AN INVESTIGATION OF THE ARTERIAL TO ALVEOLAR P_{CO_2} GRADIENT IN SCUBA DIVERS

by

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AN INVESTIGATION OF THE ARTERIAL TO ALVEOLAR P_{CO_2} GRADIENT IN S.C.U.B.A. DIVERS

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ABSTRACT

The differences in carbon dioxide tensions between arterial blood and simultaneously sampled alveolar and end-tidal gas, $P(a-A)CO_2$ and $P(a-ET)CO_2$, were investigated in 13 experienced SCUBA divers. Arterial blood gas tensions were estimated from arterialized-venous blood, sampled from a dorsal hand vein. Samples were taken after heating the hand to 40-45 degrees C. for the duration of the experiment. The validity of the technique was checked by measurement of the arterialized-venous oxygen tension. Alveolar PCO_2 was defined as the carbon dioxide tension in the lungs at 60% of the expiratory time duration. $P(a-A)CO_2$ and $P(a-ET)CO_2$ were measured at rest and during steady-state exercise (400 KPM/min.), while subjects breathed from a low resistance mouthpiece and from an open circuit demand regulator.

The $P(a-ET)CO_2$ and $P(a-A)CO_2$ gradients ranged from 9.99 to -5.88 mmHg and 9.68 to -5.74 mmHg respectively. Both PCO_2 gradients were positive while subjects breathed from the low resistance mouthpiece. These gradients became negative while subjects breathed from the SCUBA regulator. The reversal of the PCO_2 difference ($P<0.05$) was accompanied by an increase in both $PETCO_2$ and $PACO_2$, with no significant change in $PaCO_2$. The divers exhibited a modified respiratory pattern when breathing from the SCUBA regulator relative to the low resistance

mouthpiece. Ventilation decreased ($P<0.05$) with a corresponding decrease in respiratory frequency and an increase in tidal volume.

Best subset multiple linear regression analyses performed on the data generated equations predicting the PCO2 difference.

The validity of the multiple regression equations obtained by these analyses was then tested using independent data which included PETCO2 and PaCO2. The best predictive equation estimated the P(ET-a)CO2 differences of the independent data with an accuracy of ± 2.54 MSE, (mean square error).

PaCO2 cannot be assumed to equilibrate with PACO2 or PETCO2. Differences depend on a number of respiratory factors, and can be closely estimated using the predictive equation given.

DEDICATION

For my father

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I. Introduction

Efficient gas exchange requires continuous readjustments of the pulmonary circulation and pulmonary ventilation to control oxygen and carbon dioxide exchange across the alveolar-capillary membrane. One of the principle assumptions of cardio-respiratory physiology has been that alveolar carbon dioxide tension, (P_ACO_2), is in close equilibrium with arterial carbon dioxide tension, (P_aCO_2). This is thought to occur because of the high diffusion rate of carbon dioxide across the alveolar-capillary membrane and the steep carbon dioxide dissociation curve.

Until recently, it has generally been accepted that the transfer of carbon dioxide across the alveolar-capillary membrane occurs by simple diffusion. The assumption that P_aCO_2 is in equilibrium with P_ACO_2 constitutes an essential hypothesis regarding conventional analysis of alveolar gas exchange.

Since the carbon dioxide tension in the blood entering the alveolar capillary is greater than that in the alveolar gas, there is an exchange process which approaches an equilibrium level determined by the extent to which the exchange process has proceeded during the transit time of the blood in the pulmonary capillary. Measurement of the value of arterial blood P_CO_2 and expired alveolar P_CO_2 agree within acknowledged variations in

the definition of "alveolar" PCO2. Gas tension differences between end-tidal PCO2 and arterial PCO2 are considered as indices of the efficiency of pulmonary gas exchange.

Recent experimental evidence has suggested the possible existence of a negative PCO2 difference between arterial blood and alveolar gas, P(a-A)CO2. These studies have measured P(a-A)CO2 gradients during rebreathing and hypercapnic procedures. However, the existence of a negative P(a-A)CO2 difference has not been investigated during normal steady state gas exchange. Studies have measured P(a-ET)CO2 gradients as being representative of P(a-A)CO2 gradients. Several errors are associated with this assumption which may lead to observation of a false PCO2 gradient. The apparent finding of a negative P(a-A)CO2 difference during normal gas exchange conditions would invalidate the basic hypothesis of conventional gas exchange physiology, where PACO2 is in close equilibrium with PaCO2. If a negative P(a-A)CO2 gradient exists, simple passive diffusion across the alveolar-capillary membrane may not be sufficient to explain the exchange of carbon dioxide within the lungs.

Several mechanisms have been proposed to explain this apparent negative P(a-A)CO2 difference;

1. Ventilation/perfusion inequalities in the lungs,

2. Cyclic variations in alveolar gas composition during

respiration,

3. Transit time delays in exchange of alveolar gas during respiration,

4. Slow equilibration between CO2/HCO3-/H+ in the blood during transit time in the pulmonary capillary,

5. The effects of a negatively charged pulmonary capillary surface producing an ionic gradient within the pulmonary capillary, (Wein Effect).

The above controversy shows the necessity to confirm or refute the existence of a negative arterial blood to alveolar gas $\underline{P}CO2$ difference under normal gas exchange conditions.

II. Review of Literature

Introduction

One of the functional assumptions of respiratory physiology has been that pulmonary end-capillary carbon dioxide tension (PcCO2) is in equilibrium with alveolar carbon dioxide tension (PACO2) in the lungs. As a result, it is now generally accepted that the transfer of carbon dioxide across the alveolar-capillary membrane occurs by simple diffusion, (Forster, 1964; Cherniack, et al., 1972; Ganong, 1977; West, 1978).

During the later part of the last century, physiologists attempted to measure the diffusing capacity of the lungs in order to prove the existence of gas secretion by the lungs. At the turn of the century there were two schools of thought on the basic mechanisms of pulmonary gas exchange (Gurtner 1977). One group of researchers suggested that CO2 could be excreted by the lungs, whereas another group suggested that all pulmonary gas exchange took place by simple diffusion alone.

Haldane (1922) compared the carbon dioxide tension of alveolar gas (PACO2) and arterial blood (PaCO2) in dogs breathing room air and various hypercapnic gas mixtures.

Although the data showed significant P(a-A)CO2 differences when elevated CO2 levels were present in the inspired gas mixture, (negative P(a-A)CO2 gradient), Haldane believed that CO2 secretion was present under all experimental conditions (Haldane, 1922). Since Haldane's observations several groups of researchers have reported elevated PACO2 above PaCO2, under various experimental conditions (Asmussen and Nielson, 1956; Collier, 1956; Gurtner, et al., 1967; Jones, et al., 1967; Clark, 1968; Daly, et al., 1968; Denison, et al., 1969; Gurtner, et al., 1969; Jones, et al., 1969; Whipp and Wasserman, 1969; Clausen, et al., 1970; Denison, et al., 1971; Field, et al., 1971; Lazslo, et al., 1971; Jones, et al., 1972; Gurtner, 1977; Jones, et al., 1979).

The evidence has suggested that, during certain steady state conditions, a paradoxical negative PCO2 difference exists between arterial blood and alveolar gas (negative P(a-A)CO2 gradient). These findings imply that the exchange of CO2 across the alveolar-capillary membrane cannot be explained entirely on the basis of passive diffusion.

Rebreathing Experiments

The majority of literature reports support the existence of a negative P(a-A)CO2 gradient during rebreathing experiments while subjects were exercising (Jones, et al., 1967; Daley, et al., 1968; Denison, et al., 1969; Jones, et al., 1969; Denison, et al., 1971; Jones, et al., 1972; Jones, et al., 1977). Additional rebreathing studies, with subjects inspiring hypercapnic gas mixtures, where there is no net movement of CO2 across the alveolar-capillary membrane, have revealed similar findings (Gurtner, et al., 1967; Lazslo, et al., 1968; Gurtner, et al., 1969; Jones, et al., 1969; Lazslo, et al., 1971; Jennings and Chen, 1975; Gurtner, et al., 1977).

Jones, et al. (1969) reported that, during rebreathing experiments with hypercapnic gas mixtures in equilibrium, where there was no net movement of CO2 across the alveolar-capillary membrane, the PCO2 of the lung-bag system was elevated above the PCO2 of simultaneously sampled arterial blood. The absence of a net movement of CO2 would indicate that an equilibrium had been reached between the PCO2 of the alveolar gas and pulmonary capillary blood. Jones, et al. (1969) suggested that the higher oxygen content of the rebreathed gas mixture may have led to rapid oxygenation of the pulmonary capillary hemoglobin, liberating CO2 and increasing the H+ content of the blood. This,

combined with prevention of CO2 elimination, may be responsible for the apparent negative P(a-A)CO2 gradient. When this hypothesis was tested, avoiding oxygenation by rebreathing a CO2-N2 mixture, only a slight reduction in the negative P(a-A)CO2 gradient was observed.

Similar results were reported by Denison, et al. (1969) using the same experimental conditions. From their results, it was concluded that both mixed-venous PCO2 (PvCO2), and PaCO2, were lower than PACO2 when subjects rebreathed elevated CO2-O2 and CO2-N2 gas mixtures. Therefore, the possible mechanism described above cannot explain the observed negative P(a-A)CO2 gradient during rebreathing experiments.

The negative P(a-A)CO2 gradient may be caused by the rates of reactions between CO2, HCO3-, and H+ within the blood (Forster, 1972; Forster and Crandall, 1975), or by the maintenance of an H+ gradient across the alveolar-capillary membrane, (Gurtner, et al., 1969).

Gurtner et al. (1969) measured the hydrogen ion and plasma bicarbonate levels in the mixed-venous blood of dogs during rebreathing experiments. Their results were similar to those observed by Denison, et al. (1969) and Jones, et al. (1969), for steady state differences between PACO2 and PaCO2 when there was no net gas exchange. The negative P(a-A)CO2 gradient was related to the(H+) and (HCO3-) of the mixed-venous blood and the rate of pulmonary blood flow. These findings would imply that the

negative P(a-A)CO2 gradient increased with an increase in the (H+) of the blood flowing to the lungs.

Lazslo, et al. (1971) and Jones, et al. (1972) have argued that obstruction of normal CO2 excretion during rebreathing interfers with the true equilibrium PCO2 gradient between the pulmonary capillary blood and alveolar gas. They have suggested that the (HCO3-) and (H+) in the lung water and mixed-venous blood are continuously changing during rebreathing experiments and these electrolyte changes in the blood may act to slow gas equilibration. Failure to reach ionic equilibrium within the transit time of the blood in the lungs may be responsible for the observed negative P(a-A)CO2 gradient during short rebreathing experiments. This and the proposed hypothesis by Gurtner, et al. (1967) would imply an increase in the negative P(a-A)CO2 gradient with an increase in the (H+) of the blood flowing to the lungs.

Evidence has accumulated to question the assumption of rapid and complete equilibration of PACO2 and PaCO2 at the alveolar-capillary membrane and of the true identity of the PCO2 in the blood leaving the pulmonary-end capillaries with the blood in the systemic arteries.

Forster, (1972) proposed the "Delayed Equilibrium Hypothesis" to describe the slow changes of PCO2, (H+), and (HCO3-) occurring in the blood leaving the pulmonary end-capillaries. This hypothesis predicts that the PCO2 of the

blood increases after leaving the pulmonary end-capillary, resulting in a positive P(a-A)CO2 gradient (Forster and Crandall, 1975).

Gurtner, et al. (1969) believe that the negative P(a-A)CO2 gradient observed during rebreathing experiments cannot be explained by the "Delayed Equilibrium Hypothesis". Gurtner (1977) suggests that this mechanism could account for only 25% of the observed negative P(a-A)CO2 gradient. To explain the remaining difference, Gurtner in 1972, proposed the "Charged Membrane Hypothesis", suggesting that the negative PCO2 gradient is proportional to the H+ activity in the blood. The hypothesis is dependent on a transient chemical disequilibrium between H+ and HCO3- ions. Blood flow through the pulmonary capillaries produces a negative electrical field towards the periphery of the capillary wall, known as the "Wein Effect". As a result, an H+ ion gradient develops near the capillary wall repelling HCO3- ions. This produces a greater concentration of H+ ions towards the periphery of the capillary wall compared with the bulk phase of the blood flow. The gradient is maintained continuously by blood flow. The (H+) increases at the periphery of the capillary as a result of H+ ion dissociation from plasma proteins, decreasing the pH of the blood and driving carbonic acid dissociation, which elevates the capillary PCO2 at the alveolar-capillary membrane. Gurtner (1972) explains that it is this transient concentration of CO2 which is in equilibrium with

the alveolar gas, whereas the bulk phase of the pulmonary capillary blood maintains a lower PCO2 level. This theory can also be used to explain the direct relationship between the negative P(a-A)CO2 gradient and changes in the (H+) and (HCO3-) in the blood.

Forster (1977) disagrees with the "Charged Membrane Hypothesis", stating that at the present time it is not technically possible to measure directly the PCO2 in an alveolus and its pulmonary end-capillary blood supply, let alone a transient ionic gradient within the pulmonary capillaries. Forster questions the validity of an H+ and HCO3- ion gradient within the pulmonary capillary and the existence and maintenance of a non-uniform distribution between these ions over the entire length of the pulmonary capillary. In addition, the amount of energy required to maintain a PCO2 gradient between the perimeter and bulk phase of the blood would represent 14% of the total resting metabolism of man or 100 times the mechanical energy available in the blood flowing through the lungs (Effros, 1972). These factors alone call into question the proposed mechanism outlined by Gurtner to explain the existence of a negative P(a-A)CO2 gradient. Forster (1977) questions how far CO2 exchange has proceeded during the time of blood flow through the pulmonary capillaries.

Hypercapnic Gas Mixtures

Of more direct interest to this study is the relationship between the P(a-A)CO2 gradient under more normal physiological steady-state gas exchange conditions. Negative P(a-A)CO2 gradients have been observed while subjects were breathing hypercapnic gas mixtures.

Laszlo, et al. (1971) observed end-tidal CO2 levels (PETCO2) that exceeded PaCO2 when subjects breathed hypercapnic gas mixtures. Jennings and Chen (1975) also observed a negative P(a-A)CO2 gradient in conscious dogs during acute and chronic exposure to hypercapnic gas mixtures. Gurtner, et al. (1977) observed a negative P(a-A)CO2 gradient during extreme hypercapnia in dogs, in which the magnitude of the negative PCO2 gradient was directly proportional to the (H+) and (HCO3-) of the mixed-venous blood.

The above studies have documented the paradoxical behaviour of CO2 in the lungs under two separate experimental conditions.

1. With net gas exchange eliminated using rebreathing techniques to overcome the possible influence of ventilation-perfusion inequalities.
2. During steady-state gas exchange with subjects breathing hypercapnic gas mixtures.

Both approaches require the maintenance of an abnormal physiological condition.

Elevated PETCO2

Several researchers have performed experiments under normal gas exchange conditions during exercise. P(a-A)CO2 gradients were not measured but elevated PETCO2 levels were observed (Goff and Bartlett, 1957; Jarrett, 1966; Wood and Bryan, 1970; Dennedts and Anthonisen, 1973; Doell, et al., 1973).

Additional studies have reported that SCUBA (self-contained underwater breathing apparatus) divers have elevated PETCO2 levels when compared with non-divers, both at normal and increased ambient pressures while subjects were exercising breathing room air (Cherniack and Snidal, 1956; Schaefer, 1958; Froeb, 1960; Lanphier, 1963; Milic-Emili and Tyler, 1963; Broussolle, et al., 1969; Barnett, et al., 1970; Lally, et al., 1974; Anthonisen, 1976; Florio, et al., 1979).

The primary cause for the increased PETCO2 is thought to be related to the increase in barometric pressure. An increase in the absolute pressure will cause respiratory gases to become denser, resulting in an increase in respiratory resistance. This causes an overall increase in the work of breathing from the combined effects of both an increase in resistance to airflow in the respiratory passages and respiratory resistance imposed by

an external breathing apparatus. These factors will cause the divers to hypoventilate and increase PETCO2 at increased ambient pressures. There is an inverse correlation between pulmonary ventilation and PETCO2.

In addition to the above findings, some researchers have observed a change in the breathing pattern particular to SCUBA divers which reduces their work of breathing (Lanphier, 1963). SCUBA divers showed similar breathing patterns when PETCO2 was elevated through exercise or rebreathing hypercapnic gas mixtures at normal barometric pressures. Divers adapt to higher levels of CO2 with a characteristic hypoventilation and change in breathing pattern (Florio, et al., 1979). With SCUBA divers, there appears to be a trade-off between ventilation, PETCO2, and the work of breathing which results in retention of CO2. Tolerance to elevated PETCO2 may develop as an alternative to an increase in the work of breathing which would be required to maintain CO2 within normal limits during exercise and under hyperbaric conditions.

Asmussen and Neilsen (1956) observed that PETCO2 was greater than PaCO2 during exercise. They put forward the explanation that ventilation-perfusion inequalities were responsible for the observed negative gradient. Whipp and Wasserman (1969) investigated the P(a-ET)CO2 gradient during graded exercise to exhaustion and observed a decrease in the P(a-ET)CO2 gradient with increasing exercise until PETCO2 was

greater than PaCO2. Whipp and Wasserman explain that the decrease in the P(a-ET)CO2 gradient observed may be due to an adjustment in the ventilation-perfusion ratio during exercise, necessary for efficient gas exchange. However, a change in the ventilation-perfusion ratio cannot explain the negative P(a-ET)CO2 gradient, which therefore must be due to an increase in the CO2 delivery to the lungs.

A number of respiratory variables are known to influence the PCO2 gradient, independently or in relation to other variables (Jones, et al., 1979). Stepwise multiple linear regression analysis was performed on the data to generate the following equation, predicting the relationship between these variables and the P(a-ET)CO2 gradient during exercise.

$$P(ET-a)CO2 = -6.7 + 0.11*PETCO2 + 1.73*VT + 1.10*\dot{V}CO2$$

There was an increase in the negative P(a-ET)CO2 gradient proportional to the increase in VCO2 and VT during the respiratory cycle, when subjects breathed at 15, 30, and 45 breaths per minute (deliberate manipulation of breathing frequency). The observed negative P(a-ET)CO2 gradient could be abolished by increasing the respiratory frequency (Jones, et al., 1966; Jones, et al., 1979). The negative P(a-ET)CO2 gradient was inversely related to the frequency of breathing and directly related to tidal volume, carbon dioxide production and

minute ventilation.

From the above review, it would appear that a negative P(a-ET)CO2 gradient may occur during exercise or when CO2 exchange in the lungs is impaired. These findings have important implications regarding gas exchange physiology as understood at the present time, since several common physiological measurements are dependent on the assumption that an equilibrium exists between PACO2 and PaCO2.

One example involves the calculation of physiological dead space using the Bohr Equation. The equation assumes that PACO2 can be used to estimate PaCO2. If PACO2 overestimates PaCO2, then the calculated dead space using the Bohr equation is also overestimated. Another example involves the calculation of cardiac output using the indirect Fick Equation. Lower estimates for cardiac output will be derived if a negative P(a-A)CO2 gradient exists during exercise, since CO2 equilibrium will occur at a higher partial pressure during rebreathing than expected from the CO2 dissociation curve, thus causing an overestimate in the venous PCO2. Assessment of the subject's ventilatory response to CO2 will yield lower values for PACO2 then would occur using PaCO2. In addition, if negative P(a-A)CO2 gradients occur under normal gas exchange conditions, a given PaCO2 level could be maintained at a lower level of alveolar ventilation, which would be beneficial during heavy exercise loads.

The existence of a negative P(a-A)CO2 gradient would invalidate the basis of conventional analysis for alveolar gas exchange physiology, (Jones, et al., 1969; Piiper and Scheid, 1971; Scheid and Piiper, 1980).

PETCO2 cannot be used to represent PACO2 due to the cyclic variations during the later part of the respiratory cycle (Young, 1955; Berengo and Cutillo, 1961). There will always be differences between the average value for PACO2 and PETCO2 due to these cyclic variations in CO2 during the respiratory cycle, especially with exercise (Dubois, et al., 1951). The average composition of the alveolar portion of expired air (as used in the Bohr Equation) does not equal the average composition of air in the alveoli (Krogh, 1910; Krogh, 1913). Similar finding were reported by Suskind, et al., 1950, Dubois, et. al., 1951, Filley, et al., 1954, and Bartels, et al., 1954. An overestimate of the mean PACO2 may lead to a negative P(a-A)CO2 gradient.

Piiper and Scheid (1971), and Scheid and Piiper (1980), have presented critical reviews examining the experimental evidence for the existence of a negative P(a-A)CO2 gradient. Their reviews have devoted much space to the identification of possible sources of experimental error which may have led to the assumption of a negative P(a-A)CO2 gradient. After conducting their own experiments in an attempt to consider all possible sources of errors, Scheid and Piiper have concluded that at the present time there is not adequate evidence to reverse the

traditional theories regarding the positive direction of the $\underline{P}(\underline{a}-\underline{A})CO_2$ gradient in the human lung.

Purpose of the Study

The exact physiological implications of an elevated alveolar CO2 tension relative to arterial CO2 tension are at present unclear. Under normal circumstances there is generally considered to be an equilibrium between alveolar and arterial PCO2.

Several studies have documented the existence of a negative P(a-A)CO2 gradient while subjects were rebreathing or inspiring hypercapnic gas mixtures. Additional studies have suggested that trained SCUBA divers maintain elevated end-tidal carbon dioxide tensions. The breathing apparatus of SCUBA divers causes an increased resistance to breathing and accentuates PETCO2

Since the studies of SCUBA divers have not included measurements of arterial carbon dioxide tensions, one can only speculate on the exact levels of arterial PCO2 which accompany the alveolar hypercapnia measured in these divers.

This study has examined the P(a-A)CO2 and P(a-ET)CO2 gradients in trained SCUBA divers exercising under normal steady-state gas exchange conditions, without rebreathing or hypercapnia procedures, to determine the direction of the PCO2 gradient during exercise while subjects breath from a low resistance mouthpiece and open circuit SCUBA demand regulator. The thesis of this study is that equilibrium between arterial

PCO2 and alveolar PCO2 cannot be assumed under these conditions. This hypothesis does not suggest that a gradient between PETCO2 and PaCO2 or PACO2 and PaCO2 is particular to SCUBA divers. The PCO2 gradient is dependent on changes in respiratory variables during exercise. Since the purpose of this study was to examine whether or not a gradient exists between PETCO2 and PaCO2 or PACO2 and PaCO2 as opposed to comparing divers with non-divers, control subjects were not appropriate.

A definitive answer to the controversy regarding the existence of a negative P(a-A)CO2 gradient during normal gas exchange conditions would have a substantial impact on essential assumptions underlying several "classical principles" of respiratory physiology.

III. Methods, Materials and Procedure

Subjects

The subjects were 11 male and 2 female divers. Each subject was trained in self-contained underwater breathing apparatus (SCUBA) and was an active diver logging more than 50 hours diving per year.

The subjects performed no strenuous physical activity and ate no large meals for at least 4 hours before testing. Upon volunteering, subjects were required to sign an Informed Consent Form and fill out a Medical History Form. The subjects were then given a brief outline of the entire experiment and their responsibilities.

Each subject was required to exercise on a bicycle ergometer while breathing room air through a low resistance mouthpiece and an open circuit SCUBA demand regulator, outlined in Figures 1 and 2.

The SCUBA used consisted of an 80 cu.ft. compressed air cylinder (U.S. Divers) and a two-stage demand valve regulator (Voit Trieste II).

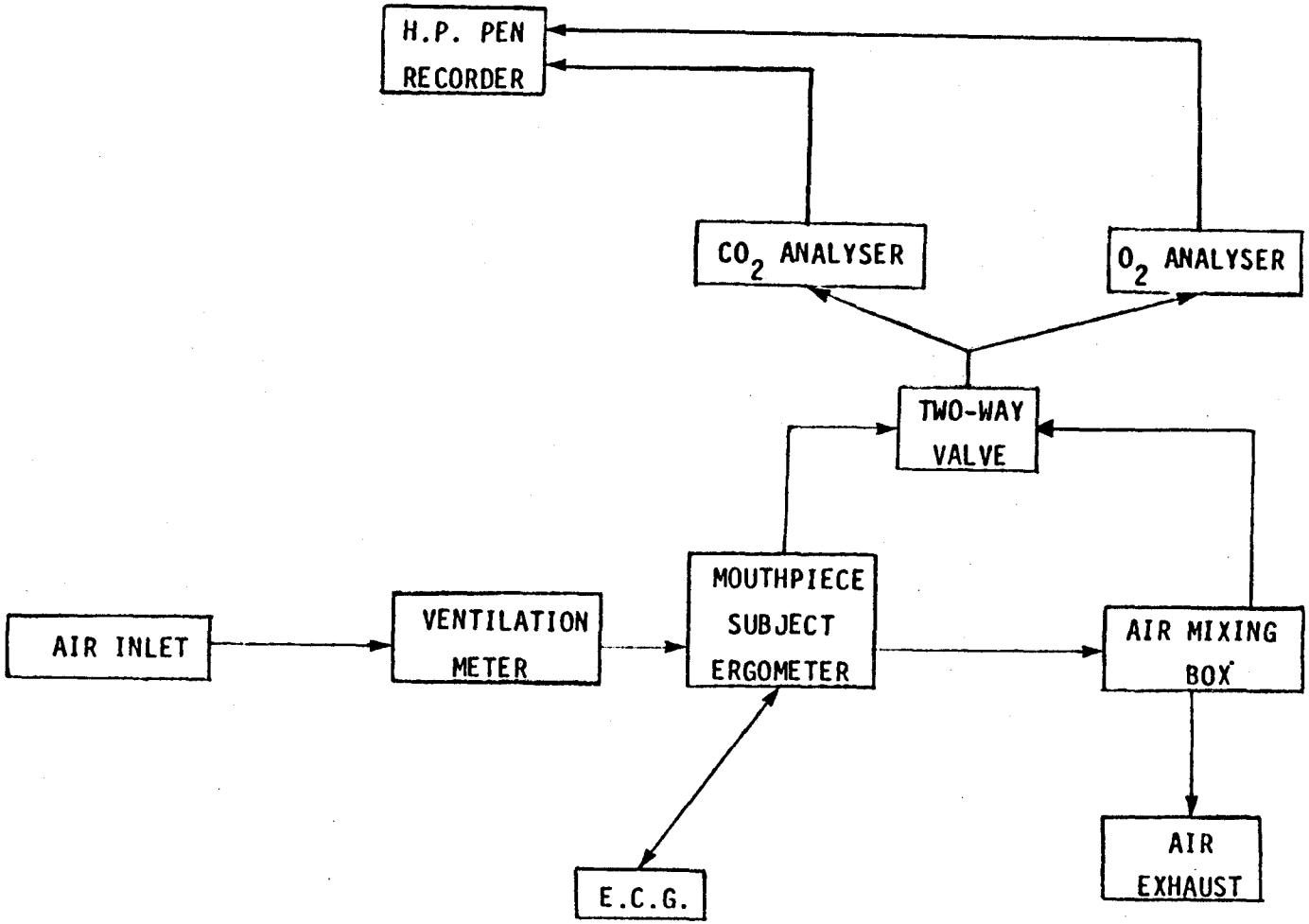

Figure 1. Schematic diagram of the apparatus and instrumentation used in the study during exercise condition A, (without the added respiratory resistance from the SCUBA apparatus).

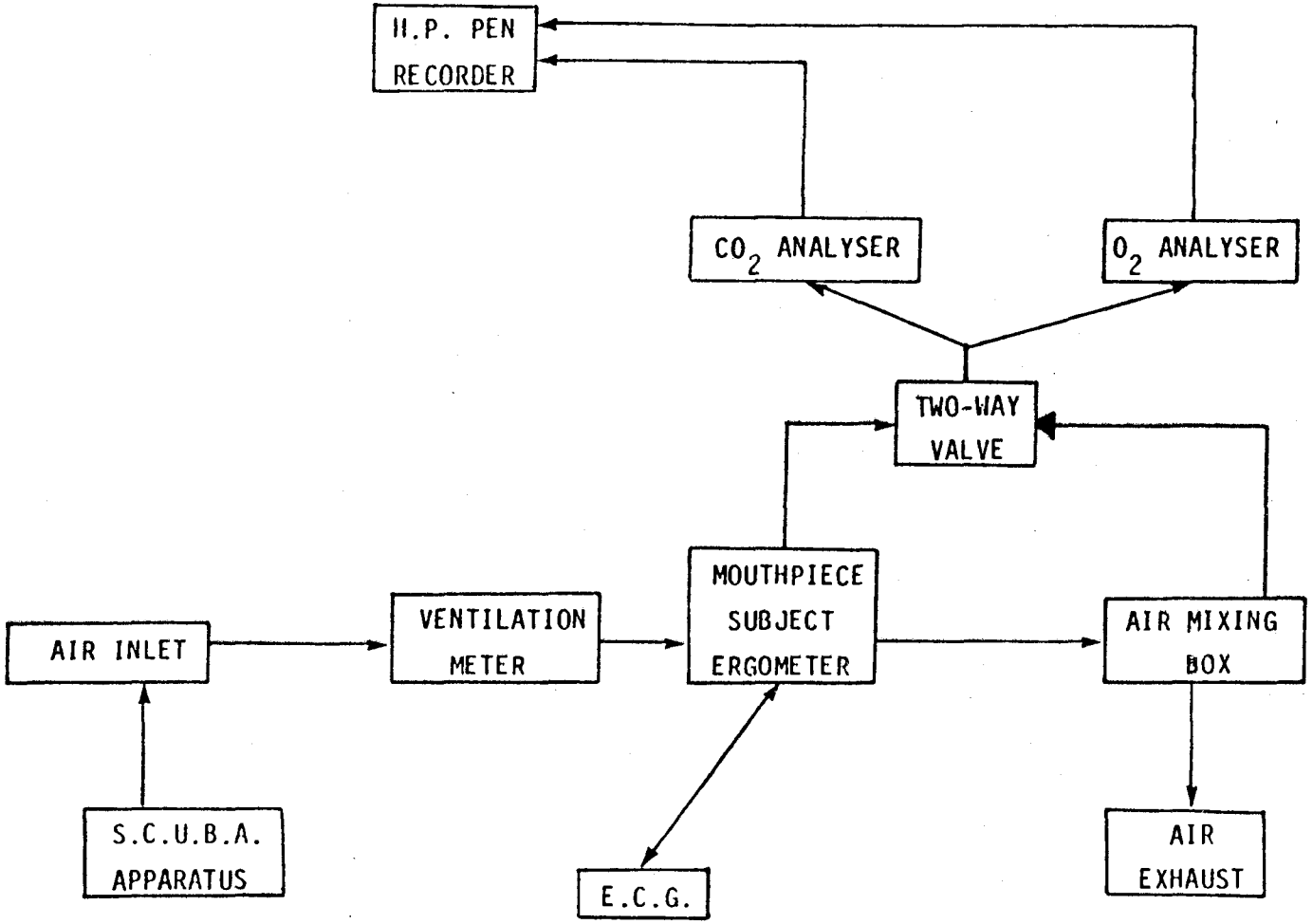

Figure 2. Schematic diagram of the apparatus and instrumentation used in the study during exercise condition B, (with the added respiratory resistance from the SCUBA apparatus).

Data Collection

Data collected prior to each experiment included room temperature and barometric pressure and the subject's age, height and weight.

Table 1 outlines the variables measured and calculated during the rest, warm-up, and exercise conditions A and B for each experiment. Table 2 outlines the experimental conditions and respective sample periods.

Blood Sampling

Due to the medical risks associated with arterial blood sampling, blood gas analysis was performed using the arterialized-venous blood sampling technique described by Forster, et al., (1972). Arterial PCO2, PO2 and pH are determined from arterialized-venous blood samples. In further discussions, the term PaCO2 will refer to arterialized-venous PCO2 measurements. The major advantage of venous versus arterial blood sampling for PaCO2 and pH is that multiple samples can be obtained while avoiding inherent risks to the subjects associated with direct arterial punctures, especially while exercising under non-clinical supervision. Catheterization permits repeated sampling during exercise studies without affecting the subject's performance.

MEASURED VARIABLES

$\dot{V}E$ BTPS (L/min.	Sampled every minute T1 to T8.
Fr (Br./min.)	Sampled every minute T1 to T8.
HR (B/min.)	Sampled during the final 15 sec. of every minute T1 to T8.
P_aO_2 (mmHg)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.
P_aCO_2 (mmHg)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.
pH (units)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.
P_AO_2 (mmHg)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.
P_ACO_2 (mmHg)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.
$P_{ET}O_2$ (mmHg)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.
$P_{ET}CO_2$ (mmHg)	Sampled during the final 20 sec. of every sample period (5 min.) T1 to T8.

CALCULATED VARIABLES

VT BTPS (Liters)	Calculated from $\dot{V}E$ (BTPS) and Fr for every minute T1 to T8.
$\dot{V}O_2$ STPD (L/min.)	Calculated from respiratory gases and $\dot{V}E$ (BTPS-STPD) for every minute T1 to T8.
$\dot{V}CO_2$ STPD (L/min.)	Calculated from respiratory gases and $\dot{V}E$ (BTPS-STPD) for every minute T1 to T8.
R	Calculated from $\dot{V}CO_2$ (STPD) and $\dot{V}O_2$ (STPD) for every minute T1 to T8.
$(P_{ET}-P_a)CO_2$ (mmHg)	Calculated from $P_{ET}CO_2$ and P_aCO_2 for every sample period T1 to T8.
$(P_A-P_a)CO_2$ (mmHg)	Calculated from P_ACO_2 and P_aCO_2 for every sample period T1 to T8.

Table 1. Variables measured and calculated during each experiment with their respective sample period duration.

Exercise Condition	Sample Period	Sample Period Duration
Rest	T 1	5 min.
Warm-up	T 2	5 min.
Exercise A	T 3	5 min.
Exercise A	T 4	5 min.
Exercise A	T 5	5 min.
Exercise B	T 6	5 min.
Exercise B	T 7	5 min.
Exercise B	T 8	5 min.

Table 2. Outline of the experimental conditions and their associated sample periods with respective time duration.

Prior to blood sampling, the hand was heated in a hot water bath (41-45^{o}C.) for 10-15 minutes. This procedure ensured a high level of arterialization as the collateral arterioles were dilated. Arterial oxygen tensions greater than 85 mmHg were used to indicate high levels of arterialization. Blood flow increased to an extent that arterialized-venous blood gas tensions were not appreciably altered by tissue metabolism. The venous catheter, (Abbott Laboratories 21 gauge Butterfly Infusion Catheter), was placed in a dorsal hand vein and secured using waterproof tape. This permitted the subjects to place their hand in the hot water bath for the duration of the experiment. Blood clotting was prevented by repeatedly flushing the catheter with a heparinized saline solution, (10% heparin) before and after sampling. Arterialized-venous blood samples were drawn from the dorsal hand vein catheter into 5 cc. disposable syringes. The dead space was filled with the heparinized saline solution. Blood samples were analysed immediately to minimize possible alteration of the blood gas and pH values by continued metabolism.

P_aCO_2, P_aO_2, and pH were measured with an Instrument Laboratories IL 213-03 pH Blood/Gas Analyser. The sampling electrodes were calibrated before and after each sample according to the procedures outlined by the manufacturer. (The sensitivities for the blood-gas analyser were P_{O_2} $\pm$0.1 mmHg, P_{CO_2} $\pm$0.1 mmHg, pH $\pm$0.003.) To avoid the possible sink

properties associated with PCO2 electrodes, the electrode was calibrated before each measurement with a calibration gas containing a CO2 tension similar to expected blood CO2 tensions.

Heart Rate

Heart rate (HR) was recorded on an electrocardiograph (Fukuda Durshi FD-13) during the last ten seconds of each minute throughout the test conditions. A CM5 transthoracic ECG lead was used for these measurements.

Minute Ventilation

Inspiratory minute ventilation ($\dot{V}I$ STPD), was measured using a low resistance ventilation meter (Parkinson-Cowan CD-4 Chatham, Ontario).

Room air or air from the SCUBA passed through the ventilation meter to the inspiratory side of a modified two-way, low resistance, demand valve mouthpiece (Collins, Boston Mass., dead space 70 ml), connected in series by Collins hose (I.D. 31.5 mm.) (Figure 1 and 2).

Respiratory Gas Sampling

Respiratory gas was sampled directly from the mouthpiece or from an expired gas mixing box depending on the position of the 3-way sampling valve (Figures 1 and 2). The valve permitted direct breath by breath measurement of both inspiratory and

expiratory FCO2 and FO2 during each respiratory cycle as well as measurement of mixed-expired FCO2 and FO2.

The respiratory gases were continuously monitored using a Godart Capnograph CO2 analyser (Type 146 Mark 4 Godarthstatham), and an Applied Electrochemistry O2 analyser, (S-3A/IO2 Analyser). The output from each analyser was recorded on a Hewlett-Packard 4-channel pen recorder (model 7404). Each gas was recorded across two channels of the pen recorder to double the gain and increase the accuracy of measurement ($\pm$ 0.02% for FCO2 and $\pm$ 0.02% for FO2).

Calibration gases prepared to a gravametric standard ($\pm$ 0.01% for FCO2 and $\pm$ 0.01% for FO2) were used to calibrate the gas analysers and pen recorder. Calibration graphs were then constructed from the known oxygen and carbon dioxide fractions in the calibration gases, as shown in Figures 3 and 4. The calibration were used to minimize random error associated with individual calibration gases. The fractions of oxygen and carbon dioxide in room air have been included for each curve to show there was no systematic error with the calibration graphs.

Both CO2 and O2 were measured as fractions of the total inspired and expired gas mixture. By measuring O2 and CO2 as fractions in the expired air, errors associated with temperature corrections, water vapor saturation and total gas pressure at the recording site were eliminated. Knowing the barometric pressure, it was possible to determine the partial pressure of

CO2 and O2 in the respiratory gases. Conversion to gas partial pressure at alveolar conditions assumed complete water vapor saturation at body temperature (37°C.).

Respiratory Resistance

Figure 5 outlines the difference in breathing resistance between the two exercise conditions when the subjects breathed through the low resistance mouthpiece and open circuit SCUBA regulator. A mechanical respirator, operating at a frequency of 20 cycles/min. and tidal volume of 1 L/min., was used to simulate breathing patterns, using the experimental apparatus outlined in Figures 1 and 2. Inspiratory and expiratory pressures were measured with a Validyne differential pressure transducer (model DP 45 ±25 cm H2O). Frequency and tidal volume were measured with an SE Labs displacement transducer (model 353 ±15 cm.). Inspiratory pressure increased from 0.66 cm H2O during exercise condition A to 11.80 cm H2O during exercise condition B. Expiratory pressure increased from 0.53 cm. H2O during exercise condition A to 0.93 cm. H2O during exercise condition B.

Alveolar and End-tidal PCO2

PACO2 was determined from a single breath recording using the fraction of CO2 in the expired air at the time corresponding to 60% of the duration of the expiratory phase, according to the following equation (47=vapor pressure of water in the lungs, PB=barometric pressure) (Figure 6).

$$PACO2 = FACO2 * (PB - 47)$$

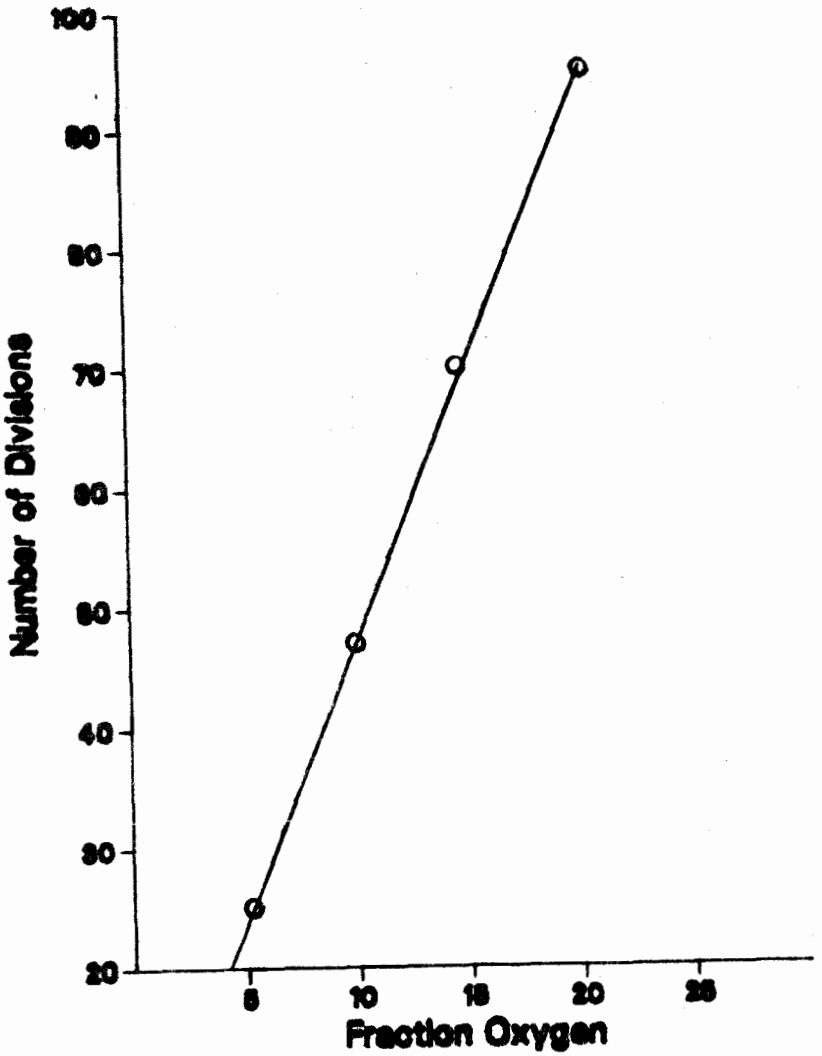

Figure 3. Calibration graph for the oxygen analyser derived from the known fractions of oxygen in the calibration gases.

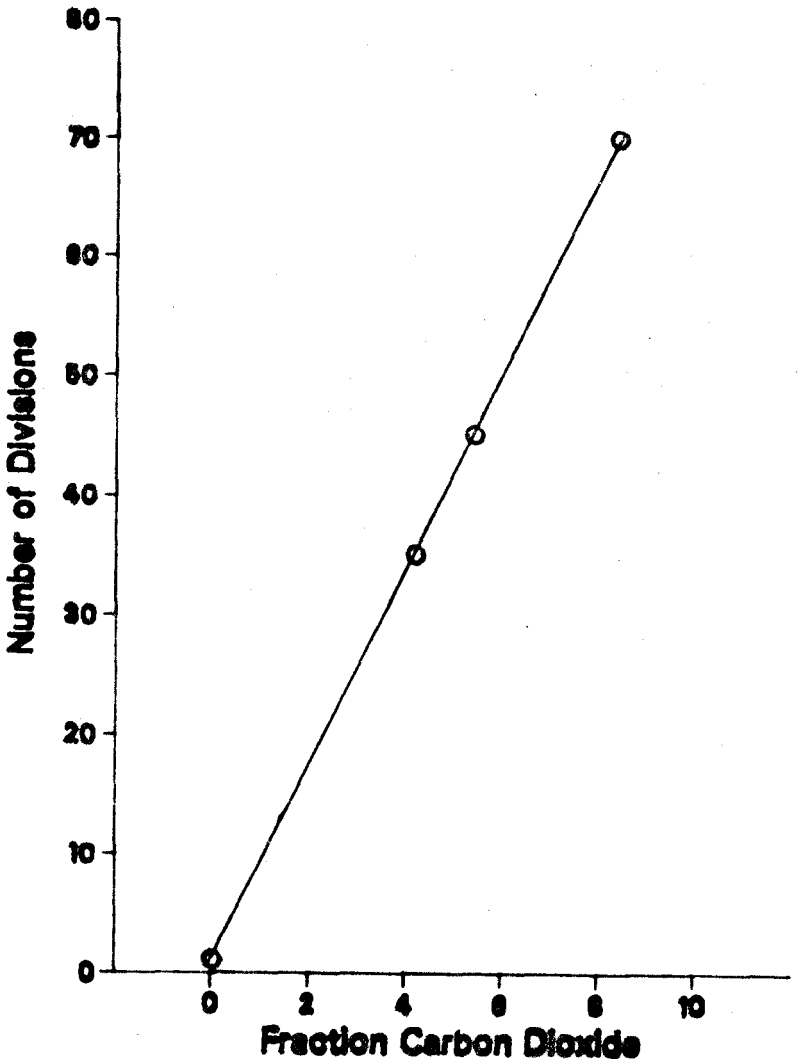

Figure 4. Calibration graph for the carbon dioxide analyser derived from the known fractions of carbon dioxide in the calibration gases.

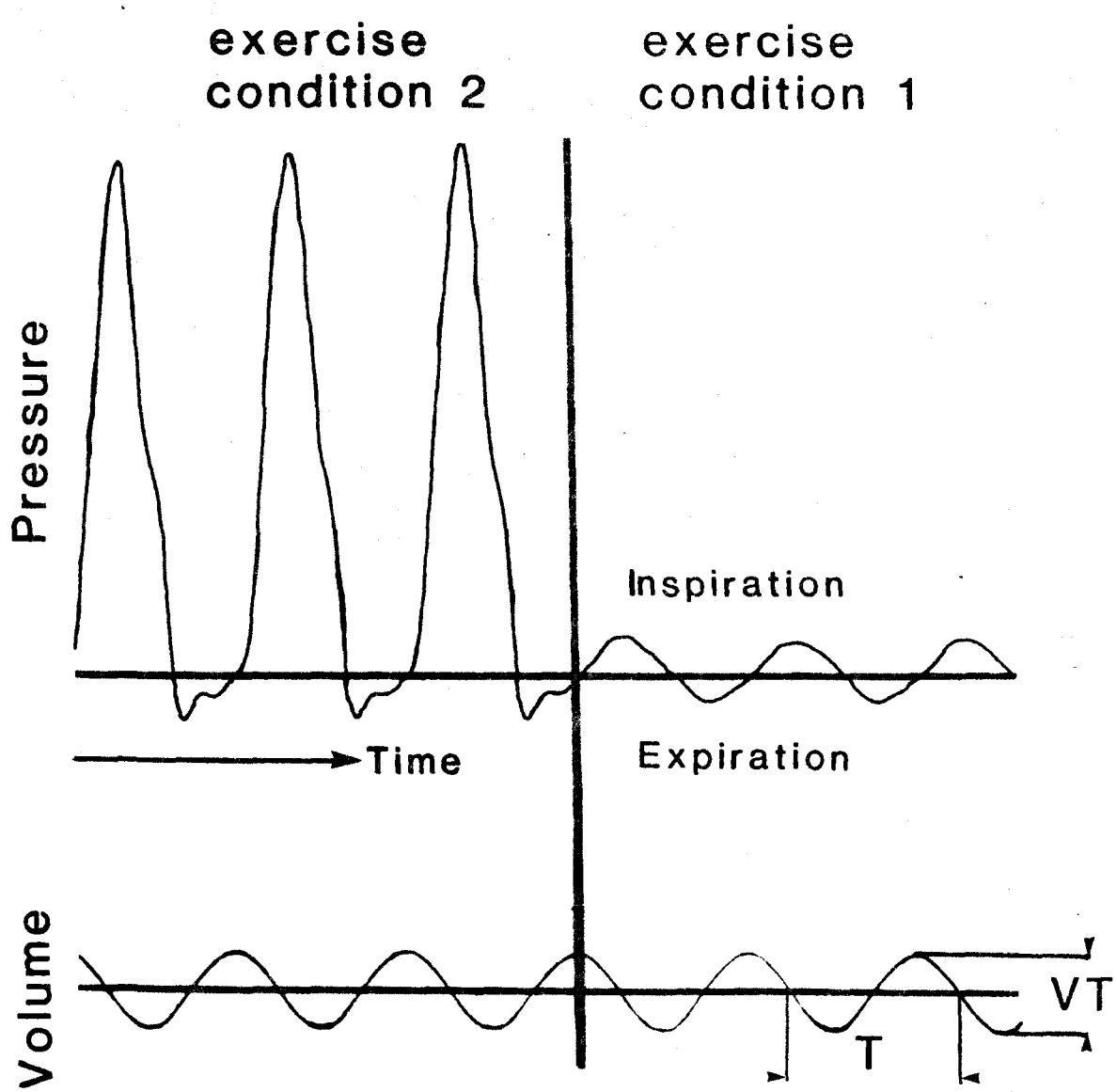

Figure 5. The change in respiratory resistance between the two exercise conditions, breathing from the open circuit SCUBA regulator and the low resistance mouthpiece, as determined using a mechanical respirator.

VT=Tidal Volume
T =Period

Subsequent discussion regarding PACO2 will refer to the CO2 tension corresponding to 60% of the expiratory phase duration. Several researchers agree that this is the best approximation for mean PACO2 (Dubois, et al., 1951; Young, 1955; Berengo and Cutillo, 1961). Although this approximation has been used for both rest and exercise, the original analysis by Dubois, et al., 1951, was based on resting data.

PETCO2 was determined from a single breath recording using the fraction of CO2 in the expired air at 100% of the duration of the expiratory phase, according to the following equation (Figure 6).

PETCO2 = FETCO2 * (PB - 47)

The measured values for FACO2 and FETCO2, were averaged over 3-4 complete respiratory cycles. These values were then used to calculate PACO2 and PETCO2.

PAO2 and PETO2 were calculated according to the following equations (Figure 7).

PAO2 = FAO2 * (PB - 47)

PETO2 = FETO2 * (PB - 47)

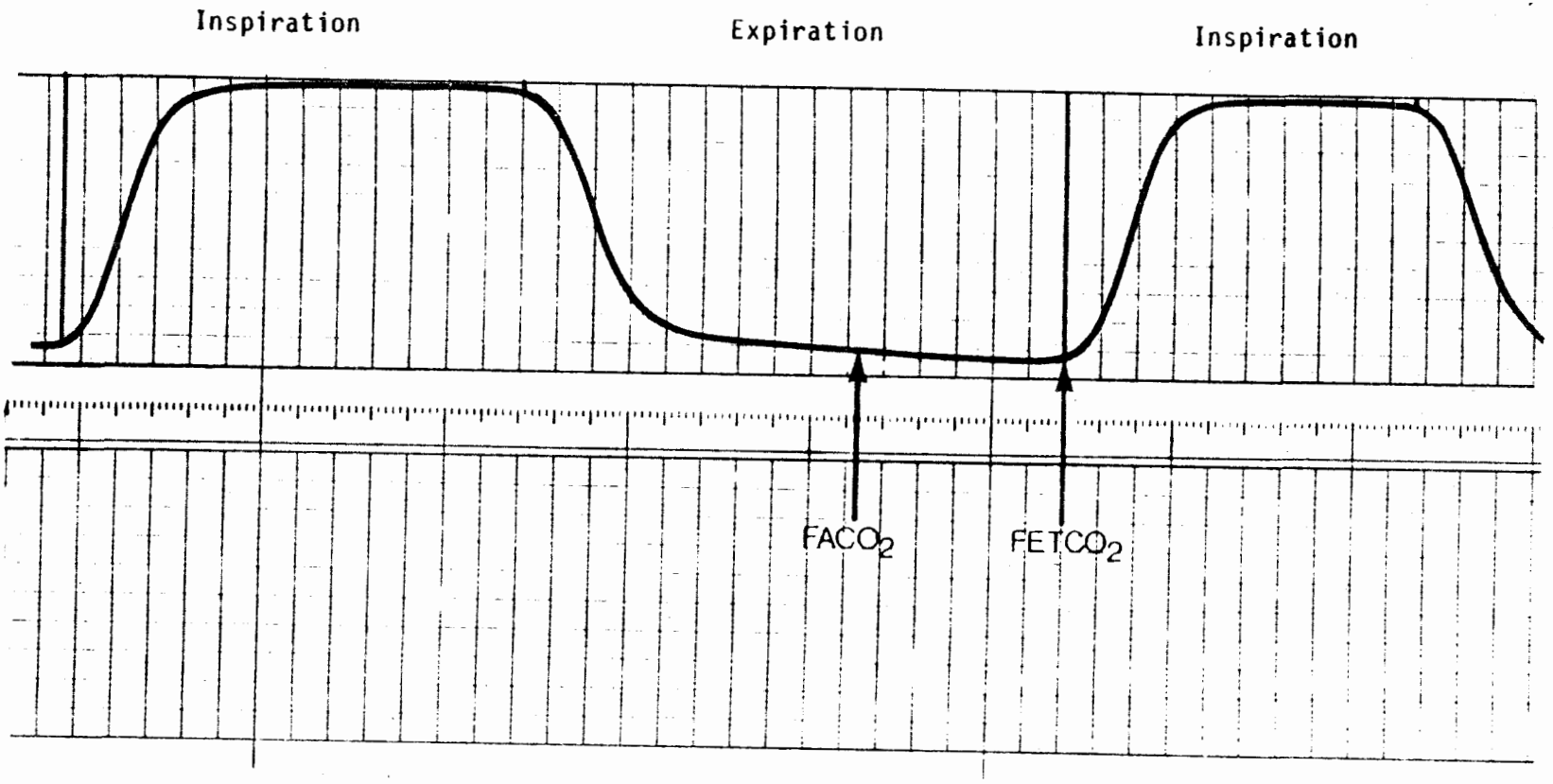

Figure 6. The fraction of carbon dioxide in the respiratory gas was continuously monitored across two channels of the Hewlett-Packard pen recorder. Alveolar carbon dioxide, FACO2, was determined at the point in time representing 60% of the expiratory duration. End-tidal carbon dioxide was determined at the point representing the end of the expiratory phase, (see text).

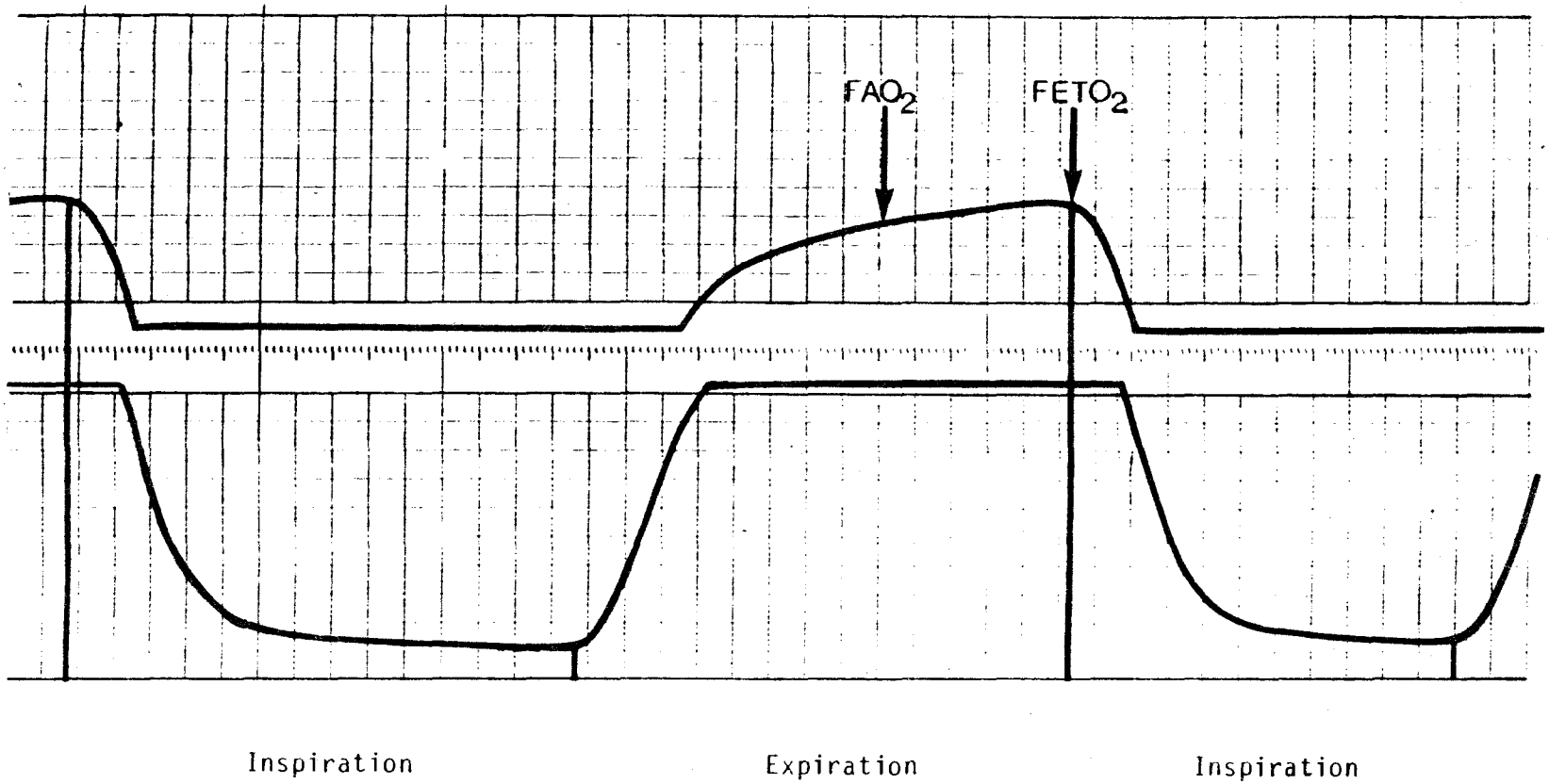

Figure 7. The fraction of oxygen in the respiratory gas was continuously monitered across two channels of the Hewlett-Packard pen recorder. Alveolar oxygen, FAO_2, was determined at the point in time corresponding to 60% of the expiratory duration. End-tidal oxygen, $FETO_2$, was determined at the point in time corresponding to the end of the expiratory phase, (see text).

Mixed-expired CO2 and O2 fractions were calculated from the average values measured over a 1 minute period on the pen recorder trace. The values for FCO2 and FO2 were then used to calculate oxygen consumption and carbon dioxide production.

Tidal Volume

Tidal volume (VT) was calculated by dividing the minute ventilation ($\dot{V}E$) measured during each minute of the sample period by the respiratory frequency(FR), as outlined in the following equation.

$$\dot{V}E = (VT/FR)$$

Minute Carbon Dioxide Production and Oxygen Consumption

Minute CO2 production ($\dot{V}CO2$), and O2 consumption ($\dot{V}O2$), were calculated using the measured values for mixed-expired CO2 and O2 and minute ventilation according to the following equations.

$$\dot{V}CO2 = (FECO2 * \dot{V}E) - (FICO2 * \dot{V}I)$$

$$\dot{V}O2 = (FIO2 * \dot{V}I) - (FEO2 * \dot{V}E)$$

$$\dot{V}E = (\dot{V}I * FIN2/FEN2)$$

Rest Condition

After completion of the catheterization procedure, the subjects rested for thirty minutes prior to the start of the warm-up and exercise conditions.

Heart rate was measured during the last 10 seconds of each minute for the final 5 minutes of the rest condition.

Minute ventilation and respiratory frequency were measured continuously throughout the rest condition.

FETCO2, FETO2, FACO2, FAO2, PaCO2, PaO2 and pH were measured during the last thirty seconds of the rest condition. All values were averaged over 3-4 complete respiratory cycles.

Warm-up Condition

Prior to the exercise condition, the subjects performed a five minute warm-up on a bicycle ergometer (Quinton Instruments), at a workrate of 200 kilopond meters per minute (Kpm/min.) and pedal frequency of 60 cycles per minute.

HR, $\dot{V}E$, FR were measured and respiratory gas analysis and blood-gas analysis were performed as outlined previously.

At the end of the five minute warm-up period, the workrate was increased to 400 Kpm/min. for the duration of the two exercise periods, which lasted 15 minutes each. This workrate was chosen to minimize possible interaction processes associated with anaerobic metabolism. In addition, the method described by

Dubois, et al. 1951 to determine PACO2, has not been proven for exercise.

Exercise Condition

After completion of the warm-up phase, subjects exercised at a constant workrate of 400 kpm/min.

HR, $\dot{V}E$, FR were measured and respiratory gas analysis and blood gas analysis were performed as outlined for the rest and warm-up conditions. After completion of three, 5-minute sample periods (exercise condition A, T3 to T5) while breathing room air with low respiratory resistance, the subjects continued to exercise at the same workrate for three additional 5-minute sample periods (exercise condition B, T6 to T8). During exercise condition B, the subjects breathed room air with added resistance from an external breathing apparatus provided by the SCUBA (Figure 1B).

PCO2 Gradients

The study examined variables which may influence the difference between (PETCO2 and PaCO2) and (PACO2 and PaCO2) during exercise.

Best Subset multiple linear regression analysis was performed on the data to yield equations which relate P(ET-a)CO2 and P(A-a)CO2 gradients to the measured variables. This method of multiple linear regression analysis chooses the best subset

of variables, from the independent variables entered into the analysis, to describe the equations predicting $\underline{P}(\underline{ET}-\underline{a})CO2$ and $\underline{P}(\underline{A}-\underline{a})CO2$. The "best" subset selection was determined by the adjusted $\bar{R}^2$ (Theil, 1971) and Mallows' Cp (Daniel and Wood, 1971) criteria.

The ultimate assessment of the merit of a regression equation is how well it fits new data. The five "best" subsets of variables predicting the $\underline{P}(\underline{ET}-\underline{a})CO2$ gradient were cross-validated (application of regression coefficients to data from other studies), using the data reported by Jones, et al. (1969), in which $\underline{Pa}CO2$ and $\underline{PET}CO2$ had been measured, to determine the best regression equation. A similar cross-validation of the equations predicting the $\underline{P}(\underline{A}-\underline{a})CO2$ gradient was not possible using the data reported.

Errors between the predicted and measured $\underline{P}(\underline{ET}-\underline{a})CO2$ gradient were calculated from the following equation,

Error = Predicted $\underline{P}(\underline{ET}-\underline{a})CO2$ - Measured $\underline{P}(\underline{ET}-\underline{a})CO2$

The mean square error was then calculated from the predicted and measured $\underline{P}(\underline{ET}-\underline{a})CO2$ difference.

Systematic errors between the predicted and measured $\underline{P}(\underline{ET}-\underline{a})CO2$ gradient were then determined by plotting the error against the measured $\underline{P}(\underline{ET}-\underline{a})CO2$ gradient.

In addition to the cross-validation study, the best regression equation, as determined from the cross-validation study, was used to predict the P(ET-a)CO2 gradient from data reported by Morrison, et al. (1976), in which PETCO2 was measured.

Non-invasive Estimates of PaCO2

The same regression analysis was used to derive an equation to predict PaCO2 from PETCO2 and other non-invasive measurements.

Best subset multiple linear regression analysis was also performed on the data to derive an equation predicting PaCO2 from both non-invasive and invasive measurements.

Statistical Analysis

Statistical analysis of the results were performed on an IBM 370/155 in the Simon Fraser Computing Center.

An integrated system of computer programs, "BMDP", (Biomedical Computing Programs. University of California 1979), were used for the storage, file manipulation, data transformation, basic statistical analysis and regression analysis of the data.

IV. Results

Subject Data

Individual heart rates, ventilation, respiratory frequency, respiratory gas analysis and blood-gas analysis for each subject during rest, warm-up, and exercise conditions A and B are given in Appendix I.

Subject data collected prior to the start of each experiment are given in Table 3. Each subject was tested according to the same experimental procedures as, outlined in Tables 1 and 2.

The mean and standard error for alveolar and end-tidal oxygen and carbon dioxide tensions during the rest, warm-up and exercise conditions are given in Table 4.

The mean and standard error for heart rates, ventilation, respiratory frequencies and tidal volumes during the rest, warm-up and exercise conditions are given in Table 5.

The mean and standard error for arterial oxygen and carbon dioxide tensions and arterial pH during the rest, warm-up and exercise conditions are given in Table 6.

Subject	Age (years)	Weight (Kg.)	Height (cm.)	Temperature (°C.)	Barometric Pressure
1	25	75.5	180	19.5	735.5
2	27	71.0	175	20.5	732.5
3	35	95.0	188	19.5	734.5
4	24	70.5	173	21.0	732.0
5	29	76.5	180	19.5	732.5
6	33	68.0	175	19.5	735.5
7	38	73.5	177	20.5	741.5
8	26	86.0	183	19.0	732.0
9	30	84.0	175	19.5	739.0
10	28	75.0	173	20.0	742.0
11	27	61.5	169	19.5	736.5
12	29	77.0	178	21.0	740.5
13	31	85.5	182	20.0	737.5

Table 3. Subject data and environmental measurements collected prior to the start of each experiment.

Exercise Condition	$\dot{V}E$ BTPS (L/min.)	Fr (Br./min.)	HR (B/min.)	VT BTPS (Liters)
T1	9.05 ± 0.39	14.9 ± 0.42	70.9 ± 0.71	0.604 ± 0.01
T2	17.41 ± 0.85	23.4 ± 0.76	83.0 ± 0.74	0.742 ± 0.02
T3	24.13 ± 1.03	29.1 ± 0.90	102.2 ± 0.87	0.827 ± 0.01
T4	25.65 ± 1.08	30.2 ± 0.97	105.5 ± 0.83	0.846 ± 0.01
T5	24.77 ± 1.26	29.7 ± 1.05	109.6 ± 0.85	0.830 ± 0.02
T6	20.72 ± 1.20	25.1 ± 0.90	112.7 ± 0.89	0.820 ± 0.02
T7	19.63 ± 1.08	24.3 ± 1.15	115.2 ± 0.81	0.804 ± 0.01
T8	20.69 ± 1.44	25.2 ± 1.27	118.5 ± 0.88	0.814 ± 0.02

Table 4. Calculated mean values for each exercise condition and respective sample period during the experiment. Values for each sample period are the means + S.E.M. (n=13).

Exercise Condition	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)
T1	117.13 ± 0.54	30.60 ± 1.05	115.88 ± 0.46	32.74 ± 1.03
T2	107.08 ± 0.51	35.43 ± 1.28	105.73 ± 0.49	36.59 ± 1.32
T3	103.55 ± 0.49	38.29 ± 0.88	102.03 ± 0.47	39.52 ± 0.96
T4	101.60 ± 0.48	38.19 ± 0.85	99.18 ± 0.51	38.98 ± 0.90
T5	100.82 ± 0.49	38.92 ± 0.83	99.43 ± 0.55	39.71 ± 0.90
T6	97.51 ± 0.47	40.66 ± 0.73	96.03 ± 0.54	41.75 ± 0.78
T7	95.45 ± 0.56	41.74 ± 0.73	94.15 ± 0.57	42.78 ± 0.77
T8	94.94 ± 0.59	42.53 ± 0.85	93.29 ± 0.59	43.61 ± 0.93

Table 5. Calculated mean values for each exercise condition and respective sample period during the experiment. Values for each sample period are means + S.E.M. (n=13).

Exercise Condition	$\dot{V}CO_2$ STPD (L/min.)	$\dot{V}O_2$ STPD (L/min.)	R	P_aCO_2 (mmHg)	P_aO_2 (mmHg)	pH
T1	0.323 ±0.027	0.409 ±0.031	0.804 ±0.038	36.8 ±0.50	89.7 ±0.43	7.435 ±0.003
T2	0.683 ±0.029	0.789 ±0.036	0.819 ±0.040	39.0 ±0.86	90.2 ±0.44	7.410 ±0.009
T3	1.004 ±0.031	1.204 ±0.041	0.842 ±0.037	40.1 ±0.74	90.4 ±0.46	7.476 ±0.007
T4	1.096 ±0.035	1.312 ±0.048	0.829 ±0.036	40.0 ±0.72	90.8 ±0.50	7.482 ±0.008
T5	1.068 ±0.039	1.257 ±0.047	0.853 ±0.035	40.3 ±0.71	90.2 ±0.48	7.475 ±0.007
T6	0.908 ±0.037	1.071 ±0.048	0.845 ±0.037	40.6 ±0.79	91.0 ±0.46	7.483 ±0.006
T7	0.875 ±0.039	0.975 ±0.038	0.916 ±0.041	40.5 ±0.88	91.0 ±0.48	7.496 ±0.006
T8	0.945 ±0.058	1.035 ±0.052	0.912 ±0.039	41.1 ±0.93	90.7 ±0.44	7.503 ±0.005

Table 6. Calculated mean values for each exercise condition and respective sample period during the experiment. Values for each sample period are means + S.E.M. (n=13).

PCO2 Gradients

The mean and standard error for the partial pressure gradients between end-tidal and arterial carbon dioxide tensions P(ET-a)CO2 and alveolar and arterial carbon dioxide tensions P(A-a)CO2 during the rest, warm-up and exercise conditions A and B are given in Table 7.

Exercise Condition	$(\underline{PET}-Pa)CO_2$ (mmHg)	$(\underline{PA}-Pa)CO_2$ (mmHg)
T1	-4.03 ± 0.76	-6.02 ± 0.68
T2	-2.40 ± 0.59	-3.56 ± 0.53
T3	-0.60 ± 0.43	-1.83 ± 0.33
T4	-1.02 ± 0.28	-1.81 ± 0.23
T5	-0.58 ± 0.30	-1.37 ± 0.29
T6	1.19 ± 0.43	0.11 ± 0.48
T7	2.37 ± 0.40	1.25 ± 0.49
T8	2.54 ± 0.33	1.46 ± 0.26

Table 7. Calculated mean values for each exercise condition and respective sample period during the experiment. Values for each sample period are means + S.E.M. (n=13).

Variables Influencing the PCO2 Gradient

P(a-ET)CO2 Differences

The P(a-ET)CO2 difference decreased from rest to exercise condition A. This was accompanied by increases in ventilation, respiratory frequency, tidal volume, minute oxygen consumption, minute carbon dioxide production, end-tidal PCO2, and arterial PCO2. During exercise condition B, the P(a-ET)CO2 difference became negative. This change was accompanied by decreases in ventilation, respiratory frequency, minute oxygen consumption and minute carbon dioxide production, and increases in tidal volume, end-tidal PCO2, and arterial PCO2, relative to the values in exercise condition A.

The five best subsets of variables derived by the multiple linear regression analysis are outlined in Table 8. The units for each variable used in the regression equation are outlined in Tables 4,5 and 6.

Best subset multiple linear regression analysis chooses variables which minimize the selection criterion and adjusts the correlation coefficient according to the number of related variables.

Predicted values for the P(a-ET)CO2 gradient, derived from

equation 1, Table 8, were plotted against the measured values for the $\underline{P}(\underline{a}-\underline{ET})CO_2$ gradient (Figure 8).

Five Best Equations From The Multiple Linear Regression Analysis	M.S.E. Using The Data From Jones, et al., (1979)
1. $\underline{P(ET-a)}CO2=0.49*\dot{V}E+0.52*\underline{PET}CO2-0.22*Fr-5.68*\dot{V}CO2-20.42$ (Cp=4.00 Adj. r^2=0.713)	25.47
2. $\underline{P(ET-a)}CO2=0.24*\dot{V}E+0.51*\underline{PET}CO2+5.73*VT-6.13*\dot{V}CO2-24.63$ (Cp=4.89 Adj. r^2=0.711)	29.25
3. $\underline{P(ET-a)}CO2=0.29*\dot{V}E+0.52*\underline{PET}CO2-5.55*\dot{V}CO2-22.03$ (Cp=5.92 Adj. r^2=0.705)	5.04
4. $\underline{P(ET-a)}CO2=0.48*\dot{V}E+0.52*\underline{PET}CO2+0.27*VT-0.21*Fr-5.72*\dot{V}CO2-20.60$ (Cp=6.00 Adj. r^2=0.711)	25.79
5. $\underline{P(ET-a)}CO2=0.49*\underline{PET}CO2+10.86*VT+0.17*Fr-5.63*\dot{V}CO2-27.75$ (Cp=7.25 Adj. r^2=0.704)	45.30

Table 8. The five best equations predicting the $\underline{P(ET-a)}CO2$ gradient from the present study were used to determine the mean square error predicting the PCO2 gradient from the data reported by Jones, et al., (1979).

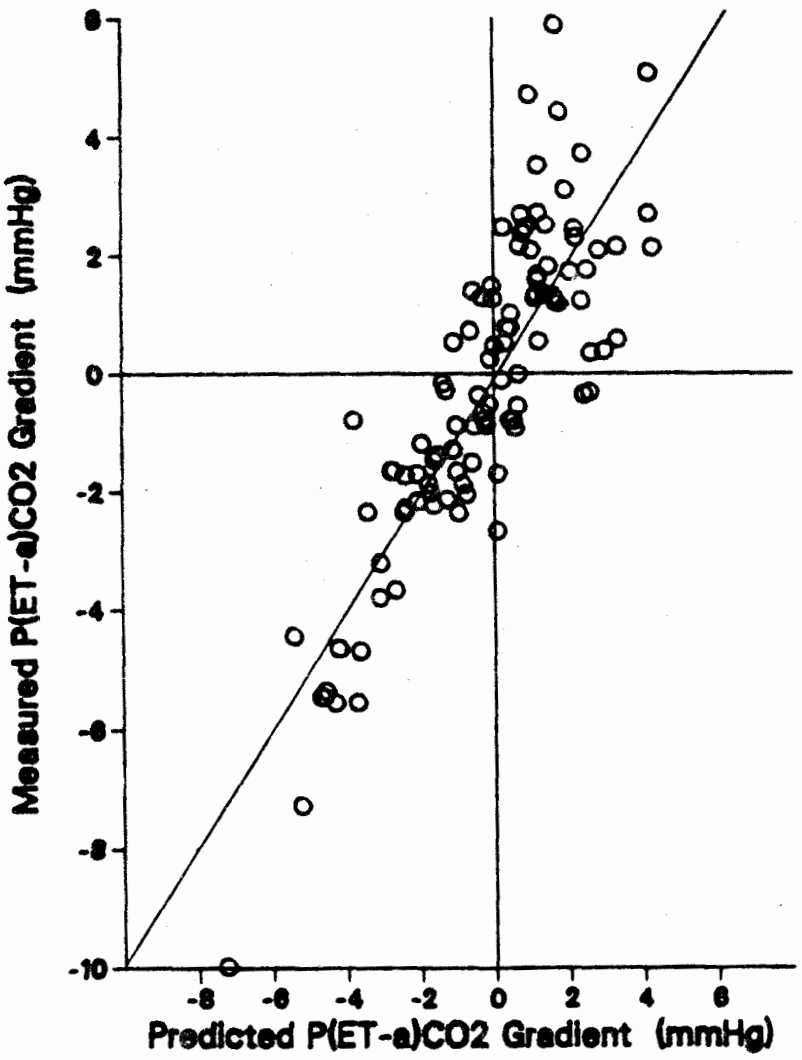

Figure 8. The measured P(ET-a)CO2 gradient plotted against the predicted P(ET-a)CO2 gradient using the data from the present study.

P(a-A)CO2 Difference

The P(a-A)CO2 difference decreased from rest to exercise condition A. This was accompanied by increases in ventilation, respiratory frequency, tidal volume, minute oxygen consumption, minute carbon dioxide production, alveolar PCO2, and arterial PCO2. During exercise condition B, the P(a-A)CO2 difference became negative. This change was accompanied by decreases in ventilation, respiratory frequency, minute oxygen consumption, and minute carbon dioxide production and increases in tidal volume, alveolar PCO2, and arterial PCO2, relative to the values in exercise condition A.

The five best subsets of variables derived by the multiple linear regression analysis are outlined in Table 9. The units for each variable used in the regression equations are outlined in Tables 4, 5 and 6.

Predicted values for the P(a-A)CO2 gradient, derived from equation 1, Table 9, were plotted against the measured values for the P(a-A)CO2 gradient (Figure 9).

Five Best Equations From The Multiple Linear Regression Analysis

1. $\underline{P(A-a)}CO2 = 0.45*\dot{V}E + 0.52*\underline{PA}CO2 - 0.16*Fr - 5.31*\dot{V}CO2 - 21.58$

   ($Cp = 4.02$ Adj. $r^2 = 0.724$)

2. $\underline{P(A-a)}CO2 = 0.30*\dot{V}E + 0.51*\underline{PA}CO2 - 5.09*\dot{V}CO2 - 22.69$

   ($Cp = 4.18$ Adj. $r^2 = 0.721$)

3. $\underline{P(A-a)}CO2 = 0.26*\dot{V}E + 0.51*\underline{PA}CO2 + 4.52*VT - 5.60*\dot{V}CO2 - 24.80$

   ($Cp = 4.35$ Adj. $r^2 = 0.723$)

4. $\underline{P(A-a)}CO2 = 0.41*\dot{V}E + 0.52*\underline{PA}CO2 + 0.98*VT - 0.14*Fr - 5.39*\dot{V}CO2 - 22.23$

   ($CP = 6.00$ Adj. $r^2 = 0.721$)

5. $\underline{P(A-a)}CO2 = 0.49*\underline{PA}CO2 + 9.96*VT + 0.19*Fr - 5.20*\dot{V}CO2 - 28.25$

   ($Cp = 6.20$ Adj. $r^2 = 0.718$)

Table 9. The five best equations predicting the $\underline{P(A-a)}CO2$ gradient from the present study.

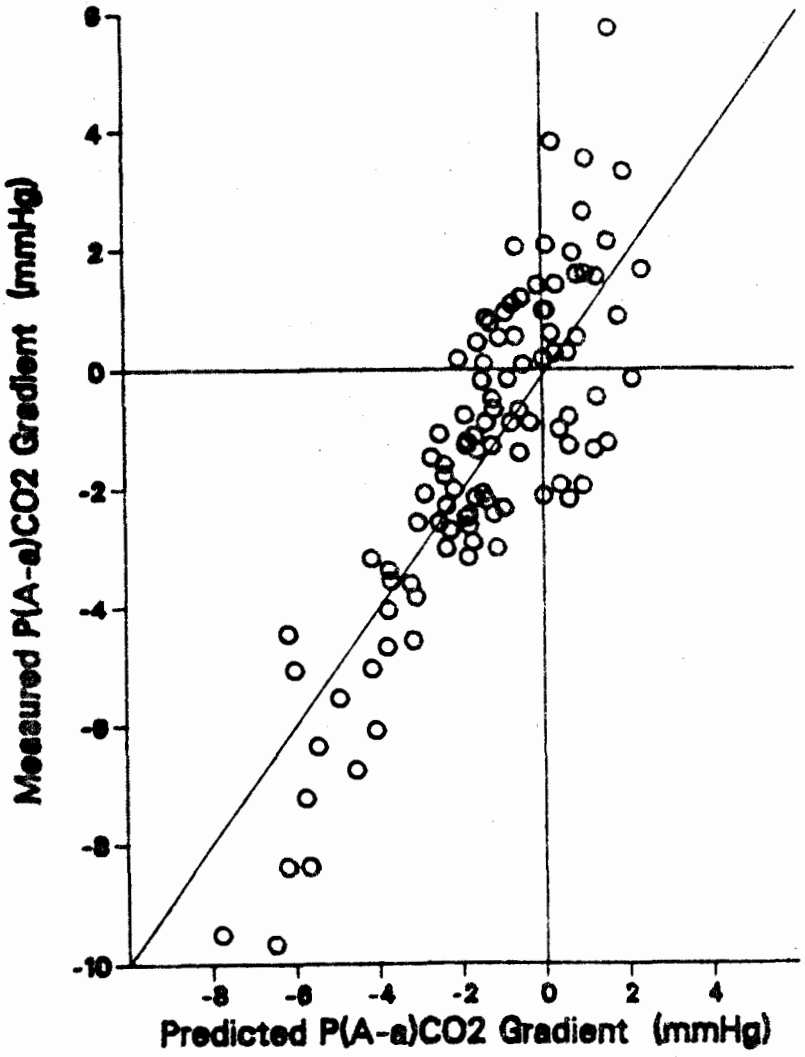

Figure 9. The measured P(A-a)CO2 gradient plotted against the predicted P(A-a)CO2 gradient using the data from the present study.

Prediction of PaCO2

PaCO2 increased from rest to exercise condition A. This was accompanied by an decrease in arterial pH. During exercise condition B, PaCO2 remained constant relative to the values in exercise condition A. Arterial pH also remained constant between the two exercise conditions.

Best subset multiple linear regression analysis yielded the following equations to predict PaCO2 from invasive and noninvasive measurements respectively,

$$PaCO2 = -0.42*\dot{V}E + 0.48*PETCO2 + 0.19*Fr + 4.45*\dot{V}CO2 - 11.40*pH + 105.47$$

$$PaCO2 = -0.51*\dot{V}E + 0.48*PETCO2 + 0.23*Fr + 5.74*\dot{V}CO2 + 20.24$$

The units for each variable used in the regression equation are outlined in Tables 4,5 and 6.

Predicted values for PaCO2, derived from both invasive measurements and noninvasive measurements, were compared with the measured values for PaCO2 (Figures 10 and 11 respectively).

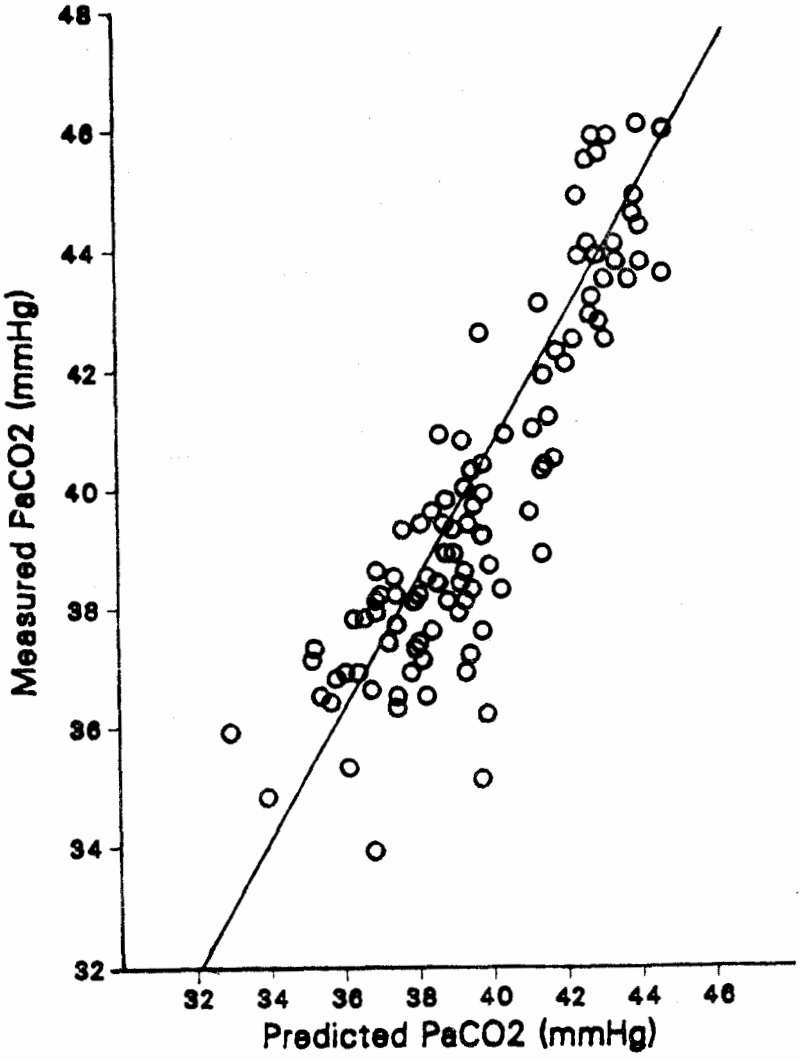

Figure 10. The measured arterial PCO2 plotted against the predicted arterial PCO2 using the data from the present study, (invasive measurements).

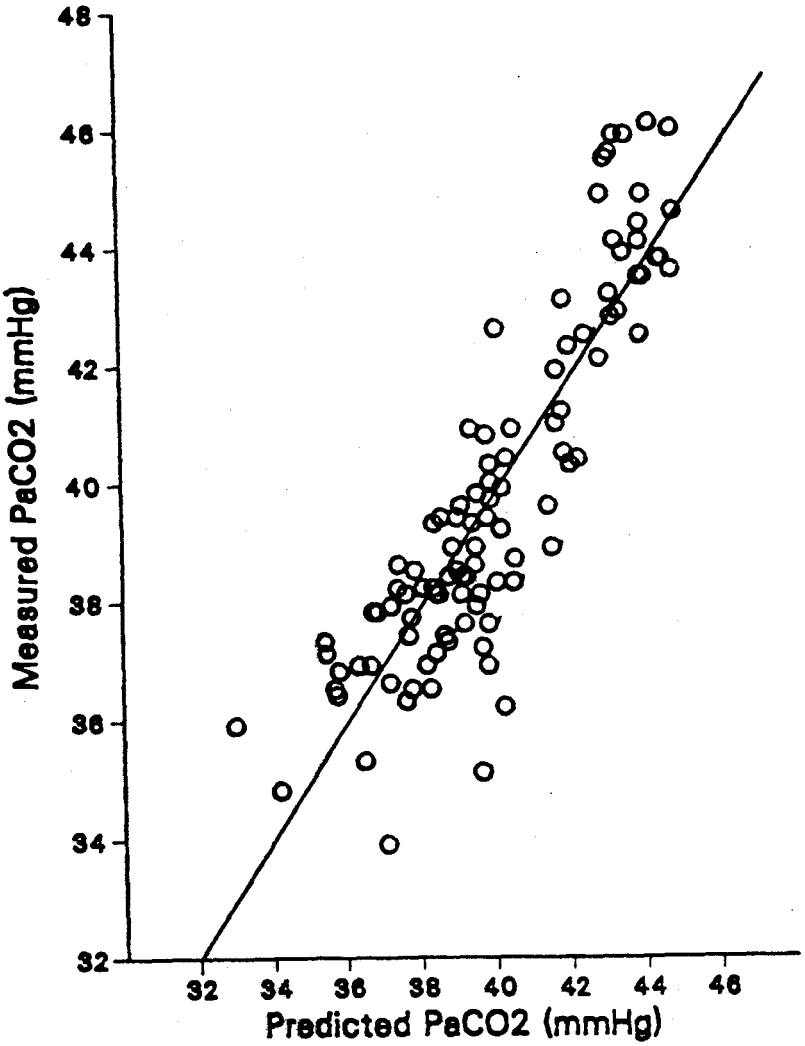

Figure 11. The measured arterial PCO2 plotted against the predicted arterial PCO2 using the data from the present study, (non-invasive measurements).

Statistical Analysis

Paired t-Test

Paired t-Tests (BMDP3D) were used to compare differences ($P<0.05$) between individual variables across one or more sample periods (Table 10).

Ventilation increased significantly from rest through exercise condition A. This change was accompanied by a significant increase in respiratory frequency and tidal volume from rest through exercise condition A. During exercise condition B, ventilation decreased significantly relative to exercise condition A. Respiratory frequency decreased significantly during exercise condition B relative to exercise condition A. Tidal volume did not change significantly between the two exercise conditions.

Both alveolar $\underline{P}CO2$ and end-tidal $\underline{P}CO2$ increased during each exercise condition, (T1 to T8, Table 5). The highest values were measured during exercise condition B. $\underline{PA}CO2$ and $\underline{PET}CO2$ were significantly greater during exercise condition B relative to exercise condition A.

There was no significant change in arterial $\underline{P}CO2$ measurements between the two exercise conditions. Arterial pH

did not change significantly during the two exercise conditions (Table 6).

Minute oxygen consumption increased significantly with the start of exercise. Maximal values were measured during exercise condition A. Mean $\dot{V}O_2$ decreased 18% during exercise condition B relative to exercise condition A. The decrease in $\dot{V}O_2$ was significant.

Minute carbon dioxide production also increased significantly with the onset of exercise, reaching maximal values during exercise condition A. There was a 14% decrease in mean $\dot{V}CO_2$ during exercise condition A relative to exercise condition B. The decrease in VCO_2 was significant.

Paired t-Tests were also used to test for significant ($P<0.05$) differences between $PaCO_2$ relative to $PETCO_2$, and for $PaCO_2$ relative to $PACO_2$, during each complete sample period, T1 through T8 (Table 11). complete sample period, T1 through T8 (Table 11).

There was a significant difference between $PaCO_2$ and $PETCO_2$ during sample periods T1, T2, T4, T6, T7, and T8. The $P(a-ET)CO_2$ difference was positive for sample periods T1, T2 and T4 and negative for sample periods T6, T7, and T8.

There was a significant difference between $PaCO_2$ and $PACO_2$ during sample periods T1 through T5, T7 and T8. The $P(a-A)CO_2$ difference was positive for sample periods T1 through T5 and negative for sample periods T7 and T8. At rest through exercise

condition A, the $\underline{P}(\underline{a}-\underline{ET})CO2$ and $\underline{P}(\underline{a}-\underline{A})CO2$ differences were positive. During exercise condition B, both $\underline{P}CO2$ gradients became negative. The mean $\underline{P}(\underline{ET}-\underline{a})CO2$ and $\underline{P}(\underline{A}-\underline{a})CO2$ gradient ranged from -4.03 mmHg to 2.54 mmHg and -6.02 mmHg to 1.46 mmHg respectively (Figure 12). There was a significant difference for both $\underline{P}(\underline{ET}-\underline{a})CO2$ and $\underline{P}(\underline{A}-\underline{a})CO2$ gradients during exercise condition A relative to exercise condition B.

Sample Periods	$\dot{V}E$ (BTPS)	$\underline{PA}CO_2$ (mmHg)	$\underline{PET}CO_2$ (mmHg)	$\underline{Pa}CO_2$ (mmHg)	Fr (Br./min.)	$P(\underline{ET-a})CO_2$ (mmHg)	$P(\underline{A-a})CO_2$ (mmHg)	$\dot{V}CO_2$ (STPD)	VT (BTPS)
(T1-T2)	*	*			*		*	*	*
(T2-T3)	*				*		*	*	*
(T2-T6)		*	*			*	*	*	
(T3-T5)									
(T6-T8)									
(T3-T5)-(T6-T8)	*	*	*		*	*	*	*	

Table 10. Paired t-tests were used to determine significant differences between individual variables for the sample periods outlined ($P<0.05$ n=104).

* denotes significance

Exercise Condition	P(ET-a)CO2 (mmHg)	P(A-a)CO2 (mmHg)
T1	S**	S**
T2	S**	S**
T3		S**
T4	S**	S**
T5		S**
T6	S*	
T7	S*	S*
T8	S*	S*

Table 11. Statistical analysis of the direction of the CO2 Gradient between P(ET-a)CO2 and P(A-a)CO2 using paired t-Tests ($P<0.05$ n=104).

S* Significant positive gradient

S** Significant negative gradient

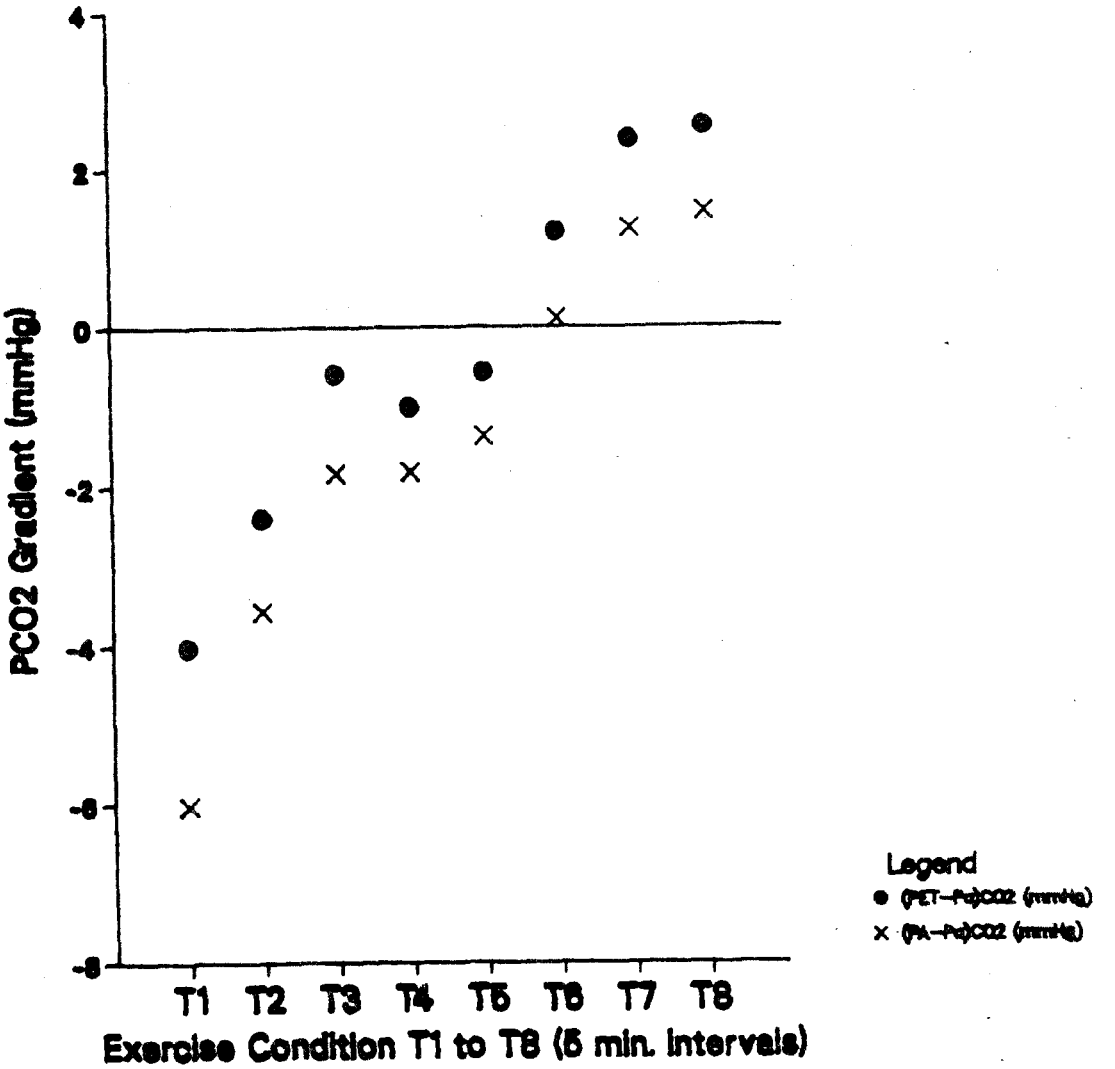

Figure 12. The P(ET-a)CO2 and P(A-a)CO2 gradients measured during each exercise condition, T1 to T8. The plotted values are the means for each sample period.

Validation Study

From the cross-validation study, equation 3 was chosen as the best equation for predicting the P(ET-a)CO2 gradient (Table 8). This equation was used to predict the P(ET-a)CO2 gradient from the data reported by Jones, et al. (1979). The mean square error between the predicted and measured PCO2 gradient was 5.01 (Table 12.) The mean square error using the equation from their study was 1.65.

Using the data from this study, the mean square errors using equations 1 and 3 were 1.99 and 2.04 respectively (Table 12). From the equation derived by Jones, et al., (1979), the mean square error was 9.32. The errors between the predicted and measured PCO2 gradient, using the above equations, were compared with the measured PCO2 gradient from the respective studies (Figures 13 and 14).

Table 13 presents an estimate of the P(ET-a)CO2 gradient which should occur for divers working at increased ambient pressures. The estimates in Table 13 were derived using predictive equation 3 and the data reported by Morrison, et al., (1976).

Equations Predicting The $\underline{P(ET-a)}CO_2$ Gradient From This Study	M.S.E. Using The Data From Jones, et al., (1979)	M.S.E. Using The Data From Present Study
1. $\underline{P(ET-a)}CO_2=0.49*\dot{V}E+0.52*\underline{PET}CO_2-0.22*F_T-5.69*\dot{V}CO_2-20.42$	25.47	1.99
2. $\underline{P(ET-a)}CO_2=0.29*\dot{V}E+0.52*\underline{PET}CO_2-5.55*\dot{V}CO_2-22.03$	5.01	2.04
Equation Predicting The $\underline{P(ET-a)}CO_2$ Gradient From Jones, et al., (1979)		
1. $\underline{P(ET-a)}CO_2=0.11*\underline{PET}CO_2+1.73*VT+1.10*\dot{V}CO_2-6.7$	1.65	9.32

Table 12. Validation study comparing the mean square errors between the present data population and the data population reported by Jones, et al., (1979) to determine the best equation predicting the $\underline{P(ET-a)}CO_2$ gradient.

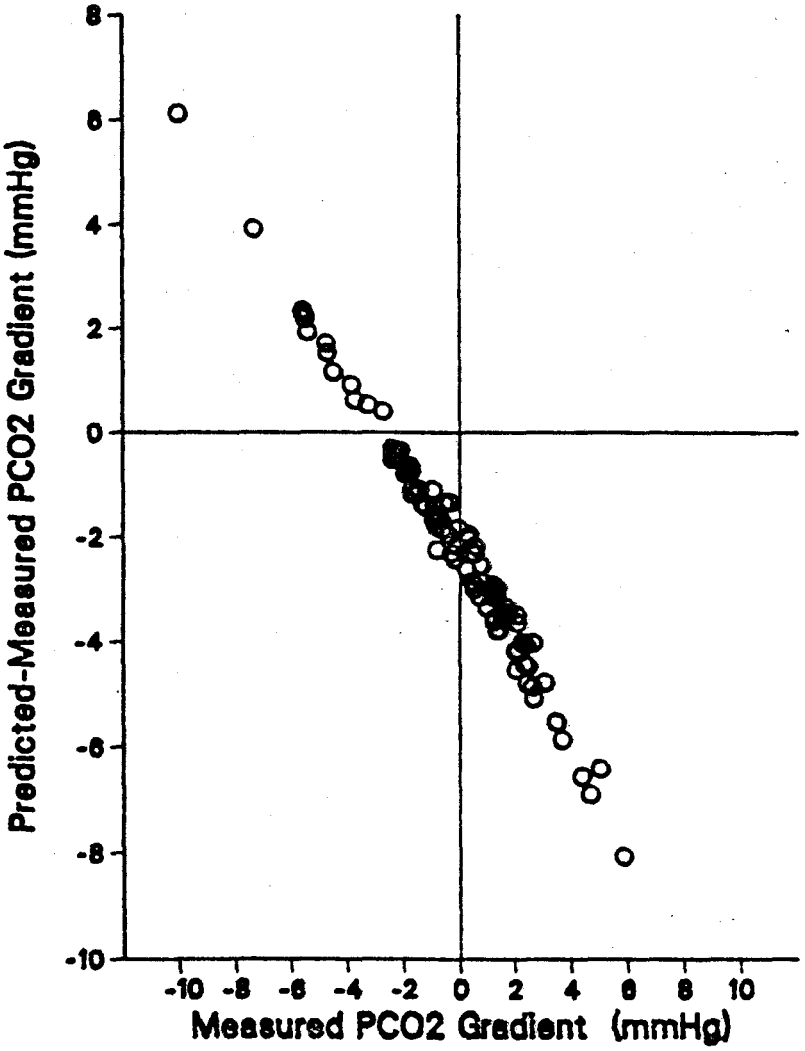

Figure 13. The error between the predicted and measured P(ET-a)CO2 gradient plotted against the measured P(ET-a)CO2 gradient showing the systematic error in the equation derived by Jones, et al., (1979), using the data from the present study.

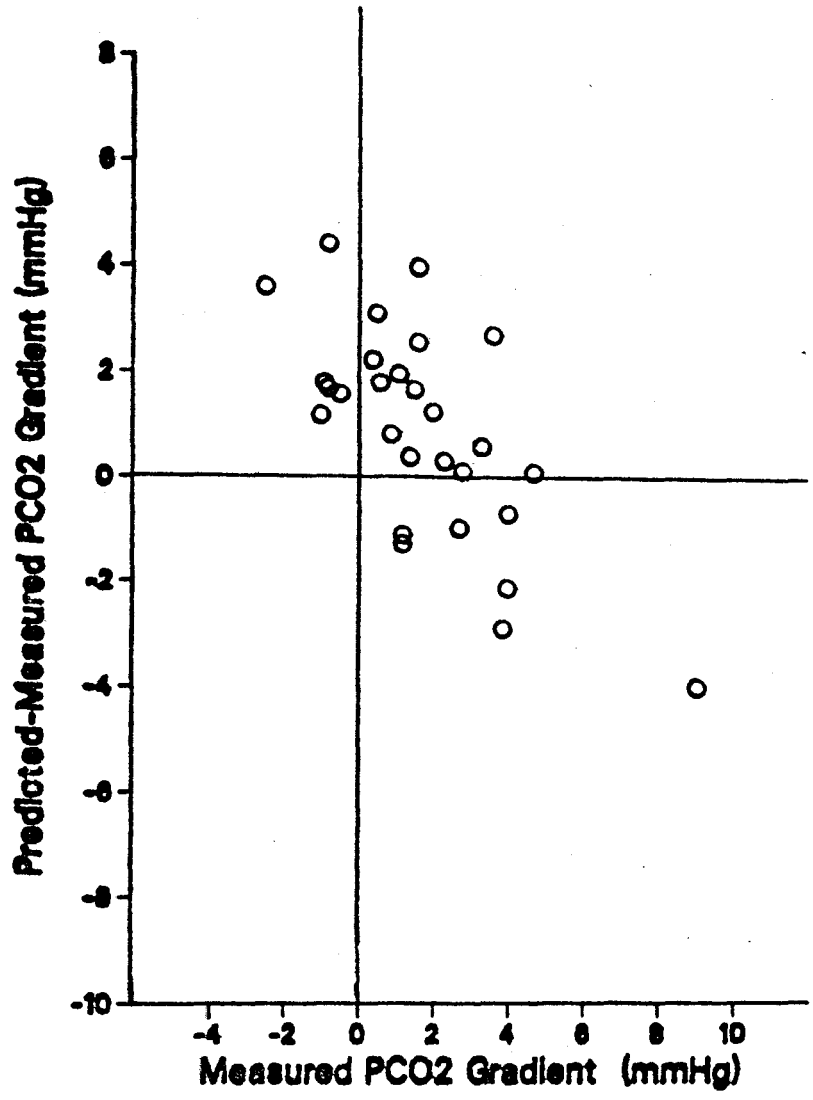

Figure 14. The error between the predicted and measured P(ET-a)CO2 gradient plotted against the measured P(ET-a)CO2 gradient showing the systematic error in Equation 1, derived in the present study, using the data reported by Jones, et al., (1979).

Subject	JB	JM	AG	JT	IM
Surface					
Rest	-3.47	-1.25	-0.95	-2.63	1.71
0 Kpm/min.	-0.29	-0.86	-0.85	1.42	2.39
250 Kpm/min.	1.84	0.42	1.33	4.36	4.51
500 Kpm/min.	3.19	2.02	4.39	4.57	6.92
750 Kpm/min.	4.62	2.58	7.51	4.68	4.80
1000 Kpm/min.		3.74			
4 ATA					
Rest	-0.42	-0.77	-1.79	-3.39	2.88
0 Kpm/min.	-0.66	0.57	1.60	1.79	7.41
250 Kpm/min.	3.30	1.30	3.56	3.80	11.25
500 Kpm/min.	7.04	4.14	6.74	4.25	15.25
750 Kpm/min.	6.22	4.91	6.93		9.82
1000 Kpm/min.					
4 ATA SABA					
Rest	-0.99	-0.94	-1.50	-2.44	4.31
0 Kpm/min.	0.21	-0.41	1.20	0.57	5.27
250 Kpm/min.	1.73	1.28	4.27	2.55	11.50
500 Kpm/min.	3.18	3.17	3.66	2.98	13.21
750 Kpm/min.	6.58	3.77	6.23	4.80	9.21
1000 Kpm/min.		6.15			

Table 13. Estimates of the $\underline{P}(\underline{ET}-a)CO2$ gradients which should occur for divers exercising at increased ambient pressures, according to equation 3, (Table 8), and the data reported by Morrison et al., (1976).

V. Discussion

The primary aim of this study was to examine whether negative P(a-A)CO2 gradients occur in a population of SCUBA divers while subjects breathed from a low resistance mouthpiece and from an open circuit demand regulator.

A second aim of the study was to generate regression equations which accurately predicted the P(a-A)CO2 and P(a-ET)CO2 differences from measured and calculated variables.

PCO2 Gradients

The present series of experiments has demonstrated the existence of negative P(a-A)CO2 gradients in SCUBA divers. The negative PCO2 gradients were present only during exercise, when subjects breathed through an open circuit demand regulator.

During rest, alveolar PCO2 and end-tidal PCO2 were significantly lower than arterial PCO2, (-6.02 mmHg ±0.68) and (-4.03 mmHg ±0.76) respectively. When subjects breathed through the low resistance mouthpiece, exercise caused a decrease in the PCO2 gradient. Alveolar PCO2 and end-tidal PCO2 were in close equilibrium with arterial PCO2. When subjects exercised while breathing through the open circuit demand regulator, there was a change in the equilibrium between PACO2, PETCO2 and PaCO2. These changes resulted in negative P(a-A)CO2 and P(a-ET)CO2 gradients.

Alveolar and end-tidal PCO2 increased relative to arterial PCO2. Reversal of the PCO2 gradient indicates a modification in PACO2 and PETCO2 independent of mean PaCO2.

Since the alveolar hypercapnia experienced by the divers was not accompanied by an increase in arterial PCO2 (see Table 6), measurements of alveolar or end-tidal PCO2 alone cannot accurately predict arterial PCO2. Hence, if PaCO2 is to be predicted with accuracy, a multiple linear regression equation consisting of a number of respiratory variables is necessary. The equations derived to predict PaCO2, from both invasive and non-invasive measurements, can accurately predict PaCO2 relative to PETCO2 (adjusted r =0.885 and 0.881 respectively, Figures 10 and 11). Calculation of PaCO2 using either of these equations reduces errors inherent in equating PaCO2 directly with PETCO2.

Factors Influencing Measured PCO2 Gradients

Several factors related to alveolar and arterial PCO2 measurements may account for the reversal of the P(a-ET)CO2 and P(a-A)CO2 gradients. Identification of a negative P(a-A)CO2 gradient suggests that simple passive diffusion may not be the only mechanism determining the exchange of carbon dioxide within the lungs.

1. Alveolar PCO2 Measurements

Elevated PETCO2 and PACO2 can result from cyclical variations in alveolar gas composition during respiration. The average composition of the alveolar portion of the expired air and the average composition of the air in the alveoli are not the same (DuBois, et al., 1952; Young, 1955; Asmussen and Nielsen, 1956). A possible reason why PETCO2 is higher than PaCO2 is that the alveolar samples represent the last part of the alveolar expired air, which undergoes large changes in composition during the respiratory cycle.

At rest, relative to exercise, alveolar ventilation is reduced. There is an increase in time for gas flow through the dead space in the lungs. These factors contribute to a more even alveolar gas composition decreasing, cyclical variations in PACO2. Exercise causes an increase in alveolar ventilation and a decrease in time for gas flow through the dead space. This causes greater fluctuations in PACO2 when sampled during the expiratory phase. In addition, the increased carbon dioxide produced during exercise is evolved into a diminishing lung volume during the expiratory phase. This results in a greater carbon dioxide tension (PETCO2) at the end of the expiratory cycle. These combined effects lead to an elevation in PCO2 during expiration which is greater than the average CO2 tension in the lungs. To estimate mean expired PACO2, a measure was taken at the time representing 60% of the expiratory duration of

the alveolar gas volume, Figure 4. Using this measurement, it was possible to estimate mean expired PACO2 DuBois, et al. 1952; Young, 1955).

These fluctuations of alveolar gas composition during the respiratory cycle may lead to overestimation of PaCO2 from measurements of PETCO2 or PACO2, in the absence of direct arterial sampling.

The increase in PACO2 was also influenced by the divers' respiratory pattern. Exercise, while subjects breathed through the low resistance mouthpiece, caused an increase in ventilation. This was accompanied by an increase in respiratory frequency and tidal volume. Alveolar PCO2 increased in response to the increased metabolic CO2 production associated with exercise. Arterial PCO2 also increased relative to the resting values. The respiratory pattern was modified when the divers breathed through the open-circuit demand regulator. Ventilation and respiratory frequency decreased while tidal volume increased. The decreased respiratory frequency resulted in prolonged inspiratory and expiratory phases. Both the lower frequency and the relative hypoventilation accentuate cyclical fluctuations in alveolar gas composition, leading to an elevation in measured PACO2 and PETCO2 and an apparent carbon dioxide retention. There was no accompanying change in PaCO2 between the two exercise conditions.

2. Arterial PCO2 Measurements

It is generally assumed that alveolar PCO2 achieves equilibrium with arterial PCO2 at the time of gas exchange across the alveolar-capillary membrane. Any change in the PCO2 of the blood during transit time between the pulmonary capillaries and the sample site may reflect a "spurious" PCO2 gradient which does not exist across the alveolar-capillary membrane.

The magnitude and direction of the PCO2 gradient measured is dependent on any change in blood PCO2 during this period of time. Results from this study cannot be extended to suggest whether or not the PCO2 of the blood increases or decreases during the time of transit between the pulmonary capillaries and the sample site. Arterialized-venous blood sampling masks changes in blood PCO2 during this period of time.

Several researchers have proposed mechanisms, related to changes in blood PCO2, which may account for the existence of an apparent negative PCO2 gradient (Gurtner, et al., 1972; Forster, 1972; Forster, et al., 1975). The findings from these studies have been presented in the literature review. It is unlikely that the mechanisms outlined in these studies can explain the negative PCO2 gradient observed during this study, using measurements of PACO2 and PaCO2. Since PaCO2 did not change between the two exercise conditions, alveolar PCO2 increased for a constant value of PaCO2. This mechanism would therefore

require a differing amount of change in blood PCO2 between the pulmonary capillaries and the site of measurement in the two exercise conditions.

The equations generated to predict PaCO2 from invasive and non-invasive measurements incorporate a number of respiratory variables including PETCO2. Although end-tidal CO2 tensions are greater than alveolar CO2 tensions during the respiratory cycle, PETCO2 may contribute to a better estimate of PaCO2 in regression equations, as the equation corrects for systematic errors.

The equation predicting PaCO2 from non-invasive measurements was compared with a similar equation derived from experiments conducted by Jones, et al. (1979). The methods used to generate the equations in each study were different. Jones, et al. (1979) derived their equation using stepwise multiple linear regression analysis. Stepwise regression analysis predetermines the order of variables entered into the regression equation, starting with the first variable and adding successive variables according to the highest correlation. This type of regression analysis precludes certain combinations of variables from the regression analysis. The equations from this study were derived using best subset multiple linear regression analysis.

The problem of variable selection increases as the number of "redundant" variables increases. Inclusion of such variables allows the regression equation to "fit" artifacts in the data

thereby producing misleading values of r^2. For example, a data set of 10, if fitted by a regression equation having 10 independent variables, will automatically provide a perfect correlation. The accuracy of the predictive equation when applied to another data set is however low. Unlike stepwise multiple linear regression analysis, best subset multiple linear regression analysis chooses the best subset of variables,from the variables entered into the analysis, to derive the predictive equation. Therefore, only the variables minimizing the selection criterion are included in the regression equation. This selection criterion minimizes Mallows' Cp. In addition, the best subset is selected using an adjusted r correlation coefficient, which adjusts the correlation coefficient according to the number of degrees of freedom in the analysis for related variables.

3. Sampling Techniques

Another factor which complicates direct comparisons between PACO2 and PaCO2 involves the method of averaging each sample. Both PACO2 and PaCO2 were sampled over several complete respiratory cycles. PaCO2 is time averaged while PACO2 is volume averaged over the same period. Therefore, the negative PCO2 gradient may reflect an artifact associated with volume averaging and time averaging the samples. The sampling techniques from this study are unable to define these errors.

The relative hypoventilation associated with exercise, while subjects breathed through the open-circuit demand regulator, may magnify these errors.

Several physiological calculations are dependent on the assumption that an equilibrium exists between PACO2 and PaCO2. The results from this study suggest that direct measurements of PACO2 overestimate PaCO2 during exercise, and underestimate PaCO2 at rest. Therefore, these calculations would also overestimate or underestimate arterial PCO2 as used in the Bohr Equation and indirect Fick Equation. Due to the sensitivity of these equations to the value of PaCO2, this P(a-A)CO2 gradient is likely to lead to large errors of estimates in alveolar volume deadspace and cardiac output in certain circumstances. It is more accurate to predict PaCO2 from an equation incorporating respiratory variables, as derived in this study.

P(a-A)CO2 Gradient

It becomes apparent from the above discussion that several factors may account for the apparent existence of a negative P(a-A)CO2 gradient. These factors are inherently related to the methods of sampling alveolar and arterial PCO2. Errors associated with these techniques have been discussed previously (Scheid and Piiper, 1980). The sampling techniques employed in this study have minimized several of these errors as outlined.

Whereas Jones, et al., (1979) were able to indentify a negative PCO2 gradient between end-tidal PCO2 and arterial PCO2, their results do not suggest a negative PCO2 gradient between alveolar PCO2 and arterial PCO2. The results from this study have been extended to include measurements of PACO2 and PaCO2, hopefully eliminating errors associated with PETCO2 due to cyclical variations in alveolar gas composition. In the absence of direct arterial PCO2 sampling, the equations generated from this study can predict the PCO2 gradient according to the experimental conditions outlined. These findings, which relate the PCO2 gradient to PACO2, $\dot{V}CO_2$, Fr, and $\dot{V}E$ are consistent with the theoretical relationships that influence fluctuations in alveolar gas composition (Dubois, et al., 1951; Young, 1955).

Changes in Oxygen Consumption

Exercise, at normal barometric pressures with the addition of an external respiratory resistance, has been shown to cause a decrease in oxygen consumption (Silverman, et al. 1951; Cooper (1960); Tabakin and Hanson 1960; Spioch, et al. 1962; Hermansen, et al. 1972) In addition, Thompson and Sharkey (1966) have shown that when subjects breath against the external resistance of a respiratory protective mask, there is a significant increase in recovery oxygen consumption. This suggests that an O2 debt occurs during exercise which is greater than the O2 debt under

normal conditions. Morrison, et al. (1976) observed a decrease in $\dot{V}O_2$ when subjects breathed from SABA (Royal Naval Swimmers' Air Breathing Apparatus) at increased barometric pressure when compared with breathing from a low resistance valve at the same pressure.

The above studies have shown a reduction in oxygen consumption with the addition of an external respiratory resistance. The results of this study at normal barometric pressures also suggest that oxygen consumption may be reduced when subjects use underwater breathing apparatus, but the findings require further investigation. A decrease in VO_2 with the addition of an external breathing resistance may represent an increase in the efficiency of oxygen extraction to satisfy the increased cost of breathing which occurs with the addition of an external breathing apparatus.

Cain and Otis (1949) and Zechman, et al. (1957) have suggested that retention of carbon dioxide during resistive breathing may indicate a compromise in which CO_2 tensions are elevated so additional energy is not expended to reduce CO_2 tensions to preresistance levels. This is consistent with the observations of Cherniack and Snidal (1956) where there was a decreased sensitivity to CO_2 in normal subjects breathing against resistance. Oxygen consumption may decrease with an altered response to CO_2 added to the control of respiration.

Validation Study

It is important to validate any derived equation by testing the prediction against data obtained from other independent investigations. Equation 1 was selected as the best equation to predict the P(ET-a)CO2 gradient, using the data from the present study according to best subsets regression analysis and the mean square error. However, as determined in Table 8, the validation process revealed that equation 3, although slightly weaker in predicting the measured data set, gave a much superior prediction of the data reported by Jones, et al., (1979). Thus, the cross-validation analysis suggests that according to the mean square error, equation 3 includes the best subset of variables to predict the PCO2 gradient in data taken from other populations (Table 12).

There will be an optimum number of variables in any regression equation which is likely to provide the best results in cross-validation comparisons. The optimum number will include variables having a strong influence while rejecting redundant variables which, although capable of improving the correlation to the specific data sample, do not improve the relationship with the general population. Systematic errors may also overemphasize the contribution from certain variables, especially if the data is limited to a restricted range of values, causing errors in the predictive equation when related to data from other studies. From Table 8 and Figure 14, it

appears that both these shortcomin In particular, there appears to be a systematic error related to tidal volume in the equation when compared with the data from Jones, et al., (1979), (Figure 16). A large systematic error is also noted in the equation derived by Jones, et. al., (1979), Figure 13, when compared with the data of this study, which may result from the narrow range in PETCO2, Figure 15. This equation appears to rely strongly on the PETCO2 term, which is perhaps underemphasized. From Table 12, it can be seen that equation 3 gave the best predictive results for the PCO2 gradient from the measured variables according to the mean square errors.

Equation 3 was applied to the data reported by Morrison, et al., (1976), Table 13. The results suggest the existence of a negative P(a-ET)CO2 and P(a-A)CO2 gradient during hyperbaric exposures. Unfortunately, it is not possible to confirm these findings since PaCO2 was not measured.

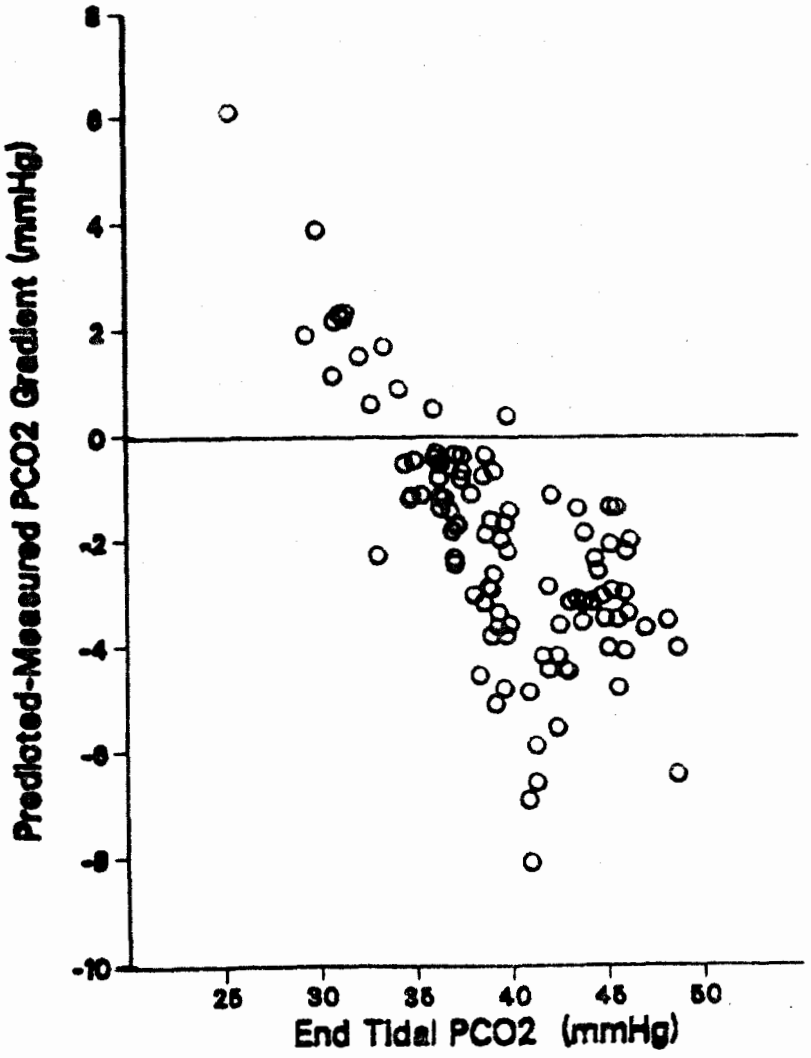

Figure 15. The error between the predicted and measured P(ET-a)CO2 gradient plotted against end-tidal PCO2 showing the systematic error in the equation derived by Jones, et al., (1979) using the data from the present study.

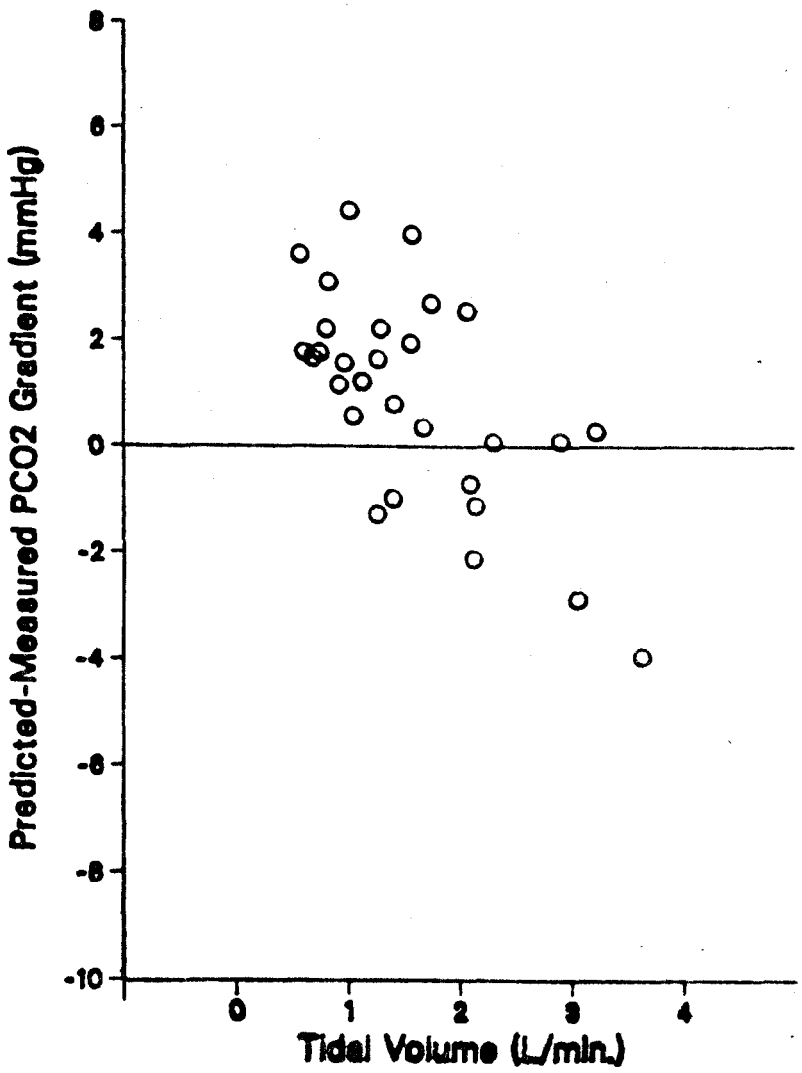

Figure 16. The error between the predicted and measured P(ET-a)CO2 gradient plotted against tidal volume showing the systematic error in equation 1 derived from this study, using the data reported by Jones, et al., (1979).

PCO2 Gradient Related To Previous Studies

The existence of a negative P(a-A)CO2 gradient in SCUBA divers is related to previously reported changes associated with prolonged exposure to increased ambient pressures (Lanphier, 1969; Lally, et al., 1974; Morrison, et al., 1976; Morrison, et al., 1979; Morrison, et al., 1981).

These changes indicate that SCUBA divers develop a physiological adaptation to carbon dioxide or a reduced sensitivity to carbon dioxide as a respiratory stimulus (Lanphier, 1969).

SCUBA divers working under hyperbaric conditions, are exposed to an increased work of breathing from the increased density of their breathing mixture, increased resistance from an external breathing apparatus, and hydrostatic pressure gradients acting on the lungs. The work of breathing does not increase sufficiently to compensate for these factors, and alveolar PCO2 increases relative to normal conditions. An increased tolerance to elevated PACO2 may be beneficial to SCUBA divers as an alternative to the increased work of respiration necessary to maintain PACO2 within normal limits.

The measured response of variables related to the subjects breathing pattern observed in this study were similar to previously documented studies. Zechman, et al., (1957) and

Morrison, et al., (1976) measured a significant decrease in the subjects ventilatory response to exercise at increased ambient pressures, breathing through SCUBA apparatus. SCUBA divers exhibit a slower, deeper breathing pattern when compared with non-divers at increased ambient pressures (Florio, et al., 1979). Their respiratory frequency decreases and tidal volume increases. These divers have been termed "Carbon Dioxide Retainers". The apparent hypoventilation presumably occurs through a process of respiratory adaptation related to an increase in the work of breathing during hyperbaric exposures. It has been suggested that this modified breathing pattern is selected to minimize the overall work of breathing.

Hypoventilation impairs CO2 elimination from the lungs with subsequent elevation in PACO2 (Milic-Emili and Tyler, 1963; Hamilton 1967; Miller, et al. 1971; Fagraeus, et al. 1974; Matthews and Howell, 1975). Prolonged inspiratory pauses which are a notable feature of divers' ventilatory patterns, also reduce the work of breathing but may lead to carbon dioxide retention. Post inspiratory and expiratory pauses also accentuate cyclical variations in PACO2 (Goff and Bartlett, 1957). Alveolar ventilation does not increase sufficiently to compensate for the lower respiratory frequency leading to carbon dioxide retention. The significant changes in ventilation, respiratory frequency, and tidal volume between the two exercise conditions found in the present study indicate that changes in

these variables are similar to the slow, deep breathing pattern exhibited by SCUBA divers in the previous studies.

Consequences of Increased Tolerance to Carbon Dioxide

An increased tolerance to carbon dioxide allows SCUBA divers to work longer underwater because of an improvement in oxygen utilization (lower ventilatory equivalent for oxygen, VE/VO2). This response is beneficial for gas exchange economy during heavy exercise. The results from the present study suggest that arterial PCO2 can be maintained at a lower level of alveolar ventilation. The PACO2 and PETCO2 levels experienced during hyperbaric exposures are generally higher than witnessed in this study at 1ATA.

Tolerance to elevated CO2 tensions may appear as a fortuitous adaption beneficial to SCUBA divers working under hyperbaric conditions. But carbon dioxide retention may be a potentiating factor in oxygen poisoning and nitrogen narcosis (Case and Haldane, 1941; Lanphier, 1975; Schaefer, 1975; Wood, 1975). Carbon dioxide retention may also contribute to the etiology of unexplained losses of consciousness occurring in divers at increased pressures (Morrison, et al., 1976).

Therefore, adaptation to elevated carbon dioxide levels may present a serious hazard for the working diver. However, due to the presence of a substantial negative PCO2 gradient, it is not possible to assess to what extent elevated PACO2 and PETCO2 are

reflected by a true CO2 retention as measured by elevated PaCO2 levels. The extent of PaCO2 retention is open to question.

Summary

The existence of P(a-A)CO2 differences have been investigated during steady-state conditions of rest and exercise. At rest a positive P(a-A)CO2 gradient was measured having a mean value of 6.02 mmHg. This gradient progressively decreased in the presence of light to moderate exercise. A negative PCO2 gradient was present during exercise, when subjects breathed through an open-circuit demand regulator, (mean gradient 1.46 mmHg). Possible factors contributing to the negative PCO2 gradient have been discussed.

Arterial PCO2 did not change significantly during the two exercise conditions. The negative PCO2 gradient was accompanied by an increase in PACO2 and PETCO2. These results indicate that changes in ventilatory pattern, not changes in arterial PCO2, were responsible for the negative PCO2 gradients observed under these exercise conditions. The increases in PACO2 and PETCO2 observed during this study were dependent on changes in these respiratory variables.

Best subset multiple linear regression analysis was used to derive equations predicting the P(ET-a)CO2 and P(A-a)CO2 gradients from both invasive and non-invasive measurements.

The equations predicting the P(ET-a)CO2 gradients were compared in a cross validation study using an independent data

population.

One cannot extend the results to suggest additional transport mechanisms underlying CO2 exchange in the lungs. The debate regarding the existence of additional mechanisms remains open for future investigations.

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Appendix 1

Individual Subject Data

Measured and calculated subject data for each exercise condition and sample period T1 to T8 respectively

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	8.57	14	74	0.612
2	8.21	15	72	0.547
3	10.01	16	70	0.626
4	7.49	13	65	0.576
5	10.56	16	80	0.660
6	10.72	15	64	0.715
7	8.55	14	71	0.612
8	10.07	13	78	0.629
9	10.01	17	70	0.589
10	11.09	17	72	0.652
11	6.85	12	66	0.571
12	7.45	14	66	0.532
13	8.01	15	74	0.534

Sample period T1

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	21.76	29	80	0.750
2	19.23	25	79	0.769
3	17.30	26	78	0.665
4	16.68	24	77	0.695
5	13.25	20	97	0.660
6	13.09	20	71	0.655
7	16.94	21	90	0.807
8	20.56	24	96	0.857
9	18.09	23	86	0.787
10	22.05	26	83	0.848
11	13.69	20	80	0.685
12	14.91	23	77	0.648
13	18.76	23	85	0.816

Sample period T2

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	26.70	33	107	0.809
2	28.47	32	89	0.890
3	28.67	31	113	0.925
4	26.80	33	96	0.838
5	22.12	27	112	0.819
6	19.42	25	86	0.777
7	22.77	26	110	0.876
8	26.08	32	113	0.815
9	24.88	30	107	0.829
10	27.45	32	95	0.858
11	16.85	23	95	0.733
12	20.01	27	105	0.741
13	23.15	28	99	0.840

Sample period T3

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	30.22	36	113	0.839
2	30.03	34	96	0.883
3	34.55	38	115	0.909
4	24.63	29	95	0.849
5	23.47	30	111	0.782
6	22.93	28	88	0.819
7	24.44	28	120	0.873
8	25.15	27	113	0.898
9	22.99	30	106	0.851
10	27.27	29	107	0.909
11	24.05	28	95	0.829
12	19.97	28	108	0.713
13	23.78	35	104	0.849

Sample period T4

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	30.94	34	116	0.884
2	26.15	31	94	0.844
3	35.93	39	123	0.921
4	19.38	27	98	0.717
5	22.38	28	117	0.799
6	19.51	26	90	0.750
7	25.01	30	122	0.843
8	24.67	27	114	0.914
9	24.00	29	109	0.828
10	26.14	29	107	0.901
11	21.07	26	100	0.843
12	22.63	30	115	0.754
13	24.22	30	110	0.807

Sample period T5

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	26.81	30	117	0.894
2	21.76	26	100	0.837
3	30.77	33	124	0.932
4	17.37	24	102	0.724
5	14.92	22	119	0.678
6	15.90	21	99	0.757
7	21.58	24	118	0.899
8	21.08	25	115	0.843
9	21.06	25	112	0.842
10	22.16	25	120	0.886
11	18.86	22	102	0.857
12	18.42	25	117	0.737
13	18.67	24	120	0.778

Sample period T6

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	23.62	29	122	0.814
2	21.77	27	109	0.806
3	24.73	30	127	0.824
4	20.15	27	106	0.746
5	13.95	19	122	0.734
6	13.08	18	95	0.727
7	19.74	23	119	0.858
8	20.96	23	116	0.911
9	22.14	26	115	0.852
10	24.05	29	116	0.829
11	14.42	18	104	0.801
12	17.17	23	123	0.747
13	19.38	24	124	0.808

Sample period T7

Subject	$\dot{V}E$ BTPS (L/min.)	FB (Br./min.)	HR (B/min.)	VT BTPS (Liters)
1	28.04	32	124	0.876
2	24.10	29	115	0.831
3	28.93	32	131	0.904
4	19.22	26	110	0.739
5	17.66	23	121	0.768
6	13.99	19	101	0.736
7	21.95	25	116	0.878
8	20.76	23	120	0.903
9	24.35	28	118	0.870
10	24.98	29	118	0.861
11	15.41	21	112	0.734
12	15.27	21	127	0.727
13	14.27	19	128	0.751

Sample period T8

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	110.16	32.33	109.33	34.94	-1.36	-3.97
2	118.24	30.22	117.01	30.85	-4.45	-5.08
3	120.31	31.35	119.48	32.24	-4.66	-5.55
4	116.45	24.38	114.74	25.56	-9.99	-9.52
5	106.93	38.25	105.77	40.01	-0.89	-2.65
6	101.43	35.78	99.47	37.15	-2.25	-3.62
7	116.07	29.16	114.52	30.94	-5.46	-7.42
8	124.56	27.62	123.30	30.02	-7.28	-9.68
9	122.52	28.37	121.10	31.44	-5.46	-8.39
10	121.02	26.41	119.54	29.43	-5.37	-8.33
11	122.87	29.43	121.94	33.10	-0.80	-4.47
12	123.55	30.74	122.86	35.42	-1.68	-6.36
13	118.63	33.70	117.39	34.53	-2.37	-3.20

Sample period T1

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	101.71	37.49	100.73	38.85	0.45	-0.91
2	109.42	33.41	108.39	34.28	-3.82	-4.69
3	114.44	35.68	112.61	36.09	-2.31	-2.72
4	109.60	32.95	108.78	31.24	-5.56	-3.85
5	92.75	42.84	92.13	43.53	-0.54	-1.23
6	88.64	42.98	85.00	43.87	-0.03	-0.92
7	107.94	30.34	106.71	31.55	-5.55	-6.76
8	109.01	32.53	107.61	34.88	-1.72	-4.07
9	110.82	32.34	109.64	35.02	-2.38	-5.06
10	115.06	31.92	113.41	32.81	-3.69	-4.58
11	109.74	33.10	108.73	34.82	-1.68	-3.40
12	114.77	32.11	114.08	33.50	-4.70	-6.09
13	109.10	42.95	106.68	45.23	0.33	-1.95

Sample period T2

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	99.83	38.76	98.11	39.18	-1.72	-2.14
2	101.29	36.40	100.22	39.00	0.50	-2.10
3	116.88	39.12	115.16	41.66	2.06	-0.48
4	100.22	38.98	99.33	39.39	0.99	0.58
5	94.19	42.98	92.41	44.76	1.26	-0.52
6	92.06	43.19	90.35	44.42	0.52	-0.71
7	100.70	36.88	98.97	37.50	-1.90	-2.52
8	95.98	35.47	95.08	36.30	-1.91	-2.73
9	102.60	35.79	100.87	36.61	-1.49	-2.31
10	111.08	35.22	109.36	36.38	-1.32	-2.48
11	109.94	35.51	108.94	36.89	-1.21	-2.59
12	110.82	35.72	109.78	36.06	-3.24	-3.57
13	110.55	43.71	107.86	45.57	-0.33	-2.19

Sample period T3

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	99.83	38.35	98.11	38.73	-2.07	-2.45
2	100.29	35.99	97.68	37.29	-0.91	-2.21
3	104.84	36.51	104.02	36.99	-0.81	-1.29
4	105.35	35.55	103.64	36.37	-1.53	-2.35
5	92.54	43.59	91.03	44.56	0.76	-0.21
6	82.81	41.68	81.10	42.16	-0.94	-1.42
7	96.40	38.61	95.49	39.52	-0.38	-1.29
8	102.90	35.47	101.17	36.34	-2.16	-3.03
9	97.43	36.20	96.53	37.12	-0.18	-1.1-
10	109.36	35.42	108.81	36.21	-2.39	-3.18
11	102.25	37.78	101.01	37.99	-1.41	-1.62
12	103.68	37.10	102.98	37.45	-1.75	-2.10
13	110.13	44.26	107.72	46.06	0.56	-1.24

Sample period T4

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	100.73	38.28	99.01	38.73	-0.57	-1.02
2	99.40	36.88	98.57	39.00	-0.80	-2.92
3	105.56	36.99	105.74	36.99	-0.81	-0.81
4	101.04	36.73	100.22	36.85	-2.05	-2.17
5	91.03	44.42	89.32	45.93	1.33	-0.18
6	90.49	43.87	88.77	44.22	1.32	0.97
7	93.76	39.10	92.92	39.73	-0.67	-1.30
8	102.00	36.30	101.17	37.20	-0.90	-1.80
9	101.70	36.61	99.98	37.10	-0.30	-0.79
10	99.89	37.76	98.17	39.13	0.23	-1.14
11	106.18	38.27	104.11	38.61	-1.69	-2.03
12	107.15	37.10	106.45	37.51	-2.19	-2.60
13	110.69	43.64	108.20	45.23	-0.37	-1.96

Sample period T5

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	92.95	40.90	91.23	41.31	3.71	3.30
2	93.43	40.72	92.54	43.74	1.64	-1.38
3	100.58	38.23	101.41	38.36	2.06	1.93
4	97.61	37.68	95.90	38.98	1.38	0.08
5	89.32	44.76	87.54	45.59	1.79	0.96
6	90.14	44.56	88.09	45.95	3.09	2.06
7	96.40	39.31	94.66	39.87	-0.13	-0.69
8	98.54	37.20	96.81	39.97	1.27	-1.50
9	95.70	38.34	93.98	38.61	0.71	0.43
10	100.17	41.53	99.89	42.56	1.56	0.53
11	100.67	39.58	99.15	39.91	-2.69	-3.02
12	105.07	41.26	102.98	41.96	0.76	0.06
13	107.03	44.49	104.27	46.26	0.36	-1.36

Sample period T6

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	97.29	40.00	95.56	40.90	4.70	3.80
2	91.72	41.47	90.83	42.84	2.44	1.07
3	99.69	40.84	100.58	40.98	5.88	5.74
4	99.33	37.68	98.50	38.09	0.51	-0.92
5	89.80	44.90	88.22	45.93	2.43	1.40
6	90.35	44.76	88.70	44.90	1.70	1.56
7	88.55	40.35	87.72	41.95	2.36	0.75
8	92.52	38.45	90.79	39.76	1.46	0.15
9	87.91	39.23	86.19	40.96	2.66	0.93
10	99.54	42.56	98.18	43.46	1.16	0.26
11	100.67	42.06	99.43	43.09	1.19	0.16
12	98.13	44.38	97.44	45.08	2.28	1.58
13	105.30	45.92	101.85	48.20	2.10	-0.18

Sample period T7

Subject	PAO2 (mmHg)	PACO2 (mmHg)	PETO2 (mmHg)	PETCO2 (mmHg)	(PET-Pa)CO2 (mmHg)	(PA-Pa)CO2 (mmHg)
1	94.67	40.42	92.12	41.31	4.41	3.52
2	92.54	40.81	90.83	42.43	2.13	0.51
3	105.88	39.12	104.03	39.19	2.69	2.62
4	89.95	40.28	89.05	42.40	3.50	1.38
5	86.72	45.93	85.88	46.13	1.73	1.53
6	85.00	45.72	83.97	48.69	5.07	2.12
7	92.02	41.67	90.29	42.99	2.49	1.17
8	96.81	38.93	95.98	39.35	1.25	0.83
9	93.08	39.23	91.36	39.65	2.45	2.03
10	96.11	44.62	94.39	45.31	1.21	0.52
11	100.53	42.75	99.29	43.78	1.28	0.25
12	96.05	45.77	94.11	47.02	2.12	0.87
13	104.82	47.64	101.50	48.68	2.68	1.64

Sample period T8

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	0.407	0.349	0.857	92.3	36.3	7.425
2	0.406	0.318	0.783	90.9	35.3	7.418
3	0.496	0.368	0.742	92.5	36.9	7.430
4	0.309	0.224	0.734	89.9	35.8	7.458
5	0.556	0.462	0.831	86.4	40.9	7.441
6	0.553	0.464	0.816	87.6	39.4	7.427
7	0.446	0.301	0.699	90.5	36.4	7.448
8	0.429	0.357	0.830	91.4	37.3	7.438
9	0.400	0.337	0.845	89.5	36.9	7.429
10	0.344	0.233	0.729	90.8	34.8	7.453
11	0.301	0.247	0.860	86.1	33.9	7.433
12	0.341	0.260	0.851	88.6	37.1	7.429
13	0.328	0.289	0.881	90.3	36.9	7.421

Sample period T1

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH (unit)
1	0.855	0.713	0.834	91.9	38.4	7.411
2	0.889	0.743	0.836	90.4	38.1	7.390
3	0.781	0.671	0.859	93.1	38.4	7.426
4	0.727	0.622	0.886	88.7	36.8	7.449
5	0.872	0.644	0.738	90.2	44.1	7.325
6	0.815	0.642	0.788	89.9	43.9	7.383
7	0.805	0.627	0.779	90.2	37.1	7.435
8	0.946	0.827	0.874	90.5	36.6	7.420
9	0.865	0.719	0.834	90.3	37.4	7.413
10	0.917	0.815	0.889	90.6	36.5	7.436
11	0.702	0.504	0.718	85.5	36.5	7.426
12	0.726	0.525	0.723	89.7	38.2	7.417
13	0.926	0.823	0.889	91.4	44.9	7.403

Sample period T2

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	1.021	0.979	0.959	90.7	40.9	7.392
2	1.301	1.126	0.865	89.6	38.5	7.394
3	1.320	0.989	0.749	92.7	39.6	7.419
4	1.400	1.103	0.788	89.1	38.4	7.441
5	1.363	1.125	0.825	91.3	43.5	7.354
6	1.090	0.874	0.802	90.3	43.9	7.346
7	1.055	0.958	0.904	89.4	39.4	7.411
8	1.487	1.102	0.741	90.7	38.2	7.414
9	1.157	1.025	0.886	91.4	38.1	7.396
10	1.299	1.112	0.856	91.1	37.7	7.422
11	0.904	0.730	0.808	87.1	38.1	7.418
12	1.021	0.941	0.922	90.3	39.3	7.389
13	1.219	1.091	0.836	90.9	45.9	7.396

Sample period T3

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	1.586	1.314	0.828	89.9	40.8	7.388
2	1.434	1.182	0.824	91.4	38.2	7.399
3	1.572	1.251	0.796	94.6	37.8	7.430
4	1.225	0.887	0.724	90.4	37.9	7.435
5	1.532	1.198	0.782	89.4	43.8	7.323
6	1.366	1.067	0.781	89.2	43.1	7.388
7	1.341	1.151	0.858	90.9	39.9	7.401
8	1.296	1.060	0.818	89.6	38.5	7.411
9	1.140	0.944	0.828	90.1	37.3	7.384
10	1.275	1.097	0.860	90.3	38.6	7.413
11	1.246	1.132	0.909	89.9	39.4	7.395
12	1.006	0.922	0.917	92.1	39.2	7.392
13	1.218	1.043	0.856	92.4	45.5	7.410

Sample period T4

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	1.182	1.134	0.959	88.4	39.3	7.389
2	1.294	1.051	0.812	92.5	39.8	7.385
3	1.619	1.382	0.854	90.3	37.8	7.437
4	0.903	0.787	0.872	91.2	38.9	7.433
5	1.364	1.149	0.842	90.9	44.6	7.339
6	1.163	0.909	0.782	88.4	42.9	7.376
7	1.483	1.103	0.744	91.5	40.4	7.393
8	1.250	1.083	0.866	90.3	38.1	7.405
9	1.237	0.973	0.787	87.6	37.4	7.397
10	1.261	1.154	0.915	89.9	38.9	7.402
11	1.024	0.994	0.971	90.3	40.3	7.404
12	1.297	1.035	0.789	89.6	39.7	7.399
13	1.266	1.128	0.891	91.7	45.6	7.416

Sample period T5

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	1.082	0.892	0.824	90.3	37.6	7.410
2	1.478	1.033	0.699	91.7	42.1	7.368
3	1.500	1.201	0.801	91.3	36.3	7.448
4	0.863	0.725	0.840	93.1	37.6	7.438
5	0.803	0.786	0.978	93.6	43.8	7.395
6	0.928	0.744	0.802	89.7	42.5	7.370
7	1.271	0.940	0.739	90.4	40.0	7.399
8	1.108	0.962	0.868	90.0	38.7	7.391
9	1.058	0.931	0.880	89.4	37.9	7.412
10	1.091	1.051	0.963	91.0	41.0	7.397
11	0.934	0.857	0.918	90.7	42.6	7.419
12	0.889	0.843	0.948	91.7	41.2	7.414
13	0.920	0.836	0.837	90.6	45.9	7.411

Sample period T6

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	1.021	0.935	0.916	91.3	36.2	7.419
2	1.024	0.971	0.932	92.3	40.4	7.373
3	1.049	0.960	0.915	91.9	35.1	7.461
4	0.924	0.840	0.909	92.4	38.6	7.425
5	0.801	0.734	0.916	92.1	43.5	7.409
6	0.726	0.613	0.848	90.1	43.2	7.414
7	1.012	0.948	0.937	88.5	39.6	7.407
8	1.140	0.969	0.850	91.0	38.3	7.399
9	1.055	0.990	0.938	90.6	38.4	7.425
10	1.159	1.097	0.947	89.6	42.3	7.418
11	0.736	0.653	0.887	90.1	41.9	7.430
12	0.808	0.793	0.981	92.3	42.8	7.420
13	0.964	0.878	0.926	91.0	46.1	7.426

Sample period T7

Subject	$\dot{V}O_2$ STPD (L/min.)	$\dot{V}CO_2$ STPD (L/min.)	R	PaO2 (mmHg)	PaCO2 (mmHg)	pH (unit)
1	1.201	1.076	0.899	91.1	36.9	7.415
2	1.202	1.114	0.927	92.9	40.3	7.379
3	1.259	1.147	0.911	91.8	36.5	7.455
4	0.906	0.802	0.885	90.5	38.9	7.430
5	1.026	0.939	0.914	90.7	44.4	7.436
6	0.801	0.669	0.835	92.3	43.6	7.432
7	1.209	1.096	0.907	89.7	40.5	7.422
8	1.049	0.955	0.910	90.8	38.1	7.432
9	1.149	1.068	0.930	90.3	37.2	7.424
10	1.352	1.301	0.962	87.3	44.1	7.431
11	0.757	0.704	0.931	91.9	42.5	7.425
12	0.786	0.714	0.908	90.5	44.9	7.435
13	0.752	0.704	0.936	89.9	46.0	7.433

Sample period T8

Appendix 2

Review of Basic Respiratory Physiology

Introduction

The following introduction outlines some of the basic considerations necessary to understand the transport of gases and blood through the lungs, gas exchange across the alveolar-capillary membrane and the transport of oxygen and carbon dioxide by the blood.

Respiration involves two processes;

External respiration, the absorption of O2 and removal of CO2 from the body,

Internal respiration, the gaseous exchange between cells and their fluid medium.

The lungs act as a gas-exchanger for O2 and CO2 between the air and blood. Atmospheric air becomes available to the gas-exchanging surfaces, (alveolar-capillary membrane), through a system of branching airways, the bronchial tree, which terminates as thin walled sacs, the alveoli. The

alveolar-capillary membrane separates alveolar air from the blood in the lungs, carried by the pulmonary-arterial network. The alveoli are surrounded by the pulmonary capillaries forming a continuous network for gas exchange between the blood and lungs. During the passage of blood through the alveoli, O2 is loaded and CO2 is unloaded. The pulmonary veins collect the arterialized capillary blood for transport to the left atrium and ventricle and subsequent distribution to the tissues via the systemic arterial network.

At rest, man breathes 12-15 times/min., (6-7 liters/min.). The inspired air mixes with the "air" already present in the alveoli and by simple diffusion O2 enters the blood in the pulmonary capillaries while CO2 enters the alveoli, (Cherniack, 1972; West, 1974). Alveolar ventilation is that portion of the total air ventilated which reaches the alveoli and takes part in gas exchange. (Miller, 1947; Ganong, 1977).

Partial Pressure Differences Between Alveolar Gas and Pulmonary Capillary Blood

Gas diffuses from areas of high pressure to areas of low pressure according to Fick's Law of Diffusion, "The rate of gas transfer through a sheet of tissue is proportional to the tissue area, the difference in gas partial pressure between the two sides, its solubility in the liquid and inversely proportional to the tissue thickness", (West, 1978). The area of the

blood-gas barrier in the lungs, (alveolar-capillary membrane), is extremely large, (50-100 square meteres), with a thickness of less than 0.5 um, making the membrane ideal for diffusion of gases such as O2 and CO2, (Bouhnys, 1977; West, 1978).

The continuous exchange of gases between alveolar air and the pulmonary capillary blood can only be maintained if the partial pressure of O2 in the alveoli, (PAO2), is higher and the partial pressure of CO2, (PACO2), is lower than the corresponding partial pressures in the venous blood arriving at the alveoli, (West, 1978). This is accomplished during ventilation by the discontinuous rhythmic dilution of alveolar air, which contains negligable CO2 and has a higher PO2 , (Rahn and Farhi, 1964).

Alveolar Gas Exchange

Oxygen diffuses continually into the pulmonary capillaries from the alveoli, while CO2 continually diffuses into the alveoli from the blood in the pulmonary capillaries. During steady state conditions, the inspired air mixes with the alveolar "air", replenishing O2 and diluting CO2. Part of the alveolar air is expired during successive expirations. The O2 content of the alveolar air will then decrease and its CO2 content will increase until the next inspiration, (Forster, 1964).

Lung Volumes

The amount of air that moves into the lungs with each inspiration is called the tidal volume, (VT). The gas remaining in the lungs following a normal expiration is the functional residual capacity, (FRC). The exhaled volume of air following maximal inspiration and expiration is called the vital capacity, (Vc). The air remaining in the lungs after a maximal expiration is the residual volume, (RV).

Portions of the respiratory system serve as conducting airways and do not contribute to gas exchange, forming the anatomical dead space (VD). The portion of inspired air occupying the anatomical dead space is not available to the alveoli for gas exchange. (West, 1978). The volume of air available for gas exchange is called the alveolar volume, ($\dot{V}A$).

The volume of the lungs which does not eliminate carbon dioxide is called the physiological dead space. Under normal conditions, the anatomical and physiological dead space are very nearly equal. The anatomical dead space contributes to the physiological dead space.

However,in patients with lung disease, the physiological dead space is increased when underperfused alveoli are ventilated or when normally perfused alveoli are overventilated, (West, 1970).

The tidal volume is the sum of the physiological dead space and the "ideal" ventilated alveolar volume,

Diffusing Capacity for Oxygen and Carbon Dioxide

The PO2 of alveolar air, (PAO2) is approximately 100 mmHg and the PO2 of the venous blood in the pulmonary artery, (PvO2) is approximately 40 mmHg. Oxygen diffuses across this pressure gradient into the blood. Diffusion of O2 is rapid even though the blood remains in the pulmonary capillaries for a relatively short period of time, (0.5-1.0 sec.), (Forster and Crandall, 1975). This period of time is adequate to raise the arterial PO2, (PaO2) to 97 mmHg, (Cherniack, 1972; West, 1978).

The PCO2 of the venous blood, (PvCO2) is approximately 45 mmHg. whereas the PCO2 of the alveolar air, (PACO2) is approximately 40 mmHg. Carbon dioxide diffuses from the venous blood into the alveoli along this pressure gradient. The PCO2 of the blood leaving the pulmonary capillaries is approximately 40 mmHg. Since CO2 diffuses readily through the alveolar-capillary membrane, seldom does lung perfusion hinder CO2 exchange in the alveoli, (Forster, 1964; West, 1978).

Distribution of Alveolar Ventilation

Radioactive tracing techniques have demonstrated that a greater portion of the inspired air is distributed to the bottom of the lungs than to the top of the lungs during normal breathing in the upright posture, (Bouhnys, 1959; West, 1978). The difference in the distribution of air is caused by

differences in the force of gravity and pleural pressures within the lung, (West, 1978). Air spaces at the apex of the lung tend to fill somewhat less on inspiration than at the base resulting in regional differences in distribution of alveolar ventilation.

Distribution of Pulmonary Blood Flow

In the upright human lung, blood flow decreases from the bottom to the top of the lung, (Rahn and Farhi, 1964; West, et al., 1964; Hughes, et al., 1968). This distribution is affected by changes in posture and with exercise. Mild exercise will increase blood flow within the lungs and reduce regional differences throughout the lungs, (West, 1978). The uneven distribution of blood flow results from hydrostatic pressure differences within the blood vessels of the lungs, (Rahn and Farhi, 1964).

Distribution of Ventilation and Perfusion

The non-uniform distribution of inspired air and pulmonary blood flow within the lungs results in an unequal alveolar gas composition in different parts of the lungs. Gas exchange in the lungs depends on the amount of ventilation reaching the alveoli, ($\dot{V}A$) and the amount of blood, ($\dot{Q}$) circulating through the pulmonary capillaries, (West, 1962; Farhi, 1967). If alveolar air and pulmonary blood do not reach individual alveolar units at equal rates, the ratio of ventilation to perfusion, ($\dot{V}A/\dot{Q}$),

will vary throughout different regions in the lungs, (0.6 at the top and 3.0 at the bottom: West, 1978).

Normally ($\dot{V}A/\dot{Q}$) is between 0.8 and 1.0 in larger regions of the lungs. Increased perfusion leads to lower ($\dot{V}A/\dot{Q}$) ratios and increases PACO2 while increased ventilation leads to higher ($\dot{V}A/\dot{Q}$) ratios and decreases PACO2, (Rahn and Farhi, 1964; Farhi, 1967; West, 1970).

The uptake of O2 and the production of CO2 are determined by the metabolic needs of the body, (Cherniack, 1972). Ventilation and blood flow in the lungs adapts to maintain adequate transfer of O2 and CO2 between the tissues and the atmosphere. The alveolar air composition varies with inspiration and expiration and with location in the lungs according to the ($\dot{V}A/\dot{Q}$) ratio, (West, 1978). Regional differences in the ($\dot{V}A/\dot{Q}$) ratio results in differences between alveolar and arterial gas partial pressures, (Roughton and Forster, 1957; Cherniack, 1972; West, 1978).

Gas Transport Between the Lungs and Tissues

Oxygen and carbon dioxide transport to and from the tissues would be grossly inadequate if dissolved O2 did not combine with hemoglobin in the blood and CO2 did not enter into a series of reversible chemical reactions, (Cherniack, 1972). The presence of hemoglobin increases the O2-carrying capacity of the blood 70 times and the chemical reactions which combine CO2

increases the CO2 content of the blood 20 times.

Oxygen Transport

Oxygen in the pulmonary capillaries is transported as dissolved O2 in physical solution in the plasma or in combination with hemoglobin in the red blood cells, (Roughton, 1964; Cherniack, 1972; West, 1978). The amount of O2 dissolved in the plasma is directly proportional to the partial pressure, (0.03 ml/mmHg/L of plasma). The amount of O2 in physical solution in the plasma is about 3.0 ml/L of plasma, (Roughton, 1964).

Most of the O2 is carried by the red blood cells in combination with hemoglobin as oxyhemoglobin. One gram of hemoglobin is capable of combining chemically with 1.34 ml of O2, (West, 1978). With a hemoglobin content of approximately 15 g/100ml of blood, the blood is capable of transporting 20.10 ml of O2/100ml of blood. The saturation of hemoglobin depends on the partial pressure of O2 in the plasma, where O2 is bound at high partial pressures in the lungs and released at low partial pressures in the tissues, (Cherniack, 1972). The amount of O2 released to the tissues is also dependent on the PCO2, pH and temperature of the blood, (West, 1978).

Oxyhemoglobin releases more O2 when the PaCO2 increases, temperature increases or pH decreases. The effects of these variables act as important safeguards for maintenance of O2

exchange between the tissues and the lungs.

In vivo, the hemoglobin in the blood at the end of the pulmonary capillaries is about 97.5% saturated with O2, ($\underline{P}O2$=97 mmHg), whereas the hemoglobin in the systemic arterial blood is only 97.0% saturated with O2 due to a slight admixture with shunted venous blood, (Cherniack, 1972). Arterial blood contains 19.8 ml of O2/100 ml of blood, (0.29 ml in solution and 19.5 ml bound to hemoglobin), (West, 1978). In venous blood the hemoglobin is 75% saturated and the total O2 content is about 15.2 ml of O2/100 ml of blood, (West, 1978). Therefore, the tissues remove about 4.6 ml of O2 from each 100 ml of blood, (0.17 ml in solution and the remainder from oxyhemoglobin), (West, 1978).

Bohr Effect

The release of O2 from the blood to the tissues is enhanced by a decrease in pH, increase in temperature or an increase in $\underline{Pa}CO2$. A change in any one of these factors will decrease the affinity of hemoglobin for O2 and promote the release of O2 to the tissues and subsequent binding of H+ ions. The binding of H+ ions will increase the capacity for hemoglobin to transport CO2.

Haldane Effect

The dissociation of carbonic acid, (H2CO3), liberates HCO3- and H+ ions. Hydrogen ions are bound to hemoglobin as follows,

$$HbO2 + H+ \longleftrightarrow HHb + O2$$

Since reduced hemoglobin is less dissociated than oxyhemoglobin, the presence of reduced hemoglobin in the blood will enhance the binding of CO2, while the oxygenation of hemoglobin in the pulmonary capillaries enhances the unloading CO2. Deoxygenation of the blood increases its capacity to transport CO2.

The interactions of O2 and CO2 binding to hemoglobin are known as the Bohr and Haldane Effects.

Buffering Systems and Acid-Base Balance

Transport of CO2 in the blood involves major pH buffering systems and is closely linked with the processes that maintain the body's acid-base balance. Therefore, a brief discussion of acid-base balance is nessecary before the mechanisms of CO2 transport can be fully understood.

The terms acid and base are usually applied to proton (or hydrogen ion) donors or acceptors. The acidity or alkalinity of a solution is expressed by the term pH, which is the negative logarithm to the base 10 of the hydrogen ion concentration, (a

decrease or an increase of one pH unit represents a tenfold change in the opposite direction of the hydrogen ion concentration).

Buffers

The capacity of an acid-base mixture to resist changes in pH is called its buffer action, and a mixture that can do this is called a buffer. The reaction of a solution that contains both an acid and base can be expressed by the equation,

pH = pK + log (buffer anion/undissociated buffer)

Where pK is a constant that varies depending on the type of acid or base involved.

Henderson-Hasselbalch Equation

The relationship between carbon dioxide, (carbonic acid), and the anion bicarbonate in the plasma, which is reflected in the Henderson-Hasselbalch equation, is quantitatively the most important buffering system of the extra-cellular fluid. The Henderson-Hasselbalch equation is used to establish the existence of an acid-base disturbance in the body,

pH = pK + log (HCO3-/H2CO3)

where the pK for blood at body temperature is 6.10.

Since the concentration of H_2CO_3 is a thousand times less than that of dissolved carbon dioxide which, in turn, is proportional to the partial pressure of carbon dioxide, the equation may be rewritten,

$$pH = 6.10 + \log (HCO_3^-/0.0301 * PCO_2)$$

The balance between bicarbonate and dissolved carbon dioxide (or CO_2 tension) is maintained at about 20:1. The bicarbonate level is normally 24 mEq/L and the dissolved carbon dioxide is about 1.2 mEq/L and the pH is about 7.4, (range 7.35 to 7.45).

Bicarbonate-Carbonic Acid Reactions

Some of the dissolved carbon dioxide in the plasma reacts with water to produce carbonic acid (a process called hydration) which, in turn, dissociates into bicarbonate and hydrogen ions.

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow HCO_3^- + H^+$$

Hydration of carbon dioxide in the plasma is a very slow chemical reaction, and the concentration of dissolved carbon dioxide is about one thousand times greater than the concentration of carbonic acid. Consequently only a small amount of bicarbonate is formed in the plasma. The hydration of carbon dioxide to carbonic acid is rapid within the red blood cells

because they contain the enzyme carbonic anhydrase, so that considerable bicarbonate is formed in the red blood cells. When carbonic acid dissociates into bicarbonate and hydrogen ions, the pH of the blood is not altered significantly. The hydrogen ions are buffered by hemoglobin and bicarbonate moves into the plasma because the concentration in the red blood cell is much higher than in the plasma.

The power of this reaction is dependent on the ability of the lungs to ventilate CO2, leading to a rapid readjustment of (H+) with a decrease in (HCO3-). The respiratory system plays an important role in the regulation of the acid-base balance of the body.

Proteins as Buffers

Amino acids are capable of acting as either an acid or a base. The amino group, (NH2-), can accept protons to form (NH3) and the carboxyl groups (COOH), can donate protons to form (COO-). Amino acid buffers in the body exert a powerful action to limit the decrease in blood pH with the addition of H+ ions. At the pH of the body, (7.4), amino acids buffer protons.

Hemoglobin as a Buffer

Hemoglobin contains many amino acids and therefore acts as an important buffer in the body. A change in oxyhemoglobin to the reduced state will lead to a large assimilation of free H+ ions. This is important when the blood releases O2 into the

tissues, binding H+ ions produced during metabolism or secondary to the production of CO2.

The buffer systems of the body remain in dynamic equilibrium.

Carbon Dioxide Transport

In the blood, CO2 is physically dissolved as well as chemically bound for transport from the tissues to the lungs, (Comroe, 1974). These complex physiochemical events enhance the transport of large amounts of CO2 when the partial pressure differences between venous and arterial blood PCO2 levels are small. The majority of CO2 produced by the tissues passes into the red blood cells and is either carried as HCO3- ions or bound to hemoglobin as a carbamino compound. Some of the CO2 is also carried in the plasma as HCO3- ions or as dissolved CO2.

At normal body temperature, (37.0 C), 0.03 mM/L of CO2 is dissolved in the plasma/mmHg PCO2, (Rahn and Farhi, 1964; Ganong, 1977). Therefore, arterial PCO2, (PaCO2=40 mmHg), contains 1.2 mM/L of CO2 dissolved in the plasma and 1.38 mM/L of CO2 dissolved in the venous blood, (PvCO2=46 mmHg).

Hydrogen and bicarbonate ions diffuse from the red blood cell into the plasma. The H+ ions are buffered by the hemoglobin molecule, where the capacity of the buffer to remove H+ ions determines how much CO2 can be bound as HCO3- in the plasma. A decrease in the O2 saturation of hemoglobin as blood passes

through the tissue will increase the buffering capacity of hemoglobin as more H+ ions are bound to deoxygenated hemoglobin then oxyhemoglobin.

$HbO_2 \longleftrightarrow HbO_2^- + H^+$ where,

$HbO_2 \longleftrightarrow Hb^- + O_2$ allowing,

$Hb^- + H^+ \longleftrightarrow HHb$ to form.

HHb is a weak acid which buffers H+ ions formed during the dissociation of H_2CO_3.

Since the red blood cell membrane is relatively impermeable to cations, the diffusion of HCO_3^- out of the red blood cell creates an ionic imbalance in the red blood cell. Ionic neutrality is maintained within the red blood cell by an equivalent influx of Cl- ions into the red blood cell, known as the "Chloride Shift", (Ganong, 1977). The chloride shift permits rapid exchange of CO_2 in the red blood cell, which enables large amounts of HCO_3^-, formed in the red blood cell, to be carried by the plasma.

Arterial blood contains 47.3 ml of CO_2 /100 ml of blood, (2.2 ml dissolved, 2.2 ml as carbamino compound, and 42.9 ml as HCO_3^-). In the tissues, 3.7 ml of CO_2 /100 ml of blood is added, (0.4 ml in solution, 0.8 ml as carbamino compounds and 2.5 ml as

HCO3-). The pH of the venous blood decreases from approximately 7.40 to 7.36 promoting the release of O2 from hemoglobin, (Bohr Effect), and enhancing the transport of CO2 in the blood, (Haldane Effect). In the lungs, this process is reversed and 3.7 ml of CO2 /100 ml of blood diffuses into the alveoli, (200 ml of CO2 /min. during rest), (Boutnys, 1977; West, 1978).