

Anaerobic threshold and respiratory gas exchange during exercise

KARLMAN WASSERMAN, BRIAN J. WHIPP,
SANKAR N. KOYAL, AND WILLIAM L. BEAVER

Department of Medicine, Harbor General Hospital, Torrance 90509; and

University of California, Los Angeles, School of Medicine, Los Angeles, California 90024

WASSERMAN, KARLMAN, BRIAN J. WHIPP, SANKAR N. KOYAL, AND WILLIAM L. BEAVER. *Anaerobic threshold and respiratory gas exchange during exercise*. *J. Appl. Physiol.* 35(2): 236-243. 1973.—Alterations in gas exchange were studied in man during exercise increasing in increments of 15 w each minute, to determine the noninvasive indicators of the onset of metabolic acidosis (anaerobic metabolism). Expired airflow and CO₂ and O₂ tensions at the mouth during the breath were continuously monitored with rapidly responding gas analyzers. These measurements were recorded directly as well as processed by a minicomputer, on-line, to give minute ventilation ($\dot{V}E$), CO₂ production ($\dot{V}CO_2$), O₂ consumption ($\dot{V}O_2$), and the gas exchange ratio (R), breath-by-breath. The anaerobic threshold (AT) could be identified by the point of 1) nonlinear increase in $\dot{V}E$, 2) nonlinear increase in $\dot{V}CO_2$, 3) an increase in end-tidal O₂ without a corresponding decrease in end-tidal CO₂, and 4) an increase in R, as work rate was increased during an incremental exercise test. Of these measurements, R was found least sensitive. The AT was determined in 85 normal subjects between 17 and 91 years of age, by these techniques. The lower limit of normal was 45 w ($\dot{V}O_2 \approx 1$ liter/min), while values for very fit normal adults were as high as 180 w. The patients studied with cardiac disease above functional class I have lower anaerobic thresholds than the least fit normal subjects. The 1-min incremental work rate test is associated with changes in gas exchange which can be used as sensitive on-line indicators of the AT, thus bypassing the need for measuring arterial lactate or acid-base parameters to indicate anaerobiosis.

metabolic acidosis; nonlinear changes in $\dot{V}E$; end-tidal CO₂ tension; end-tidal O₂ tension; gas exchange ratio; anaerobic metabolism; work performance and fitness; CO₂ production; O₂ consumption; noninvasive indicators of anaerobic metabolism in man

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. Naimark 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 threshold¹ in a group of patients with heart disease. More recently, Clode and Campbell (6) have attempted to apportion the R increase into metabolic, 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 (PET_{CO₂}) and O₂ tensions (PET_{O₂}), 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 sub-

¹ The anaerobic threshold is defined as the level of work or O₂ consumption just below that at which metabolic acidosis and the associated changes in gas exchange occur.

jects and patients. The purpose of this report is to describe the exercise test for detecting the anaerobic threshold which we find most useful, and the physiological basis for the measurement of $\dot{V}E$, $\dot{V}CO_2$, and the combination of PET_{CO_2} and PET_{O_2} as alternate measurements to R as indicators of the anaerobic threshold.

THEORETICAL CONSIDERATIONS

The relationship between oxygen supply and lactic acid production are related by the Hill-Meyerhof concept of inadequacy in O_2 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 O_2 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 O_2 supply for the energy transformations are, as we have measured them, described in Fig. 1. The first consequence of the inadequate O_2 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. CO_2 can be readily exhaled into the atmosphere, thereby preventing accumulation of this acid in the body tissues. The additional CO_2 formed by this buffering is exhaled via the lungs, resulting in an increase in $\dot{V}CO_2$ and R. A stimulus resulting from the increase in $\dot{V}CO_2$ 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 O_2 required for the work rate being performed alters O_2 uptake kinetics (28). If the subject could do the work completely aerobically, the steady-state $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ is delayed during a constant work rate above the anaerobic threshold. This contrasts with the $\dot{V}O_2$ 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 subjects² 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 CO_2 and O_2 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 CO_2 and O_2 were sampled at the mouthpiece and measured with a Beckman model LB-1 or LB-2 CO_2 analyzer and a Westinghouse 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 CO_2 was 0.160 and 0.200 sec in the case of O_2 . 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

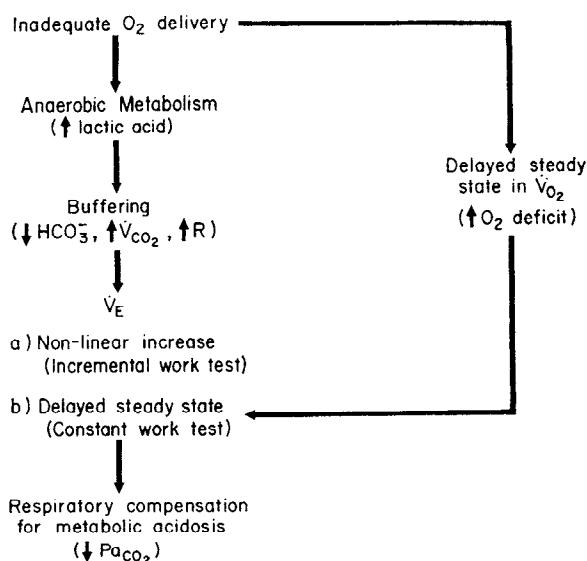


FIG. 1. Alterations in gas exchange which result from exercising at work rates above the anaerobic threshold. See text for a complete description of the flow of physiological responses depicted in this figure.

²These 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, CO_2 and O_2 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 $\dot{V}\text{E}$, $\dot{V}\text{CO}_2$, $\dot{V}\text{O}_2$, and R (2) were displayed on-line on the recorder in addition to the directly recorded expired flow, and CO_2 and O_2 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 CO_2 production and minute ventilation deviate from linearity³ 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 O_2 tension between inspired and end-tidal values without a comparable change in end-tidal CO_2 (hyperventilation with respect to O_2) 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 (2).

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 CO_2 stores reach a new steady state. This limits the usefulness of the measurement of R .

³Linearity, in this regard, refers to equal increments in response for equal increments in work rate. The "0"-w work rate is not used to establish the linear direction of the $\dot{V}\text{E}$ and $\dot{V}\text{CO}_2$ curves for the lower work rates because of the unique exercise duration of this work rate and the difficulty in knowing the amount of work being done. Thus the lowest point establishing the relationship of $\dot{V}\text{E}$ and $\dot{V}\text{CO}_2$ and work rate was 15 w in this study.

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

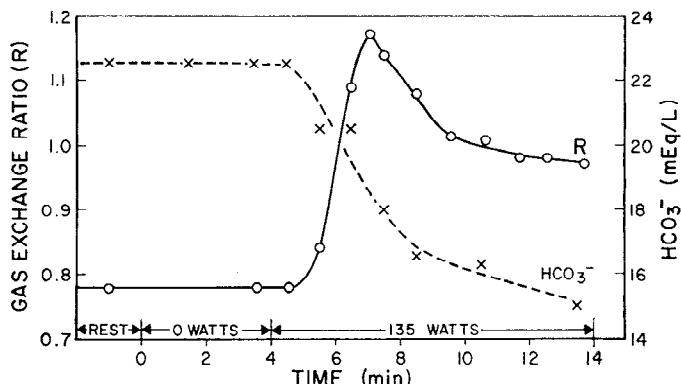


FIG. 2. Relationship between the increase in the gas exchange ratio (R) during suprathreshold exercise (135 w) and time of bicarbonate decrease. A period of unloaded cycling was done before the suprathreshold work was started, since exercise of any work intensity is usually associated with an increase in total body RQ.

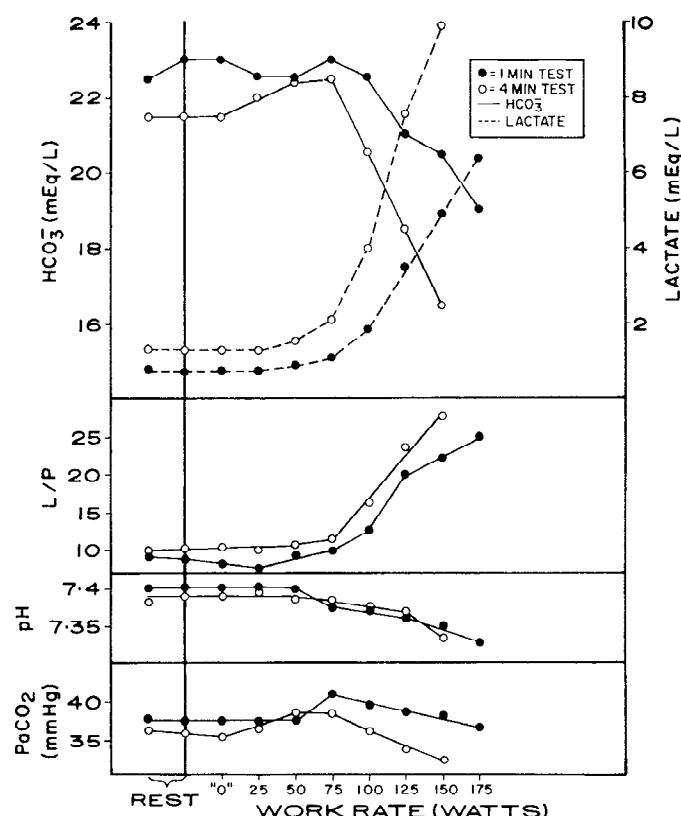


FIG. 3. Changes in lactate, bicarbonate, L/P ratio, pH, and Paco_2 during a 1-min (●) and 4-min (○) incremental work test.

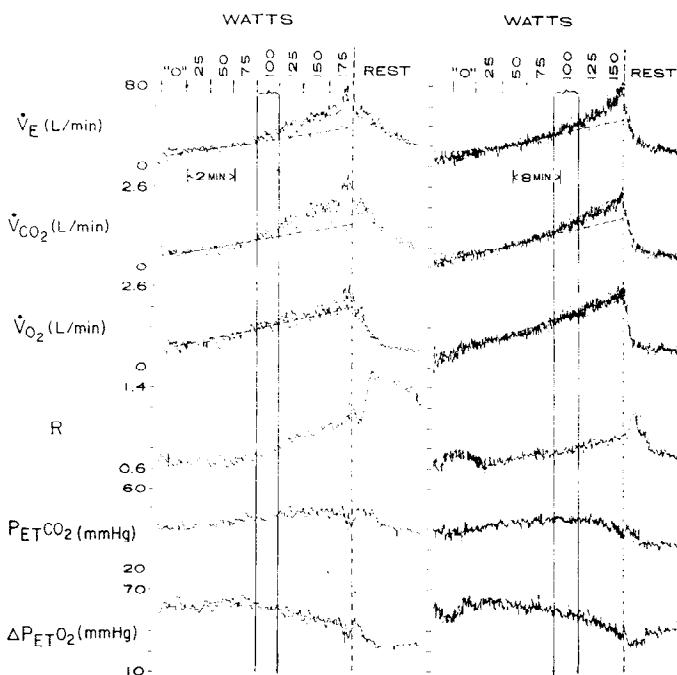


FIG. 4. Measurements of ventilatory gas exchange, breath-by-breath, for the 1- and 4-min incremental work tests described in Fig. 3.

the 4-min test. However, changes from control values occur at the same work rate.

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 ΔPET_{O_2} (difference between the inspired and end-tidal O_2 tensions) without any (1-min test) or a smaller change (4-min test) in PET_{CO_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 PET_{CO_2} and ΔPET_{O_2} in which ΔPET_{O_2} is noted to decrease while PET_{CO_2} does not change. The respiratory control

mechanism appears to be sensitively set to regulate CO_2 so that the nonproportional increase in $\dot{V}CO_2$ results in a parallel increase in $\dot{V}E$ (Fig. 5). $\dot{V}E$ increases out of proportion to $\dot{V}O_2$ above the AT with the consequent increase in PET_{O_2} or decrease in ΔPET_{O_2} . While R increases at a faster rate at work rates above the AT, the AT is visualized better from the changes in PET_{CO_2} and PET_{O_2} and the nonlinear increases in $\dot{V}E$ and $\dot{V}CO_2$. 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 $\dot{V}O_2$ s.

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.

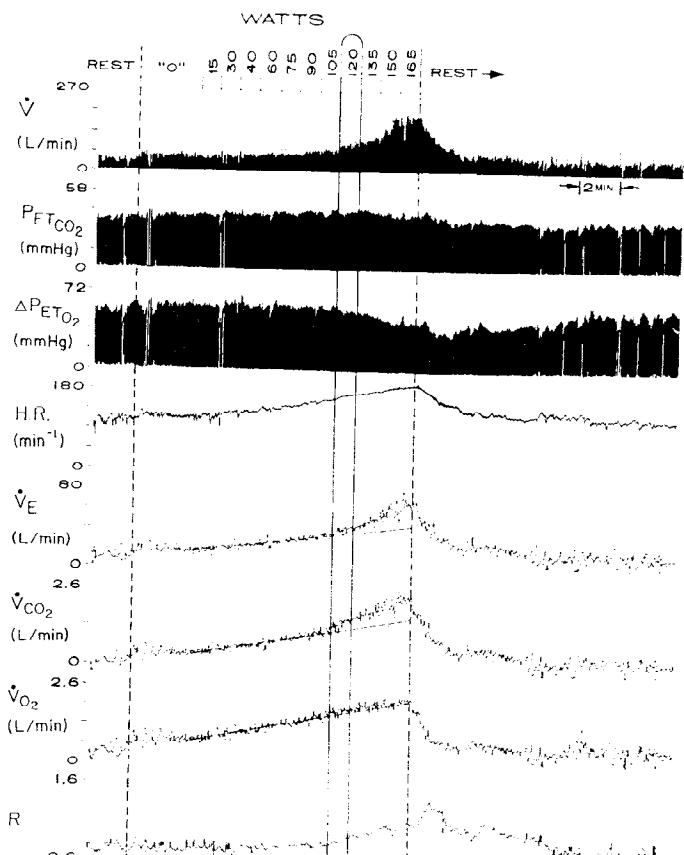


FIG. 5. Measurements in ventilatory gas exchange during an incremental work test. Work load at "0" w (unloaded pedaling) lasted for 4 min. Each additional increment in work rate was one minute in duration. Symbols are defined in text.

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 $\dot{V}O_2$ pattern is her limited cardiac output,

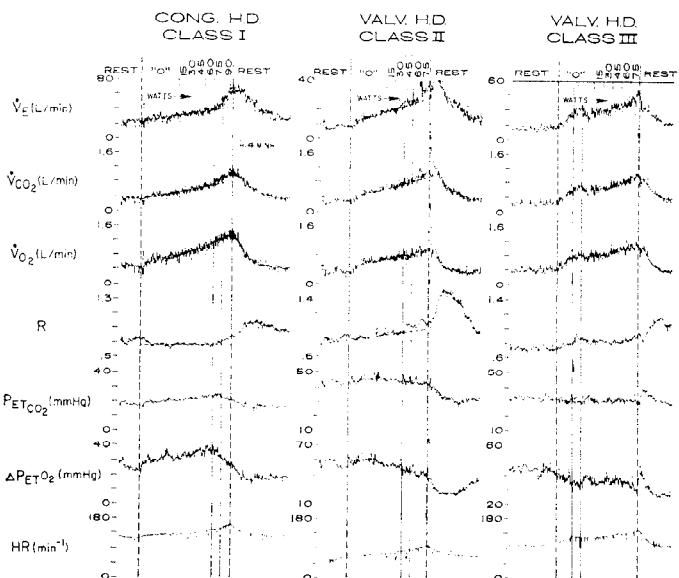


FIG. 6. Measurements of ventilatory gas exchange breath-by-breath for three subjects with heart disease. See text for further details.

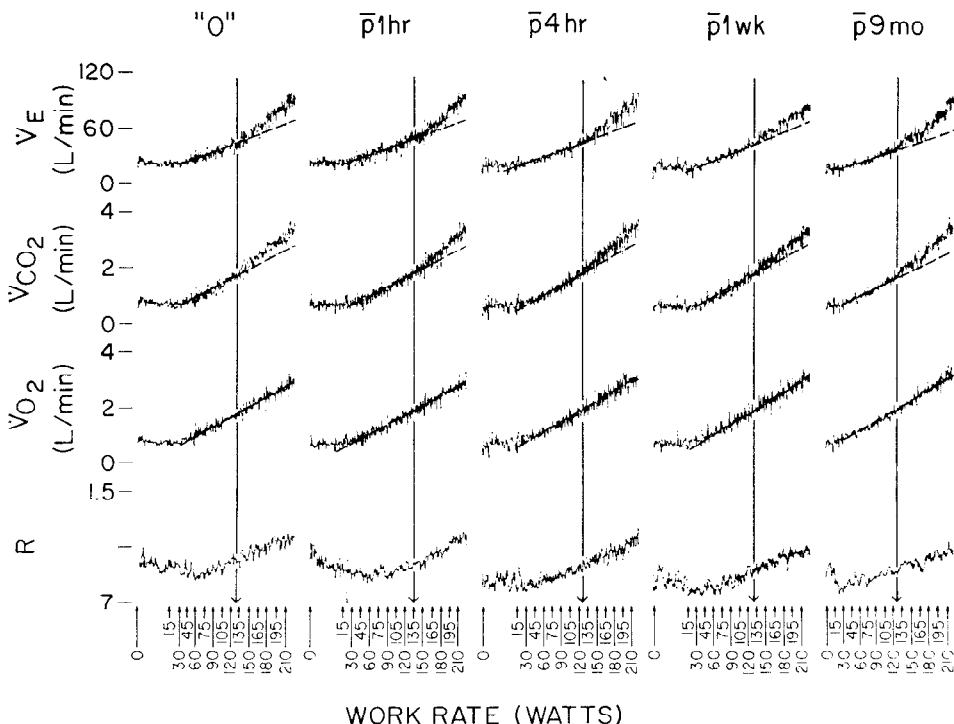


FIG. 8. Reproducibility of anaerobic threshold (AT) studies for a relatively fit 35-year-old male. Tests were performed three times on the same day and 1 week and 9 months later. Large vertical arrow indicates the AT for each study. Each interval of work above "0" w lasted 1 min.

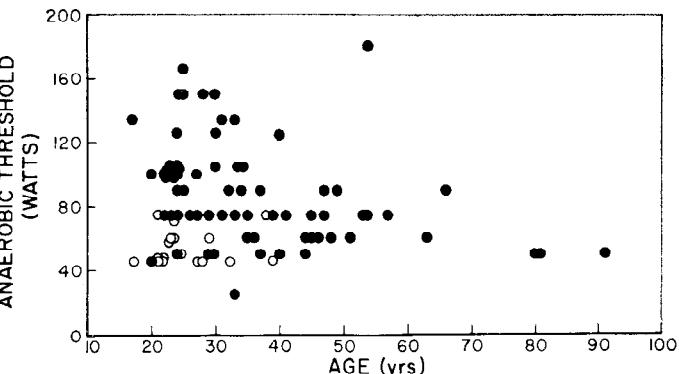


FIG. 7. Anaerobic threshold values for 85 normal subjects. Solid points are males and circles are females.

similar to that described by Meakins and Long (21). The further increase in $\dot{V}O_2$, 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 digitalis might have prevented the normal heart rate response and therefore the $\dot{V}O_2$ 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 $\dot{V}O_2$ of approxi-

mately 1 liter/min, the $\dot{V}O_2$ 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 nonlinear increase in $\dot{V}E$. However, the decrease in P_{ETCO_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 $\dot{V}E$ in this study as compared to the air-breathing study until 45 w is reached (Fig. 9). In contrast to the air-breathing study, $\dot{V}E$ is observed to increase linearly until 75 w in the case of O_2 breathing. Thus we would attribute the nonlinear hy-

perpnea 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

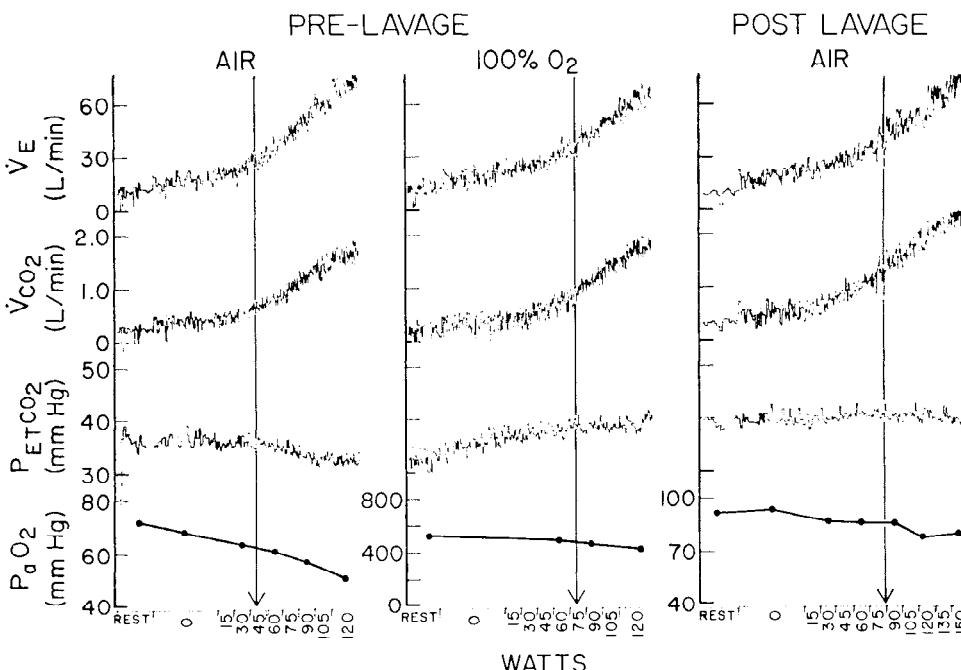


FIG. 9. Effect of exercise arterial hypoxemia on anaerobic threshold (AT) measurement (prelavage-air), effect of correcting the hypoxemia (prelavage-100% O_2), and effect of correcting the hypoxemia by therapy (postlavage-air). Vertical arrow indicates the apparent AT for each study. Each interval of work above "0" w lasted 1 min.

TABLE 1. Δ Lactate, Δ bicarbonate, minute ventilation (\dot{V}_E), change in gas exchange ratio from rest (ΔR), and heart rate at a work rate of 200 w

Subj	Δ Lactate, mEq/liter	Δ Bicar- bonate, mEq/liter	\dot{V}_E , liters/min	ΔR	Heart Rate, min ⁻¹
JJ	1.90	1.50	59.70	0.09	156
GN	2.70	4.40	81.10	0.10	163
WL	5.00	3.80	78.80	0.11	151
MC	5.10	6.00	84.90	0.12	153
CC	9.70	7.10	151.00	0.19	186

quantities (27). It is because of this buffering that $\dot{V}CO_2$ increases out of proportion to $\dot{V}O_2$.

The sensitivity of the respiratory control mechanism to $Paco_2$ and pH makes $\dot{V}E$ one of the prime gas exchange parameters in the study of the AT. As shown in Figs. 4 and 5, $\dot{V}E$ increases in response to the increase in $\dot{V}CO_2$ while maintaining PET_{CO_2} constant during the 1-min incremental work test. The precision with which ventilation increases to eliminate the increased CO_2 produced from buffering, without letting PET_{CO_2} change, becomes manifest in a decrease in ΔPET_{O_2} . Thus a simultaneous study of PET_{CO_2} and PET_{O_2} is a very sensitive way of detecting the AT. These are measurements which can be recorded directly from transducers and do not require a computer for special computations.

The simultaneous measurements of PET_{CO_2} and PET_{O_2} also permit the investigator to rule out hyperventilation with regard to CO_2 as the cause for an increase in R , since the increase in R during the 1-min incremental work rate test is associated with an increasing PET_{O_2} without a concomitant decrease of PET_{CO_2} . 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 PET_{CO_2} and $Paco_2$ (Figs. 3 and 4).

The extent to which $\dot{V}E$ 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 decrease in bicarbonate below and the increase in R above the resting values, as well as the 6th min $\dot{V}E$ and heart rate for 200-w work rate. The subjects are ranked in increasing order of their Δ lactate. It is evident that there are striking differences in $\dot{V}E$ between the man with the lowest lactate and bicarbonate change and the highest. ΔR and heart rate were less discriminatory. The first four subjects were not separable according to heart rate. The differences in ΔR for these subjects were small although in the right direction. $\dot{V}E$, being so easily measured, is an excellent determinant to use in order to detect the AT during an incremental exercise test.

Another approach for detecting the AT is the study of O_2 uptake kinetics during constant work rate exercise tests (28). Breath-by-breath measurements of V_o_2 reveal that a 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 $\dot{V}o_2$ which reaches a delayed constant value is associated with anaerobic metabolism (28). Previous studies

indicate that $\dot{V}o_2$ 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 $\dot{V}o_2$ 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 $\dot{V}o_2$ of less than 500 ml/min at the AT. Our normal subjects who are least fit have an AT $\dot{V}o_2$ -work equivalent of approximately 1 liter/min. Thus, it would appear that patients with functionally significant heart disease cannot exercise to the level of $\dot{V}o_2$ 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 $\dot{V}E$ during an incremental exercise test and look for the point at which the $\dot{V}E$ -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.

B. J. Whipp is an Established Investigator of the American Heart Association.

W. L. Beaver is a Senior Scientist, Central Research, Varian Associates, Palo Alto, Calif.

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Requests for reprints should be sent to: K. Wasserman, Division of Respiratory Medicine, Harbor General Hospital.

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DIRECTIONS-1985

Anaerobic threshold: review of the concept and directions for future research

JAMES A. DAVIS

Laboratory of Applied Physiology, California State University,
Long Beach, 1250 Bellflower Boulevard,
Long Beach, CA 90840

ABSTRACT

J.A. DAVIS. Anaerobic threshold: review of the concept and directions for future research. *Med. Sci. Sports Exerc.*, Vol. 17, No. 1, pp. 6-18, 1985. Although the term anaerobic threshold was introduced 20 years ago, the concept that an exercise-induced lactic acidosis occurs at a particular oxygen uptake which varies among subjects is over 50 years old. The surge of new interest in the parameter relates to its strong relationship to prolonged exercise performance. The average marathon running speed has been shown to be closely related to the running speed at the anaerobic threshold. Numerous studies have shown that the parameter can be validly measured during incremental exercise from the gas exchange consequences of the increased carbon dioxide and hydrogen ion levels in blood resulting from bicarbonate buffering of lactic acid. Refinement of the noninvasive detection scheme has made the parameter attractive to investigators in preventative, rehabilitative, and occupational medicine and to researchers in the exercise sciences. Controversy exists regarding the specific cause for the onset of exercise-induced metabolic acidosis. As experimentation continues to unravel the mechanisms of lactate production and ventilatory control during exercise, the anaerobic threshold concept can be further evaluated.

LACTATE, VENTILATORY CONTROL, VENTILATORY EQUIVALENTS FOR $\dot{V}O_2$ AND $\dot{V}CO_2$, METABOLIC ACIDOSIS, GAS EXCHANGE, EXERCISE TESTING, ENDURANCE PERFORMANCE

The renewed interest over the last 10 years in the anaerobic threshold concept stems largely from a series of papers (25,47,53,60) which report that endurance exercise performance is well correlated to the highest oxygen uptake that can be achieved during exercise before a systematic increase in blood lactate concentration occurs, i.e., the anaerobic threshold. This attribute has important implications in the exercise sciences and in occupational, preventative, and rehabilitative medicine. In recent years, however, several authors have challenged the anaerobic threshold concept and the methods for its detection. In an attempt to clarify the issues involved, I will put forward a current description of the concept, discuss the major controversies, and

finally suggest areas of future research which might be productive.

BRIEF HISTORY

In the early part of this century, Douglas and his colleagues (9,20,52) observed that a series of work rates could be performed without any change in blood lactate concentration from the resting value. As the work rate was increased beyond a certain level, they observed an increase in blood lactate concentration. They also observed that the carbon dioxide (CO_2) combining power of the blood (essentially the bicarbonate concentration [HCO_3^-]) was reduced with increased blood lactate and that breathing was stimulated "to expel the CO_2 set free as the sodium bicarbonate concentration in the blood is diminished" (20). In 1924, Hill et al. (33) postulated that lactate increased during muscular exercise because of an inadequacy of oxygen available for the energy requirements of the contracting muscles. Wasserman and McRoy (66), in 1964, introduced the term "anaerobic threshold" and elaborated on the concept that pulmonary gas exchange measured at the mouth could be used to detect the onset of metabolic (lactic) acidosis. In later work, Wasserman and his colleagues (16,18,71) further refined the noninvasive measurement of the anaerobic threshold. In the early 1960's, Hollmann (34), working in Germany, independently described the anaerobic threshold concept and its noninvasive detection. Much of the interest in the anaerobic threshold in Europe and Scandinavia today undoubtedly stems from Hollmann's early work and his linkage of the anaerobic threshold to endurance performance.

CURRENT CONCEPT OF THE ANAEROBIC THRESHOLD

The anaerobic threshold concept is as follows. At low exercise intensities, the level of blood lactate concentra-

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tion is the same as it is at rest. At some particular exercise intensity, which varies among subjects, blood lactate concentration begins to increase. As the work rate increases still further, blood lactate progressively rises throughout the exercise period. Because of its low pK , lactic acid will be almost completely dissociated, and it is buffered predominantly by the bicarbonate system (67), i.e., lactic acid + sodium bicarbonate \rightarrow sodium lactate + carbonic acid (H_2CO_3). The hydrogen ion (H^+) derived from the production of lactic acid is responsible for the evolution of both H_2CO_3 and CO_2 in accordance with the reaction:



The enzyme carbonic anhydrase catalyzes the carbonic acid to CO_2 and H_2O reaction so that CO_2 is quickly formed, and any disequilibrium between H_2CO_3 and CO_2 is minimized. The rapid conversion of H_2CO_3 to CO_2 and H_2O is thought to occur both intracellularly and just as H_2CO_3 enters the muscle vasculature. Effros and Weissman (21) found evidence that carbonic anhydrase is likely to be located on the endothelial surface of the muscle vasculature. A less active form of the enzyme is contained within muscle cells. Consequent to the buffering of lactic acid, the partial pressure of CO_2 (PCO_2) and H^+ of venous capillary blood increases. Because ventilatory control mechanisms try to maintain homeostasis of arterial PCO_2 ($PaCO_2$) and of H^+ , the "excess" CO_2 and increased H^+ from the buffering of lactic acid causes ventilation to increase. For exercise above the anaerobic threshold, ventilation responds to two different CO_2 sources. One is the metabolic CO_2 generated from aerobic metabolism. The second is the excess CO_2 resulting from the buffering of lactic acid. Thus, the "excess" ventilation that occurs above the anaerobic threshold is due to the excess CO_2 and increased H^+ . Wasserman et al. (72) have shown that subjects who have had their carotid bodies surgically removed have much less excess ventilation for work rates above the anaerobic threshold (Figure 1). Their excess ventilation appears to be in response to the excess CO_2 but not to H^+ , because they fail to develop respiratory compensation for exercise-induced lactic acidosis; i.e., they do not have a fall in $PaCO_2$ at high work rates. This suggests that the carotid bodies, through stimulation by H^+ , mediate the dominant component of the acute ventilatory response to metabolic acidosis.

In recent years, the term "anaerobic threshold" has been the target of considerable controversy, with the accuracy of the word "anaerobic" and the word "threshold" being questioned. Hill et al. (33) and, later, Wasserman and McIlroy (66) felt that the increase in blood lactate was inextricably linked to the onset of local muscle hypoxia at a certain work rate. Wasserman used the word "anaerobic" to indicate that O_2 supply was

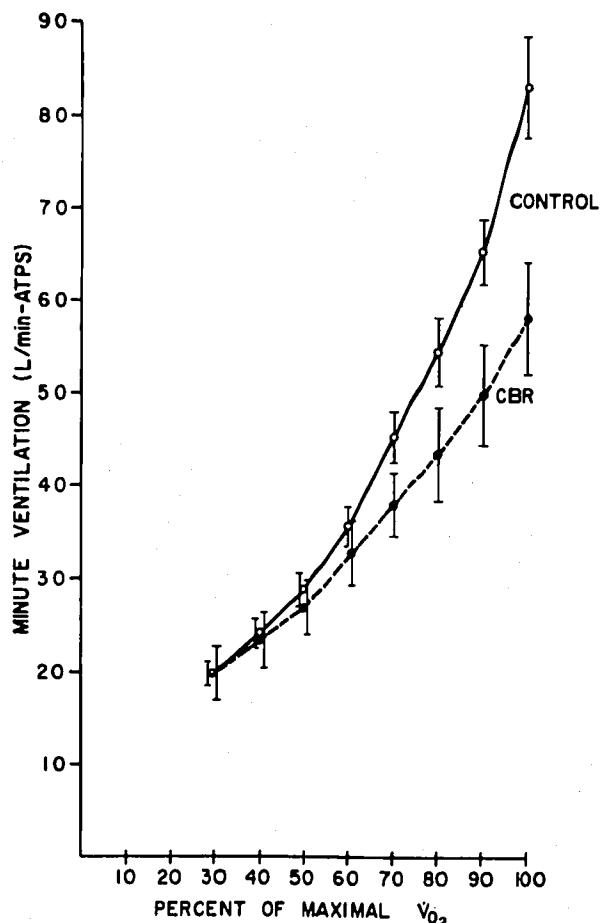


Figure 1—Average \dot{V}_E response, expressed as a percent of $\dot{V}O_{2\max}$ for a 1-min incremental cycle ergometer exercise test for 11 normal (control) subjects and six carotid body resected (CBR) subjects. Vertical bars at each point represent ± 1 SE. Reproduced, with permission, from Wasserman et al. (72).

insufficient for the working muscle's energy needs to be exclusively supported by aerobic metabolism [though others using the word have not asserted this mechanistic inference (15)]. Recently, investigators have challenged the idea that muscle hypoxia is the cause of the increase in blood lactate at a particular work rate (8,19,27,35). They emphasize that blood lactate concentration is the net result of lactate production and lactate removal. Thus, the rise in blood lactate concentration may not necessarily indicate the onset of increased lactate production by the exercising muscle. Increased lactate production, they argue, could have occurred much earlier but may not have caused an increased blood lactate concentration because lactate removal had also increased. It is known that nonexercising muscle (22), the liver (63), the kidney (85), and the heart (74) can metabolize lactate. Two reports (40,46) have shown, using steady-state exercise, that for work rates below approximately 50–60% of the maximal oxygen uptake ($\dot{V}O_{2\max}$), muscle lactate does not increase. As shown in Figure 2, the pattern of change is the same for blood and muscle lactate. This supports

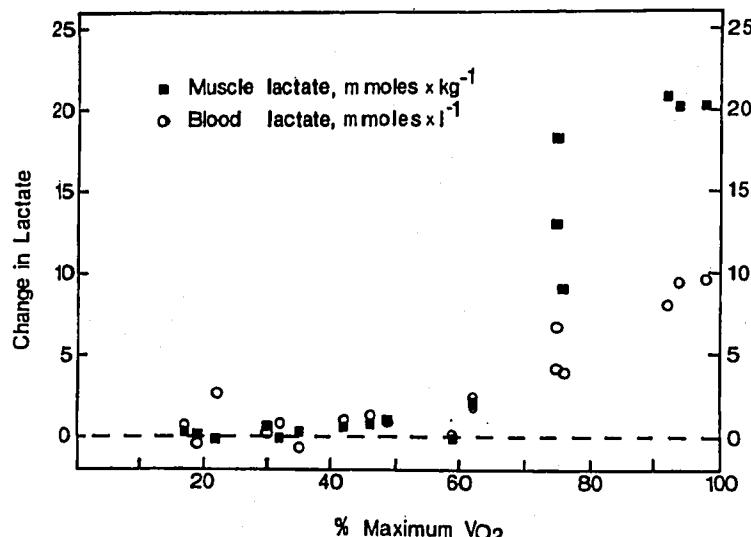


Figure 2—Relationship of change in muscle and arterialized venous blood lactate concentrations expressed as a percent of $\dot{V}O_{2\text{max}}$. Reproduced, with permission, from Knuttgen and Saltin (46).

the idea that the initial increase in blood lactate concentration does reflect the onset of increased lactate production in working muscle. The debate over the "anaerobic" portion of the term has caused some investigators to use a less mechanistic descriptor, e.g., lactate threshold (12).

Use of the word "threshold" has also been challenged. Some believe that during incremental exercise, blood lactate begins to increase during the initial work rates (8,13,80). Hence, they do not find evidence for a "threshold" or a range of work rates where blood lactate remains at its resting value. Part of this discrepancy can be explained by differences in data analysis. In an attempt to demonstrate the average response of their data, some investigators have "pooled" the individual data (8,13). But pooling data to determine a mean anaerobic threshold is invalid, because it will always produce a lower mean value than the mean of the individual values, owing to the artifact of the non-uniform weighting imposed by pooling graphical data (cf. 15). For example, as shown in Figure 3, hypothetical subject #1 has a clear lactate break point at a $\dot{V}O_2$ of $1 \cdot \text{min}^{-1}$, and the corresponding value for subject #2 is $2 \cdot \text{min}^{-1}$. Graphical pooling of the data dampens the clear individual break points and results in a pooled mean anaerobic threshold that is still at $1 \cdot \text{min}^{-1}$.

RELATION OF THE ANAEROBIC THRESHOLD TO EXERCISE ENDURANCE PERFORMANCE

Perhaps the most attractive aspect of the anaerobic threshold in the exercise sciences is its relation to endurance performance. In an important early study on this specific topic, Farrell et al. (25) showed that of the various indices purported to predict endurance performance (running economy, relative body fat, $\dot{V}O_{2\text{max}}$, percentage of slow-twitch muscle fibers, and the anaerobic threshold), the treadmill velocity corresponding to the lactate anaerobic threshold yielded the highest cor-

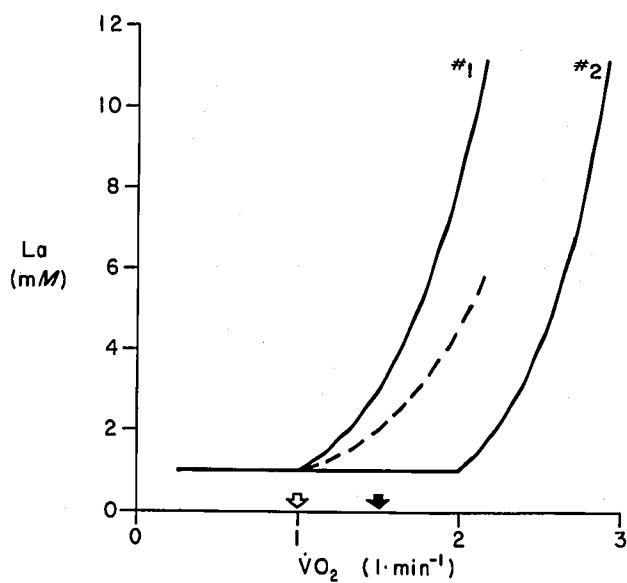


Figure 3—A diagrammatic representation which demonstrates the error made when lactate data are pooled to find the "mean" anaerobic threshold (cf. 15). The lactate break point for subject 1 occurs at $1 \cdot \text{min}^{-1}$, whereas the corresponding value for subject 2 is $2 \cdot \text{min}^{-1}$. The dashed line is obtained by adding each consecutive pair of lactate data points together. For example, at a $\dot{V}O_2$ of $1.5 \cdot \text{min}^{-1}$, subject 1's value (which has not changed from the resting value of 1 mM) is added to subject 2's value (which has increased to 3 mM) to give 4 mM . The "pooled" response is then one half of 4 mM , or 2 mM . The pooled anaerobic threshold value is shown at the open arrow, while the correct value is shown at the closed arrow. The pooled line terminates at $2.15 \cdot \text{min}^{-1}$ because that represents the last consecutive pair of lactate data points common to both subjects.

relation ($r = 0.98$) with marathon running performance in 13 runners. The "race pace" of the marathon runners was, on average, within $8 \text{ m} \cdot \text{min}^{-1}$ of the running velocity at the anaerobic threshold (see Figure 4). Powers et al. (53), using nine runners, showed that the anaerobic threshold correlated highly ($r = 0.94$) with 10-km racing times. They found much smaller and nonsignificant correlations for running economy ($r = 0.51$) and $\dot{V}O_{2\text{max}}$ ($r = 0.32$). Kumagai et al. (47)

compared 5- and 10-km times to the anaerobic threshold and $\dot{V}O_{2\text{max}}$ in 17 runners. They found correlations of 0.95 and 0.84, respectively, for race pace vs the anaerobic threshold. Corresponding correlations for $\dot{V}O_{2\text{max}}$ were 0.65 and 0.67.

Other investigators (43,58) have chosen to use the running speed at a blood lactate concentration of 4 mM and relate this value to endurance performance. For reasons not clear they have named this point, which is approximately four times greater than the resting blood lactate concentration, the "onset of blood lactate accumulation" or OBLA. They, too, have reported high

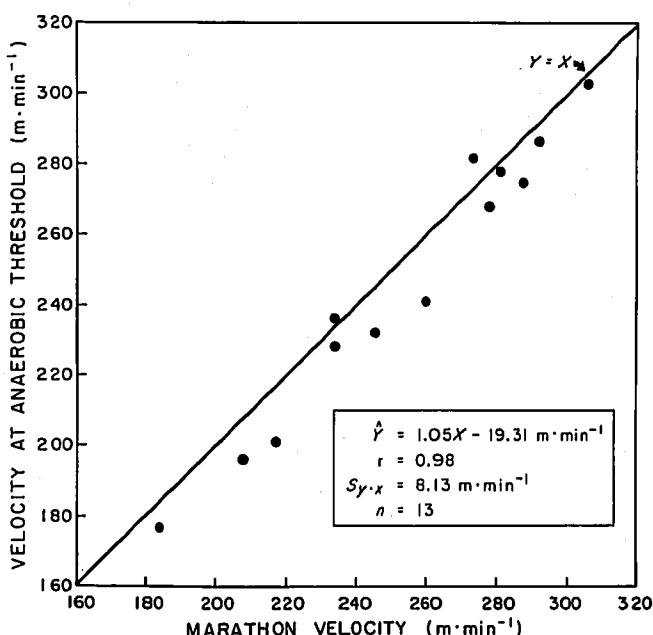


Figure 4—Comparison of marathon velocity and the velocity at the anaerobic threshold in 13 runners from the data of Farrell (24).

correlations between running performance and OBLA. Recently, Tanaka et al. (60) compared the anaerobic threshold and OBLA to marathon running performance. They found that the average marathon running speed was nearly identical to the running speed at the anaerobic threshold determined on the treadmill and was significantly lower than that found for OBLA. For activities with durations between 30 and 60 min, investigators have reported that blood lactate concentrations between 3 and 5 mM can be sustained (45,59). This demonstrates that shorter duration endurance events can be performed above the anaerobic threshold.

The postulated rationale for the close relationship between the anaerobic threshold and endurance performance relates to the rate of muscle glycogen breakdown. Because long-term, high-intensity exercise results in, and is perhaps ultimately limited by, muscle glycogen depletion (41,56), exercise just below the anaerobic threshold would result in a much slower reduction of the muscle glycogen stores than exercise above the anaerobic threshold and would therefore be tolerable for much longer periods of time. This is because glycogen is used at a rate that is 18–19 times faster during anaerobic glycolysis compared to oxidative phosphorylation for the same energy (ATP) yield. Boyd et al. (4) have demonstrated that elevations in blood lactate concentration inhibit lipolysis in exercising man and thus force obligatory carbohydrate utilization.

The anaerobic threshold, in both absolute terms and expressed as a percentage of $\dot{V}O_{2\text{max}}$, is high in the endurance-trained athlete. For example, in sedentary individuals, the anaerobic threshold occurs at ~50–60% of $\dot{V}O_{2\text{max}}$ (16,17), whereas in endurance-trained athletes it occurs at ~70–80% of $\dot{V}O_{2\text{max}}$ (25). Also, the anaerobic threshold is quite sensitive to exercise train-

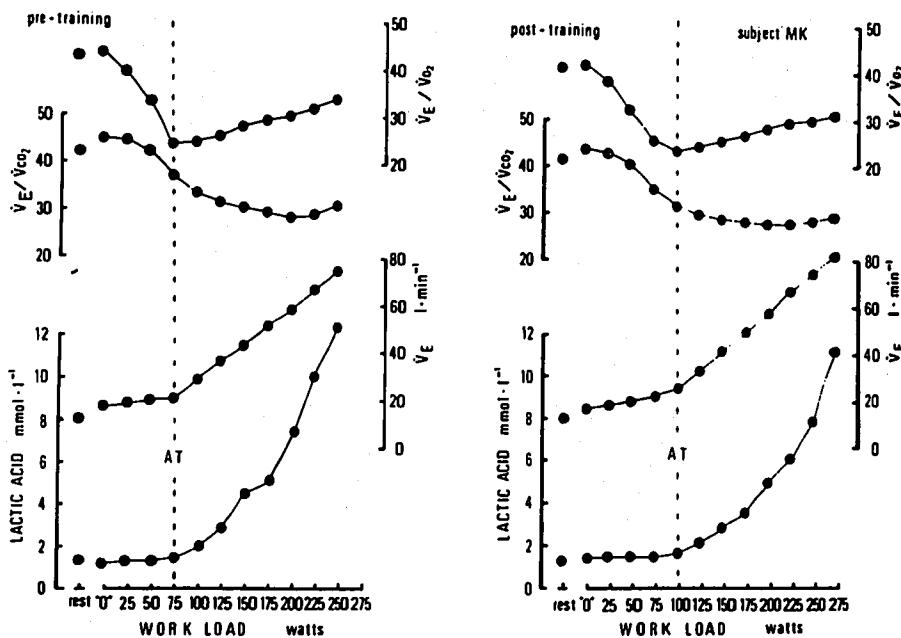


Figure 5—Comparison of the lactate and gas exchange anaerobic thresholds before and after endurance training in seven subjects. The anaerobic threshold, pre- and post-training, is indicated by the dashed vertical lines. Reproduced, with permission, from Yoshida et al. (83).

ing. Davis et al. (16) studied nine healthy middle-aged men before and after 9 weeks of strenuous endurance training. Whereas $\dot{V}O_{2\text{max}}$ increased by 25%, the anaerobic threshold increased 44%. Yoshida et al. (83) found similar results after 8 weeks of training in seven healthy male college students (see Figure 5).

ANAEROBIC THRESHOLD DETERMINED FROM BLOOD LACTATE CONCENTRATION

A technical problem with interpreting the time course of blood lactate is pointed out by the recent study of Yoshida et al. (84). They found that the anaerobic threshold is systematically higher if the venous blood break point is compared to the arterial blood break point. The investigators suggested that the likely cause for this finding was the uptake of lactate from the forearm muscles before the blood reached the venous sampling site (antecubital vein). The authors did not mention whether they controlled the activity of the forearm muscles. Jorfeldt et al. (40) found a 30–50% uptake of lactate with light forearm exercise. Many subjects tend to tighten their grip on the cycle handgrips as the work rate increases in an effort to stabilize their upper torso. Given that the anaerobic threshold discerned from changes in ventilation and gas exchange has been validated in studies using venous (7,17,39),

arterialized venous (55), and arterial (82) blood sampling, it is likely that possible differences between these sampling sites is small if forearm muscle movement is minimized. Thus, use of the venous blood lactate break point can cause errors unless a concerted attempt is made by the investigators to minimize any forearm exercise during the test (cf. 15).

Conflicting information has been published concerning the possibility that the lactate anaerobic threshold may be influenced by the rate of increase in work rate. Hughson et al. (37) reported that slow ramp testing ($8 \text{ W} \cdot \text{min}^{-1}$) yielded lower anaerobic threshold values than those found for fast ramp testing ($65 \text{ W} \cdot \text{min}^{-1}$). Conversely, Wasserman et al. (71) found similar anaerobic threshold values during exercise testing for both 1- and 4-min increment durations (the increment size was 25 W for both tests). The most comprehensive study to date on this topic was recently reported by Yoshida (81). Duplicating the design of Wasserman et al. (71), Yoshida also found similar anaerobic thresholds for the 1- and 4-min increment durations.

ANAEROBIC THRESHOLD DETERMINED FROM VENTILATION AND GAS EXCHANGE

The ability to detect the anaerobic threshold noninvasively is an important feature of the parameter. Car-

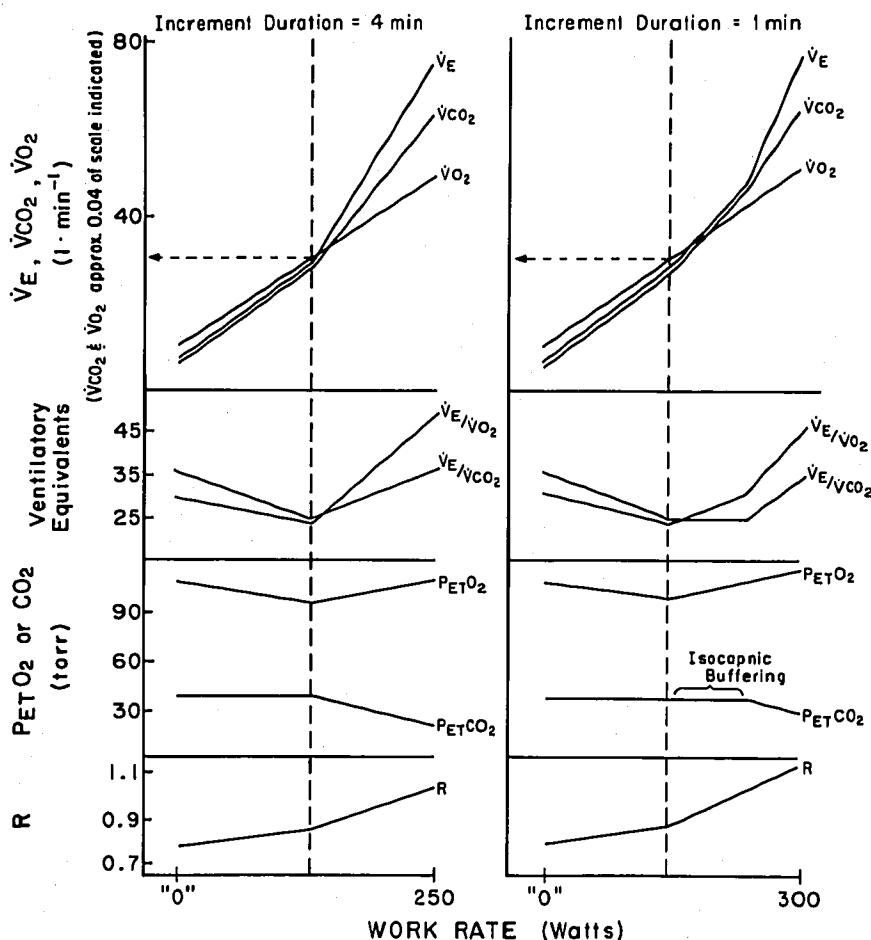


Figure 6—Diagrammatic representation of changes in minute ventilation (V_E), oxygen uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), ventilatory equivalent for $\dot{V}CO_2$, ($V_E/\dot{V}CO_2$), ventilatory equivalent for $\dot{V}O_2$ ($V_E/\dot{V}O_2$), end-tidal PCO_2 ($P_{ET}CO_2$), end-tidal PO_2 ($P_{ET}O_2$), and the gas exchange ratio (R) for 4-min and 1-min incremental exercise tests. The vertical dashed lines denote the break points in ventilation and gas exchange according to the detection scheme outlined in the text. The $\dot{V}O_2$ at the anaerobic threshold is indicated by the horizontal arrow line. Modified from Wasserman and Whipp (68).

diologists (48,73), pulmonary physiologists (23, 30,65), and exercise scientists (7,25,53) have found the measurement useful in their respective fields. The non-invasive detection of the anaerobic threshold has gone through several refinements. Initially, it was suggested that departures in the linearity of ventilation (\dot{V}_E) and carbon dioxide output ($\dot{V}CO_2$) plus an abrupt increase in the gas exchange ratio (R) could be used as markers for the onset of a metabolic acidosis (17,71). While these are valid indices, they are not optimal, because it is often difficult to judge the $\dot{V}O_2$ value at which \dot{V}_E , $\dot{V}CO_2$, and R begin to increase *more steeply*. A better detection scheme would involve determining the anaerobic threshold as the break point from a variable that is decreasing or is relatively unchanging over a number of work rates before it begins to increase.

Two variables have this pattern of response during incremental exercise. They are the ventilatory equivalent for $\dot{V}O_2$ ($\dot{V}_E/\dot{V}O_2$) and end-tidal P_{O_2} ($P_{ET}O_2$). During the early work rates of an incremental test, both variables decrease because the physiological dead space to tidal volume ratio (V_D/V_T) decreases. The decrease becomes less steep as the work rate continues to increase. At some point, $\dot{V}_E/\dot{V}O_2$ and $P_{ET}O_2$ begin to systematically increase (see Figures 5 and 6). But other events can also cause these two variables to increase, e.g., anxiety, pain, hypoxemia, and volitional hyper-ventilation. How then can one be sure that the increases in $\dot{V}_E/\dot{V}O_2$ and $P_{ET}O_2$ are due to an exercise-induced lactic acidosis and not to some other ventilatory stimulus?

The answer involves the concept of "isocapnic buffering." Wasserman et al. (64) have shown that for "rapid" incremental exercise tests, \dot{V}_E and $\dot{V}CO_2$ increase at the same rate for a few work rates beyond the anaerobic threshold (see Figure 6). This is evident by the fact that $\dot{V}_E/\dot{V}CO_2$ does not increase at the anaerobic threshold but remains stable (as does V_D/V_T), implying that arterial PCO_2 is unchanged in this region where buffering of lactic acid is occurring (hence the term isocapnic buffering). Thus, the criterion of the systematic increase in $\dot{V}_E/\dot{V}O_2$ without a concomitant increase in $\dot{V}_E/\dot{V}CO_2$ is the most specific gas exchange method for detection of the anaerobic threshold. Caiozzo et al. (7) compared several gas exchange indices of anaerobic threshold detection and found that, indeed, the ventilatory equivalent criterion yielded the best agreement with blood lactate estimates of the anaerobic threshold.

Isocapnic buffering does not occur when the increment duration is long, e.g., 4 min (see Figure 6). During these so-called "steady-state" incremental exercise tests, both ventilatory equivalents begin to increase at the same $\dot{V}O_2$. As the duration of the work rate increment is shortened, the region of isocapnic buffering becomes larger, exceeding $1 \text{ l} \cdot \text{min}^{-1}$ of $\dot{V}O_2$ above the anaerobic threshold for rapid incremental exercise tests (77). Why

this difference in the gas exchange response exists between slow and fast incremental exercise tests is currently not known. The optimal protocol for the non-invasive detection of the anaerobic threshold would appear to be one that 1) maximizes the investigator's ability to observe the isocapnic buffering region and 2) results in a clear break point in $\dot{V}_E/\dot{V}O_2$.

Numerous studies have examined the validity of the noninvasive determination of the anaerobic threshold. Five teams of researchers (7,17,39,55,82) have found close agreement between the anaerobic threshold, determined noninvasively and by blood lactate. Typical of these studies is the investigation of Caiozzo et al. (7). The systematic increase in $\dot{V}_E/\dot{V}O_2$ without a concomitant increase in $\dot{V}_E/\dot{V}CO_2$ yielded anaerobic thresholds highly correlated ($r = 0.93$) with those determined from the break point in blood lactate in 16 subjects. The noninvasive vs invasive anaerobic threshold linear regression equation was nearly equal to the line of identity and had a small standard error of estimate.

Three other studies have examined the validity of the noninvasive determination of the anaerobic threshold and have reported results that are not as encouraging. Green et al. (27) used a computer algorithm to select the anaerobic threshold from both the ventilation and lactate data. The validity of this algorithm has been challenged by others (80) and is questioned below. Yeh et al. (80) used four observers to select the gas exchange anaerobic threshold and found a large variation in their selections. However, the observers who selected the anaerobic threshold in this study did not seem to carefully follow the stated anaerobic threshold detection criteria (14). A plot of the average selection (in an attempt to reduce the observer "noise") of the gas exchange vs the lactate anaerobic threshold demonstrates good agreement between the two detection methods (cf. 14). Powers et al. (54) also compared anaerobic thresholds discerned from gas exchange and lactate responses during incremental exercise. They reported a correlation coefficient of 0.63 but failed to point out that in only one of their 13 subjects was there a sizeable difference ($690 \text{ ml} \cdot \text{min}^{-1}$) between the two methods. In 8 of the 13 subjects, the gas exchange and lactate anaerobic thresholds occurred at identical $\dot{V}O_2$ values. In four of the five other subjects, the difference between the two methods averaged $188 \text{ ml} \cdot \text{min}^{-1}$. Were it not for the single discrepant subject, the correlation coefficient would have been 0.94.

One of the problems with the gas exchange anaerobic threshold is that detection can be difficult even when the correct criteria are used. Orr et al. (51) recognized this and proposed to make the determination by a computerized algorithm. Using a multi-segment linear regression method, the anaerobic threshold is selected as the point where the plot of \dot{V}_E vs $\dot{V}O_2$ becomes non-linear. To validate the algorithm, they did not compare it to the blood lactate anaerobic threshold but instead

compared it to the result of four observers, selecting the anaerobic threshold from plots of \dot{V}_E vs $\dot{V}O_2$. In a later paper, Green et al. (27) used the same algorithm and reported that the anaerobic threshold determined from the \dot{V}_E vs $\dot{V}O_2$ plot occurred at a significantly higher $\dot{V}O_2$ than the lactate anaerobic threshold. Panel A of Figure 7 reproduces the plot of data from the subject which Green et al. felt most representative of their results. Panel B shows the $\dot{V}_E/\dot{V}O_2$ values as computed from the data in Panel A. As can be seen, the algorithm overestimates both the lactate and gas exchange anaerobic thresholds, whereas the systematic increases in $\dot{V}_E/\dot{V}O_2$ and blood lactate occur within 50 $\text{ml} \cdot \text{min}^{-1}$ of each other.

Hagberg et al. (28) used patients with McArdle's syndrome in an attempt to examine the gas exchange anaerobic threshold concept. The investigators hypothesized that because these patients do not produce lactate during exercise, owing to a muscle enzyme deficiency, they should not demonstrate the gas exchange changes associated with the anaerobic threshold. Yet when these patients exercised, $P_{ET}O_2$ increased at a similar fraction of $\dot{V}O_{2\max}$ as seen in the healthy control subjects, even

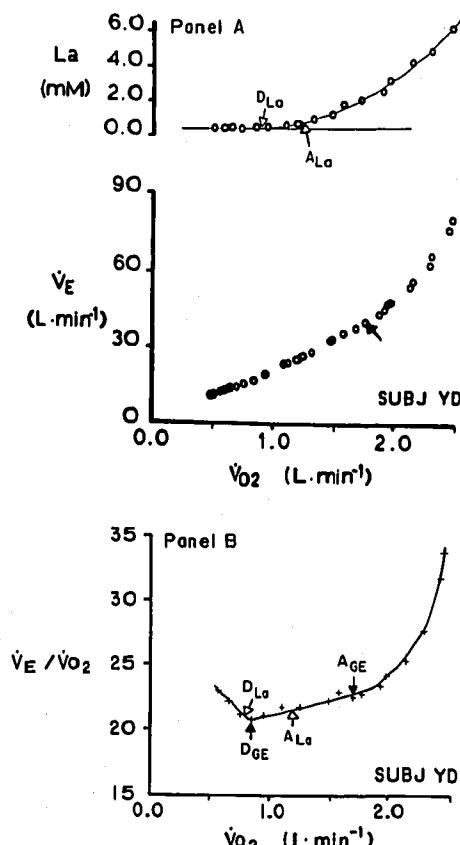


Figure 7—Panel A is taken from Green et al. (27). Added to the figure are A_{La} , which is the computer algorithm's selection for the lactate anaerobic threshold, and D_{La} , which is my selection aided by horizontal and curved lines superimposed on the data points. Panel B shows the $\dot{V}_E/\dot{V}O_2$ data which were derived from Panel A. D_{la} and D_{GE} are my selections for the lactate and gas exchange anaerobic thresholds, respectively; A_{la} and A_{GE} are the algorithm's selections.

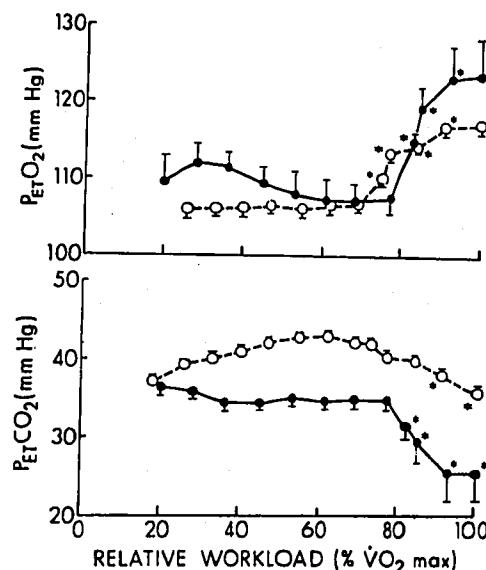


Figure 8—Average $P_{ET}O_2$ and $P_{ET}CO_2$ responses to incremental exercise in 26 normal subjects (open circles) and four patients (filled circles) with McArdle's syndrome expressed as a percent of $\dot{V}O_2$ max. Reproduced, with permission, from Hagberg et al. (28).

though blood lactate did not increase. This finding led Hagberg et al. to suggest that changes in ventilation and gas exchange are independent of increases in blood lactate. In response, Whipp (75) has pointed out that because exercise-induced pain is the chief symptom of McArdle's syndrome patients, the gas exchange changes noted by Hagberg et al. were likely to have been caused by pain or "the apprehension of its impending induction." As stated earlier, the gas exchange response to pain, anxiety, etc. can be distinguished from that corresponding to a metabolic acidosis. The data seen in Figure 8 [reproduced from Hagberg et al. (28)], though presented as averaged responses, demonstrates this nicely. Note that in the patients there is no region of isocapnic buffering; $P_{ET}O_2$ increases at the same point that $P_{ET}CO_2$ increases. Yet in the healthy subjects, isocapnic buffering is evident from 70% of $\dot{V}O_2$ max to about 84% of $\dot{V}O_2$ max where $P_{ET}CO_2$ begins to systematically decrease.

The test-retest reproducibility of the gas exchange anaerobic threshold has been recently investigated by Davis et al. (16), Caiozzo et al. (7), and Powers et al. (53). All groups found excellent agreement with repeat incremental exercise testing. No study to date has reported the test-retest reproducibility of the lactate anaerobic threshold.

The gas exchange anaerobic threshold detection scheme, as currently used, has a major limitation. Some subjects have such an erratic breathing pattern that noninvasive detection of the parameter is not possible. Even in those subjects who have a regular breathing pattern, irregular breathing near the anaerobic threshold may obscure the ability to discern the parameter correctly. As suggested nearly a decade ago (17), repeat

tests are sometimes necessary in order to secure an accurate estimate of the parameter using the noninvasive gas exchange technique.

IMPORTANCE OF THE ANAEROBIC THRESHOLD

A parameter that can predict the highest metabolic rate which can be maintained for long periods of time has application in a number of areas. The interpretation of impairment/disability exercise evaluations has been less than optimal in the past. The primary objective of these tests is to determine if the individual has enough cardiopulmonary reserve to perform his/her job over an 8-h period. To simply state, as the American Lung

Association has (1), that the individual should be able to exercise at 30–40% of his/her $\dot{V}O_{2\text{max}}$ seems arbitrary. A more rational criterion for impairment would require that the metabolic cost of the occupation not exceed the individual's anaerobic threshold. The use of the anaerobic threshold as an important criterion for impairment/disability evaluations is gaining acceptance in occupational medicine (30).

A consequence of the anaerobic threshold is that exercise which causes a lactic acidosis results in a "drift" in $\dot{V}O_2$ (Figure 9) during constant work rate exercise (29,78). Work rates below the anaerobic threshold allow $\dot{V}O_2$ to reach a steady state in about 3 minutes. For work rates slightly above the anaerobic threshold, the time to steady state is prolonged. Work rates that are well above the anaerobic threshold cause the $\dot{V}O_2$ to drift up to the subject's $\dot{V}O_{2\text{max}}$. Because the $\dot{V}O_2$ drift only occurs at work rates above the anaerobic threshold, its occurrence is likely to be related to the increased lactate. Infusions of lactate (3) and catecholamines (61) have been shown to increase $\dot{V}O_2$, and therefore these substances, which only appear to increase above the anaerobic threshold, are possible mediators. Increases in body temperature may also account for part of the drift. Work rates above the anaerobic threshold also have a pronounced effect on the ventilatory response. For constant work rate exercise that is below the anaerobic threshold, \dot{V}_E , tidal volume (V_T), and breathing frequency (f) achieve a steady state within 5 min. The corresponding variables have a markedly different response for constant work rate exercise above the anaerobic threshold as \dot{V}_E and f drift up while V_T drifts down (see Figure 10).

The differences in lactate concentration, substrate availability, body temperature, ventilatory response, and catecholamine levels for constant work rate exercise above the anaerobic threshold suggest that it is important for investigators to recognize the exercise domain

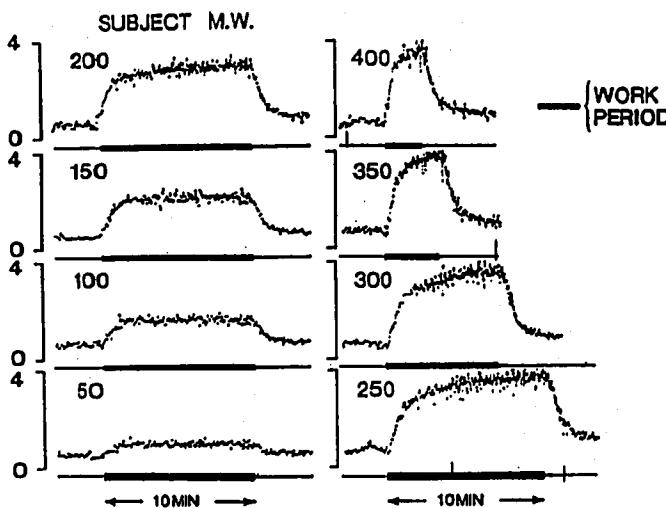


Figure 9—Breath-by-breath display of $\dot{V}O_2$ in response to eight different work rates preceded and followed by unloaded cycling. Note the absence of a steady state for work rates greater than 150 W for this subject, whose anaerobic threshold corresponded to a steady-state work rate of approximately 170 W. The subject's $\dot{V}O_{2\text{max}}$, determined from an incremental exercise test, was $3.67 \text{ L} \cdot \text{min}^{-1}$, which is the peak value of the $\dot{V}O_2$ drift seen in the 250, 300, 350, and 400 W tests. Modified from Whipp and Mahler (77).

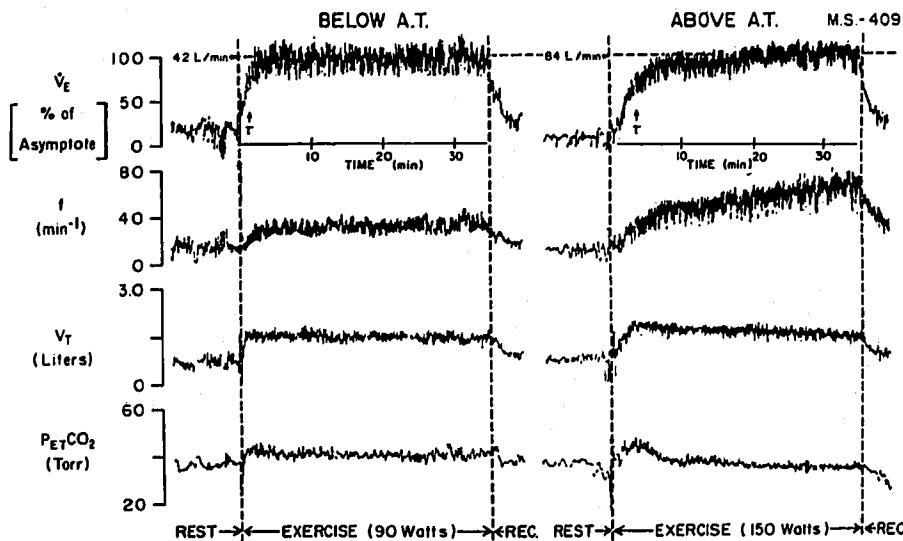


Figure 10—Differential effect of prolonged cycle ergometer exercise on breath-by-breath values for \dot{V}_E , f , V_T , and $P_{ET}CO_2$ when performed below and above the anaerobic threshold. Reproduced, with permission, from Wasserman et al. (69).

used for their studies. Currently, many investigators attempt to equate exercise intensity by using the same fraction of $\dot{V}O_{2\text{max}}$ for each subject. But if, say, 60% of $\dot{V}O_{2\text{max}}$ is above the anaerobic threshold for one subject and below the anaerobic threshold for a second subject, then the physiological response to exercise is likely to be different. For many physiological functions, a better approach for equating the exercise intensity would be to use the same fraction of the anaerobic threshold.

POSTULATED MECHANISMS FOR THE ANAEROBIC THRESHOLD

The term "anaerobic threshold" was selected by Wasserman and McIlroy (66) because they assumed that an increase in blood lactate and the lactate/pyruvate ratio (71) during incremental exercise was due to an O_2 deficiency somewhere in the working muscle. This O_2 deficiency could occur if the balance of blood perfusion to metabolism in contracting motor units was well-matched at low-to-moderate exercise intensities, but at higher work rates perfusion could lag behind local metabolic rate resulting in a hypoxic state for the metabolically active motor units. Adjacent motor units that are inactive (not recruited) might be overperfused relative to their metabolic rate, and their venous PO_2 would be relatively high. Endurance training has been shown to increase the anaerobic threshold (16,83) and cause a proliferation of capillaries in muscle (2). The increased blood supply supported by these new capillaries could improve the local matching of perfusion to metabolism in recruited motor units and delay the onset of a hypoxic state. This hypothesis is very difficult to examine experimentally. The *overall* perfusion to metabolism ratio appears to be adequate, based on the oxygen flow into and out of the muscle (femoral vein PO_2 is not low enough to suggest whole muscle hypoxia). But global adequacy does not preclude local hypoxemia.

Numerous experimental interventions that acutely alter O_2 delivery alter the anaerobic threshold and the level of blood lactate concentration at sub-maximal work rates. Each of these interventions have been reviewed recently by Wasserman (65). Two interventions that provide support for the O_2 delivery mechanism of the anaerobic threshold are an increase in carboxyhemoglobin ($COHb$) and acute isovolemic anemia. Vogel and Gleser (62) found that the blood lactate concentration was higher at all work rates when $COHb$ levels were raised to 19% by breathing a carbon monoxide-air mixture. The lactate anaerobic threshold was also reduced by this intervention. Woodson et al. (79) used acute isovolemic anemia to alter O_2 delivery. This intervention raised the arterial lactate concentration at submaximal work rates and lowered the anaerobic threshold.

Holloszy (35) has challenged the concept that increased O_2 delivery can be responsible for training-

induced decreases in blood lactate at a given submaximal work rate. He argued that if untrained muscles are hypoxic during submaximal work rates and if improved O_2 delivery is responsible for lower muscle lactate production, then the trained subject should have a higher $\dot{V}O_2$ than the untrained subject at a given work rate. That is, if the muscle tissue is hypoxic, so that O_2 delivery was the factor limiting $\dot{V}O_2$, then $\dot{V}O_2$ should be increased if the O_2 delivery following training is improved. For this argument to be valid, the exercise domain must be considered. In the domain below the anaerobic threshold, where everyone seems to agree that oxygen delivery is adequate, exercise training should not alter the steady-state $\dot{V}O_2$. There is abundant experimental evidence which supports this contention (cf. 16). In the exercise domain above the anaerobic threshold where there is an upward drift in $\dot{V}O_2$, exercise training has two predictable consequences: 1) a decrease in "steady-state" $\dot{V}O_2$ owing to a lower blood lactate concentration at any given work rate; the rate of $\dot{V}O_2$ drift is a function of blood lactate concentration (77); and 2) an increased $\dot{V}O_2$ owing to a less hypoxic state (Holloszy's suggestion). The former seems to be quantitatively more important than the latter, as suggested by the data of Yoshida et al. (83). They found, for a work rate well above the anaerobic threshold, that the "steady-state" $\dot{V}O_2$ was lower after exercise training, i.e., the $\dot{V}O_2$ drift was diminished.

A second postulated mechanism is that at the anaerobic threshold the oxidative capacity of muscle is exceeded, even though O_2 delivery is adequate (70). It seems possible that the oxidative machinery (oxidative enzymes and mitochondria) may not be able to process the delivered O_2 at high levels of exercise. Exercise endurance training results in increasing the capacity of the oxidative enzymes (35) and the number and size of mitochondria (44). These increases may correspond with the increase seen in the anaerobic threshold after training. On the other hand, it is difficult to envision how acute decreases in O_2 delivery (e.g., isovolemic anemia), which are known to increase blood lactate levels, could be accounted for by this proposed mechanism.

A third suggested mechanism involves the pattern of muscle fiber recruitment during incremental exercise. At low-to-moderate work rates, the slow-twitch (high oxidative) fibers are predominantly recruited. At higher work rates, the fast-twitch (high glycolytic) fibers are increasingly recruited, with a resultant progressive increase in lactate production. Clausen (10) has suggested that the increase recruitment of fast-twitch fibers could account for the increase in blood lactate. Nagata et al. (49) analyzed myoelectric signals which reflect motor unit requirement and hypothesized that the onset of a nonlinear increase in the integrated electromyogram represented the progressive recruitment of fast-twitch fibers. They showed that this increase occurred at the

same $\dot{V}O_2$ as the onset of lactic acidosis in ten college students. Nagata et al. suggested that a decrease in intracellular pH, caused by the increase in lactate above the anaerobic threshold, interferes with excitation-contraction coupling and the ability of the muscle to maintain force. To compensate, more fast-twitch fibers are recruited. Note, however, that this change in muscle fiber recruitment is in response to lactic acidosis, not the cause of it. Again, it seems difficult to account for acute changes in O_2 delivery by this mechanism.

A fourth mechanism has been suggested by Donovan and Brooks (19) and Brooks and Fahey (5). They hypothesized that the systematic increase in blood lactate observed for work rates greater than 50–60% $\dot{V}O_{2\max}$ could be due not to an increased lactate production but instead to a reduced hepatic clearance, with the net result being an increase in blood lactate. They postulated that an increased vasoconstriction, mediated by the sympathetic nervous system, occurs with progressively intense exercise and reduces blood flow to the liver. This would then diminish that organ's ability to remove lactate from the blood and would allow the production of lactate to outstrip removal. The above hypothesis is an extension of the Donovan and Brooks study which used isotopic tracers in the rat before and after endurance training (19). They concluded that the reason blood lactate is reduced at a particular work rate after exercise training is not due to a reduced lactate production by the muscle but to an increased lactate removal. Several studies have clearly demonstrated reduced lactate production (measured via muscle biopsy) following endurance training (31,42,57). This important discrepancy raises questions about the validity of the isotopic tracer approach in the study of lactate metabolism. Indeed, Ferminet et al. (26) have suggested that the use of isotopic tracers may not be valid for the study of lactate metabolism *in vivo*, due to numerous uncertainties.

Lastly, it has been suggested that the anaerobic threshold is a function of the metabolic substrates used for energy production. Studies in humans (11) and rats (32) have shown that when free fatty acid levels are increased during exercise, a greater reliance on fatty acid oxidation and a decreased lactate concentration occurs. Ivy et al. (38) demonstrated a small increase in both the gas exchange and lactate anaerobic thresholds after increasing blood free fatty acid levels from 0.3 to 1.5 mM by ingestion of a fatty meal about 5 h before the incremental exercise test (see Table 1). The investigators suggested that their dietary intervention resulted in an increased fatty acid oxidation in muscle which reduced the rate of lactate production. Their results, they asserted, demonstrate that the onset of a metabolic acidosis is not solely due to an O_2 deficiency. Hughes et al. (36) attempted to alter substrate availability by having subjects perform exhaustive exercise

TABLE 1. Alteration of substrate availability by ingestion of a fatty meal on the magnitude of the anaerobic threshold, expressed as a percent of $\dot{V}O_{2\max}$ in nine subjects. Taken from the data of Ivy et al. (38).

Anaerobic Threshold	Control	After Fatty Meal
Lactate	53.9 ± 2.6	59.8 ± 2.6*
Gas exchange	54.3 ± 2.6	60.3 ± 3.9*

Values are mean ± SE.

* $P < 0.05$.

TABLE 2. Effect of high-intensity exercise designed to lower muscle glycogen stores on the magnitude of the anaerobic threshold, expressed as a percent of $\dot{V}O_{2\max}$. Taken from the data of Hughes et al. (36).

Anaerobic Threshold	Control	After Exhaustive Exercise
Lactate	70.1 ± 4.6	81.1 ± 3.4
Gas exchange	72.5 ± 2.8	71.6 ± 2.4

Values are mean ± SE.

designed to lower their muscle glycogen content. This intervention produced somewhat different results (see Table 2) than those found by the dietary manipulation. The lactate anaerobic threshold increased, but the gas exchange anaerobic threshold remained unchanged.

AVENUES OF FURTHER RESEARCH

The recent flurry of publications concerning the anaerobic threshold has improved our understanding of the physiologic mechanisms underlying exercise. However, these same publications have raised questions; further studies are required to enhance our understanding of the anaerobic threshold.

An issue that clearly needs to be resolved is the correctness of the "threshold" concept in the term anaerobic threshold. Are the data of Jorfeldt et al. (40) and Knutgen and Saltin (46) correct (see Figure 2), or is there an increase in muscle lactate well before the blood lactate increase can be observed, as suggested recently by Green et al. (27)? The ideal technique needed to answer this question would allow the non-invasive study of intracellular events in humans during exercise. That technique exists today as nuclear magnetic resonance. Once some of the practical problems involved with human studies are resolved, nuclear magnetic resonance should be able to tell us if there is a threshold for the fall of intracellular pH during incremental exercise, and if so, whether or not it corresponds to the anaerobic threshold.

A mathematical method might be developed which could be programmed on a computer and which would allow the gas exchange anaerobic threshold to be determined objectively and with repeatability. This method would need to be validated against blood lactate break point estimates of the anaerobic threshold. The method should make use of the isocapnic buffering concept to guard against selecting values that are not associated with an exercise-induced metabolic acidosis. Ideally, the method should de-emphasize the need for a brisk ventilatory response to metabolic acidosis. In individ-

uals who have reduced peripheral chemoreception [e.g., possibly highly trained athletes (6)] or a reduced ventilatory pump response [e.g., due to airways obstruction (50)], the current detection criteria are not optimal.

Endurance training is known to increase the anaerobic threshold in healthy individuals. How much the anaerobic threshold is altered by exercise training in patients with various systemic diseases is largely unknown. Also unknown is the optimal training regimen that will stimulate these changes. For example, can one train below his/her anaerobic threshold and still improve the parameter? Does interval training produce greater changes in the anaerobic threshold than continuous training? Because no other measure better predicts endurance performance, it is important to define how the anaerobic threshold concept can be used to optimize the metabolic and cardiopulmonary benefits of chronic exercise.

CONCLUSION

The anaerobic threshold concept has been the subject of controversy during recent years. However, much of the debate has centered, not on the fundamental concept, but on the descriptor of the concept. Regardless of semantic arguments, there is good reason to believe that the anaerobic threshold concept will have enduring importance. Firstly, it has widespread utility because it can be measured noninvasively, using specific pulmonary gas exchange criteria. Secondly, it can be used to accurately predict exercise tolerance. This attribute has applications as diverse as determining the physiological potential of marathon runners and providing differential diagnostic information for patients with cardiopulmonary impairment. As experimentation continues to unravel its basic mechanisms, the anaerobic threshold concept will continue to evolve.

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DIRECTIONS-1985

Anaerobic threshold: review of the concept and directions for future research

GEORGE A. BROOKS

*Exercise Physiology Laboratory, Department of Physical Education,
University of California,
Berkeley, CA 94720*

ABSTRACT

G.A. BROOKS. Anaerobic threshold: review of the concept and directions for future research. *Med. Sci. Sports Exerc.*, Vol. 17, No. 1, pp. 22-31, 1985. The concentration of lactate in the blood is the result of (1) those processes which produce lactate and contribute to its appearance in the blood and (2) those processes which catabolize lactate after its removal from the blood. Consequently, the concentration of lactate in the blood provides minimal information about the rate of lactate production in muscle. The accumulation of lactate beyond the lactate threshold [T_{lact}] does provide an indication that the mechanisms of lactate removal fail to keep pace with lactate production. Lactate is produced in skeletal muscle as a direct result of increased metabolic rate and glycolytic carbon flow. Factors which influence lactate production in muscle include: the V_{max} of lactic dehydrogenase (LDH), which is several times greater than the combined activities of enzymes which provide alternative pathways of pyruvate metabolism; the K_m of LDH for pyruvate, which is sufficiently low to assure maximal stimulation of LDH in the conversion of pyruvate to lactate; and the K'_{eq} of pyruvate to lactate conversion, which exceeds 1000. Recent studies on dog gracilis muscle *in situ* clearly indicate that lactate production occurs in contracting pure red muscle for reasons other than an O_2 limitation on mitochondrial ATP production. In addition to failure of the essential assumption of the anaerobic threshold [T_{an}] hypothesis that there exist limitations on O_2 availability in muscles of healthy individuals during submaximal exercise, several groups of investigators have produced results which indicate that parameters associated with changes in pulmonary minute ventilation [i.e., the ventilatory threshold, T_{vent}] do not always track changes in blood lactate concentration. Therefore, the T_{an} hypothesis fails on the bases of theory and prediction. A series of kinetic tracer experiments to better understand lactate kinetics during exercise is proposed.

LABTATE PRODUCTION, TRACER KINETICS, SKELETAL MUSCLE, HEART, LIVER, TRAINING, LACTATE CLEARANCE, LDH, ENZYME KINETICS, GLYCOLYSIS, GLYCOGENOLYSIS

By request of the Editor, this article is pointed at criticism of the anaerobic threshold concept. This article is to be read and contrasted with the accompanying article by Davis, which presents arguments in favor of the anaerobic threshold hypothesis. It is

These are the invited comments of the author which have not been evaluated or processed by the review procedures established by the Editorial Board of *Medicine and Science in Sports and Exercise*.

hoped that the scientific community will benefit from this open presentation of ideas on this subject.

The anaerobic threshold, T_{an} , has been the subject of numerous reports (e.g., Refs. 8, 52, and 53). In the main, the experimental approach in experiments supporting the T_{an} hypothesis has been the same, with only minor variations in protocol. Those reports have evoked a significant number of responses by other investigators who have subjected the T_{an} concept to rigorous testing. Among these investigators are Hughes et al. (28), Segal and Brooks (50), Heigenhauser et al. (21), Hagberg et al. (19), Hughson et al. (30), Green et al. (17), and Yeh et al. (53). These investigations have failed to confirm the assumptions and predictions of the T_{an} hypothesis. Further, the T_{an} has been an issue of concern in three recent reviews (2,33,43). On theoretical as well as empirical grounds, Åstrand (2), Jones and Ersam (33), and Molé (43) have dismissed the T_{an} as an inappropriate and overly simplistic explanation of indirectly related phenomena.

TERMINOLOGY

Before launching into this discussion, a review of pertinent terminology and concepts is indicated.

Lactic acid. A product of glycogenolysis and glycolysis. The intracellular enzymes which process carbohydrates (the common sugar glucose being the simplest carbohydrate) produce lactic acid as a function of their metabolism. This is because the terminal enzyme of the glycolytic pathway (LDH) has the greatest catalytic activity (V_{max}) of any glycolytic enzyme. The conversion of pyruvate to lactate occurs with a standard free energy change ($\Delta G'$) of -6.0 kcal/mol and an equilibrium constant of over 1,000 (37). Additionally, the catalytic activity of LDH exceeds by many times the combined catalytic activities of enzymes which provide alternative pathways for pyruvate metabolism.

TABLE 1. Enzymatic activity (V_{max}) of LDH vs competing enzymes for pyruvate carbon removal.

	Rat gastrocnemius @30°C ($\mu\text{mol} \cdot \text{min}^{-1}$)	
	Sedentary	Trained
LDH* (44)	677	625
Pyruvate oxidase (14)	0.65	1.35
Malic enzyme (14)	0.69	1.04
GPT (14)	22.7	42.0
LDH/pyruvate oxidase	1041/1	446/1
LDH/others	28/1	14/1

*Data from the references cited.

(Table 1). Further, the Michaelis-Menten constant (k_M) for the conversion of pyruvate to lactate is on the order of 0.08 mM (13,35). Therefore, at concentrations of pyruvate found in muscle during sub-maximal exercise, substrate concentration is sufficient to support maximal catalytic activity of LDH in the production of lactate. For the reasons of LDH activity, thermodynamic equilibrium and k_M , pyruvic acid formation will inevitably lead to lactic acid formation. Thus, seen in the context of the enzymatic regulation of cellular metabolism, lactic acid production is as much a part of carbohydrate metabolism as is the production of CO_2 from respiration. However, whereas CO_2 is an end product, lactic acid is an intermediate product.

At physiological pH, lactic acid almost completely dissociates to hydrogen and lactate ions; therefore the terms lactic acid and lactate are used synonymously. In most cases, substitution of one term for the other is appropriate. In some cases, however, such as in equations of chemical balance or when describing lactate-lactic acid transport across membranes, precision in terminology is required.

Aerobic and anaerobic. Aerobic means "with air" (oxygen), whereas anaerobic means "without oxygen." In their studies of metabolism by unicellular organisms, pioneer biochemists such as Pasteur compared the rates of glycolysis when air was present and when it was eliminated. Pasteur discovered that when O_2 was absent, yeast broke down glucose and produced lactic acid at a much faster rate than when O_2 was present. This is the classic and well-known "Pasteur Effect."

While it is true that the rate of glycolysis in isolated cells and in cells of intact functioning organisms will be accelerated when O_2 is not present, the presence of lactic acid in blood or any other tissue of a healthy individual does not necessarily mean that there was anaerobiosis (i.e., metabolism limited by availability of O_2). As noted above, lactic acid is formed as the result of the characteristics of the glycogenolytic and glycolytic pathway enzymes, including lactic dehydrogenase. When metabolism is accelerated, lactic acid will inevitably be formed. [For a detailed description, see Ref. 4, pp. 67-95; also Ref. 45, p. 167.]

Production. The rate of formation of a metabolite

($\text{mg} \cdot \text{min}^{-1}$), such as lactic acid, can be measured if an isotopic tracer molecule is injected or infused into an individual. The more rapidly an individual is producing lactic acid, the greater the dilution of tracer. Thus, by measuring the extent of tracer dilution, the rate of metabolite production can be determined.

An alternative term for production is the rate of "appearance" (R_a), or entry into the blood.

Removal. The rate of removal of lactic acid can also be measured by tracer technology. The rate of removal is alternatively termed "rate of disappearance" and is abbreviated R_d .

Steady state. When the rate of entry of lactate into the blood is equivalent to the rate of disappearance from the blood, the blood concentration does not change. Thus, in the steady state, $R_a = R_d$. In the steady state, it is assumed that the rates of appearance in and disappearance from the blood equal the intracellular production and removal rates.

Turnover. Turnover (R_t) is the rate of metabolic renewal. Because in the steady state the processes of lactate production are balanced by the processes of removal, there is an equivalence of turnover, appearance and disappearance ($R_t = R_a = R_d$ in the steady state).

Accumulation. When the rate of production of a metabolite is greater than its removal ($R_a > R_d$), the concentration will increase. *In vivo*, a metabolite such as lactic acid can accumulate because production increases, because removal decreases, or both. Lactate accumulates when $R_a > R_d$ in a non-steady-state condition. Unfortunately, many individuals inappropriately use the term "production" when they actually measure "accumulation."

Metabolic clearance rate. The metabolic clearance rate ($MCR = R_d / [\text{blood metabolite}]$) is a parameter which describes the volume of blood and other body fluids (ml) from which the metabolite is cleared (removed) per unit of time (min). Thus, the MCR of lactic acid is an important parameter of lactate removal and provides a means of describing the interactions between rate of removal, blood concentration, and blood flow.

Oxidation. By collecting expired air following the injection or infusion of carbon isotope tracer and by analyzing the breath for isotopic CO_2 , the percentage of lactate oxidized (% Ox) as well as the rate of lactate oxidation (R_{ox} , in $\text{mg} \cdot \text{min}^{-1}$) can be calculated.

Lactate threshold. Initially, during a progressive exercise test, such as on a cycle ergometer where the resistance to pedalling is continually increased, lactate accumulation will be a linear function of the power output and oxygen consumption rate ($\dot{V}\text{O}_2$). Eventually, however, there will occur a workload at which lactate will accumulate in a non-linear (disproportionally high) fashion. This workload at which blood lactate

concentration abruptly increases is termed the lactate threshold [T(lact)] or the lactate break point.

Ventilatory threshold. Initially, during a progressive exercise test, the rate of pulmonary minute ventilation ($\dot{V}E$) will increase linearly with increments in work rate. Eventually, however, there will occur a workload at which $\dot{V}E$ will increase non-linearly. This workload at which $\dot{V}E$ abruptly increases is termed the ventilatory threshold [T(vent)] or the ventilatory break point.

It is the contention of Wasserman et al. (53) that the T(lact) is the same thing as the T(vent).

Anaerobic threshold, T(an). It is the hypothesis of Wasserman et al. that T(lact) = T(vent) and is caused by anaerobiosis (absence of O_2) in muscle (52). Therefore, the T(vent) has been called the "anaerobic threshold" [T(an)].

MAJOR FAILINGS OF THE ANAEROBIC THRESHOLD HYPOTHESIS

In validating a hypothesis, the burden of proof falls on the proponent of that hypothesis. To be considered valid, a hypothesis must be supported on solid bases. Further, the concept must withstand testing by independent researchers. As shall be demonstrated herein, the T(an) hypothesis must be considered unproven, because there has been no attempt to validate it and because numerous attempts to test predictions of the hypothesis have failed.

First major failing. The key component of the T(an) hypothesis that muscle tissue is anaerobic during sub-maximal exercise is untested, and because several lines of evidence suggest that the anaerobic condition does not exist in muscle during sub-maximal exercise, the T(an) hypothesis cannot be supported.

Second major failing. Because the T(an) is based on a theoretical construct which is no longer accepted (i.e., the O_2 deficit-debt relationship), the basis of the T(an) hypothesis is undermined.

Third major failing. Because in the T(an) model the T(vent) is the end result of a linked series of causes and effects, and because several of the proposed links in the model have been demonstrated to not hold, the model fails critical testing and must be considered invalid. In particular, the failure of pulmonary minute ventilation to accurately and reliably track changes in blood lactate concentration renders the T(an) concept unusable.

Fourth major failing. In recent years studies utilizing isotopic tracers have been performed to quantitate lactic acid production in animal and human subjects during rest and graded exercise. Because results of those crucial studies are in conflict with predictions of the T(an) hypothesis, the model must be seriously questioned.

NO VALIDITY OF THE ANAEROBIC THRESHOLD HYPOTHESIS

The hypothesis that contracting skeletal muscle tissue becomes anaerobic at a work rate which corresponds to 50–75% of $\dot{V}O_{2\text{max}}$, has not been tested by proponents of the T(an). Indeed, the notion that there exists muscle anoxia when significant reserves exist in cardiac output, muscle blood flow, capillary dilatation, and arterial venous O_2 difference [$(a-v)O_2$] does not seem reasonable. Reviewers such as Åstrand (2) have commented on this.

Although there have been no attempts by proponents of the T(an) hypothesis to demonstrate muscle anaerobiosis in humans or other mammals during either sub-maximal or maximal exercise, data collected by other investigators are relevant. During maximal leg exercise, Pirnay et al. (46) obtained blood samples from the deep femoral vein. During maximal exercise the femoral PvO_2 did not fall below 10 Torr, and during exercise at about 50% $\dot{V}O_{2\text{max}}$, PvO_2 was between 20 and 40 Torr. These results indicate that significant concentrations of O_2 were present in venous blood draining the active muscle bed. The O_2 tension in venous blood was much greater than the critical mitochondrial O_2 tension.

The critical mitochondrial O_2 tension is the partial pressure of O_2 , below which the maximal mitochondrial respiratory rate (State 3) cannot be supported. Estimates (6) of the critical mitochondrial O_2 tension place it between 0.1 and 0.5 Torr. It is unlikely that the critical muscle mitochondrial O_2 partial pressure is achieved in healthy subjects during sub-maximal exercise at sea level altitudes (46).

In a unique investigation, Jobsis and Stainsby (32) utilized fluorometric techniques to study mitochondrial NADH/NAD⁺ during concentration of dog muscle *in situ*. When those muscle preparations were stimulated to contract at exercise intensities sufficient to produce maximal O_2 consumption and a significant net efflux of lactate, the mitochondrial redox state reflected by the NADH/NAD⁺ ratio was more oxidized than it was during rest. These limited data on a mammalian muscle preparation stimulated to a workload which elicits $\dot{V}O_{2\text{max}}$ indicate that the critical mitochondrial O_2 tension was not achieved.

In a recent investigation on dog gracilis muscle, Connell et al. (7) concluded that lactate accumulation in contracting skeletal muscle *in situ* is due to causes other than a simple O_2 limit on mitochondrial ATP production. Dog gracilis is a pure red muscle containing only type I and IIa fibers. In their experiments, Connell et al. observed lactate accumulation in dog gracilis during mild (10% $\dot{V}O_{2\text{max}}$) exercise. Further, up to a contraction rate which elicited 70% of $\dot{V}O_{2\text{max}}$ (wherein tissue ATP and CP levels were well maintained), lactate ac-

cumulation was linearly related to twitch (work) rate. These results suggest that lactate accumulation is related to increments in work and metabolic rate. Additionally, Connell et al. observed that lactate accumulation was not reduced by increasing blood flow or inducing capillary dilatation. Further, these investigators utilized myoglobin cryomicroscopy techniques to determine the O_2 tension throughout the muscle tissue. Anoxic areas (i.e., areas in which the local PO_2 approached the critical mitochondrial O_2 tension) were found neither during exercise nor during the transition from rest to exercise. The minimum PO_2 did not drop below 2 Torr, which is significantly above the critical mitochondrial O_2 tension. As a result of these observations, Connell et al. concluded that "anoxic loci were never present in muscles that accumulated lactate." Clearly, we must conclude that lactate accumulation occurs for reasons other than O_2 tension.

On exercising humans, Green et al. (17) have utilized muscle biopsy procedure and other techniques to study the interrelationships among muscle lactate level, blood lactate level, and pulmonary ventilation during progressive exercise. These workers concluded that muscle lactate concentration increases significantly before either the T(lact) (based on blood concentration) or the T(vent) occur. Thus, the results of Green et al. (17) on human leg muscle during exercise appear to be consistent with those of Connell et al. (7) on dog gracilis *in situ*. Muscle lactate accumulation occurs when mitochondrial function is not limited by the presence of O_2 .

So we ask, "Where is the data to support the primary and essential contention of an anaerobic threshold hypothesis; where is data to support the hypothesis that skeletal muscle in healthy individuals is anaerobic during submaximal exercise at altitudes near sea level?" The data available are contrary to the primary assumption of the T(an) hypothesis.

O_2 DEFICIT- O_2 DEBT THEORY AS A BASIS FOR THE ANAEROBIC THRESHOLD HYPOTHESIS

The premise of the T(an) hypothesis is that a deficit in O_2 consumption precipitates the cascade of events which leads to the T(vent) during submaximal exercise. The classical O_2 deficit-debt theory was recently reviewed by Gaesser and Brooks (15) within the context of developing a contemporary understanding of those factors which cause the rate of O_2 consumption to remain significantly above resting levels for a time after exercise. It is certainly the case that the work of Hill and associates (22-25) and Meyerhof (40-42) represent some of the classical reports of modern muscle physiology, energetics, and biochemistry. However, for reasons that the engenderer investigators could not know,

when particular aspects of results they obtained on isolated amphibian muscles contracting *in vitro* were extrapolated to intact functioning mammals, inappropriate conclusions were reached (15, 20). In particular, the hypothesis that a majority of lactate formed during exercise is converted to glycogen during recovery is not supported by the evidence (5, 10).

While it is understandable that particular aspects of a 50-yr-old theory not be appropriate in a contemporary context, it is inappropriate that a hypothesis submitted for contemporary consideration is based upon a paradigm that is no longer completely accepted. Basing the T(an) on the presumption of an O_2 deficit during submaximal exercise is a serious mistake. Further, this is apparently a mistake that the classical investigators avoided.

Because the T(an) is based on a classical but flawed theory, we must conclude that the T(an) hypothesis is without basis.

LINKAGE BETWEEN BLOOD LACTATE AND PULMONARY MINUTE VENTILATION

The T(an) theory predicts that increments in blood lactate concentration (misunderstood to represent production) result in increments in pulmonary minute ventilation. Such is not the case. In glycogen-depleted subjects, Segal and Brooks (50) observed significantly lower blood lactate responses but significantly higher pulmonary minute ventilations at given exercise work rates. Subsequently, Hughes et al. (28), and Heigenhauser et al. (21) observed the same result.

In their studies of glycogen-depleted subjects during cycle ergometer exercise, Hughes et al. (28) observed that the T(lact) occurred at a significantly greater workload and % $\dot{V}O_{2\text{max}}$ than during exercise in the normal glycogen state. However, in comparison to the T(lact) during exercise in the glycogen-depleted state, the work load and % $\dot{V}O_{2\text{max}}$ at which the T(vent) occurred shifted to a lesser work load during the glycogen-depleted state. Further, Hughes et al. found that in comparison to slow ergometer pedaling (50 rpm) in the normal glycogen state, during fast pedaling (90 rpm) in the normal glycogen state the T(vent) occurred at a lesser work load.

In addition, the relationship between break points in blood lactate concentrations and pulmonary minute ventilation were studied by Hagberg et al. (19) in McArdle's syndrome patients. During incremental exercise tests, McArdle's patients, who lack the enzyme phosphorylase, had no blood lactate response. However, McArdle's syndrome patients demonstrated a definite T(vent) at a work rate which elicited approximately 70% of $\dot{V}O_{2\text{max}}$. Results of experiments by Hag-

berg et al. are not consistent with the notion of an T(an), because there is no linkage between T(lact) and T(vent).

Results of these studies (16,19,20,28,47,50) strongly suggest that the observed correlations between T(vent) and T(lact) are coincidental. During exercise, pulmonary minute ventilation is usually driven by a combination of neural and humoral mechanisms. In the absence of a humoral signal (as in McArdle's patients), in response to a modified humoral signal (as in glycogen depletion), or in response to different input from higher centers or from peripheral proprioceptors (such as when the speed of movement is varied), the respiratory center in the brain will still produce an appropriate ventilatory response.

In experiments on subjects who were studied before and after intense training on a bicycle ergometer, Gaesser et al. (16) observed a definite uncoupling between changes in $\dot{V}O_{2\text{max}}$ and T(vent). Whereas $\dot{V}O_{2\text{max}}$ increased 10% in response to training, T(vent) did not change. Further, Poole and Gaesser (47) observed a shift of T(lact) to higher percentages of $\dot{V}O_{2\text{max}}$ and maximal exercise power output in trained subjects. However, in response to training, the shift in T(vent) was far less pronounced. Thus, training resulted in a clear separation between T(vent) and T(lact). These results of Gaesser et al. are in contrast with an earlier published report by Davis et al. (8) on the effects of training on the T(vent). In that study, conclusions were made about the effects of training on the balance of aerobic and glycolytic metabolism without benefit of a single measurement of blood lactate level or lactate production.

In their recent text, Brooks and Fahey (Ref. 4, p. 210) acknowledged that at its inception the T(an) concept represented a reasonable and attractive hypothesis because it offered the possibility that an intracellular event could be determined on the basis of noninvasive T(vent) measures. Unfortunately, because of the above-stated and other reasons, it is now appropriate to move onto other ideas. Further, on the basis of recent experience, the basic utility of the T(vent) procedure as an alternative to T(lact) determination must be seriously questioned. The determination of T(vent) offers little advantage in comparison to the T(lact) when T(lact) determination is used in conjunction with ECG. This is because the measurement of pulmonary ventilatory rate and end tidal concentrations of ventilatory gases

require the use of expensive, computerized laboratory equipment. In contrast, the assay of lactate in blood sampled from fingertip, ear lobe, or forearm venipuncture is far less expensive and is a common laboratory procedure. Any of these blood sampling modes can be used with little discomfort to subjects, especially if the discomfort of wearing head gear for T(vent) determination can be dispensed with. In one day, a trained laboratory technician can assay hundreds of samples with excellent precision and reproducibility. Further, there have appeared on the market several automated lactate assay devices which cost a fraction of the ventilatory determination apparatus. So from the standpoints of accuracy, convenience, and cost-effectiveness, the T(vent) procedure cannot be justified as a substitute for the T(lact).

TRACER STUDIES ON LACTATE METABOLISM

Today we realize that the concentration of lactic acid in the blood represents the result of all those processes which add lactate to and remove it from the circulation. Therefore, we can dismiss measurements of pulmonary gas exchange or blood lactate concentration as being informative of the rate of lactic acid production. Lactate is always produced, even in well-oxygenated, healthy, resting individuals. The three investigations which report lactate turnover rates in resting individuals are in good agreement (Table 2). Further, in the study of Mazzeo et al. (39), the fraction of total glycolytic carbon flux which passes through lactate (approximately 50%) reflects the importance of lactate as a metabolic intermediate. The dynamic nature of lactate turnover in the resting individual cannot be detected from measurements of blood lactate concentration alone. The low and invariable blood lactate concentrations in resting individuals lead to the false conclusion that lactate is not being produced in the resting individual. To the contrary, lactate levels are low and stable in healthy individuals during rest because production is balanced by removal.

Studies on the turnover of lactic acid in animals during exercise have revealed a direct relationship between metabolic rate ($\dot{V}O_2$) and lactate turnover (9-12,31). One example is the result of Donovan and Brooks (10), who observed a correlation of 0.86 between $\dot{V}O_2$ and lactate R_t in rats during exercise (Figure 1). This high correlation reflects the coordinated regulation

TABLE 2. Lactate turnover and oxidation in resting humans.

Study	Year	Tracer	R_t ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$)	%Ox	% of CHO $\dot{V}CO_2$ from lactate oxidation
Kreisberg et al. (36)	1970	^{14}C	81.4 ± 5.0	$11.5 \pm 1.5^*$	—
Searle and Cavalieri (49)	1972	^{14}C	100.6 ± 20.9	$87.4 \pm 20.7^*$	—
Mazzeo et al. (38, 39)	1984	^{13}C	123.4 ± 20.7	49.3 ± 3.3	48.0

*Uncorrected for bicarbonate retention.

Values are mean \pm SE.

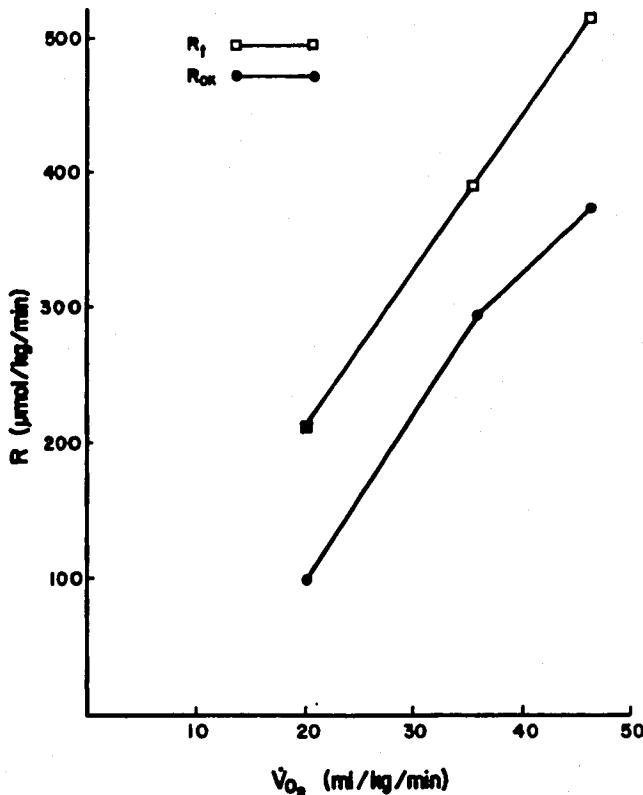


Figure 1—Rates of lactate turnover (R_t) and oxidation (R_{ox}) in rats during rest and two levels of steady state exercise. Note the strong relationships among these three parameters of metabolism. Redrawn from Donovan and Brooks (10); $n = 20$ for each point.

of metabolism. Increased rates of metabolism produced by exercise result in increased rates of glycolytic carbon flux. Increased rates of glycolytic carbon flux result in increased rates of lactic acid production.

Lactate turnover has been studied in detail in several mammalian species during exercise, and a few lactate tracer studies have been performed on humans. Using low doses of [$U-^{14}\text{C}$]lactate, Jorfeldt (34) studied lactate metabolism in contracting human forearm muscle. Additionally, using a very small dose of the same tracer (5 μCi), Hubbard (27) studied lactate metabolism in resting and exercising humans. Although the dosages and methodologies employed did not allow quantitation of the effect of exercise on lactate metabolism, together the results strongly suggest that lactate turnover and oxidation are elevated during exercise and that skeletal muscle is an important site of lactate catabolism. These results of Jorfeldt and Hubbard have been confirmed by Mazzeo et al. (38, 39), who utilized the stable, non-radioactive tracer [^{13}C]lactate to study lactate turnover in humans during rest and graded exercise. The results of Mazzeo et al. (39) confirm the linear relationship between lactate R_t and $\dot{V}O_2$ in humans during submaximal work (up to 75% $\dot{V}O_{2\text{max}}$).

While tracer studies on animals during rest and exercise reveal a direct, linear relationship between lactate R_t and $\dot{V}O_2$, the relationship between lactate R_t and

blood lactate concentration during steady-state exercise is not linear. This non-linear relationship between lactate R_t and blood lactate concentration was described by Eldridge in dogs (11, 12) and confirmed by Donovan and Brooks (10) on rats using continuous infusions of [$U-^{14}\text{C}$]lactate. As indicated in Figure 2, in the transition from rest to exercise, small increments in blood lactate concentrations belie large increments in lactate production rate.

Also as suggested in Figure 2, endurance training has the effect of shifting the lactate R_t vs blood concentration curve to the left. This shift exacerbates the problem of predicting lactate production from measurements of blood lactate concentration.

The curvilinear relationship between lactate R_t and blood lactate concentration observed initially in dogs and rats has been confirmed in humans by Mazzeo et al. (39). Although the effects of such variables such as training and genetic endowment remain to be studied in detail in humans, the effects of these variables were apparent in the population studied to date.

At the very least, the curvilinear relationship between lactate production and blood lactate concentration has

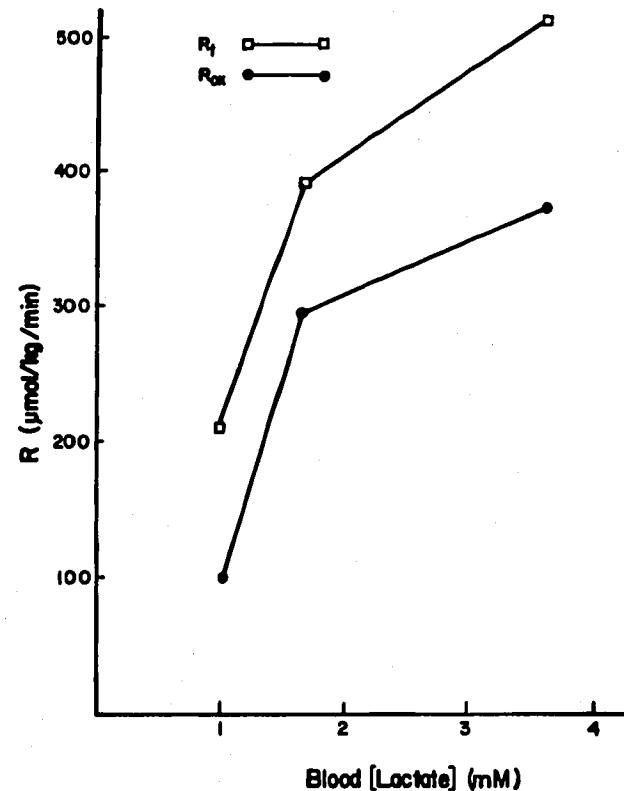


Figure 2—Relationships between lactate turnover (R_t) and oxidation (R_{ox}) and blood lactate concentration in rats during rest and two levels of exercise. Note that small changes in blood lactate concentration in the transition from rest to easy exercise indicate tremendous increases in R_t and R_{ox} . These results are opposite those predicted on the basis of "anaerobic threshold" theory and demonstrate why measures of blood lactate concentration cannot be used to indicate lactate production. Redrawn from Donovan and Brooks (10); $n = 20$ for each point.

critically important, probably lethal implications for the concept of an anaerobic threshold. Whereas, according to T(an) theory, small changes in blood lactate concentration below the T(lact) are thought to indicate only small increments in lactate production, in fact small changes in blood lactate concentration in easy exercise obtain despite very large increases in lactate production. This is so because the increases in lactate appearance are nearly matched by increases in lactate removal due to greater clearance. It has been well documented by Issekutz et al. (31) and others (10-12) that for a given blood lactate concentration, the production of lactate may be five times greater during exercise than during rest.

During exercise, the main route of lactate removal is through oxidation. This conclusion is firmly supported by results of studies on dogs (9,11,12), rats (10), and humans (38,39). In Table 3, results are portrayed on three mammalian species exercising at about 50% of $\dot{V}O_{2\text{max}}$. In each case, the majority of lactate is removed through oxidation. Further, as illustrated in Figure 1, the absolute rate of lactate oxidation remains directly related to the metabolic rate up through and including hard exercise. The relationship displayed between lactate oxidation rate and metabolic rate for exercising rats (Figure 1) has been confirmed for exercising humans by Mazzeo et al. (39). For humans exercising at approximately 75% of $\dot{V}O_{2\text{max}}$, Mazzeo et al. found that approximately 75% of the lactate turnover was removed through oxidation.

EXPLANATION OF A PHENOMENON

Based on the results of tracer kinetic studies, it is now possible to develop a reasonable explanation of the T(lact). As suggested in Figure 3, the upward inflection in blood lactate concentration is due to an inequality of lactate appearance in the blood (Ra) and its disappearance from the blood (Rd).

To provide preliminary support for this hypothesis, in Figure 4 are provided data on one subject continuously infused with [^{13}C]lactate and studied during rest and three exercise intensities. These data were obtained in collaboration with E.W. Gertz and colleagues (J. Wisneski, R. Neese, and W. Stanley). As suggested in Figure 5, both Ra and Rd are highly correlated to work

TABLE 3. Oxidation as a pathway of lactate removal during rest and exercise in three mammalian species.

Study	Species	Rest % $\dot{V}O_2$	Easy exercise (approximately 50% $\dot{V}O_{2\text{max}}$) % $\dot{V}O_2$
Issekutz et al., 1976 (31)	Dog	50	55
Donovan and Brooks, 1983 (10)	Rat	45.7 ± 3.4	74.9 ± 3.2
Mazzeo et al., 1984 (39)	Human	49.3 ± 3.3	87.0 ± 2.8

Values are mean \pm SE.

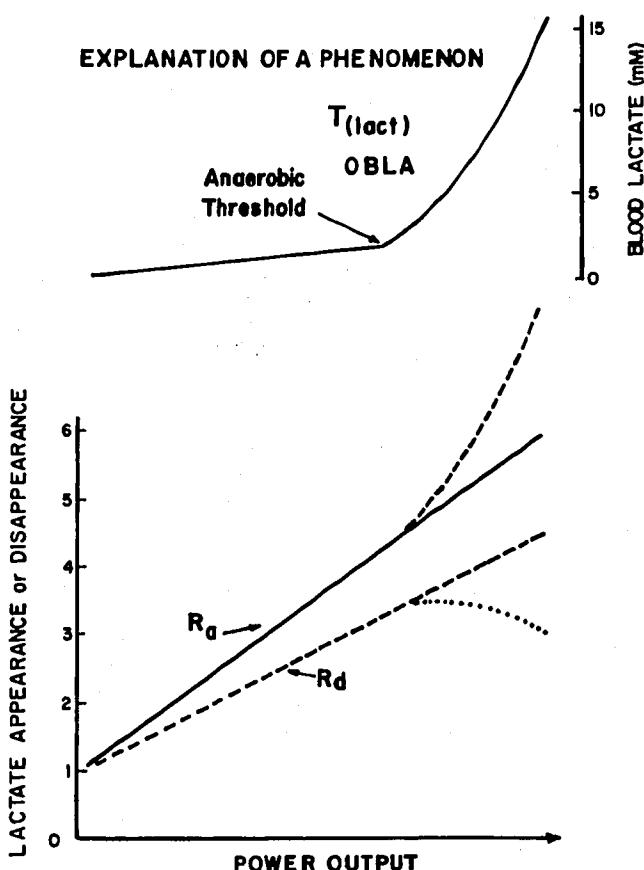


Figure 3—A model explaining the lactate threshold [T(lact)], phenomenon in terms of the difference between rates of lactate appearance (Ra) and disappearance (Rd). During exercise tasks of progressively increasing intensity, both Ra and Rd (expressed in arbitrary units) increase, but the increase in Rd lags the increase in Ra. Therefore, lactate accumulates. According to this model, blood lactate concentration is only indirectly related to lactate production. Detailed studies with laboratory animals (10,31) and preliminary experiments on humans indicate that Ra increases directly with exercise intensity. This increase may be linear, or more likely, may demonstrate an exponential rise at high intensities due to the autonomic stimulation of glycogenolysis and recruitment of type IIb muscle fibers. In humans, Ra may exceed Rd due to shunting of blood flow away from the liver and kidneys and an inability of the exercising muscle to extract and oxidize lactate at a high enough rate.

rate and $\dot{V}O_2$, but the slopes of Ra and Rd are different. Therefore, there occurred an accumulation of blood lactate because Ra > Rd.

In the explanatory figure (Figure 3), which is supported by the results as displayed in Figure 5, the T(lact) is clearly not due to a sudden increase in production of lactate. The blood lactate response is a curve because the difference between the Ra and Rd curves is a non-linear function of the $\dot{V}O_2$.

EXPLANATION OF AN EXPLANATION

In the absence of direct data to support the notion of muscle anaerobiosis during submaximal exercise, Wasserman (51) cites indirect evidence. Central among the evidence to support the concept of an T(an) is the

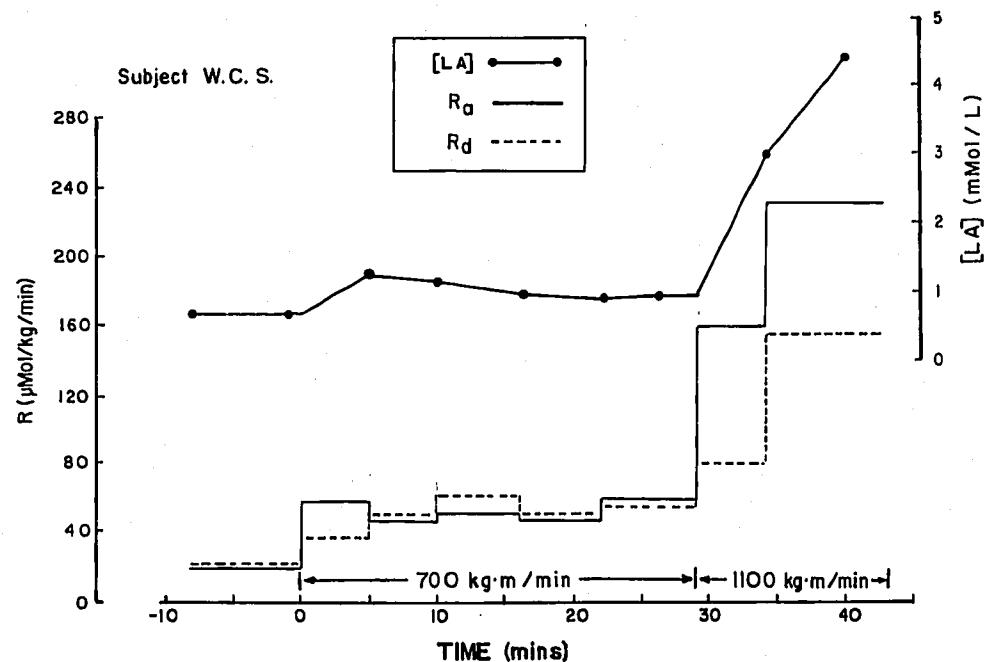


Figure 4—Rates of lactate appearance (R_a) and disappearance (R_d) measured in one subject during rest and graded exercise using a primed-continuous infusion of $[U-^{13}C]$ lactate. In the transitions from rest to exercise at $700 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$ and during exercise at $1100 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$, $R_a > R_d$. Therefore, blood concentration increases. For this subject, after 5 min, $700 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$ represents steady-state exercise because R_a approximates R_d .

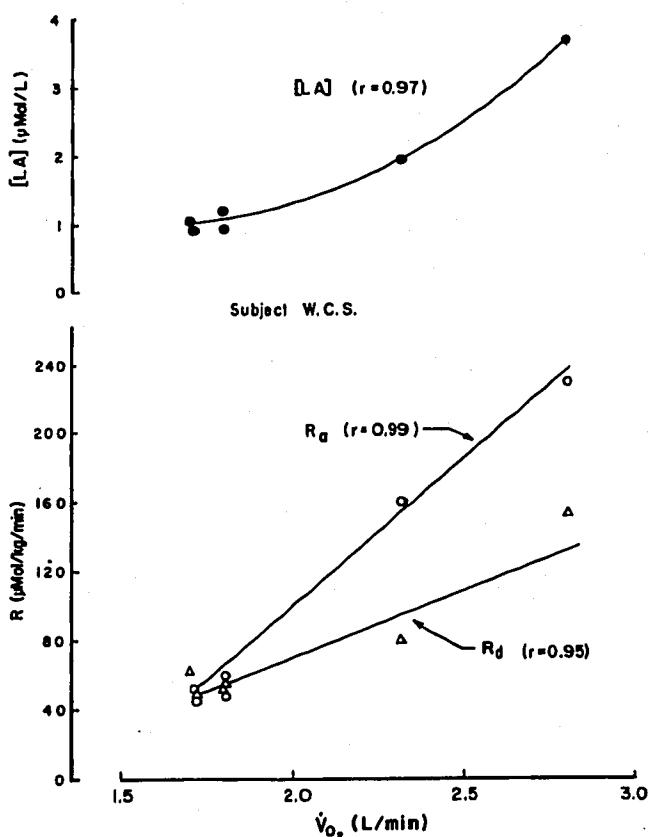


Figure 5—Results from the human experiment displayed in Figure 4 replotted against $\dot{V}\text{O}_2$. The results are similar to those obtained previously on animals (Figure 1) and support the model displayed in Figure 3. Future research should be directed at explaining the tissue and cellular mechanisms behind these results.

observation that blood lactate levels are lower in subjects who exercise while breathing hyperoxic gas mixtures. The fact is that such references prove nothing about anaerobiosis and lactate production (which has never been measured under hyperoxic exercise conditions). When measured correctly (54), submaximal $\dot{V}\text{O}_2$

is unaffected in subjects inhaling enriched O_2 -containing gas mixtures. Because the $\dot{V}\text{O}_2$ does not increase during submaximal exercise while breathing O_2 -enriched gas, the results clearly indicate the individuals were not hypoxic during exercise while breathing air. The fact that blood lactate concentrations are lower when subjects inspire enriched O_2 -containing gas mixtures may indicate that hyperoxia increases lactate clearance. The mechanism of increased clearance is probably increased perfusion of tissues and organs capable of removing lactate. One such organ is the liver, which receives an increased blood flow during exercise when hyperoxic gas mixtures are inspired (26,29,48). Additionally, hyperoxia may decrease the apparent k_M of lactate oxidation by mitochondrial enzymes and electron transport chain components (39). In subjects exercising at submaximal intensities while breathing hypoxic gas mixtures, blood lactate is significantly higher than during either normoxia or hyperoxia (1). However, during hypoxic exercise, the $\dot{V}\text{O}_2$ is the same as during normoxia or hyperoxia. Again the equivalence of $\dot{V}\text{O}_2$ in all three conditions indicates adequacy of tissue oxygenation. Elevated blood lactate levels during hypoxia (relative to normoxia or hyperoxia) suggest decreased lactate clearance during hypoxia.

RESEARCH DIRECTIONS

Based on these findings, the following questions represent research directions for 1985.

What are the relationships between lactate R_a and $\dot{V}\text{O}_2$ and between lactate R_d and $\dot{V}\text{O}_2$ during a progressive exercise test? These relationships could be studied using the continuous isotope infusion technique.

What is the site of lactate removal? Because contracting skeletal muscle represents the major site of oxidative

catabolism and because lactate is removed mainly through oxidation, it is hypothesized that active skeletal muscle is the major site of lactate removal. This hypothesis could be confirmed by a combination of isotope tracer and arterial-venous difference measurements across active and inactive muscle beds.

What is the role of the heart in removing lactate from the circulation? It is known that the heart has a high relative blood flow and that it has a high oxidative capacity. It is hypothesized that the heart removes a significant though minor amount of the lactate formed. Again, a study involving the continuous infusion of tracer lactate and arterial-venous (coronary sinus) would be required.

What is the role of the liver in removing lactate from the blood and how significant is gluconeogenesis from lactate in maintaining blood glucose homeostasis during hard, prolonged exercise? It is hypothesized that training improves the liver's role in maintaining blood glucose homeostasis in heavy exercise through one or a combination of adaptations. Among these are superior cardiac output, maintenance of hepatic blood flow in hard exercise, damped autonomic response, and induction of hepatic gluconeogenic enzymes.

What is the role of training on blood lactate production and clearance during exercise? In the laboratory rat, the major observed effect of training on lactate metabolism during exercise was an increase in the lactate metabolic clearance rate. Does the human respond to training with an enhanced metabolic clearance rate?

How is the rate of lactate production affected by activity of the autonomic nervous system? Among the factors involved here are vasoconstriction and shunting of blood flow away from gluconeogenic organs and stimulation of muscle glycogenolysis. Therefore, are changes in lactate Ra and Rd related to catecholamine release during exercise?

How does muscle fiber type and fiber recruitment during exercise affect lactate production and blood lactate concentration? When fast glycolytic (Type IIb) fibers are recruited, the rate of lactate production is likely to increase. Investigations correlating muscle EMG with lactate Ra may be helpful.

How is the transport of lactate across muscle and other cell membranes mediated? Results of Eldridge et al. (12) and Donovan and Brooks (10) (Figure 2) suggest that the transport of lactate becomes saturated. Therefore, lactate transport may involve more than simple diffusion; facilitated or active transport mechanisms may be involved. These mechanisms may be symport or antiport in nature. Therefore, studies on the mechanism of lactate transport across cell membranes would be very informative. Also, how do blood lactate kinetics differ between healthy and coronary artery disease patients? Tracer studies of lactate metabolism across the heart are potentially of significant diagnostic use (17). Whether procedures to study blood lactate kinetics in CHD patients will provide useful diagnostic information remains to be determined.

On a final note, it needs to be mentioned that while utilization of the T(vent) procedure to identify an "anaerobic threshold" in healthy individuals is an appropriate subject for scientific discussion, utilization of the T(vent) procedure for diagnostic purposes is completely without basis. Interpretation of results of T(vent) procedures on CHD and other patients could potentially be injurious to them.

Supported by DHHS NIH Grant AM19577. Data in Figures 4 and 5 are the result of collaborative studies with E.W. Gertz and associates at the Cardiovascular Research Institute, Department of Medicine, University of California, San Francisco, and the San Francisco Veteran's Administration Hospital. Their efforts and helpful discussion are appreciated. The constructive comments of C.M. Donovan, R.S. Mazzeo, W.C. Stanley, and T. Willis are also appreciated.

The term "anaerobic threshold" was selected as a means to cross-reference these two manuscripts included in Directions—1985.

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DIRECTIONS-1985

Response to Brooks' manuscript

JAMES A. DAVIS

Laboratory of Applied Physiology, California State University, Long Beach, 1250 Bellflower Boulevard, Long Beach, CA 90840.

The Editor-in-Chief has invited me to write a brief critique of Dr. Brooks' spirited exposition. Fully formed critiques of several questions raised in his paper are contained in my article. The aim here is to examine additional points not previously covered. To avoid replication of a lengthy reference list, please refer to my article for each italicized reference. New references are listed at the end of this critique, beginning with Ref. 101.

Dr. Brooks' Directions paper contains a litany of arguments suggesting that the increase in blood lactate at the anaerobic threshold may not be caused by inadequate oxygen delivery. As stated previously (101), inadequate oxygen delivery is only one of several hypotheses which may account for the phenomenon. Resolution of this specific mechanism will not occur until techniques are developed which allow determination of mitochondrial oxygen tension during exercise in man. Dr. Brooks' singular interest in mechanisms has resulted in his inability to appreciate what the anaerobic threshold represents and why it is important. The anaerobic threshold is the $\dot{V}O_2$ at which there is a simultaneous acceleration in the concentrations of muscle and blood lactate. As shown in Figure 2 of my paper, muscle and blood lactate remain near resting levels at light and moderate work rates. At approximately 50% of $\dot{V}O_{2\text{max}}$, they both begin to increase. As work rate is further increased, muscle and blood lactate concentrations continue to accelerate. This well-accepted (104) pattern of lactate change has been shown by Knuttgen and Saltin (46) and Jorfeldt et al. (40). Dr. Brooks cites the recent study of Green et al. (27) as providing evidence that the onset of muscle lactate increase occurs well before the onset of blood lactate increase. But because of problems in the Green et al. study, this conclusion should be questioned. Green et al. administered a 1-min incremental exercise test to each of 10 subjects. At a work rate corresponding to "79%" of the

anaerobic threshold, a blood sample and muscle biopsy were taken. At this work rate, muscle and blood lactate were elevated above resting levels. By definition, if blood lactate is elevated at a given work rate, that work rate is above the anaerobic threshold. Thus, the "79%" value designated by Green et al. was incorrect. The misjudgement of the onset of lactic acidosis could have been a consequence of using a computer algorithm shown previously to provide overestimates of the anaerobic threshold (101).

What is the significance of the accelerated increase in muscle and blood lactate? The ability to sustain long-term exercise has been shown to be critically dependent upon the anaerobic threshold (25,47,53,60). For example, marathon runners do not run at some arbitrary fraction of their $\dot{V}O_{2\text{max}}$. They run at a pace that is within ~5% of their anaerobic thresholds (25). The anaerobic threshold is an important determinant of sustained exercise tolerance because of the detrimental muscle and systemic effects of elevated lactate concentration. Lactic acidosis in muscle is known to accelerate creatine phosphate breakdown and inhibit glycolysis (104). Also, a decrease in muscle pH interferes with calcium triggering of muscle contraction (104). Systemically, lactic acidosis inhibits lipolysis and thus accelerates carbohydrate utilization. As a consequence, muscle glycogen, a key substrate for long-term exercise performance, will be utilized at a much faster rate and depleted at an earlier point in time. Acceleration of carbohydrate metabolism increases CO_2 end products. Further, CO_2 is loaded into the venous blood owing to bicarbonate buffering of lactate. In order to maintain PCO_2 homeostasis in the alveolar air and arterial blood, the ventilatory requirements are necessarily greater. Finally, significant lactic acidosis is associated with an upward drift in $\dot{V}O_2$ which further taxes the cardiovascular system. The utility of the anaerobic concept is *not* dependent on the mechanism of blood lactate increase but instead on the high degree of association, found experimentally and predicted theoretically, between endurance exercise tolerance and the onset of lactic acidosis.

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A necessary assumption of the invasive anaerobic threshold determination is that the initial increase in blood lactate corresponds to the initial increase in muscle lactate. This assumption has been challenged by Dr. Brooks because usual sites of blood sampling (e.g., the brachial artery) are far removed from the site of lactate release. As there are intervening organs between the two sites which are known to metabolize lactate, the concentration of lactate released by the muscle will be greater than that sampled at the brachial artery. But the assumption does not require a quantitative relationship between lactate in the venous effluent and the brachial artery. Instead, it is assumed that some measurable portion of the lactate in the venous effluent will reach the brachial artery. This seems reasonable based on the similar lactate break points for muscle and arterial blood evident in the data of Knutgen and Saltin (46) and Jorfeldt et al. (40).

In his section entitled "The linkage between blood lactate and pulmonary minute ventilation," Dr. Brooks raises two concerns. First, he asserts that lactic acidosis is not associated with increases in minute ventilation, because Segal and Brooks (106) found that blood lactate and $\dot{V}CO_2$ were reduced but ventilation increased in subjects exercising at the same work rate after glycogen reduction. The intervention used to lower glycogen stores was long-term intense exercise to exhaustion. This intervention leads to a chronic reduction in PCO_2 (103). Examination of the alveolar ventilation equation ($\dot{V}_A = \dot{V}CO_2 \cdot k / PaCO_2$) demonstrates that $\dot{V}CO_2$ is not the sole factor determining the level of ventilation—if $\dot{V}CO_2$ is held constant and PCO_2 is lowered, ventilation will increase. The glycogen reduction study of Segal and Brooks did not contravene the alveolar ventilation equation.

Secondly, he doubts the excellent agreement reported by others for the anaerobic threshold measured invasively and noninvasively. As evidence, he cites the study of Hughes et al. (36). These authors demonstrated that glycogen reduction or a fast pedal rate increased the work rate at which the noninvasive anaerobic threshold occurred. But the anaerobic threshold is the \dot{VO}_2 , not the work rate, at which the break point in blood lactate occurs (102). The \dot{VO}_2 at which the lactate break point occurred was not altered by glycogen reduction or increased pedal rate. Hughes et al. also reported that their noninvasively measured anaerobic thresholds did not correlate well with their lactate break point measurements of the parameter. Unlike previous validation studies (7,55,82,107), which used the upward break point in the \dot{V}_E/\dot{VO}_2 vs \dot{VO}_2 curve as a marker of the noninvasive anaerobic threshold, Hughes et al. used "the point after which \dot{V}_E began to increase nonlinearly." Caiozzo et al. (7) compared \dot{V}_E and \dot{V}_E/\dot{VO}_2 as indices of the anaerobic threshold. The \dot{V}_E index re-

sulted in a lower correlation and a larger scatter (the standard error of estimate was 30% higher) compared to \dot{V}_E/\dot{VO}_2 . The chance Hughes et al. had of finding good agreement between the two detection methods would have been enhanced had they used the standard gas-exchange (as opposed to ventilatory) criterion.

In this context it is worth mentioning the recent study of Smith and O'Donnell (107), who examined anaerobic threshold changes during a 36-wk endurance training study. To validate their noninvasive detection method, they compared gas exchange and arterial lactate responses to incremental exercise in four subjects prior to exercise training. Excellent agreement was found between the increases, from a prior stable base line, in blood lactate and \dot{V}_E/\dot{VO}_2 for each subject. An isocapnic buffering region between the initial increases in \dot{V}_E/\dot{VO}_2 and $\dot{V}_E/\dot{V}CO_2$ was documented for each subject. This type of careful validation of the noninvasive gas exchange detection procedure should be performed before initiating a study using the anaerobic threshold measurement. It is evident from recent publications that some investigators do not or cannot obtain agreement between the gas exchange and blood lactate detection methods. In some instances this has resulted because the wrong noninvasive index was used (36) or because an invalid computer algorithm was used (27). In other instances the cause is less evident, but inexperience with gas-exchange measurements is a possibility (cf. 80).

Dr. Brooks' previous arguments do not prepare us for his "final note." We are told that determination of the anaerobic threshold by gas exchange "is completely without basis" in patients with cardiac and/or pulmonary disease. We are not informed, however, what characteristics these patients might have that invalidate either the concept or its methods of measurement. An accumulating body of literature indicates that anaerobic threshold determination is a valuable addition in the assessment of fitness for such patients and, indeed, is useful in differential diagnosis. An abnormally low anaerobic threshold has been shown to have diagnostic importance in patients with cardiac (48,73) and pulmonary disease (105). It would be most unfortunate if the statement that this measurement in patients "could potentially be injurious to them" was taken at face value. The anaerobic threshold concept is proving useful in an increasing number of clinical centers. It is undeniable that further research needs to be done, both in elucidation of the determinants of the anaerobic threshold in various disease states and in validation of the gas exchange technique in patients with exercise limitation owing to cardiopulmonary disorders. However, the progress made to date in applying the anaerobic threshold concept in the clinical setting is a strong predictor that it will have lasting value.

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DIRECTIONS-1985

Response to Davis' manuscript

G.A. BROOKS

*Exercise Physiology Laboratory, University of California,
Berkeley, CA 94720*

In his paper on the anaerobic threshold hypothesis, Dr. Davis has missed the key and central issues. In the concluding remarks of his position paper, Davis states that "debate has centered, not on the fundamental concept [of the anaerobic threshold], but on the descriptor of the concept." This is not the case! As expressed in my position paper, the central objections to the concept of the anaerobic threshold are fundamental, and not "semantic" as concluded by Davis. Davis expresses the belief that a muscle anaerobic threshold occurs during sub-maximal exercise and that this "threshold" can be predicted from measurements of pulmonary ventilation. However, there is no indisputable scientific evidence to establish such beliefs. In his paper, Davis is concerned with the nuances of how to predict the anaerobic threshold from plots of $\dot{V}E$, $\dot{V}ETO_2$, $\dot{V}E/\dot{V}O_2$, and $\dot{V}E/\dot{V}CO_2$. Unfortunately, in the absence of a firm theoretical basis to support the concept of an "anaerobic threshold," in terms of understanding metabolic regulation and the control of ventilation, these graphings are of questionable value.

In his paper, Davis ignores the fact that lactate is produced by muscle under fully aerobic conditions. As suggested from the tracer experiments on resting individuals (12) and as demonstrated recently by Connell et al. (2) on dog gracilis muscle contracting *in situ*, lactate production occurs under fully oxygenated conditions. Lactate production does not necessarily imply anaerobiosis, i.e., oxygen-limited ATP production. These points are developed in my position paper.

In his paper, Davis also ignores the key concept that measurements of blood or muscle lactate concentration provide no direct information on the rate of lactate production. In fact, blood lactate concentration merely reflects the balance of lactate entry into and removal from the blood (12). The key observation used to support the hypothesis of an anaerobic threshold is that

during progressive-intensity exercise, there occurs a power output at which the concentration of blood lactate begins a steep increase. This observation has been misconstrued as evidence of a sudden increase in lactate production.

From isotope tracer studies of lactate metabolism in resting and exercising individuals, it is well established that the rate of lactate production is directly related to the overall metabolic rate assessed by the $\dot{V}O_2$. With exercising dogs, Issekutz et al. (14) have clearly shown that during exercise the rate of lactate production can be three to five times higher than during rest, while the blood lactate concentration remains at resting levels. This fact alone makes it difficult to accept the hypothesis of the anaerobic threshold.

Davis' position paper incorrectly assumes that an abrupt increase in pulmonary ventilation [i.e., the T(vent)] can be interpreted as an increase in blood lactate concentration [i.e., the T(lact)]. Davis, unfortunately, uses these terms interchangably. Clearly, the ventilatory response to any stress, such as exercise, is the result of several inputs. Of these, the ventilatory response to lactic acidosis, which is sensed at the peripheral chemoreceptors, provides only one component in the overall regulation of pulmonary ventilation during exercise (1). In his paper, Davis indicates that factors such as pain and anxiety can affect ventilation. If we assume that these, as well as other neural and humoral factors, can affect ventilation, then the position that the event of lactic acidosis can be predicted from pulmonary measurements becomes confusing at best. Numerous attempts (9,11,13) to test the linkage between the T(vent) and T(lact) have shown these variables to be uncoupled under a variety of circumstances.

By his references to the work of others, Davis does not adequately defend the hypothesis of an anaerobic threshold. For instance, a point made in the discussion section of the lactate tracer study on rats by Donovan and Brooks (3) is criticized. This criticism fails to conceptually distinguish between the experimental result (the effect of training on lactate metabolic clearance

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rate during exercise) and a point of discussion regarding the clearance of blood lactate by particular tissues. Moreover, Davis further criticizes the study of Donovan and Brooks (3): "several studies have clearly demonstrated reduced lactate production (measured by muscle biopsy) following endurance training." However, this statement confuses metabolite concentration with rate of production. In addition, the statement attributed to Freminet et al. (7) by Davis concerning the appropriateness of tracer techniques for studies *in vivo* is presented out of context. Clearly, Freminet is an individual who has contributed much to the field of lactate tracer kinetics; he has recently published a review on the subject (6). It is certain that the techniques of tracer methodology will be a subject for continued advancement in the future. However, it is also certain that the current procedures of venous tracer lactate infusion, arterial blood sampling, and use of carbon-labelled (as opposed to hydrogen) lactate tracer, as described in my accompanying position paper, provide a firm basis upon which to understand the effects of exercise on lactate metabolism.

As shown in Table 2 of his position paper, Davis has misrepresented the terminology and experimental results of Hughes et al. (13). Those investigators clearly demonstrated that glycogen depletion results in an uncoupling of the T(lact) and T(vent). Similarly, the results of Hagberg et al. (11), who demonstrated an uncoupling of the T(vent) and T(lact) in McArdle's syndrome patients, is not fairly represented. It is extremely presumptuous to attribute the results of Hagberg et al. to pain and anxiety in the McArdle's patients during exercise. Previously, Hagberg et al. (10) addressed this point and reported that the patients did not suffer pain during the experimental procedures used.

Davis' interpretations of the findings by Vogel and Gleser (16), and by Woodson et al. (17) are questionable. In neither of these studies was the "lactate anaerobic threshold" determined as stated by Davis.

The statements on muscle physiology by Davis can be challenged. For example, the speculation that changes in muscle fiber recruitment pattern in progressive exercise are due to lactic acidosis, rather than the converse, will, in my judgment, find minimal support. The many studies which established the size principle in muscle fiber recruitment (e.g., Ref. 5), as well as the several studies of muscle fiber glycogen depletion (e.g., Ref. 8), run contrary to the position of Davis that lactic acidosis causes changes in muscle fiber recruitment pattern during progressive intensity exercise. Similarly, Davis' description (under the section on "Mechanisms of the Anaerobic Threshold") of how muscle perfusion

is matched to regional metabolism will be read with interest by those who study the autoregulation of blood flow (e.g., Ref. 4).

In his paper, Davis refers to the findings of others [e.g., Karlsson and Jacobs (15)] who have demonstrated a correlation between performance in endurance activities and the power output which elicits the onset of blood lactate accumulation (OBLA). The OBLA has incorrectly been interpreted by Davis as the point at which areas in exercising muscle become anaerobic. It is difficult to imagine that muscle anaerobiosis exists during sustained sub-maximal exercise when significant reserves in $\dot{V}O_2$, cardiac output, muscle blood flow, and muscle capillary dilatation exist. Rather, the elevated blood lactate levels which occur and are maintained during sustained exercise are likely due to a metabolic clearance rate which is insufficient to keep blood lactate at resting levels. This interpretation of the elevation in blood lactate concentration during prolonged, sub-maximal exercise is based on the results of tracer studies and is explained in more detail in my accompanying position paper. Davis' position on significance of the correlation between the OBLA and exercise performance is an example of how application of "anaerobic threshold theory" to interpretation of a simple observation can result in erroneous conclusions.

In conclusion, it is my opinion that the position paper of Davis is similar in essence to the reports supporting the hypothesis of an anaerobic threshold. Unfortunately, the paper avoids the critical issues. The paper is very selective in its interpretation of the literature, and the physiological explanations of mechanisms thought to underlie the anaerobic threshold are inadequate. The anaerobic threshold hypothesis fails because it requires the acceptance of three separate and invalid assumptions. These are that: 1) muscle lactate production results from oxygen-limited ATP production; 2) changes in blood lactate concentration are due solely to changes in muscle lactate production; and 3) pulmonary ventilation tracks blood lactate level. Therefore, the directions for future research suggested by Davis are not likely to meaningfully contribute to our understanding of muscle metabolism during exercise. It is time to approach the understanding of the control of muscle metabolism and pulmonary ventilation by direct methods. Finding the inflection points in lines on graph paper is not likely to contribute to our understanding of metabolic and cardiopulmonary integration. Furthermore, insistence on the validity of the anaerobic threshold hypothesis is speculative at best, and at worst contributes to misunderstanding among those least prepared to interpret the literature.

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HPER 6760 Exercise Science Seminar

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The validity of the heart rate deflection threshold test for determination of the maximal lactate steady state

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Manuscript Number: JSCR-08-1072

Title: The validity of the heart rate deflection threshold test for determination of the maximal lactate steady state

Short Title: The validity of the heart rate deflection threshold

Article Type: Original Investigation

Keywords: lactate, Conconi test, running intensity.

Manuscript Region of Origin: BRAZIL

Abstract: The purpose of this study was to investigate the validity of the heart rate deflection threshold (HRDT) test in the determination of the velocity at the maximal lactate steady state (MLSS). Fifteen untrained male took part in a 3-km running performance on 400-m track and completed a comprehensive battery of laboratory tests. Performance velocity at HRDT was strongly correlated with the MLSS running velocity ($r = 0.84$; $R^2 = 0.71$; $P < 0.0001$). HRDT running velocity (mean \pm SD $9.0 \pm 1.3\text{-km.h}^{-1}$) was not significantly different ($P > 0.05$) from MLSS velocity ($9.3 \pm 1.3\text{-km.h}^{-1}$). A high agreement was observed between methods (Bland and Altman analysis). It is concluded that the HRDT was an accurate method to predict MLSS velocity in the present study.

1 The validity of the heart rate deflection threshold test for determination of the maximal
2 lactate steady state

3 Running head: The validity of the heart rate deflection threshold

4
5 Laboratory of Exercise Physiology

6
7 Paulo H.S.M. de Azevedo

8 Vitor K.P. Carrara

9 Gustavo M. Rissato

10 João M.P. Duarte

11 Runer A. Marson

12
13 Department of Physical Education

14 Anhanguera College of Bauru

15 3, Moussa Nakhl Tobias, Bauru – SP – Brazil

16 CEP: 17.021.100

17 Phone: (5514) 3239-9147

18 e-mail: paulohazevedo@yahoo.com.br

19
20 Financial support: AESA

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The purpose of this study was to investigate the validity of the heart rate deflection threshold (HRDT) test in the determination of the velocity at the maximal lactate steady state (MLSS). Fifteen untrained male took part in a 3-km running performance on 400-m track and completed a comprehensive battery of laboratory tests. Performance velocity at HRDT was strongly correlated with the MLSS running velocity ($r = 0.84$; $R^2 = 0.71$; $P < 0.0001$). HRDT running velocity (mean \pm SD $9.0 \pm 1.3\text{-km.h}^{-1}$) was not significantly different ($P > 0.05$) from MLSS velocity ($9.3 \pm 1.3\text{-km.h}^{-1}$). A high agreement was observed between methods (Bland and Altman analysis). It is concluded that the HRDT was an accurate method to predict MLSS velocity in the present study.

Keywords: lactate, Conconi test, running intensity.

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2 Introduction
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The maximal lactate steady state (MLSS) has been defined as the highest blood lactate concentration that increases by no more than 1 mmol.L^{-1} between 10 and 30-min of constant velocity/workload test (3,23). This physiological index is important because it has been used to prescribe endurance exercise training programs (20). However, two to five constant workload exercise test of up 20 to 30-min duration is usually required to determine MLSS (23).

Conconi et al. (8) reported that heart rate (HR) as a function of speed is not linear up to the maximum and that the speed corresponding to the deflection point also corresponds to the speed of the second lactate threshold. So, the heart rate deflection threshold (HRDT) is a non-invasive test of the anaerobic threshold. Thus, determination of the HRDT is supposed to be too an indirect measure of MLSS utilizing incremental exercise test, due to its correlation whit ventilatory threshold (VT) (19) and second lactate threshold (LT2) (14). These investigations suggest that knowledge of the heart rate kinetics may provide to reveal certain indicators of the intensity of exercise equivalent to MLSS. But, a number of studies has produced contradictory results (16,18,24). Thus, the aim of the present research was to establish whether HRDT velocity corresponding to the MLSS intensity.

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The Ethics Committee for Human Research at Anhanguera College approved the methods used in this study (32/2008). All experimental procedures complied with the current laws for human studies. Potential subjects were introduced to all testing equipment and procedures. After completing the informed consent procedure, 15

physically active men (23.4 ± 3.9 years old, 71 ± 10.1 kg body weight, 175 ± 0 cm height, 19.8 ± 5.1 % body fat), who were students at Anhanguera College, volunteered to participate in this investigation. The number of subjects was determined for provide appropriate statistical power ($\beta=80\%$; $\alpha=5\%$). Body density was estimated by the skinfold technique, from which body composition was determined using the Siri formula for estimation of percent body fat and fat-free mass (11). The subjects had been involved in recreational training programs (e.g. endurance running, resistance training, and soccer) for the previous 6 months, consisting of at least 20-min of exercise three times per week on a regular basis. All of the subjects were advised not to have any extenuating physical practice 48 hours before the tests.

Design

The tests were performed in the Exercise Physiology Laboratory at Anhanguera College and at 400-m track. Three to six tests were performed on separate days at the same time of day. The subjects were instructed to have their last meal at least 3-h before testing, arrive at the laboratory in a rested and fully hydrated state and to avoid strenuous exercise in the 48-h preceding a test session. The first test was a 3000-m time trial (V3000) on 400-m track. In the second test the volunteers performed an incremental test for HRDT determination. The third test was a constant velocity lasted 30-min around HRDT. The incremental and constant velocity test was performed on a treadmill (Movement LX-150). The heart rate (HR) was monitored continuously during all tests using a Polar Accurex Plus (Kempele, Finland). Before each test session the subjects performed a warm-up consisting of low intensity running for 5-min at about ($6-7.5 \text{ km h}^{-1}$).

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2 Test 1: The 3000-m velocity test (V3000)
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11 The subjects ran 3000-m as quickly as possible and the mean running velocity
12 was calculated for each subject (V3000). The V3000 was used to prescribe the
13 velocities of the treadmill runs during the incremental tests to determine the HRDT
14 (22).
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17 Test 2: Incremental test for HRDT determination
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20 Initial running velocity was about 65% of the individual's V3000. The incline
21 was set at 1% (15), with 0.5-km.h^{-1} increments at each 3-min stage. The HRDT was
22 identify when the running velocity at which heart rate began to increase less rapidly
23 with increments in running velocity during the incremental exercise test, by means of
24 third order polynomial fit (confidence 95%) (17). The maximal distance (D_{max}) between
25 perpendicular line and polynomial fit was considered HRDT (17). Standardized verbal
26 encouragement was given to the subjects to continue the test until they were exhausted.
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28 The heart rate (HR) was continuously monitored by a heart rate monitor (Polar Accurex
29 Plus, Finland) and values recorded every three minutes during incremental exercise test.
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31 The HR corresponding to HRDT ($HRDT_{HR}$) was the values registered at HRDT velocity
32 during incremental exercise test and is also reported as percent of the peak HR
33 (% $HRDT_{HR}$).
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50 Test 3: Determination of MLSS
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53 On subsequent occasions (3–5 visits), participants completed a series of
54 constant-speed treadmill runs, each of 30-min duration, for the determination of the
55 MLSS. An ear lobe capillary blood sample was taken during a 45-s time period for
56 blood lactate concentration ($[Lac^-]$) analysis at rest and during 5-min intervals
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throughout the run at which point participants were asked to step astride the treadmill.

The velocity of the first constant work rate test corresponded to a 5% below HRDT measured during the incremental exercise test. The MLSS was defined as the running speed that produced no more than a 1-mmol.L^{-1} increase in $[\text{Lac}^-]$ between 10 and 30-min of exercise (3). MLSS was determined with a precision of 0.5-km.h^{-1} . If during the first constant work-rate test a steady state or a decrease in lactate was observed, further subsequent 30-min constant work-rate tests from 0.5-km.h^{-1} higher work-rate were performed on separate days until no $[\text{Lac}^-]$ steady state could be maintained. MLSS was calculated as the mean $[\text{Lac}^-]$ measured at 10 and 30-min of the MLSS.

The heart rate (HR) was continuously monitored by a heart rate monitor (Polar Accurex Plus, Finland) and values recorded every five minutes during constant velocity tests. The HR corresponding to MLSS (MLSS_{HR}) was the mean of the values registered during MLSS testing and is also reported as percent of the peak HR (% MLLS_{HR}).

Blood collection and laboratory analysis

The $25\text{-}\mu\text{L}$ of capillary blood was collected from the ear lobe using heparinized and calibrated microcapillaries during MLSS tests. The $25\text{-}\mu\text{L}$ was deposited into Eppendorf tubes containing $50\text{-}\mu\text{L}$ of 1% sodium fluoride (NaF). The $[\text{lac}^-]$ was determined from this sample by using a blood lactate analyzer (Yellow Springs 1500). The $[\text{lac}^-]$ results were corrected by the volume of the blood sampled within the Eppendorf tubes and are presented in mmol.L^{-1} concentrations.

Statistical Analysis

Firstly, the Shapiro-Wilk test was applied to the sample for normality, and because data were found to be normal, a parametric statistic test was used. Data are

1 presented as means with standard deviations (\pm SD). Pearson product moment
2 correlations were used to quantify the relationships between MLSS and HRDT. Paired
3 t-test was used to compare MLSS and HRDT velocity. The limit of statistical
4 significance was set at 5% ($P \leq 0.05$). The Bland-Altman method was additionally
5 applied in order to assess the agreement of the results. Data was analyzed using the
6 Statistical Package for Social Sciences (SPSS), version 13.0 for Windows.
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Results

19 Table 1 contains the variables determined from the incremental velocity tests
20 (HRDT intensity, HR_{peak} , HR at HRDT and % $HRDT_{HR}$) and at the constant velocity
21 tests (MLSS intensity, HR at MLSS and % $MLSS_{HR}$). No statistically significant
22 differences were found ($P > 0.05$) between MLSS and HRDT regarding physiological
23 and performance index. Figure 1 show the time course of the HR response in a typical
24 subject for the Conconi test.
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33 [FIGURE 1 HERE]
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36 The MLSS and HRDT velocities presented Pearson's correlation coefficient of
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38 0.84 ($R^2=0.71$; $P<0.0001$). The correlation between the $HRDT_{HR}$ and $MLSS_{HR}$ was no
39 significant ($r=0.50$; $R^2=0.25$; $P=0.6$).
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42 [TABLE 1 HERE]
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45 The analysis of agreement between the methods based on the Bland-Altman
46 methodologies shows that HRDT underestimated MLSS by 0.47-km.h^{-1} , on average,
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1 within a 95% confidence interval (Fig. 2). For MLSS_{HR} and HRDT_{HR} high agreement is
2 found too, while MLSS_{HR} underestimated HRDT by 1-bpm (Fig. 3).

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7 [FIGURE 2 and 3 HERE]

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12 Discussion

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14 The main finding of this study was that the validity of HRDT to predict MLSS

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16 velocity (Table 1; Figure 2). These suggest that HRDT and MLSS (gold standard) could

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18 be used interchangeably to demarcate the boundary between oxidative and anaerobic

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20 lactic metabolism. Thus, our results indicate that HRDT and MLSS maybe correspond

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22 to the equivalent physiological phenomenon. Others studies have show high correlation

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24 when investigated the relationship between the anaerobic threshold and HRDT, which

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26 occur in response to incremental exercise (8), HRDT and ventilatory threshold (19),

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28 second lactate threshold (LT2) (14).

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34 The MLSS is an important physiological index because it has been used to

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36 prescribe endurance exercise training programs (1,4,20). However, two to five constant

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38 workload exercise test of up 20 to 30-min duration is usually required to determine

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40 MLSS (23), limiting its use for training programs. Therefore, several studies were

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42 performed to propose a simple method for determining the MLSS, time to conduct the

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44 test relatively short and inexpensive marker (8,10,16,24).

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48 Some authors have reported that the HRDT does not occur, but this is a linear

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50 relationship between heart rate and velocity/power during incremental exercise test (16).

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52 Was suggested that the HRDT is protocol dependent (6,12,24). Vachon et al., 1999 (24),

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54 concluded that the HRDT is not an accurate predictor of LT. Jones and Doust (16)

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56 compared HRDT, lactate turnpoint and OBLA (fixed 4-mmol.L⁻¹) with MLSS. The

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1 authors suggested that the Conconi test is invalid for the determination of the lactate
2 turnpoint and MLSS. In the present study high correlation and agreement were observed
3 between HRDT and MLSS velocity. This difference of results between studies may be
4 due the specifics protocols used and methodologies for determining deviation of heart
5 rate from linearity. Our results provided evidence that HRDT can be determined during
6 an incremental test in nonathlete individuals for this specific protocol and methodology.
7

8 The stage length of present study is in accordance of previous researches (7).
9 According to these authors, 3-min of stage was sufficient for blood and muscle lactate
10 equilibrium during incremental exercise test. So, blood lactate concentration can not be
11 considered due to the longer stage as reported by Vachon et al. (24). Additionally, has
12 been reported that the blood lactate does not promote muscle fatigue (21) and cardiac
13 muscle using most of the lactate as an oxidative fuel (9).

14 According to present data, it seems that the methodology here used to determine
15 HRDT is valid for estimation of MLSS intensity. No statistically significant difference
16 was observed in the velocity regarding HRDT versus MLSS (Table 1), and a good
17 correlation was found as well ($r = 0.84$; $R^2=0.71$; $P<0.0001$). These data suggest that
18 MLSS (Fig. 2) can be accurately estimated by using the dynamic response to heart rate
19 during a 3-min incremental effort increased by 0.5-km.h^{-1} , pause of 45-s and a total of
20 6-10 stages.

21 It was observed good agreement (Fig. 2) between the velocity associated to
22 HRDT and that associated to MLSS. The MLSS was found to be slightly superior to the
23 HRDT (0.47-km.h^{-1}). Six subjects exhibited identical GT and MLSS velocities. These
24 data suggest that HRDT is a simple method to estimate the MLSS.

25 The heart rate corresponding to HRDT was not found to be statistically different
26 from MLSS_{HR} , with good agreement between them (Fig. 3). The percentage HR_{peak} was
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not different between HRDT and MLSS. These data are clinically important because heart rate is largely used for controlling the training intensity. In the present study, the heart rate values regarding MLSS are in agreement with those found elsewhere (2,5,20). For HRDT heart rate values was found below of the others studies (16,18), but, percent of maximum heart rate it is similar to previous researches (13,17,25).

We can conclude that the validity of HRDT to predict MLSS velocity. High agreement was observed between methods. No difference is found for heart rate at HRDT velocity and MLSS velocity. Our results provided evidence that HRDT can be determined during an incremental test in nonathlete individuals for this specific protocol and methodology.

PRACTICAL APPLICATIONS

In the present study, HRDT was in agreement with the running speed corresponding to the maximal lactate steady state. Utilizing the D_{max} methodology between perpendicular line and polynomial fit by means of third order polynomial fit, the HRDT could be properly identified in all of the subjects. So, the data from the current study would be useful when prescribing running exercise programs to allow for sufficient intensity training sessions.

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Table 1: Selected variables obtained from constant and incremental velocity tests (mean \pm SD).

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Figure 1 – Heart rate responses to 1 subject during incremental run tests. Subject
5 showed an HR plateau on Conconi treadmill protocol, in which 3-min stages were used.
6 HR deflection threshold (arrow).

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Figure 2 – Results of the Bland–Altman analysis of agreement for MSSL and HRDT
9 measurements. The continued lines indicate de means of the differences and the dashed
10 lines indicate the limits of agreement between measurements.

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Figure 3 – Results of the Bland–Altman analysis of agreement for MLSS_{HR} and
13 HRDT_{HR} measurements. The continued lines indicate de means of the differences and
14 the dashed lines indicate the limits of agreement between measurements.

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Table 1

	HRDT	MLSS
Velocity (km.h ⁻¹)	9.0±1.3	9.3±1.3
HR _{peak} (bpm)	191.7±8.0	-
HR at (bpm)	174.1±7.4	174.2±5.2
%HR	90±2.1	91±4.2

Figure

Figure 1

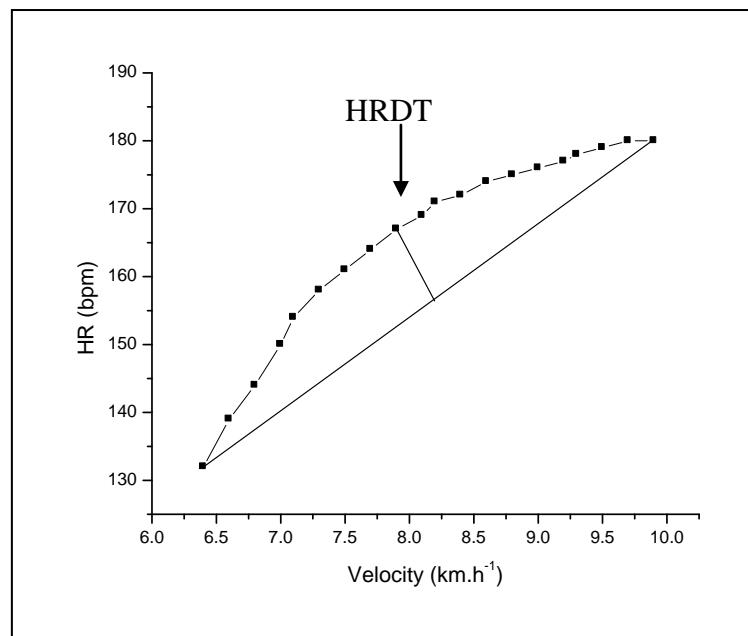


Figure 2

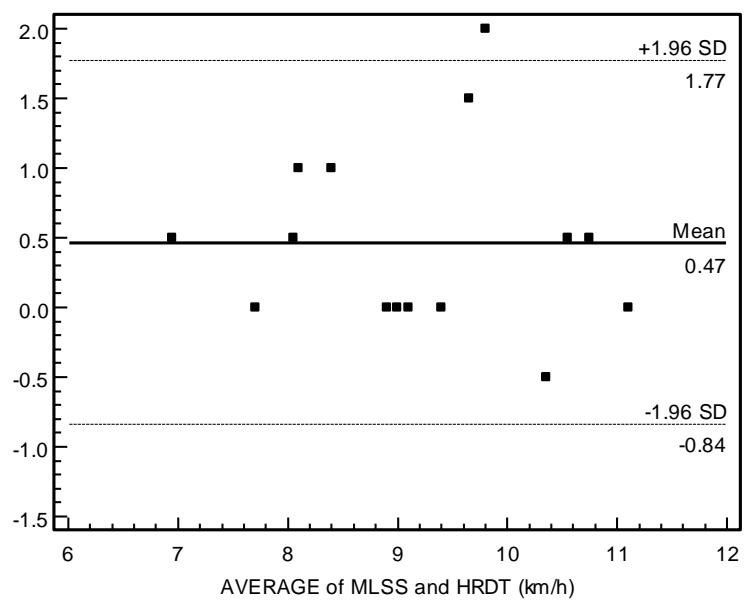


Figure 3

