FACTORS INFLUENCING VENTILATION, GAS EXCHANGE AND ARTERIAL BLOOD OXYGENATION DURING EXERCISE IN MAN


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Factors Influencing Ventilation, Gas Exchange and Arterial Blood Oxygenation During Exercise in Man.

1. At rest and during sub anaerobic steady-state exercise, alveolar and arterial carbon dioxide and oxygen partial pressures are maintained relatively constant by a ventilation which is proportional to both carbon dioxide output and oxygen uptake. Hypoxemia occurs in highly trained athletes at high work intensities. The magnitude of the fall in arterial oxygen tension is related to the degree of relative hypoventilation. Hypoxemia has also been observed following the onset of exercise. To test whether this is similarly related to the degree of hypoventilation 12 normal subjects performed a series of runs, of varying duration, at near maximal intensity, on an electrically driven treadmill. Ventilation and gas exchange variables were computed on a breath-by-breath basis. Arterial blood samples were drawn from the radial artery at regular intervals. Ventilation, oxygen uptake and carbon dioxide output all exhibited a typical three phase response. The kinetics of oxygen uptake were significantly faster than that of carbon dioxide output. The kinetics of ventilation and carbon dioxide output were virtually identical. Occurring simultaneously with the onset of phase II was a fall in ventilatory equivalent, end tidal oxygen partial pressure and arterial oxygen tension. In the first 2 minutes of exercise, there were significant correlations between these 3 variables. As exercise continued, arterial oxygen tension remained depressed while ventilatory equivalent and end tidal oxygen partial pressure returned to resting levels. This data suggests that larger gas stores for carbon dioxide than oxygen causes a kinetic disparity between oxygen uptake and carbon dioxide output following the onset of exercise. As ventilation is proportional to carbon dioxide output hypoventilation occurs with respect to oxygen uptake. This causes a fall in end tidal oxygen partial pressure and a concomitant fall in arterial oxygen tension. However, as exercise continues, an increasing dissociation of end tidal oxygen partial pressure and arterial oxygen tension occurs. This further suggests that factors other than hypoventilation also contribute to hypoxemia following the onset of exercise.

2. The degree of hypoventilation and hypoxemia occurring following the onset of exercise exhibits considerable individual variability. The extent
to which this is related to the mode of exercise and the frequency of limb movement was studied in 12 normal subjects. Six cyclists each performed an incremental test to maximum on a bicycle ergometer and a series of 2 minute constant load trials using 4 different combinations of load and pedal frequency. Six runners each performed an incremental test to maximum on an electrically driven treadmill and a series of 2 minute constant load trials using 2 different combinations of grade and stride frequency. In all of the incremental tests, ventilation and gas exchange variables were determined from mixed expired samples collected during the last 30 seconds of each 3 minute increment. In all of the 2 minute constant load trials ventilation and gas exchange variables were computed on a breath-by-breath basis. The relationships of ventilation to oxygen uptake and ventilation to carbon dioxide output were constant and independent of pedal frequency during cycling in both the non steady-state and steady-state. However, these relationships were significantly different when both cycling and running on a grade were compared with running on the flat. This was true in both the non steady-state and the steady-state. While running on the flat there was slight hyperventilation with respect to both oxygen uptake and carbon dioxide output, with a slight increase in end tidal oxygen and a slight fall in end tidal carbon dioxide partial pressure. While cycling and running on a grade there was a marked hypoventilation with respect to both oxygen uptake and carbon dioxide output with a large increase in end tidal carbon dioxide and a large fall in end tidal oxygen partial pressure. Entrainment of breathing frequency to movement frequency occurred for varying amounts of time in all subjects. Entrainment interfered with the normal breathing frequency. During running on the flat, a ventilation appropriate to the carbon dioxide output was achieved by compensatory changes in tidal volume. During running up steep grades and cycling with high loads, ventilation was compromised by entrainment of breathing to a lower than normal movement frequency, at a time when tidal volume had attained maximal exercise values. This caused significantly lower than normal ventilatory equivalents for oxygen and carbon dioxide, significant increases in end tidal carbon dioxide partial pressure and significant falls in end tidal oxygen partial pressure. This data suggests that the entrainment of breathing frequency to slow movement frequencies, in certain exercise modes, can cause hypoventilation and a fall in end tidal oxygen partial pressure. It is hypothesised that this in turn will be reflected in the arterial oxygen tension.
3. Sensitivity to carbon dioxide at rest correlates with steady state exercise ventilation. Exercise ventilation increases in proportion to carbon dioxide output in both the non steady-state and the steady-state. It is therefore likely that sensitivity to carbon dioxide at rest will also correlate with exercise ventilation in the non steady-state. The relationship between the resting hypercapnic response and ventilation was studied in 12 normal subjects while running and cycling at near maximal intensities. Sensitivity to carbon dioxide, expressed as the increase in ventilation per Torr increase in end tidal carbon dioxide partial pressure, was determined in all subjects at rest by rebreathing a gas mixture containing 5% carbon dioxide and 40% oxygen. To facilitate comparisons between individuals of different size, the relationship was expressed per m$^2$ body surface area. Ventilation and gas exchange variables were computed on a breath-by-breath basis. Ventilation was expressed per litre output of carbon dioxide. Occlusion pressure was also measured at regular intervals throughout the 2 minute trial and the relationship to ventilation examined. There were significant correlations between exercise ventilation and the resting hypercapnic response throughout nearly all of the 2 minute trials. No significant correlations were found between occlusion pressure and exercise ventilation. This data suggests that the individual variability in ventilation and the fall in end tidal oxygen partial pressure following the onset of exercise can, to some extent, be predicted from the resting hypercapnic response.
FACTORS INFLUENCING VENTILATION, GAS EXCHANGE AND ARTERIAL BLOOD OXYGENATION DURING EXERCISE IN MAN

GENERAL INTRODUCTION

A. Energy and Muscular Contraction

In man, work is done by the shortening of muscle. This is brought about in the myofibril of the muscle by the sliding of thin actin filaments in between thicker myosin filaments as a result of the formation of cross bridges (Needham 1971, Murray and Weber 1974). The energy required to achieve this is obtained by splitting of the high energy phosphate molecule, adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and phosphate (P$_j$).

ATP stores in the muscle are low and must be constantly replenished if contraction is to continue for an extended period of time. Two mechanisms are responsible for replenishing the ATP stores of the muscle.

1. **Phosphoryl Creatine (PC)** This exists in limited supply in the muscle and provides a rapidly available source of high energy phosphate. Phosphoryl creatine combines with ADP to form creatine (C) and ATP.

   \[ \text{PC} + \text{ADP} \rightarrow \text{C} + \text{ATP} \]  

2. **Oxidative Phosphorylation** This involves a series of reactions in which the energy obtained from the oxidation of various fuels is used in the resynthesis of ATP and PC from ADP, C and P$_j$.

   For carbohydrates (i.e. glucose):
   \[ \text{Glucose-6-P} + 6\text{O}_2 + 37\text{P}_j + 37\text{ADP} \rightarrow 6\text{CO}_2 + 37\text{ATP} + 6\text{H}_2\text{O} \]  

   Fats (i.e. free fatty acids) are first esterified with coenzyme A (Co A). For palmitic acid the equation is as follows:

   \[ \text{Palmitoyl Co A} + 23\text{O}_2 + 131\text{P}_j + 131\text{ADP} \rightarrow 16\text{CO}_2 + 131\text{ATP} + 146\text{H}_2\text{O} \]
These oxidative processes involve transfer of electrons to an electron acceptor, or oxidizing agent. The principal electron acceptor is nicotinamide adenine dinucleotide (NAD), which is thereby reduced to NADH. The hydrogen (H\textsuperscript{+}) of NADH is removed through two pathways. In the presence of oxygen (i.e. aerobic metabolism), electrons are transferred along the electron carrier chain to molecular oxygen:

\[
2\text{NADH} + 2\text{H}^+ + \text{O}_2 \rightarrow 2\text{NAD}^+ + 2\text{H}_2\text{O} \quad (4)
\]

In the absence of oxygen (i.e. anaerobic metabolism), H\textsuperscript{+} is accepted by pyruvate, formed from glycolysis, and lactate is produced:

\[
\text{Pyruvate} + \text{NADH} + \text{H}^+ \rightarrow \text{Lactate} + \text{NAD}^+ \quad (5)
\]

The relative yield of ATP molecules depends on whether aerobic or anaerobic processes are used and whether carbohydrates or fats are the fuel. The aerobic oxidation of either carbohydrates or fats are the processes of choice due to their greater yield of ATP and infinite capacity. The availability of oxygen determines whether the energy is derived aerobically or anaerobically. When oxygen delivery to the muscle is compromised, anaerobic processes are of particular importance. This occurs at the onset of exercise, due to the delayed adaptation of the oxygen transport system, and in high intensity exercise, when the energy demand exceeds the individuals ability to transport oxygen.

At rest, approximately 250 mls/min of oxygen is taken up by the blood. The carbon dioxide given out from the blood is usually slightly less (about 200 mls/min). The ratio of the carbon dioxide produced to the oxygen used during metabolism is the respiratory quotient (R.Q.). The R.Q. at any time is dependent only on the fuel being oxidized. From equations (2) it can be seen that for the aerobic breakdown of glycogen the R.Q. is \(6/6 = 1.0\). From equation (3) it can be seen that for the aerobic breakdown of palmitic acid (i.e. fats) the R.Q. is \(16/23 = 0.7\).

Anaerobic glycolysis itself does not contribute to the R.Q. of muscle. However, the lactic acid produced reacts with the bicarbonate of the tissue fluids to produce carbonic acid, which in turn dissociates to produce carbon dioxide. No additional carbon dioxide is being produced at the tissue, therefore the R.Q. has not changed. However, the total amount of
carbon dioxide evolved at the lungs increases. The ratio of carbon dioxide output to oxygen uptake at the lungs is known as the respiratory exchange ratio (R). R.Q. and R will differ during anaerobic metabolism and when the oxygen or carbon dioxide stores of the body are changing.

Diet, eating patterns and the intensity and duration of exercise are the most important factors determining the choice of fuels. At rest and during light exercise, equal usage of carbohydrates and fats occurs and the R.Q. is about 0.84. During short, high intensity exercise, carbohydrates become the fuel of choice and R.Q. increases towards 1.0. In moderate to low intensity exercise of long duration, fats are the preferred fuel and R.Q. decreases towards 0.7. A meal causes an increase in R.Q. due to inhibition of lipolysis in adipose tissue (Havel et al 1963, Jones and Haddon 1973).

B. The Pathway of Oxygen and Carbon Dioxide

In its passage from the air around us to the mitochondria of the active tissue, oxygen is transported via two systems and across two barriers. Carbon dioxide moves in the reverse direction. The two systems and two barriers are as follows:

1. The Respiratory System This consists of the upper respiratory tract which terminates at the trachea. The trachea subdivides into two main branches, the right and left main bronchi which supply the left and right lungs. The bronchi in turn divide in an effectively dichotomous fashion into lobar and segmental bronchi, then into numerous bronchioles which eventually terminate in blind pouches called alveoli. The trachea, bronchi and bronchioles make up the conducting airways and function to lead inspired air to the gas exchanging regions of the lung. They take no part in gas exchange and thereby constitute what is known as the anatomical dead space. The volume of the anatomical dead space is about 150 mls in the normal 70 kg man.

2. Blood Circulatory System Blood is pumped through the pulmonary system by the contractions of the right ventricle. The pulmonary artery after leaving the heart divides and enters the lungs. It then subdivides until ultimately blood flows through millions of short thin walled capillaries surrounding the alveoli. Blood returns to the left atria of the heart in the pulmonary vein. It then passes to the left ventricle from whence it is
pumped, via the aorta, to all the tissues of the body.

3. **Gas-Blood Barrier** Air is brought to the alveoli by the pumping action of the respiratory system. Blood is brought to the surrounding capillaries by the pumping action of the heart. The movement of oxygen into the venous blood depends on the diffusing capacity of lung tissues that separate the air and blood, the partial pressure of oxygen in the air and blood, and the chemical environment of haemoglobin. There are about 300 million alveoli in the two lungs of man, with diameters varying from 75 to 300 microns. The surface area of the alveolar membrane is large (about 50 to 100 m²) and exceedingly thin (about 1 micron). The surface area of the capillary bed is of a similar size. The thickness of the capillary wall is about 0.1 micron and the diameter of each vessel is about 10 to 14 micron. It is through these membranes that gas exchange occurs. The large surface area and thinness of the membranes ensures a high diffusion capacity and rapid movement of oxygen.

4. **Blood-Tissue Barrier** The unloading of oxygen in the tissue capillaries is similarly determined by the diffusing capacity of the peripheral tissues, the partial pressure of oxygen in the blood and the tissues, and the chemical environment of haemoglobin. Tissue cells continually use oxygen thereby lowering the partial pressure and ensuring an adequate pressure gradient. An abundance of capillaries ensures that diffusion distances are short. The lowering of plasma oxygen partial pressure and the uptake of carbon dioxide aid in the release of oxygen from haemoglobin.

5. **Oxygen Cascade** The transfer of oxygen from air to muscle, via the above pathway, and the movement of carbon dioxide in the reverse direction, can be considered as a series of cascades in which various mechanisms influence the differences in carbon dioxide and oxygen partial pressure at various sites. The fall in partial pressure, as oxygen moves through the pathway in the "perfect" lung, is presented in Figure 1.

At 1 atmosphere pressure, the partial pressure of oxygen in dry air is 20.9% of 760 = 159 Torr. As the air is inhaled it becomes saturated with water vapour at body temperature. The partial pressure of moist air is therefore 20.9% of (760-47) = 149 Torr. The partial pressure of expired air is about 16% of (760-47) = 114 Torr. This is less than that of moist inspired air due to the uptake of oxygen into the blood at the alveoli.
The partial pressure of oxygen in the alveoli depends upon the matching of airflow and blood flow. In a perfect gas exchanger, where the matching of airflow and bloodflow is entirely uniform, the partial pressure of oxygen is approximately 100 Torr. This is clearly much less than the partial pressure of inspired air. The partial pressure of oxygen in the arterial blood is the same as that in the alveolar (i.e. 100 Torr). Due to a number of factors (which are discussed in detail in section II) the partial pressure of oxygen in arterial blood of the "normal" lung is usually 5-10 Torr lower than that of the alveoli.

The partial pressure of oxygen in the peripheral tissues varies from place to place but is in general very low, perhaps as low as 1 Torr at the mitochondria. The partial pressure in mixed venous blood is about 40 Torr.

Throughout this pathway oxygen moves by diffusion from areas of high to low partial pressure. In a similar way carbon dioxide moves in the opposite direction. The partial pressure of carbon dioxide in the mixed venous blood, arterial blood, expired air and inspired air being approximately 70, 40, 34 and 0 Torr respectively.

Figure 1: The fall in oxygen partial pressure from air to the tissues in a "perfect" lung. In the "perfect" lung the alveolar gas and the arterial blood have the same oxygen partial pressure.
C. Ventilation and Alveolar Gas Homeostasis

The prime function of the lung is one of gas exchange. In simple terms the lung can be though of as a single gas filled compartment separated from the blood by the alveolar membrane. Oxygen moves from the air into the venous blood and carbon dioxide moves out from the blood to the air through this membrane.

1. Alveolar Gas Homeostasis The alveolar gas composition reflects the balance between the removal of oxygen and delivery of carbon dioxide in the mixed venous blood (i.e. perfusion) and the addition of oxygen and removal of carbon dioxide with each breath (i.e. alveolar ventilation). In the perfect lung at rest, the ratio of alveolar ventilation to perfusion (\(V_A/Q_c\)) is 1.0 (West 1974) and the alveolar gas partial pressures are maintained constant and equal to those of arterial blood.

In the normal individual at rest, ventilation-perfusion inequalities exist and the lung does not act in a perfect manner. However, despite the constantly changing metabolic demands of the body, as reflected in the oxygen uptake, mean oxygen and mean carbon dioxide partial pressures of both the alveoli and arterial blood remain virtually unchanged (Jones and Haddon 1973, Wasserman 1976, Oren et al 1981a, Phillipson et al 1981b). This is a reflection of how well ventilation is matched to the uptake of oxygen and the production of carbon dioxide at rest.

2. Alveolar Ventilation At rest approximately 5000 mls of inspired air is drawn into the alveoli per minute. This is known as the alveolar ventilation (\(V_A\)). If we assume the fraction of carbon dioxide in the inspired air to be zero, alveolar ventilation for a given carbon dioxide output (\(\dot{V}CO_2\)) can be defined by the mixed alveolar carbon dioxide concentration (\(FACO_2\)).

\[
\dot{V}_A = \dot{V}CO_2 / FACO_2
\]  

Or where carbon dioxide is expressed as a partial pressure:

\[
\dot{V}_A = \dot{V}CO_2 * K / PACO_2
\]  

In this equation \(K\) converts fractional concentrations to partial pressure.
and corrects ventilation to conditions at body temperature (BTPS): K is 0.863 when carbon dioxide output is expressed in ml/min STPD and ventilation in l/min BTPS, at a barometric pressure of 760 Torr and temperature 37°C.

3. **Total Ventilation** Total ventilation (VE), as recorded at the mouth, is the product of tidal volume (VT) and breathing frequency (f). At rest approximately 7500 ml/min of air is inspired at the mouth. Approximately 2300 mls of this does not reach the alveoli and therefore does not take part in gas exchange. This volume of gas is referred to as the dead space ventilation (VD). This includes both gas that resides in the conducting airways (i.e. anatomical dead space) and gas that resides in functionally inefficient alveoli. Together they constitute the physiological dead space. Dead space ventilation is usually expressed as a proportion of the total (i.e. VD/VT). VD/VT at rest is about 2300/7500 = 30%. This may be calculated using the Bohr Enghoff equation.

\[
\frac{V_D}{V_T} = \frac{P_{ACO_2} - P_{ACO_2}}{P_{ACO_2}}
\]

(8)

This equation assumes that arterial and alveolar carbon dioxide partial pressures are equal in the perfect lung and that any disturbances that increase the difference between arterial and alveolar carbon dioxide partial pressure will increase the dead space fraction (Jones 1984).

Ventilation is therefore the sum of both alveolar and dead space ventilation:

\[
\dot{V_E} = \dot{V_A} + \dot{V_D}
\]

(9)

From (7)

\[
\dot{V_E} = \frac{\dot{V}_{CO_2}}{P_{ACO_2}} + \dot{V_D}
\]

(10)

or

\[
\dot{V_E} = \frac{\dot{V}_{CO_2}}{P_{ACO_2}} \cdot \left(1 - \frac{V_D}{V_T}\right)
\]

(11)

Arterial carbon dioxide partial pressure is the closest "effective" estimate of ideal alveolar carbon dioxide partial pressure (Jones et al 1975). This is still only an approximation because even normal
inhomogeneity of ventilation-perfusion ratios will lead to differences in the partial pressure of carbon dioxide in the alveolar and arterial blood. However, the effect is usually small at rest (Riley and Cournard 1951).

Therefore:

\[ \dot{V}E = \frac{\dot{V}CO_2}{PaCO_2 \cdot (1 - VD/VT)} \]  

(12)

Carbon dioxide output, arterial carbon dioxide partial pressure and the ratio of dead space to tidal volume are the three determining variables of ventilation. Therefore, equation (12) describes the changes in ventilation necessary to maintain constancy of the partial pressures of arterial gases.

From this equation it can be seen that increasing ventilation, decreasing dead space ventilation or the ratio of dead space to tidal volume, or decreasing carbon dioxide output, will cause alveolar and arterial carbon dioxide partial pressure to fall and approach the partial pressure of inspired air (Jones et al 1977, Oren et al 1981a). Decreasing ventilation, increasing dead space ventilation or the ratio of dead space to tidal volume, or increasing carbon dioxide output, will cause alveolar and arterial carbon dioxide partial pressure to increase towards that of venous blood (Sackner et al 1980, Ward et al 1980, Wasserman 1978).

The converse is true for oxygen as oxygen uptake and alveolar oxygen partial pressure are related to carbon dioxide output and alveolar carbon dioxide partial pressure by the respiratory exchange ratio.

\[ \dot{VO}_2 = \frac{\dot{V}CO_2}{R} \]  

(13)

and

\[ PAO_2 = PIO_2 - PACO_2 + \frac{PACO_2 \cdot FI0_2(1-R)}{R} \]  

(14)

where \( PIO_2 \) is the partial pressure of oxygen in the inspired air. Equation (14) is known as the alveolar gas equation. It was derived by Riley and Cournard (1951) and enables ideal alveolar oxygen partial pressure to be calculated from \( R \) and alveolar carbon dioxide partial pressure at a known inspired gas composition.

The rate of ventilation is thus effectively coupled to the metabolic
activity of the cells. With any increase in cellular oxygen requirement and carbon dioxide production breathing must keep pace if alveolar and arterial gas tensions are to be maintained at resting levels. A failure to match ventilation to the metabolic activity of the cell will cause alveolar and arterial partial pressures of oxygen and carbon dioxide to deviate from normal values.

4. **Ventilatory Equivalent** The close correlation between ventilation and carbon dioxide output allows one to use the ratio of ventilation to carbon dioxide output to define normal ventilation. This ratio is called the ventilatory equivalent. The ventilatory equivalent for carbon dioxide (VE/VCO₂) is normally about 26 litres per litre (D'Urzo et al 1987). Lesser values indicate hypoventilation with respect to carbon dioxide production and will result in an increase in alveolar partial pressure. Greater values indicate hyperventilation with respect to carbon dioxide production and will result in a decrease in alveolar partial pressure.

Similarly, there is a close correlation between ventilation and oxygen uptake. The ventilatory equivalent for oxygen (VE/VO₂) is normally about 24 litres per litre (D'Urzo et al 1987). Lesser values indicate hypoventilation with respect to oxygen uptake and will result in a decrease in alveolar partial pressure. Greater values indicate hyperventilation with respect to oxygen uptake and will result in an increase in alveolar partial pressure.

D. **Control of Ventilation at Rest:**

1. **Respiratory Centre** - The rhythmicity of inspiration and expiration is controlled by neurons located in the reticular formation of the medulla. Interaction between two cell types within this centre are apparently responsible for the inherent rhythmicity of the centre (West 1974). This inherent rhythm is itself modified by impulses impinging upon it. Cortical factors along with reflexes from chemoreceptors, the lung, chest wall and arterial baroreceptors constitute the main inputs to the respiratory centre (see Section I for detailed discussion).

2. **Chemoreceptors** - Chemoreceptors are structures which respond to changes in the chemical composition and partial pressure of gases in the blood or other fluid around it. These variations are then encoded into neural
information and passed to the respiratory centre. The main chemoreceptors are located centrally on the ventral surfaces of the medulla near the exits of the 9th and 10th cranial nerves and peripherally in the carotid bodies, which lie in the bifurcation of the common carotid artery, and in the aortic bodies which lie above and below the aortic arch.

Chemoreceptors have an extremely high metabolic rate and a high blood flow per unit mass (Biscoe 1971). Two cell types are evident: Type I and Type II. Sensory nerves are closely associated with both cell types. It is the sensory nerves that are thought to be the transducers with the cells functioning to modulate their activity (Osborne and Butler 1975).

3. **Response to Stimuli** At rest, direct proportional control of ventilation occurs. Changes in pH and the partial pressure of oxygen and carbon dioxide in the arterial blood are detected by the chemoreceptors. The resulting signals from the chemoreceptors induce compensatory changes in ventilation. If the pH falls, the partial pressure of oxygen decreases, or the partial pressure of carbon dioxide increases, then ventilation increases. Conversely, if the pH rises, the partial pressure of oxygen increases, or the partial pressure of carbon dioxide decreases, then ventilation decreases

(a) **Hypercapnia** - Carbon dioxide is the most important stimulus in the control of ventilation. The stimulation to the increase in ventilation during hypercapnia is mediated primarily through the central medullary receptor with only minor contributions from peripheral arterial chemoreceptors (Heeringa et al 1979). The contribution of the peripheral chemoreceptors apparently increases with the degree of simultaneous hypoxia and during exercise (Schlaefke 1981, Jeyaranjan et al 1987).

(b) **Hypoxia** - Ventilation increases in acute hypoxia (Asmussen and Neilsen 1957, Hornbein and Roos 1962, Flenley et al 1979). This increase is due mainly to an increase in peripheral arterial chemoreceptor input (Hornbein and Roos 1962). The ventilatory response to hypoxia is considered to be faster than the response of ventilation to hypercapnia (Gardner 1980).

(c) **Metabolic acidosis** - Lactic acid (HLa) production during anaerobic metabolism contributes to an increase in ventilation in two ways. It leads to an increase in arterial carbon dioxide partial pressure, and hence
output, and it adds \([H^+]\), an independent ventilatory stimulus. The acid
base status of the body is represented by the application of the law of
mass action to the equation:

\[
HLa \rightleftharpoons H^+ + La^- 
\] (15)

\[
H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2 + H_2O 
\] (16)

\[
[H^+] = K \text{PCO}_2/[HCO_3^-] 
\] (17)

Equation (17) indicates that there is a linear relationship between \([H^+]\)
and PCO\(_2\). In metabolic acidosis there is an increase in \([H^+]\).
Physiological compensation depends on alterations in partial pressure of
carbon dioxide as a result of changes in ventilation, resulting in turn
from changes in the \(H^+\) stimuli.

The acute response to acidosis is mediated via the peripheral chemore­
ceptors. A decrease in pH has been shown to increase carotid sinus nerve
activity and increase ventilation (Gray 1968). No hyperventilation in
response to increased \([H^+]\) is observed in patients with carotid body
resection (Whipp and Wasserman 1969). The minor role played by central
receptors is probably due to the slow rate at which metabolic acids cross
the blood brain barrier (Wasserman et al 1975a).

E. Conclusions

The functioning of all living cells is dependent upon a constant supply of
oxygen and the removal of carbon dioxide. This in turn is dependent upon
the matching of ventilation to the uptake of oxygen and the removal of
carbon dioxide. The importance of carbon dioxide in the control of
ventilation is reflected in the close correlation between ventilation and
carbon dioxide output.

In the normal individual, under resting conditions, the uptake of oxygen
and the removal of carbon dioxide is accomplished with minimal demands
being placed upon the respiratory and cardiovascular systems. More over,
the control of ventilation is such that the partial pressures of oxygen and
carbon dioxide in the alveolar and arterial blood are maintained remarkably
constant, with in strict limits. The question arises as to whether these
control mechanisms are sufficient to both meet the metabolic demands of the tissue and also maintain constancy of gas tensions in the alveolar and arterial blood during both steady-state and non steady-state exercise.

To investigate further the relationship between ventilation and gas partial pressures in the alveoli and arterial blood, gas exchange and arterial blood gases were measured in human subjects during both steady-state and non steady-state exercise. The results of this study are reported in four sections.

Section I: This documents the changes in ventilation and gas exchange that occur following the onset of exercise.

Section II: This relates the changes in arterial gas contents that occur following the onset of exercise to the changes in ventilation and gas exchange.

Section III: This examines the effect of exercise mode and the entrainment of breathing frequency to limb movement frequency on ventilation and gas exchange during both steady-state and non steady-state exercise.

Section IV: This looks at the relationship between resting chemosensitivity to carbon dioxide, respiratory drive and ventilation in non steady-state exercise.
SECTION I

VENTILATION AND GAS EXCHANGE
DURING NON STEADY-STATE EXERCISE

INTRODUCTION

A. Steady-State Exercise:

Steady-state exercise is aerobic exercise in which the energy requirements are met totally by the oxygen that is taken up at the mouth. The oxygen uptake and carbon dioxide output at the mouth are therefore the same as that in the tissue, the gas stores of the body are unchanging and R equals RQ (Farhi and Rahn 1955). During steady-state exercise, oxygen uptake, ventilation, cardiac output and heart rate have typically stabilized and remain essentially constant as long as the exercise is continued.

1. Oxygen Uptake In the steady-state, with increasing exercise intensity, there is a proportional increase in oxygen uptake. This relationship is linear up to high intensities of exercise. Eventually a point is reached where further increases in exercise intensity produce no further increase in oxygen uptake. This constitutes the individual's maximal oxygen uptake. The maximal oxygen uptake reflects the individual's ability to transport oxygen, produce energy aerobically and perform high intensity physical work.

In high intensity exercise, oxygen needs can increase more than 10 fold compared to resting conditions. Maximal oxygen uptakes in young males average 3.4 l/min while values in excess of 6 l/min have been observed in endurance trained athletes (Astrand and Rodhal 1970). Carbon dioxide output increases proportionally.

The relationship between the uptake of oxygen and the output of the heart is expressed by the Fick equation

\[ \dot{V}O_2 = Q \times (CaO_2 - CvO_2) \]  

Where Q is the cardiac output and CaO$_2$ and CvO$_2$ are the oxygen content of arterial and venous blood respectively. Oxygen uptake can therefore
increase through either increases in cardiac output, increases in arterio-venous oxygen content difference, or a combination of both.

Cardiac output has been shown to increase proportionally with increases in oxygen uptake during exercise of moderate to high intensities (Faulkner et al 1977). This relationship is consistent within subjects but shows considerable intersubject variability, due mainly to differences in resting cardiac output (Yamaguchi et al 1986). This relationship suggests that the arterio-venous oxygen difference remains unchanged during moderate to high steady-state exercise and that changes in oxygen uptake result only from changes in cardiac output.

2. **Ventilation** At low to moderate exercise intensities ventilation increases in proportion to both oxygen uptake and carbon dioxide output. Eventually, as exercise intensity is increased a point is attained above which ventilation increases faster than oxygen uptake (Wasserman et al 1967, Hagan and Smith 1984). This point has generally been termed the anaerobic threshold and occurs at about 60% of the maximal oxygen uptake (Davis et al 1976). The increase in ventilation at this point is traditionally thought to be due to two phenomena which act to stimulate ventilation. Firstly, metabolic acidosis causes an increase in blood $[\text{H}^+]$. Secondarily, buffering of lactic acid causes an increase in carbon dioxide production.

At very high work intensities, or where heavy work is continued for an extended period of time, ventilation increases out of proportion to not only oxygen uptake but to carbon dioxide output as well. Under these conditions increases in body temperature, increases in catecholamines and arterial hypoxemia may occur and contribute to the increase in ventilation (Dempsey et al 1980, Martin et al 1979).

3. **Alveolar and Arterial Gas Partial Pressures** At work loads below the anaerobic threshold the alveolar and arterial partial pressures of oxygen and carbon dioxide are typically maintained at, or about, resting levels by changes in ventilation proportional to the rate of oxygen uptake and carbon dioxide output (Eisle et al 1967, Wasserman et al 1967, and Whipp 1981). Due to the constancy of the arterial carbon dioxide partial pressure this is termed the "period of isocapnic buffering" (Wasserman et al 1977a).
The ventilation during exercise above the anaerobic threshold is still proportional to the carbon dioxide production. Alveolar and arterial carbon dioxide partial pressures are therefore still regulated at resting levels. However, since the rate of oxygen uptake retains its linear relation to work, the lung is hyperventilating with respect to oxygen. The ventilation is therefore above that required to maintain alveolar oxygen tension constant and it subsequently increases (Margaria et al 1933, Owles 1930, Wasserman et al 1973).

At high work intensities, when the ventilation also increases out of proportion to the carbon dioxide output, alveolar and arterial carbon dioxide partial pressures are driven down to constrain the fall in pH and maintain the acid base status of the blood (Wasserman et al 1977a, Wasserman and Whipp 1975).

B. Non Steady-State Exercise:

Non steady-state exercise is exercise in which the energy requirements are not met fully by the oxygen that is being taken in at the mouth. The balance of energy is provided from oxygen stores and by anaerobic mechanisms. Because the gas stores are changing R will not equal RQ. During non steady-state exercise, oxygen uptake, ventilation, cardiac output and heart rate are typically changing and continue to do so until the steady-state is attained or the exercise is terminated.

1. Oxygen Uptake The energy requirement of the muscle at the onset of exercise is proportional to the steady-state oxygen consumption i.e. the oxygen uptake that would be achieved if the work load was maintained for a long enough time for a constant value to be attained. At the onset of exercise, oxygen uptake as measured at the mouth, lags behind the energy requirements of the muscle due to the slowness in the adaptation of the cardiovascular system. As a consequence an oxygen deficit is incurred during the first minutes of exercise. This deficit is a measure of the amount of energy drawn by the working muscle from sources other than oxidative phosphorylation derived from the oxygen uptake through the mouth. These sources comprise the net high-energy phosphate breakdown, lactate production and the depletion of oxygen stores in the lung, blood and tissue.
Oxygen Uptake Kinetics in Moderate Exercise

Initially, interest in the time course of oxygen uptake was focused on the recovery period because of its relationship to the oxygen deficit (Berg, 1947). The time course of oxygen uptake at the onset of exercise was first extensively studied by Henry (1951) and Henry and De Moor (1956). Oxygen consumption in exercising muscles responds to constant load work as a single exponential function (Kushmerick and Paul 1976, Mahler 1978, Piper et al 1968, Whipp and Mahler 1980, Mohrman et al 1973). Early attempts to characterize the oxygen uptake response at the onset of exercise also implied a single exponential function. Studies by Margaria et al (1965), Cerretelli et al (1966b), Bason et al 1973, Davies et al 1972, Margaria (1967), Di Prampero et al 1970, Whipp (1971), Diamond et al 1977, Weltman and Katch (1976), Cerretelli et al 1977, and Hagberg et al (1978) have all revealed a mono-exponential increase in oxygen uptake from rest to steady-state. As long as the work rate was below the anaerobic threshold, the adjustment in oxygen uptake was complete within 2 minutes with a half time of approximately 30-35 seconds.

With the advent of breath-by-breath techniques, three discrete phases in the oxygen uptake response to constant load work have come to be recognized (Whipp and Wasserman 1972, Linnarsson 1974). Ventilation, following the onset of exercise, exhibits a similar three-phase response (see Figure 2).

**Phase I** This is characterized by a rapid initial increase and a subsequent plateauing which lasts for 15-20 seconds after the onset of exercise. This was first recorded by Auchincloss et al (1966). Phase I contributes to approximately 40% of the total increase in oxygen uptake in subjects working just below their anaerobic threshold (Whipp et al 1982). Linnarsson (1974) found Phase I to account for 50% of the change in light exercise and 35% in moderate exercise, suggesting that the increase is constant and independent of the work intensity. As the intensity of work increases, the phase I increase becomes an ever decreasing percentage of an increasing steady-state oxygen uptake.

**Phase II** This is the secondary exponential rise in oxygen uptake. In light and moderate exercise, it was completed within 90-120 seconds. The Phase II response is significantly longer when the work rate is above the subjects anaerobic threshold compared with transitions below it. Oxygen uptake continues to change slowly well after the second minute of exercise.

**Phase III** This is the sum of phase I and phase II and in exercise below the anaerobic threshold constitutes the steady state response.

The slow increase in oxygen uptake in stage III that occurs during work loads above the anaerobic threshold has been attributed by Henry (1951) to the increased liver metabolism associated with the removal of lactic acid from the blood. This contention is supported by recent work of Whipp and Wasserman (1986). However, Hagberg et al (1978), in working subjects at 80% of maximum, observed a rise in oxygen uptake but no change in plasma lactate concentration.

The increase in oxygen uptake could be accounted for by an increase in temperature and by the increased metabolic costs of the increase in ventilation. This was supported by the work of Dempsey and Riddan (1976) who have shown that eliminating the rise in core temperature during exercise eliminates the continued rise in oxygen uptake. On the contrary, the slow rise in oxygen uptake observed by Linnarsson (1974) was too large to be accounted for by the metabolic cost of the increase in ventilation that took place at the same time (Hughes et al 1968). Wasserman et al (1967) contended that the increase in oxygen uptake reflected a delay in the adaptation of the cardio-vascular system needed to cover the energy cost of the working muscle. The fact that heart rate and cardiac output in heavy exercise also increase continually throughout phase III further supports this assumption.

(b) **Relationship Between Oxygen and Cardiovascular Kinetics** In the non steady-state the relationship between the uptake of oxygen and output of the heart is also expressed by the Fick equation. Increases in oxygen uptake are similarly achieved by increases in either cardiac output, increases in arterio-venous oxygen content difference, or a combination of both.

**Phase I** The initial increase in oxygen uptake is thought to be the consequence of a sudden increase in cardiac output (Krough and Lindgard 1913, Wasserman et al 1974, Linnarsson 1974, Whipp and Mahler 1980, Taylor et al 1987) occurring prior to any change in arterio-venous oxygen tension.

If the initial increase in oxygen uptake is dependent on cardiac output Gilbert et al (1966) postulated that the kinetics of oxygen uptake should be changed significantly by altering the magnitude of the speed of response of cardiac output, but should be relatively insensitive to changes in ventilation. This was confirmed by Auchincloss et al (1966) who found that varying the ventilatory pattern by changing tidal volume at fixed frequencies had no effect on the kinetics of oxygen uptake.

Wasserman et al (1981) found that when ventilation was constrained to resting levels, the alveolar carbon dioxide partial pressure increased and the alveolar oxygen partial pressure decreased within the first exercise breath. Similarly, exercise started during a prolonged expiration caused an immediate fall in alveolar oxygen partial pressure and an increase in carbon dioxide partial pressure. Mixed venous oxygen tension would not have changed in such a short time, therefore an increase in arterio-venous oxygen difference would not be expected. Cardiac output must have increased in proportion to oxygen uptake. Furthermore, the magnitude of the initial oxygen uptake did not vary as a function of work rate, suggesting that the initial increase in cardiac output at the start of exercise is unaffected by work rate. Work rate dependent changes in cardiac output and oxygen uptake occur later in time when mixed venous gas tensions start to reflect the muscle metabolic rate.

**Phase II** Increases in cardiac output also contribute to the phase II increase in oxygen uptake. However, most of the increase is due to an increase in arterio-venous oxygen difference resulting from the appearance in the lung of venous blood with a lowered partial pressure of oxygen (Asmussen 1965, Krough and Lindgard 1913, Weissman et al 1982, Whipp and Ward 1985). The 15-20 second time delay in the onset of Phase II corresponds to the transit time of blood from the working muscle to the lung. The secondary phase II response is therefore thought to be humorally mediated (Asmussen 1965, Cunningham 1974a, Dejours 1964).

Cardiac output is the product of heart rate and stroke volume. Opinions
have differed as to the significance of changes in heart rate and stroke volume in contributing to the increase in cardiac output, and hence oxygen uptake, at the onset of exercise.

**Stroke Volume** In the first 15 seconds some increase in stroke volume could be expected (Saltin et al. 1970). The approximate doubling of stroke volume at the onset of exercise was observed by Loeppky et al. (1981). In supine exercise it is generally accepted that stroke volume remains constant and increases in cardiac output result from increases in heart rate alone. Jones et al. (1970) showed that in the transition from rest to exercise in the supine position the time course in change of oxygen uptake and heart rate were practically identical. Similar time constants for oxygen uptake and heart rate have also been observed in upright work (Lennarsson 1974) and sinusoidal work (Casaburi et al. 1977). This suggests, that under these conditions, stroke volume doesn’t change and that changes in heart rate alone are responsible for the increase in cardiac output.

**Heart Rate** Beat by beat registration of heart rate has identified a two phase increase following the onset of exercise. An initial rapid increase is followed by a secondary slower increase (Broman and Wigertz 1971, Karlsson et al. 1975, Lennarsson 1974, Wigertz 1971). A transient levelling off, or even decrease, in heart rate has been observed between the two phases (Beaver and Wasserman 1968, Fujihara et al. 1973a, Karlsson et al. 1975, Lennarsson 1974).

A latency of about 0.5 seconds has been shown to occur between the initiation of muscular contraction and the first detectable change in heart rate (Petro et al. 1970). The rapidity of this response suggests primary neural control. Peripheral reflexes from working muscles (McCloskey and Mitchell 1972, Coote et al. 1971, Pauley 1971), radiation to the vasomotor centres (Freyschuss 1970, Goodwin et al. 1972) and reflex mediation by arterial baroreceptors are some of the possible mechanisms.

The rapid increase in heart rate is not changed by beta blockers and therefore it is not mediated by an increase in sympathetic activity (Fagreus and Lennarsson 1976). A decrease in the initial heart rate response by blocking of the parasympathetic system with atropine would support the claim that the initial changes in heart rate are effected through the withdrawal of vagal tone (Craig and Cummings 1963, Freyschuss
The slower secondary increase in heart rate occurs at about the time of the onset of the phase II ventilatory component, suggesting that it may be linked to some blood borne signal. The secondary increase in heart rate has also been linked to an increase in sympathetic activity (Maciel et al 1986). Concomitant to this secondary increase in heart rate is a slow increase in cardiac output (Jones et al 1970).

2. Ventilation A three phase response, similar to that of oxygen uptake, has been found by most researchers (Bennett and Fordyce 1985). It consists of an immediate increase at the start of exercise then a plateauing for 15-20 seconds, a slower secondary increase to steady-state and a steady-state level (Figure 2).

Figure 2 Schematic representation of the time course of ventilation at the onset of exercise. The abbreviations I, II, and III represent the three phases of the ventilatory response.
Phase I - Wasserman (1978), Jensen et al (1971), Whipp (1983), Bledsoe (1981), Jensen (1972), Pearce and Milhorn (1977), Dejours (1959), Matell (1963), Linnarsson (1974), Bledsoe and Hornbein (1981) and Greco et al (1978) have all observed the phase I ventilatory response. It begins within the duration of half a breath. The changes occur if initiated in either inspiration or expiration and effect both rate and depth of breathing (Jensen et al 1972, Paulev 1971, Ward 1979, Greco et al 1986). The magnitude of the response varies considerably. In some studies this variability was related to the load (Asmussen and Nielsen 1948, Dejours et al 1961, Jensen et al 1971, Pearce and Milhorn 1977). In moderate work the magnitude of the phase I response constituted up to 50% of the total ventilatory response (Dejours 1963a). In heavier work it was a lesser fraction of the total (Bledsoe and Hornbein 1981). These findings support the concept of a tension feedback from the exercising limbs as a source of the phase I response signal (Asmussen 1973). Others found the magnitude of the phase I response in ventilation to be relatively constant and unrelated to the work load (Dempsey et al 1985, Jensen 1972, Whipp 1983). The fact that subjects can consciously affect the size of the first breath of exercise may explain the disagreement about the effect of work load on the phase I ventilatory response.

Beaver and Wasserman (1968) found the magnitude of the response varied among subjects and in some subjects the change was slow and only occurred after an initial delay. Fujihara et al (1973b) found a greater response following an impulse work change than following a step change in work. It therefore seems that both intra-individual differences and the choice of work profile as well as the work intensity are of importance in determining the magnitude of the response. It has also been suggested that phase I may be due to conditioning, for when cued by a preparatory warning, ventilation changes were found to frequently precede the actual onset of exercise (Torelli and Brandi 1961, Beaver and Wasserman 1970).

Phase II - This occurs some 10-20 seconds after the onset of exercise and just prior to an increase in alveolar carbon dioxide partial pressure (Fujihara et al 1973b). It appears likely that carbon dioxide, or some other metabolite released in the exercising limbs, must reach a central location where receptors are stimulated. In low work rates phase II is relatively short and ventilation reaches steady-state within 3 minutes. At higher work rates additional stimuli (possibly an increase in \([H^+]\)),
continue to stimulate ventilation prolonging phase II. Alveolar oxygen partial pressure increases as part of the respiratory compensation for the metabolic acidosis.

Phase III - The phase III ventilatory response during sub anaerobic threshold exercise represents the steady-state response. The response of ventilation in relation to oxygen uptake and carbon dioxide output has been discussed above.

3. Alveolar and Arterial Gas Partial Pressures In order to maintain constant the partial pressures of oxygen and carbon dioxide in the alveoli and arterial blood at the onset of exercise the rate of change of ventilation must match the rate of change of both oxygen uptake and carbon dioxide output.

During phase I ventilation increases in proportion to oxygen uptake and carbon dioxide output and there is relative constancy of alveolar and arterial partial pressures for both oxygen and carbon dioxide. During phase II oxygen and carbon dioxide change at different rates. As both cannot be matched to ventilation changes in alveolar partial pressures occur. These changes are discussed in detail below. The changes in ventilation and alveolar gases occurring during phase III are the same as that in the steady-state. This is discussed in detail above.

C. Control of Ventilation During Exercise

1. Chemoreceptors - Many investigators have suggested that arterial gas tensions and pH remain too close to resting values during moderate steady-state exercise to account for the changes in ventilation (Asmussen 1967, Cunningham 1967, Dejours 1967) thereby ruling out the possibility of simple proportional control of ventilation mediated via the chemoreceptors. This is further supported by the fact that ventilation in steady-state exercise is relatively normal in hyperoxia (Asmussen and Nielsen 1958, Wilson and Welch 1975, Casaburi et al 1980, Jeyaranjan et al 1987) and in carotid body resected subjects (Lugliani et al 1971).

By contrast, there is also evidence supporting the involvement of chemoreceptors in the normal ventilatory response to moderate steady-state exercise (Ward et al 1987). Hornbein and Roos (1962) showed that the
ventilatory equivalent for oxygen during light exercise increased from 23 to 29 litres/litre when breathing 13-14% oxygen. Dejours (1963a), Stockley (1978), and Whipp (1981) all found that subjects responded to surreptitious substitution of oxygen for air. Also, in heavy exercise, the increase in ventilation that is thought to provide respiratory compensation for the acidosis does not occur in hyperoxia or in carotid body resected patients (Wasserman et al 1975a, Whipp and Wasserman 1980).

The role of the chemoreceptors in the Phase I hyperpnoea of non steady-state exercise is conflicting. Asmussen (1973) and Casaburi et al (1980) found that the ventilation kinetics were slowed by hyperoxia whereas the normal increase in cardiac output and heart rate persisted. Conversely, others have found that neither hypoxia (Cunningham 1974b), carotid body resection (Whipp 1981, Wasserman et al 1975b), hyperoxia (Dejours 1963b), hypercapnia (Ward 1979) nor cuff occlusion (Asmussen et al 1943) affect the phase I hyperpnoea. Similarly, Gardner et al (1986) could find no significant differences in the kinetics of heart rate, oxygen uptake, carbon dioxide output or ventilation in recovery from exercise in hypoxia.

There is considerable support for the role of the carotid bodies in phase II. Hyperoxia delayed the onset of phase II and decreased its kinetics (Cunningham et al 1968, Linnarsson 1974, Cunningham 1974b, Casaburi et al 1978a, Griffiths et al 1980). Induced acidosis decreased and induced alkalosis increased the half time of the phase II increase (Oren et al 1981b). Subjects with bilateral carotid body resection decreased phase II kinetics in moderate exercise despite the amplitude of both phases being similar to controls (Wasserman et al 1975b). Phase II kinetics were also increased by hypoxia (Griffiths et al 1980).

If moderate steady-state exercise is isocapnic simple proportional control by arterial carbon dioxide partial pressure and pH is not possible. Other carbon dioxide linked control mechanisms have therefore been proposed.

(a) Oscillation Hypothesis - Although arterial carbon dioxide partial pressure and pH remain essentially constant during light to moderate exercise (Wasserman et al 1967) and blood flow shows little respiratory fluctuation (Kawakami et al 1970), exercise increases the rate of oxygen and carbon dioxide exchange in the lung (Cochrane et al 1982, DuBois et al 1952, Jones et al 1966, Allen and Jones 1984) and the fluctuations in
alveolar gas composition (Band et al 1969a, 1969b, Kreuzer 1975, Band et al 1980). Yamamoto and Edwards (1960) proposed that changes in the rate of exchange of alveolar carbon dioxide and the amplitude of oscillations in arterial carbon dioxide partial pressure during exercise, in the absence of changes in mean arterial carbon dioxide partial pressure, might provide feed forward stimulation to regulate ventilation. This work was further supported by Biscoe and Purves (1967a, 1967b), Black and Torrance (1971), Goodman et al (1974) and Plass-Link et al (1978) who found similar oscillations in the output of the carotid bodies.

(b) Disequilibrium Theory Carbonic anhydrase, present in the red blood cell but not the plasma, catalyzes the hydration of carbon dioxide to carbonic acid in the blood.

\[
\text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \tag{2}
\]

This reaction continues in the venous plasma and systemic arteries with a 90% response time in excess of 1 minute. Transit time to the carotid bodies and central chemoreceptors are 4-6 and 8-10 seconds respectively (Millar et al 1974). Samples of arterial blood which are collected in a syringe and subsequently analysed for carbon dioxide and pH will evidence the equilibrium values of these variables. The partial pressure of carbon dioxide will be higher and [H\text{+}] lower than that sensed by the chemoreceptors. These differences could be significant during exercise owing to both the increased blood flow and higher mixed venous to arterial difference.

2. Carbon Dioxide Flow A close correlation between ventilation and carbon dioxide output has been observed in humans during cycling (Davis et al 1980) and running (Flenley et al 1979). This close correlation between ventilation and carbon dioxide output has suggested a causal linkage. Yamamoto and Edwards (1960) first proposed that carbon dioxide flow to the lung was the primary stimulus to ventilation. This led to the carbon dioxide flow hypothesis (Wasserman et al 1977b). This postulates that receptors sensitive to carbon dioxide flow to the lungs might control ventilation precisely and thereby maintain arterial isocapnia. In support of these arguments they have further cited that, alveolar carbon dioxide partial pressure and pH remain unchanged in the transition from rest to exercise, isocapnic hyperpnoea occurs in the steady-state, and a reduction

The stimuli for such a mechanism have not been conclusively verified. A number of possibilities have been proposed, including a possible role of the peripheral chemoreceptors. Changes in carbon dioxide kinetics lead those of ventilation (Casaburi et al 1978b) providing a small arterial carbon dioxide error signal downstream from the pulmonary capillaries. This could provide a stimulus to peripheral chemoreceptors to increase ventilation. Coupling of carbon dioxide output and ventilation is interfered with in hyperoxia (Casaburi et al 1980, Griffiths et al 1980) and in carotid body resected subjects (Wasserman et al 1975) both providing further evidence that ventilation-carbon dioxide coupling in the non steady-state is influenced by the carotid bodies.

Large carbon dioxide stores in the body mean that carbon dioxide produced in the muscle is greater than that delivered to the lungs. It is the flow of carbon dioxide to the lungs to which ventilation is coupled (Whipp 1981). It is therefore unlikely that the muscles are the site of chemoreception. Also, Brown et al (1976), by injecting propanolol during exercise, rapidly decreased heart rate and cardiac output thereby decreasing the carbon dioxide flux to the lung. Ventilation subsequently decreased despite the fact that carbon dioxide production in the muscle would be maintained, if not increased.

Evidence for the existence of venous chemoreceptors has been provided in newborn animals (Kollmeyer and Kleiman 1975). They have also been postulated in the rabbit (Linton et al 1976), cat (Ponte and Purves 1978) and dog (Yamamoto and Edwards 1960, Greco et al 1978, Fordyce and Grodins 1980, Bennett et al 1984). However, no such mechanisms are suggested in humans (Cropp and Comroe 1961, Storey and Butler 1963).

Evidence for cardiac or pulmonary mechanoreceptors comes from a variety of workers (Kan et al 1979, Uchida 1976, Kostreva et al 1979, Ledsome 1977, Huszczuk et al 1981). Sheldon and Green (1982), Green and Sheldon (1983), and Green and Schmidt (1984) demonstrated that increases in pulmonary artery carbon dioxide tension or pulmonary blood flow can produce increases in ventilation in dogs. This response is mediated via the phrenic nerve.
However, Clifford et al (1986) found that denervation of these receptors changed only the rate of breathing and not the ventilation. Receptors responding to ventricular pressure have been demonstrated by Jones et al (1982) and Lloyd (1986). Pulmonary receptors, sensitive to carbon dioxide, have also been demonstrated in the avian lung (Burger et al 1974, Beon et al 1980), the rabbit, (Trenchard et al 1984), cat (Delpierre et al 1981) and the dog (Banzell et al 1978, Russell et al 1984).

Correlations between ventilation and carbon dioxide have been found extensively in the steady-state and by a number of workers in the non steady-state (Wasserman and Whipp 1983). However, such correlations are not proof of a causative relationship. The only valid test of the role of carbon dioxide flow is to be found in its experimental manipulation under carefully controlled conditions. However, even when the carbon dioxide flow is manipulated the ventilation response may not be linked specifically to the change in flow. There may be an accompanying change in arterial carbon dioxide tension that is sufficient to explain the observed ventilatory response on the basis of conventional chemoreception.

Also, the time lag between the arrival of hypercapnic blood at the lungs and the onset of the ventilatory response, following the release of peripheral occlusion, suggests that the response is to humoral stimuli mediated by receptors down stream of the lung and not to changes in cardiac output mediated by pulmonary receptors (Stanley et al 1985 and 1987). This confirms the findings of Sylvester et al (1973), Gonzalez et al (1977) and Hilderbrant et al (1979) and is contrary to the concept of the carbon dioxide flow hypothesis.

3. Other Humoral Factors

(a) Hydrogen Ion Concentration An increase in \([H^+]\) is a recognized stimulus to ventilation at rest, however there is much conflicting evidence as to the importance of \([H^+]\) as a stimulus to changes in ventilation during exercise (Roston et al 1987).

Hyperventilation may occur without stimulus from increased \([H^+]\). Patients with muscle phosphorylase deficiency and blocking of glycogenolysis (McArdles syndrome) show a hyperventilatory response to heavy exercise despite the absence of metabolic acidosis (Hagberg et al 1982). In other
cases, hyperventilation may not occur despite the presence of clearly sufficient chemical stimuli. If the work rate increment is 1 minute or less, ventilation increases in proportion to carbon dioxide output, as for sub anaerobic threshold work, and there is no respiratory compensation despite substantial increases in \([H^+]\) (Casaburi et al 1976, Wasserman et al 1977a). Similarly, at high work rates, in some trained athletes, there is an actual hypoventilation despite high blood \([H^+]\) (Dempsey et al 1985). Furthermore, Farrell and Ivy (1987) found a normal linear ventilatory response in incremental exercise even with elevation of \([H^+]\) by prior exercise.

(b) **Temperature** Significant increases in core body temperature can increase ventilation. This effect is probably partially mediated via the carotid bodies (Cotes 1955, Cunningham and O'Riordan 1957). Changes in body temperature during moderate exercise are small and do not appear to influence the ventilatory response. However, during prolonged exercise, significant increases in body temperature occur. They may influence ventilation via carotid body stimulation (Henry and Bainton 1974).

c) **Catecholamines** Infusion of norepinephrine increases ventilation at rest (Cunningham 1963). Plasma norepinephrine and epinephrine levels rise in exercise (Christensen et al 1979). Norepinephrine increases in proportion to exercise intensity (Flandrois et al 1977) and rises to plateau at about 10 times resting levels in prolonged exercise (Ahlborg and Felig 1982). Norepinephrine levels and ventilation are also higher during hypoxia than when breathing air (Clancey et al 1975). These observations support the notion that norepinephrine can provide an additional drive to ventilation during exercise.

4. **Neurogenic Mechanisms** The initial phase I increase in ventilation occurs rapidly (Dejours 1964). It appears when blood flow to and from the exercising muscle is stopped by pneumatic cuffs (Asmussen et al 1943, Nielsen and Asmussen 1963, Sargent et al 1981), and it failed to occur in the recipient when blood collected from exercising limbs of dogs was infused into the arterial supply of limb muscle of a second animal (Kao 1963). This suggests that the initial hyperpnoea of exercise is not elicited by blood born factors but is of neurogenic origin (Bennett 1984). This has led to the search for other possible stimuli.
(a) Cortical Radiation Krough and Lindhard (1913) first suggested that nerve impulses from the higher centres driving muscular exercise also "irradiate" to the respiratory centres, so giving a proportional increase in ventilation. There has been renewed interest in this possibility due to recent work of Eldridge et al (1981a, 1981b) which found that electrical stimulation of hypothalamic motor areas also induced rapid responses in ventilation and gas exchange. This appeared to indicate that hypothalamic command signals were responsible for the proportional driving of both locomotion and respiration during exercise.

The following findings further support the role of cortical factors in exercise hyperpnoea. Central nervous system depression by narcotics altered the breathing pattern of phase I (Favier et al 1983). The initial ventilatory response was decreased in size during electrically induced work (Krough and Lindhard 1917). Removal of peripheral stimuli to the respiratory centres did not produce a step decrease in respiratory activity, as expected, but was followed by a slow decline in both cats (Eldridge 1976) and humans (Trawadrous and Eldridge 1974, Swanson et al 1976). This suggests that the respiratory centre is capable of sustaining ventilation independent of peripheral stimuli. Hyperventilation occurred when work tasks where modified to increase the conscious effort required for their completion e.g. following partial paralysis by curarization (Asmussen 1965), following simultaneous activation of antagonists (Goodwin et al 1972) and following hypnotic suggestion (Daley and Overly 1966, Morgan et al 1973).

Contrary to the above, the following findings appear to refute the role of central cortical stimuli in exercise hyperpnoea. The alveolar partial pressure of oxygen and carbon dioxide show little or no change during phase I whereas a neurogenic drive to ventilation would be expected to cause hyperventilation with an increase in oxygen and a decrease in carbon dioxide partial pressures (Pan et al 1983). Bypassing cortical drive by electrical stimulation of the muscles caused an increase in ventilation and heart rate that were just as rapid and appropriate to carbon dioxide elimination as that occurring in normal volitional exercise (Asmussen et al 1943, Adams et al 1981). Based on curarization and leg cuff experiments (Asmussen et al 1964, 1965) a role for gamma efferents was proposed. However, blockade of this system to the legs by infiltrating lidocaine into the lumbar peridural space produced no change in the ventilation response.
to exercise (Hornbein et al 1969). Prior hyperventilation (Ward et al 1983) and transitions from one work load to another, as opposed to exercise starting from rest (Hughson and Morrisey 1982), decreased the magnitude of the phase I response.

(b) Peripheral Afferents The role of neurogenic afferents from the exercising limbs in exercise hyperpnoea is supported by a number of investigations. Phase I hyperpnoea is not shown by subjects with paraplegia during passive movements of the legs, whereas it is observed in normal individuals (Daley and Overly 1966). Direct stimulation of Type I and II hind limb muscle afferents, including those from Golgi tendon organs and muscle spindles, caused an increase in ventilation (Koizumi et al 1961, Senapati 1966, Gautier et al 1969). Drugs that suppress spindle activity cause a decrease in the ventilatory response (Flandrois et al 1967). High frequency mechanical vibration of the tendons of biceps or triceps brachialis stimulated muscle spindle afferents resulting in an increase in ventilation and a fall in alveolar carbon dioxide partial pressure (Jammes et al 1981). Two afferent pathways from exercising limbs have been postulated. One consisting of Type I and II fibres located in the lateral columns of the spinal cord (Kao 1963) and a second consisting of small myelinated and nonmyelinated Type III and IV fibres in the dorsal root (Mitchell and McCloskey 1972). Cold block of lateral column afferents (Tibes 1977) and blockade of small diameter dorsal root afferents (McCloskey and Mitchell 1972) both altered the ventilatory response to exercise.

On the contrary, evidence refuting the role of peripheral afferents is as follows. Section of Type I and II fibres in the dorsal columns in dogs failed to interfere with the normal ventilatory response (McCloskey and Mitchell 1972). This is supported by the work of Whipp (1981) and Wasserman et al (1981). Stimulation of muscle spindles failed to induce hyperpnoea (Hornbein et al 1969, Hodgson and Mathews 1968, Lietner and Dejours 1971). Tabetic subjects, with complete loss of proprioceptive reflexes from leg and lower trunk, showed normal ventilatory and alveolar carbon dioxide responses (Asmussen et al 1943). Also, a normal phase I increase in ventilation was observed during electrically induced limb movements in subjects with complete spinal section (Adams et al 1981).

5. Cardiodynamic Hyperpnoea: The main evidence for a nonmetabolic
neurogenic stimulus for hyperpnoea is circumstantial, being based on the rapidity of the phase I response and the observation by most that the hyperventilation is isocapnic (Beaver and Wasserman 1968, Suskind et al 1950, Wasserman et al 1977a, 1977b, Weissman et al 1977, Weissman et al 1980). Wasserman et al (1974) proposed a mechanism that explained the hyperpnoea in terms of both the immediacy of response and the isocapnia of alveolar gas.

They proposed that the rapid increase in cardiac output at the onset of exercise would cause pulmonary carbon dioxide flux to increase. Such an increase, if not matched by an increase in ventilation, would result in a down stream error signal in pH, and partial pressure of oxygen and carbon dioxide. This could be sensed by rapidly responding chemoreceptors and thus provide a humoral stimulus to the early hyperpnoea of exercise. The short circulation time between the pulmonary capillaries and these receptors would ensure the rapidity of the response.

Alveolar and arterial partial pressures of oxygen and carbon dioxide do not change systematically during phase I, indicating that ventilation increases proportionally to oxygen uptake and carbon dioxide output and hence must reflect the increasing blood flow. This supports the concept of cardiodynamic hyperpnoea at the onset of exercise.

Further supporting evidence is as follows. Ventilation decreases both at rest (Galletti 1961, Stremel et al 1979) and during exercise (Huszczuk et al 1982, Oren et al 1981a) when blood flow through the lungs and heart was reduced using a cardiopulmonary bypass. Increasing cardiac output with pacing increased ventilation (Wasserman et al 1974). This increase was not dependent on carotid body receptors. Decreasing cardiac output by infusing beta blocking drugs caused a decrease in ventilation (Brown et al 1976). However, this isocapnic hypopnoea persisted only until venous carbon dioxide rose to bring carbon dioxide flux back to normal. Cardiac output then rose again.

Evidence refuting cardiodynamic hyperpnoea is as follows. In many other species, and sometimes in humans, hyperventilation and hypocapnia are the typical response at the onset of exercise (Forster et al 1984b, Adams et al 1981, Band et al 1980, Broman and Wigertz 1971, Casaburi et al 1977). The dissociation of cardiovascular and ventilatory variables suggests that
hyperpnoea is not cardiodynamic. Furthermore, oxygen uptake does not decrease during the depression of cardiac output by circulatory occlusion, nor does ventilation increase as cardiac output increased when the occlusion was released (Fordyce et al 1982). The increase in ventilation occurring when cardiac output was increased by cardiac pacing had a delay of 20 seconds suggesting that it was mediated by peripheral chemoreception and not cardiodynamic hyperpnoea (Jones et al 1981). Also, there was no correlation between the instantaneous increment in ventilation and the intensity of exercise in dogs, and the ventilatory transients were unaffected by the administration of beta adrenergic blocking agents, despite a definite slowing of the speed of adaptation in the heart (Favier et al 1983).

Mechanisms that mediate the cardiodynamic hyperpnoea are unlikely to involve known chemoreceptors. The transit delays in the lung, the likely change in error signal and the chemoreflex gains are not compatible with such a mechanism. Also, neither carotid body resection (Wasserman et al 1975b), hypoxia, hyperoxia nor hypercapnia (Cunningham 1974a), affect the magnitude of the phase I increase.

D. Oxygen and Carbon Dioxide Gas Stores of the Body

In the body, oxygen and carbon dioxide are stored either as a gas, in physical solution, or in chemical combination. When ventilation is temporarily insufficient to meet the metabolic requirement for oxygen, or to remove the carbon dioxide that is produced, the body uses these stores to limit the rate of change in the gas tensions of the blood and tissues (Rahn 1964).

1. Magnitude and Forms of Carbon Dioxide Storage. The total amount of carbon dioxide stored in the body depends on the volume and buffering capacity of the noncarbonate buffers of the body, as well as the mean partial pressure of carbon dioxide in the tissues. The quantity of carbon dioxide stored in the lung, blood and tissues of a 70 kg man have been estimated to be more than 120 litres. Approximately 0.2 litres (0.16%) is stored in the lung, 2.7 litres (2.20%) in the blood and 120 litres (97.64%) in other tissues (Farhi 1963).

In the lung, carbon dioxide is stored mainly as a gas in the functional
residual capacity. Some is also stored as bicarbonate in lung tissue (Hyde et al 1968, Sackner et al 1964). In blood, some carbon dioxide is in physical solution but most is in the form of bicarbonate. About 10% of the carbon dioxide in the blood is combined directly with haemoglobin (Roughton 1943). Tissues other than blood contain most of the carbon dioxide stored in the body. Over 90% of this tissue carbon dioxide is stored in bone as carbonate (Rahn 1964).

2. Magnitude and Forms of Oxygen Storage. The total amount of oxygen stored in the body depends upon the partial pressure of oxygen and the ability of specific blood and tissue proteins to combine with oxygen (Roughton and Kendrew 1949). The quantity of oxygen stored in the lung, blood and tissue of a 70 kg man has been estimated to be only about 2 litres. Approximately 0.5 litres (25%) is stored in the lung, 1.2 litres (60%) in the blood and 0.3 litres (15%) in the tissue (Rahn 1964).

Most of the oxygen in the body is stored in the blood, both in physical solution and in combination with haemoglobin (Rahn 1964). Therefore, as long as the blood remains saturated, blood oxygen capacity (ml/100ml) reflects approximately the oxygen stores of the body. Oxygen is found in lesser amounts in the lung, as a gas, and in the tissues, both in physical solution and in combination with myoglobin (Wittenberg 1965).

3. Relationship Between Oxygen and Carbon Dioxide Gas Stores. The amount of oxygen and the amount of carbon dioxide stored in the body are related via a number of mechanisms. Firstly, the amount of carbon dioxide produced is a function of the amount of oxygen consumed (Farhi and Rahn 1955) with the exact ratio being dependent upon the fuel being oxidized. Secondarily, the ability of the blood to store oxygen and carbon dioxide depends on the tension of both gases. The blood oxygen content, at a given partial pressure, decreases as the partial pressure of carbon dioxide increases (Bohr et al 1904). This is known as the Bohr effect. The blood carbon dioxide tension, at a given partial pressure, decreases as the partial pressure of oxygen increases, (Christiansen et al 1914). This is known as the Haldane effect. Excessive high or low tensions, of either gas, may depress metabolism (Tenney and Lamb 1965), and alter the gas stores.

4. Adjustment of Gas Stores. The total level of oxygen and carbon dioxide stores in the body can be rapidly adjusted by alterations in the level of
ventilation or cardiac output (Cherniack and Longobardo 1970). Variations in circulation and ventilation affect the gas stores to different degrees. Ventilatory changes alter the gas stores in the lung, blood and tissue. Circulatory changes alter the gas stores in the blood and tissue only (Suskind and Rahn 1954). Also, because of the different configurations of the oxygen and carbon dioxide dissociation curves of the blood, ventilatory changes are more effective in altering tissue stores of carbon dioxide and circulatory alterations are more effective in altering tissue stores of oxygen.

Additional mechanisms exist to adjust the total amount of oxygen and carbon dioxide contained in the body at any given blood oxygen and carbon dioxide tension. An decrease in blood bicarbonate concentration can be produced by renal absorption of bicarbonate (Woodbury 1965). Also, renal secretion of erythropoietin, by increasing the haemoglobin concentration, can increase blood oxygen capacity even though the partial pressure of oxygen remains unchanged (Reynañlarje et al 1968, Vaghan and Pace 1956).

5. Changes in Gas Stores at the Onset of Exercise: At the onset of exercise the oxygen requirements of the tissue exceed that which is delivered by the respiratory and circulatory systems. Oxygen stores in the tissue are small and are rapidly depleted. A fall in mixed arterial and venous oxygen tension indicate that some oxygen is also obtained from blood stores. Further oxygen is obtained from the lung stores. This is reflected in a decrease in functional residual capacity. However, most of the energy deficit is made up from anaerobic sources from within the active tissue.

In comparison, the tissues ability to store carbon dioxide is large (Yano 1986). With exercise, carbon dioxide is stored in the blood and the venous tension and bicarbonate concentration both increase. The magnitude of the increase is proportional to the work rate (Jones and Jurkowski 1979). At the onset of exercise more carbon dioxide is stored in the tissue than oxygen is given up. Therefore, the carbon dioxide being given out at the mouth is disproportionately less than the oxygen being taken in. This is reflected in a transient fall in the respiratory exchange ratio.

E. Hypothesis:

Present concepts of ventilatory control stress the regulation of arterial
carbon dioxide as well as the tight coupling between ventilation and carbon dioxide output. This proportionality between ventilation and carbon dioxide output is maintained through a wide range of intensities of steady-state exercise. However, there are conflicting reports as to whether proportionality is maintained at the onset of exercise when the regulation of ventilation is no longer under simple proportional control but subject to a variety of rapidly changing neural and humoral stimuli. Favier et al (1983) have observed a delayed coupling of ventilation and carbon dioxide at the onset of exercise. On the contrary, coupling was reported by Wasserman and Whipp (1983).

If coupling between ventilation and carbon dioxide is not maintained at the onset of exercise, alveolar and arterial carbon dioxide partial pressures will not be held at resting levels. If coupling between ventilation and carbon dioxide output is maintained, but the rates of increase in oxygen uptake and carbon dioxide output are different, then both alveolar and arterial oxygen partial pressures will not be held at resting levels. Only when coupling is maintained between all three variables will both oxygen and carbon dioxide partial pressures in the alveolar and arterial blood be held constant at resting levels.

At the onset of exercise the rate of change of carbon dioxide output is slower than the rate of change of oxygen uptake due to the greater capacity of the body to store carbon dioxide. It is postulated that if proportionality between ventilation and carbon dioxide is maintained there will be a relative hypoventilation with respect to oxygen uptake and a concomitant fall in alveolar and arterial oxygen partial pressure.
METHODS (Section 1)

A. Subjects

The subjects (n=6) were male athletes, aged 18 to 22 years, and of higher than normal cardio-vascular fitness. Maximal oxygen uptake for the group averaged 58.33 ± 5.28 mls.kg\(^{-1}\).min\(^{-1}\). They were all non smokers with no history of respiratory or cardio-vascular impairment. Resting flow volume loops were obtained on each subject prior to the exercise test. Vital capacity, forced expiratory volume, peak flow and mid expiratory flow, for all subjects, were within the normal range (Jones et al 1975).

The subjects were selected for this study on the basis of availability and their prior experience of exercising in the laboratory situation. All were familiar with the bicycle ergometer and with exercising while breathing through a mouth piece. Prior to the testing session the procedures and purpose of the experiment were explained in full.

B. Experimental Protocol

The subjects performed six 2 minute rides on a bicycle ergometer (Monark Model 869) with a minimum of 20 minutes rest between each ride. The power output was set at 300 watts. This work load was selected in order to produce a near maximal effort. Subjects set their own pedal frequency while the load was automatically adjusted to maintain a constant power output. The positioning of the seat and handlebars was adjusted by each subject for his own comfort. Each ride started from complete rest. The full load was imposed immediately at the onset of exercise. All subjects were able to completed all 6 trials.

C. Equipment

The subjects breathed through a low resistance breathing valve (Koegel Y valve). Oxygen and carbon dioxide partial pressures were measured continuously using a mass spectrometer (Perkin Elmar Model 1100). Expired flow was measured with a pneumotachograph (Fleisch Model 3), pressure transducer (Validyne DP-45) and carrier demodulator (Validyne CD-15). Heart rate was recorded using an electrocardiogram (Avionics Model 3000). The electrical outputs of the electrocardiogram, flow transducer and mass
spectrometer under went analog to digital conversion and were then transmitted to a minicomputer (Digital PDP 11/10). All electrical outputs were also recorded on a strip chart recorder (Gould Brush 2600).

Time of breath, oxygen uptake, carbon dioxide output, ventilation, respiratory exchange ratio, end tidal oxygen partial pressure, end tidal carbon dioxide partial pressures and heart rate were calculated on a breath by breath basis. A detailed account of the equipment and algorithms used in the breath by breath system, along with methods of calibration and a comparison with conventional methods, are given in Appendix B.

D. Data Analysis

Respiratory and circulatory functions exhibit spontaneous fluctuations which will be superimposed as a "noise" on the basic response pattern and become noticeable when breath-by-breath or beat-by-beat recordings are made (Beaver and Wasserman 1968). In order to reduce the noise and enhance the basic response pattern, repeated identical experiments for each individual were ensemble averaged. The background noise is thereby reduced by a factor proportional to the number of determinations (Linnarsson 1974).

The ensemble averaging was performed as follows: The data collected from the 6 separate runs for each subject were pooled. It was then grouped into 2 second time intervals from an initial point 20 seconds before the onset of exercise, and averaged to give mean values. The raw data and means for each parameter for subject JA were plotted and are presented in Figures 1.1.1 to 1.6.1 as an example of a typical response. Correlations between selected parameters for all subjects were determined using the Pearson product moment correlation. Significance was accepted at the 0.05 level.

The time constant (T) is defined as the time in seconds for an exponential process to achieve 63% of the difference between the pre exercise and the steady-state response. The time constant was determined for ventilation, oxygen uptake and carbon dioxide output from the mean subject response. No attempt was made to mathematically describe the kinetics of the response. All were assumed to be monoexponential. The pre exercise value was defined as the average of all measurements recorded in the 20 seconds prior to the onset of exercise. The steady-state value was defined as the average of all measurements made in the last 20 seconds of the trial.
RESULTS (Section I)

Age, height, weight, maximal oxygen uptake, vital capacity, forced expiratory volume, peak flow and mid expiratory flow for each of the 6 subjects, together with mean values, are listed in Table 1.1.

For the 6 subjects mean time constants for oxygen uptake, carbon dioxide output and ventilation were 26.5 ± 1.92 seconds, 34.5 ± 1.93 seconds and 35.3 ± 2.11 seconds respectively. Significant correlations were found between ventilation and carbon dioxide output (r=0.9759 ± 0.015), ventilation and oxygen uptake (r=0.9346 ± 0.023) and ventilatory equivalent for oxygen and end tidal oxygen (r=0.9538 ± 0.016). Data for the 6 subjects are summarized in Table 1.2.

The description below, and the data in Figures 1.1.1 to 1.6.1, relates to subject JA. They are typical of the response to exercise found in all subjects and are similar to that recorded by other investigators.

A. Oxygen Uptake - Carbon Dioxide Output

Oxygen uptake (Figure 1.1.1) increased 2 fold within the first 1-2 breaths after the onset of exercise from a pre exercise average of 548 ± 150 to 1061 ± 201 mls/min, this being approximately 17% of the total increase. It remained relatively constant for about 20 seconds then increased in an apparently exponential manner over the next 40 seconds. Oxygen uptake then plateaued to average 3520 ± 220 mls/min for the last 40 seconds of the run. The final value was more than 6 times pre-exercise values.

Carbon dioxide output (Figure 1.1.1) increased 2 fold within the first 1-2 breaths after the onset of exercise from a pre exercise average of 564 ± 156 to 1139 ± 184 mls/min; approximately 22% of the total increase. It remained relatively constant for about 20 seconds then increased gradually over the next 80 seconds. Carbon dioxide output then plateaued to average 3228 ± 180 mls/min in the last 20 seconds of the run. The final value for carbon dioxide being more than 5 times pre-exercise values.

Changes in the respiratory exchange ratio (Figure 1.1.2) reflect the different rates of change in oxygen uptake and carbon dioxide output. At the onset of exercise the respiratory exchange ratio increased from an
average of 1.03 ± 0.08 to 1.13 ± 0.05. It then fell rapidly to attain minimal values (0.72) about 40 seconds into the trial. Over the next 60 seconds the respiratory exchange ratio increased gradually to plateau over the last 20 seconds at an average of 0.91 ± 0.02.

B. Ventilation:

Ventilation (Figure 1.2.3) increased 2 fold within the first 1-2 breaths after the onset of exercise from an average of 15.53 ± 3.65 to 32.49 ± 4.75 litres/min. This was approximately 28% of the total increase. This initial increase reflects changes in both tidal volume and breathing frequency. Ventilation remained relatively constant for about 20 seconds then increased gradually over the next 80 seconds. Ventilation finally plateaued to average 76.81 ± 5.22 litres/min in the last 20 seconds of the run. The final value being more than 5 times pre-exercise values.

Tidal volume (Figure 1.2.1) increased from an average of 845 ± 134.10 to 1176 ± 140.41 mls within the first 1-2 breaths after the onset of exercise. It remained relatively constant for about 20 seconds then increased gradually over the next 50 seconds. This secondary increase in tidal volume is largely responsible for the phase II increase in ventilation. Tidal volume then plateaued to average 2186 ± 103.64 mls in the last 50 seconds of the run. The final value being more than 2.5 times pre-exercise values and approximately 34% of the vital capacity.

Breathing frequency (Figure 1.2.2) increased at the onset of exercise from an average of 17.78 ± 2.13 to 29.41 ± 3.69 /min. This increase occurred within the first 1-2 breaths. Breathing frequency remained relatively constant for the next 60 seconds then rose gradually over the remainder of the run. The secondary increase in breathing frequency coincided with the plateauing of tidal volume and accounts for most of the increase in ventilation over the last part of the ride. Maximal values averaged 38.42 ± 2.86 breaths/min.

C. Ventilation Vs Carbon Dioxide Output

The changes in ventilation closely follow those of carbon dioxide output (Figure 1.3.1) with a correlation coefficient of 0.9931 (Figure 1.3.2). In the first 20 seconds ventilation leads carbon dioxide output and a relative
hyperventilation occurs. During phase II carbon dioxide leads ventilation with a relative hypoventilation. This hypoventilation persists throughout the duration of the trial.

These changes are reflected in the ventilatory equivalent for carbon dioxide (Figure 1.3.3). This increased initially then fell after 20 seconds and remained reduced throughout the remainder of the trial. The ventilatory equivalent for carbon dioxide averaged $23.81 \pm 0.75$ litres/litre for the last 60 seconds of the trial.

The changing ventilation with respect to the carbon dioxide output is also reflected in the end tidal carbon dioxide partial pressure (Figure 1.3.4). At the onset of exercise it fell from an average of $40.47 \pm 1.34$ to $38.46 \pm 1.25$ Torr. After about 15 seconds it rose above resting levels to remain essentially constant through out the remainder of the trial. The end tidal carbon dioxide partial pressure averaged $43.51 \pm 1.07$ Torr over the last 60 seconds of the trial.

D. Ventilation Vs Oxygen Uptake

The time course of changes in ventilation and oxygen uptake at the onset of exercise were less closely linked (Figure 1.4.1) with a correlation coefficient of 0.9578 (Figure 1.4.2). Oxygen uptake and ventilation increased immediately at the onset of exercise then plateaued for approximately 15 seconds. The secondary increase in oxygen uptake was at a faster rate than that of ventilation.

The difference in rate of change of ventilation and oxygen uptake is reflected in the ventilatory equivalent for oxygen (Figure 1.4.3). At the onset of exercise the ventilatory equivalent increased from an average of $27.78 \pm 2.55$ to $31.04 \pm 2.50$ litres. After about 15 seconds it then fell rapidly to attain minimal values ($18.26 \pm 0.96$ litres) 35 seconds into the run. The ventilatory equivalent gradually increased over the next 60 seconds to plateau over the last 20 seconds at an average of $21.60 \pm 0.78$ litres.

The changes in ventilation with respect to oxygen uptake are also reflected in the end tidal oxygen (Figure 1.4.4). At the onset of exercise the end
tidal oxygen partial pressure increased from an average of 110.53 ± 3.55 to 115.09 ± 2.66 Torr. After about 15 seconds it then fell rapidly to attain minimal values (95.60 ± 1.62 Torr) 40 seconds into the run. End tidal oxygen gradually increased over the next 60 seconds to plateau at an average of 102.47 ± 1.38 Torr.

The time course of changes in ventilatory equivalent and end tidal oxygen were virtually identical (Figure 1.5.1) with a correlation coefficient of 0.9688 over the whole range of ventilatory equivalent values (Figure 1.5.2) and 0.9876 for those values below steady-state (i.e. below a ventilatory equivalent of 24 litres/litre).

E. Heart Rate

Heart rate increased at a greater rate than either oxygen uptake, carbon dioxide output or ventilation (Figure 1.6.1). It rose exponentially from an average of 83.52 ± 3.55 beats/min prior to exercise to a maximum of 181.73 ± 4.91 beats/min during the last 10 seconds of the run. A slight plateauing of heart rate occurred about 15 seconds after the onset of exercise.
Table 1.1 Subject Personal Data. (Section I - Cyclists)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Height (cms)</th>
<th>Weight (kgs)</th>
<th>( \dot{V}O_2 ) Max (ml/kg)</th>
<th>FVC (mls)</th>
<th>FEV(_1) (mls)</th>
<th>PEFR (l/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>21</td>
<td>178.1</td>
<td>66.2</td>
<td>62.14</td>
<td>5807</td>
<td>4877</td>
<td>9.02</td>
</tr>
<tr>
<td>TH</td>
<td>22</td>
<td>166.0</td>
<td>65.3</td>
<td>64.77</td>
<td>4998</td>
<td>3720</td>
<td>8.60</td>
</tr>
<tr>
<td>ND</td>
<td>18</td>
<td>184.9</td>
<td>79.6</td>
<td>52.55</td>
<td>5832</td>
<td>5166</td>
<td>11.38</td>
</tr>
<tr>
<td>GH</td>
<td>22</td>
<td>189.1</td>
<td>74.5</td>
<td>63.72</td>
<td>7671</td>
<td>5552</td>
<td>10.34</td>
</tr>
<tr>
<td>ML</td>
<td>18</td>
<td>185.2</td>
<td>82.7</td>
<td>53.19</td>
<td>6112</td>
<td>5082</td>
<td>10.94</td>
</tr>
<tr>
<td>JA</td>
<td>18</td>
<td>171.5</td>
<td>83.0</td>
<td>53.59</td>
<td>6357</td>
<td>5266</td>
<td>12.53</td>
</tr>
</tbody>
</table>

Mean 19.83 179.13 75.22 58.33 6129 4943 10.47
Std D ±1.86 ±8.18 ±7.26 ±5.28 ±806 ±584 ±1.35

Table 1.2 Time constants for oxygen, carbon dioxide and ventilation. Correlation coefficients for ventilation vs carbon dioxide output, ventilation vs oxygen uptake and ventilatory equivalent for oxygen vs end tidal oxygen partial pressure.

<table>
<thead>
<tr>
<th>Subject</th>
<th>( \dot{O}_2 )</th>
<th>( \dot{CO}_2 )</th>
<th>VE</th>
<th>VE-( \dot{V}CO_2 )</th>
<th>VE-( \dot{V}O_2 )</th>
<th>VE-ETO(_O_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>26.50</td>
<td>34.50</td>
<td>35.20</td>
<td>0.9875</td>
<td>0.9611</td>
<td>0.9588</td>
</tr>
<tr>
<td>TH</td>
<td>29.00</td>
<td>36.60</td>
<td>39.20</td>
<td>0.9815</td>
<td>0.9367</td>
<td>0.9762</td>
</tr>
<tr>
<td>ND</td>
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<td>33.90</td>
<td>33.80</td>
<td>0.9771</td>
<td>0.9366</td>
<td>0.9386</td>
</tr>
<tr>
<td>GH</td>
<td>33.90</td>
<td>41.20</td>
<td>42.30</td>
<td>0.9469</td>
<td>0.8912</td>
<td>0.9504</td>
</tr>
<tr>
<td>ML</td>
<td>28.80</td>
<td>37.10</td>
<td>35.80</td>
<td>0.9693</td>
<td>0.9243</td>
<td>0.9297</td>
</tr>
<tr>
<td>JA</td>
<td>33.70</td>
<td>38.30</td>
<td>36.00</td>
<td>0.9931</td>
<td>0.9578</td>
<td>0.9688</td>
</tr>
</tbody>
</table>

Mean 29.42 36.93 37.05 0.9759 0.9346 0.9538
Std D ±3.46 ±2.43 ±2.85 ±0.0150 ±0.0232 ±0.0162
Figure 1.1.1. Comparison of rate of change in oxygen uptake and carbon dioxide output during 2 minutes of cycling. Power output = 300 watts. (Subject JA).

Figure 1.1.2. Changes in the respiratory exchange ratio during 2 minutes of cycling. Power output = 300 watts. (Subject JA).
Figure 1.2.1 Changes in tidal volume during 2 minutes of cycling. Power output = 300 watts. (Subject JA).

Figure 1.2.2. Changes in breathing frequency during 2 minutes of cycling. Power output = 300 watts. (Subject JA).
Figure 1.2.3 Changes in ventilation during 2 minutes of cycling. Power output = 300 watts. Subject JA.

Figure 1.3.1. Comparison of rate of change in carbon dioxide output and ventilation during 2 minutes of cycling. Power output = 300 watts. (Subject JA).
Figure 1.3.2. Plot of carbon dioxide output against ventilation during 2 minutes of cycling. Power output = 300 watts. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. r=0.9931. (Subject JA).

Figure 1.3.3. Changes in the ventilatory equivalent for carbon dioxide during 2 minutes of cycling. Power output = 300 watts. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. (Subject JA).
Figure 1.3.4. Changes in end tidal carbon dioxide during 2 minutes of cycling. Power output = 300 watts. Normal values = 40 Torr. (Subject JA).

Figure 1.4.1. Comparison of rate of change in oxygen uptake and ventilation during 2 minutes of cycling. Power output = 300 watts. (Subject JA).
Figure 1.4.2. Plot of oxygen uptake against ventilation during 2 minutes of cycling. Power output = 300 watts. Normal ventilatory equivalent for oxygen = 24 litres/litre. \( r=0.9578 \). (Subject JA).

Figure 1.4.3. Changes in the ventilatory equivalent for oxygen during 2 minutes of cycling. Power output = 300 watts. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject JA).
Figure 1.4.4 Changes in end tidal oxygen during 2 minutes of cycling. Power output = 300 watts. (Subject JA).

Figure 1.5.1. Comparison of the rate of change in the ventilatory equivalent for oxygen and end tidal oxygen during 2 minutes of cycling. Power output = 300 watts. (Subject JA).
Figure 1.5.2. Plot of ventilatory equivalent for oxygen against end tidal oxygen during 2 minutes of cycling. Power output = 300 watts. $r = 0.9688$. (Subject JA).

Figure 1.6.1. Changes in heart rate during 2 minutes of cycling. Power output = 300 watts. (Subject JA).
DISCUSSION - (Section 1)

At the onset of exercise, the rate of change of carbon dioxide output was slower than the rate of change in oxygen uptake. This was reflected in a transient fall in the respiratory exchange ratio. Ventilation increased in proportion to the increase in carbon dioxide output resulting in relative constancy of alveolar carbon dioxide partial pressure. Ventilation with respect to the oxygen uptake was low with the ventilatory equivalent for oxygen showing a transient fall after a short delay. This fall in ventilatory equivalent correlated highly with the fall in end tidal oxygen partial pressure.

A. Considerations in Interpreting Results

1. Oxygen Uptake Conventional measurements of oxygen uptake are obtained from mixed expired gas samples collected over an extended period of time using open circuit techniques. In the steady-state these accurately reflect gas exchange at both the alveolar membrane and the muscle. New research techniques, such as fast responding gas analyzers and computer facilities, have made it possible to measure gas transfer on a breath-by-breath basis, and so elucidate the kinetics of oxygen uptake, carbon dioxide output and ventilation in the transition from rest to exercise. However, if the kinetics of gas exchange are to be obtained with maximum fidelity it will not suffice merely to collect mixed expired gas for shorter intervals and perform analysis more rapidly. The oxygen uptake resulting from such a procedure will vary in an erratic fashion if no account is taken of the changing gas stores of the body.

The body stores of oxygen include the lung, arterial and venous blood and tissue myoglobin. Muscle myoglobin saturation does not change in the transition from rest to moderate exercise (Di Prampero 1983). Arterial oxygen tension exhibit transient falls at the onset of exercise (Young and Woolcock 1978) and venous oxygen tension decreases progressively as exercise intensity is increased (Edwards et al 1972). However, it is the gas stores of the lung which constitute the greatest store of oxygen and undergoes the greatest changes at the onset of exercise.

At the end of a maximal forced expiration some gas still remains in the lung. This is called the residual volume and equals about 1200 ml (i.e.
20% of total lung volume). At the end of a normal expiration much more air remains in the lung. This is called the functional residual capacity and equals about 2400 mls (i.e. 40% of total lung volume). The functional residual capacity acts as a buffer against extreme changes in alveolar gas concentrations with each breath. If there were no functional residual capacity alveolar oxygen partial pressure would decrease to that of venous blood at end of expiration and rise to near 149 Torr with deep inspiration. Blood oxygen content, would in turn, fluctuate widely with each breath.

Functional residual capacity decreases with increasing exercise intensity such that oxygen uptake kinetics at the mouth lag behind those at the alveolar membrane (Linnarsson 1974, Ward et al 1979, Wessel et al 1979, Inman et al 1987). However, as functional residual capacity kinetics are faster than those of oxygen uptake and carbon dioxide output, and since the stores of oxygen in the body are very small relative to the metabolic demands of exercise, these effects are only most likely significant in the early portion of metabolic non steady-state. This was confirmed by Linnarsson (1974) who found that the response of oxygen uptake at the mouth was in general only slower than that at the alveolar membrane during the first 15-20 seconds but there after the two time courses agreed closely.

Computerised breath-by-breath systems capable of measuring gas exchange at the pulmonary membrane have been developed by a number of investigators (Auchincloss 1966, Linnarsson 1974, Beaver et al 1981, Giezendanner et al 1983, Swanson et al 1983). The system utilized in this study measured gas exchange at the mouth only. With this system, the increase in oxygen uptake and carbon dioxide output at the onset of exercise will be underestimated. However, the changes in ventilatory equivalent, end tidal oxygen and end tidal carbon dioxide, which are central to the hypothesis proposed in this section, all occur during phase II i.e. 15-20 seconds after the onset of exercise. This is at a time when functional residual capacity has stabilized and gas exchange at the mouth is not significantly different from that at the pulmonary membrane.

2. Alveolar Gas Tensions End tidal oxygen and end tidal carbon dioxide partial pressures are widely used as indices of both alveolar and arterial gas tensions. However, the partial pressures of both oxygen and carbon dioxide in the alveoli fluctuate cyclically with breathing such that the end tidal values are not representative of the average composition of
alveolar gas during a breath. These fluctuations have been ascribed to simultaneous gas exchange (Du Bois et al 1952) but other factors such as ventilation-perfusion mismatching in combination with sequential emptying of the lung also contribute (Guy et al 1976, Gronlund et al 1987).

Fluctuations in alveolar gas tensions are greatest at high tidal volumes, high carbon dioxide outputs and low frequencies of breathing (Jones et al 1979). For carbon dioxide, at rest, there is little change in alveolar gas compositions during the breathing cycle, and end tidal values closely approximate mean alveolar values (Jones et al 1966). During exercise, when metabolic carbon dioxide output, tidal volume and ventilation are all increased, fluctuations in alveolar gas tensions also increase. Although there may be no change in mean alveolar tension, end tidal carbon dioxide partial pressure will rise and even exceed that in the arterial blood (Lamb et al 1965, Jones et al 1979). For oxygen the same mechanism leads to significantly lower end tidal than mean alveolar values during heavy exercise.

Mean alveolar gas tensions can be more accurately estimated from measures of functional residual capacity, vital capacity and end tidal values (Jones et al 1979). Alternately mixed expired alveolar samples can be used to estimate mean alveolar values. In this study end tidal values were used to represent mean alveolar values. Small increases in end tidal carbon dioxide and large falls in end tidal oxygen were observed. It was felt that these changes in end tidal partial pressures adequately reflected the pattern of change in mean alveolar partial pressure.

**B. Oxygen Uptake Kinetics**

The increased uptake of oxygen at the onset of exercise reflects the integrated action of a multitude of respiratory, circulatory and metabolic changes. It is the failure of these adjustments to keep pace with energy demands, in response to an abrupt work load, that is the cause of the slow rise in oxygen uptake by the blood in the initial phase of muscular work.

In this study, a two phase increase in oxygen uptake was observed at the onset of exercise (Figure 1.1.1). The time constant for this combined response averaged $26.52 \pm 1.92$ seconds. This agrees closely with previous observations, such as those of Margaria et al (1965), Casaburi et al
Immediately following the onset of work, heart rate showed a rapid increase followed by a short lasting plateau (Figure 1.6.1). The timing of this plateau corresponded with the start of the phase II increase in both ventilation and oxygen uptake. Heart rate then exhibited a gradual secondary rise which persisted throughout the remainder of the trial. The kinetics of the heart rate response were considerably faster than those of both carbon dioxide and ventilation and were more closely aligned to that of oxygen uptake. This supports the contention that the increase in oxygen uptake is related to the increase in cardiac output, as reflected in the increase in heart rate.

C. Carbon Dioxide Kinetics

Carbon dioxide output also increased at the onset of exercise in an apparently exponential manner (Figure 1.1.1). However, the response was appreciably slower than that of oxygen. The time constant for the 6 subjects averaged $34.53 \pm 1.93$ seconds. This compares with values described by Linnarsson (1974), Wasserman et al (1974), Casaburi et al (1977), Hughson and Morrissey (1982) and Whipp et al (1982).

The kinetic dissociation of oxygen uptake and carbon dioxide output at the onset of exercise is unlikely to reflect changes in the ratio of muscle oxygen consumption and carbon dioxide production. It is more likely to reflect the influence of intervening gas stores. The tissue stores for carbon dioxide are larger than those of oxygen (Farhi and Rhan 1955, Wasserman et al 1977a, Jones et al 1979). The buffering action of these large peripheral stores cause changes in mixed venous carbon dioxide tension, at the onset of exercise, to occur less rapidly than the corresponding changes in mixed venous oxygen tension (Edwards et al 1972). Hence the time constants for oxygen uptake and carbon dioxide output will be appreciably different. This has been demonstrated by other workers (Casaburi et al 1978a, Margaria et al 1965, Whipp 1981, Diamond et al 1977, Hughson and Inman (1985) and is supported by the findings of this study.

Edwards et al (1972) observed that the mixed venous oxygen tension at the lung fell about 15 seconds after the onset of exercise, whereas the mixed
venous carbon dioxide tension did not start to increase at the lung until approximately 30 seconds after the onset of exercise. For the first 15 seconds while mixed venous tensions of both oxygen and carbon dioxide are not changing, increases in both oxygen uptake and carbon dioxide output will depend solely on changes in cardiac output (Whipp et al 1982). The respiratory exchange ratio will remain at, or about, resting levels (Davies 1968). After about 15 seconds, corresponding to the transit time between the muscles and the lung, the fall in mixed venous oxygen tension will increase the arterio-venous oxygen difference and cause a secondary increase in oxygen uptake. The rise in oxygen uptake now exceeds the rise in carbon dioxide output. This is reflected in a fall in the respiratory exchange ratio. A secondary rise in carbon dioxide output occurs approximately 30 seconds after the onset of exercise when blood with elevated mixed venous carbon dioxide partial pressure reaches the lung. At this point the respiratory exchange ratio will rise back towards levels more representative of the uptake of oxygen and production of carbon dioxide in the muscles. Such changes could explain the response of the expiratory exchange ratio as observed in this study.

D. Ventilation Kinetics

Following the onset of exercise, ventilation showed an immediate rapid increase, then a plateau, followed approximately 20 seconds later by a secondary slower increase (Figure 1.2.3). This secondary increase lasted approximately 80 seconds. Ventilation then remained essentially constant throughout the remainder of the trial. This response is essentially the same as that described by a number of previous workers (Wasserman 1978, Pearce and Milhorn 1977, Whipp 1983, Linnarsson 1974).

For the first 70 seconds of the run tidal volume exhibited the same basic response as ventilation (Figure 1.2.1). It increased abruptly within the first breath then plateaued. After a delay of about 20 seconds it increased slowly to plateau again approximately 70 seconds after the onset of exercise. No further change in tidal volume occurred through out the remainder of the run. Breathing frequency almost doubled within the first 3-4 seconds and then remained essentially constant for the next 60 seconds when a secondary increase occurred (Figure 1.2.2).

Increases in ventilation were essentially dictated for the first 60-70
seconds by the changes in tidal volume. Tidal volume then remained constant at about 34% of the vital capacity. Limiting values of tidal volume in exercise of similar magnitude have been observed by a number of workers (Hey et al 1966, Cotes et al 1970, Jones 1984). Further increase in ventilation where then brought about by changes in the breathing frequency.

It is not known whether the constancy of the breathing frequency was in any way related to the frequency of leg movement. The entrainment of breathing frequency to leg movement has been observed by a number of workers (Bramble and Carrier 1983). It is possible that breathing frequency was initially entrained to leg movement and that this entrainment was only interrupted when tidal volume reached maximal exercise values. Further increases in ventilation could then only be achieved by increases in rate.

The initial increase in tidal volume results from an increase in expiratory activity and is associated with a drop in functional residual capacity. This may reflect a simple mechanical relationship between leg and trunk movements when the abdominal muscles are abruptly engaged at the onset of dynamic leg exercise (Grimby et al 1968). The slower secondary increase in tidal volume is taken to a similar degree from the inspiratory and expiratory reserve volumes (Lind and Hesser 1984). It occurs at a time when blood from working muscles can be assumed to have reached arterial or medullary chemoreceptors and is therefore probably of humoral origin.

E. Alveolar Gas Tensions

The kinetics of oxygen uptake and carbon dioxide output are markedly different. As ventilation cannot track both variables following the onset of exercise, either alveolar oxygen or alveolar carbon dioxide (or both) will not be regulated at resting levels during this transition. Thus the kinetic differences between ventilation, carbon dioxide output and oxygen uptake become critical determinants of the alveolar gas tensions.

Typically in phase I oxygen uptake, carbon dioxide output and ventilation increase at a similar rate and the end tidal carbon dioxide, end tidal oxygen and the respiratory exchange ratio remain stable (Jensen 1972, Casaburi et al 1978a, Whipp et al 1982, Pearce and Milhorn 1977, Wasserman et al 1977a). In this study, a slight hyperventilation with an increase in
end tidal oxygen and respiratory exchange ratio, and a decrease in end tidal carbon dioxide, occurred. Beaver and Wasserman (1968) and Linnarsson (1974) found the heart rate response to be slower than that of ventilation suggesting a disproportional increase in ventilation and cardiac output in phase I. In this study the heart rate response lead that of ventilation and was therefore unlikely to be the cause of the hyperventilation.

Reasons for the hyperventilation are not readily apparent. They may relate to extrametabolic factors such as afferent impulses from the limbs. All subjects were of above average fitness and cycling at high leg speeds. Running as compared to walking at the same metabolic rate is known to induce a higher ventilation in athletes (McMurray and Alborn 1982). Dempsey et al (1984) also observed hyperventilation in athletes running at high work intensities.

1. **Ventilatory Equivalent for Carbon Dioxide** The time constant for ventilation was slightly longer than that for carbon dioxide output though there was strong correlation of carbon dioxide output and ventilation among subjects ($r=0.9759 \pm 0.015$). This supports the findings of Casaburi et al (1976), Karlsson et al (1975) and Whipp et al (1984). This relationship persists through both phase I and phase II (Figure 1.3.2) and is the same as that found in the steady-state.

The small kinetic dissociation between ventilation and carbon dioxide output predicts that transitional changes in end tidal carbon dioxide partial pressure should be small. Indeed at the onset of phase I end tidal carbon dioxide increased slightly above resting levels and was constant for the remainder of the run (Figure 1.3.4). It is worth remembering that these end tidal values probably over estimate mean alveolar values and that the changes in alveolar carbon dioxide tension would indeed be even smaller.

The finding that carbon dioxide output leads ventilation and that their kinetics are highly correlated among subjects is not proof of a causative relationship, but it does support the argument of Wasserman and Whipp (1983) of a tight functional coupling of the hyperpnoea of exercise to carbon dioxide production in the non steady-state.

2. **Ventilatory Equivalent for Oxygen** In this study, the time constant for
ventilation was appreciably slower than that for oxygen uptake. Similar results were found by Wade and Bishop (1962) and Wigertz (1970). The ventilation-oxygen uptake relationship was linear through phase I though nonlinear throughout phase II (Figure 1.4.2).

The ventilatory equivalent for oxygen was slightly elevated during phase I but fell at the onset of phase II and remained depressed through out the remainder of the trial (Figure 1.4.3). The increase in ventilatory equivalent for oxygen during phase I may in part be an artifact resulting from the under estimation of oxygen uptake due to its measurement at the mouth and not the alveolar membrane. The relative hypoventilation, due to the dissociation of ventilation and oxygen uptake at the onset of phase II, inevitably caused changes in alveolar gas composition. End tidal oxygen partial pressure exhibited a large transient fall (Figure 1.4.4). There was a strong correlation between this fall in end tidal oxygen partial pressure and the preceding fall in ventilatory equivalent for oxygen ($r=0.9688$). This is suggestive of a functional coupling between the ventilation at the onset of exercise and the fall in alveolar oxygen tension (Figure 1.5.2).

F. Conclusions

At the onset of exercise the rate of change of carbon dioxide output is slower than the rate of change of oxygen uptake due to the greater capacity of the body to store carbon dioxide. The increase in ventilation is proportional to the increase in carbon dioxide output. Alveolar carbon dioxide partial pressure therefore remains relatively constant. However, there is a relative hypoventilation with respect to oxygen uptake and end tidal oxygen partial pressure falls. It is postulated that this fall in end tidal oxygen partial pressure would cause a concomitant fall in arterial oxygen partial pressure. This will be further investigated in Section II.
ARTERIAL BLOOD OXYGENATION DURING NON STEADY-STATE EXERCISE

INTRODUCTION

As mentioned previously, the prime function of the lung is to exchange oxygen and carbon dioxide between the alveoli and the pulmonary capillary blood. Together with ventilation, the properties of the membrane itself and the anatomical arrangement by which the air and blood are brought into close proximity to one another, influence the effectiveness of this exchange.

A. Alveolar Arterial Gas Tension Differences

Differences exist between the partial pressures of oxygen and carbon dioxide in the alveoli and the arterial blood. These differences have been extensively studied at rest in normal subjects (Asmussen and Nielsen 1960, Ayres et al 1964, Fahri and Rhan 1955, Filley et al 1954, Hesser and Matell 1965, Jones et al 1966, Wasserman et al 1967). Approximate values for oxygen and carbon dioxide differences between the alveoli and the arterial blood are 6-10 and 3-5 Torr respectively.

The differences in oxygen and carbon dioxide tensions between alveoli and the arterial blood may be considered as indicies of the efficiency of gas exchange (Whipp and Wasserman 1969). These differences are caused by one or a combination of the following four things (West 1974).

1. **Veno-Atrial Shunt** In the normal subject, part of the bronchial venous blood empties into the pulmonary veins and blood from the Thebesian veins drains from the myocardium directly into the left side of the heart. The addition of this poorly oxygenated blood into the pulmonary venous blood causes a decrease in arterial oxygen tension (hypoxemia) and an increase in the alveolar-arterial oxygen difference.

The effect of shunting is dependent upon the amount of blood shunted and the oxygen content of the blood. A fall in mixed venous oxygen tension will cause a fall in arterial oxygen tension without a change in the actual
shunt fraction. Also, because of the shape of the oxygen dissociation curve the effect on the alveolar-arterial oxygen difference will be large at high arterial oxygen tensions and almost negligible at low arterial oxygen tensions.

In the normal individual at rest the blood that bypasses the gas exchange surfaces of the lung due to shunting constitutes about 1-2% of the total cardiac output (Mellangaard 1966). At normal venous and arterial blood gas tensions this would result in a fall in arterial oxygen tension of up to 5 Torr. This is at least half of the normal resting alveolar-arterial oxygen difference. The flow through the Thebesian veins accounts for about two thirds of the shunted blood (Gledhill et al 1977).

By giving a patient 100% oxygen to breathe true anatomical shunt can be distinguished from other causes of hypoxemia because only with a true anatomical shunt does hypoxemia remain.

2. Ventilation-Perfusion Ratio Inequality The "perfect" lung model assumes that the share of the total blood volume and the share of the total ventilation going to each lung unit is the same and that all the lung units behave in an identical way. However, in practice it is known that the ventilation-perfusion ratio actually decreases down the lung. Blood flow increases rapidly down the lung because the weight of the column of blood in the upright position increases the perfusion pressure and therefore the blood flow at the base (Anthonisen and Milic-Emili 1966, Kaneko et al 1966, West and Dollery 1960, West 1965). There is also a gradient in ventilation down the lung due to the effect of the weight of the lung itself on the pleural pressure down the lung (Bryan et al 1964, Bjure 1971). These gradients in blood flow and ventilation down the lung produce a gradient in the ventilation-perfusion ratio down the lung.

In any alveolus, or small gas exchange region, as the ventilation-perfusion ratio is gradually decreased, alveolar oxygen partial pressure approaches that of mixed venous blood (40 Torr). As the ventilation-perfusion ratio is gradually increased, alveolar oxygen partial pressure approaches that of inspired gas (149 Torr). Other things being equal, lungs with ventilation-perfusion inequality are not able to transfer as much oxygen and carbon dioxide as a lung which is uniformly ventilated and perfused, thereby resulting in hypoxemia.
In the "perfect" lung at rest the ventilation-perfusion ratio is approximately equal to 1. However, due to the decrease in ventilation-perfusion ratio down the normal lung actual values ranging from 0.63 to 1.69 have been observed (Morpurgo et al 1975). It has been estimated that this inequality is responsible for approximately half of the normal resting alveolar-arterial oxygen difference (Sylvester et al 1981).

3. Hypoventilation Alveolar oxygen partial pressure depends on a balance between the rate at which oxygen is removed from the lung by the blood and the rate at which it is replenished by alveolar ventilation. If ventilation is reduced, alveolar hypoxia and arterial hypoxemia occur. Hypoventilation is not evident in the normal lung at rest. Alveolar ventilation is sufficient to maintain normal oxygen and carbon dioxide partial pressures. Hypoxemia caused by hypoventilation has been observed during haemodialysis (Romaldini et al (1984). Carbon dioxide is removed from the blood by the dialyser. Ventilation is subsequently depressed causing alveolar hypoxia and hypoxemia.

4. Diffusion Oxygen moves across the alveolar membrane by passive diffusion because the partial pressure in the alveolar gas is higher than that in the blood. Diffusion through tissue is described by Fick's law. With respect to the lung, the rate of transfer of gas is proportional to the alveolar membrane area and the difference in gas partial pressure between the two sides and is inversely proportional to its thickness. The rate at which oxygen moves into the blood also depends on the rate of chemical combination of oxygen with haemoglobin (which itself varies with the partial pressure of oxygen in the blood) and the volume of blood in the pulmonary capillaries.

Alveolar oxygen tension is about 100 Torr. Mixed venous oxygen tension is about 40 Torr. The driving pressure of \((100-40) = 60\) Torr between the gas and the blood at the venous end of the pulmonary capillary, moves oxygen rapidly across the alveolar membrane. This causes the partial pressure of oxygen in the blood to rise quickly. However, the rise in oxygen partial pressure in the capillary blood decreases the driving pressure so that the oxygen partial pressure increases at a progressively slower rate as blood transverses the capillary.

Indirect measurements show that the mean capillary transit time of the
whole lung during rest is about 1.0 seconds (Wagner 1977). At rest, at sea level, after only about one third of the time available in the pulmonary capillary the partial pressure of oxygen in the arterial blood becomes very nearly equal to that of the alveolar gas. Inequalities in ventilation and perfusion down the lung mean that there is a vertical gradient of capillary transit times in the lung (Wagner et al 1986). This situation may change to influence gas exchange during exercise.

Diffusion limitations have long been accepted at altitude but they are generally considered to be unlikely at sea level in the normal individual (Asmussen and Nielsen 1960, Staub 1963, Cohen et al 1971, West and Wagner 1980).

B. Disease Induced Hypoxemia:

Arterial hypoxemia has been demonstrated in patients with a variety of lung diseases (Donald et al 1952, Storstein 1955, Refsum and Kim 1967, Lourenco et al 1965).

1. Anatomical Shunt The increased right to left shunting of blood is most severe in patients with congenital heart disease and those with atrial and ventricular septal defects. Pulmonary conditions such as atelectasis, pulmonary oedema and abnormal arterio-venous connections through fistulae may also result in arterial hypoxemia from this cause (West 1974).

2. Ventilation-Perfusion Ratio Inequality Ventilation-perfusion ratio inequality is the mechanism which is responsible for the hypoxemia of the majority of lung diseases and is the most common cause of cyanosis. It is responsible for the hypoxemia of chronic obstructive lung disease, pneumonia and pulmonary fibrosis. It is capable of decreasing arterial oxygen tension to half normal values and seriously limiting work capacity. In addition, the ventilation-perfusion ratio inequality also interferes with the transfer of carbon dioxide so that carbon dioxide retention may occur (West 1977).

3. Hypoventilation Depression of the respiratory centre by drugs or anesthesia, damage to the medulla by disease, diseases affecting the nerve supply to the muscles of the thorax or the muscles themselves, injury to the chest wall and obstruction to the upper airways can all cause hypoxemia
due to hypoventilation. Because the lung itself is normal, hypoxemia due to hypoventilation can usually be remedied if the precipitating cause can be removed (West 1974).

Asthma (Feisal and Fulcihan 1979) and chronic obstructive pulmonary disease (Pande et al 1974) increase the dead space fraction thereby decreasing effective alveolar ventilation. At rest this is compensated by an increase in total ventilation. However, compensatory increases in total ventilation during exercise are limited and hypoxemia results.

4. Diffusion Limitation Lung diseases which tend to thicken the alveolar membrane, such as interstitial fibrosis, sarcoidosis, asbestosis and alveolar carcinomatosis impede the diffusion of oxygen thereby causing hypoxemia. The effects of such diseases are much accentuated by exercise or the inhalation of a gas mixture low in oxygen (West 1974).

C. Altitude Induced Hypoxemia:

Hypoxemia at altitude relates mainly to the effect of the reduced oxygen partial pressure of the inspired air (West and Wagner 1980). The barometric pressure decreases with distance above the earth's surface. At 5000 metres barometric pressure is only 380 Torr. The partial pressure of oxygen of moist inspired gas is therefore 20.9% of (380-47) = 69 Torr. The effect of this reduced alveolar pressure can be predicted to cause hypoxemia as follows. Mixed venous oxygen partial pressure falls to about 20 Torr. A red blood cell passing through the pulmonary capillary will now be exposed to a driving pressure of only (69-20) = 49 Torr. The rate of movement of oxygen across the alveolar membrane will be correspondingly slower, possibly resulting in hypoxemia and an appreciable increase in alveolar-arterial oxygen difference. Furthermore, if exercise is combined with the hypoxia of altitude severe hypoxemia may result and work capacity will be markedly reduced (Johnson 1967, West and Wagner 1980, Sutton and Jones 1983).

Diffusion limited hypoxemia has been demonstrated at simulated altitudes (West et al 1962, Sylvester et al 1981). Sylvester et al (1981) considered the contribution of shunt and ventilation-perfusion ratio inequality to be minimal. However, recent investigations have found that the severe hypoxemia induced while exercising at simulated altitude, not only reflects

D. Exercise Induced Hypoxemia

Oxygen uptake is dependent upon blood flow (i.e. cardiac output) and the arterial and venous oxygen contents. During exercise oxygen uptake is thought to be limited by blood flow with arterial blood remaining highly saturated.

I. Steady-State Moderate Intensity Exercise

During moderate steady-state exercise the alveolar-arterial carbon dioxide difference decreases (Jones et al 1966, Wasserman et al 1967). There is disagreement with respect to the magnitude of the alveolar-arterial oxygen difference. Lithenthal et al (1957), Wasserman et al (1967), Asmussen and Nielsen (1957), and Jones et al (1966) found increases during exercise, while Hesser and Matell (1965) found a decrease.

Whipp and Wasserman (1969) suggested that these inconsistencies may be due to either blood tensions being uncorrected for temperature, different body positions during exercise, or differences in exercise intensities. They subsequently demonstrated an initial decrease in the alveolar-arterial oxygen difference in light exercise and then a progressive increase as exercise intensity was increased. Similar findings were reported by Dempsey et al (1982). The increase in the alveolar-arterial oxygen difference, with increasing work intensity, resulted from both a decrease in arterial oxygen tension and a rise in alveolar oxygen partial pressure.

To what extent do veno-atrial shunts, ventilation-perfusion mismatching, diffusion limitation and hypoventilation contribute to the observed fall in arterial oxygen tension during steady-state moderate intensity exercise?

(a) Veno-Atrial Shunt A two fold increase in shunt was observed in moderate exercise by Gledhill et al (1977). They postulated that the increase in shunt fraction during exercise probably came from the heart whose oxygen consumption increases with increasing work intensity. These findings are in disagreement with Harris et al (1976) who found that the
shunt fraction remains relatively unchanged during moderate exercise.

Mixed venous oxygen partial pressure falls progressively with increasing exercise intensity (Edwards et al 1972). Arterial oxygen tension would therefore fall due to blood with a reduced oxygen partial pressure passing through a normally small anatomical shunt. This is supported by the work of Whipp and Wasserman (1969), Raynaud et al (1973), Dempsey et al (1982) Sandoval et al (1983) and probably explains, in part, the increase in alveolar-arterial oxygen difference observed during high work rates.

(b) Ventilation-Perfusion Inequality A rapid and extensive recruitment of the lung apex for pulmonary blood flow occurs at low exercise intensity (West and Dollery 1960, Harf et al 1978, Mohsenifar et al 1983). Tidal volume also increases with concomitant activation of previously non ventilated or underventilated alveoli (Bryan et al 1964, Bake et al 1968, Jones and Clark 1969, Milette et al 1969). As a result there is a reduction in the number of alveoli with low ventilation-perfusion ratios. The resultant distribution of ventilation-perfusion ratios in the lung improves gas exchange by greatly enlarging the gas blood exchange interface. The improving gas exchange in turn probably explains the slight decrease in alveolar-arterial oxygen difference observed during light exercise (Dereks 1980).

As exercise intensity increases, no further redistribution of blood flow in the lung occurs (Harf et al 1978). Considerable intraregional ventilation-perfusion inhomogeneity therefore still exists in the normal lung in moderate to severe exercise (Gledhill et al 1978). Indeed there is some suggestion that as exercise intensity increases ventilation-perfusion mismatching actually increases again (Torre-Bueno et al 1985, Gale et al 1985). Hammond et al (1986a) has observed that ventilation-perfusion inequalities increase as a function of oxygen uptake. This must also account, in part, for the increasing alveolar-arterial oxygen difference with increasing exercise intensity.

(c) Hypoventilation No hypoventilation is evident in humans in either walking or cycling at a moderate steady-state. Total ventilation and alveolar ventilation increase in proportion to the increase in metabolic rate resulting in constancy of alveolar oxygen and carbon dioxide partial pressures (Asmussen 1965, Dejours 1964, Whipp 1981). If the exercise
intensity is above the anaerobic threshold, and the exercise duration is longer than 4 minutes, hyperventilation ensues with an increase in alveolar oxygen partial pressure. This constitutes respiratory compensation for the developing metabolic acidosis.


A number of factors could contribute to the increase in diffusing capacity during exercise. Some believe that the changes in the lungs diffusing capacity reflect solely the changes in pulmonary capillary volume and hence the changing size of the exchange surface (Karp et al 1968, Roughton and Forster 1957, Vreim and Staub 1973). The compliance of the pulmonary capillary bed is known to be high (Eklund and Holmgren 1967), therefore small increases in pulmonary vascular pressure during exercise will elicit substantial increases in pulmonary capillary blood volume.

In sustained exercise, hyperventilation occurs causing the alveolar partial pressure of oxygen to rise above 120 Torr. Increases in $[\text{H}^+]$, temperature and 2,3 diphosphoglycerate all contribute to a right shift in the oxy-haemoglobin dissociation curve (Klein et al 1980). This causes a greater unloading of oxygen at the tissue and a reduction in mixed venous oxygen tension. The rise in alveolar oxygen partial pressure and the fall in mixed venous oxygen tension help the diffusion process by increasing the driving pressure.

The decrease in oxygen affinity of haemoglobin will also hinder oxygenation of venous blood at the lung. However, due to the shape of the oxy-haemoglobin dissociation curve, the right shift causes greater falls in venous oxygen partial pressure than in arterial oxygen partial pressure. This is true on theoretical grounds (Grant 1982) and has been demonstrated experimentally by Frans et al (1979).
Exercise increases cardiac output and hence blood flow through the lung. This reduces severely the transit time of a single red blood cell through a pulmonary capillary. In the normal untrained subject, exercising at an oxygen uptake of 3.0 l/min, the pulmonary blood flow is about 20 l/min. This reduces the time available to complete equilibrium from about 1.0 second to about 0.35 seconds (Staub et al 1962, Gledhill et al 1977). However, it appears that even with reductions in transit time of up to one third of normal, the increase in diffusion capacity and the increased pressure gradient enable the normal lung to oxygenate blood effectively during moderate to severe exercise (Dempsey et al 1982).

It is therefore unlikely that the increase in alveolar-arterial oxygen difference observed during moderate steady-state exercise results from either increased shunting, hypoventilation or diffusion limitation. Changes in the ventilation-perfusion ratios are a more likely cause.

2. Steady State High Intensity Exhaustive Exercise

During high intensity exercise Asmussen and Nielsen (1957) found an increase in arterial oxygen tension. However, this result was not typical in that a significant fall in arterial oxygen tension has been reported by a number of other investigators (Suskind et al 1950, Filley et al 1954, Holmgren and Linderholm 1958, Asmussen and Nielsen 1960, Rowell et al 1964, Gledhill et al 1980, Dempsey et al 1982, Powers et al 1984, Hammond et al 1986a, Williams et al 1986, Powers and Williams 1987).

The fall in arterial oxygen tension ranged from 10-40 Torr and in most cases was not transient but persisted throughout the duration of the trial. Dempsey et al (1984) found that hypoxemia only occurred when work was greater than 85% of maximum and the oxygen uptake exceeded 3.5 l/min and that it was independent of mode and could be alleviated by prior work.

To what extent do veno-atrial shunts, ventilation-perfusion mismatching, diffusion limitation and hypoventilation contribute to the observed fall in arterial oxygen tension during steady state high intensity exhaustive exercise?

(a) Shunt. It is unlikely that the hypoxemia was due to veno-atrial shunt as only mild hyperoxia restored arterial oxygen tension to resting levels

(b) Ventilation Perfusion Inequality Ventilation-perfusion ratio inequalities persisted in heavy exercise (Overfield and Kylstra 1969, Torre-Bueno et al 1985, Gale et al 1985, Hammond et al 1986a) and may have contributed to the fall in arterial oxygen tension. However, the ventilation-perfusion inequalities were not sufficient to explain all of the observed fall in arterial oxygen tension.

(c) Hypoventilation The magnitude of the ventilatory response was the major determinant of exercise induced hypoxemia. Those with greatest hypoventilation had the lowest alveolar oxygen partial pressures and the greatest fall in arterial oxygen tension. Raising the partial pressure of oxygen in the alveoli by raising the inspired oxygen, or enabling a greater ventilatory response by replacing nitrogen in the inspired air with helium, lessened the fall in arterial oxygen tension (Dempsey et al 1985). Thus hypoventilation played a primary role in the exercise induced hypoxemia.

(d) Diffusion Limitation Dempsey et al (1985) proposed that the high sensitivity of exercise induced hypoxemia to changes in alveolar oxygen partial pressure is indicative of a diffusion limitation and incomplete end pulmonary capillary oxygen saturation, secondary to an inadequate time for equilibrium of red cells with alveolar oxygen in the pulmonary capillary.

Alveolar-capillary diffusion is usually not considered to be limiting either at rest or during light to moderate exercise. However, it may be limiting during high intensity exercise. In high intensity exercise, red blood cell transit time in the pulmonary capillary is reduced due to an increase in blood flow. Hermansen et al (1970) found mean maximal cardiac output in highly trained athletes to be 36 l/min. Assuming an anatomical veno-atrial shunt of 1.5% of the total cardiac output, pulmonary blood flow can be estimated to be near 35.5 l/min. This is normally compensated for by an expansion in the pulmonary blood volume of up to three times normal values (Dempsey et al 1980). However, even assuming a maximal volume of 250 ml, mean red blood cell transit time could be as low as 0.25 seconds. Furthermore, assuming a normal distribution of transit times, with a standard deviation of 0.1 seconds, almost 25% of the transit times would be less than 0.2 seconds.
It is therefore possible that in individuals with extremely high work capacities and maximal cardiac output, red blood cell transit time in the pulmonary capillary could be reduced to such an extent that diffusion is limiting.

E. Hypothesis

Arterial hypoxemia in normal individuals during moderate intensity exercise results primarily from an increase in ventilation-perfusion inequalities (Hammond et al 1986a). Arterial hypoxemia in athletes induced during high intensity exercise is directly related to the relative hypoventilation (Dempsey et al 1985). Those that ventilate the least have the greatest falls in arterial oxygen tension.

Hypoxemia has been observed at the onset of moderate to severe exercise in normal subjects (Barr et al 1964, Bjurstedt and Wigertz 1971, Young and Woolcock 1978, Oldenberg et al 1979). The fall in arterial oxygen tension occurred approximately 15-20 seconds after the onset of exercise and was transient in nature.

Relative hypoventilation and a concomitant fall in end tidal oxygen occur approximately 15-20 seconds after the onset of moderate to heavy exercise (see Section I). The timing of the fall in end tidal oxygen correlates highly with the timing of the fall in arterial oxygen tension as observed by Young and Woolcock (1978) and Oldenberg et al (1979).

It is hypothesized that the hypoxemia occurring at the onset of exercise is largely related to the degree of relative hypoventilation and the subsequent fall in alveolar oxygen partial pressure, and not to increases in veno-atrial shunts or increases in ventilation-perfusion inequalities, and that the mechanisms responsible are the same as those causing hypoxemia in athletes in steady-state high intensity exercise.
METHODS (Section II)

A. Subjects

All subjects (n=12) were Army personnel, male, aged 19-30 years, non-smokers, with no history of respiratory or cardiovascular impairment. Resting flow volume loops were obtained on each subject prior to the exercise test. Vital capacity, forced expiratory volume, peak flow and mid-expiratory flow, for all subjects, were within the normal range (Jones et al 1975).

A wide range of fitness levels were included. Maximal oxygen uptake for the 12 subjects ranged from 47.9 to 63.58 mls.kg\(^{-1}\).min\(^{-1}\). No subject had previous experience of running on the treadmill. All were selected on the basis of availability. Prior to testing each procedure was explained in full. Prior to catheterization each subject gave informed consent in writing. All protocols were reviewed and approved by The Princess Margaret Hospital Ethical Committee.

B. Experimental Protocol

In a preliminary session lung function was assessed and the subject was taught to run on the treadmill. They then underwent an incremental work test to maximum. The treadmill was set at 0% grade and 10 kph. The subject ran for 3 minutes. They then rested for 3 minutes. The treadmill grade was increased by 3% and another run performed. The incremental pattern was repeated until the subject could no longer cope with the work load imposed. The maximal oxygen uptake was used to determine the intensity of the subsequent blood collection trials.

Prior to the second session a catheter was inserted into the radial artery. The subject then completed one or more runs on the treadmill. The number of runs, the intensity of the runs, their duration, and the time at which blood samples were taken were as follows:

Series I: 1 run of approximately 2 minutes duration at 12 kph and 10% grade. Arterial blood samples were drawn at rest prior to the run and at approximately 8-10 second intervals.
Series 2: 2 runs of 2 minutes duration at a speed and grade estimated to elicit a theoretical oxygen uptake of 120% of maximum. The 2 runs were completed on the same day with a minimum of 20 minutes rest between runs. Arterial blood samples were drawn at rest prior to the run. During the run the first four blood samples were drawn as quickly as possible. The remaining blood samples were drawn at 20 second intervals. A total of 10 samples were obtained per subject.

Series 3: 2 runs of 5 minutes duration. The first at a speed and grade estimated to be 75% of maximum and the second at a speed and grade estimated to be 100% of maximum. The 2 runs were completed in the same order on the same day with a minimum of 20 minutes rest between runs. Blood samples were drawn prior to exercise and 10 secs, 30 secs, 1 min, 2 mins, 3 mins, 4 mins and 5 mins into exercise.

The intensity of the run in Series 2 and Series 3 were calculated as follows. The treadmill speed was set at 13 kph and the elevation required to elicit a theoretical oxygen uptake of a set percentage of maximum was calculated from the subjects maximal oxygen uptake (Shephard 1972).

\[
\% \text{ grade} = \frac{(W-V \times 4.61 - 7.7)}{(V \times 0.37)}
\]

Where \( V \) = Treadmill speed (13 kph)
\( W \) = Percentage of subjects maximal oxygen uptake

Time elapsed is recorded at the end of each breath. The time at which a blood sample is drawn is recorded as the time at the end of the concurrent breath. The corresponding respiratory data is calculated as the average of 3 breaths. The 2 breaths prior to the time of blood sampling and the 1 breath following. A total time of 5-8 seconds.

C. Equipment

During the incremental run oxygen uptake was calculated from expired gas collected in the last minute of each 3 minute increment. Expired air passed via a breathing valve (Koegel Y valve) and a short length of flexible tubing (Collins 32mm) to a series of four meteorological balloons. Continuous collection and analysis was made possible by a rotating valve system. Gas volumes were measured with a Tissot spirometer. Inspired and
expired concentrations of oxygen, carbon dioxide and nitrogen were measured with a mass spectrometer (Perkin Elmar Model 1100). All gas volumes were corrected and expressed as Standard Temperature and Pressure Dry (STPD). Heart rate was recorded by electrocardiogram (Avionics Model 3000) in the last 10 seconds of each increment.

During the experimental runs heart rate and respiratory parameters were measured using the breath-by-breath system as described in Appendix B. Blood samples were drawn and stored under anaerobic conditions. They were analysed as soon as possible after the trial for pH and oxygen and carbon dioxide partial pressures (Radiometer Copenhagen BMS-3). The pH electrode was calibrated using standardised pH buffers. The blood gas electrodes were calibrated using blood that had been equalibrated with gas mixtures of known oxygen and carbon dioxide partial pressure. All measurements were performed at 37°C.

D. Data Analysis

Correlations between parameters and between subjects were determined using the Pearson product moment and Spearman's rank order methods. The significance of differences between responses was assessed using the student's t test. Significance was accepted at the 0.05 level.
RESULTS (Section II)

Age, height, weight, maximal oxygen uptake, vital capacity, forced expiratory volume, peak flow and mid expiratory flow for each of the 12 subjects, together with mean values, are listed in Table 2.1, Table 2.2 and Table 2.3.

Series 1: This was a preliminary study where the subjects ran at the same absolute work load. Different degrees of fitness, as indicated by their maximal oxygen uptake, meant that the relative intensity of the work load was different for each subject.

The changes in end tidal oxygen were similar to those observed in Section I. End tidal oxygen initially increased, then 10-20 seconds later it decreased and continued to fall attaining minimum values approximately 30-70 seconds after the onset of exercise. End tidal oxygen then increased over the last 50 seconds of the trial returning to pre exercise levels in 2 of the 3 subjects. (Figure 2.1.1).

Arterial oxygen tension held relatively constant for 20 seconds then fell to attain minimum values 60-90 seconds after the onset of exercise. Arterial oxygen tension remained depressed throughout the remainder of the trial. In no subject did it return to pre exercise levels (Figure 2.1.2).

The time course and the magnitude of the fall in end tidal oxygen and arterial oxygen tension were different for each of the 3 subjects. However, in each subject the changes in end tidal oxygen appeared to be matched by corresponding changes in arterial oxygen tension. The subject with the greatest fall in end tidal oxygen partial pressure had the greatest fall in arterial oxygen tension. The subject with the smallest fall in end tidal oxygen partial pressure also had the smallest fall in arterial oxygen tension.
Table 2.1 Subject Personal Data (Section II - Series 1)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Height (cms)</th>
<th>Weight (kgs)</th>
<th>VO₂ Max (ml/kg)</th>
<th>FVC (mls)</th>
<th>FEV₁ (mls)</th>
<th>PEFR (l/sec)</th>
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<tr>
<td>ML</td>
<td>19</td>
<td>176.6</td>
<td>74.5</td>
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<td>GC</td>
<td>20</td>
<td>183.4</td>
<td>80.2</td>
<td>52.25</td>
<td>6090</td>
<td>4935</td>
<td>11.93</td>
</tr>
<tr>
<td>BM</td>
<td>30</td>
<td>183.1</td>
<td>81.0</td>
<td>53.14</td>
<td>6394</td>
<td>5485</td>
<td>10.66</td>
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</table>

Mean: 23.00 181.03 80.23 55.55 5866 4962 10.86
Std D: ±4.97 ±3.14 ±4.69 ±1.26 ±546 ±424 ±0.80

Table 2.2 Subject Personal Data (Section II - Series 2)

<table>
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<tr>
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<th>Height (cms)</th>
<th>Weight (kgs)</th>
<th>VO₂ Max (ml/kg)</th>
<th>FVC (mls)</th>
<th>FEV₁ (mls)</th>
<th>PEFR (l/sec)</th>
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<td>MB</td>
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<td>47.90</td>
<td>5056</td>
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<td>10.71</td>
</tr>
</tbody>
</table>

Mean: 24.67 175.77 77.47 49.19 5510 4886 10.43
Std D: ±2.49 ±6.04 ±11.92 ±0.99 ±452 ±606 ±0.51

Table 2.3 Subject Personal Data (Section II - Series 3)

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<th>Age (yrs)</th>
<th>Height (cms)</th>
<th>Weight (kgs)</th>
<th>VO₂ Max (ml/kg)</th>
<th>FVC (mls)</th>
<th>FEV₁ (mls)</th>
<th>PEFR (l/sec)</th>
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<td>67.1</td>
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<td>63.58</td>
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<td>4327</td>
<td>10.19</td>
</tr>
<tr>
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<td>67.5</td>
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<td>53.59</td>
<td>5289</td>
<td>4574</td>
<td>9.87</td>
</tr>
</tbody>
</table>

Mean: 23.83 172.80 69.13 57.37 5585 4473 10.30
Std D: ±2.19 ±3.99 ±9.90 ±4.24 ±226 ±105 ±0.62
Figure 2.1.1. Changes in end tidal oxygen during 2 minutes of treadmill running. Velocity = 12 kph. Grade = 10%. (3 subjects).

Figure 2.1.2. Changes in arterial oxygen tension during 2 minutes of treadmill running. Velocity = 12 kph. Grade = 10%. (3 subjects).
Series 2: In this series of experiments an attempt was made to equate the work loads by relating them to the individuals maximal oxygen uptake. The absolute work load differed from subject to subject. Also, as the time at which the blood samples were drawn differed from subject to subject statistical comparisons were not possible.

Ventilatory equivalent for oxygen (Figure 2.2.1) and end tidal oxygen (Figure 2.2.2), in all 6 subjects, fell from pre exercise levels, within 10 seconds after the onset of exercise, to reach minimum levels within 40 seconds. Over the remaining course of the run both ventilatory equivalent and end tidal oxygen recovered towards pre exercise levels. In all subjects the ventilatory equivalent for oxygen fell below normal resting values indicating a relative hypoventilation with respect to oxygen uptake.

Arterial oxygen tension (Figure 2.2.3) remained constant for approximately 20 seconds then fell to attain minimal levels within 50 seconds of the onset of exercise. At their lowest level, values for arterial oxygen tension ranged from 84 to 63 Torr. In all subjects, arterial oxygen tension remained well below pre exercise levels throughout the remainder of the run. This was reflected in a widening of the alveolar-arterial oxygen difference. The time course of changes in arterial oxygen tension lagged behind that of ventilatory equivalent and end tidal oxygen.

End tidal carbon dioxide (Figure 2.2.4) increased soon after the onset of exercise and remained elevated throughout the trial. This was accompanied by similar increases in arterial carbon dioxide tension (Figure 2.2.5).

Blood pH fell significantly in subject #1 but remained at, or near, resting levels for most of the trial in subjects #2 and #3 (Figure 2.2.6). There was a slight tendency for pH to fall in the last 20 seconds of the trial in these two subjects.

There was both a similarity in response when the 2 runs of each subject were compared and considerable differences in response between the 3 subjects. Greatest falls in ventilatory equivalent, end tidal oxygen and arterial oxygen tension were recorded by subject #1. The least falls were recorded by subject #3. This difference in response can be further observed when the relationship between carbon dioxide output and ventilation is examined (Figure 2.2.7). The slope for subject #1 was
significantly less than that of the other 2 subjects.

Significant correlations were demonstrated between ventilation and carbon dioxide output \((r=0.9419)\), ventilatory equivalent for oxygen and end tidal oxygen \((r=0.7889)\), ventilatory equivalent for oxygen and arterial oxygen tension \((r=0.7888)\), end tidal oxygen and arterial oxygen tension \((r=0.6372)\) and end tidal carbon dioxide and arterial carbon dioxide tension \((r=0.8879)\). These are presented graphically in Figures 2.2.7 to 2.2.11.
Figure 2.2.1. Changes in ventilatory equivalent for oxygen during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. Normal ventilatory equivalent for carbon dioxide = 24 litres/litre. (3 subjects, 2 trials each).

Figure 2.2.2. Changes in end tidal oxygen during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects, 2 trials each).
Figure 2.2.3. Changes in arterial oxygen tension during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects, 2 trials each).

Figure 2.2.4. Changes in end tidal carbon dioxide during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects, 2 trials each).
Figure 2.2.5. Changes in arterial carbon dioxide tension during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects, 2 trials each).

Figure 2.2.6. Changes in plasma pH during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects, 2 trials each)
Figure 2.2.7. Plot of carbon dioxide output against ventilation during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects, 2 trials each). $r = 0.7988$

![Figure 2.2.7](image)

Figure 2.2.8. Plot of ventilatory equivalent for oxygen against end tidal oxygen during 2 min. of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. $r = 0.7889$ (3 subjects, 2 trials each).

![Figure 2.2.8](image)
Figure 2.2.9. Plot of ventilatory equivalent for oxygen against arterial oxygen tension during 2 min. of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. $r = 0.7888$ (3 subjects, 2 trials each).

Figure 2.2.10. Plot of end tidal oxygen against arterial oxygen tension during 2 minutes of treadmill running at a power output estimated to be 120% maximal oxygen uptake. $r = 0.6372$ (3 subjects - 2 trials each).
Figure 2.2.11. Plot of end tidal carbon dioxide against arterial carbon dioxide tension during 2 minutes of treadmill running at a power output estimated to be 120% of maximal oxygen uptake. (3 subjects - 2 trials each). ($r = 0.8879$).
Series 3  Significance differences exist between exercise and pre exercise values for the ventilatory equivalent for oxygen, end tidal oxygen, arterial oxygen tension and alveolar-arterial oxygen difference. These differences are evident when working at both 75% and 100% of maximal oxygen uptake. Student's t scores and the significance of differences in pre exercise and exercise values of the ventilatory equivalent for oxygen, end tidal oxygen, end tidal carbon dioxide, arterial oxygen tension, arterial carbon dioxide tension, alveolar-arterial oxygen difference and alveolar-arterial carbon dioxide difference are presented in Table 2.4 and Table 2.5.

Oxygen uptake (Figure 2.3.1), heart rate (Figure 2.3.2), minute ventilation (Figure 2.3.3), end tidal carbon dioxide (Figure 2.3.9), arterial carbon dioxide tension (Figure 2.3.10) and pH (Figure 2.3.13) were all higher at the greater work intensity. The ventilatory equivalent for oxygen (Figure 2.3.4), end tidal oxygen (Figure 2.3.5) and arterial oxygen tension (Figure 2.3.6) were all lower the greater the work intensity. The significance of these differences for each parameter at each time interval is presented in Table 2.6.

At both work intensities the ventilatory equivalent for oxygen (Figure 2.3.4) and end tidal oxygen (Figure 2.3.5) returned to typical resting values by the end of the 3rd minute. On the contrary, arterial oxygen tension (Figure 2.3.6) remained depressed throughout the 5 minutes of the run. This trend resulted in a gradual increase in end tidal-arterial oxygen difference at both work intensities (Figures 2.3.7 and 2.3.8).

End tidal carbon dioxide (Figure 2.3.9) and arterial carbon dioxide tension (Figure 2.3.10) increased at the onset of exercise, remained relatively constant for the next 3 minutes, then fell slightly in the 5th minute. This was true at both work intensities. The rate of increase at the onset of exercise was faster at the higher work intensity. The end tidal-arterial carbon dioxide difference at both exercise intensities (Figures 2.3.11 and 2.3.12) reversed after about 20 seconds and remained relatively constant throughout the remainder of the run.
Figure 2.3.1. Comparison of the rate of change in oxygen uptake during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).

Figure 2.3.2. Comparison of the heart rate response during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).
Figure 2.3.3. Comparison of the rate of change in ventilation during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).

![Ventilation Graph](image)

Figure 2.3.4. Comparison of the rate of change in the ventilatory equivalent for oxygen during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. Normal ventilatory equivalent for oxygen = 24 1/1. (n=6).

![Ventilatory Equivalent Graph](image)
Figure 2.3.5. Comparison of the rate of change in end tidal oxygen during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).

Figure 2.3.6. Comparison of the rate of change in arterial oxygen tension during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).
Figure 2.3.7. End tidal-arterial oxygen difference during 5 minutes of treadmill running at a power output estimated to be 75% of maximal oxygen uptake. (n=6).

Figure 2.3.8. End tidal-arterial oxygen difference during 5 minutes of treadmill running at a power output estimated to be 100% of maximal oxygen uptake. (n=6).
Figure 2.3.9. Comparison of the rate of change in end tidal carbon dioxide during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).

Figure 2.3.10. Comparison of the rate of change in arterial carbon dioxide tension during 5 minutes of treadmill running at power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).
Figure 2.3.11. End tidal-arterial carbon dioxide difference during 5 minutes of treadmill running at a power output estimated to be 75% of maximal oxygen uptake. (n=6).

Figure 2.3.12. End tidal-arterial carbon dioxide difference during 5 minutes of treadmill running at a power output estimated to be 100% of maximal oxygen uptake. (n=6).
Figure 2.3.13. Comparison of the rate of change in plasma pH during 5 minutes of treadmill running at a power outputs estimated to be 75% and 100% of maximal oxygen uptake. (n=6).
Table 2.4  Student's t scores and the significance of differences in pre exercise and exercise values of ventilatory equivalent for oxygen, end tidal oxygen, end tidal carbon dioxide, arterial oxygen tension, arterial carbon dioxide tension, alveolar-arterial oxygen difference and alveolar-arterial carbon dioxide difference at 10, 30, 60, 120, 180, 240 and 300 seconds after the onset of exercise. Exercise intensity approximately 75% of maximal oxygen uptake.

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>10</th>
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<th>120</th>
<th>180</th>
<th>240</th>
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Table 2.5  Student's t scores and the significance of differences in pre exercise and exercise values of ventilatory equivalent for oxygen, end tidal oxygen, end tidal carbon dioxide, arterial oxygen tension, arterial carbon dioxide tension, alveolar-arterial oxygen difference and alveolar-arterial carbon dioxide difference at 10, 30, 60, 120, 180, 240 and 300 seconds after the onset of exercise. Exercise intensity approximately 100% of maximal oxygen uptake.

<table>
<thead>
<tr>
<th>Time (secs)</th>
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Table 2.6  Student's t scores and the significance of differences in oxygen uptake, carbon dioxide output, respiratory exchange ratio, heart rate, ventilation, ventilatory equivalent for oxygen, end tidal oxygen, arterial oxygen tension, end tidal carbon dioxide, arterial carbon dioxide tension, and pH at work intensities of 75% and 100% of maximal oxygen uptake. Comparisons were made at 10, 30, 60, 120, 180, 240 and 300 seconds after the onset of exercise.

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>Rest</th>
<th>10</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
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DISCUSSION - (Section II)

The maintenance of relative constancy of the blood gas tensions at rest and the isocapnia of moderate steady-state exercise is considered the norm in humans. In other species i.e. ponies (Forster et al 1984a, Pan et al 1983), goats (Bisgard et al 1982, Smith et al 1983) and dogs (Clifford et al 1983, Flandrois et al 1974, Kirlin et al 1987) direct blood gas measurements have shown that hyperventilation and hypocapnia is the typical response to moderate exercise.

The widely held assumption that arterial oxygen and carbon dioxide tensions are also held constant in the non steady-state traditionally comes from bloods taken after the completion of exercise. However, if the changes are transient they may not be detected after exercise has ceased (Ries et al 1983).

Evidence suggesting changes in arterial oxygen tension at the onset of exercise first came from measurements of end tidal oxygen partial pressure. Relative hypoventilation and transient falls in end tidal oxygen occurred approximately 15 seconds after the onset of strenuous exercise. These were observed in Section I, confirming the findings of others (Linnarsson 1974, Pearce and Milhorn 1977). A concomitant fall in arterial oxygen tension was implied but not measured directly.

In this section arterial oxygen tension and the kinetics of oxygen uptake, carbon dioxide and ventilation have been measured and their interrelationships examined in an attempt to confirm the existence of a fall in arterial oxygen partial pressure at the onset of exercise and its relationship to measures of ventilation and end tidal oxygen.

A. Hypoxemia at the Onset of Exercise

Suskind et al (1950) studied 10 normal subjects running on a treadmill and found a mean fall in arterial oxygen tension of 14 Torr at 2 minutes. Arterial oxygen tension then slowly rose back to resting levels during the remaining 4 minutes of the exercise period.

Matell (1963) observed that in light bicycle exercise, after a small transient fall, arterial oxygen tension rose and remained about 5 Torr
above resting levels throughout the remainder of the work period. Arterial oxygen saturation did not change significantly throughout the exercise period.

Bjurstedt and Wigertz (1970) examined the response of arterial oxygen tension to supine submaximal leg exercise in which the work load was varied sinusoidally between the extremes of 250 and 1050 kpm/min. The basic response of arterial oxygen tension to a change in work load was a transient change in the other direction. The change in arterial oxygen tension averaged 15 Torr and followed the change in work by approximately 15 seconds.

Large decreases in arterial oxygen tension (as much as 27 Torr) were measured during the first 90 seconds of slow stair-climbing exercise by Young and Woolcock (1978). Patients with chronic obstructive pulmonary disease recorded similar but smaller (10 Torr) decreases in arterial oxygen tension (Young and Woolcock 1979).

Oldenberg et al (1979) compared a free paced stairclimb to cycle ergometry at equivalent power outputs and found the fall in arterial oxygen saturation to be greater in stairclimbing than in cycling (i.e. equivalent to a fall in arterial oxygen tension of 27 and 16 Torr respectively).

In this study, falls in arterial oxygen tension of up to 30 Torr occurred in untrained subjects while running on a treadmill at high work intensities. The fall in arterial oxygen tension occurred some 10-15 seconds after the onset of work. The magnitude and time course of the falls in arterial oxygen tension in this study are similar to those found by the above investigators.

B. Considerations in Interpreting Results

Large changes in arterial oxygen tension have been recorded in this and above mentioned studies. There is some question as to whether the methods employed actually measure and reflect the physiological state. Errors can arise due to the following considerations:

1. Temperature Effect The degree of hypoxemia may be over estimated if alveolar and arterial gas tensions are not determined at the actual body or
blood temperature. Bradley et al (1956) estimated that a $1^\circ$C increment in temperature of blood sealed in an anaerobic environment will raise carbon dioxide partial pressure by 4.4% and oxygen partial pressure by 6% in the physiological range. Thus if arterial blood samples are drawn anaerobically at $38^\circ$C from a subject exercising at sea level and subsequently analysed for oxygen partial pressure and carbon dioxide partial pressure at $37^\circ$C, the partial pressure of oxygen will be about 6 Torr too low and the partial pressure of carbon dioxide 8-9 Torr too high, if due temperature corrections are not made.

Water vapour pressure is also altered by the change in temperature but in the opposite direction. This will offset the above mentioned effects of temperature. At $38^\circ$C arterial oxygen tension will be underestimated by about 0.5 Torr due to the higher intratracheal partial pressure of water at this temperature.

In this study arterial oxygen tensions were determined at $37^\circ$C. Due to the short exercise period (2 min in most trials) and the timing of the peak fall in arterial oxygen tension (10-40 sec after the onset of exercise) it is unlikely that temperature effects will markedly influence the results nor the conclusions drawn. The fall in arterial oxygen tension averaged over 20 Torr. Even assuming a $1^\circ$C increase in temperature and the underestimation of arterial oxygen partial pressure by 6%, the falls observed in this study would still be large and significant.

2. Blood Sampling Technique In the sitting position spontaneous time variations occur in arterial pH, and the partial pressures of oxygen and carbon dioxide at half minute intervals or longer (Barr et al 1964). The variations in arterial carbon dioxide partial pressure averaged 2.2% and in oxygen partial pressure averaged 3.3%. Therefore, if the blood sample is drawn over a rather short time interval (i.e. 30 sec or less) the partial pressures of oxygen and carbon dioxide may not be representative of the actual in vivo mean values.

It is not known whether these fluctuations persist, or are even accentuated, during exercise. In this study the blood samples were drawn over a 5-10 second period. However, the observed fall in arterial oxygen tension would still be significant with a 3.3% underestimation, even combined with the above temperature effects.
C. **Causes of Hypoxemia at the Onset of Exercise**

Changes in arterial oxygen tension at the onset of exercise occur as a result of complex interactions involving the body stores of oxygen, oxygen consumption, changes in ventilation-perfusion relationships, and the rate of adaptation of ventilation and cardiac output.

1. **Hypoventilation and Diffusion Limitation** Dempsey et al (1981) found that in athletes running on a treadmill at high work rates, the magnitude of the ventilatory response was the major determinant of exercise induced hypoxemia. He postulated that the failure to increase ventilation adequately, combined with the very rapid transit time of some red blood cells through the pulmonary capillary bed, could result in a failure of complete diffusion equilibrium for oxygen.

Hypoventilation accompanied by falls in arterial oxygen tension were found at the onset of exercise in this study and in the studies of Barr et al (1964), Bjursted and Wigertz (1970), Young and Woolcock (1978) and Oldenberg et al (1979). Furthermore Oldenberg et al (1979) found that the degree of hypoxemia could be changed by manipulating the ventilatory response. Hypoxemia was greater and ventilation lower when stairclimbing as compared to cycling. The differences in arterial oxygen saturation being correlated with the differences in ventilation. Also, the fall in arterial oxygen saturation could be prevented by overbreathing during stairclimbing or induced by controlled underbreathing during cycling.

Significant correlations between ventilation, end tidal oxygen and arterial oxygen tension were observed in this study. This lends further support to the concept that, as in high intensity steady-state exercise, the degree of hypoxemia in the non steady-state is related to the degree of relative hypoventilation.

2. **Veno-Atrial Shunt and Ventilation Perfusion Inequalities** The veno-atrial shunt and ventilation-perfusion distributions have not been measured, so their contribution to the observed falls in arterial oxygen tension, in this study, can only be speculated upon.

Changes in true anatomical shunt would not be expected at the onset of exercise. However, the mixed venous oxygen tension falls considerably
about 15 to 20 seconds after the onset of exercise (Edwards 1969). The passage of blood with a lowered oxygen content through a normal sized right to left shunt would contribute to the fall in arterial oxygen tension (Cook et al 1979).

Inequalities in the ventilation-perfusion ratios have been demonstrated in steady-state exercise (Gale et al 1985). These inequalities have been shown to increase with increasing exercise intensity and are said to account for approximately 50% of the increase in alveolar-arterial oxygen difference in the steady-state (Hammond et al 1986a). Furthermore, as is the case with true anatomical shunt, a fall in venous oxygen tension will cause a decrease in arterial oxygen tension at any given ventilation-perfusion distribution.

In series 2, two out of the three subjects showed only transient falls in ventilatory equivalent (Figure 2.2.1) and end tidal oxygen partial pressures (Figure 2.2.2). In the later part of the trial both subjects were hyperventilating with respect to oxygen and end tidal values had returned to resting levels, or above. Conversely arterial oxygen tension (Figure 2.2.3) remained depressed below resting levels throughout the 2 minutes of the trial.

Similarly in series 3, at both work intensities, ventilatory equivalent (Figure 2.3.4) and end tidal oxygen (Figure 2.3.5) fell transiently then increased to remain above resting levels for the last 3 minutes of the 5 minute trial. Again arterial oxygen tension (Figure 2.3.6) remained depressed below resting levels throughout the whole 5 minutes of the trial. The alveolar arterial oxygen difference (Figures 2.3.7 and 2.3.8) consequently increased.

The ability to change the degree of hypoxemia by manipulating the ventilatory response (Oldenberg et al 1979) and the correlation between hypoventilation and arterial oxygen tension demonstrated in this study, and by a number of other investigators (Barr et al 1964, Bjursted and Wigertz 1970, Young and Woolcock 1978, Dempsey et al 1982), suggests that the initial transitory fall in arterial oxygen tension is, at least in part, due to the relative ventilation occurring at the onset of exercise. However, this relationship is not maintained into the steady-state. The hypoxemia occurring under these conditions must therefore be due to either:
veno-arterial shunting, falls in mixed venous oxygen tension with a given shunt and ventilation-perfusion distribution, worsening of the ventilation-perfusion distribution, or some combination of these.

D. Cause of Hypoventilation at the Onset of Exercise

In moderate to high intensity steady-state exercise normal compensatory hyperventilation generally enables blood gas homeostasis to be maintained at, or near, resting levels. At the onset of exercise, relative hypoventilation occurs and there is a concomitant fall in arterial oxygen tension. Opinions differ as to the role of humoral stimuli, mechanical constraints on breathing, and differences in the kinetics of ventilation and oxygen uptake, in causing such changes.

1. Humoral Stimuli

In moderate to high intensity steady-state exercise arterial blood gas tension changes, metabolic acidosis, and increases in temperature and catecholamines represent known humoral stimuli to breathe. When combined, these could exert a powerful synergist effect on total ventilatory output (Wasserman et al 1975, Dempsey et al 1977). There is conflicting evidence as to whether the ventilatory response in the non steady-state is related to these humoral stimuli.

(a) Arterial Carbon Dioxide and Oxygen Partial Pressures

In the steady-state there is proportionality between carbon dioxide output and ventilation and constancy of alveolar and arterial gas tensions. In series 2 of this study, in all 3 subjects, the relationship between carbon dioxide output and ventilation is similarly linear (Figure 2.2.7). However, in subject #1, the ventilatory equivalent for carbon dioxide is considerably less than normal, indicative of hypoventilation with respect to carbon dioxide output. This is reflected in higher than normal end tidal (Figure 2.2.4) and arterial (Figure 2.2.5) carbon dioxide partial pressures. In subjects #2 and #3 the ventilatory equivalent for carbon dioxide is slightly greater than normal, indicative of slight hyperventilation with respect to carbon dioxide output. This is reflected in slightly lower than normal end tidal (Figure 2.2.4) and arterial (Figure 2.2.5) carbon dioxide partial pressures.

All 3 subjects also show falls in the ventilatory equivalent for oxygen uptake (Figure 2.2.1). This is indicative of hypo-ventilation with
respect to oxygen uptake and is reflected in decreases in end tidal oxygen (Figure 2.2.2) and arterial oxygen partial pressure (Figure 2.2.3). The degree of hypoventilation and the falls in end tidal and arterial carbon dioxide partial pressure being greatest in subject #1.

Neither arterial oxygen nor carbon dioxide partial pressures are therefore maintained at resting levels. Thus it can be argued that, rather than the blood gas tensions being the primary stimuli for the control of ventilation, it would appear that the blood gas tensions are a consequence of the ventilatory responses to other mechanisms.

(b) Metabolic Acidosis In heavy exercise Gledhill et al (1980) found that the fall in arterial oxygen tension was inversely related to the degree of acidosis i.e. acidosis seemed to stimulate ventilation and minimize hypoxemia. Elevating haematocrits decreased the acidosis. This in turn decreased the hyperventilatory response and lead to a lowering of arterial oxygen tension. Similarly, the rise in arterial oxygen tension following the transient fall at the onset of exercise observed by Matell (1963) was related to the increasing metabolic acidosis and compensatory hyperventilation. This was supported by the work of Whipp and Wasserman (1986) who found no increase in lactic acid and no compensatory hyperventilation during exercise when the work increments were less than 4 minutes in duration.

On the contrary, Dempsey et al (1982a) found that the ventilatory response was not related to differences in humoral stimuli. Compensatory hyperventilation was either minimal or absent and uncorrelated with the magnitude of metabolic acidosis and/or hypoxemia (Dempsey et al 1982a). Furthermore, in series 2 of this study, subject #1 exhibited both the largest falls in pH (Figure 2.2.6) and the largest fall in ventilatory equivalent. This further suggests that the compensatory hyperventilation is not related to the degree of metabolic acidosis.

(c) Catecholamines and Temperature Increases in both catecholamines and temperature are known stimuli to ventilation. However, in this study, arterial oxygen tensions had reached minimal values and was starting to rise within 40 seconds of the onset of exercise. It is unlikely that the temperature or catecholamines had changed sufficiently within this time and that they would constitute a significant stimuli to ventilation.
From the results of this, and other studies, it therefore appears unlikely that the ventilatory response at the onset of exercise is related to the differences in humoral stimuli.

2. Mechanical Constraints on Breathing Breathing a less dense gas mixture, such as oxygen in helium, increases total gas flow in the lungs by decreasing turbulence (Murphy et al 1969) and resistance to turbulent flow in the large upper airways (Comroe et al 1962, Murphey et al 1969). The reduced turbulence allows higher flow with unchanged ventilatory drive and a reduction in the cost of breathing (Nattie and Tenney 1970, Ward et al 1980).

At rest, and at low work rates, there is no change in ventilation while breathing a mixture of helium (80%) and oxygen (20%). In high intensity exercise, ventilation, ventilatory equivalent and respiratory rate are all increased, relative to air, by breathing a helium-oxygen mixture (Nattie and Tenney 1970, Spittler et al 1980, Hussain et al 1985, Maillard et al 1986). The cost of breathing, as indicated by the oxygen uptake, is also decreased (Ward et al 1982a). Dempsey et al (1982a) also observed hyperventilation and a reduction in the typical fall in arterial oxygen tension while breathing helium. It appears therefore that the respiratory system could have corrected the hypoventilation and hypoxemia, with air breathing, if ventilation had increased.

Similarly, an increase in respiratory drive (i.e. $P_{O.1}$) with resistive loading during exercise (Lind and Hesser 1984, D'Urzo et al 1987) and a reduction in ventilation with mechanical unloading of the respiratory system by inspiratory assistance during exercise (Poon et al 1987) have also been reported.

The above findings suggest that mechanical characteristics of the airways may normally exert an important influence on ventilation such that during exercise of high intensity, a marked dissociation might therefore exist between inspiratory neural drive and mechanical input (Nattie and Tenney 1970, Ward et al 1982a, Dempsey et al 1985). The following factors could possibly contribute to this dissociation. They may also operate to limit ventilation at the onset of exercise.

(a) Limitations To Flow: At high work rates, due to increased carbon
dioxide production, the ventilations required to maintain blood gas homeostasis may be very high. Flow resistive work will therefore increases. Hypoxemia in the horse, (an obligatory nasal breather), has been attributed to just such an increase in flow resistive work (Thorsten et al 1983).

The possibility of mechanical limitations to airflow generation occurring in humans during high intensity exercise is supported by the findings that: In normal subjects, during moderate intensity exercise, the tidal flow volume loop is situated well within the maximum flow volume curve obtained at rest (Grimby et al 1971, Stubbings et al 1980a). However, during high intensity exercise, airflows approach, and may even reach, their volume specific maximum (Grimby et al 1971, Hesser et al 1981, Olafsson and Hyatt 1969, Jensen et al 1980, Stubbings et al 1980). Athletes can attain about 90% of their resting maximal breathing capacity during high intensity exercise as opposed to about 70% of the maximum attained by normal subjects (Shephard 1966, Hesser et al 1981, Folinsbee et al 1983). Exercise ventilation and work capacity are reduced in normal subjects when the resistance to flow is increased by breathing dense gases (Wood and Bryan 1978).

However, the flows required to maintain normal ventilation at the onset of exercise are well below that found in high intensity steady-state exercise. It is therefore unlikely that mechanical limitations to air flow generation occurs at the onset of exercise in this study.

(b) Fatigue of Respiratory Muscles One explanation, for at least part of the absence of compensatory hyperventilation during heavy exercise, may be that inspiratory drive is reflexly inhibited to prevent inspiratory muscle fatigue.

Diaphragmatic fatigue occurs when the diaphragm develops pressures greater than 40% of maximum (Roussos and Macklem 1977). Inspiratory muscle fatigue develops if the pleural pressure generated is greater than 50-70% of maximum (Roussos et al 1979). It is considered that such critical levels are attained during exercise when ventilations exceed about 60% of maximum breathing capacity (Freedman 1970, Tenney and Reese 1968). Fatigue also occurs more quickly at low inspired oxygen (Jardim et al 1981) and when the subjects breath at high lung volumes (Roussos et al 1979).
The following observations further support the contention that respiratory muscle fatigue can occur: Training of inspiratory muscles improved both strength and endurance of respiratory muscles and lead to improved exercise tolerance in patients with chronic airflow limitation (Grassino et al 1979). Decrements in respiratory muscle strength and endurance occurred after marathon running (Loke et al 1982). Prior ventilatory work decreased heart rate, ventilation, oxygen uptake and performance of subsequent maximal running (Martin et al 1982). However, on the contrary, Morgan et al (1987) found that inspiratory muscle training did not increase exercise performance or maximal oxygen uptake in cyclists.

In high intensity exercise limb muscle can fatigue in relatively short periods of time. It is probable that during such exercise inspiratory muscles also operate at a potentially fatiguing level. However, the endurance properties of respiratory muscles are greater than limb muscles (Gandevia et al 1983). This combined with the fact that exercise is not maintained for an extended period time would suggest that inspiratory muscle fatigue did not contribute significantly to the hypoventilation observed at the onset of exercise.

(c) Energetics of Respiratory Muscle Contraction

Little oxygen is consumed by the respiratory muscles at rest and during light exercise (Bartlett et al 1958). However, the oxygen consumed increases as ventilation increases (Levison and Cherniack 1968, Kastardis et al 1986). Anholm et al (1987) estimated that at ventilations above 160 l/min respiratory muscles use nearly 500 ml/min of oxygen and consume 4 l/min of the total available blood supply. In theory, there is a level of ventilation above which any further increase in oxygen uptake would be consumed entirely by the respiratory muscles and not result in increasing the oxygen supply to the rest of the body. Estimates for this limiting value vary from 120 to 170 l/min (Margaria et al 1960, Otis 1954, Shephard 1966). Ventilation may therefore be reflexly suppressed so that oxygen supply to the other tissue is not compromised at the cost of a reduction in arterial oxygen tension.

Although such limiting levels of ventilation are readily attained by athletes during long term high intensity exercise the ventilation required to maintain arterial oxygen tension at normal resting levels at the onset of exercise would be considerably less. It is therefore unlikely that this mechanism is responsible for the hypoventilation observed at the onset of
exercise.

3. Kinetics of Ventilation and Oxygen Uptake Bjursted and Wigertz (1971) observed that during exercise the rate of change of heart rate preceded that of ventilation for up to 3 minutes with a time delay of 15 seconds. As the exercise was performed in the supine position, it was assumed that stroke volume was relatively constant and that adjustments in cardiac output were effected almost exclusively through changes in heart rate. Therefore, the rate of changes in cardiac output, and hence oxygen uptake, probably also preceded that of ventilation.

Similar relationships between the rates of change in ventilation and oxygen uptake, in the transient phase, were suggested by Jones et al (1970). In Section I, it was seen that the muscle to lung circulation time ensured that the mixed venous tensions for oxygen and carbon dioxide remained unchanged for at least the first 15 seconds. In this period changes in oxygen uptake and carbon dioxide output resulted only from changes in cardiac output. Therefore the rate of change of heart rate, cardiac output, oxygen uptake and carbon dioxide output were approximately the same. As ventilatory changes follow both those of oxygen and carbon dioxide, alveolar and arterial partial pressures, for both oxygen and carbon dioxide, were held constant at resting levels.

After about 15 seconds mixed venous oxygen tension falls reflecting the increased utilization of oxygen at the tissue. Due to the greater capacity of the body to store carbon dioxide mixed venous carbon dioxide tension remains virtually unchanged. Oxygen uptake now increases due to both increases in cardiac output and an increase in the difference in arterio-venous oxygen content. Carbon dioxide output increases due almost solely to an increase in cardiac output. Therefore the rate of change of oxygen uptake exceeds the rate of change of carbon dioxide output.

Ventilation can not track both oxygen uptake and carbon dioxide output. Ventilation increases in proportion to the output of carbon dioxide. Alveolar carbon dioxide partial pressure therefore remains relatively constant. However, there is a relative hypoventilation with respect to oxygen uptake and end tidal oxygen partial pressure falls. It is postulated that this fall in end tidal oxygen partial pressure causes a concomitant fall in arterial oxygen partial pressure.
Young and Woolcock (1979) also postulated that the arterial oxygen tension at the onset of exercise was sensitive to a discrepancy between the rate of change in ventilation and the rate of change in oxygen uptake. They concluded that a faster rate of increase in alveolar ventilation, or a slower rate of increase in oxygen uptake, were the most likely causes of the smaller non steady-state decrease in arterial oxygen tension that they observed in patients with airway obstruction.

Oldenburg et al (1979) observed smaller ventilations and larger falls in arterial oxygen tension while stair climbing than while cycling. Total ventilation was 20.3% less while stair climbing and the fall in arterial oxygen tension correlated with this decrease in ventilatory response. Oldenburg et al (1979) concluded that, although the oxygen uptake was the same for both stairclimbing and cycling, the transients may have differed, and that it was the differences in the transients of ventilation, carbon dioxide output and oxygen uptake that were significant in determining arterial oxygen tension.

In the section II study, significant correlations were found between the ventilatory equivalent for oxygen and end tidal oxygen, the ventilatory equivalent for oxygen and arterial oxygen tension, and end tidal oxygen tension and arterial oxygen tension. This supports the contention that the fall in arterial oxygen tension, occurring approximately 15 seconds after the onset of exercise, is related to the relative hypoventilation and the concomitant fall in end tidal oxygen.

E. Effect of Work Intensity on Oxygen and Ventilation Kinetics

Maintenance of alveolar gas partial pressures is dependent upon similar kinetics for ventilation, oxygen uptake and carbon dioxide output. At the onset of exercise oxygen uptake kinetics are significantly faster than those of ventilation. Carbon dioxide output and ventilation kinetics are similar. Alveolar carbon dioxide partial pressure is therefore maintained but there is a transient fall in alveolar oxygen partial pressure. Changes in work intensity may preferentially change the kinetics of one parameter causing changes in both the magnitude and timing of the changes in alveolar gas tensions.

1. Oxygen Uptake Kinetics. Reports are conflicting as to the effect of
work intensity on both the kinetics of ventilation and the kinetics of oxygen uptake. Margaria et al (1965) and Di Prampero et al (1970) reported that the pattern of rise in oxygen uptake to steady-state, when considered as a single exponential process, is the same regardless of work intensity. On the contrary, Astrand and Saltin (1961b) and Cerretelli et al (1977) found that as the work load increased the maximum level of oxygen uptake was more rapidly attained. However, most have found that the oxygen uptake kinetics are delayed as the work intensity increases above the anaerobic threshold (Whipp and Wasserman 1972, Linnarsson et al 1974). Hagberg et al (1978) reported a doubling of the half time when the exercise intensity was increased from 25% to 75% of the maximal oxygen uptake.

When the oxygen uptake response is partitioned into 2 phases conflicting results have also been obtained. Cooper et al (1985) found the magnitude of the phase I response to increase slightly with increasing exercise intensity while phase II kinetics were the same for the two different work rates. On the contrary Linnarsson (1974) found that as the intensity was increased the magnitude of the phase I response was unchanged but became an ever decreasing percentage of an increasing steady-state oxygen uptake. However, phase II kinetics increased with increasing exercise intensity (Whipp and Wasserman 1986).

2. Ventilation Kinetics Asmussen and Nielsen (1948) and Asmussen (1973) both found ventilation in the transition from rest to exercise to roughly correlate with the intensity of the exercise. Astrand and Christensen (1963) and Beaver and Wasserman (1970) could find no such relationship between ventilation and work intensity.

When the ventilatory response is partitioned into 2 phases, again, conflicting results have been obtained. Beaver and Wasserman (1968) found great variability in the magnitude of the phase I response. Others have found the phase I ventilatory response to be independent of intensity (Bledsoe and Hornbein 1981). Like oxygen uptake, it therefore becomes a decreasing percentage of an increasing steady-state ventilatory response.

Although there is conflicting opinion as to the magnitude of the phase I ventilatory and oxygen uptake responses with increasing exercise intensity, there is agreement that the duration of the phase I response decreases with increasing intensity. Phase I is related to the transit time between the
muscle and the lung. Cardiac output increases with increasing exercise intensity therefore transit time decreases. There is also agreement that the phase II ventilatory response is prolonged in exercise above the anaerobic threshold (Whipp and Wasserman 1972).

The overall response is the sum of the phase I response and the phase II response. It is possible that at sub anaerobic work loads a small increase in intensity will cause a decrease in the phase I kinetics with no change in the phase II kinetics, hence an overall decrease in kinetics. At work loads just above the anaerobic threshold an increase in intensity may cause a decrease in phase I kinetics that is balanced by a similar increase in phase II kinetics such that the overall kinetics are unchanged. At higher work loads an increase in intensity may cause an increase in phase II kinetics that exceeds the decrease in phase I kinetics such that the overall kinetics increases. This could explain the variability in the observed responses.

4. Alveolar Oxygen Partial Pressure With increasing exercise intensity phase I becomes shorter. The fall in end tidal oxygen partial pressure should therefore occur earlier with increasing exercise intensity.

The magnitude of the fall in end tidal oxygen partial pressure is dependent upon the ratio of ventilation and oxygen uptake i.e. the ventilatory equivalent for oxygen uptake. If the changes in ventilation and oxygen uptake are proportional the ventilatory equivalent, relative hypoventilation and end tidal oxygen partial pressure will all remain unchanged. For the ventilatory equivalent to decrease and end tidal oxygen partial pressure to fall with an increase in exercise intensity, the increase in oxygen uptake must be proportionally faster than the increase in ventilation. Oxygen uptake is tied to the cardiac output. The kinetics of oxygen uptake would be expected to decrease or remain unchanged. Ventilation increases at higher work intensities due to the stimulus of additional humoral and neural factors. Hence an increase in ventilatory equivalent and less of a fall in end tidal oxygen partial pressure is more likely as the exercise intensity is increased above the anaerobic threshold.

In this study, at the higher work intensity, oxygen uptake (Figure 2.3.1), carbon dioxide output, and ventilation (Figure 2.3.3) were higher and the
ventilatory equivalent for oxygen (Figure 2.3.4), and end tidal oxygen (Figure 2.3.5) were lower at each of the 8 sample times. However, none of these differences were significant (Table 2.6). At the higher work intensity, arterial oxygen tension (Figure 2.3.6) was significantly lower at 1 sample time and arterial carbon dioxide tension (Figure 2.3.10) was significantly higher at 2 the sample times (Table 2.6). The significant differences in blood gas tensions may therefore reflect increasing ventilation-perfusion inequalities and decreasing mixed venous oxygen tension rather than a fall in ventilatory equivalent for oxygen uptake.

The timing of the fall in end tidal oxygen (Figure 2.3.5) and arterial oxygen tension (Figure 2.3.6) at the two different work intensities were not significantly different. The differences in intensity, as determined from the differences in oxygen uptake, were small. Also, the blood sampling rate was low. Any differences in timing would be small and probably not detected using the current rate of sampling.

F. Conclusions

Hypoxemia occurs during high intensity steady-state exercise in athletes and persists for as long as the exercise is continued. Hypoxemia also occurs at the onset of low to moderate intensity exercise in both athletes and normal subjects. In these circumstances the fall in arterial oxygen tension is usually transient in nature. In this study, hypoxemia occurred at the onset of moderate to high intensity exercise in normal untrained subjects. It occurred at two different work intensities and persisted for the 5 minute duration of the trial.

Hypoventilation with respect to oxygen uptake, resulting from the delayed increase in carbon dioxide output and ventilation, undoubtedly contributes to the initial fall in arterial oxygen tension at the onset of exercise. However, it does not account for all of the fall, as arterial oxygen tension remains depressed throughout the 5 minutes of the trial whereas the ventilatory equivalent for oxygen and end tidal oxygen partial pressure return to normal steady-state levels. Ventilation-perfusion distribution changes and a decreasing mixed venous oxygen tension with a given shunt and given ventilation-perfusion distribution, must also contribute to the fall in oxygen tension occurring at the onset of exercise.
SECTION III

EFFECT OF EXERCISE MODE AND ENTRAINMENT OF BREATHING FREQUENCY TO GAIT ON VENTILATION AND GAS EXCHANGE DURING EXERCISE

INTRODUCTION


However, ventilatory control is more complex and involves more than simply matching of overall ventilation to the carbon dioxide production and maintaining constancy of arterial carbon dioxide tension. It seems that a breathing pattern must be generated, that provides the necessary gas flow, while minimizing the muscular work performed by the lung and chest wall (Otis 1954, Mead 1960, Stubbing et al 1980a). Therefore, like overall ventilation, other indices of ventilation, including breathing frequency, tidal volume, expiratory flow rate and functional residual capacity, must be regulated in a precise and highly predictable fashion.

A. Breathing Pattern and Ventilatory Kinetics

Overall ventilation is the product of tidal volume and breathing frequency. Consequently, increases in ventilation can result from increases in either tidal volume, breathing frequency, or both. Alternatively, the relationship between tidal volume and breathing frequency may change. For example, changes in tidal volume may be compensated for by opposite changes in breathing frequency such that overall ventilation remains constant.

1. Normal Breathing Pattern At rest, inspiration is an active process involving contraction of both the diaphragm and external intercostal muscles. Expiration is passive, due to the elastic recoil of the lung, and is typically followed by an "expiratory" pause. Expiratory duration (TE)
is therefore longer than inspiratory duration (TI).

With increasing intensity of work, increases in ventilation are brought about initially by increases in tidal volume (Lind and Hesser 1984a). Up to a tidal volume of approximately 1.4 litres inspiratory and expiratory duration remain constant, indicating that breathing frequency is unchanged. In the range of tidal volume from 1.4-2.4 litres, both inspiratory and expiratory duration decrease as tidal volume increases, indicating an increase in breathing frequency. Inspiratory duration and total breath duration (Ttot) fall but the ratio between them (TI/Ttot) remains relatively constant (Bradley 1977).

Maximum tidal volume is about 2.4 litres, approximately 50% of vital capacity (VC) (Hey et al 1966, Lind and Hesser 1984a, Jones 1984). Gallagher et al (1987) found that tidal volume plateaued at a similar percentage of vital capacity in submaximal exercise with hypercapnia. This suggests that the plateauing of tidal volume during maximal exercise is not due to stimuli related to the high levels of exercise but is a function of the level of ventilation. When maximal tidal volume is attained increases in ventilation can only then be achieved by increases in breathing frequency.

As breathing frequency increases expiration becomes active (Clark et al 1983, Kay et al 1975a). The muscles of the abdominal wall and the internal intercostals are the main muscles of expiration. First the "expiratory pause" is eliminated, then expiratory duration is decreased, and finally inspiratory duration is decreased. Because expiratory duration decreases faster than inspiratory duration, total breath duration decreases faster than inspiratory duration. This causes the ratio TI/Ttot to increase.

The increase in tidal volume at the onset of exercise is achieved by a decrease in functional residual capacity. This is brought about by enhanced expiratory activity of the internal intercostal muscles, and/or a rise in abdominal pressure, due to contraction or increased tone of the abdominal muscles. In light exercise expiration remains active with the further increases in tidal volume being due to further decreases in functional residual capacity. In moderate and heavy exercise further increases in tidal volume are taken equally from inspiratory and expiratory reserve volumes (Lind and Hesser 1984a).
The decrease in functional residual capacity with increasing exercise intensity is important in terms of work optimization. Cha et al (1987) estimated that exercise in which the functional residual capacity decreases requires up to 34% less elastic work compared with exercise performed with a fixed functional residual capacity at a given volume.

2. Control of Breathing Pattern
At the onset of exercise the increase in tidal volume and inspiratory flow are parallel with the increase in gas exchange and occur over a 3 minute period. The changes in inspiratory duration, total breath duration and breathing frequency are faster than that of gas exchange, occurring within 1 minute (Szekely et al 1982). The different time course of these two groups of parameters suggests that they are controlled by different mechanisms. It is possible that neural factors control inspiratory duration, total breath duration and breathing frequency, while gas exchange and humoral factors control tidal volume, inspiratory flow and ventilation.

There is also, in the control of ventilation, some interaction between expiratory and inspiratory duration. Some investigators have concluded that expiratory duration is determined by the previous inspiratory duration (Bradley 1977, Gautier 1980). Others have suggested that expiratory duration is, at least partially, determined by laryngeal regulation of resistance to expiratory flow (Bartlet et al 1973, England and Bartlet 1982, Gautier et al 1973, Remmers and Bartlet 1977).

3. Influence of Breathing Pattern on Oxygen uptake
Most investigators agree that the spontaneous breathing frequency minimizes the work of breathing. This assumes that deviations from the spontaneous breathing pattern will somehow be less efficient.

Kennard and Martin (1984) compared the oxygen cost of walking using breathing frequencies that ranged from the lowest sustainable to a frequency twice the spontaneous frequency. Tidal volume was not controlled. Ventilation was 65% higher at the highest breathing frequency. However, oxygen uptake was constant and independent of breathing frequency suggesting that the spontaneous breathing frequency does not minimize oxygen uptake.
Auchincloss et al (1966) found that small variations in breathing pattern following the onset of work did not alter the time course of oxygen uptake at the alveolar membrane. They felt that this was due to the buffering effect of the considerable oxygen stores within the lung.

Boutellier and Farhi (1986) examined the effect of breathing pattern on cardiac output and found frequency to have no effect. However, changes in tidal volume had a significant effect on cardiac output. This effect was greater in the sitting position than the supine and was probably mediated by the facilitation of venous return due to the greater ventilatory movements as tidal volume increased. Oxygen uptake is the product of cardiac output and the difference in arterio-venous oxygen content. Changes in cardiac output due to changes in breathing pattern may therefore induce changes in oxygen uptake.

B. Factors Affecting Breathing Pattern and Ventilatory Kinetics

Faster kinetics for oxygen uptake than for ventilation at the onset of exercise cause a relative hypoventilation with respect to oxygen uptake and a transient fall in alveolar and arterial oxygen partial pressures. Any changes in the normal kinetics of either oxygen uptake or ventilation will effect the extent to which alveolar and arterial oxygen partial pressure will change at the onset of exercise. Breathing pattern, and therefore the kinetics of ventilation and oxygen uptake, are known to be influenced by the following:

1. Mode of Activity The ventilatory kinetics and the values obtained at steady-state, closely relate to the oxygen uptake and power output of the active muscles. However, it also depends on the muscles that are exercising (Cerretelli et al 1977). Arm exercise gives higher ventilation, for the same oxygen uptake, than leg exercise (Asmussen and Nielsen 1946). Bicycling with one leg gives a higher ventilation and lower alveolar carbon dioxide partial pressure, per oxygen uptake, than bicycling with two legs (Klausen et al 1982). Running, compared with walking at the same oxygen uptake, produces higher ventilations (McMurry and Alborn 1982). Cycling, compared with stairclimbing at the same oxygen uptake, produces a higher ventilation (Oldenberg et al 1979).

The mode of exercise also influences the breathing pattern. Bainton (1972)
found that increments of speed on a treadmill caused increases in ventilation by increasing breathing frequency. Increases in grade caused increases in tidal volume.

In the steady-state, the maximal oxygen uptake and maximal heart rates vary with the mode (Astrand and Saltin 1961). This probably reflects the different muscle mass used and the different speed and tensions developed by the different muscles (Hermansen et al 1970, Asmussen and Hemmingsen 1958). Mode also affects the kinetics of oxygen uptake. Cerretelli et al (1977) found that the oxygen kinetics were slower for arm cranking than leg pedalling at equivalent power outputs. During the same power outputs, oxygen uptake and ventilation were higher during lifting tasks than in bicycle ergometry (Petrofsky and Lind 1978).

Cockcroft et al (1985) also found mode to effect arterial oxygen saturation during exercise. Desaturation in patients with chronic obstructive pulmonary disease was significantly greater when exercising on the treadmill than when exercising on the bicycle.

2. Posture In the upright posture at rest, gravitational effects limit venous return and keep stroke volume relatively low. Removing the gravitational effects, by assuming the supine position, increases stroke volume to the same extent that it would be increased by upright exercise (Bevegard et al 1960, Loeppky et al 1981, Poliner et al 1980, Rushmer 1959, Thadani and Parker 1978). Therefore, at the onset of exercise, increases in cardiac output from the supine position result only from increases in heart rate. Cardiac output therefore increases more slowly than it would if exercise had been initiated from the upright position. Typically associated with the slower increase in cardiac output is a slower increase in ventilation (Karlsson et al 1975, Weiler-Revell et al 1982, 1983).

Weissman et al (1986) found that when respiration was compared at equivalent work loads, the greater ventilation observed in the upright posture was due to a greater tidal volume and greater mean inspiratory flows.

Various combinations of pedalling and cranking in different postures (Nag 1984) also produced different patterns in the rise in oxygen uptake from rest to work. This was partially explained by the different musculature
involved in different tasks and partially by the postural influence on cardiac output (Convertino et al 1984a).

3. Prior Exercise The response times for ventilation, oxygen uptake and heart rate have been compared between work starting from complete rest with work starting from prior lower intensity exercise. Conflicting results have been found.

Beaver and Wasserman (1968), Davies (1968), Casaburi et al (1977), and Diamond et al (1977), have found that work starting from prior exercise has no effect on the kinetics of either oxygen uptake, heart rate or ventilation.

Flenley and Warren (1983), Whipp et al (1982), Hughson and Morrissey (1982, 1983), and Linnarsson (1974) found that prior exercise decrease the kinetics. This they explain as follows. At the onset of exercise the oxygen requirements at the muscle are not fully met by the oxygen transport system due to its delayed adaptation. The bodies oxygen stores are therefore depleted. This leads to a reduction in mixed venous oxygen tension. Imposition of a higher work load will only lead to a moderate further reduction of mixed venous oxygen tension. Therefore, in order to meet the oxygen demand the time of adaptation of ventilation and oxygen uptake must be decreased.

Davies et al (1972), Dawson et al (1977), and Di Prampero (1970) found that prior exercise increases the kinetics. This they explain as follows. Prior exercise increases the stroke volume. Increases in cardiac output and oxygen uptake for subsequent increases in work load are dependent solely on increases in heart rate. They therefore tend to be slower than those occurring when exercise is started from complete rest (Astrand and Rohdel 1970, Bevegard et al 1960). Hence the increased kinetics of oxygen uptake and ventilation in exercise to exercise transitions.

C. Entrainment of Breathing to Movement Frequency

Ventilation is regulated to maintain constancy of arterial blood gases and to minimize the cost of breathing. It has been suggested that this regulation can be further modified by additional stimuli arising from the muscles (Sutton and Jones 1979).
Limb muscles are endowed with mechanosensitive endings that are capable of influencing breathing pattern. These endings are believed to be stimulated by exercise and are thought to play a role in the control of ventilation and breathing pattern during exercise (Dejours 1964, Tallarida et al 1981, Tallarida et al 1983, Waldrop et al 1986). They may explain the differences in ventilatory response to different exercise modes and to the changes in pedal and stride frequency (Bechbach and Duffin 1977, Dejours 1967, Jasinkas et al 1980, McMurray and Alborn 1982).

There is species differences in the control of ventilation and arterial carbon dioxide tension during moderate steady-state exercise. The human response to exercise is one of isocapnia. The response of non human species to exercise is one of hyperventilation and hypocapnia. The hyperventilation in non humans results from increases in frequency as opposed to increases in tidal volume. Some of this species difference may be related to the stricter locomotion-respiratory rate coupling observed in the quadruped (Forster et al 1984b). This in turn is related, at least in part, to the effect of locomotor stresses on chest wall deformations (Bramble and Carrier 1983). This is not a consideration for bipedal humans.

However, humans have also been shown to entrain their breathing to the movement frequency (Bramble and Carrier 1983). It is possible that stimuli from mechanoreceptors, together with rhythmic interference with the mechanisms of breathing, derived from the upper body activity that occurs during walking and running, may also act as an additional stimulus for ventilation in humans and dictate their breathing pattern. In this way the breathing frequency may be selected to minimize, not only the cost of breathing, but the overall energy cost of exercise (Bechbach and Duffin 1977).

D. Hypothesis

At high exercise intensities tidal volume increases to attain near maximum values in the first few breaths, with little change throughout the remainder of the exercise period. Subsequent increases in ventilation result primarily from changes in breathing rate. In certain exercise modes, particularly where the movement rate is slow, entrainment may
dictate a breathing rate which is lower than that required to produce a ventilation capable of maintaining alveolar and arterial gas tensions constant within strict limits. It is hypothesised that the entrainment of breathing rate to movement frequency, in certain modes of exercise, causes a relative hypoventilation and a subsequent fall in alveolar oxygen tension.
METHODS (Section III)

Series I.

A. Subjects

The subjects were the same 6 that took part in Section I.

B. Experimental Protocol

Each subject performed 4 separate incremental tests on a mechanically braked bicycle ergometer (Monark Model 869). No more than 2 trials were performed on any one day. A minimum of 30 minutes rest was allowed between any 2 trials. In each of the 4 trials the power output was first set at 50 watts. The subject cycled for 3 minutes. He then rested for 3 minutes. The power output was increased by 50 watts and a second 3 minute work bout was performed. This incremental pattern was repeated until a maximum of 7 increments were completed.

The pedal cadence selected was different for each trial: 60 rpm for trial #1, 80 rpm for trial #2, and 100 rpm for trial #3. In all these trials a metronome and a digital display were used to help the subject maintain the desired cadence. In trial #4 the subject selected his own cadence. The bicycle ergometer automatically adjusted the load to the pedal cadence to ensure that the power output remained constant at the chosen level.

C. Equipment

Ventilation, oxygen uptake and carbon dioxide output were determined by conventional open circuit spirometry. In each trial expired air was collected in the last minute of each 3 minute increment in meteorological balloons. Heart rate was recorded by electrocardiogram in the last 10 seconds of each increment. The equipment and procedures were the same as that described in Series I Section II.

Changes in mouth pressure associated with breathing were measured by a pressure transducer (Validyne DP-45) inserted into the breathing valve. The output from the pressure transducer passed to a computer (Digital PDP 11/10) and was used to determine breathing frequency and inspiratory and
expiratory durations for each breath. The interruption of a light source by the passage of the pedal during each revolution was detected and used to fire a Schmitt trigger. The output from the Schmitt trigger in turn passed to the computer and was used in determining the pedal frequency.

D. Data Analysis

The data from all 6 subjects were pooled. Means were calculated and plotted against either oxygen uptake or carbon dioxide. Curves were fitted to the relationships between carbon dioxide and oxygen uptake, ventilation and oxygen uptake, and ventilation and carbon dioxide output. The significance of the differences between the 4 combinations of load and pedal frequency and the 2 combinations of speed and treadmill grade were then assessed.

Series 2.

A. Subjects

All 6 subjects were male, aged 18-34 years, competitive track athletes and of above average fitness. Maximal oxygen uptake for the group averaged $57.02 \pm 8.99 \text{ mls.kg}^{-1}\text{min}^{-1}$. They were also nonsmokers, with no history of respiratory or cardio-vascular impairment. Resting flow volume loops were obtained on each subject prior to the exercise test. Vital capacity, forced expiratory volume, peak flow and mid expiratory flow, for all subjects, were within the normal range (Jones et al 1975).

B. Experimental Protocol

Each subject performed 2 separate incremental tests on a treadmill. Both trials were performed in the same order on the same day with a minimum of 30 minute rest between trials. In trial #1 the treadmill was set at 15% grade and 5 kph. The subject walked/ran for 3 minutes. He then rested for 3 minutes. The speed was increased by 1 kph and a second 3 minute work bout was performed. This incremental pattern was repeated until a maximum of 7 increments were completed. In trial #2 the treadmill was set at 0% grade and 11 kph. The subject ran for 3 minutes. He then rested for 3 minutes. The speed was increased by 1 kph and a second 3 minute work bout was performed. This incremental pattern was repeated until a maximum of 7
increments were completed.

C. **Equipment**

Ventilation, oxygen uptake, carbon dioxide output, heart rate, breathing frequency and inspiratory and expiratory durations were measured using the same equipment and procedures as described in Series 1 above.

A switch was inserted into the heel of the shoe of the runner. On heel strike an electrical circuit was completed and used to fire a Schmitt trigger. The output from the Schmitt trigger in turn passed to the computer and was used in determining the stride frequency.

D. **Data Analysis**

The data from all 6 subjects were pooled. Means were calculated and plotted against either oxygen uptake or carbon dioxide. Curves were fitted to the relationships between carbon dioxide and oxygen uptake, ventilation and oxygen uptake, and ventilation and carbon dioxide output. The significance of the differences between the 4 combinations of load and pedal frequency and the 2 combinations of speed and treadmill grade were then assessed.

**Series 3**

A. **Subject**

One subject (TH) was used in this series of experiments. He was selected because of his tendency to entrain his breathing frequency to the pedal frequency.

B. **Experimental Protocol**

The subject performed 6 trials on an electrically braked bicycle ergometer (Elmar-Schonander Model EM 369). Each trial was of 2 minutes duration at a power output of 300 watts. Three trials were performed using a cadence of 60 rpm and 3 trials using a cadence of the subject's own choice. All trials were performed on the same day with a minimum of 20 minutes rest between trials. The order in which the trials were completed was randomly
assigned.

B. **Equipment**

Ventilation, oxygen uptake, carbon dioxide output, end tidal oxygen, end tidal carbon dioxide and heart rate were calculated breath-by-breath using the equipment and procedures outlined in Section I. Output from the pressure transducer in the breathing valve and the Schmitt trigger were recorded on a pen recorder. Pedal cadence, breathing frequency and inspiratory and expiratory durations were calculated manually from the resulting trace.

C. **Data Analysis**

The data from each of the 3 trials in each of the 2 conditions were pooled. It was then grouped into 5 second intervals and averaged to give mean values. The raw data and means for each parameter, under both conditions, where then plotted against time (Figures 3.9.1 to 3.11.2). Differences were evaluated using the Student's t test. Significance was accepted at the 0.05 level.

### Series 4

A. **Subject**

One subject (SW) was used in this series of experiments. He was selected because of his tendency to entrain his breathing frequency to the stride frequency.

B. **Experimental Protocol**

The subject performed 6 trials on the treadmill. In 3 trials he walked up a 16% grade at 6 kph for 2 minutes. In 3 trials he ran on 0% grade at 12 kph for 2 minutes. The 2 combinations of grade and speed had been selected such that the oxygen requirements, and therefore the work performed, should be identical. All 6 trials were performed on the same day with a minimum of 20 minutes rest between trials. The order in which the trials were performed was randomly assigned.
C. **Equipment**

Ventilation, oxygen uptake, carbon dioxide output, end tidal oxygen, end tidal carbon dioxide and heart rate were calculated breath by breath using the equipment and procedures outlined in Section 1. Output from the pressure transducer in the breathing valve and the Schmitt trigger attached to the heel switch were recorded on a pen recorder. Stride cadence, breathing frequency and inspiratory and expiratory durations were calculated manually from the resulting trace.

D. **Data Analysis**

The data from each of the 3 trials in each of the 2 conditions were pooled. It was then grouped into 5 second intervals and averaged to give mean values. The raw data and means for each parameter under both conditions were then plotted against time (Figure 3.12.1 to Figure 3.14.2). Differences were evaluated using the Student's t test. Significance was accepted at the 0.05 level.

**Entrainment**

The equipment and procedures used to assess the degree of entrainment of breathing frequency to limb cadence is outlined and discussed in detail in Appendix C. Variability and differences in response were assessed using a coefficient of variability and the student's t test. Significance was accepted at the 0.05 level.
RESULTS (Section III)

Personal details for all subjects in Series 1 and Series 2 are summarized in Table 1.1 and Table 3.1 respectively.

Series 1: During each trial the pedal frequency was set and the ergometer automatically adjusted the load to maintain a constant power output. Assuming equal subject efficiencies, one would expect oxygen uptake at any power output to be constant and independent of the pedal frequency. However, at each of the 6 workloads on the bicycle ergometer oxygen uptake (Figure 3.1.1) and ventilation (Figure 3.1.2) increased with increasing pedal frequency. This may be due to a failure of the ergometer to accurately adjust the load at higher pedal frequencies or an actual difference in oxygen costs associated with the higher leg speed. The significance of these differences in oxygen uptake and ventilation are presented in Tables 3.3 and 3.4.

Series 2 The data from Series 1 (i.e. cycling on the bicycle) and Series 2 (i.e. running on the treadmill) are considered together. Because of the differences in oxygen uptakes with changing pedal frequencies at the same power output, and the difficulty of matching work loads on the bicycle and treadmill, all parameters are compared by plotting them, not against time, but against either oxygen uptake or carbon dioxide output.

The carbon dioxide output for a given oxygen uptake was higher while running than while cycling and higher while running on the flat than running on a grade. There were no significant differences when the 4 pedal frequencies on the bicycle are compared (Figure 3.2.1). When expressed as the respiratory exchange ratio (i.e. the ratio of carbon dioxide output to oxygen uptake) it can be seen that the relationship is curvilinear with a secondary increase occurring at an oxygen uptake of about 2.5 l/min (Figure 3.2.2). The respiratory exchange ratio at the onset of exercise is at, or below, normal resting levels but in all exercise modes increases to above resting levels with increasing work intensity.

For any given oxygen uptake, the ventilation while running on the flat was significantly higher than that obtained while either running up a 15% grade or cycling at any of the four different pedal frequencies (Figure 3.3.1). There were no significant differences in the ventilation for any given
oxygen uptake when running on a grade and cycling at any of the 4 different pedal frequencies were compared. However, when the relationship was expressed as a ventilatory equivalent for oxygen (i.e. the ratio of ventilation to oxygen uptake), the ventilation while running at grade did appear to be slightly lower than that for cycling at the equivalent oxygen uptake (Figure 3.3.2). The relationship between ventilation and oxygen uptake with increasing work intensity was curvilinear with ventilation increasing faster than oxygen uptake.

For any given carbon dioxide output, the ventilation while running on the flat was significantly higher than that obtained while cycling at any of the four different pedal frequencies (Figure 3.4.1). The ventilation while cycling, in turn, was significantly higher than while running up a grade. This was confirmed when the ventilatory equivalents for carbon dioxide (i.e. the ratio of ventilation to carbon dioxide output) were compared (Figure 3.4.2). Again the relationship between ventilation and carbon dioxide output with increasing work intensity was curvilinear.

While running on the flat on the treadmill, at all work intensities, the ventilatory equivalent for oxygen (Figure 3.3.2) and the ventilatory equivalent for carbon dioxide (Figure 3.4.2), were above normal values, indicating a relative hyperventilation. While cycling in all but 2 of the 24 trials both ventilatory equivalents were lower than normal values, indicating relative hypoventilation. While running up a grade on the treadmill, at all work intensities, both ventilatory equivalents were considerable lower than normal values indicating quite substantial hypoventilation.

Mean values for the ventilatory equivalents of oxygen and carbon dioxide, showing the differences between the exercise modes, are presented in Table 3.2. For oxygen, both running on a grade and cycling at all 4 pedal frequencies had significantly lower ventilatory equivalents than running on the flat (p<0.01). There were no significant differences between running on the grade and cycling. For carbon dioxide, ventilatory equivalents when running on the grade were significantly lower than cycling at all 4 pedal frequencies (P<0.01), which in turn were significantly lower than running on the flat (P<0.01). There were no significant differences between cycling at any of the 4 pedaling frequencies.
It has been postulated that breathing frequency may be in some way related to stride frequency. This idea is supported by the findings in Series 2, Section III of this study. In this series of experiments step changes in stride frequency during the transition from walking to running up a 15% grade on the treadmill (Figure 3.1.7) were accompanied by similar step changes in breathing frequency (Figure 3.1.8). This further supports the contention of a relationship between breathing and movement frequencies.
Table 3.1 Subject Personal Data (Section III - Runners)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Height (cms)</th>
<th>Weight (kgs)</th>
<th>VO₂ Max (ml/kg)</th>
<th>FVC (ml/s)</th>
<th>FEV₁ (ml/s)</th>
<th>PEFR (l/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>23</td>
<td>179.3</td>
<td>66.8</td>
<td>53.10</td>
<td>5552</td>
<td>4728</td>
<td>10.40</td>
</tr>
<tr>
<td>SW</td>
<td>21</td>
<td>175.4</td>
<td>67.1</td>
<td>46.17</td>
<td>5806</td>
<td>5056</td>
<td>10.53</td>
</tr>
<tr>
<td>KO</td>
<td>32</td>
<td>184.2</td>
<td>63.6</td>
<td>56.26</td>
<td>6123</td>
<td>4776</td>
<td>9.55</td>
</tr>
<tr>
<td>SS</td>
<td>22</td>
<td>166.0</td>
<td>65.3</td>
<td>61.89</td>
<td>4789</td>
<td>3682</td>
<td>9.14</td>
</tr>
<tr>
<td>PM</td>
<td>26</td>
<td>181.8</td>
<td>65.9</td>
<td>72.34</td>
<td>5438</td>
<td>4597</td>
<td>10.13</td>
</tr>
<tr>
<td>ED</td>
<td>21</td>
<td>175.9</td>
<td>63.8</td>
<td>49.50</td>
<td>5589</td>
<td>4723</td>
<td>9.94</td>
</tr>
</tbody>
</table>

Mean: 24.17 177.10 65.42 56.54 5549 4601 9.80
Std D ±3.89 ±5.84 ±1.35 ±8.63 ±406 ±457 ±0.67

Table 3.2. Means and standard deviations for the ventilatory equivalents for oxygen (VE/VO₂) and carbon dioxide (VE/VO₂) for each of the 6 exercise modes.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Bicycle Ergometer</th>
<th>Treadmill</th>
</tr>
</thead>
<tbody>
<tr>
<td>rpm-grade</td>
<td>60  80  100</td>
<td>0%  15%</td>
</tr>
<tr>
<td>VO₂</td>
<td>21.10  20.34  21.09</td>
<td>20.55  25.06  19.03</td>
</tr>
<tr>
<td>±1.60</td>
<td>±1.55  ±1.61</td>
<td>±1.31  ±0.69  ±0.84</td>
</tr>
<tr>
<td>VO₂</td>
<td>25.41  24.15  24.82</td>
<td>24.12  27.24  21.46</td>
</tr>
<tr>
<td>±1.70</td>
<td>±0.68  ±1.08</td>
<td>±0.69  ±0.40  ±0.20</td>
</tr>
</tbody>
</table>
Figure 3.1.1. Effect of 4 different pedal frequencies on oxygen uptake during an incremental work test on the bicycle ergometer. Increments in power output were 50 watts. (n=6).

Figure 3.1.2. Effect of 4 different pedal frequencies on ventilation during an incremental work test on the bicycle ergometer. Increments in power output were 50 watts. (n=6).
Table 3.3: Student's t scores (t) and the significance of differences (p) in oxygen uptake while cycling at constant work load but different pedal frequencies. (Figure 3.1.1)

<table>
<thead>
<tr>
<th>Power (watts)</th>
<th>60 Vs 80 (rpm)</th>
<th>60 Vs 100 (rpm)</th>
<th>80 Vs 100 (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>3.53</td>
<td>10.15</td>
<td>4.70</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>100</td>
<td>1.18</td>
<td>3.74</td>
<td>3.43</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>150</td>
<td>1.91</td>
<td>2.38</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>200</td>
<td>1.44</td>
<td>3.25</td>
<td>2.39</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>0.02</td>
<td>---</td>
</tr>
<tr>
<td>250</td>
<td>2.18</td>
<td>6.00</td>
<td>2.87</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>300</td>
<td>2.38</td>
<td>1.83</td>
<td>-0.60</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Table 3.4: Student's t scores (t) and the significance of differences (p) in minute ventilation while cycling at constant work load but different pedal frequencies. (Figure 3.1.2)

<table>
<thead>
<tr>
<th>Power (watts)</th>
<th>60 Vs 80 (rpm)</th>
<th>60 Vs 100 (rpm)</th>
<th>80 Vs 100 (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.01</td>
<td>2.77</td>
<td>3.85</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>100</td>
<td>0.44</td>
<td>2.96</td>
<td>3.34</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>150</td>
<td>0.82</td>
<td>1.72</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>200</td>
<td>1.92</td>
<td>6.73</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>250</td>
<td>0.47</td>
<td>1.92</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>300</td>
<td>0.93</td>
<td>1.04</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
Figure 3.2.1. Effect of 4 different pedal frequencies and 2 different grades on the plot of oxygen uptake against carbon dioxide output during an incremental work test. (n=6).

Figure 3.2.2. Effect of 4 different pedal frequencies and 2 different grades on the respiratory exchange ratio during an incremental work test. (n=6).
Figure 3.3.1. Effect of 4 different pedal frequencies and 2 different grades on the plot of oxygen uptake against ventilation during an incremental work test. (n=6).

Figure 3.3.2. Effect of 4 different pedal frequencies and 2 different grades on the ventilatory equivalent for oxygen during an incremental work test. Normal ventilatory equivalent for oxygen = 24 litres/litre. (n=6).
Figure 3.4.1. Effect of 4 different pedal frequencies and 2 different grades on the plot of carbon dioxide against ventilation during an incremental work test. (n=6).

Figure 3.4.2. Effect of 4 different pedal frequencies and 2 different grades on the ventilatory equivalent for carbon dioxide during an incremental work test. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. (n=6).
Figure 3.5.1. Comparison of the changes in breathing frequency during treadmill running at two different grades. (n=6).

Figure 3.5.2. Comparison of the changes in stride frequency during treadmill running at two different grades. (n=6).
Entrainment During Steady-State Exercise

Entrainment of breathing frequency to movement frequency occurred, to some degree, in all subjects. The length of time which entrainment was evident varied from subject to subject and trial to trial. Only in one trial did a subject (SW) entrain for the total duration of the run. This subject entrained over 50% of the time in all 6 trials and was later used, along with subject TH, to examine the effect of entrainment on a number of physiological parameters during non steady-state exercise.

In three out of the four trials on the bicycle ergometer the pedal frequency was set and remained essentially constant. In the fourth trial the subjects chose their own pedal frequency. Although the frequency chosen differed from subject to subject it was maintained essentially constant throughout the duration of the trial. On the treadmill, stride frequency was determined by the speed of the belt and the stride length of the subject. Belt speed at each work load was the same for each subject. However, different stride lengths gave different stride frequencies. Although different, the stride frequency for each subject remained relatively constant throughout the duration of the run. Therefore, all shifts from periods of entrainment to periods of non entrainment resulted from changes in breathing frequency and not from changes in movement frequency. An example of this can be seen in Figures 3.6.3 and 3.6.4.

The ratio of movement frequency to breathing frequency varied from 2:1 to 5:1. The higher the work intensity the lower the ratio. A ratio of 2:1 was the most common.

The pattern of entrainment and non entrainment varied considerably between subjects and between trials for some subjects. Figures 3.6.1, 3.7.1 and 3.8.1 are three examples of different patterns of entrainment and non entrainment. Plots of entrainment ratio against time are also shown for the same three examples in Figures 3.6.2, 3.7.2 and 3.8.2.

1. Example #1 (Figure 3.6.1) At the start of exercise the subject exhibited partial entrainment at a ratio varying from 4:1 to 5:1. 82 seconds into the trial a step change in breathing frequency resulted in the complete entrainment of breathing frequency to pedal frequency at a ratio of 4:1 (Figure 3.6.2). This was maintained throughout the remainder of the trial.
2. **Example #2** (Figure 3.7.1) Periods of entrainment and non entrainment alternate throughout the trial. The time for which entrainment is evident varies from 5 to 40 seconds. The entrainment ratio remains constant at 2:1 throughout the trial (Figure 3.7.2).

3. **Example #3** (Figure 3.8.1) Periods of entrainment and non entrainment, at different entrainment ratios, are interspersed throughout the duration of the run. Initially the subject shows no sign of entrainment. Subsequent shifts in breathing frequency produce entrainment ratios of 3:1, 4:1, 3:1, and 5:1 (Figure 3.8.2). Finally, a breathing frequency is adopted which results in no entrainment to movement frequency.

Both at rest and during exercise there is considerable variability in the duration of the total breath as well as the inspiratory and expiratory phase. During entrainment this variability decreases significantly. This is shown graphically for example #1 in Figures 3.6.4, 3.6.5, and 3.6.6. Means and coefficients of variance for pedal frequency, breath frequency, inspiratory duration and expiratory duration, for each of the three examples, are presented in Tables 3.5, 3.6 and 3.7
Figure 3.6.1. Time from the onset of inspiration until the right pedal reaches the bottom of its arc. Power output = 100 watts at 100 rpm. The vertical line designates the start of entrainment. (Subject ML).

Figure 3.6.2. The ratio of pedal frequency to breathing frequency during 3 minutes cycling. Power output = 100 watts at 100 rpm. The vertical line designates the start of entrainment. (Subject ML).
Figure 3.6.3. Pedal frequency during 3 minutes cycling. Power output = 100 watts at 100 rpm. The vertical line designates the start of entrainment. (Subject ML).

Figure 3.6.4. Breathing frequency during 3 minutes cycling. Power output = 100 watts at 100 rpm. The vertical line designates the start of entrainment. (Subject ML).
Figure 3.6.5. Inspiratory duration during 3 minutes cycling. Power output = 100 watts at 100 rpm. The vertical line designates the start of entrainment. (Subject ML).

Figure 3.6.6. Expiratory duration during 3 minutes cycling. Power output = 100 watts at 100 rpm. The vertical line designates the start of entrainment. (Subject ML).
Figure 3.7.1. Time from the onset of inspiration until the right pedal reaches the bottom of its arc. The vertical lines designates the start and end of periods of entrainment. Power output = 250 watts at 80 rpm. (Subject GH).

Figure 3.7.2. The ratio of pedal frequency to breath frequency during 3 minutes cycling. The vertical lines designates the start and end of periods of entrainment. Power output = 250 watts at 80 rpm. (Subject GH).
Figure 3.8.1. Time from the onset of inspiration until the right pedal reaches the bottom of its arc. The vertical lines designates the start and end of periods of entrainment. Power output = 150 watt. (Subject ND).

Figure 3.8.2. The ratio of pedal frequency to breathing frequency during 3 minutes cycling. The vertical lines designates the start and end of periods of entrainment. Power output = 150 watts. (Subject ND).
Table 3.5: Means and coefficients of variance for pedal frequency, breath frequency, inspiratory duration and expiratory duration in subject J.A. during periods of entrainment and non-entrainment while cycling at 100 watts. (Figure 3.6.1 to Figure 3.6.6)

<table>
<thead>
<tr>
<th>Entrainment</th>
<th>Time (secs)</th>
<th>Pedal Fr. (rpm)</th>
<th>Breath Fr. (/min)</th>
<th>TI (secs)</th>
<th>TE (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>41 - 81</td>
<td>98.21</td>
<td>20.22</td>
<td>1.44</td>
<td>1.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.01</td>
<td>16.70</td>
<td>22.08</td>
<td>20.50</td>
</tr>
<tr>
<td>Yes</td>
<td>81 - 123</td>
<td>98.25</td>
<td>24.45</td>
<td>1.18</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.80</td>
<td>3.36</td>
<td>3.33</td>
<td>3.54</td>
</tr>
</tbody>
</table>

Table 3.6: Means and coefficients of variance for pedal frequency, breath frequency, inspiratory duration and expiratory duration in subject A.L. during periods of entrainment and non-entrainment while cycling at 250 watts. (Figures 3.7.1 and 3.7.2)

<table>
<thead>
<tr>
<th>Entrainment</th>
<th>Time (secs)</th>
<th>Pedal Fr. (rpm)</th>
<th>Breath Fr. (/min)</th>
<th>TI (secs)</th>
<th>TE (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>41 - 73</td>
<td>79.76</td>
<td>39.64</td>
<td>0.75</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.75</td>
<td>2.94</td>
<td>4.52</td>
<td>4.29</td>
</tr>
<tr>
<td>No</td>
<td>76 - 111</td>
<td>79.94</td>
<td>34.82</td>
<td>0.86</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.01</td>
<td>8.05</td>
<td>9.68</td>
<td>8.48</td>
</tr>
<tr>
<td>Yes</td>
<td>114 - 143</td>
<td>79.73</td>
<td>39.81</td>
<td>0.74</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.80</td>
<td>3.55</td>
<td>4.33</td>
<td>4.57</td>
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<tr>
<td>No</td>
<td>146 - 179</td>
<td>79.75</td>
<td>34.78</td>
<td>0.88</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.20</td>
<td>10.30</td>
<td>22.00</td>
<td>11.53</td>
</tr>
</tbody>
</table>
Table 3.7: Means and coefficients of variance for pedal frequency, breath frequency, inspired time and expired time in subject A.L. during periods of entrainment and non-entrainment while cycling at 150 watts. (Figures 3.8.1 and 3.8.2)

<table>
<thead>
<tr>
<th>Entrainment</th>
<th>Time (secs)</th>
<th>Pedal Fr. (rpm)</th>
<th>Breath Fr. (/min)</th>
<th>TI (secs)</th>
<th>TE (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>49 - 70</td>
<td>80.70</td>
<td>29.20</td>
<td>0.94</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.49</td>
<td>6.40</td>
<td>7.22</td>
<td>7.24</td>
</tr>
<tr>
<td>Yes</td>
<td>71 - 84</td>
<td>82.54</td>
<td>28.46</td>
<td>1.00</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.30</td>
<td>2.98</td>
<td>3.56</td>
<td>4.85</td>
</tr>
<tr>
<td>Yes</td>
<td>86 - 95</td>
<td>81.84</td>
<td>21.42</td>
<td>1.41</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.69</td>
<td>6.75</td>
<td>4.07</td>
<td>3.87</td>
</tr>
<tr>
<td>No</td>
<td>99 - 122</td>
<td>83.42</td>
<td>28.23</td>
<td>1.01</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.47</td>
<td>12.56</td>
<td>17.41</td>
<td>12.11</td>
</tr>
<tr>
<td>Yes</td>
<td>122 - 152</td>
<td>83.58</td>
<td>17.67</td>
<td>1.76</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.59</td>
<td>7.73</td>
<td>6.12</td>
<td>7.70</td>
</tr>
<tr>
<td>No</td>
<td>152 - 180</td>
<td>84.26</td>
<td>20.35</td>
<td>1.31</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.63</td>
<td>15.14</td>
<td>10.31</td>
<td>10.31</td>
</tr>
</tbody>
</table>
Series 3: Ventilation and other respiratory parameters were compared in subject TH when cycling at the same power output using two different combinations of pedal frequency and load. In the first 3 rides, pedal frequency was set at 60 rpm. In the second 3 rides, the subject selected his own pedal frequency. Pedal frequency in these rides increased exponentially to plateau, at an average of 108.34 rpm, 30 seconds after the onset of exercise (Figure 3.9.1). At all sample intervals pedal frequency in the 2 conditions were found to be significantly different (Table 3.8).

As in Series I the ergometer was relied upon to adjust the load to the pedal frequency in order to maintain the power output, and hence the oxygen uptake, constant. However, at all sample intervals the oxygen uptake was found to be significantly higher at the higher pedal frequencies (Figure 3.9.2. and Table 3.8). In order to make comparisons all parameters were compared, not at the same time, but at the same oxygen uptake or carbon dioxide output.

Breathing frequency, tidal volume, expiratory duration, ventilation and end tidal oxygen tended to be lower and end tidal carbon dioxide tended to be higher at the lower pedal frequencies. However, these differences were only significant in 43 of the 120 comparisons made (Tables 3.9 and 3.10).

The time course of the changes in ventilatory equivalent for oxygen was different for the two pedal frequencies (Figure 3.10.1). At the higher pedal frequency it fell quicker and rose again to attain near resting values by the end of the ride. At the lower pedal frequency the fall was of similar magnitude but occurred more slowly and it remained depressed below normal values through to the end of the ride. The differences in ventilatory equivalent for oxygen were significant during the initial fall and during the last 70 seconds of the ride (Table 3.11).

The time course of changes in ventilatory equivalent for carbon dioxide was only different for the 2 pedal frequencies from 15 to 25 seconds after the onset of exercise (Figure 3.11.1). No significant differences in ventilatory equivalent were evident in the second half of the ride (Table 3.11).

The ventilatory equivalent for both oxygen and carbon dioxide were above normal values for the first 20 seconds of the ride (Figures 3.10.2. and
3.11.2.). This is indicative of a relative hyperventilation with respect to both oxygen uptake and carbon dioxide output. After 20 seconds both the ventilatory equivalent for oxygen and carbon dioxide were below normal values (Figures 3.10.2. and 3.11.2.). This is indicative of a relative hypoventilation with respect to both oxygen uptake and carbon dioxide output.
Figure 3.9.1. Comparison of pedal frequency during 2 minutes cycling. 3 trials at each of the 2 frequencies. Power output = 300 watts. (Subject TH).

Figure 3.9.2. Comparison of oxygen uptake during 2 minutes cycling. 3 trials at 2 pedal frequencies. Power output = 300 watts. (Subject TH).
Table 3.8: Student's t scores (t) and significance of differences (p) in pedal frequency and oxygen uptake while cycling at 300 watts for 2 minutes at 60 rpm and at a cadence of the subjects own choice. (Figures 3.9.1 and 3.9.2)

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>Pedal Frequency</th>
<th>Oxygen Uptake</th>
<th>Time (secs)</th>
<th>Pedal Frequency</th>
<th>Oxygen Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>t 3.99</td>
<td>6.86</td>
<td>61-65</td>
<td>t 53.97</td>
<td>8.14</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>t 19.66</td>
<td>31.97</td>
<td>66-70</td>
<td>t 50.99</td>
<td>17.14</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>t 40.09</td>
<td>4.90</td>
<td>71-75</td>
<td>t 55.21</td>
<td>7.83</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>t 58.35</td>
<td>6.44</td>
<td>76-80</td>
<td>t 54.52</td>
<td>11.18</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>t 48.48</td>
<td>32.68</td>
<td>81-85</td>
<td>t 59.08</td>
<td>7.68</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>t 55.50</td>
<td>12.73</td>
<td>86-90</td>
<td>t 53.53</td>
<td>7.74</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>t 53.23</td>
<td>19.95</td>
<td>91-95</td>
<td>t 42.80</td>
<td>7.01</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-40</td>
<td>t 58.34</td>
<td>15.02</td>
<td>96-100</td>
<td>t 55.12</td>
<td>6.79</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-45</td>
<td>t 51.92</td>
<td>11.86</td>
<td>101-105</td>
<td>y 71.59</td>
<td>15.03</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-50</td>
<td>t 50.10</td>
<td>8.64</td>
<td>106-110</td>
<td>t 68.64</td>
<td>5.59</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-55</td>
<td>t 46.76</td>
<td>6.70</td>
<td>111-115</td>
<td>t 57.79</td>
<td>7.62</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56-60</td>
<td>t 50.65</td>
<td>15.63</td>
<td>116-120</td>
<td>t 56.82</td>
<td>5.66</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.10.1. Changes in the ventilatory equivalent for oxygen during 2 minutes of cycling. 3 trials at 2 pedal frequencies. Power output = 300 watts. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject TH).

Figure 3.10.2. Plot of oxygen uptake against ventilation during 2 minutes of cycling. 3 trials at 2 pedal frequencies. Power output = 300 watts. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject TH).
Figure 3.11.1. Changes in the ventilatory equivalent for carbon dioxide during 2 min. of cycling. 3 trials at 2 pedal frequencies. Power output = 300 watts. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. (Subject TH).

Figure 3.11.2. Plot of carbon dioxide output against ventilation during 2 minutes of cycling. 3 trials at 2 pedal frequencies. Power output = 300 watts. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. (Subject TH).
Table 3.9: Student's t scores (t) and significance of differences (p) for breathing frequency, tidal volume, inspiratory duration and expiratory duration while cycling at 300 watts for 2 minutes at 60 rpm and a cadence of the subject's own choice.

<table>
<thead>
<tr>
<th>V0₂ (litres)</th>
<th>B Freq.</th>
<th>VT</th>
<th>TI</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 - 1.1</td>
<td>3.74</td>
<td>1.52</td>
<td>0.86</td>
<td>0.37</td>
</tr>
<tr>
<td>1.2 - 1.3</td>
<td>1.47</td>
<td>2.34</td>
<td>-0.04</td>
<td>-2.15</td>
</tr>
<tr>
<td>1.4 - 1.5</td>
<td>2.31</td>
<td>4.11</td>
<td>-0.63</td>
<td>-1.33</td>
</tr>
<tr>
<td>1.6 - 1.7</td>
<td>-1.80</td>
<td>-5.03</td>
<td>-1.01</td>
<td>-0.42</td>
</tr>
<tr>
<td>1.8 - 1.9</td>
<td>1.82</td>
<td>1.22</td>
<td>0.41</td>
<td>2.08</td>
</tr>
<tr>
<td>2.0 - 2.1</td>
<td>1.00</td>
<td>2.27</td>
<td>0.13</td>
<td>-0.23</td>
</tr>
<tr>
<td>2.2 - 2.3</td>
<td>1.45</td>
<td>10.63</td>
<td>4.23</td>
<td>-2.27</td>
</tr>
<tr>
<td>2.4 - 2.5</td>
<td>1.49</td>
<td>0.60</td>
<td>-2.84</td>
<td>-1.77</td>
</tr>
<tr>
<td>2.6 - 2.7</td>
<td>4.98</td>
<td>2.68</td>
<td>-1.19</td>
<td>-2.74</td>
</tr>
<tr>
<td>2.8 - 2.9</td>
<td>0.38</td>
<td>1.15</td>
<td>1.11</td>
<td>1.91</td>
</tr>
<tr>
<td>3.0 - 3.1</td>
<td>1.85</td>
<td>1.05</td>
<td>-0.79</td>
<td>-2.17</td>
</tr>
<tr>
<td>3.2 - 3.3</td>
<td>0.56</td>
<td>0.10</td>
<td>1.21</td>
<td>1.48</td>
</tr>
<tr>
<td>3.4 - 3.5</td>
<td>5.15</td>
<td>1.26</td>
<td>-1.12</td>
<td>-0.72</td>
</tr>
<tr>
<td>3.6 - 3.7</td>
<td>3.11</td>
<td>0.65</td>
<td>-2.09</td>
<td>-2.28</td>
</tr>
<tr>
<td>3.8 - 3.9</td>
<td>4.43</td>
<td>3.57</td>
<td>-3.83</td>
<td>-2.75</td>
</tr>
</tbody>
</table>
Table 3.10: Student's t scores (t) and significance of differences (p) in inspiratory flow, minute ventilation, end tidal oxygen and end tidal carbon dioxide while cycling at 300 watts for 2 minutes at 60 rpm and a cadence of the subjects own choice.

<table>
<thead>
<tr>
<th>VO2 (litres)</th>
<th>VT/TI</th>
<th>VE</th>
<th>ETO2</th>
<th>ETCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 - 1.1</td>
<td>1.02</td>
<td>2.75</td>
<td>3.70</td>
<td>3.10</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>0.05</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>1.2 - 1.3</td>
<td>2.61</td>
<td>1.54</td>
<td>3.10</td>
<td>5.27</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>1.4 - 1.5</td>
<td>3.37</td>
<td>1.53</td>
<td>2.20</td>
<td>2.60</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>1.6 - 1.7</td>
<td>-2.53</td>
<td>-2.74</td>
<td>-0.24</td>
<td>1.44</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>1.8 - 1.9</td>
<td>2.76</td>
<td>2.59</td>
<td>0.41</td>
<td>0.39</td>
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<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2.0 - 2.1</td>
<td>1.16</td>
<td>0.91</td>
<td>1.01</td>
<td>0.98</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2.2 - 2.3</td>
<td>5.32</td>
<td>1.01</td>
<td>1.42</td>
<td>0.42</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2.4 - 2.5</td>
<td>4.38</td>
<td>3.66</td>
<td>0.83</td>
<td>0.06</td>
</tr>
<tr>
<td>p</td>
<td>0.02</td>
<td>0.05</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2.6 - 2.7</td>
<td>5.32</td>
<td>4.74</td>
<td>1.32</td>
<td>2.27</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2.8 - 2.9</td>
<td>-0.01</td>
<td>0.46</td>
<td>1.83</td>
<td>3.10</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>3.0 - 3.1</td>
<td>1.85</td>
<td>1.35</td>
<td>-0.50</td>
<td>1.11</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>3.2 - 3.3</td>
<td>0.88</td>
<td>0.69</td>
<td>0.05</td>
<td>0.31</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>3.4 - 3.5</td>
<td>1.05</td>
<td>0.79</td>
<td>3.20</td>
<td>1.81</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>0.01</td>
<td>-----</td>
</tr>
<tr>
<td>3.6 - 3.7</td>
<td>0.58</td>
<td>0.10</td>
<td>2.75</td>
<td>3.47</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>3.8 - 3.9</td>
<td>1.83</td>
<td>0.50</td>
<td>4.21</td>
<td>6.44</td>
</tr>
<tr>
<td>p</td>
<td>-----</td>
<td>-----</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table 3.11: Student's t scores (t) and significance of differences (p) in ventilatory equivalent for oxygen and carbon dioxide while cycling at 300 watts for 2 minutes at 60 rpm and at a cadence of the subjects own choice. (Figures 3.10.2 and 3.11.2)

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>( \text{VE/VO}_2 ) (l/l)</th>
<th>( \text{VE/VCO}_2 ) (l/l)</th>
<th>Time (secs)</th>
<th>( \text{VE/VO}_2 ) (l/l)</th>
<th>( \text{VE/VCO}_2 ) (l/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>t 0.43</td>
<td>-1.06</td>
<td>61-65</td>
<td>t -3.48</td>
<td>-0.39</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>----</td>
<td>p 0.01</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>6-10</td>
<td>t -1.15</td>
<td>0.08</td>
<td>66-70</td>
<td>t -6.84</td>
<td>-2.92</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>----</td>
<td>p 0.01</td>
<td>0.02</td>
<td>----</td>
</tr>
<tr>
<td>11-15</td>
<td>t 4.85</td>
<td>5.18</td>
<td>71-75</td>
<td>t -7.19</td>
<td>-2.79</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>16-20</td>
<td>t 8.14</td>
<td>2.47</td>
<td>76-80</td>
<td>t -7.49</td>
<td>-2.69</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.05</td>
<td>p 0.01</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>21-25</td>
<td>t 9.82</td>
<td>3.92</td>
<td>81-85</td>
<td>t -4.98</td>
<td>-0.91</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>p 0.01</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>26-30</td>
<td>t 3.64</td>
<td>0.50</td>
<td>86-90</td>
<td>t -5.20</td>
<td>-3.23</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>----</td>
<td>p 0.01</td>
<td>0.02</td>
<td>----</td>
</tr>
<tr>
<td>31-35</td>
<td>t 2.15</td>
<td>1.13</td>
<td>91-95</td>
<td>t -7.27</td>
<td>-2.08</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>----</td>
<td>p 0.01</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>36-40</td>
<td>t -1.66</td>
<td>-2.94</td>
<td>96-100</td>
<td>t -5.82</td>
<td>-2.50</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>0.02</td>
<td>p 0.01</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>41-45</td>
<td>t 0.60</td>
<td>1.44</td>
<td>101-105</td>
<td>t -3.48</td>
<td>-0.51</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>----</td>
<td>p 0.01</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>46-50</td>
<td>t -5.34</td>
<td>-2.77</td>
<td>106-110</td>
<td>t -6.45</td>
<td>-1.44</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.05</td>
<td>p 0.01</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>51-55</td>
<td>t -4.55</td>
<td>-1.43</td>
<td>111-115</td>
<td>t -4.82</td>
<td>-3.13</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>----</td>
<td>p 0.01</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>56-60</td>
<td>t -4.56</td>
<td>-2.43</td>
<td>116-120</td>
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<td>-2.24</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.05</td>
<td>p 0.01</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
Series 4: Ventilation and other respiratory parameters were compared in subject SW while exercising on the treadmill at two different combinations of speed and grade. In the first 3 trials the grade was set at 16% and the speed at 6 kph. In the second 3 trials the subject ran on the flat (i.e. 0% grade) at 12 kph. Stride frequency averaged 72.6 and 84.8 per minute respectively in the two conditions. At all sample intervals stride frequencies, in the 2 conditions, were found to be significantly different (Figure 3.12.1 and Table 3.12).

In only 3 of the 24 sample periods were there significant differences in oxygen uptake between the 2 conditions (Figure 3.12 2 and Table 3.12). In 2 instances the significant differences occurred early in the run indicating a different rate of change in oxygen uptake. Only in 1 sample period in the steady-state was there a significant difference in oxygen uptake. Again, in order to make comparisons, all parameters were compared, not at the same time, but at the same oxygen uptake.

Breathing frequency, inspiratory flow, ventilation, and end tidal oxygen tended to be lower, and inspiratory duration, expiratory duration, tidal volume and end tidal carbon dioxide tended to be higher while running at 16% grade. These differences were significant in 61 of the 88 comparisons (Tables 3.13 and 3.14).

The time course of the changes in ventilatory equivalent for oxygen was different for the two stride frequencies (Figures 3.13.1 and 3.13.2). During running at 16% grade the fall was quicker, of greater magnitude and was sustained throughout the duration of the run. During running on the flat the fall was smaller and only transient with a return to normal levels after about 60 seconds. Student's t scores and the significance of these differences are presented in table 3.15.

Throughout the entire duration of the trial, the ventilatory equivalent for carbon dioxide (Figures 3.14.1 and 3.14.2) was significantly lower while running at 16% grade as compared with running on the flat (Table 3.11). Student's t scores and the significance of these differences are presented in table 3.15.
Figure 3.12.1. Comparison of stride frequency during 2 minutes treadmill running. 3 trials at 2 combinations of speed and grade. (Subject SW).

Figure 3.12.2. Comparison of oxygen uptake during 2 minutes treadmill running. 1 subject 3 trials at 2 combinations of speed and grade. (Subject SW).
Table 3.12: Student's t scores (t) and significance of differences (p) in stride frequency and oxygen uptake while running on the treadmill at equivalent work outputs but different grades. (Figures 3.12.1 and 3.12.2)

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>Stride Frequency</th>
<th>Oxygen Uptake</th>
<th>Time (secs)</th>
<th>Stride Frequency</th>
<th>Oxygen Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>t 6.89</td>
<td>1.74</td>
<td>61-65</td>
<td>t 12.61</td>
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</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>t 12.21</td>
<td>1.46</td>
<td>66-70</td>
<td>t 10.14</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>t 13.68</td>
<td>0.63</td>
<td>71-75</td>
<td>t 12.97</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
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<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>t 12.64</td>
<td>-0.88</td>
<td>76-80</td>
<td>t 13.72</td>
<td>-1.07</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>t 13.40</td>
<td>-2.88</td>
<td>81-85</td>
<td>t 16.95</td>
<td>-0.74</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>t 16.95</td>
<td>-2.50</td>
<td>86-90</td>
<td>t 12.32</td>
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</tr>
<tr>
<td></td>
<td>p 0.01</td>
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<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>t 11.49</td>
<td>-1.87</td>
<td>91-95</td>
<td>t 13.77</td>
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<td></td>
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<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>36-40</td>
<td>t 10.63</td>
<td>0.35</td>
<td>96-100</td>
<td>t 8.92</td>
<td>-2.19</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>41-45</td>
<td>t 15.88</td>
<td>-1.40</td>
<td>101-105</td>
<td>t 9.86</td>
<td>-3.43</td>
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<tr>
<td></td>
<td>p 0.01</td>
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<td></td>
<td>p 0.01</td>
<td>0.01</td>
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<tr>
<td>46-50</td>
<td>t 14.25</td>
<td>-1.08</td>
<td>106-110</td>
<td>t 14.57</td>
<td>-0.45</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
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</tr>
<tr>
<td>51-55</td>
<td>t 15.04</td>
<td>-0.15</td>
<td>111-115</td>
<td>t 18.35</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
<tr>
<td>56-60</td>
<td>t 10.92</td>
<td>-0.03</td>
<td>116-120</td>
<td>t 14.58</td>
<td>-1.83</td>
</tr>
<tr>
<td></td>
<td>p 0.01</td>
<td></td>
<td></td>
<td>p 0.01</td>
<td></td>
</tr>
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</table>
Figure 3.13.1. Changes in the ventilatory equivalent for oxygen during 2 minutes of treadmill running. 3 trials at 2 combinations of speed and grade. Power output = 300 watts. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject SW).

Figure 3.13.2. Plot of oxygen uptake against ventilation during 2 minutes of treadmill running. 3 trials at 2 combinations of speed and grade. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject SW).
Figure 3.14.1. Changes in the ventilatory equivalent for carbon dioxide during 2 minutes of treadmill running. 3 trials at 2 combinations of speed and grade. Power output = 300 watts. Normal ventilatory equivalent for carbon dioxide = 26 l/l. (Subject SW).

Figure 3.14.2. Plot of carbon dioxide output against ventilation during 2 minutes of treadmill running. 3 trials at 2 combinations of speed and grade. Normal ventilatory equivalent for carbon dioxide = 26 litres /litre. (Subject SW).
Entrainment During Non Steady-State Exercise

Bicycle Ergometer - Example #1. In all 3 trials, the subject TH entrained at or soon after the onset of exercise (Figure 3.15.1), maintained the pattern of entrainment at a 2:1 ratio for 70-80 seconds (Figure 3.15.2), then increased the breathing frequency thereby breaking away from the pattern of entrainment, and maintained the new breathing frequency for the remainder of the trial.

The pattern of entrainment, entrainment ratio, pedal frequency, breathing frequency, inspiratory duration, expiratory duration, tidal volume, ventilation, end tidal oxygen, end tidal carbon dioxide and ventilatory equivalent for oxygen and carbon dioxide were plotted against time and presented in Figures 3.15.1 to 3.15.14.

Four time intervals each of 10 seconds duration were defined as follows:

(a) 20 to 11 seconds prior to cessation of entrainment.
(b) 10 seconds prior to the time of cessation of entrainment.
(c) Time of cessation of entrainment to 10 seconds after.
(d) 11 to 20 seconds after the cessation of entrainment.

By comparing the mean response between all 4 time intervals the significance of changes in a variety of parameters at the cessation of entrainment was assessed.

Pedal frequency remains constant throughout the trial (Figure 3.15.3). There were no significant differences between any of the four time intervals (Table 3.17). The movement in and out of entrainment results from changes in breathing frequency (Figure 3.15.4 and Table 3.18) not from changes in pedal frequency. Tidal volume (Figure 3.15.7 and Table 3.22) was the only other parameter not to show significant changes at the cessation of entrainment.

For entrainment ratio (Figure 15.13.2), inspiratory duration (Figure 3.15.5), expiratory duration (Figure 3.15.6) and end tidal carbon dioxide (Figure 3.15.10), there were no significant differences between time intervals (1) and (2) or (3) and (4). There were significant differences between time intervals (1) and (3), (1) and (4), (2) and (3), (2) and (4).
This suggests that all these parameters significantly decreased when entrainment of breathing frequency to stride frequency ceased 76 seconds after the onset of exercise (Tables 3.16, 3.19, 3.20 and 3.26).

For breathing frequency (Figure 3.15.4), ventilation (Figure 3.15.8), end tidal oxygen (Figure 3.15.9) and ventilatory equivalent (Figure 3.15.11) there were no significant differences between time intervals (1) and (2) or (3) and (4). There were significant differences between time intervals (1) and (3), (1) and (4), (2) and (3), (2) and (4). This in turn suggests that all these parameters significantly increased when entrainment of breathing frequency to stride frequency ceased 76 seconds after the onset of exercise (Tables 3.18, 3.21, 3.24, 3.25).

The ventilatory equivalents for oxygen (Figures 3.15.11 and 3.15.12) and carbon dioxide (Figures 3.15.13 and 3.15.14) reveal a slight hyperventilation with respect to oxygen and carbon dioxide at the onset of exercise. After approximately 20 seconds both fall below normal values indicating a relative hypoventilation with respect to oxygen and carbon dioxide. At the cessation of entrainment, despite increases in the ventilatory equivalents for both oxygen and carbon dioxide, they remain below normal values and the relative hypoventilation persists.
Table 3.13: Student’s t scores (t) and significance of differences (p) in breathing frequency, tidal volume, inspiratory duration and expiratory duration while running on the treadmill at equivalent work outputs but different grades.

<table>
<thead>
<tr>
<th>VO2 (litres)</th>
<th>B Freq.</th>
<th>VT</th>
<th>TI</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 - 1.3</td>
<td>t 5.41</td>
<td>2.13</td>
<td>-4.21</td>
<td>-1.70</td>
</tr>
<tr>
<td>p 0.01</td>
<td>----</td>
<td>0.02</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>1.4 - 1.5</td>
<td>t 2.50</td>
<td>1.27</td>
<td>-2.09</td>
<td>-1.83</td>
</tr>
<tr>
<td>p ----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>1.6 - 1.7</td>
<td>t 4.47</td>
<td>-1.46</td>
<td>-4.25</td>
<td>-2.60</td>
</tr>
<tr>
<td>p 0.01</td>
<td>----</td>
<td>0.01</td>
<td>0.05</td>
<td>----</td>
</tr>
<tr>
<td>1.8 - 1.9</td>
<td>t 5.78</td>
<td>-1.84</td>
<td>-3.58</td>
<td>-5.08</td>
</tr>
<tr>
<td>p 0.01</td>
<td>----</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>2.0 - 2.1</td>
<td>t 4.95</td>
<td>-0.85</td>
<td>-3.52</td>
<td>-4.23</td>
</tr>
<tr>
<td>p 0.01</td>
<td>----</td>
<td>0.05</td>
<td>0.05</td>
<td>----</td>
</tr>
<tr>
<td>2.2 - 2.3</td>
<td>t 4.38</td>
<td>-0.27</td>
<td>-3.70</td>
<td>-3.26</td>
</tr>
<tr>
<td>p 0.01</td>
<td>----</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>2.4 - 2.5</td>
<td>t 7.41</td>
<td>-2.47</td>
<td>-4.28</td>
<td>-4.60</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>2.6 - 2.7</td>
<td>t 9.21</td>
<td>-2.94</td>
<td>-7.07</td>
<td>-5.34</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>2.8 - 2.9</td>
<td>t 10.11</td>
<td>-3.78</td>
<td>-7.88</td>
<td>-6.95</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>3.0 - 3.1</td>
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<td>-7.97</td>
<td>-8.92</td>
</tr>
<tr>
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<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>3.2 - 3.3</td>
<td>t 14.84</td>
<td>-8.09</td>
<td>-11.38</td>
<td>-9.44</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>----</td>
</tr>
</tbody>
</table>
Entrainment During Non Steady-State Exercise

Treadmill - Example #2 Entrainment of breathing frequency to movement frequency was evident during all 6 trials performed by subject SW on the treadmill. The effect of entrainment on the breathing pattern was most evident while exercising at grade.

Two successive trials on the treadmill at 16% grade and 6 kph were performed 20 minutes apart. The results from those two trials are compared in this section. The speed and grade were identical in each trial. In the subject's opinion, he was fully recovered between each trial. The work done and hence the oxygen uptake were expected to be similar in the 2 trials.

The stride frequency (Figure 3.16.5) and oxygen uptake (Figure 3.16.6) were not significantly different at any of the 24 sample intervals (Table 3.27).

In trial #1 the subject entrained at the ratio of 2:1 for the entire duration of the run (Figures 3.16.1 and 3.16.2). In trial #2 the same subject initially entrained at a 2:1 ratio. After about 20 seconds into the trial he decreased his breathing frequency to partial entrainment at a ratio of approximately 3:1 (Figures 3.16.3 and 3.16.4).

The decrease in breathing frequency occurring in trial #2 (Figure 3.16.7) was brought about by increases in both inspiratory duration (Figure 3.16.9) and expiratory duration (Figure 3.16.10). This was accompanied by a corresponding increase in tidal volume (Figure 3.16.8). However, the increase in tidal volume was not large enough to counteract the effect of the decrease in breathing frequency. Ventilation was therefore lower than in the previous trial. Significant differences between trial #1 and trial #2 values persisted in all 4 parameters for the remainder of the trial (Table 3.28).

Ventilation (Figure 3.16.9), inspiratory flow (Figure 3.16.10), ventilatory equivalent for oxygen (Figure 3.16.11) and end tidal oxygen (Figure 3.16.13) and the ventilatory equivalent for carbon dioxide (3.16.14) were all lower in the second trial. End tidal carbon dioxide (3.16.16) was higher during the second trial. The differences in trial #1 and trial #2 increased with time. The significance of these differences are presented in Table 3.29.
The respiratory exchange ratio for oxygen (Figure 3.16.11) and carbon dioxide (Figure 3.16.14) indicate a relative hyperventilation for the first 20 seconds of the exercise. Both then fell and remained below normal values for the remainder of the trial. This is indicative of a relative hypoventilation with respect to both oxygen uptake and carbon dioxide output.
Figure 3.15.1. Time from the onset of inspiration to heel strike during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).

Figure 3.15.2. The ratio of pedal frequency to breath frequency during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).
Figure 3.15.3. Pedal frequency during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).

Figure 3.15.4. Breathing frequency during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).
Figure 3.15.5. Inspiratory duration during 2 minutes cycling. Power output = 300 watts at 80 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).

Figure 3.15.6. Expiratory duration during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).
Figure 3.15.7. Tidal volume during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).

Figure 3.15.8. Ventilation during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).
Figure 3.15.9. End tidal oxygen during 2 minutes cycling. Power output = 300 watts at 80 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).

Figure 3.15.10. End tidal carbon dioxide during 2 minutes cycling. Power output = 300 watts at 60 rpm. Vertical lines designate 10 second intervals before and after entrainment ceased. (Subject TH).
Figure 3.15.11. Changes in ventilatory equivalent for oxygen during 2 minutes of cycling. Vertical lines designate 10 second intervals before and after entrainment ceased. Normal ventilatory equivalent = 24 l/l. Power output = 300 watts at 60 rpm. (Subject TH).

Figure 3.15.12. Plot of oxygen uptake against ventilation during 2 minutes of cycling. Power output = 300 watts at 60 rpm. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject TH).
Figure 3.15.13. Changes in the ventilatory equivalent for carbon dioxide during 2 min. of cycling. Vertical lines designate 10 sec. intervals before and after en- trainment ceased. Power output = 300 watts at 60 rpm. Normal ventilatory equivalent = 24 l/l. (Subject TH).

Figure 3.15.14. Plot of carbon dioxide output against ventilation during 2 minutes of cycling. Power output = 300 watts at 60 rpm. Normal ventilatory equivalent = 26 litres /litre. (Subject TH).
Table 3.14: Student’s t scores (t) and the significance of differences (p) in inspiratory flow, minute ventilation, end tidal oxygen and end tidal carbon dioxide while running on a treadmill at equivalent work outputs but different grades.

<table>
<thead>
<tr>
<th>VO₂ (litres)</th>
<th>FLOW</th>
<th>VE</th>
<th>ETO₂</th>
<th>ETCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 - 1.3</td>
<td>t 5.88</td>
<td>4.79</td>
<td>0.45</td>
<td>0.33</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>1.4 - 1.5</td>
<td>t 4.26</td>
<td>4.44</td>
<td>10.95</td>
<td>-1.21</td>
</tr>
<tr>
<td>p 0.05</td>
<td>0.05</td>
<td>0.01</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>1.6 - 1.7</td>
<td>t 4.06</td>
<td>5.59</td>
<td>6.29</td>
<td>-1.89</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>1.8 - 1.9</td>
<td>t 1.98</td>
<td>1.96</td>
<td>3.60</td>
<td>-2.10</td>
</tr>
<tr>
<td>p -----</td>
<td>-----</td>
<td>0.01</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>2.0 - 2.1</td>
<td>t 1.55</td>
<td>1.32</td>
<td>4.38</td>
<td>-0.63</td>
</tr>
<tr>
<td>p -----</td>
<td>-----</td>
<td>0.05</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>2.2 - 2.3</td>
<td>t 3.20</td>
<td>3.38</td>
<td>2.89</td>
<td>-0.52</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>2.4 - 2.5</td>
<td>t 1.13</td>
<td>1.16</td>
<td>3.31</td>
<td>-3.99</td>
</tr>
<tr>
<td>p -----</td>
<td>-----</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>2.6 - 2.7</td>
<td>t 4.28</td>
<td>4.28</td>
<td>2.67</td>
<td>-4.94</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>2.8 - 2.9</td>
<td>t 3.52</td>
<td>3.95</td>
<td>4.70</td>
<td>-9.63</td>
</tr>
<tr>
<td>p 0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>3.0 - 3.1</td>
<td>t 1.39</td>
<td>3.12</td>
<td>1.91</td>
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</tr>
<tr>
<td>p -----</td>
<td>-----</td>
<td>0.01</td>
<td>-----</td>
<td>0.01</td>
</tr>
<tr>
<td>3.2 - 3.3</td>
<td>t 2.10</td>
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<td>2.65</td>
<td>-7.76</td>
</tr>
<tr>
<td>p -----</td>
<td>-----</td>
<td>0.02</td>
<td>0.01</td>
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</table>
Table 3.15: Student’s t scores (t) and significance of the differences (p) in ventilatory equivalent for oxygen and carbon dioxide while running on the treadmill at equivalent work outputs but different grades.

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>VE/VO₂ (l/l)</th>
<th>VE/VO₂ (l/l)</th>
<th>Time (secs)</th>
<th>VE/VO₂ (l/l)</th>
<th>VE/VO₂ (l/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
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<td>61-65</td>
<td>t -2.52</td>
<td>-4.30</td>
</tr>
<tr>
<td>p</td>
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<td>0.01</td>
<td>p</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>6-10</td>
<td>t -6.61</td>
<td>-3.98</td>
<td>66-70</td>
<td>t -5.49</td>
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</tr>
<tr>
<td>p</td>
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<td>0.01</td>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>11-15</td>
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<td>71-75</td>
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</tr>
<tr>
<td>p</td>
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<td>0.01</td>
<td>p</td>
<td>0.01</td>
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</tr>
<tr>
<td>16-20</td>
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<td>-4.96</td>
<td>76-80</td>
<td>t -4.34</td>
<td>-7.02</td>
</tr>
<tr>
<td>p</td>
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<td>p</td>
<td>0.01</td>
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</tr>
<tr>
<td>p</td>
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<td>0.01</td>
<td>p</td>
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<tr>
<td>26-30</td>
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<td>86-90</td>
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<td>-4.08</td>
</tr>
<tr>
<td>p</td>
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<td>0.02</td>
<td>p</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>31-35</td>
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<td>91-95</td>
<td>t -4.18</td>
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</tr>
<tr>
<td>p</td>
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<td>0.05</td>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>36-40</td>
<td>t -2.24</td>
<td>-2.63</td>
<td>96-100</td>
<td>t -4.04</td>
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</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.05</td>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>41-45</td>
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<td>-2.20</td>
<td>101-105</td>
<td>t -0.45</td>
<td>-5.57</td>
</tr>
<tr>
<td>p</td>
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<td>0.01</td>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>46-50</td>
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<td>106-110</td>
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<td>-3.63</td>
</tr>
<tr>
<td>p</td>
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<td>0.02</td>
<td>p</td>
<td>0.01</td>
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<td>-5.18</td>
<td>111-115</td>
<td>t -3.15</td>
<td>-6.10</td>
</tr>
<tr>
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<td>0.01</td>
<td>p</td>
<td>0.02</td>
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<td>-8.43</td>
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<td>p</td>
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<td>0.01</td>
<td>p</td>
<td>0.01</td>
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Table 3.16: Student's t scores (t) and significance of the differences (p) in entrainment ratio during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (secs)</th>
<th>Mean</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>1</td>
<td>57 - 66</td>
<td>1.98</td>
<td>-0.14</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>67 - 76</td>
<td>1.98</td>
<td>13.93</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>77 - 86</td>
<td>1.69</td>
<td>0.02</td>
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</table>

Table 3.17: Student's t scores (t) and significance of the differences (p) in pedal frequency during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (secs)</th>
<th>Mean</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>57 - 66</td>
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<td>0.81</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>67 - 76</td>
<td>62.34</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>77 - 86</td>
<td>62.12</td>
<td>1.45</td>
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<td>87 - 96</td>
<td>61.67</td>
<td></td>
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</table>
Table 3.18: Student's t scores (t) and significance of the differences (p) in breathing frequency during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (secs)</th>
<th>Mean (/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>57 - 66</td>
<td>31.78</td>
</tr>
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</tr>
<tr>
<td></td>
<td>87 - 96</td>
<td>36.70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.31</td>
<td>-5.23</td>
<td>-4.04</td>
</tr>
<tr>
<td>2</td>
<td>-6.30</td>
<td></td>
<td>-4.73</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
</tbody>
</table>

Table 3.19: Student’s t scores (t) and significance of the differences (p) in inspiratory duration during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (secs)</th>
<th>Mean (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>57 - 66</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>67 - 76</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>77 - 86</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>87 - 96</td>
<td>0.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.70</td>
<td>6.27</td>
<td>5.50</td>
</tr>
<tr>
<td>2</td>
<td>6.52</td>
<td></td>
<td>5.80</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-0.77</td>
<td></td>
</tr>
</tbody>
</table>

p-Values: 0.01
Table 3.20: Student's t scores (t) and significance of the differences (p) in expiratory duration during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (secs)</td>
<td>57 - 66</td>
<td>67 - 76</td>
<td>77 - 86</td>
<td>87 - 96</td>
</tr>
<tr>
<td>Mean (secs)</td>
<td>0.84</td>
<td>0.83</td>
<td>0.74</td>
<td>0.73</td>
</tr>
<tr>
<td>t</td>
<td>0.39</td>
<td>5.36</td>
<td>5.95</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.21: Student's t scores (t) and significance of the differences (p) in inspiratory flow during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (secs)</td>
<td>57 - 66</td>
<td>67 - 76</td>
<td>77 - 86</td>
<td>87 - 96</td>
</tr>
<tr>
<td>Mean (l/sec)</td>
<td>2.27</td>
<td>2.33</td>
<td>2.78</td>
<td>2.69</td>
</tr>
<tr>
<td>t</td>
<td>0.80</td>
<td>3.91</td>
<td>6.16</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>0.02</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (secs)</td>
<td>57 - 66</td>
<td>67 - 76</td>
<td>77 - 86</td>
<td>87 - 96</td>
</tr>
<tr>
<td>Mean (l/sec)</td>
<td>2.27</td>
<td>2.33</td>
<td>2.78</td>
<td>2.69</td>
</tr>
<tr>
<td>t</td>
<td>0.80</td>
<td>3.91</td>
<td>6.16</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>0.02</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.22: Student's t scores (t) and significance of the differences (p) in tidal volume during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (secs)</td>
<td>57 - 66</td>
<td>67 - 76</td>
<td>77 - 86</td>
<td>87 - 96</td>
</tr>
<tr>
<td>Mean (l)</td>
<td>1.94</td>
<td>2.01</td>
<td>2.01</td>
<td>1.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th>p</th>
<th>t</th>
<th>p</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.20</td>
<td>----</td>
<td>-0.18</td>
<td>----</td>
<td>-0.09</td>
<td>----</td>
</tr>
<tr>
<td>2</td>
<td>0.02</td>
<td>----</td>
<td>0.04</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>0.03</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

Table 3.23: Student's t scores (t) and significance of the differences (p) in ventilation during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (secs)</td>
<td>57 - 66</td>
<td>67 - 76</td>
<td>77 - 86</td>
<td>87 - 96</td>
</tr>
<tr>
<td>Mean (l/min)</td>
<td>63.29</td>
<td>66.31</td>
<td>79.33</td>
<td>75.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th>p</th>
<th>t</th>
<th>p</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.59</td>
<td>0.01</td>
<td>-10.60</td>
<td>0.01</td>
<td>-6.62</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>----</td>
<td>0.01</td>
<td>-9.61</td>
<td>0.01</td>
<td>-5.42</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>2.90</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
Table 3.24: Student’s t scores (t) and significance of the differences (p) in ventilatory equivalent during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (secs)</th>
<th>Mean (l/l)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57 - 66</td>
<td>19.53</td>
<td>-0.51</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>67 - 76</td>
<td>19.66</td>
<td>-10.79</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>77 - 86</td>
<td>21.64</td>
<td>-14.57</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>87 - 96</td>
<td>21.85</td>
<td>-10.79</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 3.25: Student’s t scores (t) and significance of the differences (p) in end tidal oxygen during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Time (secs)</th>
<th>Mean (Torr)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57 - 66</td>
<td>98.38</td>
<td>-0.47</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>67 - 76</td>
<td>98.58</td>
<td>-9.62</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>77 - 86</td>
<td>102.37</td>
<td>-13.20</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>87 - 96</td>
<td>102.55</td>
<td>-13.20</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table 3.26: Student’s t scores \( (t) \) and significance of the differences \( (p) \) in end tidal carbon dioxide during periods of entrainment and non entrainment in subject T.H. while cycling at 300 watts.

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (secs)</td>
<td>57 - 66</td>
<td>67 - 76</td>
<td>77 - 86</td>
<td>87 - 96</td>
</tr>
<tr>
<td>Mean (Torr)</td>
<td>44.03</td>
<td>44.52</td>
<td>42.86</td>
<td>43.52</td>
</tr>
<tr>
<td>( t )</td>
<td>-1.20</td>
<td>3.51</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td>( p )</td>
<td>----</td>
<td>0.02</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>( t )</td>
<td>5.01</td>
<td>3.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p )</td>
<td>0.01</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t )</td>
<td>-4.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p )</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.16.1. Time from the onset of inspiration until heel strike during 2 minutes of treadmill running. Speed = 6kph. Grade = 16%. First of 2 trials. (Subject SW).

Figure 3.16.2. The ratio of pedal frequency to breath frequency during 2 minutes of treadmill running. Speed = 6 kph. Grade = 16%. First of 2 trials. (Subject SW).
Figure 3.16.3. Time from the onset of inspiration until heel strike during 2 minutes of treadmill running. Speed = 6kph. Grade = 16%. Second of 2 trials. (Subject SW).

Figure 3.16.4. The ratio of pedal frequency to breath frequency during 2 minutes of treadmill running. Speed = 6 kph. Grade = 16%. Second of 2 trials. (Subject SW).
Figure 3.16.5. Comparison of stride frequency during 2 minutes treadmill running. Speed = 6 kpm. Grade = 16%. 1 subject 2 trials. (Subject SW).

Figure 3.16.6. Comparison of oxygen uptake during 2 minutes treadmill running. Speed = 6 kpm. Grade = 16%. 1 subject 2 trials. (Subject SW).
Table 3.27: Student's t scores (t) and significance of the differences (p) in stride frequency and oxygen uptake during 2 trials on the treadmill at 16% grade and 6 kph (Figures 3.16.5 and 3.16.6).

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>Stride Freq.</th>
<th>Oxygen Uptake</th>
<th>Time (secs)</th>
<th>Stride Freq.</th>
<th>Oxygen Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>t -0.58</td>
<td>-3.68</td>
<td>61-65</td>
<td>t -0.62</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td>0.05</td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>t -0.01</td>
<td>-0.05</td>
<td>66-70</td>
<td>t 1.82</td>
<td>-0.57</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>t -1.91</td>
<td>0.24</td>
<td>71-75</td>
<td>t 1.08</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>t -0.46</td>
<td>0.90</td>
<td>76-80</td>
<td>t 2.21</td>
<td>2.89</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>t -2.12</td>
<td>-0.05</td>
<td>81-85</td>
<td>t 1.25</td>
<td>-0.05</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>26-30</td>
<td>t 0.83</td>
<td>-1.39</td>
<td>86-90</td>
<td>t 0.67</td>
<td>-0.81</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>31-35</td>
<td>t 0.62</td>
<td>2.34</td>
<td>91-95</td>
<td>t 1.05</td>
<td>-0.12</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>36-40</td>
<td>t -0.22</td>
<td>-1.87</td>
<td>96-100</td>
<td>t 0.26</td>
<td>-1.19</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>41-45</td>
<td>t -0.51</td>
<td>-0.34</td>
<td>101-105</td>
<td>t 1.75</td>
<td>-1.10</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>46-50</td>
<td>t -0.18</td>
<td>1.30</td>
<td>106-110</td>
<td>t 0.26</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>51-55</td>
<td>t 1.03</td>
<td>-0.45</td>
<td>111-115</td>
<td>t -0.16</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
<tr>
<td>56-60</td>
<td>t -1.75</td>
<td>1.29</td>
<td>116-120</td>
<td>t -0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p -----</td>
<td></td>
<td></td>
<td>p -----</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.16.7. Comparison of breathing frequency during 2 minutes treadmill running. Speed = 6 kpm. Grade = 16%. 1 subject 2 trials. (Subject SW).

Figure 3.16.8. Comparison of tidal volume during 2 minutes treadmill running. Speed = 6 kpm. Grade = 16%. 1 subject 2 trials. (Subject SW).
Figure 3.16.9. Changes in ventilation during 2 minutes of treadmill running. Comparison of 2 trials. Speed = 6 kph. Grade = 16%. (Subject SW).

Figure 3.16.10. Changes in inspiratory flow during 2 minutes of treadmill running. Comparison of 2 trials. Speed = 6 kph. Grade = 16%. (Subject SW).
Figure 3.16.11. Changes in ventilatory equivalent for oxygen during 2 minutes of treadmill running. Comparison of 2 trials. Speed = 6 kph. Grade = 16%. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject SW).

Figure 3.16.12. Plot of oxygen uptake against ventilation during 2 minutes of treadmill running. Speed = 6 kph. Grade = 16%. Normal ventilatory equivalent for oxygen = 24 litres/litre. (Subject SW).
Figure 3.16.13. Changes in end tidal oxygen during 2 minutes of treadmill running. Comparison of 2 trials. Speed = 6 kph. Grade = 16%. (Subject SW).

Figure 3.16.14. Changes in the ventilatory equivalent for carbon dioxide during 2 minutes of treadmill running. Comparison of 2 trials. Speed = 6 kph. Grade = 16%. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. (Subject SW).
Figure 3.16.15. Plot of carbon dioxide output against ventilation during 2 minutes of treadmill running. Speed = 6 kph. Grade = 16%. Normal ventilatory equivalent for carbon dioxide = 26 litres/litre. (Subject SW).

Figure 3.16.16. Changes in end tidal carbon dioxide during 2 minutes of treadmill running. Comparison of 2 trials. Speed = 6 kph. Grade = 16%. (Subject SW).
Table 3.28: Student’s t scores (t) and the significance of the differences (p) in breathing frequency, tidal volume, inspiratory duration and expiratory duration during two 2 minute runs on the treadmill at 16% grade and 6 kph (Figures 3.16.7 to 3.16.10).

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>B Freq.</th>
<th>VT</th>
<th>TI</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 10</td>
<td>t 2.36</td>
<td>-1.84</td>
<td>-1.58</td>
<td>-2.49</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>11 - 20</td>
<td>t 1.35</td>
<td>-2.20</td>
<td>-0.78</td>
<td>-1.81</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>21 - 30</td>
<td>t 12.67</td>
<td>-6.89</td>
<td>-15.02</td>
<td>-6.10</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>31 - 40</td>
<td>t 5.74</td>
<td>-6.97</td>
<td>-3.62</td>
<td>-3.75</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>41 - 50</td>
<td>t 18.70</td>
<td>-8.05</td>
<td>-20.32</td>
<td>-18.55</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>51 - 60</td>
<td>t 28.61</td>
<td>-7.13</td>
<td>-14.92</td>
<td>-15.43</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>61 - 70</td>
<td>t 10.10</td>
<td>-8.99</td>
<td>-5.09</td>
<td>-10.20</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>71 - 80</td>
<td>t 14.81</td>
<td>-6.30</td>
<td>-7.34</td>
<td>-16.01</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>81 - 90</td>
<td>t 18.47</td>
<td>-8.73</td>
<td>-15.02</td>
<td>-8.99</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>91 - 100</td>
<td>t 27.20</td>
<td>-8.86</td>
<td>-16.90</td>
<td>-11.31</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>101 - 110</td>
<td>t 21.33</td>
<td>-6.14</td>
<td>-16.77</td>
<td>-9.07</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>111 - 120</td>
<td>t 19.50</td>
<td>-5.50</td>
<td>-15.22</td>
<td>-9.42</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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</tr>
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</table>
Table 3.29: Student’s t scores (t) and the significance of the differences (p) in inspiratory flow, minute ventilation, ventilatory equivalent and end tidal oxygen during two 2 minute runs on the treadmill at 16% grade and 6 kph (Figures 3.16.9, 3.16.10, 3.16.11 and 3.16.13).

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>VT/TI</th>
<th>VE</th>
<th>VE/VO2</th>
<th>ETO2</th>
</tr>
</thead>
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<tr>
<td>1 - 10</td>
<td>t -0.41 p ----</td>
<td>-2.94 p ----</td>
<td>-3.26 p ----</td>
<td></td>
</tr>
<tr>
<td>11 - 20</td>
<td>t -2.57 p 0.05</td>
<td>-3.02 p 0.05</td>
<td>-4.17 p 0.01</td>
<td></td>
</tr>
<tr>
<td>21 - 30</td>
<td>t 0.75 p ----</td>
<td>-0.09 p ----</td>
<td>-0.66 p ----</td>
<td></td>
</tr>
<tr>
<td>31 - 40</td>
<td>t -1.21 p ----</td>
<td>0.16 p ----</td>
<td>0.23 p ----</td>
<td></td>
</tr>
<tr>
<td>41 - 50</td>
<td>t 0.41 p ----</td>
<td>2.79 p 0.05</td>
<td>5.26 p 0.01</td>
<td></td>
</tr>
<tr>
<td>51 - 60</td>
<td>t 3.22 p 0.05</td>
<td>7.91 p 0.01</td>
<td>11.74 p 0.01</td>
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</tr>
<tr>
<td>61 - 70</td>
<td>t 1.02 p ----</td>
<td>6.36 p 0.01</td>
<td>3.23 p 0.05</td>
<td></td>
</tr>
<tr>
<td>71 - 80</td>
<td>t 2.43 p ----</td>
<td>5.84 p 0.01</td>
<td>3.52 p 0.02</td>
<td></td>
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<tr>
<td>81 - 90</td>
<td>t 3.15 p 0.05</td>
<td>4.82 p 0.01</td>
<td>4.87 p 0.01</td>
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<tr>
<td>91 - 100</td>
<td>t 4.82 p 0.01</td>
<td>6.48 p 0.01</td>
<td>8.95 p 0.01</td>
<td></td>
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<td>101 - 110</td>
<td>t 5.30 p 0.01</td>
<td>10.55 p 0.01</td>
<td>9.15 p 0.01</td>
<td></td>
</tr>
<tr>
<td>111 - 120</td>
<td>t 1.83 p ----</td>
<td>6.51 p 0.01</td>
<td>6.59 p 0.01</td>
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</tr>
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</table>
DISCUSSION (Section III)

It is apparent that the traditional concepts of isocapnic hyperpnoea cannot explain the whole ventilatory response in exercising man and that ventilation is determined by many interacting influences. In this Section III, it has been found that the mode of activity and the entrainment of breathing frequency to limb movement frequency results in modification of the normal breathing pattern and overall ventilatory response.

A. Considerations in Interpreting the Results

1. Bicycle Ergometer There are different efficiencies at different rates of limb movement while pedalling a bicycle. Therefore, the rate at which work is done on the flywheel of a bicycle ergometer is not perfectly independent of the pedalling rate.

Seabury et al (1977) estimated that the internal work required to accelerate and decelerate the leg equals from 5-30% of the external work. This internal work increases with increasing pedal rate. Therefore, the force pushing the pedaling becomes a smaller percentage of the total work at higher pedal frequencies (Davis and Hull 1981, Lafortune and Cavanagh 1983). Hence, one would expect the oxygen cost of pedalling to increase with increasing pedal frequency.

Coast et al (1986) found that the oxygen uptake at any work load varied by as much as 10%, depending on the rate of pedalling. As the pedal rate increased from 40-80 rpm work rate increased by about 8 watts. This gave a predicted rise in oxygen uptake of about 80 ml/min.

In this study, oxygen uptake increased with increasing pedal frequency at all power outputs. To some extent, this must reflect an actual increase in internal work. However, it may also reflect greater external work due to the inability of the bicycle ergometer to adjust the load to ensure that the power output remained constant at the chosen level.

2. Oxygen Equivalent of Work Because changing pedal or stride frequency results in a change in oxygen uptake at a given power output, changes in ventilation and carbon dioxide output are to be expected. However, it is not possible to tell whether the changes in ventilation and carbon dioxide
output are due to the changes in oxygen uptake alone, or whether the changing pedal or stride frequency also influence the ventilation and carbon dioxide output. By changing pedal or stride frequency and maintaining a constant oxygen uptake, changes in ventilation and carbon dioxide output are more likely to relate to the frequency of limb movement (Bramble and Carrier 1983, Hanson et al 1982, McMurray and Alborn 1982).

This study examined the effects on ventilation of different combinations of pedal frequency and load while cycling, and different combinations of stride frequency and grade while running on the treadmill. Because the oxygen uptakes were not matched at each of the power outputs the responses were assessed by plotting each parameter against oxygen uptake and then comparing the slope for each of the four pedal frequencies and two grades used.

3. **Treadmill vs Ground Running** Significant differences exist between treadmill and ground locomotion. Several studies have been done comparing the metabolic energy expenditure. However, of more significance are those studies which have demonstrated differences in the kinematics of locomotion i.e. the difference in stride length and cadence while walking and running at the same speed (Murray et al 1985). Entrainment of breathing frequency to stride frequency on the treadmill, in certain circumstances, may cause hypoventilation and be detrimental to gas exchange. Running at the same speed on the ground may be achieved with a significantly different stride frequency. Entrainment of breathing frequency to this new stride frequency may not readily occur. Even if it does occur it may not interfere with either ventilation or gas exchange.

B. **Ventilatory Response to Different Modes of Exercise**

Numerous investigators have concluded that the type of exercise influences the ventilatory response (D'Angelo and Torelli 1971, Fordyce et al 1982). The results of this Section III tend to support this contention.

1. **Steady-State**

(a) **Cycling** The relationship between carbon dioxide and oxygen uptake (Figure 3.2.1), and the relationship between ventilation and oxygen uptake (Figure 3.3.1), while cycling, were at first linear. At work intensities
greater than about 2.5 to 3.0 l/min, both carbon dioxide and ventilation increased faster than oxygen uptake. The secondary increase is more obvious when the respiratory exchange ratio (Figure 3.2.2) and the ventilatory equivalent for oxygen (Figure 3.3.2) are plotted against oxygen uptake. This secondary increase is probably a consequence of the increasing metabolic acidosis with increasing work intensities above the anaerobic threshold.

The relationship between ventilation and carbon dioxide (Figure 3.4.1) was also curvilinear. The secondary increase in ventilation is again more obvious when the ventilatory equivalent for carbon dioxide is plotted against oxygen uptake (Figure 3.4.2). This secondary change occurs later and is not as large as the changes in the ventilatory equivalent for oxygen.

Only at the highest work loads is proportionality between carbon dioxide output and ventilation compromised. The trials in this study were progressive in nature and increasing body temperature and catecholamine levels are likely. This may account for the disproportionate increase in ventilation with respect to carbon dioxide production at the high work intensities.

The ventilatory equivalent for oxygen ranged from about 19 litres/litre, at the lowest work intensity, to about 23 litres/litre at the highest work intensity. The ventilatory equivalent for carbon dioxide similarly ranged from about 23 to 26 litres/litre. As normal resting values are 24 and 26 litres/litre for oxygen and carbon dioxide respectively, while cycling, there is hypoventilation with respect to both oxygen uptake and carbon dioxide output over the full range of exercise intensities.

Oxygen uptake (Figure 3.1.1) and ventilation (Figure 3.1.2) increased with increasing pedal frequency at each of the 6 power outputs. However, when comparing the four different pedal frequencies, over the full range of exercise intensities, the carbon dioxide (Figure 3.2.1) and ventilation (Figure 3.3.1) at any oxygen uptake were not significantly different. Therefore, the differences in carbon dioxide output and ventilation at each power output related solely to the differences in oxygen uptake and were independent of the pedal frequencies.
(b) **Running** In both running modes the relationship between carbon dioxide and oxygen (Figure 3.2.1), ventilation and oxygen uptake (Figure 3.3.1), and ventilation and carbon dioxide (Figure 3.4.1) were similar to that found while cycling. The respiratory exchange ratio (Figure 3.2.2) and the ventilatory equivalent for oxygen (Figure 3.3.2) also show a similar 2 phase increase with the secondary increase again occurring at an oxygen uptake of about 2.5 to 3.0 l/min.

Carbon dioxide output, at all power outputs, was higher while running on the flat than while running on the grade. It cannot be determined as to what extent this reflects hyperventilation or an actual increase in carbon dioxide production. Hyperventilation without a concomitant increase in production will cause a decrease in arterial carbon dioxide tension (Hanson et al 1982). Neither arterial carbon dioxide tension nor end tidal carbon dioxide were measured in this study. Essen (1978) and Gonyea (1980) have suggested that carbon dioxide output could also increase due to a greater proportion of Type II fibres being recruited during running. These rely on carbohydrates as a fuel and would effect an increase in carbon dioxide production.

McMurray and Alborn (1985) found the same ventilation while running at a given submaximal oxygen uptake, regardless of the alterations in stride frequency. This was supported by the work of Kay et al (1975b) and Dejours (1967) but contrary to the findings of McMurray and Alborn (1982). In this study the ventilation at any given oxygen uptake was lower running on a grade than when running on the flat. This was true over a range of speeds from 6-14 kph.

The mean ventilatory equivalent for oxygen for running on the flat was about 25 litres/litre and about 19 litres/litre for running on the grade. This suggest a slight hyperventilation with respect to oxygen uptake for running on the flat and a marked hypoventilation when running on a grade.

While running on the flat the ventilatory equivalent for carbon dioxide (Figure 3.4.2) also increased with increasing work intensity. However, no such increase was evident while running up a grade. When running up a grade the subjects performed one less work increment than when running on the flat. Increases in metabolic acidosis, temperature and catecholamines are time dependent. In a shorter time the rise in [H⁺], temperature and
catecholamines would be less. Hence the extra metabolic stimuli to ventilation would be less.

The mean ventilatory equivalent for carbon dioxide for running on the flat was about 27 litres/litre and about 21 litres/litre for running on the grade. This suggest a slight hyperventilation with respect to carbon dioxide for running on the flat and a marked hypoventilation when running on a grade.

As with McMurray and Alborn (1982) the increase in ventilation was due entirely to a greater frequency of breathing. It is possible that the two are related and that a degree of entrainment of breathing frequency to limb movement has occurred. Such entrainment could also explain the failure of the ventilatory equivalent for carbon dioxide to increase at high work intensities while running on a grade. A rises in ventilation may have been prevented by entrainment of breathing frequency to a low rate at a time when tidal volume had reached maximum values. The identical step changes in breathing frequency (Figure 3.5.1) and stride frequency (Figure 3.5.2) observed while running on the grade certainly lend support to the notion that entrainment of breathing frequency to limb movement is occurring while running on a grade.

2. Non Steady-State

(a) Cycling When the two combinations of pedal frequency and load on the bicycle ergometer were compared both, the pedal frequencies (Figure 3.9.1) and the oxygen uptakes (Figure 3.9.2) were significantly different throughout the whole duration of the trial. These differences and their significance are presented in Table 3.8. As in the steady-state, the differences in oxygen uptake at the same power output probably reflect both an increase in internal work with increasing pedal frequency and greater external work due to the inability of the bicycle ergometer to adjust the load to ensure that the power output remained constant at the chosen level.

When breathing frequency, tidal volume, inspiratory duration, expiratory duration, inspiratory flow, ventilation, end tidal oxygen and end tidal carbon dioxide were compared, under the two conditions, no consistent significant differences were evident (Tables 3.9 and 3.10).
The relationship between ventilation and oxygen uptake (Figure 3.10.2) was linear up to an oxygen uptake of about 1.4 l/min. Ventilation then plateaued as oxygen uptake increased to nearly 3 l/min. A secondary increase in ventilation then occurred. The general pattern of the response was identical for both pedal frequencies.

The ventilatory equivalent for oxygen (Figure 3.10.1) averaged about 32 litres/litre for the first 10 to 15 seconds then fell rapidly to attain minimal values of about 19 litres/litre 25 to 30 seconds after the onset of exercise. The ventilatory equivalent then rose gradually during the remaining 90 seconds of the trial. At both pedal frequencies there was hyperventilation with respect to oxygen uptake at the onset of exercise. The fall in ventilatory equivalent after 10 to 15 seconds meant that there was relative hypoventilation with respect to oxygen uptake for the remainder of the trial.

With the high pedal frequency, the initial fall in ventilatory equivalent occurred earlier passing below normal values after 15 seconds and attaining minimal values approximately 25 seconds after the onset of exercise. The ventilatory equivalent then rose to attain normal resting values just prior to the completion of the trial. With the low pedal frequency, the fall in ventilatory equivalent occurred later, passing below normal values after 20 seconds and not reaching minimal values to about 30 seconds after the onset of exercise. The ventilatory equivalent then rose slowly but remained well below normal resting levels at the end of the trial. These differences and their significance are presented in Table 3.11.

The maximal oxygen uptake at the low pedal frequency was about 4 l/min as compared to nearly 5 l/min at the high pedal frequency. The ventilation at the low pedal frequency was about 80 l/min as compared to 120 l/min at the high pedal frequency. Also, the cardiac output would be higher and the transit time between the muscle and the lung would be less at the high pedal frequency. The differences in the timing of the response is probably a consequence of these differences in work intensities. The differences in the magnitude of the response over the later part of the trial may be related more to the differences in pedal frequency.

(b) Running When the two combinations of speed and grade on the treadmill were compared, stride frequencies (Figure 3.12.1) were significantly
different throughout the whole duration of the trial. No such differences were found in oxygen uptake (Figure 3.9.2). The differences in stride frequency and oxygen uptake and their significance are presented in Table 3.12.

When the two conditions were compared breathing frequency, inspiratory flow, ventilation and end tidal oxygen were significantly higher and tidal volume, inspiratory duration, expiratory duration and end tidal carbon dioxide were significantly lower when running on the flat. These differences and their significances are presented in Tables 3.13 and 3.14.

The relationship between ventilation and oxygen uptake (Figure 3.13.2) during the first 2 minutes of running was similar to that occurring while cycling, but not as clearly defined. For both running on the flat and running on a grade the initial response was similar. However, the plateauing of ventilation was not as obvious as that occurring during cycling, particularly when running on the flat. During phase II, throughout the range of oxygen uptakes studied, ventilation was significantly higher while running on the flat.

The ventilatory equivalent for oxygen (Figure 3.13.1) was above 34 litres/litre at the onset of exercise then fell rapidly to attain minimal values 45 to 50 seconds after the onset of exercise. The ventilatory equivalent then rose gradually during the remaining 90 seconds of the trial. The pattern of the response was identical for both conditions. However, the magnitude of the response differed. While running on a grade, the initial fall in ventilatory equivalent occurred almost immediately passing below normal values after approximately 20 seconds and attaining minimal values approximately 50 seconds after the onset of exercise. The ventilatory equivalent then rose slowly but remained below normal resting levels at the end of the trial. While running on the flat, the fall in ventilatory equivalent again occurred soon after the onset of exercise. It passed below normal values after 30 seconds and reached minimal values about 50 seconds after the onset of exercise. The ventilatory equivalent then rose to attain normal resting values about 40 seconds prior to the completion of the trial.

At both pedal frequencies there was hyperventilation with respect to oxygen uptake at the onset of exercise. The fall in ventilatory equivalent meant
that there was relative hypoventilation with respect to oxygen uptake after about 30 seconds. Hypoventilation was evident while running on the grade throughout the remainder of the trial. Ventilation returned to normal 40 seconds prior to completing the trial while running on the flat.

The pattern of change in oxygen uptake and the maximal oxygen uptake for running on the flat and running on a grade were identical. The differences in the ventilation and carbon dioxide response throughout the trial must therefore related, not to the oxygen uptake, but to the differences in the combination of treadmill grade and speed i.e. the different modes of exercise.

C. Coupling of Ventilation and Carbon Dioxide Output

1. Steady State  Despite varying pedal and stride frequencies if the work remains the same then the oxygen uptake and carbon dioxide production should remain the same and ventilation should be unaffected if carbon dioxide is the stimulus. Consequently, the ventilatory equivalent for carbon dioxide and the arterial carbon dioxide tension should remain relatively constant.

(a) Cycling  Casaburi et al (1978b) found only small fluctuations in end tidal carbon dioxide with varying pedal frequency. Kay et al (1975b) similarly found that the relationship between ventilation and carbon dioxide output was independent of pedal speed. In this study there were no significant differences in the relationships between ventilation, oxygen uptake and carbon dioxide output at each of the 4 pedal frequencies studied.

It appears that, while cycling, the ventilation and carbon dioxide output for a given oxygen uptake is not affected by the force or speed of muscle contraction. Limb movement per se does not act as an additional stimulus to ventilation. Ventilation instead is linked to metabolism by the associated carbon dioxide production. This supports the findings of Brown et al (1976), Casaburi et al (1977), and Wasserman et al (1977b).

(b) Running  In ponies running on a treadmill, ventilation was not tightly coupled to carbon dioxide production (Pan et al 1983). As treadmill speed was increased there was a divergence of ventilation and carbon dioxide
output with a concomitant decrease in end tidal carbon dioxide and increase in end tidal oxygen.

On the contrary, McMurray and Ahlborn (1982) found that during moderate intensity running in athletes the ventilatory equivalent for carbon dioxide and the arterial carbon dioxide tension were both within the normal range. However, during walking at a similar power output arterial carbon dioxide tension increased and the ventilatory equivalent for carbon dioxide decreased to 20 litres/litre. Also, during running in nonathletes, the ventilatory equivalent for carbon dioxide increased to 29 litres/litre and the arterial carbon dioxide tension fell (McMurray and Smith 1985).

In the later two cases, carbon dioxide stores are changing and carbon dioxide output is not representative of carbon dioxide production. The respiratory exchange ratio does not reflect metabolic substrate. This is indicative of an uncoupling of ventilation and carbon dioxide output. It appears that stride frequency in some way provides a considerable stimulus for ventilation independent of carbon dioxide thereby causing hyper-ventilation at high stride frequencies and hypventilation at low frequencies (Comroe 1944, Kao 1963, Eldridge et al 1981, McMurray and Smith 1985).

An apparent uncoupling of ventilation and carbon dioxide output is also evident during steady-state exercise in this study. The ventilatory equivalent for carbon dioxide while running on a grade and while running on the flat were significantly different. They averaged about 21 and 27 litres/litre respectively. These values are similarly indicative of hypoventilation while running on the grade (i.e. low stride frequencies) and hyperventilation while running on the flat (i.e. high stride frequencies).

2. Non Steady State

(a) Cycling There was a good correlation between ventilation and carbon dioxide throughout the 2 minutes of cycling (Figure 3.11.2). The relationship was essentially identical for both pedal frequencies.

The ventilatory equivalent for carbon dioxide (Figure 3.11.1) was about 29 litres/litre at the onset of exercise. After about 10 seconds it fell to
attain minimal values about 25 seconds after the onset of exercise. The ventilatory equivalent remained constant at about 24 litres/litre throughout the remainder of the trial. The timing of the response was different for the two pedal frequencies. The ventilatory equivalent while pedalling at the higher frequency fell quicker passing below normal resting values after 12 seconds. The ventilatory equivalent while pedalling at the slower frequency fell more slowly passing below the normal resting level after about 20 seconds. Both remained below normal resting levels for the remainder of the trial indicating a hypoventilation with respect to carbon dioxide. There was a tendency for the ventilation equivalent while pedalling at the higher frequency to be slightly higher during the second half of the trial. These differences and their significance are presented in Table 3.11.

As with the ventilatory equivalent for oxygen, it is likely that the differences in the timing of the response are a consequence of the differences in work intensities. The differences in the magnitude of the response over the second half of the trial may be related to the differences in pedal frequency.

(b) Running The correlation between ventilation and carbon dioxide (Figure 3.14.2) throughout the 2 minutes of running was not as close as that observed during cycling, although it was linear in nature. The relationship was again essentially identical for both pedal frequencies.

The ventilatory equivalent for carbon dioxide (Figure 3.14.1) averaged about 30 litres/litre at the onset of exercise. It remained constant for about 25 seconds then it fell to attain minimal values about 60 seconds after the onset of exercise. The ventilatory equivalent remained relatively constant throughout the remaining 60 seconds of the trial. The pattern of the response for the two pedal frequencies was similar though the magnitude of the response was significantly different.

The fall in ventilatory equivalent while running on a grade was greater. It passed below normal resting values after 40 seconds and remained below for the remainder of the trial. This is indicative of hypoventilation with respect to carbon dioxide. The fall in ventilatory equivalent while running on the flat was less. At all times during the trial it remained above normal resting levels. This is indicative of hyperventilation with
respect to carbon dioxide. These differences and their significance are presented in Table 3.15.

As with the ventilatory equivalent for oxygen it is likely that the differences in the magnitude of the response can be related to the differences in pedal frequency.

D. Uncoupling of Ventilation and Carbon Dioxide Output

Certain humoral factors are known to override the precise coupling of ventilation and carbon dioxide output during exercise (Hanson et al 1982). They include: metabolic acidosis, elevations in temperature, elevations in catecholamines, and hypoxemia. The influence of neural afferents has also been postulated.

1. Humoral Factors A greater degree of metabolic acidosis has been demonstrated during cycling than during running at equivalent work outputs (DeCoster et al 1969, Glassford et al 1965, Hollman and Kastner 1969, Niederberger et al 1974, Scherrer 1969, Koyal et al 1976) and during cycling than during stairclimbing at equivalent work outputs (Oldenberg et al 1979, Shephard et al 1968). This is thought to be due to a smaller muscle mass generating the same power output thereby causing the mean metabolic rate per unit of contracting muscle to be higher. Anaerobiosis would therefore become manifest at a lower oxygen uptake. A lower leg blood flow during cycling may also contribute to the increased lactate and higher ventilation while cycling (Matell 1963). The fact that a greater degree of metabolic acidosis results in a higher ventilation indicates normal respiratory control via carotid bodies (Wasserman et al 1975b).

In this study, ventilation and carbon dioxide output were higher during cycling than during running at grade (running at grade being comparable to stair climbing) but contrary to the above results, they were also higher during running on the flat than during cycling.

The degree of muscular involvement in each of the modes and the lactate production can only be surmised as neither were measured. However, it is possible that muscle involvement was greater in cycling than running in this study. All subjects were experienced athletes. Competitive cyclists tend to employ considerable upper body movement when cycling. Much more so
than the untrained individual. Conversely experienced endurance runners employ far less upper body movement in running than the untrained subject. Running at grade involves considerable exaggerated upper body movement. Thus the lactate production could relate to the muscle involvement and explain the observed differences in ventilation.

This postulated variance in lactate production may also explain the timing of the secondary rise in ventilatory equivalent for carbon dioxide. This occurred earlier i.e. at a lower oxygen uptake, in running on the flat than cycling and not at all in running at grade.

2. Neural Afferents Three types of studies have been used to demonstrate the possible role of neural afferents from muscle in stimulating ventilation during exercise.

(a) Studies in which muscle afferents have been anatomically defined and stimulated to produce alterations in ventilation (Comroe and Schmidt 1943, Kao 1963, McCloskey and Mitchell 1972).

(b) Studies in which passive limb movements have been shown to evoke changes in ventilation (Bahnson et al 1949, Beirman and Ralston 1963, Comroe and Schmidt 1943, Flandrois et al 1967, Lloyd and Patrick 1963).

(c) Studies in which the ventilatory response to exercise is different using different patterns of limb movement e.g. different pedalling rates (Beirman and Ralston 1963, Cardus 1969, Kay et al 1975b, Lloyd and Patrick 1963, Sipple and Gilbert 1966, Casaburi et al 1978b).

Results from the latter type of studies are inconclusive. Altering the pedal rate has been shown to alter the neurogenic stimuli from the limbs (Gautier et al 1969, Kao et al 1955, Tibes 1977). The role of these afferents in the ventilatory response is supported by studies in dogs (Bainton 1972) ponies (Pan et al 1983) and humans (Hanson et al 1982, McMurray and Ahlborn 1982) which show that changes in treadmill speed but not changes in grade produce hypocapnia. Contrary to this are further studies in ponies (Forster et al 1984) and humans (Bahnson et al 1949, Beirman and Ralston 1963, Cardus 1969, Kay et al 1975, Lloyd and Patrick 1963, Casaburi et al 1977, Casaburi et al 1978b, McMurray and Smith 1985) which suggest that the frequency of limb movement is not a major factor in regulating the ventilatory response to exercise and that the increase in ventilation is only proportional to the increase in metabolic rate.
It is known that metabolic disturbances can change the level at which arterial carbon dioxide partial pressure is regulated (Caiozzo et al 1987). In people with chronic metabolic acidosis arterial carbon dioxide partial pressure will be regulated at some value less than the normal 40 Torr. Conversely, in people with chronic metabolic alkalosis arterial carbon dioxide partial pressure is regulated at a value greater than the normal 40 Torr. These changes do not represent uncoupling of ventilation and carbon dioxide output. Instead the slope of the ventilation carbon dioxide relationship has increased in a predictable manner as described by the alveolar ventilation equation (Caiozzo et al 1987).

In this study, the ventilatory equivalent for carbon dioxide in the steady-state averaged about 21, 24 and 27 litres/litre for running on a grade, cycling and running on the flat, respectively. In the non steady-state, the ventilatory equivalent for carbon dioxide while running on the treadmill on the flat was about 28 litres/litre. While running on a treadmill on a grade, and while cycling, the ventilatory equivalent for carbon dioxide was about 24 litres/litre.

The normal ventilatory equivalent for carbon dioxide is about 26 litres/litre. It is postulated that, under these conditions, carbon dioxide is the only stimulus to ventilation. The upward displacement of the ventilation carbon dioxide output relationship, without change in the slope, (e.g. during running on the flat) suggests that additional humoral or neural stimuli have had an additive effect. The downward displacement of the ventilation carbon dioxide output relationship, without change in the slope, (e.g. during running on a grade) suggests that the normal ventilatory response has been interfered with. Possibly ventilation has been limited by the entrainment of breathing frequency to stride frequency at a time when tidal volume has reached its maximum.

Certain modes of exercise cause vertical displacement of the carbon dioxide-ventilation relationship. Rather than representing an uncoupling of the carbon dioxide ventilation relationship it may indicate a changing of the level at which the arterial carbon dioxide partial pressure is regulated.

E. Entrainment of Breathing Frequency to Movement Frequency

The different findings are possibly due to experimental design (see Appendix C). In particular, it is claimed that neurogenic factors have not been satisfactorily separated from possible metabolic influences on respiratory pattern. Experiments designed to eliminate this complication indicate that neurogenic mechanisms have little, if any, effect on the entrainment of breathing to the pattern of limb movement (Casaburi et al 1978a).

In this study, entrainment of breathing frequency to movement frequency occurred to some degree in all subjects. It occurred over a wide range of pedal frequencies while cycling, and at a variety of stride frequencies while running on a grade and running on the flat. It occurred at all exercise intensities. The extent of entrainment varied from individual to individual and from trial to trial. Some entrained the whole duration of the trial. Others completed whole trials with no evidence of entrainment at all.

2. Ratios and Ratio shifts. In the quadruped the ratio of limb movement to breathing frequency is usually 1:1. This is dictated by the cyclic loading of chest wall during locomotion. Humans use a wide variety of coupling ratios ranging from 1:1 to 5:1 (Figure 3.8.2). Most prominent over a wide range of speeds and stride frequencies is 2:1. A 1:1 ratio is common while ascending sloped surfaces where the metabolic demand is high, the stride frequency is low, and the cyclic loading of the body is high. On flat ground a 4:1 or 2:1 ratio is more common.

Shifts in coupling ratio occur quickly and smoothly over as little as 1 or
2 breaths. Shifts are not normally associated with changes in gait but with changes in the breathing frequency. Most changes are involuntary and the subject is unaware of the change in ratio even though this may mean an abrupt and very large change in breathing frequency.

Because humans can vary the entrainment ratio at any particular stride frequency, the breathing rate of a human can be substantially lower than that of a quadruped. It has been suggested that there exists a specific rate and depth of breathing that optimizes ventilatory efficiency. Shifts in coupling ratio may therefore related to the control of respiratory efficiency and thereby, the overall energetic costs of locomotion (Bramble and Carrier 1983).

3. Consequences of Entrainment In the quadruped the thoracic complex is subjected to direct impact loading on each stride making a synchronization of gait and breathing mechanically advantageous. Humans utilize a striding bipedal gait. The question then arises as to whether there is any advantage in synchronizing the respiratory and locomotor movements.

Dejours et al (1961) studied the time course of ventilation in two series of treadmill exercise. In one the grade was kept constant and the speed varied. In the other the speed was kept constant and the grade varied. Ventilation increased in proportion to work load in both series of experiments. However, the respiratory frequency was slower at the work load with the lower stride frequency and higher grade. This suggests that ventilatory timing may in part be determined by the frequency of leg movement. As ventilation was the same at any given work load tidal volume must be inversely related to the frequency of leg movement, such that ventilation is held constant. This suggests that it is only when normal compensatory changes in tidal volume are prevented that entrainment of breathing frequency to stride frequency will produce changes in ventilation.

(a) Entrainment to High Rates The relative tachypnea and hyperventilation associated with running at high running velocities can be due to entrainment to the high stride frequency. In high intensity exercise this is usually advantageous to gas exchange and acid base regulation at the relatively small expense of some efficiency and a departure from steady-state homeostatic conditions.
Hyperventilation eliminates relatively "low" ventilation-perfusion regions present in the lung at rest (Dempsey et al. 1977, Gledhill et al. 1978) and prevents excessive widening of the alveolar-arterial gradient, thereby maintaining arterial oxygen tension near resting levels. It also causes hypocapnia. This is important in the regulation of $[H^+]$, especially during transient states of metabolic acidosis occurring during abrupt transitions in exercise intensity.

Hyperventilation is disadvantageous if accomplished by a preferential increase in respiratory rate (Frostell et al. 1983). This may result in an abnormally high ratio of dead space to tidal volume. A given level of alveolar ventilation can only then be maintained by excessively high levels of ventilation. Volumes exceeding 70-80% of maximum exercise ventilation and approaching "maximal sustainable ventilation" may be needed (Roussos and Macklem 1977). This may elicit a high flow resistive component (Stubbing et al. 1980b) resulting in either muscular fatigue or significantly increased consumption of total oxygen uptake by the respiratory muscles (Gallagher et al. 1987).

(b) Entrainment to Low Rates Entrainment of breathing to low rates of movement, may be efficient in terms of the energy cost of breathing, but may also result in hypoventilation and ultimately significant falls in end tidal oxygen and arterial oxygen tension.

Maximal exercise tidal volumes are approximately 50% of the vital capacity. These maximal values can be attained rapidly at the onset of high intensity exercise. If the breathing frequency is constrained by entrainment to a slow movement frequency, total ventilation may be limited by the inability to further increase tidal volume. Hypoventilation and ultimately hypoxemia will ensue. Two examples of this are presented in this study.

(i) The subject (TH) exercised at 300 watts on a bicycle ergometer at a pedal frequency of 60 rpm. Soon after the onset of exercise he entrained his breathing to pedal frequency at a ratio of 2:1 (Figure 3.15.2). The rise in ventilation (Figure 3.15.8) paralleled the increase in tidal volume (Figure 3.15.7). Tidal volume plateaued after 60 seconds averaging 1970 mls (47% of VC). Ventilation plateaued at 67 l/min being constrained by the entrainment of breathing frequency and by tidal volume reaching its maximal exercise limit. Ventilation was held constant for approximately 20
The ventilatory equivalent for oxygen (Figure 3.15.11) and the end tidal oxygen (Figure 3.15.9) predictably fell approximately 15 seconds after the onset of exercise due to the disproportionate increases in oxygen uptake and ventilation in the non steady-state. End tidal oxygen was held low by the constraint of the normal rise in ventilation. Approximately 80 seconds after the onset of exercise breathing frequency (Figure 3.15.4) exhibited a step increase of some 25%. The pattern of entrainment had been broken. Ventilation (Figure 3.15.8), the ventilatory equivalent for oxygen (Figure 3.15.11) and the end tidal oxygen (Figure 3.15.9) all exhibited substantial step increases. End tidal carbon dioxide (Figure 3.15.10) similarly exhibited a step decrease.

(ii) The subject (SW) exercised on the treadmill at the same velocity and same grade on two consecutive trials 20 minutes apart. The entrainment of breathing frequency to movement frequency at different ratios resulted in marked differences in breathing pattern and exercise ventilation. In trial #1 the subject entrained at a ratio of 2:1 (Figure 3.16.2). In trial #2 the subject partially entrained at a ratio of 3:1 (Figure 3.16.4). Movement frequency was dictated by the speed of the treadmill and remained essentially constant throughout the trial. Changes in entrainment ratio in trial #2 were brought about by a 50% decrease in breathing frequency (Figures 3.16.7). Tidal volume (Figure 3.16.9) increased approximately 30%, but became limiting and only partially compensating for the decrease in breathing rate. Hypoventilation occurred with the decrease in ventilation (Figure 3.16.9) causing the ventilatory equivalent for oxygen (Figure 3.16.15) and the end tidal oxygen (Figure 3.16.13) to be significantly lower than in trial #1.

4. Causes of Entrainment The exact mechanisms responsible for entrainment are unknown. It has been postulated that entrainment can result from either, feedback from peripherally located proprioceptors (Dejours et al 1957) producing a ventilatory stimulus secondary to mechanical excitation during muscular contraction (Comroe and Schmidt 1943), feedforward stimuli during movement through cortical or subcortical "irradiation" to respiratory muscles (Di Marco et al 1981, Eldridge et al 1981a, Krough and Lindhard 1913), or possibly from the reflex effects on diaphragmatic activity of excessive intra abdominal pressure changes generated in
synchrony with the vertical force of each foot plant (Grillner et al 1978).

It is unlikely that the primary stimulus is from peripheral receptors that have an output proportional to the frequency of limb movement, as shifts in entrainment ratio usually result from changes in breathing frequency and not changes in movement frequency. It is more likely that other stimuli, probably metabolic, trigger the changes in breathing frequency. However, such adjustments in breathing pattern are only possible within the constraints imposed by locomotion (Paterson et al 1986).

5. **Proposed Entrainment Mechanism** Haas et al (1986) proposed the existence of a central respiratory pattern generator (CPG) with an autonomous oscillator system whose frequency was primarily determined by metabolic drive. Normal variations in breathing frequency, such as occur at rest, were assumed to result from the introduction of noise into the CPG.

Entrainment of breathing involves driving the CPG by a second oscillatory system. Normally the CPG is exposed to noise from the higher centres, resulting in relatively large variations in breathing frequency. When the CPG is exposed to a pacemaker with oscillations of a different frequency the interaction of the two oscillations results in relative entrainment. The frequency of the external oscillator has a magnetic effect on the oscillations of the CPG pulling it to its external frequency.

Entrainment in this study was shown to significantly decrease the variability in breathing frequency and its components, inspiratory and expiratory duration. This lends support to the mechanism proposed above.

6. **Factors Increasing Susceptibility to Entrainment** Entrainment may be affected by enforcement from other sensory stimuli, severity of exercise, frequency of movement, degree of fitness, degree of familiarity with exercise procedure, increased dead space and whether the exercise is steady-state or not (Bechbache and Duffin 1977).

(a) **Complimentary Sensory Input** Observed differences in the occurrence of entrainment may relate to the method used to impose the exercise rhythm. Some subjects have allowed the subject to choose their own rhythm (Bramble 1983, Jasinskas et al 1980, Kohl et al 1981) whereas others use a metronome
or other form of pacing device (Bannister et al. 1954, Bechbache and Duffin 1977, Kay et al. 1975a, Kelman and Watson 1973).

The use of a metronome, flashing light, digital display or any combination of these has been found by most investigators to enhance entrainment (Asmussen 1973, Bechbache and Duffin 1977). Some have actually found no entrainment in the absence of some form of pacing (Kay et al. 1975b, Yonge and Petersen 1983). On the contrary Jasinskas et al. (1980) found no enhancement of entrainment by additional external stimuli and suggested that entrainment is initiated by the movement itself.

Hass et al. (1986) has postulated that additional external stimuli act by increasing the signal to noise ratio to the CPG. Wilke et al. (1975) found that when the primary stimulus (in this case rhythmical music) was combined with a second oscillator (tapping), of the same frequency, the net signal to the CPG increases and entrainment was reinforced.

(b) Habituation Familiarity with the activity seems to enhance entrainment. Bramble and Carrier (1983) found entrainment common in experienced runners. Phase locking occurred within the first 4-5 strides. Whereas inexperienced runners showed little or no tendency to synchronize breathing and stride frequency. Hass et al. (1986) found that entrainment of breathing frequency to musical rhythm was more evident in musically trained subjects. Kohl et al. (1981) found evidence of entrainment in 70-100% of racing cyclists as compared to only 25-63% of non cyclists.

(c) Mechanical Constraints Bramble and Carrier (1983) suggest that running is one mode of exercise in humans that is likely to impose mechanical constraints on breathing that would require the respiratory cycle to be synchronized with the gait. Running and breathing both rely on cyclic movements of the thoracic complex (ribs, sternum and associated musculature). Also, while running the body is alternately accelerated and decelerated in the vertical plane. As the viscera are not firmly attached to the body frame they can be expected to shift position within the abdominal cavity. This could literally constitute a "visceral piston" the movements of which could influence respiration by altering abdominal and intra thoracic volume and pressures.

Alterations in the mechanics of breathing with increased involvement of the
upper body in the exercise would also be expected to increase the incidence of entrainment. Clark et al (1983) has suggested that entrainment is more likely in oarsmen as they are accustomed to doing rhythmical exercise requiring co-ordination of the trunk muscles with all four extremities. The trend towards increased entrainment from cycling (20-33%) to walking (53%) to treadmill running (80%) would also support the idea that exercises requiring upper body involvement must desirably be synchronized with breathing (Bechbache and Duffin 1977).

E. Conclusions

In this study, there was a close correlation between ventilation and carbon dioxide output and a remarkable consistancy of the ventilatory equivalent for carbon dioxide. This occurred, throughout the duration of the trial, in all exercise modes, and in both the steady-state and the non steady-state. This relationship between ventilation and carbon dioxide output implies that the selection of tidal volume, inspiratory duration, total breath duration, and ultimately ventilation, is essentially related to the metabolic production of carbon dioxide.

1. Exercise Mode Although there were significant correlations between ventilation and carbon dioxide output and consistency of the ventilatory equivalent for carbon dioxide in each mode, there were significant differences in the ventilatory equivalent for carbon dioxide when comparing the different modes.

The ventilatory equivalents for carbon dioxide was higher while running on the flat than when cycling or running on a grade. This may reflect the additive effects of additional humoral and neural stimuli to ventilation. Exercise intensity was above the anaerobic threshold in all trials. The accumulation of lactate in the blood would act as a stimulus to increased ventilation. Due to differences in the relative muscle mass being used, in the different exercise modes, the rate of production and accumulation of lactate would vary. Therefore, the stimulus to ventilation from lactate would vary. Neural afferents from the moving limbs may also stimulate ventilation during exercise. This stimulus to ventilation, if proportional to the limb movement frequency, would be greater while running on the flat.

The ventilatory equivalent for carbon dioxide was lower while running on a
grade than when cycling or running on the flat. This may reflect limitations to ventilation resulting from the entrainment of breathing frequency to the low movement frequencies that occur while running on a grade.

The postulated variance in lactate production and neural stimuli from the moving limbs and the degree of entrainment of breathing frequency to movement frequency could all contribute to the differences in ventilatory equivalent for carbon dioxide occurring during the different exercise modes in this study.

2. Entrainment The results of this section support the existence of entrainment. The occurrence varies from individual to individual and from time to time within the same individual. Entrainment, when present, modifies the spontaneous breathing frequency. If the changes in breathing frequency are not accompanied by compensatory changes in tidal volume the normal ventilatory response will also be interfered with. At high work intensities entrainment of breathing to slow movement frequencies, when tidal volume has reached maximal values, will result in hypoventilation and a fall in end tidal oxygen partial pressure.

3. Ventilatory Response It is apparent that the traditional concepts of isocapnic hyperpnea can not explain the whole ventilatory response and that ventilation is determined by many interacting influences. These influences vary with the different exercise modes, at different intensities of exercise, and in different individuals.

The mode of activity provides stimuli which can result in modification of the normal breathing pattern. This in turn can modify the normal ventilatory response. If the ventilatory response is modified such that hypoventilation occurs, alveolar and arterial gas tensions will not be maintained at normal resting levels. Alveolar oxygen partial pressure will fall resulting in hypoxemia.
CHEMOSENSITIVITY AND OCCLUSION PRESSURE AS PREDICTORS OF EXERCISE HYPERPNOEAE AT THE ONSET OF EXERCISE

Introduction - Section IV

It is the kinetics of ventilation as a function of the carbon dioxide output and oxygen uptake response which determines the alveolar gas tensions during the non steady-state of exercise. Other factors being equal, this in turn determines the partial pressure of oxygen and carbon dioxide in the arterial blood. The degree of hypoventilation and hypoxemia observed, following the onset of exercise in Section II, showed considerable individual variability. The contribution of exercise intensity, exercise mode and the degree of entrainment to this variability was examined in sections II and III. Sex, race, age, health, fitness, diet and size of the subject have been shown to modify the kinetics of ventilation, oxygen uptake and carbon dioxide output at the onset of exercise and could therefore contribute to the variability of the response. The variability may also partially relate to the significantly different breathing patterns and ventilatory responses which occur between normal healthy untrained individuals (Shea et al 1987a, 1987b). This section discusses the significance of these possible causes, in light of the results of Sections II and III, and looks into ways of predicting the ventilatory response of the individual at the onset of exercise with a view to predicting the likely degree of hypoxemia.

A. Factors Contributing to Individual Variability

1. Sex In mild bicycle exercise, cardiac output and stroke volume are decreased in males as compared to females working at the same oxygen uptake (Stevens 1987). The changes in cardiac output are a consequence of the higher haemoglobin concentration and a greater oxygen extraction due to the larger muscle mass in males (Freedson et al 1979).

Spiro et al (1974) observed no differences in the ventilatory response between males and females. However, Aitken et al (1986) observed that gender affected ventilatory control in a number of ways. At a given work load, even when corrected for size, men had both higher ventilation and higher oxygen uptake. Conversely women had lower ventilatory equivalents for carbon dioxide and higher end tidal carbon dioxide partial pressures.
Demore (1977) also observed differences between the sexes in the oxygen debt curve.

2. **Race** Cerney (1987) found at rest, a significantly lower lung volume in sex, height, age and weight matched black subjects, as compared to white subjects. Also, the black subjects, at any given level of ventilation, had a higher breathing frequency and a lower tidal volume.

3. **Age** There is a suggestion that both the capacity of the circulation for delivering oxygen and the ability of the active tissue to use oxygen decrease with age (Robinson 1958). The oxygen requirements at any submaximal work load are greater in the elderly (Astrand 1960). However, despite this, most investigators have found that the dynamic response of oxygen uptake is independent of age. No differences in oxygen uptake kinetics during exercise transitions below the anaerobic threshold were observed between a group of 7-9 year olds and 15-18 year olds (Cooper et al 1985). This is supported by de Vries et al (1982) who found no differences in oxygen uptake response using submaximal work rates between a group of older (60-90 year) and younger men (21-29 year).

On the contrary, Macek and Vavra (1980) reported faster kinetics in 10-11 year old boys than in 20-22 year old men. Cooper et al (1985) suggest that this may relate to the methodology in that the work loads imposed were a percentage of maximal oxygen uptake. The maximal oxygen uptake was significantly lower in boys. It is possible that the faster kinetics of young subjects represented a response to a relatively lower work rate and did not indicate a growth related difference (Lamarra 1982).

Gerstenblith et al (1987) found similar kinetics for cardiac output and oxygen uptake at the onset of exercise in young and old people. However, in young people the increase in cardiac output was achieved primarily through increases in heart rate. In older people the increase in cardiac output, due to the decreased ability to increase heart rate, was achieved primarily through increases in stroke volume.

4. **Disease** The normal ventilatory and oxygen uptake response to exercise is affected by disease induced alterations in gas exchange kinetics, dead space fraction, arterial carbon dioxide tension and the mechanics of breathing. Such changes in ventilation are reflected in the ventilatory
equivalent for carbon dioxide. In general, conditions in which the ventilatory requirement for the regulation of carbon dioxide and pH have increased will cause the ventilatory equivalent to be displaced upwards and steepened in slope. Such patients typically show a low arterial carbon dioxide tension.

(a) Changed Kinetics Ventilation, oxygen uptake and carbon dioxide output kinetics were all significantly slower in chronic obstructive pulmonary disease due to a slowing of the rate of change of cardiac output. This could result from a slower rate of increase in muscle metabolism (Beaver et al 1973, Young and Woolcock 1978), higher pulmonary vascular resistance (Matthay and Berger 1981, Slutsky et al 1980), changes in intrathoracic pressure affecting left ventricular transmural pressure and thus afterload to the left ventricle (Buda et al 1979, Matthay and Berger 1981), or primary myocardial dysfunction (Matthay and Berger 1981, Slutsky et al 1981).

In patients with coronary disease, stroke volume is reduced and there is a decrease in heart rate kinetics (Zimmerman et al 1966). In the steady state and at low work rates cardiac output is kept within the normal expected range by an increase in heart rate. At high work loads heart rate reaches a maximum and the inability to raise stroke volume limits cardiac output and oxygen uptake. Work capacity is therefore reduced.

(b) Dead Space Fraction The dead space fraction at rest is normally about 25-30%. In exercise, because tidal volume increases with relatively little change in anatomical and alveolar dead space, the dead space fraction actually decreases. A high dead space fraction at rest and during exercise is usually indicative of ventilation-perfusion mismatching and may reflect disease of the airways, lung parenchyma or vasculature (Mohsenifar et al 1985).

Breathing at a higher frequency, and with a lower tidal volume, will result in a high ventilation-perfusion ratio and cause the partial pressure of carbon dioxide in the alveolar gas to decrease. Conversely a low ventilation-perfusion ratio will contribute little carbon dioxide to the alveolar gas but cause arterial carbon dioxide tension to increase. Both conditions increase the dead space component of total ventilation (Jones et al 1966). At any metabolic rate, unless ventilation is increased by an
amount equal to the increase in dead space, alveolar ventilation will be compromised (Ward and Whipp 1980). The resulting hypoventilation means that arterial and alveolar partial pressures for carbon dioxide will not be maintained at normal resting levels.

c) Changes in Arterial Carbon Dioxide Tension Over the range of work rates within which arterial carbon dioxide tension is regulated, it may be considered as a set point for the ventilatory control process (Whipp et al 1984). The positioning of this set point will influence the magnitude of the exercise hyperpnoea. The lower the set point the greater the ventilation required to regulate arterial carbon dioxide tension. The higher the set point the lower the ventilation required to regulate arterial carbon dioxide tension. A low set point may results from the effects of regional lung distortion on vagal mechanoreceptors and hypoxemia (Whipp et al 1984). This will increase the ventilation requirements of exercise. A high set point occurs in primary hypoventilation syndromes (Whipp et al 1984). This will decrease the ventilatory response to exercise. Both interfere with the normal ventilation kinetics.

d) Mechanical Limitation to Breathing Unlike normal subjects, in patients with chronic airflow limitation exercise ventilation frequently attains maximum breathing capacity (Clark et al 1969, Potter et al 1971). Tidal flow volume loops have also been observed to attain the maximum flow volume curve (Clark et al 1969, Leaver et al 1971, Potter et al 1971, Stubble et al 1980a). In these patients there is a mechanical limitation to further increases in flow. Therefore, exercise ventilation is limited and the normal kinetics of ventilation interfered with.

5. Fitness and Training Training increases athletic capacity by improving performance of cardiac and skeletal muscle (Jones et al 1975). Most workers consider that no such adaptation is seen in the lung and that training therefore does not appreciably alter pulmonary function (Raven 1977). However, the following differences in athletes and non athletes have been observed.

(a) Breathing Pattern The hyperpnoea of exercise involves changes in both the rate and depth of breathing. Typically, following the onset of exercise, tidal volume increases more than rate. As exercise continues and metabolic acidosis occurs, increases in rate predominate. The extent and
timing of these changes depend upon the individuals fitness.

The maximum tidal volume is about 50% of the vital capacity (Hey et al 1966, Cotes et al 1970, Lind and Hesser 1984a, Jones 1984). This is true in both athletes and non athletes (Folinsbee et al 1983). The difference being that athletes have larger vital capacities than normal and therefore larger maximal tidal volumes. This is related to their larger body size and not due to their athletic ability (Wilmore and Haskell 1972). Only in swimmers has a difference in vital capacity between athletes and non athletes been observed, that is not related to their size (Raven 1977). The use of a larger percentage of the vital capacity has been observed in exercise, but this is usually accompanied by an increase in alveolar carbon dioxide partial pressure (Martin and Weil 1979) or an increase in dead space (Kelman and Watson 1973).

The level of work at which metabolic acidosis occurs is also higher in fit subjects (Hickson et al 1978, Wasserman 1978). The increase in breathing rate therefore occurs later and at high work levels. Also, athletes (fit subjects) are capable of attaining significantly higher respiratory rates than non athletes (Folinsbee et al 1983). This, combined with their larger maximal tidal volumes, means that athletes can attain significantly higher ventilations than non athletes.

(b) Maximum Breathing Capacity Maximum breathing capacity is usually measured over 15 seconds while exercise, at or near maximal oxygen uptake, may last for several minutes. The level of ventilation in exercise rarely reaches these values. When maximum breathing capacity is determined over a longer period of time it is limited by fatigue of the ventilatory muscles (Leith and Bradley 1976, Roussos et al 1979) and the ventilation attained only slightly exceeds that obtained in maximal exercise (Freedman 1970).

Athletes working at maximum intensity can sustain a higher percentage of their maximum breathing capacity; nearly 90% as compared to about 70% in normal subjects (Shephard 1966, Hesser et al 1981, Folinsbee et al 1983). It is possible that in non athletes, exercise ventilation may be limited by the onset of fatigue of the respiratory muscles. This is supported by the work of Leith and Bradley (1976) who found that endurance training increased the level of hyperpnoea that could be sustained for 7-15 minutes by 19%.
(c) **Oxygen Uptake Kinetics** In the steady-state the oxygen uptake at a given work rate has been found to be both independent of the fitness of the subject (Astrand and Rodahl 1970, Whipp and Wasserman 1972) and to be lower with increasing fitness (Casaburi et al 1987). However, there is agreement that individuals with higher fitness (i.e. higher maximal oxygen uptake) have faster oxygen kinetics at the onset of exercise (Whipp and Wasserman 1972, Hagberg et al 1978, Hichson et al 1978, Weltman and Katch 1976), as well as faster adjustment of oxygen uptake in the recovery from exercise (Hagberg et al 1980).

The reduced time constant for oxygen uptake may result from either an increased rate of oxygen delivery per unit time, due to redistribution of blood flow, or an increase in cardiac output (Hughson and Morrisey 1983). Alternatively, it may be due to increased oxygen extraction and utilization resulting from changes at the cellular level (Pendergast et al 1980), or a combination of both.

Various training techniques have also been shown to increase oxygen kinetics (Berry and Moritani 1985). Trained athletes have been shown to possess: increased heart rate (and presumably cardiac output) kinetics (Hagberg et al 1980), increased levels of myoglobin (Holloszy and Booth 1976), increased oxidative capacity of muscles (Kiessling et al 1971, Morgan et al 1971), increased mitochondrial density (Gollnick et al 1971), increased muscle fibre area (Faulkner et al 1971), and increased muscle capillary density (Andersen and Henricksson 1977). All of these changes could contribute to the faster oxygen uptake kinetics in the trained state.

Further support for the effect of fitness on oxygen uptake kinetics comes from studies which show a slowing in the adaptation of the oxygen uptake after enforced bed rest (Ebfeld et al 1984, Convertino et al 1984b). This was associated with a slow response of cardiac output due to orthostatic factors limiting stroke volume.

(d) **Ventilatory Response** Endurance athletes have a lower ventilation than untrained people at equal relative work loads (Byrne-Quinn et al 1971, Hirshman et al 1975, Miyamura et al 1976a, Jones 1976, Martin et al 1979, Casaburi et al 1987a, 1987b). It has been suggested that this is a consequence of training and the difference in fitness between athletes and
non athletes. This is supported by the finding that exercise ventilation is inversely related to maximal oxygen uptake (Morrison et al 1983). The lower ventilation may be related to the smaller increase in heart rate and arterial lactate concentration in the athlete at any given work load (Rasmussen et al 1975, Sutton and Jones 1979). Training may also lower the respiratory quotient with the lower carbon dioxide output causing a proportional decrease in ventilation.

Low exercise ventilation in athletes will lessen the work requirement of the ventilatory muscles, decrease the oxygen requirement and lessening the likelihood of fatigue. However, it cannot promote performance by enhancing arterial blood oxygenation or by improving elimination of carbon dioxide. On the contrary, hypoventilation may cause arterial hypoxemia and a retention of carbon dioxide.

From the above it can be seen that there are a number of individual differences which could alter the kinetics of gas exchange and therefore contribute to the variability in the degree of hypoventilation and arterial hypoxemia occurring at the onset of exercise in Section II. However, the subjects studied in Section II were all male caucasians, of similar age and fitness, with no known impairment of heart lung or circulation. Furthermore, they all performed the same activity at the same intensity. It is therefore unlikely that factors such as sex, age, race, health and fitness contributed to the observed variability in this study. It is more likely that the variability relates to the inherited or acquired differences in individual breathing patterns and ventilatory responses.

B. Sensitivity to Carbon Dioxide

The most important input to the respiratory centres, in the control of ventilation, is the partial pressure of carbon dioxide in the arterial blood. According to traditional concepts of ventilatory control, changes in arterial carbon dioxide partial pressure are sensed by chemoreceptors in the central nervous system and the carotid bodies. Ventilation is subsequently adjusted in order to maintain arterial carbon dioxide partial pressure constant within very strict limits.

A rise in arterial carbon dioxide tension causes ventilation to increase and a fall in arterial carbon dioxide tension causes ventilation to
decrease. However, the effect of a given increase in arterial carbon dioxide tension on the ventilatory response is quite variable and will depend in part on the individuals' "chemosensitivity". This is defined as the increase in ventilation in litres per minute per Torr increase in the partial pressure of carbon dioxide. Values in the range of 1 to 4 litres per minute per Torr are considered normal (Read 1967).

There are two methods in common use for investigating the ventilatory response to carbon dioxide stimulation. In the steady-state method, the subject inhales a gas mixture containing a low percentage of carbon dioxide (2-3%) and 40% oxygen. This continues until ventilation and alveolar carbon dioxide partial pressures are constant (15-20 minutes). Then while carbon dioxide inhalation continues ventilation and alveolar carbon dioxide partial pressure are recorded for 2 minutes. The procedure is then repeated 1-3 times with gas mixtures containing different concentrations of carbon dioxide in oxygen.

In the rebreathing method, the subject rebreathes a gas mixture for up to 4 minutes. The gas mixture initially contains 5% carbon dioxide and 40% oxygen. The ventilation and alveolar carbon dioxide partial pressure are recorded on a breath-by-breath basis.

In both methods the slope of the ventilatory response from rest to hyperpnoea is derived from the linear regression relating changes in ventilation to changes in alveolar carbon dioxide partial pressure. The rebreathe method has the advantage of simplicity in that a measure can be obtained within a single trial. It is also not as time consuming and therefore less likely to be affected by increasing temperature, particularly during exercise. The results for both methods are reported to be not significantly different (Read 1967, Clark 1968, Kelly et al 1982).

C. Respiratory Drive

Ventilation is controlled by the respiratory centre. Many stimuli impinge upon this centre. Its output in turn appears as a multitude of motor neuron discharges. Many attempts have been made to quantify this output. The following are the most common methods employed.

I. Ventilation and its Components Traditionally respiratory centre output
has been measured in terms of pulmonary ventilation and its components, tidal volume and breathing frequency. Pulmonary ventilation being the product of the two. This has proved unsatisfactory in that while ventilation is the ultimate outcome of the respiratory centre activity, it is influenced by a number of mechanical and peripheral factors which alter the resistance and compliance of the respiratory system. This may cause variations in ventilation which do not reflect variations in the activity of the respiratory centres. A number of other ways of assessing the respiratory centre output have been proposed.

2. **Breath Duration and its Subdivisions** The study of total breath duration (Ttot) and its subdivisions, inspiratory duration (TI) and expiratory duration (TE) has been used to provide information concerning mechanisms which can influence tidal volume (VT) and breathing frequency. This lead to the formulation of the "Hering-Breuer" threshold curve by Clark and Euler (1972) and the concept formulated by Milic-Emili and Grunstein (1976) of studying ventilation in terms of inspiratory flow (VT/TI) and the inspiratory duty cycle (TI/Ttot).

\[ \dot{V}E = 60 \times (VT/TI) \times (TI/Ttot) \]

where VT/TI reflects the drive components of ventilation and TI/Ttot reflects the timing components of ventilation.

3. **Respiratory Mechanical Work Rate** The rate of work of the respiratory muscles has been used as a measure of respiratory centre output (Cherniack and Snidal 1956). However, the method is difficult to apply accurately and the result is influenced by such factors as lung volume (Flenley et al 1971) and the speed of contraction of the respiratory muscles (Pengelly et al 1971).

4. **Diaphragm Electromyography** Lourenco and Miranda (1968) quantified the electromyograph of the diaphragm with an oesophageal electrode. However, the method is hard to standardize and has the disadvantage in that it represents the output supplied to only one of the muscles which power the respiratory pump.

5. **Peak Occlusion Pressure** Grunstein et al (1973) occluded the airway of anesthetized cats at functional residual capacity and measured the
amplitude of the tracheal pressure generated in the following inspiratory effort. At relaxed functional residual capacity the elastic recoil of the respiratory system is zero and the pressure measured is the net pressure developed by the respiratory muscles.

Since there is no flow of gas during this maneuver and lung volume only changes a small amount due to compression, the measurement is not influenced by many of the mechanical factors, such as flow resistance and compliance of the lung-chest system, which are involved in the transformation of respiratory centre output into ventilatory function. Also, because the respiratory muscles can be expected to shorten much less during the occluded breath than during unobstructed breathing, their force velocity relations should have a relatively small influence on the measured pressure.

6. Occlusion Pressure at 0.1 Seconds It is impossible to measure peak occlusion pressure in conscious humans because when one occludes the airway of a conscious subject, the subject will modify his inspiratory effort. Therefore, the peak inspiratory pressure cannot be relied upon or interpreted in the same way as in anesthetized cats. However, Whitelaw et al (1975) observed a delay between the onset of inspiration against an occluded airway and the subjects reaction to it. The reaction of the normal subject was never less than 0.15 seconds. The fall in pressure in the first 0.15 seconds would therefore represent the respiratory output unaltered by the imposed load. The occlusion pressure developed 0.1 seconds after the onset of inspiration was subsequently adopted as an index of respiratory centre output.

Euler (1977) gave support to the concept that the respiratory centre is functionally divided into two parts. A generator of central inspiratory activity produces a rising ramp of activity with each inspiration and sets the rate of lung volume increase, and a timer controls inspiratory duration according to volume related stimuli received from lung afferents. These reflexes are carried in the vagi and modify tidal volume and breathing rate. However, they produce differences in ventilation that do not reflect differences in the true respiratory centre output (Guz and Widdicombe 1970). The rate of increase of pressure in the early part of an occluded breath, and therefore occlusion pressure at 0.1 seconds, are free of this vagal influence.
Occlusion pressure at 0.1 seconds therefore represents a measure of respiratory centre activity that is non invasive, reproducible, simple to make and measures the activity of all muscles involved in inspiration. It is also unaffected by respiratory system resistance and compliance or by volume related reflex activity.

D. Hypothesis

Clinical tests will normally discern abnormal ventilatory responses due to disease. The effects of age, sex and fitness on the ventilatory response are known and can be predicted. However, there is still considerable individual variability in the ventilatory response of clinically normal nonathletic people of the same sex and age. The following two procedures have been employed in an attempt to identify those individuals that are likely to exhibit the greatest hypoventilation, and hence hypoxemia, at the onset of exercise.

1. Carbon Dioxide Sensitivity Masuyama et al (1986) found that the hypoxic response of subjects at sea level was predictive of their tolerance to altitude. Sensitivity to carbon dioxide at rest has been shown to correlate with ventilation in both athletes and non athletes during mild to moderate steady-state exercise (Martin et al 1978, 1979). Those with low ventilatory chemoresponses tended to have low exercise ventilations. It is hypothesised that this relationship will be maintained in the non steady-state and that measures of chemosensitivity will therefore be a predictor of hypoventilation at the onset of exercise.

2. Occlusion Pressure The mouth pressure 0.1 seconds after the start of inspiration against an occluded airway ($P_{0.1}$) is a measure of respiratory drive and represents the pressure potential that is available for inspiration (Hesser and Lind 1983). Ventilation is a measure of the resulting flow. There exists a close correlation between $P_{0.1}$ and ventilation in the steady-state. It is hypothesised that this relationship will be maintained in the non steady-state, and therefore, those with a low drive will be most susceptible to hypoventilation at the onset of exercise.
METHODS (Section IV)

A. Subjects

The 12 subjects used in this section were the same 12 subjects used in Section III. Body surface area (BSA) was estimated for each subject using the method of Du Bois (Comroe et al 1955).

\[ \text{BSA (m}^2\text{)} = \text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184 \]  

B. Experimental Protocol

1. Chemosensitivity In a preliminary session the physiologic responsiveness to carbon dioxide was measured by having the subject rebreathe a gas mixture containing 5% carbon dioxide and 40% oxygen in nitrogen. Two rebreathe trials were performed 15 minutes apart. Each trial continued for 4 minutes or until the carbon dioxide concentration in the rebreathe mixture exceeded 10%. The slopes of the regression of the 2 trials were averaged. The correlation between the determinations from the two trials was 0.7262. The average values are presented in Table 4.1.

2. Occlusion Pressure Each subject performed 6 work trials of 2 minutes duration during which occlusion pressure was measured approximately every 7th breath. All 6 trials were performed on the same day with a minimum of 20 minutes rest between trials. The cyclists cycled on an electrically braked bicycle ergometer (Elmar-Schonander Model EM 369) at a power output of 300 watts. The track athletes ran on the treadmill (Quinton Model 18-60) at a grade of 10% and a speed of 12 kph.

C. Equipment

1. Chemosensitivity During the carbon dioxide rebreathe, tidal volume was measured by a spirometer (Ohio Model 840). The carbon dioxide partial pressure was monitored continuously by a mass spectrometer probe inserted in the mouth piece (Perkin Elmar Model 1100). The outputs from the spirometer and mass spectrometer were passed to a computer (Digital PDP-11) which calculated and plotted end tidal carbon dioxide and minute ventilations on a breath by breath basis (Tektronix Model 4012). The resistance to flow in the circuit was 0.12 cm H$_2$O.litres$^{-1}$.sec$^{-1}$. 
2. **Oclusion Pressure** A detailed account of the development, operation and validation of the equipment used for measuring occlusion pressure is given in Appendix D.

D. Data Analysis

1. **Chemosensitivity** For each subject, the hypercapnic ventilatory response was expressed as the increase in ventilation in litres per minute per Torr increase in carbon dioxide (l.min⁻¹.Torr⁻¹ CO2). The slope of the response curve was calculated by linear least squares regression. Because much of the variability in carbon dioxide chemoresponsiveness among subjects is due to variability in size (Hirshman et al 1975, Rebuck et al 1974) the value of the slope was normalised for size differences by division by body surface area in m². Ventilation was expressed per unit metabolic rate (VE/VO₂).

For each subject, data from the 6 trials were pooled. Mean ventilations were determined for each successive 10 second interval. Correlations (Pearson's Product Moment) of ventilation with the hypercapnic ventilatory response were determined separately, for cycling on the bicycle ergometer and running on the treadmill, for each of the 12 time intervals.

2. **Oclusion Pressure** Due to individual differences in total breath duration, the time at which occlusion pressure was measured during the 2 minute trial, and therefore the time at which all parameters were calculated, differed from subject to subject. In order to make comparisons between subjects oxygen uptake, occlusion pressure, inspiratory flow, ventilation, ventilatory equivalent and end tidal oxygen data, from the 6 trials performed by each subject, were pooled. It was then grouped into 10 second time intervals and averaged to give mean values. These mean values were then compared.

For each subject the increase in ventilation in litres was expressed per minute per cm H₂O increase in occlusion pressure (l.min⁻¹.cm H₂O⁻¹). This value was then normalised for body size by dividing by body surface area in m². Ventilation was expressed per unit metabolic rate (VE/VO₂).

For each subject, data from the 6 trials were pooled. Mean values were calculated for each successive 10 second interval. Correlations (Pearson's
Product Moment) of ventilation with the occlusion ventilatory response were determined separately for cycling on the bicycle ergometer and running on the treadmill, for each of the 12 time intervals.

For all 6 cyclists the raw data and means for oxygen uptake, occlusion pressure, inspiratory flow, ventilation, ventilatory equivalent for oxygen and end tidal oxygen were also plotted against time. Correlations between selected parameters were determined using Spearman's rank order method. Significance was accepted at the 0.05 level.
RESULTS (Section VI)

A. Chemosensitivity to Carbon Dioxide

During the rebreathe manoeuver, end tidal carbon dioxide and ventilation were calculated and plotted on a breath-by-breath basis. An example of such a plot is presented in Figure 4.1.1. In this way, the increase in ventilation (l/min) per Torr increase in carbon dioxide (i.e the hypercapnic ventilatory response) was determined for each subject. These values were then corrected for differences in body size and the mean of the two trials calculated. The uncorrected (SL) and corrected (SL/m²) values for all 12 subjects are presented in Table 4.1. The regression lines for the 6 cyclists and the 6 runners are presented in Figure 4.2.1 and Figure 4.2.2.

Significant positive correlations were found between ventilation (VE/VCO₂) and hypercapnic ventilatory response (SL/m²) in all but 2 of the 12 time intervals during both the 2 minute ride on the bicycle ergometer and the 2 minute run on the treadmill. Correlations and their significance for all 12 time intervals while cycling and running are presented in Table 4.2.

B. Occlusion Pressure

Each subject performed 6 identical trials. All trials were conducted at the same absolute work load (i.e. 10% grade and 12 kph). Oxygen uptake was essentially the same for all subjects during the 2 minutes of cycling.

Oxygen uptake, occlusion pressure, inspiratory flow, ventilation, ventilatory equivalent for oxygen and end tidal oxygen were plotted against time for the 6 cyclists (Figures 4.4.1 to 4.4.6). Breath-by-breath data and mean values for each of the 12 time intervals were included.

In this study, the subject who generated the highest occlusion pressures clearly exhibited the highest inspiratory flows and the highest ventilations along with the lowest falls in ventilatory equivalent and end tidal oxygen. Conversely, the subject who generated the lowest occlusion pressures exhibited the lowest inspiratory flows and the lowest ventilations along with the greatest falls in ventilatory equivalent for oxygen and end tidal oxygen. However, the overall correlations between occlusion pressure and inspiratory flow, occlusion pressure and
ventilation, and ventilatory equivalent and end tidal oxygen, for the 6 subjects, were not consistently significant (Table 4.3).

The increase in ventilation (l/min) per cm H₂O increase in occlusion pressure was determined for all subjects. These values were then corrected for differences in body size. The uncorrected (S2) and corrected (S2/m²) values for all 12 subjects are presented in Table 4.1. The regression lines for occlusion pressure Vs ventilation were calculated and are presented for the 6 cyclists and the 6 runners in Figures 4.3.1. and Figure 4.3.2.

There was a tendency for those subjects with the greatest slope (i.e. the greatest impedance) to have the lowest ventilations. However, the correlations between ventilation (̇VE/̇VCO₂) and the occlusion pressure ventilatory response (S2/m²) were not significant at any of the 12 time intervals during the 2 minute ride on the bicycle ergometer or the 2 minute run on the treadmill. Correlations and their significance for all 12 time intervals while cycling and running are presented in Table 4.2.
Table 4.1: Body surface area (BSA), hypercapnic ventilatory response ($S_1$), hypercapnic ventilatory response corrected for size ($S_1/m^2$), occlusion pressure ventilatory response ($S_2$) and occlusion pressure ventilatory response corrected for size ($S_2/m^2$). BSA = weight$^{0.425}$ X height$^{0.725}$ X 0.007184

<table>
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<th>Subject</th>
<th>BSA m$^2$</th>
<th>$S_1$</th>
<th>$S_1/m^2$</th>
<th>$S_2$</th>
<th>$S_2/m^2$</th>
</tr>
</thead>
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<td>4.37</td>
<td>2.39</td>
<td>5.76</td>
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</tr>
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<tr>
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<td>0.68</td>
<td>6.53</td>
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<td>7.65</td>
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Figure 4.1.1. Plot of end tidal carbon dioxide against ventilation while rebreathing a gas mixture of 4% carbon dioxide in 40% oxygen at rest. (Read method for determining sensitivity to carbon dioxide).
Figure 4.2.1. Regression lines for plot of end tidal carbon dioxide against ventilation while rebreathing a gas mixture of 4% carbon dioxide in 40% oxygen at rest. Data from 6 cyclists.

![Graph of Figure 4.2.1](image1)

Figure 4.2.2. Regression lines for plot of end tidal carbon dioxide against ventilation while rebreathing a gas mixture of 4% carbon dioxide in 40% oxygen at rest. Data from 6 runners.

![Graph of Figure 4.2.2](image2)
Figure 4.3.1. Regression lines for plot of ventilation against occlusion pressure. Data from 6 cyclists.

Figure 4.3.2. Regression lines for plot of ventilation against occlusion pressure. Data from 6 runners.
Table 4.2: Correlations (r) and their significance (p) between hypercapnic ventilatory response (SI/m²) and ventilation (VE/VCO₂), and occlusion pressure ventilatory response (S2/m²) and ventilation at 10 second intervals during a 2 minute trial on the bicycle ergometer and treadmill.

<table>
<thead>
<tr>
<th>Time</th>
<th>Hypercapnic Response</th>
<th>Occlusion Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bicycle</td>
<td>Treadmill</td>
</tr>
<tr>
<td>0 - 10</td>
<td>r</td>
<td>0.7530</td>
</tr>
<tr>
<td></td>
<td>p</td>
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</tr>
<tr>
<td>11 - 20</td>
<td>r</td>
<td>0.8947</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.01</td>
</tr>
<tr>
<td>21 - 30</td>
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<tr>
<td>31 - 40</td>
<td>r</td>
<td>0.6927</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>----</td>
</tr>
<tr>
<td>41 - 50</td>
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</tr>
<tr>
<td></td>
<td>p</td>
<td>----</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>p</td>
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</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>p</td>
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</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>p</td>
<td>0.05</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>p</td>
<td>0.05</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>p</td>
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</tr>
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</tr>
<tr>
<td></td>
<td>p</td>
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</tr>
<tr>
<td>111 - 120</td>
<td>r</td>
<td>0.7668</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Figure 4.4.1. The rate of change of oxygen uptake during 2 minutes of cycling. Comparison between 6 subjects. Power output = 300 watts.

![Graph showing the rate of change of oxygen uptake during 2 minutes of cycling.]

Figure 4.4.2. The rate of change of occlusion pressure during 2 minutes of cycling. Comparison between 6 subjects. Power output = 300 watts.

![Graph showing the rate of change of occlusion pressure during 2 minutes of cycling.]
Figure 4.4.3. The rate of change of inspiratory flow during 2 minutes of cycling. Comparison between 6 subjects. Power output = 300 watts.

Figure 4.4.4. The rate of change of ventilation during 2 minutes of cycling. Comparison between 6 subjects. Power output = 300 watts.
Figure 4.4.5. The rate of change of ventilatory equivalent for oxygen during 2 minutes of cycling. Comparison between 6 subjects. Power output = 300 watts. Normal ventilatory equivalent for oxygen = 24 litres/litre.

Figure 4.4.6. The rate of change of end tidal oxygen during 2 minutes of cycling. Comparison between 6 subjects. Power output = 300 watts.
Figure 4.3  Correlations (r) and their significance (p) between occlusion pressure (PO.1), inspiratory flow, ventilation, ventilatory equivalent and end tidal oxygen during 2 minutes cycling at 300 watts. (10 second time intervals)

<table>
<thead>
<tr>
<th>Time (secs)</th>
<th>PO.1/Flow</th>
<th>PO.1/VE</th>
<th>Flow/VE</th>
<th>VEVO2/ETO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>r -0.09</td>
<td>-0.09</td>
<td>0.54</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>11 - 20</td>
<td>r 0.31</td>
<td>0.09</td>
<td>0.77</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>----</td>
<td>0.01</td>
</tr>
<tr>
<td>21 - 30</td>
<td>r 0.60</td>
<td>0.49</td>
<td>0.94</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>31 - 40</td>
<td>r 0.66</td>
<td>0.66</td>
<td>0.83</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
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<td>----</td>
</tr>
<tr>
<td>41 - 50</td>
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<td>0.31</td>
<td>0.94</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>51 - 60</td>
<td>r 0.54</td>
<td>0.54</td>
<td>0.83</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>0.05</td>
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<tr>
<td>61 - 70</td>
<td>r 0.83</td>
<td>0.77</td>
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<td></td>
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<tr>
<td>71 - 80</td>
<td>r 0.83</td>
<td>0.71</td>
<td>0.89</td>
<td>0.49</td>
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<tr>
<td></td>
<td>p 0.05</td>
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<tr>
<td>81 - 90</td>
<td>r 0.60</td>
<td>0.71</td>
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<td>0.66</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>0.01</td>
<td>----</td>
</tr>
<tr>
<td>91 - 100</td>
<td>r 0.71</td>
<td>0.77</td>
<td>0.89</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>p ----</td>
<td>----</td>
<td>0.05</td>
<td>----</td>
</tr>
<tr>
<td>101 - 110</td>
<td>r 0.83</td>
<td>0.83</td>
<td>1.00</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>p 0.05</td>
<td>0.05</td>
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</tr>
<tr>
<td>111 - 120</td>
<td>r 0.83</td>
<td>0.94</td>
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<td>0.83</td>
</tr>
<tr>
<td></td>
<td>p 0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>
The degree of hypoventilation and hypoxemia occurring following the onset of exercise shows considerable individual variability. The contribution of exercise intensity, exercise mode and entrainment to this variability was examined in sections II and III. The extent to which this variability is related to inherent differences in the ventilatory response of the subject is examined in this Section IV.

A. Chemosensitivity

The relationship between the individual ventilatory response to carbon dioxide at rest (i.e. the hypercapnic ventilatory response) and the ventilation occurring in non steady-state exercise was investigated with a view to predicting which individuals are more likely to exhibit significant hypoventilation and hypoxemia at the onset of exercise.

1. Sensitivity to Carbon Dioxide at Rest

The partial pressure of carbon dioxide in the arterial blood is the most important input to the respiratory centre in the control of ventilation at rest. Changes in arterial carbon dioxide partial pressure induce compensatory changes in ventilation such that arterial carbon dioxide partial pressure is regulated within very strict limits. The normal resting level for arterial carbon dioxide partial pressure is about 40 Torr. However, the level at which the arterial carbon dioxide partial pressure is regulated (Whipp et al 1984), and the magnitude of the ventilatory response to a given change in the arterial carbon dioxide partial pressure (Hughes et al 1968), both show considerable individual variability.

Arterial carbon dioxide partial pressure can be manipulated by inspiration of hypercapnic gas mixtures. The gas mixture is rebreathed until the alveolar carbon dioxide partial pressure equilibrates with that in the arterial blood. The alveolar partial pressure of carbon dioxide and the ventilation are then measured. In this way the change in ventilation induced by a known change in arterial carbon dioxide partial pressure can be calculated.

The chemosensitivity to carbon dioxide ranges normally from about 1 to 4 litres.min⁻¹.Torr⁻¹ change in carbon dioxide partial pressure. It is
reduced by various drugs and in patients with restrictive lung disease (Hirshman et al 1975) and it is often low in athletes. Miyamura et al (1976b), Godfrey et al (1971), Byrne-Quinn et al (1971), Rebuck et al (1971) have shown that the sensitivity to carbon dioxide is reduced in endurance athletes. However, others have reported similar sensitivities between athletes and non athletes (Saunders et al 1976, Mahler et al 1982).

There are also conflicting opinions as to whether the inherent hypercapnic response can be modified. For example, does the training of the athlete decrease the sensitivity to carbon dioxide, or are they good endurance athletes because they inherit a low sensitivity to carbon dioxide. Most reports on the effect of training on the control of ventilation relate to possible changes in the resting response of athletes to carbon dioxide and hypoxia. Two studies which have examined the effect of training on sensitivity to carbon dioxide have reached opposite conclusions. One has found a reduction in sensitivity (Blum et al 1979) and the other no change in sensitivity (Bradley et al 1980).

Although the possibility that sensitivity to carbon dioxide can be changed by training has not been excluded, it is more likely that individual responses have a genetic component (Collins et al 1978). Low sensitivities to carbon dioxide have been shown to occur in familial clusters independent of training. Scoggin et al (1978) found that the immediate family members of those athletes which had low sensitivities to carbon dioxide similarly had low chemosensitivities.

2. Sensitivity to Carbon Dioxide During Steady-State Exercise In the past, the idea that hypoventilation during exercise may be associated with a low sensitivity to carbon dioxide at rest had been discounted, because arterial carbon dioxide partial pressure remained near resting levels during exercise. Only mixed venous carbon dioxide tension rises with exercise and no venous chemoreceptors are known to exist. It was therefore felt that direct proportional control of ventilation was not occurring during exercise.

However, Rebuck et al (1972), Martin et al (1978), and Martin et al (1979) found significant correlations between sensitivity to carbon dioxide at rest and ventilation over a wide range of exercise intensities. Those with the lowest resting chemosensitivities had the lowest steady-state exercise
ventilations. This suggested that the arterial carbon dioxide partial pressure was also an important input to the respiratory centre, in the control of ventilation during exercise.

One explanation is that respiratory sensitivity to carbon dioxide increases with exercise (Dejours 1964, Asmussen and Nielsen 1957, Weil et al 1972). Increased carbon dioxide sensitivity could amplify the effect of any small changes in arterial carbon dioxide partial pressure which may result from large increases in mixed venous carbon dioxide partial pressure during exercise. Thereby, a near constant arterial carbon dioxide partial pressure, which would provide little ventilatory stimulation at rest, would become a significant stimuli for ventilation during exercise.

However, experiments testing for increased sensitivity to carbon dioxide during exercise have produced inconclusive results. When measured as the slope of the hypercapnic ventilatory response, carbon dioxide sensitivity during exercise has been reported to increase (Cunningham et al 1963, Weil et al 1973, Miyamura et al 1976a, Duffin et al 1980), decrease (Miyamura et al 1976b, Clark and Godfrey 1969), or remain unchanged (Asmussen and Nielsen 1957, Martin et al 1978, Bradley et al 1980, Kelley et al 1982). The different results could be due to a number of factors, including differences in the exercise intensity, the mode of exercise and the technique used for measuring sensitivity to carbon dioxide.

The failure to find a consistent increase in carbon dioxide sensitivity during exercise leaves unexplained how proportional control of ventilation can occur during exercise when only minor changes in arterial carbon dioxide partial pressure are taking place. However, this in itself does not distract from the findings of Rebuck et al (1972), Martin et al (1978), and Martin et al (1979) of a correlation between carbon dioxide sensitivity and steady-state exercise ventilation in both athletes and non athletes.

3. Sensitivity to Carbon Dioxide During Non Steady-State Exercise The measures of hypercapnic ventilatory response ranged from 0.97 to 4.37 litres.min\(^{-1}\).Torr\(^{-1}\) and 0.56 to 2.39 litres.min\(^{-1}\).Torr\(^{-1}\).m\(^2\)\(^{-1}\) when corrected for body size. Although the subjects in this study were all competitive athletes and successful at the local level, only one was of national standard and none had competed with success internationally. The range in the measures of chemosensitivity obtained are therefore not unexpected.
The correlations between the hypercapnic ventilatory response at rest and the ventilatory response during both cycling and running were significant in 10 of the 12 time intervals (Table 4.2). Those subjects with the lowest hypercapnic response at rest exhibited the greatest degree of hypoventilation and the lowest end tidal oxygen partial pressures. One could therefore predict, on the basis of their hypercapnic ventilatory response at rest, that subjects with low values would exhibit the greatest hypoventilation and the greatest falls in arterial oxygen tension at the onset of exercise.

Sensitivity to carbon dioxide at rest correlates with steady-state exercise ventilation. Exercise ventilation increases in proportion to carbon dioxide output in both the steady-state and non steady-state. It is therefore not surprising that sensitivity to carbon dioxide at rest also correlates with exercise ventilation in the non steady-state.

B. Occlusion Pressure

The relationship between the occlusion pressure and the ventilation occurring at rest and in non steady-state exercise was investigated with a view to predicting which individuals are more likely to exhibit significant hypoventilation and hypoxemia at the onset of exercise.

1. Methodological Problem Considerable variability existed in the values of PO.1 obtained while exercising on the treadmill. It was felt that most of this variability related to the difficulty in recording mouth pressure with a pressure transducer under these circumstances. Movement artifacts due to vibration from the treadmill, considerable body movement due to the action of running at high intensity, and the way in which the breathing valve and shutter mechanism were suspended, all interfered with the recording of the pressure signal. This interference was such that, in some subjects, in some runs, the computer logic was unable to consistently and accurately detect the beginning of inspiration and expiration.

Although the results from the runs on the treadmill are included their validity is in doubt. This is why the correlations between hypercapnic ventilatory response and exercise ventilation, and occlusion pressure ventilatory response and exercise ventilation, while cycling on the bicycle ergometer and while running on the treadmill, were performed separately.
No difficulty was encountered in recording occlusion pressure at rest or while exercising on the bicycle ergometer. Under these circumstances the results were both consistent and reliable.

2. **Occlusion Pressure-Exercise Ventilation Relationships** In this study there was a tendency for those with the highest $P_{0.1}$ to have the highest exercise ventilation and those with the lowest $P_{0.1}$ to have the lowest exercise ventilations, but this relationship was not significant (Table 4.2). The failure to find a significant correlation between $P_{0.1}$ and exercise ventilation must in part relate to the nature of the measurement itself.

The occlusion pressure measured at 0.1 seconds is used as a measure of respiratory centre activity. However, the same $P_{0.1}$ in two individuals will not result in the same ventilation, thus rendering the interpretation of results more difficult. This variability in the relationship between occlusion pressure and ventilation between subjects is due to the shape of the occlusion pressure curve, the large number of factors that take part in the conversion of static pressure to flow of gas, the different patterns of breathing employed by the different subjects and neural influences from both higher centres and peripheral afferents.

(a) In any individual, as the output of the respiratory centre increases, the occlusion pressure wave increases its amplitude without changing its shape. Therefore, the relationship between the pressure measured at 0.1 seconds and the total output of the respiratory centre is fixed. However, although consistent in one individual, the relationship between $P_{0.1}$ and the output of the respiratory centre varies from subject to subject.

In some subjects the occlusion pressure rises rapidly at the onset of inspiration, but more slowly later on. In such cases $P_{0.1}$ would be relatively large compared to the total output of the respiratory centre. In other subjects the occlusion wave rises slowly at the beginning of inspiration and more rapidly at the end. In these cases $P_{0.1}$ may be relatively small compared to the total output (Whitelaw 1975).

(b) The occlusion pressure is a potential pressure developed by the respiratory muscles when contracting isometrically. In normal breathing, as the muscle shortens in producing ventilation, not all the potential
pressure is realized in the resulting ventilation. The amount lost varies from subject to subject due to differences in the functional residual capacity, in configuration of the chest wall, in intrinsic properties of the respiratory muscles and in the strength of these muscles. Therefore, the effectiveness of the contraction of the respiratory muscles varies from subject to subject.

(c) As was mentioned in the introduction to this section, tidal volume is determined for each breath by a combination of two mechanisms (Euler 1977). A central inspiratory activity generator, which determines the rate of inspiratory discharge, and a timer which controls inspiratory duration. PO.1 only gives information on the former of these two mechanisms. However, ventilation also depends on the time spent in inspiration and expiration. Therefore, different patterns of breathing, irrespective of the PO.1, will result in different ventilations. The mode of exercise, the use of a mouth piece and associated respiratory apparatus, and the entrainment of breathing frequency to movement frequency are just three factors that may modify breathing pattern and ventilation at the onset of exercise (see Section III).

3. Inspiratory Impedance PO.1 represents the pressure potential available for inspiration. VT/TI is a measure of the resulting flow. The relationship between PO.1 and VT/TI (i.e. the ratio PO.1/(VT/TI)), therefore constitutes an estimate of the respiratory system impedance (Derenne et al 1976, 1978, Sorti et al 1978, Gautier et al 1980, Lind and Hesser 1984b, Fordyce and Whetstone 1987). The validity of PO.1/(VT/TI) as a measure of impedance has been questioned, because it is the ratio of two terms determined during different portions of the inspiratory cycle (Weil 1986). Also, such measures of impedance are underestimated when compared with more classical methods of determination (Fordyce and Whetstone 1987). Therefore, to distinguish it from the more classical methods of determination, it has been termed the "effective inspiratory impedance".

Effective inspiratory impedance varies from subject to subject and is a function of lung compliance, breathing rate and respiratory airway resistance (Hesser and Lind 1984b).

(a) Compliance is the volume change per unit pressure change. It is related to the elastic properties of the lung. Compliance increases with
age and diseases such as emphysema. It decreases in alveolar oedema, when the lung has remained under ventilated for a long time, and when pulmonary venous pressure is increased (West 1977). Recent studies have indicated that compliance actually decreases with increasing work load (Stubbing et al 1980). Decreases in compliance cause an increase in impedance.

(b) Increases in breathing frequency cause increases in respiratory system impedance. However, the frequency dependent increase in impedance while cycling at 200 watts has been calculated to account for less than half of the total increase in impedance (Mead 1979).

(c) Changes in airway resistance with increasing intensity of work is the main cause of increasing respiratory impedance during exercise. This increase in resistance is a function of the rate and type of flow, the lung volume, the density and viscosity of the inspired gas and the extent of contraction of bronchial smooth muscle.

4. Inspiratory Impedance During Non Steady-State Exercise $P_{0.1}$, VT/TI and ventilation all increase with increasing exercise intensity. Some have found the relationship between $P_{0.1}$ and VT/TI and $P_{0.1}$ and ventilation to be linear while others have found $P_{0.1}$ to increase at a faster rate than both ventilation and VT/TI (Lind and Hesser 1984a). This progressive divergence of the $P_{0.1}$ and ventilatory response reflects an increase in respiratory impedance as breathing frequency and airway resistance increase with increasing work intensity.

The relationship of $P_{0.1}$ to ventilation depends upon the relative amounts of time spent in inspiration and expiration. Expiratory duration decreases faster than inspiratory duration as expiration becomes active at high work intensities. The ratio of inspiratory duration to total breath duration (TI/Ttot) therefore increases. As ventilation is the product of VT/TI and TI/Ttot, ventilation must increase at a faster rate than VT/TI. As a consequence, as the work load increases, the ration $P_{0.1}/(VT/TI)$ increases at a faster rate than the ratio $P_{0.1}$/ventilation.

The slope of $P_{0.1}/(VT/TI)$ differed from subject to subject. There was a tendency for exercise ventilation to be less in those with a high $P_{0.1}/(VT/TI)$ but this relationship was not significant. This again demonstrates the ample reserves of the respiratory system and the likelihood that flow
was not limiting ventilation during exercise in this study.

The fact that $P_{O,1}$ did not increase at a significantly faster rate than ventilation and $VT/TI$ and that the relationship between them was linear further supports the contention that flow was not limiting. The linearity of the relationship in this study as opposed to the curvilinear relationship demonstrated by Lind and Hesser (1984a) may be a reflection of the significantly lower ventilations achieved by the subjects in this study.

C. Conclusions

1. Chemosensitivity Sensitivity to carbon dioxide at rest has been shown to correlate with ventilation during mild to moderate steady-state exercise. This relationship was also evident, in this study, in the non steady-state. Ventilation correlated significantly with the hypercapnic ventilatory response throughout most of the first two minutes of exercise. Those with low ventilatory chemosensitivity tended to have the lowest exercise ventilations. Measures of chemosensitivity may therefore be good predictors of hypoventilation and hypoxemia at the onset of exercise.

2. Occlusion Pressure Although there was a tendency for those with high occlusion pressures to have the greatest ventilations, and vice versa, the close correlation between $P_{O,1}$ and ventilation, that existed in the steady state, was not maintained in the non steady-state. Therefore, an assessment of ventilatory drive, through measures of occlusion pressure, was not reliable as a predictor of hypoventilation at the onset of exercise.
During exercise, the oxygen requirement of the muscle may increase 10 fold. Carbon dioxide output increases proportionally. At the onset of exercise, due to the delayed adaptation of the cardio-respiratory system, there is an oxygen deficit and an accumulation of carbon dioxide in the muscle. The short fall in oxygen is met partially by the stores of oxygen in the muscle and surrounding tissues. The balance of the energy requirement is derived from anaerobic processes.

The tissues ability to store oxygen is small. Myoglobin stores are rapidly depleted and there is an immediate decrease in the partial pressure of oxygen in the venous blood. Conversely the tissues ability to store carbon dioxide is considerable. Carbon dioxide is taken up by the surrounding tissues delaying the increase in carbon dioxide in the venous blood.

The initial increase in oxygen uptake and carbon dioxide output are due to the increase in cardiac output alone. A secondary increase results from the increase in the difference in gas partial pressure between venous and arterial blood. Due to the greater stores for carbon dioxide than oxygen, the increase in veno-atrial carbon dioxide difference and the secondary increase in carbon dioxide output occurs some 10-20 seconds later than the increases in veno-atrial oxygen difference and oxygen uptake.

The alveolar partial pressure of oxygen and carbon dioxide reflect a balance between the movement of gas between the alveoli and the air by the alveolar ventilation and the exchange of gases between the alveoli and the venous blood due to diffusion. Ventilation must be proportional to the oxygen uptake and the carbon dioxide output if both the oxygen and carbon dioxide partial pressures are to be regulated in the alveoli. Because of the kinetic disparity between oxygen uptake and carbon dioxide at the onset of exercise ventilation can not follow both. Therefore, either oxygen, carbon dioxide, or both gases, will not be regulated constant.

In all trials in this study there was proportionality between carbon dioxide output and ventilation and relative hypoventilation with respect to oxygen uptake. This was reflected in a fall in the ventilatory equivalent for oxygen. This in turn caused a fall in the end tidal oxygen partial pressure.
Oxygen and carbon dioxide move between the alveoli and venous blood by simple diffusion. Other things being equal, a fall in alveolar oxygen partial pressure should therefore cause a fall in arterial oxygen partial pressure. In Section II falls in arterial oxygen partial pressure were observed at the onset of exercise. In the first 2 minutes these falls in arterial oxygen tension correlated with the falls in end tidal oxygen partial pressure and could be assumed to have been caused by them.

The degree of hypoventilation and the extent of the fall in end tidal oxygen partial pressure showed considerable individual variability. Normally ventilation is proportional to carbon dioxide output and the ventilatory equivalent for carbon dioxide is held constant at about 26 litres/litre. Under some circumstances, other stimuli to ventilation, such as the accumulation of lactic acid and neural afferents from the exercising limbs, have an additive effect, causing the ventilatory equivalent for carbon dioxide to increase. In this study, during high intensity exercise, entrainment of breathing frequency to low movement frequencies, when tidal volume had reached maximal exercise values, caused marked hypoventilation and significant falls in end tidal oxygen partial pressure.

Although there is a close correlation between ventilation and carbon dioxide output there is individual variability with respect to the level at which arterial carbon dioxide partial pressure is regulated and the change in ventilation induced by a known change in arterial carbon dioxide partial pressure. Those with low chemosensitivities to carbon dioxide at rest have been shown to have low steady-state exercise ventilations. This relationship was also demonstrated during non steady-state exercise in this study.

Hypoxemia has been demonstrated at the onset of moderate to high intensity exercise. In all cases it was related to the degree of relative hypoventilation and the subsequent fall in end tidal oxygen partial pressure. The degree of hypoventilation in turn showed considerable individual variability. The likelihood of hypoventilation and hypoxemia occurring is related to the inherent sensitivity of the individual to carbon dioxide at rest and the nature of the exercise performed. It appears that individuals with low chemosensitivity at rest and those engaging in activities involving low movement frequencies are those most likely to incur the greatest falls in arterial oxygen tension at the onset of exercise.
APPENDIX A

CONFIGURATION OF THE RESPIRATORY PHYSIOLOGY LABORATORY
AT THE PRINCESS MARGARET HOSPITAL

A.1 Introduction

Most of the research reported in this thesis was performed in the Respiratory Laboratory at The Princess Margaret Hospital. The laboratory is equipped with a Digital Equipment Corporation (DEC) PDP 11/10 mini-computer and a Perkin Elmar respiratory mass spectrometer. These form the nucleus of the laboratory. In addition, there are a large number of other pieces of equipment which are routinely used in the study of respiratory and exercise physiology.

A.2 Computer

The PDP 11/10 provides the main computing power and primary data collection functions of the laboratory. The configuration (Figure 1A) comprises an 11/10 processor with the Extended Arithmetic Element and 24k words of 16 bit core memory. Disk storage comprises three RK05j removable cartridge disks each providing 2.5Mb of data and program storage. Terminals are connected via two DL-11 serial line interfaces. A Teleray 10M VDU provides general purpose editing facilities and an LA-36 Decwriter serves as the system printer. Graphical output is provided by a Tektronix 4012 storage vector graphics terminal with a resolution of 1024 points by 780 points on a 210 mm by 160 mm screen. A Tektronix 4631 dry silver paper copier allows an exact copy of the screen to be made at any time. A DR-11k provides 16 bit parallel I/O facilities. Analog to digital conversion is by way of a Laboratory Peripheral System (LPS-11) providing a 12 bit A/D converter and a 16 channel analogue multiplexor allowing data collection from any of the 16 channels. A real time programmable clock (KW-11p) provides accurate timing for the data collection and also provides 2 Schmitt trigger inputs allowing for the generation of remote triggering events from anywhere in the laboratory. Data rates in excess of 6kHz may be obtained. The operating system is RT-11 V3-b. This is a single user system providing real time capabilities. Most programing was done in FORTRAN IV with some assembly language programming in MACRO-11.
A.3 Mass Spectrometer

A Perkin Elmar MGA-1100 Medical Gas Analyzer was used to measure the partial pressures of oxygen and carbon dioxide. It is of a fixed sector design. Whilst it is not possible to vary which gases are measured, the fixed sector design exhibits exceptional stability over a period of several months and requires only minimal adjustment and calibration in routine work.

In respiratory mode, output is available from 6 channels (Table 1A). Whilst 8 channels are available in anaesthetic mode it is at the expense of decreased accuracy and slower response in the carbon dioxide measurement. The accuracy of the MGA-1100, as stated by the manufacturers, is 0.1% of full scale in respiratory mode (Perkin Elmar Manual). Calibration of the mass spectrometer was done using a Wosthoff gas mixing pump and/or gravimetric gas mixtures.

A.4 Laboratory Bus

All the instruments in the laboratory are connected via a 24 channel analogue bus to the LPS-II of the computer (see Figure 1A). The output signals from the equipment may be logged by the computer by tapping into the bus at any point. Such a system provides considerable flexibility in the positioning and moving of equipment within the laboratory as each item need have only one cable connected to it. The bus can also be used to provide signals for display on either a 6 channel Gould Brush 2600 pen recorder or as an X-Y plot on a Tektronix 630 storage oscilloscope.

Equipment that is coupled to the bus includes 2 Ohio 840 101 dry rolling seal spirometers providing both flow and volume signals, several Validyne DP-45 variable reluctance pressure transducers, that may be used directly or coupled to Fleisch pneumotachographs for flow measurements, and an Avionics heart rate monitor.

A.5 Exercise Testing Equipment

This consists of a Quinton programmable treadmill, an Avionics heart rate monitor and ECG recorder, an Elena Schonander bicycle ergometer and an assortment of mouthpieces, breathing valves, tubing and bags for the
collection of expired gas samples. This equipment is housed in the room next to the laboratory. The analogue and data communication buses are extended into this room for computerised logging of exercise tests.

Table 1A  MGA-1100 output channels and their characteristics.

<table>
<thead>
<tr>
<th>Gas</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂</td>
<td>0-100%</td>
</tr>
<tr>
<td>O₂</td>
<td>0-100%</td>
</tr>
<tr>
<td>CO₂</td>
<td>0-10%</td>
</tr>
<tr>
<td>He</td>
<td>0-10%</td>
</tr>
<tr>
<td>C¹⁸O</td>
<td>0-1%</td>
</tr>
<tr>
<td>C₂H₂</td>
<td>0-2%</td>
</tr>
</tbody>
</table>

RESPIRATORY MODE

ANAESTHETIC MODE  As above but with the following additions.

<table>
<thead>
<tr>
<th>Gas</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>0-10%</td>
</tr>
<tr>
<td>N₂O</td>
<td>0-100%</td>
</tr>
<tr>
<td>Halothane</td>
<td>0-10%</td>
</tr>
</tbody>
</table>

Note 1:  CO cannot be measured as this has the same mass as N₂, thus only C¹⁸O can be used.

Note 2:  In anaesthetic mode the carbon dioxide is measured at mass fraction 12 and nitrous oxide at mass 44.
Figure 1A. Configuration of The Princess Margaret Hospital Respiratory Laboratory data logging and analysis system.
APPENDIX B

AN ONLINE BREATH-BY-BREATH COMPUTER BASED SYSTEM FOR THE MEASUREMENT OF VENTILATION AND GAS EXCHANGE DURING EXERCISE.

B.1 Introduction

The use of minicomputers has made it possible to observe the breath-by-breath variations in a number of physiological variables associated with respiration. Analog signals can be digitized and derived variables of physiological significance can be calculated on line for each breath. In this way the time course of changes in oxygen uptake, carbon dioxide output, respiratory exchange ratio, ventilation, end tidal oxygen, end tidal carbon dioxide and heart rate, at the onset of exercise, can be studied. Several such systems have been described in the literature (Beaver et al 1973, Linnarsson and Lindborg 1974, Pearce et al 1977).

B.2 Methods

The subject breathes through a mouthpiece connected to a two way breathing valve (Koegel Y valve). The valve has a dead space of 50 mls and functions to separate the inspired and expired air. Only the expired air is analysed and used in the calculation of the following variables.

Expired air passes through a 1 metre length of flexible tubing (Collins 32mm) to a pneumotachograph (Fleisch model 3). This in turn is connected to a differential pressure transducer (Validyne DP-45) with a 2 cm diaphram and a carrier demodulator (Validyne CD-15). The pneumotachograph system was assumed to be linear through the range of flows encountered in this study. Some have disputed this linearity (Yeh et al 1982) and recommend calibration over a wide range of flows. The accuracy of the results obtained with this system did not warrant such an approach (see B.8 Validation).

Inspired and expired air is sampled via a probe inserted on the mouthpiece side of the breathing valve. The air is drawn via a small lumen sampling line to a mass spectrometer (Perkin Elmar Model 1200) where oxygen and carbon dioxide partial pressures are measured continuously. Heart rate is
obtained from a cardiotachometer (Avionics Model 3000) using standard leads.

The electrical output of the pressure transducer and the oxygen and carbon dioxide channels of the mass spectrometer are amplified and displayed on a strip chart recorder (Gould Brush 2600). These outputs, along with that from the cardiotachometer, also pass to an analog to digital converter (Laboratory Peripheral System - LPS11) which digitizes the analog signal. A programmable real time clock provides the timing signal for the processor to sample the four input channels at a predetermined rate.

Breathing apparatus with high flow resistance can interferes with the breathing pattern and alter normal ventilation (Askanazi et al 1980). The resistance to flow between the breathing valve and the Fleisch pneumotachograph in the above system was measured with a U-tube manometer during steady unidirectional flow rates ranging from 1 to 6 l/sec. The resistance to flow averaged 0.42 cm H$_2$O литres$^{-1}$ sec$^{-1}$. This is low when compared with values reported for other systems (Lenox and Koegel 1974).

B.3 Calibration

The signal from the cardiotachometer is sampled at the end of each breath. One volt is equivalent to 50 beats per minute. The LPS values for known frequencies were determined. The following calibration factor was derived and used to calculate heart rate in beats per minute from the LPS values obtained during the actual experimental runs.

\[
\text{Heart Rate} = (((168 \times (LPS \text{ value} - 2287)) / 639) + 62)
\]

The mass spectrometer was calibrated for oxygen and carbon dioxide prior to each session using gases of known partial pressure. Computer calibration factors for oxygen and carbon dioxide are calculated based on data input during a calibration subroutine. A linear 2 point calibration is used. Two samples of differing gas concentrations are introduced. One is room air and the other a sample of mixed expired gas. The voltages generated for oxygen and carbon dioxide when the two samples are passed through the analog to digital converter give LPS values that correspond to the partial pressures of the gases. The LPS values are recorded and the partial pressures, as given by the mass spectrometer, are then entered via the
keyboard. The calibration factors for oxygen and carbon dioxide are then calculated as follows: (All variables are defined on page 260.)

\[
\begin{align*}
\text{SCALEO} & = \frac{1}{(\text{IAIRO} - \text{ICALO})} \times (\text{FAIRO} - \text{FCALO}) \\
\text{SCALEC} & = \frac{1}{(\text{ICALC} - \text{IAIRC})} \times (\text{FCALC} - \text{FAIRC})
\end{align*}
\]

The flow channel is calibrated by passing air through the pneumotachograph using a calibration pump of known volume. The calibration procedure first records the LPS value at zero flow (RFLO0). It then integrates 6 calibration pump cycles and calculates a mean value for the volume. This is then compared with the actual volume which was established from spirometer water calibration. A conversion factor is then derived in order to get the computer output to exactly equal the calibration volume. The flow calibration (RFLOCL) is calculated in mls/sec as follows:

Sample flow channel to get flow in LPS units.
Integrate flow to get volume.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Flow.dt \times \text{(LPS units X frames)}</td>
</tr>
<tr>
<td>Max-Min Volume</td>
<td>\text{DVOL} \times \text{(LPS units X frames)}</td>
</tr>
<tr>
<td>\text{DVOL}</td>
<td>2013 mls</td>
</tr>
<tr>
<td>1 LPS unit</td>
<td>2013 mls / \text{DVOL} / \text{frames}</td>
</tr>
<tr>
<td>1 frame</td>
<td>\text{sample rate} \times \text{(SR X secs)}</td>
</tr>
<tr>
<td>1 LPS unit</td>
<td>2013 mls / \text{DVOL} / (\text{SR X secs})</td>
</tr>
<tr>
<td>Flow Calibration</td>
<td>2013 mls / \text{DVOL} / (\text{SR X secs})</td>
</tr>
</tbody>
</table>

The flow calibration factor can be further modified by applying a correction factor in retrospect. This correction factor is found by comparing gas volumes measured with a Tissot spirometer with the gas volumes calculated by the computer.

\[
\text{New RFLOCL} = \text{Old RFLOCL} \times \frac{\text{Tissot Volume}}{\text{Computer Volume}}
\]

B.4 Mass Spectrometer Transit Time

The oxygen and carbon dioxide partial pressure output signals are delayed in time with respect to the flow signal (Figure 1B, 2B, 3B). This delay represents the time required to transport the air sample from the mouth piece to the mass spectrometer and the rise time inherent in the mass
spectrometers response (Bates et al 1983). This delay time must be measured and introduced into the program so that the gas concentrations and the flow signals are in phase and can be multiplied and integrated in each sample interval to give the oxygen uptake and carbon dioxide production for each breath. Mitchell (1979) revealed that the effect of not accounting for the analyzer response time results in a 20% underestimation of the gas exchange rate. The realigned trace is presented in Figure 4B.

The delay time was found to vary depending on the inlet used and on the extent of protrusion of the capillary into the mouth piece. This made it essential that the delay time was checked prior to each experimental run.

The delay time was determined by blasting pure oxygen into the breathing valve while sampling the oxygen and flow channels. This produced a square wave for both oxygen and flow. Oxygen and flow are then plotted against time. Tracings such as those in Figure 5B are produced. The onset of the oxygen and flow spikes are then marked with vertical cursors and the delay time calculated as the difference between the two.

B.5 Computer Programs

(a) Calibration When the data acquisition program is first run the calibration file is read from disk (Digital Decpack rko5). The calibration factors for oxygen and carbon dioxide are displayed. These may be accepted or recalculated by running the mass spectrometer calibration subroutine.

Barometric pressure, ambient temperature and the dead space of the breathing valve are all entered via the keyboard. Mass spectrometer transit time may be either entered or recalculated. The LPS value for zero flow (RFLOO) is entered and the flow calibration factor (RFLOCL) is either entered via the keyboard or recalculated by running the flow calibration subroutine.

(b) Data Acquisition The data acquisition program has two modes of operation. In the first mode values of breath duration, oxygen uptake, carbon dioxide output, respiratory exchange ratio, ventilation, end tidal oxygen, end tidal carbon dioxide and heart rate are printed after each breath. In the second mode of operation the screen is divided into three and oxygen uptake, end tidal carbon dioxide and respiratory exchange ratio
are plotted concurrently with a vector being drawn after every breath (Figure 9B). The scales for both the X and Y axis may be either set or default values accepted.

During the run a Schmitt trigger is used to signal the time of an event. Event markers may be dropped as follows. To start data sampling the Schmitt trigger is pressed (and released) once. Thereafter, each time the trigger is pressed the time from the onset of sampling is recorded and stored as the variable "EVENT" along with other parameters for the breath. If the second sampling option is in effect a line is also drawn on the 3 plots to coincide with the end of the breath during which the Schmitt trigger was pressed. If the trigger is pressed twice in quick succession, i.e. not separated by an exhalation, the first will mark an event, the second will stop data sampling. Computer analysis will only use data up to the time indicated by the first event marker. Data logged after this event will be ignored.

At the end of sampling, total time of sampling and mean values for oxygen uptake, carbon dioxide output and ventilation are calculated and printed.

With both operating modes, data may be written to disk. Files for writing to disk have one record per breath. Each record is unformatted and contains the following real variables: breath duration, oxygen uptake, carbon dioxide output, tidal volume, end tidal oxygen, end tidal carbon dioxide, heart rate and "EVENT". The last record contains -1, mean oxygen uptake, mean carbon dioxide output, total ventilation and total time.

File names are created in numerical sequence, i.e. EX0001.DAT, EX0002.DAT, until one is found that does not exist. A file of that name is then opened with a length of 50 blocks. The file is then closed and reopened so that it is not lost if the system fails.

The first record of the file is 6 integers and they are used as follows. The first contains the number of real values per record (NVAL), the second contains the highest block number written (starting at zero), and the third to sixth are unused.

On the first call to the data output module the number of real values per record (NVAL) is written into the first word of the file. For this and
subsequent calls to the data output module "NVAL" real values are transferred to the disk file as sequential records starting after the first 6 integers.

At the end of sampling the operator enters a 6 letter file name via the keyboard. The old file is then copied to the new until the last block written. The new file is then closed. This means that the new file is only as long as the actual data written by the data output module. The 50 block original file still remains as a back up.

(c) **Printing Results** A print program allows you to list the data file. It is printed almost exactly as the data would have appeared on the screen had the first operational procedure been selected. In addition "EVENTS" are indicated as they occur in the stored data.

When called, the print program asks for the file name. The number of real values per record (NVAL) is read from the first block and written into the common block. "NVAL" real variables, (starting after the first 6 integers), are then passed back to the calling program and printed on the screen or line printer as required. In subsequent calls sequential records in the file are returned. If the first record in the word is equal to -1 the remaining variables in the word are read and then the file is closed.

(d) **Data Analysis** An analysis program is also available. It allows the plotting of data against time in either real form or as a percentage of maximum values. Parameters may also be plotted against each other. The axes may be adjusted with the range being selected by cursors or from the keyboard. The cursors and the keyboard may also be used to select ranges over which average values may be computed.

**B.6 End of Breath Logic**

The duration of one breath is defined as being from the beginning of inspiration to the end of expiration. End of breath logic has been developed to accurately detect the end of expiration. The following variables have been defined and are used in its determination.

(a) **BOBCO2** This is the partial pressure of carbon dioxide in Torr that end tidal carbon dioxide must exceed on expiration before end of breath
logic can be true.

(b) **EOBCO2** This is a fraction \( \leq 1 \). The instantaneous partial pressure of carbon dioxide must fall below \( EOBCO2 \times ETO2 \) before end of breath logic can be true.

(c) **IDELAY** The number of frames of data (one frame of data is collected every 0.02 of a second) for which end of breath logic must be true in succession before the final "end of breath" is declared.

When \( BOBC02=20 \) Torr, \( EOBC02=0.5 \), \( IDELAY=1 \) and end tidal oxygen = 110 Torr, for end of breath logic to be true the instantaneous partial pressure of carbon dioxide must first rise above 20 Torr, and then fall below half its maximum value for this expiration (i.e. 55 Torr). Flow must also be zero and the tidal volume must be greater than the dead space of the breathing valve.

Using single character non echoing input from the keyboard it is possible to change the end of breath logic while the program is running. On receipt of these commands \( BOBC02 \) and \( EOBC02 \) are either increased or decreased by 10%. The keys are accepted at the end of the breath and acted upon immediately if valid.

B.7 **Calculations**

The analog to digital convertor samples the outputs of the flow, oxygen and carbon dioxide channels 50 times per second. The time to digitize all four channels is less than 100 usec at the beginning of each sampling cycle.

(a) In the remainder of the interval between sampling times the following computations are made:

**Tidal Volume**

To convert raw data to ml (STPD) / frame

\[
RFLOCl = RFLOCl \times STPD / \text{sample rate}
\]

For each frame instantaneous flow

\[
FLOWI = (IFLOW \times RFLO0) \times RFLOCl
\]

This is summed for each frame to give tidal volume
SUMV = SUMV + FLOWI

Oxygen Flow

Instantaneous oxygen concentration
GASOI = (IGASO - ICALO) * SCALEO + FCAO
Flow of oxygen per frame in mls/min
OFLOW = FLOWI * GASOI
This is summed for each frame to give the total flow of oxygen during exhalation
SUMO = SUMO + OFLOW

Carbon Dioxide Flow

Instantaneous carbon dioxide concentration
GASOC = (IGASC - IAIRC) * SCALEC + FAIRC
Flow of carbon dioxide per frame in mls/min
CFLOW = FLOWI * GASCI
This is summed for each frame to give the total flow of carbon dioxide during exhalation.
SUMC = SUMC + CFLOW

(b) During inspiration the following parameters are calculated:

Breath Duration

The time between successive end of breaths
\[ T = (T1 - T2) \text{ seconds} \]

Ventilation

\[ \dot{V}E = \frac{SUMV}{T} \times 60 \times 1000 \text{ litres/min} \]

End Tidal Oxygen

The lowest partial pressure of oxygen during exhalation
\[ ETO2 = GASOI \times (PB - 47) \text{ Torr} \]
End Tidal Carbon Dioxide

The highest partial pressure of carbon dioxide during exhalation
\[ ETCO2 = GASI \times (PB - 47) \text{ Torr} \]

Oxygen Uptake and Carbon Dioxide Output

The inspired air is composed of two components. The expired air that remains in the breathing valve at the end of expiration and room air.

The volume of each gas inspired from the valve

\[ VALVEO = VV \times ETO2 \]
\[ VALVEC = VV \times ETCO2 \]
\[ VALVEN = VV - VALVEO - VALVEC \]

The volume of each gas inspired from air

\[ EN = SUMV - SUMC - SUMO \]
\[ AIRN = EN - VALVEN \]
\[ AIRC = FAIRC \times AIRN / FAIRN \]
\[ AIRO = FAIRO \times AIRN / FAIRN \]

Net changes for each gas

\[ \dot{V}O2 = AIRO - (SUMO - VALVEO) \]
\[ \dot{V}CO2 = SUMC - VALVEC - AIRC \]

These are then converted to ml(STPD)/min

\[ \dot{V}O2 = VO2 / T \times 60 \]
\[ \dot{V}CO2 = VCO2 / T \times 60 \]

Respiratory Exchange Ratio (R)

\[ R = VCO2 / VO2 \]
B.8 Validation

The accuracy of the system is influenced by a number of factors. The significance of the linearity of flow and the transit time of the mass spectrometer have already been discussed. The accuracy is also influenced by the frequency at which the input signals are sampled by the analog to digital converter and the signal noise. Signal noise affects the accuracy with which the true value of the signal is measured at the time of sampling. Numerical filters can be used to reduce the effects of signal noise, but the filters may also affect the true signal. Bernard (1977) demonstrated that a trapezoid rule integration at a sample rate of 30 Hz with no numerical filter can provide satisfactory data.

This system assumes flow to be linear, corrects for mass spectrometer transit time, uses a trapezoid rule integration procedure and samples at a rate of 50 Hz with no numerical filters. The results have proved to be both reliable and accurate.

The accuracy of the computer derived variables was assessed by comparing them with conventional methods for determining oxygen uptake, carbon dioxide output and ventilation. Three subjects each performed 8 trials of 3 minute duration. The intensity of the trials ranged from resting to moderate to severe exercise. Expired air was collected in the third minute in a meteorological balloon. The oxygen and carbon dioxide partial pressures of aliquot samples were measured by mass spectrometer. Volume was measured by Tissot spirometer. Oxygen uptake, carbon dioxide and ventilation was calculated by the conventional nitrogen correction technique. For comparison, the same variables were calculated for the same time interval by the computer. The data together with the line of identity is plotted in Figures 6B, 7B and 8B. Equations for the line of regression and r values are also given. There was no significant difference between the regression line for the experimentally determined points and the line of identity.
GLOSSARY OF TERMS

The standard symbols for respiratory physiology are used, with the following special symbols and interpretations.

AIRC = volume of carbon dioxide inspired from air
AIRN = volume of nitrogen inspired from air
AIRO = volume of oxygen inspired from air
EN = volume of expired nitrogen
FAIRC = fraction of carbon dioxide in room air
FAIRN = fraction of nitrogen in room air
FAIRO = fraction of oxygen in room air
FCALC = fraction of carbon dioxide in calibration gas
FCALO = fraction of oxygen in calibration gas
FLOWC = flow of carbon dioxide per frame
FLOWO = flow of oxygen per frame
FLOWI = instantaneous flow
GASCI = instantaneous flow of carbon dioxide
GASOI = instantaneous flow of oxygen
IAIRC = LPS value for carbon dioxide pp of air
IAIRO = LPS value for oxygen pp in air
ICALC = LPS value for carbon dioxide pp in calibration gas
ICALO = LPS value for oxygen pp in calibration gas
IFLOW = LPS value for flow
RFLOO = LPS value at zero flow
RFLOCL = flow calibration factor
SCALEC = carbon dioxide calibration factor
SCALEF = flow calibration factor
SCALEO = oxygen calibration factor
STPD = correction factor to give volumes in STPD
SUMC = carbon dioxide flow for one expiration
SUMO = oxygen flow for one expiration
SUMV = total flow during one expiration
T = breath duration
T1, T2 = time at beginning and end of breath
VALVEC = volume of carbon dioxide inspired from valve
VALVEN = volume of nitrogen inspired from valve
VALVEO = volume of oxygen inspired from valve
VV = volume of valve
Figure 1B  Oxygen partial pressure trace from the mass spectrometer during a normal breathing cycle. Sample rate 50 Hz.

Figure 2B  Carbon dioxide partial pressure trace from the mass spectrometer during a normal breathing cycle. Sample rate 50 Hz.
Figure 3B Instantaneous flow trace from the Fleisch pneumotachograph during a normal breathing cycle. Sample rate 50 Hz.

Figure 4B. Oxygen and carbon dioxide trace realigned with respect to flow. This accounts for transit delays in the mass spectrometer.
Figure 5B. Determination of mass spectrometer transit time by comparing the response time of flow and oxygen to surreptitious introduction of oxygen into the breathing valve.

Figure 6B. Comparison of oxygen uptake as obtained from conventional mixed expired samples and online breath-by-breath procedures.

\[ Y = 1.0073 \times X + 0.0119 \]

\[ r = 0.9993 \]
Figure 7B Comparison of carbon dioxide output as obtained from conventional mixed expired samples and online breath-by-breath procedures.

\[ Y = 0.9984 \times X + 0.0076 \]

\[ r = 0.9996 \]

Figure 8B Comparison of ventilation as obtained from displacement measures of expired samples and online breath-by-breath procedures using a pneumotachograph.

\[ Y = 0.9786 \times X + 1.1537 \]

\[ r = 0.9997 \]
Figure 9B  Output to the screen during normal operational mode. A vector for oxygen uptake, end tidal carbon dioxide and respiratory exchange ratio is plotted at the end of each breath.
APPENDIX C

A COMPUTER BASED DATA ACQUISITION SYSTEM FOR STUDYING THE RELATIVE TIMING OF BREATHING AND LIMB MOVEMENT ON A BREATH-BY-BREATH BASIS.

C.1 Introduction

The entrainment of breathing rate to movement of the limbs is common among quadrupeds and has been demonstrated during cycling and running in humans (Bramble and Carrier 1983). The failure of some researchers to show entrainment (Kay et al 1975b, Kellman and Watson 1973) may be a reflection of the methods used rather than the existence or not of entrainment.

The simplest method for detecting entrainment is to measure breathing frequency and determine if it is related to some sub multiple of the limb movement frequency. This assumes that if entrainment is present the frequencies will be in some integer ratio to one another. More recently, sophisticated averaging techniques using cross correlations and post stimulus histograms of breath occurrence times relative to limb movement times have been used to search for entrainment (Jasinskas et al 1980).

However, averaging methods such as these, no matter how sophisticated, do not allow for interrupted or shifting patterns of breathing and movement frequency (Parker et al 1985). Consequently computer based data acquisition systems have been designed to study the relative timing of breathing and limb movement on a breath-by-breath basis.

C.2 Methods

The subject breathed through a mouthpiece attached to a breathing valve (Koegel Y valve). Mouth pressure was measured at the mouth piece with a pressure transducer (Validyne DP-45) and carrier demodulator (Validyne CD-15).

Pedal period was measured during cycling by using a photoelectric beam relay to detect the right foot as it passed through the bottom of its pedal arc. When the beam was interrupted the electrical pulse generated activated a Schmitt trigger which in turn passed to the computer (Digital PDP-11).
Stepping period during walking and running on the treadmill was measured with a microswitch attached to the heel of the right shoe. This emitted an electrical pulse as the right heel touched the treadmill with each stride. Again the electrical pulse was made to activate a Schmitt trigger which passed to the computer.

The output of the pressure transducer and Schmitt trigger were amplified and displayed on a strip chart recorder. They also passed to an analog to digital converter which digitized the analog signal. A programmable real time clock provided the timing signal for the computer to sequentially sample the 2 input channels at the selected rate of 100 samples per second.

C.3 Computer Programs

(a) Calibration: This program enables channel numbers and calibration values to be entered and stored on disk. For pressure a linear two point calibration is used.

(b) Data Acquisition: This program relies on the mouth pressure signal for the identification of the onset of inspiration and expiration. An inspiratory signal is accepted if it lasts more than 0.1 sec, the system was previously in expiration, the duration of the previous expiration exceeded 0.3 sec, and mouth pressure has dropped more than 0.4 cm H₂O relative to the ambient pressure. An expiratory signal is accepted if it lasts more than 0.1 sec, the system was previously in inspiration and the duration of the previous inspiration exceeded 0.3 sec.

At run time, file names are entered and the pressure calibrations are obtained from file on disk. Data sampling starts on the first recorded firing of the Schmitt trigger and is stopped by a keyboard command. After each sampling a completion routine checks to see if the Schmitt trigger has fired, whether an inspiratory or expiratory signal has been accepted, or whether a halt command has been entered.

If the Schmitt trigger has fired, or an inspiratory or expiratory signal has been accepted, the time at which it occurred is displayed and logged in memory. If a halt command is received, sampling is stopped, all data in memory is written to disc and a hard copy record is printed.
(c) **Analysis:** This program reads the file off disk. The time of each heel strike from the immediately preceding onset of inspiration is calculated and plotted against running time (Figure 1C). The regular pattern occurring between 20 and 70 seconds into the run indicates that entrainment is occurring in these breaths. The large variability occurring before and after this indicates that no entrainment occurred in these breaths. In this example a slight drift in the timing is evident.

The inspiratory and expiratory durations, total breath duration and the ratio of stride frequency to breath frequency is calculated for each breath and a hard copy record is printed.

**C.4 Validation**

The success of this technique as a means of detecting entrainment of breath frequency to gait is dependent upon the accuracy with which the computer detects the onset of inspiration and expiration. This was verified by comparing the onset of inspiration and expiration obtained manually from the strip chart records with the corresponding values obtained by computer analysis. The data together with the line of identity is presented in Figures 2C, 3C and 4C. Equations for the line of regression and r values are also given.
Figure 1C. Entrainment of breathing frequency to stride frequency as represented by plotting time of foot strike after the onset of inspiration against time.

Figure 2C. Comparison of inspiratory duration obtained manually from strip chart recordings with corresponding values obtained by computer analysis.

\[ Y = 0.9873 \times X + 0.0105 \]

\[ r = 0.9887 \]
Figure 3C. Comparison of expiratory duration obtained manually from strip chart recordings with corresponding values obtained by computer analysis.

\[ Y = 0.9950 \times X + 0.0055 \]

\[ r = 0.9878 \]

Figure 4C. Comparison of total breath duration obtained manually from strip chart recordings with corresponding values obtained by computer analysis.

\[ Y = 1.0029 \times X - 0.0061 \]

\[ r = 0.9994 \]
APPENDIX D

A COMPUTER BASED DATA ACQUISITION SYSTEM FOR THE MEASUREMENT OF BREATHING PATTERN AND OCCLUSION PRESSURE

D.1 Introduction

Occlusion pressure is defined as the static pressure generated by the respiratory muscles at functional residual capacity against an obstructed airway 0.1 seconds after the onset of inspiration. The occlusion pressure is easy to measure and reproducible in each subject. It is unaffected by respiratory system resistance and compliance or by volume related reflex activity. It is an overall index of the neuromuscular component of the respiratory output and an indicator of the pressure potential available for inspiration at any point in time (Whitelaw et al 1975). As such it has become recognised as the best means available for assessing the output of the respiratory centres.

D.2 Methods

To determine occlusion pressure the subject breathed through a mouthpiece attached to a breathing valve (Koegel Y valve). The valve had a dead space of 50 mls and functioned to separate the inspired and expired flow of gas. Mouth pressure was measured at the mouthpiece with a pressure transducer (Validyne DP-45). Inspired and expired oxygen and carbon dioxide partial pressures were measured for each breath by continuous sampling at the mouth with a mass spectrometer (Perkin Elmar MGA-1100). The expired side of the valve was connected to a pneumotachograph (Fleisch 3) and a pressure transducer (Validyne DP-45) by one metre of 32 mm diameter flexible tubing. The electrical output of the two pressure transducers and the mass spectrometer under went analog to digital conversion (LPS-11) and were then transmitted to a digital mini computer (PDP 11/10). All four variables (mouth pressure, flow, oxygen partial pressure and carbon dioxide partial pressure) were also displayed continuously on a strip chart recorder (Gould Brush 2000).

Attached to the inspired side of the valve was the occlusion device. This consisted of a wide calibre plastic tube with a pneumatically driven perspex shutter. Signals passed from the computer via a digital to analog
converter (LPS-II) to activate a solenoid valve (Wixom Model 600). The solenoid valve in turn controlled the direction of air flow passing to a double acting pneumatic cylinder (Schrader-Bellows M.12 16010 40mm) thereby opening and closing the shutter.

The mass spectrometer and pneumotachograph were calibrated as outlined in Appendix B. For pressure a linear two point linear calibration was used.

Care was taken to ensure that the subject had no prior warning of the closing of the shutter. A screen was placed between the subject and the occlusion device so that the subject could not see the movement of the shutter. Vibrations in the valve and mouth piece caused by the closure of the shutter were minimized by adjusting the speed with which the shutter closed. The subject was also isolated from the noise of the apparatus by putting cotton wool in their ears and applying light weight headphones which played, at high volume, music of their choice. All subjects indicated that they were unaware of the actual closing of the shutter.

Control of the speed at which the shutter closed, at the onset of expiration, was achieved by controlling the air supply to the pneumatic cylinder with an adjustable valve (Martonair M/678F). This was regulated so that the maximum time between signaling of the shutter to close by the computer and the time at which the shutter was fully occluded was no more than 0.3 seconds. This was in accordance with the criteria for detecting the onset of inspiration as outlined above.

The speed at which the shutter opened was maximized according to the air pressure and the calibre of the pneumatic tubing. The noise of the shutter opening, or the vibration it caused, was of no concern as the measurement of occlusion pressure had already been made. It was more important that unrestricted inspiratory flow be restored as soon as possible so that minimal interference to the normal breathing pattern took place.

The dead time between signalling of the shutter to open by the computer and the return to unrestricted flow was measured and allowed for so that the shutter began to open and unrestricted flow was restored as soon as possible after the measurement of occlusion pressure was made.

D.3 Data Acquisition Program
The minicomputer is programmed both to control the function of the occlusion device and to measure occlusion pressure. To control the device the onset of inspiration and expiration must be reliably obtained. Both are determined from the mouth pressure signal. Criteria for the acceptance of inspiratory and expiratory signals were the same as that outlined in Appendix C.

The program is activated in the first instance with a Schmitt trigger. The computer samples the four input channels through the A/D converter at 50 hertz, continuously logging all data in memory. A completion subroutine examines each data sample to detect the occurrence of an inspiratory or expiratory trigger.

At the onset of expiration of the third breathing cycle a signal is passed from the computer to close the shutter thereby excluding the inspired line to the breathing valve. The shutter stays closed through the remainder of expiration. 0.06 seconds after the onset of inspiration in the next breathing cycle a signal is passed from the computer to withdraw the shutter. The dead time for this operation is about 0.05 seconds. The shutter therefore begins to open approximately 0.01 seconds after the measurement of P0.1 has been completed. Unrestricted flow is resumed shortly after this.

Sampling continues to the end of the following expiratory phase. All data is then stored on disk for subsequent analysis. The keyboard is then checked for a halt command. If none has been received the sampling cycle is then repeated.

The timing of the sampling cycle is such that occlusion pressure is measured on every 6th to 7th breath. The number of breaths in the sampling cycle prior to the closing of the shutter can be varied thereby altering the rate at which occlusion pressure can be measured.

**D.4 Calculation of Results**

At the completion of data collection a second program is used to calculate the results. Occlusion pressure is calculated as the pressure recorded 0.1 seconds after the onset of inspiration against the occluded airway. Inspiratory duration, expiratory duration and total breath duration are
calculated from the pressure trace using the same criteria for the determination of the beginning of inspiration and the beginning of expiration as outlined in Appendix C. Mouth pressure is then plotted against time with the beginning of each inspiratory and expiratory phase being indicated (Figure 1D). This enables a visual check on the accuracy of the computer derived values.

The beginning of inspiration and expiration as determined from the mouth pressure trace will not coincide with that determined from the carbon dioxide trace. The difference representing the transit time delay in the mass spectrometer. The trace of carbon dioxide against time is plotted (Figure 2D). The beginning of inspiration and expiration for each breath are then determined manually by positioning vertical cursors on the carbon dioxide trace. Flow against time is then plotted (Figure 3D). The onset of inspiration and expiration as determined from the mouth pressure trace should coincide with the rise and fall of the flow trace from zero levels. The oxygen and carbon dioxide data are then adjusted in time so that the onset of inspiration and expiration as determined from the carbon dioxide trace coincides with that determined from the pressure and flow traces. The realigned data is then replotted (Figure 4D). Oxygen uptake, carbon dioxide output, ventilation and end tidal gas partial pressures are then calculated as in appendix B.

D.5 Exercise Studies

The mouth piece, breathing valve, occlusion device and associated equipment were suspended from a boom enabling its use in exercise studies. The changes in the mouth pressure trace with increasing exercise intensity can be seen in Figures 5D, 6D and 7D. With increasing exercise intensity inspiratory and expiratory duration decreases and the amplitude of the normal rise and fall in mouth pressure with each breath increases (Figure 5D). The occlusion pressure (Figure 6D), and the rate at which the occlusion pressure falls (Figure 7D) also increase.

(a) Linearity of Response The linearity of the response was assessed in six subjects by comparing occlusion pressure obtained directly from the pressure trace with that obtained from the line of best fit through the data points obtained in the first 0.1 seconds of inspiration against the occluded airway.
In 4 of the 6 subjects there were no significant differences between the two values at any of the 6 work loads. The 2 remaining subjects reacted to the occlusion by inhibiting inspiration. The latency of this response for subject SE appeared to decrease as the work intensity increased (Figures 8D and 9D). This resulted in significant differences in the values of occlusion pressure obtained from the pressure trace and those obtained from the regression line at high work intensities (Figure 10D). Student's t scores and the significance of these differences over the range of 6 work loads are presented in Table 1D.

(b) Relationship Between $P_{O_2}$ Flow and Ventilation Some researchers have demonstrated a linear relationship between occlusion pressure and inspiratory flow, and occlusion pressure and ventilation, during incremental work tests. Other investigators believe that the increase in occlusion pressure is faster than the rate of increase in ventilation and inspiratory flow due to increasing impedance in the respiratory system (Lind and Hesser 1984b). To verify this 6 subjects each cycled for 3 minutes at 6 different work intensities. Ventilation and inspiratory flow were both plotted against occlusion pressure. The correlation coefficients for the linear regression of occlusion pressure on ventilation and inspiratory flow were both high in all subjects. However, in 2 of the 6 subjects parabolic regression lines showed a significantly better fit. Figures 11D to 14D show an example where parabolic regressions give a significantly better fit.

(c) Consistency of Response In any one individual the same occlusion pressure should mean the same neural output from the respiratory centre and result in the same ventilations and inspiratory flows. One subject (JA) performed 6 trials on a bicycle ergometer. Each trial was of 2 minutes duration at a power output of 300 watts. Three trials were performed at a cadence of 60 rpm and 3 trials at a cadence of the subject's own choosing (average 109.24 rpm).

Oxygen uptakes and ventilations were higher at the higher pedal frequency. However, regressions for the plots of occlusion pressure against ventilation and occlusion pressure against inspiratory flow for the 2 cadences were not significantly different (Figures 15D and 16D).

(d) Interbreath Variability In previous steady-state experiments where
occlusion pressure was measured ventilation and inspiratory flow were calculated from the tidal volume and duration of the 3 breaths immediately preceding the occlusion (Whitelaw et al 1975). In the non steady-state with the rapid changes in tidal volume and breath duration, mean values may not produce ventilations and flows representative of those occurring at the time of the occlusion.

In computerised breath by breath systems the tidal volume and breath duration of the actual occluded breath have been used for calculating ventilation and inspiratory flow (Lind and Hesser 1984b). However, typically when comparing the breath of the occlusion with the breath preceding the occlusion, breath duration is shorter. i.e. the occlusion interferes with the normal breathing pattern.

One subject performed 3 trials cycling on a bicycle ergometer for 2 minutes at 300 watts. Tidal volume, inspiratory and expiratory duration, total breath duration and inspiratory flow were calculated for the breath prior to occlusion (B1), the breath of occlusion (B2), the breath after occlusion (B3), and the average of all 3 breaths (BA). Mean values are presented in Table 2D.

Inspiratory duration, expiratory duration and total breath duration were shorter and inspiratory flow and ventilation greater for the breath of occlusion when compared to the breath prior to occlusion. There were no significant differences between the breath during occlusion and the breath after occlusion and the average of all 3 breaths for any of the parameters studied (Table 3D).

Analysis of variance revealed that the regression line for the average values of ventilation and flow against occlusion pressure showed a significantly better fit than those calculated from any single breath. Consequently the average of the breath preceding occlusion, the breath during occlusion and the breath after occlusion was used in calculating ventilation and inspiratory flow in these studies.
Figure 1D. Mouth pressure trace during normal breathing and during inspiration against an occluded airway. Vertical lines indicate the beginning of inspiration and expiration.

Figure 2D. Trace of carbon dioxide partial pressure showing how the onset of inspiration and expiration are defined by the positioning of cursors on the screen.
Figure 3D. Trace of instantaneous flow showing how the onset of inspiration and expiration are defined by the positioning of cursors on the screen.

Figure 4D. Correction for mass spectrometer transit time and the subsequent alignment of the oxygen, carbon dioxide, pressure and flow traces.
Figure 5D. Mouth pressure trace during an occluded breath at three different work intensities. Power output = 50, 100, and 200 watts.

Figure 6D. Mouth pressure trace showing the extent and timing of the fall in pressure at three different work intensities. Power output = 50, 100 and 200 watts.
Figure 7D. Mouth pressure showing the individual sample points and differences in negative slope with increasing work intensities. Power output = 50, 100 and 200 watts.

Figure 8D. Mouth pressure showing the individual sample points and the relative linearity of the response with increasing work intensities. Power output = 0, 50 and 100 watts.
Figure 9D. Mouth pressure showing the individual sample points and the relative linearity of the response with increasing work intensities. Power output = 150, 200 and 250 watts.

Figure 10D. Comparison of occlusion pressures measured at 0.1 seconds with those calculated from the regression line at different work intensities.
Figure 11D. Linear relationship between occlusion pressure and inspiratory flow with increased work intensity.

Figure 12D. Curvilinear relationship between occlusion pressure and inspiratory flow with increased work intensity.
Figure 13D. Linear relationship between occlusion pressure and ventilation with increased work intensity.

Figure 14D. Curvilinear relationship between occlusion pressure and ventilation with increased work intensity.
Figure 15D. Comparisons of the relationship between occlusion pressure and ventilation while cycling at 2 different pedal frequencies. A linear fit.

Figure 16D. Comparisons of the relationship between occlusion pressure and ventilation while cycling at 2 different pedal frequencies. A curvilinear fit.
Table ID: Significance of difference at increasing power outputs between PO.1 calculated from the raw data (top figure) and PO.1 calculated from the regression line drawn through the first 5 data points (bottom figure). (Subject S.E.)

<table>
<thead>
<tr>
<th>Power</th>
<th>N</th>
<th>Means</th>
<th>Std. D</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>6</td>
<td>1.40 ±0.82</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.42 ±0.93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>7</td>
<td>2.69 ±0.90</td>
<td>1.51</td>
<td>0.180</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2.51 ±0.71</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>7</td>
<td>3.42 ±1.61</td>
<td>2.91</td>
<td>0.027</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3.16 ±1.60</td>
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</tr>
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<td>125</td>
<td>7</td>
<td>11.15 ±2.48</td>
<td>3.13</td>
<td>0.014</td>
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</tr>
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<td></td>
<td></td>
<td>11.99 ±2.82</td>
<td></td>
<td></td>
<td></td>
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<td>150</td>
<td>8</td>
<td>13.35 ±1.30</td>
<td>3.16</td>
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<td></td>
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<td>14.08 ±1.53</td>
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<td>175</td>
<td>7</td>
<td>19.87 ±4.29</td>
<td>7.95</td>
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<td></td>
<td></td>
<td>21.50 ±4.61</td>
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Table 2D: Means and standard deviations for ventilation, inspiratory flow, inspiratory duration, expiratory duration and total breath duration for the breath before occlusion (B1), the breath during occlusion (B2), the breath after occlusion (B3) and the average of these 3 breaths (BA). (n=62)

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation</td>
<td>61.89</td>
<td>66.37</td>
<td>65.72</td>
<td>64.66</td>
</tr>
<tr>
<td>Inspiratory Flow</td>
<td>±16.41</td>
<td>±13.67</td>
<td>±17.63</td>
<td>±15.39</td>
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<tr>
<td>Inspiratory Duration</td>
<td>2.30</td>
<td>2.36</td>
<td>2.30</td>
<td>2.32</td>
</tr>
<tr>
<td>Expiratory Duration</td>
<td>±0.67</td>
<td>±0.47</td>
<td>±0.64</td>
<td>±0.56</td>
</tr>
<tr>
<td>Total Breath Duration</td>
<td>1.30</td>
<td>1.24</td>
<td>1.23</td>
<td>1.26</td>
</tr>
<tr>
<td>Expiratory Duration</td>
<td>±0.32</td>
<td>±0.19</td>
<td>±0.21</td>
<td>±0.19</td>
</tr>
<tr>
<td>Expiratory Duration</td>
<td>1.06</td>
<td>0.96</td>
<td>0.90</td>
<td>0.97</td>
</tr>
<tr>
<td>Expiratory Duration</td>
<td>±0.19</td>
<td>±0.20</td>
<td>±0.18</td>
<td>±0.15</td>
</tr>
<tr>
<td>Total Breath Duration</td>
<td>2.36</td>
<td>2.20</td>
<td>2.13</td>
<td>2.23</td>
</tr>
<tr>
<td>Expiratory Duration</td>
<td>±6.48</td>
<td>±0.38</td>
<td>±0.36</td>
<td>±0.31</td>
</tr>
</tbody>
</table>

Table 3D: Student's t scores (t) and significance of differences (p) in ventilation between the breath before occlusion (B1), the breath during occlusion (B2), the breath after occlusion (B3) and the average of these three breaths (BA). (n=62)

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>BA</th>
</tr>
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<tr>
<td>B1 t</td>
<td>-3.84</td>
<td>-2.97</td>
<td>-4.00</td>
<td></td>
</tr>
<tr>
<td>B1 p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>B2 t</td>
<td>0.49</td>
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<td></td>
</tr>
<tr>
<td>B2 p</td>
<td>-</td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>B3 t</td>
<td></td>
<td></td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>B3 p</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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</tbody>
</table>
Table 4D: Student’s t scores (t) and significance of differences (p) in inspiratory flow between the breath before occlusion (B1), the breath during occlusion (B2), the breath after occlusion (B3) and the average of these three breaths (BA). (n=62)

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td></td>
<td>-0.91</td>
<td>0.01</td>
<td>-0.55</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td></td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td>0.91</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td></td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td></td>
<td>-0.58</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td></td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

Table 5D: Student’s t scores (t) and significance of differences (p) in inspiratory duration between the breath before occlusion (B1), the breath during occlusion (B2), the breath after occlusion (B3) and the average of these three breaths (BA). (n=62)

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td></td>
<td>1.32</td>
<td>1.38</td>
<td>1.38</td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td></td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td>0.19</td>
<td>-0.83</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td></td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td></td>
<td>-1.09</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>----</td>
<td></td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
Table 6D: Student's t scores (t) and significance of differences (p) in expiratory duration between the breath before occlusion (B1), the breath during occlusion (B2), the breath after occlusion (B3) and the average of these three breaths (BA). (n=62)

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>B1</td>
<td>3.67</td>
<td></td>
<td></td>
<td>4.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>B2</td>
<td>1.80</td>
<td>-0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td></td>
<td>-3.53</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Table 7D: Student's t scores (t) and significance of differences (p) in total breath duration between the breath before occlusion (B1), the breath during occlusion (B2), the breath after occlusion (B3) and the average of these three breaths (BA). (n=62)

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>B1</td>
<td>2.60</td>
<td>2.91</td>
<td>3.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>0.95</td>
<td>-0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.95</td>
<td>-0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td></td>
<td>-2.29</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>
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