To the Graduate Council:

I am submitting herewith a thesis written by Alexander J. Rouch II entitled "Comparison of the Oxygen Cost of Breathing and Lactatemia During Exercise between Nitrogen-Oxygen Breathing and Helium-Oxygen Breathing." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Life Sciences.

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COMPARISON OF THE OXYGEN COST OF BREATHING AND LACTATEMIA DURING EXERCISE BETWEEN NITROGEN-OXYGEN BREATHING AND HELIUM-OXYGEN BREATHING

A Thesis

Presented for the

Master of Science

Degree

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Alexander J. Rouch II

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DEDICATION

To my father who taught me the most important lesson in life; never, never give up.

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ABSTRACT

The purpose of this study was to compare the oxygen cost of breathing during exercise when inspiring mixtures of either 80% nitrogen/20% oxygen (N_2-O_2) or 80% helium/20% oxygen (He-O_2). Four male subjects exercised on a bicycle ergometer for 20 minutes at a rate of approximately 60% of their $\dot{V}O_2$ max. During the final 10 minutes of exercise, they hyperventilated voluntarily at a breathing rate of 60 breaths per minute. The minute ventilation achieved during hyperventilation with He-O_2 was significantly higher than that with N_2-O_2 ($p < 0.05$), but there was no significant difference in the oxygen cost of breathing between the two gases ($p > .5$). The average cost of breathing for He-O_2 was 3.9 ml/l at an average ventilation of 81.8 l/min; the average cost of breathing for N_2-O_2 was 3.5 ml/l at an average ventilation of 56.1 l/min. Lactate concentration was measured to determine if voluntary isocapnic hyperventilation caused increased blood lactate levels. No significant difference was found in lactate concentration between the two gases and between the two exercise periods of normal ventilation and voluntary hyperventilation. This study suggests that one can sustain a higher ventilation with He-O_2 without increasing the O_2 cost of that ventilation.

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CHAPTER I

INTRODUCTION

The work of breathing is a complicated and misunderstood measurement which deserves more attention from physiologists. An effective way to study the work of breathing is to change the density of the gas that is breathed. By doing this, one can compare the work of the respiratory apparatus between gases of different densities. Helium has often been substituted for nitrogen to study metabolic differences encountered when breathing these two gases. The study of metabolism has been enhanced by helium-nitrogen comparisons. Consequently, helium substitution provides the opportunity to conduct controlled studies on the work of breathing.

The physiological effects of substituting helium (He) for nitrogen (N_2) in the inspired air are poorly understood. Some believe helium to be beneficial because it reduces the density of the gas mixture and thus makes breathing easier. Others feel that the effects of using helium are so misunderstood that it should not be used as the diluent in artificial atmospheres (29, 35).

There is a conflict among investigators on the effect of helium-oxygen ($He\text{-}O_2$) breathing on the metabolic rate ($\dot{V}O_2$). Spitler et al. and Murphy et al. report a lower maximal oxygen uptake ($\dot{V}O_2$ max) when helium is substituted for nitrogen in the inspired air (50, 66). Others report higher $\dot{V}O_2$ max values when one breathes helium (11, 18, 67).

The main disagreement between these two sets of studies centers around the effect of breathing He-O_2 on pulmonary ventilation during high work rates. In the studies which show a higher $\dot{V}O_2$ for He-O_2, the ventilations achieved during high work rates for helium breathing greatly exceed those for air. In the studies which show a lower $\dot{V}O_2$ max for He-O_2, the reported ventilations between the two gases are not significantly different, and the investigators of these studies attribute the difference in the $\dot{V}O_2$ max to a lower O_2 cost of breathing with helium. To date, the O_2 cost of breathing during exercise with these two gases has not been compared.

Several investigators have reported an increase in blood lactate accumulation from hyperventilation during rest (9, 12, 16, 17, 31, 71). However, only a few studies have examined the effect of exercise hyperventilation on lactate accumulation (41, 48). One such study by Graham et al. reported an inverse relationship between the increase in lactate and the percentage of CO_2 in the inspired air (26). For some physiological reason yet to be determined, adding CO_2 to the inspired air will reverse the effect of increased lactate from hyperventilation. Recently however, Martin et al. reported a significant increase in lactate accumulation during isocapnic hyperpnea at rest (41).

Information on the O_2 cost of breathing between He-O_2 and air is obviously needed. In addition, more investigation is required on the effect of hyperventilation on lactate accumulation. It was the purpose of this study to compare the O_2 cost of breathing during exercise between He-O_2 and air, and to examine the effects of isocapnic hyperventilation on lactate.

CHAPTER II

REVIEW OF RELATED LITERATURE

The review of literature is organized into three major categories: 1) oxygen cost of breathing, 2) helium-oxygen breathing, and 3) lactate accumulation during hyperventilation.

A. OXYGEN COST OF BREATHING

O_2 Cost of Breathing During Exercise

The oxygen cost of breathing during exercise has received little attention from exercise physiologists. The contribution of the cost of breathing to the entire metabolic rate during exercise is perceived to be minimal. Cardiovascular capacity and the metabolism of the working skeletal muscles are believed to be the primary limiting factors during exercise; thus, these factors are given more consideration than the increased pulmonary ventilation. Recent research suggests, however, that the work of breathing during steady state exercise may cost as much as 10% of the total metabolic rate, and this could have a major role in exercise tolerance.

There are several reasons why scientists have a low regard for the O_2 cost of breathing during exercise. These stem from the following observations: 1) during exercise when the maximal oxygen uptake is reached, pulmonary ventilation increases without reaching a distinct plauteau; 2) a subject can voluntarily hyperventilate above the ventilation achieved at maximal work; 3) during heavy work, the alveolar

oxygen tension increases and the carbon dioxide tension decreases, thus providing an effective gas exchange in the lungs (1). These reasons, although true, are not sufficient enough to totally disregard the effect of the work of breathing in exercise. They actually suggest that the respiratory muscles do not fatigue. Even though maximal ventilation is rarely achieved during maximal work, enough evidence exists showing that the breathing muscles are fatigable and can limit performance (42, 44, 69).

Work of Breathing Components

The work of breathing is divided into three main components: 1) work required to expand the lungs against its elastic forces (compliance work); 2) work required to overcome the viscous resistance of the lungs and chest wall (tissue resistance work); and 3) work required to overcome airway resistance as air moves into the lungs (airway resistance work) (65). During inspiration, the pressure inside the lungs and the volume of air change. Since work is the result of a force (f) moved through a distance (d), the work done in breathing can be determined from the change in the intrapleural pressure which represents the force, and the change in lung volume which represents the distance. In this case, pressure can be expressed in units of cm-H_2O and distance in l. Thus,

$$\text{work}(\text{cm-}H_2O\text{-l}) = f(\text{cm-}H_2O) \times d \text{ (l)}.$$

The pressure-volume diagram of Figure 1 illustrates the three components of the work of breathing. The work to overcome elasticity

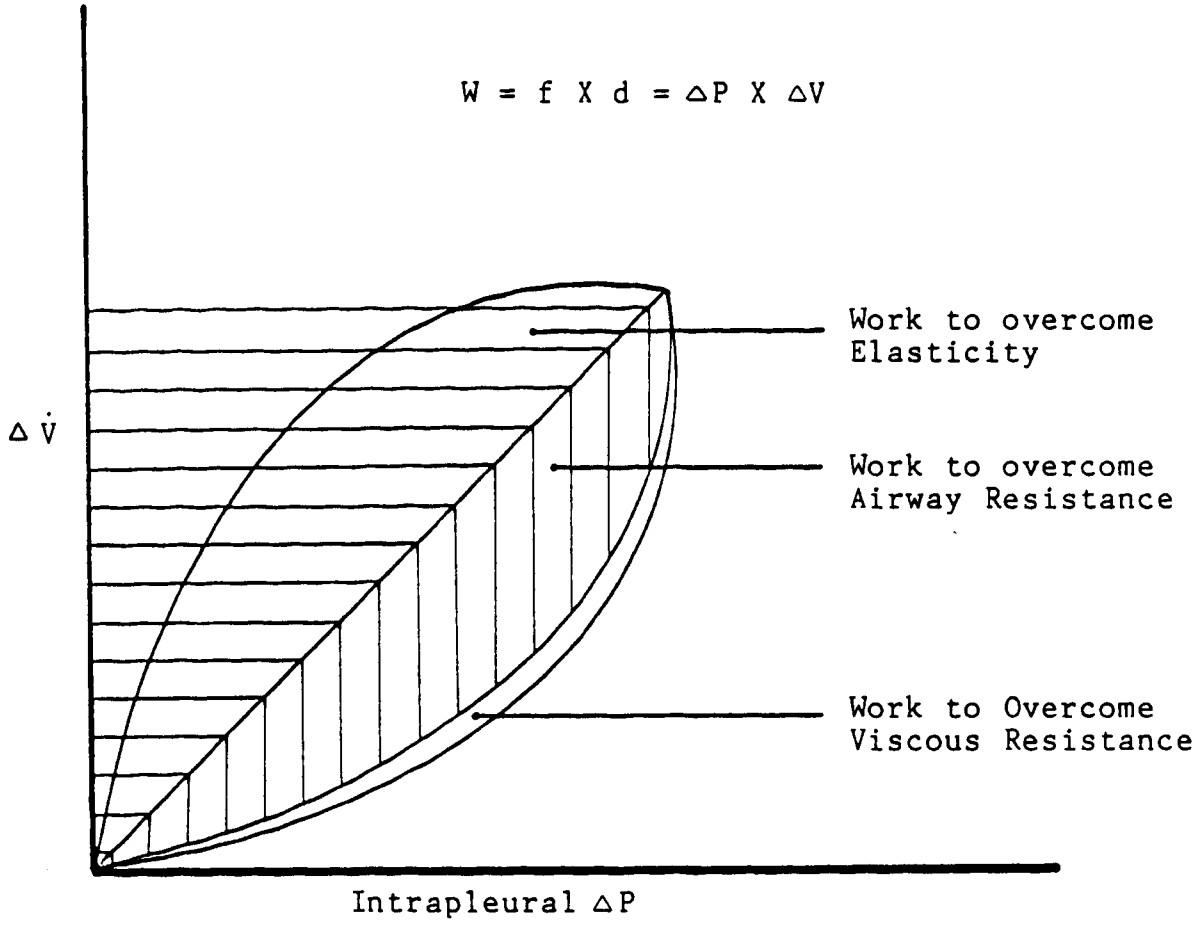

Figure 1. The Work of Breathing.

Slonim, N. B. & Hamilton, L. H. Respiratory Physiology. 4th ed. St. Louis: The C. V. Mosby Company, 1981, p. 84.

constitutes about 65% of the work of breathing. The work done to overcome airway resistance is roughly 80% of the nonelastic work of breathing (65). Viscous resistance is small for healthy people.

O_2 Cost of Breathing Curve

The oxygen cost of breathing is expressed in units of milliliters of oxygen per liter of ventilation (ml/l). This value might be particularly useful for clinicians; however, it is not used as a pulmonary function test. The main reason it is probably not used as a pulmonary function test, as Bartlett suggests, stems from the fact that standardized procedures for determining the O_2 cost of breathing do not exist (4). In addition, the values obtained from different techniques vary considerably. This will be shown later.

The oxygen cost of breathing at rest is low compared to the total body O_2 uptake (55). The cost of breathing increases in a curvilinear fashion as the minute ventilation increases, and Otis suggests that the work of breathing, although not important at normal conditions, becomes important during intense work, and even during moderate work for patients with chronic pulmonary lung obstruction (55). Figure 2 illustrates this concept. Therefore we can at least say that the O_2 cost of breathing at rest amounts to a very small percentage of the total $\dot{V}O_2$, and that the O_2 cost of breathing increases as ventilation increases.

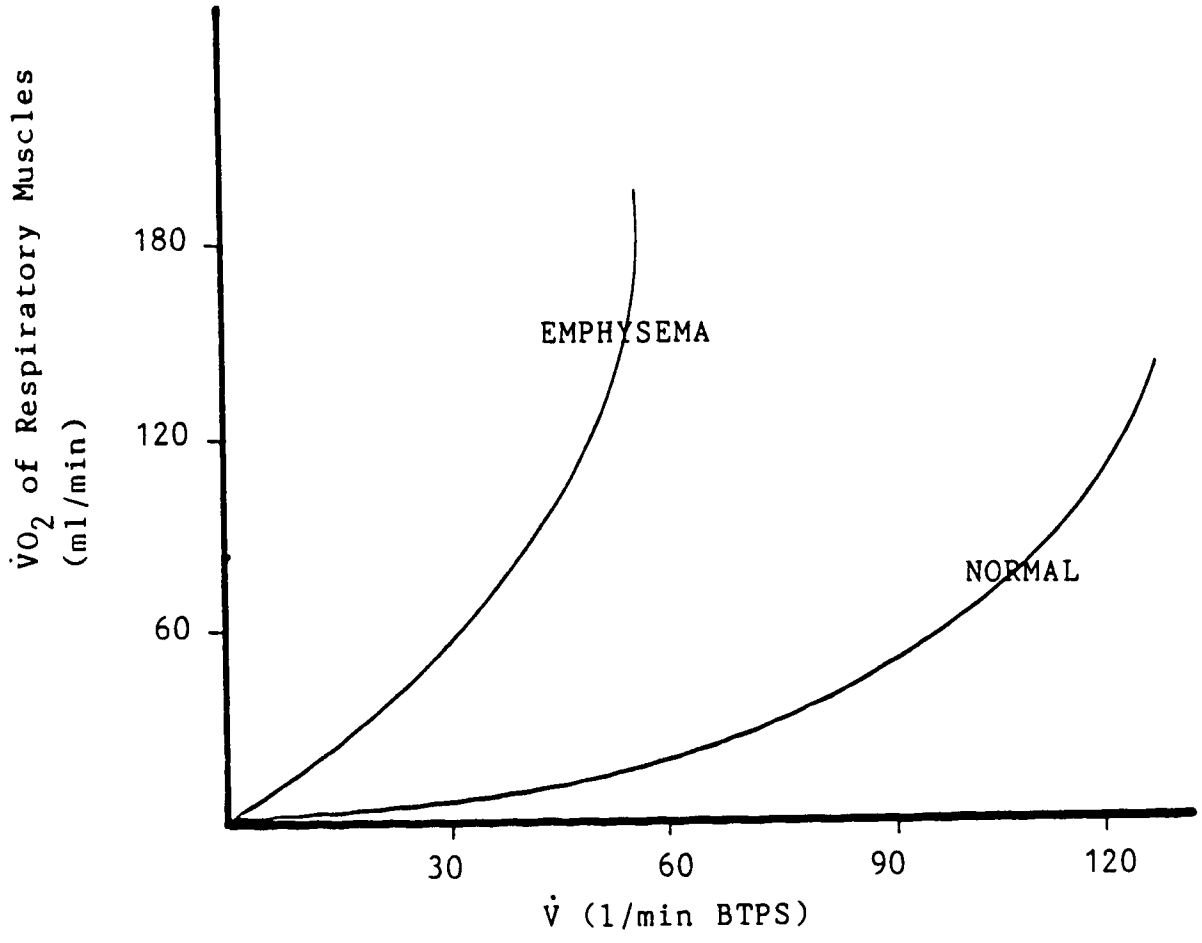

Figure 2. Oxygen Cost of Breathing Curves.

Campbell, E. J. M., E. K. Westlake, and R. M. Cherniack. Simple methods of estimating oxygen consumption and efficiency of the muscles of breathing. J. Appl. Physiol., 1957, 11 (2), 306.

Measuring the O_2 Cost of Breathing

It is not feasible to measure the oxygen cost of the respiratory muscles directly. This is done indirectly by measuring the oxygen uptake during normal conditions and then measuring the oxygen uptake during the same conditions but with an increased ventilation. This method is valid only if the additional work during hyperventilation is aerobic and does not affect the non-respiratory metabolic rate. That the total ventilation could be increased without affecting non-respiratory oxygen consumption has been supported (15). A steady state metabolic rate during periods of hyperventilation can be attained. This will be discussed shortly.

Pulmonary ventilation must increase to measure the O_2 cost of breathing. Three general methods are used to increase pulmonary ventilation. These include voluntary hyperventilation, increasing the inspired CO_2 fraction, and increasing anatomical dead space. Bartlett et al. suggested that the dead space technique is the best of the three methods because it avoids the unsteady state of voluntary hyperventilation and the difficulties of regulating the work of breathing that occur when the CO_2 in the inspired air is increased (4).

Otis stated that voluntary hyperventilation invariably resulted in higher O_2 costs of breathing than with the same ventilation stimulated by CO_2 (55). Conflicting opinions exist as to why this is so. Liljestrand believed voluntary hyperventilation was unnatural, and that the mechanical effort to voluntarily hyperventilate resulted in inefficient breathing muscle movements (38). Others contend that

voluntary hyperventilation increases the O_2 requirement of the ventilatory muscles because of a lowering of alveolar and arterial PCO_2 (53, 55). Table 1 illustrates the results from different methods of measuring the O_2 cost of breathing. Two important observations can be made from the table: 1) as the ventilation increases, the cost of breathing increases which further supports Figure 2 and 2) the variability within a particular study and thus within subjects is often high.

Reported values of the cost of breathing at rest vary among investigators, employing different methods of measurement, from .5 to 10 ml/l (55). Otis suggested that the different methods of determining the cost of ventilation and the failure of some investigators to obtain measurements during the steady state cause the large range of breathing cost measurements (55). Obtaining the O_2 cost of ventilation without achieving steady state conditions can lead to an overestimation of oxygen uptake ($\dot{V}O_2$), and thus an invalid O_2 cost of breathing result.

The reason for this overestimation of $\dot{V}O_2$ can be explained by Murray's O_2 storage phenomenon (51). An abrupt increase in ventilation raises the alveolar PO_2. This causes the body's O_2 stores to come into equilibrium at a higher partial pressure. The attainment of this equilibrium requires time. During the first few minutes of hyperventilation, the $\dot{V}O_2$ represents metabolic O_2 as well as O_2 taken up by body tissue, blood, and alveolar tissue to equilibrate with the higher alveolar oxygen tension.

Bradley and Leith defined the steady state period during hyperventilation as that period when the mean O_2 consumption varied less

Table 1. Comparisons of the O_2 Cost of Breathing

Investigator	Method	$\dot{V}$	Cost ml/L
Bartlett	DS	40	0.8-1.2
		80	1.0-2.2
		120	1.8-2.8
		180	5.7-9.8
Milic-Emili and Petit	DS	40	0.2-0.3
		80	0.4-0.5
		100	0.6-0.7
Campbell et al.	CO_2	40	0.2-0.3
		80	0.4-0.5
		100	0.6-0.7
Levison and Cherniack	CO_2	10	0.7-3.2
		30	1.9-6.5
		40	3.0-6.0
		50	1.9-5.5
		60	1.7-6.1
McKerrow and Otis	HV	250	2.8-8.5
McGregor and Becklake	HV	55	1.3-5.5
Shepard	HV	85	1.2
		90-140	3.8-8.7
Bradley and Leith	HV	103-250	4.4-4.7
Martin	HV	35-65	2.0
		65-95	6.0
		95-125	9.0
Murry	HV	10-40	3.5

DS--Deadspace; HV--Hyperventilation.

than 10% (7). They reported 3 minutes for the attainment of the steady state when subjects increased their ventilation from rest to about 200 l/min. Farhi and Rahn suggested 7 minutes for the attainment of the steady state with hyperventilation (19).

Respiratory Alkalosis

Voluntary hyperventilation causes a decrease in the PCO_2 of blood and a lowering of the hydrogen ion concentration. This results in a respiratory alkalosis which can, in time, affect oxygen uptake (9, 13). During hyperventilation in humans, Karetzky and Cain reported that a decrease in the hydrogen ion concentration enhanced $\dot{V}O_2$ (13). This has also been reported with animal experiments (9, 33, 34). McNair suggested that a decrease in the $PACO_2$ from hypocapnic hyperventilation could increase the O_2 cost of breathing (48). This increase may be related to the effect of a lower $PACO_2$ on the respiratory airways.

Bronchial muscle contraction, which increases airway resistance, is associated with decreasing end-tidal CO_2 tensions (54). Newhouse measured a 133% increase in flow resistance when the $PACO_2$ fell from 45-50 mmHg to 20-25 mmHg (53). This flow resistance represents the airway resistance work explained earlier. Thus for ventilations between 32 and 48 l/min, the work required to breathe was significantly greater when the $PACO_2$ was lower. Another problem with the low $PACO_2$ is physical performance. Balke reported a significant decrease in psychomotor performance when $PACO_2$ fell below 25 mmHg (2).

These findings illustrate the important difference between hypocapnic and isocapnic hyperventilation. To reiterate from a previous

section, a valid O_2 cost of breathing measurement assumes that the increase in $\dot{V}O_2$ from hyperventilation is caused by the additional work of only the respiratory muscles. Since airway resistance increases with hypocapnia, one can suggest that the O_2 cost of breathing is probably higher during hypocapnic hyperventilation than it is during isocapnic hyperventilation. Under hypocapnic conditions where respiratory alkalosis occurs, the increase in $\dot{V}O_2$ from hyperventilation may be attributed partially to other sources in addition to the respiratory muscles. Therefore, the assumption above may not be valid with hypocapnic conditions because it has not been determined how respiratory alkalosis increases the O_2 uptake.

If motor performance is adversely affected by a lowered PCO_2, the work of the non-respiratory muscles may change during hypocapnic hyperventilation. When measuring the O_2 cost of breathing during exercise, it is imperative that the work of the non-respiratory muscles is unchanged between periods of normal ventilation and hyperventilation. Therefore, maintaining desired motor performance could be difficult with hypocapnic hyperventilation.

Optimal Breathing Frequency

Changes in the breathing frequency will affect the work of breathing. From the data obtained by Liljestrand in 1918, Otis suggested that at least for the ranges Liljestrand studied (frequency 5-25/min; ventilation 5-35 l/min), given ventilations are performed with a lower total energy cost the higher the frequency (55).

Nonelastic work increases with increasing breathing rates at constant pulmonary as well as constant alveolar ventilation. The overall elastic work will decrease with increasing breathing rates because of smaller tidal volumes. Bartlett et al. suggested that the optimal breathing rate for a given pulmonary ventilation depends on the elastic and nonelastic work of breathing (4). They described the nonelastic work variations with different breathing rates as a consequence of the time "loss" or volume "deficit" associated with flow reversal patterns of the breathing cycle. The energy cost of this volume "deficit" will at some time equal the energy saved by the lesser resistances met in fast shallow breathing. Figure 3 illustrates this concept.

If a subject is given the freedom to choose combinations of breathing rates and tidal volumes over a large number of tests, an optimal ventilation-O_2 uptake curve can be obtained (4). In addition, the existence of such a wide variety of ventilation-O_2 uptake curves could be a result of the large deviations from the optimal breathing rate. Bradley and Leith reported that spontaneously chosen frequency varied among subjects for a given ventilation and suggested that the optimum for frequency was broad, or that it was imperfect (7). Suffice it to say that the breathing rate cannot go unnoticed in these types of studies.

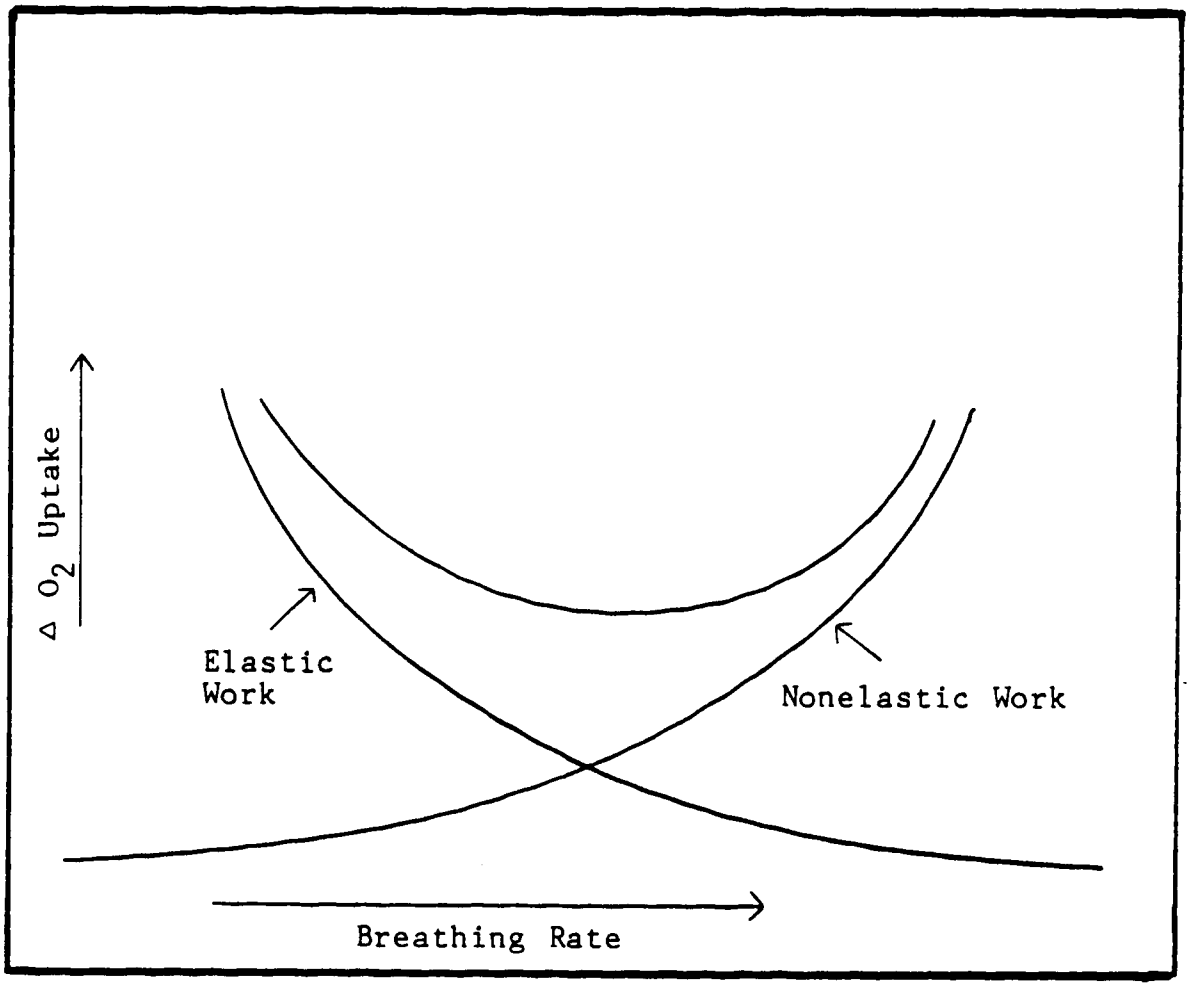

Figure 3. Oxygen Cost of Breathing with Varying Breathing Rates.

Bartlett, R. G., H. F. Brubach, and H. Specht. Oxygen Cost of Breathing. J. Appl. Physiol., 1958, 12 (3), 423.

The cumulative effect, as indicated by the curve in the middle, results in an optimum breathing frequency which varies with variations in the pulmonary minute volume.

B. HELIUM-OXYGEN BREATHING

Physical Properties of Helium

Helium exists in the monatomic form (He) rather than the diatomic form (He_2) and is classified as a member of the "rare" gases. The atomic weight of helium is 2.0000, and its 2 electrons provide a complete 1S electron shell, which makes helium chemically unreactive (52). A 21% oxygen and 79% helium mixture has a viscosity 1.1 times that of air, a density .34 times that of air, and a thermal conductivity 6.5 times that of air (6, 25).

Possible Effects of Helium Substitution

Barach established the use of helium as a therapeutic gas in 1936 when he defined its potential usefulness in anaesthesia and for treatment of airway obstruction (3). Helium is well known for its use in hyperbaric physiology and deep-sea diving. Helium has no toxic effect on the lungs, and unlike nitrogen, it will not cause narcosis at pressures above 5 atmospheres (28). Helium is nonirritating to airways and is reported to be absent of any pharmacologic activity (45). The consequence of these physical properties of helium is that $He-O_2$ mixtures may reduce the work of breathing because its low density should reduce the airway resistance work.

However, the use of helium in the treatment of chronic obstructive pulmonary disease (COPD) is not firmly established (45). Mathewson claims that the effectiveness of helium with asthmatic patients has considerable variability. Raimondi found that exercise tolerance was

better with a 35%-65% oxygen-nitrogen mixture than with a 21%-79% oxygen-helium mixture (59). There is some evidence that He-O_2 mixtures may reduce ventricular fibrillation following heart attacks (57). Pifarre proposed that breathing He-O_2 mixtures develops collateral circulation faster than air yielding more blood flow through the ischemic areas.

If a He-O_2 mixture reduces the O_2 cost of breathing during exercise, then patients with COPD and asthma would benefit from helium substitution. At any rate, the beneficial effects of substituting helium for nitrogen in the inspired air are not established.

The Reynolds Number

The principal effect of breathing He-O_2 is the reduction of airway resistance. Air flow into the lungs at rest and at low ventilations is predominantly laminar. During exercise when the velocity of flow increases, the flow becomes turbulent. Turbulence results in a greater airway resistance and requires more muscular effort to maintain a given ventilation. The type of air flow depends on the velocity of flow, the density and viscosity of the gas, and the diameter of the airway. The Reynolds number (R = density x velocity x diameter/viscosity) provides a numerical indication of the type of flow. This results in a dimensionless number, where a value greater than 2000 usually means turbulent flow is occurring and a value less than 2000 usually means laminar flow is occurring (28).

The Metabolic Effects of He-O_2 Mixtures

Different investigators have reported conflicting results on the effect of He-O_2 breathing on $\dot{V}O_2$ values. Some report higher $\dot{V}O_2$

values with He-O_2 while others report no difference or lower $\dot{V}O_2$ values for He-O_2 (11, 18, 20, 30, 50, 66, 67). If He-O_2 breathing does reduce the O_2 cost of breathing, then the total $\dot{V}O_2$ for a given work rate should be less for He-O_2 than for air. This may be the case, however, only if the work rate is not sufficiently high.

Murphy et al. found no difference in $\dot{V}O_2$ between the two gases at mild work rates but did find a significant decrease in $\dot{V}O_2$ with He-O_2 at higher work rates (50). They attributed these results to a higher O_2 cost of breathing with air caused by an increased amount of turbulence in the tracheo-bronchial tree. This reasoning seems sound when one considers the effect of gas density on the Reynolds number. Spitler et al. also found significantly lower $\dot{V}O_2$ values with He-O_2 at maximal and near maximal work rates (66). Their reasoning falls in line with that of Murphy's, centering around the decreased resistance to air flow and the accompanying decrease in the energy cost of breathing. Hoar et al. found lower $\dot{V}O_2$ values when scuba divers exercised underwater breathing a mixture of 36% He, 20% O_2, and 43% N_2 than for air (30).

Tait tested four subjects and found higher $\dot{V}O_2$ values for He-O_2 breathing though these values were not significant (67). Brice and Welch found that during intense work and at maximal work, the $\dot{V}O_2$ is significantly higher for He-O_2 breathing than for air (11). In addition, they found no difference in $\dot{V}O_2$ between the two gases at mild work rates.

Fagraeus reported higher $\dot{V}O_2$ max values for He-O_2 under hyperbaric conditions (18). The pulmonary ventilation value under these conditions was significantly higher for He-O_2 breathing. Although these conditions were at environmental conditions of 3ATA, the results are still in direct disagreement with those of Spitler, Murphy, and Hoar.

Why do some investigators report higher $\dot{V}O_2$ max values for He-O_2 while others report lower? Differences in pulmonary ventilation between He-O_2 and air seem to be the primary factor in this conflict. Murphy reported the same ventilation values for the two mixtures at intense work rates (50). Spitler et al. found slightly higher ventilations for He-O_2 during maximal work and similar ventilations between the two gases at mild work rates (66). Brice and Welch, on the other hand, found significantly higher minute ventilations for He-O_2 during maximal work and suggested that the increased $\dot{V}O_2$ values could be caused by the alkalotic effects induced by a higher ventilation (11).

This review explicity describes the need to compare the O_2 cost of breathing during exercise between He-O_2 and air. If it is shown that during exercise at high ventilations the cost of breathing for He-O_2 is lower than that for air, the studies of Spitler et al., Hoar et al., and Murphy et al. will be supported. On the other hand, if there is no difference in the O_2 cost of breathing between these two gases, and the pulmonary ventilation for He-O_2 is higher than that for air, the studies of Brice and Welch, Tait, and Fagraeus will be supported.

C. LACTATE ACCUMULATION DURING HYPERVENTILATION

Passive hyperventilation has been associated with increased lactate levels in animals (9, 34, 71). Hyperventilation also induces increased lactate levels in humans (41, 48). Eichenholz et al. observed that increased lactate levels from hyperventilation can be prevented with the addition of 4% CO_2 to the inspired air during hyperventilation (16). Huckabee and Zborowska-Sluis and Dossetor reported similar results (31, 71).

Graham et al. reported the effects of hypercapnia on metabolic responses in steady state exercises (26). Their subjects performed 30 minutes of work on a bicycle ergometer at two work intensities, 50% and 65% of $\dot{V}O_2$ max, and they inspired a gas containing 0, 2, 4, or 6% carbon dioxide. As the amount of CO_2 in the inspired air increased, the pulmonary R value ($\dot{V}CO_2/\dot{V}O_2$) decreased. Bicarbonate concentration and PaO_2 increased with CO_2 in the inspired air. In addition, lactate accumulation showed a significant inverse relationship with inspired CO_2 levels. The physiological reasons for this inverse relationship are unknown. Possible reasons will be discussed later.

Recently, Martin et al. reported a significant increase in lactate accumulation during isocapnic voluntary hyperventilation (41). The ventilations achieved in this study were equivalent to and exceeded those of maximal work. The subjects in this study hyperventilated while being seated, and did not perform exercise. Seated hyperpnea is obviously different from exercise-induced hyperpnea, but the results warrant further investigation.

Increased lactate from hyperventilation could indicate ventilatory muscle fatigue. The role of the breathing muscles in exercise is undetermined. As earlier stated, it is generally believed that the contribution of the respiratory apparatus to whole-body fatigue in exercise is negligible. However, the evidence reported by Martin and others possibly shows that this traditional belief is wrong.

It should also be emphasized that ventilatory muscle training increases maximal voluntary ventilation, vital capacity, and ventilatory endurance time (7, 63). The breathing muscles can be trained, and supplemental ventilatory muscle training may be useful to a standard exercise program. The oxygen cost of breathing during exercise might be indicative of ventilation capacity. A lower O_2 cost of breathing during heavy exercise may provide more O_2 for other active muscles. If breathing He-O_2 reduces the O_2 cost of breathing, then breathing He-O_2 may yield more oxygen to non-respiratory muscles.

Although increased blood lactate from hyperventilation does not verify respiratory muscle fatigue, this response should be further investigated. Martin et al. had to increase the amount of CO_2 in the inspired air as the subjects increased their hyperventilation to maintain isocapnia. Their finding of an increased blood lactate contradicts Graham's results of decreased lactate with increased CO_2 in the inspired air.

Measuring lactate accumulation during voluntary isocapnic hyperventilation during exercise will add new and needed evidence on the contribution of respiratory muscle fatigue to whole-body fatigue. Also,

this might help us determine the effect of gas density on respiratory work in exercise. If more lactate accumulates from hyperventilation with air than helium, this could indicate that breathing air requires a higher work rate for the breathing muscles.

CHAPTER III

METHODS

A. SUBJECTS

Four healthy male subjects volunteered to participate in the study. The subjects were experienced with laboratory procedures and the experimental protocol. Each subject exercised regularly 3 to 4 times per week. One subject, subject #4, competed as a cyclist and trained at least 5 days per week. Table 2 lists the physical characteristics of the subjects.

B. PILOT TESTS

Voluntary hyperventilation is not natural, so it was necessary to have the subjects practice before the formal experiment. Each subject performed a number of pilot tests (2 to 3) until it was assured that he could maintain a steady state condition of voluntary hyperventilation during exercise.

C. MAXIMAL OXYGEN UPTAKE TEST

The four subjects completed a maximal oxygen uptake test on a Monark bicycle ergometer at a pedal rate of 60 or 72 revolutions per minute (subject's preference). During this progressive exercise test, the resistance was increased by increments of .5 kg (4.9N) every 2 minutes until exhaustion. Expired air was collected in Douglas bags

Table 2. Physical Characteristics of Subjects

Subject	Age	Wt (kg)	$\dot{V}O_2$ max (ml/kg min)	$\dot{V}O_2$ max (l/min)	Submax Workload $\%\dot{V}O_2$ max
1	30	63	50.3	3.21	61
2	45	70	45.0	3.15	62
3	26	70	46.7	3.27	63
4	29	80	55.9	4.47	54

during the last minute of each work rate beginning at the 2.0 kg (19.6N) resistance setting.

Oxygen uptake was calculated from the O_2 and CO_2 expired fractions in the Douglas bags. Table 2 lists the $\dot{V}O_2$ max value of each subject. This $\dot{V}O_2$ max was used to set the work rate in the experiment for each subject.

D. EXPERIMENTAL PROTOCOL

Each subject performed four experimental tests. Two of these tests were with voluntary hyperventilation and two were without. The latter two, one with a 79%-21% N_2-O_2 mixture and one with a 79%-21% He-O_2 mixture, consisted of a 20-minute ride at a pedal rate of 60 revolutions per minute (rpm) and a work rate of approximately 60% $\dot{V}O_2$ max. These rides were conducted to assure that each subject maintained a constant steady state for the entire exercise period.

The test rides with voluntary hyperventilation, one with a 79%-21% N_2-O_2 mixture and one with a 79%-21% He-O_2 mixture, were also 20 minutes in duration. During the first 10 minutes the subjects breathed normally; during the final 10 minutes the subjects increased their ventilation by breathing in cadence to a metronome so that the breathing rate during the final 10 minutes of the hyperventilation rides was 60 breaths per minute.

During the final 10 minutes of these rides, CO_2 was added to the inspired air from a cylinder tank containing 100% CO_2. An assistant adjusted the amount of added CO_2 by monitoring the end-tidal CO_2

readings from a CO_2 analyzer (Beckman LB-1). The assistant made sure that the end-tidal CO_2 reading during the voluntary hyperventilation phase was the same as that during the normal ventilation phase. Thus, isocapnia was maintained.

The inspired air flowed from a compressed air tank to a warmed humidification chamber to a 200-liter Douglas bag which was used as a reservoir. Large bore tubing (40mm ID) connected the reservoir to a dry test gas meter (Parkinson-Cowan model CD-4). The same type of tubing was used to connect the gas meter to a low resistance Koegel breathing valve. By using this breathing valve and the large bore tubing, air resistance was minimized.

Expired gas was mixed in a 9-liter mixing chamber, and also collected in Douglas bags during minutes 8-9 and 18-19 of each test ride.

The order of assignment of a given test (with or without voluntary hyperventilation, and with N_2-O_2 or He-O_2) was random, and the subject was unaware of the composition gas used for a particular test. Because helium breathing can be detected by voice changes, the subjects breathed room air for 2 minutes post exercise to ensure the blind nature of the study.

All tests were conducted in the same room under the following conditions: Room Temperature--22-24°C; Barometric Pressure--730-745 mmHg; Relative Humidity--40-65%.

E. DESCRIPTION OF MEASUREMENTS

The open circuit method was used to determine oxygen consumption. Expired air was analyzed for O_2 and CO_2 fractions by an Applied Electrochemistry Model S-3A and a Beckman LB-2 analyzer, respectively. Both analyzers were calibrated, before each bag analysis, using two gas mixtures that were analyzed by the Micro-Scholander technique (62). The following equations were used to calculate oxygen uptake (56):

$$\dot{V}O_2 = \dot{V}I\ [FIO_2 - (FEO_2 \times FIN_2/FEN_2)]$$

$$\dot{V}O_2 = \dot{V}E\ [(FIO_2 \times FEN_2/FIN_2) - FEO_2]$$

Inspired minute ventilation was measured from the Parkinson-Cowan gas meter fitted with a rotary potentiometer. A servoamplifier on a DMP-48 Physiograph picked up the output and provided a continuous reading of ventilation and frequency. Expired ventilation was measured by expelling the gas in the Douglas bag through a Parkinson-Cowan gas meter. The volume was read from the dial on the meter. It was previously determined that no calibration changes occur in the Parkinson-Cowan gas meter when the gas changes from air to He-O_2 (10).

The oxygen cost of breathing was calculated by the following equation:

$$(\text{ml } O_2/\text{l}) = \Delta\dot{V}O_2(\text{ml/min})/\Delta\dot{V}(\text{l/min})\ \text{BTPS}$$

$\Delta\dot{V}O_2 = \dot{V}O_2$ (from minute 18-19 - voluntary hyperventilation phase) - $\dot{V}O_2$ (from minute 8-9 - normal ventilation phase).

$\Delta\dot{V}$ = $\dot{V}$ (from minute 18-19 - voluntary hyperventilation phase) - $\dot{V}$ (from minute 8-9 - normal ventilation phase).

Disposable ECG electrodes were placed on the subject's chest to monitor heart rate. Heart rate was recorded with these electrodes connected to a biotachometer (BT-1200). The output was fed to the DMP-4B Physiograph which provided a continuous record of heart rate.

The humidity of the inspired gas was measured by monitoring the wet-bulb temperature. A Yellow Springs Tele-Thermometer (model 46-TUC) provided the output from two probes that were placed on the outlet side of the gas meter. This placement provided the most accurate reading by being as close as possible to the subject.

F. BLOOD SAMPLING

Fingertip blood samples were collected at minute 9-10 and within 1 minute post-exercise (2 collections per test) and analyzed in duplicate. The subject's hand was kept warm by a heating pad which was wrapped around the handle bar on the ergometer.

Each blood sample was placed in a small well on a spot plate. The well was coated with 4% NaF solution which prevented clotting and inhibited glycolysis. The blood and NaF were mixed and then drawn into two separate 50 microliter samples and each placed into 2 ml of 7% perchloric acid. Each sample was mixed well by shaking, then centrifuged, and the supernatant was frozen for later lactate analysis.

A fluorometric modification of the Gutman-Wahlefeld method was used to determine lactic acid concentration (27). A Turner Model 430 Spectro-fluorometer was used in this assay.

G. STATISTICAL ANALYSIS

Data were analyzed by comparing mean values with a Paired T test.

CHAPTER IV

RESULTS

A. TEST RIDES WITHOUT VOLUNTARY HYPERVENTILATION

Mean data were compared between the two phases of the control rides (minutes 8-10 and minutes 18-20 of the rides without hyperventilation). No significant difference was found in any of the following variables: $\dot{V}O_2$, $\dot{V}$, lactate. In addition, each of these variables was compared with its corresponding variable measured in minute 8-10 of the test rides with voluntary hyperventilation (in this phase, the subject was still ventilating normally). Again, no significant differences were found in any of the variables during these three exercise periods. Tables 9 and 10 in the Appendix include the mean data of the control rides and of phase 1 of the hyperventilation rides.

McNair who also studied voluntary hyperventilation during exercise reported the same results (48). With the results of her study and this one, it can now be assumed (for healthy subjects who have completed a pilot training program) that no significant change will occur in $\dot{V}$, $\dot{V}O_2$, or lactate during a moderate steady state exercise test. With this assumption which is based on the range of the reported p values ($p > .3$-$.8$), investigators conducting future similar studies may deem the control tests unnecessary.

B. TEST RIDES WITH VOLUNTARY HYPERVENTILATION

Mean data were compared for minutes 8-10 and 18-20. Minutes 1-10 (Phase 1) were with normal ventilation, and minutes 10-20 (Phase 2) were with voluntary hyperventilation at a constant breathing rate of 60 breaths per minute. Table 3 summarizes the entire data of the study by listing the mean values of the following variables, $\dot{V}$, $\dot{V}O_2$, lactate, O_2 cost of breathing, $\Delta\dot{V}$, and $\Delta\dot{V}O_2$.

C. PULMONARY VENTILATION

Figure 4 shows the $\dot{V}$ for Phase 1. No significant difference between $\dot{V}$ of N_2-O_2 and $\dot{V}$ of He-O_2 was found in this phase.

Figure 5 shows the $\dot{V}$ for Phase 2. Here, $\dot{V}$ during voluntary hyperventilation was significantly higher for He-O_2 ($p < 0.05$). The $\Delta\dot{V}$ for He-O_2 and N_2-O_2 is presented in Table 4. $\Delta\dot{V}$ for He-O_2 was significantly higher than that for N_2-O_2 ($p < 0.05$). ($\Delta\dot{V}$ = $\dot{V}$ in Phase 2 - $\dot{V}$ in Phase 1).

D. O_2 COST OF BREATHING

Table 5 shows the O_2 cost of breathing for He-O_2 and N_2-O_2. There was no significant difference in this measurement between the two gases ($p > .5$). Two subjects had higher O_2 costs with He-O_2, and two had higher O_2 costs with N_2-O_2.

Table 3. Summary Data Table of Mean Values

	N_2-O_2 Phase		He-O_2 Phase	
	1	2	1	2
$\dot{V}$ (l/min) BTPS	61.7	117.7*	63.9	145.7*
$\dot{V}O_2$ (l/min)	2.10	2.30	2.07	2.38
LA (mM)	2.4	2.9	2.1	2.1
O_2 Cost of Breathing (ml/l)	3.5		3.9 ($p > .5$)	
$\Delta\dot{V}$ (l/min)	56.1*		81.8*	
$\Delta\dot{V}O$ (ml/min)	200		315 ($p > .1$)	

*Significantly different ($p < .05$).

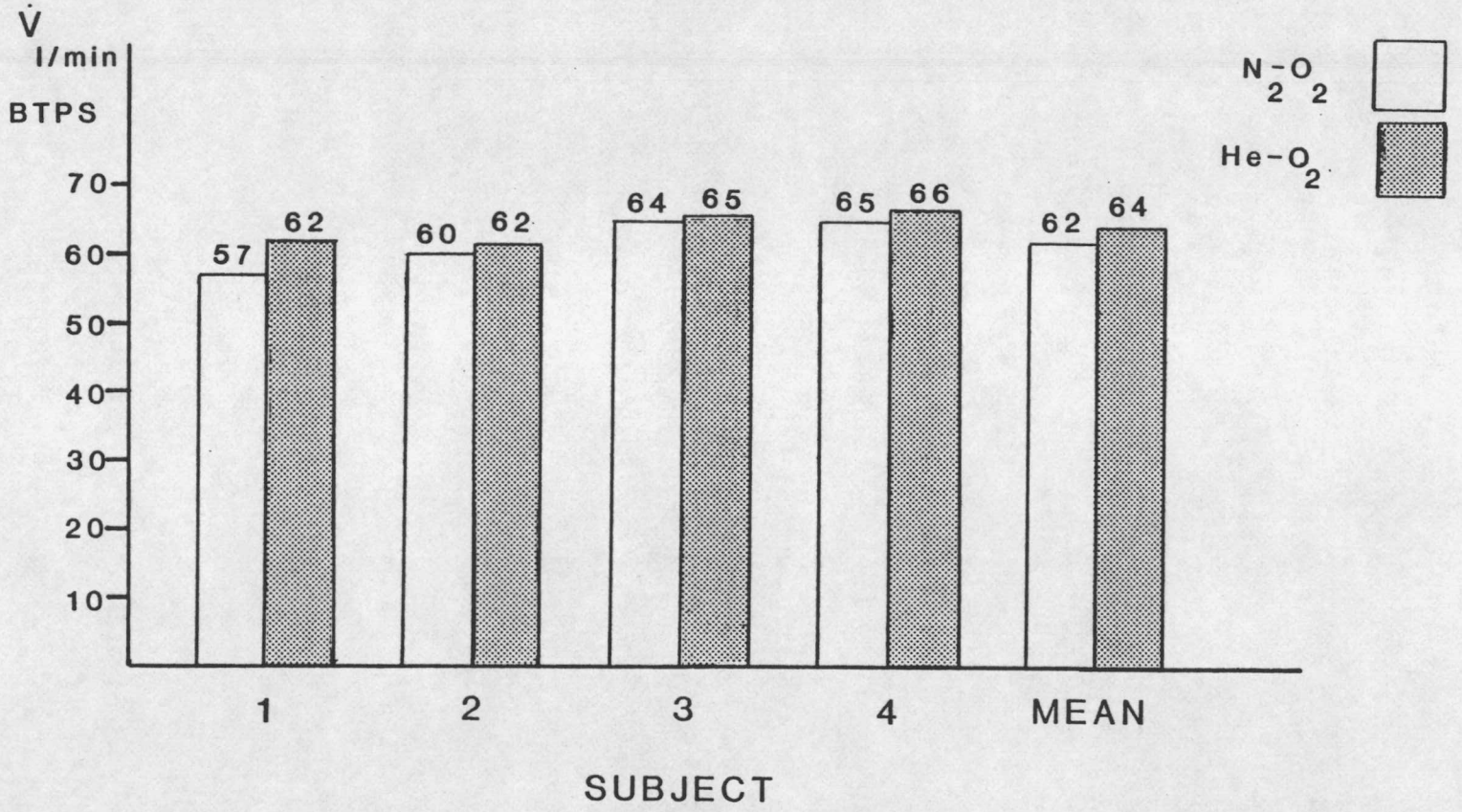

Figure 4. Ventilation during Phase 1.

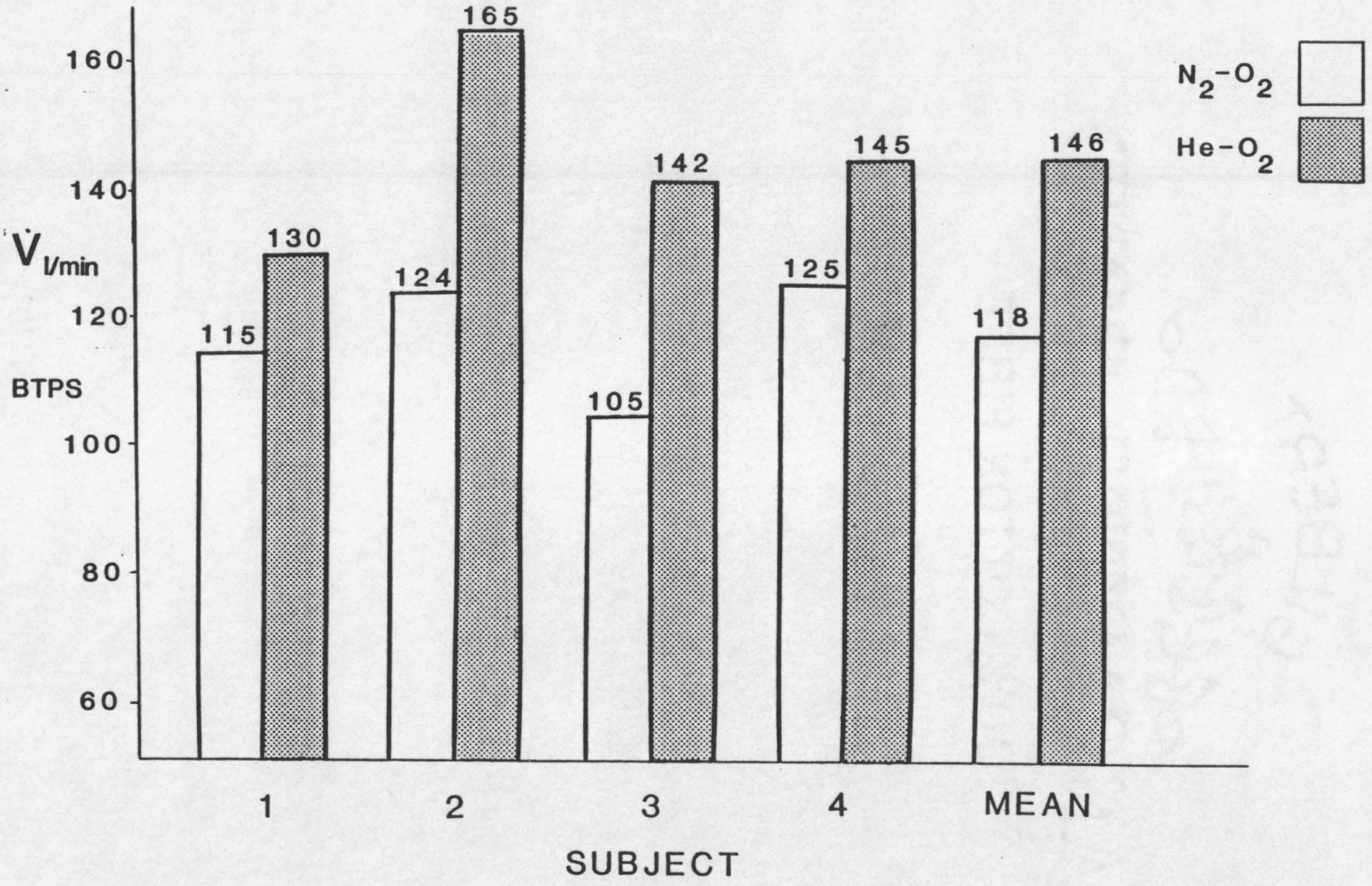

Figure 5. Ventilation during Phase 2. Mean Values are Significantly Different ($p < .05$).

Table 4. $\Delta\dot{V}$ from Isocapnic Voluntary Hyperventilation during Exercise

	$\Delta\dot{V}$ (l/min) BTPS	
	N_2-O_2	He-O_2
Subject		
1	58.7	68.4
2	64.2	103.6
3	41.5	76.5
4	59.9	78.6
$\bar{X}$	56.1	81.8*
SEM	5.0	7.6

*Significantly different ($p < 0.05$).

$\Delta\dot{V}$ = $\dot{V}$ (Phase 2) - V (Phase 1).

Table 5. Oxygen Cost of Breathing for N_2-O_2 and He-O_2 during Voluntary Hyperventilation

	O_2 Cost of Breathing (ml/l)	
	N_2-O_2	He-O_2
Subject		
1	3.8	2.8
2	3.1	3.7
3	3.0	2.6
4	4.2	6.3
$\bar{X}$	3.5	3.9
SEM	0.3	0.9

E. OXYGEN UPTAKE

$\dot{V}O_2$ measured in Phase 1 and Phase 2 for N_2-O_2 and He-O_2 are listed in Table 6. Although not significant, the $\dot{V}O_2$ that resulted from voluntary hyperventilation with He-O_2 is higher than that for N_2-O_2. The $\Delta\dot{V}O_2$ ($\dot{V}O_2$ in Phase 2 - $\dot{V}O_2$ in Phase 1) for He-O_2 and N_2-O_2 is presented in Table 7. This further illustrates the higher $\dot{V}O_2$ for He-O_2 in Phase 2.

F. LACTATE

Table 8 lists the lactate concentrations measured in Phase 1 and Phase 2 for He-O_2 and N_2-O_2. No significant difference was found for either phase of both gases, although the mean [LA] for Phase 2 with N_2-O_2 was slightly higher than Phase 1.

Table 6. Oxygen Uptake between N_2-O_2 and He-O_2 during Exercise with Normal Ventilation and Voluntary Hyperventilation

	$\dot{V}O_2$ (l/min)			
	N_2-O_2		He-O_2	
	Phase		Phase	
	1	2	1	2
Subject				
1	1.95	2.17	1.94	2.13
2	1.94	2.14	1.82	2.20
3	2.06	2.19	2.08	2.28
4	2.44	2.69	2.43	2.92
$\bar{X}$	2.10	2.30	2.07	2.38
SEM	0.12	0.13	0.13	0.18

Table 7. $\Delta\dot{V}O_2$ from Isocapnic Voluntary Hyperventilation between N_2-O_2 and He-O_2

	$\Delta\dot{V}_2$ (ml/min)	
	N_2-O_2	He-O_2
Subject		
1	220	190
2	200	380
3	130	200
4	250	490
$\bar{X}$	200	315
SEM	25.5	72.8

Table 8. Lactate Concentration for N_2-O_2 and He-O_2 during Exercise with Normal Ventilation and Isocapnic Voluntary Hyperventilation

	LA(mM)			
	N_2-O_2		He-O_2	
	Phase		Phase	
	1	2	1	2
Subject				
1	2.8	2.8	2.1	2.0
2	4.6	5.2	3.0	3.3
3	1.2	2.8	2.4	2.3
4	0.9	0.7	0.8	0.7
$\bar{X}$	2.4	2.9	2.1	2.1
SEM	0.8	0.9	0.5	0.6

CHAPTER V

DISCUSSION

The first purpose of this study was to compare the oxygen cost of breathing during exercise between inspired mixtures of 79%-21% N_2-O_2 and 79%-21% He-O_2. This comparison was needed because of the existing conflict among different investigators on the metabolic effects of breathing He-O_2. This was discussed in Chapter II and will be elaborated on in this chapter.

Measuring the lactate accumulation from isocapnic hyperventilation was the second purpose of the study. This was needed because of the existing controversy of the effect of respiratory muscle fatigue in exercise, and of the recent data from Martin et al. (41) showing a significant increase in blood lactate from seated isocapnic voluntary hyperventilation.

The Discussion will be divided into separate sections on the measured variables, i.e. Pulmonary Ventilation, O_2 Cost of Breathing, Oxygen Uptake, and Lactate.

A. PULMONARY VENTILATION

The finding of no significant difference in pulmonary ventilation between the gases during mild work rates (Figure 4, p. 32) is in agreement with other studies (6, 11, 20, 21, 50, 67). The $\dot{V}$ for He-O_2 in Phase 1 was 1 to 2 l/min higher than that for N_2-O_2. Others have

reported higher (though not significant) $\dot{V}$ for $He\text{-}O_2$ during mild work rates (20, 66).

The $\dot{V}$ in voluntary hyperventilation was significantly higher for $He\text{-}O_2$. During intense exercise, $\dot{V}$ for $He\text{-}O_2$ has been reported to be significantly higher than that for air (11, 66, 67, 70).

However, the differences reported in the literature are not consistent. Spitler et al. reported a difference in $\dot{V}$ of 16 l/min between the two gases at maximal work. Brice and Welch reported a difference of 36 l/min, Tait reported 30 l/min, and Fagraeus reported 31 l/min. The mean difference in $\dot{V}$ found in my study in the voluntary hyperventilation period was 28 l/min, $He\text{-}O_2$ being higher.

Why is Spitler's reported $\dot{V}$ value not higher? Brice and Welch provide an explanation (11). Errors are involved when $\dot{V}$ measurements are made with gases of different densities and viscosities. Brice and Welch suggest that Spitler's use of a pneumotachograph may have underestimated the $\dot{V}$ when $He\text{-}O_2$ was used. The consequence of an underestimation of $\dot{V}$ is an invalid $\dot{V}O_2$ measurement from the open circuit technique of measuring O_2 uptake.

If this is true, would the same result occur when using the Parkinson Cowan gas meter, as was done in this study? The answer is no because this gas meter was calibrated with both gases before the experiments, and no calibration differences between gases were found. A previous study supports this finding (10).

Why was there a significant difference in $\dot{V}$ during voluntary hyperventilation between the two gases? When the breathing rate

increased to 60 breaths per minute, more turbulence probably occurred with N_2-O_2 than with He-O_2. Tenney and Reese (68) suggested that most of the resistance to breathing at high levels of ventilation is caused by turbulence. By substituting a less dense gas (He-O_2 is .34 times as dense as air), a greater flow rate is possible. Going back to the description of the Reynolds number in Chapter II, this value for N_2-O_2 must have been significantly higher than that for He-O_2.

When exactly does this difference in ventilation occur? Spitler et al. (66) reported that the difference occurs at about 85% of $\dot{V}O_2$ max. Brice and Welch (11) reported a lower value of about 70-75% $\dot{V}O_2$ max. Brice and Welch define this period as the "breaking point"--that point where $\dot{V}$ for He-O_2 begins to greatly exceed that for air. The studies of Brice and Welch, and Spitler et al. used normal healthy subjects. The work intensity required to elicit this breaking point for patients with chronic pulmonary lung obstruction or emphysema is probably considerably less. Therefore, for these people, I suggest that helium substitution should prove beneficial for exercise tolerance at moderate and maybe even low work rates.

B. O_2 COST OF BREATHING

There was no significant difference in the O_2 cost of breathing between He-O_2 and N_2-O_2. This statement does not mean much by itself. Obviously additional information needs to be added. Voluntary hyperventilation was performed at a constant breathing rate of 60 breaths per minute. Pulmonary ventilation for He-O_2 was significantly higher

than that for N_2-O_2. It can now be said that under similar conditions, one can ventilate more with He-O_2 than with N_2-O_2 without significantly increasing the O_2 cost of the extra ventilation.

One might also assume from these results that the O_2 cost of breathing for He-O_2 is less than that for N_2-O_2 for equivalent ventilations. However, a study needs to be conducted where the $\dot{V}$ rather than the breathing rate is held constant for both gases. This should then fully answer the question of whether He-O_2 is less costly to breathe.

Referring to Table 1, p. 10, the results for the O_2 cost of breathing reported in this study are in rather good agreement with those of others (7, 46, 51, 64). As stated earlier, it is believed by some investigators that the reason for the O_2 cost of breathing not becoming a pulmonary function test is because of the lack of standardized procedures for making this measurement. I believe it is time to reexamine this issue. The range of values being reported for the O_2 cost of breathing seems at least to be more conforming than what Otis reported them to be in 1954 (55).

An excessive O_2 cost of breathing value might indicate to a clinician or respiratory therapist the type of treatment needed for a patient. Or it might indicate to an athlete the need for respiratory muscle training.

Bradley and Leith reported that ventilatory muscle training leads to a significant increase in the level of hyperpnea that could be sustained for a period of 7-15 minutes (7). In a previous study by the same investigators, maximal voluntary ventilation (MVV) was

significantly increased after a 5-week respiratory muscle training period (36). Unpublished data from this lab shows similar results. If the cost of breathing can be reduced for a given level of exercise, it may be possible to provide other muscles with more oxygen. The point to be made here is that the O_2 cost of breathing may be a valuable measurement not only for clinicians but also for serious athletes.

It cannot be overemphasized, however, that to make this measurement, standardized conditions are essential. Should the test be conducted with exercise? If exercise is conducted, then what mode should be performed? Should isocapnia be maintained? Should a constant breathing rate be maintained or would it be better to let the subject choose a desired breathing rate? All of these conditions can affect the final outcome, but nevertheless, the usefulness of the O_2 cost of breathing deserves more attention.

C. OXYGEN UPTAKE

The $\dot{V}O_2$ during Phase 1 showed only a slight difference between $He\text{-}O_2$ and $N_2\text{-}O_2$. Others have reported no significant difference in $\dot{V}O_2$ between these two gases during mild work (6, 11, 21, 30, 50, 66). The $\dot{V}O_2$ for Phase 2, although not significant, was considerably higher for $He\text{-}O_2$, i.e. p approaches .05. This result agrees with the results of a higher $\dot{V}O_2$ for $He\text{-}O_2$ breathing at intense work (11, 18, 67).

During voluntary hyperventilation, the average tidal volume for $He\text{-}O_2$ was 2.4 l and the average tidal volume for $N_2\text{-}O_2$ was 2.0 l.

Referring back to Figure 3, p. 14, the elastic work for He-O_2 was obviously higher than that for N_2-O_2 because of a larger lung and chest wall expansion. The nonelastic work for He-O_2 may have been lower, higher or equivalent to that of N_2-O_2. Remember that a significantly greater volume of gas was ventilated with He-O_2. Therefore, the work of breathing may have been greater for He-O_2 during voluntary hyperventilation, thus causing the higher $\dot{V}O_2$. But from examination of the mean values of the O_2 cost of breathing, $\Delta\dot{V}$, and $\Delta\dot{V}O_2$ (Table 3, p. 31), I doubt this explanation.

The difference between the mean values of the O_2 cost of breathing for both gases (Table 3) was only 0.4 ml/l with He-O_2 being higher. This value seems too small to account for the higher $\dot{V}O_2$ of He-O_2 breathing during voluntary hyperventilation. So the question still stands. Why is the $\dot{V}O_2$ higher for He-O_2 breathing during voluntary hyperventilation?

One possible explanation might be a higher state of alkalosis with He-O_2. Even this seems unlikely since end-tidal CO_2 was kept constant throughout voluntary hyperventilation. The only way to satisfactorily determine this is to make accurate blood gas measurements during the voluntary hyperventilation phase. A future study making these measurements could help determine the effect of alkalosis on $\dot{V}O_2$.

The large differences in $\dot{V}$ during voluntary hyperventilation between the two gases could cause significant acid-base changes in the body. Inducing passive hyperventilation on dogs, Cain (13) concluded

that the hydrogen ion concentration was the primary factor in setting $\dot{V}O_2$. Others have also found changes in $\dot{V}O_2$ from acid-base changes in the body (33, 34, 61).

The important point that the results of this study show is that the O_2 cost of breathing cannot be totally responsible for the higher $\dot{V}O_2$ value found with He-O_2.

D. LACTATE

Isocapnic voluntary hyperventilation did not result in a significant increase in blood lactate. This agrees with other studies where CO_2 is added to the inspired air (16, 26, 71). It has been clearly shown that hypocapnic hyperventilation will increase blood lactate concentration (9, 16, 31, 48). It has been suggested that this increased lactate accumulation is a compensatory mechanism for the reduction in the [H+] from alkalosis (6, 31). By adding CO_2 to the inspired air, this reduction in [H+] is prevented. CO_2 functions as an acid in body fluids, and as the PCO_2 increases, the [H+] will also increase so long as other compensatory mechanisms remain unchanged.

Graham et al. suggested some possible physiological mechanisms for the reduction in lactate from higher CO_2 levels (26). There could be an increased removal of lactate by the liver, heart, and skeletal muscle. The release of lactate into the blood may have been depressed. Glycolysis may have been inhibited by the addition of CO_2 to the inspired air.

Poortmans et al. and Issekutz et al. reported that lactate removal by the heart and resting skeletal muscle is proportional to blood lactate concentration (32, 58). Hence, from the low lactate concentrations reported in this study, enhanced removal by the heart and other tissues seems unlikely.

As for the reduction in the release of lactate into the blood by the active muscle, Graham et al. suggested that the acid-base shifts required to reduce lactate release need to be extreme (26). Mainwood reported that decreasing the pH will inhibit the rate of lactate release for a given intramuscular lactate accumulation (39). Maintaining a constant end tidal CO_2, as was done in my study, prevented any severe acid-base shift that could slow down this lactate release.

Phosphofructokinase has been shown to be inhibited by decreasing the pH (72). Gimenez and Florentz suggested that increasing $PaCO_2$ will inhibit glycolysis (24). It is difficult to say if this mechanism contributed to the low lactate levels from voluntary hyperventilation in my study. The precise amount of CO_2 that was added to the inspired air was not measured. It might be possible that too much CO_2 was added and glycolysis was thus inhibited. I think not, however, because a steady state was maintained by each subject during voluntary hyperventilation, and the end tidal CO_2 readings were closely monitored. The present study cannot firmly establish why lactate did not increase with hyperventilation.

Martin et al. reported a significant increase in blood lactate when subjects voluntarily hyperventilated at rest (41). CO_2 was also

added to the inspired air to keep end tidal CO_2 fractions constant. The ventilations that induced this increase (138 ± 7 l/min) were comparable to those of this study (131 ± 18 l/min). Why did Martin find this increase and I did not?

This difference in findings could be from the fact that Martin's subjects were not exercising. Martin suggested that the absence of exercise in his study would, if anything, underestimate the lactate response of the breathing muscles from hyperventilation. The large vasodilation caused by active muscle in exercise could reduce ventilatory blood flow and O_2 uptake below the levels found in seated hyperventilation. He also suggested that since seated hyperpnea increases the alveolar PO_2 to about 140 Torr, which would result in a 1 or 2% increase in arterial O_2 content, an underestimation of respiratory lactate production in exercise could be made.

Vasodilation occurs in the vascular beds in the active muscles during exercise. This may limit ventilatory muscle blood flow during intense exercise. However, the cardiac output during exercise is probably much higher than that found in seated hyperpnea and a lower ventilatory muscle blood flow in exercise is unlikely. The higher arterial O_2 content from seated hyperpnea seems too small to be attributed to the underestimation that Martin refers to.

Seated hyperpnea that achieves $\dot{V}$ levels found at maximal exercise requires a strenuous amount of respiratory work. Accessory muscles are also used to achieve these high $\dot{V}$ values at rest. When one performs this work, I am not sure that the cardiac output is high

enough to provide the ventilatory muscles an adequate blood flow thus a sufficient O_2 supply. In addition, accessory muscles could be functioning anaerobically. Breathing patterns in seated hyperpnea may be different from those in exercise-induced hyperpnea. This might also explain Martin's high O_2 cost of breathing results in a previous study where seated hyperpnea was also used (44). I suggest that there is a significant difference in the O_2 cost and work of the respiratory muscles between hyperventilation at rest and hyperventilation in exercise.

There is a need to further investigate the effect of respiratory muscle work on lactate accumulation. The physiological mechanisms for a reduction in blood lactate from a higher PCO_2 are still undetermined. Respiratory muscle fatigue remains a controversial issue. The actual site of increased lactate production from hyperventilation has not been completely identified.

E. SUMMARY

The results of this study lead to one main conclusion: when breathing He-O_2 during exercise, one can ventilate more than with N_2-O_2 without significantly increasing the O_2 cost of that extra ventilation.

I suggest that for an equivalent $\dot{V}$, the O_2 cost of breathing with He-O_2 is lower than that for N_2-O_2. Another study is required to make this determination.

Breathing He-O_2 results in significantly higher pulmonary ventilations at high breathing rates and work rates. The $\dot{V}O_2$ for He-O_2 breathing is not different from N_2-O_2 breathing at mild work rates, but is higher during work rates which induce a high $\dot{V}$.

Lactate accumulation does not significantly increase with isocapnic voluntary hyperventilation at exercise.

LIST OF REFERENCES

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1. Astrand, P. O., and K. Rodahl. Textbook of Work Physiology. Second ed. New York: McGraw-Hill Book Company, 235-236, 1977.

2. Balke, B., and J. P. Lillehel. Effect of hyperventilation on performance. J. Aviation Med. 9:371-374, 1956.

3. Barach, A. L. The use of helium as a new therapeutic gas. Anesth. Analg. 14:210-215, 1935.

4. Bartlett, R. G., Jr., H. F. Brubach, and H. Specht. Oxygen cost of breathing. J. Appl. Physiol. 12(3):413-424, 1958.

5. Boerboom, L. E., and J. N. Boelkins. Hemodynamics in awake rabbits during hyperbaric helium-oxygen exposure. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48:281-283, 1980.

6. Bowers, R. W., and E. L. Fox. Metabolic and thermal responses of man in various He-O_2 and air environments. J. Appl. Physiol. 23(4):561-565, 1967.

7. Bradley, M. E., and D. E. Leith. Ventilatory muscle training and the oxygen cost of sustained hyperpnea. J. Appl. Physiol. 45(6): 885-892, 1978.

8. Brauer, R. W., and R. O. Way. Relative narcotic potencies of hydrogen, helium, nitrogen, and their mixtures. J. Appl. Physiol. 20:20-31, 1970.

9. Brice, A. G. The effects of respiratory alkalosis on the hind limb and in situ skeletal muscle in the dog. Knoxville, TN: The University of Tennessee, 1984. 95 p. Dissertation.

10. Brice, A. G. The metabolic responses to helium-oxygen breathing during exercise. Knoxville, TN: The University of Tennessee, 1980. 71 p. Thesis.

11. Brice, A. G., and H. G. Welch. Metabolic and cardiorespiratory responses to He-O_2 breathing during exercise. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 54(2):387-392, 1983.

12. Cain, S. W. Aerterial lactate responses in dogs made apneic or breathing nitrogen. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 42(1):39-43, 1977.

13. Cain, S. M. Increased oxygen uptake with passive hyperventilation of dogs. J. Appl. Physiol. 28(1):4-7, 1970.

14. Campbell, E. J. M., E. K. Westlake, and R. M. Cherniack. Simple methods of estimating oxygen consumption and efficiency of the muscles of breathing. J. Appl. Physiol. 11(2):303-308, 1975.

15. Cherniack, R. M. Work of breathing and the ventilatory response to CO_2. Handbook of Physiology. W. O. Fenn and H. Rahn (Eds.) American Physiological Society, Washington, D.C. Baltimore: Waverly Press, Inc., Section 3, Volume 2:1469-1474, 1964.

16. Eichenholz, A., R. A. Mulhausen, W. E. Anderson, and F. M. MacDonald. Primary hypocapnia: A cause of metabolic acidosis. J. Appl. Physiol. 17(2):283-288, 1962.

17. Eldridge, F. Anaerobic metabolism of the respiratory muscles. J. Appl. Physiol. 21(3):853-857, 1966.

18. Fagraeus, L. Maximal work performance at raised air and helium-oxygen pressures. Acta Physiol. Scand. 91:545-556, 1974.

19. Farhi, L. E., and H. Rahn. Gas stores of the body and the unsteady state. J. Appl. Physiol. 7:472-484, 1955.

20. Flynn, E. T., D. E. Evans, K. M. Greene, D. C. LeGrys, and R. P. Layton. Adrenergic and cardiopulmonary responses to exercise with air and helium-oxygen at 1 ATA. (Abstract). Seventh Symposium on Underwater Physiology 1980, Athens, Greece.

21. Fox, E. L., H. S. Weiss, R. L. Bartels, and E. P. Hiatt. Thermal responses of man during rest and exercise in a helium-oxygen environment. Arch. Environ. Health. 13:23-38, 1966.

22. Freedman, S. Sustained maximum voluntary ventilation. Respiration Physiol. 8:230-244, 1970.

23. Fritts, H. W., J. Filler, A. P. Fishman, and A. Cournand. The efficiency of ventilation during voluntary hyperpnea. J. Clin. Invest. 38(2):1339-1348, 1959.

24. Gimenez, M., and M. Florentz. Effects of hypercapnia on the glycolytic metabolism enzyme activity and myoglobin of stimulated skeletal muscle in the rat. Bull. Europ. Physiopath. Resp. 15:269-284, 1974.

25. Glauser, S. C., E. M. Glauser, and B. F. Rusy. Gas density and the work of breathing. Respiration Physiol. 2:344-350, 1967.

26. Graham, T. E. The effects of hypercapnia on the metabolic response to steady-state exercise. Guelph, Ontario: The University of Guelph, 1980.

27. Gutmann, I., and A. W. Wahlefeld. L-(+)-Lactate determination with lactate dehydrogenase and NAD. In: Methods of enzymatic analysis. Edited by H. U. Bergmeyer. 2nd English Ed. New York: Academic Press, Inc., pp. 1464-1468, 1974.

28. Guyton, A. C. Textbook of Medical Physiology. Sixth ed. Philadelphia: W. B. Saunders Company, 1981.

29. Hawkins, I. K. Helium effect on skeletal muscle of mice. Aerospace Med. 44(4):374-378, 1973.

30. Hoar, P. F., L. W. Raymond, H. C. Langworthy, R. E. Johnsonbaugh, and J. Sode. Physiological responses of men working in 25.5°C water, breathing air or helium tri-mix. J. Appl. Physiol. 40(4): 605-610, 1976.

31. Huckabee, W. E. Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or lactate or glucose and of hyperventilation. J. Clin. Invest. 37:244-254, 1958.

32. Issekutz, B., W. A. S. Shaw, and A. C. Issekutz. Lactate metabolism in resting and exercising dogs. J. Appl. Physiol. 40:312-319, 1976.

33. Khambatta, H. J., and S. F. Sullivan. Carbon dioxide production and washout during passive hyperventilation alkalosis. J. Appl. Physiol. 37:665-669, 1974.

34. Karetzky, M. E., and S. M. Cain. Oxygen uptake stimulation following Na-La-lactate infusion in anaesthetized dogs. Amer. J. Physiol. 216(6):1468-1490, 1969.

35. Latterell, R. L. Nitrogen and helium-induced anoxia: Different lethal effects on rye seeds. Science. 153:69-70, 1966.

36. Leith, D. E., and M. Bradley. Ventilatory muscle strength and endurance training. J. Appl. Physiol. 41(4):508-516, 1976.

37. Levison, H., and R. M. Cherniack. Ventilatory cost of exercise in chronic obstructive pulmonary disease. J. Appl. Physiol. 25(1):21-27, 1968.

38. Liljestrand, G. Skand. Arch. Physiol. 35:199, 1918.

39. Mainwood, G. W., and P. Worsley-Brown. The effects of extracellular pH and buffer concentration on the efflux of lactate from frog sartorius. J. Physiol. 250:1-22, 1975.

40. Margaria, R., G. Milic-Emili, J. M. Petit, and G. Cavagna. Mechanical work of breathing during muscular exercise. J. Appl. Physiol. 15(3):354-358, 1960.

41. Martin, B. J., H. Chen, and J. A. Kolka. Anaerobic metabolism of the respiratory muscles during exercise. Med. Sci. Sports Exerc. 16(1):82-86, 1984.

42. Martin, B. J., M. Heintzelman, and H. Chen. Exercise performance after ventilatory work. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52(6):1581-1585, 1982.

43. Martin, B. J., K. E. Sparks, C. W. Zwillich, and J. V. Weil. Low exercise ventilation in endurance athletes. Med. Sci. Sports. 11(2):181-185, 1979.

44. Martin, B. J., and J. M. Stager. Ventilatory endurance in athletes and non-athletes. Med. Sci. Sports Exerc. 13(1):21-26, 1981.

45. Mathewson, H. S. Helium-Who needs it? Respiratory Care. 27(11): 1400-1401, 1982.

46. McGregor, M., and M. R. Becklake. The relationship of oxygen cost of breathing to respiratory mechanical work and respiratory force. J. Clin. Invest. 40:971-980, 1961.

47. McKerrow, C. B., and A. B. Otis. Oxygen cost of hyperventilation. J. Appl. Physiol. 9:375-379, 1956.

48. McNair, K. I. The oxygen cost and hyperlactatemia of voluntary hyperventilation during exercise. Knoxville, TN: The University of Tennessee, 1979. 37 p. Thesis.

49. Milic-Emili, G., and J. M. Petit. Mechanical efficiency of breathing. J. Appl. Physiol. 15(3):359-362, 1960.

50. Murphy, T. M., W. H. Clark, I. P. B. Buckingham, and W. A. Young. Respiratory gas exchange in exercise during helium-oxygen breathing. J. Appl. Physiol. 26(3):303-307, 1969.

51. Murray, J. F. Oxygen cost of voluntary hyperventilation. J. Appl. Physiol. 14(2):187-190, 1959.

52. Nebergall, W. H., F. C. Schmidt, and H. F. Holtzclaw, Jr. General Chemistry. Third ed. Lexington: D. C. Heath and Co., p. 77, 1968.

53. Newhouse, M. T., M. R. Becklake, P. T. Macklem, and M. McGregor. Effect of alterations in end-tidal CO_2 tension on flow resistance. J. Appl. Physiol. 19(4):745-749, 1964.

54. Nissell, O. The action of oxygen and CO_2 on the bronchioles and vessels of isolated perfused lungs. Acta. Physiol. Scand. 21:573, 1-62, 1950.

55. Otis, A. B. The work of breathing. Physiol. Rev. 34:449-457, 1954.

56. Otis, A. B. Quantitative relationships in steady-state gas exchange. In: Handbook of Physiology, Sec. 3, Vol. II, W. Fenn and H. Rahn (Eds.). Washington, D. C.: American Physiological Society, 1964, pp. 681-698.

57. Pifarre, R., M. D. Raghunath, R. M. Vanecko, F. S. Chua, J. U. Balis, and W. E. Neville. Effect of oxygen and helium mixtures on ventricular fibrillation. J. Thorac. Cardiovasc. Surg. 60:648-652, 1970.

58. Poortmans, J. R., J. Delescaille-Vanden Bossche, and R. Leclercq. Lactate uptake by inactive forearm during progressive leg exercise. J. Appl. Physiol. 45:835-839, 1978.

59. Raimondi, A. C., R. H. T. Edwards, D. M. Denison, D. G. Leaver, D. G. Spencer, and J. A. Siddorn. Exercise tolerance breathing a low density gas mixture, 35% oxygen and air in patients with chronic obstructive bronchitis. Clin. Sci. 39:675-685, 1970.

60. Raymond, L., R. B. Weiskopf, M. L. Halsey, A. Goldfein, E. I. Eger, and J. W. Severinghaus. Possible mechanism for the antiarrhythmic effect of helium in anesthetized dogs. Science. 176:1250-1252, 1972.

61. Riggs, T. E., A. W. Shaffer, and C. A. Guenter. Physiologic effects of passive hyperventilation on oxygen delivery and consumption. Proc. Soc. Exp. Biol. Med. 140:1414-1417, 1972.

62. Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. J. Biol. Chem. 167:235-250, 1947.

63. Shepard, R. J. The maximum sustained voluntary ventilation in exercise. Clin. Sci. 32:167-176, 1967.

64. Shepard, R. J. The oxygen cost of breathing during vigorous exercise. Quart. J. Exper. Physiol. 51:336-350, 1966.

65. Slonim, N. B., and L. H. Hamilton. Respiratory Physiology. Fourth ed. St. Louis: The C. V. Mosby Company, 1981.

66. Spitler, D. L., S. M. Horvath, K. Kobayashi, and J. A. Wagner. Work performance breathing normoxic nitrogen or helium gas mixtures. Eur. J. Appl. Physiol. 43:157-166, 1980.

67. Tait, G. T. Exercise performance in men breathing selected mixtures of nitrogen-oxygen and helium-oxygen. State College, PA: The Pennsylvania State University, 1969. 94 p. Dissertation.

68. Tenney, S. M., and R. E. Reese. The ability to sustain great breathing efforts. Respiration Physiol. 5:187-201, 1968.

69. Whiting, W. G. Mechanical efficiency of breathing at selected ventilatory loads. Toronto: University of Guelph, 1981. 72 p. Dissertation.

70. Wilson, D., and H. G. Welch. Effects of varying concentrations of N_2/O_2 and He/O_2 on exercise tolerance in man. Med. Sci. Sports Exerc. 12:380-384, 1980.

71. Zborowska-Sluis, D. T., and J. B. Dossetor. Hyperlactatemia of hyperventilation. J. Appl. Physiol. 22(4):746-755, 1967.

72. Zborowska-Sluis, D. T., and G. A. Klassen. Carbon dioxide mediated glycolysis II. Resp. Physiol. 19:162-175, 1973.

APPENDIX

Table 9. Mean Data from Phase 1 and Phase 2 of the Control Ride with N_2-O_2 and Phase 1 of the Experimental Ride with N_2-O_2

	Phase		
	C1	C2	E1
$\dot{V}$ (l/min) BTPS	61.5	61.2	61.7
$\dot{V}O_2$ (l/min)	2.11	2.15	2.10
LA (mM)	2.3	2.4	2.4

C1--Minutes 1-10 of the Control Ride.

C2--Minutes 11-20 of the Control Ride.

E1--Minutes 1-10 of the Experimental Ride with Hyperventilation (normal ventilation was maintained during E1).

No significant difference was found between the following comparisons:

$\dot{V}$	C1 vs C2 ($p > .5$)	C2 vs E1 ($p > .8$)
$\dot{V}O_2$	C1 vs C2 ($p > .3$)	C2 vs E1 ($p > .4$)
LA	C1 vs C2 ($p > .4$)	C2 vs E1 ($p > .8$)

Table 10. Mean Data from Phase 1 and Phase 2 of the Control Ride with He-O_2 and Phase 1 of the Experimental Ride with He-O_2

	Phase		
	C1	C2	E1
$\dot{V}$ (l/min) BTPS	62.4	62.1	63.9
$\dot{V}O_2$ (l/min)	2.15	2.14	2.07
LA (mM)	1.5	1.6	2.1

C1--Minutes 1-10 of the Control Ride.

C2--Minutes 11-20 of the Control Ride.

E1--Minutes 1-10 of the Experimental Ride with Hyperventilation (normal ventilation was maintained during this phase).

No significant difference was found between the following comparisons:

$\dot{V}$	C1 vs C2 ($p > .4$)	C2 vs E1 ($p > .4$)
$\dot{V}O_2$	C1 vs C2 ($p > .5$)	C2 vs E1 ($p > .4$)
LA	C1 vs C2 ($p > .5$)	C2 vs E1 ($p > .4$)

Table 11. Individual Data of Ventilation during Control Rides

	$\dot{V}$ (l/min) BTPS			
	N_2-O_2		He-O_2	
	Phase		Phase	
	1	2	1	2
Subject				
1	62.6	63.0	62.9	63.2
2	60.0	59.4	58.8	57.6
3	62.4	61.0	67.4	67.1
4	60.9	61.3	60.3	60.3
$\bar{X}$	61.5	61.2	62.4	62.1
SEM	0.6	0.7	1.9	2.0

Table 12. Individual Data of $\dot{V}O_2$ during Control Rides

	$\dot{V}O_2$ (l/min)			
	N_2-O_2 Phase		He-O_2 Phase	
	1	2	1	2
Subject				
1	1.99	2.04	2.00	2.01
2	2.05	2.01	2.05	2.06
3	2.00	2.06	2.15	2.10
4	2.41	2.47	2.38	2.38
$\bar{X}$	2.11	2.15	2.15	2.14
SEM	0.1	0.1	0.1	0.1

Table 13. Individual Data of Lactate during Control Rides

	LA(mM)			
	N_2-O_2		He-O_2	
	Phase		Phase	
	1	2	1	2
Subject				
1	2.5	3.2	1.8	1.5
2	3.6	3.5	2.2	2.8
3	2.2	2.2	1.2	1.2
4	0.7	0.7	0.6	0.7
$\bar{X}$	2.3	2.4	1.5	1.6
SEM	0.6	0.6	0.4	0.5

VITA

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