

To the Graduate Council:

I am submitting herewith a dissertation written by Richard Paul Adams entitled "The Relationship of Exercise Performance to Variations in Blood Acid-Base Status Induced by Changes in the Inspired Oxygen Fraction." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Zoology.

Hugh G. Welch
Hugh G. Welch, Major Professor

We have read this dissertation
and recommend its acceptance:

Edward T. Howley

Roland Berg

James M. Liles

Michael H. Sims

Accepted for the Council:

L. Evans Bell
Vice Chancellor
Graduate Studies and Research

Thesis
796
.A335
cop. 2

THE RELATIONSHIP OF EXERCISE PERFORMANCE TO VARIATIONS IN
BLOOD ACID-BASE STATUS INDUCED BY CHANGES IN THE
INSPIRED OXYGEN FRACTION

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Richard Paul Adams

December 1979

1406074

ACKNOWLEDGEMENTS

I am especially indebted to Dr. Hugh Welch for his constant encouragement, aid, and advice throughout my graduate work. It was his guidance that gave direction to my studies.

I am also grateful to those who served as technicians and subjects in this study, namely, Ron Cox, Kim McNair, Korinne Riley, Linda Sundall, Hugh Welch, Cathy Welch, Ken Wessling, Rick Ellis, Steve Lemay, Bob Seals, Marty Sonnenfeldt, Dave West, and Andy Woods. Their enthusiasm, accuracy, and promptness made possible the collection of the data for this study.

A special thanks to my parents, Dr. Percy G. Adams and Pauliene Serger Adams. Without their continual encouragement towards academic achievement, this goal would never even have been formulated, and, without their aid with the technicalities of the English language, this dissertation might never have been completed.

ABSTRACT

This study was undertaken to investigate two possible limiting factors in human exercise performance. Six subjects rode a bicycle ergometer on three different occasions breathing either a 17%, 21%, or 60% oxygen mixture. In addition to rest and recovery periods, each subject worked for 10 minutes at 55% of maximal oxygen uptake and then to exhaustion at about 91% of maximal oxygen uptake. The values measured included performance time, inspired and expired gas fractions, minute ventilation, heart rate, and "arterialized" venous PO_2 , PCO_2 , and pH. Oxygen uptake, carbon dioxide output, respiratory exchange ratio, $[H^+]$ and, $[HCO_3^-]$ were calculated.

The results indicated that performance times were longer in hyperoxia than in normoxia or hypoxia. However, contrary to other published literature, oxygen uptake was not different at exhaustion in normoxia as compared to hypoxia ($p > .1$) or hyperoxia ($p = .09$). Also, during exercise the higher inspired oxygen fractions were generally associated with decreased HLa and increased $[H^+]$, PCO_2 , and $[HCO_3^-]$. However, at exhaustion $[H^+]$ was not different under any inspired oxygen fraction ($p = .8$).

These results support the contention that oxygen is not a limiting factor for exercise of the intensity and duration used in this study. The results also suggest that $[H^+]$ is limiting for such exercise and that the effect of oxygen on performance is related to control of $[H^+]$.

TABLE OF CONTENTS

CHAPTER	PAGE
I. INTRODUCTION.	1
II. REVIEW OF THE LITERATURE, ...	11
Arterial Hydrogen Ion Concentration ($[H^+]$).	12
Oxygen Uptake ($\dot{V}O_2$)	16
Carbon Dioxide Output ($\dot{V}CO_2$).	26
Respiratory Exchange Ratio (R).	29
Minute Ventilation ($\dot{V}$).	29
Lactic Acid (HLA)	33
PCO_2	42
Bicarbonate Concentration ($[HCO_3^-]$)	45
Heart Rate (HR)	45
Summary	51
III. METHODS	52
Protocol.	52
Measurements and Recordings	56
Calculations.	60
Statistics.	61
IV. RESULTS	62
Parameter Trends.	62
Results of Statistical Analyses by Test Section	78

CHAPTER	PAGE
V. DISCUSSION.	92
General Effects of Oxygenation.	92
Oxygen Uptake and Carbon Dioxide Output	94
Oxygen and Hydrogen Ion: A Comparison of Effects in the Blood	97
Ventilation ($\dot{V}$)	101
Lactic Acid	103
Blood and Muscle [H^+]	107
Mechanisms for [H^+] Limitation of Performance	111
Summary	112
BIBLIOGRAPHY.	114
VITA.	124

LIST OF TABLES

TABLE	PAGE
2.1. Effects of Acid-Base Variation on Arterial $[H^+]$	13
2.2. Effects of Oxygen Variation on Arterial $[H^+]$	15
2.3. Effects of Acid-Base Variation on $\dot{V}O_2$	17
2.4. Effects of Oxygen Variation on $\dot{V}O_2$	21
2.5. Effects of Acid-Base Variation on $\dot{V}CO_2$	27
2.6. Effects of Oxygen Variation on $\dot{V}CO_2$	28
2.7. Effects of Acid-Base Variation on R.	30
2.8. Effects of Oxygen Variation on R	31
2.9. Effects of Acid-Base Variation on $\dot{V}$	32
2.10. Effects of Oxygen Variation on $\dot{V}$	34
2.11. Effects of Acid-Base Variation on Arterial HLa	37
2.12. Effects of Oxygen Variation on Arterial HLa.	40
2.13. Effects of Acid-Base Variation on Arterial PCO_2	43
2.14. Effects of Oxygen Variation on Arterial PCO_2	44
2.15. Effects of Acid-Base Variation on Arterial $[HCO_3^-]$	46
2.16. Effects of Oxygen Variation on Arterial $[HCO_3^-]$	47
2.17. Effects of Acid-Base Variation on HR	48
2.18. Effects of Oxygen Variation on HR.	49
3.1. Subject Personal Data.	53
4.1. p Values for Comparison of Rest Data Prior to Breathing the Gas Mixture and After Breathing the Gas Mixture for 14 Minutes (T x S)	80

TABLE	PAGE
4.2. Comparison of Rest Values Under Three Levels of $FI O_2$ (Low= Hypoxia, Air=Normoxia, Hi=Hyperoxia)	82
4.3. Comparison of Low Work Blood Values Under Three Levels of $FI O_2$	82
4.4. Comparison of Ventilatory and HR Low Work Values (Min. 3-10) Under Three Levels of $FI O_2$	84
4.5. Comparison of High Work Blood Values Under Three Levels of $FI O_2$	85
4.6. Comparison of Ventilatory and HR Data at High Work Under Three Levels of $FI O_2$	86
4.7. Comparison of Blood Values at Exhaustion Under Three Levels of $FI O_2$	87
4.8. Comparison of Ventilatory and HR Data at Exhaustion Under Three Levels of $FI O_2$	88
4.9. Comparison of Blood Values During Recovery Under Three Levels of $FI O_2$	89
4.10. Comparison of Ventilatory and HR Values During Recovery Under Three Levels of $FI O_2$	91

LIST OF FIGURES

FIGURE	PAGE
4.1. Performance Times to Exhaustion under 17%, 21%, and 60% Inspired Oxygen.	63
4.2. Mean PO_2 Values.	64
4.3. Mean $[H^+]$ Values	67
4.4. Mean $\dot{V}O_2$ Values.	69
4.5. Mean $\dot{V}CO_2$ Values	70
4.6. Mean R Values.	71
4.7. Mean Ventilation Values.	73
4.8. Mean HLa Values.	74
4.9. Mean PCO_2 Values	76
4.10. Mean $[HCO_3^-]$ Values.	77
4.11. Mean Heart Rate Values	79
5.1. Comparison of the Effects of Oxygen and Hydrogen Ion on Selected Variables During Rest, Submaximal and Maximal Work Rates	99
5.2. Pathways for the Effects of Oxygen on $[H^+]$	109

LIST OF ABBREVIATIONS

ADP---Adenosine Diphosphate

ATP---Adenosine Triphosphate

CaCO_2 CvO_2 CaCO_2 CvCO_2 ---The arterial or venous content or concentration of oxygen or carbon dioxide

CO_2 ---carbon dioxide

FIO_2 FEO_2 FICO_2 FECO_2 ---The fraction of oxygen or carbon dioxide in the inspired or expired gas mixture

GLY---glycolysis

$[\text{H}^+]_a$ $[\text{H}^+]_i$ ---Arterial or intracellular hydrogen ion concentration

$[\text{HCO}_3^-]_a$ $[\text{HCO}_3^-]_i$ ---Arterial or intracellular bicarbonate concentration

HLa---Lactic acid

HR---Heart rate

La^- ---Lactate ion

O_2 ---Oxygen

PCO_2 PO_2 PaCO_2 PaO_2 ---Partial pressure of carbon dioxide or oxygen
(a = in arterial blood)

pH---negative log of the hydrogen ion concentration

Pi---Inorganic phosphate

R---Respiratory exchange ratio

$\dot{V}$ ---Minute ventilation

$\dot{V}\text{CO}_2$ ---Carbon dioxide output

$\dot{V}\text{I}$ ---Minute inspired ventilation

$\dot{V}\text{O}_2$ ---Oxygen uptake

$\dot{V}\text{O}_2$ max---Maximal oxygen uptake

DEFINITION

PARAMETER---an arbitrary constant each of whose values characterizes a member of a system (as a family of curves); a characteristic element; used here to refer to the various quantities measured which are affected by variable oxygen levels. The word is not defined here in the statistical sense.

CHAPTER I

INTRODUCTION

There have been many studies over the years which have attempted to designate a factor or factors limiting physical performance. For exhausting exercise of moderate duration the factors generally resolve into two possibilities. One school of thought--perhaps the largest and surely the more popular--believes that oxygen availability at the muscle is limiting, in other words, that the body is just not capable of delivering enough oxygen to the tissue (Ekblom et al., 1975; Hill et al., 1924; Horstman et al., 1976; Krebs, 1971; Margaria et al., 1972). The other viewpoint holds, however, that the muscle is presented with all the oxygen it can use and that the limiting factors must lie elsewhere, for example, in the ability of that muscle to utilize the oxygen. In this view, some factor other than oxygen is limiting (Cronin et al., 1962; Doll et al., 1968; Jöbsis & Stainsby, 1968; Kaijser, 1970; Pirnay et al., 1972; Sahlin, 1978; Stainsby, 1973).

Many studies have been conducted to show that oxygen limits physical performance. One of the most frequently used techniques has been the simple, direct approach which concludes that if increasing the amount of oxygen available to the system yields better performance, then the oxygen supply must previously have been inadequate. The large majority of performance studies on human subjects, whether or not they find that O_2 availability is the limiting factor, show increased performance with increased

presentation of oxygen to the subject (Asmussen et al., 1948; Ekblom et al., 1975; Hughes et al., 1968; Linnarsson et al., 1974; Wilson & Welch, 1975; Wyndham et al., 1970). The only exception I have found among studies using human subjects is that of Kaijser (1970). Kaijser's study, however, used hyperbaric conditions to achieve elevated oxygen pressures. On the other hand, investigations using in situ dog muscle preparations do not show changes in performance with hyperoxygenation (Welch et al., 1974; Wilson & Stainsby, 1978).

The evidence on human exercise in hyperoxia, although supportive of the contention that O_2 availability limits performance, does not, however, require the interpretation that oxygen is in short supply under normal circumstances. The administration of increased oxygen, one may argue, may be causing some other factor to change and this factor itself or other factors in a chain of events may be limiting performance. Since most investigators realize this possibility, performance studies usually also measure the oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) in order to show more exactly what is happening within the body. The reason for taking these measurements is that if the body can be shown to take up more oxygen when more is presented, then the conclusion can be drawn that oxygen is normally limiting. According to this argument, if the body can take up more oxygen when more is available, then it would have taken up more under normoxic conditions if it had been available.

When looking at human maximal oxygen uptake ($\dot{V}O_{2 \text{ max}}$), one sees few exceptions (Fagraeus et al., 1974) to the finding that $\dot{V}O_{2 \text{ max}}$ increases or decreases as the inspired oxygen fraction ($FI O_2$) increases or decreases

respectively (Asmussen et al., 1948; Banister et al., 1970; Ekblom et al., 1975; Margaria et al., 1972; Welch et al., 1974, 1977; Wilson et al., 1975; Wyndham et al., 1970). These studies are somewhat inconsistent, however, in that they have found very large variations in the degree of change of $\dot{V}O_2$ with different oxygen levels. That is, inspired oxygen fractions under .5 (Hill et al., 1924; Nielsen & Hansen, 1937) have yielded up to 40% increases in $\dot{V}O_2$; Welch et al. (1974) have reported 30% increases in $\dot{V}O_2$ with an FI_{O_2} of .6; while an FI_{O_2} of 1.0 (Margaria et al., 1961) has given 10% increases. Equally improbable results have been obtained by using other gas fractions.

The reason for these variations lies with the difficulty in measuring $\dot{V}O_2$ under conditions of increased FI_{O_2} (Hill et al., 1924). Techniques for overcoming the errors inherent in the open-circuit method of measuring $\dot{V}O_2$ have, however, become increasingly better in recent years. With these improvements in technique, the values for $\dot{V}O_2$ under hyperoxic conditions have been decreasing, that is, approaching those found with normoxia. The elevated $\dot{V}O_2$ under hyperoxic conditions, nevertheless, seems consistent with the concept that O_2 availability is a limiting factor.

If oxygen use is increased, then carbon dioxide production must also be increased. That is, $\dot{V}CO_2$ must reflect $\dot{V}O_2$. But if there has been one consistent and practically unanimous finding, it is that $\dot{V}CO_2$ at exhaustion does not increase with hyperoxia. It has either been the same or lower when compared with normoxic controls (e.g., Welch et al., 1977). That is, most studies reveal that $\dot{V}O_2$ increases while $\dot{V}CO_2$ does not. Carbon dioxide storage has been shown to be an inadequate explanation for

the difference between $\dot{V}O_2$ and $\dot{V}CO_2$ (Clode et al., 1967; Wilson et al., 1975). So far only one other plausible alternative has been presented to deal with the difference in the trends of $\dot{V}O_2$ and $\dot{V}CO_2$: the possibility of a substrate shift to fatty acids from carbohydrate in the presence of high oxygen levels (Wilson et al., 1975; Wilson & Stainsby, 1978). Such a shift would produce less CO_2 for a given $\dot{V}O_2$. This remains a possibility.

For the studies using in situ preparations, the preponderance of evidence demonstrates that neither $\dot{V}CO_2$ nor $\dot{V}O_2$ increases with hyperoxia. Apparently there is only one study which shows increased $\dot{V}O_2$ during maximal stimulation of the muscle in oxygen, and this study poses at least two inherent problems: not only was $\dot{V}O_2$ calculated from a questionable derivation of arterial oxygen concentration ($CaCO_2$) but the authors also gave no measurements of $\dot{V}CO_2$ with which to compare it (Horstman et al., 1976). These problems do not exist in the studies showing no increase in $\dot{V}O_2$ (Welch et al., 1974; Wilson & Stainsby, 1978).

Since carbon dioxide output does not increase with hyperoxia, and since $\dot{V}O_2$ should reflect $\dot{V}CO_2$, $\dot{V}O_2$ should not increase. Despite this fact, and perhaps due to the technical difficulties, pulmonary $\dot{V}O_2$ measurements do increase with oxygen. However, evidence obtained from studies on blood flow (Q) reveal that working tissue $\dot{V}O_2$ does not increase with increased FIO_2 . These studies have shown that flow through a given area is dependent on the arterial PO_2 of the blood, with hypoxia increasing and hyperoxia decreasing flow (Cronin et al., 1962; Dempsey et al., 1975; Haddy & Scott, 1968; Hughes et al., 1968; Kenmure et al., 1972; Reich

et al., 1970; Ross et al., 1962; Stainsby, 1973; Welch et al., 1974; Wilson & Stainsby, 1978).

Bird & Telfer (1966), in a study on resting forearm blood flow, indicated that an increase in the blood O_2 concentration of 10.1% with increased FI_{O_2} was offset by a blood flow decrease of 11.2%. Welch et al. (1977) have recently shown in exercising human subjects that the increase in CaO_2 in the leg during bicycle work in hyperoxia is almost exactly matched by decreased Q to the same area so that there is no significant difference in oxygen delivery to the working muscle (O_2 delivery = $CaO_2 \times Q$). The same study demonstrates that $\dot{V}O_2$ and $\dot{V}CO_2$ values in the limb with hyperoxia were not significantly different from those in the normoxic condition.

These studies imply that if the pulmonary $\dot{V}O_2$ does increase in hyperoxia, it is not due to an increased $\dot{V}O_2$ at the working tissue since increasing the availability of oxygen at the pulmonary level does not increase its availability at the tissues. Such a conclusion lends support to the in situ dog studies which also show no increase in $\dot{V}O_2$ (Welch et al., 1974; Wilson & Stainsby, 1978). In addition, it is consistent with the concept that oxygen delivery is not limiting, most studies having shown that performance increases with increased FI_{O_2} even without a concomitant increase in working tissue $\dot{V}O_2$.

In reviewing the presentation to this point, it should be clear that there are objections to the theory that the availability of oxygen limits performance. Although studies on performance and $\dot{V}O_2$ using in situ

preparations do not support the conclusion that oxygen delivery limits performance, studies using human subjects employed for the same purpose do support such a conclusion. The human pulmonary $\dot{V}O_2$ studies, however, become less significant when one considers the implications of the $\dot{V}CO_2$ data. Furthermore, the blood flow experiments of Bird & Telfer (1966) and Welch et al., (1977) bring into question the idea that it is oxygen itself which is enhancing performance since oxygen delivery does not increase with hyperoxia.

The investigation of oxygen as a limiting factor in human performance is the first of the two lines of research that I am trying to tie together; the other is the study of the acid-base status of the body during exercise. Many investigators have looked at factors involved in the acid-base balance, factors such as hydrogen ion concentration ($[H^+]$), lactic acid (HLA), PCO_2 and bicarbonate (HCO_3^-). Nearly every one of these variables has at one time or another been claimed to be a major factor in the limitation of human performance. The most critical of these, however, seems to be the $[H^+]$, with any limitations by the other factors deriving from their interaction with it (Nahas, 1971).

Jones and co-workers, in a series of experiments inducing alkalosis or acidosis, showed that performance on a cycle ergometer could be enhanced or depressed by ingestion of $NaHCO_3$ or NH_4Cl respectively (Jones et al., 1975, 1976, 1977). That is, induced alkalosis increased performance while acidosis reduced it. While the idea had been suggested earlier (Asmussen et al., 1948; Dennig et al., 1931; Klausen & Knuttgen, 1971; Margaria et al., 1971; Poulus et al., 1974), these were the first studies designed specifically to demonstrate the changes.

From these two lines of research, the studies of oxygen and acid-base status, several facts emerge which, when tied together, form the basis for the present study. First, even though variations in human performance correspond to changes in the inspired oxygen fraction, in light of the $\dot{V}CO_2$ and blood-flow data, these variations may not be due to an increased use of oxygen in the tissue. And second, performance also varies inversely with $[H^+]$. The central purpose of this study, then, is to begin with these two facts and demonstrate that the relationship between inspired oxygen and performance may be due to the action of oxygen leading to changes in $[H^+]$.

One major finding of the present study is that at exhaustion pulmonary $\dot{V}O_2$ in hyperoxic or hypoxic conditions is not significantly different from the normoxic control. The literature, concluding that $\dot{V}O_2$ increases with FI_{O_2} , almost unanimously disagrees with this finding. The present study shows a non-significant 4.8% increase with 60% O_2 and a 3.7% decrease with 17% O_2 as compared with 21% O_2 . These are much smaller changes than have previously been reported. $\dot{V}CO_2$ also shows no significant change but displays a tendency to be inversely related to FI_{O_2} . In light of the great care taken, including gas analysis by two separate methods for determination of $\dot{V}O_2$ values, I believe that these results are accurate. They also fit more closely with what would be expected from $\dot{V}CO_2$ and blood-flow results obtained elsewhere. There is evidence that previous results showing increased $\dot{V}O_2$ have not been accurate because of technical difficulties.

Although the control of ventilation ($\dot{V}$) was not designed as a part of this study, several conclusions about such control may be drawn from the results. First, during exercise $\dot{V}$ varies inversely with FI_{O_2} . Further, with any change in work rate, $\dot{V}$ in hypoxia always reacts fastest. It seems obvious then that PO_2 has some effect on $\dot{V}$. Second, due to the speed of the ventilatory reaction to changes in work output, the controlling mechanism must react quickly, perhaps via neural inputs from the muscles. Third, it would seem very likely that there is an interaction between PO_2 chemoreceptors and "work receptors." That is, there would seem to be a progressive resetting of one receptor as input to the other is varied.

The second major product of this study is the support for the hypothesis that $[H^+]$ is a limiting factor to performance. Since I have demonstrated that oxygen is most likely not limiting for work of the intensity and duration used in this study, and since arterial $[H^+]$ at exhaustion is the same under all conditions, I have developed the possibility that variations in performance with variations in FI_{O_2} are the result not of changes in oxygen use but of changes in $[H^+]$. In order to understand the mechanisms for control of $[H^+]$, however, it is necessary to first look at HLa. Here, PO_2 seems to have no effect on the fairly constant rate of release of HLa. Since the peak values are widely different from each other, however, there is obviously an effect on the total amount produced. And since lactate is produced only during the first few minutes of exercise, the suggestion is that the rate of release of HLa is rather low relative to the amount produced. That is, there is a limit to the rate at which HLa can be released.

Despite the fact that the rate of release is the same, there are differences in the total HLa produced. Although changes in HLa with hyperoxia are most likely due neither to relief of anaerobiosis nor to changes in $[H^+]$, they may be related to the ADP+Pi/ATP ratio. At the onset of work glycolysis may compete with oxidative phosphorylation for available ADP and Pi, and thus inhibit respiration. Lactate would be produced until oxidative phosphorylation obtains the necessary ADP and begins to compete effectively with glycolysis. Since varying $FI O_2$ does not alter O_2 delivery, then the effect of $FI O_2$ on HLa production most likely occurs by means of PO_2 . The hypothesis proposed here is that in hyperoxia increased PO_2 may somehow more quickly make ADP available to oxidative phosphorylation, thereby depressing glycolysis, an action which will in turn reduce HLa, with a consequent lowering of $[H^+]$.

The $[H^+]$ in arterial blood reflects a balance among several factors. These factors are primarily two--the formation of H^+ by dissociation of HLa and the removal of H^+ via HCO_3^- and PCO_2 with ventilation. I have argued that in hypoxia there is a larger formation of HLa during increases in work levels. Under all conditions of $FI O_2$ used here, however, the release rate of HLa is the same, and due to this limited rate of release, the larger amount of HLa produced in hypoxia stays in the muscle longer. Most of this HLa dissociates to H^+ and lactate and thereby increases the muscle acidity. As the muscle acidity increases, the rate of diffusion of H^+ into the blood increases and at some point surpasses the ventilatory capability to counter it. At this point the rate of change in blood

levels increases to such an extent that it surpasses those rates in the normoxic and hyperoxic conditions. Thus the initial trend for a lower $[H^+]$ in hypoxia is the result of a more severe hyperventilation, while the later increases are caused by the greater release of H^+ from the larger muscle store of HLa.

In this and other studies, the $[H^+]$ in the blood at exhaustion is the same under all imposed conditions. That is most likely not a coincidence. The $[H^+]$ in the muscle is of course always much higher than in blood, but blood levels at exhaustion may correlate well with muscle levels. That is, $[H^+]$ may be the same under all conditions in the muscle as well as in the blood. If so, then muscle $[H^+]$ would be a strong candidate for one factor limiting human performance during exercise of the intensity and duration used in this study.

There are, then, two major points which arise from this study. The first is the finding that $\dot{V}O_2$ at exhaustion does not vary with changes in FI_{O_2} . This result strongly implies that oxygen is not a limiting factor in performance of the intensity and duration used here. The second point is the proposal of an hypothesis whereby $[H^+]$ is a limiting factor to performance. According to this hypothesis, variations in performance with variations in FI_{O_2} are the result not of changes in oxygen use but of changes in $[H^+]$, the $[H^+]$ being in turn a reflection of the effect of PO_2 on lactate and ventilation.

CHAPTER II

REVIEW OF THE LITERATURE

The purpose of this chapter is not only to review the results of other studies in this field but also to build a foundation on which to base much of the discussion to be given later. There are several methods of presenting a review of the literature. Due to the large number of studies considered, the need to deal with information on several variables, and the confusion that exists concerning the trends in those variables, this review is presented primarily in tabular form.

The effects of oxygen and acid-base variations as variables on each of nine parameters are shown here with 75-100 studies having been considered. Whenever possible the predominant effects of the variables on each parameter will be identified and some conclusion drawn. Often, however, a determination is not possible: as when the literature is evenly balanced on opposing views or when there are insufficient data available. Further, because of some aspect of the methods used, the results of several investigations included here should be accepted only with careful consideration. In those cases warning will usually be given.

One example in which acceptance of results should be carefully weighed is the use of hyperbaric methods of increasing PO_2 . There are two basic ways of presenting extra oxygen to a subject. First, the fraction of oxygen in inspired air at normal atmospheric pressure can be increased (increased FI_{O_2}). This is known as hyperoxygenation. Second, by increasing the ambient pressure (increased ATA--atmospheres absolute,

1 ATA = 760mm Hg) with either normal or elevated gas fractions, the PO_2 of the inspired gas (PIO_2) will be increased. This may be called hyperbaric oxygenation. Although each of these methods is standard, several investigations have shown that the studies using hyperbarism should be viewed in a manner different from those using normal pressures. The reason is that hyperbarism produces not only increased PO_2 but also increased gas densities and hypercapnia (Cook, 1970; Fagraeus et al., 1973, 1974). As a result, while the present investigation considers the hyperbaric studies and frequently cites them, it gives primary consideration to investigations using only normal pressures.

A word of explanation concerning the tabular review is in order at this point. Most of each table is self-explanatory. The results column, however, is confusing at first glance. The results are presented as a series of arrows. A single arrow indicates that the method used yielded an increase or decrease--according to the direction of the arrow--in the parameter measured. Three arrows indicate the relationship between variable and parameter. For example, when considering the effects of oxygen variation on $[H^+]$, $\uparrow\rightarrow\downarrow$ signifies that an increase ($\uparrow$) in O_2 yields ($\rightarrow$) a decrease ($\downarrow$) in $[H^+]$. An "NC" indicates no change in the parameter.

I. ARTERIAL HYDROGEN ION CONCENTRATION ($[H^+]$)

Effects of Acid-Base Variation (Table 2.1)

The purpose of this comparison is merely to show that with the infusion of substances or the inducement of acid-base changes by other methods such as CO_2 breathing, the effects are exactly as should be

TABLE 2.1

EFFECTS OF ACID-BASE VARIATION ON ARTERIAL $[H^+]$

Reference	Method	Results	Species	Work	Comments
Karetzky & Cain	1969 NaHCO ₃ Na-L-Lactate	+	Dog	Rest	controlled $\dot{V}$, anesthetized
Patterson & Sullivan	1978 NaHCO ₃	+	Dog	Rest	controlled $\dot{V}$, anesthetized
Mithoeffer & Karetzky	1968 HCl, HLa	+	Dog	Rest	controlled $\dot{V}$, anesthetized
Harken	1976 CO ₂	+	Dog	Elect. Stim.	tetanic contr., controlled perfusion
Hirche et al.	1975 THAM, NaHCO ₃ HCl	+	Dog	Elect. Stim.	tetanic contr. controlled $\dot{V}$.
Takeshita	1962 5% CO ₂	+	Human	Rest	
Jones et al.	1977 NH ₄ Cl NaHCO ₃	+	Human	Submax	33,66% $\dot{V}O_2$ max
Poulus et al.	1974 NaHCO ₃	+	Human	Submax Maximal	progressive test
Kindermann et al.	1977 NaHCO ₃ , THAM	+	Human	Submax Maximal	light warm up 400m run

expected. That is, acidic infusions and CO_2 breathing produce increased arterial $[\text{H}^+]$, while basic infusions or ingestions decrease the concentration.

What is not reviewed in Table 2.1 is the effect of those changes in the muscle. Adler et al. (1965) felt that induced changes in extracellular pH do not reflect changes in intracellular pH which they concluded to be a complex function of the $[\text{HCO}_3^-]$ and PCO_2 with PCO_2 being the more important. They showed further (1) that it is necessary to make rather large acidic shifts in extracellular pH in order to affect the muscle cell but (2) that small alkaline shifts are quickly observed inside the cell.

Waddell & Bates (1969) agreed that infusions of NaHCO_3 and HCl affect extracellular pH as would be predicted but that intracellular pH is much less affected. They concluded, however, that CO_2 has a more profound effect within the cell. Mithoeffer & Karetzky (1968) also noted that there is a large difference in the effects of infused organic and mineral acids due to their differing abilities to diffuse into the total body water.

Effects of Oxygen Variation (Table 2.2)

Although the discrepancies can in many cases be explained, the results of studies on the effects of oxygen on $[\text{H}^+]$ are somewhat inconsistent (Table 2.2). In rest, for example, only Banister et al. (1970) present data contrary to the prevailing trend. Their study used hyperbaric conditions, a fact which may have adversely affected their results. Taunton et al. (1970), on the other hand, using the same general procedures

TABLE 2.2

EFFECTS OF OXYGEN VARIATION ON ARTERIAL $[H^+]$

Reference	Method (% O ₂)	Results of O ₂ on $[H^+]$	Work	Comments
Banister et al.	100%-2ATA	↑↑↑	Rest	Hyperbaric
Taunton et al.	21, 100%-2ATA	↑↑↑	Rest	Hyperbaric
Boismare et al.	4.5%	↑↑↑	Rest	Dog, controlled V. anesth.
Huckabee	10, 13%	↑↑↑	Rest	Humans & Dogs
Naimark et al.	11-12%	↑↑↑	Rest	
Takeshita	10%	↑↑↑	Rest	
Taunton et al.	21, 100%-2ATA	↑↑↑	Submax	Hyperbaric, 161-290 watts
Banister et al.	100%-2ATA	↑↑↑	Submax	Hyperbaric, 242 watts
Hughes et al.	11, 16, 33%	↑↑↑ ↑↑↑	Submax	Progressive test
Eklom et al.	50%, CO	NC	Submax	30% V _{O2} max
Gautier et al.	45%	NC	Submax	90 watts, 36-70% V _{O2} max
Naimark et al.	11-12%	NC	Submax	97 watts
Asmussen & Nielsen	33, 99%	↑↑↑	Submax	87-116 watts
Pirnay et al.	12.5%	NC	Maximal	Progressive test
Asmussen & Nielsen	100%	NC	Maximal	232 watts
Eklom et al.	33, 99%	NC	Maximal	6-minute max
Hughes et al.	50%, CO	↑↑↑	Maximal	Progressive test
	11, 16, 33%	↑↑NC		

found the expected trend; that is, during rest, $[H^+]$ varies directly with $FI O_2$.

In Table 2.2 are the results of 7 studies showing almost all possible effects of O_2 on $[H^+]$ during submaximal exercise. Only those 2 employing hyperbaric conditions, however, claim an inverse relationship and can therefore probably be set aside. The remaining differences in the results cannot be easily explained. It should be noted, however, that those studies showing no change in $[H^+]$ with O_2 changes use very low work rates while those showing a direct relationship between $[H^+]$ and O_2 are at slightly higher work rates. The few studies available basically agree that at exhaustion $[H^+]$ is the same regardless of $FI O_2$. Hughes et al. (1968) are the only group showing a difference in $[H^+]$ at exhaustion and this only with hyperoxia.

II. OXYGEN UPTAKE ($\dot{V}O_2$)

Effects of Acid-Base Variation (Table 2.3)

Among those studies which demonstrate that acid-base variations do produce changes in $\dot{V}O_2$, most agree that it is the $[H^+]$ which controls the process. This conclusion was reached, for example, by Huckabee (1958) and Karetzky & Cain (1970), each of whom held $[H^+]$ constant while varying $FICO_2$ and found no change in $\dot{V}O_2$. Despite the seeming consistency in the results of the studies listed in Table 2.3, problems do exist, however, especially when studies employing humans are compared with those using dogs.

TABLE 2.3

EFFECTS OF ACID-BASE VARIATION ON $\dot{V}O_2$

Reference	Method	Results of $[H^+]$ on $\dot{V}O_2$	Species	Work	Comments
Canzanelli et al.	1939 NaOH HCl	↑↑↑ ↑↑↑	Guinea Pig	in Vitro	Within phys. range
Gevers & Dowdle	1963 $NaHCO_3$	NC	Rat	in Vitro	
Patterson & Sullivan	1976 $NaHCO_3$	↑↑↑	Dog	Rest	Controlled $\dot{V}$, anesthetized
Karetzky & Cain	1969 $NaHCO_3$ Na-L-Lactate	↑↑↑	Dog	Rest	Controlled $\dot{V}$, anesthetized
Mithoeffer & Karetzky	1968 HLa HCl	↑↑↑	Dog	Rest	Controlled $\dot{V}$, anesthetized
Usinger & Spaich	1970 CO_2	↑↑↑	Dog	Rest	Controlled $\dot{V}$, anesthetized
Cain	1970 HCl	↑↑↑	Dog	Rest	Passive hyperventilation, anesthetized
Harken	1976 CO_2	↑↑↑ ↑↑↑	Dog	Rest	Controlled perfusion, $\dot{V}O_2$ by Fick, anesthetized

TABLE 2.3 (CONTINUED)

Reference		Method	Results of $[H^+]$ on $\dot{V}O_2$	Species	Work	Comments
Theye et al.	1977	ventilatory control	NC	Dog	Rest	Controlled $\dot{V}$ anesthetized
Huckabee	1958	5% CO_2 $[H^+]$ constant	NC	Dog	Rest	$[H^+]$ constant, hyperventilation, anesthetized
Karetzky & Cain	1970	2,3,5,7% CO_2 , $[H^+]=k$	NC	Human	Rest	$[H^+]$ constant, hyperventilation
Takeshita	1962	5% CO_2	+++	Human	Rest	
Hirche et al.	1975	HCl, THAM $NaHCO_3$	NC or +++	Dog	Tetanic Max Stimula- tion	Controlled $\dot{V}$, $\dot{V}O_2$ by Flick, gastroc. preparation
Jones et al.	1977	$NaHCO_3$ NH_4Cl	NC	Human	Submax	33 & 66% $\dot{V}O_2$ max.
Asmussen et al.	1948	NH_4Cl	NC	Human	Maximal	322 watts
Poulus et al.	1974	$NaHCO_3$	NC	Human	Submax & Max	Progressive test
Luft et al.	1971	15 mm Hg PCO_2	+++ +++	Human Human	Submax Maximal	Progressive test

With few exceptions, all in situ and in vitro studies show increased $\dot{V}O_2$ with decreased $[H^+]$ and vice versa. Harken (1976) noted that a change of .1 pH unit yields a 10% $\dot{V}O_2$ change and that variations in PCO_2 are not necessary to produce the change. Cain (1970) demonstrated this relationship in anesthetized dogs and observed that the sensitivity to change is much greater with alkalosis than with acidosis. Patterson & Sullivan (1978) obtained similar results by the infusion of $NaHCO_3$ and noted that only when PCO_2 is normal or below normal does $\dot{V}O_2$ increase as $[H^+]$ decreases. In fact, they found that increased PCO_2 negates the effect of decreased $[H^+]$ on $\dot{V}O_2$. Theye et al. (1977), however, questioned the theory that in dog studies limb $\dot{V}O_2$ increases as $[H^+]$ decreases. They concluded that the $\dot{V}O_2$ increase may be due to muscle twitches and fasciculations that result from decreased levels of ionized blood calcium produced by certain perfusates commonly used in these studies.

Although the findings in Table 2.3 are consistent when dogs are the experimental animals, it is possible that the results are affected by the anesthesia, the controlled ventilation, or fasciculations so that a conclusion based solely on those dog studies is not warranted. Unfortunately, there are few studies on humans at rest and those that have been done do not agree with those using animals. There is only one study during rest which does not hold $[H^+]$ constant, and since its results are available only in the English abstract of a Japanese article, the details of its methods cannot here be evaluated (Takeshita, 1962). In addition, that study used CO_2 to produce the acid-base variations, and while the fact is not apparent in the dog studies, it may be possible that acidosis

produced by this method has an effect different from that produced by infusion of acidic substances (Waddell & Bates, 1969). Such a possibility may also exist for the conclusions of Luft et al. (1971). Using CO_2 during submaximal work, they also obtained results which disagree with the predominant trend. With these exceptions noted, acid-base variations do not produce changes in $\dot{V}\text{O}_2$ during submaximal and maximal exercise.

Effects of Oxygen Variation (Table 2.4)

The trend at rest is consistent. Decreases in FIO_2 to 10-12% cause decreased $\dot{V}\text{O}_2$ while increased FIO_2 causes no change. The only exception is in the results of Ekblom et al. (1975), who found no change with hypoxia. Their hypoxia was produced by CO poisoning (14% HbCO), with PO_2 normal or even slightly elevated.

For experiments conducted during submaximal exercise, while there may seem to be general disagreement in Table 2.4, there is a definite trend. During the lower submaximal tests the situation is the same as in rest; that is, there is no change in $\dot{V}\text{O}_2$ with hyperoxia and there is a depression with hypoxia. As the work rate increases, $\dot{V}\text{O}_2$ becomes directly related to FIO_2 . There seem to be only two exceptions to this trend. The first is the study of Ekblom et al. (1975) at both 30 and 70% $\dot{V}\text{O}_2$ max. Although the problem with their hypoxic data (normal PO_2) has been stated earlier, the problems with the hyperoxic data cannot be explained from their presentation. The other exception is the study of Byrd & Horvath (1970). Using 100% O_2 , they found an inverse relationship between $\dot{V}\text{O}_2$

TABLE 2.4

EFFECTS OF OXYGEN VARIATION ON $\dot{V}O_2$

Reference		Method (% O_2)	Results of O_2 on $\dot{V}O_2$	Species	Work	Comments
Bean	1945	O_2 Review of literature prior to 1945, all possibilities found, mostly resting $\dot{V}O_2$				
Huckabee	1958	10%	+++	Human	Rest	Dogs also
Naimark et al.	1965	11-12%	+++	Human	Rest	
Gautier et al.	1978	45%	NC	Human	Rest	
Eklom et al.	1975	50%, CO	NC	Human	Rest	Hypoxia by 14% HbCO
Korkushko & Ivanov	1976	70%	NC	Human	Rest	
Linnarsson et al.	1974	.68 & 1.4 ATA	NC	Human	Submax	Hyperbaric, 147 watts, 50% $\dot{V}O_2$
Fagraeus et al.	1974	4.5 ATA	NC	Human	Submax	Hyperbaric, 50 watts
Byrd & Horvath	1970	100%	NC	Human	Submax	25% $\dot{V}O_2$ max.
Eklom et al.	1975	50%, CO	+++ ++NC	Human	Submax	30% $\dot{V}O_2$ max, Hypoxia=14% HbCO
Gautier et al.	1978	45%	NC	Human	Submax	90 watts 36-70% $\dot{V}O_2$ max.
Naimark et al.	1965	11-12%	+++	Human	Submax	97 watts

TABLE 2.4 (CONTINUED)

Reference	Method (% O ₂)	Results of O ₂ on $\dot{V}O_2$	Species	Work	Comments
Asmussen & Nielsen	1955	100%	Human	Submax	0-175 watts, 100% closed circuit
Asmussen & Nielsen	1958	33,99%	Human	Submax	87-116 watts open circuit
Nielsen & Hansen	1937	45%	Human	Submax	145-175 watts
Welch et al.	1977	100%	Human	Submax	Working leg, 150 watts
Fagraeus et al.	1974	4.5 ATA	Human	Submax	Hyperbaric 100, 150 watts
Byrd & Horvath	1970	100%	Human	Submax	50,67% $\dot{V}O_2$ max.
Cronin et al.	1962	11%	Human	Submax	
Wilson et al.	1975	60%	Human	Submax	40,80% $\dot{V}O_2$ max.
Eklom et al.	1975	50%, CO	Human	Submax	70% $\dot{V}O_2$ max, hypoxia=14% HbCO
Banister et al.	1970	100%-2ATA	Human	Submax	Hyperbaric, 242 watts, assumed R for $\dot{V}O_2$
Nielsen & Hansen	1937	45%	Human	Submax	260 & 290 watts
Welch et al.	1974	60%	Human	Submax	Mild-strenuous
Hughes et al.	1968	11,16,33%	Human	Submax	Progressive test

TABLE 2.4 (CONTINUED)

Reference	Method (% O ₂)	Results of O ₂ on $\dot{V}O_2$	Species	Work	Comments
Pedersen & Welch	1976	50,80%	Human	Submax	Progressive test
Welch et al.	1974	100%	Dog	Elect. Stim.	Gastrocnemius
Wilson & Stainsby	1978	100%	Dog	Elect. Stim.	Gastroc., 8 volts .2 sec, 1-4/sec.
Horstman et al.	1977	HbO ₂ 73,62%; 100% O ₂	Dog	Elect. Stim.	Gracilis, 4-6 volts .001 sec, 1-16/sec. $\dot{V}O_2$ from derived CaO ₂ by Fick
Stanek et al.	1979	60%	Pony	Submax	Pulmonary
Welch et al.	1977	100%	Pony	Submax	Cardiovasc. fick
Fagraeus et al.	1973	.68,1.14,1.4, 2,3 ATA	Human	Maximal	Working leg, 200-300 watts
Linnarsson et al.	1974	.68,1.4 ATA	Human	Maximal	Supramax $\dot{V}O_2$, hyperbaric
Wyndham et al.	1970	.83,1.14, ATA	Human	Maximal	318 watts, hyperbaric
Taunton et al.	1970	21%-2 ATA 100%-2 ATA	Human	Maximal	Progressive max, hyperbaric
					161-290 watts, hyperbaric

TABLE 2.4 (CONTINUED)

Reference	Method (% O ₂)	Results of O ₂ on $\dot{V}O_2$	Species	Work	Comments
Pirnay et al.	1973	100%-1,2ATA	Human	Maximal	Hyperbaric, closed circuit, progressive test
Asmussen et al.	1948	12%	Human	Maximal	322 watts
Asmussen & Nielsen	1958	33, 99%	Human	Maximal	232 watts
Nielsen & Hansen	1937	45%	Human	Maximal	300-400 watts
Hughes et al.	1968	11, 16, 33%	Human	Maximal	Progressive
Margaria et al.	1972	100%	Human	Maximal	Closed circuit, supramax $\dot{V}O_2$
Welch et al.	1974	25, 50, 75%	Human	Maximal	95% $\dot{V}O_2$ max.
Wilson et al.	1975	60%	Human	Maximal	92% $\dot{V}O_2$ max.
Eklom et al.	1975	50%, CO	Human	Maximal	6 min. max, hypoxia=14% HbCO

and FI_{O_2} . Theirs is the only study, however, at any level of exercise using any method which finds that $\dot{V}O_2$ decreases as FI_{O_2} increases. Although one cannot be sure, since their methods section is very short on useful information, one problem may be that it is almost impossible to use 100% O_2 with what seems to be an open circuit method. The reason for this difficulty is that the equation for calculating $\dot{V}O_2$ from that method becomes indeterminate when the inspired N_2 fraction is zero.

There are three studies in this review which used electrical stimulation of dog muscle in situ. Welch et al. (1974) and Wilson & Stainsby (1978) each found no difference in $\dot{V}O_2$ with 100% O_2 compared to air. Horstman et al. (1977) found $\dot{V}O_2$ to vary with O_2 but, as pointed out earlier, there are drawbacks to the techniques used in that study: (1) $\dot{V}O_2$ was calculated from a questionable method of deriving $CaCO_2$; (2) there was no description of the method of producing the high and low oxygen conditions; and (3) there were no $\dot{V}CO_2$ results to substantiate the $\dot{V}O_2$ data. Until that study can be verified with a direct method, the studies showing no change should be accepted for in situ preparations.

There is only one study which measures $\dot{V}O_2$ by both pulmonary and cardiovascular methods. Stanek et al. (1979) exercised ponies at a high submaximal work rate and showed that $\dot{V}O_2$ at the pulmonary level increased with hyperoxia while $\dot{V}O_2$ determined by cardiovascular methods did not.

While there is no exception to the finding that during exhausting work pulmonary $\dot{V}O_2$ varies directly with FI_{O_2} , the results of Welch et al. (1977), however, show that $\dot{V}O_2$ of the working limb does not change with hyperoxia. This last study, on humans, agrees with the in situ studies.

The trend in the results of experiments ranging from rest through exhausting work now become more obvious. The lower the work rate, the less effect O_2 has on $\dot{V}O_2$, except in cases of very low $FI O_2$ where there is a depressed $\dot{V}O_2$. At higher work rates pulmonary $\dot{V}O_2$ is definitely affected by O_2 . The only real exceptions are in those cases where the $\dot{V}O_2$ is measured directly at the muscle ($\dot{V}O_2 = Q \times (CaO_2 - CvO_2)$).

III. CARBON DIOXIDE OUTPUT ($\dot{V}CO_2$)

Effects of Acid-Base Variation (Table 2.5)

Unfortunately, there are few data on this subject and the information available is contradictory; even the studies on dogs do not agree. Since there is no obvious reason to doubt any of the results, the only justifiable conclusion that can be drawn at this time is that changes in $[H^+]$ probably do not cause changes in $\dot{V}CO_2$ during submaximal work. There may, however, be an inverse relation at exhaustion.

Effects of Oxygen Variation (Table 2.6)

There are no data available on $\dot{V}CO_2$ at rest in those articles reviewed. The results show that during exercise there is either no change or only a slight inverse relationship between $\dot{V}CO_2$ and O_2 . The hyperbaric studies involving maximal exercise provide the only exceptions to this trend. Perhaps the most helpful study here is that of Welch et al. (1977) in which $\dot{V}CO_2$ was measured both at the pulmonary and muscle levels. They found no change in $\dot{V}CO_2$ at the leg but a decreased pulmonary $\dot{V}CO_2$ when the subject breathed 100% O_2 .

TABLE 2.5
EFFECTS OF ACID-BASE VARIATION ON $\dot{V}CO_2$

Reference		Method	Results of $[H^+]$ on $\dot{V}CO_2$	Species	Work	Comments
Mithoeffer & Karetzky	1968	HLa, HCl	$\uparrow\rightarrow\uparrow$	Dog	Rest	Controlled $\dot{V}$, anesthetized
Patterson & Sullivan	1978	$NaHCO_3$	$\uparrow\rightarrow\uparrow$	Dog	Rest	Controlled $\dot{V}$, anesthetized
Jones et al.	1977	$NaHCO_3$ NH_4Cl	NC	Human	Submax	33,66% $\dot{V}O_2$ max
Poulus et al.	1974	$NaHCO_3$	NC $\uparrow\rightarrow\uparrow$	Human Human	Submax Maximal	Progressive test

TABLE 2.6

EFFECTS OF OXYGEN VARIATION ON $\dot{V}O_2$

Reference	Method (% O_2)	Results of O_2 on $\dot{V}O_2$	Species	Work	Comments
Welch et al.	1974	100%	Dog	Elect. Stim.	Gastroc. prep.
Wilson & Stainsby	1978	100%	Dog	Elect. Stim.	Gastroc. prep.
Fagraeus et al.	1974	21%-4.5ATA 100%	Human	Submax	50,100,150 watts
Banister et al.	1970	100%-2ATA	Human	Submax	Hyperbaric, 242 watts
Taunton et al.	1970	21%-2ATA	Human	Submax	161-290 watts, Hyperbaric, 97 watts
Naimark et al.	1965	11-12%	Human	Submax	40% $\dot{V}O_2$ max
Wilson et al.	1975	60%	Human	Submax	80% $\dot{V}O_2$ max
Welch et al.	1974	60%	Human	Submax	Mild-strenuous
Welch et al.	1977	100%	Human	Submax	150 watts, pulmonary
Welch et al.	1977	100%	Human	Submax	Working leg
			Human	Maximal	150 watts, Working leg
			Human	Maximal	pulmonary
Fagraeus et al.	1973	.68, 1.14, 1.4, 2.3 ATA	Human	Maximal	Hyperbaric
			Human	Maximal	Supramaximal $\dot{V}O_2$
Taunton et al.	1970	100%-2ATA	Human	Maximal	Hyperbaric, 161, 210
			Human	Maximal	242-290 watts

IV. RESPIRATORY EXCHANGE RATIO (R)

Effects of Acid-Base Variation (Table 2.7)

Because the data show basically no change in $\dot{V}O_2$ with acid-base changes, the table for R looks exactly like the table for $\dot{V}CO_2$ and therefore the same conclusions must be drawn. There is probably no change in R during submaximal work though there may be an inverse relation between acidity and R at exhaustion.

Effects of Oxygen Variation (Table 2.8)

The results of this tabulation reflect the changes in both $\dot{V}CO_2$ and $\dot{V}O_2$. R decreases with hyperoxia both as a result of increases in $\dot{V}O_2$ and decreases in $\dot{V}CO_2$.

V. MINUTE VENTILATION ($\dot{V}$)

Effects of Acid-Base Variation (Table 2.9)

Though several groups show no change in ventilation with acid-base changes under some conditions, the predominant trend is for acidemia to increase ventilation and alkalemia to decrease it. In their review, Mitchell et al. (1972) built the case for $[H^+]$ in brain and cerebro-spinal fluid (CSF) as being at least a partial contributor to ventilatory control. They noted that because of the different diffusion patterns into CSF, increased PCO_2 causes $\dot{V}$ increases larger than those resulting from equivalent amounts of infused mineral acids. Sylvester et al. (1973), for example, infused CO_2 -laden blood into dogs and showed that a 1 mm Hg rise in PCO_2

TABLE 2.7
EFFECTS OF ACID-BASE VARIATION ON R

Reference		Method	Results of $[H^+]$ on R	Species	Work	Comments
Mithoeffer & Karetzky	1968	HCl, HLa	↑→↑	Dog	Rest	Controlled $\dot{V}$, anesthetized
Patterson & Sullivan	1978	$NaHCO_3$	↑→↑	Dog	Rest	Controlled $\dot{V}$, anesthetized
Jones et al.	1977	$NaHCO_3$ NH_4Cl	NC	Human	Submax	33,66% $\dot{V}O_2$ max
Poulus et al.	1974	$NaHCO_3$	NC ↑→↑	Human Human	Submax Maximal	Progressive

TABLE 2.8

EFFECTS OF OXYGEN VARIATION ON R

Reference	Method (% O ₂)	Results of O ₂ on R	Species	Work	Comments
Wilson & Stainsby	1978	100%	Dog	Elect. Stim.	Gastroc. prep.
Welch et al.	1974	100%	Dog	Elect. Stim.	Gastroc. prep.
Welch et al.	1977	100%	Human	Submax Maximal	150 watts 200-200 watts, working legs
Gautier et al.	1978	45%	Human	Submax	90 watts
Naimark et al.	1965	11-12%	Human	Rest Submax	97 watts
Welch et al.	1974	60%	Human	Submax	Mild to severe
Wilson et al.	1975	60%	Human	Submax	40, 80% V _O 2 max
Fagraeus et al.	1974	4.5 ATA	Human	Submax	Hyperbaric; 50, 100, 150 watts
Fagraeus et al.	1973	.68, 1.14, 1.4, 2, 3ATA	Human	Maximal	Hyperbaric, Supramax V _O 2
Taunton et al.	1970	2 ATA	Human	Maximal	161-290 watts

TABLE 2.9

EFFECTS OF ACID-BASE VARIATION ON $\dot{V}$

Reference	Year	Method	Results of $[H^+]$ on $\dot{V}$	Species	Work	Comments
Sylvester et al.	1973	CO ₂ laden Blood	+CO ₂ →→	Dog	Rest	[H ⁺] not re- ported
Jones et al.	1977	NH ₄ CL NaHCO ₃	→→→ →→→	Human	Submax	33,66% $\dot{V}O_2$ max
Luft et al.	1971	15mm Hg PCO ₂	→→→ NC	Human Human	Submax Maximal	Progressive test
Poulus et al.	1974	NaHCO ₃	NC	Human	Submax Maximal	Progressive test

increased $\dot{V}$ by .6 l/min. In Table 2.9 the differences cannot apparently be explained on the basis of differences between CO_2 and infusates. Even the difference between the findings of Poulus et al. (1974) and Jones et al. (1977), each of whom used NaHCO_3 , cannot be explained since each group used approximately the same amounts of acid or base. The only apparent difference is that Jones et al. used capsule ingestion while Poulus et al. infused a solution.

Effects of Oxygen Variation (Table 2.10)

Here the trend in $\dot{V}$ is fairly obvious for conditions of rest. Discounting the hyperbaric study, hyperoxia produces increased $\dot{V}$. Unfortunately, other than with hypobaria, there seem to be only two studies using hypoxia at rest. One is on dogs and shows increased $\dot{V}$ (Huckabee, 1958), while the other produces hypoxia by the CO poisoning method, with PO_2 the same as or higher than in the control (Ekblom et al., 1975).

The tendency during work is also fairly obvious. With few exceptions, one already noted (Ekblom et al., 1975), very light work shows no change in $\dot{V}$ due to O_2 ; however, as work rate increases from about 30-40% $\dot{V}\text{O}_2$ max, an inverse relation appears and becomes more pronounced at exhaustion. There is no readily apparent explanation for the discrepancy presented by the data of Hughes et al. (1968) during maximal work.

VI. LACTIC ACID (HLA)

Effects of Acid-Base Variation (Table 2.11)

At rest there is a tendency for increased $[\text{H}^+]$ to decrease HLA and for alkalosis to bring about an increase in HLA. However, there is only

TABLE 2.10
EFFECTS OF OXYGEN VARIATION ON $\dot{V}$

Reference	Method (% O ₂)	Results of O ₂ on $\dot{V}$	Species	Work	Comments
Bean	1945 O ₂	↑↑↑	Review of pre-1945 literature		
Huckabee	1958 10,13,15%	↑↑↑	Dog	Rest	
Fagraeus et al.	1974 21%-4.5ATA 100%-1ATA	NC	Human	Rest	Hyperbaric
Ekblom et al.	1975 50%, CO	↑↑↑ ↓→NC	Human	Rest	Hypoxia=14% HbCO, PO ₂ =same
Dripps & Comroe	1947	↑↑↑	Human	Rest	
Asmussen & Nielsen	1958 33,99%	↑↑↑	Human	Rest	
Korkushko & Ivanov	1976 70%	↑↑↑	Human	Rest	
Fagraeus et al.	1974 21%-4.5ATA 100%-1ATA	NC	Human	Submax	50,100 watts
		↑↑↑	Human	Submax	150 watts, Hyperbaric
Banister et al.	1970 100%-2ATA	↑↑↑	Human	Submax	Hyperbaric, 242 watts
Bird & Telfer	1966 100%-1,2ATA	↑↑↑	Human	Submax	Hyperbaric
Asmussen & Nielsen	1958 33,99%	NC	Human	Submax	87 watts
Gautier et al.	1978 45%	NC	Human	Submax	90 watts

TABLE 2.10 (CONTINUED)

Reference	Method (% O ₂)	Results of Q ₂ on V	Species	Work	Comments
Ekblom et al.	1975	50%, CO	Human	Submax	30% $\dot{V}O_2$ max
Byrd & Horvath	1970	100%	Human	Submax	25, 50, 67% $\dot{V}O_2$ max
Welch et al.	1977	100%	Human	Submax	150 watts
Welch et al.	1974	60%	Human	Submax	Mild-severe
Wilson et al.	1975	60%	Human	Submax	40, 80% $\dot{V}O_2$ max
Ekblom et al.	1975	50%, CO	Human	Submax	70% $\dot{V}O_2$ max, hypoxia=14% HbCO, PO ₂ same
Pirnay et al.	1973	100%-1ATA	Human	Submax	Progressive test
Hughes et al.	1968	11, 16, 33%	Human	Submax	Progressive test
Pedersen & Welch	1976	50, 80%	Human	Submax	Progressive test
Taunton et al.	1970	21%-2ATA 100%-2ATA	Human	Maximal	161-240 watts, Hyperbaric
Wyndham et al.	1970	.83, 1.14ATA	Human	Maximal	Progressive test, Hyperbaric
Fagraeus et al.	1973	.68, 1.14, 1.4, 2, 3 ATA	Human	Maximal	Supramax $\dot{V}O_2$, Hyperbaric
Pirnay et al.	1973	100%-1, 2ATA	Human	Maximal	Progressive test, Hyperbaric
Hughes et al.	1968	11, 16, 33%	Human	Maximal	Progressive test

TABLE 2.10 (CONTINUED)

Reference		Method (% O ₂)	Results of Q ₂ on V	Species	Work	Comments
Welch et al.	1974	25, 50, 75%	+++	Human	Maximal	95% $\dot{V}O_2$ max
Welch et al.	1977	100%	+++	Human	Maximal	200-300 watts
Asmussen & Nielsen	1958	33, 99%	+++	Human	Maximal	232 watts
Wilson & Welch	1975	40, 60, 80, 100%	+++	Human	Maximal	110% $\dot{V}O_2$ max
Ekblom et al.	1975	50%, CO	+++ +NC	Human	Maximal	6-Minute max, 14% HbCO, PO ₂ same

TABLE 2.11

EFFECTS OF ACID-BASE VARIATION ON ARTERIAL HLa

Reference	Method	Results on $[H^+]$ on HLa	Species	Work	Comments
Gevers & Dowdle	1963	1963	1963	1963	1963
Uf	NaHCO ₃	↑↑↑	Rat	in Vitro	
Klassen & Zborowska-Sluis	7%CO ₂ in O ₂	↑↑↑	Rat	in Vitro	
	3.5-35mm Hg PCO ₂ , $[H^+]=k$	↑CO ₂ ↑↑	Dog	in Vitro	$[H^+]=\text{constant}$, erythrocytes
Zborowska-Sluis & Klassen	5.5% CO ₂ , $[H^+]=k$	↑CO ₂ ↑↑	Dog	in Vitro	Erythrocytes $[H^+]=\text{constant}$
Huckabee	NaHCO ₃	↑↑↑	Dog	Rest	Anesthetized, controlled $\dot{V}$
Karetzky & Cain	NaHCO ₃ Na-L-Lactate	↑↑↑	Dog	Rest	Anesthetized, controlled $\dot{V}$
Harken	CO ₂	↑↑↑	Dog	Rest	Controlled perfusion, anesthetized
Cain	HCl	↑↑↑	Dog	Rest	Anesthetized, hyperventilation
Huckabee	5% CO ₂ , $[H^+]=k$	NC	Dog	Rest	Hyperventilation
Tobin	NaHCO ₃ , THAM	↑↑↑	Cat	Rest	Anesthetized
Takeshita	5% CO ₂	NC/↑↑↑	Human	Rest	

TABLE 2.11 (CONTINUED)

Reference	Method	Results of $[H^+]$ on HLa	Species	Work	Comments
Hirche et al.	1975 NaHCO ₃ , THAM HCl	+++ +++	Dog	Elect. Stim.	Anesthetized, controlled $\dot{V}$, muscle HLa +++
Kindermann et al.	1977 NaHCO ₃ , THAM	+++	Human	Submax	Light warm up
Jones et al.	1977 NH ₄ Cl	+++	Human	Submax	33,66% $\dot{V}O_2$ max
	NaHCO ₃	+++		Maximal	95% $\dot{V}O_2$ max
Asmussen et al.	1948 NH ₄ Cl	NC	Human	Maximal	322 watts
Kindermann et al.	1977 NaHCO ₃ , THAM	NC	Human	Maximal	400m run
Margaria et al.	1971 NaHCO ₃	NC +++	Human	Maximal	Supramax $\dot{V}O_2$

one study which is not in vitro or on anesthetized animals. That one study is the previously mentioned investigation of Takeshita (1962), the details of which are unavailable. Nevertheless, since there is no evidence to the contrary, these results can probably be accepted.

What is less certain is what causes the HLa variations. Huckabee (1958) held $[H^+]$ constant and found HLa unchanged when his dogs breathed 5% CO_2 ; variations in HLa resulted only from $[H^+]$ changes. However, another group found that CO_2 does have an effect at constant $[H^+]$ (Klassen & Zborowska-Sluis, 1971; Zborowska-Sluis & Klassen, 1972). These last were in vitro studies on canine red blood cells and may not reflect what happens in vivo.

There is no agreement on the affects of acid-base changes on HLa during maximal exercise. Jones et al. (1977) found that with .3 g/kg, the inverse relationship shown during submaximal work was again apparent. Margaria et al. (1971), found the same relationship when 12 g $NaHCO_3$ was administered within one hour. They also found, however, that a much smaller dose produced no change. The differences cannot be explained. Kindermann et al. (1977) found no change when using about 16g within 2 hours and Asmussen et al. (1948) also found no change after administering 15g NH_4Cl the day before and 5g prior to the test.

Effects of Oxygen Variation (Table 2.12)

With several exceptions, most of which can be explained, the trend here is for HLa to be depressed in hyperoxia and elevated in hypoxia. Of the 21 studies considered, 12 observed this trend at rest and at any work

TABLE 2.12

EFFECTS OF OXYGEN VARIATION ON ARTERIAL HLa

Reference	Method (% O ₂)	Results of O ₂ on HLa	Work	Comments
Huckabee	1958	5,7,8,10, 13,15%	Rest	Humans & Dogs
Banister et al.	1970	100%-2ATA	Rest	Hyperbaric
Linnarsson et al.	1974	.68,1.4 ATA	Rest	Hyperbaric
Takeshita	1962	10%	Rest	
Naimark et al.	1965	11-12%	Rest	
Banister et al.	1970	100%-2ATA	Submax	Hyperbaric,242 watts
Linnarsson et al.	1974	.68,1.4 ATA	Submax	Hyperbaric,147 watts
Gautier et al.	1978	45%	Submax	90 watts
Naimark et al.	1965	11-12%	Submax	97 watts
Welch et al.	1977	100%	Submax	150 watts
Eklblom et al.	1975	50%, CO	Submax	70% $\dot{V}O_2$ max, hypoxia = 14% HbCO
Wilson et al.	1975	60%	Submax	80% $\dot{V}O_2$ max
Hughes et al.	1968	11,16,33%	Submax	Progressive
Pedersen & Welch	1976	50,80%	Submax	Progressive
Welch et al.	1977	100%	Maximal	200-300 watts

TABLE 2.12 (CONTINUED)

Reference		Method (% O ₂)	Results of O ₂ on HLa	Work	Comments
Cunningham & Critz	1972	16,100%	↑↑↑ ↑↑↑	Maximal	95% $\dot{V}O_2$ max
Asmusen et al.	1948	12,100%	↑↑NC ↑↑↑	Maximal	322 watts
Ekblom et al.	1975	50%, CO	↑↑↑ ↑↑↑	Maximal	6-minute max
Hughes et al.	1968	11,16,33%	↑↑↑ ↑↑↑	Maximal	Progressive
Margaria et al.	1972	100%	NC	Maximal	Supramax $\dot{V}O_2$
Fagraeus et al.	1973	.68,1.14,1.4, 2,3 ATA	NC	Maximal	Hyperbaric, Supramax $\dot{V}O_2$
Linnarsson et al.	1974	.68,1.4 ATA	NC	Maximal	Hyperbaric, 318 watts

load. Of the studies disagreeing, 4 are hyperbaric. Two others are the studies of Takeshita (1962) and Ekblom et al. (1975) previously mentioned. Of the three remaining, that of Hughes et al. (1968), at both submaximal and maximal work loads, may be explained by noting that it was one of the very few non-hyperbaric studies finding decreased $[H^+]$ with hyperoxia. The two remaining cases, each finding no change with 100% O_2 , are unexplained (Asmussen et al., 1948; Margaria et al., 1971).

VII. PCO_2

Effects of Acid-Base Variation (Table 2.13)

Due to the contradictory nature of the results in this table, it is difficult to make a determination of the trends during rest. Cain (1970) found that there was no change in PCO_2 due to HCl infusion; the passive hyperventilation no doubt offset any effect of the HCl. There does not seem to be any way to analyze the varying results of the other rest studies in Table 2.13. However, the data showing an inverse relationship agree with the results obtained during exercise and may therefore be the more accurate. With exercise the inverse relationship between PCO_2 and acidosis is clear. The only exception is the study of Poulus et al. (1974); these data cannot be explained.

Effects of Oxygen Variation (Table 2.14)

The results are again somewhat confusing for conditions of rest. It can probably be concluded, however, that hypoxia produces a decreased PCO_2 but that the effect of hyperoxia is not obvious. The same problems

TABLE 2.13

EFFECTS OF ACID-BASE VARIATION ON ARTERIAL PCO_2

Reference	Method	Results of $[\text{H}^+]$ on PCO_2	Species	Work	Comments
Karetzky & Cain	1969 NaHCO_3 Na-L-Lactate	$\uparrow\uparrow\uparrow$	Dog	Rest	Anesthetized, controlled $\dot{V}$
Patterson & Sullivan	1978 NaHCO_3	$\uparrow\uparrow\uparrow$	Dog	Rest	Anesthetized, controlled $\dot{V}$
Mithoeffer & Karetzky	1968 HCl , HLa	$\uparrow\uparrow\uparrow$	Dog	Rest	Anesthetized, controlled $\dot{V}$
Cain	1970 HCl	NC	Dog	Rest	Anesthetized, passive hyperventilation
Hirche et al.	1975 HCl NaHCO_3 , THAM	$\uparrow\uparrow\uparrow$ $\uparrow\uparrow\uparrow$	Dog	Elect. Stim.	Anesthetized, controlled $\dot{V}$, tetanic, gastroc.
Jones et al.	1977 NH_4Cl NaHCO_3	$\uparrow\uparrow\uparrow$ $\uparrow\uparrow\uparrow$	Humans	Submax	33,66% $\dot{V}\text{O}_2$ max
Poulus et al.	1974 NaHCO_3	NC $\uparrow\uparrow\uparrow$	Humans	Submax	ex < 75% $\dot{V}\text{O}_2$ max ex > 75% $\dot{V}\text{O}_2$ max
Kindermann et al.	1977 NaHCO_3 , THAM	$\uparrow\uparrow\uparrow$	Humans	Maximal	400m run

TABLE 2.14
EFFECTS OF OXYGEN VARIATION ON ARTERIAL PCO_2

Reference		Method (% O_2)	Results of O_2 on PCO_2	Work	Comments
Banister et al.	1970	100%-2ATA	↑↑↑	Rest	Hyperbaric
Boismare et al.	1975	4.5%	↑↑↑	Rest	Dogs, anesthetized, controlled $\dot{V}$
Naimark et al.	1965	11-12%	↑↑↑	Rest	
Korkushko & Ivanov	1978	70%	NC	Rest	
Banister et al.	1970	100%-2ATA	↑↑↑	Submax	Hyperbaric, 242 watts
Gautier et al.	1978	45%	↑↑↑	Submax	90 watts
Naimark et al.	1965	11-12%	↑↑↑	Submax	97 watts
Ekblom et al.	1975	50%, CO	NC	Submax	30,70% $\dot{V}O_2$ max, hypoxia by 14% HbCO with PO_2 same

exist for exercise conditions. One of these 4 studies is a hyperbaric study and another is the investigation of Ekblom et al. (1975), whose results are questionable. The other 2 studies indicate that PCO_2 increases or decreases with $FI O_2$ changes in the same directions. This relationship is most likely due to ventilatory depression or elevation with hyperoxia and hypoxia respectively.

VIII. BICARBONATE CONCENTRATION ($[HCO_3^-]$)

Bicarbonate Concentration ($[HCO_3^-]$) (Tables 2.15, 2.16)

Due to the paucity of data at hand, definite conclusions cannot be drawn concerning the effects of either oxygen or acid-base variations on $[HCO_3^-]$. However, for acid-base variations (Table 2.15) there seems to be an inverse relationship at rest and a direct relationship with exercise. For changes in $FI O_2$ (Table 2.16) there are no data during resting conditions. For exercise conditions, the trend seems to be that hyperoxia produces elevated $[HCO_3^-]$ levels.

IX. HEART RATE (HR)

Heart Rate (HR) (Tables 2.17, 2.18)

Heart rate is not a critical variable in the present study. The measurements presented later were recorded merely to supply information normally provided in studies such as this and because of the simplicity of the measurement. For those reasons, the literature is analyzed only briefly.

Acid-base changes (Table 2.17) seem to produce no corresponding changes in HR in either submaximal or maximal work. In the case of oxygen

TABLE 2.15
EFFECTS OF ACID-BASE VARIATION ON ARTERIAL $[\text{HCO}_3^-]$

Reference	Year	Method	Results of $[\text{H}^+]$ on $[\text{HCO}_3^-]$	Species	Work	Comments
Karetzky & Cain	1969	NaHCO_3 Na-L-Lactate	↑↑↑	Dog	Rest	Anesthetized, controlled $\dot{V}$
Mithoeffer & Karetzky	1968	HCl, HLa	↑↑↑	Dog	Rest	Anesthetized
Jones et al.	1977	NaHCO_3 NH_4Cl	↑↑↑ ↑↑↑	Human	Submax	33,66% $\dot{V}\text{O}_2$ max
Luft et al.	1971	15mm Hg PCO_2	↑↑↑	Human	Maximal	
Kindermann et al.	1977	NaHCO_3 , THAM	↑↑↑	Human	Maximal	400m run

TABLE 2.16

EFFECTS OF OXYGEN VARIATION ON ARTERIAL $[\text{HCO}_3^-]$

Reference		Method (% O_2)	Results of O_2 on $[\text{HCO}_3^-]$	Work	Comments
Gautier et al.	1978	45%	↑↑↑	Submax	90 watts
Taunton et al.	1970	21, 100%-2ATA	↑↑↑	Maximal	Hyperbaric, 160-290 watts

TABLE 2.17

EFFECTS OF ACID-BASE VARIATION ON HR

Reference	Year	Method	Results of $[H^+]$ on HR	Species	Work	Comments
Mitchell et al.	1972		NC			Review
Jones et al.	1977	$NH_4Cl, NaHCO_3$	NC	Human	Submax	33,66% $\dot{V}O_2$ max
Poulus et al.	1974	$NaHCO_3$	NC	Human	Submax Maximal	Progressive test
Luft et al.	1971	15mm Hg PCO_2	NC ↑→↑	Human Human	Submax Maximal	Progressive test
Kindermann et al.	1977	$NaHCO_3, THAM$	NC	Human	Submax Maximal	light warm up 400m run

TABLE 2.18

EFFECTS OF OXYGEN VARIATION ON HR

Reference	Method (% O ₂)	Results of O ₂ on HR	Work	Comments
Bean	1945	↑↑↑	Rest	Review
Boismare et al.	1975	↑↑↑	Rest	Dog, controlled $\dot{V}$, anesthetized
Banister et al.	1970	↑↑↑	Rest	Hyperbaric
Fagraeus et al.	1974	↑↑↑	Rest	Hyperbaric
Kaijser	1970	↑↑↑	Rest	Hyperbaric
Kenmure et al.	1972	↑↑↑	Rest	Hyperbaric
Fagraeus et al.	1974	NC	Rest	
Korkushko & Ivanov	1976	NC	Rest	
Fagraeus et al.	1974	↑↑↑	Submax	50,100,150 watts, hyperbaric
Asmussen & Nielsen	1955	↑↑↑ ↑↑↑	Submax	0-175 watts
Byrd & Horvath	1970	↑↑↑	Submax	25,50,67% $\dot{V}O_2$ max
Welch et al.	1977	↑↑↑	Submax	150 watts
Eklblom et al.	1975	↑↑↑ ↑↑↑	Submax	30,70% $\dot{V}O_2$ max
Pirnay et al.	1973	↑↑↑	Submax	Progressive test
Welch et al.	1974	NC	Submax	Mild-strenuous

TABLE 2.18 (CONTINUED)

Reference	Method (% O ₂)	Results of O ₂ on HR	Work	Comments
Pedersen & Welch	1976	50, 80%	Submax	Progressive test
Hughes et al.	1968	11, 16, 33%	Submax	Progressive test
Taunton et al.	1970	21%-2ATA 100%-2ATA	Maximal	Hyperbaric, 161-240 watts
Banister et al.	1970	100%-2ATA	Maximal	Hyperbaric, 242 watts
Wyndham et al.	1970	.83, 1.14ATA	Maximal	Hyperbaric, progressive
Fagraeus et al.	1973	.68, 1.14, 1.4, 2, 3 ATA	Maximal	Supramaximal $\dot{V}O_2$, Hyperbaric
Pirnay et al.	1972	100%-1, 2ATA	Maximal	Hyperbaric, progressive
Eklom et al.	1975	50%, CO	Maximal	6-minute max, hypoxia=14% HbCO & PO ₂ same
Wilson et al.	1975	60%	Maximal	92% $\dot{V}O_2$ max
Welch et al.	1974	25, 50, 75%	Maximal	95% $\dot{V}O_2$ max
Cunningham & Critz	1972	16, 100%	Maximal	95% $\dot{V}O_2$ max
Wilson & Welch	1975	40, 60, 80, 100%	Maximal	110% $\dot{V}O_2$ max
Margaria et al.	1972	100%	Maximal	Supramaximal $\dot{V}O_2$
Hughes et al.	1968	11, 16, 33%	Maximal	Progressive test

variations (Table 2.18), once the hyperbaric studies and the others with obvious problems are discarded, it seems that oxygen has no effect on HR, either at rest or with maximal exercise. There does, however, seem to be a slight inverse relationship during submaximal loads. As Kaijser (1970) noted, the trend is for the differences in HR due to $FI O_2$ to decrease with increasing work load.

X. SUMMARY

The variables reviewed in this chapter were selected as factors which might aid in explaining the relationship between inspired oxygen and exercise performance, a relationship based on grounds other than increased O_2 use. Whenever there was adequate information available, the review has shown the predominant trends. The following chapters present the methods and results of the measurement of those same variables in this study.

CHAPTER III

METHODS

I. PROTOCOL

Six males participated as subjects in this study (see Table 3.1 for personal data). All were active and were conducting personal running programs. None was specifically trained as a cyclist.

All subjects voluntarily gave written consent after having been informed of their rights as subjects, most of them after having seen someone else perform the test. The subjects were asked to try to keep their activities as constant as possible and to come to the test in a post-absorptive state. The tests were performed under fairly uniform environmental conditions ($T^{\circ}C$:21.5-26.0; P_b :736-745 Torr; relative humidity: 48-63%).

The subjects were first given a continuous maximal oxygen uptake test on a bicycle ergometer (Monark) with constant RPM(75-77) and progressive increments of .5kg in resistance at 2-minute intervals until exhaustion. At a later time, the subjects were given another maximal oxygen uptake ($\dot{V}O_2$ max) test which was similar to the protocol to be followed in the actual experiments. These tests consisted of riding for 10 minutes at approximately 55% of $\dot{V}O_2$ max followed immediately by a ride to exhaustion at 100% of $\dot{V}O_2$ max. The subjects then underwent several training rides to further familiarize themselves with the equipment. These rides were also

TABLE 3.1
SUBJECT PERSONAL DATA

Subject	Test* Order	Age (Yrs)	Height (CM)	Weight (KG)	Max $\dot{V}O_2$		Watts		Percent Max	
					L/M	ML/KG·MIN	Low	High	Low	High
1	2,3,1	22	173	73.6	4.01	54.5	147	258	55.5	93.9
2	3,2,1	28	178	69.1	4.05	58.6	147	258	52.0	87.8
3	1,3,2	24	183	73.4	4.35	59.3	147	294	52.1	97.6
4	1,2,3	26	180	73.4	4.46	60.8	151	302	51.5	97.8
5	3,1,2	18	180	72.3	3.70	51.2	129	202	57.8	90.8
6	2,1,3	22	188	65.7	4.56	69.4	184	248	59.6	76.9
$\bar{X}$		23	180	71.3	4.19	59.0	151	260	54.8	90.8

*1 = hypoxia, 2 = normoxia, 3 = hyperoxia.

used to determine an appropriate workload which would lead to exhaustion in approximately 10 minutes following a previous 10-minute ride at 55% of $\dot{V}O_2$ max. This prediction was not always successful.

After these preliminary rides, the subjects were tested 3 times, each subject waiting approximately one week between two successive tests. The tests were performed in an identical manner except that the inspired oxygen fraction (FI_{O_2}) was changed each time ($\bar{X} = .1682, .2093, .6003$ in N_2). The six possible orderings of the three tests were assigned in a random fashion (see Table 3.1 for orders) and the subjects were unaware of what gas they were breathing. They had been told previously only that they would be breathing gases at various inspired O_2 fractions. In order to give as few cues as possible, the bicycle ergometer was enclosed in curtains and all monitoring equipment and technicians, with the exception of the nurse drawing the blood samples, were placed out of view of the subject. Since the digital displays on the analyzers monitoring the gas fractions readily indicated to the technician which gas was being inspired, a double-blind study was not deemed feasible.

The test protocol called for the subject to report to a quiet room approximately 30 minutes before coming into the testing room. While in the quiet room, he lay on a bed for several minutes and had his hand warmed with an electric heating pad. An infusion needle (Deseret Minicath-PRN, 21 gauge, 3/4" with 3-inch extension length) was inserted into a superficial vein on the back of the hand and taped down to minimize movement. During the periods when samples were not being drawn, the needle

was periodically flushed with saline containing about 50 units of heparin per ml. The hand was continuously warmed throughout the test to help ensure better "arterialization" of the blood. Electrodes for monitoring heart rate were also placed on the subject at this time.

After a short rest, the subject was brought to the test room, where he sat on a bicycle ergometer, the hand grip of which had been modified to help keep the blood sampling area as stable and flat as possible. The subject then sat quietly, breathing room air for 10 minutes, following which he put on the mouthpiece and noseclip and breathed that day's gas mixture for an additional 15 minutes. A blood sample was drawn at the end of each of these periods. Ventilatory data collection began at minute 12 of the prebreathing period and continued throughout the test. At the end of the prebreathing period, the subject began pedalling the ergometer at a rate which was approximately 55% of $\dot{V}O_2$ max (Table 3.1, page 53) and continued for 10 minutes. Blood samples were taken at minutes 5 and 9 of this period (hereafter referred to as the low-work period). The work rate was then increased to a higher level ($\bar{X} = 91\% \dot{V}O_2$ max, Table 3.1, page 53) at which he rode until exhaustion (high-work period). Blood samples were taken every 4 minutes beginning at minute 3 of this period. A 2-speed electric fan was provided for the comfort of the subject and was controlled by the subject from the handlebars.

The subjects had been told previously that they should make every effort to maintain pedal frequency as long as possible and that when they could no longer do so they should stop abruptly rather than slow down gradually. Subjects were given no outside encouragement to continue;

they were, however, kept informed if their pedal frequency varied. Upon exhaustion the subject continued to breathe the gas mixture while sitting at rest on the bicycle for an additional 20-minute recovery period. Blood samples were taken every 4 minutes beginning at minute 3 of this period.

II. MEASUREMENTS AND RECORDINGS

Pedal Frequency (fp), Inspiratory Minute Volume ($\dot{V}_I$), Heart Rate (HR)

Pedal frequency was both recorded (physiograph Narco-Biosystems, Type PMP-4A) and monitored on a digital display via the signal from a microswitch attached to the bike frame and tripped by the crankshaft. Any variations of greater than ± 3 RPM were reported to the subject who was also listening to a metronome and watching a speedometer dial marked at the appropriate RPM.

Inspired gas was provided from high pressure cylinders. It was bubbled through heated water in a 2-liter aspirator bottle to ensure 100% saturation and then passed into a 120-liter Tissot gasometer which acted as a reservoir. From there the gas passed through a Parkinson-Cowan CD4 dry-test gas meter (with potentiometer coupled to the physiograph) and then directly to the mouthpiece. The mouthpiece was a Daniels valve with minimal deadspace and resistance. Heart rate was recorded from a 3-lead connection via a biotachometer (Narco Biosystems, BT-1200) connected to the physiograph.

Gas Fractions (FEO_2 , $FECO_2$, FIO_2 , $FICO_2$)

The expired gas passed through a 32 cm length of tubing into a 5-liter mixing chamber and then into the room. The inspired and expired

connections were flexible plastic 34 mm ID tubing. Expired gas fractions were monitored continuously from an Applied Electrochemistry S-3A O_2 analyzer and a Beckman LB-2 CO_2 analyzer and recorded by hand at 15-second intervals. These analyzers sampled from the mixing chamber by way of a 1-foot length of 6 mm ID tubing. The analyzers were frequently calibrated against known gases during the test.

At predesignated intervals (usually 4 minutes), 50cc samples were drawn from the mixing chamber into glass syringes and later analyzed by the Scholander method (Scholander, 1947). The expired gas fractions obtained from the Scholander and from the electronic analyzers were used to calculate separate values for oxygen uptake and carbon dioxide output. The accuracy of the measurement was demonstrated when it was found that the values for $\dot{V}O_2$ and $\dot{V}CO_2$ calculated from the two sets of gas fractions were not significantly different (two-tailed Student's t-test for related measures: $p(\dot{V}O_2) = .25$, $p(\dot{V}CO_2) = .24$). For both $\dot{V}O_2$ and $\dot{V}CO_2$ the difference between the means was less than 1ml/min.

The Douglas bag method of gas collection and analysis was not used because of the inherent difficulty of obtaining a pure sample. Drawing directly from the mixing chamber prevented any problems of contamination from diffusion of gases in or out of Douglas bags as well as from inability to completely empty the bags prior to collection.

Inspired gas fractions were checked by the same electronic analyzers before and after the test. On three occasions during each test samples were drawn from the outlet side of the CD4 for Scholander analysis.

Lactic Acid (HLA), pH, PCO_2 , PO_2

All variables measured from "arterialized" venous blood samples with the exception of PO_2 have previously been shown to accurately reflect arterial values (Forster et al., 1972). Blood was therefore drawn from a superficial vein on the back of the hand and used to determine HLA, pH and PCO_2 as well as PO_2 . The blood samples were drawn at designated intervals throughout the test into 1ml matched tuberculin syringes whose dead space had been flushed with saline containing approximately 300 units of heparin per ml. This blood was used for determinations of HLA, pH, PCO_2 , and PO_2 .

Approximately .3cc of the sample was placed immediately into a spot-plate well which had previously been coated with .05 ml of a 4% NaF solution and then dried. The blood and NaF were mixed and two separate 50 μ l samples were taken and each placed into 2ml of 7% $HClO_4$. These samples were shaken by hand and iced until the end of the test. Upon completion of the test the samples were centrifuged and the supernatant fluid frozen for subsequent lactate analysis. The analysis was performed according to a modification of the fluorometric enzymatic method of Gutmann & Wahlefeld (1974).

From the remaining .7cc of the blood sample, two separate determinations for pH, PCO_2 and PO_2 were made. The analyses were made at 37°C using a BMS MK2 Blood MicroSystem with PHM73 pH/Blood Gas Monitor (Radiometer, Copenhagen) calibrated frequently with gases analyzed by the Scholander method and with Radiometer buffers. The analyses were performed

within 10 minutes of sampling to overcome any problems with deterioration of the sample (Fletcher, 1966).

In order to gauge the reproducibility of the measurement, one blood sample on each test was taken before the subject inspired the given gas. These samples, therefore, gave three comparable resting values while he was breathing room air. A comparison of these samples yielded p values from .1 to .75 ($[\text{HCO}_3^-]$: .75, $[\text{H}^+]$: .57, PO_2 : .53, PCO_2 : .24, HLA : .1). The low probability for lactate was due to a slightly higher average value for that parameter while the subjects were breathing room air prior to the hypoxic tests. The average value prior to the hypoxic tests was 1.4mM/l as opposed to .9mM/l prior to the normoxic and hyperoxic tests. At present this difference is not explainable.

During the analysis of the data some PCO_2 values were lower than expected. Subsequent checks of the PCO_2 electrode using equilibrated liquids (Tonometer 237, Instrumentation Laboratory) showed that the higher PCO_2 readings were indeed below the actual values. Unfortunately, the slope of the graph of the actual value vs Radiometer readings was not constant from day to day so no correction could be applied. However, there is not a great discrepancy in the values--especially below 35mm Hg--and those values from 50mm Hg are at the most 10mm Hg low. As a result, the PCO_2 and bicarbonate values presented should be viewed with this fact in mind--the higher values may be a little low.

III. CALCULATIONS

Oxygen Uptake ($\dot{V}O_2$), Carbon Dioxide Output ($\dot{V}CO_2$), Respiratory Exchange Ratio (R)

$\dot{V}O_2$ and $\dot{V}CO_2$ were calculated using the Haldane equation and transformation for $\dot{V}I$ (Otis, 1964; Wilmore & Costell, 1973).

$$\dot{V}O_2 = \dot{V}I \times \left[FIO_2 - \frac{FEO_2 \times FIN_2}{FEN_2} \right]$$

Also,

$$\dot{V}CO_2 = \dot{V}I \times \left[\frac{FECO_2 \times FIN_2}{FEN_2} - FICO_2 \right]$$

R was taken as the ratio of $\dot{V}CO_2/\dot{V}O_2$.

Hydrogen Ion Concentration ($[H^+]$)

$[H^+]$ was calculated from the measured pH by the conversion: $[H^+] = \text{antilog}(-\text{pH})$. $[H^+]$ is used throughout this paper as being much more descriptive than pH (Stewart, 1978).

Bicarbonate Concentration ($[HCO_3^-]$)

$[HCO_3^-]$ was calculated from PCO_2 and $[H^+]$ data according to the equation: $[HCO_3^-] = K a PCO_2/[H^+]$

where

$$K = (\text{antilog}((-pK) = 6.1)) = 794 \times 10^{-9}$$

and,

$$a = .0301.$$

Therefore, $[HCO_3^-] = (24 \times 10^{-9}) \times (PCO_2/[H^+])$ (Davenport, 1974).

As explained above there may be a systematic error in the PCO_2 which causes the given data to be low at the higher values. Any such error would of course be carried directly into the bicarbonate calculations and cause them also to yield low values. Nevertheless, trends and changes relative to $FI O_2$ are still valid.

IV. STATISTICS

Repeated Measures Designs were used for the primary statistical analysis since each subject performed under all conditions. In some instances, Treatments (O_2 level) x Subjects (TxS) was called for; in other cases Treatments (O_2 level) x Treatments(time) x Subjects (TxTxS) was the better method (Bruning & Kintz, 1968). The Tukey a (HSD) test was used for a posteriori analysis when overall significant differences were indicated between treatments. When interaction significance was of importance the data were retabbed and repeated measures analyses were performed on two levels at a time (Lindquist, 1953).

There were six subjects. This number is not unusual for such a complex study. However, it is often difficult to set an exact significance level for an n this small. Therefore, in order to let each reader interpret the results where the significance might be questionable, actual probabilities are reported whenever possible. Tukey a analysis was performed only at .1, .05, and .01 levels. In the results an arbitrary decision was made to call any $p < .05$ significant, and to leave $p > .05$ open to interpretation, noting $.1 > p > .05$ as "marginally significant" or "approaching significance."

CHAPTER IV

RESULTS

The results presented in this chapter will be shown in two ways. First, the trends through the entire test for each parameter will be presented. This presentation is based on the statistics given later in the chapter but should provide a somewhat clearer picture of what is actually happening to each measure as the test progresses. Approximate values for each parameter are shown on the graphs presented. Second, the differences revealed in the statistical analyses will be given. In order to supply them, the experiment is divided into its various sections (Rest, Low Work, High Work, Exhaustion, Recovery) and each parameter is presented within that section. Tables of probability values are provided covering most statistics performed.

I. PARAMETER TRENDS

Mean performance times to exhaustion are shown in Figure 4.1. Hyperoxia improves performance and hypoxia reduces it. The other graphs presented here require a brief explanation. Each figure is divided into six periods (See Figure 4.2). Period I represents 10 minutes during which the subject sits at rest breathing from the room. Period II is a further 15 minute rest period with the subject breathing one of the three gas mixtures which he will continue to breathe for the remainder of the test. With period III exercise begins. The subject works for 10 minutes

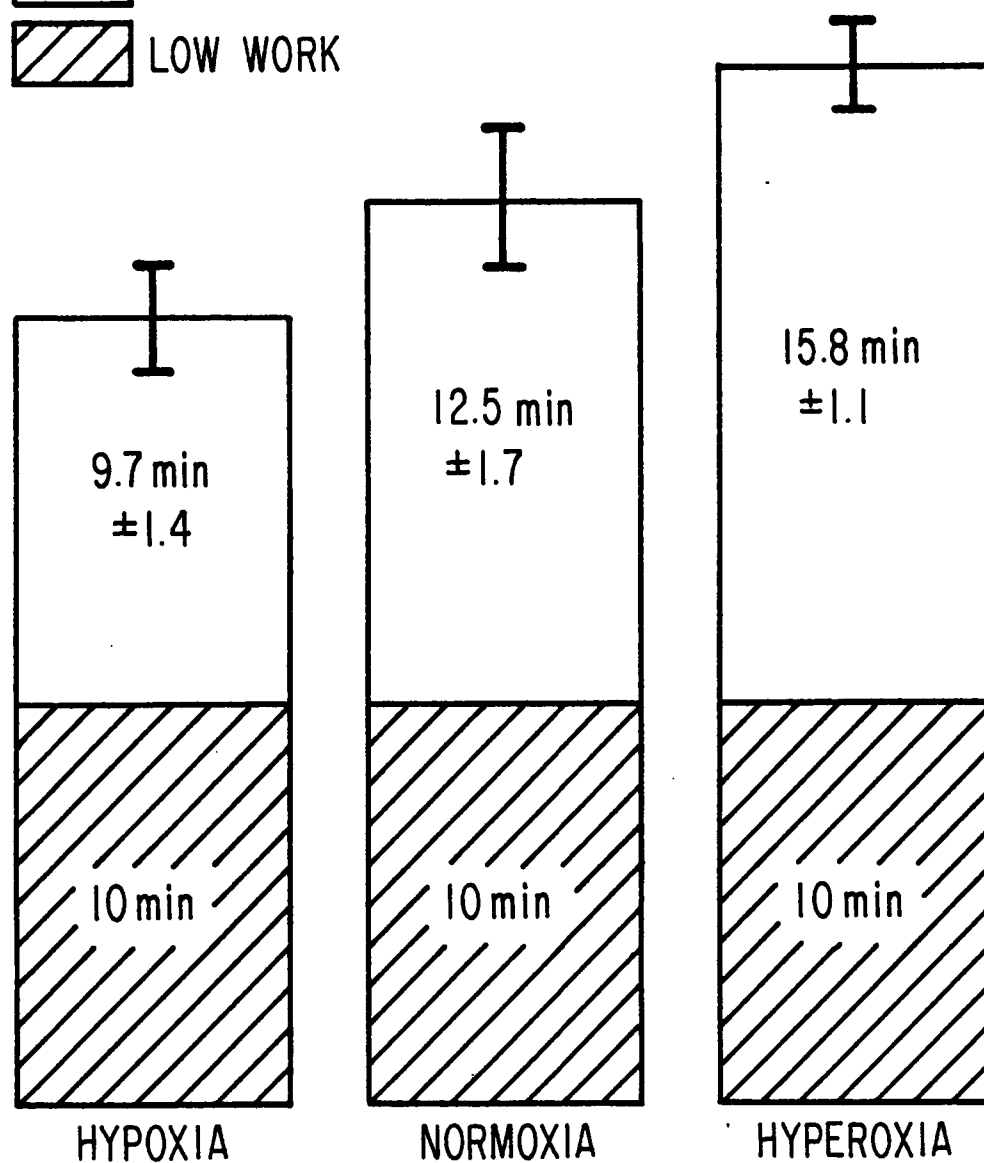
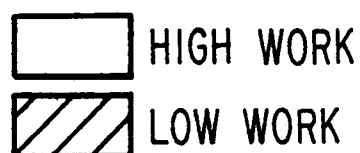


Figure 4.1. Performance times to exhaustion under 17%, 21% and 60% inspired oxygen. (+/- S.E.M.)

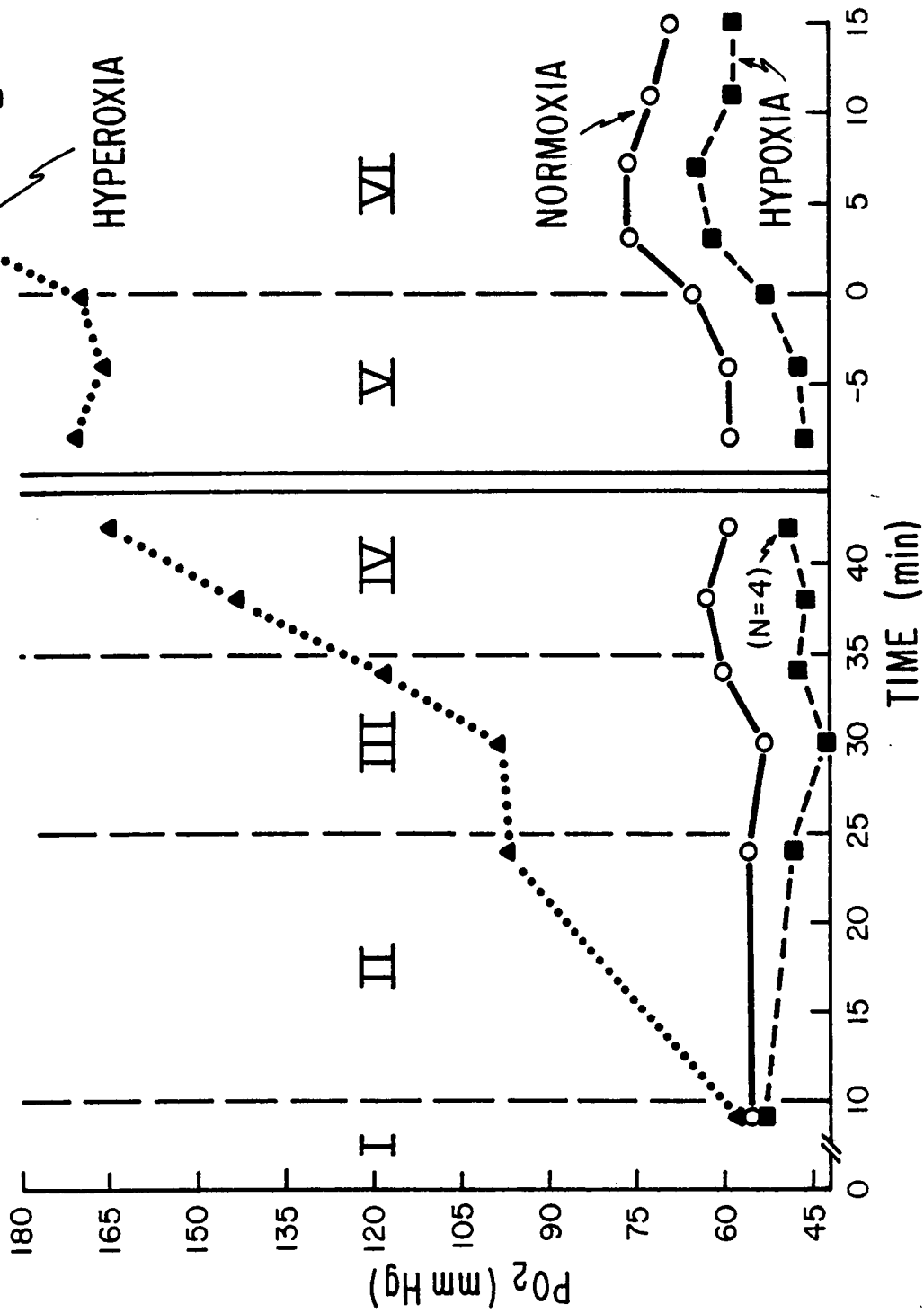


Figure 4.2. Mean P_{O_2} values. I = Rest breathing room air; II = Rest breathing gas mixture; III = Low Work; IV = Beginning High Work; V = end of High Work; VI = Recovery.

at approximately 55% $\dot{V}O_2$ max during this time. Period IV represents the first nine minutes of the exercise to exhaustion at 91% $\dot{V}O_2$ max and period V shows the last seven minutes of the same exercise. The division between periods IV and V was necessary because these are performance studies and unfortunately not all people become exhausted after the same amount of time. Therefore period IV was necessary to show trends relative to the onset of work and period V to show the trends relative to the cessation of work. If each subject on each test had performed exactly the same amount of time this division would not have been necessary. Because it is necessary there is some overlap between these two periods. For example, in normoxia the average time to exhaustion is 12.5 minutes (Figure 4.1, page 63). Of this time, the first seven minutes are shown in period IV and the last eight in period V. Therefore the middle 2.5 minutes are shown in each period. For hypoxia, the middle 4.5 minutes appear in each period while for hyperoxia there is no overlap. Exhaustion is represented by the line of division between periods V and VI with period VI displaying the data during recovery.

The graphs do present the data accurately, and in most cases one can see an approximate picture of the trend for each gas for the entire test by mentally moving the appropriate right half curve across to the left until its starting point hits the left hand curve. In doing so, one sees that a high-work period curve of approximately the correct mean time for that gas will be generated. It must be emphasized that the first point on the right hand curve does not correspond to the last point on the left hand curve except rather generally in the case of hyperoxia.

There are two blood samples in period IV; the second point in hypoxia only is based on $n=4$. All other points for both ventilatory and acid-base data are based on $n=6$.

PO_2 (Figure 4.2, page 64)

Since the trends in PO_2 in this study were so obvious and not of great interest except to reflect the "arterialization" of the blood, most statistical analyses were not performed. PO_2 was highest in hyperoxia and lowest in hypoxia throughout.

Hydrogen Ion Concentration ($[H^+]$) (Figure 4.3)

There was no difference between rest values before and after putting in the mouthpiece (Rest 1 & 2) for any gas, nor was there any effect due to FI_{O_2} on the second resting sample. In low work the levels of $[H^+]$ were lower in hypoxia than in either normoxia or hyperoxia--which were not different from each other. The samples at minutes 5 and 9 of this work load (low 1 & 2) revealed no significant difference (NSD also non significantly different) NSD from each other. In high work, this trend continued; that is, hypoxic values were lower than hyperoxic while normoxic values were not different from those at either extreme. During this period the lower hypoxic values were increasing faster than with the other gases. As a result, at exhaustion $[H^+]$ revealed NSD at any level. By the first recovery sample 3 minutes later, the hypoxic value was significantly higher than for the hyperoxic while the normoxic value was intermediate and showed NSD from either of the others. Hypoxic values remained highest during recovery, with the initial high recovery value falling fastest toward normal. Overall, from minute 3-15 of recovery, FI_{O_2} did not bring about significant differences.

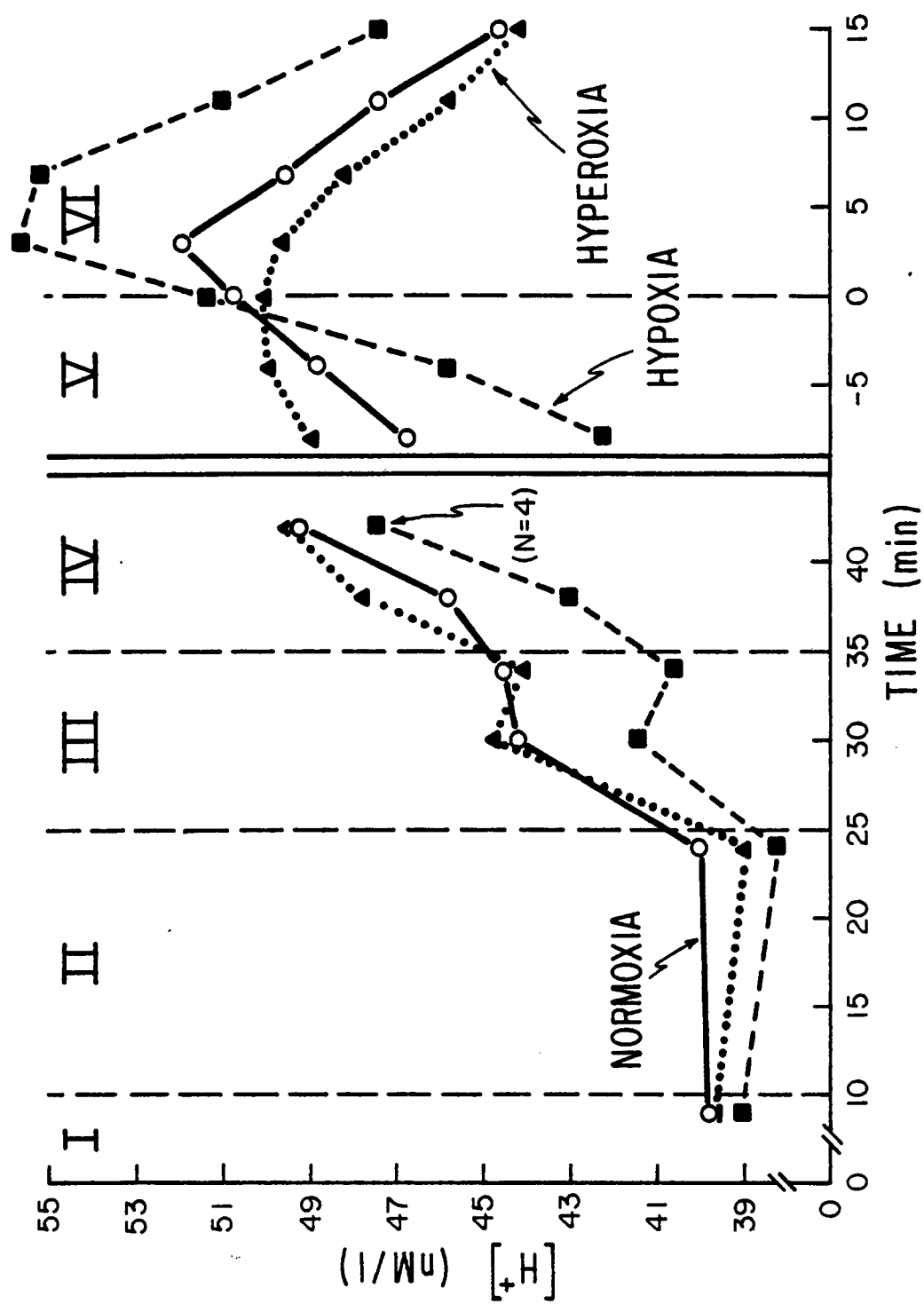


Figure 4.3. Mean $[H^+]$ values. Legend as in Figure 4.2.

Oxygen Uptake ($\dot{V}O_2$) (Figure 4.4)

During rest, $\dot{V}O_2$ decreased with hypoxia but showed no difference in the hyperoxic-normoxic comparison. During low work the three values revealed NSD. In minutes 3-6 of high work, the hypoxic values were lower than the hyperoxic, but the normoxic value showed NSD from either of those. At exhaustion, although normoxia was still not different from the extremes, the normoxic-hyperoxic difference was approaching significance. Immediately after work, the higher hyperoxic values dropped fastest and no pairs revealed significant differences for the remainder of recovery.

Carbon Dioxide Output ($\dot{V}CO_2$) (Figure 4.5)

$\dot{V}CO_2$ at rest yielded NSD between any two level of inspired O_2 . In low work the increased $\dot{V}CO_2$ was higher during hypoxia than during each of the other oxygen levels. At the high work load, only the hypoxia-hyperoxia comparison showed a significant difference, with hypoxic $\dot{V}CO_2$ being greater. At exhaustion no FI_{O_2} comparisons showed a significant difference. This remained the case through recovery.

Respiratory Exchange Ratio (R) (Figure 4.6)

During rest and low work, R values did not vary significantly as a result of variations in FI_{O_2} . During high work and at exhaustion the R was greater under hypoxic than under hyperoxic conditions. In each of these last two cases the normoxic R remained intermediate and in high work was significantly different only under hyperoxic conditions and at exhaustion only under hypoxic conditions. During recovery the differences again showed NSD for any level of FI_{O_2} .

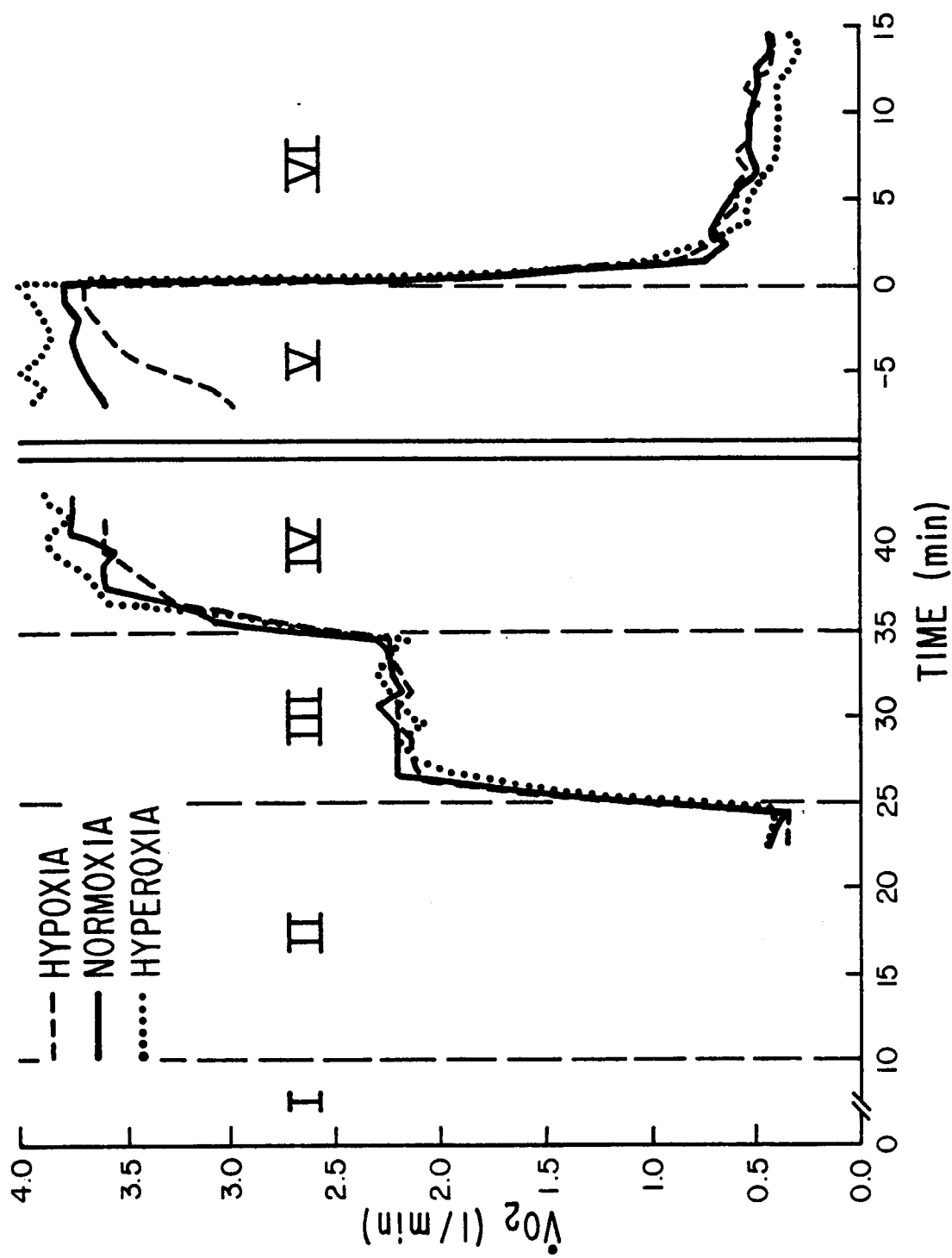


Figure 4.4. Mean $\dot{V}O_2$ values. Legend as in Figure 4.2.

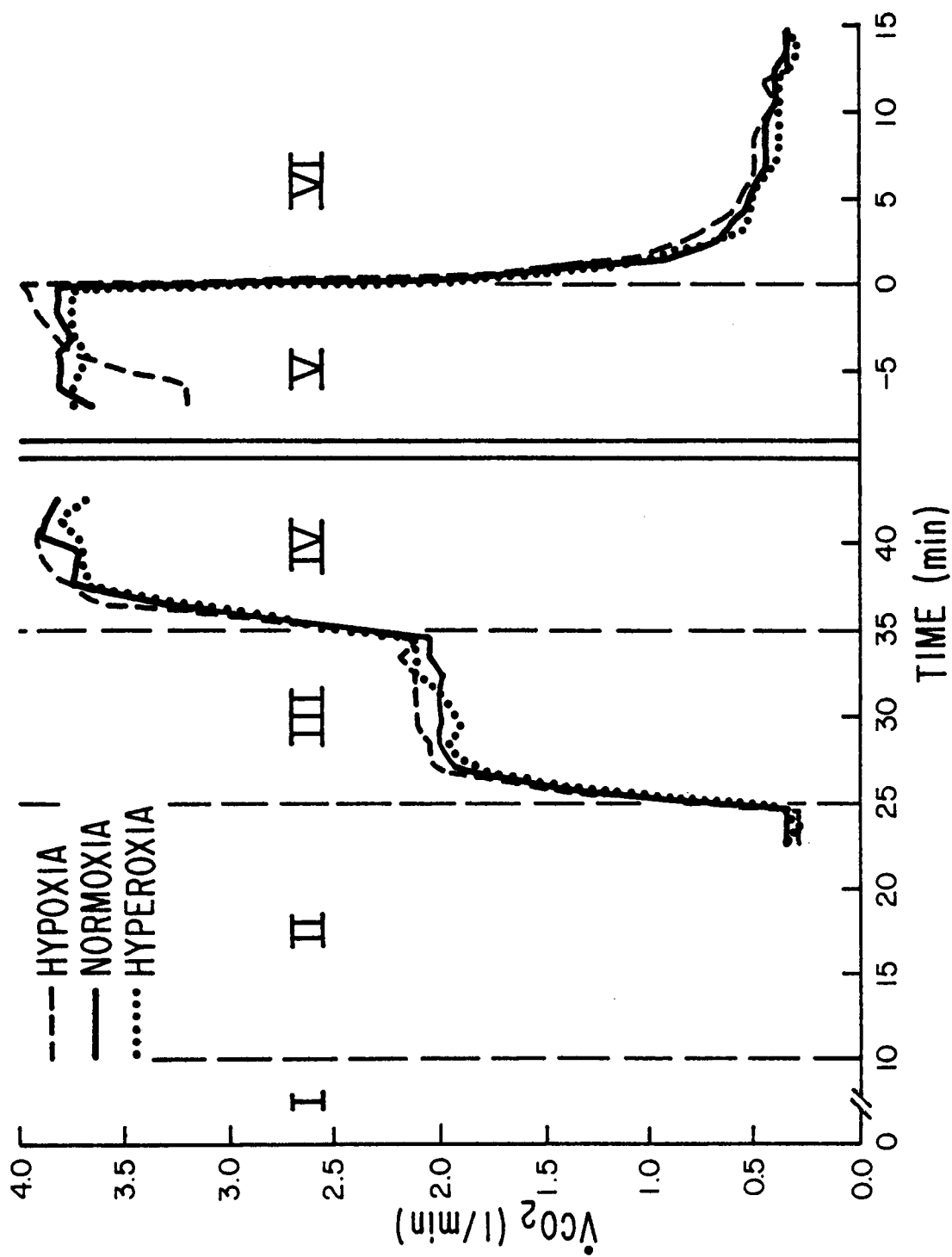


Figure 4.5. Mean $\dot{V}CO_2$ values. Legend as in Figure 4.2.

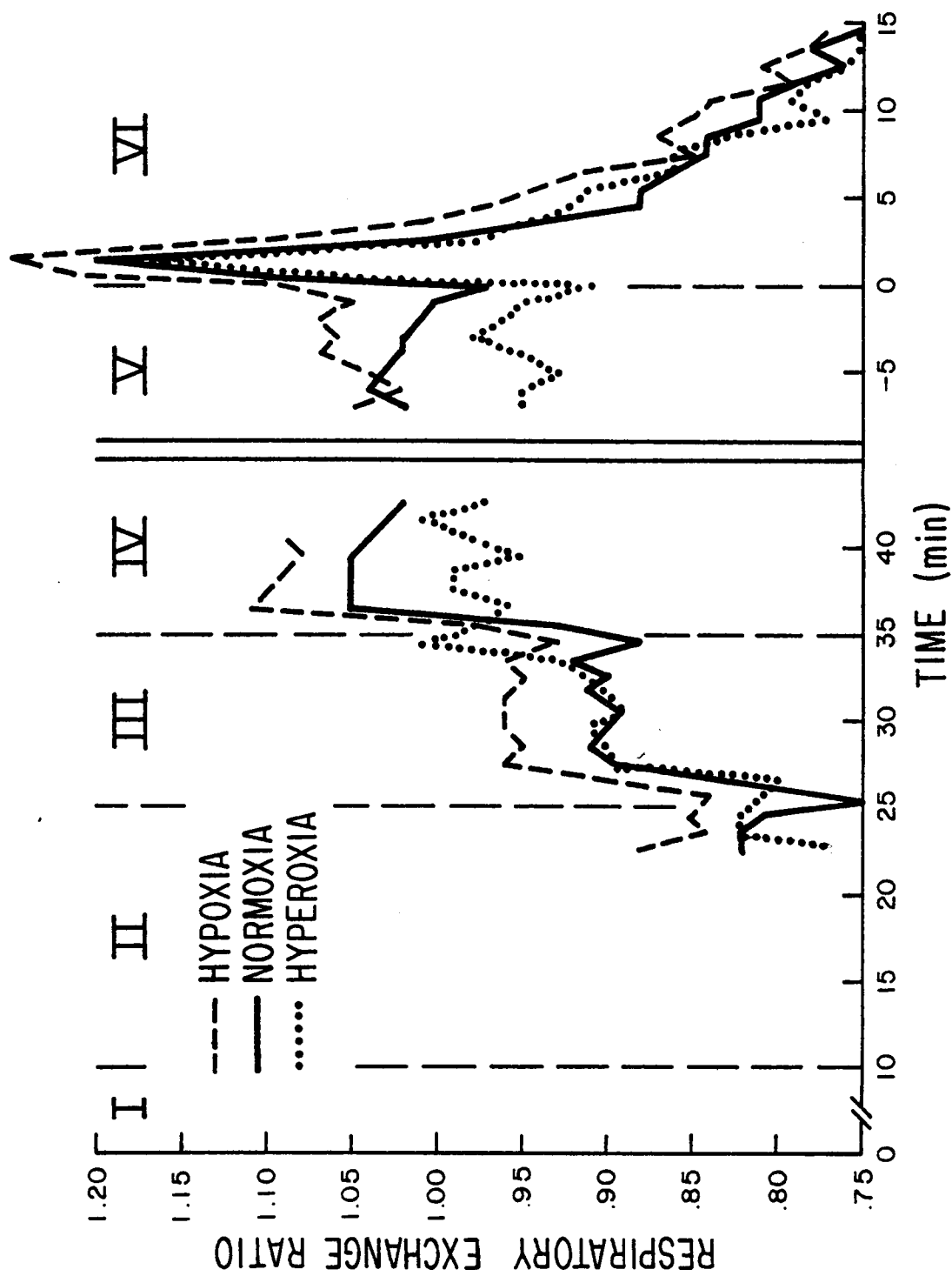


Figure 4.6. Mean R values. Legend as in Figure 4.2.

Inspiratory Minute Volume ($\dot{V}I$) (Figure 4.7)

At rest, while normoxic $\dot{V}I$ did not differ from either extreme, the hyperoxic-hypoxic comparison did yield a significant difference. Thus, at rest, there was a tendency for $\dot{V}I$ to increase with increased FI_{O_2} and decrease with decreased FI_{O_2} . At the onset of work, however, hypoxic $\dot{V}I$ increased faster and surpassed hyperoxic ventilation. During low work, the $\dot{V}I$ under hypoxic conditions was significantly different from the other values; hyperoxia, while being NSD from normoxia, produced the lowest values. During the jump to high work, the hypoxic $\dot{V}I$ again increased faster than the hyperoxic, the normoxic rate remaining intermediate. During minutes 3-6 of high work and at exhaustion the trend remained the same, with hypoxic $\dot{V}I$ greater than normoxic, which was in turn greater than hyperoxic $\dot{V}I$. Upon completion of the work, the highest values (hypoxia) decreased fastest so that analysis of values for minutes 3-15 of recovery showed NSD for any FI_{O_2} comparisons, although hypoxic values continued to decrease fastest.

Lactic Acid (HLA) (Figure 4.8)

There was no effect on HLA due to putting in the mouthpiece and breathing any gas. There was also no effect of FI_{O_2} on the value obtained at Rest 2. During low work, hypoxia produced significantly higher values than during normoxia. Hyperoxia was intermediate but yielded NSD from the other two conditions. HLA did not increase significantly during this period (low 1 to low 2).

Over the first two samples at high work, the separation in HLA values due to FI_{O_2} continued, with hypoxic now also higher than hyperoxic

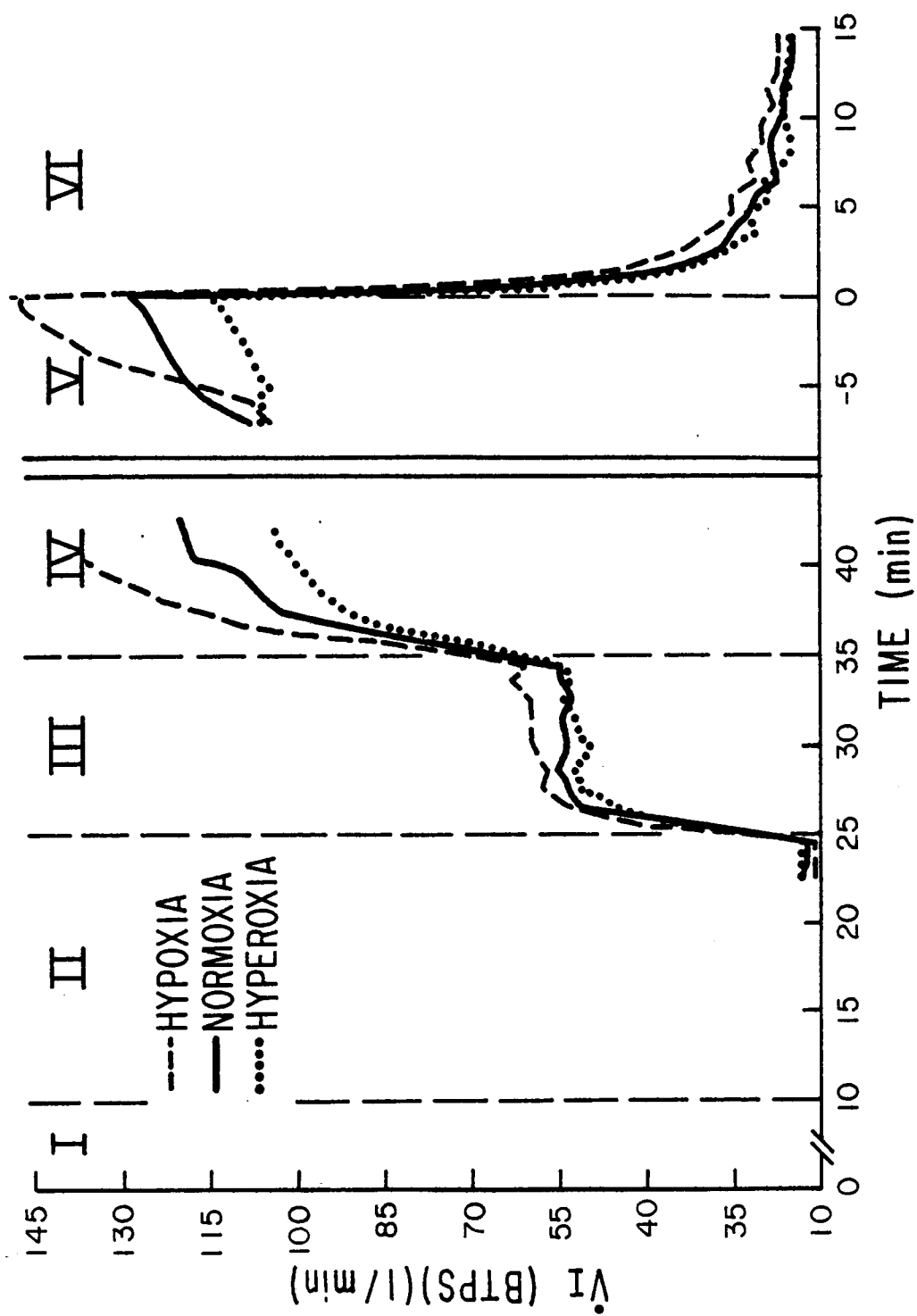


Figure 4.7. Mean Ventilation values. I = Rest breathing room air II = Rest breathing gas mixture; II = Low Work; IV = Beginning High Work; VI = Recovery.

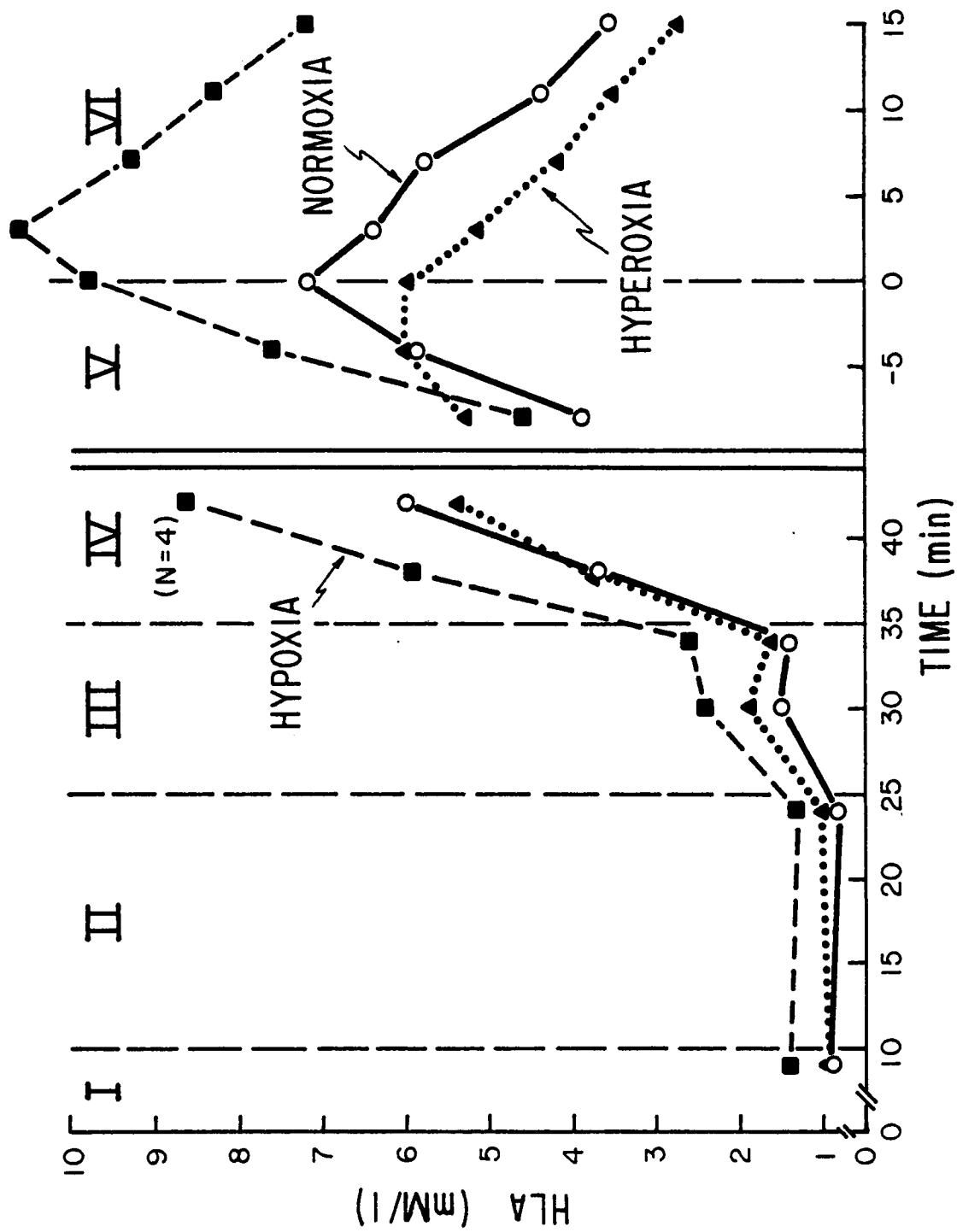


Figure 4.8. Mean HLa values. Legend as in Figure 4.7.

values but with normoxia and hyperoxia still revealing NSD. The level of HLa did increase between the first two samples at high work (from High 1 to High 2), but there was NSD in the rate of increase due to FIO_2 . At exhaustion, the picture for HLa was exactly the same as during early high work. This state continued into recovery, although the high HLa value in hypoxia decreased fastest toward normal so that the only significant difference was that HLa in hypoxia was higher than in hyperoxia.

PCO_2 (Figure 4.9)

In all cases PCO_2 decreased to some degree as a result of breathing through the mouthpiece, but variations in FIO_2 resulted in NSD for the values at Rest 2. During low work there was still no difference in PCO_2 , although the hypoxic value dropped rapidly between Low 1 and 2 while at the other inspired fractions it stayed relatively constant. In high work, the PCO_2 values were highest in hyperoxia, and with each paired comparison there was a significant difference. The trend at all inspired fractions was for PCO_2 to decrease. At exhaustion, this trend continued except that the hypoxic-normoxic comparison now showed NSD. In recovery, the values began a return upward, with the rate unaffected by FIO_2 . Throughout recovery, hypoxic PCO_2 values were lower than hyperoxic, while normoxic values provided NSD when compared with either extreme. Even after 20 minutes of recovery, PCO_2 had not returned to baseline levels.

Bicarbonate Concentration ($[\text{HCO}_3^-]$) (Figure 4.10)

When the subjects breathed with the mouthpiece, $[\text{HCO}_3^-]$ decreased somewhat for all gases except hyperoxia. FIO_2 produced no effect, however, on the Rest 2 sample. This similarity in values continued through

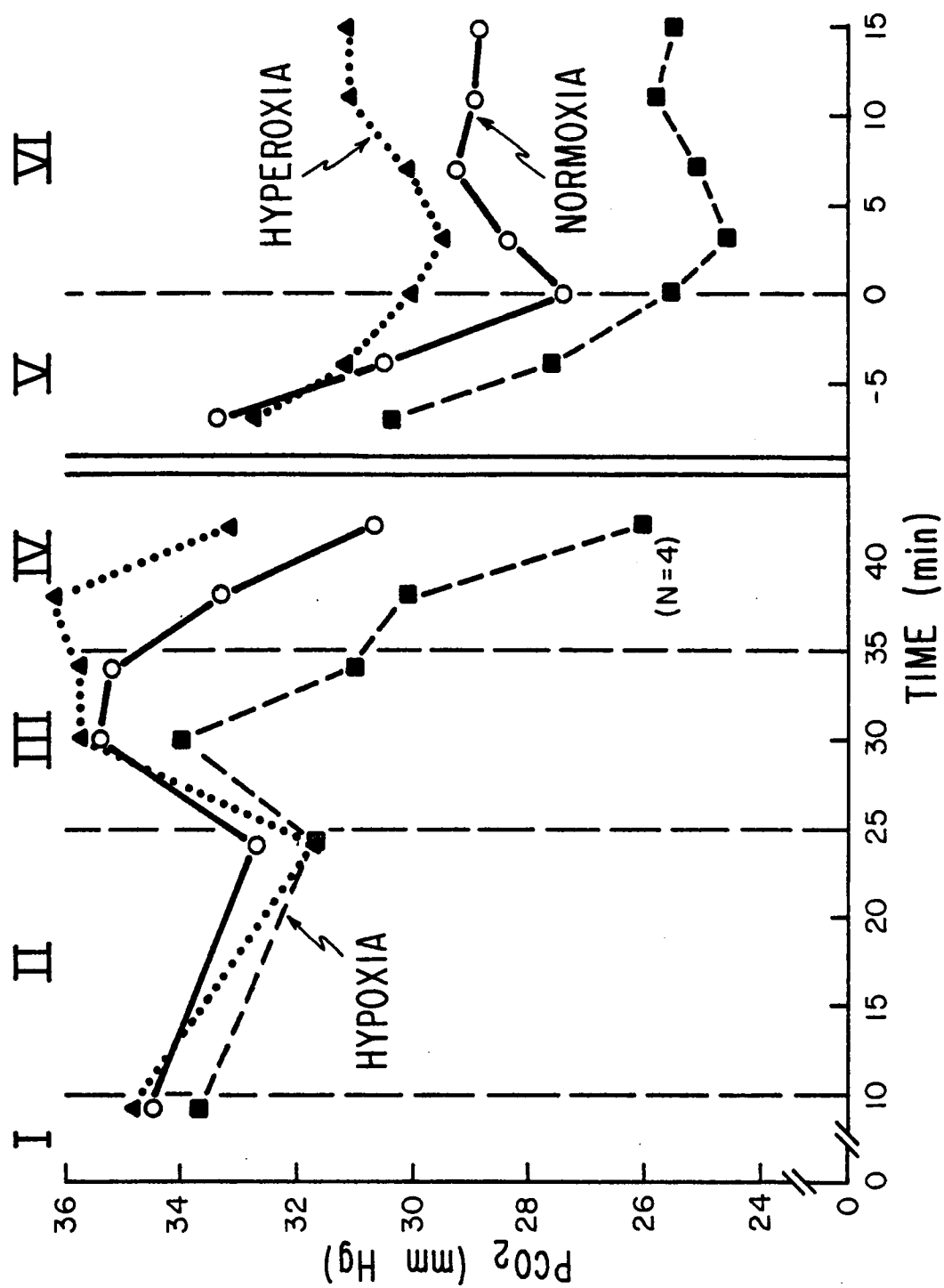


Figure 4.9. Mean PCO_2 values. Legend as in Figure 4.7.

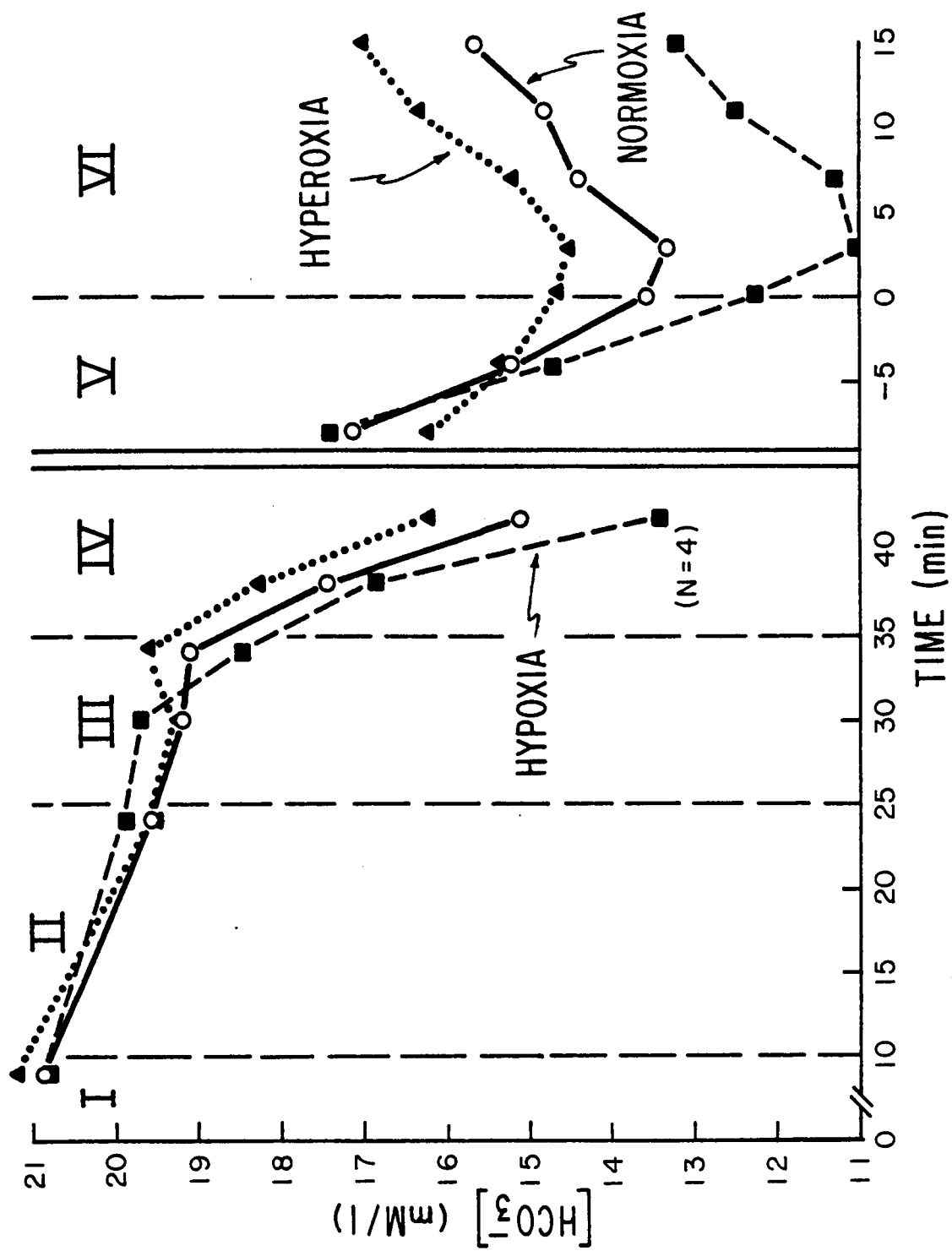


Figure 4.10. Mean $[\text{HCO}_3^-]$ values. Legend as in Figure 4.7.

low work although the rate of change signaled variations to come, with hypoxia decreasing slightly, normoxia constant, and hyperoxia essentially constant but showing a slight increase. At high work (High 1 & 2), hypoxic values were significantly lower than hyperoxic, but normoxia still yielded NSD when compared with values at each of the other levels. The differences at exhaustion were the same as during high work. During recovery the respective levels were also the same; that is, hypoxic values were lowest, but the trend was an increase toward normal at rates that were not significantly affected by FIO_2 .

Heart Rate (HR) (Figure 4.10)

Variations in FIO_2 did not produce any significant differences in resting HR, but at low work hypoxia showed higher values than hyperoxia, with normoxia intermediate and revealing NSD. Overall during this low work period, both hypoxic and hyperoxic values increased faster than normoxic values; however, during minutes 3-6 of high work, there were no significant differences a fact that continued to be true at exhaustion and through recovery.

II. RESULTS OF STATISTICAL ANALYSES BY TEST SECTION

In this statistical presentation, the experiment is divided into its various periods (Rest through Recovery) and each parameter is presented within each period. In order to simplify the text, most probability values are provided in tables. For any probability (p value) less than .05 the differences are considered significant. Probabilities less than

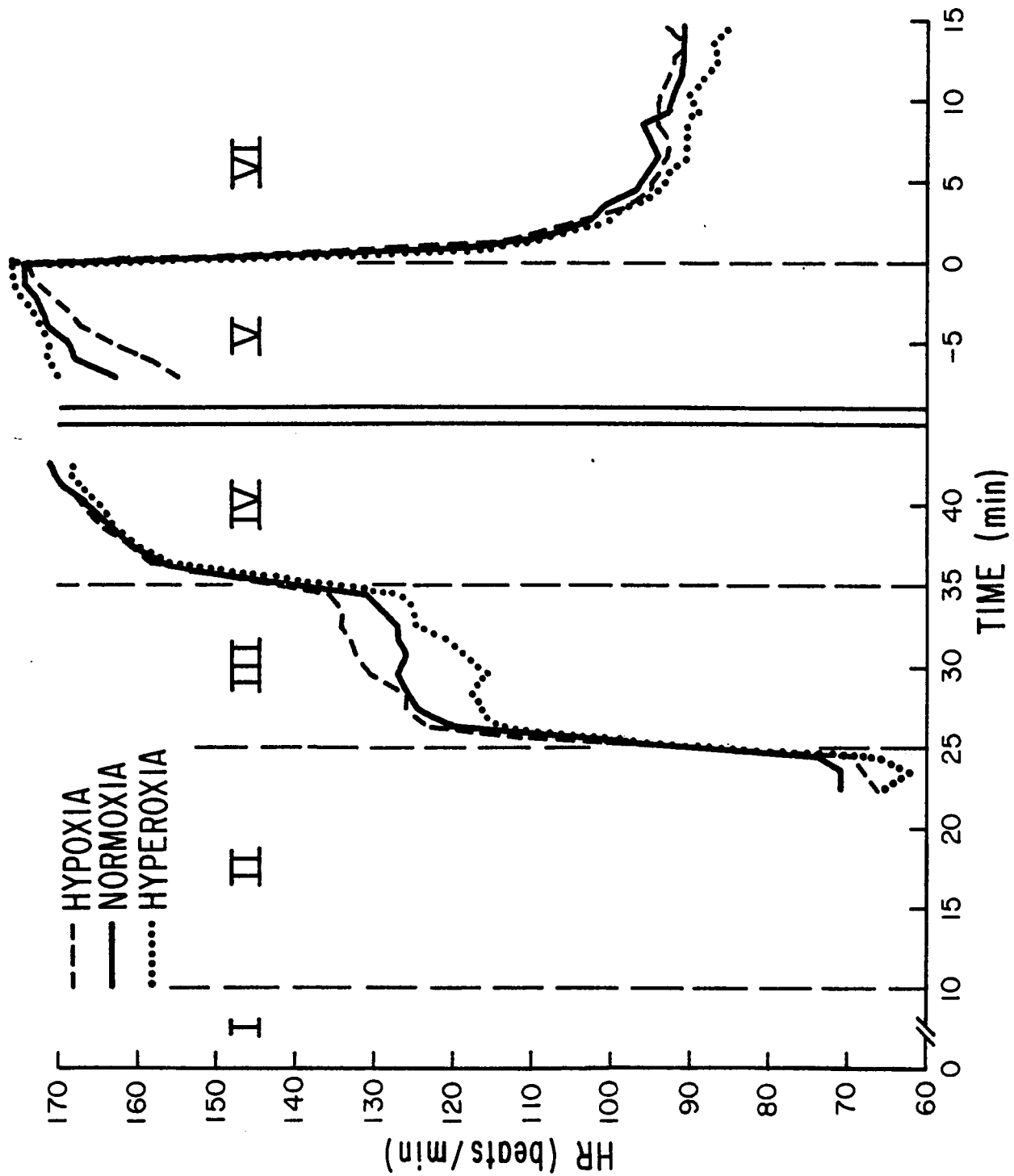


Figure 4.11. Mean Heart Rate values. Legend as in Figure 4.7.

.1 and greater than .05 are considered marginally significant. Exact probabilities are given for all repeated measures analyses above .001 and where these are significant the probability range derived from the Tukey HSD test is given for each paired comparison.

Rest

Table 4.1 shows probabilities for blood data at rest. Here the values obtained prior to inserting the mouthpiece and inspiring the given gas are compared with these obtained after inspiring the gas for 14 minutes. In the shift from room air to hypoxia, the PO_2 , PCO_2 , and bi-carbonate all decreased. Probabilities for HLa and $[H^+]$ show NSD (no significant difference--also non-significantly different). For the change from room air to the normoxic mixture, $[HCO_3^-]$ was decreased and

TABLE 4.1

p VALUES FOR COMPARISON OF REST DATA PRIOR TO BREATHING THE GAS MIXTURE AND AFTER BREATHING THE GAS MIXTURE FOR 14 MINUTES.
(T x S)

Variable	Hypoxia	Normoxia	Hyperoxia
PO_2	.04	.43	.10
PCO_2	.002	.08	.16
$[HCO_3^-]$	.02	.03	.19
$[H^+]$	.16	.67	.59
HLa	.32	.36	.68

PCO_2 marginally so. Probabilities for HLa , $[\text{H}^+]$, and PO_2 revealed NSD. Switching from room air to hyperoxia produced a slightly increased PO_2 while other values were NSD.

A comparison of the effect of the three inspired gases on the second rest sample (14 minutes after beginning to inspire the given gas) showed NSD for any parameter other than PO_2 ($p(\text{HLa})=.14$, $p([\text{H}^+])=.22$, $p(\text{PCO}_2)=.76$, $p([\text{HCO}_3^-])=.95$). That is, at rest inspired O_2 has no significant effect on any of these measured blood variables.

Table 4.2 shows the probabilities for ventilatory and heart rate data at rest. Comparison was made of the average rest values for the 3 minutes prior to exercise while breathing the given gas mixture. The comparison between the three O_2 levels for $\dot{\text{V}}\text{O}_2$ and $\dot{\text{V}}\text{I}$ by Tukey HSD analysis showed for $\dot{\text{V}}\text{O}_2$ (1) that hypoxia produced only marginally lower values than normoxia or hyperoxia; and (2) that for normoxia vs hyperoxia there was NSD. For $\dot{\text{V}}\text{I}$, the comparison of hypoxia and hyperoxia was significant while the normoxic comparison with each of these was not. These results indicate a slight tendency for $\dot{\text{V}}\text{I}$ to vary directly with FIO_2 during rest.

Low Work (55% $\dot{\text{V}}\text{O}_2$ max)

Table 4.3 shows the probabilities for the blood data during low work. Samples were taken at minutes 5 and 9 of this period. Analysis for the effects of FIO_2 showed no difference for $[\text{HCO}_3^-]$. The PCO_2 was marginally significant overall but with no definite trend, Tukey analysis showing NSD for any pair compared. HLa means were different by Tukey analysis only with the hypoxia-normoxia comparison, with HLa slightly

TABLE 4.2

COMPARISON OF REST VALUES UNDER THREE LEVELS OF FIO_2
 (LOW=HYPOXIA, AIR=NORMOXIA, HI=HYPEROXIA).
 (T x T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$\dot{\text{V}}\text{O}_2$	.05	.1>p>.05	.1> p>.05	p>.1
$\dot{\text{V}}\text{I}$	.06	p>.1	.05>p>.01	p>.1
HR	.14			
$\dot{\text{V}}\text{CO}_2$	.26			
R	.20			

TABLE 4.3

COMPARISON OF LOW WORK BLOOD VALUES UNDER THREE LEVELS OF FIO_2 .
 (T x T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
PCO_2	.07	p>.1	p>.1	p>.1
HLa	.03	.1>p>.05	p>.1	p>.1
$[\text{H}^+]$	.001	.01>p	.01>p	p>.1
$[\text{HCO}_3^-]$	.89			

higher in hypoxia. For $[H^+]$, hypoxia yielded a significant lowering from normoxia and hyperoxia but showed NSD between normoxic and hyperoxic values.

Analysis for differences between samples at minutes 5 and 9 showed all probabilities greater than .14 except for PO_2 . Since such a finding indicates no significant increase or decrease during this period, one can reasonably assume that the body was in a "steady state."

Throughout these analyses a significant interaction is interpreted as a significant difference in the rate of change of a variable due to the effect of FIO_2 . Of the significant interactions at this stage only PCO_2 ($p=.008$) and $[HCO_3^-]$ ($p=.02$) are of interest. Hyperoxic PCO_2 and normoxic PCO_2 are relatively level through this period while the hypoxic PCO_2 falls rapidly. For $[HCO_3^-]$, hypoxia shows a decrease, normoxia shows no change, and hyperoxic values, while essentially level, show a slight increase.

Table 4.4 shows ventilatory and HR probabilities during low work. Since the blood data for this period indicate a steady state, the values for the ventilatory data from minute 3-10 were averaged to obtain one steady state value. The effects of oxygen on $\dot{V}O_2$ and R were NSD. Tukey analysis of $\dot{V}CO_2$ showed hypoxic values to be higher than either normoxic or hyperoxic values while normoxic $\dot{V}CO_2$ results revealed NSD from hyperoxic values. For $\dot{V}I$, only the normoxia-hyperoxia pair were NSD, each of the other comparisons giving an increase in $\dot{V}I$ with decreased FIO_2 . Analysis of the $\dot{V}I$ data from the last rest value through the second work value

TABLE 4.4
COMPARISON OF VENTILATORY AND HR LOW WORK VALUES (MIN 3-10)
UNDER THREE LEVELS OF FIO_2 .
(T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$\dot{\text{VCO}}_2$	.01	.05>p>.01	.05>p>.01	p>.1
$\dot{\text{V}}\text{I}$	<<.001	.01>p	.01>p	.01>p
$\dot{\text{V}}\text{O}_2$	.38			
R	.26			

($p=.02$ for interaction) showed that with the onset of work ventilation increases faster during hypoxia than during hyperoxia ($p=.003$) with normoxic $\dot{\text{V}}\text{I}$ increasing at an intermediate rate but NSD from either extreme FIO_2 ($p=.19$ & $.47$).

Steady state HR values showed (min 4-10) overall $p=.02$ (TxTxS) for the effect of O_2 ; however, Tukey analysis produced no comparison with $p<.1$. Steady state HR interaction ($p<.001$) analysis showed significant interaction for each of the three rates though the trends were not in the same direction. The analysis showed that HR in both hypoxia ($p=.005$) and hyperoxia ($p=.015$) increased at a faster rate than in normoxia and that hyperoxic HR increased faster than hypoxic ($p=.011$).

High Work (91% $\dot{\text{V}}\text{O}_2$ max)

A comparison was made of the first and second blood samples (minutes 3 and 7 of this period) on those subjects who performed at least 7 minutes

at this work load (n=4). For the effects due to O_2 (Table 4.5), $[H^+]$ and

TABLE 4.5
COMPARISON OF HIGH WORK BLOOD VALUES UNDER
THREE LEVELS OF FI_{O_2}
(T x T x S) (n=4) ²

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$[H^+]$	.06	$p>.1$	$.05>p>.01$	$p>.1$
$[HCO_3^-]$	.06	$p>.1$	$.1>p>.05$	$p>.1$
HLa	.02	$.05>p>.01$	$.01>p$	$p>.1$
PCO_2	.001	$.05>p>.01$	$.01>p$	$.05>p>.01$

$[HCO_3^-]$ each revealed hypoxic values lower than hyperoxic. Lactate levels were higher in hypoxia than in normoxia or hyperoxia, but normoxia was NSD from hyperoxia. PCO_2 showed a difference between each of the three pairs, with hyperoxic levels higher than normoxic, which were in turn higher than hypoxic.

With only 4 subjects included in the analysis, the comparison for time showed that $[H^+]$ did not change significantly from minute 3 to 7 of this period, ($p=.13$) while lactate increased ($p=.03$) and PCO_2 ($p=.008$) and $[HCO_3^-]$ ($p=.01$) decreased. Despite the fact that $[H^+]$ showed no significant change between samples at minutes 3 and 7 (perhaps due to the

small $n=4$), there was a significant interaction ($p=.02$) due primarily to the lower initial concentration in hypoxia increasing faster than under either of the other conditions.

An analysis of the rate of change in $\dot{V}I$ at the onset of high work (interaction $p<<.001$) indicated that hypoxic $\dot{V}I$ increased faster than normoxic ($p=.007$) or hyperoxic $\dot{V}I$ ($p<<.001$). Normoxic $\dot{V}I$, while increasing at an intermediate rate, was NSD from hyperoxic $\dot{V}I$ ($p=.16$).

The values for $\dot{V}I$, $\dot{V}O_2$, $\dot{V}CO_2$, R , and HR were averaged for minutes 3-6 of this period. These values reflect averages for the period after the initial large increase due to the jump in work load. Repeated measures analysis showed all but HR to be affected by O_2 level (Table 4.6). Tukey HSD analysis indicated that for $\dot{V}I$ all pairs were different, with hypoxia

TABLE 4.6
COMPARISON OF VENTILATORY AND HR DATA AT HIGH WORK
UNDER THREE LEVELS OF FIO_2
(T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$\dot{V}I$	$<<.001$	.01>p	.01>p	.01>p
R	$<.001$	$p>.1$	.01>p	.01>p
$\dot{V}O_2$	.03	$p>.1$	.01>p	$p>.1$
$\dot{V}CO_2$	.03	$p>.1$	.01>p	$p>.1$
HR	.72			

values highest. $\dot{V}O_2$ was different only between hypoxia (lower) and hyperoxia. $\dot{V}CO_2$, with the same significance level, had hypoxic values greater than hyperoxic and again neither of the other differences were significant. R data analysis revealed that during hyperoxia R was lower than either normoxia or hypoxia but that normoxic and hypoxic values were NSD.

Exhaustion

Values for PCO_2 , $[HCO_3^-]$, HLa, and $[H^+]$ at exhaustion were calculated where necessary from the equation of the straight line connecting the last value obtained during exercise and the first value during recovery (minute 3 of recovery). Probabilities for the effects on blood data due to O_2 are indicated in Table 4.7. $[H^+]$ was NSD ($p=.8$). HLa analysis

TABLE 4.7
COMPARISON OF BLOOD VALUES AT EXHAUSTION
UNDER THREE LEVELS OF FIO_2
(T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$[H^+]$	.80			
HLa	.005	.05>p>.01	.01>p	p>.1
PCO_2	.007	p>.1	.01>p	.1>p>.05
$[HCO_3^-]$	.01	p>.1	.05>p>.01	p>.1

showed that hypoxic values were higher than normoxic and hyperoxic values but that hyperoxic and normoxic values revealed NSD. PCO_2 data analysis indicated that hyperoxic PCO_2 was greater than hypoxic but only slightly larger than normoxic while normoxic and hypoxic values were NSD. $[\text{HCO}_3^-]$ showed a somewhat similar pattern, with hypoxia producing lower results than hyperoxia but the intermediate normoxic value NSD from either extreme.

For HR and ventilatory data (Table 4.8), the values for the last 3 minutes prior to exhaustion were averaged for Treatments x Subjects analysis. All except HR revealed some significance although $\dot{\text{VCO}}_2$ was marginal. For $\dot{\text{V}}\text{I}$, all pairs were different, with hypoxic ventilation highest and a progressive decrease with increased FIO_2 . $\dot{\text{V}}\text{O}_2$ analysis showed that while the value for hypoxia was lower than that for hyperoxia, normoxic and hypoxic values were NSD and normoxic and hyperoxic values only marginally different. Analysis of R data indicated hypoxic values

TABLE 4.8
COMPARISON OF VENTILATORY AND HR DATA AT EXHAUSTION
UNDER THREE LEVELS OF FIO_2 .
(T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$\dot{\text{V}}\text{I}$	$<<.001$	$.01>p$	$.01>p$	$.01>p$
$\dot{\text{V}}\text{O}_2$	.009	$p>.1$	$.01>p$	$.1> p>.05$
R	.004	$.05>p>.01$	$.01>p$	$p>.1$
$\dot{\text{V}}\text{CO}_2$	.09			
HR	.52			

greater than for either normoxic or hyperoxic levels of FI_{O_2} , while these levels did not produce differences from each other.

Performance time (Figure 4.1, page 63) was taken as the length of time from beginning of low work until voluntary cessation of high work. The repeated measures probability was .003. Tukey analysis revealed that 60% O_2 yielded better performances than 17% O_2 ($p < .01$) or 21% O_2 ($p < .05$) while 17% and 21% O_2 performances were NSD ($.15 > p > .1$).

Recovery

Blood samples were taken at minutes 3, 7, 11, and 15 of recovery. TxTxS analysis indicated significances below the .05 level for all blood parameters due to the effect of O_2 (Table 4.9). However, $[H^+]$ analysis by Tukey HSD revealed no differences between pairs of O_2 levels. PCO_2 and $[HCO_3^-]$ showed differences below the .1 level only in the hypoxic-hyperoxic comparison, with the lower FI_{O_2} producing the lower PCO_2 and $[HCO_3^-]$ values. Lactate analysis revealed hypoxic values higher than hyperoxic but only marginally higher than normoxic values, while values at these last two levels yielded NSD.

TABLE 4.9
COMPARISON OF BLOOD VALUES DURING RECOVERY
UNDER THREE LEVELS OF FI_{O_2} .
(T x T x S)

Variable	Effects of O_2	Tukey HSD		
		low vs air	low vs hi	air vs hi
$[H^+]$	.03	$p > .1$	$p > .1$	$p > .1$
PCO_2	<.001	$p > .1$	.05 > $p > .01$	$p > .1$
$[HCO_3^-]$	<.001	$p > .1$	.01 > p	$p > .1$
HLA	<<.001	.1 > $p > .05$	.05 > $p > .01$	$p > .1$

Analysis for the time factor indicated that PCO_2 ($p=.09$) and $[HCO_3^-]$ ($p<<.001$) were now increasing, with HLa ($p<<.001$) and $[H^+]$ ($p<.01$) decreasing toward normal values. The rate of change of PCO_2 and $[HCO_3^-]$ during recovery was not affected by O_2 level ($p=.61$ & $.35$). However, for $[H^+]$ and HLa, the hypoxic FI_{O_2} --for which the highest values were obtained at minute 3 of recovery--yielded the most rapid decreases (interaction $p([H^+])=.03$, $p(HLa)=.07$).

Analysis of data for the first 2 minutes of recovery shows that the rate of change in $\dot{V}I$ is affected by FI_{O_2} , ($p=.006$) with hypoxic ventilation--which was the highest at exhaustion--dropping faster than normoxic or hyperoxic ventilation ($p=.02, .02$). The normoxic rate was intermediate and revealed NSD from hyperoxia ($p=.15$). The trend was also for the higher $\dot{V}O_2$ values produced during hyperoxia to drop faster ($p=.08$).

Three 4-minute averages were taken for the HR and ventilatory variables during the period from minutes 3-15 of recovery, and these averages were analyzed (TxTxS). The effect of FI_{O_2} on the values during this period (Table 4.10) showed NSD for $\dot{V}O_2$, R, or HR. $\dot{V}I$ and $\dot{V}CO_2$ changes, while showing some overall significance as a result of O_2 variation, produced no differences greater than .1 when submitted to Tukey HSD analysis. The effect of O_2 on the rate of change provided NSD (all $p>.3$) for any variable except $\dot{V}I$ ($p=.005$), where the previously higher values in hypoxia were still decreasing fastest toward normal.

TABLE 4.10
COMPARISON OF VENTILATORY AND HR VALUES DURING RECOVERY
UNDER THREE LEVELS OF FIO_2
(T x T x S)

Variable	Effects of O_2	Tukey HSD		
		Low vs air	Low vs hi	air vs hi
$\dot{V}\text{I}$	.02	$p > .1$	$p > .1$	$p > .1$
$\dot{V}\text{CO}_2$	.08	$p > .1$	$p > .1$	$p > .1$
$\dot{V}\text{O}_2$	.36			
R	.28			
HR	.39			

CHAPTER V

DISCUSSION

With only one major and several minor exceptions, the results obtained in this study agree with the prevalent trends exhibited in the literature covering hypo- and hyperoxygenation. The one major disagreement lies in the comparison of pulmonary $\dot{V}O_2$ at exhaustion. That difference will be thoroughly discussed here. Other differences are minor, and in all cases the trends found in this study correspond to those found in the literature. Often, however, the literature is evenly divided on opposing views or simply lacking in data. In those cases the results of this study were used to exhibit the trends.

I. GENERAL EFFECTS OF OXYGENATION

There were several reasons for choosing the gas fractions used in this study. The 60% O_2 level was chosen as being high enough to provide a large elevation in PO_2 without being so high as to make accurate measurements of $\dot{V}O_2$ difficult. The 17% O_2 level was chosen as being low enough to provide a definite depression in arterial PO_2 (PaO_2) without being below the "critical level," that is, without causing a true tissue hypoxia (e.g. Stainsby, 1973).

In looking at the graphs of Chapter IV collectively it is fairly obvious that for most parameters hypoxia has the greater effect. This is

true despite the large increase in PO_2 with hyperoxia compared to the small decrease with hypoxia. In most cases the hyperoxic and normoxic parameters are closely grouped, while the hypoxic data is consistently different from the other two. What this trend indicates is that small decreases in PO_2 are related to relatively large changes in the parameters while larger increases in PO_2 cause only slight changes in the opposite direction. These results hold true not only for all the acid-base data but also to some extent for the ventilatory data. These results may in fact be fundamentally related to the effect of PO_2 on ventilation. The one important exception to this, however, is the performance trend. Performance in hypoxia is shown to not be significantly different from normoxic performance while hyperoxia yields significantly better performances.

The reason for this difference in the degree of change shown with large increases as opposed to small decreases in PO_2 is not readily apparent. There may indeed be several reasons. One factor which must be considered but which does not answer the question is the relationship of PO_2 to the oxy-hemoglobin dissociation curve. Decreasing FI_{O_2} 20% from .21 to .17 lowers the quantity of O_2 (CaO_2) in blood about 2 vol%, while increasing FI_{O_2} 285% from .21 to .6 increases the CaO_2 at most only about the same amount. Another possible reason for the difference in the degree of change may lie in the observations of Adler et al. (1965) and Cain (1970). Each of these investigators observed that while a large acidosis was required to achieve physiological variations due to the buffering ability of the body, a much smaller alkalosis produced effects. Adler pointed

out that since most stresses normally placed on the body are of an acid nature the body has developed the ability to deal with them while alkalosis is a rather uncommon phenomenon. Another possibility along the same lines is that historically hypoxia is a condition which the body has experienced (altitude) and to which it has learned to adapt. Hyperoxia on the other hand is a condition not naturally encountered and therefore a condition which the body does not deal with well. At present, however, these speculations cannot be verified.

II. OXYGEN UPTAKE AND CARBON DIOXIDE OUTPUT

A major finding of the present study is that at exhaustion pulmonary $\dot{V}O_2$ in hyperoxic or hypoxic conditions is not significantly different from the normoxic control. As discussed in detail earlier, the literature almost unanimously agrees that $\dot{V}O_2$ increases with increased FI_{O_2} . In this study there is a non-significant 4.8% increase with 60% O_2 and a 3.7% decrease with 17% O_2 as compared with 21% O_2 . These are much smaller changes than have previously been reported. $\dot{V}CO_2$ also shows no significant change but displays a tendency to be inversely related to FI_{O_2} . In light of the great care taken, including gas analysis by two separate methods for determination of $\dot{V}O_2$ values, I believe that these results are accurate. They also fit more closely with what would be expected from $\dot{V}CO_2$ and blood-flow results obtained elsewhere.

In the study of Welch et al. (1977) $\dot{V}CO_2$ was measured both at the working limb and at the pulmonary level. Since they used 100% O_2 and the open circuit method, they could not measure $\dot{V}O_2$ at the pulmonary level.

They found that in the active limb $\dot{V}CO_2$ did not change from normoxic to hyperoxic conditions, although there was a slight decrease at the lung. The $\dot{V}O_2$ at the muscle also did not change. Stanek et al. (1979), using ponies as the experimental animal, measured $\dot{V}O_2$ by the cardiovascular Fick method and also at the lung. They found that while there was an increase in pulmonary $\dot{V}O_2$ with 60% O_2 , the direct Fick $\dot{V}O_2$ did not change. Those findings combined with the present study provide grounds for concluding that reports of increased $\dot{V}O_2$ with $FI O_2$ were caused by technical difficulties.

$\dot{V}O_2$ and $\dot{V}CO_2$ measurements made at the muscle are direct applications of the Fick principle and when performed in a competent manner are not subject to large systematic errors ($\dot{V}O_2 = Q \times (CaO_2 - CvO_2)$). Pulmonary measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ from gas exchange data are another matter. Recalling the necessary equations:

$$\dot{V}O_2 = \dot{V}I \times (FI O_2 - (FE O_2 \times FIN_2 / FEN_2))$$

and

$$\dot{V}CO_2 = \dot{V}I \times ((FE CO_2 \times FIN_2 / FEN_2) - FI CO_2),$$

we see that there are three critical quantities in each: ventilation, the expired O_2 or CO_2 fraction, and the ratio of inspired to expired nitrogen. These are critical factors because any change or error in them affects the end result in a multiplicative manner.

Measurement of $\dot{V}CO_2$ is a relatively simple matter since during the hyperoxic or hypoxic conditions considered here the pulmonary CO_2 values

do not change to any great extent among the different conditions. Any errors in those values, then, would be of the same magnitude at any FI_{O_2} . Therefore the FE_{CO_2} can be removed from the list of critical factors for that equation. That is not true for $\dot{V}O_2$. Variations in FI_{O_2} change FE_{O_2} proportionally and as the difference in FI_{O_2} between normoxic and experimental conditions increases, the likelihood of error increases. It is the accurate measurement of the gas fractions which is most critical and which most often fails. Those errors in measurement of gas fraction should be the same at rest and low work as at exhaustion. However, a look at the review table for the effects of O_2 on $\dot{V}O_2$ (Table 2.4, page 21) shows that at rest and at very light work there is no change in $\dot{V}O_2$ with FI_{O_2} but that as work increases so do the differences. These results also hold true for $\dot{V}CO_2$ except that a higher work rate is required, that is, the differences begin to appear only at very high and maximal work.

It should in fact be the case that errors in measurement of the gas fractions are the same at all levels of work rate. The reason that significant differences in $\dot{V}O_2$ and, to some degree, $\dot{V}CO_2$ occur at higher work rates lies with the other critical factors in the equations for those values. Basically, there are in the equations two error multiplier factors for $\dot{V}CO_2$ and three for $\dot{V}O_2$. In each case one of the factors is $\dot{V}$. As $\dot{V}$ increases, errors are compounded. As work increases so does $\dot{V}$ and therefore so do the magnifications of any errors in gas fractions. Although at low work the errors do not produce significant changes, at high work these same errors are compounded. By inference, the reason previous studies have reported increased $\dot{V}O_{2\text{ max}}$ with increased FI_{O_2} is

that the high maximal ventilations obtained in exercise compounded the errors made in the collection and analysis of expired gas. The present study was able to minimize those errors and did not find an increased $\dot{V}O_2$ at exhaustion.

III. OXYGEN AND HYDROGEN ION: A COMPARISON OF EFFECTS IN THE BLOOD

During exercise the blood becomes acidic. While in all cases the blood is acidic relative to the resting condition, increased levels of inspired oxygen bring about a slight relative acidemia, and hypoxic conditions show a relative alkalemia as compared to normoxic conditions. This being the case, it is possible to make a comparison of the effects of hypoxia with induced alkalosis and of hyperoxia with induced acidosis. By combining the information from the literature review with the results of this study, I was able in Figure 5.1 to make such a comparison.

Figure 5.1 is rather complicated and requires some explanation. In the figure, a comparison is made of the effects of variations in $FI O_2$ with the effects of induced variations in arterial $[H^+]$. This comparison is made for each of three work conditions: rest, submaximal work, and maximal work. Variations in $FI O_2(O_2)$ are hypoxic(hypo) to hyperoxic(hyper). Variations in $[H^+]$ are from a relatively basic state (base) to a relatively acidic state (acid). The arrows point in the direction of an increase or decrease of a parameter under mentioned conditions while "NC" indicates no change in the parameter. In the comparison of the effects of O_2 and H^+ , an "O" indicates agreement, an "X" shows disagreement, and a "?" means that while trends may be indicated there is very little data available.

Figure 5.1. Comparison of the effects of oxygen and hydrogen ion on selected variables during rest, submaximal and maximal work rates.

Arrows point in the direction of increase or decrease of a variable under mentioned conditions. NC=no change. O=agreement, X=disagreement between the effects due to oxygen and to hydrogen ion. ?=data incomplete for the effects of O_2 or $[H^+]$ as indicated.

	REST				SUBMAXIMAL				MAXIMAL			
	O ₂		H ⁺		O ₂		H ⁺		O ₂		H ⁺	
	HYPO	HYPER	BASE	ACID	HYPO	HYPER	BASE	ACID	HYPO	HYPER	BASE	ACID
[H ⁺]	↗		○	↘	↗	↘	○	↘	↗	○	↘	↘
$\dot{V}O_2$	↘	NC	P	NC	↘	↘	○	NC	↘	×	NC	NC
$\dot{V}CO_2$	NC	NC	P	P	↘	↘	○	NC	↘	P	↘	↘
R	NC	NC	P	P	↘	↘	P	NC	↘	P	↘	↘
$\dot{V}$	↘	↘	○	↘	↘	↘	×	↘	↘	×	NC	↘
HL _a	↘	↘	○	↘	↘	↘	○	↘	↘	×	NC	↘
PCO ₂	NC	NC	P	P	↘	↘	×	↘	↘	×	↘	↘
[HCO ₃ ⁻]	NC	NC	P	↘	↘	↘	○	↘	↘	P	↘	↘
HR	NC	NC	○	NC	↘	↘	×	NC	NC	○	NC	NC

Figure 5.1

For example, in Figure 5.1, under resting conditions, HLa increases with hypoxia and decreases with hyperoxia. It also increases under basic conditions and decreases under acidic conditions. Agreement is indicated between the effects of increased (decreased) FI_{O_2} and increased (decreased) $[H^+]$.

As can be seen from Figure 5.1, while in rest there is a general lack of data, there are no discrepancies; hypoxia produces results similar to induced alkalosis and hyperoxia to induced acidosis. In maximal exercise there are three major differences, two of which appear at sub-maximal work rates while the third is only partially apparent there.

The first difference is that acid-base changes produce no changes in $\dot{V}O_2$ while most reports of changes from normoxia to hyperoxia show increases in $\dot{V}O_2$. As discussed in the previous section, the explanation for this may be that hyperoxia does not produce significantly increased $\dot{V}O_2$. Again, if the oxygen studies do fall in line with the acid-base data, the results of most in situ preparation studies, of the blood-flow studies, and of all $\dot{V}CO_2$ data then become clear.

During maximal work, the other two discrepancies, $\dot{V}$ and PCO_2 , are related and are, in this case, due to the differences in PO_2 . Ventilation has been known for many years to be affected by chemoreceptors sensitive to PO_2 . In the present study, during exercise, increased PO_2 yields a decreased $\dot{V}$ relative to normoxia. As a result of the decreased $\dot{V}$ in hyperoxia, PCO_2 is relatively elevated and as a further result the blood becomes more acidic than in normoxia. This would tend to increase $\dot{V}$.

However, any attempt by the relative acidosis resulting from hyperoxia to increase ventilation is overcome by the effect of the increased PO_2 on the chemoreceptors and $\dot{V}$ is depressed. On the other hand, in the infusion studies when there are only changes in acid-base status to be dealt with, acidosis does produce a relative increase in $\dot{V}$ and consequently a relative depression of PCO_2 in an attempt to correct the acidic imbalance. Thus in the control of ventilation, the effects of oxygen changes and induced acid-base changes do not parallel each other.

IV. VENTILATION ($\dot{V}$)

While the design of this investigation did not specifically include the study of the control of ventilation, the role of $\dot{V}$ in the acid-base balance of the body requires that we look closely at its reaction to changes in $FI O_2$. During rest, hyperoxia and hypoxia stimulate and depress $\dot{V}$ respectively--relative to each other. The reasons are not clear. Such results are probably not related to arterial acid-base changes produced metabolically. In the present study, the arterial acid-base changes during rest are not significant.

On the other hand, what does change is the PO_2 . The high PO_2 in hyperoxia most likely interferes with the CO_2 transport from the tissue, thereby causing a slight acidosis which leads to the elevated $\dot{V}$. It may also be that during rest PO_2 has a completely different effect on chemoreceptors than that found with exercise. These questions also remain unanswered.

Once exercise starts, the relationship is reversed; hypoxia produces the highest ventilations. Furthermore, with any change in work rate such as onset of low or high work or cessation of work, ventilation in hypoxic conditions always reacts fastest. Its rate of increase or decrease is more rapid than in the normoxic condition, and hyperoxic $\dot{V}$ changes most slowly. It seems obvious, therefore, that PO_2 has some effect.

As can be seen from Figure 4.7 (page 73) the changes with onset of exercise and, especially, with recovery are almost instantaneous. Due to the speed of the ventilatory reaction to changes in work output, the controlling mechanism cannot require a chain of events such as production of H^+ (Kozłowski et al., 1971). It must be a mechanism which reacts quickly: perhaps work rate or stretch "receptors" giving neural inputs from the working muscle.

Most likely PO_2 and some mechanism similar to a "work receptor" do, therefore, help in the control of $\dot{V}$. Asmussen & Nielsen (1958) concluded that there was no reason for assuming an interaction between PO_2 and work rate. The present study, however, agrees with the work of Kozłowski et al. (1971), who proposed that such a connection should exist. Even Asmussen & Nielsen showed that the hyperventilation of heavy work could be abolished by increasing PO_2 but drew their conclusion because the same thing did not occur during light work rates. As the present study shows, however, there is an effect at low rates even though it is smaller. It would seem very likely then that an interaction between chemoreceptors sensitive to PO_2 and "work receptors" may occur. That is, there would seem to be

a progressive resetting of one receptor as input to the other is varied. As work rate increases, for example, a given change in PO_2 has a greater effect on $\dot{V}$.

As mentioned in the previous section, in addition to the direct effects of PO_2 , there is another aspect to the question of ventilatory control during exercise at varied FI_{O_2} . As shown in the literature review, both oxygen and acid-base variations affect $\dot{V}$. With exercise, $\dot{V}$ is affected by increased acidity. With the inclusion of FI_{O_2} variations, $\dot{V}$ is not only affected by PO_2 changes at the chemoreceptors but, as will be developed later, by the effects of varied oxygen levels on the acidity of the blood and tissues. There are two ways then that $\dot{V}$ is controlled with varied FI_{O_2} . One is the direct effect of PO_2 ; the other is the indirect effect of acidic changes produced by changes in FI_{O_2} .

V. LACTIC ACID

In order to understand the mechanisms for control of $[H^+]$ it is necessary to first look at HLa. The left side of the graph of HLa (Figure 4.8, page 74) reveals the similarity in the curves for different O_2 fractions. This similarity is even more striking when the curve for hypoxia is "normalized" to adjust for the unexplained high pre-test value. This similarity in the curves indicates that PO_2 has no effect on the fairly constant rate of release of HLa. Since the peak values are widely different, however, there is obviously an effect on the total amount produced. Although Hirche et al. (1975) and others have noted that muscle produces lactate only during about the first 2-4 minutes of exercise,

blood levels in the present study continue to rise at a steady rate throughout exercise. Tests of longer duration, however, have found that after initial rises blood levels decrease during exercise. This decrease indicates that after the initial production of HLa there is very little more, if any, made (Stainsby & Welch, 1966; Hirche et al., 1971). The suggestion that can be drawn from this observation is that the rate of release is rather low relative to the amount produced. That is, there is a limit to the rate at which HLa can be released. As a result, a long time is required for the complete equilibration. Once the muscle levels have decreased below the point where the rate of release is no longer limiting, then blood levels also decrease.

We have seen that the total amount of HLa produced varies inversely with the FIO_2 (Figure 4.8, page 74). For example, less lactate is produced in hyperoxia. Two factors which might produce these HLa changes in hyperoxia can be eliminated. First, the blood flow studies show that there is no more oxygen delivery to the tissue with hyperoxia than during normoxia and presumably, though it is unproven, no less with the degree of hypoxia used in this study. If the O_2 delivery does not vary, then during hyperoxia the slowing of glycolysis to produce less lactate cannot be the result of an alleviation of anaerobic conditions. Second, as discussed in Chapter II, increased acidity depresses HLa. It will later be argued that muscle tissue is certainly no more acidic under hyperoxic conditions than during normoxia. It cannot therefore be said that the decreased HLa in hyperoxia is caused by changes in $[\text{H}^+]$. Changes in HLa

with hyperoxia are due then neither to relief of anaerobiosis nor to changes in $[H^+]$. As several authors have noted, however, there is an effect of the ADP+Pi/ATP ratio on glycolysis (Gevers & Dowdle, 1963; Ui, 1966; Lehninger, 1975). In addition, this ratio has an effect on oxidative phosphorylation.

For example, at rest oxidative phosphorylation is limited by the availability of ADP (Chance, 1959). This is because during rest there is not a great demand for energy and ATP levels are high. At the onset of work, glycolysis may compete with oxidative phosphorylation for available ADP and Pi. This inhibition of respiration by glycolysis due to the removal of ADP is known as the Crabtree effect (Krebs, 1971). Even under aerobic conditions glycolysis, since it occurs in the cytoplasm, should initially have an advantage over oxidative phosphorylation which is one membrane further removed within the mitochondria. Therefore, lactate would be produced until the electron transport chain obtains ADP and begins to compete effectively with glycolysis (Pasteur effect).

As shown in this study, less HLa appears in the blood during hyperoxia. In order for glycolysis to produce less HLa during hyperoxia, oxidative phosphorylation must be given a competitive edge. That is, some mechanism must exist whereby oxidative phosphorylation is provided with more ADP when $FI O_2$ is increased. Since increasing $FI O_2$ does not increase O_2 delivery, the effect is most likely mediated through an increased PO_2 . Such a mechanism would also cause a decreased PO_2 to enhance the Crabtree effect with consequent increases in HLa. If PO_2 has the indicated effects, then oxidative phosphorylation would reach the

required level of ATP production more quickly during hyperoxia. At the same time at the onset of work the glycolytic system would produce less lactic acid in hyperoxia and more in hypoxia. These effects of PO_2 on glycolysis and oxidative phosphorylation would explain the difference in total amount of HLa produced under the different conditions of FI_{O_2} .

Under the hypothesis presented here, whatever the mechanism, it would have to act within a minute or so in order to have an effect before normal amounts of lactate are produced. It would also have to act either to impede glycolysis, thus providing more ADP to oxidative phosphorylation, or to decrease ADP transit time from the site of ATP usage to within the mitochondria.

This theory would at first glance seem to disagree with that of Hirche et al. (1975). However, those authors induced acid-base changes by infusion in order to change HLa. They argued that with the onset of work the same amount of HLa was produced under all conditions and that the blood levels were due to differing dispersion rates from muscle. The changes in HLa in the present study were produced by varying FI_{O_2} . I argue that with the onset of work, different amounts of HLa are produced under the different conditions and that the blood levels are due to reasonably constant dispersion rates from muscle. The argument proposed here that different amounts of HLa are produced in the muscle is predicated on effects due to PO_2 . Hirche et al. did not vary PO_2 and would, therefore, not have obtained different amounts of HLa. It may also be that different dispersion rates are obtained with the degree of change in $[H^+]$ that they used. The acid-base changes in that study, while within physiological ranges, were quite outside those obtained here.

VI. BLOOD AND MUSCLE $[H^+]$

The second major result of this study concerns the trends in arterial $[H^+]$. Since I have demonstrated that oxygen is very likely not limiting for work of the intensity and duration used in this study, the finding that $[H^+]$ at exhaustion is the same under all conditions is especially noteworthy. For these reasons, I have turned to $[H^+]$ as a possible limiting factor.

My results can be interpreted to support the theory that $[H^+]$ limits performance. If $[H^+]$ does limit performance, and since $[H^+]$ increases with exercise, the cessation of work would then be the result of an increased concentration of H^+ , that is, acidosis. On the other hand, the results of the comparison made in section 5.4, showing a strong similarity in the effects of hyperoxia and acidosis, seem to contradict this fact. In that comparison, hyperoxia is seen to affect almost all parameters in a manner identical to induced acidosis. Nevertheless, hyperoxia yields the longest performance times among the various $FI O_2$ levels while acidosis is associated with shortened performance times. The inconsistency here of course is that these are blood conditions and nothing has yet been said about the degree of acidosis in the muscle. That is, while hyperoxia and induced acidosis have similar effects in arterial blood, they may differ with respect to effects on intracellular conditions. Despite some conclusions to the contrary (Patterson & Sullivan, 1978), there is evidence that it may be the muscle or intracellular conditions which are important (Sahlin, 1978; Kaijser, 1970).

The differences between hyperoxia and induced acidosis with respect to intracellular effects may depend upon the fact that there is a great deal of difference between generating H^+ from external sources and from within the muscle. Inducing acidosis or alkalosis by infusion or ingestion does not always affect intracellular variables in ways that might be expected (Adler et al., 1965; Mithoeffer & Karetzky, 1968; Waddell & Bates, 1969). The use of hyperoxia, on the other hand, may not induce changes in acid-base parameters in the same way that infusion or ingestion do. It rather should have an effect upon some facet of the internal production or distribution of those variables. If $[H^+]$ is limiting some aspect of muscle performance, there are two ways oxygen could have an effect on it to vary that limitation: it could cause either a decreased H^+ production in or an increased H^+ removal from the muscle.

Figure 5.2 is a diagram of the pathways whereby changes in $FI O_2$ might affect performance. The symbols in parenthesis (+ or -) indicate the relationship between the quantities above and below. A "+" indicates that an increase (decrease) in the quantity below brings about an increase (decrease) in the quantity above. A "-" indicates that an increase (decrease) in the quantity below brings about a decrease (increase) in the quantity above. Quantities enclosed in heavy boxes were measured in this study, others were not. Dotted arrows indicate unknown mechanisms. Solid arrows indicate well known effects and the dashed arrow indicates a pathway of lesser importance than the solid arrow in the opposite direction.

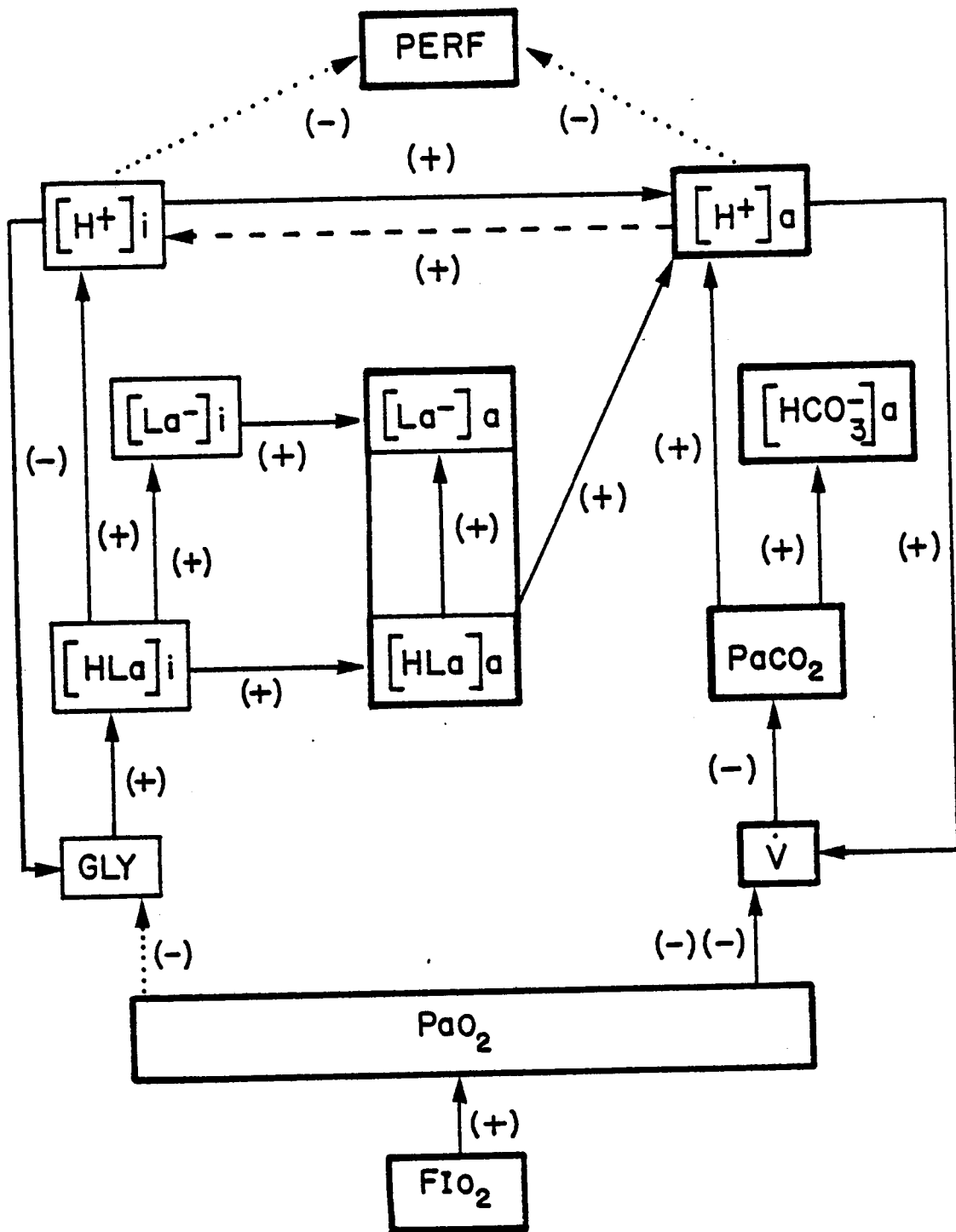


Figure 5.2. Pathways for the effects of oxygen on $[H^+]_i$.

As seen in this study, arterial $[H^+]$ at rest is not different under varied O_2 levels. During work, $\dot{V}O_2$ and $\dot{V}CO_2$ increase but are not different under the various conditions indicating metabolic rate to be about the same. However, arterial $[H^+]$ is lower in hypoxia. As seen from PCO_2 and HCO_3^- levels (Figures 4.9 and 4.10, pages 76 and 77) there is a great variation in the buffering that occurs at the different O_2 levels. The increased $\dot{V}$ of hypoxia has lowered PCO_2 significantly from control values while the decrease in hyperoxic $\dot{V}$ has caused a relative increase in PCO_2 . Due to the hyperventilation of hypoxia there is a consequent lowering of $[H^+]$. The arterial levels during low work are an inverse reflection of the ventilation.

Arterial $[H^+]$ is not, however, completely a reflection of ventilation. I have argued that in hypoxia there is a larger formation of HLa. Under all conditions of $FI O_2$ used here, the release rate of HLa is the same. Due to the limited rate of release, the larger amount of HLa produced in hypoxia stays in the muscle longer. Most of this HLa dissociates to H^+ and lactate and thereby increases the muscle acidity. As the muscle acidity increases, the rate of diffusion of H^+ into blood increases and at some point surpasses the ventilatory capability to counter it. At this point the rate of change in blood levels increases to such an extent that it surpasses those rates in the normoxic and hyperoxic conditions. Thus the initial trend for lower $[H^+]$ in hypoxia is the result of a more severe hyperventilation while the later increases are caused by the greater release of H^+ from the larger muscle store of HLa.

The fact that blood $[H^+]$ at exhaustion in this study was the same under all conditions may simply be a coincidence. It may be that the oxygen fractions utilized affected the formation of HLa and, therefore, $[H^+]$ to just the extent necessary for work of this duration. On the other hand, under this hypothesis, the trends will always be in the direction indicated. Hyperoxia would produce a faster increase in $[H^+]$ at first due to a relative hypoventilation, thus allowing less respiratory compensation. The hyperoxic $[H^+]$ would then approach a maximum slowly because of a smaller $[H^+]$ gradient from muscle. Hypoxic $[H^+]$ would have a slow initial build-up due to a relative hyperventilation, and, as a result, subsequent faster release from the muscle due to a higher gradient. It may, therefore, also not be a coincidence that the H^+ levels are the same at exhaustion.

Muscle $[H^+]$ is of course always much higher than that in blood (e.g. Sahlin, 1978), but blood levels at exhaustion may correlate well with muscle levels. That is, $[H^+]$ may be the same under the three conditions in muscle as well as in the blood. If so, then muscle $[H^+]$ would be a strong candidate for one factor limiting human performance during exercise of the intensity and duration used in this study.

VII. MECHANISMS FOR $[H^+]$ LIMITATION OF PERFORMANCE

There are several mechanisms which provide possible avenues whereby elevated $[H^+]$ might limit performance. The chemiosmotic-coupling theory of oxidative phosphorylation has as one tenet the necessity for a $[H^+]$ gradient across the mitochondrial membrane (Lehninger, 1975). It may be

that once a critical level of H^+ is reached, external to the mitochondria, the impermeability of the membrane to H^+ under normal conditions breaks down. Should this condition occur, the internal alkalotic "sink" would be destroyed, thereby stopping or altering the process of ATP generation. Progressive development of fatigue might occur either as more and more mitochondria are inactivated or as the alkalotic "sinks" are gradually destroyed.

Fuchs (1970) has shown that if $[H^+]$ is increased, the troponin-C binding site in the muscle is less able to bind calcium. Without calcium, actin and myosin cannot interact and the muscle does not contract. This decreasing ability to bind calcium could also proceed in a graded manner. That is, as $[H^+]$ increases, more and more fibers will be affected until performance is terminated.

Another similar possibility is that increased levels of H^+ cause the amount of calcium released from the sarcoplasmic reticulum to be depressed. Such a depression prevents the inhibition of troponin-C and a consequent loss of contractile process (Nakamaru & Schwartz, 1970).

VIII. SUMMARY

I have in this discussion attempted to point out several facts and open several possibilities in the control of mechanisms limiting human performance. I have argued that O_2 does not limit performance since, as shown in this study, $\dot{V}O_2$ at exhaustion in hyperoxia does not increase, and I have at length discussed the reasons why other reports show

increased $\dot{V}O_2$. Finally, I have advanced a theory for performance limitations based on $[H^+]$ as it is controlled by the action of PO_2 on lactate production and ventilation and have suggested several possible mechanisms by which $[H^+]$ could affect performance.

BIBLIOGRAPHY

BIBLIOGRAPHY

- Adler, S., A. Roy & A. S. Relman. Intracellular acid-base regulation. J. Clin. Invest. 44(1):8-30, 1965.
- Albers, C. Carbon dioxide and the utilization of oxygen. In K. E. Schaeffer & G. Nahas (Eds.), CO₂ and Metabolic Regulations: Proceedings, International Congress of Physiological Sciences Satellite Symposium 1971. Berlin: Springer 1974.
- Asmussen, E. & M. Nielsen. The cardiac output in rest and work at low and high oxygen pressures. Acta Physiol. Scand. 35:73-83, 1955.
- Asmussen, E. & M. Nielsen. Pulmonary ventilation and the effect of oxygen breathing in heavy exercise. Acta Physiol. Scand. 43:365-378, 1958.
- Asmussen, E., W. V. Dobeln, & M. Nielsen. Blood lactate and oxygen debt after exhaustive work at different oxygen tensions. Acta Physiol. Scand. 15:57-62, 1948.
- Bean, J. W. Effects of oxygen at increased pressure. Physiol. Rev. 25:1-147, 1945.
- Banister, E. W., J. E. Taunton, T. Patrick, P. Oforsagd, & W. R. Duncan. Effect of oxygen at high pressure at rest and during severe exercise. Respir. Physiol. 10:74-84, 1970.
- Bannister, R. G., & D. J. C. Cunningham. The effects on the respiration and performance during exercise of adding oxygen to the inspired air. J. Physiol. (London) 125:118-137, 1954.
- Bird, A. D., & A. B. M. Telfer. The effects of oxygen at 1 and 2 atmospheres on resting forearm blood flow. Surgery, Gynecology & Obstetrics 123: 260-268, 1966.
- Boismare, F., M. LePoncin, & L. Hapille. Modifications hemodynamiques provoques par l'hypoxie chez le chen. Comptes Rendues des Seances de la Societe de Biologie 169(6):1458-1463, 1975.
- Bruning, J. L. & B. L. Kintz. Computational Handbook of Statistics. Glenview: Scott, Foresman, 1968.
- Byrd, R. J. & S. M. Horvath. Cardiovascular and ventilatory responses to exercise breathing 100 percent oxygen. Int. Z. Angew. Physiol. 28: 263-268, 1970.

- Cain, S. M. Increased oxygen uptake with passive hyperventilation of dogs. J. Appl. Physiol. 28:4-7, 1970.
- Canzanelli, A., M. Greenblat, G. A. Rogers, & D. Rapport. The effect of pH changes on the in-vitro O₂ consumption of tissues. Amer. J. Physiol. 127:290-295, 1939.
- Chance, B. Quantitative aspects of the control of oxygen utilization. CIBA Found. Symp. Regulation of Cell Metabolism. Boston: Little, Brown, 1959.
- Clode, M., T. J. H. Clark, & E. J. M. Campbell. The immediate CO₂ storage capacity of the body during exercise. Clin. Sci. 32:161-165, 1967.
- Cook, J. C. Work capacity in hyperbaric environments without hyperoxia. Aerospace Med. 41:1133-1135, 1970.
- Cronin, R. F. P., & D. J. MacIntosh. The effect of induced hypoxia on oxygen uptake during muscular exercise in normal subjects. Can. J. Biochem. Physiol. 40:717-726, 1962.
- Cunningham, D. A., & J. B. Critz. Effect of hypoxia and physical activity on plasma enzyme levels in man. Int. Z. Angew. Physiol. 30:302-308, 1972.
- Cunningham, D. J. C., D. G. Shae, S. Lahiri, & B. B. Lloyd. The effect of maintained ammonium chloride acidosis on the relation between pulmonary ventilation and the alveolar oxygen and carbon dioxide in man. Qtrly. J. Exptl. Physiol. & Cognate Med. Sci. 46:323-334, 1961.
- Danforth, W. H. Activation of glycolytic pathway in muscle. In B. Chance & R. W. Estabrook (Eds.), Control of Energy Metabolism. New York: Academic, 1965.
- Davenport, H. W. The ABC of Acid-Base Chemistry. (6th ed. Rev.), Chicago: Univ. Chicago, 1974.
- Dempsey, J. A., J. M. Thompson, S. C. Alexander, H. V. Forster, & L. W. Chosy. Respiratory influences on acid-base status and their effects on O₂ transport during prolonged muscular work. In H. Howald & J. R. Poortmans (Eds.), Metabolic Adaptations to Prolonged Physical Exercise. Basel: Kirkhauser, 1975.
- Dennig, H., J. H. Talbott, H. T. Edwards, & D. B. Dill. The effect of acidosis and alkalosis upon the capacity for work. J. Clin. Invest. 9:601-613, 1931.

- Doll, E., J. Keul, & C. Maiwald. Oxygen tension and acid-base equilibria in venous blood of working muscle. Amer. J. Physiol. 215:23-29, 1968.
- Dripps, R. D., & J. H. Comroe. The effect of inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation of normal individuals. Amer. J. Physiol. 149:277-291, 1947.
- Eklblom, B., R. Huot, E. M. Stein, & A. T. Thorstensson. Effect of changes in arterial oxygen content on circulation and physical performance. J. Appl. Physiol. 39(1):71-75, 1975.
- Fagraeus, L. Maximal work performance at raised air and helium-oxygen pressures. Acta Physiol. Scand. 91:545-556, 1974.
- Fagraeus, L., C. M. Hesser, & D. Linnarsson. Cardio-respiratory responses to graded exercise at increased ambient air pressure. Acta Physiol. Scand. 91:259-274, 1974.
- Fagraeus, L., J. Karlsson, D. Linnarsson, & B. Saltin. Oxygen uptake during maximal work at lowered and raised ambient air pressures. Acta Physiol. Scand. 87:411-421, 1973.
- Fletcher, E. C. Allowance for changes in oxygen saturation, pH, PCO_2 , and PO_2 in blood drawn for analysis. Brit. J. Dis. Chest. 60:182-184, 1966.
- Forster, H. V., J. A. Dempsey, J. Thompson, E. Vidruk, & G. A. DoPico. Estimation of arterial PO_2 , PCO_2 , pH, and lactate from arterialized venous blood. J. Appl. Physiol. 32(1):134-137, 1972.
- Fuchs, F. The interaction of cations with the calcium binding site of Troponin-C. Biochem. Biophys. Acta. 221:407-409, 1970.
- Gautier, H., D. Maillard, J. Vincent, & D. Zaoui. Gas exchanges during exercise in normoxia and hyperoxia. Resp. Physiol. 33:199-211, 1978.
- Gevers, W., & E. Dowdle. The effect of pH on glycolysis in vitro. Clin. Sci. 25:343-349, 1963.
- Glass, G. V. & J. C. Stanley, Statistical Methods in Education and Psychology. Englewood Cliffs: Prentice-Hall, 1970.
- Gutmann, I. & A. W. Wahlefeld. L-(+)-Lactate determination with lactate dehydrogenase and NAD. In H. U. Bergmeyer (Ed.), Methods of Enzymatic Analyses. New York: Academic, 1974.

- Haddy, F. J. & J. B. Scott. Metabolically linked vaso-active chemicals in local regulation of blood flow. Physiol. Rev. 48:688-707, 1968.
- Hagberg, J. M., F. J. Nagel, & J. L. Carlson. Transient O_2 uptake responses at the onset of exercise. J. Appl. Physiol. 44(1):90-92, 1978.
- Harken, A. H. Hydrogen ion concentration and oxygen uptake in an isolated canine hindlimb. J. Appl. Physiol. 40(1):1-5, 1976.
- Hill, A. V., C. N. H. Long, & H. Lupton. Muscular exercise, lactic acid, and the supply and utilization of oxygen. Proceedings of the Royal Society of London. 97:84-138, 1924.
- Hirche, H., U. Wacker, & H. D. Langohr. Lactic acid formation in the working gastrocnemius of the dog. Int. Z. Angew. Physiol. 30:52-64, 1971.
- Hirche, H., V. Hombach, H. D. Langohr, U. Wacker, & J. Busse. Lactic acid permeation rates in working gastrocnemii of dogs during metabolic alkalosis and acidosis. Pflug. Arch. 356:209-222, 1975.
- Horstman, D. H., M. Gleser, & J. Delehunt. Effects of altering O_2 delivery on $\dot{V}O_2$ of isolated, working muscle. Amer. J. Physiol. 230(2):327-334, 1976.
- Huckabee, W. E. Relationships of pyruvate and lactate during anaerobic metabolism. J. Clin. Invest. 37:244-271, 1958.
- Hughes, R. L., M. Clode, R. H. T. Edwards, T. J. Goodwin, & N. L. Jones. Effect of inspired O_2 on cardiopulmonary and metabolic responses to exercise in man. J. Appl. Physiol. 24:336-347, 1968.
- Jobsis, F. F. & W. N. Stainsby. Oxidation of NADH during contractions of circulated mammalian skeletal muscle. Respir. Physiol. 4:292-300, 1968.
- Jones, N. L., J. R. Sutton, J. Lin, G. Ward, W. Richardson, & C. J. Tows. Effect of acidosis on exercise performance and muscle glycolysis in man. Clin. Res. 23:636A, 1976. (Abstract).
- Jones, N. L., J. R. Sutton, R. Taylor, & C. J. Tows. Effect of acidosis and alkalosis on exercise performance and metabolism. Fed. Proc. 34:444, 1975. (Abstract)
- Jones, N. L., J. R. Sutton, R. Taylor, & C. J. Tows. Effect of pH on cardiorespiratory and metabolic responses to exercise. J. Amer. Physiol. (Resp. Env. Ex. Physiol.) 43(6):959-964, 1977.

- Kaijser, L. Limiting factors for aerobic muscle performance. Acta Physiol. Scand. Suppl. 346, 1970.
- Kaijser, L. Oxygen supply as a limiting factor in physical performance. In J. Keul (Ed.), Limiting Factors of Physical Performance. Stuttgart: Georg Thieme, 1973.
- Kaijser, L. The influence of oxygen under hyperbaric pressure on the physical working capacity. Life Sci. 9:151-158, 1970.
- Karetzky, M. S. & S. M. Cain. Effect of carbon dioxide on oxygen uptake during hyperventilation in normal man. J. Appl. Physiol. 28:8-12, 1970.
- Karetzky, M. S. & S. M. Cain. Oxygen uptake stimulation following Na-L-Lactate infusion in anesthetized dogs. Amer. J. Physiol. 216(6): 1486-1490, 1969.
- Kenmure, A. C. F., W. R. Murdoch, I. Hutton, & A. J. V. Cameron. Hemodynamic effects of oxygen at 1 and 2 ATA pressure in healthy subjects. J. Appl. Physiol. 32:223-226, 1972.
- Kindermann, W., J. Keul, & G. Huber. Physical exercise after induced alkalosis. Eur. J. Appl. Physiol. 37:197-204, 1977.
- Klassen, G. A. & D. T. Zborowska-Sluis. Carbon dioxide mediated glycolysis: A signal system. Proc. Int. Union Physiol. Sci. XXV Int. Cong. 9:37A, 1971 (Abstract)
- Klausen, K., D. B. Dill, & S. M. Horvath. Exercise at ambient and high oxygen pressure at high altitude and at sea level. J. Appl. Physiol. 29(4):456-463, 1970.
- Klausen, K., & H. G. Knuttgen. Effect of high blood lactate concentration on maximal work performance. Proc. Int. Union Physiol. Sci. XXV Int. Cong. 9:38A, 1971. (Abstract).
- Korkushko, O. V., & L. A. Ivanov. Hyperoxia effect on the indices of external respiration, cardiovascular function and gas composition of the blood. Kosmicheskaya Biologiya Aviakosmicheskaya Meditsina 10(2): 45-50, 1976. ([Abstract])
- Kozlowski, S., B. Rasmussen, & W. G. Wilkoff. The effect of high oxygen tensions on ventilation during severe exercise. Acta Physiol. Scand. 81:385-395, 1971.
- Krebs, H. A. The Pasteur effect and the relations between respiration and fermentation. Essays in Biochem. 7:1-34, 1971.

- Lehninger, A. L. Biochemistry (2nd ed.). New York: Worth, 1975.
- Lindquist, E. F. Design and Analysis of Experiments in Psychology and Education. Boston: Houghton Mifflin, 1953.
- Linnarsson, D., J. Karlsson, L. Fagraeus, B. Saltin. Muscle metabolites and oxygen deficit with exercise in hypoxia and hyperoxia. J. Appl. Physiol. 36(4):399-402, 1974.
- Luft, U. C., S. Finkelstein, & J. C. Elliott. Respiratory gas exchange, acid-base balance and electrolytes during and after maximal work breathing 15mm Hg PICO₂. In K. E. Schaeffer & G. Nahas (Eds.), CO₂ and Metabolic Regulations: Proceedings, International Congress of Physiological Sciences Satellite Symposium 1971. Berlin: Springer-Verlag, 1974.
- Margaria, R., E. Camporesi, P. Aghemo, & G. Sassi. The effect of O₂ breathing on maximal aerobic power. Pflug. Arch. 336:225-235, 1972.
- Margaria, R., P. Aghemo, & G. Sassi. Effect of alkalosis on performance and lactate formation in supramaximal exercise. Int. Z. Angew. Physiol. 29:215-223, 1971.
- Margaria, R., P. Cerretelli, S. Marchi, & L. Rossi. Maximum exercise in oxygen. Int. Z. Angew. Physiol. 18:465-467, 1961.
- McGilvery, S. Use of fuels for muscular work. In H. Howald & J. R. Poortmans (Eds.), Metabolic Adaptations to Prolonged Physical Exercise. Basel: Kirkhauser, 1975.
- Minakami, S. The hydrogen ion concentration and erythrocyte glycolysis. Biochem. Biophys. Res. Comm. 17(6):748-750, 1964.
- Mitchell, J. W., K. Wildenthal, & R. L. Johnson, Jr. The effects of acid-base disturbance on cardiovascular and pulmonary function. Kidney Int. 1:375-389, 1972.
- Mithoeffer, J. C., & M. S. Karetzky. Comparative effects of organic and mineral acid on acid-base balance & gas exchange. J. Lab. Clin. Med. 72(6):924-932, 1968.
- Nahas, G. G. Mechanisms of carbon dioxide and pH effects on metabolism. In K. E. Schaefer & G. Nahas (Eds.), CO₂ and Metabolic regulations: Proceedings, International Congress of Physiological Sciences Sattelite Symposium 1971. Berlin: Springer-Verlag, 1974.
- Naimark, A., N. L. Jones, & S. Lal. The effect of hypoxia on gas exchange and arterial lactate and pyruvate concentration during moderate exercise in man. Clin. Sci. 28:1-13, 1965.

- Nakamaru, Y., & A. Schwartz. Possible control of intracellular calcium metabolism by $[H^+]$: sarcoplasmic reticulum of skeletal and cardiac muscle. Biochem. Biophys. Res. Comm. 41:830-836, 1970.
- Nielsen, M. & O. Hansen. Maximale körperliche arbeit bei atmung O_2 -reicher luft. Skand. Arch. Physiol. 76:37-59, 1937.
- Otis, A. B. Quantitative relationships in steady-state gas exchange. In W. O. Fenn & H. Rahn (Eds.), Handbook of Physiology: Respiration. (Vol. I). Washington: American Physiological Society, 1964.
- Patterson, R. W., & S. F. Sullivan. Determinants of oxygen uptake during sodium bicarbonate infusion. J. Appl. Physiol. (Resp. Env. Ex. Physiol.) 45(3):399-402, 1978.
- Pedersen, P. K., & H. G. Welch. Oxygen breathing, selected physiological variables and perception of effort during submaximal exercise. In G. Borg (Ed.), Physical Work and Effort. (Wenner-Gren, Vol. 28). Oxford & New York: Pergamon, 1976.
- Pirnay, F., M. Lamy, J. Dujardin, R. Deroanne, J. M. Petit. Analysis of femoral venous blood during maximum muscular exercise. J. Appl. Physiol. 33(3):289-292, 1972.
- Pirnay, F., R. Marechal, J. Dujardin, M. Lamy, R. Deroanne, & J. M. Petit. Exercise during hyperoxia and hyperbaric oxygenation. Int. Z. Angew. Physiol. 31:259-268, 1973.
- Poortmans, J. R., J. Delescaille-Vanden Bossche, R. Leclerq. Lactate uptake by inactive forearm during progressive leg exercise. J. Appl. Physiol. (Resp. Env. Ex. Physiol.) 45(6):835-839, 1978.
- Poulus, A. J., H. J. Docter, & H. G. Westra. Acid-base balance and subjective feelings of fatigue during physical exercise. Eur. J. Appl. Physiol. 33:207-213, 1974.
- Reich, T., J. Tuckman, N. E. Naftchi, J. H. Jacobson. Effect of normo- and hyperbaric oxygenation on resting and post exercise calf blood flow. J. Appl. Physiol. 28(3):275-279, 1970.
- Ross, J. M., H. M. Fairchild, J. Weldy, & A. C. Guyton. Autoregulation of blood flow by oxygen lack. Amer. J. Physiol. 202(1):21-24, 1962.
- Rowell, L. B., K. K. Kraning II, T. O. Evans, J. W. Kennedy, J. R. Blackmon, & F. Kusumi. Splanchnic removal of lactate and pyruvate during prolonged exercise in man. J. Appl. Physiol. 21(6):1773-1783, 1966.

- Sahlin, K. Intracellular pH and energy metabolism in skeletal muscle of man. Acta. Physiol. Scand. Suppl. 455, 1978.
- Sahlin, K., A. Avestrand, R. Brandt, & E. Hultman. Intracellular pH and bicarbonate concentration in human muscle during recovery from exercise. J. Appl. Physiol. (Resp. Env. Ex. Physiol.) 45(3):474-480, 1978.
- Schaffer, S. W., B. Safer, C. Ford, J. Illingworth, & J. R. Williamson. Respiratory acidosis and its reversibility in perfused rat heart: regulation of citric acid cycle activity. Amer. J. Physiol. 234(1): H40-H51, 1978.
- Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cc samples. J. Biol. Chem. 167(1):235-250, 1947.
- Stainsby, W. N., & H. G. Welch. Lactate metabolism of contracting dog skeletal muscle in situ. Amer. J. Physiol. 211:177-183, 1966.
- Stainsby, W. N. Critical oxygen tensions in muscle. In J. Keul (Ed.), Limiting Factors of Physical Performance. Stuttgart: Georg Thieme, 1973.
- Stanek, K. A., F. J. Nagle, G. E. Bisgard, & W. C. Byrnes. Effect of hyperoxia on oxygen consumption in exercising ponies. J. Appl. Physiol. (Resp. Env. Ex. Physiol.) 46(6):1115-1118, 1979.
- Stewart, P. A. Independent and dependent variables of acid-base control. Resp. Physiol. 33:9-26, 1978.
- Sylvester, J. T., B. J. Whipp, & K. Wasserman. Ventilatory control during brief infusions of CO₂-laden blood in the awake dog. J. Appl. Physiol. 35(2):178-186, 1973.
- Takeshita, S. Changes of serum lactate and pyruvic acid in hypoxia and hypercapnea, especially effects of respiratory changes of blood pH upon lactic acid level. Jap. Arch. Int. Med. 9:12-30, 1962.
- Taunton, J. E., E. W. Banister, T. R. Patrick, P. Oforsagd, & W. R. Duncan. Physical work capacity in hyperbaric environments and conditions of hyperoxia. J. Appl. Physiol. 28:421-427, 1970.
- Theye, R. A., G. A. Gronert, & J. J. A. Heffron. Oxygen uptake of canine whole body and hind limb with hypocapnic alkalosis. Anesthesiology 47(5):416-422, 1977.
- Tobin, R. B. In vivo influences of hydrogen ions on lactate and pyruvate of blood. Amer. J. Physiol. 207(2):601-605, 1964.

- Ui, M. The role of phosphofructokinase in pH-dependent regulation of glycolysis. Biochem. Biophys. Acta 124:310-322, 1966.
- Usinger, W., & P. Spaich. Sauerstoffverbrauch und kreislauf bei akuten änderungen des arteriellen pH. Int. Z. Angew. Physiol. 28:181-192, 1970.
- Verhaeghe, R. H., R. R. Lorenz, M. A. McGrath, J. T. Shepard, & P. M. Vanhoutte. Metabolic modulation of neurotransmitter release--adenosine, adenine nucleotides, potassium, hyperosmolarity, and hydrogen ion. Fed. Proc. 37:208-211, 1978.
- Waddell, W. J., & R. G. Bates. Intracellular pH. Phys. Revs. 49(2); 285-329, 1969.
- Welch, H. G., J. P. Mullin, G. D. Wilson, J. Lewis. Effects of breathing O₂ enriched gas mixtures on metabolic rate during exercise. Med. Sci. Sports 6(1):26-32, 1974.
- Welch, H. G., F. Bonde-Petersen, T. Graham, K. Klausen, & N. Secher. Effects of hyperoxia on leg blood flow and metabolism during exercise. J. Appl. Physiol. (Resp. Env. Ex. Physiol.) 42(3):385-390, 1977.
- Wilmore, J. H., & D. L. Costill. Adequacy of the haldane transformation in the computation of exercise $\dot{V}O_2$ in man. J. Appl. Physiol. 35(1): 85-89, 1973.
- Wilson, B. A., H. G. Welch, & J. N. Liles. Effects of hyperoxic gas mixtures on energy metabolism during prolonged work. J. Appl. Physiol. 39(2):267-271, 1975.
- Wilson, B. A., & W. N. Stainsby. Effects of O₂ breathing on RQ, blood flow, and developed tension in in situ dog muscle. Med. Sci. Sports 10(3):167-170, 1978.
- Wilson, D. G., & H. G. Welch. Effects of hyperoxic gas mixtures on exercise tolerance in man. Med. Sci. Sports 7(1):48-52, 1975.
- Wyndham, C. H., N. B. Strydom, A. J. Rensburg, & G. G. Rogers. Effects on maximal oxygen intake of acute changes in altitude in a deep mine. J. Appl. Physiol. 29:552-555, 1970.
- Zborowska-Sluis, D. T., & G. A. Klassen. The effect of carbon dioxide and H⁺ on canine erythrocyte glycolysis. Resp. Physiol. 15:96-103, 1972.

VITA

Richard Paul Adams was born in Columbus, Ohio on August 30, 1947. He attended the Webb School of Knoxville, Tennessee and graduated in June 1965. The following September he entered The University of North Carolina at Chapel Hill and in June 1969 received a Bachelor of Arts degree with a major in International Studies. He served as an officer in the United States Marine Corps from September 1969 through June 1973. In September 1973 he began course work at The University of Tennessee, Knoxville leading to his acceptance into graduate school there.

He entered the Graduate School at The University of Tennessee, Knoxville, with a National Science Foundation Graduate Fellowship in September 1975 and received the Doctor of Philosophy degree with a major in Zoology in December 1979. He is a member of the American College of Sports Medicine and the American Physiological Society.