1989

The Lactate Threshold and Carbon Dioxide Flow to the Lung as Predictors of Ventilation During Exercise.

Becky Anne Baker
Louisiana State University and Agricultural & Mechanical College

Follow this and additional works at: https://digitalcommons.lsu.edu/gradschool_disstheses

Recommended Citation
https://digitalcommons.lsu.edu/gradschool_disstheses/4759

This Dissertation is brought to you for free and open access by the Graduate School at LSU Digital Commons. It has been accepted for inclusion in LSU Historical Dissertations and Theses by an authorized administrator of LSU Digital Commons. For more information, please contact gradetd@lsu.edu.
INFORMATION TO USERS

The most advanced technology has been used to photograph and reproduce this manuscript from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book. These are also available as one exposure on a standard 35mm slide or as a 17" x 23" black and white photographic print for an additional charge.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI
University Microfilms International
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
313/761-4700 800/521-0600
The lactate threshold and CO₂ flow to the lung as predictors of ventilation during exercise

Baker, Becky Anne, Ph.D.
The Louisiana State University and Agricultural and Mechanical Col., 1989
THE LACTATE THRESHOLD AND CO₂ FLOW TO THE LUNG AS PREDICTORS OF VENTILATION DURING EXERCISE

A dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The School of Health, Physical Education, Recreation and Dance

by

Becky Anne Baker
B.S., Ashland College, 1969
M.A., Eastern Kentucky University, 1980
August 1989
ACKNOWLEDGEMENTS

I would like to express my thanks to Dr. Steve Dodd for his advice and help as major professor since January, 1989. His expertise and understanding has helped make the transition from one major professor to another to be without strife and loss of time in the completion of my degree. I would also like to thank my minor professor, Dr. Harold Silverman, for his guidance and teaching, as well as the other members of my committee, Dr. B. Don Franks, Dr. Yuruk Iyriboz, Dr. Dennis K. Landin, and Dr. Gerard Berggren for their time spent in reviewing the manuscript.

I would like to thank Gable Church for her statistical assistance. Dr. Ron Byrd and Dr. Michael Mangum have also made important contributions through their teaching and words of encouragement. I would also like to thank Uncle Zara, Phyllis Lefeaux, and a very special group of friends for their support. Most of all, my gratitude extends to my gracious subjects, my mentor, Dr. Scott K. Powers, and to Mother and Dad, who taught me to trust God and commit my work to Him.
# TABLE OF CONTENTS

## ACKNOWLEDGEMENTS

ix

## ABSTRACT

ix

## INTRODUCTION

1

## Chapter

1. REVIEW OF LITERATURE

3

   The Lactate Threshold

3

   The Ventilatory Threshold

6

   The Control of Ventilation during Exercise

8

2. ASSIGNMENT OF THE LACTATE THRESHOLD VALUE USING LOG-LOG AND SEMILOG TRANSFORMATIONS

13

   Methods

14

   Results

18

   Discussion

26

3. PREDICTION OF THE VENTILATORY THRESHOLD BY THE LACTATE THRESHOLD

34

   Methods

35

   Results

37

   Discussion

45

4. THE VENTILATORY RESPONSE TO CO₂ FLOW AND EXERCISE

54

   Methods

55

   Results

58

   Discussion

65

## SUMMARY

74
LIST OF TABLES

Table
1. Lactate Threshold (Means ± Std. Error) ........................................................... 19
2. ANOVA table for Testing Differences in the Lactate Threshold for 10 Subjects ........................................................... 20
3. Mean Square Error (Means ± Std. Error) ........................................................... 21
4. ANOVA Table for Testing Differences in the Mean Square Errors of the Piecewise Regressions for 10 Subjects ........................................................... 22
5. Lactate Thresholds Found by Each Method/Model Combination ................... 24
6. Mean Square Errors (in Logarithmic Units) of Piecewise Regressions .................. 25
7. Comparison of Log-log and Semilog Analyses of Lactate vs. \( \dot{V}O_2 \) Relationship ........................................................... 26
8. Lactate and Ventilatory Thresholds for Each Subject ........................................... 38
9. Descriptive Statistics of Lactate and Ventilatory Thresholds ............................... 39
10. Tests for Significant Difference between the Lactate Threshold and the Ventilatory Threshold ........................................................... 40
11. Results of Linear Regressions of the Lactate Threshold on the Ventilatory Threshold ........................................................... 46
12. Slopes and Intercepts of the \( \dot{V}E-\dot{V}T CO_2 \) Regressions ...................................... 59
13. Comparison of \( \dot{V}E-\dot{V}T CO_2 \) Regressions ........................................................... 60
14. Stepwise Regression of $\dot{V}_E$ vs. $\dot{V}_{TCO_2}$ and $P_{ETCO_2}$ with $\dot{V}_{TCO_2}$ Entered First.......................................................................................................................64

15. Division of Ventilatory Response to Exercise at 400 Kpm·Min$^{-1}$ into 1) the Component Dependent upon CO$_2$ Flow, and 2) the Component Independent of CO$_2$ Flow........................................................................................................72
LIST OF FIGURES

Figure

1. Lactate Concentration vs. O₂ Uptake................................................................. 15
2. Log Lactate Concentration vs. Log \( \dot{V}O_2 \)....................................................... 17
3. Predicted Values of Exponential That Best Fits Data of Subject 1.................. 31
4. Predicted and Actual Values of Subject 1 When Data is Fit to an Exponential............................................................................................................ 33
5. Plots of \( \dot{V}E \), \( \dot{V}E/\dot{V}O_2 \), and \( \dot{V}E/\dot{V}CO_2 \) Used to Determine Ventilatory Threshold of Subject 1............................................................... 36
7. Beaver Log-log Lactate Threshold vs. Ventilatory Threshold.......................... 42
8. Baker Semilog Lactate Threshold vs. Ventilatory Threshold......................... 43
9. Beaver Semilog Lactate Threshold vs. Ventilatory Threshold.......................... 44
10. Line of Best Fit of the Baker Log-log Lactate Threshold vs. the Ventilatory Threshold................................................................................. 47
11. Line of Best Fit of the Beaver Log-log Lactate Threshold vs. the Ventilatory Threshold................................................................................. 48
12. Line of Best Fit of the Baker Semilog Lactate Threshold vs. the Ventilatory Threshold.......................................................... 49
13. Line of Best Fit of the Beaver Semilog Lactate Threshold vs. the Ventilatory Threshold................................................................................. 50
14. Line of Best Fit of the Baker Semilog Lactate Threshold vs. the Ventilatory Threshold When the Lactate Threshold is Less than 2 Liters Minute⁻¹................................................................. 51
15. Ventilatory Response of Subject 3 to CO₂ Inhalation at Rest and during Constant Rate Exercise of 400 Kpm ..............................................................62

16. Ventilatory Response of Subject 3 to CO₂ Inhalation at Rest and to Metabolic CO₂ during Exercise at Different Levels of Work Rate ......................................................................................................................................................63

17. Drawing the Components of the Ventilatory Response of Subject 2 ..............................................................................................................................................................................67

18. Addition of Vectors to Partition the Ventilatory Response of Subject 2 to Exercise ........................................................................................................................................................................69

19. Hypothetical Intercept Vectors during Exercise at 600 and 800 Kpm·Min⁻¹ ........................................................................................................................................................................71
ABSTRACT

Three studies were performed to determine the relationship between blood lactate, CO₂ flow to the lung, and ventilation during exercise. First, the method of determining the lactate threshold by use of log-log and semilog transformations developed by Beaver and his colleagues was modified to provide an objective method of determining the threshold which resulted in a significantly better fit (p<.05) of the log-log model to the data. Second, to test the theory that the increase in CO₂ flow to the lung due to bicarbonate buffering of H⁺ from lactic acid causes the rise in ventilation out of proportion to \( \dot{V}O₂ \) at the ventilatory threshold, the lactate thresholds of these subjects were used to predict their ventilatory thresholds. The lactate threshold determined by the modified log-log model/method was a poor predictor with an insignificant relationship between the lactate and ventilatory thresholds (p>.05). In the third study, six subjects were tested during 4 sessions to determine the relationship between ventilation and CO₂ flow to the lung during exercise and also during rest and exercise while CO₂ was being inhaled. This relationship was expressed by the regression of minute ventilation (\( \dot{V}_E \)) vs. the minute rate of CO₂ expired (\( \dot{V}_{T\text{CO}_2} \)). Results showed no significant differences (p>.05) between the slopes of the \( \dot{V}_E - \dot{V}_{T\text{CO}_2} \) regression during rest and exercise with CO₂ inhalation, but the intercepts were significantly different (p<.05). The slope of the \( \dot{V}_E - \dot{V}_{T\text{CO}_2} \) regression during incremental exercise was significantly greater than during rest with CO₂ inhalation, with the intercepts not significantly
different, showing that the regression at rest with CO$_2$ inhalation could not be extended to explain the ventilatory response to exercise. However, the ventilatory response to incremental exercise could be explained by dividing the response into two components: 1) that component dependent upon CO$_2$ flow to the lung, and 2) a component independent of CO$_2$ flow to the lung and quantified by the difference in intercepts between the ventilatory response to $\dot{V}_T CO_2$ at rest and during exercise with CO$_2$ inhalation. In conclusion, these studies do not support the theory that CO$_2$ flow is the primary stimulus of exercise hyperpnea.
INTRODUCTION

Ventilation during exercise is a subject of intrigue and the question of control is perplexing. The search for the major stimulus of exercise hyperpnea has occupied the efforts of numerous physiologists in the past three decades, but the problem is complex and complicated by the integration of both neural and humoral influences. There exists the possibility that no one stimulus in itself is both sufficient and necessary to the control of ventilation during exercise.

One of the theories of ventilatory control during exercise is linked to CO₂ delivery to the lung as a consequence of CO₂ production in the muscle and bicarbonate buffering of hydrogen ion released by the production of lactic acid. During light and moderate exercise, ventilation is in direct proportion to metabolic CO₂ production and VO₂, while blood lactate levels remain near resting values. Then as the work rate increases during incremental exercise, lactic acid production increases and a marked rise in blood lactate occurs. Additional CO₂ is delivered to the lung as a result of bicarbonate buffering of the lactic acid. It is then that VE begins to increase out of proportion to VO₂ while continuing to follow V̇CO₂ (6, 8). The workrate above which a marked rise in blood lactate occurs is termed the lactate threshold (7), and because some investigators (8, 80) believe this is the work rate signalling a greater increase in anaerobic metabolism, it is also called the anaerobic threshold. These investigators propose that the nonlinear rise in ventilation, with isocapnic buffering, is a direct result of
the additional CO$_2$ delivered to the lung (8). Finally at even higher
workrates, as arterial bicarbonate levels decrease and hydrogen ion
concentration increases, the carotid bodies respond to strengthen the
ventilatory stimulus. VE then increases out of proportion to VOCO$_2$ (84).

In spite of the close coupling of ventilation to VOCO$_2$ during exercise,
the exact mechanism by which CO$_2$ flow to the lung may increase ventilation
has not been elucidated. While some investigators have expressed doubts
that there really is a threshold of blood lactate (92), lack of reliability in
selecting the threshold (37) and an ability to uncouple the lactate and
ventilatory thresholds (44) has brought uncertainty about the cause and
effect relationship between blood lactate and ventilation. In addition,
studies in animals have shown a neurogenic control component in exercise
claimed to be sufficient to explain the hyperpnea (49). Other animal studies
have shown CO$_2$ flow to increase ventilation, but without sufficient gain to
explain exercise hyperpnea (39, 40).

The purpose of the studies of this dissertation was to further
investigate the relationships between the lactate threshold, ventilation
during exercise, and CO$_2$ flow to the lung in order to test the hypothesis that
CO$_2$ flow to the lung is the primary stimulus of ventilation during moderate
exercise and during the transition from moderate to heavy exercise. First,
the technique commonly used to assign a value to the threshold was
modified in an attempt to more accurately determine that value. Then using
the modified method, the lactate thresholds of 10 subjects were compared
to their ventilatory thresholds. Finally, the theory that CO$_2$ flow to the lung
is the main stimulus for hyperpnea during moderate exercise was tested in
6 subjects by increasing CO$_2$ flow by CO$_2$ inhalation.
The relationship between lactic acid formation, muscular contraction, and fatigue has been studied since the 1800's (76). In 1907, Fletcher and Hopkins (33) clearly demonstrated that lactic acid was a metabolic product of living tissue, that it could be produced under anaerobic conditions, that fatigue was associated with an increase in lactic acid, and hyperoxia depressed lactic acid formation. In 1914, Christiansen, Douglas, and Haldane (15) showed that CO$_2$ was formed from the combination of lactic acid and bicarbonate in the blood during severe exercise, and in 1930 Douglas's student Owles (61) demonstrated that there exists a critical metabolic level below which blood lactic acid does not increase substantially and above which there is a marked increase. Since then, the nonlinear rise in blood lactate that occurs above a threshold work rate (the lactate threshold) during incremental exercise has been described by numerous investigators (11,24).

The use of the term "anaerobic threshold" in describing the lactate threshold first appeared in the literature in a report by Wasserman and McIlroy (81) in which they defined the anaerobic threshold as the level of oxygen consumption at which anaerobic metabolism becomes important, corresponding to the point at which the concentration of bicarbonate in arterial blood decreases and the concentration of lactate rises. In later
papers Wasserman and colleagues have referred to the anaerobic threshold as the level of O\textsubscript{2} consumption just below that at which metabolic acidosis and the associated changes in gas exchange occur (85). They consider it as the \( \dot{V}O_2 \) above which there is cardiovascular insufficiency in meeting tissue O\textsubscript{2} requirements and have used it as an aid in the differential diagnosis of exertional dyspnea (79). Subsequently, an incremental exercise test to determine the anaerobic threshold has been widely used by clinicians and investigators.

The anaerobic threshold is considered a very useful measure because it aids the assessment of exercise tolerance in patients with chronic heart failure (55,87), essential hypertension (50), ischemic heart disease (23), pulmonary vascular disease (48), and chronic obstructive pulmonary disease (54). It has also been used in predicting endurance capacity and/or performance in trained runners (30, 67, 70) trained and untrained cyclists (5,78), and competitive racewalkers (42). Alterations in the anaerobic threshold due to endurance training (25, 74), detraining (69), diet manipulation (44, 93), hyperoxia and hypoxia (43), caffeine ingestion (36, 66), thermal dehydration (29), testing mode (26), protocol (94), and sampling site (92, 95) have all been investigated. The anaerobic threshold has been used to determine exercise intensities for training and competition (34) and in laboratories to distinguish between moderate and heavy work rates (89). Noninvasive methods to determine the anaerobic threshold are widely used. The most commonly used noninvasive method is the determination of the ventilatory threshold, though that in itself has been determined in varying ways (13). Also suggested as noninvasive measures of the anaerobic threshold are respiratory frequency (47), the velocity-
heart rate relationship (21, 14), and the use of integrated electromyograms (57).

Although the anaerobic threshold is such a useful measure, there has been considerable controversy over the term and whether the rise in blood lactate at the anaerobic threshold is really due to anaerobic conditions in exercising skeletal muscle (11, 22, 43, 75). Some investigators believe that there is really no threshold, but that the increase in blood lactate is exponential (37, 92). Others claim the ventilatory threshold does not necessarily coincide with the lactate threshold (37, 44, 45, 58, 68).

Traditionally, the choice of experienced investigators, who visually inspect the graph of blood lactate vs. $\dot{V}O_2$ and pick a break point, has been the criterion measure of the anaerobic threshold. However, the lack of agreement between investigators in choosing the threshold (37) has pointed out the necessity of finding a better and more accurate method for determining the lactate threshold, if indeed it does exist. There also needs to be a better method for testing whether there is a threshold.

Beaver, Wasserman, and Whipp (7) have proposed a method for improving the detection of the lactate threshold by using a log-log transformation. Each subject performs an incremental exercise test, and blood lactate is measured during every other work stage. From the graph of blood lactate vs. $\dot{V}O_2$, the investigators visually select a division point as the data point where the steep portion of the curve begins. This point divides the curve into two segments, and the division point is considered to belong to both segments since the authors found no statistical reason for assigning it to one or the other segment. A straight line of best fit is then fitted to logarithmic transformations of each of the two segments of data.
points using linear regression analysis, and the intersection of these two lines is determined to be a more precise threshold.

Beaver et al. (7) also used a semilog model, transforming the lactate values but not the $\dot{V}O_2$ values, and fit two lines using the same method as for the log-log model. They argued that the log-log model was better because it appeared to fit the data in the vicinity of the threshold better than did the semilog model although there was no significant difference in the fit of the models as determined by pooled mean square error of the two lines for each model.

**The Ventilatory Threshold**

Beaver and colleagues also proposed a new method in determining the anaerobic threshold by gas exchange called the V-slope method (8). After a process of filtering and correcting for fluctuations in $P_{ETCO_2}$ (highest tension of CO$_2$ in expired alveolar gas), on the graph of $\dot{V}E$ vs. $\dot{VO}_2$, the data points above that portion of the curve referred to as isocapnic buffering are eliminated. Then a line is drawn through the isocapnic buffering portion of the curve, and another line through the lower portion of the curve. The intersection of the two lines is the anaerobic threshold, and Beaver and colleagues are careful to distinguish this as the point at which there is an increase in $\dot{V}CO_2$ due to bicarbonate buffering of H+, pointing out that just looking at $\dot{V}E$ vs. $\dot{VO}_2$ does not take into consideration that many times ventilatory insensitivity, obstructive lung disease, and obesity may cause $\dot{V}E$ and $\dot{V}CO_2$ to be uncoupled and therefore the ventilatory threshold may not represent the anaerobic threshold. Although useful for breath by breath systems and protocols with small increments and many data points, it is not
feasible to use that method with systems and protocols with fewer data points.

Orr, Green, Hughson, and Bennett (60) have used a computer program to determine the ventilatory threshold, with an algorithm that performed successive iterations that divided the data ($\dot{V}_E$ vs. $\dot{V}O_2$) into three parts and fit a line of best fit to each part. The iteration that resulted in the least pooled residual sums of squares was then used to determine the threshold by computing the intersection of the first two lines. They also used an algorithm that divided the data into two parts, as well as fitting exponential or power functions to the curvilinear region of the function, but did not find them to provide a better fit.

Caiozzo et al. (13) studied different methods of picking the ventilatory threshold and concluded the best criteria to be the point at which the ventilatory equivalent for $O_2$ begins a systematic increase with no concomitant increase in the ventilatory equivalent for $CO_2$. The criteria regarding the condition that the ventilatory equivalent for $CO_2$ not increase at the threshold was stressed so that hyperventilation was not occurring due to neural or other factors, and so that it was clear that the threshold picked represented the increase in ventilation under isocapnic conditions and due to the increase in $CO_2$ flow from the buffering of $H^+$ as lactic acid production increased. However, Davis (24) pointed out that in one-minute increment tests, the delay in the increase in $\dot{V}_E/\dot{V}CO_2$ was evident, but during 4-minute increment tests, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ both increased at the same workrate.
The Control of Ventilation during Exercise

The debate over the control of ventilation during exercise has centered around neural control versus humoral control (27, 28, 35, 49, 65, 82, 90). Clearly, there are chemoreceptors sensitive to arterial PO$_2$, PCO$_2$ and pH that modulate ventilation during rest, but during moderate exercise the mean arterial levels of these agents do not show a measurable change (2). However, the constancy with which arterial PCO$_2$ appears to be regulated and the close coupling of $\dot{V}_E$ to $\dot{V}$CO$_2$ has led some investigators (82) to hypothesize that CO$_2$ return to the lung (\dot{V}C \dot{V}$CO_2$) is the primary stimulus for exercise hyperpnea during moderate exercise.

The theory that the stimulus for exercise hypernea is CO$_2$ flow to the lung rather than mean arterial PCO$_2$ has prompted the search for chemoreceptors sensitive to lung CO$_2$ flow. It has been suggested that C-fiber endings located in the lung parenchyma close to pulmonary capillaries are sensitive to CO$_2$ and could be important in regulating ventilation (27, 17, 77). Also in the dog there exist slowly adapting pulmonary stretch receptors closely associated with the smooth muscle of the airways that are sensitive to the volume of air entering the lung, the distending pressure across the airways, and to an increased PCO$_2$ in the airways (18, 39, 56). However, it has not yet been convincingly demonstrated that these receptors or any others respond to physiological changes in the CO$_2$ flow to the human lung, either in the blood or airways (56).

In spite of the lack of clear evidence that CO$_2$ receptors exist in humans that are sensitive to CO$_2$ flow to the lung, the CO$_2$ flow hypothesis appears plausible. Yamamoto and Edwards (91) infused blood that had been loaded with CO$_2$ into the inferior vena cava of rats. Ventilation increased in proportion to the venous CO$_2$ load, resulting in an isocapnic hyperpnea.
Yamamoto and Edwards concluded that perhaps arterial PCO$_2$ was regulated by a mechanism that sensed oscillations of PCO$_2$ and pH within the breathing cycle. Band, Cameron, and Semple (3) subsequently showed that venous CO$_2$ loading does change the oscillations of PCO$_2$ and pH in arterial blood in the cat, and others (10, 38, 51) have shown that afferent neural discharge from the carotid sinus nerve oscillates with the arterial oscillation and may be a control signal. Band, Wolff, Ward, Cochrane, and Prior (4) have reported oscillations in arterial CO$_2$ tension in humans which become steeper during exercise. However, the fact that carotid body denervation does not significantly alter the steady state exercise ventilation in humans (52, 86) casts doubt on this mechanism as the primary stimulus for ventilatory control during exercise (29).

Nevertheless, other experiments with venous CO$_2$ loading or unloading indicate a close relationship between $\dot{V}_E$ and the venous CO$_2$ load. Although some investigators have claimed that small changes in P$_a$CO$_2$ could explain the ventilatory response (9), others report an isocapnic hyperpnea (12, 62, 82, 83), indicating that the venous CO$_2$ load was itself sufficient to explain the hyperpnea. Phillipson, Duffin, & Cooper (63) concluded that respiratory rhythmicity is critically dependent on stimuli related to $\dot{V}$CO$_2$. They demonstrated that when metabolic CO$_2$ was removed from mixed venous blood of awake intact sheep, there was a proportional reduction in $\dot{V}_E$. As the rate of CO$_2$ removal became equivalent to the metabolic rate, apnea ensued, with maintenance of normal values of arterial PCO$_2$, pH, and PO$_2$. Green and Sheldon (41) and Sheldon and Green (72) have shown that in dogs $\dot{V}_E$ increased in proportion to pulmonary blood flow and mixed venous PCO$_2$ when each was changed independently while arterial PCO$_2$ was maintained at normal levels. Green and Schmidt (40) later concluded that the
mechanism of hypernea induced by changes in pulmonary blood flow was caused by stimulation of CO₂-sensitive pulmonary receptors. These increases in \( \dot{V}_E \) could be blocked by vagotomy.

Since in the human lung it is not feasible to manipulate CO₂ flow by venous CO₂ infusion, an alternative is to add CO₂ to the inspired airstream. In 1963 Fenn and Craig (31, 32) proposed a different method of administering CO₂ to subjects. When a constant percentage of CO₂ is inhaled, the ventilatory response affects the amount of CO₂ inspired. The greater the ventilatory response, the greater the total CO₂ inspired. However, if CO₂ were injected into the inspired airstream at a constant rate, the total amount of CO₂ inspired would not depend upon the ventilatory response, provided the frequency of breathing was fairly constant, but would be a function of the rate of CO₂ delivery. This method of CO₂ administration would more nearly mimic the way in which metabolic CO₂ is emptied into the bloodstream, and as Fenn and Craig proposed, it seems possible that alveolar PCO₂ would be more easily held isocapnic as is done during exercise with an increased CO₂ load to the lung. However, from experimental data they concluded that the ventilatory response to exogenous CO₂ was different than the response to endogenous CO₂ because alveolar and arterial PCO₂ were allowed to increase. Fenn and Craig believe this is a tradeoff that the respiratory control center allows in order to avoid the extra work it would take to keep PCO₂ levels isocapnic.

Most experiments that have been done to test the ventilatory response to CO₂ through CO₂ inhalation, whether using Fenn's method of administration or by giving a certain percentage of CO₂, have defined the response as a response to changes in arterial or alveolar PCO₂. Comparisons of ventilatory sensitivity during rest and during exercise have brought
differing conclusions. Some investigators report parallel slopes of the $\dot{V}_E$-\(P_a\text{CO}_2\) relationship (2), indicating the same sensitivity, while others (16, 64, 88) report a greater slope and sensitivity during mild and moderate exercise.

Alternatives to the CO\textsubscript{2} flow theory of exercise hyperpnea include two neurogenic theories. A series of very elaborate experiments by Kao (49) gave good evidence of a peripheral neurogenic drive. When electrically stimulating the hind limb of dogs whose blood leaving the limb was diverted to a second dog, increases in ventilation were found, though less than what would be expected during exercise of that intensity. When the head of the so-called neural dog was perfused by the isocapnic blood of a third dog, the increases in ventilation were similar to that expected during exercise of an intact dog, indicating that although there was a peripheral neurogenic drive, the CO\textsubscript{2}-filled blood from the exercising limb was important in preventing hypocapnia which would then depress ventilation. The main objections to a peripheral neurogenic component being the primary stimulus of exercise hyperpnea is that the experiments have not been repeated and that spinal cord transections do not block the hyperpnea when hind limbs are electrically stimulated (1).

A central neurogenic component of exercise has also been hypothesized and tested by Eldridge (28) who in decorticated cats stimulated subthalamic regions of the central nervous system to initiate limb locomotion. Proportional to increased muscular contraction were increases in phrenic nerve activity. This was true also when sensory feedback was eliminated by muscle paralysis. The explanation was that the central neural mechanism that initiated and sustains muscular contraction irradiated to also initiate increases in ventilation.
In addition to these theories, Asmussen (2) has suggested a theory whereby the sensitivity of the carotid bodies to hypoxia is increased during exercise by sympathetic outflow to the carotid bodies. Others suggest a fast component of ventilation at the onset of exercise is neural, while a slower component is humoral (53).

In summary, the exact mechanisms for the increase in ventilation during exercise are not known. Theories of CO_2 return to the lung from the exercising muscles and central or peripheral neurogenic drives are the most plausible at this time. The link between the lactate threshold and the ventilatory threshold, in substantiation of the CO_2 flow theory, is thought to be a result of the increase in CO_2 return to the lung from the bicarbonate buffering of H⁺.

Although this study does not elucidate mechanisms, it contributes to the plausibility of these theories by 1) testing to see if the lactate and ventilatory thresholds occur at the same workrate, as would be expected if the increase in blood lactate caused the increase in ventilation by increasing CO_2 return to the lung, and 2) testing to see if the regression line representing the ventilatory response to CO_2 inhalation during rest is sufficient to explain the ventilatory response to exercise (metabolic) CO_2.
The lactate threshold is a physiological measurement commonly made in laboratories and clinical settings during incremental exercise testing in order to evaluate or predict performance (5, 30, 42, 46, 79). Previously, the threshold was chosen as that workrate just before the rapid rise in blood lactate, and its precision was dependent upon the size increment of work rate and frequency of blood samples. Recently, however, Beaver, Wasserman, and Whipp (7) have proposed a method to increase that precision. They use a log-log transformation and fit the data to two straight lines. The lactate threshold (LT) is found as the intersection of those two lines, and it is not necessarily one of the workrates at which the subject worked. It makes sense that the true LT would only by coincidence be the precise workrate at which the increments were chosen, so the purpose of the method seems justified. However, it seems that the method as described by Beaver et al. introduces a bias that reduces its precision and that the method could be improved to eliminate that bias. The bias comes from their forcing the "division point" to belong to both straight lines. In reality, the division point would only belong to both lines if it were the true threshold. If it is not, it is influencing the regression of a line to which it does not belong. In addition, the ability among investigators to choose breakpoints has been
questioned (37, 92). There is a need for a more objective method of choosing the threshold.

The purpose of this study was to modify the Beaver method of determining the lactate threshold by 1) removing the stipulation that the division point belong to both straight lines, and 2) replacing investigator subjectivity with computer objectivity by use of repeated pairs of regressions to find the pair with the best fit.

**Methods**

Twelve male subjects performed an incremental exercise test on a cycle ergometer until volitional fatigue. The work rate began at 30 watts and was increased every three minutes by 30 watts. During the last 30 seconds of each stage arterialized venous blood samples were drawn from an indwelling catheter placed in a superficial vein on the dorsal aspect of the hand. Minute ventilation and oxygen consumption were measured during the third minute of each stage. The blood samples were assayed for lactic acid according to the enzymatic technique described by Sigma (73). This assay is based on the principle that the conversion of pyruvic acid to lactic acid is reversible in the presence of an excess of NAD+ and LDH. At a highly alkaline pH and with addition of hydrazine to form a complex with the pyruvate, nearly all the lactate is converted to pyruvate and the amount of NAD+ converted to NADH, determined spectrophotometrically, is a measure of the lactate.

Using the method of Beaver et al., the plots of blood lactate vs. \( \dot{V}O_2 \) for each subject were submitted to two independent, experienced investigators. The investigators visually selected a division point as the data point where the steep portion of the curve began (Figure 1). If the
Figure 1. Lactate Concentration vs. O₂ Uptake. Division point (D), indicated by arrow, was determined by visual inspection. Redrawn from Beaver, et al. (2).
investigators did not agree, a third investigator arbitrated to pick the division point. This division point divided the curve into two segments and the division point was considered to belong to both segments. Both coordinates (lactate and $\dot{V}O_2$) were transformed to logarithms (base 10), and a straight line was fitted to each of the two segments of data points using least squares linear regression analysis. The intersection of these two lines was determined to be the threshold (Figure 2).

This same method was applied to a semilog transformation of the data. After the division point was chosen, the lactate data was transformed to logarithms and plotted against $\dot{V}O_2$. The threshold was found by fitting two regressions to the two segments of data and calculating the intersection of those two lines.

Alternately, the data for each subject was first transformed according to the log-log model, that is, both blood lactate and $\dot{V}O_2$ were transformed to logarithms. Then using the proposed (Baker) method, an algorithm divided the data successively into two parts and fit lines of best fit to each part until all possibilities were tried. The intersection of each pair of lines resulting from each iteration was calculated. Then, using piecewise regression to fit each pair, the iteration with the least mean square error was chosen, and the lactate threshold was determined to be the intersection of the two lines fit in that iteration. Second, blood lactate was transformed to logarithms, but $\dot{V}O_2$ was left untransformed (semilog model). The Baker method was similarly used on this data to determine the lactate threshold.

Once the intersection point for each subject was found by both the Beaver method and the Baker method for both models, piecewise regression was used to compare the fit of the data by each method and by each model.
Figure 2. Log Lactate Concentration vs. Log $\dot{V}O_2$. Transformed division point (Dt) is assumed to belong to both regression lines. Lactate threshold (LT) is intersection of the two linear regression lines. Redrawn from Beaver, et al. (2).
The piecewise regression used a single model \( Y_i = B_0 + B_1 X_{11} + B_2(X_{11}-LT)X_{12} + e_i \), where \( X_{11} \) is \( \dot{V}O_2 \) and \( X_{12} \) is an indicator variable defined as 1 if \( X_{11}>LT \) and is defined as 0 if \( X_{11}\leq LT \) to fit each subject's data using the predetermined intersection point (LT) as the point where the slope changed (59). Differences in the lactate threshold and in the fit of the methods and models (determined by mean square error) were then tested using 2 x 2 factorial ANOVA with repeated measures.

Results

The means (\( N = 10 \)) of the lactate thresholds found by each method, each model, and each method/model combination are shown in Table 1. One subject was eliminated from the study because the investigators could not pick a break point, and another subject was eliminated except in the comparison of the Baker log-log and Beaver log-log method/model combination because the Beaver semi log method resulted in a negative threshold. There were no significant differences (\( p>0.05 \)) between the thresholds for the ten subjects found by either method or model or method/model combination. These results are shown in Table 2.

Table 3 shows the means (\( N=10 \)) of the mean square errors, in logarithmic units, of the piecewise regressions fit each subject’s data. Table 4 is the ANOVA table for the comparisons of the mean square errors. The mean square errors of the log-log model were significantly different (\( p<0.05 \)) from the mean square errors of the semi log model. In the comparison of the 10 subjects in which all four method/model combinations of the lactate threshold could be determined, there were no significant differences (\( p>0.05 \)) in the mean square errors between methods. However, because there were 11 subjects in which the threshold could be determined
Table 1. Lactate Threshold (Means $^1$ ± Std. Error)

<table>
<thead>
<tr>
<th></th>
<th>Baker</th>
<th>Beaver</th>
<th>Mean of both methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-log</td>
<td>1.816 ± 0.131</td>
<td>1.711 ± 0.096</td>
<td>1.763 ± 0.080</td>
</tr>
<tr>
<td>Semilog</td>
<td>1.662 ± 0.193</td>
<td>1.545 ± 0.155</td>
<td>1.603 ± 0.121</td>
</tr>
<tr>
<td>Mean of both models</td>
<td>1.739 ± 0.115</td>
<td>1.628 ± 0.115</td>
<td></td>
</tr>
</tbody>
</table>

$^1$Values are in units of $\dot{V}O_2$ (1-minute$^{-1}$); N=10.

There were no significant differences ($p>0.05$) between thresholds found by either method, model, or method/model combination.
Table 2. ANOVA Table for Testing Differences in the Lactate Threshold for 10 Subjects

<table>
<thead>
<tr>
<th></th>
<th>df</th>
<th>Sums of Squares</th>
<th>Mean Square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>9</td>
<td>6.2100</td>
<td>.6900</td>
<td>11.277**</td>
</tr>
<tr>
<td>Method</td>
<td>1</td>
<td>.1229</td>
<td>.1229</td>
<td>2.009 NS</td>
</tr>
<tr>
<td>Model</td>
<td>1</td>
<td>.2568</td>
<td>.2568</td>
<td>4.197 NS</td>
</tr>
<tr>
<td>Method x Model</td>
<td>1</td>
<td>.0004</td>
<td>.0004</td>
<td>.0065 NS</td>
</tr>
<tr>
<td>Error</td>
<td>27</td>
<td>1.6521</td>
<td>.0612</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>8.2422</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** p<0.01
Table 3. Mean Square Error (Means ± Std. Error)

<table>
<thead>
<tr>
<th></th>
<th>Baker</th>
<th>Beaver</th>
<th>Mean of both methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-log</td>
<td>0.0017 ± 0.0005</td>
<td>0.0025 ± 0.0006</td>
<td>0.0021 ± 0.0004&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Semilog</td>
<td>0.0027 ± 0.0006</td>
<td>0.0029 ± 0.0005</td>
<td>0.0028 ± 0.0004&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean of both models</td>
<td>0.0022 ± 0.0004</td>
<td>0.0027 ± 0.0004</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Means are in logarithmic units, N=10
Significant differences (p<0.05) were found between values labeled "a".
Table 4. ANOVA Table for Testing Differences in the Mean Square Errors of the Piecewise Regressions for 10 Subjects

<table>
<thead>
<tr>
<th></th>
<th>df</th>
<th>Sums of Squares</th>
<th>Mean Square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>9</td>
<td>.009560</td>
<td>.001062</td>
<td>16.824**</td>
</tr>
<tr>
<td>Method</td>
<td>1</td>
<td>.000254</td>
<td>.000254</td>
<td>4.025 NS</td>
</tr>
<tr>
<td>Model</td>
<td>1</td>
<td>.000483</td>
<td>.000483</td>
<td>7.645*</td>
</tr>
<tr>
<td>Method x Model</td>
<td>1</td>
<td>.000068</td>
<td>.000068</td>
<td>1.085 NS</td>
</tr>
<tr>
<td>Error</td>
<td>27</td>
<td>.001705</td>
<td>.000063</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>.012070</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** p<0.01
* p<0.05
for the log-log model, the following apriori comparisons of the Baker log-log and Beaver log-log thresholds and mean square errors were made by paired t-tests. No significant differences (p>0.05) were found between the thresholds, whose means ± standard errors for the log-log model were 1.760 ± .131 vs. 1.673 ± .095 for Baker and Beaver methods, respectively. There were significant differences (p<0.05) in the mean square errors (.0022 ± .0005 vs. .0028 ± .0006), indicating the Baker method did provide a better fit than the Beaver method for the log-log model.

Tables 5 and 6 show the individual thresholds and mean square errors. Table 7 compares the log-log and semilog models, as well as the Baker and Beaver methods, in a way similar to that done by Beaver (7). Since no division point was chosen by the Baker method, deviations of the LT for the Baker log-log and semilog models are in reference to the division point chosen by the Beaver method. The deviation is defined as the difference between the division point (the data point predetermined by the investigators) and the LT as determined by the particular method-model combination for a given subject. The slopes of the two portions of the curve, above and below the LT, are given. Note that for the log-log model, the slope represents the change in lactate in logarithmic units divided by the change in \( \dot{V}O_2 \) in logarithmic units. However, the slope of the semilog model represents the change in lactate in logarithmic units divided by the change in \( \dot{V}O_2 \) in arithmetic units. Thus, the slopes of the semilog model are less than those of the log-log model and can only be compared by changing all values to arithmetic units.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Log-log Baker</th>
<th>Log-log Beaver</th>
<th>Semilog Baker</th>
<th>Semilog Beaver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.453</td>
<td>1.366</td>
<td>1.257</td>
<td>1.257</td>
</tr>
<tr>
<td>2</td>
<td>1.855</td>
<td>1.907</td>
<td>1.790</td>
<td>1.810</td>
</tr>
<tr>
<td>3</td>
<td>2.580</td>
<td>1.856</td>
<td>2.689</td>
<td>1.963</td>
</tr>
<tr>
<td>4</td>
<td>2.006</td>
<td>2.015</td>
<td>2.003</td>
<td>1.987</td>
</tr>
<tr>
<td>5</td>
<td>1.344</td>
<td>1.454</td>
<td>1.456</td>
<td>1.143</td>
</tr>
<tr>
<td>6</td>
<td>1.758</td>
<td>1.820</td>
<td>1.545</td>
<td>1.649</td>
</tr>
<tr>
<td>7</td>
<td>1.742</td>
<td>1.800</td>
<td>1.560</td>
<td>1.612</td>
</tr>
<tr>
<td>9</td>
<td>2.296</td>
<td>2.062</td>
<td>2.503</td>
<td>2.258</td>
</tr>
<tr>
<td>10</td>
<td>1.247</td>
<td>1.117</td>
<td>1.097</td>
<td>1.069</td>
</tr>
<tr>
<td>11</td>
<td>1.878</td>
<td>1.714</td>
<td>0.717</td>
<td>0.700</td>
</tr>
<tr>
<td>Mean</td>
<td>1.816</td>
<td>1.711</td>
<td>1.662</td>
<td>1.545</td>
</tr>
<tr>
<td>± Std. Error</td>
<td>0.131</td>
<td>0.096</td>
<td>0.193</td>
<td>0.155</td>
</tr>
</tbody>
</table>
Table 6. Mean Square Errors (in Logarithmic Units) of Piecewise Regressions

<table>
<thead>
<tr>
<th>Subject</th>
<th>Log-log Baker</th>
<th>Log-log Beaver</th>
<th>Semilog Baker</th>
<th>Semilog Beaver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0001</td>
<td>0.0005</td>
<td>0.0011</td>
<td>0.0011</td>
</tr>
<tr>
<td>2</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.0003</td>
</tr>
<tr>
<td>3</td>
<td>0.0017</td>
<td>0.0038</td>
<td>0.0003</td>
<td>0.0026</td>
</tr>
<tr>
<td>4</td>
<td>0.0006</td>
<td>0.0006</td>
<td>0.0011</td>
<td>0.0011</td>
</tr>
<tr>
<td>5</td>
<td>0.0008</td>
<td>0.0011</td>
<td>0.0036</td>
<td>0.0036</td>
</tr>
<tr>
<td>6</td>
<td>0.0037</td>
<td>0.0044</td>
<td>0.0049</td>
<td>0.0044</td>
</tr>
<tr>
<td>7</td>
<td>0.0019</td>
<td>0.0020</td>
<td>0.0042</td>
<td>0.0043</td>
</tr>
<tr>
<td>9</td>
<td>0.0005</td>
<td>0.0029</td>
<td>0.0022</td>
<td>0.0027</td>
</tr>
<tr>
<td>10</td>
<td>0.0041</td>
<td>0.0053</td>
<td>0.0048</td>
<td>0.0049</td>
</tr>
<tr>
<td>11</td>
<td>0.0040</td>
<td>0.0044</td>
<td>0.0045</td>
<td>0.0045</td>
</tr>
<tr>
<td>Mean</td>
<td>0.0017</td>
<td>0.0025</td>
<td>0.0027</td>
<td>0.0029</td>
</tr>
<tr>
<td>± Std. Error</td>
<td>0.0005</td>
<td>0.0006</td>
<td>0.0006</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
Table 7. Comparison of Log-log and Semilog Analyses of Lactate vs. \( \dot{V}O_2 \) Relationship using Baker and Beaver Methods

<table>
<thead>
<tr>
<th></th>
<th>Baker method</th>
<th></th>
<th>Beaver method</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log-log</td>
<td>semilog</td>
<td>log-log</td>
<td>semilog</td>
</tr>
<tr>
<td>Mean ( \dot{V}O_2 ) at LT (1/min) ±SEM</td>
<td>1.816±.131</td>
<td>1.662±.193</td>
<td>1.711±.096</td>
<td>1.545±.155</td>
</tr>
<tr>
<td>Mean ( \dot{V}O_2 ) at division point ±SEM</td>
<td>---</td>
<td>---</td>
<td>1.692±.107</td>
<td>1.692±.107</td>
</tr>
<tr>
<td>Deviation of LT from division point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (peak to peak)</td>
<td>-.226-.730</td>
<td>-.723-.839</td>
<td>-.116-.274</td>
<td>-.740-.298</td>
</tr>
<tr>
<td>Range (size)</td>
<td>.956</td>
<td>1.562</td>
<td>.390</td>
<td>1.038</td>
</tr>
<tr>
<td>Mean deviation±S.D.</td>
<td>.124±.310</td>
<td>-.030±.447</td>
<td>.019±.119</td>
<td>-.146±.295</td>
</tr>
<tr>
<td>Mean of the absolute value of the deviations</td>
<td>.254±.205</td>
<td>.316±.299</td>
<td>.090±.075</td>
<td>.232±.225</td>
</tr>
<tr>
<td>Mean lactate at LT (mmoles-liter(^{-1}))</td>
<td>2.316±.338</td>
<td>2.417±.519</td>
<td>1.923±.222</td>
<td>1.945±.236</td>
</tr>
<tr>
<td>Slope of curve above LT (mean±SEM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>logarithmic units</td>
<td>3.532±.652</td>
<td>.602±.098</td>
<td>2.897±.223</td>
<td>.512±.041</td>
</tr>
<tr>
<td>arithmetic units</td>
<td>340.4</td>
<td>4.00</td>
<td>78.89</td>
<td>3.25</td>
</tr>
<tr>
<td>Slope of curve below LT (mean±SEM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>logarithmic units</td>
<td>.760±.206</td>
<td>.388±.150</td>
<td>.747±.203</td>
<td>.375±.168</td>
</tr>
<tr>
<td>arithmetic units</td>
<td>.575</td>
<td>2.443</td>
<td>.558</td>
<td>2.37</td>
</tr>
</tbody>
</table>
Discussion

Four method-model combinations were used to determine the lactate threshold of 10 subjects. No significant differences were found in the thresholds determined by each of those combinations. This finding is not surprising, since in most cases the elimination of bias skewed the determination of the threshold by only about 100 milliliters when the division of the data by the Baker method was near the division point picked by the Beaver method. This was so in most cases.

Beaver et al. (7) found that the semi log method tended to result in lower thresholds than the log-log method. That was also true in the present study. Although there were no statistically significant differences, in seven of the ten subjects the Baker semi log method resulted in lower thresholds than the Baker log-log method; the Beaver semi log method gave lower thresholds than the Beaver log-log method in eight of ten subjects. In addition, although the mean of the thresholds found by the Baker method tended to be higher than the mean found by the Beaver method for both log-log (1.816 ± .131 vs. 1.711 ± .096) and semi log (1.662 ± .193 vs. 1.545 ± .155) models, only five of ten thresholds were higher for the log-log model, and six of ten were higher for the semi log model.

The reason for the lower thresholds of the semi log model is not clear. It is also interesting that although the thresholds (\(\dot{V}O_2\)) were lower, the mean lactate at the threshold was slightly higher than that of the log-log models. This is consistent with the finding that the slope of the curve below the LT was greater for the semi log model (2.443 and 2.371 mmoles·L⁻¹ for the Baker and Beaver methods, respectively) compared to the log-log model (0.575 and 0.559 mmoles·L⁻¹). However, the slopes after the threshold are less for the semi log models (3.999 and 3.250 mmoles·L⁻¹).
compared to the log-log models (340 and 79 mmoles·l⁻¹). It thus appears that the semilog model may overestimate the lactate at and prior to the threshold, but underestimates it after the threshold. This may be due to the transformation of the data which reduces the variance of lactate as \( \dot{V}O_2 \) increases. In many subjects the last data point of the semilog model tended to influence and reduce the slope beyond the LT more than it did in the log-log model. Beaver et al., in their study (7), also concluded that some systematic bias in the semilog transformation resulted in a poorer fit in the region near the LT, and that after the threshold lactate rose faster than the semilog model.

It is clear from the comparisons of the deviations of the LT from the predetermined division point (Table 7) that the Beaver method, particularly the log-log model, does influence the LT toward it. The mean of the deviations about the division point was merely 19 ml for Beaver's log-log model, with the mean distance (mean of the absolute values of the deviations) from the division point being 90 ml. The range about the division point was 390 mls for the Beaver log-log method compared to 956 mls for the Baker log-log method. The Baker method allowed more freedom in the model by not requiring the division point to belong to both lines as well as not predetermining the data into two segments. In some cases the division of the data was not the same as that for the Beaver method.

It is also apparent that the Baker method resulted in greater individual differences in the LT than the Beaver method. A comparison of the ranges and standard deviations of the LT for each method shows that the range for the Baker log-log model was 1.383 liters·minute⁻¹ compared to 0.945 for the Beaver log-log model; the range for the Baker semilog model was 1.972 compared to 1.558 for the Beaver semilog model. The standard
deviations were greater for the Baker method as well (0.414 vs. 0.304 for the log-log model; 0.609 vs. 0.489 for the semilog model).

It thus would seem that the main differences between the Baker method and the Beaver method have to do with freedom vs. control and objectivity vs. subjectivity. The Beaver method gives the investigator a degree of control over the data and the picking of the breakpoint, perhaps preventing the choice of an aberrant threshold caused by the influence of a data point that has some obvious measurement error. However, it is a subjective method and is surely influenced by the preconceived idea of where the breakpoint should be. Also the ability of different investigators to pick the same breakpoint has been shown to vary considerably. Yeh (92) reported an average range of variation of 0.51 minute\(^{-1}\) with differences from 0.05 to 0.931 minute\(^{-1}\). Gladden (37) found absolute differences ranging from 0.11 to 0.41 1 - minute\(^{-1}\). In the present study the two investigators who picked the division points disagreed in their choice in five of the twelve subjects, and a third investigator had to arbitrate. In contrast to the Beaver method, the Baker method is objective and allows freedom in fitting the data and in finding the best fit.

The differences in the log-log and semilog models are a result of the transformations of the data. As Beaver points out (7), data that follows a power-law function \(y=\alpha x^b\) would fall on a straight line when the data is transformed to a log-log plot. Data that follows an exponential function \(y=a^{10^{bx}}\) would result in a straight line when the data is transformed to a semilog plot. Because the data is fit to two straight lines rather than one argues that there is a breakpoint in the data, a point at which the slope \(b\) changes. Although Beaver found no significant difference in the fit of the two models to his data, he argued that the log-log model was a better fit,
mainly because the log-log model appeared to fit the data better in the region surrounding the division point and the calculated threshold. We found a significant difference in the fit of the two models, with the log-log model having significantly smaller mean square errors. These results seem to indicate that there is indeed a threshold, in contrast to those investigators (37, 92) who suggest there is no real threshold, but that the increase in lactate is actually exponential. We were able to test this, using piecewise regression to fit the semilog transformed data as explained earlier. The model $Y_j = B_0 + B_1X_{i1} + B_2(X_{i1}-LT)X_{i2} + e_i$, where $B_1$ is the slope of the line below the threshold and $B_1 + B_2$ is the slope of the line above the threshold, allowed for testing of $B_2$ to see if it were significantly different from zero. In other words, we were able to test whether the slopes were different. It is interesting that using the Baker method, in only four of ten subjects was $B_2$ significantly different from zero. Using the Beaver method, in only three of the ten subjects was $B_2$ significantly different from zero. Although this tends to suggest that a single exponential would fit the data of most subjects, the fact that the log-log model significantly fit the data better and had a smaller slope before the threshold argues that a single exponential does not completely describe the delay in the rise of blood lactate.

It is also interesting to take an exponential function and plot it on a log-log plot. Figure 3 shows a plot of predicted values for the exponential function that best fit subject 1's data. One can imagine, with few data points particularly in the curvilinear region, that this exponential data could be fit by two linear regressions. However, if those points outside the physiological range are eliminated and the predicted values are compared to the actual values, it appears that if one attempts to fit two straight lines
Figure 3. Predicted Values of Exponential That Best Fits Data of Subject 1, Showing How a Log-log Plot of an Exponential Can Look Like Two Straight Lines.
to the data, the first line would have a slope greater than what is normally found below the lactate threshold. This is shown in Figure 4. Therefore, again one would conclude that this analysis indicates that there is a threshold at which blood lactate begins to rise more rapidly, and that the log-log model is the better model to use to determine that threshold.

In summary, Beaver's method of determining a more precise lactate threshold by using log-log and semilog transformations was modified to eliminate bias and subjectivity. No significant differences were found in the lactate thresholds determined by the four method-model combinations. However, the log-log model had a significantly better fit than the semilog model, and the Baker log-log model a significantly better fit than the Beaver log-log model. Therefore, it is suggested that the Beaver log-log method of determining the lactate threshold be modified by use of a computer algorithm that successively divides a log-log transformation of the data into two parts. The lactate threshold may then be chosen as the intersection of the two regression lines determined by the iteration with the smallest mean square error when fit by piecewise regression.
Figure 4. Predicted and Actual Values of Subject 1 When Data is Fit to an Exponential.
CHAPTER 3

PREDICTION OF THE VENTILATORY THRESHOLD
BY THE LACTATE THRESHOLD

The concept of the anaerobic threshold has been developed by
Wasserman and colleagues (79, 85) and as such assumes the direct linking
of the lactate threshold (the \( \dot{V}O_2 \) above which there occurs a nonlinear rise
in blood lactate) and the ventilatory threshold. The theory behind the link
regards the control of ventilation during moderate exercise and proposes
that \( CO_2 \) flow to the lung is the primary stimulus for exercise hyperpnea
(82). Therefore, as the production of lactic acid increases during
incremental exercise, the buffering of \( H^+ \) by bicarbonate provides an added
source of \( CO_2 \) above that of metabolic \( CO_2 \). Consequently, at metabolic rates
of 50-75% \( \dot{V}O_2 \) max a simultaneous nonlinear rise in \( \dot{V}CO_2 \) and \( \dot{V}_E \) occurs
relative to \( \dot{V}O_2 \) during a period of isocapnic buffering. The threshold of this
nonlinear rise in \( \dot{V}_E \) (the ventilatory threshold) may be detected by the point
at which a systematic rise in the ventilatory equivalent for \( O_2 \) (\( \dot{V}_E/\dot{V}O_2 \))
occurs, with a decrease or lack of increase in the ventilatory equivalent for
\( CO_2 \) (\( \dot{V}_E/\dot{V}CO_2 \)) (13, 24).

In contrast to Wasserman et al., other investigators raise doubts that
the ventilatory and lactate thresholds coincide and have given evidence that
the coupling of \( \dot{V}_E \) to \( \dot{V}CO_2 \) can be manipulated by such things as diet or
pedaling frequency (44), with resulting dissociation of the ventilatory and
lactate thresholds. In addition, the subjectivity inherent in the choosing of the thresholds makes it difficult to decisively conclude whether the thresholds do coincide. In turn, it is difficult to infer a cause and effect.

The purpose of this study was to determine if the Baker method of determining the lactate threshold, as a more objective method described in the previous chapter, resulted in identical thresholds for lactate and ventilation. In addition, the relationship between blood lactate and ventilation was studied by using the lactate thresholds determined from the previous study to predict the ventilatory thresholds of each subject.

**Methods**

The lactate thresholds determined for each subject in the previous chapter were compared to their ventilatory thresholds. Graphs of $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ were plotted against $\dot{V}O_2$ (Figure 5) and given to two independent investigators to select the ventilatory threshold using the following criteria:

1. The $\dot{V}O_2$ at which $\dot{V}_E/\dot{V}O_2$ exhibits a systematic increase, and
2. The $\dot{V}O_2$ at which $\dot{V}_E$ begins to increase nonlinearly.

Caiozzo's (13) criterion for selecting the anaerobic threshold by an increase in $\dot{V}_E/\dot{V}O_2$ included the condition that there was no concomitant increase in $\dot{V}_E/\dot{V}CO_2$. However, this was for an increment of one minute duration. Davis (24) reported that when the increment duration is four minutes, both ventilatory equivalents increase at the same $\dot{V}O_2$. Therefore, since the increment duration was three minutes for the data presented here, the criterion that there was no concomitant rise in $\dot{V}_E/\dot{V}CO_2$ was not applied. If the two investigators did not agree in their determination of the ventilatory threshold, a third investigator arbitrated.
Figure 5. Plots of $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ Used to Determine Ventilatory Threshold of Subject 1.
Once the ventilatory thresholds were determined, paired t-tests were used to test significant differences between the lactate and ventilatory thresholds, and plots of the lactate threshold vs. the ventilatory threshold were made to show the scatter around the line of identity. Then least squares linear regression was used to see which method/model gave the lactate threshold that best predicted the ventilatory threshold.

**Results**

The lactate thresholds found by each method/model in the previous study and the ventilatory threshold for each subject are listed in Table 8. One subject was eliminated from the study because the investigators could not pick a lactate threshold nor a ventilatory threshold according to the specified criterion. Another subject was eliminated because the Beaver semilog method resulted in a negative threshold. Descriptive statistics of the different thresholds may be compared in Table 9. Table 10 shows the results of the paired t-tests. The Beaver semilog lactate threshold was significantly different (p<0.05) from the ventilatory threshold, but all other combinations of method and model to determine the lactate threshold resulted in no significant differences (p>0.05) from the ventilatory threshold. Comparing the mean difference between the lactate threshold and ventilatory threshold (Table 8) and plotting the ventilatory threshold against the lactate thresholds with the line of identity as reference (Figures 6–9) show that, although the differences were not statistically significant, the lactate threshold tended to be less than the ventilatory threshold. This was particularly true of the semilog models. The Baker log-log lactate threshold had the least mean difference from the ventilatory
Table 8. Lactate and Ventilatory Thresholds for Each Subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lactate thresholds</th>
<th>Ventilatory threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baker log-log</td>
<td>Beaver log-log</td>
</tr>
<tr>
<td>1</td>
<td>1.453</td>
<td>1.366</td>
</tr>
<tr>
<td>2</td>
<td>1.855</td>
<td>1.907</td>
</tr>
<tr>
<td>3</td>
<td>2.580</td>
<td>1.856</td>
</tr>
<tr>
<td>4</td>
<td>2.006</td>
<td>2.015</td>
</tr>
<tr>
<td>5</td>
<td>1.344</td>
<td>1.454</td>
</tr>
<tr>
<td>6</td>
<td>1.758</td>
<td>1.820</td>
</tr>
<tr>
<td>7</td>
<td>1.742</td>
<td>1.800</td>
</tr>
<tr>
<td>9</td>
<td>2.296</td>
<td>2.062</td>
</tr>
<tr>
<td>10</td>
<td>1.247</td>
<td>1.117</td>
</tr>
<tr>
<td>11</td>
<td>1.878</td>
<td>1.714</td>
</tr>
<tr>
<td>Thresholds</td>
<td>Mean</td>
<td>Standard Error</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker log-log</td>
<td>1.816</td>
<td>.131</td>
</tr>
<tr>
<td>Baker semilog</td>
<td>1.662</td>
<td>.193</td>
</tr>
<tr>
<td>Beaver log-log</td>
<td>1.711</td>
<td>.096</td>
</tr>
<tr>
<td>Beaver semilog</td>
<td>1.545</td>
<td>.155</td>
</tr>
<tr>
<td>Ventilatory</td>
<td>1.904</td>
<td>.095</td>
</tr>
</tbody>
</table>
Table 10. Tests for Significant Difference between the Lactate Threshold and the Ventilatory Threshold

<table>
<thead>
<tr>
<th>Method/Model</th>
<th>p</th>
<th>mean difference (LT-VT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>log-log</td>
<td>.5193</td>
<td>-.088</td>
</tr>
<tr>
<td>semilog</td>
<td>.1456</td>
<td>-.242</td>
</tr>
<tr>
<td>Beaver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>log-log</td>
<td>.0753</td>
<td>-.193</td>
</tr>
<tr>
<td>semilog</td>
<td>.0156*</td>
<td>-.359*</td>
</tr>
</tbody>
</table>

*Lactate threshold significantly different from the ventilatory threshold*
Figure 6. Baker Log-log Lactate Threshold vs. Ventilatory Threshold. Line of Identity is Shown.
Figure 7. Beaver Log-log Lactate Threshold vs. Ventilatory Threshold. Line of Identity is Shown.
Figure 8. Baker Semilog Lactate Threshold vs. Ventilatory Threshold. Line of Identity is Shown.
Figure 9. Beaver Semilog Lactate Threshold vs. Ventilatory Threshold. Line of Identity is Shown.
threshold (-.088), and the reason for this can be seen better by observing a scatter of data points around both sides of the line of identity (Figure 6).

The results of the linear regressions of the lactate threshold on the ventilatory threshold showed that the lactate threshold determined by the Baker and Beaver semilog methods \( p = .052 \) and .054) best predicted the ventilatory threshold. However, they were poor predictors \( R^2 = .394 \) and .389). The regressions of all the method/model combinations of the lactate threshold on the ventilatory threshold may be compared in Table 11. Figures 10-13 are graphs of the regressions. Note that the Baker log-log lactate threshold, determined in the previous study to be the threshold from the model that best fit the data and in this study to have the least mean difference from the ventilatory threshold, was the poorest predictor of the ventilatory threshold, with a slope not significantly different from zero and \( R^2 = .129 \).

**Discussion**

Although paired t-tests showed no significant differences \( p > .05 \) between the lactate and ventilatory thresholds in three of the four method/model determinations of the lactate threshold, the lactate thresholds were not good predictors of the ventilatory threshold. The best predictors were the lactate thresholds determined by the semilog models. Closer examination of the Baker semilog lactate threshold as a predictor of the ventilatory threshold (Figure 8) reveals that for lactate thresholds less than 2 liters·minute\(^{-1}\) the Baker semilog lactate threshold is a fairly good predictor of the ventilatory threshold, with \( R^2 = .85 \) and the line of best fit almost parallel to the line of identity (Figure 14). It suggests a delay in the ventilatory threshold of approximately .525 liters·minute\(^{-1}\) of oxygen consumption, or in the protocol used in this study, 1-2 increments of work.
Table 11. Results of Linear Regressions of the Lactate Threshold on the Ventilatory Threshold

<table>
<thead>
<tr>
<th>Method/Model</th>
<th>p</th>
<th>R²</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log-log</td>
<td>.3088</td>
<td>.129</td>
<td>.298</td>
</tr>
<tr>
<td>semilog</td>
<td>.0520</td>
<td>.394</td>
<td>.248</td>
</tr>
<tr>
<td>Beaver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log-log</td>
<td>.1439</td>
<td>.247</td>
<td>.277</td>
</tr>
<tr>
<td>semilog</td>
<td>.0538</td>
<td>.389</td>
<td>.249</td>
</tr>
</tbody>
</table>
Figure 10. Line of Best Fit of the Baker Log-log Lactate Threshold vs. the Ventilatory Threshold.
Figure 11. Line of Best Fit of the Beaver Log-log Lactate Threshold vs. the Ventilatory Threshold
Figure 12. Line of Best Fit of the Baker Semilog Lactate Threshold vs. the Ventilatory Threshold
Figure 13. Line of Best Fit of the Beaver Semilog Lactate Threshold vs. the Ventilatory Threshold
Figure 14. Line of Best Fit of the Baker Semilog Lactate Threshold vs. the Ventilatory Threshold When the Lactate Threshold is Less than 2 Liters·minute⁻¹.

\[ y = 0.6525 + 0.9056x \]
rate. A delay in the ventilatory threshold would not be expected if the increase in ventilation were a result of a greater CO₂ flow to the lung brought about by bicarbonate buffering of H⁺, especially in protocols with 3 minute stages. However, if the semilog model actually overestimates lactate at low work rates, as reported by Beaver et al. (7) and confirmed by Baker in the previous study, the delay may be a result of that overestimation. Why it is a better predictor of the ventilatory threshold than the log-log model, which seems to be a better predictor of the actual rise in lactate, is still unclear. Neither is it clear why the semilog lactate threshold is a fairly good predictor when the threshold occurs at lower workrates, but not at higher workrates. It may be because the semilog model tends to overpredict lactate below the threshold and underpredicts it above the threshold.

The Baker log-log lactate threshold, found to be the best method/model for determining the lactate threshold in the previous paper, had the least mean difference from the ventilatory threshold, but was the worst predictor of the ventilatory threshold. One must conclude, if the Baker log-log model selects the lactate threshold determined by the best fit of the data, that the point of marked rise in blood lactate is not sufficient to predict the nonlinear rise in ventilation. It appears that although the semilog model did not fit as well, and although the "threshold" determined by that model may not really distinguish that point where the rapid rise in lactate actually begins, it is a better predictor of the ventilatory threshold, especially when the threshold is below 2 liters·minute⁻¹. Therefore, the semilog model may be the better model to use when interested in the relationship between lactate and ventilation.
In summary, although the Baker log-log model was shown in the previous study to provide a better fit of the data, the lactate threshold was not a good predictor of the ventilatory threshold. This suggests the coupling of the two thresholds by CO₂ flow to the lung may not adequately explain the exercise hyperpnea at workrates approximately 50-75% \( \dot{V}O₂ \) max.
CHAPTER 4
THE VENTILATORY RESPONSE TO CO₂ FLOW
AND EXERCISE

The stimulus that is both sufficient and necessary for the hyperpnea of moderate exercise has been the object of search by numerous physiologists of this century. One of these theories of exercise hyperpnea is that increased CO₂ flow to the lung is responsible for the increase in ventilation. Wasserman and his colleagues (82) argue that an isocapnic hyperpnea during moderate exercise indicates a close link between ventilation and the rate at which CO₂ is delivered to the lungs. They claim that the increases in ventilation in proportion to CO₂ flow point to the existence of a CO₂-sensitive mechanism that accounts for the hyperpnea. Although CO₂-sensitive receptors have not been proven to exist in the human lung, animal studies (62, 63, 72) have shown a proportional increase or decrease in ventilation as CO₂ flow to the lung, by way of intravenous infusions, has been increased or decreased, respectively. However, the relatively small gain found by Sheldon and Green (72) and Green et al. (39) during intravenous infusion of CO₂ in dogs raises doubt that CO₂ flow is the primary stimulus for exercise hyperpnea.

The purpose of this study was to test the hypothesis that, in humans, increases in ventilation during moderate, incremental exercise may be
explained by the ventilatory response to an increase in CO$_2$ flow to the lung brought about by CO$_2$ inhalation at rest.

**Methods**

Six healthy, moderately trained male volunteers performed eight steady state tests on each of 4 days to determine their ventilatory response to an increase in CO$_2$ flow to their lungs brought about by either CO$_2$ inhalation or exercise or both. CO$_2$ was injected into the inspiratory airstream at a constant rate so that the amount of CO$_2$ added was independent of ventilation and in such a way mimicked the way in which metabolic CO$_2$ is added to the venous bloodstream. The rate of total CO$_2$ expired ($\dot{V}_T$CO$_2$) during steady state was taken as the CO$_2$ flow to the lung. Regressions of $\dot{V}_E$ on $\dot{V}_T$CO$_2$ were compared for differences in slope and/or intercept in the following situations:

1. During the first session, the subject was given four levels of CO$_2$, one level each during four steady state tests while sitting at rest on a cycle ergometer. The tests were repeated for a total of eight steady state tests in order to determine if the ventilatory responses to CO$_2$ (the $\dot{V}_E$-$\dot{V}_T$CO$_2$ regressions) were identical for the two sets of four tests.

2. Session 2 was similar to session 1 except that the subject exercised at a work rate of 400 kpm·min$^{-1}$ while being given the levels of CO$_2$. The two $\dot{V}_E$-$\dot{V}_T$CO$_2$ regression lines of this session were tested to see if they were identical.

3. During session 3, four levels of CO$_2$ were given during 4 tests at rest and during 4 tests during exercise. The regressions of the $\dot{V}_E$-$\dot{V}_T$CO$_2$ relationship during rest were compared with those during exercise to
determine if ventilatory sensitivity to CO₂ was the same during rest and exercise.

4. During session 4, four levels of CO₂ were given during 4 tests at rest. The regression of \( \dot{V}_E - \dot{V}_T \text{CO}_2 \) during these 4 tests was compared with the regression of 4 exercise tests at different work rates (200, 300, 400, and 600 kpm·min⁻¹) with no CO₂ inhalation so that the increase in CO₂ flow was a result of the increase in metabolic rate. This was done to determine if the ventilatory sensitivity to CO₂ at rest (the \( \dot{V}_E - \dot{V}_T \text{CO}_2 \) regression) could be extended to explain the increase in ventilation during moderate exercise.

The subjects were asked to refrain from caffeine-containing beverages and foods for at least 48 hours before each testing session, and they reported to the laboratory 4 hours postprandial. Prior to the first session, each subject came to the laboratory for orientation, during which they became adjusted to the breathing apparatus and performed an incremental exercise test to volitional exhaustion to determine \( \dot{V}_O_2 \text{max} \). The four steady-state testing sessions lasted approximately three hours each and consisted of eight steady state tests per session. Three subjects completed session 1 before session 2, and the other three subjects completed session 2 before session 1. The order of the tests belonging to each regression were counterbalanced within each session and CO₂ levels were randomly applied. During session 3, the order of the CO₂ levels was randomly applied over the resting tests and over the exercise tests, and the order of the tests was counterbalanced with respect to rest and exercise. During session 4, the order of the CO₂ levels was randomly applied over the resting tests, the order of the work rates was randomly applied over the exercise tests, and the order of the resting and exercise tests was counterbalanced.
Each of the steady state sessions consisted of eight tests in which the subject sat on a Quinton uniwork cycle ergometer model 845, breathing through a low-resistance nonrebreathing Rudolph's valve whose inspiratory side was connected by tubing to a 3.4 liter mixing chamber open at the opposite end and into which CO$_2$ was injected as the inspiratory air moved through it. The amount of CO$_2$ injected into the mixing chamber each minute was controlled by a Vacumed flowmeter which was calibrated with a Collins basic clinical spirometer P-1255. The four levels of CO$_2$ delivery were 0, .41, .66, and .90 liters·minute$^{-1}$. The expiratory side of the subject's breathing valve was connected by tubing to a mixing chamber in a Beckman metabolic cart, from which expiratory gas samples were taken to determine expiratory O$_2$ and CO$_2$ fractions. Expiratory volumes were measured by a turbine in the metabolic cart. Each steady state test lasted approximately 8 1/2 minutes. End-tidal PCO$_2$ was sampled continuously and recorded by a Beckman recorder connected to a Beckman LB-2 carbon dioxide analyzer. During the sixth minute inspired fractions of O$_2$ and CO$_2$ were measured by sampling from the inspiratory tubing just prior to the inspiratory port of the Rudolph's valve. $\dot{V}_E$ and expiratory O$_2$ and CO$_2$ fractions were measured during minutes 7 and 8. $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated using the inspiratory fractions from minute 6 with the expiratory fractions of minutes 7 and 8. $\dot{V}TCO_2$ was calculated as $\dot{V}_E$ times FECO$_2$ for minutes 7 and 8. As soon as the measurement of minute 8 was completed, the CO$_2$ flow to the inspiratory mixing chamber was turned off, but the subject remained on the system until the mixing chamber was completely flushed and measurement at the mouth showed FICO$_2$ to be zero. Heart rate was calculated from an ECG strip taken the last 10 seconds of minutes 7 and 8 by a 1500 B Hewlett Packard electrocardiograph. The percent O$_2$ saturation was recorded from a
Biox II-A ear oximeter the last 10 seconds of minutes 7 and 8. Ten minutes was allowed between each steady state test.

The data for each subject was analyzed separately. Eight regressions ($\dot{V}_E$ vs. $\dot{V}_T\text{CO}_2$) were fit for each subject using least squares linear regression. Tests for differences in slope and intercept were made for the comparisons discussed above according to Neter and Wasserman (59). Then, pooling the slopes and intercepts, the same comparisons were tested for the subjects as a group. Regressions of $\dot{V}_E$ vs. $P_{ET}\text{CO}_2$ were run for each subject for all tests at rest, then for all tests during exercise with CO$_2$ inhalation to see if $P_{ET}\text{CO}_2$ could account for the increases in $\dot{V}_E$. Stepwise regression was then run for each subject under varying conditions to determine which factor explained the most variance in ventilation. Finally, analysis of the ventilatory response to incremental exercise with no CO$_2$ inhalation was made using vectors.

**Results**

Slopes and intercepts of the $\dot{V}_E$-$\dot{V}_T\text{CO}_2$ regressions for each subject are shown in Table 12. Results for the comparisons of the two regressions for each session are listed in Table 13 for each subject. Combining the data of all six subjects, ANOVA of the slopes and intercepts gave the following results, which appear to reflect the individual results of most subjects:

1. Results showed no significant differences in slopes or intercepts at rest for the two $\dot{V}_E$-$\dot{V}_T\text{CO}_2$ regressions during session 1.

2. Similar results were found for the ventilatory response to $\dot{V}_T\text{CO}_2$ during exercise.
<table>
<thead>
<tr>
<th>Line</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
<th>Subject 6</th>
<th>Mean ± St. Err.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intercept</td>
<td>18.823</td>
<td>2.939</td>
<td>4.299</td>
<td>4.871</td>
<td>4.31</td>
<td>4.037</td>
</tr>
<tr>
<td>3</td>
<td>slope</td>
<td>11.038</td>
<td>17.51</td>
<td>15.107</td>
<td>13.546</td>
<td>17.172</td>
<td>14.301</td>
</tr>
<tr>
<td></td>
<td>intercept</td>
<td>9.027</td>
<td>5.008</td>
<td>3.708</td>
<td>5.538</td>
<td>3.712</td>
<td>5.266</td>
</tr>
<tr>
<td></td>
<td>intercept</td>
<td>10.458</td>
<td>3.312</td>
<td>3.038</td>
<td>5.949</td>
<td>4.398</td>
<td>4.04</td>
</tr>
<tr>
<td>8</td>
<td>slope</td>
<td>9.19</td>
<td>29.741</td>
<td>27.034</td>
<td>23.413</td>
<td>27.938</td>
<td>20.926</td>
</tr>
<tr>
<td></td>
<td>intercept</td>
<td>22.599</td>
<td>2.666</td>
<td>2.07</td>
<td>4.546</td>
<td>1.78</td>
<td>5.158</td>
</tr>
</tbody>
</table>

Lines 1 and 2 are the regressions of the tests at rest with CO₂ inhalation from Session 1.
Lines 3 and 4 are the regressions of the tests during exercise at 400 km·min⁻¹ with CO₂ inhalation from Session 2.
Line 5 is the regression of the tests at rest with CO₂ inhalation from Session 3.
Line 6 is the regression of the tests during exercise at 400 km·min⁻¹ with CO₂ inhalation from Session 3.
Line 7 is the regression of the tests at rest with CO₂ inhalation from Session 4.
Line 8 is the regression of the incremental exercise tests with no CO₂ inhalation from Session 4.
Table 13. Comparison of $\dot{V}_E - \dot{V}_{CO_2}$ Regressions.

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>s</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td>1 vs. 2</td>
<td>Intercept</td>
<td>ns</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>ns</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>3 vs. 4</td>
<td>Intercept</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>5 vs. 6</td>
<td>Intercept</td>
<td>s</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>s</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Slope</td>
<td>ns</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
</tbody>
</table>

1 vs. 2 is the test of rest with CO$_2$ vs. rest with CO$_2$ on the same day.
3 vs. 4 is the test of exercise with CO$_2$ vs. exercise with CO$_2$ on the same day.
5 vs. 6 is the test of rest with CO$_2$ vs. exercise with CO$_2$.
7 vs. 8 is the test of rest with CO$_2$ vs. exercise without CO$_2$ inhalation.
3. The results from session 3 showed that the slopes of the $\dot{V}_E - \dot{V}_{TCO_2}$ regression lines for rest and exercise were not significantly different, but that the intercepts were significantly different.

4. The results from session 4 showed that the ventilatory response to metabolic CO$_2$ (the $\dot{V}_E - \dot{V}_{TCO_2}$ regression line) had a significantly greater slope than the $\dot{V}_E - \dot{V}_{TCO_2}$ response at rest with CO$_2$ inhalation. However, the intercepts were not significantly different.

Figures 15 and 16 are graphs of the regressions of subject 3, illustrating the results from sessions 3 and 4 as listed above.

In addition to the $\dot{V}_E - \dot{V}_{TCO_2}$ regressions, the regressions of $\dot{V}_E$ vs. PETCO$_2$ showed that there was a significant ($p<.01$) positive relationship between $\dot{V}_E$ and PETCO$_2$ at rest for 5 of the 6 subjects and for all 6 subjects during exercise with CO$_2$ inhalation. However, the stepwise regression which forced $\dot{V}_{TCO_2}$ as the first variable in the regression equation showed that once the variance attributable to $\dot{V}_{TCO_2}$ was accounted for, there was in most cases a strong negative correlation between $\dot{V}_E$ and PETCO$_2$ (Table 14).

Moreover, given the variables $\dot{VO}_2$, $\dot{VO}_2$, $\dot{V}_{TCO_2}$, PETCO$_2$, HR, and workrate, stepwise regression for 5 of 6 subjects showed $\dot{V}_{TCO_2}$ and either $\dot{VO}_2$, $\dot{VO}_2$, or workrate accounting for 99% of the variance in $\dot{V}_E$ when considering all testing conditions (all tests of rest and exercise with CO$_2$ inhalation and exercise with no CO$_2$ inhalation). When considering resting tests only, $\dot{V}_{TCO_2}$ was always the first variable entered for each subject, with PETCO$_2$ being the second (with a negative correlation), and together they accounted for 99% of the variance in $\dot{V}_E$ for 5 subjects, 93% for the other subject. During exercise at 400 kpm·min$^{-1}$, with CO$_2$ inhalation, again $\dot{V}_{TCO_2}$ was always the first variable entered. PETCO$_2$ was the second
Figure 15. Ventilatory Response of Subject 3 to CO₂ Inhalation at Rest and during Constant Rate Exercise of 400 kpm·min⁻¹.
Figure 16. Ventilatory Response of Subject 3 to CO₂ Inhalation at Rest and to Metabolic CO₂ during Exercise at Different Levels of Work Rate.
Table 14. Stepwise Regression of $V_E$ vs. $\dot{V}_{TCO2}$ and $PETCO2$ with $\dot{V}_{TCO2}$ Entered First

### At Rest with CO₂ Inhalation

<table>
<thead>
<tr>
<th>Subject</th>
<th>$R^2$ for $\dot{V}_{TCO2}$</th>
<th>Std. Error</th>
<th>Partial Correlation of $PETCO2$</th>
<th>$R^2$</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.311</td>
<td>2.367</td>
<td>-.953</td>
<td>.937</td>
<td>.727</td>
</tr>
<tr>
<td>2</td>
<td>.951</td>
<td>.71</td>
<td>-.863</td>
<td>.988</td>
<td>.364</td>
</tr>
<tr>
<td>3</td>
<td>.989</td>
<td>.562</td>
<td>-.527</td>
<td>.989</td>
<td>.486</td>
</tr>
<tr>
<td>4</td>
<td>.989</td>
<td>.592</td>
<td>-.712</td>
<td>.994</td>
<td>.423</td>
</tr>
<tr>
<td>5</td>
<td>.984</td>
<td>.574</td>
<td>-.705</td>
<td>.992</td>
<td>.414</td>
</tr>
<tr>
<td>6</td>
<td>.984</td>
<td>.572</td>
<td>-.705</td>
<td>.992</td>
<td>.414</td>
</tr>
</tbody>
</table>

### During Exercise with CO₂ Inhalation

<table>
<thead>
<tr>
<th>Subject</th>
<th>$R^2$ for $\dot{V}_{TCO2}$</th>
<th>Std. Error</th>
<th>Partial Correlation of $PETCO2$</th>
<th>$R^2$</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.666</td>
<td>1.655</td>
<td>-.968</td>
<td>.979</td>
<td>.427</td>
</tr>
<tr>
<td>2</td>
<td>.907</td>
<td>1.42</td>
<td>-.878</td>
<td>.979</td>
<td>.695</td>
</tr>
<tr>
<td>3</td>
<td>.986</td>
<td>.595</td>
<td>.162</td>
<td>PETCO₂ not entered</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>.947</td>
<td>1.083</td>
<td>-.767</td>
<td>.978</td>
<td>.711</td>
</tr>
<tr>
<td>5</td>
<td>.992</td>
<td>.479</td>
<td>-.339</td>
<td>PETCO₂ not entered</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>.957</td>
<td>.815</td>
<td>-.684</td>
<td>.977</td>
<td>.608</td>
</tr>
</tbody>
</table>
variable entered for 4 of the 6 subjects, \( \dot{V}CO_2 \) being entered second for one subject and \( \dot{V}O_2 \) second for the other subject.

Summarizing the results of the stepwise regression, it would appear that both CO\(_2\) flow (\( \dot{V}_{TCO_2} \)) and metabolic rate (represented by workrate, \( \dot{V}O_2 \), or \( \dot{V}CO_2 \)) are important in determining \( \dot{V}E \). However, when the work rate is the same, then CO\(_2\) flow is the most important variable. \( P_{ETCO_2} \) may account for some of the variance, but it is negatively correlated to \( \dot{V}E \).

**Discussion**

The two main findings of this study are:

1. The slopes of the ventilatory response to CO\(_2\) (\( \dot{V}_{TCO_2} \)) are the same at rest and during exercise with CO\(_2\) inhalation, but the intercepts are different.

2. The slope of the ventilatory response to CO\(_2\) during exercise without CO\(_2\) inhalation is steeper than the ventilatory response to rest or exercise during CO\(_2\) Inhalation. However, the intercept is not significantly different from the intercept at rest.

It is clear from these data that the regression of \( \dot{V}_{TCO_2} \) on \( \dot{V}E \) at rest with CO\(_2\) inhalation cannot be extended to explain the ventilatory response to exercise. It is also clear from the comparison of the ventilatory responses to rest and exercise, both with CO\(_2\) inhalation, that although the slopes of the response to CO\(_2\) inhalation are the same, there is a difference in the responses that is represented by the difference in intercepts. The stepwise regression suggests that this component is related to metabolic rate, although it is not clear whether that component is the workrate itself, \( \dot{V}O_2 \), \( \dot{V}CO_2 \), or some other factor closely correlated to the metabolic rate. These results are not surprising. The \( \dot{V}E \) vs. \( P_{aCO_2} \) relationship has
previously been shown to form parallel lines, with the $\dot{V}_E$ response shifted upward as workrate increases. Asmussen (2) claims that the sensitivity to CO$_2$ has not changed from rest to different levels of exercise, but that the "idling" speed of the respiratory center has changed, possibly due to a neurogenic component increasing the state of arousal of the brain.

The finding that the $\dot{V}_E$-$\dot{V}_T$CO$_2$ slope is steeper during exercise without CO$_2$ inhalation is at first surprising. However, the uniqueness of this study is that it looks at the sensitivity of ventilation to CO$_2$ in a new way, defining it not as the ventilatory response to $P_a$CO$_2$ but as a response to CO$_2$ flow to the lung ($\dot{V}_T$CO$_2$). Because of this, it is possible to show that the ventilatory response to CO$_2$ during exercise is actually the sum of the following two components:

1. the ventilatory response to $\dot{V}_T$CO$_2$, as quantified by the slope of the $\dot{V}_E$-$\dot{V}_T$CO$_2$ regression for constant-rate exercise during CO$_2$ inhalation (which is approximately the same as the slope at rest), and

2. the ventilatory component that is due to the difference in intercepts of the $\dot{V}_E$-$\dot{V}_T$CO$_2$ regressions at rest and exercise with CO$_2$ inhalation.

This may be shown by the use of vectors. In the following example, the data is that of subject 2. The data for all days at rest with CO$_2$ inhalation were pooled, as well as that of all days during exercise with CO$_2$ inhalation.

First (Figure 17), draw the line of the regression of exercise with no CO$_2$ inhalation (vector 3). To make it simple use the y-intercept ($0,b_1$) and the point $(1, a_1+b_1)$ in the equation $y_1=a_1x+b_1$. [$y = 29.741x + 2.666$]

Second (Figure 17), start at the y-intercept at rest (with CO$_2$ inhalation). From this resting intercept, draw the line (vector 2) which
Figure 17. Drawing the Components of the Ventilatory Response of Subject 2.
stands for the slope of the regression of $\dot{V}_E - \dot{V}_T \text{CO}_2$ during exercise with CO$_2$ inhalation (which for most subjects is the same as during rest). Again, to make it easy to draw the line, use the y-intercept $(0, b_2)$ and the point $(1, a_2 + b_2)$ in the equation $y_2 = a_2x + b_2$. [slope = 14.253; resting intercept = 3.449]

Third (Figure 17), draw a vertical vector which stands for the ventilation due to the difference in intercepts between rest and exercise at 400 kpm·min$^{-1}$, both with CO$_2$ inhalation. [resting intercept = 3.449; exercise intercept = 16.568]

Fourth (Figure 18), move this vector so that its tail sits on the line representing the ventilatory response to exercise during CO$_2$ inhalation (from the second step). Place it at the $\dot{V}_T \text{CO}_2$ equal to the metabolic CO$_2$ measured at 400 kpm·min$^{-1}$, the same work rate at which the subject cycled during CO$_2$ inhalation. [$\dot{V}_T \text{CO}_2 = \text{metabolic CO}_2 = 0.870$]

Fifth (Figure 18), in all subjects the sum of the two vectors (labeled 1 and 2) accounted for all, or very close to all, of the ventilation at 400 kpm·min$^{-1}$ during exercise with no CO$_2$ (vector 3). It is important to note that vector 2 was drawn its particular length from the difference in intercepts prior to moving it. Its length was not changed after setting its tail upon the head of vector 1.

The difference in intercepts between rest and exercise with CO$_2$ inhalation does not seem to be a difference between rest and exercise per se, but a difference which is dependent upon differences in metabolic rates or intensities of metabolic states. The results of the stepwise regressions support this, but the following data support it as well. One subject was
Figure 18. Addition of Vectors to Partition the Ventilatory Response of Subject 2 to Exercise.
tested at rest, 184 kpm·min⁻¹, and 367 kpm·min⁻¹ during CO₂ inhalation with the following $\dot{V}_e-\dot{V}_rCO₂$ regressions:

- **rest**
  \[ y = 3.0906 + 17.966x \]

- **184 kpm·min⁻¹**
  \[ y = 7.1051 + 17.5212x \]

- **367 kpm·min⁻¹**
  \[ y = 10.3463 + 16.8189x \]

Notice the difference in intercepts, with approximately the same slopes. This suggests that had each subject of the present study been tested also at 600 or 800 kpm·min⁻¹ with CO₂ inhalation, there would be greater differences in intercepts between rest and higher workrates. It would then be possible to add the vertical vectors due to those differences to the vector 1 at the appropriate $\dot{V}_rCO₂$ and account for the ventilation at 600 or 800 kpm·min⁻¹ without CO₂ inhalation. This possibility is illustrated in Figure 19.

Essentially then, what this study has done is to partition the ventilatory response to CO₂ during exercise into two components, the ventilatory response to $\dot{V}_rCO₂$ (which at steady state is assumed to be equal to the CO₂ flow to the lung) and another component that depends upon the intensity of exercise. This second component appears to be independent of CO₂ flow.

It was also possible to quantify for each subject the ventilatory response due to CO₂ flow and that due to the intercept component. These comparisons are shown in Table 15. There appears to be quite a bit of variability between subjects in the percent ventilation due to CO₂ flow and that independent of CO₂ flow. The percent due to CO₂ flow ranged from 21% to 70%; that due to the intercept component ranged from 30% to 79%. The intercept component of exercise hyperpnea appears to be dependent upon intensity of exercise for the reasons explained above. It could be a neural
Figure 19. Hypothetical Intercept Vectors during Exercise at 600 and 800 kpm·min⁻¹.
Table 15. Division of Ventilatory Response to Exercise at 400 km-min\(^{-1}\) into 1) the Component Dependent upon CO\(_2\) Flow and 2) the Component Independent of CO\(_2\) Flow.

<table>
<thead>
<tr>
<th>Subject</th>
<th>(\Delta V\text{E})</th>
<th>% due to CO(_2) flow</th>
<th>% independent of CO(_2) flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.6</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>22.3</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>21.4</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>16.7</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>17.1</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>15.1</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>
component due to either central input to the respiratory center (28) or peripheral afferents (49). It is suggested that these afferent signals may be related to work rate as muscle contractions are sensed by mechanoreceptors (20) or metabolic products as sensed by chemoreceptors in the muscle (53).

This study makes another important point. Fenn and Craig (31, 32) had thought that injecting CO₂ into the inspiratory airstream might mimic the dumping of metabolic CO₂ into the bloodstream, and that the ventilatory response might be similar to the ventilatory response to exercise with maintenance of alveolar CO₂. However, they concluded this was not the case. Redefining ventilatory response in terms of changes in Ʌ่อยCO₂ rather than in terms of changes in alveolar or arterial PCO₂, this study shows that the ventilatory response to CO₂ flow to lung during CO₂ inhalation is really the same as during exercise with metabolic increases in CO₂ flow to the lung. This argument considers the ventilatory response to CO₂ during exercise to be only the slope vector and that the intercept component of exercise hyperpnea is not really a response to CO₂, but a ventilatory response to a factor as yet unknown but related to metabolic rate.

In summary, this study has shown that the ventilatory response to Ʌ่อยCO₂, or the rate of total CO₂ (endogenous + exogenous) expired, during CO₂ inhalation is the same at rest and during exercise at 400 kpm-min⁻¹. However, there appears to be an additional ventilatory response during exercise that is not related to CO₂ flow. This study does not support the theory that CO₂ flow is the primary stimulus of the hyperpnea of moderate exercise, although it does suggest that CO₂ flow may be the stimulus for a portion of the hyperpnea.
SUMMARY

Three studies were made to more accurately define the relationship between $\dot{V}_E$, $\dot{V}CO_2$, and blood lactate during exercise. The first study showed that the Baker modification of the Beaver log-log method of determining the lactate threshold significantly improved the fit of the model to the data, along with adding objectivity, and that the log-log model fit the data better than the semilog model. In the second study the Beaver semilog method showed significant differences between the lactate and ventilatory thresholds, but the differences were not significant for the other method/models. However, the belief that the lactate and ventilatory thresholds coincide was not supported because of the large variation around or above the line of identity. The lactate threshold was not a good predictor of the ventilatory threshold. Evidence was not sufficient to support a close link between additional CO$_2$ from the buffering of lactic acid and increased ventilation during exercise. The third study suggests that although CO$_2$ flow may be a component of the ventilatory response to exercise, there is another component independent of CO$_2$ flow. Together the last two studies indicate that the lactate threshold may not always coincide with the ventilatory threshold because of another component of exercise hyperpnea independent of CO$_2$ flow to the lung.
REFERENCES


14. CELLINI, M., P. VITIELLO, A. NAGLIATI, P. G. ZIGLIO, S. MARTINELLI, E.
    BALLARIN, AND F. CONCONI. Noninvasive determination of the anaerobic

15. CHRISTIANSEN, J., C. G. DOUGLAS, AND J. S. HALDANE. The absorption
    and dissociation of carbon dioxide by human blood. *J. Physiol.* (London)
    48:244-271, 1914.

16. CLARK, J. M., R. D. SINCLAIR, AND J. B. LENOX. Chemical and nonchemical

17. COLERIDGE, H. M., AND J. C. G. COLERIDGE. Impulse activity in afferent
    vagal C-Fibers with endings in the intrapulmonary airways of dogs.

18. COLERIDGE, H. M., J. C. G. COLERIDGE, AND R. B. BANZETT. Effect of CO₂
    on afferent vagal endings in the canine lung. *Resp. Physiol.* 34:135-
    151, 1978.

19. COLERIDGE, J. C. G., AND H. M. COLERIDGE. Afferent vagal C fibre
    innervation of the lungs and airways and its functional

20. COMROE, J. H., JR., AND C. F. SCHMIDT. Reflexes from the limbs as a
    factor in the hyperpnea of muscular exercise. *Am. J. Physiol.* 138:536-
    547, 1943.


61. OWLES, W. H. Alterations in the lactic acid content of the blood as a result of light exercise, and associated changes in the CO₂-combining power of the blood and in the alveolar CO₂ pressure. J. Physiol. (London) 69:214-237, 1930.


VITA

Becky Anne Baker was born July 29, 1947, in Huntington, Indiana, and lived in North Manchester, Indiana, until graduating from Manchester High in 1965. She attended Ashland College, Ashland, Ohio, from 1965-69, graduating with a B.S. in Education with a major in elementary education. She returned to North Manchester for two years, teaching fourth grade in the public schools, then moved to Lost Creek, Kentucky, to teach at Riverside Christian School. In 1978-79 she attended Eastern Kentucky University in Richmond, Kentucky, to become certified in secondary physical education, then returned to Riverside Christian School while completing the M.A. in Education with a major in physical education from Eastern Kentucky University in 1980. In 1981 she matriculated to Louisiana State University to study in the School of Health, Physical Education, Recreation, and Dance. In August, 1989, she completed requirements for the Ph.D. in physical education with a major in exercise science and a minor in physiology.

Becky has the following publication and research presentations:


DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Becky Anne Baker

Major Field: Physical Education (Exercise Physiology)

Title of Dissertation: The lactate threshold and CO₂ flow to the lung as predictors of ventilation during exercise.

Approved:

[Signatures]

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Date of Examination:

July 26, 1989