MECHANISMS OF EXERCISE - INDUCED HYPOXEMIA IN TRAINED ENDURANCE ATHLETES

Anthony John Rice B.Ed, M.Ed (Studies)

Department of Medicine, University of Adelaide

Submitted: March 1999

DISCLOSURE AND CONSENT

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Signed ..... Date 26/8/99

Anthony J. Rice

DEDICATION

This thesis is dedicated to my wife, Kristan, who has given me unconditional love and support from the first day I met her. Thank you Kristan, I know a time will come when I will be able to provide you with the same level of commitment as you have shown me.

ACKNOWLEDGEMENTS

I would like to gratefully acknowledge my supervisors, Professor Garry Scroop, Dr Christopher Gore and Associate Professor Raffaele Scicchitano without whom this thesis would not have been possible. I would also like to thank Dr Mark Holmes, Dr Andrew Thornton, Kustas Tiivas, and the entire Department of Thoracic Medicine, Royal Adelaide Hospital for their support and patience throughout the time it has taken me to complete this work. I would like to conclude by thanking all of the subjects who have been involved with this thesis.

PUBLICATIONS, PRESENTATIONS AND AWARDS

Publications

- **Rice, A. J.**, G. C. Scroop, C. J. Gore, A. T. Thornton, M.J. Chapman, H.W. Greville, M.D. Holmes, and R. Scicchitano. Exercise-induced hypoxaemia in highly trained cyclists at 40% peak oxygen uptake. ***Eur.J.Appl.Physiol.*** 79(4): 353-359, 1999.

- **Rice, A. J.**, A.T. Thornton, C.J. Gore, G.C. Scroop, H.W. Greville, H. Wagner, P.D. Wagner and S.R. Hopkins. Pulmonary gas exchange during exercise in highly trained cyclists with arterial hypoxemia. (accepted) ***J.Appl.Physiol.*** 1999.

- Barker, R., S.R. Hopkins, N. Kellog, I.M. Olfert, T. Brutsaert, T.P. Gavin, P. Entin, **A.J. Rice**, and P.D. Wagner. Measurement of cardiac output during exercise by open circuit acetylene uptake. (accepted) ***J.Appl.Physiol.*** 1999

- **Rice, A.J.**, G.C. Scroop, A.T. Thornton, N.S. McNaughton, K.J. Rogers, H.W. Greville, R. Scicchitano, and C.J. Gore. Effects of training discipline and exercise modality on arterial blood gases during intense exercise. (submitted) ***Resp. Physiol.*** 1999.

Presentations

- Oral Presentation: Oxygen diffusion limitation and inadequate hyperventilation results in arterial hypoxemia in trained cyclists. **Thoracic Society of Australia and New Zealand, Adelaide, March 1998.**

- Oral Presentation: Exercise-induced hypoxemia in trained cyclists begins with the onset of exercise and is related to inadequate hyperventilation and the alveolar to arterial oxygen pressure difference**. Sports Medicine Australia, Adelaide, October 1998.**

Awards

- Allen and Hanburys Research Fellowship. **Thoracic Society of Australia and New Zealand, Canberra, March 1999.**

- Young Investigator Award, **Thoracic Society of Australia and New Zealand, Adelaide, March 1998.**

- Highly commended oral presentation, **Sports Medicine Australia, Adelaide, October 1998.**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

ABSTRACT

The primary purpose of this doctoral thesis was to investigate the mechanisms of exercise-induced hypoxemia (EIH) which is reported to occur in ~50% of trained endurance athletes whose peak oxygen consumption ($\dot{V}O_{2peak}$) exceeds 68 $ml.kg^{-1}.min^{-1}$. The phenomenon has been reported at exercise intensities greater than 70% of $\dot{V}O_{2peak}$ and is characterised by a significant reduction in arterial oxygen tension (PaO_2) and arterial oxygen saturation, and an excessive widening of the alveolar-arterial oxygen tension difference ($A\text{-}aDO_2$). The suggested mechanisms for EIH include an inadequate hyperventilatory response to exercise, an end-capillary oxygen diffusion limitation, ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality and an intra or extra-pulmonary shunt. The role and relative contribution from each of these factors remain uncertain.

The first study in this thesis identified the prevalence of EIH in a group of young, competitive endurance-trained cyclists. In contrast to previous studies, EIH in this subject group was found to occur at much lower exercise intensities (~40% $\dot{V}O_{2peak}$) than previously reported. It was also shown that PaO_2 during moderate and maximal exercise was strongly associated with alveolar oxygen tension (PAO_2) and $A\text{-}aDO_2$. Importantly, this initial experimental series allowed an otherwise homogeneous group of trained athletes to be divided for further study on the basis of the presence or absence of EIH.

These two sub-groups were then enrolled in a second protocol to explore some of the suggested mechanisms of EIH. Using the multiple inert gas elimination technique (MIGET), the contributions of end-capillary oxygen diffusion limitation and $\dot{V}_A/\dot{Q}$ inequality to EIH were measured at rest and during exercise at ~30%, 60% and 90% of $\dot{V}O_{2peak}$. The results of this second study demonstrated that those athletes with EIH had significantly greater levels of end-capillary oxygen diffusion limitation when compared with the sub-group without EIH. Furthermore, when both sub-groups were combined, PaO_2 at 90% $\dot{V}O_{2peak}$ could be accurately predicted from a combination of the lung diffusing capacity for oxygen, minute ventilation ($\dot{V}_E$, BTPS) and $\dot{V}_A/\dot{Q}$ inequality, which respectively, accounted for 31%, 24% and 17% of the measured variance. This study is the first to use MIGET to explore the phenomenon of EIH in trained athletes and the results suggest a multifactorial etiology with a dominant role for end-capillary oxygen diffusion limitation and inadequate hyperventilation, and a lesser contribution from $\dot{V}_A/\dot{Q}$ inequality.

Although not specifically identified, literature reports suggest that EIH is more severe with treadmill running than cycling, which could reflect ventilatory differences between the two exercise modes. Given the strong link between ventilation and EIH identified in the earlier sections of this thesis, the final experimental series explored the effect of exercise mode on the severity of EIH with attention directed specifically at an etiological role for inadequate hyperventilation. The differences in arterial blood gases and metabolic function were assessed in thirteen endurance-trained subjects during five minutes of high

intensity exercise on both a cycle and treadmill ergometer. The results indicated that the degree of EIH was ergometer specific and strongly associated with $\dot{V}_E$. It was concluded that the greater level of ventilation on the cycle ergometer was stimulated by higher arterial blood lactic acid levels consequent upon a greater relative work load placed on the lower limb muscles.

In summary, this thesis identifies for the first time that EIH occurs at a much lower exercise intensity than reported previously (~40% $\dot{V}O_{2peak}$) and that the exercise mode changes the severity of the phenomenon. The novel approach of using inert gas measurements to examine the mechanism of EIH has demonstrated that while EIH has a multifactorial etiology, end-capillary oxygen diffusion limitation and inadequate hyperventilation are primary factors with $\dot{V}_A/\dot{Q}$ inequality involved to a lesser extent.

1 INTRODUCTION

1.1 DEFINITION OF EXERCISE-INDUCED HYPOXEMIA

Clinically, exercise-induced hypoxemia (EIH) and arterial oxygen (O_2) desaturation co-exist and are often used to describe the same phenomenon. Desaturation has been defined as a decrease in arterial O_2 saturation (SaO_2) of ≥2% as measured by CO-oximetry (Mohler, Collier, et al. 1982), although 4% appears as the more standard value in the literature (Ries, Farrow, et al. 1985; Zeballos & Weisman 1991). Other definitions for desaturation include a reduction in SaO_2 below 88% and/or arterial O_2 tension (PaO_2) below 55 mm Hg (Shigeoka & Stults 1992). In contrast, some authors have described EIH in healthy subjects to be a significant reduction in PaO_2 (Rowell, Taylor, et al. 1964), which in some cases can be as little as 5-10 mm Hg (Harms, McClaran, et al. 1998; Préfaut, Bourgouin-Karaouni, et al. 1988).

In the trained athlete, EIH has been defined as a decline in SaO_2 below 92% (Harms & Stager 1995; O'Kroy & Martin 1989; Powers, Lawler, et al. 1989). The relevance of this ceiling is that maximal O_2 consumption ($\dot{V}O_{2max}$) is lowered by 1% for every 1% decline in SaO_2 below 92% (O'Kroy & Martin 1989; Powers, Lawler, et al. 1989). Other workers have defined EIH statistically as a change in PaO_2 of >18 mm Hg, which corresponds to four standard deviations away from the mean maximal exercise-induced change in PaO_2 in healthy

untrained people (Powers, Dodd, et al. 1991; Powers, Martin, et al. 1992). However, changes in PaO_2 as small as 8 mm Hg have been used to define EIH in some studies involving athletes (Anselme, Caillaud, et al. 1994).

As will be stated in Section 1.4, the main aim of this doctoral thesis was to investigate the mechanisms of EIH in healthy trained athletes. Due to the nature of the investigations there was only one study (see Section 4) where a distinction in PaO_2 needed to be made between two subjects groups. In that study the two groups were matched for $\dot{V}O_{2peak}$ but the respective group mean PaO_2's during exercise were significantly different. The two groups were chosen based on the definition provided by Rowell et al. (1964) using a limit of >12 mm Hg as the ceiling for a significant reduction in PaO_2 during exercise.

1.2 GENERAL BACKGROUND

1.2.1 Consequences of exercise-induced hypoxemia

One major consequence of EIH is that it cancels the beneficial effects of increased hemoglobin concentration, thus reducing the O_2 carrying capacity of arterial blood and ultimately limiting $\dot{V}O_{2max}$. Arterial hemoglobin concentration increases 10-15% during severe exercise when plasma water is lost into the active muscle cells due to the rise in muscle osmolarity (Harrison 1985). In a healthy, untrained subject, SaO_2 decreases slightly from ~97% to no lower than 94% during maximal exercise (Dempsey & Johnson 1992). This desaturation, combined with the relative hemoconcentration, results in arterial O_2 carrying capacity increasing from ~20 $ml.100ml^{-1}$ at rest to ~22 $ml.100ml^{-1}$ at $\dot{V}O_{2max}$, while the actual O_2 content of arterial blood rises from ~19 $ml.100ml^{-1}$ to ~20 $ml.100ml^{-1}$. This relatively minor desaturation reduces the arterial O_2 content of a healthy, untrained subject by approximately 2 $ml.100ml^{-1}$, which theoretically reduces $\dot{V}O_{2max}$ from 3.4 $l.min^{-1}$ to 3.0 $l.min^{-1}$ (Rowell, Taylor, et al. 1964). One major difference between a healthy, untrained subject and the trained endurance athlete is that the latter has an extremely high maximal cardiac output ($\dot{Q}_{max}$) which attenuates any reduction in O_2 delivery to the skeletal muscles (O_2 delivery = $\dot{Q}$ x O_2 content). In the trained endurance athlete, O_2 carrying capacity at $\dot{V}O_{2max}$ is similar to that of a healthy, untrained subject (~22 $ml.100ml^{-1}$), but due to the effects of EIH, O_2 content can be as low as 18 $ml.100ml^{-1}$ representing a SaO_2 of ~85% (Rowell, Taylor, et al. 1964). This reduction in arterial O_2 content

lowers the potential to widen the arterio-venous O_2 difference by ~4 ml.100ml^{-1} at $\dot{V}O_{2max}$. Coupled with a $\dot{Q}_{max}$ approaching ~35 l.min^{-1}, the maximal O_2 carrying capacity in trained athletes without EIH would be ~7.7 l.min^{-1} (35 l.min^{-1} x 22 ml.100ml^{-1}) (Rowell 1993). However, in athletes experiencing marked EIH, maximal O_2 carrying capacity can be reduced to ~6.3 l.min^{-1} (35 l.min^{-1} x 18 ml.100ml^{-1}). Based on an 85% extraction at the tissue level (Rowell 1993), $\dot{V}O_{2max}$ will be reduced from ~6.5 l.min^{-1} [35 l.min^{-1} x (0.85 x 22 ml.100ml^{-1})] to ~5.4 l.min^{-1} [35 l.min^{-1} x (0.85 x 18 ml.100ml^{-1})] as a result of EIH. The functional importance of EIH was demonstrated by Powers et al. (1989) where the effects of EIH were reversed by breathing a slightly hyperoxic gas mixture (F_IO_2=0.26) which increased the mean $\dot{V}O_{2max}$ from 5.0 to 5.7 l.min^{-1}. This effect is even more pronounced in the thoroughbred racehorse where desaturation from 98% to 77% is not uncommon, and maximal O_2 carrying capacity is reduced correspondingly from 97 l.min^{-1} to 74 l.min^{-1} (Bayly, Hodgson, et al. 1989).

1.2.2 Initial reports of exercise-induced hypoxemia

In 1958, Holmgren and Linderholm (1958) were the first to describe EIH in a group of junior endurance athletes. They demonstrated a wide variation in the blood gas response to maximal exercise. While several subjects showed a large reduction in PaO_2, some to as low as 57 mm Hg, others remained near rest values. The average PaO_2 for the thirteen subjects was 78.8 mm Hg, corresponding to an mean SaO_2 of 94%. Rowell et al. (1964) later demonstrated

that SaO_2 declined from a mean resting value of approximately 98% to 85% during maximal exercise in trained subjects. In addition, four subjects underwent three months of endurance training with a subsequent 15% increase in $\dot{V}O_{2max}$, but during maximal exercise SaO_2 decreased by a further 2-3%.

Following these initial studies, investigation into EIH remained dormant until 1980 when Gledhill et al. (1980) demonstrated a significant reduction in PaO_2 (22 mm Hg) during near-maximal exercise in well trained subjects. A systematic and comprehensive investigation of EIH was conducted in 1984 by Dempsey and coworkers (1984). Sixteen trained runners (mean $\dot{V}O_{2max}$; 72.2 $ml.kg^{-1}.min^{-1}$) completed a variety of protocols aimed at identifying the mechanisms responsible for EIH. It was observed that the subjects with the most pronounced EIH exhibited little or no alveolar hyperventilation, maintained arterial PCO_2 ($PaCO_2$) values near resting levels, and markedly widened the alveolar-arterial O_2 tension difference ($A\text{-}aDO_2$), sometimes in excess of 40 mm Hg. Importantly, the study also demonstrated, using mild hypoxia, hyperoxia and a reduced density inspired gas (helium-O_2 mixture), that PaO_2 changed in proportion to alveolar PO_2 (PAO_2), suggesting that adequate alveolar hyperventilation was a key determinant of arterial oxygenation. In conclusion, Dempsey et al. (1984) stated that "hypoxemia may be attributed to a diffusion limitation secondary to very short red cell transit times in at least a portion of the pulmonary circulation". This conclusion, together with those of earlier workers provided the impetus for a large number of studies that have addressed the prevalence and mechanisms of EIH in trained endurance athletes.

1.2.3 Prevalence of exercise-induced hypoxemia

Using the physiological definition of an SaO_2 <92% (Powers, Lawler, et al. 1989), the prevalence of EIH in trained males and females performing heavy exercise has been shown to range from 0% (Brown, Knowlton, et al. 1993) to 76% (Dempsey, Hanson, et al. 1984; Gore, Hahn, et al. 1996; Harms, McClaran, et al. 1998; Harms & Stager 1995; Miyachi & Tabata 1992; Norton, Squires, et al. 1995; Pedersen, Mandoe, et al. 1996; Powers, Dodd, et al. 1988; Powers, Lawler, et al. 1989; Powers, Martin, et al. 1992; St Croix, Harms, et al. 1998; Warren, Cureton, et al. 1991; Williams, Powers, et al. 1986). In an attempt to define EIH more clearly, a number of workers (Powers, Dodd, et al. 1988; Williams, Powers, et al. 1986) have proposed that EIH in healthy male subjects occurs in ~40-50% of those with a $\dot{V}O_{2max}$ in excess of 68 $ml.kg^{-1}.min^{-1}$ during exercise of an intensity >70% $\dot{V}O_{2max}$ (Powers, Dodd, et al. 1984). Older male athletes also experience EIH, but at lower exercise intensities, and to a much larger degree than young athletes (Préfaut, Anselme, et al. 1994). Data collected on the female athlete are sparse, but the limited number of studies suggest that EIH may affect a greater percentage and occur at a lower $\%\dot{V}O_{2max}$ in females than males (Gore, Little, et al. 1997; Harms, McClaran, et al. 1998; St Croix, Harms, et al. 1998).

1.2.4 Characteristics of exercise-induced hypoxemia in trained endurance athletes

The data of Dempsey et al. (1984) provide a clear picture of the characteristics of EIH in the trained endurance athlete. The athlete with EIH has a large metabolic capacity (>68 $ml.kg^{-1}.min^{-1}$ or 4.5 $l.min^{-1}$) with normal pulmonary function when compared to race, age and height predicted values. However, they appear to have a blunted (often termed 'inadequate') hyperventilatory response to exercise (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Harms, McClaran, et al. 1998; Miyachi & Tabata 1992) which limits the rise in PAO_2, maintains $PaCO_2$ near resting levels, and is associated with a decrease in both PaO_2 and SaO_2 below resting levels. The mechanisms behind the inadequate hyperventilatory response to exercise in the athlete with EIH remain unclear, but suggestions include; a specific training response (Hopkins & McKenzie 1993), reduced chemosensitivity (Harms & Stager 1995), excess mechanical load placed on the chest wall (Dempsey, Hanson, et al. 1984), and mechanical limitations to air flow (Aaron, Seow, et al. 1992).

A key characteristic exhibited by the athlete with EIH is significant pulmonary gas exchange inefficiency, as evidenced by an excessive widening of their A-aDO_2. Recent work has demonstrated that A-aDO_2 is directly associated with $\dot{V}O_2$ (Johnson, Saupe, et al. 1992; Norton, Squires, et al. 1995; Warren, Cureton, et al. 1991) and is maximal at $\dot{V}O_{2max}$. The explanations for an increase in the A-aDO_2 in healthy, untrained subjects during exercise include; intra and

extra-pulmonary shunt, ventilation perfusion inequality and end-capillary O_2 diffusion limitation (Figure 1.1).

A number of recent reports have suggested that histamine (Anselme, Caillaud, et al. 1994; Préfaut, Anselme, et al. 1997) and dietary polyunsaturated fatty acids (Aguilaniu, Flore, et al. 1995; Aguilaniu, Flore, et al. 1998) may play an accessory role in the development of EIH in the trained athlete, and that the latter may be linked to cell membrane fluidity and thus O_2 diffusion. These reports are yet to be corroborated, but will be discussed in more detail, along with all potential mechanisms believed to contribute to EIH, in the following sections.

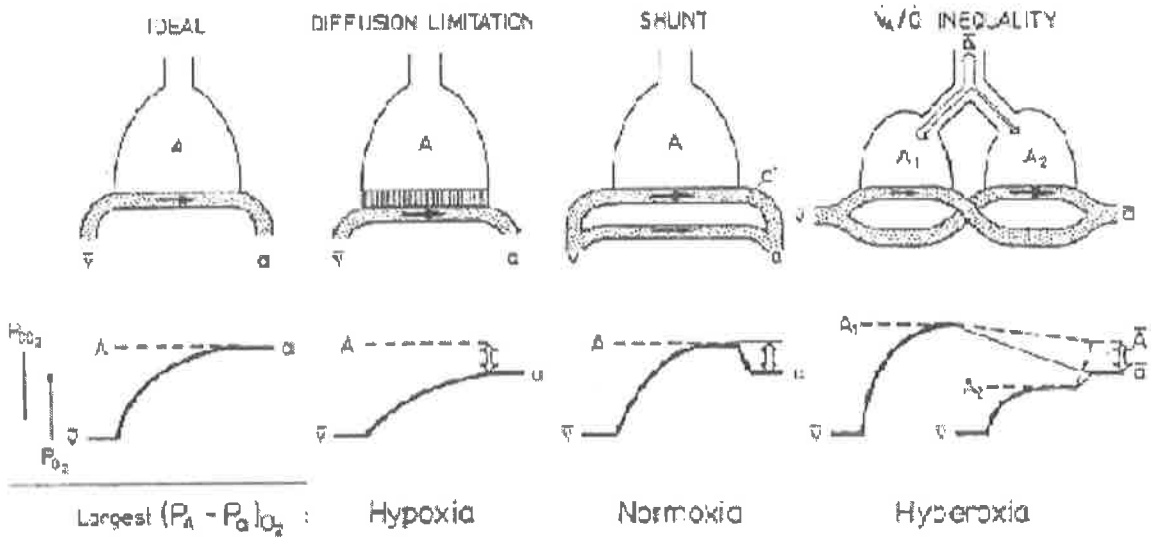


Figure 1.1 Models showing the mechanisms for a widened alveolar-arterial O_2 tension difference (A-aDO_2) by end-capillary O_2 diffusion limitation, shunt and ventilation-perfusion inequality ($\dot{V}_A/\dot{Q}$ inequality). A-aDO_2 is indicated by the open arrows. Reproduced from Piiper (1994).

1.3 POSSIBLE MECHANISMS RESPONSIBLE FOR EXERCISE-INDUCED HYPOXEMIA

1.3.1 Inadequate hyperventilation

By definition, inadequate hyperventilation, sometimes referred to as relative hypoventilation, is an alveolar ventilation below the rate metabolically required to maintain arterial blood gases at normal values (Powers, Martin, et al. 1993). A cardinal marker of hypoventilation is an increase in $PaCO_2$ above normal resting levels. As this has not been demonstrated during heavy exercise in the trained athlete, the belief is that hypoventilation is not responsible for EIH in athletes. Despite this, Dempsey (1987) and Dempsey and co-workers (1984) have suggested that an inadequate hyperventilatory response may contribute to differing magnitudes of EIH between athletes. As such, the term inadequate hyperventilation will be used to describe, herein, an alveolar ventilation which is insufficient to maintain PaO_2 within a normal range.

1.3.1.1 Ventilation at rest

Ventilation at rest depends entirely upon cyclical respiratory-muscle excitation by the motor nerves to the diaphragm and the intercostal muscles. The phasic contraction to these muscle groups is the result of fluctuations in the membrane potentials of the respiratory motorneurons. These alternating rhythmic

phases of depolarisation and hyperpolarisation originate from the medulla oblongata, and are referred to as the central respiratory drive. It remains controversial as to how the brain generates alternating cycles of firing and quiescence in the medullary inspiratory neurons, but afferent impulses from the pulmonary stretch receptors and synaptic input from various areas of the pons (pneumotaxic centre) are believed to have strong influences.

One of the many inputs to the medulla inspiratory neurons for the involuntary control of ventilation arises from the peripheral and central chemoreceptors. The peripheral chemoreceptors are located in the bifurcation of the carotid arteries (Heymans & Heymans 1927) and on the arch of the aorta, and are known as the carotid and aortic bodies. The carotid bodies play a more important role in the control of ventilation at rest. The peripheral chemoreceptors are sensitive to changes in PaO_2, hydrogen ion concentration ($[H^+]$) and $PaCO_2$, and at rest have been shown to contribute approximately 10-15% of the ventilatory drive to breathe (Dejours, Labrousse, et al. 1957; Dejours, Labrousse, et al. 1958). A low PaO_2 will increase the rate at which the peripheral chemoreceptors receptors discharge impulses to the medulla (Page 209: Dejours 1981). The resulting increase in ventilation provides more O_2 to the alveoli and minimises the drop in PaO_2. However, it is important to note that PaO_2 generally needs to fall below 60 mm Hg before this response occurs. The answer to the apparent lack of response by the peripheral chemoreceptors to small reductions in PaO_2 can be found by examining the shape of the oxyhemoglobin dissociation curve. Total arterial O_2 content is not significantly reduced until the PaO_2 falls

below 60 mm Hg, therefore any increase in ventilation above a PaO_2 of 60 mm Hg is not necessary.

In contrast to PaO_2, the peripheral chemoreceptors are highly sensitive to changes in $PaCO_2$, with even a 2-5 mm Hg increase in $PaCO_2$ resulting in a nearly 100% increase in minute ventilation. The opposite can also happen, where a reduction in $PaCO_2$ removes the stimulus to ventilate, thereby allowing the metabolically produced CO_2 to accumulate and return $PaCO_2$ to normal. In this manner, $PaCO_2$ at rest is stabilised at the normal value of ~40 mm Hg. The effects of increased $PaCO_2$ and decreased PaO_2 not only exist as independent inputs to the medulla, but can manifest synergistic interactions as well. Acute ventilatory responses to a combined low PaO_2 and high $PaCO_2$ are considerably greater than the sum of the individual responses.

The central chemoreceptors are a group of neurons located in three bilateral regions (rostral, caudal and intermediate chemosensitive zones) on the ventral surface of the medulla (Berndt, Fenner, et al. 1969; Cherniack, von Euler, et al. 1979; Loeschcke, De Lattre, et al. 1970). These regions are sensitive only to the $[H^+]$ of their environment produced by changes in the $PaCO_2$ and the cerebrospinal fluid $[H^+]$ (Bruce & Cherniack 1987).

Experiments in humans during periods of rest have demonstrated that the sensitivity of the central chemoreceptors is very low when the $PaCO_2$ is below ~40 mm Hg (Casey, Duffin, et al. 1987; Duffin & McAvoy 1988). However, above this threshold, ventilation increases approximately 3 $l.min^{-1}.mm\ Hg^{-1}$

increase in $PaCO_2$ (Duffin 1990). Of the two sets of chemoreceptors involved with the regulation of ventilation in response to changes in $PaCO_2$, the central chemoreceptors are the most important, accounting for about 70% of the stimulus to ventilate at rest.

1.3.1.2 Ventilation during exercise

The chemical factors that result in altered ventilation at rest (Section 1.3.1.1) are not necessarily the primary forces that act to increase ventilation up to twenty fold during maximal exercise. Generally, in the healthy subject, only the appearance of lactic acid in the blood, and not an increase in $PaCO_2$ or a decrease in PaO_2 will occur during exercise. This change in the $[H^+]$ is partly responsible for stimulating hyperventilation during severe exercise (Wasserman, Beaver, et al. 1990). In addition, it has been suggested as early as 1938 that stimulation of the carotid sinus by potassium (K^+) could also result in alterations in minute ventilation (von Euler 1938). Numerous investigations have demonstrated that K^+ is released from the contracting muscles during exercise and that the consequent increase in plasma K^+ concentration ($[K^+]$) is directly related to the intensity of exercise (De Lanne, Barnes, et al. 1959; Wilkerson, Horvath, et al. 1982). This suggests that the stimulation of the peripheral chemoreceptors by potassium may play a minor role in the control of ventilation during exercise. Therefore, although the chemical stimuli do not appear to be the primary regulators of ventilation during exercise, there is a consensus that the fine adjustment of

alveolar ventilation during moderate exercise and heavy exercise is strongly influenced by the peripheral and central chemoreceptors (Harrison, Harrison, et al. 1932; Kao 1963).

The abrupt alteration in the level of ventilation at the onset and cessation of exercise occurs too rapidly to be explained by alterations of the chemical composition of the blood. It has been suggested that other factors must therefore play a role in the regulation of ventilation during exercise (Krough & Lindhard 1913; Zuntz & Geppert 1886). These factors are thought to include; 1) receptors in the joints and muscle spindles which are stimulated by the frequency of physical movements that accompany muscle contraction (Jammes, Mathiot, et al. 1981; Kelsey & Duffin 1992; Takano 1988), 2) increases in blood temperature (Cotes 1955), 3) increases in hydrostatic blood pressure (Harrison, Harrison, et al. 1932), and 4) the appearance of catecholamines in the blood (Clark, Galloway, et al. 1997).

Given the extensive range of factors involved in the control of ventilation at rest, most authors (Comroe 1944; Grodins 1950; Lambertsen 1961; Mateika & Duffin 1995; Schmidt 1959; Whipp & Davis 1979) believe that any number of factors will determine the absolute level of ventilation during exercise depending on its mode, intensity and duration.

Mateika and Duffin (1995: p 1) stated that "the physiological function of pulmonary ventilation is to ensure a gas exchange in the lungs which matches that of tissue metabolism, so that respiratory homeostasis is maintained." The

increase in O_2 consumption and carbon dioxide production that accompanies exercise necessitates an increase in alveolar ventilation in order to maintain respiratory homeostasis. During exercise of light and moderate intensity, alveolar ventilation increases in direct proportion to the O_2 consumption. However, during heavy exercise, alveolar ventilation shows a large disproportionate increase that is coincident with an increased contribution of anaerobic metabolism to the overall work output. This relative hyperventilation serves to maintain $PaCO_2$ at rest levels, but also provides a large diffusion gradient for O_2 across the lung blood:gas interface. In the normal, healthy untrained subject, the hyperventilation that accompanies exercise is more than sufficient to result in significant arterial hypocapnia and maintain PaO_2 values near resting levels (Astrand & Rodahl 1986). Any reduction in the magnitude of the ventilatory response to exercise would thus result in arterial eucapnia (possibly even hypercapnia) and hypoxemia, a response which has been documented in the trained athlete during near exhaustive work (Dempsey, Hanson, et al. 1984; Powers, Dodd, et al. 1988; Powers, Martin, et al. 1992; Préfaut, Anselme, et al. 1994; Rowell, Taylor, et al. 1964; Thompson, Dempsey, et al. 1974).

1.3.1.3 Causes of an inadequate hyperventilatory response to exercise

Theoretically, inadequate hyperventilation in response to exercise can contribute to arterial hypoxemia by reducing PAO_2 and thus the driving force for O_2 to transfer across the lung blood:gas interface (Dempsey, Hanson, et al. 1982;

Dempsey, Hanson, et al. 1984; Powers, Martin, et al. 1993). However, there are opposing views about the role of inadequate hyperventilation in the etiology of EIH. While a number of reports have used inadequate hyperventilation to explain at least part of the observed EIH in their subjects (Caillaud, Anselme, et al. 1993; Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Harms, McClaran, et al. 1998; Miyachi & Shibayama 1992; Miyachi & Tabata 1992; Préfaut, Anselme, et al. 1994; Turcotte, Kiteala, et al. 1997), others have suggested that inadequate hyperventilation plays no role in the development of EIH (Buono & Maly 1996; Hopkins & McKenzie 1989; Norton, Squires, et al. 1995; Powers, Martin, et al. 1992). An inadequate hyperventilatory response to exercise can be attributed to a number of possible causes, including; low hypoxic and hypercapnic ventilatory responses (Harms & Stager 1995), ventilatory response which lags behind metabolic demand (Young & Woolcock 1978), respiratory muscle fatigue (Bye, Farkas, et al. 1983), decreased sensitivity to sensory stimuli (Harms, McClaran, et al. 1998), and mechanical limitations, such as inspiratory and expiratory flow limitations (Johnson, Saupe, et al. 1992). A recent explanation states that inadequate hyperventilation during both near-maximal and maximal exercise is a consequence of a sub-optimal balance between the flow of blood to, and O_2 consumption of, the respiratory muscles compared to the locomotor muscles (Harms, Babcock, et al. 1997; Harms, Wetter, et al. 1998; Hopkins & McKenzie 1993; Johnson, Saupe, et al. 1992). A combination of one or all of the above factors would decrease minute ventilation below its theoretical optimum, and result in a reduced driving pressure for O_2 across the lung blood:gas interface, thereby resulting in EIH.

1.3.1.3.1 Hypoxic and hypercapnic ventilatory responses

As stated in Section 1.3.1.1, PaO_2 and $PaCO_2$ play an accessory role in the control of ventilation via the peripheral chemoreceptors. These responses are often referred to as the hypoxic and hypercapnic ventilatory drives for O_2 and CO_2, respectively. The estimated contribution of hypoxic drive to the overall exercise ventilation is 16-30% (Hopkins & McKenzie 1993; Martin, Weil, et al. 1978; Stockley 1978; Whipp & Davis 1979). During rest and moderate exercise, hypoxic and hypercapnic drives are positively associated with each other (Martin, Weil, et al. 1978; Rebuck & Campbell 1974), and with exercise ventilation (Martin, Weil, et al. 1978; Rebuck, Jones, et al. 1972). Between near-maximal to maximal exercise however, this relationship is not as well defined. Several reports support their influence (Mahler, Moritz, et al. 1982; Harms & Stager 1995) while others demonstrate little effect (Dempsey, Hanson, et al. 1984; Hopkins & McKenzie 1989). The latter studies suggest that other ventilatory stimuli override any contribution of both hypoxic and hypercapnic drives.

Trained endurance athletes demonstrate a blunted ventilatory response to exercise which is believed to be a result of habitual training (Byrne-Quinn, Weil, et al. 1971; Martin, Weil, et al. 1978). This response may be due in part to a reduction in the chemosensitivity to sensory stimuli (Harms, McClaran, et al. 1998; Martin, Weil, et al. 1978). The question remains as to whether this response is a training adaptation or maladaptation. It has been hypothesised that a reduction in the level of ventilation during absolute exercise work loads provides additional blood flow to the working locomotor muscles and, during maximal

exercise, reduces O_2 costs incurred by the respiratory muscles (Otis 1954). Thus, it may be that the trained endurance athlete tolerates sub-optimal arterial oxygenation and O_2 delivery as a result of a blunted ventilatory response, rather than incur the exorbitantly high O_2 costs of ventilation (Hopkins & McKenzie 1993).

1.3.1.3.2 Mechanical limitations to ventilatory flow

Flow is a rate defined by the relationship of volume to time. With respect to pulmonary ventilation, flow is related to the length and diameter of the conducting airways, the driving pressure, and the viscosity of the air in the airway (Hopkins & McKenzie 1993). Pulmonary function during rest is measured using static tests such as forced expiratory volume in 1 second ($FEV_{1.0}$) and the maximal expiratory flow-volume (MEFV). Tidal volume during rest falls well within the MEFV curve, however, in circumstances such as maximal exercise these limits are often approached or even exceeded suggesting flow limitation (Aaron, Seow, et al. 1992; Chapman, Emery, et al. 1998; Hesser, Linnarsson, et al. 1981; Jensen, Lyager, et al. 1980; McClaran, Harms, et al. 1998; Olafsson & Hyatt 1969). In addition to directly measured tidal volume flow limitation, many investigators have used an increase in end-expiratory lung volume during exercise as an indication of flow limitation (Babb, Viggiano, et al. 1991; Johnson, Saupe, et al. 1992; Koulouris, Dimopoulou, et al. 1997; Pellegrino, Brusasco, et al. 1993; Rodarte 1997). Flow limitation constitutes a mechanical constraint for

ventilation, and its presence implies that any further increase in expiratory flow must take place at an increased lung volume (Rodarte 1997). Of all the studies investigating mechanical limitations to flow during exercise, the work of Johnson et al. (1992) is the most relevant to EIH. Their subjects ($\dot{V}O_{2max}$; 73 ± 1 $ml.kg^{-1}.min^{-1}$) demonstrated significant arterial hypoxemia during short term maximal exercise (PaO_2 at $\dot{V}O_{2max}$ was 78.0 ± 6.2 mm Hg) together with significant mechanical limitations coincident with the attainment of $\dot{V}O_{2max}$. More importantly, when the stimulus to breathe during maximal exercise was increased using either hypercapnia (end-tidal PCO_2; 65 mm Hg) or hypoxemia (arterial O_2 saturation; 75%), minute ventilation, inspiratory pressure and expiratory pressure failed to increase. The authors concluded that "during maximal exercise, highly trained individuals often reach mechanical limits of the lung and respiratory muscle for producing alveolar ventilation" (Johnson, Saupe, et al. 1992:p 874). In support of this conclusion, Dempsey et al. (1984) demonstrated a 10 mm Hg increase in PAO_2 with a concomitant rise in PaO_2 of 5-15 mm Hg during inhalation of a low density normoxic helium mixture. This result was attributed to the reduction of turbulent flow and flow resistance and the consequent mechanical 'unloading' of the respiratory muscles, thus allowing for a greater mechanical reserve to ventilate during exercise. In contrast, other authors (Norton, Squires, et al. 1995; Buono & Maly 1996) have suggested that mechanical factors do not limit ventilation during maximal exercise. This is supported by the fact that pulmonary ventilation during exercise does not reach the same level as that attained during maximal voluntary ventilation (Hesser, Linnarsson, et al. 1981). There are several explanations for this discrepancy.

Firstly, individuals tend to breathe at higher lung volumes during forced maximal voluntary breathing and therefore have higher expiratory flow (Olafsson & Hyatt 1969). This problem was demonstrated clearly by Johnson et al. (1992) where end-expiratory lung volumes increased during progressive incremental exercise and were significantly different from rest at exercise intensities greater than 90% $\dot{V}O_{2max}$. Secondly, during exercise there may be a decreased resistance to flow as a result of bronchodilation, secondary to increased sympathetic or decreased parasympathetic drive (Jensen, Lyager, et al. 1980). In addition, maximum flow during exercise may be increased by an increase in the elastic recoil pressure of the lung (Hopkins & McKenzie 1993). Thus, it appears that caution is required when comparing results obtained at rest with those measured during near-maximal exercise, particularly when investigating the possibility of mechanical limitations influencing the degree of alveolar ventilation. Overall, there is a general consensus that flow limitation due to mechanical constraints of the lung are present during maximal exercise, and that these can be potential contributors to arterial hypoxemia in the trained endurance athlete.

1.3.1.3.3 Oxygen and blood flow cost of exercise ventilation

The respiratory muscles require a portion of the cardiac output (and O_2 delivery) in order to overcome a number of forces that act against respiration. Otis et al. (1950) proposed that these forces were the elastic recoil of the chest and lungs, as well as the non-elastic forces of viscous and turbulent air resistances,

deformation of tissue, and friction from organ movements across each other. All of these elastic and non-elastic forces change with changing ventilatory magnitudes and as such, Otis (1954) argued that a critical level of ventilation could be reached during exercise beyond which any increase in O_2 consumption would go directly to the respiratory muscles. In the male this level was estimated at 140 $l.min^{-1}$ (BTPS), although further work demonstrated it to be even lower (Shephard 1966). In the trained endurance athlete minute ventilation in excess of 200 $l.min^{-1}$ is not uncommon during heavy to maximal exercise, thus it is interesting to speculate on the additional O_2 and blood flow cost of such high levels of respiratory work.

The O_2 cost of respiration during mechanical stress or heavy exercise has been directly measured in many animal models and varies from 15 $ml.min^{-1}.100g^{-1}$ in the dog (Reid & Johnson 1983; Robertson, Foster, et al. 1977; Rochester & Bettini 1976) to as high as ~60 $ml.min^{-1}.100g^{-1}$ in the exercising pony (Manohar 1986; Manohar, Goetz, et al. 1988). In the human, these experiments are more difficult ethically, due to the invasiveness of the techniques. Consequently, the most widely accepted technique in humans is to measure the additional O_2 consumption above resting values required during voluntary ventilation. Caution is required when interpreting the results because differences in the methods employed to increase ventilation can have a marked effect on the type and level of ventilation achieved (Coast, Rasmussen, et al. 1993). There has been a wide variation in the estimated O_2 cost of ventilation during maximal exercise, ranging from 3% (Milic-Emili, Petit, et al. 1962) to as much as 25% (Fritts, Filler, et al. 1959) of $\dot{V}O_{2max}$. Many investigators have demonstrated that

the relationship between the O_2 cost of ventilation and actual minute ventilation is not linear but it is more accurately modelled by an exponential or third order polynomial, where there is a rapid rise in the O_2 cost of ventilation as the upper limit of minute ventilation is reached, and the curve shifts to the right or left depending on the respiratory rate chosen (Aaron, Johnson, et al. 1992; Anholm, Johnson, et al. 1987; Bartlett, Brubach, et al. 1958; Coast, Rasmussen, et al. 1993; Milic-Emili, Petit, et al. 1962; Milic-Emili & Petit 1960; Margaria, Milic-Emili, et al. 1960; Weiner, Suo, et al. 1989). It is particularly relevant that while exercising, the naturally selected tidal volume and respiratory rate provides the most efficient compromise between the level of ventilation and the O_2 cost of ventilation (Mead 1960; Otis, Fehn, et al. 1950). In addition trained subjects have a lower O_2 consumption for a given level of pulmonary ventilation than do untrained individuals (Milic-Emili, Petit, et al. 1962).

A major problem with adequate hyperventilation (i.e. one that maintains blood gas homeostasis) is that the required level of ventilation is excessively large. For example, to achieve a $PaCO_2$ of ~30 mm Hg and a PAO_2 of ~115 mm Hg at a carbon dioxide production ($\dot{V}CO_2$) of 3-4 $l.min^{-1}$, the level of ventilation required is ~120 $l.min^{-1}$. If however, the gas tensions were to remain constant and the $\dot{V}CO_2$ increased to 5-6 $l.min^{-1}$, as is the case with a trained athlete, the required ventilation would approach 240 $l.min^{-1}$ (Dempsey, Vidruk, et al. 1985). This value is generally unachievable or at least unsustainable in even the most highly trained subject. Therefore, it would appear that the level of exercise ventilation is a balance between the O_2 cost of high rates of ventilation, and the body's requirement to maintain homeostasis.

Recently, the amount of blood flow directed to the respiratory muscles has been investigated as a possible mechanism limiting both maximal ventilation and $\dot{V}O_{2max}$. Harms et al. (1998) concluded that respiratory work during maximal exercise has two important effects on the cardiovascular system: 1) up to 14-16% of the cardiac output (~5.5 $l.min^{-1}$) is directed to the respiratory muscles; and 2) local reflex vasoconstriction significantly compromises leg muscle $\dot{V}O_2$ and blood flow (Harms, Babcock, et al. 1997). Anholm et al. (1987) measured cardiac output in subjects ventilating maximally for 4 minutes and expressed the relationship between ventilation and cardiac output by the equation;

$$\text{Cardiac Output}_{\text{respiratory muscles}} = 0.00287 \text{ x minute ventilation } (l.min^{-1})^{1.452}$$

These data agree with those measured in animal models (Manohar 1988) and demonstrate that the respiratory muscles are in direct competition with the skeletal muscles for blood flow. This suggests that maximal exercise in the trained athlete is achieved by balancing respiratory muscle blood flow against the demands of the skeletal muscles to perform external work.

This leads one to speculate whether the respiratory muscles are trainable and if training would improve the efficiency of ventilation. Previously, the respiratory muscles were believed to be resistant to fatigue and thus specific training was of little importance. However, investigations from the last 10-20 years have demonstrated decreases in respiratory muscle strength after prolonged exercise (Loke, Mahler, et al. 1982) and decreases in performance following respiratory work (Mandor & Acevedo 1991; Martin, Heintzelman, et al. 1982).

Furthermore, some investigators have shown that ventilatory muscle endurance training can appreciably increase the aerobic endurance of the respiratory muscles (Boutellier 1998; Bradley & Leith 1978). The extent to which specific respiratory muscle training can impact on EIH is yet to be determined, but the hypothesis may offer some tangible benefits.

1.3.2 Intra and extra-pulmonary shunt

Even in the normal circulatory system there are areas where the venous blood is not circulated through ventilated areas of the lung (intra-pulmonary shunt) or bypasses the lung totally (extra-pulmonary shunt) (Bachofen, Hobi, et al. 1973). This veno-arterial shunt results in induction of poorly oxygenated blood into the arterial circulation and causes a decline in PaO_2. At rest, veno-arterial shunt accounts for approximately 50% of the A-aDO_2 (Gledhill, Froese, et al. 1977; Whipp & Wasserman 1969) and it has been postulated that it could account for nearly 49% of the A-aDO_2 observed during moderate exercise (Asmussen & Neilsen 1960). However, during heavy exercise, several investigators have demonstrated that veno-arterial shunt does not contribute to the increased A-aDO_2 seen in trained athletes (Dempsey, Hanson, et al. 1984; Gale, Torre-Bueno, et al. 1985; Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Powers, Martin, et al. 1992; Schaffartzik, Poole, et al. 1992; Torre-Bueno, Wagner, et al. 1985). Generally, the degree of shunt is determined by breathing an hyperoxic gas mixture while exercising. If shunt is primarily responsible for

the arterial hypoxemia, then breathing the hyperoxic gas would not alter PaO_2 as the venous blood would bypass the lung and never come into contact with the high O_2 tension. However, using this method, both Dempsey et al. (1984) and Powers et al. (1992) have demonstrated that a switch from breathing a normoxic gas mixture (room air at sea level) to a mild hyperoxic gas mixture (24-26% O_2) returned PaO_2 back to resting levels in hypoxemic athletes exercising near $\dot{V}O_{2max}$.

As stated earlier, veno-arterial shunt is comprised of two parts; intra and extra-pulmonary. It is important to make a distinction between these two components of shunt, as the former represents a physiological disturbance, whereas the latter is an anatomical disturbance. There are two main limitations of using hyperoxic gas mixtures to quantify the degree of veno-arterial shunt. First, this technique combines both components of veno-arterial shunt into a single value. Secondly, the accuracy of blood gas measurements at high O_2 tensions are well within the measurement error of the analysers and thus a high precision of measurement is not possible (Hammond, Gale, et al. 1986a). Recently, the multiple inert gas elimination technique (MIGET) has been used to distinguish between intra and extra-pulmonary shunt during exercise. Studies using this technique have demonstrated that in healthy subjects during exercise, extra-pulmonary shunt comprises less than 0.5% of cardiac output (Hammond, Gale, et al. 1986a; Torre-Bueno, Wagner, et al. 1985) and intra-pulmonary shunt is almost non-existent (Hopkins, McKenzie, et al. 1994).

1.3.3 Ventilation–perfusion inequality

Ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality describes the mismatch of pulmonary ventilation to pulmonary blood flow. In general, unless the proportion of total blood flow and total ventilation to each gas exchanging unit are the same, the overall gas exchange becomes inefficient, and with all other factors being equal, the PaO_2 falls and $PaCO_2$ rises (Wagner & West 1980). Ventilation and perfusion are not uniform throughout the upright lung at rest; the effects of gravity render the lung bases better perfused than the apices, and conversely, the apices better ventilated than the bases. Upon exercise, the increase in pulmonary artery pressure leads to a more uniform topographic perfusion distribution (Bake, Bjure, et al. 1968). However, as other factors such as large airways gas mixing and non-uniform vasoconstriction begin to play a more dominant role during exercise, there is no overall improvement in arterial oxygenation. As such, $\dot{V}_A/\dot{Q}$ inequality will tend to depress PaO_2 and widen the $A\text{-}aDO_2$ as more blood will be poorly oxygenated rather than over ventilated.

Historically, $\dot{V}_A/\dot{Q}$ inequality was measured using O_2, CO_2 and nitrogen (N_2), as these were the simplest and most readily available means of assessing inequality (Riley & Cournand 1949). The major disadvantage of using these gases for the measurement of $\dot{V}_A/\dot{Q}$ inequality was that they were unable to provide the resolution required to accurately reflect what was happening in the lung. More importantly, the gas exchange behaviour of O_2, CO_2 and N_2 in the presence of $\dot{V}_A/\dot{Q}$ inequality was dominated by the slope of their dissociation

curves in the blood, that is, their physiologic solubility (West 1970). This latter problem was especially relevant for O_2 as the slope of the oxyhemoglobin dissociation curve was considerably shallower than the slope of the CO_2 dissociation curve, thus leaving it prone to diffusion limitation and effectively limiting the resolution of the technique.

In 1967, Yokoyama and Fahri (1967) were the first to describe ventilation-perfusion measurements using MIGET. Initially, the multiple inert gases used were a mixture of methane, ethane and nitrous oxide. Yokoyama and Fahri (1967) found that the lung acted as a two compartment model; one compartment with a nearly normal ventilation-perfusion ratio and the other with a ratio of less than 0.1, of which the latter received 10-29% of the total blood flow. Currently, MIGET uses six inert gases (ether, ethane, enflurane, cyclopropane, sulphur hexaflouride, and acetone) which provide a number of additional benefits over the three inert gases used initially. The major benefit of MIGET is that it spans an enormous range of solubilities (eg. 10^5 between the solubilities of acetone and sulphur hexofluoride) enabling far more information about any $\dot{V}_A/\dot{Q}$ inequality to be obtained than would be determined using O_2, CO_2 and N_2 or methane, ethane and nitrous oxide. In addition, MIGET utilises Henry's law of solubility which means that the complicating effects of non-linear dissociation curves are avoided.

The MIGET technique relies on the mass balance principle which relates the alveolar tension of the inert gas to the gas solubility and the $\dot{V}_A/\dot{Q}$ ratio of the area of lung under consideration (Wagner & West 1980). More

specifically, in a small area of lung of homogeneous alveolar tension, the relationship between alveolar (P_A), end-capillary ($P_{c'}$) and mixed venous ($P_{\bar{v}}$) tensions of an inert gas, the blood:gas partition coefficient (λ) and the $\dot{V}_A/\dot{Q}$ ratio is given by;

$$\frac{P_{c'}}{P_{\bar{v}}} = \frac{P_A}{P_{\bar{v}}} = \frac{\lambda}{\lambda + \dot{V}_A/\dot{Q}}$$

The above relationship relies on a number of assumptions that apply to any steady state gas technique that attempts to quantify the degree of $\dot{V}_A/\dot{Q}$ inequality (Wagner & West 1980).

- Each homogenous lung unit is in a steady state of gas exchange such that the net rate of transfer of gas from capillary blood to alveolar gas exactly equals the net rate of elimination through expiration. Thus the amount of inert gas stored in the lung is constant.

- Both ventilation and blood flow are taken to be continuous in nature, thus the pulsatile nature of the two variables is not taken into account.

- The lung is treated as a collection of separate "lung units", each of which is homogeneous, receives both ventilation and blood flow, and the $\dot{V}_A/\dot{Q}$ ratio varies from unit to unit.

- Diffusion equilibration is assumed to be complete, suggesting that there are uniform tensions everywhere within the lung unit. This also implies that gases

of different molecular weight do not behave differently other than through differences in solubility.

- All lung units receive blood of the same hematocrit.

- All lung units within the lung are arranged in parallel with one another so that they receive inspired gas that traverses only their own conducting airway deadspace. Consequently, there is no transfer of gas between physically adjacent lung units.

If single lung units exchange inert gas under the above assumptions, then the behaviour of a lung that is made up of many lung units (50 units for MIGET) of different $\dot{V}_A/\dot{Q}$ ratios can be studied mathematically in a straightforward manner by employing traditional mixing equations. The attraction of MIGET is that it is able to predict an A-aDO_2 which reflects only $\dot{V}_A/\dot{Q}$ inequality and intra-pulmonary shunt. Any residual difference between the observed A-aDO_2 and the MIGET predicted A-aDO_2 is due to some combination of 1) end-capillary O_2 diffusion limitation and 2) extra-pulmonary shunt (caused by bronchial arterial-pulmonary venous anastomoses and Thebesian venous drainage into the left side of the heart).

Over the past 20 years, MIGET has been used to investigate $\dot{V}_A/\dot{Q}$ inequality in athletes at sea level and altitude (Hammond, Gale, et al. 1986a and 1986b; Hopkins, McKenzie, et al. 1994; Hopkins, Gavin, et al. 1998; Podolsky, Eldridge, et al. 1996; Schaffartzik, Poole, et al. 1992; Wagner, Gale, et al. 1986),

healthy untrained subjects at sea level and altitude (Cardús, Burgos, et al. 1997; Gale, Torre-Bueno, et al. 1985; Hammond, Gale, et al. 1986a and 1986b; Torre-Bueno, Wagner, et al. 1985; Wagner, Sutton, et al. 1987), in subjects with lung disease (Dantzker & D'Alonzo 1986; Marthan, Castaing, et al. 1985; Roca, Montserrat, et al. 1987; Wagner, Dantzker, et al. 1977; Young, Corte, et al. 1982), and in exercising animals (Erickson, Seaman, et al. 1994; Hopkins, Hicks, et al. 1995; Hopkins, Wang, et al. 1996; Wagner, Gillespie, et al. 1989). Collectively, these data suggest that $\dot{V}_A/\dot{Q}$ inequality increases linearly with exercise (Gale, Torre-Bueno, et al. 1985; Hammond, Gale, et al. 1986a; Torre-Bueno, Wagner, et al. 1985; Wagner, Gale, et al. 1986) and explains the majority of the increase in A-aDO_2 up to a $\dot{V}O_2$ of ~2.0 $l.min^{-1}$ in both healthy untrained subjects and athletes (Hammond, Gale, et al. 1986a; Hopkins, McKenzie, et al. 1994; Figure 1.2).

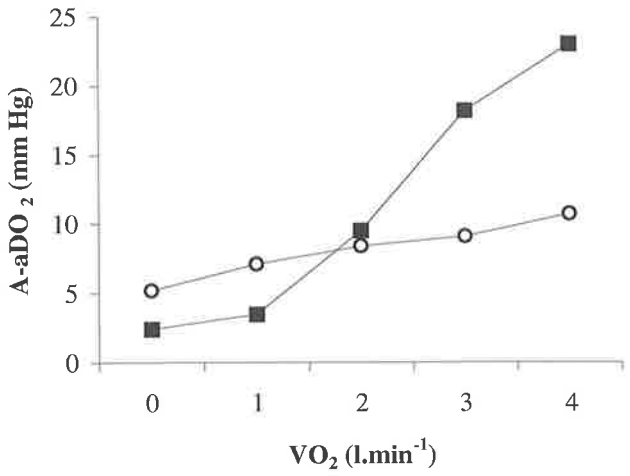


Figure 1.2 Alveolar-arterial O_2 tension difference (A-aDO_2) observed (■) and predicted (○) as a function of O_2 uptake ($\dot{V}O_2$). Higher observed A-aDO_2 compared with predicted A-aDO_2 is due to end-capillary O_2 diffusion limitation in

the absence of extra-pulmonary shunt (Adapted from Hammond, Gale, et al. 1986a).

The principal causes of an increase in $\dot{V}_A/\dot{Q}$ inequality during exercise remain unclear, but current hypotheses include; 1) increases in pulmonary artery pressures (Bevegard, Holmgren, et al. 1963; Groves, Reeves, et al. 1987; Wagner, Dantzker, et al. 1977; Wagner, Gale, et al. 1986; Wagner, Sutton, et al. 1987), 2) interstitial pulmonary edema (Hopkins, Gavin, et al. 1998; Podolsky, Eldridge, et al. 1996; Schaffartzik, Poole, et al. 1992; Schaffartzik, Arcos, et al. 1993), 3) reduced large airway gas mixing (Ross & Farhi 1960; Tsukimoto, Arcos, et al. 1990), 4) alterations in airway muscle tone (Wagner 1992), and 5) non-uniform pulmonary vasoconstriction (Houston 1960; Hultgren 1982). Interstitial pulmonary edema is considered the most attractive of these options (Wagner 1992).

Exercise can increase mean pulmonary artery and capillary wedge pressures to as high as 40 and 27 mm Hg, respectively (Bevegard, Holmgren, et al. 1963; Groves, Reeves, et al. 1987; Wagner, Gale, et al. 1986), and hypoxia attenuates this effect (Wagner, Gale, et al. 1986; Wagner, Sutton, et al. 1987). It is possible, with pressures in the range that have been described during exercise, that there is rapid transcapillary fluid movement sufficient to overload the rate of clearance and lead to temporary interstitial pulmonary edema. If the net result

was an increase in regional perivascular fluid accumulation, inhomogeneity of blood flow and thus regional hypoxemia could be exacerbated.

Recently, two studies have presented data concerning the association between the release of histamine and the development of EIH during maximal exercise (Anselme, Caillaud, et al. 1994; Préfaut, Anselme, et al. 1997). The release of histamine into the blood was used as a marker of inflammation at the pulmonary capillary level, and represented a response to mild transient pulmonary edema due to stress failure of the pulmonary capillaries. More importantly, the study of Préfaut et al. (1997) demonstrated that a reduction of histamine in the blood was concomitant with a significant reduction in arterial hypoxemia at maximal exercise intensity. These results, coupled with those presented by West et al. (1991; 1992; 1993) and Tsukimoto et al. (1991) regarding stress failure of the pulmonary capillaries, led the authors to speculate that "the inflammatory reaction is related to stress failure development". In support of this hypothesis, Hopkins et al. (1997) demonstrated an increase in the concentration of red cells and protein in bronchoalveolar lavage fluid, indicating mechanical stress of the blood:gas membrane in six well trained athletes following 7 minutes of high intensity exercise. This evidence suggests that during heavy exercise, stress failure of the pulmonary capillaries may lead to pulmonary edema and an increase in $\dot{V}_A/\dot{Q}$ inequality, with the net result being a lowered arterial O_2 tension.

There are only a few reports which have estimated interstitial pulmonary edema during exercise in humans (Gallagher, Huda, et al. 1988; Goresky, Warnica, et al. 1972; Houston 1960; Marshall, Teichner, et al. 1971;

McKechnie, Leary, et al. 1979; Podolsky, Eldridge, et al. 1996; Rasmussen, Hanel, et al. 1986; Rasmussen, Elkjaer, et al. 1988; Wagner, Sutton, et al. 1987). Of these reports, a number suggested that the estimated amount of exercise-induced edema was below the stage of alveolar flooding (Houston 1960; McKechnie, Leary, et al. 1979). In contrast, studies which used double indicator-dilution techniques showed an increase in pulmonary extravascular water during exercise (Goresky, Warnica, et al. 1972; Marshall, Teichner, et al. 1971). There is also strong indirect evidence in humans to support the link between pulmonary edema and an increase in $\dot{V}_A/\dot{Q}$ inequality (Hopkins, Gavin, et al. 1998). Changes in transthoracic electrical impedance during recovery from maximal exercise suggest augmented intrathoracic fluid volumes (Buono, Wilmore, et al. 1982). Furthermore, lung volume and function are transiently impaired after exercise (Buono, Constable, et al. 1981; O'Kroy, Loy, et al. 1992 456). The decreased vital capacity and increased residual volume after exercise have been considered as signs of small-airway closure reflecting subclinical edema. The strongest evidence for an increase in pulmonary edema with exercise comes from the animal model. Studies in dogs have demonstrated that *in situ* perfused lungs accumulate fluid when blood flow is increased four fold above resting levels (Younes, Bshouty, et al. 1987). In the sheep and goat, exercise has been shown to increase lung lymph flow up to three fold (Coates, O'Brodovich, et al. 1984), a finding which is consistent with fluid accumulation. In one of the more definitive studies, Schaffartzik et al. (1993) sacrificed pigs immediately after the had completed a maximal bout of treadmill exercise and demonstrated a significantly higher percentage of pulmonary arteries with perivascular edema when compared

with a group of non-exercised pigs. The authors concluded that this finding was consistent with both perivascular and quite possibly parenchymal interstitial edema.

Overall, there are a large number of potential mechanisms available to explain the increase in $\dot{V}_A/\dot{Q}$ inequality during exercise in normal subjects. However, rather than a single mechanism, it is more likely that a combination of factors is responsible, with a large contribution from interstitial pulmonary edema.

1.3.4 End-capillary O_2 diffusion limitation

Exercise presents a special challenge for pulmonary diffusion because of the decreases in both the O_2 tension of mixed venous blood ($P\bar{v}O_2$) and red blood cell transit time in the pulmonary capillaries. Add to this the potential problem of pulmonary edema resulting from raised hydrostatic pressures in the pulmonary artery arising due to increased cardiac output during exercise (see Section 1.3.3), and the lung must make a number of adjustments to maintain the conditions for gas diffusion during exercise. The lung of a healthy untrained individual easily manages the changes induced by heavy exercise, as evidenced by maintenance of PaO_2 and SaO_2 near resting levels. In contrast, Dempsey et al. (1984) was one of the first authors to demonstrate conclusively, that in the highly trained endurance athlete able to sustain exercise demanding a large metabolic

cost, diffusion of O_2 across the lung blood:gas interface may be impaired. Subsequent studies have reported that significant end-capillary O_2 diffusion limitation is unlikely to be present during exercise of <70% $\dot{V}O_{2max}$ (Hopkins, McKenzie, et al. 1994; Warren, Cureton, et al. 1991), but above this intensity can contribute up to 66% of the measured A-aDO_2 (Bebout, Story, et al. 1989; Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, McKenzie, et al. 1994; Martin & O'Kroy 1993; Torre-Bueno, Wagner, et al. 1985; Wagner, Gale, et al. 1986; Warren, Cureton, et al. 1991).

Equilibration of O_2 between the alveolar gas and pulmonary capillary blood during exercise is dependent upon four aspects; 1) adequate transit time of the red blood cells in the pulmonary capillary bed, 2) the effective slope of the oxyhemoglobin dissociation curve between PAO_2 and $P\bar{v}O_2$, 3) the maintenance of the extremely narrow diffusion distance that O_2 must travel to pass from the alveolar space into the pulmonary blood and, 4) the surface area available for diffusion (varies with the pulmonary capillary blood volume). End-capillary O_2 diffusion limitation is believed to occur if any two of the above conditions prevail (Dempsey, Hanson, et al. 1984).

1.3.4.1 Red blood cell transit time

In the healthy untrained subject exercising at sea level, it has been documented that adequate red cell transit time for O_2 diffusion (~≥0.4 seconds, Dempsey, Hanson, et al. 1982; Gledhill, Froese, et al. 1977) is maintained as a

result of a larger increase in the pulmonary capillary blood volume than occurs in right ventricle stroke volume (Johnson, Spicer, et al. 1960; Shepherd 1958; Staub, Bishop, et al. 1962). In the trained endurance athlete data remain equivocal (Dempsey, Hanson, et al. 1984; Hopkins, Belzberg, et al. 1996; Warren, Cureton, et al. 1991). Figure 1.3 demonstrates the role of reduced red cell transit time in the development of EIH during high intensity exercise in endurance athletes. Line A shows the computed mean transit times for red cells through the pulmonary capillaries with increasing pulmonary blood flow. Line B shows the estimated average pulmonary capillary blood volume with increasing blood flow. As long as capillary blood volume increases with pulmonary blood flow, mean transit time is sufficient to permit alveolar-capillary O_2 equilibration. In many athletes pulmonary blood flow increases well beyond 25 $l.min^{-1}$, at which point capillary blood volume may reach its morphological limit (~220 ml; Gehr, Bachofen, et al. 1978) thus causing mean transit time to fall sharply (*smaller bold arrow*). The heavy black line at the top of the figure indicates the theoretical PaO_2 as a result of reduced red cell transit times.

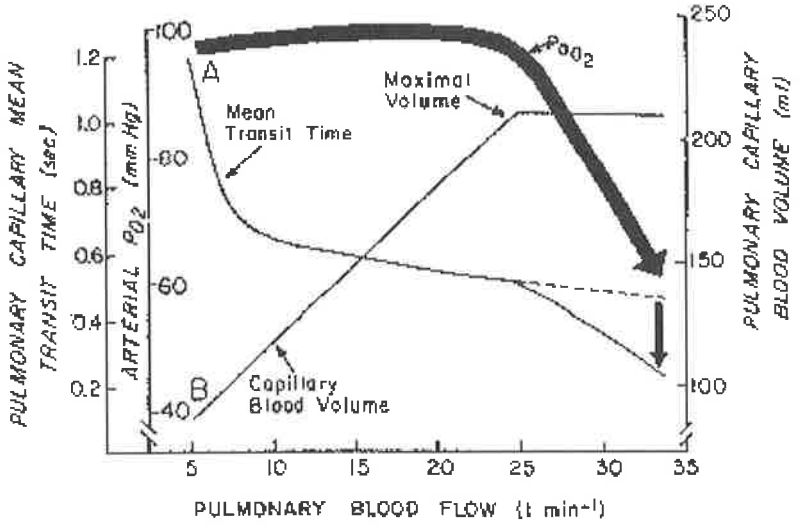


Figure 1.3 Theoretical explanation of reduced red cell transit times in trained endurance athletes. Pulmonary capillary blood volume (Line B) and pulmonary blood flow (X axis) increase linearly with increasing exercise intensity up to a pulmonary blood flow of ~25 l.min^{-1}. At higher exercise intensities, pulmonary blood flow continues to increase but capillary blood volume does not. This results in a more rapid decline in the mean transit time (Line A) which results in end-capillary O_2 diffusion limitation (Reproduced from Rowell 1993; Warren, Cureton, et al. 1991).

Presently, only two studies have attempted to measure red cell transit times in exercising athletes (Hopkins, Belzberg, et al. 1996; Warren, Cureton, et al. 1991). While both studies demonstrated a significant fall in transit time neither provided unequivocal evidence to show that transit times breached the hypothetical minimum time of 0.4 seconds required for O_2 equilibration.

However, the results from both studies must be interpreted in context of the methodologies and subjects that were used. Although Hopkins et al. (1996) measured mean whole lung pulmonary transit time, they suggested that mean transit time was not an accurate reflection due to the pulsatile nature of capillary flow. In addition, they stated that it was possible that transit times lower than the mean were present (Hopkins & McKenzie 1993). The major limitation of the work of Warren et al. (1991) was that none of their subjects exhibited significant EIH, as demonstrated by an observed A-aDO_2 <25 mm Hg at 90% $\dot{V}O_{2max}$. A further limitation was that some of the techniques used to measure red cell transit times had the potential to introduce sufficient experimental error, leading to equivocal results. These technical issues included the use of oral temperature to correct arterial blood gas data, and the use of a breath hold manoeuvre at 90% of vital capacity to measure pulmonary capillary blood volume. The latter is important because this manoeuvre could increase venous return and spuriously elevate pulmonary capillary blood volume. Therefore, there is no conclusive evidence to support or refute that reduced red cell transit times contribute to EIH. Nevertheless, it appears possible that in trained endurance athletes able to sustain extremely high metabolic rates, capillary transit times may be sufficiently compromised to result in end-capillary O_2 diffusion limitation.

1.3.4.2 Effective slope of oxyhemoglobin dissociation curve

Diffusion of O_2 during exercise is made more difficult by the fact that mixed venous blood arrives at the alveoli with a considerably lower O_2 tension than during normal resting conditions. In addition, the greater the aerobic power of the athlete and the higher the metabolic cost of near-maximal exercise, the lower the $P\bar{v}O_2$ is. If this is coupled with a potentially reduced red cell transit time (see Section 1.3.4.1), end-capillary O_2 diffusion limitation is inevitable. It is a common belief that the driving pressure for O_2 across the lung blood:gas interface ($PAO_2 - P\bar{v}O_2$) is an important determinant of the rate of equilibration between alveolar and end-capillary PO_2 (Rowell 1993). However, this is not necessarily the complete picture. Of greater importance than either of these two factors is the effective slope of the oxyhemoglobin dissociation curve compared to the solubility of O_2 in the tissue of the blood:gas barrier (Thews 1968; Wagner & West 1972). PAO_2 is one determinant of the effective slope of the dissociation curve, but of equal importance is $P\bar{v}O_2$. In Figure 1.4, two hypothetical examples are shown to illustrate this concept. Both examples are based on the same PAO_2 (Point A), but the two cases differ in $P\bar{v}O_2$ (V_1 and V_2) which alters the effective slope of the oxyhemoglobin dissociation curve between the corresponding points. Although the tension gradient between case two ($PA-PV_2$) exceeds that of case one ($PA-PV_1$), diffusion equilibration (with all other factors being equal) is more likely to occur in case one rather than case two (Wagner 1977). Thus, the time required to reach a given degree of equilibrium at a given PAO_2 is heavily dependent upon the value of $P\bar{v}O_2$, because the effective slope of the

oxyhemoglobin dissociation curve varies accordingly (Dempsey 1987; Wagner 1982).

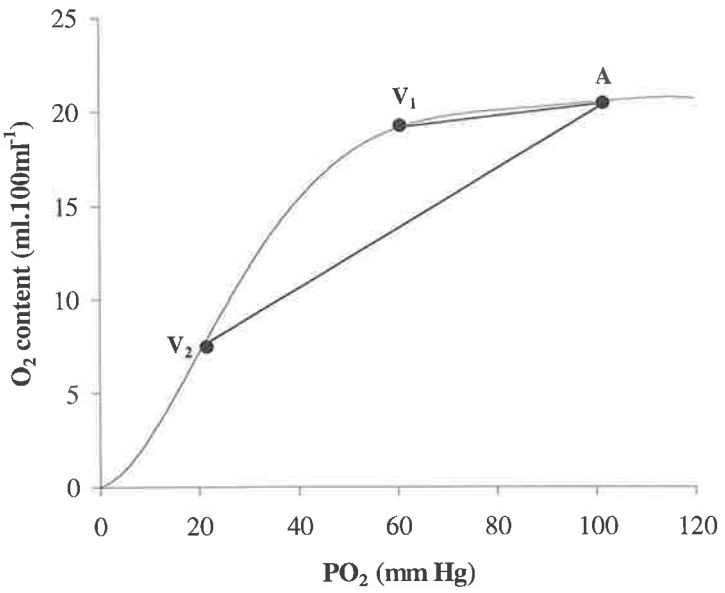


Figure 1.4 Oxyhemoglobin dissociation curve showing how the effective slope of the curve varies with $P\bar{v}O_2$ (points V_1 and V_2) when PAO_2 (point A) is constant (Adapted from Wagner 1982).

Figure 1.5 illustrates the combined effect of reduced red cell transit time and effective slope of oxyhemoglobin dissociation curve on O_2 diffusion equilibration in untrained and trained subjects. The key differences between the two samples are; 1) the differences in $P\bar{v}O_2$ (y intercept in Figure 1.5), and 2) the differences in red cell transit times. Indeed, $P\bar{v}O_2$ and red blood cell transit time are most likely lower in the trained athlete than in the untrained individual. The low $P\bar{v}O_2$ in the trained athlete means that the effective slope of the

oxyhemoglobin dissociation curve is shifted down and to the right, which results in an increased time required for alveolar to end-capillary O_2 equilibration.

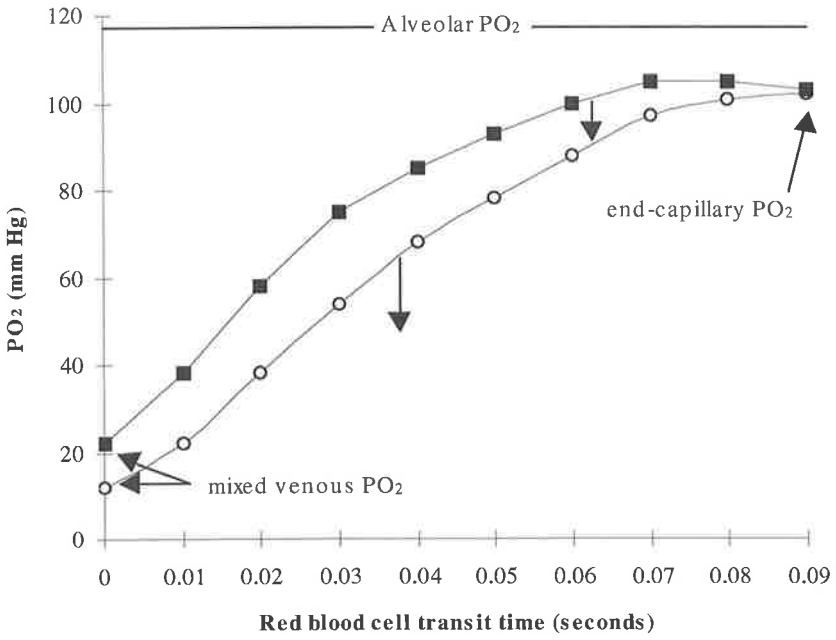


Figure 1.5 Theoretical model examining the relationship between end-capillary PO_2, $P\bar{v}O_2$ and red blood cell transit time in untrained (■) and trained (○) subjects. The vertical arrows represents the transit times available for each group of subjects. This model illustrates how end-capillary O_2 diffusion limitation might occur in trained subjects at work rates approaching $\dot{V}O_{2max}$ (Adapted from Dempsey 1987; Powers, Martin, et al. 1993; Wagner 1982).

1.3.4.3 Diffusion distance

The thickness of the alveolar membrane is known to increase in a number of disease states, an example of which is interstitial lung disease. In the normal healthy individual, the thickness of the blood:gas barrier is 0.2-0.4 μm (Gehr, Bachofen, et al. 1978) which is advantageous for passive diffusion of O_2 and CO_2 through the barrier because resistance to diffusion is proportional to the barrier thickness. Mechanical failure of this barrier may result in alveolar edema or hemorrhage, both of which will compromise gas exchange. It is generally accepted that the diffusion distance between the alveolar space and pulmonary capillaries remains constant, as extravascular fluid volume in the lung is unaltered during exercise (Marshall, Soma, et al. 1975; Vaughan, DeMarino, et al. 1976). However, Wagner et al. (1986) have demonstrated significant transcapillary fluid flux as a result of increased hydrostatic pressure and cardiac output during exercise. In theory, this could result in low grade pulmonary edema (see Section 1.3.3; Wagner 1992).

The recent work of St Croix et al. (1998) argues strongly against pulmonary edema or any other structural limitation contributing to arterial hypoxemia. They found that hypoxemia was not present immediately post-exercise nor was it exacerbated by a repeat bout of maximal exercise. These results were interpreted as evidence of a functional mechanism, only present during exercise, being responsible for EIH. Not discounting this innovative study, the sheer volume of reports that confirm in some manner the possibility of pulmonary edema during exercise cannot be ignored (see Section 1.3.3). In

further support of pulmonary edema as a potential mechanism for diffusion limitation, two studies (Aguilaniu, Flore, et al. 1995; Aguilaniu, Flore, et al. 1998) have investigated the effects of a polyunsaturated fatty acid diet (PUFA) on the development of EIH in masters athletes. They demonstrated that a PUFA rich diet minimised the decrease in PaO_2 during exercise. More importantly, the improvement in PaO_2 following PUFA was significantly associated with the decrease in A-aDO_2 (Aguilaniu, Flore, et al. 1995). The authors concluded that the improvement in EIH following PUFA could be related to an increase in alveolar-arterial O_2 conductance following improved pulmonary diffusion, possibly as a result of enhanced pulmonary cell membrane fluidity.

1.3.4.4 Surface area available for diffusion

The surface area available for diffusion is directly related to the pulmonary capillary blood volume which itself is related to cardiac output. As such, during low to moderate intensity exercise more pulmonary capillaries receive venous blood which; 1) acts to increase the surface area available for gaseous diffusion, and 2) decreases the pulmonary artery and capillary wedge pressures. No workers have investigated the possibility that EIH is related to decreased transit times in the lung as a consequence of lower recruitment of pulmonary capillaries or absolute lower pulmonary capillary blood volume, although Dempsey et al. (1984) has proposed that regional reduced red cell transit

times possibly exist. It therefore seems that further investigation is warranted to provide direct evidence regarding this hypothesis.

In conclusion, end-capillary O_2 diffusion limitation has been shown to contribute a large portion of the A-aDO_2 during intense exercise. This result is likely to be a combination of low $P\bar{v}O_2$ and reduced red blood cell transit times in the trained athlete performing intense exercise, although it is quite tenable that a reduced surface area for gaseous diffusion and pulmonary edema play accessory roles.

1.4 SUMMARY AND AIMS OF THE THESIS

The question as to which mechanism is primarily responsible for the development of EIH in trained endurance athletes remains unanswered. The majority of evidence suggests a multifactorial etiology but indirectly supports a major role for end-capillary O_2 diffusion limitation due to either reduced red cell transit time in the pulmonary capillaries, low $P\bar{v}O_2$, the development of pulmonary edema, or a combination of all three. Supporting roles in the development of EIH include inadequate hyperventilation resulting from mechanical limitation of ventilation, and increases in $\dot{V}_A/\dot{Q}$ inequality.

The aim of this doctoral study was to determine the main cause of EIH in trained endurance athletes. Specifically, the aim was to test the hypothesis that athletes who develop EIH do so because of a larger degree of end-capillary O_2 diffusion limitation.

2 GENERAL METHODS

2.1 GENERAL

The subjects described in this thesis volunteered to participate after being informed of all the potential risks. The experiment protocols were approved by the Research Ethics Committee of the Royal Adelaide Hospital and all subjects gave written informed consent (see Section 7.1). All experiments were conducted in an air-conditioned laboratory with a room temperature maintained at a mean ± SEM of 21 ± 1°C (range 19.6 – 23.3°C). Subjects were requested to arrive at the laboratory having abstained from exercise for the previous 24 hours and food and caffeine products for the previous 4 hours.

2.2 EXPERIMENTAL TECHNIQUES

2.2.1 Measurement of electrocardiogram and heart rate

Heart rate (HR) was recorded continuously during all experiments using a three lead electrocardiogram (ECG) (US-504, Criticare, Waukesha, WI) with 30 second averages displayed on an IBM-compatible (386-SX, Osborne Computers, NSW, Australia) personal computer (PC). A duplicate HR measurement system consisted of a Polar Sports Tester (PE3000, Polar, Finland, OY) that enabled the HR to be recorded every 15 seconds and later down loaded to the PC using a proprietary interface (Polar Interface, Polar, Finland, OY).

2.2.2 Determination of O_2 consumption

Oxygen consumption ($\dot{V}O_2$) was measured on-line with an indirect calorimetry system. Inspired volume was measured with a linearised pneumotachograph (Model 4813 Hans Rudolph, Kansas City, MO or #3, Fleisch, Lausanne, Switzerland) connected to a ± 2 cm H_2O differential pressure transducer (Model DP 45, Validyne, Northridge, CA), (see Section 2.2.3). The pneumotachograph was connected to the subjects via ~1.2 m of large bore tubing (Vacu·Med, Ventura, CA). Subjects breathed through a low resistance, low dead space (~170 ml) two way non-rebreathing respiratory valve (R2700, Hans Rudolph, Kansas City, MO) connected to either a mouthpiece (Hans Rudolph,

Kansas City, MO) or silicone nose and mouth breathing mask (8900 series, Hans Rudolph, Kansas City, MO). Expired air passed from the respiratory valve through ~1.2 m of large bore tubing into a 5 l baffled mixing chamber (Vacu·Med, Ventura, CA). Temporal alignment for the combined dead space in the expired respiratory circuit (~6.3 l) was taken into account in all calculations (Wasserman, Hansen, et al. 1994). Mixed expired air was sub-sampled from the mixing chamber at 550 $ml.min^{-1}$, dried using CaCl, then passed to the gas analysers for measuring O_2 (Rapid Zirconia, PK Morgan, Rainham, Kent) and CO_2 (LB-2, Beckman, Anaheim, CA) concentrations. The gas analysers were calibrated prior to and immediately following the testing protocol with two precision grade gases (BOC Gases, NSW, Australia) of known concentrations that spanned the physiological range. A 386-SX PC (Figure 2.1) was programmed to perform every 30 seconds, the standard calculations to determine the average of expired ventilation ($\dot{V}_E$, $l.min^{-1}$, BTPS and STPD), $\dot{V}O_2$ ($l.min^{-1}$, STPD), carbon dioxide production ($\dot{V}CO_2$, $l.min^{-1}$, STPD) and respiratory exchange ratio (RER; Wasserman, Hansen, et al. 1987). Peak O_2 consumption ($\dot{V}O_{2peak}$, $l.min^{-1}$, STPD) was calculated as the average of the two highest consecutive 30 second $\dot{V}O_2$ values.

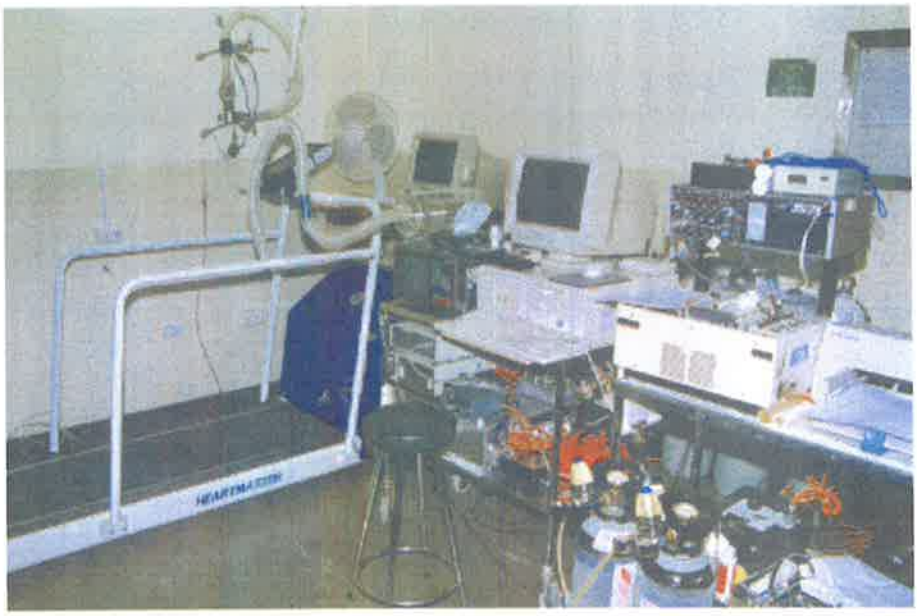


Figure 2.1 Gas analysers and 386-SX PC used to measure $\dot{V}O_2$, $\dot{V}CO_2$ and RER.

2.2.3 Assessment of inspired gas volume

Inspired gas volume ($\dot{V}_I$, $l.min^{-1}$, ATP) was measured using a linearised pneumotachograph (Model 4813 Hans Rudolph, Kansas City, MO or #3, Fleisch, Lausanne, Switzerland) connected to a ± 2 cm H_2O differential pressure transducer (DP 45, Validyne, Northridge, CA). The pneumotachograph was linearised according to Yeh et al. (1982) using at least one hundred syringe (3 l, Hans Rudolph, Kansas City, MO) strokes at varying flow rates. At the beginning of each day the pneumotachograph was calibrated with fifteen syringe strokes at different flow rates in order to reset the zero point of the digital channel used by the 386-SX PC to measure $\dot{V}_I$ ($l.min^{-1}$, ATP). Expired minute ventilation ($\dot{V}_E$, $l.min^{-1}$, BTPS and STPD) was calculated by the PC using the Haldane

transformation (Haldane 1912) from breath by breath measurements of $\dot{V}_I$ ($l.min^{-1}$, ATP).

Figure 2.2 Fleisch pneumotachograph and differential pressure transducer used to measure $\dot{V}_I$, ($l.min^{-1}$, ATP).

2.2.4 Arterial catheterisation and measurement of arterial blood gases

Each subject lay supine while a polyethylene catheter (20 gauge, Becton Dickinson, Franklin Lakes, NJ) was inserted under local anaesthesia (2% lignocaine hydrochloride, Xylocaine) into the left radial artery with the catheter tip directed towards the heart. One end of a 10 cm J-Loop (Becton Dickinson, Franklin Lakes, NJ) was attached to the catheter hub and the other end connected to an adaptor (Y adaptor, Tuta Laboratories, Australia) with two injection ports to allow simultaneous blood sampling and temperature measurement (see Section

2.2.8). A three-way tap (Baxter Health Care, NSW, Australia) was connected to the blood sampling port and a Teflon coated thermocouple (IT21, Physitemp Instruments, Clifton, NJ) was inserted through the rubber seal on the second port with the tip positioned in the hub of the radial artery catheter. The entire catheter, J-loop and injection port system was filled with heparinised saline (15 $IU.ml^{-1}$ heparin in normal saline, 0.9% w/v) to prevent clotting.

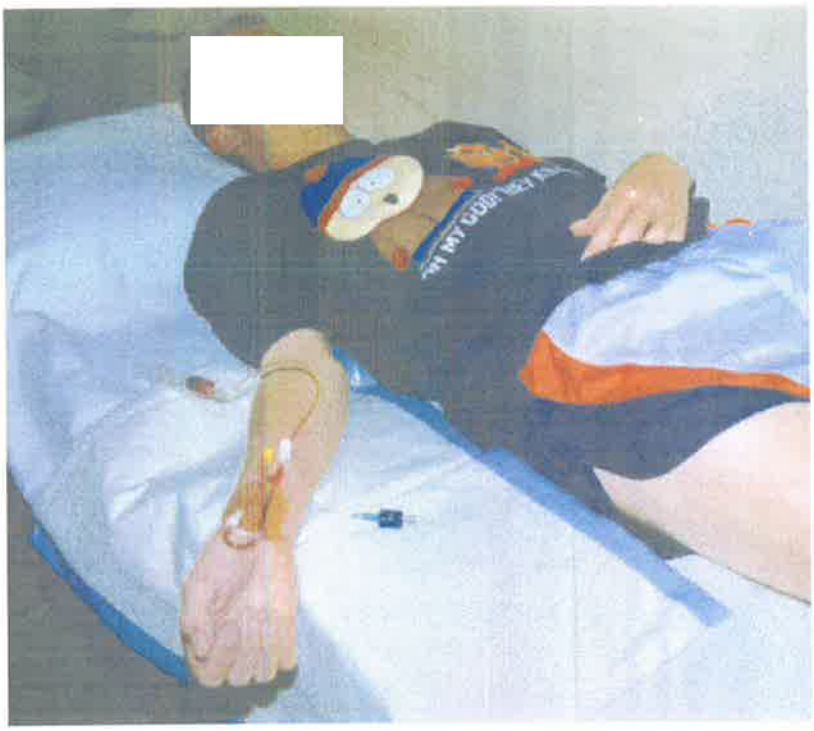


Figure 2.3 Subject with radial artery catheter *in situ*.

Prior to obtaining each arterial blood sample, the initial deadspace (2-5 ml) of the catheter system (blood-saline mixture) was withdrawn and discarded. The samples (5 ml) were then taken under anaerobic conditions into

heparinised ground glass syringes (Becton Dickinson, Franklin Lakes, NJ). The syringes were capped immediately, stored vertically in melting ice, and after prior mixing were analysed in duplicate for PaO_2, CO_2, pH and SaO_2 using a combined blood gas and CO-oximeter analyser (ABL520, Radiometer, Copenhagen). Arterial blood lactate was measured using a separate lactate module (ABL620, Radiometer, Copenhagen) connected to the blood gas analyser and CO-oximeter. Between each arterial sample the catheter system was filled with heparinised saline to prevent clotting. Blood gas and SaO_2 values were all analysed at 37°C and appropriate corrections (Severinghaus 1979) were subsequently made for either rectal or arterial blood temperatures (see Sections 2.2.7 and 2.2.8, respectively).

2.2.5 Estimation of O_2 saturation by pulse oximetry

Estimations of arterial oxyhemoglobin saturation (SpO_2) were obtained from a two wavelength infra-red sensor (US-504, Criticare, Waukesha, WI) applied to an earlobe pre-treated with a rubefacient. The signal obtained was co-ordinated with the R wave of the electrocardiogram and displayed on the digital screen of the pulse oximeter. The pulse oximeter was calibrated with an internal standard as described by the manufacturer and was equipped with a low signal alert to notify the user of perfusion related artefacts.

2.2.6 Measurement of hematocrit

Hematocrit (Hct) was determined from spun microcapillary samples (125 µl; 1024, Becton Dickinson, Franklin Lakes, NJ) withdrawn from the arterial blood syringes immediately after each blood gas measurement. Samples were spun in duplicate using an hematocrit centrifuge (Hema-C, Hawksley, Lancing, Sussex, UK) and read on a dedicated hematocrit ruler (Hawksley, Lancing, Sussex, UK). If duplicate values were different from each other by more than 1% another sample was measured with the closest two values used for subsequent analyses. The average of the duplicates was used in the multiple inert gas elimination model for determination of ventilation-perfusion distributions (see Section 2.2.14.2)

2.2.7 Measurement of rectal temperature

Rectal temperature was measured using an 8F disposable rectal/oesophageal temperature probe (Mon-A-Therm 700 series, Mallinckrodt Medical, Orange County, CA) inserted 20 cm beyond the anal sphincter. The analogue output from the temperature probe was directed to the 386-SX PC for the calculation of 30 second averages. The digital channel of the PC devoted to temperature monitoring was calibrated using an impedance generator (Bio-Medical Engineering, Royal Adelaide Hospital, Adelaide, Australia) that had previously been calibrated against a National Association of Testing Authorities (NATA) certified temperature monitor. The digital channel was calibrated

between 35 and 40°C prior to each experiment. Calibration of each rectal probe was not possible because they were single use and packaged in a sterile container. However, prior to beginning each series of experiments a single probe was calibrated in a heated and stirred water bath against a NATA certified mercury thermometer (-5-50°C). An example of a temperature probe calibration is displayed in Figure 2.4.

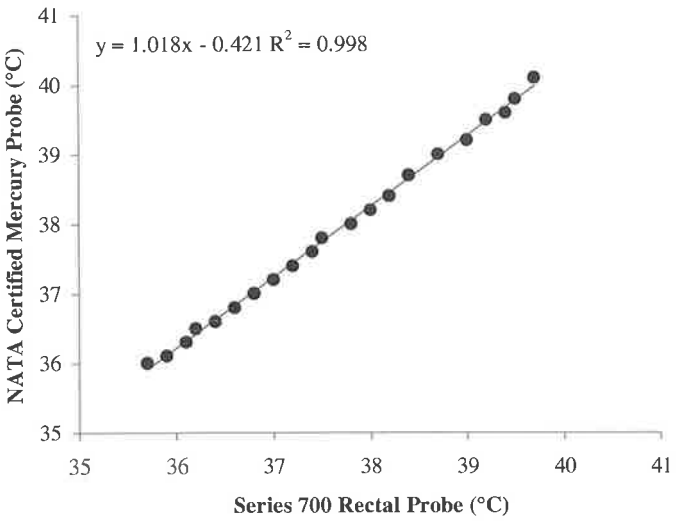


Figure 2.4 Rectal temperature probe calibration against NATA certified mercury thermometer.

2.2.8 Measurement of arterial blood temperature

Arterial blood temperature was measured and used as a potentially less invasive method compared with rectal temperature for the estimation of core temperature. It was measured with a teflon coated thermocouple (IT21,

Physitemp Instruments, Clifton, NJ, Fig 3.5) inserted into the radial artery catheter hub (see Section 2.2.4). Only the first 5 mm of the thermocouple detects temperature so no cooling effect occurred if the remainder of the thermocouple was exposed to ambient conditions. The response time of the thermocouple is reported by the manufacturer at 0.5 seconds for 95% of full scale. Thus it was suitable for the assessment of arterial blood temperature during sampling of arterial blood gases, which was usually completed under 10 seconds.

Arterial blood temperature was displayed on a digital monitor (Thermalert 5, Physitemp Instruments, Clifton, NJ, see Figure 2.5) and also recorded in real time on chart paper (Neomedix Instruments, Dee Why, NSW) via a 25mV/°C analogue output originating from the rear of the digital monitor.

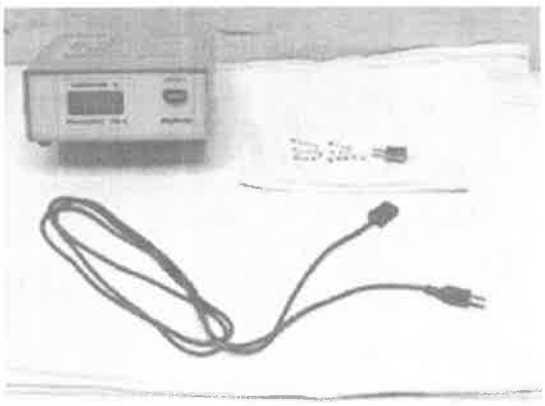


Figure 2.5 Physitemp 'Thermalert' digital monitor, 6 foot extension lead and IT 21 thermocouple.

Prior to initial sterilisation each thermocouple was calibrated in a heated and stirred water bath against a NATA certified mercury thermometer (-5-50°C) to establish a baseline calibration factor specific to that thermocouple. At the completion of each experiment a check calibration was performed under identical conditions to establish if the calibration factor had altered. If the calibration factor had shifted from the initial calibration, then a scaling factor was applied to all the arterial blood temperatures measured during the preceding experiment. Calibration occurred at the completion of the experiment because the thermocouple was required to be sterile prior to insertion into the radial artery catheter hub. An example of a calibration file for a single thermocouple is displayed in Table 2.1. The calibration factors for all the thermocouples used in this thesis remained stable.

Table 2.1 Baseline and routine calibration of a teflon-coated arterial blood temperature thermocouple (probe #4339 No.2) against a reference thermometer certified by the National Association of Testing Authorities (NATA)

4/2/97			**20/5/97**			**27/10/97**		
NATA	(#4339 No.2)	± diff	NATA	(#4339 No.2)	± diff	NATA	(#4339 No.2)	± diff
40	39.8	0.2	40	39.8	0.2	40	39.8	0.2
39	38.7	0.3	39	38.8	0.2	39	38.8	0.2
38	37.8	0.2	38	37.9	0.1	38	37.8	0.2
37	36.7	0.3	37	36.7	0.3	37	36.8	0.2
36	35.7	0.3	36	35.7	0.3	36	35.8	0.2
35	34.7	0.3	35	34.7	0.3	35	34.8	0.2
13/2/97			**7/7/97**			**8/11/97**		
NATA	(#4339 No.2)	± diff	NATA	(#4339 No.2)	± diff	NATA	(#4339 No.2)	± diff
40	39.8	0.2	40	39.8	0.2	40	39.8	0.2
39	38.7	0.3	39	38.8	0.2	39	38.8	0.2
38	37.7	0.3	38	37.8	0.2	38	37.7	0.3
37	36.7	0.3	37	36.8	0.2	37	36.8	0.2
36	35.7	0.3	36	35.8	0.2	36	35.8	0.2
35	34.7	0.3	35	34.8	0.2	35	34.8	0.2
14/4/97			**29/7/97**					
NATA	(#4339 No.2)	± diff	NATA	(#4339 No.2)	± diff			
40	39.8	0.2	40	39.7	0.3			
39	38.7	0.3	39	38.8	0.2			
38	37.7	0.3	38	37.9	0.1			
37	36.7	0.3	37	36.8	0.2			
36	35.7	0.3	36	35.8	0.2			
35	34.7	0.3	35	34.8	0.2			

2.2.9 Treadmill protocol used to measure peak O_2 consumption

$\dot{V}O_{2peak}$ was measured on a calibrated (see Section 2.2.15.1) motorised treadmill (1900 series, Marquette Electronics Inc., Milwaukee, WI; Figure 2.6). Each subject was allowed a 5 minute warm up at a brisk walking pace after which time they were instructed to complete 5 minutes of musculo-skeletal stretching. The protocol began with a 2 minute walk at 6.0 $km.hr^{-1}$ which was used to flush the $\dot{V}O_2$ measuring system with mixed expired gas. At the completion of the 2 minutes, the treadmill speed was increased to 15 $km.hr^{-1}$ for well trained runners or 13 $km.hr^{-1}$ for untrained runners and cyclists. The subjects were required to maintain these speeds for the duration of the test. The treadmill remained horizontal for the first 4 minutes of the protocol after which the treadmill elevation was increased 2% every minute. The subjects were frequently asked to give an indication of their ability to continue the test using pre-determined hand signals. An emergency stop button was located immediately in front of the subject. Verbal encouragement was provided during the terminal stages of the test to ensure each subject reached volitional exhaustion. Because $\dot{V}O_2$ was averaged every 30 seconds, the subjects were instructed to continue exercising until either 30 or 60 seconds of the final work load had been completed.

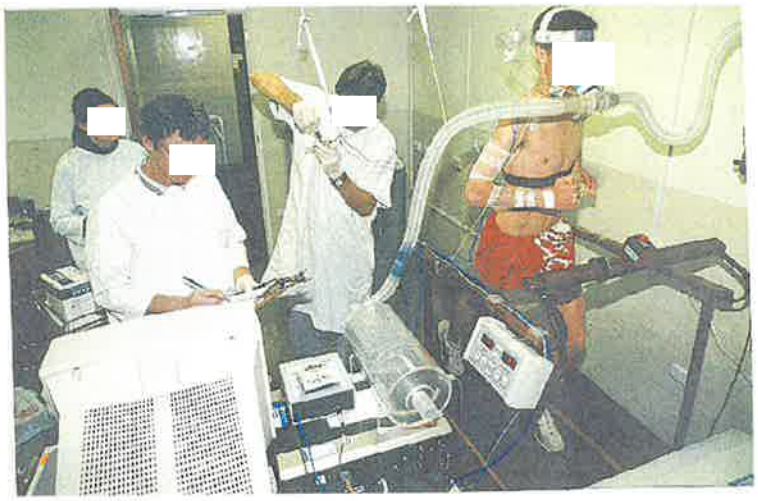


Figure 2.6 Treadmill used for assessment of running $\dot{V}O_{2peak}$

2.2.10 Air-braked cycle ergometer protocol used to measure peak O_2 consumption

$\dot{V}O_{2peak}$ tests were performed on an air-braked cycle ergometer (Peter Bundy Cycles, NSW, Figure 2.7) which was calibrated regularly against a first principle dynamic calibration rig (Woods, Day, et al. 1994; see Section 2.2.15.2). The cycle ergometer was fitted with clipless pedals (PP276, Look, France) and a special head stem (Ergo-Stem, Look, France) that allowed each subject to adopt a cycling position that replicated the position on their own bicycle. The cycle ergometer protocol began with a 5 minute warm up at 100 watts (W) followed by a brief period of musculo-skeletal stretching. The protocol began at a work load of 150 W for 1 minute with 25 W increments every minute thereafter. Power output was displayed on a video monitor in front of the subjects to indicate the target power output that was required for the duration of the each minute. The

ergometer had seven gears, which allowed each subject to chose their own pedal cadence to meet the target power output. The subjects were frequently asked to give indication of their ability to continue the test using pre-determined hand signals. Verbal encouragement was given towards the end of the test to ensure each subject reached volitional exhaustion. Because $\dot{V}O_2$ was averaged every 30 seconds, the subjects were instructed to continue exercising until either 30 or 60 seconds of the final work load had been completed.

Figure 2.7 Air-braked cycle ergometer used for assessment of cycling $\dot{V}O_{2peak}$

2.2.11 Technical error of measurement (TEM) for the treadmill and air-braked cycle ergometer protocols used to determine peak O_2 consumption

Every procedure in an exercise physiology laboratory should be precise and reliable, yet any measurement has a degree of uncertainty associated with it. Thus a measure is required to provide the user with the ability to distinguish those tests which have high precision and are repeatable in nature. The measure of precision adopted for this thesis is the technical error of measurement (TEM; Pederson & Gore 1996) defined as the standard deviation of duplicate measures taken independently of one another on the same subject. The units of the TEM are the same units as the variable measured.

$$TEM = \sqrt{MSe}$$

Where MSe = error mean square which is equal to the average variance of the paired values.

The percent TEM (% TEM) is calculated as the TEM divided by the grand mean of all paired observations.

The measure of reliability used in this thesis is the intra-class correlation coefficient (ICC), calculated from the results of an analysis of variance (ANOVA). The between subjects error and error mean squares from the ANOVA

are combined into a ratio formula to give an ICC. An ICC is always positive and has no units. Values range from 0 to 1, with values close to 1 indicating high reliability since successive measurements were in relatively close agreement.

$$ICC = \frac{MSs - MSe}{MSs + MSe}$$

Where MSs = Mean square error between subjects

2.2.11.1 TEM of treadmill peak O_2 consumption protocol

Five subjects completed two $\dot{V}O_{2peak}$ tests separated by one week. The tests were conducted at identical times of the day and followed the protocol described in Section 2.2.9. The TEM and ICC of the two $\dot{V}O_{2peak}$ tests are shown in Table 2.2.

2.2.11.2 TEM of air-braked cycle ergometer peak O_2 consumption protocol

Ten subjects completed two $\dot{V}O_{2peak}$ tests separated by one week. The tests were conducted at identical times of the day and followed the protocol described in Section 2.2.10. The TEM and ICC of the two $\dot{V}O_{2peak}$ tests are shown in Table 2.3.

Table 2.2 TEM data for the measurement of peak O_2 consumption ($l.min^{-1}$) on the treadmill ergometer

	Trial 1	Trial 2
subject 1	5.05	5.08
subject 2	4.14	4.21
subject 3	4.43	4.57
subject 4	4.79	4.48
subject 5	4.10	4.30
Grand Mean	**4.52 $l.min^{-1}$**	

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Row 1	2	10.13	5.065	0.00045
Row 2	2	8.35	4.175	0.00245
Row 3	2	9	4.5	0.0098
Row 4	2	9.27	4.635	0.04805
Row 5	2	8.4	4.2	0.02

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Subjects	1.0639	4	0.265975	16.46904	0.004393	5.192163
Within Groups	0.08075	5	0.01615			
Total	1.14465	9				

TEM =	**0.127 $l.min^{-1}$**
%TEM =	**2.8 %**
ICC =	**0.89**

Table 2.3 TEM data for the measurement of peak O_2 consumption ($l.min^{-1}$) on the air-braked cycle ergometer

	Trial 1	Trial 2
subject 1	5.04	4.78
subject 2	5.65	5.86
subject 3	5.25	5.31
subject 4	3.70	3.63
subject 5	5.58	5.60
subject 6	5.54	5.35
subject 7	5.32	5.05
subject 8	4.91	5.06
subject 9	3.98	3.82
subject 10	3.96	4.17

Grand Mean **4.88 $l.min^{-1}$**

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Row 1	2	9.82	4.91	0.0338
Row 2	2	11.51	5.755	0.02205
Row 3	2	10.56	5.28	0.0018
Row 4	2	7.33	3.665	0.00245
Row 5	2	11.18	5.59	0.0002
Row 6	2	10.89	5.445	0.01805
Row 7	2	10.37	5.185	0.03645
Row 8	2	9.97	4.985	0.01125
Row 9	2	7.8	3.9	0.0128
Row 10	2	8.13	4.065	0.02205

Table 2.3 (continued) TEM data for the measurement of peak O_2 consumption ($l.min^{-1}$) on the air-braked cycle ergometer

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	9.90942	9	1.101047	68.4305	8.49E-08	3.020382
Within Groups	0.1609	10	0.01609			
Total	10.07032	19				
TEM =	**0.127 $l.min^{-1}$**					
%TEM =	**2.6 %**					
ICC =	**0.97**					

2.2.12 Measurement of cardiac output

Cardiac output ($\dot{Q}$, $l.min^{-1}$) was measured using a quasi steady-state acetylene (C_2H_2) non-rebreathing technique. The details of this method have been previously reported and show excellent agreement with direct Fick methods for measurement of $\dot{Q}$ (Barker, Hopkins, et al. 1998). The measurement of $\dot{Q}$ utilised the identical experimental set up as that described for the $\dot{V}O_{2peak}$ testing (see Section 2.2.2). The fraction of end-tidal CO_2 ($F_{ET}CO_2$) was measured using an infra-red CO_2 analyser (Beckman LB-2, Anaheim, CA) and a strip chart recorder (Neomedix Systems, Dee Why, NSW). Once steady-state was attained (as measured by stable $F_{ET}CO_2$, HR and $\dot{V}O_2$) subjects inspired a gas mixture containing C_2H_2 (1%), O_2 (20.9 or 13.1%) and balance N_2 for approximately 30-40 breaths. End-tidal concentrations of C_2H_2 were measured using gas chromatography, and the blood:gas partition coefficient for C_2H_2 in blood was measured using the method of Wagner et al. (1974b). The steady state relationship between inspired and end tidal C_2H_2 was determined and then extrapolated back to the first breath to account for C_2H_2 recirculation. $\dot{Q}$ was calculated according to the following equation:

$$\dot{Q} = \left[\frac{\dot{V}_E * P_ECO_2 * (P_IC_2H_2 - P_{ET}C_2H_2)}{(\lambda * P_{ET}CO_2 * P_{ET}C_2H_2)} \right]$$

where: $\dot{V}_E$ = Expired minute ventilation ($l.min^{-1}$, BTPS), P_ECO_2 = mixed expired PCO_2, $P_{ET}CO_2$ = end tidal PCO_2, $P_IC_2H_2$ = inspired C_2H_2, $P_{ET}C_2H_2$ = end tidal PC_2H_2, and λ = C_2H_2 blood:gas partition coefficient (BTPS).

2.2.13 Measurement of resting pulmonary function

Pulmonary function tests were conducted in the Lung Function Laboratory of the Royal Adelaide Hospital. This laboratory recently participated in, and satisfactorily completed, a Hospital Quality Assurance program conducted by the Australian Council Healthcare Standards.

2.2.13.1 Forced expiratory volume in 1 second and forced vital capacity

Forced expiratory volume in 1 second ($FEV_{1.0}$) and forced vital capacity (FVC) manoeuvres were completed in triplicate, separated by approximately 2-3 minutes. Briefly, each subject sat quietly on a chair with a nose clip fitted. The subject then inhaled to full inspiratory capacity and exhaled as forcefully and for as long as possible through a disposable cardboard mouthpiece and ~90 cm of large diameter (50.8 mm) smooth bore respiratory

tubing (Hans Rudolph, Kansas City, MO). $FEV_{1.0}$ was measured on a 12 l rolling seal spirometer (Model 131, P.K. Morgan, Rainham, Kent, UK). FVC was calculated by computer integration of the flow signal. The spirometer was calibrated prior to every assessment with ten syringe strokes of a 3 l calibration syringe (Hans Rudolph, Kansas City, MO) at varying flow rates. Gender and age specific predicted values for $FEV_{1.0}$ and FVC were determined using the equations described by Crapo et al. (1981).

Male and Female (> 18 years of age)

Predicted $FEV_{1.0}$ (l) = [0.0414 x Height (cm)] – [0.0244 x Age (years)] – 2.19

Predicted FVC (l) = [0.06 x Height (cm)] – [0.0214 x Age (years)] – 4.65

Male and Female (< 18 years of age)

Predicted $FEV_{1.0}$ (l) = [0.044 x Height (cm)] – 3.99

Predicted FVC (l) = [0.146 x (Exp(0.0199 x Height (cm)))]

2.2.13.2 Lung diffusing capacity for carbon monoxide

Lung diffusing capacity for carbon monoxide (DL_{CO}) was measured using a standard single breath technique on a rapid response helium and carbon monoxide analyser (MasterLab, Jaeger, Würzburg, Germany). Inspired gas fractions consisted of 0.2-0.3% CO, 7-10% He, balance air. Each subject sat quietly breathing through the mouthpiece with a nose clip attached. From the end of a normal expiration, the subject exhaled to maximum expiration then followed with a full maximal inspiration. During the inspiration, the subject inhaled the test gas and was then required to hold the maximal inspiration for a period of 10 seconds. The subject exhaled normally with the first 800 ml of expirate discarded and the following portion collected in a impermeable foil bag and analysed for CO and He (Figure 2.8). The CO transfer factor was calculated (based on a standard hemoglobin concentration ([Hb]) of 14.6 g.100 ml^{-1}) and corrected for [Hb] measured during resting arterial blood samples. The equation used to calculate DL_{CO} was;

$$DL_{CO} = \dot{V}_A \times (60 / \text{actual time}) \times 0.389\ mmol.min^{-1}.kPa^{-1} \times Log[(FI_{CO} \times FA_{He}) / (FA_{CO} \times FI_{He})]$$

where; $\dot{V}_A$ (alveolar ventilation) $= k \times FI_{He} \times FA_{He} \times (\dot{V}_{IN} - \dot{V}_{DA} - \dot{V}_{AT})$

$$0.389 = (BP-47)/BP \times [273/(273 + 37)] \times (BP/760) \times 44.6 mmol.l^{-1} / (BP-47)$$

$k = 1.025$ if $CO_2 = 5\%$ and the dead space of the sample bag = 30 ml

$\dot{V}_{IN}$ = inspired volume

$\dot{V}_{DA}$ = equipment dead space (valve dead space)

$\dot{V}_{AT}$ = anatomical dead space

BP = barometric pressure (mm Hg)

FA_{CO} is assumed to be 5%

FI_{CO} = fraction of inspired CO

FA_{HE} = fraction of alveolar helium

FI_{HE} = fraction of inspired helium

Predicted values for DL_{CO} were obtained from Gaensler and Wright (1966) using the following equations;

Male > 18 years of age

$$DL_{CO} = 3.75 \times \dot{V}_A - 0.153 \times \text{age (years)} + 19.93$$

Where; $\dot{V}_A$ = (70.18 - 0.284) x Age (years) x Height (cm) x (TLC / VC) x STPD factor

TLC / VC (total lung capacity / vital capacity)

= 1.25 if Age (years) <35

= 1.305 if 35 > Age (years) <50

= 1.45 if Age (years) >50

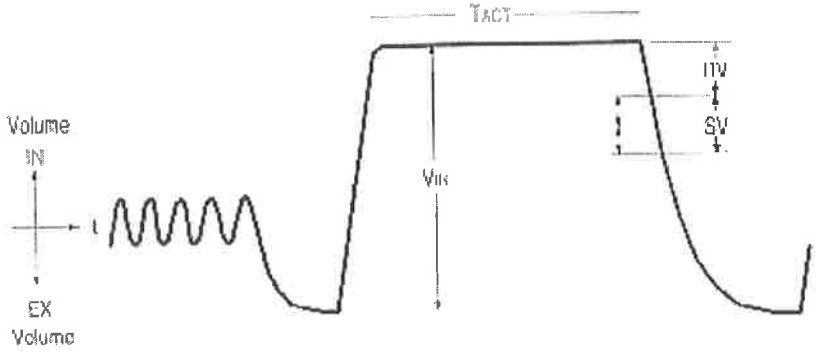


Figure 2.8 Diagram depicting the measurement of DL_{CO}

Where; IN, inspired volume; EX, expired volume; t, time; V_{IN} inspiratory capacity; T_{ACT}, breath hold time; DV, dead space volume; SV, sample volume.

2.2.13.3 Lung volume

There are two main aspects of lung mechanics: the dynamic (flow - pressure) and the static elastic (volume-pressure) components. These components can be investigated by measuring subdivisions of the total lung volume and the elastic recoil. Body plethysmography is the most rapid and accurate means of measuring the total compressible gas in the thorax, including gas trapped in poorly ventilated spaces. This is achieved by recording the changes in flow at the mouth, flow through a box wall pneumotachograph, and pressure at the mouth while the subject performs a series of breathing manoeuvres. The volume of trapped gas is extrapolated from analysis of the small changes in volume and pressure that occur when the mouthpiece is occluded and the subject expands and compresses the air in their chest by making small 'panting' efforts against the

closed mouthpiece. This is based on the assumption that in the closed system (provided the subject keeps their larynx open) the gas pressure in the mouthpiece is equal to the pressure in their alveoli since no flow can occur. Subdivisions of lung volumes measured by plethysmography are: vital capacity (VC), inspiratory capacity (IC), expiratory reserve volume (ERV), residual volume (RV), total lung capacity (TLC) and functional residual capacity (FRC).

Subdivisions of lung volumes were measured in an air-conditioned closed body box (Jaeger, Würzburg, Germany). Mouth flow was measured with a large pneumotachograph (#4, Fleisch, Lausanne, Switzerland) connected to a $\pm$ 1 cmH_2O differential pressure transducer (DP 45, Validyne, Northridge, CA). Mouth pressure was measured during occlusion using a differential pressure transducer (DP 15, Validyne, Northridge, CA). Body box flow was measured with a pneumotachograph (#4, Fleisch, Lausanne, Switzerland) connected to a $\pm$ 2 cmH_2O differential pressure transducer (DP 45, Validyne, Northridge, CA).

The subject sat comfortably in the body box, with the seat adjusted to the appropriate height for the mouthpiece. The subject was asked to breath hold for approximately 2-3 seconds just prior to the zero flow check and then to breathe normally again. After a minimum of four to five tidal breaths from FRC, the subject was instructed to breathe to TLC, followed by a slow expiration out to RV. Immediately following this manoeuvre the subjects placed their hands firmly on their cheeks and shallow panted at a rate of approximately one pant per second. The mouth shutter was depressed at approximately FRC and was occluded for approximately 5-9 seconds after which time the test was completed and the

subject was asked to breath normally. The calculation of subdivisions of lung volume from the plethysmograph is based on Boyle's law as described by DuBois et al. (1956).

Predicted values were calculated from the following equations (Goldman & Backlake 1959);

Males

$$TLC = 0.094 \times \text{Height (cm)} - 0.015 \times \text{Age (years)} - 9.17$$

$$FRC = 0.05 \times \text{Height (cm)} - 5.02$$

2.2.14 Multiple inert gas elimination technique

2.2.14.1 Experimental method

The multiple inert gas elimination technique (MIGET) of Wagner et al. (1974a) was used to measure $\dot{V}_A/\dot{Q}$ inequality in athletes. Prior to MIGET measurements each subject had two vascular catheters inserted percutaneously under local anaesthesia (1% lignocaine hydrochloride). The first was a 20 G radial arterial catheter, inserted as previously described (see Section 2.2.4). The second catheter (18 G, Insyte, Becton Dickinson, Sandy, UT) was placed in the right forearm and was used exclusively for the inert gas infusion. The infusate

was made up of six inert gases (SF_6, ethane, cyclopropane, enflurane, ether and acetone) contained in a 5% dextrose solution which was infused (Masterflex Model 7521, Barnant Corp., Barrington, IL) via a 0.22 µm high-pressure Millipore filter into the forearm vein at a rate ($ml.min^{-1}$) approximately one quarter of the expected $\dot{V}_E$ ($l.min^{-1}$, BTPS). Immediately following the onset of infusion each subject was seated on the air-braked cycle ergometer and asked to remain there for 20 minutes. At the completion of the rest period, the subjects were connected to the same respiratory circuit as described in Section 2.2.14.5. $\dot{V}_I$, mixed expired respiratory and all ancillary measurements were monitored continuously throughout rest and during each work load, as described previously (see Sections 2.2.1, 2.2.2 and 2.2.3).

2.2.14.2 Inert gas analysis

At each work load, 5 ml duplicate arterial blood samples for inert gases and 6 ml samples for arterial blood gases were collected in pre-heparinised ground glass syringes (Becton Dickinson, Franklin Lakes, NJ). Thirty ml duplicate mixed expired gas samples were simultaneously collected in ground glass syringes (Becton Dickinson, Franklin Lakes, NJ). Drawing of blood and mixed expired samples was coordinated to allow for the transit time of expired gas through the mixing chamber. The mixed expired and arterial blood inert gas samples were analysed by gas chromatography according to the method of Wagner et al. (1974b). Mixed venous inert gas tensions were calculated from the

arterial and expired samples using the Fick principle, the measured cardiac output (described in Section 2.2.12) and $\dot{V}_E$. Retention (arterial tension / mixed venous tension) and excretion (mixed expired tension / mixed venous tension) values for all six gases were used to estimate the $\dot{V}_A/\dot{Q}$ distribution as previously described (Wagner, Saltzman, et al. 1974). The log standard deviation of the perfusion distribution ($\log SD\dot{Q}$) and the log standard deviation of the ventilation distribution ($\log SD\dot{V}$) were calculated from the recovered distribution and used as overall indices of $\dot{V}_A/\dot{Q}$ inequality. Additional dispersion indices ($DISP_R$, $DISP_E$, $DISP_{R-E}$) were derived directly from the retention and excretion data (Gale, Torre-Bueno, et al. 1985). These three indices describe the extent of $\dot{V}_A/\dot{Q}$ inequality independent of the fifty compartment model. $DISP_R$ and $\log SD\dot{Q}$ are comparable in that they both are parameters of the perfusion distribution. Similarly, $DISP_E$ and $\log SD\dot{V}$ describe the ventilation distribution. $DISP_{R-E}$ is an overall index of dispersion that has no counterpart in the moment analysis using the fifty compartment model. A copy of the Fortran programs and the output files associated with MIGET are detailed in Section 7.2 to 7.7.

The algorithm of Hammond and Hempleman (1987) was used to estimate an effective pulmonary diffusing capacity for O_2 (DLO_2) assuming a uniform distribution of diffusing capacity to blood flow. It calculates the expected PaO_2 associated with the measured degree of $\dot{V}_A/\dot{Q}$ inequality, excluding the possibility of alveolar-capillary diffusion disequilibrium. Agreement between expected and measured PaO_2 therefore supports the conclusion that diffusion equilibration is complete, but if expected PaO_2 exceeds

the measured value, diffusion limitation is inferred, although extra-pulmonary shunt cannot be excluded. The calculations of DLO_2 are outlined in detail in Section 7.4, with an example of the computer data output displayed in Section 7.6.

2.2.14.3 Arterial blood gas sampling and analysis

The duplicate arterial blood gas samples (6 ml each) were kept in a melted ice slurry and analysed (ABL 520, Radiometer, Copenhagen) after gentle mixing within 20 minutes of collection. PaO_2, $PaCO_2$, pH, SaO_2 and [Hb] were run in duplicate. The blood gas analyser routinely participated in Royal College of Pathologist Quality Assurance Program certification and was calibrated at hourly intervals throughout the day. Blood gas values were measured at 37°C and appropriate corrections made for the measured changes in arterial blood temperature (Section 2.2.7) throughout exercise (Severinghaus 1979). Blood temperature was taken as the highest temperature recorded on a digital monitor (Thermalert 5, Physitemp Instruments Inc., Clifton, NJ) during the withdrawal of the 5 ml arterial inert gas and 6 ml arterial blood gas samples.

2.2.14.4 Prediction of arterial O_2 and CO_2 tension and alveolar-arterial O_2 tension difference from inert gas data

Predicted values for PaO_2, $PaCO_2$ and the A-aDO_2 [A-aDO_2 (p)] can be calculated from the recovered $\dot{V}_A/\dot{Q}$ distribution (Hammond, Gale, et al. 1986a; Kelman 1966; Kelman 1967; West 1969). These predicted values represent the arterial respiratory gas tensions and contents that would result from the measured degree of $\dot{V}_A/\dot{Q}$ inequality and intra-pulmonary shunt determined by MIGET. Consequently, A-aDO_2 (p) reflects only the A-aDO_2 due to $\dot{V}_A/\dot{Q}$ inequality and intra-pulmonary shunt, assuming 1) complete alveolar-end-capillary O_2 diffusion equilibration and 2) negligible extra-pulmonary shunts. Any statistically valid residual difference between the observed A-aDO_2 [A-aDO_2 (o)] and A-aDO_2 (p), [A-aDO_2 (o-p)] is due to some combination of 1) diffusion limitation of O_2 transport and 2) extra-pulmonary shunt (caused by bronchial arterial-pulmonary venous anastomoses and Thebesian venous drainage into the left side of the heart).

2.2.14.5 Measurement of peak O_2 consumption used for MIGET experiment

$\dot{V}O_{2peak}$ was determined with an on-line, indirect calorimetry system that measured inspired volume and both inspired and expired gas fractions. The dry inspired gas mixtures (either air; 20.93% O_2 or hypoxia; 13.1% O_2) were

contained in pressurised cylinders, verified by the distributor (BOC Gases, Chatswood, NSW) to be accurate within ± 0.1% O_2. The dry gases were passed through a heated water bath (to humidify the gas to approximately 50%) and were then stored in a 2000 l impermeable aluminium bag (Scholle Industries, Elizabeth, SA). Leading from the aluminium bag was a T piece connector and ~1.2 m of respiratory tubing (Vacu·Med, Ventura, CA). The T piece housed a rapid response temperature and relative humidity probe (HMP230, Viasala OY, Finland) as well as a sample port connected to a paramagnetic O_2 analyser (Normocap 200, Datex Medical Instruments, Tewksbury, MA) for the measurement of F_IO_2. Downstream from the respiratory tube was a linearised pneumotachograph (#3, Fleisch, Lausanne, Switzerland) and a ± 2 cm H_20 differential pressure transducer (Validyne DP45, Northridge, CA) which together with real time measurements of F_IO_2, gas temperature and relative humidity, allowed the calculation of inspired minute ventilation ($l.min^{-1}$, ATP). The subjects inhaled through a low dead space, non-rebreathing respiratory valve (R2700, Hans Rudolph, Kansas City, MO) with the expired volume directed to a 5 l baffled mixing box (Vacu·Med, Ventura, CA). Expired O_2 and CO_2 fractions were sub-sampled from the mixing box at a rate of 550 $ml.min^{-1}$, dried with $CaCl_2$ crystals and then analysed on a rapid response zirconia (PK Morgan Zirconia, Rainham, Kent) and infra-red (Beckman LB-2, Anaheim, CA) O_2 and CO_2 analyser, respectively. The gas analysers were calibrated prior to and checked for drift immediately following the test protocol with two precision grade gases of known concentration (BOC Gases, Chatswood, NSW) that spanned the physiological range. A PC was programmed to determine the 30 second averages

of $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, RER, HR and W. $\dot{V}O_{2peak}$ for each F_IO_2 was determined as the average of the two highest consecutive 30 second values.

2.2.14.6 Measurement of O_2 consumption during MIGET experiment

Following catheter insertion, subjects were seated on the cycle ergometer and connected to the same respiratory circuit as that used during the $\dot{V}O_{2peak}$ measurements (see Section 2.2.14.5) but with modifications to the expired tubing and mixing boxes. In order to minimise the loss of soluble inert gases (particularly acetone), the expired breathing circuit, which consisted of respiratory tubing (~1.5 m), a 10 l mixing box (used for resting measurements) and a 27 l mixing box (used for exercise measurements) was heated at a constant temperature (40-50°C) using heating tape (Deto.58, Fisher Scientific, Tustin, CA) and a heater controller box (11-463-46F, Fisher Scientific, Tustin, CA).

2.2.15 Calibration of treadmill and air-braked cycle ergometers

2.2.15.1 Treadmill ergometer

The treadmill speed was calibrated prior to beginning of each experiment. Briefly, a coloured piece of adhesive tape was applied to the treadmill belt and the time taken for ten complete revolutions of the belt was hand timed with a stop watch at a variety of treadmill speeds. An example treadmill speed calibration curve is displayed in Figure 2.9 and calibration data in Table 2.4.

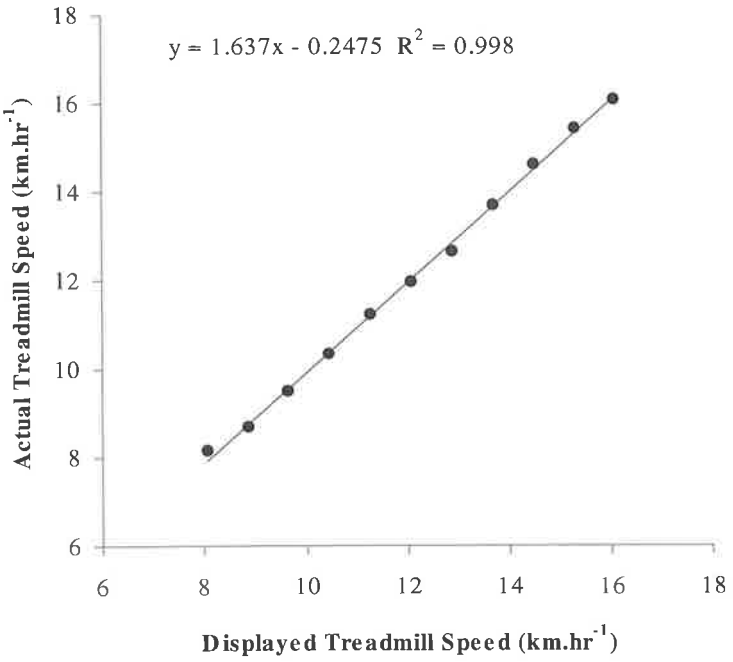


Figure 2.9 An example of treadmill speed calibration graph

Table 2.4 An example of treadmill speed calibration data

Treadmill Display		Actual Measurement				
$m.hr^{-1}$	$km.hr^{-1}$ (Calculated)	10 revs (s)	$revs.sec^{-1}$	$Revs.min^{-1}$	$Distance.min^{-1}$ (m)	$km.hr^{-1}$
5.0	8.05	14.88	0.67	40.32	135.69	8.14
5.5	8.85	13.94	0.72	43.04	144.84	8.69
6.0	9.66	12.74	0.78	47.10	158.48	9.51
6.5	10.46	11.72	0.85	51.19	172.27	10.34
7.0	11.27	10.78	0.93	55.66	187.29	11.24
7.5	12.07	10.14	0.99	59.17	199.11	11.95
8.0	12.87	9.57	1.04	62.70	210.97	12.66
8.5	13.68	8.84	1.13	67.87	228.39	13.70
9.0	14.48	8.28	1.21	72.46	243.84	14.63
9.5	15.29	7.86	1.27	76.34	256.87	15.41
10.0	16.09	7.54	1.33	79.58	267.77	16.07

Treadmill belt length - 3.365 m

2.2.15.2 Air-braked cycle ergometer

The air-braked cycle ergometer was regularly calibrated against a first principles dynamic calibration rig as per Woods et al. (1994). This calibration was performed at the South Australian Sports Institute, Kidman Park, South Australia. Data from a typical calibration are displayed in Figure 2.10.

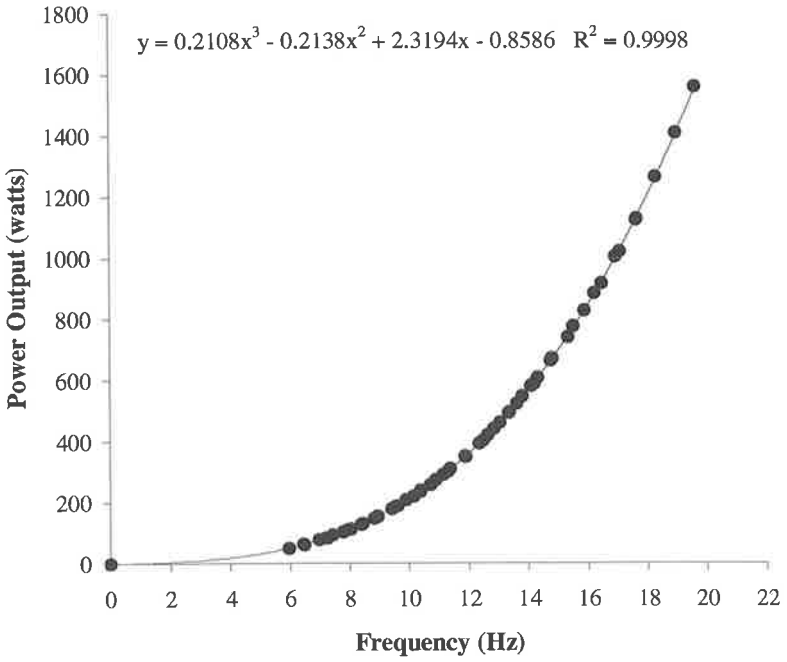


Figure 2.10 An example of the calibration curve of the air-braked cycle ergometer

2.2.16 Pneumotachograph calibration

Prior to any data collection the pneumotachograph was linearised (Yeh, Gardner, et al. 1982) with one hundred and fifty syringe strokes at varying flow rates via a 3 l calibration syringe (Hans Rudolph, Kansas City, MO). Following this, routine calibrations were performed immediately before each experiment with ten syringe strokes from the 3 l calibration syringe.

The degree of accuracy of the initial pneumotachograph linearisation was verified using a sinusoidal pump capable of flow rates in excess of 220 $l.min^{-1}$ (ATP; Gore, Catcheside, et al. 1997). Increasing volumes of air at different flow rates were passed through the pneumotachograph using the sinusoidal pump and the difference between the two measures was investigated. The data from the linearisation verification are displayed in Table 2.5.

Table 2.5 Validation of pneumotachograph linearisation using a sinusoidal pump

epoch	Time	True $\dot{V}_I$ (ATP)	Pneumotach $\dot{V}_I$ (ATP)	% Diff	Pneumotach $\dot{V}_E$ (ATP)	Pneumotach $\dot{V}_T$ (BTPS)	Pneumotach $\dot{V}_E$ (BTPS)
1	0.5		42.06		39.92	3.21	43.95
2	1.0	41.70	42.39	1.66%	40.24	3.2	44.3
3	1.5	41.70	42.35	1.57%	40.20	3.2	44.26
4	2.0		53.67		50.94	3.18	56.08
5	2.5	54.30	55.17	1.60%	52.36	3.18	57.65
6	3.0	54.30	55.15	1.56%	52.34	3.18	57.63
7	3.5		83.42		79.17	3.15	87.17
8	4.0	83.70	84.07	0.44%	79.79	3.15	87.85
9	4.5	83.70	84.06	0.43%	79.78	3.15	87.84
10	5.0		106.15		100.75	3.13	110.93
11	5.5	108.60	108.16	-0.40%	102.66	3.13	113.03
12	6.0	108.60	108.15	-0.41%	102.65	3.13	113.02
13	6.5		130.99		124.32	3.11	136.88
14	7.0	133.50	132.38	-0.84%	125.65	3.11	138.34
15	7.5	133.50	132.24	-0.94%	125.51	3.11	138.19
16	8.0		160.20		152.05	3.11	167.41
17	8.5	164.10	162.89	-0.74%	154.60	3.11	170.22
18	9.0	164.10	162.76	-0.82%	154.48	3.11	170.08
19	9.5		188.41		178.83	3.12	196.89
20	10.0	192.30	191.10	-0.62%	181.38	3.12	199.7
21	10.5	192.30	191.54	-0.39%	181.80	3.11	200.16
22	11.0		190.16		180.48	3.11	198.71
23	11.5		67.49		64.06	2.6	70.53
24	12.0	215.25	214.83	-0.19%	203.91	2.61	224.5
25	12.5	215.25	214.87	-0.18%	203.94	2.61	224.54

True $\dot{V}_I$ (ATP), inspired ventilation measured by sinusoidal pump; Pneumotach $\dot{V}_I$ (ATP), inspired ventilation measured by linearised pneumotachograph; % diff = [True $\dot{V}_I$ (ATP) – Pneumotach $\dot{V}_I$ (ATP) / True $\dot{V}_I$ (ATP)] x 100; Pneumotach $\dot{V}_E$ (ATP), expired ventilation measured by linearised pneumotachograph; Pneumotach $\dot{V}_T$ (BTPS), tidal volume measured by linearised pneumotachograph

2.3 DATA ANALYSIS

Data are expressed as means ± SEM. For all statistical tests the level of significance was established at $P<0.05$. All analyses were conducted using Statistica (Ver 5.0, Statsoft, Tulsa, OK).

More complete explanations of the statistical analyses used for each experiment are outlined in Sections 3.2.3, 4.2.7 and 5.2.8.

3 TIME COURSE OF EXERCISE-INDUCED HYPOXEMIA

3.1 INTRODUCTION

Holmgren and Linderholm (1958) and Rowell et al. (1964) provided the first descriptions of EIH during strenuous exercise. This observation was confirmed by Dempsey and colleagues (1984) who provided one of the first systematic studies during intense exercise in highly trained runners. While several subsequent studies in endurance athletes have reported a significant fall in SaO_2 with exercise intensities at or close to $\dot{V}O_{2max}$ (Powers, Martin, et al. 1992; Williams, Powers, et al. 1986) the primary mechanism of EIH remains uncertain. Several hypotheses have been put forward including intra and extra-pulmonary shunt (Dempsey, Hanson, et al. 1984; Powers, Martin, et al. 1992), inadequate hyperventilation (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Miyachi & Tabata 1992; Powers, Dodd, et al. 1984; Turcotte, Kiteala, et al. 1997), an end-capillary O_2 diffusion limitation based on low pulmonary capillary blood transit time (Dempsey, Hanson, et al. 1982; Schaffartzik, Poole, et al. 1992; Wagner, Gale, et al. 1986), and ventilation-perfusion inequalities (Hammond, Gale, et al. 1986a; Hopkins & McKenzie 1993; Hopkins, McKenzie, et al. 1994; Schaffartzik, Poole, et al. 1992; Torre-Bueno, Wagner, et al. 1985; Wagner, Gale, et al. 1986).

While EIH is reported to affect ~50% of athletes with a $\dot{V}O_{2max}$ above ~4.5 $l.min^{-1}$ or ~68 $ml.kg^{-1}.min^{-1}$ (Powers, Dodd, et al. 1984; Powers & Williams 1987; Powers, Lawler, et al. 1989), its true prevalence and severity remain uncertain. Much of this uncertainty could reflect flawed methodology. Most blood gas measurements are made at 37°C and it is critical to correct for the exercise-induced hyperthermic response to avoid overestimating any hypoxemic trend. Yet only a handful of studies have done so (Dempsey, Hanson, et al. 1984; Norton, Squires, et al. 1995; Powers, Dodd, et al. 1991; Powers, Martin, et al. 1992; Warren, Cureton, et al. 1991) while many others have not (Brown, Knowlton, et al. 1993; Caillaud, Anselme, et al. 1993; Gore, Hahn, et al. 1996; Hopkins & McKenzie 1989; Pedersen, Mandoe, et al. 1996; Préfaut, Anselme, et al. 1994; Todaro, Leonardi, et al. 1995).

Some studies of EIH have estimated SaO_2 by pulse oximetry (Harms & Stager 1995; Lama, Wolski, et al. 1996; Martin, Powers, et al. 1992; Miyachi & Tabata 1992; Powers, Dodd, et al. 1989; Williams, Powers, et al. 1986) yet it is by no means certain that such estimates provide results which can be equated with direct measurements of SaO_2 (Brown, Knowlton, et al. 1993), despite claims to the contrary (Martin, Powers, et al. 1992; Powers, Dodd, et al. 1989).

Finally, while EIH has been reported most frequently during exercise of high intensity, few studies have followed the time course of EIH throughout exercise from rest to exhaustion with appropriate corrections made for increases in core temperature. Of the two which have done so using arterial blood samples (Powers, Martin, et al. 1992; Warren, Cureton, et al. 1991) only the study of

Powers et al. (1992) showed significant EIH. However, changes were only reported at maximal exercise.

Therefore, the present study was undertaken to monitor the changes in arterial blood gases throughout incremental exercise from rest to exhaustion, with all values corrected to rectal temperature measured during sampling. Direct measurements of oxyhemoglobin saturation in arterial blood were compared with those estimated simultaneously by ear oximetry.

3.2 METHODS

3.2.1 Subjects and experimental protocol

Fifteen male cyclists participated in the study. All subjects were engaged in regular competition and had no history of lung disease. Subjects arrived at the laboratory having abstained from vigorous exercise for the previous 24 hours and food and caffeine products for the previous 4 hours.

On entering the laboratory subjects self-inserted a disposable rectal temperature probe such that the thermistor was positioned 20 cm past the anal sphincter and the probe taped securely to the buttock skin (Section 2.2.7). Chest electrodes were applied to monitor both HR and the ECG (see Section 2.2.1). A radial arterial catheter was inserted under local anaesthesia (see Section 2.2.4). SpO_2 was measured by the method described in Section 2.2.5. Subjects then assumed their accustomed racing position on a calibrated air-braked cycle ergometer with power output displayed on a video monitor. To monitor $\dot{V}O_2$, a low dead-space respiratory valve (R2700, Hans Rudolph, Kansas City, MO) was fitted to all subjects immediately prior to exercise (see Section 2.2.2). Minor modifications were made to the protocol used to elicit $\dot{V}O_{2peak}$ as described in Section 2.2.10. Briefly, the initial work load was 150 W and lasted for 2 minutes whereafter the work load was increased by 25 W every 2 minutes until volitional exhaustion. All cardio-respiratory variables and power output were monitored

throughout exercise with 30 second averages displayed in a spreadsheet program (Microsoft Excel, Microsoft Corp. Redmond, CA).

3.2.2 Blood sampling and analysis

The technique used for the sampling of arterial blood and the measurement of gas tension is described in detail in Section 2.2.4. Briefly, 5 ml arterial samples were taken anaerobically over a number of breaths into heparinised ground glass syringes during the last 30 seconds of each 2 minute work load. The syringes were capped immediately, stored vertically in melting ice and after prior mixing were analysed in duplicate for PaO_2, $PaCO_2$, pH and SaO_2. Between arterial sampling periods the catheter system was filled with heparinised saline to prevent clotting. Blood gas and SaO_2 values were all measured at 37°C and appropriate corrections (Severinghaus 1979) made subsequently for rectal temperature using the mean value measured during the last 30 seconds of each work load. The ideal alveolar gas equation (Wasserman, Hansen, et al. 1987) was used to estimate PAO_2 and the calculated A-aDO_2.

3.2.3 Data analysis

Of the fifteen subjects who participated in the study, twelve were able to complete a work load of at least 375 W. From the remaining three, one subject completed 325 W and two completed 350 W. A least squares regression model was used to fill four blank cells for the three subjects to allow a full repeated measures ANOVA to be used on all subjects up to a work load of 375 W. In total, four cells out of 165 were filled with the least squares regression method. The strength of the association between PaO_2 and other ventilatory ($\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$ and PAO_2) and blood gas variables ($PaCO_2$ and A-aDO_2) were determined at 150 W and $\dot{V}O_{2peak}$ for all fifteen subjects using the Pearson product moment correlation and multiple linear regression. A one-way repeated measures ANOVA was used to test changes in PaO_2, $PaCO_2$ and A-aDO_2 over the duration of the incremental exercise test. A two-way repeated measures ANOVA was used to determine significance between SaO_2 and SpO_2 over the duration of the incremental exercise test. When significant main effects or interactions were found, means which differed were determined post-hoc using a Tukey's honestly significant difference analysis.

3.3 RESULTS

3.3.1 General

General anthropometric, peak physiologic and resting pulmonary function data of the fifteen subjects are displayed in Table 3.1. The mean $\dot{V}O_{2peak}$ of 68.5 ± 1.6 $ml.kg^{-1}.min^{-1}$ is representative of trained endurance athletes and was achieved at a power output of 370 ± 10 W.

Table 3.1 General anthropometric, peak physiologic and resting pulmonary function data for fifteen subjects

	Mean (SEM)
Age, years	25.7 (1.4)
Height, cm	179.0 (1.3)
Weight, kg	70.0 (1.7)
$FEV_{1.0}$, % of predicted	106 (3)
FVC, % of predicted	115 (2)
$\dot{V}O_{2peak}$, $l.min^{-1}$	4.77 (0.11)
$\dot{V}O_{2peak}$, $ml.kg^{-1}.min^{-1}$	68.5 (1.6)
$\dot{V}_{Epeak}$, $l.min^{-1}$, BTPS	178.1 (3.7)
HR, $beats.min^{-1}$	187 (2)

Values are mean (SEM). $FEV_{1.0}$, forced expiratory volume in 1 second; FVC, forced vital capacity; $\dot{V}O_{2peak}$, peak O_2 consumption; $\dot{V}_E$, peak minute ventilation; HR, heart rate.

3.3.2 Arterial PO_2

Progressive incremental exercise caused a variable response in PaO_2 for the fifteen subjects (Table 3.2). There were eight subjects who had a PaO_2 value less than 90 mm Hg at $\dot{V}O_{2peak}$ with six of those having values less than 85 mm Hg. The other subjects, however, demonstrated no appreciable change in PaO_2 throughout the entire study protocol. When the data for all fifteen subjects were combined, the first exercise work load (150 W, ~40% $\dot{V}O_{2peak}$) resulted in an immediate and significant decrease in PaO_2 (Figure 3.1). A further significant decrease in PaO_2 occurred at 200 W, whereafter it remained stable but still significantly below resting values. With both the first and final work loads ($\dot{V}O_{2peak}$), PaO_2 was correlated significantly with PAO_2 [R=0.81 (Figure 3.2) and R=0.70 (Figure 3.4), respectively] and A-aDO_2 [R=-0.63 (Figure 3.3) and R=-0.86 (Figure 3.5), respectively]. PAO_2 and A-aDO_2 were not significantly correlated at either 150 W or $\dot{V}O_{2peak}$ (R=0.05 and R=0.31, respectively). When combined in a multiple linear regression model PAO_2 and A-aDO_2 explained all of the variance in PaO_2 at a work load of 150 W and 95% of the variance in PaO_2 at $\dot{V}O_{2peak}$. At $\dot{V}O_{2peak}$, PaO_2 was significantly correlated with both $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ (R=0.58 and R=0.53, respectively).

Table 3.2 Individual arterial PO_2 data for fifteen subjects during a progressive incremental exercise test

	Work Load (watts)										
Subject	Rest	150	175	200	225	250	275	300	325	350	375
1	106.7	99.7	98.6	94.3	96.0	87.6	84.6	84.6	85.5	82.7	86.1
2	106.5	104.4	103.0	92.4	94.2	97.7	92.5	92.3	92.2	92.6	93.3
3	99.5	90.4	90.3	82.7	83.3	84.3	79.4	76.8	77.6	77.2	79.7
4	109.1	97.4	92.0	87.3	93.3	89.3	85.8	88.9	87.5	84.3	81.6
5	104.0	99.5	99.5	98.9	100.8	95.7	100.4	105.5	104.6	101.2	101.2
6	100.3	92.6	90.2	85.9	84.6	86.1	80.5	80.6	79.5	80.6	80.9
7	98.7	95.2	95.2	94.6	86.6	87.0	85.3	83.2	82.3	82.2	82.5
8	97.4	92.6	97.5	94.0	90.5	91.8	91.8	88.9	88.8	91.4	88.9
9	94.1	91.8	94.6	95.1	94.0	93.4	92.6	85.4	87.9	90.7	93.9
10	99.7	92.4	85.1	83.1	80.1	78.6	79.7	81.0	77.9	77.8	77.7
11	99.6	87.9	88.7	83.5	84.9	83.5	85.1	82.0	82.7	81.9	81.3
12	99.6	95.4	95.9	94.1	89.8	90.7	88.9	90.7	87.2	84.7	89.7
13	102.2	101.4	94.1	89.6	90.8	87.5	89.4	89.1	90.3	86.0	90.1
14	104.2	98.0	97.9	96.2	95.8	95.6	96.9	97.2	98.0	97.8	96.3
15	99.6	108.9	102.0	94.7	90.1	94.1	91.9	91.5	92.3	93.7	98.6

Data are means of duplicate measures of the same sample (mm Hg).

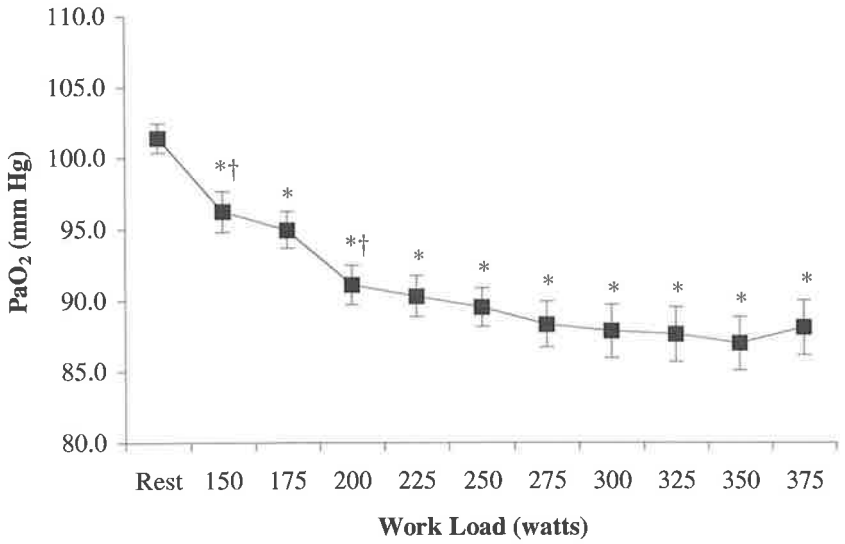


Figure 3.1 Values are means ± SEM. PaO_2 values during incremental exercise in fifteen subjects. † significantly different from previous value; * significantly different from Rest, $P<0.05$.

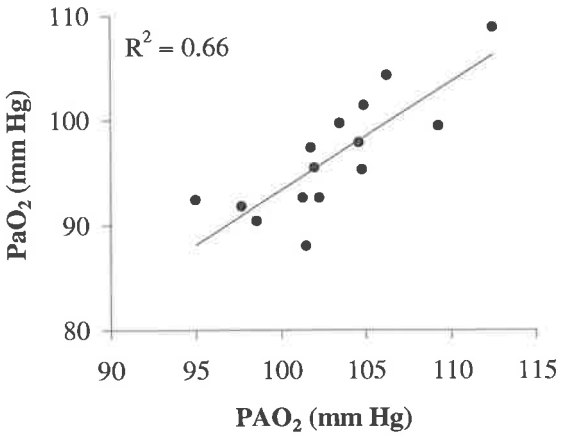


Figure 3.2 Association between PaO_2 and PAO_2 at 150 W

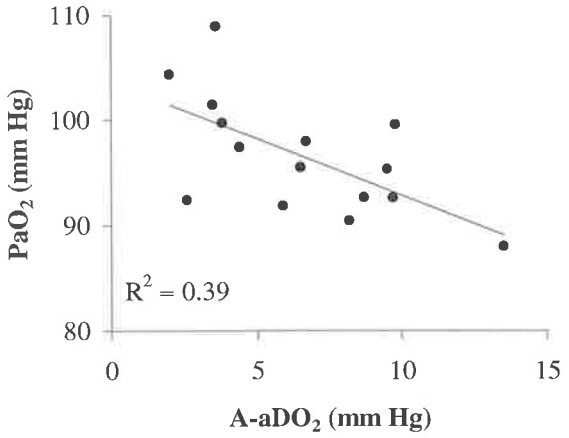


Figure 3.3 Association between PaO_2 and A-aDO_2 at 150 W

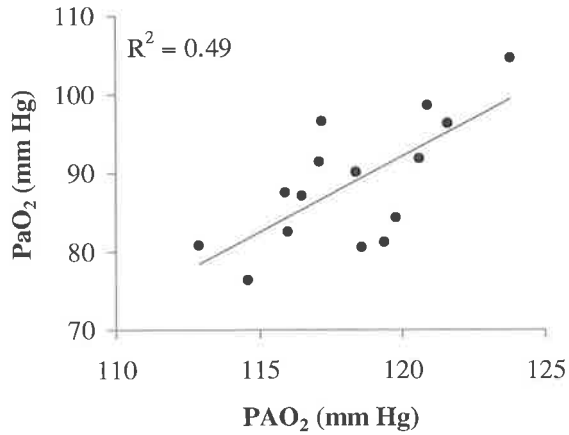


Figure 3.4 Association between PaO_2 and PAO_2 at $\dot{V}O_{2peak}$

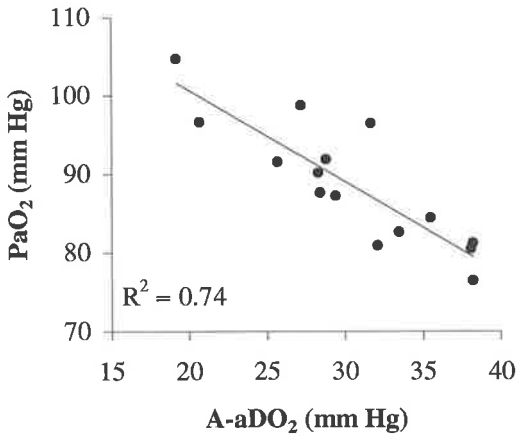


Figure 3.5 Association between PaO_2 and A-aDO_2 at $\dot{V}O_{2peak}$

3.3.3 Arterial PCO_2

A significant decrease in $PaCO_2$ was not seen until the work load exceeded 275 W (Figure 3.6) and although successive values were not significantly different thereafter, $PaCO_2$ continued to decline, with the lowest absolute value being at 375 W (34.5 ± 0.5 mm Hg). However, when $PaCO_2$ at 375 W was compared with $PaCO_2$ at 275 W, a significant difference was apparent ($P<0.0001$). $PaCO_2$ was not associated with PaO_2 at either 150 W or $\dot{V}O_{2peak}$, although the latter association was considerably stronger than the former ($R=0.07$, $P=0.79$ and $R=0.46$, $P=0.08$, respectively).

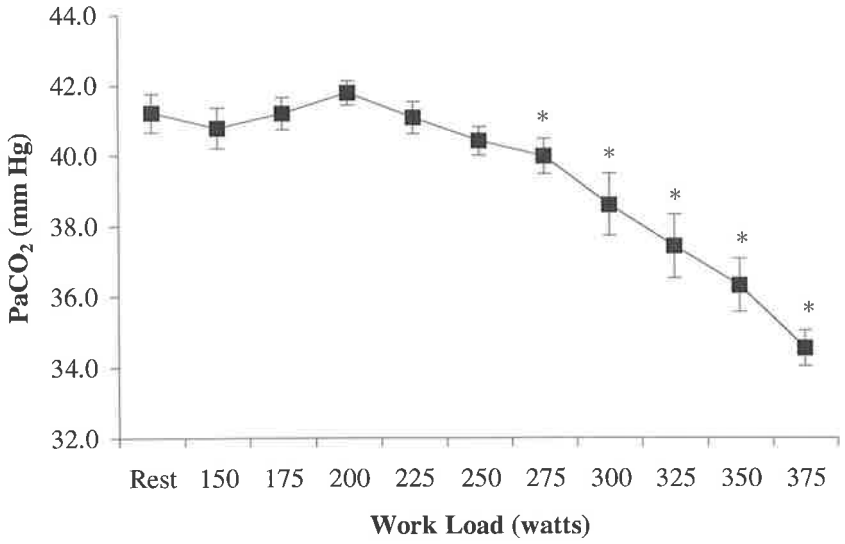


Figure 3.6 Values are means ± SEM. $PaCO_2$ values during incremental exercise in fifteen subjects. * significantly different from Rest, $P<0.05$.

3.3.4 Alveolar-arterial O_2 tension difference

There was a progressive widening of the A-aDO_2 during incremental exercise (Figure 3.7). At the end of the first work load (150 W) there was a significant increase compared with rest. All subsequent values were significantly different from rest with the value at 200 W being significantly higher than that measured at 175 W. Beyond 200 W, no work load was significantly different from the previous one. The mean A-aDO_2 value at $\dot{V}O_{2peak}$ was 28.8 ± 1.4 mm Hg (range; 18.9 – 38.4 mm Hg). At $\dot{V}O_{2peak}$ there were five subjects with A-aDO_2 values exceeding 35 mm Hg.

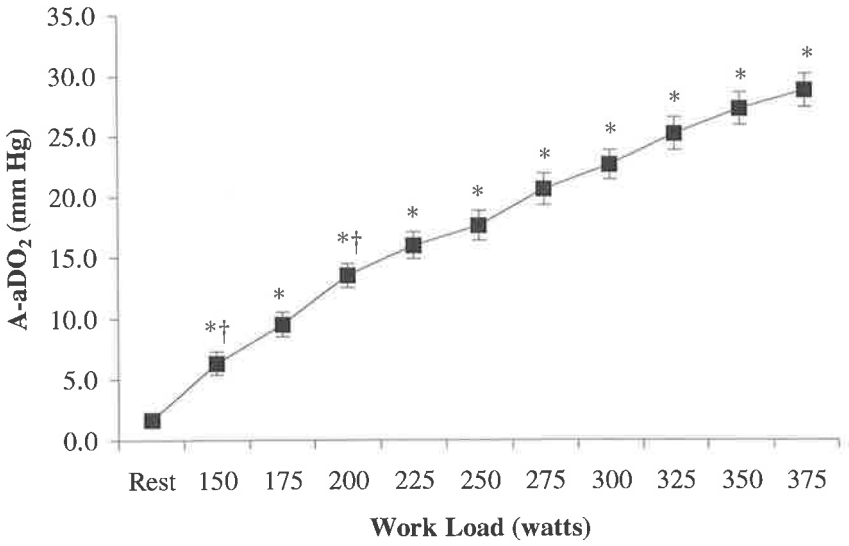


Figure 3.7 Values are means ± SEM. A-aDO$_2$ during incremental exercise in fifteen subjects. † significantly different from previous value; * significantly different from Rest, P<0.05.

3.3.5 Arterial blood (SaO_2) and pulse oximetry (SpO_2) oxyhemoglobin saturation responses

There was a progressive downward trend in SaO_2 during exercise, with work loads beyond 200 W resulting in significantly lower values than measured at rest (Figure 3.8). Successive values beyond this point were not significantly different, with the lowest value of 94.6 ± 0.3 % being recorded at 375 W. At $\dot{V}O_{2peak}$ however, nine subjects had SaO_2 values less than 94% with three of those subjects declining to <92%. The lowest individual value achieved during the exercise protocol was 90.7% (Subject 10, Table 3.1).

SpO_2 values were significantly higher than the rectal temperature corrected SaO_2 values at all work loads throughout exercise, although a significant decrease from rest only occurred during the last two work loads (Figure 3.8).

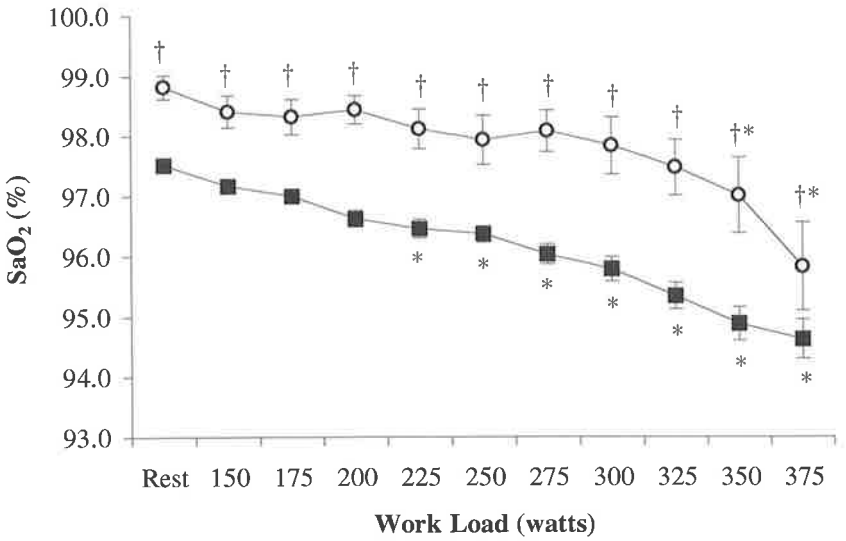


Figure 3.8 Values are means ± SEM. SaO_2 (■) and SpO_2 (○) during incremental exercise in fifteen subjects. * significantly different from Rest; † significantly different from arterial oxyhemoglobin saturation, $P<0.05$.

3.4 DISCUSSION

Previous studies, including those which have examined the time course of exercise-induced arterial hypoxemia with temperature corrected arterial blood gas samples (Powers, Martin, et al. 1992; Warren, Cureton, et al. 1991), have reported significant reductions in PaO_2 only at or near $\dot{V}O_{2max}$ (Dempsey, Hanson, et al. 1984; Pedersen, Mandoe, et al. 1996; Powers, Dodd, et al. 1984; Préfaut, Anselme, et al. 1994; Williams, Powers, et al. 1986). However, in the present study, a significant reduction in PaO_2 was seen with the first work load applied (150 W, ~40% $\dot{V}O_{2peak}$). PaO_2 continued to decline significantly until a work load of 200 W (~53% $\dot{V}O_{2peak}$) whereafter it remained stable but significantly lower than rest. Therefore, the hypoxemia in the present study appeared to be an event which began with the first work load (150 W) and stabilised well before peak aerobic power was achieved. Powers et al. (1992) collected data between 10% and 100% $\dot{V}O_{2max}$ and while they focussed their analysis on results obtained at $\dot{V}O_{2max}$, further inspection suggests that in many subjects, a significant reduction appeared as early as ~30% $\dot{V}O_{2max}$, a result which is in agreement with those from the present study. In searching for an explanation for the progressive hypoxemia during incremental exercise, consideration must be given to mechanisms which change with intensity, such as inadequate hyperventilation (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Miyachi & Tabata 1992; Turcotte, Kiteala, et al. 1997), an end-capillary O_2 diffusion limitation (Gale, Torre-Bueno, et al. 1985; Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Torre-Bueno,

Wagner, et al. 1985) and $\dot{V}_A/\dot{Q}$ inequality (Gale, Torre-Bueno, et al. 1985; Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, McKenzie, et al. 1994; Schaffartzik, Poole, et al. 1992; Torre-Bueno, Wagner, et al. 1985; Wagner, Gale, et al. 1986).

Hyperventilation during exercise results in an increase in PAO_2, which provides the necessary pressure gradient for O_2 to travel across the blood:gas barrier (Astrand & Rodahl 1986). Previous studies have demonstrated that inadequate hyperventilation during strenuous exercise contributed to arterial hypoxemia in both normoxia and hypoxia (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Miyachi & Tabata 1992). Dempsey et al. (1984) stated that the most severe hypoxemia during heavy exercise was associated with little or no alveolar hyperventilation, with $PaCO_2$ >35 mm Hg and PAO_2 <110 mm Hg. Based on the significant correlations between PaO_2 with PAO_2, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ at $\dot{V}O_{2peak}$, it appears that inadequate hyperventilation was a major contributor to arterial hypoxemia during maximal exercise in this group of subjects. However, in the present study, a significant association between PaO_2 and PAO_2 at 150 W (~40% $\dot{V}O_{2peak}$) was demonstrated, suggesting that inadequate hyperventilation was present at the end of the first work load. To my knowledge, this is the first study to demonstrate such a strong association between PAO_2 and PaO_2 during light exercise with nearly 66% of the variance in PaO_2 explained on the basis of PAO_2 alone. Dempsey et al. (1984) demonstrated the significant effect of alveolar ventilation on PaO_2 by altering the density of the inspired gas. Their results demonstrated

that both PAO_2 and PaO_2 increased to the same degree, without changing A-aDO_2. However, recent work by Buono and Maly (1996) using an identical technique (helium-O_2 breathing) to increase ventilation during intense exercise, demonstrated no change in SaO_2 measured by ear oximetry when ambient air was compared with the helium-O_2 mix, despite large increases in minute ventilation. This result is difficult to interpret due to the use of pulse oximetry of the ear to estimate SaO_2, and the fact that PAO_2 nor end-tidal PO_2 was measured. The authors also chose not to examine their data as a time course and thus the effects of inadequate hyperventilation could not be considered at different exercise intensities.

The PaO_2 values obtained during the present study are generally higher than previously reported (Dempsey, Hanson, et al. 1984; Hopkins & McKenzie 1989; Pedersen, Mandoe, et al. 1996), but similar to several others (Caillaud, Anselme, et al. 1996; Powers, Martin, et al. 1992; Warren, Cureton, et al. 1991). As suggested by Dempsey et al. (1984) the differences between studies may well depend on the mode, duration and intensity of the experimental protocol employed. The exercise protocol adopted on the air-braked cycle ergometer in the current section was identical to the protocols employed by Warren et al. (1991), Powers et al. (1992) and Caillaud et al. (1996), the three studies that display similar results to those presently reported. However, the studies of Dempsey et al. (1984) and Hopkins and McKenzie (1989) employed 5 minute, near maximal work loads on a treadmill to elicit their larger reductions in PaO_2. Thus, it appears clear that the difference between the two protocols used may help explain the smaller changes in PaO_2 measured in the present study.

During the initial work load (150 W) and at $\dot{V}O_{2peak}$, significant correlations were found between PaO_2 and A-aDO_2. An increasing A-aDO_2 during exercise is most likely due to either an end-capillary O_2 diffusion limitation or $\dot{V}_A/\dot{Q}$ inequality, although theoretically intra and/or extra-pulmonary shunt are possibilities. The available evidence suggests that arterial hypoxemia due to an end-capillary O_2 diffusion limitation, based on decreased pulmonary capillary blood transit time, is unlikely to be important at exercise intensities below ~70% $\dot{V}O_{2max}$ (Hopkins, McKenzie, et al. 1994; Warren, Cureton, et al. 1991) by which time the hypoxemia observed in the present study was maximal. However, the fact that the relative effect of A-aDO_2 on PaO_2 appears to increase during exercise of increasing intensity, suggests that the mechanisms which result in a widened A-aDO_2 change with exercise intensity, an hypothesis which is supported by the work of Hopkins et al. (1994). In that study, the multiple inert gas elimination technique was used to show that at a work load of 150 W, the A-aDO_2 due to $\dot{V}_A/\dot{Q}$ inequality increased significantly above resting levels. Interestingly, PaO_2 decreased to the same degree as in the present study (~7 mm Hg). As exercise intensity rose from light to maximal intensity, the increasing importance of end-capillary O_2 diffusion limitation on the measured A-aDO_2 became apparent. While not directly measured in the present study, it is plausible that $\dot{V}_A/\dot{Q}$ inequality exerted its greatest effect on PaO_2 during light intensity exercise, and a combination of both $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation affected PaO_2 to a larger degree at $\dot{V}O_{2peak}$, leading to the stronger correlation between PaO_2 and A-aDO_2 at $\dot{V}O_{2peak}$.

PAO_2 and A-aDO_2 are independent predictors of PaO_2 demonstrated by non-significant correlations at 150 W and $\dot{V}O_{2peak}$. This is in agreement with the observation of Dempsey et al. (1984) stating that there was no consistent relationship between PAO_2 and A-aDO_2 during exercise. The results of the multiple linear regression at both 150 W and $\dot{V}O_{2peak}$ demonstrated that at least 95% of the variance in PaO_2 could be explained by a combination of PAO_2 and A-aDO_2. These results provide indirect evidence in support of a multifactorial etiology of EIH. That is, inadequate hyperventilation, $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation may all contribute to EIH in different proportions at different exercise intensities. Therefore, studies which have focused on a single mechanism resulting in EIH (Todaro, Leonardi, et al. 1995) may not provide an accurate overall picture.

It is clear from the results of the present study that if the identification of EIH is based on SaO_2 measurements alone, whether derived directly from arterial blood or indirectly from ear oximetry, the maximal hypoxemic response will not be observed until near maximal intensity. The apparent differential rate of change in the values for O_2 saturation determined by pulse oximetry when compared with the direct arterial blood measurement is of concern, but the results are consistent with those of Woods et al. (1997) using an identical pulse oximeter. As such, the rapid fall in SpO_2 immediately prior to $\dot{V}O_{2peak}$ probably reflects factors other than a real change in arterial blood O_2 saturation. Taken together, these results suggest that if the efficiency of pulmonary gas exchange is being investigated as a potential mechanism for EIH, then PaO_2 and A-aDO_2 rather than

SaO_2 or SpO_2 must be measured directly and throughout the course of exercise, as the mechanism may well change with increasing intensity.

In conclusion, the results from the present study indicate that EIH is an intensity-dependent phenomenon. Given that a significant hypoxemic response occurred at ~40% $\dot{V}O_{2peak}$, and was strongly associated with PAO_2, inadequate hyperventilation is the most likely mechanism at low exercise intensities, with a smaller contribution from ventilation-perfusion inequality.

4 PULMONARY GAS EXCHANGE IN TRAINED CYCLISTS WITH EXERCISE-INDUCED HYPOXEMIA

4.1 INTRODUCTION

Exercise-induced hypoxemia, as evidenced by a reduction in PaO_2 and a widening of the A-aDO_2, can be found in ~50% of trained athletes capable of sustaining metabolic rates in excess of 4.5 $l.min^{-1}$ (Powers, Dodd, et al. 1988; Williams, Powers, et al. 1986). It was demonstrated in Section 3.3.2 that PaO_2 during moderate and maximal exercise was strongly associated with A-aDO_2 and PAO_2. This information combined with that already published in the area suggest that the possible mechanisms of EIH include; intra and extra-pulmonary shunt, $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation (Dempsey, Hanson, et al. 1984; Gale, Torre-Bueno, et al. 1985; Hopkins & McKenzie 1989; Hopkins, McKenzie, et al. 1994). In addition, if alveolar ventilation does not rise sufficiently to match the increase in metabolic rate during exercise, PaO_2 will decrease due to the direct effect ventilation has on PAO_2 (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Miyachi & Tabata 1992).

The multiple inert gas elimination technique (MIGET) has previously been used to measure $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation in healthy subjects while exercising at sea level, and in hypobaric and normobaric

hypoxia (Gale, Torre-Bueno, et al. 1985; Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, McKenzie, et al. 1994; Schaffartzik, Poole, et al. 1992; Torre-Bueno, Wagner, et al. 1985). However, there are few studies that have attempted to quantify the relative contributions of $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation in athletes during heavy exercise (Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, McKenzie, et al. 1994; Wagner, Sutton, et al. 1987) and none that have used trained athletes with documented EIH.

Therefore, the aim of this study was to evaluate the relative contributions of the above mentioned mechanisms of EIH in trained cyclists with EIH and compare their results with those from a similar group of trained cyclists without EIH. This was achieved by employing MIGET to investigate $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation during, and up to 45 minutes after heavy exercise. As MIGET is unable to distinguish between end-capillary O_2 diffusion limitation and extra-pulmonary shunt, and it was felt imperative to make such as distinction, $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation were also measured while breathing 13% O_2. Hypoxia increases the amount of end-capillary O_2 diffusion limitation, and decreases the degree to which extra-pulmonary shunt affects PaO_2 due to the position hypoxia places each individual on the oxyhemoglobin dissociation curve. This allows qualification of the contribution of extra-pulmonary shunt to the measured reduction in PaO_2.

4.2 METHODS

4.2.1 Subject selection and preliminary studies

Twelve healthy male cyclists were selected from a group of twenty who had previously had arterial blood samples withdrawn while completing a progressive incremental exercise test to exhaustion (see Section 7.8). All subjects had a $\dot{V}O_{2peak}$ >65 $ml.kg^{-1}.min^{-1}$ and/or 4.5 $l.min^{-1}$ and reported no history of cardiovascular or respiratory disease. The subjects were divided into two groups prior to the commencement of the study; control (n=5) and experimental (n=7) based on their lowest temperature corrected PaO_2 during the progressive incremental exercise test to exhaustion. While the control group showed a small reduction in PaO_2 during exercise (mean change, 7.6 ± 1.3 mm Hg; range 2.8 – 10.2), the experimental group demonstrated a much larger change (mean change, 16.5 ± 1.1 mm Hg; range 14.1 – 22.1, P between groups <0.005). Basic anthropometric, peak metabolic and resting pulmonary function data for the two groups are outlined in Table 4.1.

Table 4.1 Anthropometric and preliminary data for control (n=5) and experimental subjects (n=7).

	Control	Experimental
Age, yr	23.4 ± 0.7	27.9 ± 2.3
Height, cm	177.8 ± 0.3	182.3 ± 1.6
Weight, kg	68.8 ± 0.7	77.1 ± 3.8
FVC, % of predicted	109 ± 2	105 ± 3
$FEV_{1.0}$, % of predicted	106 ± 3	102 ± 3
DL_{CO}, % of predicted	139 ± 9	131 ± 3
Normoxic $\dot{V}O_{2peak}$, $l.min^{-1}$	5.01 ± 0.14	5.13 ± 0.16
Hypoxic $\dot{V}O_{2peak}$, $l.min^{-1}$	3.84 ± 0.23 *	3.67 ± 0.10 *

Data are means ± SEM. FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 second; DL_{CO}, lung diffusing capacity for carbon monoxide; $\dot{V}O_{2peak}$, peak O_2 consumption. All pulmonary function data reflect resting conditions before exercise. * Significantly different from Normoxic $\dot{V}O_{2peak}$.

4.2.2 Experimental design

Each subject was required to complete four separate visits to the laboratory. The initial two visits measured $\dot{V}O_{2peak}$ during an incremental exercise protocol while breathing either air (20.93% O_2) or a hypoxic gas mixture (13.2 ± 0.1% O_2, balance N_2). These two visits were used to establish the work loads for the subsequent components of this study. During the third visit inert gas exchange was measured during submaximal exercise while breathing both

normoxic and hypoxic mixtures. In the final visit, cardiac output ($\dot{Q}$) was measured at identical times of the day and work loads to those employed during the third visit (see Section 2.2.12). It was necessary to measure $\dot{Q}$ on a separate day as the relatively high concentration of C_2H_2 used to measure $\dot{Q}$ interferes with the measurement of MIGET inert gas concentrations. All four visits were completed within a four week period, with the final two visits completed within a week of each other.

4.2.3 Preliminary incremental exercise protocol to establish peak O_2 consumption

After entering the laboratory each subject's height and weight were recorded and chest electrodes were applied to measure both HR and ECG (see Section 2.2.1). The subjects then completed two $\dot{V}O_{2peak}$ tests as outlined in Section 2.2.14.5 using the protocol outlined in Section 2.2.10 on separate days within a two week period. The order of the $\dot{V}O_{2peak}$ tests was randomised and balanced among the twelve subjects. The starting work load for room air was 150 W and for the hypoxic gas mixture was 100 W. Subjects pedalled at these work loads for 1 minute and were then required to increase the work load by 25 W every minute thereafter until volitional exhaustion. The two highest consecutive 30 second values obtained for $\dot{V}O_2$ during the incremental protocol were averaged and the mean designated as the $\dot{V}O_{2peak}$ for the relevant inspired gas mixture (F_IO_2).

4.2.4 Subject preparation for inert gas exchange study

Prior to catheterisation each subject underwent routine pulmonary function testing (FVC, $FEV_{1.0}$ DL_{CO}) as described in Section 2.2.13. Then, under local anaesthesia (1% lignocaine hydrochloride), each subject had two catheters placed percutaneously, the detail of which has been outlined in Section 2.2.14.1. The radial arterial catheter was used to periodically sample arterial blood, while the peripheral intravenous catheter was connected to a 1000 ml infusion bag containing six inert gases [sulphur hexaflouride (SF_6), ethane, cyclopropane, enflurane, ether and acetone] dissolved in a 5% dextrose solution (Wagner, Saltzman, et al. 1974).

4.2.5 Inert gas exchange study protocol

The catheterised subjects were seated on the cycle ergometer and connected to the same respiratory circuit as used during the $\dot{V}O_{2peak}$ measurements but with modifications to the expired tubing and mixing boxes as described in Section 2.2.14.6. $\dot{V}_E$, mixed expired gas fractions and all ancillary measurements were monitored in real time throughout rest and during each work load. The exercise work loads were continuous and measurements were made for 5 minutes at each of the following points; 1) rest; 2) ~30% $\dot{V}O_{2peak}$ (light exercise); 3) ~60% $\dot{V}O_{2peak}$ (moderate exercise); 4) ~90% $\dot{V}O_{2peak}$ (heavy exercise); 5) 5 minutes post exercise; 6) 15 minutes post exercise; 7) 30 minutes

post exercise and 8) 45 minutes post exercise, for a total of eight measurement times. The order of the inspired gas concentrations (air or hypoxia) was randomised and balanced among the groups and individual exercise work loads were determined from the initial $\dot{V}O_{2peak}$ tests conducted up to three weeks prior (Section 2.2.14.5).

Mixed expired inert gas samples and arterial inert blood samples were collected simultaneously during the final 2 minutes of the eight measurement times previously outlined in Sections 2.2.14.2 and 2.2.14.3, respectively. The gas analysers, pneumotachograph and ancillary instruments were calibrated prior to rest and 5 minute post-exercise measurements, and were checked for drift immediately following the 45 minute post exercise measurement.

Post exercise pulmonary function tests ($FEV_{1.0}$, FVC, DL_{CO}) were completed within 20 minutes of the final MIGET measurement.

4.2.6 Measurement of cardiac output

$\dot{Q}$ was measured in both normoxia and hypoxia using an acetylene (C_2H_2) non-rebreathing technique which has been described in Section 2.2.12. The identical experimental system was used as that described for the $\dot{V}O_{2peak}$ testing. Each subject exercised for 5 minutes at ~30, 60 and 90% $\dot{V}O_{2peak}$ during both normoxia and hypoxia with measurements of $\dot{V}_E$, $\dot{V}O_2$ and $\dot{V}CO_2$ recorded

breath by breath and averaged every 30 seconds. Cardiac output was calculated in the final minute of exercise at each exercise intensity.

4.2.7 Data analysis

A two-factor repeated measures ANOVA was used to determine significant differences by group (control vs experimental) and work load during each F_IO_2. Where overall significance was obtained, differences between cell means were identified with Tukey's post-hoc analysis for unequal numbers. Correlation analysis was calculated using the Pearson product moment correlation test. Stepwise multiple linear regression was used to predict PaO_2 based on DLO_2, $\dot{V}_{E,}$ and $\log SD\dot{Q}$ at 90% $\dot{V}O_{2peak}$ during both normoxia and hypoxia. All the independent variables were introduced first for the analysis, and the more suitable variables were selected by the software so that the *F* value of a final multiple regression model, and partial *F* values of the independent variables became maximum and significant for the *F* distribution. Standardised regression coefficients (beta coefficients) of the independent variables, which were defined as regression coefficients standardised for the units of the variables, were considered to indicate the relative contribution of the independent variables to PaO_2 (Takano, Inaishi, et al. 1997).

4.3 RESULTS

4.3.1 Analysis according to experimental grouping of subjects

4.3.1.1 Alveolar–arterial O_2 tension difference

Exercise resulted in a significant widening of the measured A-aDO_2 in both groups during normoxia (Figure 4.1 and Table 4.2). During both moderate and heavy exercise, normoxia and hypoxia resulted in significantly larger A-aDO_2 than that at rest for both the experimental and control groups. Additionally, light exercise caused a significant widening of the measured A-aDO_2 in the hypoxia trial for both groups (Figure 4.2 and Table 4.3). The experimental group developed significantly larger A-aDO_2 values than the control group during moderate and heavy exercise while breathing air, but there was no difference between the groups during hypoxia.

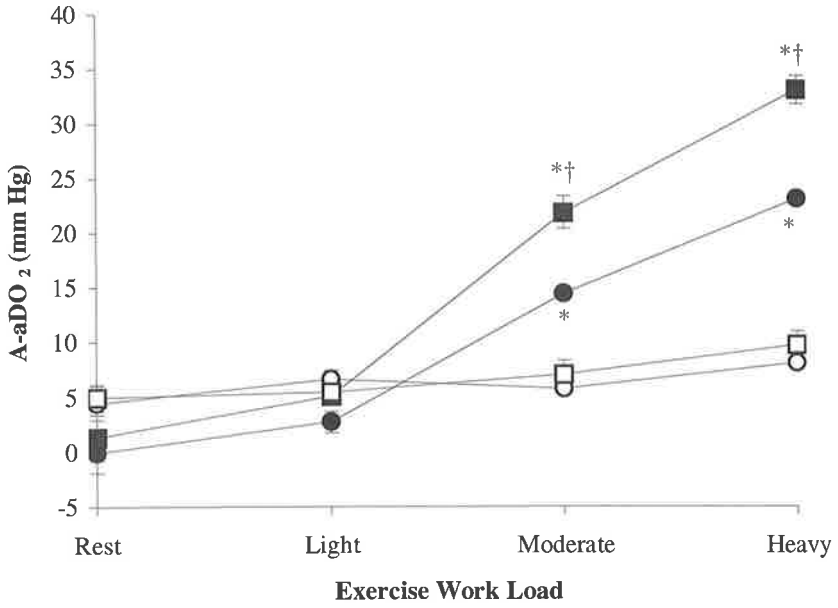


Figure 4.1 Data are means ± SEM. Observed (filled) and predicted (unfilled) alveolar-arterial O_2 tension difference (A-aDO_2) in control (circles, n=5) and experimental (squares, n=7) groups during normoxia. * significantly different from rest, † significantly different from control, $P<0.05$.

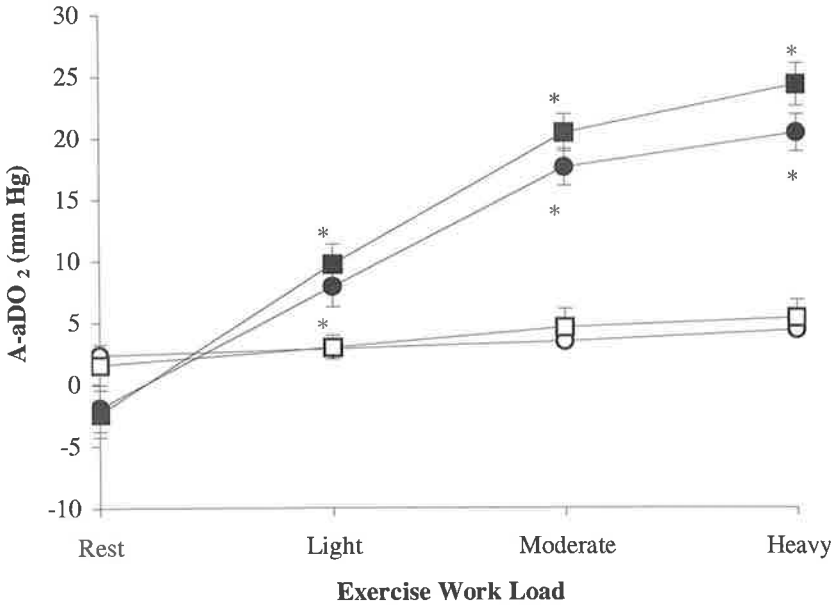


Figure 4.2 Data are means ± SEM. Observed (filled) and predicted (unfilled) alveolar-arterial O_2 tension difference in control (circles, n=5) and experimental (squares, n=7) groups during hypoxia. * significantly different from rest, † significantly different from control, $P<0.05$.

Table 4.2 Metabolic and inert gas data at rest and during exercise in control (n=5) and experimental (n=7) subjects while breathing normoxic gas

		NORMOXIA			
	GROUP	Rest	Light	Moderate	Heavy
$\dot{Q}$, l.min^{-1}	Con	6.1±0.5	15.7±0.7	24.5±1.3	30.9±2.1
	Exp	5.2±0.5	16.8±0.5	26.2±1.1	33.2±1.7
$\dot{V}O_2$, ml.min^{-1}	Con	517±54	2037±44	3459±124	4476±178
	Exp	485±37	2144±86	3482±127	4451±129
$\dot{V}CO_2$, ml.min^{-1}	Con	457±66	1716±51	3358±147	5135±214
	Exp	376±29	1799±80	3329±102	5243±111
RER	Con	0.88±0.05	0.84±0.02	0.97±0.02	1.15±0.03
	Exp	0.78±0.02	0.84±0.01	0.96±0.01	1.18±0.02
$\dot{V}_E$, l.min^{-1} (BTPS)	Con	16.8±1.8	45.8±2.4	88.8±5.4	146.7±9.6
	Exp	12.7±0.7	47.0±1.5	88.3±4.0	144.0±1.9
Lactate, mmol.l^{-1}	Con	1.9±0.3	1.7±0.3	3.1±0.4	5.9±0.3
	Exp	1.5±0.2	1.5±0.1	2.7±0.2	6.6±0.3
PaO_2, mm Hg	Con	108±4	101±2	96±3	97±3
	Exp	96±2	96±1	87±2 §†	87±2 §†
$PaCO_2$, mm Hg	Con	34±1	38±1	38±1	35±1
	Exp	39±1	40±1	40±1	37±1
A-aDO_2 (o), mm Hg	Con	0±2	3±1	14±0 *	23±0 *
	Exp	1±1	5±0	22±1 *†	33±1 *†
A-aDO_2 (o-p), mm Hg	Con	-6±3	-7±4	5±4 *	13±2 *
	Exp	-4±1	0±1	15±3 *†	23±2 *†
DLO_2, ml.min^{-1}.mm Hg^{-1}	Con	NAC	NAC	79.3±3.1	85.0±4.3
	Exp	NAC	NAC	68.8±4.2	75.1±4.2
DLO_2 / $\dot{Q}$	Con	NAC	NAC	3.2±0.1	2.7±0.1
	Exp	NAC	NAC	2.7±0.1 †	2.2±0.1 †
log SD$\dot{Q}$	Con	0.39±0.02	0.36±0..02	0.37±0.02	0.41±0.02
	Exp	0.38±0.03	0.40±0.02	0.35±0.0.2	0.37±0.02
log SD$\dot{V}$	Con	0.40±0.03	0.37±0.02	0.39±0.03	0.39±0.02
	Exp	0.43±0.05	0.43±0.05	0.36±0.02	0.38±0.02
RSS	Con	8.2±2.9	6.5±0.6	6.8±0.5	4.5±0.5
	Exp	7.0±0.8	8.1±0.8	7.2±0.4	4.3±0.3

Values are means ± SEM. Con, control group; Exp, experimental group; $\dot{Q}$ cardiac output; $\dot{V}O_2$, O_2 consumption; $\dot{V}CO_2$, CO_2 production; RER, respiratory exchange ratio; PaO_2 arterial O_2 tension; $PaCO_2$, arterial CO_2 tension; A-aDO_2 (o), observed alveolar-arterial O_2 tension difference; A-aDO_2 (o-p), difference between observed and predicted alveolar-arterial O_2 tension difference; DLO_2, lung diffusing capacity for O_2; $\log SD_{\dot{V}}$, SD of log normal ventilation distribution; $\log SD_{\dot{Q}}$, SD of log normal perfusion distribution; NAC, not appropriate to calculate; RSS, residual sum of squares. * significantly different from rest ($P<0.05$); † significantly different from control ($P<0.05$); § significantly different from light exercise [this comparison was made due to marked hyperventilation at rest in the Con group (see Section 4.3.1.7), $P<0.05$].

Table 4.3 Metabolic and inert gas data at rest and during exercise in control (n=5) and experimental (n=7) subjects while breathing hypoxic gas (F_IO_2 = 0.132)

		HYPOXIA			
	GROUP	Rest	Light	Moderate	Heavy
$\dot{Q}$, l.min^{-1}	Con	6.1±0.4	13.9±0.7	25.0±0.5	31.9±1.1
	Exp	6.8±0.9	17.6±0.9	27.5±1.1	34.3±1.4
$\dot{V}O_2$, ml.min^{-1}	Con	482±18	1598±154	3083±123	4013±107
	Exp	464±28	1764±69	2966±85	3787±91
$\dot{V}CO_2$, ml.min^{-1}	Con	427±34	1423±143	2979±152	4366±107
	Exp	371±23	1450±66	2715±70	4010±93
RER	Con	0.88±0.05	0.89±0.02	0.97±0.02	1.09±0.02
	Exp	0.80±0.02	0.83±0.02	0.94±0.02	1.06±0.03
$\dot{V}_E$, l.min^{-1} (BTPS)	Con	14.5±1.0	41.2±4.1	91.8±6.6	151.8±11.1
	Exp	13.7±0.8	46.9±2.4	91.2±3.9	141.8±5.4
Lactate, mmol.l^{-1}	Con	2.0±0.3	2.2±0.2	3.9±0.4	6.6±0.2
	Exp	1.5±0.07	1.6±0.2	3.8±0.3	7.0±0.5
PaO_2, mm Hg	Con	53±3	44±1 *	41±1 *	45±1 *
	Exp	49±1	40±1 *	37±1 *	40±1 *
$PaCO_2$, mm Hg	Con	35±2	36±1	33±0	30±1 *
	Exp	36±1	35±1	33±1	30±1 *
A-aDO_2 (o), mm Hg	Con	-2±2	8±2 *	18±1 *	20±1 *
	Exp	-2±2	10±2 *	20±2 *	24±2 *
A-aDO_2 (o-p), mm Hg	Con	-4±2	5±1 *	14±2 *	16±2 *
	Exp	-4±2	7±1 *	16±2 *	19±2 *
DLO_2, ml.min^{-1}.mm Hg^{-1}	Con	NAC	NAC	111.8±10.2	127.4±9.1
	Exp	NAC	NAC	97.6±6.4	110.9±7.7
DLO_2 / $\dot{Q}$	Con	NAC	NAC	4.5±0.4	4.0±0.4
	Exp	NAC	NAC	3.5±0.2	3.2±0.2
log SD$\dot{Q}$	Con	0.38±0.02	0.38±0.02	0.40±0.02	0.42±0.02
	Exp	0.37±0.02	0.38±0.01	0.36±0.02	0.40±0.02
log SD$\dot{V}$	Con	0.41±0.03	0.38±0.03	0.39±0.02	0.42±0.01
	Exp	0.40±0.02	0.40±0.02	0.37±0.02	0.40±0.02
RSS	Con	7.5±1.0	7.2±1.0	7.2±0.5	4.9±0.7
	Exp	6.7±0.8	8.0±1.0	6.5±0.4	4.6±0.4

Values are means ± SEM. Con, control group; Exp, experimental group; $\dot{Q}$ cardiac output; $\dot{V}O_2$, O_2 consumption; $\dot{V}CO_2$, CO_2 production; RER, respiratory exchange ratio; PaO_2 arterial O_2 tension; $PaCO_2$, arterial CO_2 tension; A-aDO_2 (o), observed alveolar-arterial O_2 tension difference; A-aDO_2 (o-p), difference between observed and predicted alveolar-arterial O_2 tension difference; DLO_2, lung diffusing capacity for O_2; $\log SD_{\dot{V}}$, SD of log normal ventilation distribution; $\log SD_{\dot{Q}}$, SD of log normal perfusion distribution; NAC, not appropriate to calculate; RSS, residual sum of squares. * significantly different from rest ($P<0.05$); † significantly different from control ($P<0.05$).

4.3.1.2 Ventilation-perfusion inequality

During both normoxic and hypoxic exercise and recovery there were no significant changes from rest in $\log SD\dot{Q}$ or $\log SD\dot{V}$ for either group (Table 4.2 and 4.3). The MIGET predicted values for A-aDO_2 (Figure 4.1 and 4.2) reflect these findings in both groups during both normoxia and hypoxia, respectively. Although there were no significant changes in $\dot{V}_A/\dot{Q}$ inequality during exercise, the predicted A-aDO_2 accounted for 30% of the observed A-aDO_2 in the experimental group and 35% in the control group during heavy exercise while breathing air.

The independently derived measures of $\dot{V}_A/\dot{Q}$ inequality during both normoxia and hypoxia are shown in Figure 4.3. Compared with rest, there were no significant differences in any dispersion index during either F_IO_2 for both the control and experimental groups throughout all exercise work loads. Additionally, there were no differences in these indexes between groups at any exercise level. Intra-pulmonary shunt was not detected in either group during rest, exercise or recovery for either F_IO_2.

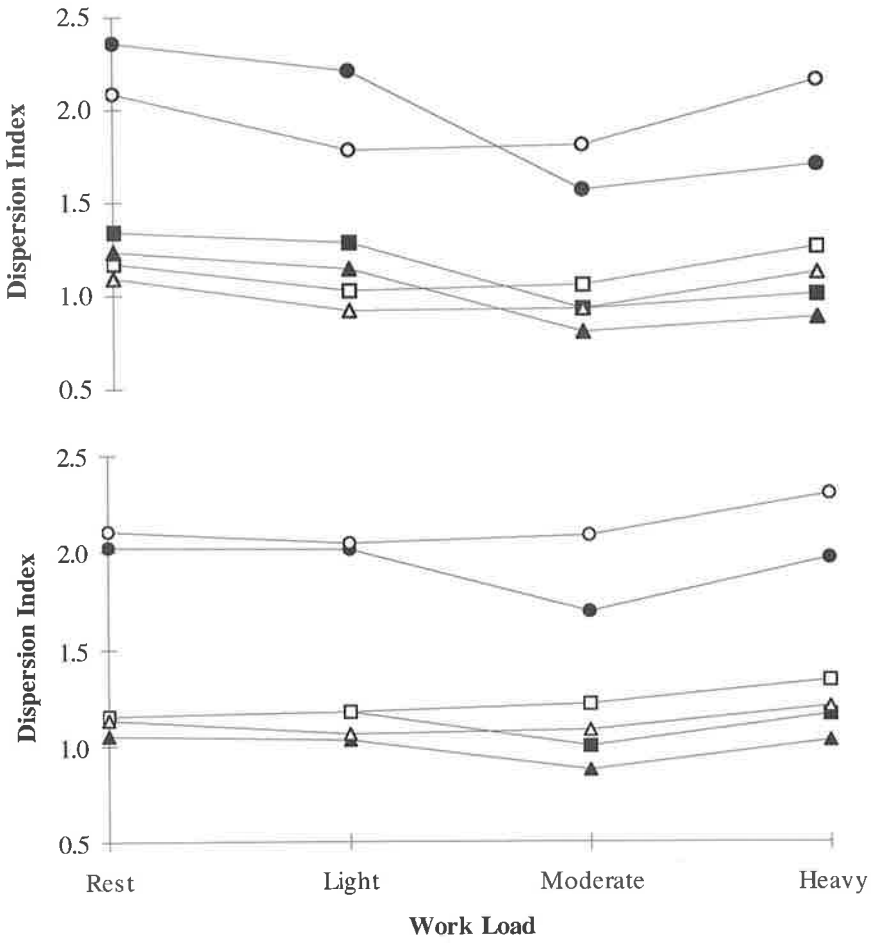


Figure 4.3 Mean $\dot{V}_A/\dot{Q}$ inequality dispersion indexes for control (n=5) and experimental (n=7) groups during normoxia (top panel) and hypoxia (bottom panel). Control $Disp_R$ (▪), Control $Disp_E$ (▲), Control $Disp_{R-E}$ (•), Experimental $Disp_R$ (□), Experimental $Disp_E$ (△) and Experimental $Disp_{R-E}$ (○) (see Section 2.14.2). There was no effect of exercise under any condition. There were no differences between subject groups under any condition. SEM bars were omitted for clarity.

4.3.1.3 Observed–predicted alveolar–arterial O_2 tension difference

During moderate and heavy exercise while breathing air, A-aDO_2 (o-p) in both control and experimental groups was significantly greater than that measured at rest (Table 4.2), and at these work loads was larger by 10 mm Hg in the experimental than the control group ($P<0.01$). During hypoxia, the A-aDO_2 (o-p) of both groups was significantly higher than rest at all exercise work loads, but there were no significant differences between the two groups at any exercise work load (Table 4.3).

4.3.1.4 Lung diffusing capacity for O_2

The estimation of DLO_2 is based on the degree to which measured PaO_2 is less than that predicted from $\dot{V}_A/\dot{Q}$ inequality alone. At rest and light exercise, and also for one control subject during moderate and heavy exercise this requirement was not met, consequently DLO_2 could not be calculated at these times. Based on the data of the remaining eleven subjects for moderate and heavy exercise during normoxia and hypoxia, DLO_2 was not different between the experimental and control groups despite the experimental group having consistently lower values at all exercise intensities (Table 4.2 and 4.3).

4.3.1.5 Cardiac Output

Cardiac output increased progressively with exercise intensity during normoxia and hypoxia for both the control and experimental groups (Table 4.2 and 4.3). There were no significant differences between the groups at any work load during either F_IO_2.

4.3.1.6 Diffusive conductance to perfusive conductance

To investigate further differences in end-capillary O_2 diffusion limitation between the two groups, the ratio of diffusing capacity for O_2 to cardiac output ($DLO_2/\dot{Q}$) was used as this represented the ratio of diffusive conductance to perfusive conductance. Table 4.2 presents the $DLO_2/\dot{Q}$ for the control and experimental group while breathing air. During both moderate and heavy exercise, the experimental group had significantly lower values for $DLO_2/\dot{Q}$ than the control group. During hypoxia however, the values between the groups were not significantly different from each other (Table 4.3), although the experimental group consistently had lower $DLO_2/\dot{Q}$ values at moderate and heavy exercise compared with the control group.

4.3.1.7 Arterial PO_2

Due to the anticipation of the onset of exercise two subjects from the control group hyperventilated during resting measurements while breathing air and thus spuriously elevated PaO_2 and reduced $PaCO_2$. For this reason, no comparisons between or within the groups were made at rest with respect to PaO_2 and $PaCO_2$ while breathing air.

When compared to the PaO_2 during light exercise, moderate and heavy exercise invoked significant arterial hypoxemia in the experimental group, whereas the control group demonstrated no significant change (Table 4.2). As such, the experimental group had a significantly lower PaO_2 (~10 mm Hg) than the control group during both moderate and heavy exercise. During hypoxia, both groups had a significantly lower PaO_2 during all exercise intensities when compared with rest (Table 4.3), but there were no significant differences between the groups.

4.3.1.8 Ventilation and arterial PCO_2

There was no significant difference between the two groups for absolute $\dot{V}_E$ ($l.min^{-1}$, BTPS) during either normoxia or hypoxia. (Table 4.2 and 4.3). When $\dot{V}_E$ ($l.min^{-1}$, BTPS) was calculated relative to body weight, $\dot{V}_E$ ($l.min^{-1}.kg^{-1}$, BTPS) during normoxic heavy exercise was higher for the control group (2.12 ± 0.33) than for the experimental group (1.91 ± 0.27), but the means

were not significantly different (P=0.25). During hypoxic heavy exercise the corresponding values were 2.20 ± 0.37 $l.min^{-1}.kg^{-1}$ for the control group compared with 1.89 ± 0.39 $l.min^{-1}.kg^{-1}$ for the experimental group (P=0.20). Normoxic exercise resulted in no significant change in $PaCO_2$ for either group and there were no significant differences between the groups during any exercise work load. Hypoxia however, resulted in a significant decline in $PaCO_2$ during moderate and heavy exercise for the experimental group and during heavy exercise for the control group (Table 4.3). There were no significant differences between the two groups during any work load.

4.3.1.9 Recovery

There were no significant changes from pre-exercise in $\log SD\dot{Q}$ or $\log SD\dot{V}$ for either group during recovery. PaO_2 and A-aDO_2 (o-p) remained at or near resting levels from 5 to 45 minutes post exercise under normoxic conditions (Figure 4.4). A-aDO_2 (o-p) during recovery from normoxic exercise was not significantly greater than zero, indicating an absence of end-capillary O_2 diffusion limitation or shunt during this time. After exercise, DL_{CO} decreased significantly within each group when compared with pre-exercise values (Figure 4.5), but there were no significant differences between groups either pre- or post-exercise. When the data of both subject groups were pooled, there were no significant changes in pulmonary function from pre to post-exercise ($FEV_{1.0}$: pre, 4.77 ± 0.68, post, 4.85 ± 0.64 l; FVC: pre, 6.01 ± 0.56, post, 6.07 ± 0.63 l).

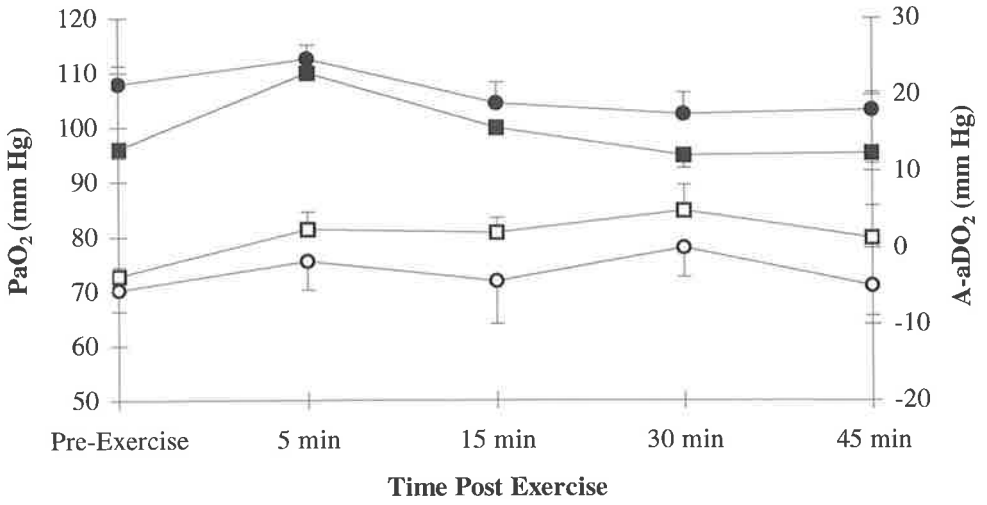


Figure 4.4 Normoxic arterial PO_2 and observed minus predicted alveolar-arterial O_2 tension difference in control (n=5) and experimental (n=7) groups pre-exercise and up to 45 minutes post-exercise. (■) PaO_2 (experimental), (●) PaO_2 (control), (□) A-aDO_2 (o-p) (experimental), (○) A-aDO_2 (o-p) (control). There were no significant differences over time or between the two groups.

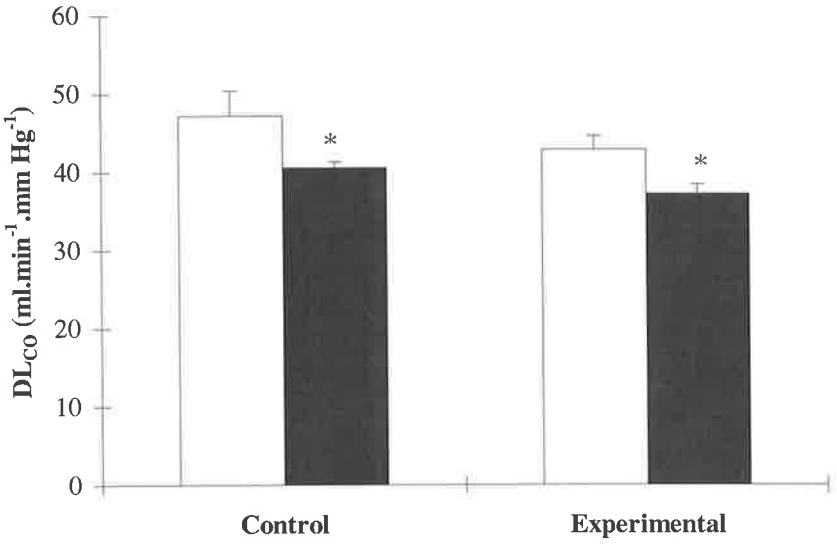


Figure 4.5 Lung diffusing capacity for carbon monoxide (DL_{CO}) pre-exercise (unfilled) and post-exercise (filled). * significantly different from pre-exercise, $P<0.05$.

4.3.2 Analysis of all subjects by linear regression

4.3.2.1 Prediction of arterial PO_2

When data for all twelve subjects were examined by linear regression analysis, $\dot{V}_E$ (l.min^{-1}.kg^{-1}, BTPS) was significantly associated with, and alone explained 37% of the variance in PaO_2 (Figure 4.6) during normoxic heavy exercise. During this work load, neither DLO_2 nor $\dot{V}_A/\dot{Q}$ inequality (represented by $\log SD\dot{Q}$) were individually significantly associated with PaO_2 (R^2=0.26 and 0.12, respectively). However, by including $\dot{V}_E$ (l.min^{-1}.kg^{-1}, BTPS), DLO_2 (ml.min^{-1}.mmHg^{-1}), and $\log SD\dot{Q}$ in a stepwise multiple linear regression model,

72% of the variance in PaO_2 was explained by the equation; 9.19 * $\dot{V}_E$ + 0.306 * DLO_2 – 0.41 * $\log SD\dot{Q}$ + 62.2 (R=0.85, Figure 4.7). The corresponding beta coefficients were 0.53, 0.68 and 0.39 for $\dot{V}_E$, DLO_2 and $\log SD\dot{Q}$, respectively. Based on the results of the R^2 and the beta coefficients, it was estimated that on average, DLO_2 accounted for 31% of the variance in PaO_2 (0.72 * 0.68 * 100 / 0.53 + 0.68 + 0.39), $\dot{V}_E$ for 24% and $\log SD\dot{Q}$ for 17%. The same regression models were evaluated for heavy exercise under hypoxic conditions. While DLO_2 was significantly associated with measured PaO_2 (R=0.58), neither $\dot{V}_E$ ($l.min^{-1}.kg^{-1}$, BTPS), nor $\log SD\dot{Q}$ were significantly related (R=0.40, P=0.20 and R=0.18, P=0.58, respectively). The stepwise multiple linear regression model included DLO_2 ($ml.min^{-1}.mmHg^{-1}$) and $\dot{V}_E$ ($l.min^{-1}.kg^{-1}$, BTPS) but not $\log SD\dot{Q}$ and was described by the equation 4.69 * $\dot{V}_E$ + 0.108 * DLO_2 + 19.98 (R=0.81). The R^2 for the multiple linear regression was 0.66 and the beta coefficients for $\dot{V}_E$ and DLO_2 were 0.59 and 0.73, respectively. Based on the R^2 and the beta coefficients it was estimated that DLO_2 accounted for 37% of PaO_2 and $\dot{V}_E$ for 29%.

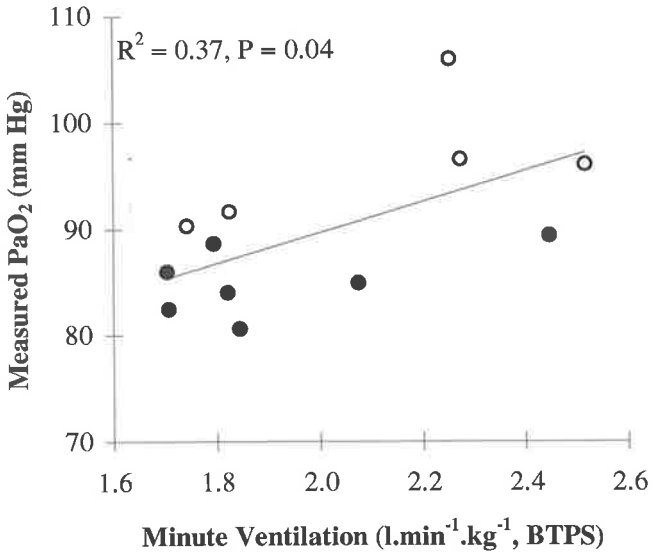


Figure 4.6 Association of measured PaO_2 with minute ventilation while performing heavy exercise under normoxic conditions, ● Experimental subjects (n=7), ○ Control subjects (n=5).

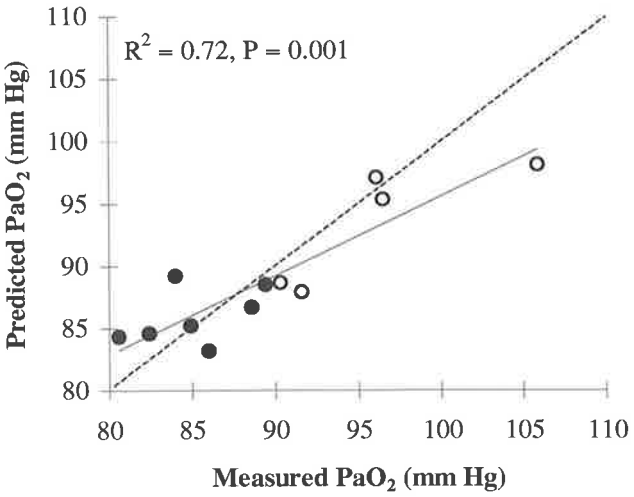


Figure 4.7 Association between measured PaO_2 and predicted PaO_2 in twelve subjects while performing heavy exercise under normoxic conditions Predicted PaO_2 calculated by the equation 9.19 * $\dot{V}_E$ + 0.306 * DLO_2 – 41 * log$SD_{\dot{Q}}$ + 62.2. Dashed line; line of identity, • Experimental subjects (n=7), o Control subjects (n=5).

4.4 DISCUSSION

4.4.1 Summary

The principal findings of this investigation are three-fold. Firstly, during heavy exercise, the subjects with exercise-induced hypoxemia developed significantly more end-capillary O_2 diffusion limitation (measured by the observed minus predicted alveolar-arterial O_2 tension difference) than control subjects matched for age, lung function and $\dot{V}O_{2peak}$. Secondly, the majority (72%) of the variance of PaO_2 during normoxic heavy exercise could be explained with a stepwise multiple linear regression model which combined the independent predictors; lung diffusing capacity for O_2 (DLO_2), minute ventilation ($\dot{V}_E$) and $\dot{V}_A/\dot{Q}$ inequality ($\log SD_{\dot{Q}}$). Within this regression model the relative contribution of the predictor variables was 31% for DLO_2, 24% for $\dot{V}_E$, and 17% for $\log SD_{\dot{Q}}$. This suggests that in this group of athletes, arterial oxygenation may have a multifactorial rather than a single cause. Lastly, no subject developed significant increases from rest in $\dot{V}_A/\dot{Q}$ inequality during exercise while breathing either air or 13.2 % O_2 (hypoxia).

4.4.2 End-capillary O_2 diffusion limitation

Previously it has been reported that substantial end-capillary O_2 diffusion limitation is evident during intense exercise, which becomes increasingly important as $\dot{V}O_2$ increases, suggesting a link between $\dot{V}O_2$ and the degree of end-capillary O_2 diffusion limitation (Hammond, Gale, et al. 1986a). In the present study, the experimental and control groups were matched for $\dot{V}O_2$ during both normoxic and hypoxic submaximal work loads which suggests that the significant difference between the two groups for A-aDO_2 (o-p) during moderate and heavy exercise is likely to be an inherent problem of pulmonary gas exchange in the experimental subjects.

Dempsey et al. (1984) suggested that diffusion limitation may result from very short red cell transit times in at least a portion of the pulmonary circulation, but only two studies have attempted to measure transit times in exercising athletes (Hopkins, Belzberg, et al. 1996; Warren, Cureton, et al. 1991). While both studies demonstrated a significant fall in transit time, neither provided unequivocal evidence to show that transit times approached the hypothetical minimum time of 0.35-0.40 seconds for O_2 equilibration (Dempsey, Hanson, et al. 1982; Gledhill, Froese, et al. 1977). In the present study there were no significant differences between the control and experimental groups with respect to cardiac output. Therefore, if reduced transit time is the major cause of greater end-capillary O_2 diffusion limitation in the experimental subjects, then this group must have either or both of the following; 1) a smaller pulmonary capillary blood

volume and/or 2) less recruitment of pulmonary capillaries at identical exercise intensities. The two groups of subjects in the present study were well matched for pulmonary function and lung size. As such, there is no obvious reason to suspect that there would be a significant difference in the pulmonary capillary structure of the two groups, however this cannot be discounted. Although no direct evidence of end-capillary O_2 diffusion limitation due to excessively brief pulmonary capillary transit times can be provided, there is evidence to suggest a link between the two. Firstly, a significant association between DLO_2 and PaO_2 during heavy exercise while breathing air was demonstrated. Secondly, the development of an alveolar-end capillary O_2 gradient in a single-compartment lung model can be shown to depend on the relative ratio of diffusive conductance to perfusive conductance ($DLO_2/\dot{Q}$; Piiper & Scheid 1980). When the ratio is >3, $\dot{V}O_2$ is perfusion limited, as would be the case in normoxia at rest. As $DLO_2/\dot{Q}$ falls below 3, end-capillary O_2 diffusion limitation becomes evident. In the present study, during normoxic heavy exercise, both the control and experimental groups had $DLO_2/\dot{Q}$ values <3, suggesting end-capillary O_2 diffusion limitation in each. More importantly however, the experimental group during normoxic moderate and heavy exercise had significantly lower $DLO_2/\dot{Q}$ values than the matched control group, indicating significantly more end-capillary O_2 diffusion limitation in the former. Finally, Hopkins et al. (1996) found whole lung transit time was significantly related to A-aDO_2 (o-p) (R=-0.58) in a group of subjects with a similar $\dot{V}O_{2max}$ to those in the present study. Although pulmonary capillary transit time and not whole lung transit time is the key measure related to gas exchange, the significant difference in A-aDO_2 (o-p) of the experimental

compared with the control subjects in the present study suggests that transit times during heavy exercise may have been low enough to significantly impair gas exchange.

Warren et al. (1991) stated that the ceiling for pulmonary capillary transit times was not breached during exercise. However, this needs to be interpreted with reference to the limitations of their study. Importantly, none of the subjects involved in that study developed significant EIH, as demonstrated by an A-aDO_2 (o) <25 mm Hg at 90% $\dot{V}O_{2max}$ compared with >33 mm Hg in the present study. This is critical because only those subjects who develop EIH are thought to compromise pulmonary capillary transit times. Another limitation included the use of a breath hold manoeuvre at 90% of vital capacity to measure pulmonary capillary blood volume. This is of major concern because this manoeuvre could increase venous return and spuriously elevate pulmonary capillary blood volume. Unfortunately, these limitations could possibly cause sufficient imprecision to obscure pulmonary capillary transit times less than 0.40 seconds during exercise.

Another possible mechanism for arterial hypoxemia during exercise is a significantly reduced $P\bar{v}O_2$ (Wagner 1982). From the 50 compartment inert gas data, $P\bar{v}O_2$ was calculated for all exercise work loads. Analysis of the results during heavy exercise while breathing air revealed no significant differences between the control and experimental groups (24 ± 2 vs 26 ± 2 mm Hg, respectively; P=0.29). Thus, in the experimental subject group, $P\bar{v}O_2$ would not be considered as the reason for the greater arterial hypoxemia measured.

Additionally, any difference between the two groups for SaO_2 would have been offset by the slightly higher $\dot{Q}$ measured in the experimental group during all exercise work loads.

Recently, St Croix et al. (1998) provided evidence to suggest that EIH was not caused by a mechanism which persisted after exercise but rather that a functionally based mechanism was responsible. These results support the hypothesis of reduced red cell transit times as a mechanism responsible for EIH, but it appears that additional direct evidence is required to confirm or refute the link between transit times and end-capillary O_2 diffusion limitation in subjects who develop EIH during high intensity exercise.

4.4.3 Extra-pulmonary shunt

The MIGET technique is unable to distinguish the relative contributions that end-capillary O_2 diffusion limitation and extra-pulmonary shunt make towards the overall A-aDO_2 (o-p). It is therefore worth exploring the potential effect extra-pulmonary shunt may have on EIH. During normoxic heavy exercise, it was calculated that the fall in PaO_2 from rest measured in the control and experimental subjects could be explained entirely by a 1.5 ± 0.2% and 3.0 ± 0.5% extra-pulmonary shunt, respectively, as opposed to end-capillary O_2 diffusion limitation. Shunts of this size are at the limits of expectation in healthy subjects. The contention that extra-pulmonary shunt could fully explain the

measured hypoxemia in both groups during normoxic heavy exercise thus appears unsound, especially considering previous studies have reported extra-pulmonary shunt values in the range of 0.18 - 2% of total cardiac output (Hammond, Gale, et al. 1986a; Torre-Bueno, Wagner, et al. 1985). Typically, extra-pulmonary shunt is measured by having the subject breathe 100% O_2, which eliminates the effects of $\dot{V}_A/\dot{Q}$ inequality and end-capillary O_2 diffusion limitation. Any residual difference between predicted and measured values while breathing 100% O_2 must be due to extra-pulmonary shunt. This method was not used in the present study because of the difficulty in measuring PaO_2 accurately when breathing 100% O_2. Indeed, the absolute O_2 content differences between air and 100% O_2 breathing are in the range of the experimental error (Hammond, Gale, et al. 1986a). For this reason hypoxia (F_IO_2=0.13) was used to demonstrate that extra-pulmonary shunt could not be the sole explanation for the hypoxemia measured during normoxic heavy exercise. Due to the steepness of the oxyhemoglobin dissociation curve at an F_IO_2 of 0.13, a 1-3% extra-pulmonary shunt would decrease measured PaO_2 by only 2-3 mm Hg. In contrast, the hypoxemia measured during hypoxic heavy exercise in the present study would require an extra-pulmonary shunt in the region of 17% for the control subjects and 24% for experimental subjects. It is unlikely that hypoxia alone would cause extra-pulmonary shunt to increase to such high levels. Therefore, it is concluded that end-capillary O_2 diffusion limitation occurred in the control and experimental subjects during heavy exercise, and that extra-pulmonary shunt comprised an extremely small component of the overall A-aDO_2 (o-p).

4.4.4 Ventilation

Inadequate hyperventilation during high intensity exercise has been proposed as a significant contributor to EIH by many authors (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Miyachi & Tabata 1992). In the present study, when all subjects (n=12) were considered by regression analysis, there was a significant association between PaO_2 and $\dot{V}_E$ ($l.min^{-1}.kg^{-1}$, BTPS) during heavy exercise under normoxic conditions. This result suggests that those subjects with severe arterial hypoxemia were likely to have a blunted hyperventilatory response to exercise. A number of possible mechanisms have been proposed for inadequate hyperventilation during heavy exercise; 1) a decreased peripheral chemoreceptor function (Byrne-Quinn, Weil, et al. 1971; Harms & Stager 1995), 2) respiratory muscle fatigue (Bye, Farkas, et al. 1983) and 3) mechanical constraints imposed on inspiratory and expiratory flow (Johnson, Saupe, et al. 1992). Regardless of the mechanism, the level of ventilation during heavy exercise while breathing air in the present study explained at least one quarter of the variance in arterial oxygenation. It appears further investigation into the possible mechanisms is warranted.

4.4.5 Ventilation–perfusion inequality

Contrary to previous studies (Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, McKenzie, et al. 1994; Torre-Bueno,

Wagner, et al. 1985) there were normal levels of $\dot{V}_A/\dot{Q}$ inequality at rest with no significant increase during exercise while breathing either normoxic or hypoxic gas mixtures. The technical quality of the inert gas data was excellent as evidenced by a low residual sum of squares under all conditions (Table 4.2 and 4.3). Consequently, it is believed that this result is a characteristic of this particular population. A recent study demonstrated that lung capacity normalised for body surface area was an important determinant in the efficiency of $\dot{V}_A/\dot{Q}$ matching, in effect suggesting that those athletes with large lungs are less likely to develop significant $\dot{V}_A/\dot{Q}$ inequality during exercise (Hopkins, Gavin, et al. 1998). This hypothesis is supported by the present study as all subjects possessed FVC and alveolar volumes greater than those predicted according to the subject's age, height and race (FVC, 107 ± 3%; alveolar volume, 166 ± 5%). Furthermore, there were no significant differences between the control and experimental groups in any pulmonary function test, which may explain the lack of difference in $\dot{V}_A/\dot{Q}$ inequality between the two groups during exercise. The reason why hypoxia did not induce significant $\dot{V}_A/\dot{Q}$ inequality in either group remains unclear, but may reflect additionally that these subjects were generally resistant to the development of exercise-induced $\dot{V}_A/\dot{Q}$ inequality.

4.4.6 Hypoxia

Hypoxia as expected, resulted in significantly lower $\dot{V}O_{2peak}$ values in both the control and experimental subjects (decrease from normoxia: control, 22.0 ± 2.9%; experimental, 26.6 ± 1.5%, P=0.14, NS). The larger, even if non-significant, reduction measured in the experimental group most likely represents their position as a group on the oxyhemoglobin dissociation curve as this has been shown to directly affect the degree of decrease in $\dot{V}O_{2peak}$ (Lawler, Powers, et al. 1988; Powers, Lawler, et al. 1989). This result has implications for those athletes who wish to pursue competition in endurance events at altitude. It is most likely, with all other factors being equal, that subjects who develop EIH during sea level exercise will have a greater reduction in performance upon ascent to altitude than will those athletes who retain PaO_2 near resting levels.

4.4.7 Recovery

DL_{CO} post-exercise was reduced significantly in all control and experimental subjects, a result which has been reported several times previously (Hanel, Teunissen, et al. 1997; Manier, Moinard, et al. 1991). The reasons behind this reduction are not fully understood. The mechanisms proposed in the literature for a reduction in post-exercise DL_{CO} are; 1) a transient change in the structure of the alveolo-capillary membrane thereby affecting the diffusing capacity (Manier, Moinard, et al. 1991) and 2) a decrease in the pulmonary

capillary blood volume (Hanel, Teunissen, et al. 1997). In the present study, A-aDO_2 (o-p), $\dot{V}_A/\dot{Q}$ relationships and PaO_2 were measured up to 45 minutes post-exercise and there were no significant changes in any of the variables from rest, suggesting no change in the alveolo-capillary structure of sufficient magnitude to affect O_2 diffusion. Secondly, previous studies have demonstrated that lung volume and function are temporarily impaired after exercise (Buono, Constable, et al. 1981; O'Kroy, Loy, et al. 1992) suggesting small airway closure and possible subclinical edema, all contributing to a decreased diffusing capacity. In the present study, no significant alteration in pulmonary function post-exercise was found. In fact, there was a slight trend towards an improvement in lung volume, vital capacity and airflow rates post-exercise. This does not support the contention that edema was present in either the control or experimental groups during either normoxic or hypoxic exercise, and thus edema is unlikely to explain the significant fall in DL_{CO} in this subject population. Based on this evidence, it is hypothesised that the most likely cause for the significant post-exercise decrease in DL_{CO} in both the control and experimental groups is a reduction in the pulmonary capillary blood volume.

4.4.8 Conclusion

In summary, this study has demonstrated that trained cyclists with significant exercise-induced hypoxemia during intense exercise developed a significantly larger observed-predicted alveolar-arterial O_2 tension difference

compared with a control group matched for age, lung function and $\dot{V}O_{2peak}$. This result has been interpreted to primarily represent differences in end-capillary O_2 diffusion limitation between the two subject groups. It has also been demonstrated that lung diffusing capacity for O_2, minute ventilation and ventilation-perfusion inequality each contribute to the level of arterial oxygenation in any subject and together explain the majority of the variance in PaO_2. Therefore, the results from the present study suggest that in this group of trained cyclists, exercise-induced hypoxemia has a multifactorial etiology related to end-capillary O_2 diffusion limitation and inadequate hyperventilation with a minor role played by ventilation-perfusion inequality.

5 EXERCISE-INDUCED HYPOXEMIA AT 95% $\dot{V}O_{2PEAK}$ IS GREATER WITH RUNNING THAN CYCLING

5.1 INTRODUCTION

Dempsey et al. (1984) demonstrated significant hypoxemia in highly trained runners performing intense exercise on the treadmill. Since then, the majority of studies investigating EIH have used cycle ergometry as it appears more convenient to obtain arterial blood samples with this exercise mode. In addition, for those studies which utilise pulse oximetry, the reading is more stable and reliable during cycle ergometry as the subject's upper body is relatively stationary (Poets & Stebbens 1997).

In Section 3, EIH was demonstrated in a group of trained cyclists performing progressive incremental exercise to exhaustion, and the degree of hypoxemia was strongly associated with the degree of alveolar oxygenation. However, neither this study, nor others where exercise was performed on a cycle ergometer (Brown, Knowlton, et al. 1993; Hopkins, McKenzie, et al. 1994; Powers, Martin, et al. 1992) were able to produce arterial hypoxemia as profound as that demonstrated by Dempsey et al. (1984) when athletes ran on a treadmill. Only one previous study has measured arterial blood gases during both treadmill and cycle exercise at similar work loads in the same subjects (Cockcroft, Beaumont, et al. 1985). The authors reported greater arterial O_2 desaturation

during treadmill exercise, which was directly related to the level of ventilation. However, the subjects in that particular study were patients with chronic obstructive pulmonary disease. As yet, no deliberate comparative study using two different ergometer modes has been reported in healthy trained athletes.

Therefore, the hypothesis to be tested was that EIH in trained endurance athletes was ergometer specific and would be exacerbated during treadmill running compared with cycle exercise. To test this hypothesis, a group of trained athletes performed exercise on a treadmill and cycle ergometer at a matched O_2 consumption, while measurements of arterial blood gases and ventilation were made.

5.2 METHODS

5.2.1 Subject selection

Thirteen healthy male athletes participated in this study (see Table 5.1). Seven were trained runners and six were trained cyclists. All subjects had a $\dot{V}O_{2peak}$ >65 $ml.kg^{-1}.min^{-1}$ and/or 4.5 $l.min^{-1}$ and gave no prior history of cardiovascular or respiratory disease. Routine pulmonary function testing (FVC, $FEV_{1.0}$, DL_{CO} and TLC) also revealed normal lung function for each (see Table 5.1).

5.2.2 Experimental design

Subjects visited the laboratory on three separate occasions within a three week period. During the first two visits a $\dot{V}O_{2peak}$ test was performed on a treadmill or cycle ergometer in a random but counterbalanced order. The final visit required each subject to complete 5 minutes of exercise on each ergometer at a work load that corresponded to ~90% of the subject's lowest $\dot{V}O_{2peak}$. Arterial blood samples were withdrawn at the end of each minute.

5.2.3 Incremental exercise protocols

Prior to beginning each experiment the subject's height and weight were recorded and chest electrodes were applied to measure HR and ECG (see Section 2.2.1).

5.2.3.1 Treadmill incremental exercise protocol

Subjects began by completing 5 minutes of exercise at 70% of their age-predicted maximum HR (HR_{max}) followed by 5 minutes of musculo-skeletal stretching. A detailed description of the treadmill protocol beyond the warm up protocol has been provided in Section 2.2.9.

5.2.3.2 Cycle incremental exercise protocol

The cycle ergometer protocol began with a 5 minute warm up similar to that for the treadmill (70% age-predicted HR_{max}). Trained cyclists began the incremental protocol on the air-braked cycle ergometer at a work rate of 150 W whereas the runners began at 100 W. Increments of 25 W occurred every minute thereafter until volitional exhaustion. A more detailed description of the cycle ergometer incremental protocol can be found in Section 2.2.10.

5.2.4 Determination of peak O_2 consumption

Section 2.2.2 describes the method used to measure $\dot{V}O_2$ and $\dot{V}O_{2peak}$ for this series of experiments.

5.2.5 Subject preparation for arterial blood gas sampling

Prior to catheterisation each subject self inserted a rectal thermocouple 20 cm beyond the anal spinchter (see Section 2.2.7). While lying supine and using local anaesthesia (1% lignocaine hydrochloride) each subject had a 20 G catheter placed in the radial artery at the right wrist as described in Section 2.2.4. For safety reasons the catheter was secured in place with two sutures. Approximately 1 m of minimum volume extension tubing was connected to the catheter hub and taped in a number of places up the subjects arm. This system allowed easy and rapid arterial blood sampling with little hindrance to the subject, especially while running.

5.2.6 Experimental protocol and arterial blood gas sampling

Following 20 minutes of recovery from the catheter insertion procedure the subjects were allowed an identical warm up and musculo-skeletal stretching period as was provided during the incremental exercise tests. The order

of ergometers was the same as the earlier incremental tests. Following the warm up, each subject spent 8 minutes at rest, either standing (treadmill) or sitting (cycle). At minute 5 of this rest period subjects were connected to the respiratory circuit, at minute 7 a resting arterial blood sample was withdrawn (see Section 2.2.4), and at minute 8 the subject was instructed to begin pedaling at the required power output. The treadmill was started 15 seconds before minute 8 to ensure that it was at the correct grade and speed for the subject's work load. The exercise protocols ceased at the end of minute 13.

5.2.7 Blood gas sampling and analysis

A detailed description of the method used to sample and analyse the arterial blood gases has been provided in Section 2.2.4.

5.2.8 Data analysis

Differences in values obtained at $\dot{V}O_{2peak}$ between the two incremental exercise protocols were analysed using a paired Student's t-test. A two-way repeated measures ANOVA was used to determine significant differences for exercise time (minute 1, 2, 3, 4 or 5) and ergometer (treadmill vs cycle). Where overall significance was obtained, differences between means were identified with a Tukey's honestly significant test for unequal numbers.

Correlation of PaO_2 with selected ventilatory and blood gas variables was performed on the pooled data of both ergometers (n=26) using the Pearson product moment correlation analysis.

5.3 RESULTS

5.3.1 General data

The highest $\dot{V}O_{2peak}$ values for each subject from either ergometer were pooled providing a mean of 70.2 ± 1.7 $ml.kg^{-1}.min^{-1}$, which is characteristic of trained endurance athletes. Mean resting pulmonary function data were above age and height predicted values (Table 5.1).

5.3.2 Incremental exercise test

Table 5.2 compares the results of the incremental exercise tests on the two ergometers. $\dot{V}O_{2peak}$ and $\dot{V}CO_{2peak}$ were not different between running and cycling, but RER was significantly lower on the treadmill compared with the cycle ergometer. Minute ventilation and associated measurements ($\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$) were significantly lower while running compared with cycling.

Table 5.1 Anthropometric, metabolic and pulmonary function data for thirteen trained subjects

	Mean	SEM
Age, years	23.7	1.7
Height, cm	177.9	1.4
Weight, kg	70.6	2.8
$\dot{V}O_{2peak}$, $l.min^{-1}$	4.92	0.13
$\dot{V}O_{2peak}$, $ml.kg^{-1}.min^{-1}$	70.2	1.7
$FEV_{1.0}$, l	4.83 (105%)	0.17
FVC, l	5.73 (104%)	0.24
DL_{CO}, ml.mm $Hg^{-1}.min^{-1}$	41.6 (131%)	2.0
TLC, l	7.40 (104%)	0.31

Values are mean ± SEM, % predicted in parentheses. $\dot{V}O_{2peak}$, pooled peak O_2 consumption from either ergometer; $FEV_{1.0}$, forced expiratory volume in 1 second; FVC, forced vital capacity; DL_{CO}, lung diffusing capacity for CO; TLC, total lung capacity.

Table 5.2 Metabolic data at the completion of a progressive cycle ergometer and treadmill ergometer test to exhaustion

	Cycle	Treadmill
$\dot{V}O_{2peak}$, $l.min^{-1}$	4.69±0.13	4.89±0.14
$\dot{V}O_{2peak}$, $ml.kg^{-1}.min^{-1}$	66.6±1.3	69.9±1.8
$\dot{V}CO_{2peak}$, $l.min^{-1}$	5.24±0.16	5.30±0.17
RER	1.12±0.02	1.08±0.04*
$\dot{V}_T$, l	2.77±0.1	2.71±0.1
$\dot{V}_E$, $l.min^{-1}$	172.7±5.6	155.9±4.7*
$\dot{V}_E/\dot{V}CO_2$	33.1±1.1	29.5±0.5*
$\dot{V}_E/\dot{V}O_2$	36.9±1.1	31.9±0.6*
Breath f, $breaths.min^{-1}$	63.3±2.5	58.2±2.3
Heart Rate, $beats.min^{-1}$	188±2	192±2

Values are means ± SEM. $\dot{V}O_{2peak}$, peak O_2 consumption; $\dot{V}CO_{2peak}$, peak carbon dioxide production; RER, respiratory exchange ratio; $\dot{V}_T$, tidal volume; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; Breath f, breath frequency. * significantly different from cycle ergometer, $P<0.05$.

5.3.3 Time course of 5 minutes of high intensity exercise

Figure 5.1 and Table 5.3 display the time course for blood gas and selected metabolic variables during 5 minutes of high intensity exercise. The work loads selected for each subject were estimated to be ~90% of their lower $\dot{V}O_{2peak}$ (treadmill or cycle ergometer) achieved during the incremental exercise tests. In reality, the treadmill work load was 95.3 ± 2.0% of the treadmill $\dot{V}O_{2peak}$ and cycle work load was 99.4 ± 1.0% of the cycle $\dot{V}O_{2peak}$.

5.3.3.1 Blood gas variables

5.3.3.1.1 Arterial O_2 tension

PaO_2 at rest was similar on each ergometer, and after the first minute of both cycling and running had dropped significantly, and to the same degree (Figure 5.1a). At the end of the second minute of exercise, PaO_2 on the cycle had increased significantly above that at minute 1 and was also significantly higher than the corresponding value on the treadmill. At minutes 2, 3, 4 and 5 of exercise, PaO_2 on the cycle was significantly higher (~8–10 mm Hg) than on the treadmill.

5.3.3.1.2 Arterial CO_2 tension

$PaCO_2$ did not change from rest values throughout the 5 minutes of treadmill exercise (Figure 5.1b). In contrast, while cycling, $PaCO_2$ rose marginally in the first minute and then fell progressively, with the values at minutes 4 and 5 of exercise being significantly lower than those measured at the same time points on the treadmill.

5.3.3.1.3 Alveolar O_2 tension and alveolar-arterial O_2 tension difference

PAO_2 was significantly elevated above rest at minute 2 and thereafter with exercise on both ergometers (Figure 5.1c). At minutes 3, 4 and 5 of exercise PAO_2 was significantly higher on the cycle ergometer compared with the treadmill. A-aDO_2 was not significantly different between the two modes of exercise and widened progressively throughout exercise to maximum values at minute 5 of 28.1 ± 1.9 and 24.3 ± 2.2 mm Hg on the treadmill and cycle ergometer, respectively (Figure 5.1d).

5.3.3.1.4 Acid-base status

Cycling induced larger changes in acid base status than did running. Arterial pH was significantly lower on the cycle ergometer compared with the treadmill at minutes 2, 3, 4 and 5 of exercise (Figure 5.1e). Arterial blood lactate

on the cycle ergometer was significantly higher than on the treadmill at minutes 3, 4 and 5 of exercise (Figure 5.1f).

5.3.3.2 Metabolic variables

Apart from rest, tidal volume on the treadmill was always lower than that on the cycle ergometer but was only significantly different at minutes 2, 3, 4 and 5 of exercise (Figure 5.1g). Minute ventilation (Figure 5.1e and Table 5.3) while running was significantly higher than that cycling at minute 1, but was significantly lower at minutes 3, 4 and 5 of exercise. Table 5.3 displays the slower rise in $\dot{V}O_2$ on the cycle ergometer, such that $\dot{V}O_2$ was significantly lower cycling than running at both minute 1 and minute 2, but not at minutes 3, 4 and 5 of exercise. $\dot{V}CO_2$ on the treadmill was lower than on the cycle ergometer at minutes 3, 4 and 5 of exercise (Table 5.3). The ventilatory equivalent for O_2 (Figure 5.1i) was significantly lower on the treadmill than the cycle ergometer at minutes 2, 3, 4 and 5 of exercise, while the ventilatory equivalent for CO_2 (Figure 5.1j) was significantly higher at minute 1 and significantly lower at minutes 4 and 5.

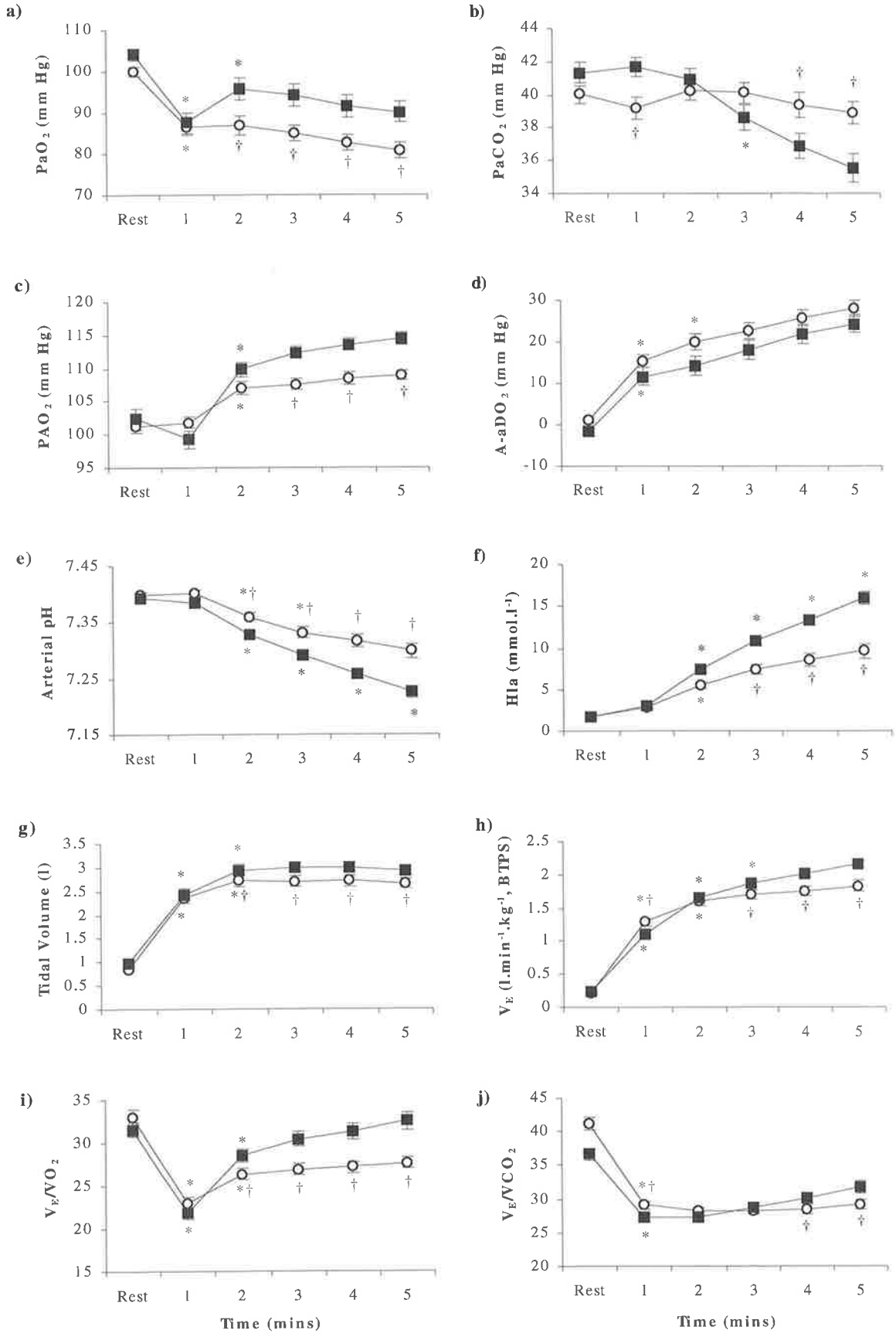

a)
PaO2 (mm Hg)
110
100
90
80
70
Rest 1 2 3 4 5
b)
PaCO2 (mm Hg)
44
42
40
38
36
34
Rest 1 2 3 4 5
c)
PAO2 (mm Hg)
120
115
110
105
100
95
Rest 1 2 3 4 5
d)
A-aDO2 (mm Hg)
30
20
10
0
-10
Rest 1 2 3 4 5
e)
Arterial pH
7.45
7.35
7.25
7.15
Rest 1 2 3 4 5
f)
Hla (mmol.l-1)
20
15
10
5
0
Rest 1 2 3 4 5
g)
Tidal Volume (l)
3.5
3
2.5
2
1.5
1
0.5
0
Rest 1 2 3 4 5
h)
VE (l.min-1.kg-1, BTPS)
2.5
2
1.5
1
0.5
0
Rest 1 2 3 4 5
i)
VE/VO2
35
30
25
20
15
Rest 1 2 3 4 5
Time (mins)
j)
VE/VCO2
45
40
35
30
25
20
Rest 1 2 3 4 5
Time (mins)

Figure 5.1 Selected variables during 5 minutes of exercise at ~95% $\dot{V}O_{2peak}$ on a cycle ergometer (■) and treadmill ergometer (○). PaO_2, arterial O_2 tension; $PaCO_2$, arterial CO_2 tension; PAO_2, alveolar O_2 tension; A-aDO_2, alveolar-arterial O_2 tension difference; Hla, arterial blood lactate; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for O_2; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for CO_2. * significantly different from previous minute, † significantly different from cycle ergometer, $P<0.05$.

Table 5.3 Selected metabolic variables during 5 minutes exercise at ~95% $\dot{V}O_{2peak}$ on a cycle and treadmill ergometer

	Ergometer	Rest	Minute 1	Minute 2	Minute 3	Minute 4	Minute 5
$\dot{V}_E$ $l.min^{-1}$	Cycle	16.3±1.1	77.2±4.2 *	116.1±4.7 *	131.1±4. *	141.1±4.4	151.2±4.9
	Treadmill	15.2±0.9	90.1±4.1 *†	112.8±5.6 *	119.1±5.1 †	123.4±5.1 †	129.0±5.4 †
$\dot{V}O_2$ $l.min^{-1}$	Cycle	0.52±0.03	3.54±0.14 *	4.08±0.15 *	4.33±0.16	4.54±0.16	4.67±0.15
	Treadmill	0.46±0.03	3.93±0.14 *†	4.27±0.16 †	4.43±0.15	4.55±0.15	4.65±0.14
$\dot{V}CO_2$ $l.min^{-1}$	Cycle	0.45±0.03	2.84±0.13 *	4.24±0.15 *	4.56±0.15	4.67±0.15	4.77±0.15
	Treadmill	0.37±0.03	3.09±0.13 *	4.01±0.18 *	4.21±0.17 †	4.34±0.17 †	4.44±0.17 †
Heart Rate $beats.min^{-1}$	Cycle	77±5	157±2 *	168±2	173±2	177±3	180±3
	Treadmill	91±4	163±3 *	171±3	176±3	179±2	182±3

Values are means ± SEM. $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, O_2 consumption; $\dot{V}CO_2$, CO_2 production; * significantly different from previous value; † significantly different from cycle ergometer, $P<0.05$.

5.3.4 Relationship between selected blood gas and ventilatory variables and PaO_2

When the data from the 13 subjects was pooled, PaO_2 was a strongly associated with $\dot{V}_E$ (relative to body weight; $l.min^{-1}.kg^{-1}$, BTPS) at each minute of exercise (range of R=0.59 to 0.75, Table 5.4). Figure 5.2 illustrates the association between these two variables at the completion of exercise. There was a strong negative relationship between A-aDO_2 and PaO_2 throughout the 5 minutes of exercise (range of R=-0.85 to -0.93, Table 5.4).

Table 5.4 Correlation of PaO_2 with selected blood gas and ventilatory variables during 5 minutes exercise at ~95% $\dot{V}O_{2peak}$

	PaO_2 (mmHg)				
	Min 1	Min 2	Min 3	Min 4	Min 5
$\dot{V}_E$, $l.min^{-1}.kg^{-1}$, BTPS	0.59*	0.60*	0.71*	0.73*	0.75*
$PaCO_2$, mmHg	-0.33	-0.50*	-0.66*	-0.70*	-0.71*
PAO_2, mmHg	0.53*	0.62*	0.65*	0.62*	0.59*
A-aDO_2, mmHg	-0.85*	-0.93*	-0.92*	-0.91*	-0.90*

Data are pooled from both ergometers (n=26). PaO_2, arterial O_2 tension; $\dot{V}_E$, minute ventilation per kilo body weight; $PaCO_2$, arterial CO_2 tension; PAO_2, alveolar O_2 tension; A-aDO_2, alveolar–arterial O_2 tension difference, * $P<0.05$.

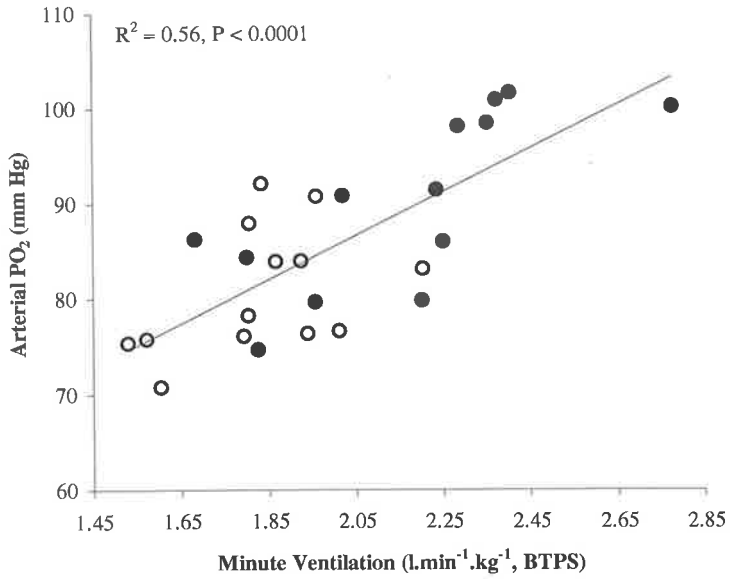


Figure 5.2 The relationship between minute ventilation (l.min^{-1}.kg^{-1}, BTPS) and arterial O_2 tension at minute 5 of exercise at ~95% $\dot{V}O_{2peak}$. Data are pooled from both ergometers (n=26), ○ treadmill ergometer, ● cycle ergometer.

5.4 DISCUSSION

The principal findings of the present study are two fold; firstly, 5 minutes of treadmill running results in lower PaO_2 values than five minutes of cycling at an equivalent O_2 consumption. This result is in agreement with Cockcroft et al. (1985) the only other workers to investigate differences in blood gases while performing matched exercise on a treadmill and cycle ergometer. While Cockcroft et al. (1985) used subjects with chronic obstructive pulmonary disease, this study demonstrates the differences in trained endurance athletes. Secondly, the degree of arterial oxygenation (PaO_2) is strongly associated with a number of ventilatory variables throughout the duration of exercise. This latter result provides direct evidence to suggest that inadequate hyperventilation plays a major role in the development of exercise induced hypoxemia during intense exercise.

Based on a comparison of the results of Dempsey et al. (1984) for subjects on a treadmill, and those from previous sections (see Sections 3 and 4) for subjects on a cycle ergometer, it was hypothesised that treadmill running would exacerbate arterial hypoxemia compared with cycling, and furthermore, that the difference in PaO_2 between the two exercise modalities could be attributed to the level of ventilation. The results of the present study support the hypotheses and provide a plausible explanation for these phenomena. Arterial blood lactate levels while cycling were significantly higher and the arterial pH significantly lower compared with running from minute 3 to 5, as has been

demonstrated previously (Bouckaert, Vrijens, et al. 1990; Bouckaert & Pannier 1995; Cockcroft, Beaumont, et al. 1985). This suggests that the relative muscle work load (O_2 consumption per kilogram of muscle mass activated) of the lower limbs while cycling was greater than the relative work load of the entire body while running (Koyal, Whipp, et al. 1976). Asmussen and Neilsen (1946) have shown that for the same subject, work with smaller muscle groups produces a larger minute ventilation for the same $\dot{V}O_2$ than work with larger muscle groups. They and others (Koyal, Whipp, et al. 1976) attributed this relative hyperventilation as a response to products of anaerobic energy metabolism appearing in the blood. In the present study, it is likely that exercise on the cycle ergometer involved less muscle mass than exercise on the treadmill at an identical O_2 consumption, and thus cycling provoked a greater acidosis with a consequent increased stimulus for ventilation (Wasserman 1978). This relative hyperventilation during cycle ergometry was sufficient to raise PaO_2 above that observed during treadmill running after minute 1 and drop $PaCO_2$ below that seen on the treadmill after minute 2.

Inadequate hyperventilation has been postulated as a key mechanism of EIH because it directly reduces the driving pressure for O_2 across the pulmonary blood:gas membrane (Hopkins & McKenzie 1993). The relative importance of inadequate hyperventilation for the development of EIH is equivocal. A number of reports suggest that inadequate hyperventilation can account for up to 50% of the arterial desaturation measured during high intensity exercise (Dempsey, Hanson, et al. 1984; Gavin, Derchak, et al. 1998; Harms & Stager 1995; Harms, McClaran, et al. 1998; Miyachi & Shibayama 1992; Miyachi

& Tabata 1992). In contrast, other researchers have not found a link between inadequate hyperventilation and EIH (Buono & Maly 1996; Hopkins & McKenzie 1989; Powers, Martin, et al. 1992). There is no conclusive reason for the differences between the studies, which have used a variety of ergometers and exercise intensities. The present study demonstrates that the lowest PaO_2 and minute ventilation ($l.min^{-1}.kg^{-1}$, BTPS) values were recorded while running on the treadmill. This result, in combination with the significant relationship between PaO_2 and $\dot{V}_E$ ($l.min^{-1}.kg^{-1}$, BTPS) throughout the 5 minutes of exercise ($R>0.59$), suggests that the hyperventilatory response during treadmill running was inadequate to compensate for the hypoxemia that occurred. The question arises as to why greater hypoxemia was tolerated on the treadmill when the subjects had the capacity to increase ventilation, as demonstrated during cycling exercise of matched intensity. The finding that hypoxemia was tolerated in the face of a stable $PaCO_2$ on the treadmill suggests that hypoxic ventilatory drives are less important in determining exercise ventilation than are hypercapnic drives, a hypothesis which has been supported by previous work (Hopkins & McKenzie 1989).

The degree of EIH reported by different authors has varied. In the present study, the mean lowest PaO_2 value was 81 mm Hg at the completion of the final minute while running on the treadmill. This is in contrast to ~72 mm Hg reported by Dempsey et al. (1984) but is similar to the value of 78 mm Hg reported by Hopkins and McKenzie (1989). The mean $\dot{V}O_2$ for the subjects at minute 5 was 4.67 ± 0.15 $l.min^{-1}$ and 4.65 ± 0.14 $l.min^{-1}$ for the cycle and

treadmill, respectively, and this was similar to the 4.56 ± 0.12 l.min^{-1} measured on the treadmill by Hopkins and McKenzie (1989). The six subjects in the study of Dempsey et al. (1984) exercised on the treadmill at a $\dot{V}O_2$ of 4.97 ± 0.10 l.min^{-1}, and since the level of desaturation is negatively associated with $\dot{V}O_2$ (Williams, Powers, et al. 1986), the lower absolute $\dot{V}O_2$ in the present study and that of Hopkins and McKenzie (1989) may explain the higher PaO_2 values. A further difference between the present study and that of Dempsey et al. (1984) was the PaO_2 at rest. Dempsey's subjects had a resting PaO_2 of ~89 mm Hg, whereas the subjects in this study had a resting PaO_2 on the treadmill of 100.1 ± 1.1 mm Hg. Dempsey et al. (1984) measured resting blood gases after 20 - 30 minutes of quiet sitting, while in the present study they were drawn after 7 minutes of rest which had been preceded by 5 minutes of exercise at 70% of age-predicted HR_{max} and 5 minutes of musculo-skeletal stretching. It is possible that the subjects in the present study were still hyperventilating during resting measurements as a result of the warm up, thus elevating PaO_2. However, the fact that the immediate pre-exercise $PaCO_2$ in the current study was above 40 mm Hg and minute ventilation was ~15 l.min^{-1} does not support this postulate. Dempsey's work was conducted in Madison, Wisconsin and the elevation of Madison airport is 262 metres (barometric pressure ~735 mm Hg) while the present study, and the research of Hopkins and McKenzie (1989) was conducted at sea level (barometric pressure ~760 mm Hg). The difference in barometric pressure would lower the ambient PO_2 from 159 mm Hg to 154 mm Hg and Gore et al. (1996) have shown that this will reduce arterial PO_2 by ~5 mm Hg. Therefore, it is plausible that the 11 mm Hg difference between the present study and that of Dempsey et al. (1984) may be

due to a combination of a lower inspired O_2 tension and the additional rest provided before sampling. However, given that the absolute lowest PaO_2 is the most critical factor in the determination of arterial O_2 saturation, it is clear that the present study was unable to induce the same level of arterial hypoxemia as the study of Dempsey et al. (1984).

In the present study, a strong inverse association was demonstrated between A-aDO_2 and PaO_2 throughout 5 minutes of high intensity exercise. This finding has been demonstrated previously in Section 3.3.2 and by a number of other authors (Harms, McClaran, et al. 1998; Hopkins & McKenzie 1989; Powers, Martin, et al. 1992). A-aDO_2 is a measure of the inefficiency of pulmonary gas exchange and increases during exercise in normal subjects. This result is attributed to a combination of three factors; intra and extra-pulmonary shunt, ventilation-perfusion inequality and end-capillary O_2 diffusion limitation (Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Wagner, Gale, et al. 1986). We have previously demonstrated significant end-capillary O_2 diffusion limitation in a group of trained cyclists (see Section 4.3.1.3). In that study, the A-aDO_2 for twelve subjects was 28 ± 2 mm Hg, which is identical to the values measured in the present study of 28 ± 2 mm Hg on the treadmill and similar to the 24 ± 2 mm Hg measured on the cycle ergometer. Interestingly, there were no significant differences between the two exercise modalities with respect to A-aDO_2 (Figure 5.1d). This suggests that the intensity of exercise is more important in determining the degree of inefficient pulmonary gas exchange than is

the type of exercise (Hammond, Gale, et al. 1986a; Torre-Bueno, Wagner, et al. 1985).

In summary, this study demonstrates that at a matched O_2 consumption, treadmill running results in significantly more arterial hypoxemia than cycling. The higher arterial O_2 tension on the cycle ergometer appears to be due to a greater ventilation, stimulated by higher arterial blood lactic acid levels consequent upon a greater relative work load placed on the lower limb muscles. This result provides further evidence in support of the role for inadequate hyperventilation in the development of exercise-induced hypoxemia.

6 SUMMARY AND CONCLUSIONS

6.1 VALIDITY OF THE DEFINITION OF EXERCISE-INDUCED HYPOXEMIA

As stated in the introduction to this thesis (see Section 1.1), the most widely accepted diagnostic criterion for EIH is a reduction in SaO_2 below 92% (Harms & Stager 1995; O'Kroy & Martin 1989; Powers, Lawler, et al. 1989). This level has been chosen because every 1% decline in SaO_2 below 92% results in a similar percentage fall in $\dot{V}O_{2max}$ (O'Kroy & Martin 1989; Powers, Lawler, et al. 1989). However, $\dot{V}O_{2max}$ has been shown to be a poor predictor of exercise performance (Snell & Mitchell 1984), and Koskolou and McKenzie (1993) reported that maximal exercise performance in highly trained endurance athletes was not significantly impaired until SaO_2 fell below 87%. Accepting 92% as the critical threshold for EIH further implies that it is an all or none phenomenon. Yet a number of workers have reported a negative linear relationship between $\dot{V}O_{2max}$ and maximal exercise SaO_2 (Williams, Powers, et al. 1986) and a further decline in both $\dot{V}O_{2max}$ and maximal SaO_2 with hypoxia (Lawler, Powers, et al. 1988), suggesting that EIH is a continuum. Regardless of the level of SaO_2 chosen, the results outlined in this thesis suggest that the physiological validity of SaO_2 as an index of EIH is questionable. Evidence is presented (Section 3.3.5) which indicates that significant arterial hypoxemia was present before a significant change in SaO_2, whether measured directly from arterial blood samples or indirectly with a pulse oximeter. Furthermore, despite many claims that pulse

oximeters yield results comparable with directly measured blood SaO_2 in exercising athletes (Martin, Powers, et al. 1992; Powers, Dodd, et al. 1989), results from this thesis (see Section 3.3.5) and other investigations suggest that this is highly unlikely (Brown, Knowlton, et al. 1993). The further implication is that where oxyhemoglobin saturation measurements have been used for the diagnosis of EIH, the reported prevalence of ~40-50% in those endurance athletes whose $\dot{V}O_{2max}$ exceeds 68 $ml.kg^{-1}.min^{-1}$ (Williams, Powers, et al. 1986; Powers, Dodd, et al. 1988), is questionable. Equally, reliance on arterial blood gas measurements is only valid if corrections are made for the corresponding core temperature changes, and this has not always been the case in published research in this area (Brown, Knowlton, et al. 1993; Caillaud, Anselme, et al. 1993; Gore, Hahn, et al. 1996; Hopkins & McKenzie 1989; Pedersen, Mandoe, et al. 1996; Préfaut, Anselme, et al. 1994; Todaro, Leonardi, et al. 1995 369). Therefore, significant arterial hypoxemia is the only valid measurement in diagnosing and determining the prevalence of EIH, with the critical variables being PaO_2 (directly measured and temperature corrected) and $A\text{-}aDO_2$, as unlike SaO_2 these are first order measurements independent of changes in pH.

6.2 MECHANISMS OF EXERCISE-INDUCED HYPOXEMIA

6.2.1 Inadequate hyperventilation

This thesis has demonstrated that the level of ventilation during exercise can contribute up to 66% of the measured variance in PaO_2 during moderate exercise (see Section 3.3.2), and anywhere up to 37% of the measured variance during heavy exercise (see Section 4.3.2.1). These data provide strong support for the role of inadequate hyperventilation in the development of EIH in trained endurance athletes. Elucidation of the mechanisms responsible for the apparent lack of adequate ventilatory response to exercise was not a specific aim of this thesis. However, the results from Section 5.3 suggest that the chemical stimulus to breathe, or specifically, the degree of lactic acidosis, was an important determinant. In contrast, the results from Sections 4 and 5 (see Section 4.3 and 5.3) suggest that at sea level, arterial hypoxia was not a powerful stimulus to ventilate. The observation that EIH occurred at such a low exercise intensity in the first series of experiments (~40% $\dot{V}O_{2peak}$) eliminates the possibility of mechanical flow limitations contributing to inadequate hyperventilation in that situation. Based on the above evidence, a tenable hypothesis is that inadequate hyperventilation contributes to EIH at low exercise intensities as a result of reduced chemosensitivity to ventilatory stimuli, and that during heavy to near-maximal exercise the influence of mechanical flow limitations (Johnson, Saupe, et al. 1992) and competition for blood flow between the skeletal muscles

and respiratory muscles (Harms, Babcock, et al. 1997; Harms, Wetter, et al. 1998) becomes increasingly important.

As suggested by Otis (1964) it appears that an inadequate hyperventilatory response at near-maximal exercise is the body's response to the conflicting demands of maintaining work output in the face of rising O_2 and blood flow costs of alveolar ventilation. Whether this response is acquired as a result of consistent training is difficult to determine, but would be a valid and worthwhile longitudinal study. The addition of mechanical flow limitation during more intense exercise only compounds the problem of ventilation at an exorbitantly high metabolic cost.

6.2.2 End-capillary O_2 diffusion limitation

This thesis has demonstrated that during moderate and heavy exercise, subjects with EIH have a significantly larger observed minus predicted A-aDO_2 (see Section 4.3.1.3), and significantly lower $DLO_2/\dot{Q}$ (see Section 4.3.1.6) compared with a group of control subjects matched for age, $\dot{V}O_{2peak}$ and pulmonary function. These results provide direct evidence in support of end-capillary O_2 diffusion limitation as a primary mechanism responsible for EIH in trained athletes, and are in agreement with the hypotheses of a number of previous investigators (Dempsey, Hanson, et al. 1984; Hopkins & McKenzie 1993; Powers, Martin, et al. 1992; Powers, Martin, et al. 1993). In fact, an end-capillary O_2

diffusion limitation, in this case estimated by DLO_2, accounted for over 30% of the variance in PaO_2 during heavy exercise. The reason for the greater degree of an end-capillary O_2 diffusion limitation in subjects with EIH remains undetermined. Possible mechanism include; is low grade pulmonary edema (Hopkins, Gavin, et al. 1998; Podolsky, Eldridge, et al. 1996; Schaffartzik, Poole, et al. 1992; Schaffartzik, Arcos, et al. 1993) due to excessively high pulmonary artery pressures (Bevegard, Holmgren, et al. 1963; Groves, Reeves, et al. 1987; Wagner, Dantzker, et al. 1977; Wagner, Gale, et al. 1986; Wagner, Sutton, et al. 1987), or a reduction in the rate of transcapillary fluid flux (Wagner, Gale, et al. 1986), although indirect evidence from this thesis (see Section 4.4.7) does not support this hypothesis. In addition, cardiac output and $P\bar{v}O_2$ values were similar between the subjects with EIH and those without, suggesting that a slower rate of O_2 equilibration between the alveoli and pulmonary capillary blood was not responsible for the differences in end-capillary O_2 diffusion limitation between the two groups (Dempsey 1987; Wagner 1982). Therefore, it is hypothesised that the subjects with EIH had critically low pulmonary capillary transit times as a result of lower capillary blood volumes in at least a portion of the lung, as suggested by Dempsey et al. (1984).

6.2.3 Ventilation-perfusion inequality

Previous studies have demonstrated significant ventilation-perfusion inequality during exercise of varying intensity (Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, McKenzie, et al. 1994; Hopkins, Gavin, et al. 1998; Schaffartzik, Poole, et al. 1992; Torre-Bueno, Wagner, et al. 1985) which was attributed to the development of interstitial pulmonary edema (Hammond, Gale, et al. 1986a; Hammond, Gale, et al. 1986b; Hopkins, Gavin, et al. 1998; Schaffartzik, Poole, et al. 1992). In the present thesis, ventilation-perfusion inequality while breathing air was normal at rest and accounted for the entire observed A-aDO_2 at 30% $\dot{V}O_{2peak}$ [light exercise (see Figure 4.1)]. In addition, log $SD_{\dot{Q}}$ accounted for 17% of the variance in PaO_2 at 90% $\dot{V}O_{2peak}$ [heavy exercise (see Section 4.3.2.1)]. However, in contrast to previous reports (Hammond, Gale, et al. 1986a; Hopkins, McKenzie, et al. 1994) no significant increase in ventilation-perfusion inequality during exercise (see Section 4.3.1.2) was found. In addition, there was no evidence post exercise to suggest the presence of interstitial pulmonary edema (see Section 4.4.7). The reasons for the lack of increase in ventilation-perfusion inequality described in this thesis remain unclear, but may be a consequence of the subjects possessing pulmonary function well above the predicted values for their age and height, as this has been demonstrated to be an important determinant in the efficiency of gas exchange during exercise (Hopkins, Gavin, et al. 1998). In addition, this finding indicates the subjects general resistance to the development of additional ventilation-perfusion inequality during exercise. The latter hypothesis is supported by the

observation that acute normobaric hypoxia did not worsen ventilation-perfusion relationships, as has been demonstrated previously (Hammond, Gale, et al. 1986b; Torre-Bueno, Wagner, et al. 1985).

6.3 SUMMARY OF PRINCIPAL FINDINGS

The aim of the experiments in the present thesis was to examine several of the proposed mechanisms of exercise-induced hypoxemia in a group of trained endurance athletes. A number of novel and important observations have been made leading to the conclusion that a different approach will be required in future research if the full etiology of this unusual phenomenon is to be resolved. The following summarises the significant observations reported in the substance of this thesis:

1. In contrast to previous studies which have reported EIH as a phenomenon associated with exercise of near-maximal intensity, the present study, undertaken during incremental exercise from ~40% $\dot{V}O_{2peak}$ to exhaustion, demonstrates that significant arterial hypoxemia is present at the beginning of the exercise protocol and is maximal by ~50% $\dot{V}O_{2peak}$. This information is vital in terms of exploring mechanisms as it suggests that any further studies of EIH should focus on exercise throughout the entire intensity spectrum rather than just near-maximal exercise. It is likely that the relative contribution from each of the proposed mechanisms change with intensity (Dempsey, Hanson, et al. 1984).

2. The conclusions in the above experiments were based on changes in arterial O_2 tension as the index of arterial hypoxemia. When direct measures and pulse oximetry estimation of oxyhemoglobin saturation were used simultaneously to identify exercise-induced hypoxemia, no significant change was detected until the work load approached near-maximal intensity. Furthermore, pulse oximetry consistently over-estimated directly-measured SaO_2 by 1-2%. Given that several previous studies investigating EIH have utilised SaO_2 as the criterion variable, and others have employed pulse oximeters to estimate SaO_2 (Harms & Stager 1995; Powers, Dodd, et al. 1984; Powers, Dodd, et al. 1988; Powers, Lawler, et al. 1989; Williams, Powers, et al. 1986) the significance of the findings reported in this thesis is clear. In any future study investigating the mechanisms of EIH, particularly throughout the entire exercise intensity spectrum, direct measurements of arterial O_2 tension are the only valid physiological measure in diagnosing significant arterial hypoxemia. Furthermore, the observation that pulse oximeters attached to the ear provide unreliable estimations of arterial O_2 saturation during exercise has substantial implications in clinical studies where they are widely employed.

3. The degree of arterial hypoxemia measured during exercise of both ~40% and 100% $\dot{V}O_{2peak}$ was strongly associated with the level of alveolar oxygenation, supporting a critical role for inadequate hyperventilation in the development of exercise-induced hypoxemia. This is a new and significant finding as the majority of previous studies have focused only on the

influence of inadequate hyperventilation during near-maximal exercise (Harms & Stager 1995; Johnson, Saupe, et al. 1992; Miyachi & Shibayama 1992; Miyachi & Tabata 1992; Norton, Squires, et al. 1995; Powers, Martin, et al. 1992 106).

4. The present thesis is the first to utilise the multiple inert gas elimination technique to measure pulmonary gas exchange in athletes with documented EIH. The results from this investigation confirmed that athletes with EIH developed significantly more end-capillary O_2 diffusion limitation than matched control subjects at work loads eliciting ~60% and 90% $\dot{V}O_{2peak}$. This result provides a stimulus for further investigation into the mechanisms of end-capillary O_2 diffusion limitation in healthy trained athletes during exercise.

5. Some athletes in the present study were resistant to the development of ventilation-perfusion inequality even with the introduction of acute hypoxia. This is the first observation to provide support for the hypothesis that lung size and lung function are important determinants in the matching of ventilation and perfusion during exercise (Hopkins, Gavin, et al. 1998).

6. This thesis has provided one of the first measurements of arterial blood gases in trained endurance athletes during high intensity exercise, using two different exercise modes (running and cycling). The results demonstrate

that in the same athlete performing exercise of matched intensity, the degree of EIH is significantly greater during running than cycling and that this is a consequence of the higher level of ventilation adopted during cycling exercise. It is hypothesised that the higher level of ventilation during cycling of matched intensity is a consequence of the higher blood lactic acid levels.

6.4 RECOMMENDATIONS FOR FURTHER STUDY

The following recommendations are made for further research into the area of exercise-induced hypoxemia;

1. Measure hypoxic and hypercapnic ventilatory drives, circulating potassium and tidal volume flow limitation during exercise in a variety of endurance trained athletes to investigate further the mechanisms responsible for an inadequate hyperventilatory response.

2. Investigate pulmonary capillary transit times in a variety of trained endurance athletes across a number of exercise intensities and regress the results against simultaneously assessed arterial blood O_2 tension (directly measured with temperature correction).

3. Investigate why some subjects develop significant $\dot{V}_A/\dot{Q}$ inequality during exercise and others do not. In addition, it would be extremely worthwhile to broncho-alveolar lavage and perform chest X-rays on endurance trained athletes before and after intense exercise in an attempt to determine lung damage and provide more direct evidence of pulmonary edema.

4. Conduct similar studies to those outlined in this thesis in well trained female athletes to obtain more information about the gender differences in the development of EIH.

5. Measure arterial blood gases in a number of sporting disciplines such as rowing and swimming where breathing entrainment is intrinsic to the exercise mode.

6. Investigate the apparent link between diet and the release of histamine during exercise and EIH. Attention may be focused on the use of anti-histamines to mediate the degree of EIH.

7 APPENDICIES

7.1 EXPERIMENTAL PROTOCOL INFORMATION SHEET

Protocol Title

Ventilation-perfusion inequality contributes to exercise induced hypoxemia in highly trained cyclists.

Purpose of Study

To investigate the changes that occur in the lungs with exercise and their effect on the blood O_2 levels in highly-trained cyclists.

Potential Benefits

The benefits to you as a subject will be minimal, although your maximum aerobic fitness, maximum workload and maximum heart pumping capacity will be measured. These may provide useful information in your training programs. Most of the benefits of this study will be realised by state and national sporting institutions where the performances of elite endurance athletes are continually being improved. It is intended that the results from this study will provide more information regarding the limitations to performance in some elite endurance-trained individuals.

Foreseeable Risks, Side Effects and Discomforts

Plastic Tube Insertion

Participation in this study may involve additional risks and discomforts. These include:

1. Discomfort of local anaesthesia for insertion of needles into arteries and veins.
2. Very small risk of the tube in the artery in your hand temporarily producing insufficient blood supply to the hand. Should symptoms of this occur, the tube will be promptly removed to prevent injury. There is a remote risk of continuing problems of obstruction of the artery.
3. Very small risk of the tubes causing clotting of blood in the vein or artery.
4. Very small risk of infection in the skin at the site of insertion of the tubes.
5. Mild bruising surrounding the tube insertion site.

Reimbursement for Loss of Time and Inconvenience

You will be paid $300 for completion of this study. If you are unable to complete the study you will be paid an hourly rate of $15/hour to compensate you for the time you have spent completing the study.

Contact numbers if any concerns arise:

1. Mr Anthony Rice Hm 8271 6303 Wk 8222 3452

2.	Dr Raffaele Scicchitano	Wk 8222 5375
3.	Dr Christopher Gore	Wk 8235 2497
4.	Dr Garry Scroop	Wk 8303 5331
5.	Dr John Myburgh	Wk 8222 5649
6.	Dr Michael James (Research Ethics Committee)	Wk 8222 5355

** Dr James is only available to discuss general aspects of the project

Prior Medical History Information Sheet:

General Information

Mr/Mrs/Ms/Miss..... Date of Birth.....

Address..... Post Code.....

Phone No. (Home)..... (Work).....

Emergency Contact..... Phone No.....

Personal Health Information

The following questions seek information that is required prior to you undertaking any physiological assessment.

Please tick the appropriate box.	Yes	No	Not Sure
1. Has your doctor ever said you have had heart trouble?	[ ]	[ ]	[ ]
2. Have you ever had pains in your heart and/or chest?	[ ]	[ ]	[ ]
3. Has your doctor ever said you have had lung disease?	[ ]	[ ]	[ ]
4. Do you have asthma?	[ ]	[ ]	[ ]
5. Do you ever feel faint or have dizzy spells?	[ ]	[ ]	[ ]
6. Has your blood pressure ever been high?	[ ]	[ ]	[ ]
7. Have you ever had any bone or joint problems such as arthritis or past injuries that may be aggravated by intense exercise?	[ ]	[ ]	[ ]
8. Have you suffered from a stroke?	[ ]	[ ]	[ ]
9. Is there any other reason why you may be unable to complete any of the tests?	[ ]	[ ]	[ ]

Please give details.....

10. If you take any medications please list them and their purpose

.....

11. Are you allergic to any medications? [ ] [ ] [ ]

If known please list.....

12. Do you smoke or have you ever smoked [ ] [ ]

regularly

I declare that to the best of my knowledge the information given in this sheet is true and accurate.

Signature..... Date.....

Consent Form

Protocol: Ventilation-perfusion inequality contributes to exercise induced hypoxemia in highly trained cyclists.

Investigators:

(1) Mr Anthony Rice B.Ed, M.Ed

(2) Dr Christopher Gore B.Ed (Hons), Ph.D

(4) Assoc. Prof. Garry Scroop MBBS, MD, Ph.D

(5) Prof. Peter Wagner MD

6) Assis. Prof. Susan Hopkins MD, Ph.D

(7) Dr John Myburgh MBBCh, DA(SA), FANZCA,

(8) Dr Mary-Anne Chapman MBBS

(9) Assoc. Prof. Raffaele Scicchitano MBBS, Ph.D,

1. The nature and purpose of the project has been fully explained to me. I understand it, and agree to take part.

2. I understand that I may not directly benefit from taking part in the study.

3. I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.

4. I understand that I can withdraw from the study at any stage, and that this will not affect my medical care now, or in the future.

5. I understand the statement concerning payment to me for taking part in this study, which is contained in the Information Sheet.

6. I have had time to discuss taking part in this study with a family member or friend.

Name of subject: .....

Signed: .....

Dated: [ ][ ]/[ ][ ]/19[ ][ ]

I certify that I have explained the study to the subject and consider that he/she understands what is involved.

Signed:..... (Investigator)

7.2 FORTRAN PROGRAM TO CALCULATE P_{50} FROM MEASURED SATURATIONS AND BLOOD GASES

```
C     PROGRAM P50 - PDW - 26/NOV/83
C
C     PROGRAM TO CALCULATE P50 FROM MEASURED SATURATIONS & BLOOD GASES
C
      CHARACTER ID,IOK
      DIMENSION PO2(100),PCO2(100),PHE(100),SATM(100),SATC(100),
     1HB(100),HCRIT(100),TEMP(100),FIO2(100),SATMUS(100),ID(40),
     2IUSED(100),PO2V(100)
      COMMON/OXY1/HBX,HCRITX,TEMPX,DP50,PO2VIR
      WRITE(*,11)
   11 FORMAT(' SEND OUTPUT TO PRINTER (1) OR DISK (0) ?')
      READ(*,*)IPR
      IF(IPR.EQ.1) OPEN(3,FILE='PRN')
      IF(IPR.EQ.0) OPEN(3,FILE=' ',STATUS='NEW')
      WRITE(*,105)
  105 FORMAT(' ENTER NAME OF SUBJECT & DATE OF STUDY, 40A1',/,
     1' ****************************************'/)
      READ(*,110)(ID(I),I=1,40)
  110 FORMAT(40A1,/)
      WRITE(3,110)(ID(I),I=1,40)
  115 FORMAT(//)
      WRITE(*,10)
   10 FORMAT(' ENTER NUMBER OF BLOOD GAS SETS')
      READ(*,*)NSETS
   20 FORMAT(I5)
      WRITE(*,75)
   75 FORMAT(' ARE YOU RUNNING AN OLD FILE (0) OR CREATING A NEW (1)')
      READ(*,*)ION
      IF(ION.EQ.0) OPEN(6,FILE=' ',STATUS='OLD')
      IF(ION.EQ.1) OPEN(7,FILE=' ',STATUS='NEW')
   76 FORMAT(I1)
      WRITE(3,85)
   85 FORMAT(3X,'% INSP O2',4X,'PO2',6X,'PCO2',8X,'PH',4X,'MEAS SAT',
     16X,'HB',6X,'HCRIT',5X,'TEMP'/)
      IF(ION.EQ.0) GO TO 500
      WRITE(7,5)NSETS
    5 FORMAT(I5)
      DO 100 I=1,NSETS
      WRITE(*,45)I
   45 FORMAT(' FOR SET NUMBER:',I5,/)
   55 WRITE(*,31)
   31 FORMAT(' ENTER % INSP O2,PO2,PCO2,PH,SAT,HB,HCT%,TEMP',/)
      READ(*,*)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
     1TEMP(I)
   40 FORMAT(7F10.2,F9.2)
      WRITE(*,40)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
     1TEMP(I)
      WRITE(*,50)
   50 FORMAT(' OK (Y) OR NOT (N)')
      READ(*,65)IOK
   65 FORMAT(A1)
      IF(IOK.EQ.'N') GO TO 55
      WRITE(3,40)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
     1TEMP(I)
      WRITE(7,40)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
     1TEMP(I)
  100 CONTINUE
      GO TO 501
  500 CONTINUE
      READ(6,5)NSETS
      DO 101 I=1,NSETS
      READ(6,40)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
```

```
     1TEMP(I)
      WRITE(*,40)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
     1TEMP(I)
 101  WRITE(3,40)FIO2(I),PO2(I),PCO2(I),PHE(I),SATM(I),HB(I),HCRIT(I),
     1TEMP(I)
 501  CONTINUE
      WRITE(*,4567)
 4567 FORMAT(' ENTER LOWER BOUND ON P50, F10.1')
      READ(*,*)P50
 4568 FORMAT(F10.1)
      WRITE(*,4569)
 4569 FORMAT(' ENTER UPPER BOUND ON P50, F10.1')
      READ(*,*)UPRP50
C     P50=15.0
C     UPRP50=30.0
      RP50=(UPRP50-P50)*10.0+1.0
      NP50=RP50
      P50=P50-0.1
      SSQMIN=10000.0
      IFLAG=0
      WRITE(*,115)
      WRITE(3,115)
      WRITE(*,120)
      WRITE(3,120)
 120  FORMAT(3X,'TRIAL P50',7X,'SUM OF SQUARES'/)
      DO 200 K=1,NP50
      P50=P50+0.1
      DP50=P50-26.8
      SSQ=0.0
      DO 300 I=1,NSETS
      IF(SATM(I).LT.20.0.OR.SATM(I).GT.85.0) GO TO 300
      HBX=HB(I)
      HCRITX=HCRIT(I)
      TEMPX=TEMP(I)
      SATC(I)=SATURA(PO2(I),PCO2(I),PHE(I))
      SUMDIF=SATM(I)-SATC(I)
      SSQ=SSQ+SUMDIF**2
 300  CONTINUE
      WRITE(3,60)P50,SSQ
      WRITE(*,60)P50,SSQ
  60  FORMAT(F10.1,F20.4)
      IF(SSQ.GT.SSQMIN) IFLAG=IFLAG+1
      IF(SSQ.LT.SSQMIN) RP50=P50
      IF(SSQ.LT.SSQMIN) SSQMIN=SSQ
C      IF(IFLAG.GE.10) GO TO 201
 200  CONTINUE
 201  CONTINUE
      DP50=RP50-26.8
      WRITE(3,197)SSQMIN,RP50
 197  FORMAT(/,' MIN SSQ IS',F8.2,'  AT A P50 OF',F6.1,'  TORR,GIVING:'
     1,//,'  SET #',3X,'VIRT PO2',4X,'MEAS SAT',3X,
     1'KELMAN SAT',5X,'DIFF',5X,'LN PO2',3X,'LN(S/(1-S))')
      DO 198 I=1,NSETS
C      IF(SATM(I).LT.20.0.OR.SATM(I).GT.85.0) GO TO 198
      HBX=HB(I)
      HCRITX=HCRIT(I)
      TEMPX=TEMP(I)
      SATC(I)=SATURA(PO2(I),PCO2(I),PHE(I))
      PO2V(I)=PO2VIR
      DIFSAT=SATM(I)-SATC(I)
      AL=ALOG(PO2V(I))
      AS=ALOG(SATM(I)/(100.0-SATM(I)))
      WRITE(3,199)I,PO2V(I),SATM(I),SATC(I),DIFSAT,AL,AS
 198  CONTINUE
 199  FORMAT(I5,3F12.2,F11.2,F10.2,F12.2)
      WRITE(*,115)
      WRITE(3,115)
      NUSED=0
      DO 400 I=1,NSETS
      IF(SATM(I).LT.20.0.OR.SATM(I).GT.85.0) GO TO 400
      NUSED=NUSED+1
      IUSED(NUSED)=I
      HBX=HB(I)
      HCRITX=HCRIT(I)
```

```
      TEMPX=TEMP(I)
      SATC(NUSED)=SATURA(PO2(I),PCO2(I),PHE(I))
      SATMUS(NUSED)=SATM(I)
400   CONTINUE
      CALL LINREG(1,NUSED,IUSED,SATMUS,SATC,SLOPE,RINTER)
      WRITE(3,115)
      CALL HILL(NSETS,PO2V,SATM,IUSED)
      END
      SUBROUTINE HILL(NSETS,PO2,SATM,IUSED)
      DIMENSION PO2(100),SATM(100),IUSED(100)
      DIMENSION X(100),Y(100)
      NP=0
      DO 100 I=1,NSETS
      IF(SATM(I).LT.20.0.OR.SATM(I).GT.85.0) GO TO 100
      NP=NP+1
      X(NP)=ALOG(PO2(I))
      Y(NP)=ALOG(0.01*SATM(I)/(1.0-0.01*SATM(I)))
 100  CONTINUE
      WRITE(3,135)
135   FORMAT(' LINEAR REGRESSION BETWEEN LOG PO2 & LOG(SAT/(1-SAT))'/)
      WRITE(3,136)
136   FORMAT(' HILL N IS THE SLOPE; P50 IS EXP(-INTERCEPT/SLOPE)'/)
      CALL LINREG(2,NP,IUSED,X,Y,SLOPE,RINTER)
      REXP=-RINTER/SLOPE
      P50=EXP(REXP)
      WRITE(3,30)SLOPE,P50
 30   FORMAT(//' HILL COEFFICIENT =',F6.1,'    P50 =',F6.1)
      RETURN
      END
      FUNCTION SATURA(PO2,PCO2,PHE)
      COMMON/OXY1/HB,HCRIT,TEMP,DP50,XX
      A1=-8532.229
      A2=2121.401
      A3=-67.07399
      A4=935960.9
      A5=-31346.26
      A6=2396.167
      A7=-67.10441
      B=0.43429*ALOG(40.0/PCO2)
      XX=PO2*10.0**(0.024*(37.0-TEMP)+0.4*(PHE-7.4)+0.06*B)
      X=26.8*XX/(26.8+DP50)
      IF(X-10.0) 1,2,2
 1    SAT=0.003683*X + 0.000584*X*X
      GO TO 3
 2    SAT=(X*(X*(X*(X+A3)+A2)+A1))/(X*(X*(X*(X+A7)+A6)+A5)+A4)
 3    SATURA=100.0*SAT
      RETURN
      END
      SUBROUTINE LINREG(IC,NP,IUSED,X,Y,SLOPE,RINTER)
      DIMENSION X(100),Y(100),IUSED(100)
      RNP=NP
      RN1=NP-1
      SUMX=0.0
      SUMY=0.0
      SUMXX=0.0
      SUMYY=0.0
      SUMXY=0.0
      NUSED=0
      DO 6 I=1,NP
      SUMX=SUMX + X(I)
      SUMY=SUMY + Y(I)
      SUMXX=SUMXX + X(I)*X(I)
      SUMYY=SUMYY + Y(I)*Y(I)
 6    SUMXY=SUMXY + X(I)*Y(I)
      XMEAN=SUMX/RNP
      YMEAN=SUMY/RNP
      XSD=SQRT((SUMXX-SUMX*SUMX/RNP)/RN1)
      IF(SUMY.EQ.0.0) GO TO 11
      YSD=SQRT((SUMYY-SUMY*SUMY/RNP)/RN1)
      RNUM=SUMXY-SUMX*SUMY/RNP
      RDENOM=SUMXX-SUMX*SUMX/RNP
      SLOPE=RNUM/RDENOM
      RINTER=YMEAN-SLOPE*XMEAN
      RD1=RDENOM
```

```
      RD2=SUMYY-SUMY*SUMY/RNP
      CORCOE=RNUM/SQRT(RD1*RD2)
   11 CONTINUE
      IF(IC.EQ.1)
     1WRITE(3,7)XMEAN,YMEAN,XSD,YSD,SLOPE,RINTER,CORCOE
    7  FORMAT('  MEAN VALUE OF MEASURED   SAT (X) =',F10.1,/,
     1'  MEAN VALUE OF CALCULATED SAT (Y) =',F10.1,/,
     1'  STANDARD DEVIATION OF MEASURED   SATURATIONS =',F10.1,/,
     1'  STANDARD DEVIATION OF CALCULATED SATURATIONS =',F10.1,/,
     1'  SLOPE OF LINEAR REGRESSION LINE =',F10.3,/,
     1'  Y INTERCEPT OF THIS LINE =',F10.3,/,
     1'  CORRELATION COEFFICIENT =',F10.3/)
      IF(IC.EQ.1) WRITE(3,10)
   10 FORMAT(6X,'#',6X,'SAMPLE',5X,'MEAS SAT (X)',3X,'CALC SAT (Y)',4X,
     1'BEST FIT Y',5X,'  DIFF'/)
      IF(IC.EQ.2)
     1WRITE(3,70)XMEAN,YMEAN,XSD,YSD,SLOPE,RINTER,CORCOE
   70 FORMAT('  MEAN VALUE OF      LOG PO2 (X)     =',F10.2,/,
     1'  MEAN VALUE OF LOG(SAT/(1-SAT)) (Y) =',F10.2,/,
     1'  STANDARD DEVIATION OF X =',F10.2,/,
     1'  STANDARD DEVIATION OF Y =',F10.2,/,
     1'  SLOPE OF LINEAR REGRESSION LINE =',F10.3,/,
     1'  Y INTERCEPT OF THIS LINE =',F10.3,/,
     1'  CORRELATION COEFFICIENT =',F10.3//)
      IF(IC.EQ.2) WRITE(3,80)
   80 FORMAT(1X,'#',6X,'SAMPLE',5X,'LOG PO2 (X)',3X,'LOG(SAT/(1-SAT))',
     1' (Y)',2X,'BEST FIT Y',3X,'  DIFF'/)
      DO 8 I=1,NP
      YCALC=RINTER + SLOPE*X(I)
      IF(IC.EQ.1) WRITE(3,9)I,IUSED(I),X(I),Y(I),YCALC,Y(I)-YCALC
      IF(IC.EQ.2) WRITE(3,90)I,IUSED(I),X(I),Y(I),YCALC,Y(I)-YCALC
    8 CONTINUE
    9 FORMAT(I7,I10,3F15.2,F14.2)
   90 FORMAT(I2,I10,2F15.2,7X,F13.2,F12.2)
      RETURN
      END.............
```

7.3 SHORT FORTRAN PROGRAM FOR DATA ENTRY OF STEADY-STATE MIGET MEASUREMENTS

```
      PROGRAM SHORT
C
C        This is a data entry program for the steady state multiple inert
C        gas elimination technique.  It creates a raw data file & a file
C        for VQDIST, the program which estimates ventilation and blood
C        flow distributions.  Entry of data is format-free.
C        Measured VO2 and VCO2 are entered as well.
C        Data files are named from the keyboard.
C
C        Updated by PDW  on DECEMBER 14, 1990
C
      CHARACTER IQ,IADDON,IOK,IFLAG,NAMRAW
      DIMENSION S(10),PC(10),PA(10),PE(10),PV(10),R(10),E(10)
      DIMENSION WT(10),ERRA(10),ERRE(10),ERRV(10),ERRPC(10),RMV(10)
      DIMENSION EMV(10),VARQT(10),QTCALC(10),PAC(10),PVC(10),PEC(10)
      DIMENSION NAMRAW(60),GA(10),GE(10),GV(10),PCC(10)
      DIMENSION HUMSLO(6),DOGSLO(6),HORSLO(6),PCFACT(6),PCBODY(6)
      DATA GA/10*1.0/,GE/10*1.0/,GV/10*1.0/
      DATA HUMSLO/2950.,1374.,2025.,3016.,4066.,805./
      DATA DOGSLO/2263.,2396.,2909.,4435.,3281.,1391./
      DATA HORSLO/1251.,2466.,3262.,2696.,3877.,2412./
      WRITE(*,1)
    1 FORMAT(' WRITE OUTPUT TO DISK (0) OR TO PRINTER (1) ?')
      READ(*,*)IOUT
      IF(IOUT.EQ.0) WRITE(*,2)
    2 FORMAT(' ENTER  DISK:NAME.EXT  OF OUTPUT DATA FILE'/)
      IF(IOUT.EQ.0) OPEN(3,FILE=' ',STATUS='NEW')
      IF(IOUT.EQ.1) OPEN(3,FILE='PRN')
      WRITE(*,3)
    3 FORMAT(' ARE DATA FOR MAN(1), DOG(2), OR HORSE(3) ?')
      READ(*,*)ISPEC
      WRITE(*,4)
    4 FORMAT(' WANT TO CORRECT FOR BODY/BATH TEMP DIFF ? 1=YES, 0=NO')
      READ(*,*)IBATH
      WRITE(*,1234)
 1234 FORMAT(' WANT TO CORRECT FOR EXPIRED ACETONE LOSS ? (YES=1/NO=0)')
      READ(*,*)IACET
      VO2=300.0
      VCO2=240.0
      TOL=99000.0
      TEMP=37.0
      PICO2=0.0
      Y1=30.0
      Y2=45.0
      X3=40.0
      X4=55.0
      SO2=0.003
      APCO2=30.0
      BPCO2=60.0
      LCASE=1
   10 WRITE(*,20)
   20 FORMAT(' THIS VERSION OF SHORT WILL WEIGHT EITHER RETENTIONS OR
     + EXCRETIONS',/,
     +' ENTER 0 FOR R (USUAL WAY) OR 1 FOR E, BUT NOT <CR>')
      READ(*,*) IRORE
C************
C     ASK WHETHER ARTERIAL OR PERIPHERAL VENOUS BLOOD IS TO BE USED
C************
      WRITE(*,25)
   25 FORMAT(' USING ARTERIAL (1) OR PERIPHERAL VENOUS (2) BLOOD ?'/)
      READ(*,*)IPAPV
      WRITE (*,30)
```

```
  30  FORMAT(' ARE DATA FROM HP (0) OR FROM BECKMAN (1) GC ?',/,
     1'  <CR> NOT ALLOWED')
      READ(*,*)IGC
      IF(IRORE.NE.0 .AND. IRORE.NE.1) GO TO 10
  40  FORMAT(' ENTER LABEL FOR DATA SET, UP TO 60 CHRS')
  50  FORMAT(60A1)
      WRITE (*,60)
  60  FORMAT(' ARE RAW DATA ALREADY ON FILE ? (Y/N)')
      READ (*,70) IQ
  70  FORMAT(A1)
      IF(IQ.EQ.'N') WRITE(*,40)
      IF(IQ.EQ.'N') READ(*,50)(NAMRAW(I),I=1,60)
      IF(IQ.NE.'Y') GO TO 130
      LCASE=3
      WRITE(*,80)
  80  FORMAT(' ENTER    DISK:FILE.EXT    FOR OLD RAW DATA FILE'/)
      OPEN(8,FILE=' ')
      READ(8,50)(NAMRAW(I),I=1,60)
      WRITE (*,90) (NAMRAW(I),I=1,60)
  90  FORMAT(' DO YOU WANT TO ADD ON TO FILE: ',/,60A1'?? (Y/N)')
      READ (*,70) IADDON
      READ(8,190) NRUNS,PBSEA,ELECT,TBATH,RER,SO2
C**************
C     IF(IADDON.NE.'Y') GO TO 150
      IF(IADDON.NE.'Y') GO TO 130
C**************
      LCASE=2
 100  WRITE (*,110) NRUNS
 110  FORMAT(I4' DATA SETS ARE ON FILE (IF INCORRECT EDIT # IN FILE|)'
     +/' ENTER # OF SETS TO ADD')
      READ (*,190) NADDON
      NTOT=NRUNS+NADDON
      WRITE (*,120) NRUNS,NADDON,NTOT
 120  FORMAT(I3' SETS IN OLD FILE +'I3' NEW SETS ='I3' TOTAL, OK?
     + (Y/N)')
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 100
 130  CONTINUE
      IF(LCASE.EQ.3) NTOT=NRUNS
      WRITE(*,140)
 140  FORMAT(' ENTER     DISK:FILE.EXT     FOR NEW RAW DATA FILE'/)
      OPEN(7,FILE=' ',STATUS='NEW')
      WRITE(7,50)(NAMRAW(I),I=1,60)
 150  CONTINUE
      WRITE(*,160)
 160  FORMAT(' ENTER     DISK:FILE.EXT     FOR VQDIST INPUT FILE'/)
      OPEN(9,FILE=' ',STATUS='NEW')
      WRITE(3,170)(NAMRAW(I),I=1,60)
 170  FORMAT(' LABEL FOR DATA SET  =  ',60A1/)
      WRITE(9,50)(NAMRAW(I),I=1,60)
      IF(IQ.EQ.'Y') GO TO 200
      WRITE (*,180)
 180  FORMAT(' ENTER # OF DATA SETS, PB SEA LEVEL,',/,
     1' BLOOD GAS ELECTRODE TEMP, & INERT GAS BATH TEMP ',/,
     2' FRACTIONAL CV OF GASES OTHER THAN SF6',/,
     3' AND O2 SOLUBILITY, ML/100 ML/TORR'/)
C
C     RER, THE (FRACTIONAL) MEASURED CV FOR GASES OTHER THAN SF6,
C     IS NORMALLY 0.03, AND IS TWICE THIS FOR SF6.
C     HOWEVER, YOU CAN ENTER ANY VALUE THAT YOU WISH
C
      READ(*,*)NRUNS,PBSEA,ELECT,TBATH,RER,SO2
      WRITE(7,190) NRUNS,PBSEA,ELECT,TBATH,RER,SO2
 190  FORMAT(I4,F7.1,2F6.1,F8.2,F8.4)
C************
C 200  IF(LCASE.EQ.2) GO TO 220
 200  IF(LCASE.EQ.2.OR.LCASE.EQ.3) GO TO 220
C************
      WRITE(9,190)NRUNS,PBSEA,ELECT,TBATH,RER,SO2
      WRITE(3,210)NRUNS,PBSEA,ELECT,TBATH,RER,SO2
 210  FORMAT(' NUMBER OF RUNS =',I5,';    SEA LEVEL PB =',F7.1,/,
     1' ELECTRODE TEMP =',F5.1,';   H2O BATH TEMP =',F7.1,/,
     2' FRACTIONAL MEASUREMENT CV (EXCEPT SF6) =',F8.2,/,
     3' AND O2 SOLUBILITY, ML/100 ML/Torr      = ',F9.4/)
```

```
      GO TO 230
 220  WRITE(7,190)NTOT,PBSEA,ELECT,TBATH,RER,SO2
      WRITE(9,190)NTOT,PBSEA,ELECT,TBATH,RER,SO2
      WRITE(3,210)NTOT,PBSEA,ELECT,TBATH,RER,SO2
 230  IF(LCASE.EQ.1) GO TO 270
      READ(8,240) NGASES,NVAQS,ZZ,VQLO,VQHI
      READ(8,250) (PC(I),I=1,NGASES)
 240  FORMAT(2I4,1X,F5.1,2X,F5.3,2X,F5.1)
 250  FORMAT(1X,6(1PE12.3))
 260  FORMAT(1X,1PE12.3,5(1PE12.3))
C*************
      IF(LCASE-2) 310,310,310
C      IF(LCASE-2) 310,310,320
C*************
 270  WRITE (*,280)
 280  FORMAT(' ENTER NGASES,NVAQS,Z,VQLO & VQHI')
      READ (*,*) NGASES,NVAQS,ZZ,VQLO,VQHI
      WRITE (*,240) NGASES,NVAQS,ZZ,VQLO,VQHI
      WRITE (*,290) NGASES
 290  FORMAT(' ENTER',I3,'   PARTITION COEFFICIENTS, BATH TEMP')
      READ (*,*) (PC(I),I=1,NGASES)
      WRITE (*,250) (PC(I),I=1,NGASES)
      WRITE (*,300)
 300  FORMAT(' OK OR NOT ? (Y/N)')
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 270
 310  WRITE(7,240) NGASES,NVAQS,ZZ,VQLO,VQHI
      WRITE(7,250) (PC(I),I=1,NGASES)
 320  WRITE(3,330)NGASES,NVAQS,ZZ,VQLO,VQHI
 330  FORMAT(' # OF GASES=',I2,';   # OF COMPTS=',I3,';   Z=',F7.2,
     1';  VQLO=',F6.3,';  VQHI=',F6.1)
      WRITE(3,340)(PC(I),I=1,NGASES)
 340  FORMAT(' PARTITION COEFFICIENTS, BATH TEMP =',
     1F7.5,2F7.3,F6.2,F6.1,F8.1)
      WRITE(3,350)
 350  FORMAT(80('-'))
      INDEX=0
      LOGAS=1
      IF(PC(1).LT.0.01) LOGAS=2
      L1=1
      IAGAIN=0
 360  DO 1350 LM=L1,NRUNS
 370  CONTINUE
      DO 380 I=1,NGASES
      E(I)=0.0
      R(I)=0.0
      EMV(I)=0.0
      RMV(I)=0.0
      WT(I)=0.0
      QTCALC(I)=0.0
 380  CONTINUE
      INDEX=INDEX+1
C************
C       IF(IQ.EQ.'Y') GO TO 610
      IF(IQ.EQ.'Y'.AND.IAGAIN.EQ.0) GO TO 610
C************
      IF(IAGAIN.EQ.1) GO TO 420
 390  IF(IPAPV.EQ.1) WRITE (*,400) LM
 400  FORMAT(//9X'SET #'I3//3X'ENTER ARTERIAL PEAKS (in mm)')
      IF(IPAPV.EQ.2) WRITE (*,401) LM
 401  FORMAT(//9X'SET #'I3//3X'ENTER PERIPHERAL VENOUS PEAKS (in mm)')
      READ (*,*) (PA(I),I=1,NGASES)
      IF(IGC.EQ.1.AND.IPAPV.EQ.1) WRITE (*,410) NGASES
 410  FORMAT(' ENTER',I3'  ARTERIAL SF6 DILUTION/FID GAINS (decimal)')
      IF(IGC.EQ.1.AND.IPAPV.EQ.2) WRITE (*,411) NGASES
 411  FORMAT(' ENTER',I3'  PERIPHERAL VENOUS SF6 DILUTION/FID GAINS')
      IF(IGC.EQ.1) READ (*,*) (GA(I),I=1,NGASES)
 420  WRITE (*,1200)(PA(I),I=1,NGASES)
      WRITE (*,1210)(GA(I),I=1,NGASES)
      WRITE (*,300)
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 390
      IF(IAGAIN.EQ.1) GO TO 460
 430  WRITE (*,440)
```

```
 440  FORMAT(3X,'ENTER EXPIRED PEAKS (decimal in mm)')
      READ (*,*) (PE(I),I=1,NGASES)
      IF(IGC.EQ.1) WRITE (*,450) NGASES
 450  FORMAT(' ENTER',I3'  EXPIRED SF6 DILUTION/FID GAINS (decimal)')
      IF(IGC.EQ.1) READ(*,*)(GE(I),I=1,NGASES)
 460  WRITE (*,1200)(PE(I),I=1,NGASES)
      WRITE (*,1210)(GE(I),I=1,NGASES)
      WRITE (*,300)
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 430
      IF(IAGAIN.EQ.1) GO TO 500
 470  WRITE (*,480)
 480  FORMAT(3X,'ENTER VENOUS PEAKS (decimal in mm)')
      READ(*,*)(PV(I),I=1,NGASES)
      IF(IGC.EQ.1) WRITE (*,490) NGASES
 490  FORMAT(' ENTER',I3'  VENOUS SF6 DILUTION/FID GAINS (decimal)')
      IF(IGC.EQ.1) READ(*,*)(GV(I),I=1,NGASES)
 500  WRITE (*,1200) (PV(I),I=1,NGASES)
      WRITE (*,1210) (GV(I),I=1,NGASES)
      WRITE (*,300)
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 470
      IF(IAGAIN.EQ.1) GO TO 530
 510  WRITE (*,520)
 520  FORMAT(' ENTER VE,QT,PB,TEMPB,TEMPR,VGA,VBA,VHA,VGV,VBV,VHV
     1 (FREE FORMAT)')
      READ(*,*)VE,QT,PB,TEMPB,TEMPR,VGA,VBA,VHA,VGV,VBV,VHV
 530  WRITE (*,535) VE,QT,PB,TEMPB,TEMPR,VGA,VBA,VHA,VGV,VBV,VHV
 535  FORMAT(F9.2,F6.2,2X,F5.1,2F6.1,6F7.2)
      WRITE (*,300)
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 510
      VEO=VE
      IF(IAGAIN.EQ.1) GO TO 600
 540  IF(PV(1).EQ.0.0) GO TO 560
      WRITE (*,550)
 550  FORMAT(' ENTER HB,HCRIT,PVO2,PVCO2,PHV,FIO2,FICO2,P50,PMAO2,PMACO2
     1,PHA,VO2 & VCO2',/,' FREE FORMAT')
      GO TO 590
 560  CONTINUE
      WRITE (*,570)
 570  FORMAT(' ENTER HB,HCRIT,VO2,VCO2,TOL,FIO2,FICO2,P50,PMAO2,PMACO2,
     1PHA, FREE FORMAT')
      WRITE (*,580)
 580  FORMAT(' TOL=20.0 will iterate mixed venous gases to match
     + VO2 & VCO2'/' TOL=99000. will use Fick calculated mixed
     + venous tensions'//)
 590  CONTINUE
      READ(*,*)HB,HCRIT,PVO2,PVCO2,PHV,FIO2,FICO2,P50,PMAO2,PMACO2,PHA,
     1VO2DUM,VCO2DM
 600  WRITE (*,1230)HB,HCRIT,PVO2,PVCO2,PHV,FIO2,FICO2,P50,PMAO2,PMACO2,
     1PHA,VO2DUM,VCO2DM
      WRITE (*,300)
      READ (*,70) IOK
      IF(IOK.EQ.'N') GO TO 540
      GO TO 620
 610  CONTINUE
      READ(8,1200) (PA(I),I=1,NGASES)
      READ(8,1210) (GA(I),I=1,NGASES)
      READ(8,1200) (PE(I),I=1,NGASES)
      READ(8,1210) (GE(I),I=1,NGASES)
      READ(8,1200) (PV(I),I=1,NGASES)
      READ(8,1210) (GV(I),I=1,NGASES)
      READ(8,1220) VEO,QT,PB,TEMPB,TEMPR,VGA,VBA,VHA,VGV,VBV,VHV
      READ(8,1230)HB,HCRIT,PVO2,PVCO2,PHV,FIO2,FICO2,P50,PMAO2,PMACO2,
     1PHA,VO2DUM,VCO2DM
 620  CONTINUE
C
C     ABILITY TO COPE WITH 1 FEWER GAS ON ANY RUN
C
      NGSS=NGASES
      IGAS=0
      DO 630 I=1,NGASES
      PCC(I)=PC(I)
```

```
      IF(PA(I).GT.0.0) GO TO 630
      IF(PE(I).GT.0.0) GO TO 630
      IF(PV(I).GT.0.0) GO TO 630
      IGAS=I
 630  CONTINUE
      IF(IGAS.GT.0) NGSS=NGASES-1
      DP50=P50-26.8
      REXP=9.0578-2290.5/(273.15+TEMPR)
      BEXP=9.0578-2290.5/(273.15+TEMPB)
      CEXP=9.0578-2290.5/(273.15+TBATH)
      SVPB=10.0**BEXP
      SVPBTH=10.0**CEXP
      IF(TEMPR.LT.TEMPB) SVPR=10.0**REXP
      IF(TEMPR.GE.TEMPB) SVPR=SVPB
      EXPFAC=(PB-SVPB)/(PBSEA-SVPB)
      PIO2=(PB-SVPB)*FIO2
      PICO2=(PB-SVPB)*FICO2
      X5=PB-SVPB-PIO2
      TEMP=TEMPB
      VC=0.01*HCRIT
      TBODY=TEMPB-(ELECT-37.0)
      IF(PHV.GT.6.5.AND.PHV.LT.8.0) CALL TEMPCR(PHV,PVCO2,PVO2,VC,
     &TBODY,PHVBT,PVCOBT,PVO2BT,BX)
      IF(PHA.GT.6.5.AND.PHA.LT.8.0) CALL TEMPCR(PHA,PMACO2,PMAO2,VC,
     &TBODY,PHABT,PACOBT,PAO2BT,BX)
      FACT=(PBSEA-SVPB)/100.0
      WRITE (*,640) INDEX
 640  FORMAT(30X,'  RUN NUMBER  ',I3,/)
      IF(TEMPB.GT.TEMPR) CORR=(273.0+TEMPB)*(PB-SVPR)/
     & ((273.0+TEMPR)*(PB-SVPB))
      IF(TBATH.GT.TEMPR) COR1=(273.0+TBATH)*(PB-SVPR)/
     & ((273.0+TEMPR)*(PB-SVPBTH))
      IF(TEMPB.LE.TEMPR) CORR=(273.0+TEMPB)/(273.0+TEMPR)
      IF(TBATH.LE.TEMPR) COR1=(273.0+TBATH)/(273.0+TEMPR)
      VE=VEO*CORR
C***********
      VESTAR=VEO*COR1
C***********
      IF(PA(1).GT.0.0.AND.IPAPV.EQ.1)
     1ERRA(1)=(2.0*RER)*(2.0*RER) + 0.212*0.212/(PA(1)*PA(1))
      IF(PA(1).GT.0.0.AND.IPAPV.EQ.2)
     1ERRA(1)=(4.0*RER)*(4.0*RER) + 0.212*0.212/(PA(1)*PA(1))
      IF(PE(1).GT.0.0) ERRE(1)=(2.0*RER)*(2.0*RER) +
     10.212*0.212/(PE(1)*PE(1))
      IF(PV(1).GT.0.0) ERRV(1)=(2.0*RER)*(2.0*RER) +
     10.212*0.212/(PV(1)*PV(1))
      ERRPC(1) = (4.0*RER)*(4.0*RER)/2.0
      DO 650 I=LOGAS,NGASES
      IF(IGAS.EQ.I) GO TO 650
      IF(PA(I).GT.0.0.AND.IPAPV.EQ.1)
     1ERRA(I)=RER*RER + 0.212*0.212/(PA(I)*PA(I))
      IF(PA(I).GT.0.0.AND.IPAPV.EQ.2)
     1ERRA(I)=(2.0*RER)*(2.0*RER) + 0.212*0.212/(PA(I)*PA(I))
      IF(PE(I).GT.0.0) ERRE(I)=RER*RER + 0.212*0.212/(PE(I)*PE(I))
      IF(PV(I).GT.0.0) ERRV(I)=RER*RER + 0.212*0.212/(PV(I)*PV(I))
C
C      PA(I) ETC MUST BE IN MM OF CHART PAPER, NOT INCHES|||||
C      AND MUST BE PRIOR TO ANY GAIN OR DILUTION MULTIPLICATION
C
      ERRPC(I) = (2.0*RER)*(2.0*RER)/2.0
 650  CONTINUE
      DO 670 I=1,NGASES
C
C     CORRECTIONS WHEN BODY AND INERT GAS BATH TEMP ARE DIFFERENT
C
      IF(IBATH.EQ.0) PCFACT(I)=1.0
      IF(IBATH.EQ.0) PCBODY(I)=PC(I)
      IF(IBATH.EQ.0) GO TO 659
      TT1=1.0/(TEMPB+273.0)
      TT2=1.0/(TBATH+273.0)
      IF(ISPEC.EQ.1) SLP=HUMSLO(I)
      IF(ISPEC.EQ.2) SLP=DOGSLO(I)
      IF(ISPEC.EQ.3) SLP=HORSLO(I)
      PCFACT(I)=EXP(SLP*(TT1-TT2))
```

```
      PCBODY(I)=PC(I)*PCFACT(I)
  659 CONTINUE
      S(I)=PCBODY(I)/FACT
      PEC(I)=GE(I)*PE(I)*EXPFAC
      IF(PA(I).EQ.0.0) GO TO 660
      IF(IPAPV.EQ.1) PAPV=1.0
      IF(IPAPV.EQ.2) PAPV=0.95
      PAC(I) = GA(I)*PA(I)*(1.0 + VHA/VBA + VGA/(VBA*PC(I)))/
     1(PCFACT(I)*PAPV)
  660 IF(PV(I).GT.0.0)
     1PVC(I) = GV(I)*PV(I)*(1.0 + VHV/VBV + VGV/(VBV*PC(I)))/PCFACT(I)
C
C     CORRECT FOR EXPIRED ACETONE LOSS BASED ON ETHER EXP/ART RATIO:
C     ACETONE "BOHR" VDVT MUST BE NO GREATER THAN THAT OF ETHER, THUS:
C
C     (Pa-PE)/Pa (acetone)  =  (Pa-PE)/Pa (ether)
C
C     OR
C
C      PE (acetone)  =  Pa (acetone) * PE (ether) / Pa (ether)
C
C     HENCE, REPLACE MEASURED PE (acetone) BY THE ABOVE IF THE ABOVE
C     IS THE LARGER NUMBER
C
      IF(IACET.EQ.0) GO TO 670
      IF(I.LT.NGASES) GO TO 670
      IF(PAC(NGASES-1).EQ.0.0.OR.PAC(NGASES).EQ.0.0) GO TO 670
      IF(PEC(NGASES-1).EQ.0.0.OR.PEC(NGASES).EQ.0.0) GO TO 670
      ETHER=PEC(NGASES-1)/PAC(NGASES-1)
  669 FORMAT(/' CORRECTING FOR EXPIRED ACETONE LOSS BY ',F7.3,/)
      IF(PV(NGASES).GT.0.0) ACEXP=0.5*ETHER*(PAC(NGASES)+PVC(NGASES))
      IF(PV(NGASES).EQ.0.0) ACEXP=    ETHER*PAC(NGASES)
      IF(PEC(NGASES).GE.ACEXP) GO TO 670
      ACEFAC= ACEXP/PEC(NGASES)
      WRITE(*,669)ACEFAC
      WRITE(3,669)ACEFAC
      PEC(NGASES)=ACEXP
  670 CONTINUE
      IF(PA(1).EQ.0.0) GO TO 690
      IF(PE(1).EQ.0.0) GO TO 710
      IF(PV(1).EQ.0.0) GO TO 730
      WRITE (*,680)
  680 FORMAT(/' PA, PE, AND PV ALL MEASURED IN THIS SET'/)
      GO TO 750
  690 WRITE (*,700)
  700 FORMAT(/' ONLY PE AND PV HAVE BEEN MEASURED - PA IS DERIVED'/)
      GO TO 750
  710 WRITE (*,720)
  720 FORMAT(/' ONLY PA AND PV HAVE BEEN MEASURED - PE IS DERIVED'/)
      GO TO 750
  730 IF(IPAPV.EQ.1) WRITE(*,740)
  740 FORMAT(/' ONLY PA AND PE HAVE BEEN MEASURED - PV IS DERIVED'/)
      IF(IPAPV.EQ.2) WRITE(*,741)
  741 FORMAT(/' PERIPHERAL VENOUS AND PE ARE MEASURED - PV IS DERIVED'/
     1' ARTERIAL = PERIPHERAL VENOUS/0.95, AND COEFF VAR ARE DOUBLED'/)
  750 CONTINUE
      IF(NGASES.EQ.6) WRITE (*,760)
  760 FORMAT(19X,'SF6',6X,'ETHANE',5X,'CYCLO',4X,'ENFLURANE',4X,
     1'ETHER',5X,'ACETONE')
      WRITE (*,770) (S(I),I=1,NGASES)
      WRITE (*,780) (PC(I),I=1,NGASES)
      WRITE (*,781) (PCBODY(I),I=1,NGASES)
  770 FORMAT(' SOLUBILITY ', 8F11.5)
  780 FORMAT(' PC, BATH T ', 8F11.5)
  781 FORMAT(' PC, BODY T ', 8F11.5)
      IF(PA(1).EQ.0.0) GO TO 940
      IF(PE(1).EQ.0.0) GO TO 980
      IF(PV(1).EQ.0.0) GO TO 1010
      VO2=VO2DUM
      VCO2=VCO2DM
      SUMTOP=0.0
      SUMBOT=0.0
      DO 790, I=1,NGASES
      IF(I.EQ.IGAS) GO TO 790
```

```
      R(I) = PAC(I)/PVC(I)
      E(I) = PEC(I)/PVC(I)
      QTCALC(I) = VESTAR*E(I)/(PC(I)*(1.0-R(I)))
      V = ERRE(I) + ERRPC(I) + ERRV(I)/((1.0-R(I))**2) +
     1ERRA(I)*R(I)*R(I)/((1.0-R(I))**2)
      VARQT(I) = QTCALC(I)*QTCALC(I)*V
      IF(QTCALC(I).LE.0.0) VARQT(I)=10.0**6
      IF (PC(I).GT.50.0) VARQT(I)=10.0**6
      SUMTOP=SUMTOP+QTCALC(I)/VARQT(I)
      SUMBOT=SUMBOT+1.0/VARQT(I)
  790 CONTINUE
      QT=SUMTOP/SUMBOT
      DO 810, I=1,NGASES
      IF(I.EQ.IGAS) GO TO 810
      IF(IRORE.NE.0) GO TO 800
      X=R(I)*R(I)*(ERRA(I)+ERRV(I))
      Y=((VE*E(I)/(QT*PCBODY(I)))**2)*(ERRE(I) + ERRPC(I) + ERRV(I))
      Z=VE*E(I)*R(I)*ERRV(I)/(QT*PCBODY(I))
      TOPT=(Y+Z)/(X + Y + 2.0*Z)
      RMV(I)=TOPT*R(I) + (1.0-TOPT)*(1.0-VE*E(I)/(QT*PCBODY(I)))
      EMV(I)=QT*PCBODY(I)*(1.0-RMV(I))/VE
      VRCE=Y - 2.0*TOPT*(Y+Z) + TOPT*TOPT*(X+Y+2.0*Z)
      WT(I) = 1.0/SQRT(VRCE)
      GO TO 810
  800 AA=QT*PCBODY(I)/VE
      ASQ=AA*AA
      RSQ=R(I)*R(I)
      ESQ=E(I)*E(I)
      BB=ESQ*ERRPC(I)+ASQ*RSQ*ERRA(I)
      CC=ASQ*ERRV(I)
      TNUM=BB+CC*R(I)
      DENOM=BB+ESQ*ERRE(I)+CC
      TOPT=TNUM/DENOM
      VRCE=TOPT*TOPT*DENOM-2.0*TOPT*TNUM+BB+CC*RSQ
      EMV(I)=TOPT*E(I)+(1.0-TOPT)*AA*(1.0-R(I))
      RMV(I)=1.0-EMV(I)/AA
      WT(I)=1.0/SQRT(VRCE)
  810 CONTINUE
      WRITE (*,819)(PCFACT(I),I=1,NGASES)
  819 FORMAT(' BODY/BATH PC',F10.5,7F11.5)
      IF(IRORE.NE.0) GO TO 870
      WRITE (*,820)(R(I),I=1,NGASES)
  820 FORMAT(' MEASURED R ',8F11.5)
      WRITE (*,830)(RMV(I),I=1,NGASES)
  830 FORMAT(' MIN VAR R  ',8F11.5)
      WRITE (*,840)(E(I),I=1,NGASES)
  840 FORMAT(' MEASURED E ',8F11.5)
      WRITE (*,850)(EMV(I),I=1,NGASES)
  850 FORMAT(' ASSOCIATED E ',F9.5,7F11.5)
C******************
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C******************
      WRITE (*,860)(WT(I),I=1,NGASES)
  860 FORMAT(' WEIGHTS (R)',8F11.1)
      GO TO 910
  870 WRITE (*,840) (E(I),I=1,NGASES)
      WRITE (*,880) (EMV(I),I=1,NGASES)
  880 FORMAT(' MIN VAR E  ',8F11.5)
      WRITE (*,820) (R(I),I=1,NGASES)
      WRITE (*,890) (RMV(I),I=1,NGASES)
  890 FORMAT(' ASSOCIATED R ',F9.5,7F11.5)
C**************
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C**************
      WRITE (*,900) (WT(I),I=1,NGASES)
  900 FORMAT(' WEIGHTS (E)',8F11.1)
  910 WRITE (*,920) (QTCALC(I),I=1,NGASES)
  920 FORMAT(' PREDICTED QT ',F9.2,7F11.2)
      WRITE (*,930) VE,QT
  930 FORMAT(/' MINUTE VENTILATION, BTPS ='F8.2,'   MEAN FICK CARDIAC
     1OUTPUT =',F7.2)
      GO TO 1050
```

```
 940  CONTINUE
      DO 960, I=1,NGASES
      IF(I.EQ.IGAS) GO TO 960
      PAC(I) = PVC(I) - VE*PEC(I)/(QT*PCBODY(I))
      R(I) = PAC(I)/PVC(I)
      RMV(I) = R(I)
      E(I) = PEC(I)/PVC(I)
      EMV(I) = E(I)
      IF(IRORE.NE.0) GO TO 950
      V = ERRE(I) + ERRV(I) + ERRPC(I)
      V = V*((VE*E(I)/(QT*PCBODY(I)))**2)
      WT(I) = SQRT(1.0/V)
      GO TO 960
 950  V=E(I)*E(I)*(ERRE(I)+ERRV(I))
      WT(I)=SQRT(1.0/V)
 960  CONTINUE
      WRITE (*,819) (PCFACT(I),I=1,NGASES)
      WRITE (*,820) (R(I),I=1,NGASES)
      WRITE (*,840) (E(I),I=1,NGASES)
C***************
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C***************
      IF(IRORE.EQ.0) WRITE (*,860) (WT(I),I=1,NGASES)
      IF(IRORE.NE.0) WRITE (*,900) (WT(I),I=1,NGASES)
      WRITE (*,970) VE,QT
 970  FORMAT(/' MEASURED MINUTE VENTILATION =',F9.2,
     1'   AND MEASURED CARDIAC OUTPUT =',F8.2)
      GO TO 1050
 980  CONTINUE
      DO 1000, I=1,NGASES
      IF(I.EQ.IGAS) GO TO 1000
      R(I) = PAC(I)/PVC(I)
      RMV(I) = R(I)
      PEC(I) = QT*PCBODY(I)*(PVC(I)-PAC(I))/VE
      E(I)=PEC(I)/PVC(I)
      EMV(I)=E(I)
      IF(IRORE.NE.0) GO TO 990
      V=R(I)*R(I)*(ERRA(I)+ERRV(I))
      WT(I) = SQRT(1.0/V)
      GO TO 1000
 990  ASQ=(QT*PCBODY(I)/VE)**2
      V=ASQ*(ERRPC(I)+R(I)*R(I)*(ERRA(I)+ERRV(I)+ERRPC(I)))
      WT(I)=SQRT(1.0/V)
1000  CONTINUE
      WRITE (*,819) (PCFACT(I),I=1,NGASES)
      WRITE (*,820) (R(I),I=1,NGASES)
      WRITE (*,840) (E(I),I=1,NGASES)
C******************
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C******************
      IF(IRORE.EQ.0) WRITE (*,860) (WT(I),I=1,NGASES)
      IF(IRORE.NE.0) WRITE (*,900) (WT(I),I=1,NGASES)
      WRITE (*,970) VE,QT
      GO TO 1050
1010  CONTINUE
      TOL=PHV
      VO2=PVO2
      VCO2=PVCO2
      IF(TOL.GT.50.0) GO TO 1020
      TOL=20.0
      PVO2=40.0
      PVCO2=45.0
1020  CONTINUE
      DO 1040 I=1,NGASES
      IF(I.EQ.IGAS) GO TO 1040
      PVC(I) = PAC(I)+ VE*PEC(I)/(QT*PCBODY(I))
      R(I)=PAC(I)/PVC(I)
      RMV(I)=R(I)
      E(I)=PEC(I)/PVC(I)
      EMV(I)=E(I)
      IF(IRORE.NE.0) GO TO 1030
      X=QT*PCBODY(I)*PAC(I)
```

```
      Y=VE*PEC(I)
      W = X*Y/((X+Y)**2)
      V=ERRA(I) + ERRE(I) + ERRPC(I)
      V = V*W*W
      WT(I) = SQRT(1.0/V)
      GO TO 1040
1030  ESQ=E(I)*E(I)
      RSQ=R(I)*R(I)
      V=ESQ*ERRPC(I)+ESQ*RSQ*(ERRA(I)+ERRPC(I)+ERRE(I))
      WT(I)=SQRT(1.0/V)
1040  CONTINUE
      WRITE (*,819) (PCFACT(I),I=1,NGASES)
      WRITE (*,820) (R(I),I=1,NGASES)
      WRITE (*,840) (E(I),I=1,NGASES)
C******************
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C******************
      IF(IRORE.EQ.0) WRITE (*,860) (WT(I),I=1,NGASES)
      IF(IRORE.NE.0) WRITE (*,900) (WT(I),I=1,NGASES)
      WRITE (*,970) VE,QT
1050  CONTINUE
C
C      NOW WRITE DATA TO DISK FOR THE LONG PROGRAM
C
C**************
C      IF(IQ.EQ.'Y') GO TO 1070
C**************
      WRITE (*,1060)
1060  FORMAT(' IS THIS SET OK OR NOT ? (Y/N)')
      READ (*,70) IFLAG
      IF(IFLAG.NE.'N') GO TO 1070
      INDEX=INDEX-1
      IAGAIN=1
      VE=VEO
      GO TO 370
1070  CONTINUE
      IAGAIN=0
      WRITE(3,640)INDEX
      WRITE(3,1075)
1075  FORMAT(22X,'GAS 1',5X,'GAS 2',5X,'GAS 3',5X,'GAS 4',5X,'GAS 5',
     15X,'GAS 6'/)
      WRITE(3,1080)(PA(I),I=1,NGASES)
1080  FORMAT(' ARTERIAL PEAKS  ',10F10.1)
      WRITE(3,1090)(GA(I),I=1,NGASES)
1090  FORMAT(' AND GAIN FACTORS',10F10.1)
      WRITE(3,1100)(PE(I),I=1,NGASES)
1100  FORMAT(' EXPIRED PEAKS   ',10F10.1)
      WRITE(3,1090)(GE(I),I=1,NGASES)
      WRITE(3,1110)(PV(I),I=1,NGASES)
1110  FORMAT(' VENOUS PEAKS    ',10F10.1)
      WRITE(3,1090)(GV(I),I=1,NGASES)
      WRITE(3,1119)(PCFACT(I),I=1,NGASES)
1119  FORMAT(' BODY/BATH PC  ',10F10.4)
      WRITE(3,1120)VE,QT,PB,SVPR,SVPB,TEMPB,TEMPR,VGA,VBA,VHA,VGV,VBV,
     1VHV
1120  FORMAT(
     1' VE  =',F7.2,'; QT   =',F7.2,'; PB   =',F5.1,/,
     2' SVPR=',F7.1,'; SVPB =',F7.1,'; TMPB =',F5.1,'; TMPR =',F6.1,';'/
     3' VGa =',F7.2,'; VBa  =',F7.2,'; VHa  =',F5.2,'; VGv  =',F6.2,
     4';  VBv =',F5.2,'; VHv=',F4.2)
      IF(PV(1).EQ.0.0) GO TO 1140
      WRITE(3,1130)HB,HCRIT,PVO2BT,PVCOBT,PHVBT,P50,PIO2,PICO2,PAO2BT,
     1PACOBT,PHABT,VO2,VCO2,VCO2/VO2
1130  FORMAT(
     1' HB  =',F7.1,'; HCT  =',F7.1,';',13X,' PvO2 =',F6.1,'; PvCO2=',
     2F5.1,'; PHv=',F4.2,/,
     3' P50 =',F7.1,'; PIO2 =',F7.1,'; PICO2=',F5.1,'; PaO2 =',F6.1,
     4'; PaCO2=',F5.1,'; PHa=',F4.2,/,
     5' VO2 =',F7.1,'; VCO2 =',F7.1,';   R  =',F5.2,';')
      GO TO 1160
1140  WRITE(3,1150)HB,HCRIT,PHV,P50,PIO2,PICO2,PAO2BT,PACOBT,PHABT,
     1PVO2,PVCO2,PVCO2/PVO2
1150  FORMAT(
```

```
     1' HB  =',F7.1,'; HCT  =',F6.1,'; TOLERANCE =',F7.1,/,
     2' P50 =',F7.1,'; PIO2 =',F6.1,'; PICO2 =',F6.1,'; PaO2 =',F6.1,
     3'; PaCO2=',F6.1,'; PHa =',F5.2,/,
     4' VO2 =',F7.1,'; VCO2 =',F6.1,';    R  =',F6.2)
1160  WRITE(3,1170)EXPFAC
1170  FORMAT(' HYPO/HYPERBARIC CORRECTION FACTOR FOR EXPIRED GAS'
     1' VALUES=',F6.3)
      IPF=0
      IF(PV(1).EQ.0.0 .OR.PA(1).EQ.0.0 .OR.PE(1).EQ.0.0) IPF=1
      IF(IPF.EQ.0) WRITE(3,680)
      IF(PV(1).EQ.0.0.AND.IPAPV.EQ.1) WRITE(3,740)
      IF(PV(1).EQ.0.0.AND.IPAPV.EQ.2) WRITE(3,741)
      IF(PA(1).EQ.0.0) WRITE(3,700)
      IF(PE(1).EQ.0.0) WRITE(3,720)
      WRITE(3,760)
      WRITE(3,770)(S(I),I=1,NGASES)
      WRITE(3,780)(PC(I),I=1,NGASES)
      WRITE(3,781)(PCBODY(I),I=1,NGASES)
      WRITE(3,819)(PCFACT(I),I=1,NGASES)
      IF(IRORE.NE.0) GO TO 1180
      WRITE(3,820)(R(I),I=1,NGASES)
      IF(IPF.EQ.0) WRITE(3,830)(RMV(I),I=1,NGASES)
      WRITE(3,840)(E(I),I=1,NGASES)
      IF(IPF.EQ.0) WRITE(3,850)(EMV(I),I=1,NGASES)
C*********
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C*********
      WRITE(3,860)(WT(I),I=1,NGASES)
      GO TO 1190
1180  WRITE(3,840)(E(I),I=1,NGASES)
      IF(IPF.EQ.0) WRITE(3,880)(EMV(I),I=1,NGASES)
      WRITE(3,820)(R(I),I=1,NGASES)
      IF(IPF.EQ.0) WRITE(3,890)(RMV(I),I=1,NGASES)
C*********
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C*********
      WRITE(3,900)(WT(I),I=1,NGASES)
1190  IF(IPF.EQ.0) WRITE(3,920)(QTCALC(I),I=1,NGASES)
      IF(IPF.EQ.0) WRITE(3,930)VE,QT
      IF(IPF.EQ.1) WRITE(3,970)VE,QT
C************
C      IF(LCASE.EQ.3) GO TO 1240
C************
      WRITE(7,1200) (PA(I),I=1,NGASES)
      WRITE(7,1210) (GA(I),I=1,NGASES)
      WRITE(7,1200) (PE(I),I=1,NGASES)
      WRITE(7,1210) (GE(I),I=1,NGASES)
      WRITE(7,1200) (PV(I),I=1,NGASES)
      WRITE(7,1210) (GV(I),I=1,NGASES)
      WRITE(7,1220) VEO,QT,PB,TEMPB,TEMPR,VGA,VBA,VHA,VGV,VBV,VHV
      IF(PV(1).GT.0.0) WRITE(7,1230) HB,HCRIT,PVO2,PVCO2,PHV,FIO2,
     &FICO2,P50,PMAO2,PMACO2,PHA,VO2,VCO2
      IF(PV(1).EQ.0.0) WRITE(7,1230) HB,HCRIT,VO2,VCO2,TOL,FIO2,FICO2,
     & P50,PMAO2,PMACO2,PHA
1200  FORMAT(6(1X,F6.1))
1210  FORMAT(1X,6(F5.0,2X))
1220  FORMAT(F7.2,F6.2,2X,F5.1,2F6.1,6F7.2)
1230  FORMAT(2(2X,F4.1),2F7.1,F9.2,1X,2F6.4,F6.1,/,2F7.1,F6.2,2F8.1)
1240  CONTINUE
      PICO2=(PB-SVPB)*FICO2
      WRITE(9,1250) VO2,VCO2,PIO2,PB,TEMP,HB,HCRIT,PICO2,BX,DP50
1250  FORMAT(F7.1,F8.1,F8.2,F7.1,3F6.1,F7.2,2F6.2)
      IF(PV(1).GT.0.0) GO TO 1280
      WRITE(9,1260) PVO2,PVCO2,Y1,Y2,X3,X4,X5,SO2
      WRITE(9,1270) PHABT,PHV,APCO2,BPCO2,PAO2BT,PACOBT
1260  FORMAT(F7.1,6F7.1,F9.5)
1270  FORMAT(F9.2,F9.2,2F6.1,2F7.1)
      GO TO 1290
1280  WRITE(9,1260) PVO2BT,PVCOBT,Y1,Y2,X3,X4,X5,SO2
      WRITE(9,1270) PHABT,PHVBT,APCO2,BPCO2,PAO2BT,PACOBT
1290  WRITE(9,1300) NGSS,NVAQS,ZZ,VQLO,VQHI,VE,SVPB,QT,TOL
1300  FORMAT(I3,I4,F6.1,F7.3,F7.1,2F8.2,F6.2,F8.0)
```

```
      IF(IGAS.EQ.0) GO TO 1320
      DO 1310 I=IGAS,NGSS
      PCC(I)=PCBODY(I+1)
      RMV(I)=RMV(I+1)
      EMV(I)=EMV(I+1)
      WT(I)=WT(I+1)
1310  CONTINUE
1320  CONTINUE
      IF(IGAS.NE.0) WRITE(9,260) (PCC(I),I=1,NGSS)
      IF(IGAS.EQ.0) WRITE(9,260) (PCBODY(I),I=1,NGSS)
      WRITE(9,1330) (RMV(I),I=1,NGSS)
      WRITE(9,1330) (EMV(I),I=1,NGSS)
C********
      IF(RMV(1).LT.0.01) WT(1)=200.0
      IF(EMV(6).LE.EMV(5)) WT(6)=1000.0
C********
      WRITE(9,1340) (WT(I),I=1,NGSS)
1330  FORMAT(F12.6,7F12.6)
1340  FORMAT(F11.2,7(F11.2,1X))
      WRITE(3,350)
1350  CONTINUE
      IF(LCASE.NE.1) CLOSE(8)
      IF(LCASE.NE.2) GO TO 1360
      L1=NRUNS+1
      NRUNS=NTOT
      IQ='N'
      LCASE=1
      GO TO 360
1360  CLOSE(9)
      IF(LCASE.NE.3) CLOSE(7)
      STOP
      END
      SUBROUTINE TEMPCR(PHP,PCO2,PO2,VC,T,PHPT,PCO2T,PO2T,BEB)
C      CORRECTS BLOOD GAS & PH VALUES TO BODY TEMP & CALCS BASE EXCESS
      REAL N,N1,MIN,MAX
      A=15.
      B=2045.
      C=-2000.
      D=2400.
      E=31100.
      F=2.4E+6
      PP=75.0
      N=-PO2*10.**(.48*(PHP-7.4))
      SO2=(N**4+A*N**3+B*N**2+C*N)/(N**4+A*N**3+D*N**2+E*N+F)
      DSO2BB=-VC*(1-SO2)*(8.5+PCO2*(.01-.05526*10.**(PHP-7.4)))
      RH=.627-.440*(PHP-7.4)
      PK=6.099-.04167*(PHP-7.4)
      HBO2NH=20.1*VC*.2658*PCO2/(.8238*PCO2+10.**(8.-PHP)/RH*
     &(8.611+10.**(8.-PHP)/RH))
      PB=(1.-VC)*PP*(.2413+.104*(PHP-7.4))
      PHC=PHP+ALOG10(RH)
      HB=20.1*VC*(10.625*PHC-.5*PHC**2-48.46)
      HCO3=.0306*PCO2*10.**(PHP-PK)*(1.+VC*(.7676*RH-1.))
      BBB=HCO3+HB+PB+HBO2NH+DSO2BB
      BEB=BBB-24.48-31.395*VC-.2413*(1.-VC)*PP
      N1=-PO2*10.**(.48*(PHP-7.4)-.0013*BEB)
      PCO2T=PCO2*10.**(.019*(T-37.))
      PHPT=PHP-(T-37.)*(.0147+.00654*(PHP-7.4))
      SO237=(N1**4+A*N1**3+B*N1**2+C*N1)/(N1**4+A*N1**3+D*N1**2+
     &E*N1+F)
      SM=-PO2*10.**(.48*(PHPT-7.4)-.0013*BEB-.024*(T-37.))
      SP=1.+ALOG10(T/37.)+.00012*(T-37.)**2
      ST=342.18*VC/(PO2*(.02114+.00516*VC))
      SA=A/SM+SP*(ST*(1.-SO237)-1.)
      SB=(D/SM+A*SP*(ST*(1.-SO237)-1.))/SM
      SC=(E/SM+SP*(B*ST-D*(1.+ST*SO237)))/SM**2
      SD=(F/SM+SP*(C*ST-E*(1.+ST*SO237)))/SM**3
      SE=-F*SP*(1.+ST*SO237)/SM**4
      MIN=0.
      MAX=1.
      CALCX=T-37.
      IF(CALCX)20,10,70
10    X=1.
      GO TO 120
```

```
20    DO 50, J=1,24
      XT=(MAX+MIN)/2.
      Y=XT**5+SA*XT**4+SB*XT**3+SC*XT**2+SD*XT+SE
      IF(Y) 40,60,30
30    MAX=XT
      GO TO 50
40    MIN=XT
50    CONTINUE
60    X=XT
      GO TO 120
70    DO 100, K=1,24
      RXT=(MAX+MIN)/2.
      Y=1.+SA*RXT+SB*RXT**2+SC*RXT**3+SD*RXT**4+SE*RXT**5
      IF(Y)80,110,90
80    MAX=RXT
      GO TO 100
90    MIN=RXT
100   CONTINUE
110   X=1./RXT
120   PO2T=X*PO2
      SL=SM*X
      SO2T=(SL**4+A*SL**3+B*SL**2+C*SL)/(SL**4+A*SL**3+D*
     &SL**2+E*SL+F)
      RETURN
      END
........
```

7.4 FORTRAN PROGRAM TO CALCULATE DLO_2

```
C     THIS PROGRAM COMBINES VQDIST WITH BOHR INTEGRATION (KELMAN CURVES)
C     BASICALLY FOLLOWS HEMPLEMAN AND GRAY, JUNE 88
C
C     THIS VERSION FINDS DLO2 ITERATIVELY BY QUADRATIC INTERPOLATION
C     USING THREE STARTING GUESSES AT DLO2 ("DM") TO CALCULATE THE THREE
C     COEFFICIENTS (A,B,C) OF:  PO2ERR = A.DM.DM + B.DM + C
C     PO2ERR IS THE DIFFERENCE BETWEEN MEASURED AND PREDICTED ARTERIAL PO2
C     THESE GUESSES ARE 0.010, 0.015 AND 0.020 OF THE MEASURED VO2
C     DLO2 IN ML/MIN/TORR AND VO2 IN ML/MIN. HOWEVER, TO ENSURE
C     NUMERICAL STABILITY, THE FIRST VALUE (0.010) IS STEPPED DOWN IF
C     ITS PO2ERR IS POSITIVE, UNTIL PO2ERR JUST BECOMES NEGATIVE, WITH DM
C     BEING 0.8 OF ITS PREVIOUS VALUE EACH STEP. SIMILARLY, THE THIRD
C     VALUE (0.020) IS STEPPED UP TO 1.2 OF ITS PREVIOUS VALUE IF ITS
C     PO2ERR IS NEGATIVE, UNTIL PO2ERR JUST BECOMES POSITIVE.
C     FOR EACH OF THESE GUESSES, THE ACTUAL PO2ERR IS COMPUTED BY RUNNING
C     THE BOHR INTEGRATION, TO GIVE 3 EQNS IN 3 UNKNOWNS (A,B,C):
C
C           PO2ERR(1) = A.DM(1).DM(1)  +  B.DM(1)  +  C
C           PO2ERR(2) = A.DM(2).DM(2)  +  B.DM(2)  +  C
C           PO2ERR(3) = A.DM(3).DM(3)  +  B.DM(3)  +  C
C
C     NEXT, THE VALUE OF DM THAT GIVES PO2ERR=0 IS CALCULATED FROM
C     THIS QUADRATIC, AND ITS ACTUAL PO2ERR COMPUTED BY RUNNING THE
C     BOHR INTEGRATION WITH THIS NEW VALUE OF DM.
C
C     THE FIRST (DM,PO2ERR) PAIR IS NOW DROPPED, THE MOST RECENT PAIR
C     RETAINED, FORMING AN UPDATED SET OF THREE (DM,PO2ERR) PAIRS, AND
C     A NEW SET OF QUADRATIC COEFFICIENTS IS COMPUTED FROM THEM.
C
C     THIS PROCESS IS REPEATED TO CONVERGENCE TO WITHIN THE DESIRED
C     TOLERANCE, CURRENTLY STATED AS PO2ERR < 0.1 TORR ABSOLUTE.
C
      PROGRAM MAIN
      CHARACTER NAME(60),IO2,ISKO2
      DIMENSION IFLAG(24),X(4),Y(4)
      DIMENSION VSAVE(20,50),QSAVE(20,50)
      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     +PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     +PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     +IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      IPRN=0
      DO 10, I=1,24
 10   IFLAG(I)=0
      WRITE(*,310)
      OPEN (8,FILE=' ')
      WRITE(*,320)
      READ(*,*)IDP
      IF(IDP.LE.0) WRITE(*,330)
      IF(IDP.LE.0) OPEN(3,FILE=' ',STATUS='NEW')
      IF(IDP.GE.1) OPEN(3,FILE='PRN')
      WRITE(*,390)
      READ(*,*)IPLTVQ
      WRITE(*,395)
      READ(*,*)IPLTRE
      IF(IPLTVQ.EQ.1) OPEN(9,FILE='VQPLOT.FYL',STATUS='NEW')
      IF(IPLTRE.EQ.1) OPEN(6,FILE='REPLOT.FYL',STATUS='NEW')
      IF(IPLTVQ.EQ.1) WRITE(*,410)
      IF(IPLTRE.EQ.1) WRITE(*,415)
      READ(8,20)(NAME(I),I=1,60)
 20   FORMAT(60A1)
      READ(8,30) NRUNS,PBSEA
```

```
 30   FORMAT(I4,F7.1)
 40   WRITE(*,50)
 50   FORMAT(' ARE THESE SETS RETENTION OR EXCRETION WEIGHTED ?'/
     + '  (0 FOR R (USUAL WAY) OR 1 FOR E)')
      READ(*,*)IRORE
      IF(IRORE.NE.0 .AND. IRORE.NE.1) GO TO 40
      WRITE(*,60)
 60   FORMAT('  ENTER SET NUMBERS TO BE SKIPPED, 20I3 FORMAT'/)
      READ(*,65)(IFLAG(I),I=1,NRUNS)
 65   FORMAT(20I3)
      WRITE(*,70)
 70   FORMAT(' DO YOU WANT O2/CO2 CALCS, D/Q INFINITE (Y/N) ?')
      READ(*,90)IO2
      IF(IO2.NE.'Y') GO TO 110
      WRITE(*,80)
 80   FORMAT(' DO YOU WANT BOHR INTEGRATION CALCULATIONS ? (Y/N)')
      READ(*,90)ISKO2
 90   FORMAT(A1)
      IF(ISKO2.NE.'Y') GOTO 110
      WRITE(*,100)
100   FORMAT(' ENTER # OF INTEGRATION STEPS (20 - 100), FREE FORMAT',/,
     1' AND FLAG SCREEN-PRINT OPTION (1=YES, 0=NO)')
      READ(*,*)NT,IPRN
      RNT=NT
110   CONTINUE
      DO 300 KK=1,NRUNS
      ISKIP=0
      DO 120 KIJ=1,NRUNS
120   IF(IFLAG(KIJ).EQ.KK) ISKIP=1
      IF(ISKIP.EQ.0) WRITE(3,130)KK,(NAME(I),I=1,60)
      IF(ISKIP.EQ.0) WRITE(*,130)KK,(NAME(I),I=1,60)
130   FORMAT(/////,' SET NUMBER :'I3'  FROM FILE: '60A1)
      IF(ISKIP.EQ.0 .AND. IRORE.EQ.0) WRITE(3,140)
      IF(ISKIP.EQ.0 .AND. IRORE.NE.0) WRITE(3,150)
140   FORMAT(' FITTING A BLOOD FLOW DISTRIBUTION TO RETENTIONS'/)
150   FORMAT(' FITTING A VENTILATION DISTRIBUTION TO EXCRETIONS'/)
      READ(8,160) GVO2,GVCO2,PIO2,PB,TEMP,HB,HCRIT,PICO2,BX,DP50
160   FORMAT(F7.1,F8.1,F8.2,F7.1,3F6.1,F7.2,2F6.2)
      READ(8,170) X(1),Y(1),X(2),Y(2),X(3),Y(3),PVN2,SO2
170   FORMAT(7F7.1,F9.5)
      ALPHA=0.0017
      READ(8,180) PHA,PHV,APCO2,BPCO2,PMAO2,PMACO2
180   FORMAT(2F9.2,2F6.1,2F7.1)
      READ(8,190) NGASES,NVAQS,Z,VQLO,VQHI,VT,PH2O,QT,TOL
190   FORMAT(I3,I4,F6.1,F7.3,F7.1,2F8.2,F6.2,F8.0)
      IF(IO2.EQ.'N') GO TO 200
      Y1=0.003*HB*(100.0-SATURA(PMAO2,PMACO2,PHA))/100.0
      PHX=7.59+Y1-0.2741*ALOG(PMACO2/20.0)
      DELPH=PHA-PHX
      APH=7.59+DELPH-0.2741*ALOG(APCO2/20.0)
      BPH=7.59+DELPH-0.2741*ALOG(BPCO2/20.0)
      IF(PHV.LE.6.0.OR.PHV.GE.8.0) GO TO 200
      Y1=0.003*HB*(100.0-SATURA(X(1),Y(1),PHV))/100.0
      PHX=7.59+Y1-0.2741*ALOG(Y(1)/20.0)
      DELPH=PHV-PHX
      APHV=7.59+DELPH-0.2741*ALOG(APCO2/20.0)
      BPHV=7.59+DELPH-0.2741*ALOG(BPCO2/20.0)
      HA1=EXP(-APH)
      HA2=EXP(-APHV)
      HB1=EXP(-BPH)
      HB2=EXP(-BPHV)
      HA=(HA1+HA2)/2.0
      HBAV=(HB1+HB2)/2.0
      APH=-ALOG(HA)
      BPH=-ALOG(HBAV)
200   CONTINUE
      FACT = (PBSEA-PH2O)/100.0
      P50=26.8+DP50
      DSPCE=0.0
      KRUN=KK
      CALL CALCVQ(IPLTRE,ISKIP,DSPCE,SUMQ,KRUN,IRORE)
      IF(SUMQ.EQ.0.0) ISKIP=1
      IF(ISKIP.EQ.1) GO TO 300
      IF(IO2.EQ.'N') GO TO 300
```

```
      KOUNT=0
      WRITE(3,210)
210   FORMAT(30X,'GAS EXCHANGE')
      FIO2=PIO2/(PB-PH2O)
      FICO2=PICO2/(PB-PH2O)
      WRITE(3,220)GVO2,GVCO2,PIO2,FIO2,PICO2,FICO2,PB,TEMP,HB,HCRIT,
     + P50,BX
220   FORMAT(/'   GVO2',4X,'GVCO2',3X,'PIO2',3X,'FIO2',2X,'PICO2',
     +2X,'FICO2'2X'PB'4X'TEMP'3X'HB'2X'HCRIT'2X'P50'2X'BX'/,
     +2F8.1,1X,F6.1,F7.4,F5.1,2X,F6.2,1X,F6.1,3(1X,F5.1),2F5.1,/)
      CALL BLOOD(PMAO2,PMACO2,AMO2C,AMCO2C)
      WRITE(3,230)APH,APCO2,PMAO2,AMO2C,BPH,BPCO2,PMACO2,AMCO2C
230   FORMAT(4X,'FIRST  BLOOD PH =',F4.2,4X,'PCO2 =',F5.2,6X,
     +'PMAO2 =',F6.2,5X,'CMAO2 =',F6.2/,4X,'SECOND BLOOD PH =',F4.2,
     +4X,'PCO2 =',F5.2,6X,'PMACO2=',F6.2,5X,'CMACO2=',F6.2/)
      WRITE(3,240)VT,QT,SO2
240   FORMAT(/,25X,'TOTAL VENTILATION=',F12.2,/,
     + 25X,'TOTAL BLOOD FLOW =',F12.2,/,
     + 25X,'O2 SOLUBILITY    =',F12.4)
      WRITE(3,250)TOL
250   FORMAT(/,25X,'TOLERANCE        =',F12.2/)
      QR=QT
      IF(X(1).NE.GVO2 .OR. Y(1).NE.GVCO2) GO TO 280
      CALL BLOOD(PMAO2,PMACO2,AMO2C,AMCO2C)
      FMVO2=-GVO2/(10.0*QT)+AMO2C
      FMVCO2=GVCO2/(10.0*QT)+AMCO2C
      IF(FMVO2.GT.0.0) GO TO 270
      WRITE(3,260) FMVO2,FMVCO2
      WRITE(*,260)FMVO2,FMVCO2
260   FORMAT(' FICK CALC MIXED VENOUS O2 CONTENT='F5.1,5X,'CO2
     + CONTENT='F5.1,6X,'THEREFORE O2 CALCS IMPOSSIBLE'////////)
      GO TO 300
270   CALL FNDTEN(PVO2,PVCO2,FMVO2,FMVCO2)
      X(1)=PVO2
      Y(1)=PVCO2
280   CONTINUE
      DO 290 IBOHR=1,2
      CALL FNDMVP(KRUN,X,Y)
      CALL WRITE
      IF(IBOHR.EQ.2) GO TO 286
      DO 285 J=1,NVAQS
      VSAVE(KK,J)=V(J)
285   QSAVE(KK,J)=Q(J)
286   IF(ISKO2.EQ.'N') GO TO 300
290   CONTINUE
300   CONTINUE
310   FORMAT(' ENTER FILE NAME.EXT FOR VQ INPUT DATA',/)
320   FORMAT(' WRITE OUTPUT TO DISK (0) OR PRINTER (1) ?')
330   FORMAT(' ENTER FILE NAME.EXT OF YOUR CHOICE FOR RESULTS')
C
C     WRITE DISTRIBUTION TO DISK FOR PLOTTING
C
      IF(IPLTVQ.EQ.0) GO TO 400
      ZERO=0.0
      VAQ(1)=0.001
      VAQ(NVAQS)=1000.
      DO 370 KK=1,NRUNS
      DO 340 KIJ=1,NRUNS
340   IF(IFLAG(KIJ).EQ.KK) GO TO 370
      IF(IPLTVQ.EQ.1.AND.KK.EQ.1) WRITE(3,355)
      IF(IPLTRE.EQ.1.AND.KK.EQ.1) WRITE(3,350)
350   FORMAT(' R & E PLOT VARIABLES FIELD IS 8 COLS, EACH 10 CHARS')
355   FORMAT('   V/Q PLOT VARIABLES FIELD IS 5 COLS, EACH 10 CHARS')
      WRITE(9,380)VAQ(1),ZERO,ZERO,Q(1),ZERO
      DO 360 J=2,NVAQS-1
360   WRITE(9,380)VAQ(J),VSAVE(KK,J),QSAVE(KK,J),ZERO,ZERO
      WRITE(9,380)VAQ(NVAQS),ZERO,ZERO,ZERO,V(NVAQS)
370   CONTINUE
380   FORMAT(5F10.3)
390   FORMAT(' WANT TO HARDCOPY PLOT THE V/Q CURVES?  0=NO, 1=YES')
395   FORMAT(' WANT TO HARDCOPY PLOT THE R & E CURVES?  0=NO, 1=YES')
400   CONTINUE
410   FORMAT(' DATA FOR HARDCOPY VA/Q  PLOTS ARE IN:      C:VQPLOT.FYL')
415   FORMAT(' DATA FOR HARDCOPY R & E PLOTS ARE IN:      C:REPLOT.FYL')
```

```
      STOP
      END
      SUBROUTINE CALCVQ(IPLTRE,ISKIP,DSPCE,SUMQ,KRUN,IRORE)
      DIMENSION S(10),PC(10),RDATA(10),EDATA(10),AD(10)
      DIMENSION WEIGHT(10),RAWDAT(10),RAD(10)
      DIMENSION SOL(50),CALCDR(50),CALCDE(50),RHOMO(50),EHOMO(50)
      DIMENSION DKK(10,10),DQ(11),DV(11)
      CHARACTER IPLCHR
      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      NGAS1=NGASES+1
      READ(8,10) (PC(I),I=1,NGASES)
10    FORMAT(1X,6(1PE12.3))
      PC(NGAS1)=0.0
      READ(8,20) (RDATA(I),I=1,NGASES)
      READ(8,20) (EDATA(I),I=1,NGASES)
20    FORMAT(8F12.6)
      READ(8,30) (WEIGHT(I),I=1,NGASES)
30    FORMAT(8(F11.2,1X))
      IF(ISKIP.EQ.1) RETURN
      DO 40, I=1,NGAS1
40    S(I)=PC(I)/FACT
      DO 50 I=1,NGASES
      IF(IRORE.EQ.0) RAWDAT(I)=RDATA(I)
50    IF(IRORE.NE.0) RAWDAT(I)=EDATA(I)
      RAWDAT(NGAS1)=1.0
      RAWDAT(NGAS1+1)=1.0
      WRITE(3,60)NGASES,NVAQS,Z
60    FORMAT(' NUMBER OF GASES ='I3/' NUMBER OF VA/Q COMPARTMENTS ='
     & I4,/,' SMOOTHING COEFFICIENT Z =',F8.2/)
      WRITE(3,70)
70    FORMAT(8X,'GAS'10X'SOL'12X'PC'14X'R'14X'E')
      DO 80, I=1,NGASES
80    WRITE(3,90)I,S(I),PC(I),RDATA(I),EDATA(I)
90    FORMAT(I10,4F15.5)
      NV=NVAQS-1
      RNV=NV
      DVQ=(ALOG(VQHI/VQLO))/RNV
      DO 110, J=1,NVAQS
      TJ=J
110   VAQ(J) = VQLO*EXP(DVQ*(TJ-1.0))
      VAQ(1)=0.0
      VAQ(NVAQS) = 10000.0
      IC=1
120   IF(IRORE.EQ.0) CALL SMOOTH(E,PC,RDATA,RAWDAT,WEIGHT,AD,IC,
     + SUMQ,IRORE)
      IF(IRORE.NE.0) CALL SMOOTH(E,PC,EDATA,RAWDAT,WEIGHT,AD,IC,
     + SUMV,IRORE)
      IF(IRORE.NE.0) GO TO 184
      VTNEW=0.0
      V(1)=0.0
      DO 140, J=1,NV
      QQ(J)=QQ(J)/SUMQ
      V(J) = QT*VAQ(J)*QQ(J)
140   VTNEW=VTNEW+ V(J)
      V(NVAQS)=VT-VTNEW
      DO 150, J=1,NVAQS
150   V(J)=V(J)/VT
C      WRITE(3,155)
C155   FORMAT(4X,'I'7X,'PC',8X,'AD/WEIGHT',8X,'RAD')
      DO 170, I=1,NGASES
      RAD(I)=0.0
      DO 160, J=1,NV
160   RAD(I)=RAD(I)+QQ(J)*PC(I)/(VAQ(J)+PC(I))
C      WRITE(3,180)I,PC(I),AD(I)/WEIGHT(I),RAD(I)
170   CONTINUE
C180   FORMAT(I5,F11.4,2F15.8)
C      WRITE(3,182) IC,QT,VT,VTNEW,VTNEW/VT
C182   FORMAT(I5,3X,'QT:'F6.3,3X,'VT:'F7.3,3X,'CALC:'F9.5,3X,
C     & 'CALC/MEAS:'F8.5)
      QQ(NVAQS)=0.0
      GO TO 198
184   QTNEW=0.0
      QQ(NVAQS)=0.0
```

```
      V(1)=0.0
      DO 186, J=2,NV
      V(J)=V(J)/SUMV
      QQ(J) = V(J)*VT/VAQ(J)
186   QTNEW=QTNEW+ QQ(J)
      V(NVAQS)=V(NVAQS)/SUMV
      QQ(1)=QT-QTNEW
      DO 188, J=1,NVAQS
188   QQ(J)=QQ(J)/QT
C      WRITE(3,189)
C189      FORMAT(4X'I'7X'PC'8X'AD/WEIGHT'8X'EXC'11X'RETEN'11X'RAD')
      DO 192, I=1,NGASES
      RAD(I)=0.0
      EXC=0.0
      DO 190, J=1,NV
      EXC=EXC+ V(J)*PC(I)/(VAQ(J)+PC(I))
190   RAD(I)=RAD(I)+QQ(J)*PC(I)/(VAQ(J)+PC(I))
      RETEN=1.0- VT*EXC/(PC(I)*QT)
C      WRITE(3,194) I,PC(I),AD(I)/WEIGHT(I),EXC,RETEN,RAD(I)
192   CONTINUE
C194   FORMAT(I5,F11.4,4F15.8)
C      WRITE(3,182) IC,QT,VT,QTNEW,QTNEW/QT
198   SHNT=QQ(1)
      DSPCE=V(NVAQS)
      SMQPO1=0.0
      SMVPO1=0.0
      SMQP1=0.0
      SMVP1=0.0
      SMQ1=0.0
      SMV1=0.0
      SMQ10=0.0
      SMV10=0.0
      SMQ100=0.0
      SMV100=0.0
      DO 240, J=2,NV
      IF(VAQ(J).GT.0.01) GO TO 200
      SMQPO1=SMQPO1 + QQ(J)
      SMVPO1=SMVPO1 + V(J)
      GO TO 240
200   IF(VAQ(J).GT.0.1) GO TO 210
      SMQP1=SMQP1 + QQ(J)
      SMVP1=SMVP1 + V(J)
      GO TO 240
210   IF(VAQ(J).GT.1.0) GO TO 220
      SMQ1=SMQ1 + QQ(J)
      SMV1 =SMV1 + V(J)
      GO TO 240
220   IF(VAQ(J).GT.10.0) GO TO 230
      SMQ10=SMQ10 + QQ(J)
      SMV10=SMV10 + V(J)
      GO TO 240
230   SMQ100=SMQ100 + QQ(J)
      SMV100=SMV100 + V(J)
240   CONTINUE
      WRITE(3,250)
250   FORMAT(//6X'RANGE'17X'BLOOD FLOW'11X'VENTILATION'/)
      WRITE(3,260)SHNT
      WRITE(3,270)SMQPO1,SMVPO1
      WRITE(3,280)SMQP1,SMVP1
      WRITE(3,290)SMQ1,SMV1
      WRITE(3,300)SMQ10,SMV10
      WRITE(3,310)SMQ100,SMV100
      WRITE(3,320)DSPCE
260   FORMAT(' VA/Q OF ZERO       ',F16.3,8X,'        ZERO')
270   FORMAT(' VA/Q RANGE    0  TO  .01'F11.3,F20.3)
280   FORMAT(' VA/Q RANGE   .01 TO  .1',F12.3,F20.3)
290   FORMAT(' VA/Q RANGE   .1 TO  1.',F13.3,F20.3)
300   FORMAT(' VA/Q RANGE  1.0 TO 10.',F13.3,F20.3)
310   FORMAT(' VA/Q RANGE 10. TO 100.',F13.3,F20.3)
320   FORMAT(' VA/Q OF INFINITY              ZERO     ',F15.3/)
      SUMQVQ=0.0
      SUMVVQ=0.0
      SUMQ=0.0
      SUMV=0.0
```

```
      DO 330, I=2,NV
      SUMQVQ=SUMQVQ + QQ(I)*ALOG(VAQ(I))
      SUMVVQ=SUMVVQ + V(I)*ALOG(VAQ(I))
      SUMQ=SUMQ + QQ(I)
330   SUMV=SUMV + V(I)
      IF(SUMQ.LE.0.0.OR.SUMV.LE.0.0) RETURN
      FQ=SUMQVQ/SUMQ
      FV=SUMVVQ/SUMV
      QBAR=EXP(FQ)
      VBAR=EXP(FV)
      SUMVRQ=0.0
      SUMVRV=0.0
      SUMSKQ=0.0
      SUMSKV=0.0
      DO 340, I=2,NV
      SUMVRQ=SUMVRQ + QQ(I)*(ALOG(VAQ(I)) - FQ)**2
      SUMVRV=SUMVRV + V(I)*(ALOG(VAQ(I)) - FV)**2
      SUMSKQ=SUMSKQ + QQ(I)*(ALOG(VAQ(I)) - FQ)**3
      SUMSKV=SUMSKV + V(I)*(ALOG(VAQ(I)) - FV)**3
340   CONTINUE
      QSD=SQRT(SUMVRQ/SUMQ)
      VSD=SQRT(SUMVRV/SUMV)
      QSKEW = SUMSKQ/SUMQ
      VSKEW = SUMSKV/SUMV
      WRITE(3,350)QBAR,QSD,QSKEW,VBAR,VSD,VSKEW
350   FORMAT(/,'       MEAN OF BLOOD FLOW  DISTRIBUTION =',F7.2,/,
     1' 2nd MOMENT OF BLOOD FLOW  DISTRIBUTION =',F7.2,/,
     2' 3rd MOMEMT OF BLOOD FLOW  DISTRIBUTION =',F7.2,//,
     3'       MEAN OF VENTILATION DISTRIBUTION =',F7.2/,
     4' 2nd MOMENT OF VENTILATION DISTRIBUTION =',F7.2/,
     5' 3rd MOMENT OF VENTILATION DISTRIBUTION =',F7.2,//)
      DO 360, I=1,NVAQS
      V(I)=V(I)*VT
360   QQ(I)=QQ(I)*QT
      VA=VT-V(NVAQS)
C      Calculation of max possible deadspace ventilation
C      by John Evans' recursion method
      DQ(NGAS1)=QT
      DV(1)=0.0
      DO 370, LL=1,NGASES
      DKK(NGASES,LL)=RAD(LL)*QT
C      DKK(NGASES,LL)=(AD(LL)/WEIGHT(LL))*QT-THIS IS NOT ACCURATE ENOUGH!
370   CONTINUE
      DO 380, KK=1,NGASES-1
      K=NGASES-KK
      K1=K+1
      DQ(K1)=(DQ(K1+1)-DKK(K1,K1))/DKK(K1,K1)
      DO 380,I=1,K
      DKK(K,I)=(PC(I)*(DKK(K1,I)-DKK(K1,K1)))/(PC(I)*DKK(K1,K1)-
     1 PC(K1)*DKK(K1,I))
      IF(K.NE.1) GO TO 380
      DQ(1)=(DQ(K1)-DKK(K,K))/DKK(K,K)
380   CONTINUE
      DO 390, L=1,NGASES
      L1=L+1
      DV(L1)=DKK(L,L)*(DV(L)+PC(L)*(DQ(L)+1.0)*DQ(L))
390   CONTINUE
      VD=VT-DV(NGAS1)
      DED=VD/VT
C**********
C     MEASURE OF DISPERSION DIRECTLY FROM DATA, AS THE SUM OF SQUARES
C     OF THE DIFFERENCES BETWEEN HOMOGENEOUS RETENTIONS AND THE BEST FIT
C     VALUES OUT OF SMOOTH.
C**********
      WRITE(3,400)
400   FORMAT(' GAS',4X,'PC',7X,'R',7X,'RH',4X,'R - RH',5X,'E',
     &7X,'E*',6X,'EH',3X,'EH - E*',1X,'R - E*')
      DISR=0.0
      DISE=0.0
      DISRE=0.0
      DO 410, I=1,NGASES
      RH=PC(I)/(PC(I)+VA/QT)
      EH=RH
C      ADD=AD(I)/WEIGHT(I)-THIS IS NOT ACCURATE ENOUGH!
```

```
      ADD=RAD(I)
      EE=PC(I)*QT*(1.0-ADD)/VT
      EXC=EE/(1.0-DED)
      DIFFR=ADD-RH
      DIFFE=EH - EXC
      DIFFRE=ADD - EXC
      DISR=DISR+DIFFR*DIFFR
      DISE=DISE+DIFFE*DIFFE
      DISRE=DISRE+DIFFRE*DIFFRE
      WRITE(3,420)I,PC(I),ADD,RH,DIFFR,EE,EXC,EH,DIFFE,DIFFRE
410   CONTINUE
420   FORMAT(I2,F10.5,8F8.5)
      DISPR=100.0*SQRT(DISR/(FLOAT(NGASES)))
      DISPE=100.0*SQRT(DISE/(FLOAT(NGASES)))
      DISPRE=100.0*SQRT(DISRE/(FLOAT(NGASES)))
      WRITE(3,430) VD,DED
430   FORMAT(/' MAX POSSIBLE DEADSPACE VENTILATION =',F7.1,
     1' L/MIN,  OR AS A FRACTION =',F5.3/)
      WRITE(3,440)DISPR,DISPE,DISPRE
440   FORMAT(' DISPERSION DIRECTLY FROM DIFFERENCES BETWEEN:',//,
     1'  BEST FIT   RETENTIONS & HOMOGENEOUS RETENTIONS IS:',F7.2,/,
     2' HOMOGENEOUS EXCRETIONS &  BEST FIT   EXCRETIONS IS:',F7.2,/,
     3'  BEST FIT   RETENTIONS *  BEST FIT   EXCRETIONS IS:',F7.2///)
      IF(IC.EQ.2)  GO TO 450
      IF(IRORE.EQ.0 .AND. V(NVAQS).GE.0.0) GO TO 450
      IF(IRORE.NE.0 .AND. QQ(1).GE.0.0) GO TO 450
      IC=2
      GO TO 120
450   CONTINUE
      YMAX=0.0
      DO 460, J=2,NVAQS
      IF(YMAX.GE.QQ(J)) GO TO 460
      YMAX=QQ(J)
460   CONTINUE
      DO 470, J=1,NV
      IF(YMAX.GE.V(J)) GO TO 470
      YMAX=V(J)
470   CONTINUE
      YMAX=1.25*YMAX
      YMAXV=YMAX
      VAQ(1)=0.0002
      VAQ(NVAQS)=990.0
      LINES=36
      IF(YMAX.EQ.0.0) GO TO 480
      IPLCHR='*'
      CALL PLOT(1,VAQ,QQ,YMAX,LINES,NVAQS,1,2,1,0,IPLCHR,KRUN)
      IPLCHR='O'
      CALL PLOT(1,VAQ,V,YMAXV,LINES,NV,2,2,1,0,IPLCHR,KRUN)
480   CONTINUE
      VAQ(1)=0.0
      SOLHI=1000.0
      SOLLO=0.0001
      DS=(ALOG10(SOLHI/SOLLO))/49.0
      DO 490, J=1,50
      TJ=J
490   SOL(J) = SOLLO*(10.0**(DS*(TJ-1.0)))
      DO 510 I=1,50
      CALCDR(I)=0.0
      CALCDE(I)=0.0
      DO 500, J=1,NV
      CALCDR(I)=CALCDR(I) + QQ(J)*SOL(I)/(SOL(I)+VAQ(J))
500   CALCDE(I)=CALCDE(I) + V(J)*SOL(I)/(SOL(I)+VAQ(J))
      CALCDR(I)=CALCDR(I)/QT
      CALCDE(I)=CALCDE(I)/VT
      VA=VT-V(NVAQS)
      RHOMO(I)=SOL(I)/(SOL(I) + VA/QT)
      EHOMO(I) = RHOMO(I)*VA/VT
510   CONTINUE
      LINES=36
      IPLCHR='.'
      CALL PLOT(2,SOL,CALCDR,1.0,LINES,50,1,6,1,0,IPLCHR,KRUN)
      IPLCHR='*'
      CALL PLOT(2,SOL,RHOMO,1.0,LINES,50,2,6,1,0,IPLCHR,KRUN)
      IPLCHR='O'
```

```
      IF(IRORE.EQ.0)CALL PLOT(2,PC,RAWDAT,1.0,LINES,NGASES,3,6,1,0,
     + IPLCHR,KRUN)
      IF(IRORE.NE.0)CALL PLOT(2,PC,RDATA,1.0,LINES,NGASES,3,6,1,0,
     + IPLCHR,KRUN)
      IPLCHR='.'
      CALL PLOT(2,SOL,CALCDE,1.0,LINES,50,4,6,1,0,IPLCHR,KRUN)
      IPLCHR='*'
      CALL PLOT (2,SOL,EHOMO,1.0,LINES,50,5,6,1,0,IPLCHR,KRUN)
      IPLCHR='O'
      IF(IRORE.EQ.0) CALL PLOT(2,PC,EDATA,1.0,LINES,NGASES,6,6,1,0,
     + IPLCHR,KRUN)
      IF(IRORE.NE.0) CALL PLOT(2,PC,RAWDAT,1.0,LINES,NGASES,6,6,1,0,
     + IPLCHR,KRUN)
      IF(IPLTRE.EQ.0) GO TO 540
      ZERO=0.0
      DO 520 J=1,50
      IF(J.LE.NGASES) WRITE(6,530)SOL(J),RHOMO(J),CALCDR(J),EHOMO(J),
     1CALCDE(J),PC(J),RAWDAT(J),EDATA(J)
      IF(J.GT.NGASES) WRITE(6,530)SOL(J),RHOMO(J),CALCDR(J),EHOMO(J),
     1CALCDE(J),ZERO,ZERO,ZERO
  520 CONTINUE
  530 FORMAT(8F10.3)
  540 CONTINUE
      RETURN
      END
      SUBROUTINE SMOOTH(E,PC,DATA,RAWDAT,WEIGHT,AD,IC,SUMQV,IRORE)
      DIMENSION WEIGHT(10),PC(10),AD(10),DATA(10),RAWDAT(10)
      DIMENSION IFLOW(50),Y(50)
      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      DIMENSION A(50,10),WT(50),FLOW(50),H(50)
      DIMENSION C(10,10),RBAR(10),RD(10)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      DOUBLE PRECISION A,WT,FLOW,H,C,RBAR,RD
C
C     GENERATE A, THE ORIGINAL CHEBYSHEV MATRIX:  S/(S+VAQ)
C
      NV=NVAQS-1
      QTVT=QT/VT
      VTQT=VT/QT
      JLO=1
      JHI=NV
      JC=1
      IF(IRORE.EQ.0) GO TO 10
      JLO=2
      JHI=NVAQS
      JC=NVAQS
   10 SSQPRE=1000000.0
      SSLOOP=1000000.0
      NEQNS=NGASES+IC
      NEQN1=NEQNS+1
      NEQN2=NEQNS+2
      DO 20 I=1,NGASES
      A(NVAQS,I)=0.0
      DO 20  J=1,NV
   20 A(J,I) = PC(I)/(PC(I) + VAQ(J))
      DO 30, J=JLO,JHI
      A(J,NGASES+1) = 1.0
      IF(IC.EQ.2 .AND. IRORE.EQ.0) A(J,NEQNS)=VAQ(J)*QTVT
   30 IF(IC.EQ.2 .AND. IRORE.NE.0) A(J,NEQNS)=VTQT/VAQ(J)
      DO 40 J=1,IC
      DATA(NGASES+J) = 1.0
   40 WEIGHT(NGASES+J) = 20000.0
      ICL=(IC-1)*NGASES + 1
      DO 50, I=ICL,NEQNS
   50 DATA(I)=DATA(I)*WEIGHT(I)
      DO 60, I=1,NEQNS
      DO 60, J=JLO,JHI
   60 A(J,I)=A(J,I)*WEIGHT(I)
      DO 70, J=2,NV
      IFLOW(J)=1
      IF(IRORE.EQ.0) WT(J)=SQRT(Z*(1.0 + QTVT*QTVT*VAQ(J)*VAQ(J)))
      IF(IRORE.NE.0) WT(J)=SQRT(Z*(1.0 + VTQT*VTQT*
     & (1.0/VAQ(J))*(1.0/VAQ(J))))
   70 CONTINUE
```

```
      IFLOW(JC)=1
      WT(1)=1.0
      WT(NVAQS)=1.0
      DO 80, I=1,NEQNS
      DO 80, J=JLO,JHI
 80   A(J,I)=A(J,I)/WT(J)
      IF(IC.EQ.2 .AND. IRORE.EQ.0) WRITE(3,90)
 90   FORMAT(' SMOOTH RERUN WITH A NON-NEGATIVE DEADSPACE CONSTRAINT -
     & AN 8th EQN WITH TOTAL V=1')
      IF(IC.EQ.2 .AND. IRORE.NE.0) WRITE(3,100)
100   FORMAT(' SMOOTH RERUN WITH A NON-NEGATIVE SHUNT CONSTRAINT -
     & AN 8th EQN WITH TOTAL Q=1')
      IF(IRORE.EQ.0) WRITE(3,110)
110   FORMAT(/3X,'ITN',2X,'LOOP',9X,'TOTAL SSQ',12X,'FIT TO R',13X,
     1'SUM Q*Q')
      IF(IRORE.NE.0) WRITE(3,120)
120   FORMAT(/3X,'ITN',2X,'LOOP',9X,'TOTAL SSQ',12X,'FIT TO E',13X,
     1'SUM V*V')
      ITER=0
      IREP=1
C
C     GENERATE THE UPPER HALF OF A*A TRANSPOSE, NOTING THAT IT IS SYMMETRIC
C
      LOOP=0
130   LOOP=LOOP+1
      IF(LOOP.GT.1) SSLOOP=SSQ
      DO 150 I=1,NEQNS
      DO 150 J=1,I
      C(J,I)=0.0
      DO 140 K=2,NV
      IF(IFLOW(K).EQ.0) GO TO 140
      C(J,I) = C(J,I) + A(K,I)*A(K,J)
140   CONTINUE
      IF(I.EQ.J) C(J,I) = 1.0 + C(J,I)
150   CONTINUE
C
C     THE SMOOTHING FACTOR IS CALLED Z. WE GENERATE MATRIX  C, WHICH IS
C     IDENTITY PLUS A x AT DIVIDED BY Z, PLUS A DATA COLUMN & A SHUNT
C     OR DEADSPACE SPECIAL COMPARTMENT COLUMN
C
      DO 160 I=1,NEQNS
      C(I,NEQN1) = DATA(I)
      IF(IFLOW(JC).GT.0) C(I,NEQN2) = A(JC,I)
160   CONTINUE
C
C     NOW SOLVE THE UNCONSTRAINED SYSTEM C x RD = DATA, USING GAUSSIAN
C     ELIMINATION WITH BACK-SUBSTITUTION
C
      DO 180, I=1,NEQNS-1
      I1=I+1
      DO 180 J=I1,NEQNS
      DO 170 K=J,NEQN1
      C(J,K) = C(J,K) -  C(I,J)*C(I,K)/C(I,I)
170   CONTINUE
      IF(IFLOW(JC).GT.0) C(J,NEQN2)=C(J,NEQN2)-
     & C(I,J)*C(I,NEQN2)/C(I,I)
180   CONTINUE
      RD(NEQNS) = C(NEQNS,NEQN1)/C(NEQNS,NEQNS)
      IF(IFLOW(JC).GT.0) RBAR(NEQNS)=C(NEQNS,NEQN2)/C(NEQNS,NEQNS)
      DO 200 I=1,NEQNS-1
      RD(NEQNS-I) = C(NEQNS-I,NEQN1)
      IF(IFLOW(JC).GT.0) RBAR(NEQNS-I) = C(NEQNS-I,NEQN2)
      NN1 = NEQN1 -I
      DO 190, K=NN1,NEQNS
      RD(NEQNS-I) = RD(NEQNS-I) - C(NEQNS-I,K)*RD(K)
      IF(IFLOW(JC).GT.0) RBAR(NEQNS-I) = RBAR(NEQNS-I) -
     & C(NEQNS-I,K)*RBAR(K)
190   CONTINUE
      RD(NEQNS-I) = RD(NEQNS-I)/C(NEQNS-I,NEQNS-I)
      IF(IFLOW(JC).GT.0) RBAR(NEQNS-I)=
     & RBAR(NEQNS-I)/C(NEQNS-I,NEQNS-I)
200   CONTINUE
      IF(IFLOW(JC).EQ.0) GO TO 230
      A1=0.0
```

```
      A2=0.0
      DO 210, I=1,NEQNS
      A1=A1 + A(JC,I)*RD(I)
      A2=A2 + A(JC,I)*RBAR(I)
210   CONTINUE
      A0=A1/A2
      DO 220, I=1,NEQNS
220   RD(I)=RD(I)-A0*RBAR(I)
C
C     NOW COMES CALCULATION OF THE Q (OR V) VALUES
C
230   DO 240 J=JLO,JHI
      FLOW(J)=0.0
      DO 240 I=1,NEQNS
      FLOW(J)=FLOW(J) + RD(I)*A(J,I)
240   CONTINUE
      IF(IFLOW(JC).GT.0) FLOW(JC) = A0
      SUM1=0.0
      DO 250 I=1,NEQNS
      SUM1=SUM1+RD(I)*RD(I)
250   CONTINUE
      SUM2=0.0
      DO 260 J=2,NV
      IF(IFLOW(J).EQ.0) GO TO 260
      SUM2=SUM2+FLOW(J)*FLOW(J)
260   CONTINUE
      SSQ=SUM1+SUM2
      WRITE(3,270)ITER,LOOP,SSQ,SUM1,SUM2
270   FORMAT(2I5,3F20.6)
C
C     WRITE(3,272)(IFLOW(JC),IFLOW(J),J=2,NV)
C272  FORMAT(10(I8,4X))
C     WRITE(3,274)FLOW(JC),((FLOW(JJ)/WT(JJ)),JJ=2,NV)
C274  FORMAT(10F12.5)
C
C     HAVING CALCULATED Q OR V VALUES, WE NOW NEED TO ENFORCE THE
C     NON-NEGATIVITY CONSTRAINT:
C
      IF(IREP.EQ.1) GO TO 280
      GO TO 300
280   IREP=2
      DO 290, I=JLO,JHI
      IF(IFLOW(I).EQ.1 .AND. FLOW(I).LE.0.0) IREP=1
      IF(IFLOW(I).EQ.1 .AND. FLOW(I).LE.0.0) IFLOW(I)=0
290   CONTINUE
      IF(IREP.EQ.1) GO TO 130
300   IREP=3
      XMIN=1.0
      DO 320 I=JLO,JHI
      IF(IFLOW(I).GT.0 .AND. FLOW(I).LE.0.0) GO TO 310
      GO TO 320
310   IREP=2
      Y(I)=H(I)/(H(I)-FLOW(I))
      IF(XMIN.GT.Y(I)) XMIN=Y(I)
320   CONTINUE
      IF(IREP.EQ.3) GO TO 350
      DO 340 I=JLO,JHI
      IF(IFLOW(I).EQ.0) GO TO 340
      IF(FLOW(I).GT.0.0) GO TO 330
      Y(I)=H(I)/(H(I)-FLOW(I))
      IF(Y(I).EQ.XMIN) IFLOW(I)=0
330   H(I)= (1.0-XMIN)*H(I)+XMIN*FLOW(I)
340   CONTINUE
      GO TO 130
350   CONTINUE
      ITER=ITER+1
      SUM1=0.0
      DO 360 I=1,NEQNS
      SUM1=SUM1+RD(I)*RD(I)
360   CONTINUE
      SUM2=0.0
      DO 370 J=2,NV
      IF(IFLOW(J).EQ.0) GO TO 370
      SUM2=SUM2+FLOW(J)*FLOW(J)
```

```
370   CONTINUE
      SSQ=SUM1 + SUM2
C*******************************
      IF(SSQ.GE.SSQPRE) GO TO 390
C*******************************
      SSQPRE=SSQ
      DO 380 I=JLO,JHI
      IF(IFLOW(I).GT.0) H(I)=FLOW(I)
      IF(IFLOW(I).GT.0) IFLOW(I)=2
      IF(IFLOW(I).EQ.0 .AND. FLOW(I).GT.0.0) IREP=1
      IF(IFLOW(I).EQ.0 .AND. FLOW(I).GT.0.0) IFLOW(I)=1
      IF(IFLOW(I).EQ.0) H(I)=0.0
380   CONTINUE
      IF(ITER.EQ.99) GO TO 410
      IF(IREP.EQ.1) GO TO 130
390   CONTINUE
C
C     CALCULATE THE ERROR AND THE APPROXIMATING DATA
C
      DO 400 I=2,NV
400   FLOW(I)=FLOW(I)/WT(I)
410   WRITE(3,420)ITER
420   FORMAT(/' ITERATION NUMBER =',I3)
      SUMQV=0.0
      SUME8=0.0
      IF(IRORE.NE.0) GO TO 470
      DO 430 J=1,NV
      IF(IFLOW(J).EQ.0) FLOW(J)=0.0
      QQ(J)=SNGL(FLOW(J))
      SUMQV=SUMQV + QQ(J)
      SUME8=SUME8+QQ(J)*VAQ(J)*QTVT
430   CONTINUE
      WRITE(3,440) SUMQV
440   FORMAT(' TOTAL BLOOD FLOW ='F10.6)
      IF(IC.EQ.2) WRITE(3,450) SUME8
450   FORMAT(' TOTAL VENTILATION='F10.6)
      WRITE(3,460)
460   FORMAT(/6X,'PC'7X,'RETENTIONS',5X,'BEST FIT'7X,'ERROR',
     15X,'RAW DATA',7X,'ERROR')
      GO TO 520
470   DO 480 J=2,NVAQS
      IF(IFLOW(J).EQ.0) FLOW(J)=0.0
      V(J)=SNGL(FLOW(J))
      SUMQV=SUMQV + V(J)
      SUME8=SUME8+V(J)*VTQT/VAQ(J)
480   CONTINUE
      WRITE(3,490)SUMQV
490   FORMAT(' TOTAL VENTILATION='F10.6)
      IF(IC.EQ.2) WRITE(3,500) SUME8
500   FORMAT(' TOTAL BLOOD FLOW ='F10.6)
      WRITE(3,510)
510   FORMAT(/6X,'PC'7X,'EXCRETIONS',5X,'BEST FIT'7X,'ERROR',
     15X,'RAW DATA',7X,'ERROR')
520   E=0.0
      DO 530 I=1,NEQNS
      E=E+RD(I)*RD(I)
      AD(I)=DATA(I)-RD(I)
530   CONTINUE
      DO 540 I=1,NEQNS
      S=PC(I)
      IF(I.GT.NGASES) S=0.0
      RAWERR=AD(I)/WEIGHT(I) - RAWDAT(I)
      WRITE(3,550)S,DATA(I),AD(I),RD(I),RAWDAT(I),RAWERR
540   CONTINUE
550   FORMAT(F10.4,F15.3,F13.3,F12.3,F13.5,F12.5)
      WRITE(3,560)E
560   FORMAT(/' REMAINING SUM OF SQUARES =',1PE10.2)
      RETURN
      END
      SUBROUTINE PLOT(IM,XX,Y,YMAX,LINES,LAST,NO,MOST,LOGX,
     1LOGY,ISYMBO,KRUN)
      DIMENSION XX(50),Y(50),ZX(8),IGRAPH(61,40),X(50)
      DIMENSION LRUN(10),INAM1(15),INAM2(15)
      DIMENSION IHEAD1(36),IHEAD2(36)
```

```
      CHARACTER INAM1,INAM2,IHEAD1,IHEAD2,IHEAD,IOK,IBLANK,IBORDE,
     1LRUN,ISYMBO,IGRAPH,IPOINT
      DATA IHEAD1/' ',' ','C','O','M','P',' ',' ',' ','V','E','N','T',
     1' ',' ','O','R',' ',' ','B','L','O','O','D','F','L','O','W',
     1' ',' ','L','/','M','I','N',' '/
      DATA IHEAD2/' ',' ','R','E','T','E','N','T','I','O','N',
     1' ',' ',' ',' ',' ','A','N','D',' ',' ',' ',' ','E','X',
     1'C','R','E','T','I','O','N',' ',' ',' '/
      DATA IBORDE/'.'/
      DATA IBLANK/' '/
      DATA INAM1/'V','E','N','T','I','L','A','T','I','O','N',
     1' ','=' ,' ','O'/
      DATA INAM2/'B','L','O','O','D','F','L','O','W',' ',' ',
     1' ','=',' ','*'/
      DATA LRUN/'0','1','2','3','4','5','6','7','8','9'/
      IWID=61
      RWID=IWID-1
      IF(IM.EQ.2) GO TO 20
      DO 10 I=7,21
      IGRAPH(I,3)=INAM1(I-6)
   10 IGRAPH(I,5)=INAM2(I-6)
   20 CONTINUE
      IF(KRUN.LT.10) IGRAPH(55,3)=LRUN(KRUN+1)
      IF(KRUN.LT.20.AND.KRUN.GE.10) IGRAPH(55,3)=LRUN(2)
      IF(KRUN.LT.20.AND.KRUN.GE.10) IGRAPH(56,3)=LRUN(KRUN-9)
      IF(KRUN.LT.30.AND.KRUN.GE.20) IGRAPH(55,3)=LRUN(3)
      IF(KRUN.LT.30.AND.KRUN.GE.20) IGRAPH(56,3)=LRUN(KRUN-19)
      IPOINT=ISYMBO
      YL=YMAX
      YS=0.0
      MATRIX=IWID*LINES
      A=LINES-1
      YSCALE=(YL-YS)/A
      XL=1000.0
      XS=0.0001
      IF(LOGX) 30,50,30
   30 DO 40 I=1,LAST
   40 X(I)=ALOG10(XX(I))
      XS=ALOG10(XS)
      XL=ALOG10(XL)
      XSCALE=(XL-XS)/RWID
   50 IF(LOGY) 60,80,60
   60 DO 70 I=1,LAST
   70 Y(I)=ALOG10(Y(I))
      YS=ALOG10(YS)
      YL=ALOG10(YL)
   80 IF(NO-1) 120,90,120
   90 CONTINUE
      MATRIX=IWID*LINES
      DO 100 I=1,LINES
      DO 100 J=1,IWID
  100 IGRAPH(J,I)=IBLANK
      XSCALE=(XL-XS)/RWID
      A=LINES-1
      YSCALE=(YL-YS)/A
      DO 110 I=1,LINES
      IGRAPH(1,I)=IBORDE
  110 IGRAPH(IWID,I)=IBORDE
  120 DO 170 I=1,LAST
      IF(XL-X(I)) 170,130,130
  130 IF(X(I)-XS) 170,140,140
  140 IF(YL-Y(I)) 170,150,150
  150 IF(Y(I)-YS) 170,160,160
  160 IX=(X(I)-XS)/XSCALE + 1.5
      IY=(Y(I)-YS)/YSCALE + 0.5
      IY=LINES-IY
      IGRAPH(IX,IY)=IPOINT
  170 CONTINUE
      IF(NO-MOST) 180,190,180
  180 RETURN
  190 CONTINUE
      WRITE(3,320)
      YES=YL+YSCALE
      DO 200 I=1,LINES
```

```
      YES=YES-YSCALE
      IF(IM.EQ.1) IHEAD=IHEAD1(I)
      IF(IM.EQ.2) IHEAD=IHEAD2(I)
200   WRITE(3,330)YES,IHEAD,(IGRAPH(J,I),J=1,IWID)
      WRITE(3,340)
      ZX(1)=0.0
      IF(IM.EQ.2) ZX(1)=0.00013
      ZX(2)=0.0013
      ZX(3)=0.013
      ZX(4)=0.13
      ZX(5)=1.0
      ZX(6)=10.0
      ZX(7)=100.0
      ZX(8)=1000.0
      WRITE(3,350)(ZX(K),K=1,8)
      IF(LOGX) 250,220,250
220   IF(LOGY) 230,310,230
230   WRITE(3,240)
240   FORMAT(26H Y IS PLOTTED ON LOG SCALE)
      GO TO 310
250   IF(LOGY) 260,280,260
260   WRITE(3,270)
270   FORMAT(34H X AND Y ARE PLOTTED ON LOG SCALES)
      GO TO 310
280   CONTINUE
      IF(IM.EQ.1) WRITE(3,290)
      IF(IM.EQ.2) WRITE(3,300)
290   FORMAT(/21X'VENTILATION - PERFUSION  RATIO,  LOG SCALE'///)
300   FORMAT(/20X'BLOOD:GAS PARTITION COEFFICIENT,  LOG SCALE'/////)
310   RETURN
320   FORMAT(11H   Y VALUES 3X,1H.,7X,1H.,7X,1H.,7X,1H.,7X,1H.,7X,1H.,
     17X,1H.,7X,1H.,7X,1H.)
330   FORMAT(1H F8.3,1X,A1,1X,101A1)
340   FORMAT(14X,1H.,7X,1H.,7X,1H.,7X,1H.,7X,1H.,7X,1H.,7X,1H.,8X,1H.,7X,
     11H.)
350   FORMAT(F17.4,F8.3,F8.2,F7.1,F8.1,F8.1,F10.1,F9.1)
      RETURN
      END

      SUBROUTINE BLOOD(PO2,PCO2,O2C,CO2C)
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      PH1=PH(PCO2,0.0)
      Y=0.003*HB*(1.0-SATURA(PO2,PCO2,PH1)/100.0)
      PH2=PH(PCO2,Y)
      SATRN=SATURA(PO2,PCO2,PH2)
      O2C=0.0139*HB*SATRN + SO2*PO2
      CO2C=CO2CON(PCO2,PH2,SATRN)
      RETURN
      END
      FUNCTION PH(PCO2,Y)
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      IF(PCO2.LT.0.001) PCO2=0.001
      IF(APH-1.0) 10,10,20
 10   PH=7.59 + Y - 0.2741*ALOG(PCO2/20.0)
      GO TO 30
 20   PH=BPH+Y+(APH-BPH)*ALOG(PCO2/BPCO2)/ALOG(APCO2/BPCO2)
 30   RETURN
      END
      FUNCTION CO2CON(PCO2,PHE,SATN)
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      P=7.4-PHE
      PK=6.086+0.042*P+(38.0-TEMP)*(0.00472+0.00139*P)
      SOL=0.0307 + 0.00057*(37.0-TEMP) + 0.00002*(37.0-TEMP)*(37.0-TEMP)
      DOX=0.59+0.2913*P-0.0844*P*P
      DR=0.664+0.2275*P-0.0938*P*P
      DDD=DOX+(DR-DOX)*(1.-SATN/100.0)
      CP=SOL*PCO2*(1.0+10.0**(PHE-PK))
      CCC=DDD*CP
      CO2CON=(HCRIT*CCC*0.01 + (1.0-HCRIT*0.01)*CP)*2.22
      RETURN
      END
      FUNCTION SATURA(PO2,PCO2,PHE)
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      KOUNT=KOUNT+1
```

```
      A1=-8532.229
      A2=2121.401
      A3=-67.07399
      A4=935960.9
      A5=-31346.26
      A6=2396.167
      A7=-67.10441
      B=0.43429*ALOG(40.0/PCO2)
      X=PO2*10.0**(0.024*(37.0-TEMP)+0.4*(PHE-7.4)+0.06*B)
      X=26.8*X/(26.8+DP50)
      IF(X-10.0) 10,20,20
   10 SAT=0.003683*X + 0.000584*X*X
      GO TO 30
   20 SAT=(X*(X*(X*(X+A3)+A2)+A1))/(X*(X*(X*(X+A7)+A6)+A5)+A4)
   30 SATURA=100.0*SAT
      RETURN
      END
      SUBROUTINE SAMEO2(PPO,PPCO,ARTO2C,CO2CT2)
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      E=0.0
      F=PIO2+10.0
   10 G=(E+F)/2.0
      CALL BLOOD(G,PPCO,O2CNT2,CO2CT2)
      A10=ABS(O2CNT2-ARTO2C)
      IF(A10-0.001) 50,50,20
   20 IF(O2CNT2-ARTO2C) 30,50,40
   30 E=G
      GO TO 10
   40 F=G
      GO TO 10
   50 CONTINUE
      PPO=G
      RETURN
      END
      SUBROUTINE FNDTEN(PPO,PPCO,ARTO2C,ARTCO2)
      DIMENSION PI(4)
      PI(1)=10.0
      PI(2)=1.0
      PI(3)=0.1
      PI(4)=0.01
      PPCO=0.0
      DO 20 K=1,4
   10 PPCO=PPCO+PI(K)
      CALL SAMEO2 (PPO,PPCO,ARTO2C,CO2CT2)
      IF(CO2CT2-ARTCO2) 10,20,20
   20 PPCO=PPCO-PI(K)
      RETURN
      END
      SUBROUTINE DETERM(U,F,G,DET)
      DIMENSION U(3),F(3),G(3),W(3)
      I=1
      J=2
      K=3
   10 W(I)=U(I)*(F(J)*G(K) - F(K)*G(J))
      IF(I-3) 20,50,50
   20 IF(I-1) 30,30,40
   30 I=2
      J=3
      K=1
      GO TO 10
   40 I=3
      J=1
      K=2
      GO TO 10
   50 DET=0.0
      DO 60 I=1,3
   60 DET=DET+W(I)
      RETURN
      END
      SUBROUTINE SUMUP(KRUN)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
```

```
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     +IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      CALL BLOOD(PVO2,PVCO2,FMVO2,FMVCO2)
      KNT=0
      DM1=0.020*GVO2
      DM2=0.025*GVO2
      DM3=0.030*GVO2
C
C     ALTERNATIVE FIRST THREE GUESSES COULD BE:
C
C     0.8*QT
C     1.0*QT
C     1.5*QT
C
   10 KNT=KNT+1
      IF(KNT.EQ.1) DM=DM1
      IF(KNT.EQ.2) DM=1.2*DM1
      IF(KNT.EQ.3) DM=DM3
   20 CC=0.0
      DD=0.0
      DLO2=0.0
      DLCO2=0.0
      IWARN2=0
      DO 30 I=1,NVAQS
      FVQQ(I)=0.0
      PO22(I)=0.0
      PCO22(I)=0.0
      PN22(I)=0.0
      RZZ(I)=0.0
      PBO2(I)=0.0
      PBCO2(I)=0.0
      OO2CON(I)=0.0
      OCCO2(I)=0.0
   30 CONTINUE
      IF(IBOHR.EQ.2) WRITE(*,40)KRUN
   40 FORMAT(//,3X'#'5X'PAO2'6X'PaO2'6X'PACO2'5X'PaCO2          SET:'I5/)
      DO 80 I=2,NVAQS-1
      IF(IBOHR.EQ.2.AND.Q(I).LE.1.E-6) GO TO 80
      GVAQ=VAQ(I)
      FI=FIO2+FICO2
      SUM=ABS(FI-1.0)
      IF(SUM.LE.0.0001) GO TO 60
      CALL VQSOLN
      IF (IWARN.EQ.1) IWARN2=1
      IF(IBOHR.EQ.2) WRITE(*,50)I,PAO2,PO2B,PACO2,PCO2B
   50 FORMAT(' ',I3,4F10.2)
      GO TO 70
   60 CALL PUREO2
   70 CONTINUE
      PBO2(I)=PO2B
      PBCO2(I)=PCO2B
      IF(IBOHR.EQ.2) CALL BLOOD(PO2B,PCO2B,O2CON,CCO2)
      FVQQ(I)=FVQ
      PO22(I)=PAO2
      PCO22(I)=PACO2
      PN22(I)=PIO2/FIO2-PAO2-PACO2
      RZZ(I)=RZ
      OO2CON(I)=O2CON
      OCCO2(I)=CCO2
      CC=CC+OO2CON(I)*Q(I)
      DD=DD+OCCO2(I)*Q(I)
      DLO2=DLO2+DDLO2*Q(I)
      DLCO2=DLCO2+DDLCO2*Q(I)
   80 CONTINUE
      FVQQ(1)=0.0
      PO22(1)=PVO2
      PCO22(1)=PVCO2
      PBO2(1)=PVO2
      PBCO2(1)=PVCO2
      RZZ(1)=0.0
```

```
      PN22(1) = PIO2/FIO2-PVO2-PVCO2
      OO2CON(1) = FMVO2
      OCCO2(1) = FMVCO2
      FVQQ(NVAQS) = 30000.0
      PO22(NVAQS) = PIO2
      PCO22(NVAQS) = PICO2
      PN22(NVAQS) = PIO2/FIO2-PIO2-PICO2
      RZZ(NVAQS) = 0.0
      OO2CON(NVAQS) = 0.0
      OCCO2(NVAQS) = 0.0
      Q(NVAQS) = 0.0
      CC=CC+OO2CON(1)*Q(1)
      DD=DD+OCCO2(1)*Q(1)
      ARTO2C = CC/QT
      ARTCO2=DD/QT
      DLO2=DLO2/(QT-Q(1))
      DLCO2=DLCO2/(QT-Q(1))
      FVO2=10.0*QT*(ARTO2C-FMVO2)
      FVCO2=10.0*QT*(FMVCO2-ARTCO2)
      CALL FNDTEN(PP1,PP2,ARTO2C,ARTCO2)
      PO2=PP1
      PCO2=PP2
      PO2ER=PO2-PMAO2
      IF(IBOHR.EQ.2) WRITE(3,90)KNT,DM,PO2ER
      IF(IBOHR.EQ.2) WRITE(*,90)KNT,DM,PO2ER
   90 FORMAT(' ITN',I3,';  DM=',F8.2,'; & PO2 ERROR=',F7.2)
      IF (IBOHR.EQ.1) GO TO 140
      IF(ABS(PO2ER).LT.0.1) GO TO 140
      IF(KNT.EQ.2) GO TO 100
      IF(KNT.EQ.3) GO TO 110
      IF(KNT.GT.3) GO TO 120
      IF(PO2ER.GT.-5.0.AND.PO2ER.LT.0.0) GO TO 99
      IF(PO2ER.LT.-10.0) DM=1.2*DM
      IF(PO2ER.LT.-10.0) GO TO 20
      IF(PO2ER.LT.-5.0) DM=1.1*DM
      IF(PO2ER.LT.-5.0) GO TO 20
      IF(PO2ER.GT.0.0) DM=0.8*DM
      IF(PO2ER.GT.0.0) GO TO 20
   99 DM1=DM
      ERR1=PO2ER
      GO TO 10
  100 DM2=DM
      ERR2=PO2ER
      GO TO 10
  110 CONTINUE
      IF(PO2ER.LE.-10.0) DM=4.0*DM
      IF(PO2ER.GT.-10.0.AND.PO2ER.LE.-5.0) DM=2.0*DM
      IF(PO2ER.GT. -5.0.AND.PO2ER.LE.-2.0) DM=1.50*DM
      IF(PO2ER.GT. -2.0.AND.PO2ER.LT. 0.0) DM=1.1*DM
      IF(PO2ER.LT.0.0) GO TO 20
      IF(PO2ER.GE.(ARTPM-0.5)) DM=0.8*DM
      IF(PO2ER.GE.(ARTPM-0.5)) GO TO 20
      DM3=DM
      ERR3=PO2ER
      GO TO 130
  120 DM1=DM2
      ERR1=ERR2
      DM2=DM3
      ERR2=ERR3
      DM3=DM
      ERR3=PO2ER
  130 T1=(ERR1-ERR2)/(DM1-DM2)
      T2=(ERR1-ERR3)/(DM1-DM3)
      A=(T1-T2)/(DM2-DM3)
      B=T1 - A*(DM1+DM2)
      C=ERR1 - B*DM1 - A*DM1*DM1
      DM=(SQRT(B*B - 4.0*A*C) - B)/(2.0*A)
      GO TO 10
  140 CONTINUE
      RETURN
      END
      SUBROUTINE PUREO2
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
```

```
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      TOL1=0.001
      PCO21=PICO2
      PCO22=PICO2+PIO2
 10   PACO2=(PCO21+PCO22)/2.0
      PAO2=PIO2+PICO2-PACO2
      CALL BLOOD(PAO2,PACO2,O2CON,COCON)
      R1=(O2CON-FMVO2)/(FMVCO2-COCON)
      CON1=1.0 + FICO2*(R1-1.0)
      FVQ=8.63*(FMVCO2-COCON)*CON1/(PACO2-PICO2)
      DIFF=ABS(GVAQ-FVQ)
      IF(DIFF.LE.TOL1) GO TO 40
      IF(GVAQ-FVQ) 20,40,30
 20   PCO21=PACO2
      GO TO 10
 30   PCO22=PACO2
      GO TO 10
 40   CONTINUE
      RZ=1.0/R1
      CCO2=COCON
      PO2=PAO2
      PCO2=PACO2
      RETURN
      END
      SUBROUTINE FNDMVP(KRUN,X,Y)
      DIMENSION X(4),Y(4),F(4),G(4),U(4)
      DIMENSION VINSP(50)
      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     +IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      IF(ARTPM.LE.1.0.AND.IBOHR.EQ.2) WRITE(3,1)
 1    FORMAT(' NOT ATTEMPTING BOHR INTEGRATION BECAUSE',/,' PREDICTED',
     1' ARTERIAL PO2 IS LESS THAN 1 TORR MORE THAN MEASURED')
      IF(ARTPM.LE.1.0.AND.IBOHR.EQ.2) RETURN
      IF(IBOHR.EQ.2) WRITE(3,5)
 5    FORMAT(//,19X,'***** BOHR INTEGRATION RESULTS *****'//)
      DO 10 I=1,50
      Q(I)=QQ(I)
 10   CONTINUE
      PVN2=PIO2/FIO2-PIO2-PICO2
      FBTPS=(273.0+TEMP)*PB*FIO2/(273.0*PIO2)
C      WRITE(3,20)
 20   FORMAT(/,8X'ITERATION'6X'PVO2'5X'PVCO2'5X'+VO2'4X'+VCO2')
      ITER=0
      NNN=3
 30   DO 70 N=1,NNN
      PVO2=X(N)
      PVCO2=Y(N)
      CALL SUMUP(KRUN)
      F(N)=FVO2-GVO2
      G(N)=FVCO2-GVCO2
      IF(NNN.EQ.3) WRITE(3,20)
      WRITE(3,40)ITER,X(N),Y(N),F(N),G(N)
 40   FORMAT(11X,I3,6X,F7.2,2X,F8.2,2F9.1)
      IF(ABS(F(N))-TOL) 50,50,70
 50   IF(ABS(G(N))-TOL) 60,60,70
 60   CONTINUE
      GO TO 190
 70   CONTINUE
      DO 80 N=1,3
      U(N)=1.0
 80   CONTINUE
      CALL DETERM(U,F,G,DET1)
      DO 90 N=1,3
 90   U(N)=X(N)
      NFLAG=0
```

```
100   CALL DETERM(U,F,G,DET2)
      IF(NFLAG-1) 110,120,120
110   X(4)=DET2/DET1
      GO TO 130
120   Y(4) = DET2/DET1
130   IF(NFLAG-1) 140,160,160
140   DO 150 N=1,3
150   U(N)=Y(N)
      NFLAG=1
      GO TO 100
160   DO 170 N=1,2
      J=4-N
      X(J)=X(J-1)
      Y(J)=Y(J-1)
      F(J)=F(J-1)
      G(J)=G(J-1)
170   CONTINUE
      X(1)=X(4)
      Y(1)=Y(4)
      NNN=1
      ITER=ITER+1
      IF(ITER-10) 180,190,190
180   GO TO 30
190   CONTINUE
      PVVO2=X(N)
      PVVCO2=Y(N)
      CALL BLOOD(PVVO2,PVVCO2,FVVO2,FVVCO2)
      IF(IBOHR.EQ.1) WRITE(3,195)
195   FORMAT(/2X'N'7X'VA'7X'Q'6X'VA/Q'3X'PO2'3X'PCO2'3X'O2CON',
     12X'CO2CON'3X'VINSP'3X'RQ')
      IF(IBOHR.EQ.2) WRITE(3,200)
200   FORMAT(/2X'N'5X'VA/Q'3X'PAO2'3X'PaO2'2X'PACO2'2X
     1'PaCO2'2X'O2CON'2X'CO2CON'3X'RQ')
      PAN2=0.0
      DO 210 I=1,NVAQS-1
      IF(IBOHR.EQ.2.AND.I.EQ.1) GO TO 210
      IF(IBOHR.EQ.2.AND.Q(I).LE.1.0E-6) GO TO 210
      VINSP(I)=V(I)*PO22(I)/PIO2 + 8.63*Q(I)*(OO2CON(I)-FMVO2)/PIO2
      IF(IBOHR.EQ.1) WRITE(3,215)I,V(I),Q(I),VAQ(I),PO22(I),PCO22(I),
     1OO2CON(I),OCCO2(I),VINSP(I),RZZ(I)
      IF(IBOHR.EQ.2) WRITE(3,220)I,VAQ(I),PO22(I),PBO2(I),
     1PCO22(I),PBCO2(I),OO2CON(I),OCCO2(I),RZZ(I)
      PAN2=PAN2+Q(I)*PN22(I)
210   CONTINUE
215   FORMAT(I3,F10.4,F9.4,F8.4,4F7.2,F8.2,F6.2)
220   FORMAT(I3,F9.4,6F7.2,F6.2)
      I=NVAQS
      VINSP(I) = V(NVAQS)
      IF(IBOHR.EQ.1) WRITE(3,230)I,V(I),Q(I),PO22(I),PCO22(I),
     1OO2CON(I),OCCO2(I),VINSP(I),RZZ(I)
230   FORMAT(I3,F10.4,F9.4,'  INF    ',4F7.2,F8.2,F6.2)
      PAN2=PVN2*(1.0-QR/QT) + PAN2/QT
      CAN2=ALPHA*PAN2
      CVN2=ALPHA*PVN2
      VN2=10.0*QT*(CAN2-CVN2)
      WRITE(3,240)PAN2,PVN2,VN2
240   FORMAT(/11X,' MIXED ARTERIAL PN2 '21X,'=',F9.1,/,
     111X,' MIXED VENOUS   PN2 '21X,'=',F9.1,/,
     211X,' N2 UPTAKE, ML/MIN  '21X,'=',F9.1/)
      RETURN
      END
      SUBROUTINE WRITE
      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     +IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      IF(IBOHR.EQ.2) GO TO 160
      AA=0.0
```

```
      BB=0.0
      EE=0.0
      FFF=0.0
      DO 10 I=1,NVAQS
      AA=AA+V(I)*PO22(I)
      BB=BB+V(I)*PCO22(I)
      EE=EE+V(I)*PN22(I)
      FFF=FFF+Q(I)*PN22(I)
   10 CONTINUE
      ALVPO2=AA/VT
      ALVPCO=BB/VT
      ALVPN2=EE/VT
      ARTPN2=FFF/QT
      O2IN=FVO2
      CO2OUT=FVCO2
      OVERAL=CO2OUT/O2IN
      RMEAS=GVCO2/GVO2
      WRITE(3,20)ALVPO2,ALVPCO,O2IN,CO2OUT,OVERAL,RMEAS
   20 FORMAT(12X,'MIXED EXPIRED  PO2                          =',F10.2,/,
     112X,'MIXED EXPIRED  PCO2                       =',F10.2,/,
     112X,'OXYGEN UPTAKE                             =',F10.2,/,
     112X,'CARBON DIOXIDE OUTPUT                     =',F10.2,/,
     112X,'PREDICTED R                               =',F10.2,/,
     112X,'MEASURED R                                =',F10.2,/)
      CALL FNDTEN(ARTPO2,ARTPCO,ARTO2C,ARTCO2)
      O2DIF=ALVPO2-ARTPO2
      CO2DIF=ARTPCO-ALVPCO
      DIFN2=ARTPN2-ALVPN2
      WRITE(3,30)ARTPO2,ARTPCO,ARTO2C,ARTCO2,O2DIF,CO2DIF,DIFN2
   30 FORMAT(12X,'ARTERIAL PO2                                =',F10.2,/,
     112X,'ARTERIAL PCO2                             =',F10.2,//,
     112X,'ARTERIAL O2 CONTENT                       =',F10.2,/,
     112X,'ARTERIAL CO2 CONTENT                      =',F10.2,/,
     112X,'MIXED ALVEOLAR-ARTERIAL PO2 DIFFERENCE  =',F10.2,/,
     112X,'MIXED ALVEOLAR-ARTERIAL PCO2 DIFFERENCE =',F10.2,/,
     112X,'MIXED ALVEOLAR-ARTERIAL PN2 DIFFERENCE  =',F10.2)
      IF(OVERAL.LE.0.0) RETURN
      GRADMP=0.0
      ARTPM=ARTPO2-PMAO2
      CONPM=ARTO2C-AMO2C
      DO 140 II=1,2
      IF(II.EQ.1) WRITE(3,40)
      IF(II.EQ.2) WRITE(3,50)
   40 FORMAT(/'  IDEAL CALCULATIONS USING PREDICTED VO2 & VCO2:'/)
   50 FORMAT(/'  IDEAL CALCULATIONS USING  MEASURED VO2 & VCO2:'/)
      P1=0.0
      P2=1.2*PVCO2
      IRCNT=0
   60 PACO2=(P1+P2)/2.0
      IRCNT=IRCNT+1
      IF(II.EQ.1) RM=OVERAL
      IF(II.EQ.2) RM=RMEAS
      IF(II.EQ.2) ARTPO2=PMAO2
      FI=FIO2+FICO2
      SUM=ABS(FI-1.0)
      IF(SUM.LE.0.0001) GO TO 70
      GO TO 80
   70 PAO2=PIO2-PACO2+PICO2
      GO TO 90
   80 PAO2=PIO2*RM+PACO2*FIO2*(1.0-RM)+PICO2-PACO2
      PAO2=PAO2/(RM+FICO2*(1.0-RM))
   90 CONTINUE
      CALL BLOOD(PAO2,PACO2,O2CONE,CCO2E)
      IF(O2CONE.EQ.FMVO2) GO TO 110
      BLOODR=(FMVCO2-CCO2E)/(O2CONE-FMVO2)
      DIFF=ABS(RM-BLOODR)
      IF(DIFF.LE.0.001) GO TO 110
      IF(IRCNT.GT.50) GO TO 110
      IF(BLOODR.GT.RM) GO TO 100
      P2=PACO2
      GO TO 60
  100 P1=PACO2
      GO TO 60
  110 CONTINUE
```

```
      CON1=1.0+FICO2*(RM-1.0)
      GVAQ=8.63*(FMVCO2-CCO2E)*CON1/(PACO2-PICO2)
      PO2IDE=PAO2
      PCO2ID=PACO2
      DEALDI=PO2IDE-ARTPO2
      DEALO2=O2CONE
      IF(II.EQ.1) GRADMP=GRADMP-DEALDI
      IF(II.EQ.2) GRADMP=GRADMP+DEALDI
      ALVDS=100.0*(PCO2ID-ALVPCO)/(PCO2ID-PICO2)
      QSQT=0.0
      IF(DEALO2.EQ.FMVO2) GO TO 120
      QSQT=100.0*(DEALO2-ARTO2C)/(DEALO2-FMVO2)
      IF(II.EQ.2) QSQT=100.0*(DEALO2-AMO2C)/(DEALO2-FMVO2)
  120 WRITE(3,130)PO2IDE,PCO2ID,DEALDI,DEALO2,ALVDS,QSQT,KOUNT,GVAQ
  130 FORMAT(12X,'IDEAL ALVEOLAR PO2                              =',F10.2,/,
     112X'IDEAL ALVEOLAR PCO2                                     =',F10.2,/,
     112X'IDEAL ALVEOLAR-ARTERIAL PO2 DIFFERENCE                  =',F10.2,/,
     112X'IDEAL O2 CONTENT                                        =',F10.2,/,
     112X'PHYSIOLOGIC DEAD SPACE PCT                              =',F10.2,/,
     112X'VENOUS ADMIXTURE PCT                                    =',F10.2,/,
     112X'NUMBER OF TIMES SATURA CALLED                           =',I10,/,
     112X'IDEAL VA/Q                                              =',F10.2)
  140 CONTINUE
      WRITE(3,150) ARTPM,CONPM,GRADMP
  150 FORMAT(/,
     1'  PREDICTED - MEASURED ARTERIAL PO2                        ='F10.2,/,
     2'  PREDICTED - MEASURED ARTERIAL CONTENT                     ='F10.2,/,
     3'  MEASURED - PREDICTED ALVEOLAR-ARTERIAL GRADIENT          ='F10.2//)
      GO TO 220
  160 CONTINUE
      IF(ARTPM.LE.1.0) GO TO 220
      AA=0.0
      BB=0.0
      EE=0.0
      FFF=0.0
      DO 180 I=1,NVAQS
      AA=AA+V(I)*PO22(I)
      BB=BB+V(I)*PCO22(I)
      EE=EE+V(I)*PN22(I)
      FFF=FFF+Q(I)*PN22(I)
  180 CONTINUE
      ALVPO2=AA/VT
      ALVPCO=BB/VT
      ALVPN2=EE/VT
      ARTPN2=FFF/QT
      O2IN=FVO2
      CO2OUT=FVCO2
      OVERAL=CO2OUT/O2IN
      RMEAS=GVCO2/GVO2
      WRITE(3,190) ALVPO2,ALVPCO,O2IN,CO2OUT,OVERAL,RMEAS
  190 FORMAT(12X,'MIXED EXPIRED  PO2                              =',F10.2,/,
     112X,'MIXED EXPIRED  PCO2                                    =',F10.2,/,
     112X,'OXYGEN UPTAKE                                          =',F10.2,/,
     112X,'CARBON DIOXIDE OUTPUT                                  =',F10.2,/,
     112X,'PREDICTED R                                            =',F10.2,/,
     112X,'MEASURED R                                             =',F10.2,/)
      CALL FNDTEN(ARTPO2,ARTPCO,ARTO2C,ARTCO2)
      O2DIF=ALVPO2-ARTPO2
      CO2DIF=ARTPCO-ALVPCO
      DIFN2=ARTPN2-ALVPN2
      WRITE(3,200) ARTPO2,ARTPCO,ARTO2C,ARTCO2,O2DIF,CO2DIF,DIFN2
  200 FORMAT(12X,'ARTERIAL PO2                                    =',F10.2,/,
     112X,'ARTERIAL PCO2                                          =',F10.2,//,
     112X,'ARTERIAL O2 CONTENT                                    =',F10.2,/,
     112X,'ARTERIAL CO2 CONTENT                                   =',F10.2,/,
     112X,'MIXED ALVEOLAR-ARTERIAL PO2 DIFFERENCE                 =',F10.2,/,
     112X,'MIXED ALVEOLAR-ARTERIAL PCO2 DIFFERENCE                =',F10.2,/,
     112X,'MIXED ALVEOLAR-ARTERIAL PN2 DIFFERENCE                 =',F10.2)
      NT=RNT
      WRITE (3,210) DDLO2,DDLCO2,NT
  210 FORMAT(/12X,'DLO2  by Bohr Integration                       =',F10.2,/,
     112X,'DLCO2 set to 5*DLO2                                    =',F10.2,/,
     212X,'NUMBER OF STEPS USED                                   =',I10,///)
      IF (IWARN2.EQ.0) GOTO 220
```

```
      WRITE(3,215)
      WRITE(*,215)
 215  FORMAT(' Possible truncation error: try smaller step size')
 220  CONTINUE
      RETURN
      END
      SUBROUTINE VQSOLN
      DIMENSION X(4),Y(4),G(4),U(4),F(4)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
C      COMMON/VQ/V(50),Q(50),QQ(50),VAQ(50)
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     + IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
C      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
C     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      TOL1=0.001
      Y(1)=PVCO2*6.0/(6.0 + GVAQ)
      Y(2)=Y(1) + 5.0
      Y(3)=Y(2)
      IF(GVAQ.LE.0.55) GO TO 20
      IF(GVAQ.GE.10.0)GO TO 10
      X(1) = PIO2-30.0
      X(2) = PIO2-60.0
      X(3) = PIO2-30.0
      GO TO 30
  10  CONTINUE
      X(1)=PIO2
      X(2)=0.95*PIO2+0.05*PVO2
      X(3) = X(1)
      GO TO 30
  20  CONTINUE
      X(1) = PVO2 + 0.1
      X(2)=X(1)+10.0
      X(3)=X(1)
  30  CONTINUE
      ITER=0
      NNN=3
  40  DO 90 N=1,NNN
      CALL BOHRI(X(N),Y(N),O2CON,CCO2)
      IF(PVN2.EQ.0.0) GO TO 50
C     N2 EXCHANGE INCORPORATED
      RZ=(FMVCO2-CCO2)/(O2CON-FMVO2)
      PAO2=X(N)
      PACO2=Y(N)
      FAO2=PAO2*FIO2/PIO2
      FACO2=PACO2*FIO2/PIO2
      FVN2=PVN2*FIO2/PIO2
      C1=1.0-FAO2-FACO2
      C2=C1-FVN2
      C3=1.0-FIO2-FICO2
      B1=GVAQ*C1/C3
      B2=8.63*ALPHA*C2/C3
      O2CON1=FMVO2 + (PIO2*(B1+B2) - PAO2*GVAQ)/8.63
      CCO21=FMVCO2 - (PACO2*GVAQ - PICO2*(B1+B2))/8.63
      GO TO 60
  50  CONTINUE
C     N2 EXCHANGE IGNORED
      ABAB=Y(N)*(1.0-FIO2) - FICO2*(PIO2/FIO2 - X(N))
      AAAA=ABAB*GVAQ/(8.63*(1.0-FIO2-FICO2))
      BBAA=PIO2-X(N)*(1.0-FICO2) - FIO2*Y(N)
      AABB=Y(N)*(1.0-FIO2) - PICO2 + FICO2*X(N)
      RZ=AABB/BBAA
      O2CON1 = FMVO2 + AAAA/RZ
      CCO21 = FMVCO2-AAAA
  60  CONTINUE
      F(N) = O2CON-O2CON1
      G(N) = CCO2-CCO21
      IF(ABS(F(N))-TOL1) 70,70,90
  70  IF(ABS(G(N))-TOL1) 80,80,90
  80  CONTINUE
      PAO2=X(N)
```

```
      PACO2=Y(N)
      GO TO 210
   90 CONTINUE
      DO 100 N=1,3
  100 U(N)=1.0
      CALL DETERM(U,F,G,DET1)
      DO 110 N=1,3
  110 U(N)=X(N)
      NFLAG=0
  120 CALL DETERM(U,F,G,DET2)
      IF(NFLAG-1) 130,140,140
  130 IF(DET1.NE.0.0) X(4) = DET2/DET1
      IF(DET1.EQ.0.0) X(4)=PAO2 + 1.0
      GO TO 150
  140 IF(DET1.NE.0.0) Y(4) = DET2/DET1
      IF(DET1.EQ.0.0) Y(4)=PACO2+1.0
  150 IF(NFLAG-1) 160,180,180
  160 DO 170 N=1,3
  170 U(N)=Y(N)
      NFLAG=1
      GO TO 120
  180 DO 190 N=1,2
      J=4-N
      X(J)=X(J-1)
      Y(J)=Y(J-1)
      F(J)=F(J-1)
      G(J)=G(J-1)
  190 CONTINUE
      X(1)=X(4)
      Y(1)=Y(4)
      NNN=1
      ITER=ITER+1
      IF(ITER-20) 200,210,210
  200 GO TO 40
  210 CONTINUE
      IF(PICO2.GT.0.0) GO TO 220
      FVQ=8.63*(FMVCO2-CCO2)/PACO2
      GO TO 230
  220 CONTINUE
      D1=(O2CON-FMVO2)/PIO2 + (FMVCO2-CCO2)/PICO2
      D2=PACO2/PICO2-PAO2/PIO2
      FVQ=8.63*D1/D2
  230 CONTINUE
      PO2=PAO2
      PCO2=PACO2
      RETURN
      END
      SUBROUTINE FTEN(X,Y,OXO2,COCON,PO2,PCO2)
C      DOUBLE PRECISION U,F,G,DET1,DET2
      DIMENSION X(4),Y(4),F(4),G(4),U(4)
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      DO 10 KK=1,4
      F(KK)=0.
      G(KK)=0.
      U(KK)=0.
   10 CONTINUE
      ITER=0
      TOL=.001
      NNN=3
   20 DO 50 N=1,NNN
      PH1=PH(Y(N),0.0)
      Y1=.003*HB*(1.-SATURA(X(N),Y(N),PH1)/100.)
      PH2=PH(Y(N),Y1)
      SATRN=SATURA(X(N),Y(N),PH2)
      FNN=.0139*HB*SATRN+SO2*X(N)-OXO2
      GNN=CO2CON(Y(N),PH2,SATRN)-COCON
      F(N)=FNN
      G(N)=GNN
      IF(ABS(FNN)-TOL)30,30,50
   30 IF(ABS(GNN)-TOL)40,40,50
   40 PO2=X(N)
      PCO2=Y(N)
      GO TO 170
   50 CONTINUE
```

```
      DO 60 N=1,3
      U(N)=1.
   60 CONTINUE
      CALL DETER(U,F,G,DET1)
      DO 70 N=1,3
      U(N)=X(N)
   70 CONTINUE
      NFLAG=0
      PNO2=X(1)
      PNCO2=Y(1)
   80 CALL DETER(U,F,G,DET2)
      IF(NFLAG-1)90,100,100
   90 IF(DET1.EQ.0.) X(4)=PNO2*1.05
      IF(DET1.NE.0.) X(4)=DET2/DET1
      GO TO 110
  100 IF(DET1.EQ.0.) Y(4)=PNCO2*.95
      IF(DET1.NE.0.) Y(4)=DET2/DET1
  110 IF(NFLAG-1)120,140,140
  120 DO 130 N=1,3
      U(N)=Y(N)
  130 CONTINUE
      NFLAG=1
      GO TO 80
  140 DO 150 N=1,2
      J=4-N
      X(J)=X(J-1)
      Y(J)=Y(J-1)
      F(J)=F(J-1)
      G(J)=G(J-1)
  150 CONTINUE
      X(1)=X(4)
      Y(1)=Y(4)
      NNN=1
      ITER=ITER+1
      IF(ITER-30)160,170,170
  160 GO TO 20
  170 CONTINUE
      X(1)=PO2
      X(2)=PO2
      X(3)=PO2+5.
      Y(1)=PCO2
      Y(2)=PCO2-5.
      IF(Y(2).LE.1.0) Y(2)=1.0
      Y(3)=PCO2
      RETURN
      END
      SUBROUTINE BOHRI(PAAO2,PAACO2,O2CONE,CCO2E)
      DIMENSION X(4),Y(4),GRADO2(5),GRADCO(5)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     + IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
      IWARN=0
      PAO2=PAAO2
      PACO2=PAACO2
      IF (DM.GT.9000.0.OR.IBOHR.EQ.1) GO TO 30
      DO 10 I=1,5
      GRADCO(I)=0.0
      GRADO2(I)=0.0
   10 CONTINUE
      O2CI=FMVO2
      CO2CI=FMVCO2
      X(1)=PVO2
      X(2)=PVO2
      X(3)=PVO2+5.
      Y(1)=PVCO2
      Y(2)=PVCO2-5.
      Y(3)=PVCO2
      X(4)=0.
```

```
      Y(4)=0.
      PASTPO=0.
      PASTPC=0.
      NT=RNT
      DDLO2=DM
      DDLCO2=5.0*DM
      DO 20 I=1,NT
      CALL CALC(X,Y,O2CI,CO2CI,FO21,FCO21)
      IF((FO21.EQ.9000.0).OR.(FCO21.EQ.9000.0)) GOTO 30
      CALL CALC(X,Y,O2CI+FO21/2.0,CO2CI+FCO21/2.0,FO22,FCO22)
      IF((FO22.EQ.9000.0).OR.(FCO22.EQ.9000.0)) GOTO 30
      CALL CALC(X,Y,O2CI+FO22/2.0,CO2CI+FCO22/2.0,FO23,FCO23)
      IF((FO23.EQ.9000.0).OR.(FCO23.EQ.9000.0)) GOTO 30
      CALL CALC(X,Y,O2CI+FO23,CO2CI+FCO23,FO24,FCO24)
      IF((FO24.EQ.9000.0).OR.(FCO24.EQ.9000.0)) GOTO 30
      O2CI=O2CI+(FO21+FO22*2.0+FO23*2.0+FO24)/6.0
      CO2CI=CO2CI+(FCO21+FCO22*2.0+FCO23*2.0+FCO24)/6.0
      CALL FTEN(X,Y,O2CI,CO2CI,PO2I,PCO2I)
      PASTPO=PO2I
      PASTPC=PCO2I
   20 CONTINUE
      IF (DM.LT.9000.) GO TO 40
C
C     COME HERE IF DM IS ESSENTIALLY INFINITE ....
C
   30 PO2I=PAO2
      PCO2I=PACO2
      IWARN=1
      CALL BLOOD(PO2I,PCO2I,O2CI,CO2CI)
   40 CONTINUE
      O2CONE=O2CI
      CCO2E=CO2CI
      PO2B=PO2I
      PCO2B=PCO2I
      RETURN
      END
      SUBROUTINE CALC(X,Y,O2CI,CO2CI,DO2CI,DCO2CI)
C
C     THIS SUBROUTINE CALCULATES DO2,DCO2 FROM OTHER INPUTS
C
      DIMENSION X(4),Y(4)
      COMMON/INERT/NVAQS,VT,QT,NGASES,FACT,Z,VQLO,VQHI
      COMMON/OXY1/HB,HCRIT,TEMP,APH,BPH,APCO2,BPCO2,KOUNT,DP50,PIO2,SO2
      COMMON/OXY2/PB,FIO2,PICO2,FICO2,VS,QS,SKEW,GVO2,GVCO2,TOL,
     + PVO2,PVCO2,FMVO2,FMVCO2,PVN2,ALPHA,SHUNT,QR,GVAQ,FVQ,PAO2,
     + PACO2,O2CON,CCO2,PO2,PCO2,FVO2,FVCO2,RZ,RM,ARTO2C,ARTCO2,AMO2C
      COMMON/O2ARAY/OO2CON(50),OCCO2(50),FVQQ(50),PN22(50),PCO22(50),
     + PO22(50),RZZ(50),PBO2(50),PBCO2(50)
      COMMON/BOHR/DM,VC,BETA,RNT,DDLO2,DDLCO2,PMAO2,PMACO2,PO2B,PCO2B,
     + IBOHR,CAIII,IPRN,ARTPM,IWARN,IWARN2
      O2C=(1.39*HB) + (SO2*PIO2)
      IF ((CO2CI.LT.0.0).OR.(O2CI.GT.O2C)) GOTO 10
      CALL FTEN(X,Y,O2CI,CO2CI,PO2I,PCO2I)
      IF ((PO2I.LE.PAO2+2.0).AND.(PCO2I.GE.PACO2-1.0)) GOTO 20
   10 IF (PO2I.GT.PAO2+2.0) DO2CI=9000.0
      IF (PCO2I.LT.PACO2-1.0) DCO2CI=9000.0
      IF (CO2CI.LT.0.0) DCO2CI=9000.0
      IF (O2CI.GT.O2C) DO2CI=9000.0
      GOTO 30
   20 CONTINUE
      DO2CI=(PAO2-PO2I)*DDLO2/(RNT*(QT-QS)*10.)
      DCO2CI=(PACO2-PCO2I)*DDLCO2/(RNT*(QT-QS)*10.)
   30 IF(IPRN.LE.0) GO TO 40
      WRITE(*,35)O2CI,CO2CI,PO2I,PCO2I
   35 FORMAT(' IN CALC, O2CI,CO2CI,PO2I & PCO2I ARE:',4F10.3)
      WRITE(*,37)PAO2,PO2I,DM,DDLO2
   37 FORMAT(' IN CALC, PAO2,PO2I,DM & DDLO2 ARE:',4F10.3)
   40 CONTINUE
      RETURN
      END
      SUBROUTINE DETER(U,F,G,DET)
C
C     THIS SUBROUTINE IS USED BY BOTH THE MATCHING PROCEDURES.
C
```

```
      DIMENSION U(4),F(4),G(4),W(4)
C      DOUBLE PRECISION U,F,G,W,D,DET
      DO 10 KK=1,4
   10 W(KK)=0.0
      I=1
      J=2
      K=3
   20 W(I)=U(I)*(F(J)*G(K)-F(K)*G(J))
      IF(I-3)30,60,60
   30 IF(I-1)40,40,50
   40 I=2
      J=3
      K=1
      GO TO 20
   50 I=3
      J=1
      K=2
      GO TO 20
   60 D=0.
      DO 70 I=1,3
      D=D+W(I)
   70 CONTINUE
      DET=D
      RETURN
      END...............
```

7.5 LONG DATA OUTPUT FROM MIGET MODEL

```
SET NUMBER :  5  FROM FILE:  NICK SHIPP 11/7/97
 FITTING A BLOOD FLOW DISTRIBUTION TO RETENTIONS

 NUMBER OF GASES =  6
 NUMBER OF VA/Q COMPARTMENTS =  50
 SMOOTHING COEFFICIENT Z =   40.00
```

GAS	SOL	PC	R	E
1	.00086	.00614	.00183	.00189
2	.01370	.09771	.03532	.02910
3	.07957	.56750	.17402	.14471
4	.31197	2.22500	.47655	.35958
5	1.39372	9.94000	.78939	.64632
6	36.69378	261.70000	.99103	.72457

ITN	LOOP	TOTAL SSQ	FIT TO R	SUM Q*Q
0	1	7.793803	.245256	7.548547
0	2	10.831910	1.353007	9.478907
0	3	13.884840	2.786967	11.097880
0	4	16.175140	5.058248	11.116890
0	5	16.742870	6.250896	10.491970
0	6	16.910160	6.365654	10.544500
0	7	20.318680	6.277416	14.041260
0	8	21.260930	8.559921	12.701000

```
ITERATION NUMBER =  1
TOTAL BLOOD FLOW =  1.000009
```

PC	RETENTIONS	BEST FIT	ERROR	RAW DATA	ERROR
.0061	.365	.500	-.134	.00183	.00067
.0977	17.273	18.699	-1.426	.03532	.00291
.5675	20.177	21.544	-1.367	.17402	.01179
2.2250	31.838	31.174	.665	.47655	-.00995
9.9400	79.137	79.382	-.245	.78939	.00244
261.7000	1858.744	1856.718	2.026	.99103	-.00108
.0000	20000.000	20000.190	-.185	1.00000	.00000

```
REMAINING SUM OF SQUARES =  8.56E+00
```

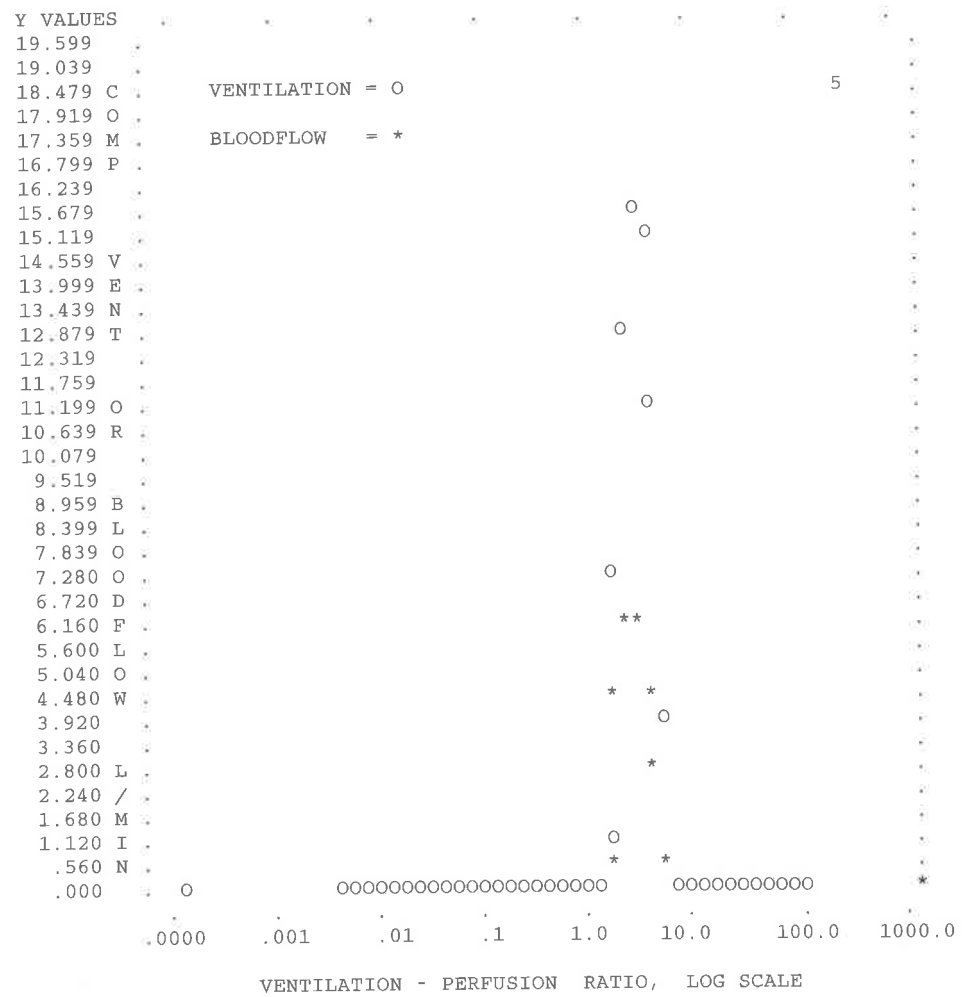
RANGE	BLOOD FLOW	VENTILATION
VA/Q OF ZERO	.000	ZERO (INTRA PULMONARY SHUNT)
VA/Q RANGE 0 TO .01	.000	.000
VA/Q RANGE .01 TO .1	.000	.000
VA/Q RANGE .1 TO 1.	.000	.000
VA/Q RANGE 1.0 TO 10.	1.000	.821
VA/Q RANGE 10. TO 100.	.000	.000
VA/Q OF INFINITY	ZERO	.179

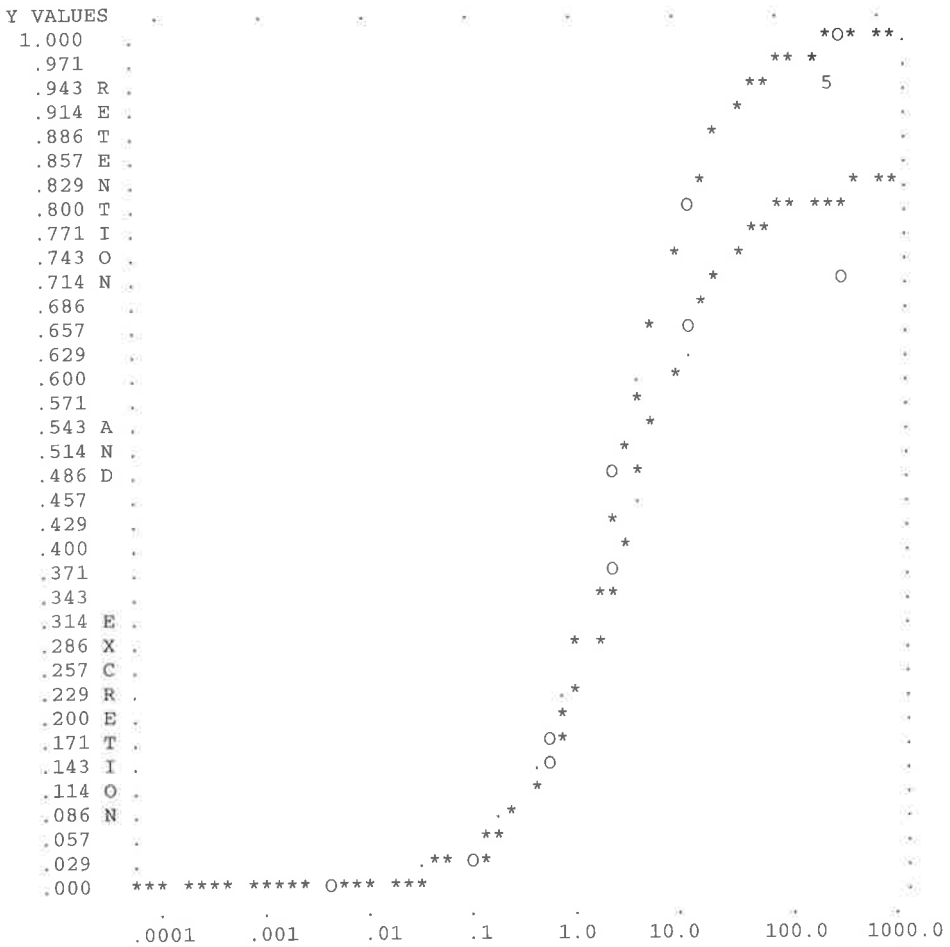
```
      MEAN OF BLOOD FLOW  DISTRIBUTION =   2.55
2nd MOMENT OF BLOOD FLOW  DISTRIBUTION =    .29 (Log SDQ)
3rd MOMEMT OF BLOOD FLOW  DISTRIBUTION =    .00

      MEAN OF VENTILATION DISTRIBUTION =   2.78
2nd MOMENT OF VENTILATION DISTRIBUTION =    .29 (LOG SDV)
3rd MOMENT OF VENTILATION DISTRIBUTION =    .00
```

GAS	PC	R	RH	R - RH	E	E*	EH	EH - E*	R - E*
1	.00614	.00250	.00230	.00020	.00189	.00230	.00230	.00000	.00020
2	.09771	.03823	.03542	.00281	.02901	.03532	.03542	.00010	.00291
3	.56750	.18580	.17580	.01000	.14265	.17367	.17580	.00213	.01213
4	2.22500	.46660	.45542	.01118	.36641	.44607	.45542	.00935	.02053
5	9.94000	.79183	.78885	.00298	.63883	.77772	.78885	.01113	.01411
6	261.70000	.98994	.98994	.00000	.81244	.98907	.98994	.00086	.00087

MAX POSSIBLE DEADSPACE VENTILATION = 14.5 L/MIN, OR AS A FRACTION = .179
DISPERSION DIRECTLY FROM DIFFERENCES BETWEEN:

BEST FIT	RETENTIONS & HOMOGENEOUS	RETENTIONS IS:	.63
HOMOGENEOUS	EXCRETIONS & BEST FIT	EXCRETIONS IS:	.60
BEST FIT	RETENTIONS * BEST FIT	EXCRETIONS IS:	1.14





BLOOD:GAS PARTITION COEFFICIENT, LOG SCALE

GAS EXCHANGE

GVO2	GVCO2	PIO2	FIO2	PICO2	FICO2	PB	TEMP	HB	HCRIT	P50	BX
3690.0	3235.0	149.8	.2100	.0	.00	760.0	36.9	14.6	44.0	27.1	1.1

FIRST BLOOD PH =7.49 PCO2 =30.00 PMAO2 = 78.50 CMAO2 = 19.67
SECOND BLOOD PH =7.30 PCO2 =60.00 PMACO2= 39.40 CMACO2= 49.24

TOTAL VENTILATION= 81.30 **(Minute Ventilation)**
TOTAL BLOOD FLOW = 25.10 **(Cardiac Output)**

TOLERANCE = 99000.00

ITERATION	PVO2	PVCO2	+VO2	+VCO2
0	17.27	54.88	91.6	-161.2

N	VA	Q	VA/Q	PO2	PCO2	O2CON	CO2CON	VINSP	RQ
1	.0000	.0000	.0000	17.27	54.88	4.97	62.13	.00	.00
2	.0000	.0000	.0061	17.63	54.94	5.14	62.09	.00	.23
3	.0000	.0000	.0075	17.68	54.94	5.16	62.08	.00	.25
4	.0000	.0000	.0092	17.74	54.95	5.19	62.07	.00	.26
5	.0000	.0000	.0112	17.81	54.95	5.23	62.06	.00	.28
6	.0000	.0000	.0137	17.90	54.95	5.27	62.04	.00	.29
7	.0000	.0000	.0168	18.01	54.95	5.32	62.02	.00	.30
8	.0000	.0000	.0206	18.15	54.96	5.39	62.00	.00	.31
9	.0000	.0000	.0252	18.31	54.97	5.47	61.97	.00	.32
10	.0000	.0000	.0308	18.51	54.97	5.57	61.93	.00	.33
11	.0000	.0000	.0377	18.76	54.98	5.69	61.89	.00	.33
12	.0000	.0000	.0462	19.06	54.99	5.83	61.83	.00	.34
13	.0000	.0000	.0565	19.42	55.00	6.01	61.77	.00	.34
14	.0000	.0000	.0692	19.87	55.01	6.23	61.69	.00	.35
15	.0000	.0000	.0847	20.42	55.02	6.49	61.59	.00	.35
16	.0000	.0000	.1037	21.09	55.03	6.81	61.47	.00	.36
17	.0000	.0000	.1269	21.90	55.03	7.19	61.32	.00	.36
18	.0000	.0000	.1553	22.89	55.03	7.65	61.14	.00	.37
19	.0000	.0000	.1901	24.11	55.03	8.20	60.92	.00	.37
20	.0000	.0000	.2327	25.59	55.00	8.87	60.65	.00	.38
21	.0000	.0000	.2848	27.41	54.95	9.65	60.32	.00	.39
22	.0000	.0000	.3486	29.63	54.85	10.57	59.91	.00	.40
23	.0000	.0000	.4266	32.36	54.69	11.64	59.43	.00	.40
24	.0000	.0000	.5222	35.72	54.43	12.87	58.84	.00	.42
25	.0000	.0000	.6391	39.89	54.02	14.25	58.13	.00	.43
26	.0000	.0000	.7823	45.18	53.38	15.72	57.29	.00	.45
27	.0000	.0000	.9575	52.06	52.40	17.18	56.31	.00	.48
28	.0000	.0000	1.1720	61.05	50.93	18.41	55.21	.00	.51
29	.8493	.5921	1.4345	71.84	48.89	19.23	54.00	.89	.57
30	7.5539	4.3023	1.7558	82.92	46.39	19.69	52.69	7.83	.64
31	12.8715	5.9893	2.1491	93.11	43.60	19.95	51.27	13.17	.72
32	15.6790	5.9606	2.6304	101.99	40.63	20.12	49.75	15.88	.82
33	15.1271	4.6984	3.2196	109.57	37.55	20.23	48.12	15.20	.92
34	10.9781	2.7858	3.9408	116.00	34.43	20.31	46.41	10.97	1.02
35	3.7221	.7717	4.8235	121.41	31.33	20.37	44.62	3.70	1.14
36	.0000	.0000	5.9038	125.97	28.29	20.42	42.77	.00	1.25
37	.0000	.0000	7.2262	129.82	25.37	20.46	40.89	.00	1.37
38	.0000	.0000	8.8448	133.05	22.59	20.50	38.98	.00	1.49
39	.0000	.0000	10.8259	135.77	19.98	20.53	37.06	.00	1.61
40	.0000	.0000	13.2507	138.06	17.57	20.55	35.15	.00	1.73
41	.0000	.0000	16.2187	139.98	15.36	20.58	33.26	.00	1.85
42	.0000	.0000	19.8514	141.60	13.35	20.59	31.41	.00	1.97
43	.0000	.0000	24.2978	142.95	11.55	20.61	29.60	.00	2.08
44	.0000	.0000	29.7402	144.09	9.95	20.63	27.84	.00	2.19
45	.0000	.0000	36.4015	145.04	8.53	20.64	26.13	.00	2.30
46	.0000	.0000	44.5549	145.84	7.29	20.65	24.49	.00	2.40
47	.0000	.0000	54.5345	146.50	6.20	20.66	22.92	.00	2.50
48	.0000	.0000	66.7495	147.06	5.26	20.67	21.41	.00	2.59
49	.0000	.0000	81.7003	147.52	4.45	20.68	19.98	.00	2.68
50	14.5190	.0000	INF	149.77	.00	.00	.00	14.52	.00

MIXED ARTERIAL PN2	=	572.8
MIXED VENOUS PN2	=	563.4
N2 UPTAKE, ML/MIN	=	7.0
MIXED EXPIRED PO2	=	111.22
MIXED EXPIRED PCO2	=	32.63
OXYGEN UPTAKE	=	3781.58
CARBON DIOXIDE OUTPUT	=	3073.84
PREDICTED R	=	.81
MEASURED R	=	.88
ARTERIAL PO2	=	96.42
ARTERIAL PCO2	=	40.85
ARTERIAL O2 CONTENT	=	20.03
ARTERIAL CO2 CONTENT	=	49.88
MIXED ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	14.80
MIXED ALVEOLAR-ARTERIAL PCO2 DIFFERENCE	=	8.22
MIXED ALVEOLAR-ARTERIAL PN2 DIFFERENCE	=	3.42

IDEAL CALCULATIONS USING PREDICTED VO2 & VCO2:

IDEAL ALVEOLAR PO2	=	101.58
IDEAL ALVEOLAR PCO2	=	40.77
IDEAL ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	5.16
IDEAL O2 CONTENT	=	20.11
PHYSIOLOGIC DEAD SPACE PCT	=	19.98
VENOUS ADMIXTURE PCT	=	.50
NUMBER OF TIMES SATURA CALLED	=	2306
IDEAL VA/Q	=	2.60

IDEAL CALCULATIONS USING MEASURED VO2 & VCO2:

IDEAL ALVEOLAR PO2	=	106.68
IDEAL ALVEOLAR PCO2	=	38.78
IDEAL ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	28.18
IDEAL O2 CONTENT	=	20.19
PHYSIOLOGIC DEAD SPACE PCT	=	15.86
VENOUS ADMIXTURE PCT	=	3.41
NUMBER OF TIMES SATURA CALLED	=	2326
IDEAL VA/Q	=	2.97

PREDICTED - MEASURED ARTERIAL PO2	=	17.92
PREDICTED - MEASURED ARTERIAL CONTENT	=	.36
MEASURED - PREDICTED ALVEOLAR-ARTERIAL GRADIENT	=	23.02 **(A-aDO_2 (o-p))**

7.6 DLO_2 OUPUT FROM MIGET MODEL

```
SET NUMBER :  5  FROM FILE:  NICK SHIPP 11/7/97
 FITTING A BLOOD FLOW DISTRIBUTION TO RETENTIONS

 NUMBER OF GASES =  6
 NUMBER OF VA/Q COMPARTMENTS =  50
 SMOOTHING COEFFICIENT Z =   40.00
```

GAS	SOL	PC	R	E
1	.00086	.00614	.00183	.00189
2	.01370	.09771	.03532	.02910
3	.07957	.56750	.17402	.14471
4	.31197	2.22500	.47655	.35958
5	1.39372	9.94000	.78939	.64632
6	36.69378	261.70000	.99103	.72457

ITN	LOOP	TOTAL SSQ	FIT TO R	SUM Q*Q
0	1	7.793803	.245256	7.548547
0	2	10.831910	1.353007	9.478907
0	3	13.884840	2.786967	11.097880
0	4	16.175140	5.058248	11.116890
0	5	16.742870	6.250896	10.491970
0	6	16.910160	6.365654	10.544500
0	7	20.318680	6.277416	14.041260
0	8	21.260930	8.559921	12.701000

```
 ITERATION NUMBER =  1
 TOTAL BLOOD FLOW =  1.000009
```

PC	RETENTIONS	BEST FIT	ERROR	RAW DATA	ERROR
.0061	.365	.500	-.134	.00183	.00067
.0977	17.273	18.699	-1.426	.03532	.00291
.5675	20.177	21.544	-1.367	.17402	.01179
2.2250	31.838	31.174	.665	.47655	-.00995
9.9400	79.137	79.382	-.245	.78939	.00244
261.7000	1858.744	1856.718	2.026	.99103	-.00108
.0000	20000.000	20000.190	-.185	1.00000	.00000

```
 REMAINING SUM OF SQUARES =  8.56E+00
```

RANGE	BLOOD FLOW	VENTILATION
VA/Q OF ZERO	.000	ZERO
VA/Q RANGE 0 TO .01	.000	.000
VA/Q RANGE .01 TO .1	.000	.000
VA/Q RANGE .1 TO 1.	.000	.000
VA/Q RANGE 1.0 TO 10.	1.000	.821
VA/Q RANGE 10. TO 100.	.000	.000
VA/Q OF INFINITY	ZERO	.179

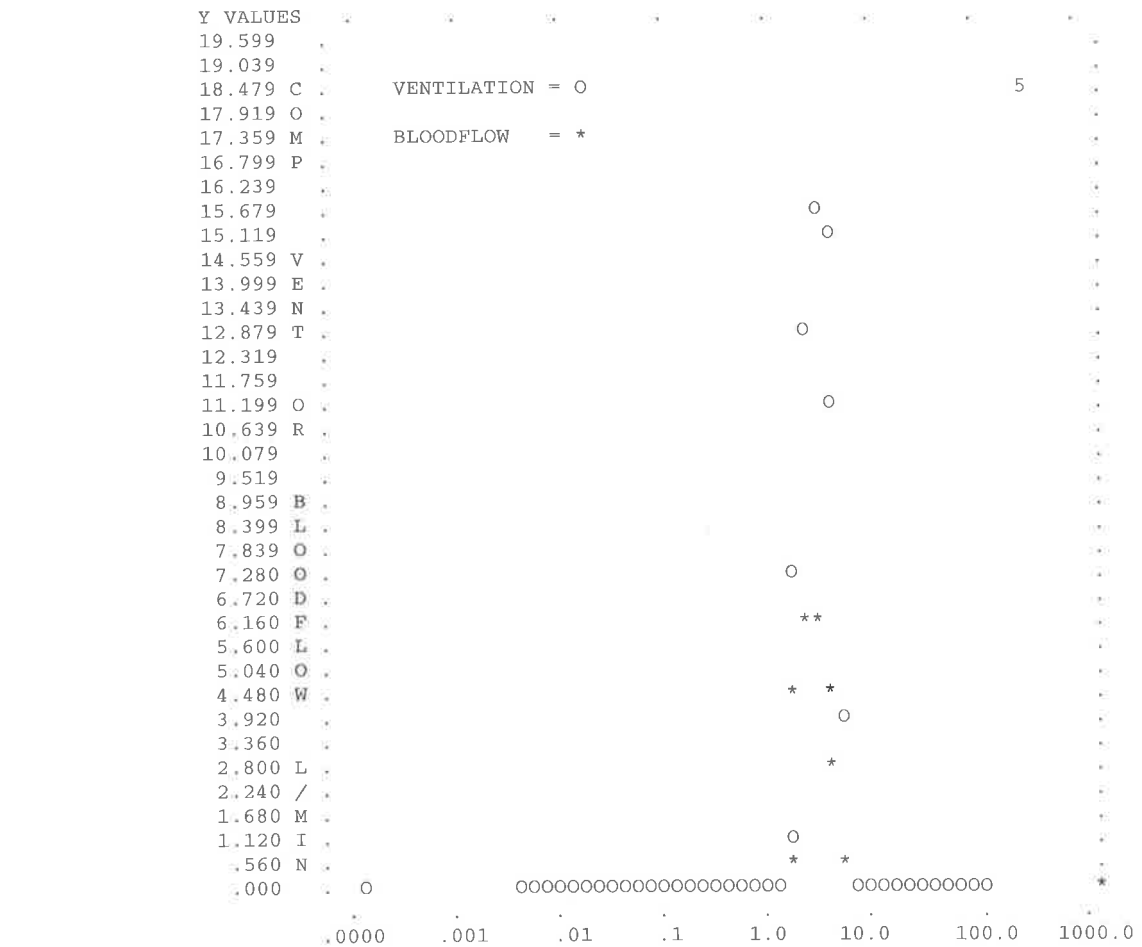
```
      MEAN OF BLOOD FLOW  DISTRIBUTION =   2.55
2nd MOMENT OF BLOOD FLOW  DISTRIBUTION =    .29
3rd MOMEMT OF BLOOD FLOW  DISTRIBUTION =    .00

      MEAN OF VENTILATION DISTRIBUTION =   2.78
2nd MOMENT OF VENTILATION DISTRIBUTION =    .29
3rd MOMENT OF VENTILATION DISTRIBUTION =    .00
```

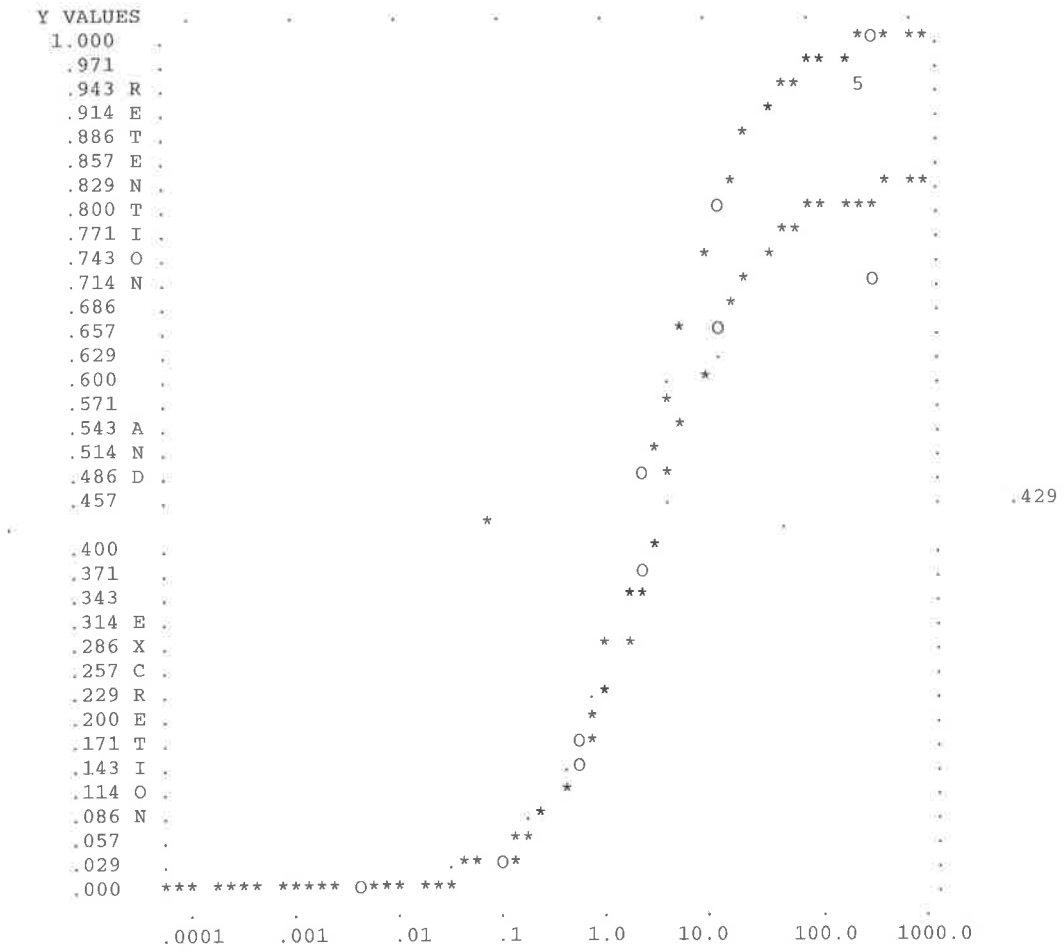
GAS	PC	R	RH	R - RH	E	E*	EH	EH - E*	R - E*
1	.00614	.00250	.00230	.00020	.00189	.00230	.00230	.00000	.00020
2	.09771	.03823	.03542	.00281	.02901	.03532	.03542	.00010	.00291
3	.56750	.18580	.17580	.01000	.14265	.17367	.17580	.00213	.01213
4	2.22500	.46660	.45542	.01118	.36641	.44607	.45542	.00935	.02053
5	9.94000	.79183	.78885	.00298	.63883	.77772	.78885	.01113	.01411
6	261.70000	.98994	.98994	.00000	.81244	.98907	.98994	.00086	.00087

MAX POSSIBLE DEADSPACE VENTILATION = 14.5 L/MIN, OR AS A FRACTION = .179

DISPERSION DIRECTLY FROM DIFFERENCES BETWEEN:

BEST FIT RETENTIONS & HOMOGENEOUS RETENTIONS IS: .63
HOMOGENEOUS EXCRETIONS & BEST FIT EXCRETIONS IS: .60
BEST FIT RETENTIONS * BEST FIT EXCRETIONS IS: 1.14





BLOOD:GAS PARTITION COEFFICIENT, LOG SCALE

GAS EXCHANGE

GVO2	GVCO2	PIO2	FIO2	PICO2	FICO2	PB	TEMP	HB	HCRIT	P50	BX
3690.0	3235.0	149.8	.2100	.0	.00	760.0	36.9	14.6	44.0	27.1	1.1

FIRST BLOOD PH =7.49 PCO2 =30.00 PMAO2 = 78.50 CMAO2 = 19.67
SECOND BLOOD PH =7.30 PCO2 =60.00 PMACO2= 39.40 CMACO2= 49.24

TOTAL VENTILATION= 81.30
TOTAL BLOOD FLOW = 25.10
O2 SOLUBILITY = .0030

TOLERANCE = 99000.00

ITERATION	PVO2	PVCO2	+VO2	+VCO2
0	17.27	54.88	91.5	-161.2

N	VA	Q	VA/Q	PO2	PCO2	O2CON	CO2CON	VINSP	RQ	
1	.0000	.0000	.0000	**17.27**	54.88	4.97	62.13	.00	.00	(P_vO2)
2	.0000	.0000	.0061	17.57	54.92	5.11	62.09	.00	.27	
3	.0000	.0000	.0075	17.62	54.92	5.13	62.08	.00	.28	
4	.0000	.0000	.0092	17.68	54.92	5.16	62.07	.00	.30	
5	.0000	.0000	.0112	17.75	54.93	5.20	62.06	.00	.31	
6	.0000	.0000	.0137	17.84	54.93	5.24	62.04	.00	.32	
7	.0000	.0000	.0168	17.95	54.93	5.30	62.02	.00	.32	
8	.0000	.0000	.0206	18.09	54.94	5.36	62.00	.00	.33	
9	.0000	.0000	.0252	18.25	54.94	5.44	61.97	.00	.34	
10	.0000	.0000	.0308	18.46	54.95	5.54	61.93	.00	.34	
11	.0000	.0000	.0377	18.70	54.96	5.66	61.89	.00	.35	
12	.0000	.0000	.0462	19.00	54.97	5.81	61.83	.00	.35	
13	.0000	.0000	.0565	19.37	54.97	5.99	61.77	.00	.35	
14	.0000	.0000	.0692	19.82	54.99	6.20	61.69	.00	.36	
15	.0000	.0000	.0847	20.36	55.00	6.46	61.59	.00	.36	
16	.0000	.0000	.1037	21.03	55.01	6.78	61.47	.00	.36	
17	.0000	.0000	.1269	21.84	55.01	7.17	61.32	.00	.37	
18	.0000	.0000	.1553	22.84	55.02	7.63	61.14	.00	.37	
19	.0000	.0000	.1901	24.05	55.01	8.18	60.92	.00	.38	
20	.0000	.0000	.2327	25.54	54.98	8.84	60.65	.00	.38	
21	.0000	.0000	.2848	27.36	54.93	9.63	60.32	.00	.39	
22	.0000	.0000	.3486	29.58	54.84	10.55	59.91	.00	.40	
23	.0000	.0000	.4266	32.31	54.68	11.63	59.43	.00	.41	
24	.0000	.0000	.5222	35.67	54.42	12.86	58.84	.00	.42	
25	.0000	.0000	.6391	39.84	54.01	14.23	58.13	.00	.43	
26	.0000	.0000	.7823	45.13	53.37	15.71	57.29	.00	.45	
27	.0000	.0000	.9575	52.01	52.40	17.17	56.32	.00	.48	
28	.0000	.0000	1.1720	61.00	50.93	18.40	55.21	.00	.51	
29	.8493	.5921	1.4345	71.80	48.89	19.23	54.00	.89	.57	
30	7.5539	4.3023	1.7558	82.90	46.39	19.69	52.69	7.83	.64	
31	12.8715	5.9893	2.1491	93.09	43.60	19.95	51.27	13.17	.72	
32	15.6790	5.9606	2.6304	101.98	40.63	20.12	49.75	15.88	.82	
33	15.1271	4.6984	3.2196	109.57	37.55	20.23	48.12	15.20	.92	
34	10.9781	2.7858	3.9408	116.00	34.43	20.31	46.41	10.97	1.02	
35	3.7221	.7717	4.8235	121.41	31.33	20.37	44.62	3.70	1.14	
36	.0000	.0000	5.9038	125.98	28.29	20.42	42.77	.00	1.25	
37	.0000	.0000	7.2262	129.82	25.37	20.46	40.89	.00	1.37	
38	.0000	.0000	8.8448	133.05	22.59	20.50	38.98	.00	1.49	
39	.0000	.0000	10.8259	135.77	19.98	20.53	37.06	.00	1.61	
40	.0000	.0000	13.2507	138.06	17.57	20.55	35.15	.00	1.73	
41	.0000	.0000	16.2187	139.98	15.36	20.58	33.26	.00	1.85	
42	.0000	.0000	19.8514	141.60	13.35	20.59	31.41	.00	1.97	
43	.0000	.0000	24.2978	142.95	11.55	20.61	29.60	.00	2.08	
44	.0000	.0000	29.7402	144.09	9.95	20.63	27.84	.00	2.19	
45	.0000	.0000	36.4015	145.04	8.53	20.64	26.13	.00	2.30	
46	.0000	.0000	44.5549	145.84	7.29	20.65	24.49	.00	2.40	
47	.0000	.0000	54.5345	146.50	6.20	20.66	22.92	.00	2.50	
48	.0000	.0000	66.7495	147.06	5.26	20.67	21.41	.00	2.59	
49	.0000	.0000	81.7003	147.52	4.45	20.68	19.98	.00	2.68	
50	14.5190	.0000	INF	149.77	.00	.00	.00	14.52	.00	

MIXED ARTERIAL PN2	=	572.8
MIXED VENOUS PN2	=	563.4
N2 UPTAKE, ML/MIN	=	4.0
MIXED EXPIRED PO2	=	111.22
MIXED EXPIRED PCO2	=	32.63
OXYGEN UPTAKE	=	3781.52
CARBON DIOXIDE OUTPUT	=	3073.83
PREDICTED R	=	.81
MEASURED R	=	.88
ARTERIAL PO2	=	96.35
ARTERIAL PCO2	=	40.85
ARTERIAL O2 CONTENT	=	20.03
ARTERIAL CO2 CONTENT	=	49.88
MIXED ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	14.87
MIXED ALVEOLAR-ARTERIAL PCO2 DIFFERENCE	=	8.22
MIXED ALVEOLAR-ARTERIAL PN2 DIFFERENCE	=	3.42

IDEAL CALCULATIONS USING PREDICTED VO2 & VCO2:

IDEAL ALVEOLAR PO2	=	101.58
IDEAL ALVEOLAR PCO2	=	40.77
IDEAL ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	5.23
IDEAL O2 CONTENT	=	20.11
PHYSIOLOGIC DEAD SPACE PCT	=	19.98
VENOUS ADMIXTURE PCT	=	.50
NUMBER OF TIMES SATURA CALLED	=	2312
IDEAL VA/Q	=	2.60

IDEAL CALCULATIONS USING MEASURED VO2 & VCO2:

IDEAL ALVEOLAR PO2	=	106.68
IDEAL ALVEOLAR PCO2	=	38.78
IDEAL ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	28.18
IDEAL O2 CONTENT	=	20.19
PHYSIOLOGIC DEAD SPACE PCT	=	15.86
VENOUS ADMIXTURE PCT	=	3.41
NUMBER OF TIMES SATURA CALLED	=	2332
IDEAL VA/Q	=	2.97

PREDICTED - MEASURED ARTERIAL PO2	=	17.85
PREDICTED - MEASURED ARTERIAL CONTENT	=	.36
MEASURED - PREDICTED ALVEOLAR-ARTERIAL GRADIENT	=	22.95

***** BOHR INTEGRATION RESULTS *****

ITN 1; DM= 73.80; & PO2 ERROR= 7.86
ITN 1; DM= 59.04; & PO2 ERROR= -6.69
ITN 1; DM= 64.94; & PO2 ERROR= .06

ITERATION	PVO2	PVCO2	+VO2	+VCO2
0	17.27	54.88	-11.2	-357.9

N	VA/Q	PAO2	PaO2	PACO2	PaCO2	O2CON	CO2CON	RQ
29	1.4345	81.47	51.90	45.33	48.76	17.34	54.59	.61
30	1.7558	88.31	60.15	43.20	46.92	18.47	53.34	.65
31	2.1491	95.36	74.28	40.79	44.71	19.42	51.97	.70
32	2.6304	102.78	95.60	38.13	42.08	20.01	50.51	.77
33	3.2196	110.09	108.95	35.25	39.18	20.21	48.98	.86
34	3.9408	116.48	116.12	32.21	36.27	20.30	47.42	.96
35	4.8235	121.89	121.71	29.13	33.45	20.36	45.85	1.06

MIXED ARTERIAL PN2	=	573.4
MIXED VENOUS PN2	=	563.4
N2 UPTAKE, ML/MIN	=	4.2
MIXED EXPIRED PO2	=	112.52
MIXED EXPIRED PCO2	=	30.54
OXYGEN UPTAKE	=	3678.76
CARBON DIOXIDE OUTPUT	=	2877.10
PREDICTED R	=	.78
MEASURED R	=	.88
ARTERIAL PO2	=	78.56
ARTERIAL PCO2	=	42.17
ARTERIAL O2 CONTENT	=	19.62
ARTERIAL CO2 CONTENT	=	50.67
MIXED ALVEOLAR-ARTERIAL PO2 DIFFERENCE	=	33.96
MIXED ALVEOLAR-ARTERIAL PCO2 DIFFERENCE	=	11.63
MIXED ALVEOLAR-ARTERIAL PN2 DIFFERENCE	=	3.22
DLO2 by Bohr Integration	=	64.94 **(DLO_2 Value)**
DLCO2 set to 5*DLO2	=	324.72
NUMBER OF STEPS USED	=	20

7.7 SHORT OUTPUT FROM MIGET MODEL

```
RUN NUMBER     5

                       GAS 1      GAS 2      GAS 3      GAS 4      GAS 5      GAS 6

ARTERIAL PEAKS          12.6      174.5      775.8      607.0     1155.0      932.8
AND GAIN FACTORS         1.0        1.0        1.0        1.0        1.0        1.0
EXPIRED PEAKS         2606.0     1950.0     2082.0      741.0     1119.0      746.4
AND GAIN FACTORS         1.0        1.0        1.0        1.0        1.0        1.0
VENOUS PEAKS              .0         .0         .0         .0         .0         .0
AND GAIN FACTORS         1.0        1.0        1.0        1.0        1.0        1.0
BODY/BATH PC          1.0248     1.0115     1.0170     1.0254     1.0344     1.0067
VE  =  81.30; QT   =  25.10; PB   =760.0
SVPR=   46.8; SVPB =   46.8; TMPB = 36.9; TMPR =  36.9;
VGa =   8.79; VBa  =   7.21; VHa  =  .70; VGv  =   .00;  VBv =  .00; VHv= .00
HB  =   14.6; HCT  =  44.0; TOLERANCE =99000.0
P50 =   27.1; PIO2 = 149.8; PICO2 =    .0; PaO2 =  78.5; PaCO2=  39.4; PHa = 7.42
VO2 = 3690.0; VCO2 =3235.0;   R   =   .88
HYPO/HYPERBARIC CORRECTION FACTOR FOR EXPIRED GAS VALUES= 1.000

ONLY PA AND PE HAVE BEEN MEASURED - PV IS DERIVED

                        SF6       ETHANE      CYCLO     ENFLURANE     ETHER      ACETONE
SOLUBILITY           .00086       .01370     .07957       .31198    1.39375     36.70026
PC, BATH T           .00599       .09660     .55800      2.17000    9.61000    260.00000
PC, BODY T           .00614       .09771     .56747      2.22506    9.94020    261.74480
BODY/BATH PC        1.02481      1.01148    1.01697      1.02538    1.03436      1.00671
MEASURED R           .00183       .03532     .17402       .47655     .78939      .99103
MEASURED E           .00189       .02910     .14471       .35958     .64632      .72457
WEIGHTS (R)          200.0        489.1      116.0         66.8      100.2      1875.6

MEASURED MINUTE VENTILATION =    81.30   AND MEASURED CARDIAC OUTPUT =   25.10
```

7.8 INDIVIDUAL SUBJECT DATA OBTAINED DURING PROGRESSIVE INCREMENTAL EXERCISE TEST TO EXHAUSTION

Subject (Group)	$\dot{V}O_{2peak}$ $ml.kg^{-1}.min^{-1}$	Resting PaO_2 mm Hg	Lowest PaO_2 mm Hg	Maximum Change	SaO_2 at $\dot{V}O_{2peak}$ %
1. (Experimental)	65.8	99.5	78.4	22.1	93.5%
2. (Control)	62.7	95.7	86.0	9.7	95.5%
3. (Experimental)	64.4	89.0	75.3	14.3	93.1%
4. (Not Used)	59.0	99.0	83.1	15.9	93.4%
5. (Not Used)	60.2	94.5	90.5	4.0	95.9%
6. (Experimental)	83.0	96.7	80.0	16.7	92.1%
7. (Not Used)	70.2	95.0	83.3	11.7	93.2%
8. (Not Used)	62.4	88.8	84.3	4.5	94.7%
9. (Control)	76.9	88.4	80.5	7.9	94.0%
10. (Experimental)	72.1	95.6	76.9	18.7	90.8%
11. (Experimental)	70.7	91.5	76.8	14.7	90.9%
12. (Not Used)	67.3	92.4	82.5	9.9	93.2%
13. (Not Used)	52.6	102.2	83.8	18.4	96.1%
14. (Experimental)	70.9	103.0	88.4	14.6	92.7%
15. (Not Used)	65.5	92.8	82.0	10.8	93.4%
16. (Not Used)	56.4	97.9	84.2	13.7	95.3%
17. (Control)	70.9	93.1	90.3	2.8	95.4%
18. (Control)	66.4	95.8	85.6	10.2	94.2%
19. (Experimental)	64.5	92.4	78.3	14.1	90.4%
20. (Control)	67.1	90.3	82.9	7.4	95.9%
Control mean (SEM)	68.8 (2.4)	92.7 (1.5)	85.1 (1.6)	7.6 (1.3)	95.0 (0.4)
Experimental mean (SEM)	70.2 (2.5)	95.4 (1.8)	79.2 (1.6)	16.5 (1.1)	91.9 (0.5)

$\dot{V}O_{2peak}$, peak O_2 consumption; PaO_2, arterial O_2 tension; SaO_2, arterial O_2 saturation. Data is corrected for arterial blood temperature measured during sampling.

8 BIBLIOGRAPHY

Aaron, E.A., Johnson, B.D., Seow, C.K. and Dempsey, J.A. (1992) Oxygen cost of exercise hyperpnea: measurement. *J.Appl.Physiol.* **72**, 1810-1817.

Aaron, E.A., Seow, C.K., Johnson, B.D. and Dempsey, J.A. (1992) Oxygen cost of exercise hyperpnea: implications for performance. *J.Appl.Physiol.* **72**, 1818-1825.

Aguilaniu, B., Flore, P., Perrault, H., Page, J.E., Payan, E. and Lacour, J.R. (1995) Exercise-induced hypoxaemia in master athletes: effects of a polyunsaturated fatty acid diet. *Eur.J.Appl.Physiol.* **72**, 44-50.

Aguilaniu, B., Flore, P., Page, E., Maitre, J., Lacour, J.R. and Perrault, H. (1998) Effects of indomethacin and polyunsaturated fatty acid diet on exercise-induced hypoxaemia in master athletes. *Eur.J.Appl.Physiol.* **77**, 81-88.

Anholm, J.D., Johnson, R.L. and Ramanathan, M. (1987) Changes in cardiac output during sustained maximal ventilation in humans. *J.Appl.Physiol.* **63**, 181-187.

Anselme, F., Caillaud, C., Couret, I., Rossi, M. and Prefaut, C. (1994) Histamine and exercise-induced hypoxemia in highly trained athletes. *J.Appl.Physiol.* **76**, 127-132.

Asmussen, E. and Neilsen, M. (1946) Studies on the regulation of respiration in heavy work. *Acta Physiol.Scan.* **12,** 171-188.

Asmussen, E. and Neilsen, M. (1960) Alveolar-arterial gas exchange at rest and during work at different oxygen tensions. *Acta Physiol.Scan.* **50,** 153-166.

Astrand, P.O. and Rodahl, K. (1986) *Textbook of Work Physiology*, 3rd Edition Provenzano, D. (Eds). New York: McGraw-Hill.

Bachofen, H., Hobi, H.J. and Scherrer, M. (1973) Alveolar-arterial N_2 gradients at rest and during exercise in healthy men of different ages. *J.Appl.Physiol.* **34**, 137-142.

Bake, B., Bjure, J. and Widimsky, J. (1968) The effect of sitting and graded exercise on the distribution of pulmonary blood flow in healthy subjects studied with the 133Xenon technique. *Scand.J.Clin.Lab.Invest.* **22**, 99-106.

Barker, R., Hopkins, S.R., Kellog, N., Olfert, I.M., Brutsaert, T., Gavin, T.P., Entin, P., Rice, A.J. and Wagner, P.D. (1998) Measurement of cardiac output during exercise by acetylene uptake. *FASEB J.* **12**, A1040.

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

Bayly, W.M., Hodgson, D.R., Schulz, D.A., Dempsey, J.A. and Gollnick, P.D. (1989) Exercise-induced hypercapnia in the horse. *J.Appl.Physiol.* **67**, 1958-1966.

Bebout, D.E., Story, D., Roca, J., Hogan, M.C., Poole, D.C., Gonzalez-Camarena, R., Ueno, O., Haab, P. and Wagner, P.D. (1989) Effects of altitude acclimatization on pulmonary gas exchange during exercise. *J.Appl.Physiol.* **67**, 2286-2295.

Berndt, J., Fenner, A. and Berger, K. (1969) Influence of calcium and magnesium on the respiratory response to changes in CSF pH. *Respir.Physiol.* **7**, 216-229.

Bevegard, S., Holmgren, A. and Jonsson, B. (1963) Circulatory studies in well trained athletes at rest and during heavy exercise with special reference to stroke volume and the influence of body position. *Acta Physiol.Scan.* **57**, 26-50.

Bouckaert, J., Vrijens, J. and Pannier, J.L. (1990) Effect of specific test procedures on plasma lactate concentration and peak oxygen uptake in endurance athletes. *J.Sports Med.Phys.Fitness* **30**, 13-18.

Bouckaert, J. and Pannier, J.L. (1995) Blood ammonia response to treadmill and bicycle exercise in man. *Int.J.Sports Med.* **16**, 141-144.

Boutellier, U. (1998) Respiratory muscle fitness and exercise endurance in healthy humans. *Med.Sci.Sports Exerc.* **30**, 1169-1172.

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

Brown, D.D., Knowlton, R.G., Sanjabit, P.B. and Szurgot, B.T. (1993) Re-examination of the incidence of exercise-induced hypoxaemia in highly trained subjects. *Br.J.Sp.Med.* **27**, 167-170.

Bruce, E.N. and Cherniack, N.S. (1987) Central chemoreceptors. *J.Appl.Physiol.* **62**, 389-402.

Buono, M.J., Constable, S.H., Morton, A.R., Rotkis, T.C., Stanforth, P.R. and Wilmore, J.H. (1981) The effect of an acute bout of exercise on selected pulmonary function measurements. *Med.Sci.Sports Exerc.* **13**, 290-293.

Buono, M.J., Wilmore, J.H. and Roby, F.B. (1982) Evidence of increased thoracic extravascular water following intense exercise in man. *Physiologist* **25**, A201.

Buono, M.J. and Maly, R. (1996) Augmented hyperventilation via normoxic helium breathing does not prevent exercise-induced hypoxemia. *Can.J.Appl.Physiol.* **21**, 264-270.

Bye, P.T., Farkas, G.A. and Roussos, C. (1983) Respiratory factors limiting exercise. *Annu.Rev.Physiol.* **45**, 439-451.

Byrne-Quinn, E., Weil, J.V., Sodal, I.E., Filley, G.F. and Grover, R.F. (1971) Ventilatory control and the athlete. *J.Appl.Physiol.* **30**, 91-98.

Caillaud, C.F., Anselme, F.M., Mercier, J. and Prefaut, C.G. (1993) Pulmonary gas exchange and breathing pattern during and after exercise in highly trained athletes. *Eur.J.Appl.Physiol.* **67**, 431-437.

Caillaud, C.F., Anselme, F.M. and Prefaut, C.G. (1996) Effects of two successive maximal exercise tests on pulmonary gas exchange in athletes. *Eur.J.Appl.Physiol.* **74**, 141-147.

Cardús, J., Burgos, F., Diaz, O., Roca, J., Barberà, J.A., Marrades, R.M., Rodriguez, R.R. and Wagner, P.D. (1997) Increase in pulmonary ventilation-perfusion inequality with age in healthy individuals. *Am.J.Respir.Crit.Care Med.* **156**, 648-653.

Casey, K., Duffin, J. and McAvoy, G.V. (1987) The effect of exercise on the central-chemoreceptor threshold in man. *J.Physiol.(Lond.)* **383**, 9-18.

Chapman, R.F., Emery, M. and Stager, J.M. (1998) Extent of expiratory flow limitation influences the increase in maximal exercise ventilation in hypoxia. *Respir.Physiol.* **113**, 65-74.

Cherniack, N.S., von Euler, C., Homma, I. and Kao, F.F. (1979) Graded changes in central chemoreceptor input by local temperature changes on the ventral surface of medulla. *J.Physiol.(Lond.)* **287**, 191-211.

Clark, A.L., Galloway, S., MacFarlane, N., Henderson, E., Aitchison, T. and McMurray, J.J. (1997) Catecholamines contribute to exertional dyspnoea and to the ventilatory response to exercise in normal humans. *Eur.Heart J.* **18**, 1829-1833.

Coast, J.R., Rasmussen, S.A., Krause, K.M., O'Kroy, J.A., Loy, R.A. and Rhodes, J. (1993) Ventilatory work and oxygen consumption during exercise and hyperventilation. *J.Appl.Physiol.* **74**, 793-798.

Coates, G., O'Brodovich, H., Jefferies, A.L. and Gray, G.W. (1984) Effects of exercise on lung lymph flow in sheep and goats during normoxia and hypoxia. *J.Clin.Invest.* **74**, 133-141.

Cockcroft, A., Beaumont, A., Adams, L. and Guz, A. (1985) Arterial oxygen desaturation during treadmill and bicycle exercise in patients with chronic obstructive airways disease. *Clin.Sci.* **68**, 327-332.

Comroe, J.H. (1944) The hyperpnea of muscular exercise. *Physiol.Rev.* **24,** 319-339.

Cotes, J.E. (1955) The role of body temperature in controlling ventilation during exercise in one normal subject breathing oxygen. *J.Physiol.(Lond.)* **129**, 554-563.

Crapo, R.O., Morris, A.H. and Gardner, R.M. (1981) Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am.Rev.Respir.Dis.* **123**, 659-664.

Dantzker, D.R. and D'Alonzo, G.E. (1986) The effect of exercise on pulmonary gas exchange in patients with severe chronic obstructive pulmonary disease. *Am.Rev.Respir.Dis.* **134**, 1135-1139.

De Lanne, R., Barnes, J.R. and Brouha, L. (1959) Changes in osmotic pressure and ionic concentrations of plasma during muscular work and recovery. *J.Appl.Physiol.* **14,** 804-808.

Dejours, P., Labrousse, Y., Raynaud, J. and Teillac, A. (1957) Stimulus oxygene chemoreflexe de la ventilation a basse altittude (50 m) chez l'homme. *J.Physiol.(Paris)* **49,** 115-119.

Dejours, P., Labrousse, Y., Raynaud, J., Girard, F. and Teillac, A. (1958) Stimulus oxygene de la ventilation au repos et au cours de l'exercisemusculaire a basse altittude (50 m) chez l'homme. *Rev.Fr.Clin.Biol.* **3**, 105-123.

Dejours, P. (1981) Control of respiration. In: Dejours, P (Ed.) *Principles of comparative respiratory physiology*, 2nd edn. Amsterdam: Elsevier-Holland Biomedical Press.

Dempsey, J.A., Hanson, D., Pegelow, D., Claremont, A. and Rankin, J. (1982) Limitations to exercise capacity and endurance: pulmonary system. *Can.J.Appl.Spt.Sci.* **7**, 4-13.

Dempsey, J.A., Hanson, P.G. and Henderson, K.S. (1984) Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J.Physiol.* **355**, 161-175.

Dempsey, J.A., Vidruk, E.H. and Mitchell, G.S. (1985) Pulmonary control systems in exercise: update. *Federation Proc.* **44**, 2260-2270.

Dempsey, J.A. (1987) Exercise-induced imperfections in pulmonary gas exchange. *Can.J.Appl.Spt.Sci.* **12**, 66S-70S.

Dempsey, J.A. and Johnson, B.D. (1992) Demand vs. capacity in the healthy pulmonary system. *Schweiz.Z.Sportmed.* **40**, 55-64.

DuBois, A.B., Botelho, S.Y., Bedell, G.N., Marshall, R. and Comroe, J.H. (1956) A rapid plethysmographic method for measuring thoracic gas volume: a comparison with nitrogen washout method for measuring functional residual capacity in normal subjects. *J.Clin.Invest.* **35**, 322-326.

Duffin, J. and McAvoy, G.V. (1988) The peripheral-chemoreceptor threshold to carbon dioxide in man. *J.Physiol.(Lond.)* **406**, 15-26.

Duffin, J. (1990) The chemoreflex control of breathing and its measurement. *Can.J.Anaesth.* **37**, 933-942.

Erickson, B.K., Seaman, J., Kubo, K., Hiraga, A., Kai, M., Yamaya, Y. and Wagner, P.D. (1994) Mechanism of reduction in alveolar-arterial PO_2 difference by helium breathing in the exercising horse. *J.Appl.Physiol.* **76**, 2794-2801.

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

Gaensler, E.A. and Wright, G.W. (1966) Evaluation of respiratory impairment. *Arch.Environ.Health* **12**, 146-189.

Gale, G.E., Torre-Bueno, J.R., Moon, R.E., Saltzman, H.A. and Wagner, P.D. (1985) Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude. *J.Appl.Physiol.* **58**, 978-988.

Gallagher, C.G., Huda, W., Rigby, M., Greenberg, D. and Younes, M. (1988) Lack of radiographic evidence of interstitial pulmonary edema after maximal exercise in normal subjects. *Am.Rev.Respir.Dis.* **137**, 474-476.

Gavin, T.P., Derchak, A. and Stager, J.M. (1998) Ventilation's role in the decline in $\dot{V}O_{2max}$ and SaO_2 in acute hypoxic exercise. *Med.Sci.Sports Exerc.* **30**, 195-199.

Gehr, P., Bachofen, M. and Weibel, E.R. (1978) The normal human lung: ultrastructure and morphometric estimation of diffusion capacity. *Respir.Physiol.* **32**, 121-140.

Gledhill, N., Froese, A.B. and Dempsey, J.A. (1977) Ventilation to perfusion distribution during exercise in health. In: Dempsey, J.A. and Reed, C.E., (Eds.) *Muscular Exercise And The Lung*, pp. 325-343. Madison, WI: University of Wisconsin Press

Gledhill, N., Spriet, L., Froese, A.B., Wilkes, D. and Meyers, E. (1980) Acid-base status with induced erythrocemia and its influence on arterial oxygenation during heavy exercise. *Med.Sci.Sports Exerc.* **12**, Abstract 122.

Goldman, H.I. and Backlake, M.R. (1959) Respiratory function tests: normal values at median altitudes and the prediction of normal results. *Am.Rev.Tuber.* **79,** 457-467.

Gore, C.J., Hahn, A.G., Scroop, G.C., Watson, D.B., Norton, K.I., Wood, R.J., Campbell, D.P. and Emonson, D.L. (1996) Increased arterial desaturation in trained cyclists during maximal exercise at 580 m altitude. *J.Appl.Physiol.* **80**, 2204-2210.

Gore, C.J., Little, S.C., Hahn, A.G., Scroop, G.C., Norton, K.I., Bourdon, P.C., Woolford, S.M., Buckley, J.D., Stanef, T., Campbell, D.P., Watson, D.B. and Emonson, D.L. (1997) Reduced performance of male and female athletes at 580 m altitude. *Eur.J.Appl.Physiol.* **75**, 136-143.

Goresky, C.A., Warnica, J.W., Burgess, J.H., Cronin, R.F.P. and Nadeau, B.E. (1972) Changes during exercise in man. *Federation Proc.* **31**, 307-311.

Grodins, F.S. (1950) Analysis of factors concerned in regulation of breathing in exercise. *Physiol.Rev.* **30**, 220-239.

Groves, B.M., Reeves, J.T., Sutton, J.R., Wagner, P.D., Cymerman, A., Malconian, M.K., Rock, P.B., Young, P.M. and Houston, C.S. (1987) Operation Everest II: elevated high-altitude pulmonary resistance unresponsive to oxygen. *J.Appl.Physiol.* **63**, 521-530.

Haldane, J.S. (1912) Methods of air analysis. In: *Methods Of Air Analysis*, Haldane J.S. (Ed) pp. 54-58. London: Charles Griffen and Co. Ltd

Hammond, M.D., Gale, G.E., Kapitan, K.S., Ries, A. and Wagner, P.D. (1986a) Pulmonary gas exchange in humans during exercise at sea level. *J.Appl.Physiol.1986.* **60**, 1590-1598.

Hammond, M.D., Gale, G.E., Kapitan, K.S., Ries, A. and Wagner, P.D. (1986b) Pulmonary gas exchange in humans during normobaric hypoxic exercise. *J.Appl.Physiol.* **61**, 1749-1757.

Hammond, M.D. and Hempleman, S.C. (1987) Oxygen diffusing capacity estimates derived from measured $\dot{V}_A/\dot{Q}$ distributions in man. *Respir.Physiol.* **69**, 129-147.

Hanel, B., Teunissen, I., Rabol, A., Warberg, J. and Secher, N.H. (1997) Restricted post-exercise pulmonary diffusion capacity and central blood volume depletion. *J.Appl.Physiol.* **83**, 11-17.

Harms, C.A. and Stager, J.M. (1995) Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. *J.Appl.Physiol.* **79**, 575-580.

Harms, C.A., Babcock, M.A., McClaren, S.R., Pegelow, D.F., Nickele, G.A., Nelson, W.B. and Dempsey, J.A. (1997) Respiratory muscle work compromises leg blood flow during maximal exercise. *J.Appl.Physiol.* **82**, 1573-1583.

Harms, C.A., Wetter, T.J., McClaren, S.R., Pegelow, D.F., Nickele, G.A., Nelson, W.B., Hanson, P.G. and Dempsey, J.A. (1998) Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J.Appl.Physiol.* **85**, 609-618.

Harms, C.A., McClaran, S.R., Nickele, G.A., Pegelow, D.F., Nelson, W.B. and Dempsey, J.A. (1998) Exercise-induced arterial hypoxaemia in healthy young women. *J.Physiol.(Lond.)* **507**, 619-628.

Harrison, T.R., Harrison, W.G., Calhoun, J.A. and Marsh, J.P. (1932) Congestive heart failure. The mechanisms of dyspnea on exertion. *Arch.Internal Med.* **50**, 690-720.

Hesser, C.M., Linnarsson, D. and Fagraeus, L. (1981) Pulmonary mechanisms and work of breathing at maximal ventilation and raised air pressure. *J.Appl.Physiol.* **50**, 747-753.

Heymans, J.F. and Heymans, C. (1927) Sur les modifications directes et sur la regulation reflexe de l'activite du centre respiratoire de la tete isolee du chien. *Arch.Int.Pharmacodyn.* **33**, 272-372.

Holmgren, A. and Linderholm, H. (1958) Oxygen and carbon dioxide tension of arterial blood during heavy and exhaustive exercise. *Acta Physiol.Scan.* **44**, 203-215.

Hopkins, S.R. and McKenzie, D.C. (1989) Hypoxic ventilatory response and arterial desaturation during heavy work. *J.Appl.Physiol.* **67**, 1119-1124.

Hopkins, S.R. and McKenzie, D.C. (1993) Respiratory factors limiting maximal aerobic exercise. *Clin.J.Sports Med.* **3**, 174-185.

Hopkins, S.R., McKenzie, D.C., Schoene, R.B., Glenny, R.W. and Robertson, H.T. (1994) Pulmonary gas exchange during exercise in athletes. I. Ventilation-perfusion mismatch and diffusion limitation. *J.Appl.Physiol.* **77**, 912-917.

Hopkins, S.R., Belzberg, A.S., Wiggs, B.R. and McKenzie, D.C. (1996) Pulmonary transit time and diffusion limitation during heavy exercise in athletes. *Respir.Physiol.* **103**, 67-73.

Hopkins, S.R., Schoene, R.B., Henderson, W.R., Spragg, R.G., Martin, T.R. and West, J.B. (1997) Intense exercise impairs the integrity of the pulmonary blood-gas barrier in elite athletes. *Am.J.Respir.Crit.Care Med.* **155**, 1090-1094.

Hopkins, S.R., Gavin, T.P., Siafakas, N.M., Haseler, L.J., Olfert, I.M., Wagner, H. and Wagner, P.D. (1998) Effect of prolonged heavy exercise on pulmonary gas exchange in athletes. *J.Appl.Physiol.* **85**, 1523-1533.

Houston, C.S. (1960) Acute pulmonary edema of high altitude. *New Eng.J.Med.* **263**, 478-480.

Hultgren, H.N. (1982) Pulmonary hypertension and pulmonary edema.: Riedesel, J.A., (Ed.) *Oxygen Transport To Human Tissues* , pp. 243-254. New York: Elsevier

Jammes, Y., Mathiot, M.J., Roll, J.P., Prefaut, C., Berthelin, F., Grimaud, C. and Milic-Emili, J. (1981) Ventilatory responses to muscular vibrations in healthy humans. *J.Appl.Physiol.* **51**, 262-269.

Jensen, J.I., Lyager, S. and Pedersen, O.F. (1980) The relationship between maximal ventilation, breathing pattern and mechanical limitation of ventilation. *J.Physiol.(Lond.)* **309**, 521-532.

Johnson, B.D., Saupe, K.W. and Dempsey, J.A. (1992) Mechanical constraints on exercise hyperpnea in endurance athletes. *J.Appl.Physiol.* **73**, 874-886.

Johnson, R.L., Spicer, W.S., Bishop, J.M. and Forster, R.E. (1960) Pulmonary capillary blood volume, flow and diffusing capacity during exercise. *J.Appl.Physiol.* **15**, 893-902.

Kao, F.F. (1963) An experimental study of the pathways involved in exercise hyperpnea employing cross circulation techniques. In: Cunningham, D.J.C. and Lloyd, B.B., (Eds.) *The Regulation Of Human Respiration*, Blackwell: Oxford Press

Kelman, G.R. (1966) Digital computer subroutine for the conversion of oxygen tension into saturation. *J.Appl.Physiol.* **21**, 1375-1376.

Kelman, G.R. (1967) Digital computer procedure for the conversion of PCO_2 into blood CO_2 content. *Respir.Physiol.* **3**, 111-116.

Kelsey, C.J. and Duffin, J. (1992) Changes in ventilation in response to ramp changes in treadmill exercise load. *Eur.J.Appl.Physiol.* **65**, 480-484.

Koskolou, M.D. and McKenzie, D.C. (1993) Arterial hypoxemia and performance during intense exercise. *Eur.J.Appl.Physiol.* **68**, 80-86.

Koulouris, N.G., Dimopoulou, I., Valta, P., Finkelstein, R., Cosio, M.G. and Milic-Emili, J. (1997) Detection of expiratory flow limitation during exercise in COPD patients. *J.Appl.Physiol.* **82**, 723-731.

Koyal, S.N., Whipp, B.J., Huntsman, D., Bray, G.A. and Wasserman, K. (1976) Ventilatory responses to the metabolic acidosis of treadmill and cycle ergometry. *J.Appl.Physiol.* **40**, 864-867.

Krough, A. and Lindhard, J. (1913) The regulation of respiration and circulation during the initial stages of muscular work. *J.Physiol.(Lond.)* **47**, 112-136.

Lama, I.L., Wolski, L.A., Coutts, K.D. and McKenzie, D.C. (1996) The relationship between test protocol and the development of exercise-induced hypoxemia (EIH) in highly trained athletes. *Eur.J.Appl.Physiol.* **74**, 330-335.

Lambertsen, C.J. (1961) Mechanical and physical aspects of respiration. In: Bard, P., (Ed.) *Medical Physiology*, pp. 559 St. Louis: Mosby

Lawler, J., Powers, S.K. and Thompson, D. (1988) Linear relationship between $\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ decrement during exposure to acute hypoxia. *J.Appl.Physiol.* **64**, 1486-1492.

Loeschcke, H.H., De Lattre, J., Schlafke, M.E. and Trouth, C.O. (1970) Effects on respiration and circulation of electrically stimulating the ventral surface of the medulla oblongata. *Respir.Physiol.* **10**, 184-197.

Loke, J., Mahler, D.A. and Virgulto, J.A. (1982) Respiratory muscle fatigue after marathon running. *J.Appl.Physiol.* **52**, 821-824.

Mahler, D.A., Moritz, E.D. and Loke, J. (1982) Ventilatory responses at rest and during exercise in marathon runners. *J.Appl.Physiol.* **52**, 388-392.

Mandor, M.J. and Acevedo, F.A. (1991) Effect of respiratory muscle fatigue on subsequent exercise performance. *J.Appl.Physiol.* **70**, 2059-2065.

Manier, G., Moinard, J., Techoueyres, P., Varene, N. and Guenard, H. (1991) Pulmonary diffusion limitation after prolonged strenuous exercise. *Respir.Physiol.* **83**, 143-154.

Manohar, M. (1986) Blood flow to the respiratory and limb muscles and to abdominal organs during maximal exertion in ponies. *J.Physiol.(Lond.)* **377**, 25-35.

Manohar, M., Goetz, T.E., Holste, L.C. and Nganwa, D. (1988) Diaphragmatic O_2 and lactate extraction during submaximal and maximal exertion in ponies. *J.Appl.Physiol.* **64**, 1203-1209.

Manohar, M. (1988) Costal vs Crural diaphragmatic blood flow during submaximal and near maximal exercise in ponies. *J.Appl.Physiol.* **65**, 1514-1519.

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

Marshall, B.E., Teichner, R.L., Kallos, T., Sugerman, H.J., Wyche, M.Q.J. and Tantum, K.R. (1971) Effects of posture and exercise on the pulmonary extravascular water volume in man. *J.Appl.Physiol.* **31**, 375-379.

Marshall, B.E., Soma, L.R. and Neufeld, G.R. (1975) Lung water volume at rest and exercise in dogs. *J.Appl.Physiol.* **39**, 7-8.

Marthan, R., Castaing, Y., Manier, G. and Guenard, H. (1985) Gas exchange alterations in patients with chronic obstructive lung disease. *Chest.* **87**, 470-475.

Martin, B.J., Weil, J.V., Sparks, K.E., McCullough, R.E. and Grover, R.F. (1978) Exercise ventilation correlates positively with ventilatory chemoresponsiveness. *J.Appl.Physiol.* **45** , 557-564.

Martin, B.J., Heintzelman, M. and Chen, H.I. (1982) Exercise performance after ventilatory work. *J.Appl.Physiol.* **52**, 1581-1585.

Martin, D., Powers, S.K., Cicale, M., Collop, N., Huang, D. and Criswell, D. (1992) Validity of pulse oximetery during exercise in elite endurance athletes. *J.Appl.Physiol.* **72**, 455-458.

Martin, D. and O'Kroy, J. (1993) Effects of acute hypoxia on the $\dot{V}O_{2max}$ of trained and untrained subjects. *J.Sports Sci.* **11**, 37-42.

Mateika, J.H. and Duffin, J. (1995) A review of the control of breathing during exercise. *Eur.J.Appl.Physiol.* **71**, 1-27.

McClaran, S.R., Harms, C.A., Pegelow, D.F. and Dempsey, J.A. (1998) Smaller lungs in women affect exercise hyperpnea. *J.Appl.Physiol.* **84**, 1872-1881.

McKechnie, J.K., Leary, W.P., Noakes, T.D., Kallmeyer, J.C., MacSearraigh, E.T. and Olivier, L.R. (1979) Acute pulmonary oedema in two athletes during a 90-km running race. *S.Afr.Med.J.* **56**, 261-265.

Mead, J. (1960) Control of respiratory frequency. *J.Appl.Physiol.* **15**, 325-336

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

Milic-Emili, G., Petit, J.M. and Deroanne, R. (1962) Mechanical work of breathing during exercise in trained and untrained subjects. *J.Appl.Physiol.* **17**, 43-46.

Miyachi, M. and Shibayama, H. (1992) Ventilatory capacity and exercise-induced arterial desaturation of highly trained endurance athletes. *Ann.Physiol.Anthrop.* **11**, 263-267.

Miyachi, M. and Tabata, I. (1992) Relationship between arterial oxygen desaturation and ventilation during maximal exercise. *J.Appl.Physiol.* **73**, 2588-2591.

Mohler, J.G., Collier, C.R., Brandt, W., Abramson, J., Kerkaik, G. and Yates, S. (1982) In: Mohler, J.G., (Ed) *Pulmonary function testing guidelines and controversies: equipment, methods and normal values*, New York: Academic Press.

Norton, K.I., Squires, B., Norton, L.H., Craig, N.P., McGrath, P. and Olds, T.S. (1995) Exercise stimulus increases ventilation from maximal to supramaximal exercise. *Eur.J.Appl.Physiol.* **70**, 115-125.

O'Kroy, J. and Martin, D. (1989) Effect of acute hypoxia and hyperoxia on maximal oxygen uptake of trained and untrained subjects. *Med.Sci.Sports Exerc.* **21**, S21.

O'Kroy, J.A., Loy, R.A. and Coast, J.R. (1992) Pulmonary function changes following exercise. *Med.Sci.Sports Exerc.* **24**, 1359-1364.

Olafsson, S. and Hyatt, R.E. (1969) Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects. *J.Clin.Invest.* **48**, 564-573.

Otis, A.B., Fehn, W.O. and Rahn, H. (1950) Mechanics of breathing in man. *J.Appl.Physiol.* **2**, 592-603.

Otis, A.B. (1954) The work of breathing. *Physiol.Rev.* **34**, 449-458.

Otis, A.B. (1964) Quantitative relationships in gas exchange. In: Fenn, W.O. and Rahn, H., (Eds.) *Handbook Of Physiology, Respiration*, Vol 1. pp. 681-698. Washington DC: American Physiological Society

Pedersen, P.K., Mandoe, H., Jensen, K., Andersen, C. and Madsen, K. (1996) Reduced arterial O_2 saturation during supine exercise in highly trained cyclists. *Acta Physiol.Scan.* **158**, 323-331.

Pederson, D.G. and Gore, C.J. (1996) Anthropometry measurement error. In: Norton, K.I. and Olds, T.S., (Eds.) *Anthropometrica* , pp. 77-96. Sydney: University of New South Wales Press

Pellegrino, R., Brusasco, V., Rodarte, J.R. and Babb, T.G. (1993) Expiratory flow limitation and regulation of end-expiratory lung volume during exercise. *J.Appl.Physiol.* **74**, 2552-2558.

Piiper, J. and Scheid, P. (1980) Blood-gas equilibration in lungs. In: West, J.B., (Ed.) *Pulmonary Gas Exchange*, pp. 132-173. New York: Academic

Piiper, J. (1994) Search for diffusion limitation in pulmonary gas exchange. In: Wagner, W.W. and Weir, E.K., (Eds.) *The Pulmonary Circulation And Gas Exchange*, pp. 1-17. New York: Futura Publishing Co

Podolsky, A., Eldridge, M.W., Richardson, R.S., Knight, D.R., Johnson, E.C., Hopkins, S.R., Johnson, D.H., Michimata, H., Grassi, B., Feiner, J., Kurdak, S.S., Bickler, P.E., Severinghaus, J.W. and Wagner, P.D. (1996) Exercise-induced $\dot{V}_A/\dot{Q}$ inequality in subjects with prior high-altitude pulmonary edema. *J.Appl.Physiol.* **81**, 922-932.

Poets, C.F. and Stebbens, V.A. (1997) Detection of movement artifact in recorded pulse oximeter saturation. *Eur.J.Pediatr.* **156**, 808-811.

Powers, S.K., Dodd, S., Woodyard, J., Beadle, R.E. and Church, G. (1984) Haemoglobin saturation during incremental arm and leg exercise. *Br.J.Sports Med.* **18**, 212-216.

Powers, S.K. and Williams, J.H. (1987) Exercise-induced hypoxaemia in highly trained athletes. *Sports Med.* **4**, 46-53.

Powers, S.K., Dodd, S., Lawler, J., Landry, G., Kirtley, M., McKnight, T. and Grinton, S. (1988) Incidence of exercise induced hypoxemia in elite endurance athletes at sea level. *Eur.J.Appl.Physiol.* **58**, 298-302.

Powers, S.K., Lawler, J., Dempsey, J.A., Dodd, S. and Landry, G. (1989) Effects of incomplete pulmonary gas exchange on $\dot{V}O_{2max}$. *J.Appl.Physiol.* **66**, 2491-2495.

Powers, S.K., Dodd, S., Freeman, J., Ayers, G.D., Samson, H. and McKnight, T. (1989) Accuracy of pulse oximetry to estimate HbO_2 fraction of total Hb during exercise. *J.Appl.Physiol.* **67**, 300-304.

Powers, S.K., Dodd, S., Criswell, D., Lawler, J., Martin, D. and Grinton, S. (1991) Evidence for an alveolar-arterial PO_2 gradient threshold during incremental exercise. *Int.J.Sports Med.* **12**, 313-318.

Powers, S.K., Martin, D., Cicale, M., Collop, N., Huang, D. and Criswell, D. (1992) Exercise-induced hypoxemia in athletes: role of inadequate hyperventilation. *Eur.J.Appl.Physiol.* **65**, 37-42.

Powers, S.K., Martin, D. and Dodd, S. (1993) Exercise-induced hypoxaemia in elite endurance athletes. Incidence, causes and impact on $\dot{V}O_{2max}$. *Sports Med.* **16**, 14-22.

Préfaut, C., Bourgouin Karaouni, D., Ramonatxo, M., Michel, F.B. and Macabies, J. (1988) A one year double-blind follow-up of blood gas tensions and haemodynamics in almitrine bismesylate therapy. *Eur.Respir.J.* **1**, 41-50.

Préfaut, C., Anselme, F., Caillaud, C. and Masse-Biron, J. (1994) Exercise-induced hypoxemia in older athletes. *J.Appl.Physiol.* **76**, 120-126.

Préfaut, C., Anselme, P.F. and Caillaud, C. (1997) Inhibition of histamine release by nedocromil sodium reduces exercise-induced hypoxemia in master athletes. *Med.Sci.Sports Exerc.* **29**, 10-16.

Rasmussen, B.S., Hanel, B., Jensen, K., Serup, B. and Secher, N.H. (1986) Decrease in pulmonary diffusion capacity after maximal exercise. *J.Sports Sci.* **4**, 185-188.

Rasmussen, B.S., Elkjaer, P. and Juhl, B. (1988) Impaired pulmonary and cardiac function after maximal exercise. *J.Sports Sci.* **6**, 219-228.

Rebuck, A.S., Jones, N.L. and Campbell, E.J. (1972) Ventilatory responses to exercise and to CO_2 rebreathing in normal subjects. *Clin.Sci.* **43**, 861-867.

Rebuck, A.S. and Campbell, E.J. (1974) A clinical method for assessing the ventilatory response to hypoxia. *Am.Rev.Respir.Dis.* **109**, 345-350.

Reid, M.B. and Johnson, R.L.J. (1983) Efficiency, maximal blood flow, and aerobic work capacity of canine diaphragm. *J.Appl.Physiol.* **54**, 763-772.

Ries, A.L., Farrow, J.T. and Clausen, J.L. (1985) Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. *Am.Rev.Respir.Dis.* **132**, 685-689.

Riley, R.L. and Cournand, A. (1949) "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lung. *J.Appl.Physiol.* **1**, 825-847.

Robertson, C.H.J., Foster, G.H. and Johnson, R.L.J. (1977) The relationship of respiratory failure to the oxygen consumption of, lactate production by, and distribution of blood flow among respiratory muscles during increasing inspiratory resistance. *J.Clin.Invest.* **59**, 31-42.

Roca, J., Montserrat, J.M., Rodriguez-Roisin, R., Guitart, R., Torres, A., Agusti, A.G. and Wagner, P.D. (1987) Gas exchange response to naloxone in

chronic obstructive pulmonary disease with hypercapnic respiratory failure. *Bull.Eur.Physiopathol.Respir.* **23**, 249-254.

Rochester, D.F. and Bettini, G. (1976) Diaphragmatic blood flow and energy expenditure in the dog. Effects of inspiratory airflow resistance and hypercapnia. *J.Clin.Invest.* **57**, 661-672.

Rodarte, J.R. (1997) "Detection of expiratory flow limitation during exercise in COPD patients". *J.Appl.Physiol.* **82**, 721-722.

Ross, B.B. and Farhi, L.E. (1960) Dead-space ventilation as a determinant in the ventilation-perfusion concept. *J.Appl.Physiol.* **15**, 363-371.

Rowell, L.B., Taylor, H.L., Wang, Y. and Carlson, W.S. (1964) Saturation of arterial blood with oxygen during maximal exercise. *J.Appl.Physiol.* **19**, 284-286.

Rowell, L.B. (1993) Limitations to oxygen uptake during dynamic exercise. In: Rowell, L.B., (Ed.) *Human Cardiovascular Control*, pp. 327-370. New York: Oxford University Press

Schaffartzik, W., Poole, D.C., Derion, T., Tsukimoto, K., Hogan, M.C., Arcos, J.P., Bebout, D.E. and Wagner P.D. (1992) $\dot{V}_A/\dot{Q}$ distribution during heavy exercise and recovery in humans: implications for pulmonary edema. *J.Appl.Physiol.* **72**, 1657-1667.

Schaffartzik, W., Arcos, J., Tsukimoto, K., Mathieu-Costello, O. and Wagner, P.D. (1993) Pulmonary interstitial edema in the pig after heavy exercise. *J.Appl.Physiol.* **75**, 2535-2540.

Schmidt, C.F. (1959) Respiration. In: Bard, P., (Ed.) *Medical Physiology*, pp. 282-312. St. Louis: Mosby

Severinghaus J.W. (1979) Simple, accurate equations for human blood O_2 dissociation computations. *J.Appl.Physiol.* **46**, 599-602.

Shephard, R.J. (1966) The oxygen cost of breathing during vigorous exercise. *Quart.J.Exper.Physiol.* **51**, 336-350.

Shepherd, R.H. (1958) Effect of pulmonary diffusing capacity on exercise tolerance. *J.Appl.Physiol.* **12**, 487-488.

Shigeoka, J.W. and Stults, B.M. (1992) Home oxygen therapy under Medicare. A primer. *West.J.Med.* **156**, 39-44.

Snell, P.G. and Mitchell, J.H. (1984) The role of maximal oxygen uptake in exercise performance. *Clin.Chest Med.* **5**, 51-62.

St Croix, C.M., Harms, C.A., McClaran, S.R., Nickele, G.A., Pegelow, D., Nelson, W.B. and Dempsey, J.A. (1998) Effects of prior exercise on exercise-induced arterial hypoxemia in young women. *J.Appl.Physiol.* **85**, 1556-1563.

Staub, N.C., Bishop, J.M. and Forster, R.E. (1962) Importance of diffusion and chemical reaction rates in O_2 uptake in the lung. *J.Appl.Physiol.* **17**, 21-27.

Stockley, R.A. (1978) The contribution of the reflex hypoxic drive to hyperpnoea of exercise. *Respir.Physiol.* **35**, 79-87.

Takano, N. (1988) Effects of pedal rate on respiratory responses to incremental bicycle work. *J.Physiol.* **396**, 389-397.

Takano, N., Inaishi, S. and Zhang, Y. (1997) Individual differences in breathlessness during exercise, as related to ventilatory chemosensitivities in humans. *J.Physiol.* **499**, 843-848.

Thews, G. (1968) The theory of oxygen transport and its application to gaseous exchange on the lung. In: Lubbers, D.W., Luft, U.C., Thews, G. and Witzleb, E., (Eds.) *Oxygen Transport In Blood And Tissue*, pp. 1-20. New York/Stuttgart: Gearg Thieme Verlag

Thompson, J.M., Dempsey, J.A., Chosy, L.W., Shahidi, N.T. and Reddan, W.G. (1974) Oxygen transport and oxyhemoglobin dissociation during prolonged muscular work. *J.Appl.Physiol.* **37**, 658-664.

Todaro, A., Leonardi, L.M., Besi, M., Faccini, P., Sardella, F., Menchinelli, C. and Gallozzi, C. (1995) Pulmonary gas exchange in athletes with exercise-induced hypoxaemia. *J.Sports Med.Phys.Fitness.* **35**, 114-123.

Torre-Bueno, J.R., Wagner, P.D., Saltzman, H.A., Gale, G.E. and Moon, R.E. (1985) Diffusion limitation in normal humans during exercise at sea level and simulated altitude. *J.Appl.Physiol.* **58**, 989-995.

Tsukimoto, K., Arcos, J.P., Schaffartzik, W., Wagner, P.D. and West, J.B. (1990) Effect of common dead space on $\dot{V}_A/\dot{Q}$ distribution in the dog. *J.Appl.Physiol.* **68**, 2488-2493.

Tsukimoto, K., Mathieu-Costello, O., Prediletto, R., Elliot, A.R. and West, J.B. (1991) Ultrastructural appearances of pulmonary capillaries at high transmural pressures. *J.Appl.Physiol.* **71**, 573-582.

Turcotte, R., Kiteala, L., Marcotte, J.E. and Perrault, H. (1997) Exercise-induced oxyhemoglobin desaturation and pulmonary diffusing capacity during high-intensity exercise. *Eur.J.Appl.Physiol.* **75**, 425-430.

Vaughan, T.R.J., DeMarino, E. and Staub, N.C. (1976) Indicator dilution lung water and capillary blood volume in prolonged heavy exercise in normal men. *Am.Rev.Respir.Dis.* **113**, 757-762.

von Euler, U.S. (1938) Reflectorische und zentrale Wirkung von Kaliumionen auf Blutdruck und Atmung. *Skand.Arch.Physiol.* **80**, 94-123.

Wagner, P.D. and West, J.B. (1972) Effects of diffusion impairment on O_2 and CO_2 time courses in pulmonary capillaries. *J.Appl.Physiol.* **33**, 62-71.

Wagner, P.D., Saltzman, H.A. and West, J.B. (1974a) Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J.Appl.Physiol.* **36**, 588-599.

Wagner, P.D., Naumann, P.F. and Laravuso, R.B. (1974b) Simultaneous measurement of eight foreign gases in blood by gas chromatography. *J.Appl.Physiol.* **36**, 600-605.

Wagner, P.D., Dantzker, D.R., Dueck, R., Clausen, J.L. and West, J.B. (1977) Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J.Clin.Invest.* **59**, 203-216.

Wagner, P.D. (1977) Diffusion and chemical reaction in pulmonary gas exchange. *Physiol.Rev.* **57**, 257-312.

Wagner, P.D. and West, J.B. (1980) Ventilation-perfusion relationships In: West, J.B. (Ed.) *Pulmonary Gas Exchange,* pp. 219-262. New York: Academic

Wagner, P.D. (1982) Influence of mixed venous PO_2 on diffusion of O_2 across the pulmonary blood:gas barrier. *Clin.Physiol.* **2**, 105-115.

Wagner, P.D., Gale, G.E., Moon, R.E., Torre-Bueno, J.R., Stolp, B.W. and Saltzman, H.A. (1986) Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J.Appl.Physiol.* **61**, 260-270.

Wagner, P.D., Sutton, J.R., Reeves, J.T., Cymerman, A., Groves, B.M. and Malconian, M.K. (1987) Operation Everest II: pulmonary gas exchange during a simulated ascent of Mt. Everest. *J.Appl.Physiol.* **63**, 2348-2359.

Wagner, P.D., Gillespie, J.R., Landgren, G.L., Fedde, M.R., Jones, B.W., DeBowes, R.M., Pieschl, R.L. and Erickson, H.H. (1989) Mechanism of exercise-induced hypoxemia in horses. *J.Appl.Physiol.* **66**, 1227-1233.

Wagner, P.D. (1992) Ventilation-perfusion matching during exercise. *Chest* **101**, 192S-198S.

Warren, G.L., Cureton, K.J., Middendorf, W.F., Ray, C.A. and Warren, J.A. (1991) Red blood cell pulmonary capillary transit time during exercise in athletes. *Med.Sci.Sports Exerc.* **23**, 1353-1361.

Wasserman, K. (1978) Breathing during exercise. *New Eng.J.Med.* **298**, 780-785.

Wasserman, K., Hansen, J.E., Sue, D.Y. and Whipp, B.J. (1987) *Principles of Exercise Testing and Interpretation, Appendix D.* Philadelphia, PA: Lea & Febiger.

Wasserman, K., Beaver, W.L. and Whipp, B.J. (1990) Gas exchange theory and the lactic acidosis (anaerobic) threshold. *Circulation* **81**, 14-30.

Wasserman, K., Hansen, J.E., Sue, D.Y., Whipp, B.J. and Casaburi, R. (1994) *Principles of Exercise Testing and Interpretation, Appendix D.* Philadelphia, PA: Lea & Febiger.

Weiner, P., Suo, J., Fernandez, E. and Cherniack, R.M. (1989) Efficiency of the respiratory muscles in healthy individuals. *Am.Rev.Respir.Dis.* **140**, 392-396.

West, J.B. (1969) Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. *Respir.Physiol.* **7**, 88-110.

West, J.B. (1970) Effect of slope and shape of dissociation curve on pulmonary gas exchange. *Respir.Physiol.* **8**, 66-85.

West, J.B., Tsukimoto, K., Mathieu-Costello, O. and Prediletto, R. (1991) Stress failure in pulmonary capillaries. *J.Appl.Physiol.* **70**, 1731-1742.

West, J.B. and Mathieu-Costello, O. (1992) High altitude pulmonary edema is caused by stress failure of pulmonary capillaries. *Int.J.Sports Med.* **13**, S54-S58.

West, J.B., Mathieu-Costello, O., Jones, J.H., Birks, E.K., Logemann, R.B., Pascoe, J.R. and Tyler, W.S. (1993) Stress failure of pulmonary capillaries in racehorses with exercise-induced pulmonary hemorrhage. *J.Appl.Physiol.* **75**, 1097-1109.

Whipp, B.J. and Wasserman, K. (1969) Alveolar-arterial gas tension differences during graded exercise. *J.Appl.Physiol.* **27**, 361-365.

Whipp, B.J. and Davis, J.A. (1979) Peripheral chemoreceptors and exercise hyperpnea. *Med.Sci.Sports* **11**, 204-212.

Wilkerson, J.E., Horvath, S.M., Gutin, B., Molner, S. and Diaz, F.J. (1982) Plasma electrolyte content and concentration during treadmill exercise in humans. *J.Appl.Physiol.* **53**, 1529-1539.

Williams, J.H., Powers, S.K. and Kelly Stuart, M. (1986) Hemoglobin desaturation in highly trained athletes during heavy exercise. *Med.Sci.Sports Exerc.* **18**, 168-173.

Wood, R.J., Gore, C.J., Hahn, A.G., Norton, K.I., Scroop, G.C., Campbell, D.P., Watson, D.B. and Emonson, D.L. (1997) Accuracy of two pulse oximeters during maximal cycling exercise. *Aust.J.Sci.Med.Sport.* **29**, 47-50.

Woods, G.F., Day, L., Withers, R.T., Ilsley, A.H. and Maxwell, B.F. (1994) The dynamic calibration of cycle ergometers. *Int.J.Sports Med.* **15**, 168-171.

Yeh, M.P., Gardner, R.M., Adams, T.D. and Yanowitz, F.G. (1982) Computerized determination of pneumotachometer characteristics using a calibrated syringe. *J.Appl.Physiol.* **53**, 280-285.

Yokoyama, T. and Farhi, L.E. (1967) The study of ventilation-perfusion ratio distribution in the anaesthetized dog by multiple inert gas washout. *Respir.Physiol.* **3**, 166-176.

Younes, M., Bshouty, Z. and Ali, J. (1987) Longitudinal distribution of pulmonary vascular resistance with very high pulmonary blood flow. *J.Appl.Physiol.* **62**, 344-358.

Young, I.H. and Woolcock, A.J. (1978) Changes in arterial blood gas tensions during unsteady-state exercise. *J.Appl.Physiol.* **44**, 93-96.

Young, I.H., Corte, P. and Schoeffel, R.E. (1982) Pattern and time course of ventilation-perfusion inequality in exercise-induced asthma. *Am.Rev.Respir.Dis.* **125**, 304-311.

Zuntz, N. and Geppert, J. (1886) Ueber die Natur der normalen Atemreize und den Ort ihrer Wirkung. *Arch.Ges.Physiol.* **38**, 337-338.