STUDIES IN VENTILATORY CONTROL IN EXERCISING HUMANS

A Thesis Submitted to the College of
Graduate Studies and Research
in partial fulfillment of the requirements
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University of Saskatchewan
Saskatoon, Canada.

By

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Saskatoon, Saskatchewan

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UNIVERSITY OF SASKATCHEWAN

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SUMMARY OF DISSERTATION

Submitted in partial fulfillment

of the requirement for the

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by

Bharath S. Krishnan

Physiology Graduate Program

University of Saskatchewan

Spring 1999

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ABSTRACT

Minute ventilation ($\dot{V}_E$, and its pattern) is the result of an interaction between the drive to breathe (from the respiratory controller) and the mechanical properties of the respiratory system. While there is abundant information about the chemoreceptor based control of exercise $\dot{V}_E$, the present studies were designed to examine the roles of other neuro-mechanical stimuli from the airways, lungs, chest wall, respiratory muscles and/or the limbs in healthy humans performing constant work-rate heavy exercise (CWHE) or maximal incremental exercise (MIE) on a cycle-ergometer. With increasing $\dot{V}_E$ during CWHE, there was a progressive increase in inspiratory (I) and a relatively greater increase in expiratory (E) muscle pressures (P_{mus}). Furthermore, the Total P_{mus} (I + E) - $\dot{V}_E$ and inspiratory tension · time index - $\dot{V}_E$ relationships were significantly linear, while post-inspiratory inspiratory activity decreased progressively throughout CWHE. However, when the load on all the respiratory muscles was significantly reduced (with flow-proportional mouth pressure assist) throughout CWHE, there was no effect on $\dot{V}_E$ (or breathing pattern) or other metabolic variables and on exercise performance. These results differ from the hyperventilatory response that results when airflow resistance is reduced with heliox (HeO_2) substituted for air as the breathing mixture. The results suggest that receptors from large and central airways play a major role in the mediation of the transient, but not the sustained $\dot{V}_E$ response to HeO_2 breathing during exercise. However, airway receptors do not appear to be involved in the mediation of $\dot{V}_E$ and breathing pattern responses during MIE, or affect the ventilatory and breathing pattern adaptations to added external deadspace during exercise. While some subjects developed spontaneous locomotor-respiratory coupling (LRC, manifesting as entrainment of breathing to pedalling frequency, coupling of I and/or E to limb movements) when pedalling freely (without imposed or fixed pedalling rates), LRC had no effect on $\dot{V}_E$ (or breathing pattern) control or metabolic variables throughout MIE. It is concluded that ventilatory control during exercise in humans, is the result of the integration of a variety of numerous and apparently "redundant" stimuli and is ultimately directed towards optimal gas exchange and maintenance of acid-base homoeostasis, while minimizing both respiratory muscle work and the oxygen cost of breathing.

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LIST OF ABBREVIATIONS

PRIMARY SYMBOLS

C - Concentration of gas in blood phase

F - Fractional concentration in the gas phase

f - frequency in general

P - Gas pressure in general

Q - Volume of blood

$\dot{Q}$ - Rate of blood flow

R - Respiratory exchange ratio in general

S - Saturation of hemoglobin with oxygen in percent

V - Gas volume in general (Pressure, temperature and water vapour tension are also to be specified

$\dot{V}$ - Gas volume per unit time; rate of gas flow

SECONDARY SYMBOLS (GAS PHASE)

A - Alveolar gas

B - Barometric

D - Dead space gas

E - Expired gas

I - Inspired gas

L - Lung

T - Tidal gas

SECONDARY SYMBOLS (BLOOD PHASE)

a - arterial blood (location specific)

c - capillary blood

v - venous blood (location specific)

$\bar{v}$ - mixed venous blood

OTHER SECONDARY SYMBOLS AND ABBREVIATIONS

ATPD - Ambient temperature, ambient pressure, dry conditions

ATPS - Ambient temperature, ambient pressure, saturated with water vapour

BTPS - Body temperature, ambient pressure, saturated with water vapour

STPD - Standard temperature (273 °K), standard pressure (760 mmHg), dry

$\overline{X}$ - Dash above any symbol used to indicate a mean value

$\dot{X}$ - Dot above any symbol used to indicate a rate

MORE SYMBOLS AND ABBREVIATIONS USED IN THE THESIS

θan, RC - Anaerobic threshold and respiratory compensation for metabolic acidosis

EELV, EILV - End-expiratory- and end-inspiratory lung volumes

FRC, VC, TLC - Functional residual, vital and total lung capacities

MVV, MVC - Maximum voluntary ventilation and maximal ventilatory capacity

$\dot{V}O_2$, $\dot{V}CO_2$, R - O_2 uptake, CO_2 output and respiratory exchange ratio

$\dot{V}O_{2,max}$, $\dot{W}max$ - Maximal oxygen uptake and maximal work rate

$\dot{V}I$, $\dot{V}E$ - Inspired and expired minute ventilation

$\dot{V}A$, $\dot{V}D$ - Alveolar and deadspace ventilation

Pa,CO_2, $P\overline{A},CO_2$, PET,CO_2 - Arterial, mean alveolar and end-tidal partial pressures of CO_2

VT, VD - Tidal volume and deadspace fraction of each breath

TI, TE, TT - Inspiratory, expiratory and total breath durations

TI/TT - Inspiratory duty-cycle

fb, fped, HR - Breathing, pedalling frequencies and heart rate

Pel, Pres, Pin - Elastic, resistive and inertial pressures on the chest wall (W) and lungs (L)

Pmus, $Pm_{0.1}$ - Respiratory muscle pressure and occlusion mouth pressure

PmusI, PmusE - Inspiratory and expiratory muscle pressures

mean PmusI/PcapI (%) - Inspiratory muscle tension · time index

PIIA, $Pmus_{IpI}$ - Post-inspiratory inspiratory (muscle) activity

LRC - Locomotor-Respiratory coupling

1. VENTILATORY REGULATION IN EXERCISING HUMANS - AN OVERVIEW

1.1. Introduction

The respiratory system is the first, and one of the most, important links in the chain of oxygen (O_2) transport to the tissues and working muscles. During the increased metabolic state of physical exercise, the rising O_2 consumption and carbon dioxide (CO_2) production by the working muscles necessitates a concomitant increase in O_2 delivery to and CO_2 removal from, these muscles. In addition to increasing O_2 transport and CO_2 removal, normal respiratory function also involves maintenance of acid-base homeostasis during exercise. While the normal physiologic response to exercise involves all the major body systems, this thesis will focus on respiratory system function and the ventilatory response during heavy exercise. Figure 1.1. summarizes the relative importance of the different cardio-respiratory adjustments

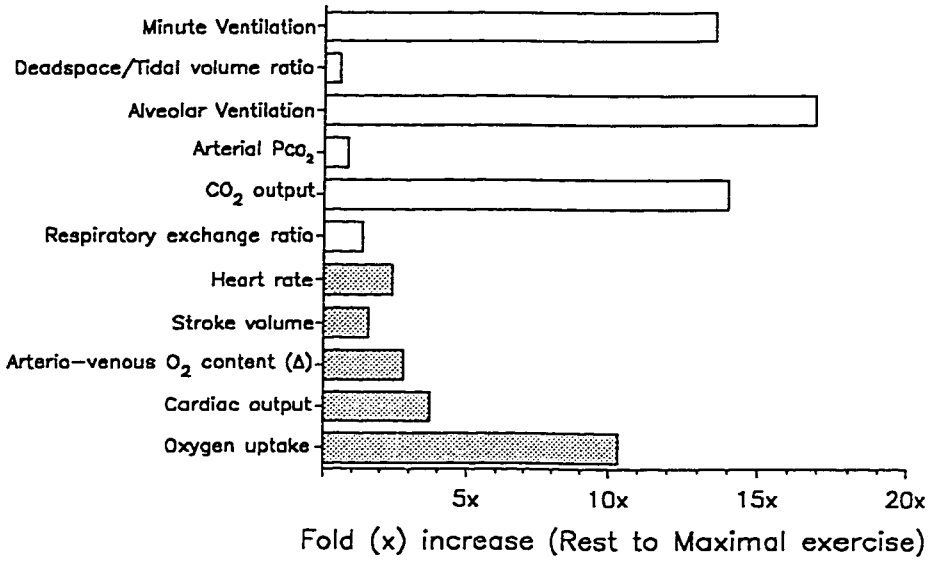

Figure 1.1. Cardio-respiratory responses during maximal exercise. [GALLAGHER, 1990].

during maximal exercise in a healthy subject and reveals that the significant increase (~10x) in O_2 uptake ($\dot{V}O_2$) from rest to maximal exercise is as a result of moderate increases in cardiac output ($\dot{Q}$, < 4x) and arterio-venous O_2 content difference ($\Delta(C_{a,O_2} - C_{\bar{v},O_2})$ < 3x). As the data also show [GALLAGHER, 1990], the dramatic increases in alveolar ventilation ($\dot{V}A$, > 17x) from resting values underscores the fact that at maximal exercise, the magnitude of increase of respiratory variables is much greater than that of the cardiovascular system variables. Both the capacity and efficiency of the respiratory pump in serving this increase in need, depend essentially on the interaction between respiratory muscle activity and mechanical properties of the components of the pump (conducting airways, lungs and chest-wall) and the control mechanisms that regulate their function during exercise. The increased ventilatory demands mean that airflow (both inspiratory and expiratory) needs to increase substantially for the maintenance of homeostasis. The energetic efficiency of the respiratory pump is however dictated by the magnitude of mechanical impedance to airflow, the determinants of which i.e., resistance and compliance of the lungs and chest wall, remain essentially unchanged during exercise [GRANATH *ET AL*, 1959; STUBBING *ET AL*, 1980; WHIPP AND PARDY, 1986]. Most of the available evidence suggests that the respiratory system in an untrained, healthy young adult at sea-level, is ideally designed to meet the ventilatory, gas exchange and acid-base homeostatic demands of even very heavy short-term exercise [DEMPSEY, 1986]. It is also currently accepted that in the average healthy human, maximal exercise or O_2 uptake capacity is determined chiefly by the "other links" in the chain of O_2 transport, *viz.* stroke volume, cardiac output and/or the oxidative capacity/perfusion of the working skeletal muscles [SALTIN & GOLLNICK, 1983; SALTIN, 1985; SALTIN AND STRANGE, 1992; SUTTON, 1992; LINDSTEDT AND HOPPELER, 1995; HOPPELER AND WEIBEL, 1998]. Thus, except in patients with lung disease and in some exceptionally fit athletes [DEMPSEY *ET*

AL, 1985; DEMPSEY AND FREGOSI, 1985], the respiratory system is considered "over-built" with respect to its O_2 transport function in most humans.

The respiratory system therefore forms part of a multi-faceted control system that is ultimately concerned with O_2 transport, CO_2 elimination and maintenance of blood-gas homeostasis. During exercise, this control system is involved not only in the generation of the appropriate (to the ventilatory need) output from the brain-stem respiratory neurons, but also ensuring that this neural output is ultimately transformed into mechanical output from the respiratory pump (muscles and chest wall) in the form of adequate alveolar ventilation and an energetically efficient breathing pattern.

Figure 1.2. provides a simple overview of the essential elements of this control system and the sequence of events that are involved in the translation of neural output ("drive") to mechanical output ("minute ventilation"). The increased drive to breathe might be as a result of acidosis, CO_2 inhalation, or more commonly, exercise. This drive is ultimately translated into airflow, through the major links in the respiratory pump *viz.* respiratory muscles, lungs and chest-wall and the airways and this translation is coordinated by two forms of feedback ("error correction"): **1)** a well documented chemical (medullary and carotid "chemoreceptors") feedback,

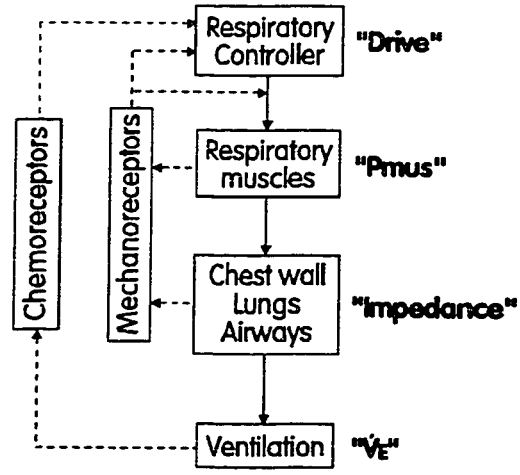

Figure 1.2. A simple overview of the respiratory control system.

conveying information about arterial blood gases and cerebral fluid acid-base status and **2)** a less well documented neuro-mechanical feedback from the respiratory pump itself ("mechanoreceptors"), from receptors that appear primarily to respond to variables related to amount of work done for each breath, e.g. the tension developed by the respiratory muscles and/or the degree of stretch in the chest wall and lung parenchyma and/or the pressure developed in the airways. Possible receptor types include those in the lung parenchyma and airways, muscle spindles and golgi tendon organs in intercostal muscles and diaphragm [COLERIDGE AND COLERIDGE, 1986; SHANNON, 1986]. These afferents may communicate directly to the brain stem or higher cortex (e.g. airway vagal afferents) or may project to reflex pathways in the phrenic nerves and the spinal cord (e.g. from muscle spindles and tendon organs). This sensory feedback could influence the pattern of recruitment of the respiratory muscles by affecting the output of the spinal motoneurons directly, or by changing the amplitude and pattern of the command signal to the respiratory muscles.

1.2. Determinants of the exercise ventilatory response.

It is well established that during exercise, the increase in minute ventilation is commensurate with the increasing rates of metabolic gas exchange and muscular effort. There is however a lack of consensus among researchers regarding the importance of each of the afore-mentioned components of the respiratory control system (figure 1.2) in ventilatory regulation during exercise. While there are many proposed control mechanisms, the conclusions drawn by different investigators from different experimental models are often contradictory and in some cases, mutually exclusive. However, the study of the ventilatory response to dynamic exercise performed under laboratory conditions (at sea level) with reference to pulmonary gas exchange and respiratory mechanical constraints, makes it possible to draw useful inferences regarding the underlying control mechanisms. As the increase in ventilation is needed not only to match metabolic gas exchange requirements of

exercise, but also to provide respiratory compensation for metabolic acidosis (see below), it is convenient to study the ventilatory response to exercise at levels below and above the effort at which metabolic acidosis occurs (anaerobic threshold, θ_{an}).

1.2.1. Chemical determinants.

During most of exercise, minute ventilation ($\dot{V}_E$) increases appropriately to match the increasing gas exchange requirements and to maintain arterial blood gas and acid-base homeostasis. Therefore, the temporal profiles of these variables *.viz.* oxygen uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), arterial blood-gases (P_{a,O_2}, P_{a,CO_2}) and acid-base status, are a significant framework within which the magnitude and appropriateness of the $\dot{V}_E$ response during exercise can be judged [WHIPP, 1981]. During exercise at moderate work rates, i.e., below the anaerobic threshold (θ_{an}), arterial pH (pH_a) can be maintained constant, as long as P_{a,CO_2} is regulated by an appropriate increase in alveolar ventilation ($\dot{V}_A$) commensurate to the level of CO_2 production ($\dot{V}CO_2$). In an ideal lung (with no ventilation-perfusion ($\dot{V}/\dot{Q}$) inequalities, with no diffusion limitations and with no right-to-left shunt), alveolar P_{CO_2} (P_{A,CO_2}) equals P_{a,CO_2} and the relationship between $\dot{V}CO_2$ and $\dot{V}_A$ is described thus:

$$P_{A,CO_2} = 863 \cdot \frac{\dot{V}CO_2}{\dot{V}_A} \qquad (1.1)$$

Equation 1.1 suggests that with P_{a,CO_2} as the regulated variable, the $\dot{V}_A$ - $\dot{V}CO_2$ relationship is linear with a slope of $863/P_{a,CO_2}$ and passes through the origin. The constant 863 is derived from the temperature, pressure and water vapour corrections that result from the conventions for reporting metabolic rate at standard temperature and pressure, dry (STPD) and ventilation at body temperature and pressure, saturated (BTPS). It follows then that the lower the P_{a,CO_2} set-point, the greater must be the increase in $\dot{V}_A$, as work rate and $\dot{V}CO_2$ increase during exercise. The quantitative temporal relationships between the different variables that determine the magnitude of $\dot{V}_A$ during exercise are summarized in figure 1.3.

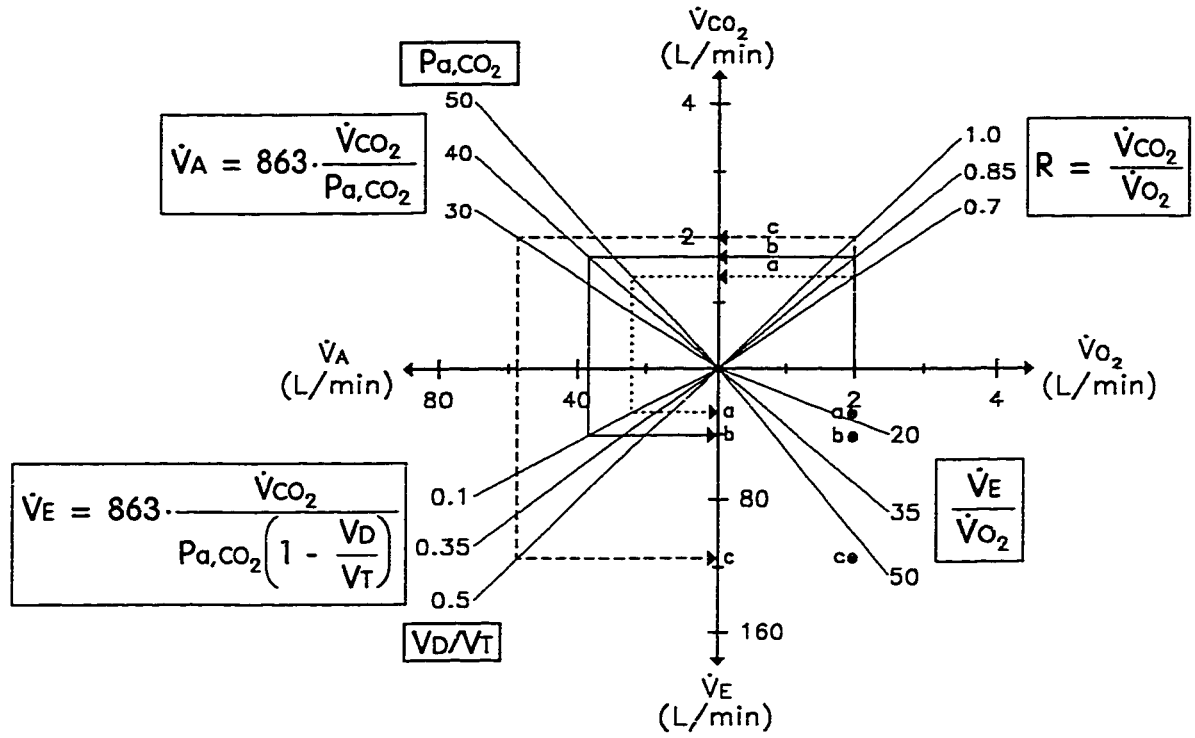

Figure 1.3. Chemical determinants of exercise ventilation. The influence of R, P_{a,CO_2} and V_D/V_T on $\dot{V}_E$ during exercise. For a given $\dot{V}_{O_2}$, $\dot{V}_E$ can be significantly altered from a normal response (solid line, arrow "b") with a particular combination of determining variables leading to a reduced (dotted line, arrow "a") or a markedly high (dashed line, arrow, "c") response. [WHIPP AND PARDY, 1986]. *(see text for details)*

However, as total ventilation ($\dot{V}_E$) includes not only alveolar ventilation but also dead space ventilation ($\dot{V}_D$) the relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ becomes:

$$\dot{V}_E = 863 \cdot \frac{\dot{V}_{CO_2}}{P_{a,CO_2}} + \dot{V}_D \qquad \textbf{(1.2)}$$

$\dot{V}_D$ is determined by the product of physiological dead space (V_D) and breathing frequency. As the $\dot{V}_E$ response to moderate exercise has been shown to be linearly related to increases in $\dot{V}_{CO_2}$ [CASABURI *ET AL*, 1978], V_D must either remain constant, or increase linearly with exercise. The latter is usually the case with increasing exercise levels. Another variable of importance is the dead space to tidal volume ratio (V_D/V_T), which is the dead space fraction of each breath, thus:

$$\dot{V}E = 863 \cdot \frac{\dot{V}CO_2}{Pa,CO_2\left(1 - \frac{VD}{VT}\right)} \qquad \textbf{(1.3)}$$

Equation 1.3 suggests that the linear $\dot{V}E$ - $\dot{V}CO_2$ relationship during moderate exercise is possible because VD/VT does not remain constant but decreases progressively during exercise. Equation 1.3 also clearly underscores the importance of each of the determinant variables ($\dot{V}CO_2$, Pa,CO_2 and VD/VT) in the regulation of $\dot{V}E$ over the range of work rates (sub-θan) over which Pa,CO_2 can be regulated. All the above equations (1.1 - 1.3) also emphasize, that the magnitude of increase in $\dot{V}E$ to effect a given decrement in Pa,CO_2 to provide respiratory compensation for the metabolic acidosis that occurs at supra-θan work rates, depends critically on the $\dot{V}CO_2$ at which the acidosis occurs. Thus the increase in $\dot{V}E$ to effect a 10 mmHg reduction in Pa,CO_2 is relatively small at low metabolic rates and becomes progressively greater as metabolic rates increase [WHIPP *ET AL*, 1984]. Given a similar Pa,CO_2 set point (e.g. 40 mmHg), the compensatory hyperpnea in a highly fit subject (with $\dot{V}CO_2 > 5\ L \cdot min^{-1}$) is significantly greater than that which is required in a sedentary subject, in whom metabolic acidosis occurs at relatively lower work rates (at $\dot{V}CO_2 < 2\ L \cdot min^{-1}$).

The maintenance of arterial acid-base homeostasis i.e. arterial H^+ (pH_a) depends on Pa,CO_2, the physical properties of CO_2 and the bicarbonate $[HCO_3^-]_a$ levels thus:

$$pHa = pK' + \log\left(\frac{[HCO3^-]a}{\alpha \cdot Pa,CO_2}\right) \qquad \textbf{(1.4)}$$

where α is the solubility constant of CO_2 in blood and K' is the apparent dissociation constant (pK' of human blood = 6.1). Under conditions when $[HCO_3^-]_a$ does not change, i.e. mild or moderate exercise, pH_a will remain constant only if Pa,CO_2 remains unaltered during exercise. During heavy and severe exercise, the metabolic acidosis that ensues results in significant reductions in $[HCO_3^-]_a$. The subsequent fall

in pH_a is then constrained by a compensatory fall in P_{a,CO_2}. However, a full respiratory compensation of the metabolic acidosis is never observed, and if at all has been shown to occur with only relatively mild degrees of metabolic acidosis [WASSERMAN *ET AL*, 1967].

During mild and moderate exercise, the magnitude of CO_2 evolved reflects the level of metabolic (mitochondrial) CO_2 formation accurately. However at higher work rates which result in increased lactate $[La^-]_a$ levels, the CO_2 evolved is derived from two additional sources. Firstly, a majority (> 90%) of the additional CO_2 is released as a result of lactate buffering by bicarbonate. Secondly, if the increases in $\dot{V}_E$ were solely dependent on metabolically released CO_2 at high work rates, it would clearly be inappropriate for the total CO_2 load and the increase in P_{a,CO_2} would then contribute to a respiratory acidosis in addition to the metabolic acidosis. If the $\dot{V}_E$ increases during exercise depended exclusively on the total CO_2 flow to the lung, there would be no respiratory compensation for the metabolic acidosis. In order to the regulate pH_a at higher work rates, P_{a,CO_2} is then lowered by the process of hyperventilation (CO_2 "blow-off"), thus contributing to the total CO_2 evolved during heavy and severe exercise.

Ventilatory control and pH_a regulation during exercise therefore depend on the simultaneous interaction of the 3 determinant variables, *viz.* $\dot{V}_{CO_2}$, P_{a,CO_2} and V_D/V_T. Figure 1.3 [WHIPP AND PARDY, 1986] illustrates the simultaneous interaction of these variables in three subjects (a, b, c), who are exercising at the same metabolic rate (oxygen uptake, $\dot{V}_{O_2} = 2\ L \cdot min^{-1}$). Subject 'b' (solid line) is a normal subject, who metabolizes a mixed substrate (carbohydate and fatty acid) has a respiratory quotient (metabolic exchange ratio, RQ) and a respiratory exchange ratio (pulmonary exchange ratio, $R = \dot{V}_{CO_2}/\dot{V}_{O_2}$, top-right quadrant, figure 1.3) of 0.85 (and thus a $\dot{V}_{CO_2}$ of $1.7\ L \cdot min^{-1}$) and requires a $\dot{V}_A$ of $\sim 37\ L \cdot min^{-1}$ to maintain a normal P_{a,CO_2} of about 40 mmHg (top-left quadrant, figure 1.2). Assuming a normal V_D/V_T ratio of 0.1

at these work intensities [JONES *et al*, 1966, HIGGS *et al*, 1967], $\dot{V}_E$ would be about ~41 L · min^{-1} (bottom-left quadrant, figure 1.3). Subject "a" (dotted line) on the other hand metabolizes free fatty acids (R = 0.7) and assuming a moderate hypoventilation (P_{a,CO_2} = 50 mmHg), requires a $\dot{V}_A$ of ~24 L · min^{-1} and with a V_D/V_T of 0.1, requires a $\dot{V}_E$ of ~27 L · min^{-1}. Subject "c" represents a patient with lung disease (e.g. Chronic Obstructive Pulmonary Disease, COPD) with a P_{a,CO_2} of 30 mmHg and an elevated V_D/V_T of 0.5, both of which (along with the elevated $\dot{V}_{CO_2}$ due to R = 1) contribute to the $\dot{V}_E$ requirements in excess of 110 L · min^{-1} for this subject. Thus, while it is possible to reliably predict the O_2 requirements for any subject (based on body mass), it is impossible to predict with any degree of precision, the $\dot{V}_E$ requirements and thus the ventilatory equivalent for O_2 (●, $\dot{V}_E/\dot{V}_{O_2}$, bottom-right quadrant) in subjects with impaired lung function, without prior knowledge of the effects of the determinants of ventilation, i.e. $\dot{V}_{CO_2}$, P_{a,CO_2} and V_D/V_T. The significant differences in ventilatory requirements among the three subjects also underscores the importance of the determinants of exercise $\dot{V}_E$ and the degree to which the elicited exercise responses may encroach (or exceed) on the metabolic and mechanical limits of the system. This is important for e.g. in patients with COPD whose maximum attainable $\dot{V}_E$ is reduced significantly, or in fit athletes who are able to achieve very high metabolic rates.

1.2.2. Mechanical determinants.

The respiratory system has two major functions: **1)** to provide for adequate gas exchange and **2)** as an energetically efficient pump that causes transfer of air in and out of the lungs with each breath. Under resting conditions, the respiratory pump is required to work at ~5% of its maximal capacity (maximal voluntary ventilation, MVV), moving ~500 - 750 ml/breath at ~10 - 15 breaths a minute. This requires ~1 - 2 % of the total body O_2 consumption (~2 - 3 ml/min). However, during exercise, the increasing metabolic demands require that the respiratory pump move larger volumes of gas with each breath and with more frequent breaths. The

ultimate response of the ventilatory pump during dynamic exercise is then the result of a complex integration of changes in tidal volume and breathing frequency. These in turn are influenced by the pressures generated by the respiratory muscles, their O_2 supply and consumption, the power output and energetic efficiency of all the active respiratory muscles.

Minute ventilation increases in the first breath at the onset of constant load exercise and continues to increase exponentially to a steady-state plateau [PEARCE AND MILLHORN, 1977; WASSERMAN *ET AL*, 1981; PARDY *ET AL*, 1984], the amplitude of which depends on exercise intensity. However, there is no ventilatory steady-state at high-intensity exercise levels. When exercise intensity increases incrementally (e.g. in 4 - 5 minute increments), minute ventilation increases in close proportion to the rate of CO_2 production, until the work rate at which metabolic acidosis occurs is reached. As discussed later, at work rates above this level and up to maximum, the ventilatory response to exercise exceeds that of the rate of CO_2 production, as it is influenced significantly by the effect of H^+ (and other stimuli) on the peripheral chemoreceptors. The close proportionality between $\dot{V}_E$ and $\dot{V}_{CO_2}$ persists for a longer duration during incremental exercise with shorter duration work rate increments (e.g. 1 minute increments). While it is abundantly clear that exercise hyperpnea depends on both chemical and neural determinants, the individual quantitative contributions of these components have not been precisely determined. The importance and the specific roles of some of the chemical determinants of exercise $\dot{V}_E$ were discussed in the previous section.

The significance of the static mechanical properties of the respiratory pump is immediately apparent in the context of increasing ventilation during exercise. This is caused both by an increase in tidal volume (V_T) and breathing frequency (f_b). While the theoretical possible maximal V_T that an exercising individual can utilize is his vital capacity (VC) [OGILVIE *ET AL*, 1955; OLAFSSON AND HYATT, 1969; JENSEN *ET AL*, 1980;

McPARLAND *ET AL*, 1991] and while it has been suggested that the theoretical maximal f_b in humans is about 300 - 400 breaths · min^{-1} [OTIS AND GUYATT, 1968], most normal humans increase their V_T to a maximal value of ~50% - 60% VC and f_b to about ~50 - 60 breaths · min^{-1} during heavy exercise [GALLAGHER AND YOUNES, 1986; BLACKIE *ET AL*, 1991]. It is clear that given the significant constraints on exercise ventilation (i.e. sufficient alveolar gas exchange and maintenance of blood-gas and acid-base homeostasis), the choice of a breathing pattern (i.e. a combination of V_T and f_b) at any level of exercise is contingent both on the minimizing the work of breathing and respecting the mechanical constraints of the respiratory system [MILIC-EMILI *ET AL*, 1960, 1962; MEAD *ET AL*, 1967; OLAFSSON AND HYATT, 1969; DEMPSEY *ET AL*, 1977, 1979, 1980; JENSEN *ET AL*, 1980; STUBBING *ET AL*, 1980].

The two most important determinants of the ventilatory response to exercise and mechanical breathing pattern are: **1)** The mechanical properties of the respiratory pump and its components (chest wall and the lungs); **2)** The mechanical properties of the conducting airways. The former is described by the pressure-volume (P - V) relationships in the respiratory system and the latter by the maximal inspiratory and expiratory flow-volume relationships, which indirectly describe the pressure-flow relationship in the airways.

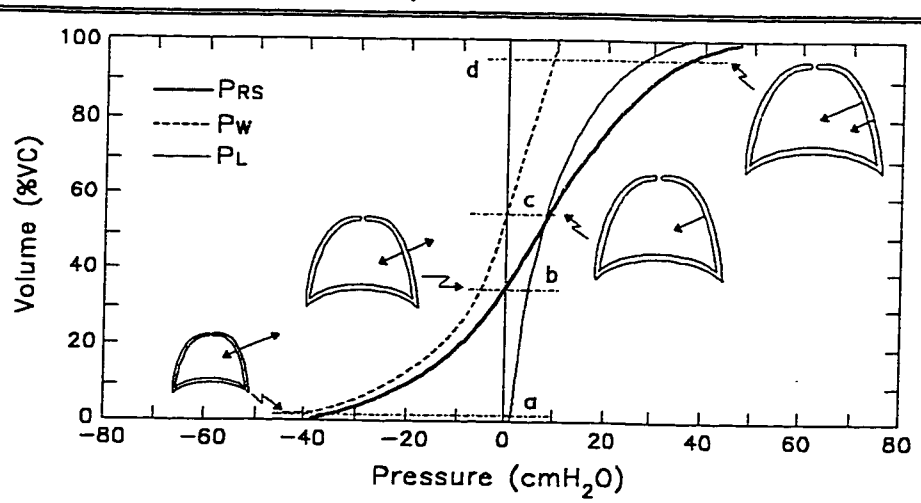

Figure 1.4. **Static pressure - volume relationships in the respiratory system.** [FENN AND RAHN, 1964].

Figure 1.4 describes the static P - V relationships [FENN AND RAHN, 1964] of the lungs (P_L, thin line), chest wall (P_W, dashed line) and the respiratory system ($P_{RS} = P_L + P_W$, thick line). The P - V relationship of the respiratory pump at any lung volume (%VC, vital capacity) is the resultant of the elastic forces across the chest wall and the lungs each of which is acts in the opposite direction to that of the other. At resting lung volume at end expiration (FRC, functional residual capacity, point "b"), these pressures are equal and opposite (the arrows in figure 1.4 indicate both the direction and magnitude) and thus $P_{RS} = 0$. As lung recoil is minimal at very low lung volumes (i.e. at RV, residual volume, point "a"), almost all the pressure across the respiratory system is accounted for by P_W. In contrast, at high lung volumes (i.e near total lung capacity, TLC, point "d"), P_{RS} is predominantly due to significant lung recoil and partly due to chest wall recoil. Figure 1.4 emphasizes the fact that at lung volumes between 30% VC and 75% VC, the P - V relationships of both the lungs and chest wall (and of the respiratory system) are significantly linear and thus changes in V_T within this range are possible with small and yet energetically efficient changes in pressure. However, the P - V relationship of the respiratory system at both lung volume extremes is significantly non-linear, as the lung and chest wall attain their elastic limits at high and low lung volumes respectively, thus contributing to a volume limit for increasing V_T.

At low levels of exercise (both incremental and constant-load protocols) an increase in $\dot{V}_E$ is possible with concomitant increases in both V_T and f_b [HEY *ET AL*, 1966; GALLAGHER *ET AL*, 1987]. At higher levels of exercise, further increases in $\dot{V}_E$ are predominantly due to an increase in f_b, as V_T remains the same or changes very little [CLARK *ET AL*, 1983; GALLAGHER *ET AL*, 1987]. A tachypneic breathing pattern is usually seen during heavy exercise. A further increase in $\dot{V}_E$ is possible in some subjects with a significant increase in f_b with a progressive fall in V_T [JENSEN *ET AL*, 1980; PEARCE AND MILLHORN, 1977; GALLAGHER *ET AL*, 1986]. The interrelationships between increasing

minute ventilation and its components (V_T, f_b and breath times) in normal subjects are described during both maximal incremental (solid line) and constant load exercise (dotted line) in figure 1.5 [SYABBALO *ET AL*, 1994].

With the increasing $\dot{V}_E$ levels of exercise, a progressive shortening of both inspiratory (T_I) and expiratory (T_E) durations contribute to the progressive increase in f_b. However, as figure 1.5 reveals, there is a greater fractional decrease in T_E than T_I such that the inspiratory duty cycle (T_I/T_T) increases from ~0.4 (resting value) to ~0.5 or more during maximal exercise [CLARK *ET AL*, 1983; MCPARLAND *ET AL*, 1992; SYABBALO *ET AL*, 1994]. As shown in the figure, normal humans show a 3 - 5 fold increase in V_T from rest to maximal exercise and maximal exercise V_T does not usually exceed 60% of VC. This increase in V_T is due a decrease in end-expiratory lung volume (EELV) and an increase in end-inspiratory lung volume (EILV). It has been shown that EELV begins to fall even with a minor increase in $\dot{V}_E$ at the start of exercise [YOUNES AND KIVINEN, 1984; HENKE *ET AL*, 1988], from resting levels (FRC) and this fall precedes the increase in

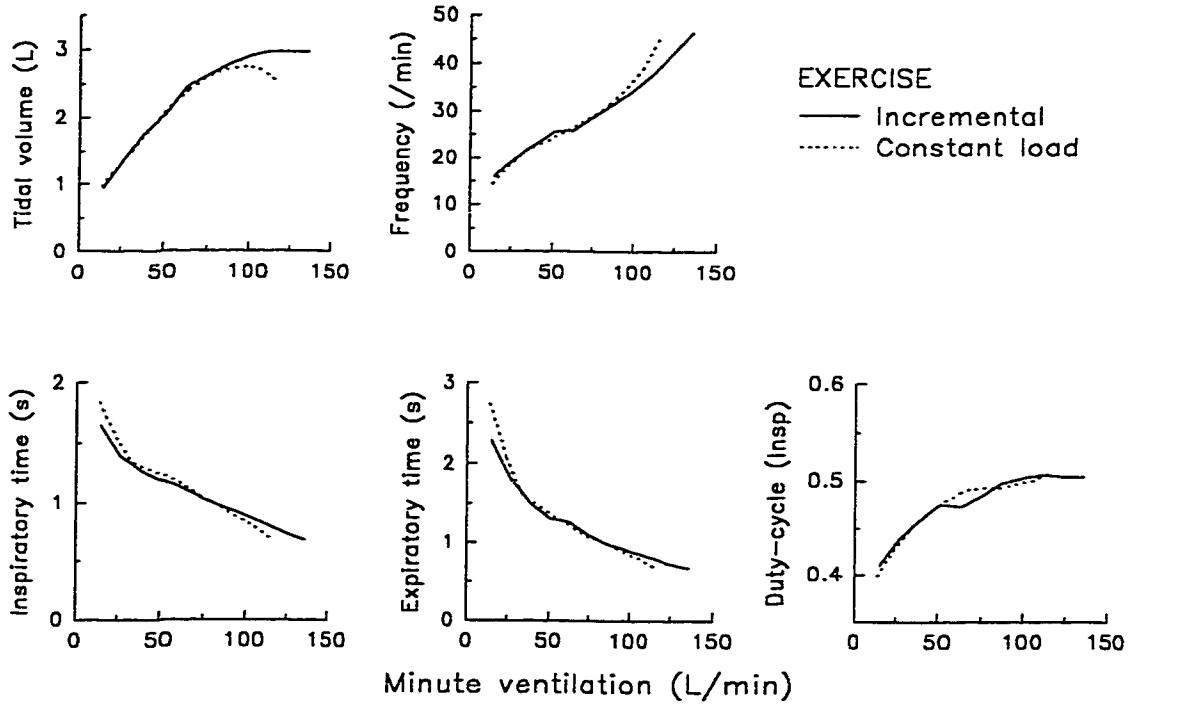

Figure 1.5. Mechanical determinants of exercise ventilation.
[SYABBALO *ET AL*, 1994]

EILV with loadless pedalling [BABB AND RODARTE, 1991]. After the initial fall at the start of exercise, data from several studies show that EELV usually stabilizes at a new level [YOUNES AND KIVINEN, 1984; HUSSAIN *ET AL*, 1985; CHA *ET AL*, 1987; GALLAGHER AND YOUNES, 1989; JOHNSON *ET AL*, 1992]. Further increases in V_T are due to increases in EILV alone.

While EELV falls at the start of exercise and remains below resting EELV position (functional residual capacity, FRC) through most of moderate exercise, it has been shown to increase towards or above FRC at higher exercise levels. This is as a consequence of expiratory flow limitation [JOHNSON *ET AL*, 1991; 1992; PELLIGRINO *ET AL*, 1993], a phenomenon by which airways are dynamically compressed at low lung volumes and have reached their capacity for effective flow generation. Furthermore, the relative greater fall in T_E results in a greater increase in mean expiratory flow (V_T/T_E) from rest to maximal exercise than the increase in mean inspiratory flow (V_T/T_I).

The maximum ventilatory capacity (MVC) represents the highest level of $\dot{V}_E$ that a subject can produce at any lung volume and is ultimately determined by the boundaries of the maximum inspiratory and expiratory flow - volume ($\dot{V}$ - V) relationships in the respiratory system [JENSEN *ET AL*, 1980; MCPARLAND *ET AL*, 1991]. Figure 1.6 summarizes the relationships between exercise tidal $\dot{V}$ - V loops and that of the maximal $\dot{V}$ - V boundaries in one subject. As seen in figure 1.6, the maximal $\dot{V}$ - V loops represent the highest inspiratory or expiratory flow (MIF and MEF) that can be generated at any given operating lung volume. For a given V_T therefore, MVC can be achieved over a range of lung volumes (within the VC) that can maximize MIF and MEF. Furthermore as both MIF and MEF are maximal only over a limited range of volumes, it results that breathing with a larger V_T would include ranges of lung volumes associated with lower MIF and MEF (i.e. a lower MVC) than would breathing with a smaller V_T [MCPARLAND *ET AL*, 1991]. Many studies suggest that this is true, i.e. breathing with V_T values greater than 50% of VC results in a reduction of MVC [BERNSTEIN *ET AL*, 1952; JENSEN *ET AL*, 1980]. This decline in maximal $\dot{V}_E$ generation with

increasing V_T values, places a mechanical limit on breathing pattern at the high $\dot{V}_E$ levels of heavy exercise. While both V_T and f_b increase simultaneously at low and moderately high levels of exercise, indefinite increases in V_T are pre-empted by the mechanical limitation of maximal $\dot{V}$ - V envelope, i.e. further increases in $\dot{V}_E$ are not possible with larger V_T breaths. Any further increase in $\dot{V}_E$ is possible therefore by increases in f_b, i.e. a tachypneic breathing pattern.

The progressively increasing mechanical constraints posed by the maximal $\dot{V}$ - V boundaries are quite evident from the data shown in figure 1.6. Data (from one subject) shown are from rest (thick solid line), start of exercise (dotted line), during moderate exercise (thin dashed line) and at end exercise (thin solid line). The tidal exercise loops are positioned with respect to the subject's VC (TLC - RV) and the resting loop is positioned at the subject's measured FRC. It is evident that with progressively increasing exercise levels, $\dot{V}_E$ increases are possible with a

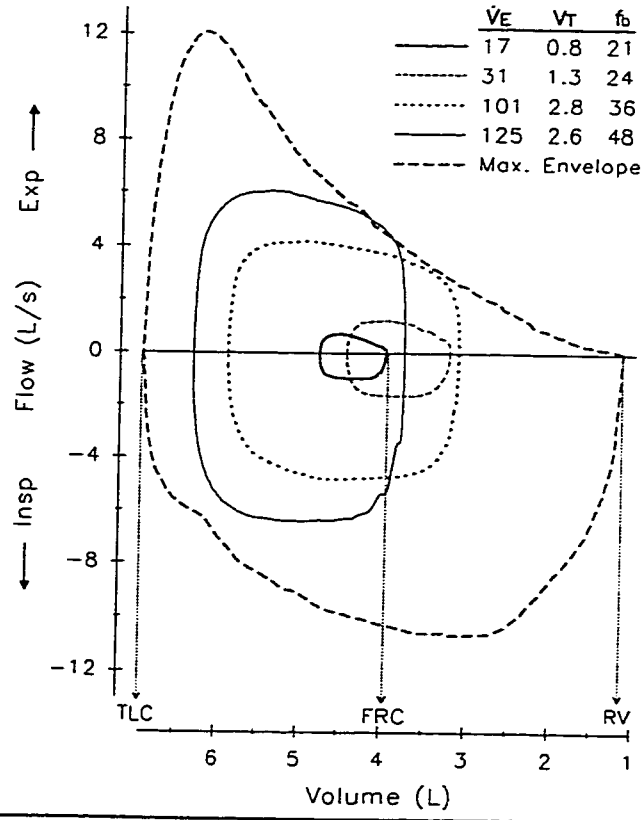

Figure 1.6. Resting, maximal and exercise tidal flow - volume relationships.

simultaneous increase in both V_T and f_b until the maximal expiratory flow is limited by the expiratory flow - volume boundary ($\dot{V}_E > 100\ L \cdot min^{-1}$). Further increases in $\dot{V}_E$ were possible in this subject only with an increase in EELV, thus moving the tidal loop away from the flow limiting segment. As figure 1.6 shows, along with an increase in EELV (to offset the expiratory flow-limitation) V_T in this subject fell slightly, both of which enable him to achieve higher expiratory flow rates, and thus a higher $\dot{V}_E$.

1.3. Ventilatory response in different exercise domains.

The inter-relationships among the various determinants of exercise $\dot{V}_E$ are valid for different forms of exercise. Arterial blood gas and acid-base homeostasis is preserved over a wide range of steady-state work rates, i.e. as long as exercise is performed without lactic acidemia. Therefore, at least during moderate exercise, the characteristics of the $\dot{V}_E$ and gas exchange responses are useful indicators of underlying regulatory mechanisms. However, as metabolic acidosis significantly influences both the ventilatory and gas exchange responses during heavy exercise, it is important to distinguish between the $\dot{V}_E$ (and gas exchange) response to exercise at work rates below and above the threshold at which a sustained metabolic acidosis occurs (anaerobic threshold, θ_{an}). Ventilatory response can thus be examined at two different exercise intensities (moderate or sub-θ_{an} and heavy or supra-θ_{an}).

1.3.1. Moderate (sub-θ_{an}) exercise.

At the onset of exercise of moderate intensity, $\dot{V}_E$ increases on the first breath [KROGH AND LINDHARD, 1913; D'ANGELO AND TORELLI, 1971; WHIPP *ET AL*, 1971] and changes in inspiratory or expiratory flow profiles are apparent within the first respiratory half-cycle [JENSEN *ET AL*, 1971; WHIPP *ET AL*, 1971; PAULEV, 1973). $\dot{V}_E$ then remains approximately constant at this new value for about 15 - 20 s and then increases thereafter in exponential fashion towards its steady-state with a time-constant (τ) of about 65 - 75 s [BROMAN AND WIGERTZ, 1971; WIGERTZ, 1971; LINNARSSON, 1974; CASABURI *ET AL*, 1978]. Based on the dynamics of the $\dot{V}_E$ response at the start of and in the early

part of moderate exercise, it is convenient to study the response of the ventilatory and gas exchange variables in three temporal domains: **1) Phase 1** - characterized by the rapid initial increase and the short subsequent plateau (ϕ_1); **2) Phase 2** - the slow rise to steady state (ϕ_2); and **3) Phase 3** - the steady state itself (ϕ_3). Figure 1.7 [WHIPP, 1981], schematically illustrates the relative changes (Δ%) in both the ventilatory and gas exchange variables at the start of moderate exercise from rest (top panel) or mild exercise (0 Watts, middle panel). Figure 1.7 also illustrates the temporal course of arterial blood gases (P_{a,CO_2}, P_{a,O_2}) in these three temporal domains (bottom panel).

Phase 1: This phase lasts from the onset of exercise to when the gas tensions in the mixed venous blood entering the pulmonary capillaries begin to change, as a result of altered tissue metabolic rate. The abrupt increases in $\dot{V}O_2$ and $\dot{V}CO_2$ that occur in ϕ_1 have been attributed to concomitant increases in pulmonary blood flow ($\dot{Q}$) [KROGH AND LINDHARD, 1913; WHIPP *ET AL*, 1982; CASABURI *ET AL*, 1989; MIYAMOTO, 1989]. $\dot{V}E$ also increases abruptly and in close proportion to the gas exchange responses and therefore alveolar gases remain stable for about 15 - 20 s [JENSEN, 1972; CASABURI *ET AL*, 1978; WHIPP *ET AL*, 1982; MIYAMOTO, 1989]. The abrupt changes in $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$

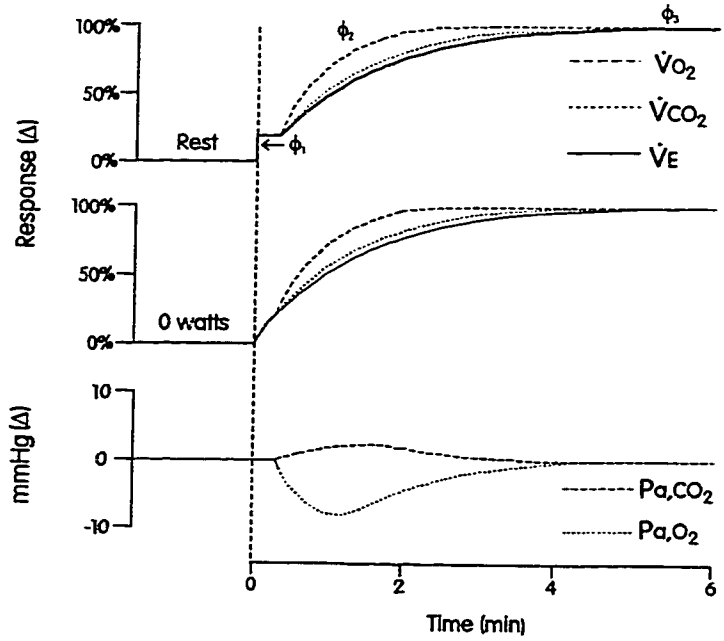

Figure 1.7. Dynamics of ventilation at the start of exercise. [WHIPP, 1981].

however are noted only at the rest → moderate exercise transition and not when exercise begins from a background of mild exercise [BROMAN AND WIGERTZ, 1971; CASABURI *ET AL*, 1978; WHIPP *ET AL*, 1982], or from rest in the supine position [KARLSSON *ET AL*, 1975; WEILER-RAVELL *ET AL*, 1982]. The similar increase of $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ suggests that the $\dot{V}E$ increases in ϕ_1 are closely coupled to increases in $\dot{Q}$. The $\dot{V}E$ increase thus correlates with the increase in stroke volume due to increased venous return as a result of increased peripheral and respiratory muscle activity [ÅSTRAND, 1970]. However, at the start of moderate exercise in supine position, or from a background of light prior exercise (middle panel, figure 1.7), there is no abrupt increase in $\dot{V}E$, as stroke volume has already increased to its constant exercise level.

Phase 2: This more prominent phase is characterized by altered pulmonary blood flow and changes in mixed venous blood composition, both exerting significant influences on rates of pulmonary gas exchange. However, unlike in ϕ_1, the kinetics of $\dot{V}O_2$ and $\dot{V}CO_2$ in ϕ_2 are considerably different: $\dot{V}O_2$ increases exponentially with a τ of 30 - 40 s, while the $\dot{V}CO_2$ increase is slower (τ = 50 - 60 s, figure 1.3) [LINNARSSON, 1974; HUGHSON AND MORRISSEY, 1982; WHIPP *ET AL*, 1982; MIYAMOTO, 1989]. As the rates of O_2 consumption and CO_2 production in the working muscles are similar, the dissociation of the $\dot{V}O_2$ and $\dot{V}CO_2$ kinetics in ϕ_2 is due mostly to the influence of intervening body CO_2 stores, i.e. some of the metabolically produced CO_2 is stored [JONES AND JURKOWSKI, 1979; WHIPP, 1981; WASSERMAN AND CASABURI, 1991; WHIPP AND WARD, 1991]. The time course of $\dot{V}E$ in ϕ_2 is similar but slightly slower than that of $\dot{V}CO_2$ and as a result $\dot{V}E$ changes (55 - 65 s) are much slower than the changes in $\dot{V}O_2$ [LINNARSSON, 1974; HUGHSON AND MORRISSEY, 1982; WHIPP *ET AL*, 1982; MIYAMOTO, 1989]. This dissociation between $\dot{V}E$ and $\dot{V}O_2$ kinetics results in a transient fall in arterial P_{O_2} (P_{a,O_2}, bottom panel figure 1.7) during ϕ_2 [YOUNG AND WOOLCOCK, 1978; OLDENBURG *ET AL*, 1979). The similarity in the temporal course of $\dot{V}E$ and $\dot{V}CO_2$ during ϕ_2 however, while underscoring the close link between the metabolic ($\Delta \dot{V}CO_2$) and

ventilatory ($\Delta \dot{V}_E$) changes during exercise, results in only small changes in arterial P_{CO_2} (P_{a,CO_2}, bottom panel, figure 1.7) [WHIPP AND WARD, 1991].

Phase 3: This steady state of the response is generally considered to be as a result of the summation of the control mechanisms in both ϕ_1 and ϕ_2. Both pH_a and arterial blood gases are thought to be maintained at or close to resting levels [WHIPP, 1981; DEMPSEY *ET AL*, 1984; FORSTER AND PAN, 1991], and there is a close proportionality between $\dot{V}_E$ and $\dot{V}_{CO_2}$ throughout ϕ_3. Furthermore the $\dot{V}_E$ - $\dot{V}_{CO_2}$ relationship does not appear to depend on the type of exercise undertaken, as square-wave, constant load and rapidly-incrementing profiles, all result in the same linear relationship [WASSERMAN *ET AL*, 1977; WHIPP, 1981].

Figure 1.8 summarizes the inter-relationships between the different ventilatory variables throughout incremental exercise (25 watts/min) to exhaustion, in one

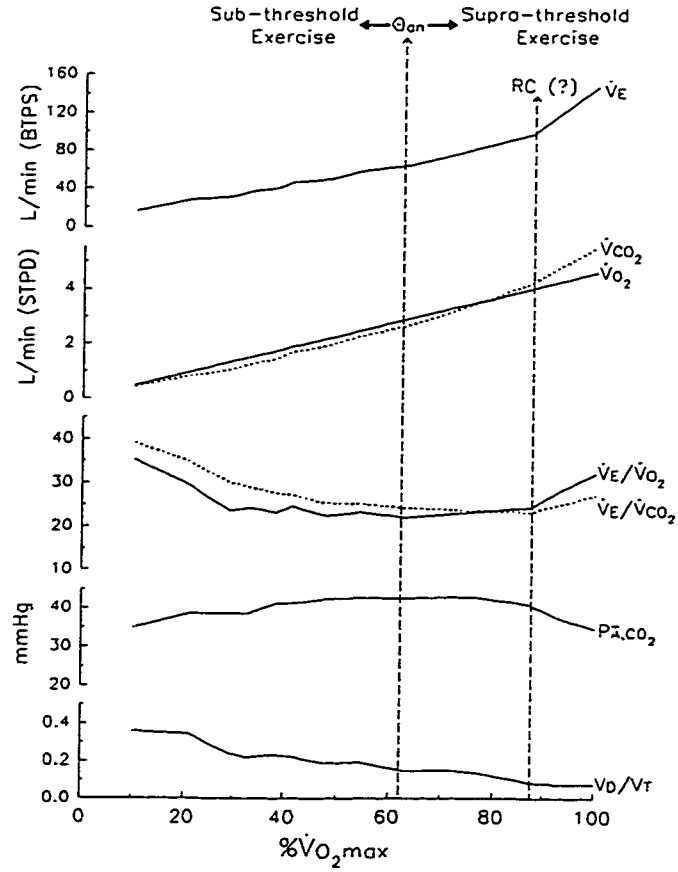

Figure 1.8. Ventilatory and metabolic responses in different exercise domains.

subject. Data from both moderate (sub-θ_{an}) and heavy (supra-θ_{an}) exercise are shown. It can be seen how the $\dot{V}_E$ response at sub-θ_{an} work loads is closely proportional to $\dot{V}_{CO_2}$. However, the ventilatory equivalent for CO_2 ($\dot{V}_E / \dot{V}_{CO_2}$) falls not linearly, but hyperbolically with increasing work rates. This is due to the hyperbolic reduction in the V_D/V_T ratio during moderate exercise (*vide.* equation 1.3) [DAVIS *ET AL*, 1978; WARD AND WHIPP, 1980].

Figure 1.8 also reveals that arterial P_{CO_2} (shown as $P_{\bar{A},CO_2}$), is maintained at or close to resting levels (~40 mmHg) during moderate exercise. However, some subjects (as in this example) hyperventilate on being connected to the mouth-piece of the breathing apparatus. Therefore the magnitude of $\dot{V}_E$ increase at the start of and in early exercise in proportion to the increased metabolic requirement, is relatively smaller, due to the initial hyperventilation. Arterial P_{CO_2} therefore increases slightly with exercise under these conditions (note the initial rise in $P_{\bar{A},CO_2}$ in early exercise). The slight change in $P_{\bar{A},CO_2}$ is therefore a consequence of the ventilatory change and not a cause of it [WHIPP, 1981].

1.3.2 Heavy (supra-θ_{an}) exercise.

Figure 1.8 also describes the temporal course of ventilatory and gas exchange variables during exercise above θ_{an}. The ventilatory response to exercise at supra-θ_{an} work rates is significantly influenced by sustained metabolic acidemia that occurs at these work rates. The rate of increase in $\dot{V}_E$ at these work intensities becomes highly non-linear and steady states are usually not attained. The rates of CO_2 clearance are also augmented, as additional CO_2 is being produced as a result of lactate buffering by sodium bicarbonate both in the working muscles and in the blood. The rate of decline in $[HCO_3]^-$ levels [OWLES, 1930] has been shown to mirror that of the rate of increase in serum lactate levels [WASSERMAN *ET AL*, 1967; BEAVER *ET AL*, 1986A; WASSERMAN AND CASABURI, 1991]. The relatively greater increase in $\dot{V}_{CO_2}$ (than $\dot{V}_{O_2}$) results in respiratory exchange ratios above unity. However, as the buffering

processes do not completely constrain the fall of pH_a, an additional ventilatory stress results in the form of respiratory compensation for the acidosis. During exercise with rapidly incremented work rates (1 minute stages, as in figure 1.8), $\dot{V}E$ retains its sub-θan proportionality to $\dot{V}CO_2$ over a significant portion of the supra-θan range of work rates [WASSERMAN AND WHIPP, 1975; WASSERMAN *ET AL*, 1977]. As a result, there is no respiratory compensation for the acidosis at these work rates and the reasons for this are yet unclear [WARD, 1994]. However, during exercise with short duration increments in work rate, there is a point in time (or work rate, pH_a etc.) when the $P\bar{A}CO_2$ is reduced to constrain the further fall in pH_a (respiratory compensation, RC, Figure 1.8) [WASSERMAN *ET AL*, 1967; WASSERMAN AND WHIPP, 1975; SUTTON AND JONES, 1979; WASSERMAN AND CASABURI, 1991]. The increases in $\dot{V}E$ henceforth is out of proportion not only to that of $\dot{V}O_2$, but also to $\dot{V}CO_2$ (Note $\dot{V}E/\dot{V}CO_2$, and $\dot{V}E/\dot{V}O_2$ in figure 1.8).

1.4. Mechanisms underlying ventilatory regulation during exercise.

The net ventilatory response to exercise is not as a result of *one* major stimulus, but due to the simultaneous influence of *several* major and minor stimuli. While there is consensus in the current literature that the primary signal to increase ventilation during exercise arises from the alterations in the metabolic environment of the working muscles ($\uparrow\dot{V}O_2$, $\uparrow\dot{V}CO_2$), there is considerable conflict regarding the specific mechanisms which are involved in ventilatory regulation during exercise. The two main proposed mechanisms that have been implicated in the control of exercise hyperpnea are, **1)** Neurogenic influences that regulate the increase in exercise $\dot{V}E$ commensurate to the level of activity (both metabolic and contractile) of the skeletal muscles and **2)** Humoral influences that relate the $\dot{V}E$ increases during moderate exercise to changes in rate of CO_2 flow to the lungs. These also include mechanisms that are based on the changes in arterial blood (pH_a, Pa,CO_2, K^+, catecholamines, body temperature etc.) that occur during heavy exercise. It is now well understood that exercise hyperpnea is determined both by neurogenic and chemical stimuli, but

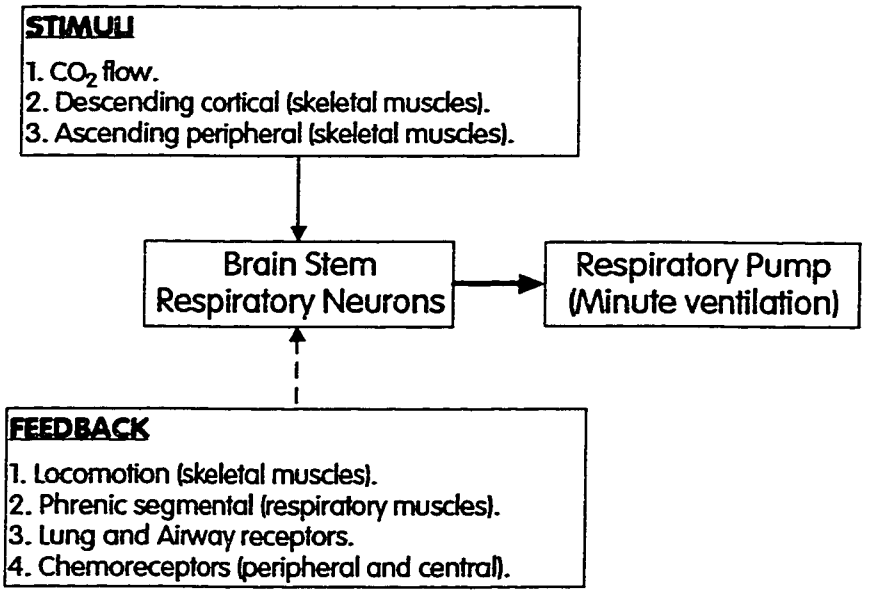

Figure 1.9. Exercise ventilatory regulation - functional pathways.

the quantitative contribution of each of these influences to the $\dot{V}_E$ increase of exercise, has been hard to define, in the complex physiological environment of heavy exercise.

Figure 1.9 summarizes some of the currently understood functional pathways, involved in the regulation of exercise $\dot{V}_E$. Respiratory active neurons in the brain-stem have been shown to receive 3 main inputs ("Stimuli"): **1)** That related to the rate of CO_2 production (CO_2 flow $= \dot{Q} \cdot C\bar{v},CO_2$) in the muscles; **2)** A descending neurogenic drive from the cortex to the locomotor muscles with projections to respiratory center neurons; **3)** An ascending neurogenic drive from type III and IV afferents from the locomotor muscles. Figure 1.9 also lists four feedback (error-correction) pathways that aid in the near-precise regulation of exercise $\dot{V}_E$: **1)** Afferents from the locomotor muscles to the cerebral cortex involved in locomotor control; **2)** Segmental afferents from the chest-wall and intercostal muscle spindles to both the cortex and the phrenic motoneurones, related primarily to the amount of work done with each breath; **3)** Lung and airway afferents to cortex; **4)** from peripheral (carotid) chemoreceptors responding to arterial Po_2, Pco_2 and pH and

central (medullary) chemoreceptors that are affected by cerebrospinal fluid (CSF) acid-base status (H^+). The following is a brief description of the possible roles of both neurogenic and humoral influences in ventilatory regulation during exercise.

1.4.1. Neurogenic mechanisms.

The immediate augmentation of $\dot{V}_E$ with the first breath at the onset of exercise (ϕ_1), well before muscle metabolites reach or stimulate peripheral and/or central chemoreceptors, suggests a strong neurogenic (non-humoral, rapid) influence on exercise hyperpnea. Possible origins of such stimuli include, reflexes from the exercising limbs [KAO, 1963; DEJOURS, 1967; MCCLOSKEY AND MITCHELL, 1972; TIBES, 1977; KAUFMAN *ET AL*, 1984; WALDROP *ET AL*, 1986], supra-bulbar regions of the central nervous system [KROGH AND LINDHARD, 1913; GOODWIN *ET AL*, 1972; ELDRIDGE *ET AL*, 1981, DIMARCO *ET AL*, 1983; ELDRIDGE *ET AL*, 1985A] and/or the central circulation [WASSERMAN *ET AL*, 1974; KOSTREVA *ET AL*, 1979; HUSZCZUK *ET AL*, 1983]. Additionally, it has been shown that the interruption of group III and IV afferents from exercising hindlimbs abolished both the hyperpnea and associated cardiovascular responses at the start of exercise, suggesting a parallel activation of both the $\dot{V}_E$ and cardiovascular responses. These conclusions are supported by evidence that the $\dot{V}_E$ response to exercise is affected by: **a)** complete transection or lateral column section of spinal cord [KAO, 1963]; **b)** cold block of hindlimb afferents [TIBES, 1977]; **c)** blockade of small fibre non- and myelinated dorsal root afferents from exercising limbs [MCCLOSKEY AND MITCHELL, 1972]. Pharmacological alteration of muscle spindle activity has also been shown to affect exercise hyperpnea [FLANDROIS *ET AL*, 1967; GAUTIER, *ET AL*, 1969]. However, as the magnitude of the ϕ_1 hyperpnea is relatively constant despite the severity of the work load [DEJOURS, 1964; JENSEN, 1972] imposed (from rest), it is unlikely that $\dot{V}_E$ regulation at the start of exercise is proportional to the recruitment of motor units or to the intensity of the imposed work load.

It has been argued [TIBES, 1977] that peripheral neurogenic mechanisms could play a major role in ϕ_2 hyperpnea also, based on temporal correlations observed between non- steady-state $\dot{V}E$ and K^+ (which stimulates both non-myelinated afferents and the carotid bodies [BAND *ET AL*, 1985]). However, these data are in contrast to those from others that have shown that hind limb de-afferentation has no effect on ϕ_2 kinetics of $\dot{V}CO_2$ [WEISSMAN *ET AL*, 1979; CROSS *ET AL*, 1982A]. Furthermore, it has been shown that temporal course of $\dot{V}E$ in electrically induced exercise is similar in both intact humans and in patients with complete spinal (thoracic and lumbar) transection [ADAMS *ET AL*, 1984; BRICE *ET AL*, 1986].

The slow nature of the $\dot{V}E$ response in ϕ_2 does not preclude involvement of neural mechanisms. For example, it has been shown that following a change in respiratory stimulus, notably a cessation of one (e.g. limb afferent or carotid body information), neural reverberations ("potentiation") within the brain stem respiratory centers are responsible for the slow decline in the observed $\dot{V}E$ response [ELDRIDGE, 1977]. However, imposed stimuli (in contrast to cessation) do not evoke such a response [ELDRIDGE AND WALDROP, 1991], and this is in striking contrast to the symmetry between both the "on" (see figure 1.9) and "off" ϕ_2-$\dot{V}E$ responses that is usually seen [CASABURI, 1977; GRIFFITHS *ET AL*, 1986].

The association of the immediate increase in $\dot{V}E$ with increases in cardiac output ($\dot{Q}$) in ϕ_1 when exercise starts from rest and the absence of such an abrupt $\dot{V}E$ increase at work-to-work transitions or in supine exercise (middle panel, figure 1.7) as a result of $\dot{Q}$ having increased earlier, has led to the suggestion that both the ventilatory and cardiovascular responses are influenced by concurrent "feed-forward" mechanisms (i.e. parallel activation). However, it has also been suggested that the cardiovascular response by itself might influence the hyperpnea of exercise ("cardio-dynamic hyperpnea" [WASSERMAN *ET AL*, 1974]), rather than a parallel activation of both cardiovascular and ventilatory control systems that result in increases in both

$\dot{Q}$ and $\dot{V}_E$. Further evidence in support of such mechanisms has been available from studies [JONES *ET AL*, 1982; HUSZCZUK *ET AL*, 1983] that have demonstrated a good correlation between right ventricular pressure (which was altered) and the $\dot{V}_E$ responses, that was preserved with vagotomy. It has also been shown that cardiac sympathetic afferents may play a role in ventilatory control [KOSTREVA *ET AL*, 1975; UCHIDA, 1986]. Studies that have used independent right ventricular and pulmonary artery pressure alterations, showed that reductions in blood flow to both the heart and the lungs resulted in a significant reduction in $\dot{V}_E$, suggesting the possible involvement of intra-thoracic sensing mechanisms [LEVINE, 1978; GREEN AND SHELDON, 1983; HUSZCZUK *ET AL*, 1986a; TRENCHARD, 1986]. While all of the above studies clearly suggest a valid link between cardiovascular and ventilatory systems in the control of exercise $\dot{V}_E$, the preservation of both the normal exercise hyperpneic response and acid base status in patients with cardiac transplantation [THEODORE *ET AL*, 1986], or in animals with artificial hearts [HUSZCZUK *ET AL*, 1986], clearly suggests that cardiac mediated mechanisms may not play a significant role in the ventilatory response to exercise.

1.4.2. Humoral mechanisms.

While it has been acknowledged that neural mechanisms are involved in the determination of both the characteristics and the magnitude of the drive to breathe during exercise, it is clear that a number of feedback mechanisms are involved in the fine control of respiration and circulation during exercise [ELDRIDGE *ET AL*, 1985A; 1985B]. Most of the support for humoral basis of ventilatory control during exercise stems from the observations that: **1)** The ϕ_2 - $\dot{V}_E$ response begins after a brief delay (ϕ_1) that is commensurate with the transit delay involved in the metabolites from the exercising limbs reaching the lungs and/or a sensor in between; **2)** The close correlation between the temporal profiles of both $\dot{V}_E$ and $\dot{V}_{CO_2}$ (an index of

pulmonary gas exchange) and **3)** The regulation of P_{a,CO_2} and pH_a close to control ("set point") values during steady-state exercise.

Of the 3 major stimuli involved in the regulation of exercise $\dot{V}_E$ (figure 1.9), CO_2 flow to the lungs forms the primary humoral stimulus. YAMAMOTO AND EDWARDS [1960] had suggested that CO_2 was sufficient for its own regulation, as it was shown that an isocapnic hyperpnea resulted with simulated exercise (↑venous return, $\uparrow C\bar{v},CO_2$). However, it has been suggested that this $\dot{V}_E$ response to experimental manipulation of CO_2 flow may not only be attributable to "specifically humoral" mechanisms, but also to conventional peripheral chemoreceptor feedback in responses to changes in arterial P_{CO_2}. For example, the slope of the $\dot{V}_A$ - $\dot{V}_{CO_2}$ slopes were identical with either venous CO_2 loading or exercise or both, in sheep [PHILLIPSON *ET AL*, 1981]. In dogs performing mild exercise, the ventilatory response to CO_2 loading/unloading resulted in changes in P_{a,CO_2}, which by itself could be attributed to for the $\dot{V}_E$ response [BENNETT *ET AL*, 1984]. Furthermore, the design of these studies limit the amount by which CO_2 flow could be increased (~2x - 3x basal levels). Thus it is not clear whether the $\dot{V}_E$ response to CO_2 loading (at higher CO_2 flows) is any different from that to increased P_{a,CO_2} either with CO_2 inhalation or during exercise in humans. Limited data from animals with higher CO_2 flows suggest that the $\dot{V}_E$ response could be attributed to the significant CO_2 retention that results [PHILLIPSON *ET AL*, 1981].

1.4.2.1. Peripheral Chemoreceptors.

Although CO_2 flow from the working muscles is a potential signal, both the exact pattern of the signal and the receptors that mediate the ventilatory response to this, are yet poorly understood. The carotid bodies in humans have been identified as perhaps the main, if not the only receptor subserving the role of peripheral ventilatory chemosensitivity [HOLTON AND WOOD, 1965; WADE *ET AL*, 1970; LUGLIANI *ET AL*, 1971; SWANSON *ET AL*, 1978; HONDA *ET AL*, 1979; HONDA, 1992]. The carotid bodies have been shown to be crucial for ventilatory responsiveness to both hypoxia

[CUNNINGHAM, 1974] and metabolic acidosis [OREN *ET AL*, 1982]. A variety of experimental approaches have been used to assess carotid chemoreceptor contribution to exercise hyperpnea in man: **1)** studies that have altered the stimulus profiles in arterial blood; **2)** studies that altered the reflex sensitivity; **3)** procedures that either stimulate or suppress activity; **4)** exercise responses in patients after carotid body resection and **5)** studies that have used oxygen-breathing techniques. It has been shown that carotid chemosensitivity in man can be reversibly abolished with hyperoxia, at least at rest and during moderate exercise *(see section 1.4.2.1).*

As the delay in the transit of metabolites from the exercising limbs to the lungs and then on to the carotid bodies is quite long, it is unlikely that the carotid bodies play any role in mediating the ϕ_1 hyperpnea. In addition, procedures that either increase carotid chemosensitivity (e.g. hypoxia) or abolish it (e.g. hyperoxia, resection) have been shown to have no significant effect on ϕ_1 hyperpnea [CUNNINGHAM *ET AL*, 1968; WASSERMAN *ET AL*, 1975; MIYAMURA *ET AL*, 1990]. However, the carotid bodies have been shown a play a major role in the mediation of ϕ_2 hyperpnea. It has been shown that hyperoxia significantly delays the onset of ϕ_2 hyperpnea in humans [WARD *ET AL*, 1987]. Procedures that accentuate carotid chemosensitivity, e.g. hypoxia [GRIFFITHS *ET AL*, 1986; WARD *ET AL*, 1987] or metabolic acidosis [OREN *ET AL*, 1982] have been clearly shown to accentuate the ϕ_2 - $\dot{V}_E$ kinetics (both in absolute terms and in comparison to those of $\dot{V}O_2$ or $\dot{V}CO_2$). Furthermore, The ϕ_2 - $\dot{V}_E$ response was significantly attenuated when carotid chemosensitivity was reduced e.g. hyperoxia [GRIFFITHS *ET AL*, 1986; WARD *ET AL*, 1987], metabolic alkalosis [OREN *ET AL*, 1982] or after intravenous infusion of dopamine [BOETGER AND WARD, 1986]. It has also been demonstrated that the ϕ_2 - $\dot{V}_E$ response is slower in patients after carotid body resection [WHIPP *ET AL*, 1993]. It follows that the carotid bodies, by their effect on ϕ_2 - $\dot{V}_E$ kinetics, significantly influence the temporal course of blood gas tensions and

acid-base status in ϕ_2, i.e. enhanced carotid body sensitivity can reverse the transient hypoxemia and slight CO_2 retention that occurs in ϕ_2 (lower panel, figure 1.7).

It has been suggested that the peripheral chemoreceptors may sense an oscillatory P_{a,CO_2} and/or $[H^+]$ signal, independent of the changes in level of the mean stimulus [YAMAMOTO AND EDWARDS, 1960; YAMAMOTO, 1977]. CROSS *ET AL* [1982B] have shown that both the magnitude and timing (when the rate of fall is greatest) of the intra-breath pH_a oscillations (index of CO_2 - H^+ changes) have significant and independent influences on $\dot{V}_E$. Furthermore, respiratory oscillations in P_{a,CO_2} have been shown to cause pH oscillations in the medullary cerebrospinal fluid (CSF) of cats [MILLHORN *ET AL*, 1984]. It has also been proposed that the effect of the intra-breath pH_a oscillations on $\dot{V}_E$ can be modulated further by the phase of the respiratory cycle at which it arrives at the medullary respiratory centers [BLACK AND TORRANCE, 1967; HOWARD *ET AL*, 1969; BAND *ET AL*, 1970; ELDRIDGE, 1972A; 1972B; CROSS *ET AL*, 1979]. While it has been shown that the amplitude of the CO_2 - pH_a oscillations increases significantly at exercise onset [BAND *ET AL*, 1980], it has been difficult to correlate these oscillations with any ventilatory change attributable to carotid chemosensitivity either in ϕ_2 [WARD *ET AL*, 1984] or in ϕ_3 [WARD, 1994]. Additionally, with the increasing ventilatory frequencies with increasing work rates, the recording of changes in pH_a amplitude has been exceedingly difficult in the past [MURPHY *ET AL*, 1987]. However, using rapidly responding intra-arterial electrodes, CROSS *ET AL* [1995] have recorded pH_a oscillations at breathing frequencies similar to that found during exercise. Using the ventilatory response to hyperoxia in both control and carotid body resected subjects, it has been suggested that the carotid bodies subserves ~20% of ϕ_3 hyperpnea [GRIFFITHS *ET AL*, 1986; JEYARANJAN *ET AL*, 1987; MACDONALD *ET AL*, 1990; WHIPP, 1994]. However, the exact nature of the stimulus (arterial CO_2 - H^+ oscillation, increased arterial K^+) that underlies this carotid body response, is not clear [CROSS *ET AL*, 1982; PATERSON, 1992].

During supra-θ_{an} exercise however, the carotid bodies appear to significantly mediate the respiratory compensation response to metabolic acidosis, that occurs at these levels of exercise. At comparable levels of metabolic acidosis, it was shown that the restoration of pH_a to normal values occurred faster during hypoxic exercise (compared to normoxia), suggesting that the degree of carotid chemosensitivity played a key role in the mediation of this response [RAUSCH *ET AL*, 1991]. Carotid body resected subjects show a markedly attenuated ventilatory response to heavy exercise and a greater fall in pH_a compared to changes in $[HCO_3]^-$ [WASSERMAN *ET AL*, 1975; WHIPP AND WASSERMAN, 1980]. Furthermore, the $\dot{V}_E$ response during supra-θ_{an} exercise has been shown to be attenuated with hyperoxia [RAUSCH *ET AL*, 1991; MCLOUGHLIN *ET AL*, 1993; SYABBALO *ET AL*, 1993]. In addition to the fall in pH_a, the contributions from other possible stimuli to peripheral chemoreceptor control of exercise $\dot{V}_E$, have been investigated. Increased circulating levels of epi- and nor-epinephrine during exercise have been implicated, but β-adrenergic blockade has been shown to have little effect on the $\dot{V}_E$ response to high intensity exercise [DODD *ET AL*, 1989]. The role of increased K^+ in the carotid body contribution to hyperventilation of heavy exercise [NEWSTEAD *ET AL*, 1990; PATERSON *ET AL*, 1990; PATERSON, 1992] has been questioned by investigators who have suggested that the hyperkalemia increases activation of Group III and IV limb afferents [TIBES *ET AL*, 1977; BUSSE *ET AL*, 1989]. The onset of respiratory compensation to metabolic acidosis at rapidly incremeted supra-θ_{an} work rates (figure 1.4) is relatively slow, i.e., $\dot{V}_E$ retains its sub-θ_{an} proportionality to $\dot{V}_{CO_2}$ over a major portion of the supra-θ_{an} range. As a result there is no change in $\dot{V}_E / \dot{V}_{CO_2}$ or fall in P_{A,CO_2}, until a point ("respiratory compensation point", RC - figure 1.8) midway between θ_{an} and maximal exercise. The functional basis of ventilatory control in this domain of work rates ("range of isocapnic buffering" [WASSERMAN *ET AL*, 1977]) is not presently clear. However, with slowly incremented work rates,

respiratory compensation has been shown to occur concurrently with the onset of metabolic acidosis [WARD AND WHIPP, 1992].

1.4.2.2. Central chemoreceptors.

The contribution of central chemosensory mechanisms to the regulation of exercise hyperpnea in humans has been inferred predominantly from indirect evidence from studies that have used hypercapnia-hyperoxia for selective central chemoreceptor stimulation, or from studies in patients with congenital central hypoventilation syndromes (CCHS). It has been suggested that due to the long latency (> 10 s) of lung-to-central chemoreceptor CO_2 transit [MILLER *ET AL*, 1974; WARD AND BELLVILLE, 1983], it is unlikely that central chemoreceptors play a role, if any, in the mediation of ϕ_1 hyperpnea. It has also been shown that hypercapnic-hyperoxia has no effect on the $\dot{V}E$ response at exercise onset [CUNNINGHAM *ET AL*, 1968]. While children with CCHS have been shown to have a similar exercise $\dot{V}E$ response to that of age matched controls [SHEA *ET AL*, 1993], the $\dot{V}E$ increase is predominantly due to an increase in f_b [PATON *ET AL*, 1993]. The lack of effect of hypercanic-hyperoxia on the $\dot{V}E$ response in patients with CCHS [PATON *ET AL*, 1993; SHEA *ET AL*, 1993] however, must be interpreted with caution. This is because, it has also been shown that progressive isocapnic-hypoxia has little or no effect on the $\dot{V}E$ response in patients with CCHS, suggesting that peripheral chemoreceptor response may also be affected.

As the response kinetics of the central chemosensors to hypercapnia are rather slow [BELLVILLE *ET AL*, 1979] and the transient (and predicted) increase in P_{a,CO_2} in ϕ_2 (bottom panel, figure 1.7) is rather small [WHIPP AND WARD, 1991], it is considered unlikely that the central chemosensors are involved in the mediation of ϕ_2 hyperpnea. Hypercapnic-hyperoxia in addition has been shown to have no effect on exercise ϕ_2 - $\tau \dot{V}E$ [WARD *ET AL*, 1987] and furthermore the ϕ_2 - $\dot{V}E$ kinetics in children with CCHS has been shown to quite similar to that of normal subjects [SHEA *ET AL*, 1993], suggesting that central chemosensory mechanisms do not play a major role in $\dot{V}E$ regulation in

ϕ_2. While in the anaesthetized cat it has been shown that medullary extracellular CO_2 - H^+ oscillations are possible at low breathing frequencies (MILLHORN *ET AL*, 1984], CSF - pH in exercising ponies has been shown to be stable over a range of work rates [BISGARD *ET AL*, 1978], suggesting that medullary chemosensors play a minor, if any, role in the regulation of $\dot{V}E$ in ϕ_3. Both the demonstrated stability of pH_a (i.e the mean stimulus) during light and moderate exercise [DEMPSEY *ET AL*, 1979] and the lack of effect of altered CSF [H^+] on exercise hyperpnea in goats [SMITH *ET AL*, 1988], suggest that the central chemosensors do not play a major role. At supra-θ_{an} work rates however, the respiratory compensation of metabolic acidosis has been shown to result in a mild alkalosis of the CSF [BISGARD *ET AL*, 1978], suggesting that the central chemosensors, by their response (i.e. reduced activity) or by their effects on peripheral chemosensor discharge [MAJCHERCZYK AND WILLSHAW, 1973] may play a constraining role in $\dot{V}E$ regulation during exercise.

1.4.2.3. Pulmonary chemoreceptors.

The lung has been shown to be an important site of detection in changes to CO_2 flow. Using extra-corporeal bypass, it has been possible to isolate/control the changes in both pulmonary blood flow and venous CO_2 flow to the lung from changes in P_{a,CO_2} [GREEN AND SHELDON, 1983]. These investigators showed that with maintained P_{a,CO_2}, increased pulmonary blood flow (8x), or increased $P_{\bar{v},CO_2}$ (~75 mmHg) caused an increase in $\dot{V}E$ that was blocked by vagotomy. This response could have been mediated by changes in pulmonary CO_2, pulmonary artery wedge pressure [KAN *ET AL*, 1979] or by C-fibre afferents [COLERIDGE AND COLERIDGE, 1984]. While the above studies implicate CO_2 flow as an important mechanism in ventilatory control, the quantitative contribution of this signal to the ventilatory response of exercise is yet unclear. Comparative $\dot{V}E$ - $\dot{Q} \cdot C\bar{v},CO_2$ data from anaesthetized [GREEN AND SHELDON, 1983] *vs.* awake exercising dogs [FAVIER *ET AL*, 1982] suggests that only a fifth of the total $\dot{V}E$ response to exercise could be explained by changes in pulmonary

blood flow and furthermore, bilateral vagotomy had no appreciable effect on the $\dot{V}_E$ response to exercise in awake dogs. While all the above studies indicate that both CO_2 flow and changes in pulmonary blood flow are important inputs in ventilatory regulation at metabolic rates commensurate with resting levels, the $\dot{V}_E$ response to exercise is influenced significantly by stimuli that are specifically related to exercise, i.e. locomotion.

1.5. Thesis objectives.

The ultimate ventilatory output of the exercising individual therefore not only needs to be appropriate for gas exchange requirements and acid-base homeostasis, but is also energetically efficient. Figure 1.10 summarizes some of the elements of the respiratory control system that have been shown to be involved in the regulation of $\dot{V}_E$ response during exercise. The possible roles of the various chemical and mechanical determinants in the regulation of exercise $\dot{V}_E$, were outlined in the previous sections. As discussed earlier, there is a wealth of

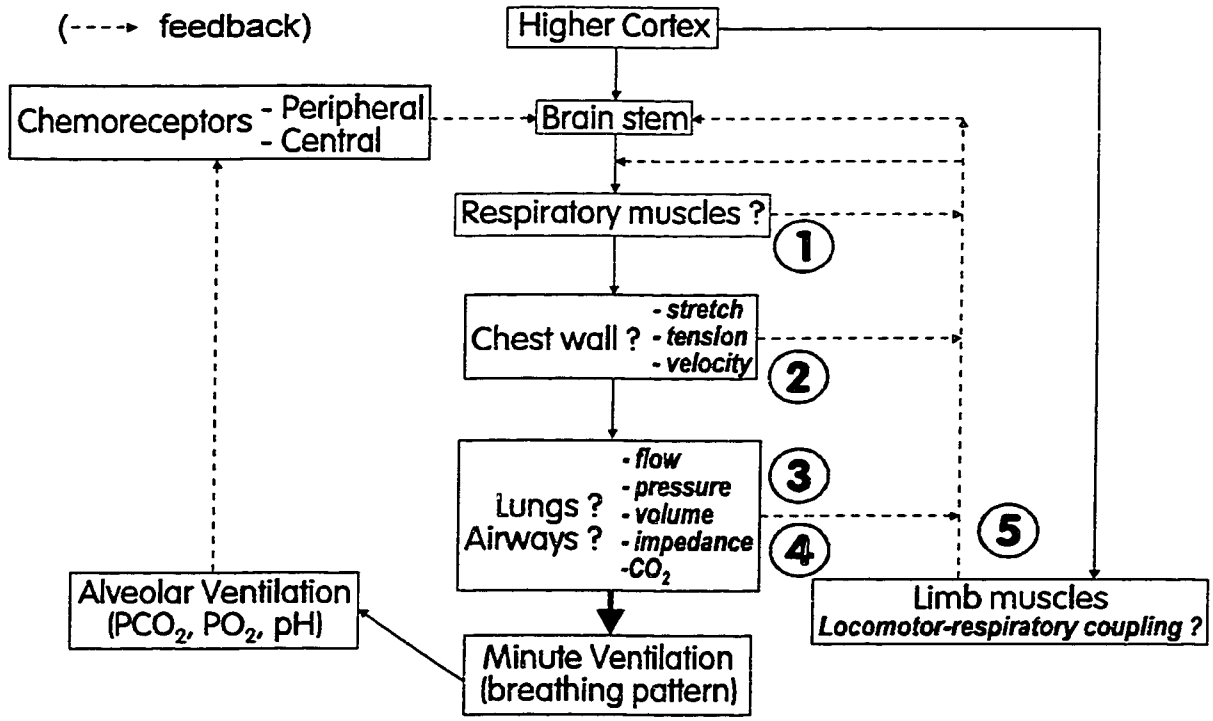

Figure 1.10. Mechanisms underlying ventilatory regulation during exercise - thesis objectives.

information available on the chemoreceptor based control of exercise $\dot{V}_E$ (left side of figure 1.10) from studies that have explored the interrelationships between $\dot{V}_E$, breathing pattern, arterial blood gases during different modes of exercise and intensities.

This thesis will focus on some of the less understood mechanisms underlying ventilatory control in normal exercising humans. As outlined in the introduction, the studies presented in the thesis are designed to explore the roles of some of the elements involved in the neuro-mechanical feedback control of exercise $\dot{V}_E$ (Right side of figure 1.10). These include: **1)** the pattern and magnitude of respiratory muscle recruitment throughout exercise and the relationship between respiratory motor output (measured as respiratory muscle pressures) and minute ventilation during exercise; **2)** the role of the intrinsic load on all the respiratory muscles ("respiratory impedance") and the effect of reducing of respiratory muscle work throughout exercise on ventilatory regulation; **3)** the mechanisms underlying the exercise hyperventilatory response that results from the reduction of airflow resistance when breathing a helium-oxygen mixture and the role of airway afferents in that response; **4)** The role of airway afferents in ventilation and breathing pattern regulation during exercise and when breathing through an added external dead space; and **5)** the mechanisms underlying locomotor-respiratory inter-dependence (e.g., the entrainment of respiratory frequency by the limb frequency) and their role in ventilation and breathing pattern during exercise. A brief overview of the currently available evidence regarding each of the above issues will be presented in the following sections. In the following chapters of this thesis, each of the above 5 questions will be addressed in separate studies in normal humans during cycle ergometry.

1.5.1. Evolution of respiratory muscle pressures during exercise.

Minute ventilation ($\dot{V}_E$) and the mechanical breathing pattern (V_T - f_b relationship) are the result of complex interactions between respiratory muscle activity and the mechanical properties of the respiratory pump (chest wall, lungs and airways). The increasing metabolic and ventilatory requirements of exercise result in a substantial increase in the command signal to all the respiratory muscles. The transformation of this command signal into an appropriately augmented ventilatory response and a mechanically efficient breathing pattern requires complex error-correction mechanisms. Figure 1.11 illustrates a simple overview of this "control system" with its main components, whereby the respiratory controller receives feedback about blood-gas tensions and acid-base status (from chemoreceptors) and also that which is related to lung and chest-wall mechanics (from mechanoreceptors). The controller then adjusts the command signal to all the respiratory muscles to provide an appropriate level of alveolar ventilation.

A number of techniques have been employed to understand the amplitude and the pattern of the command signal, in order to understand how this elaborate control system works. The command signal ("Drive") is best characterized as

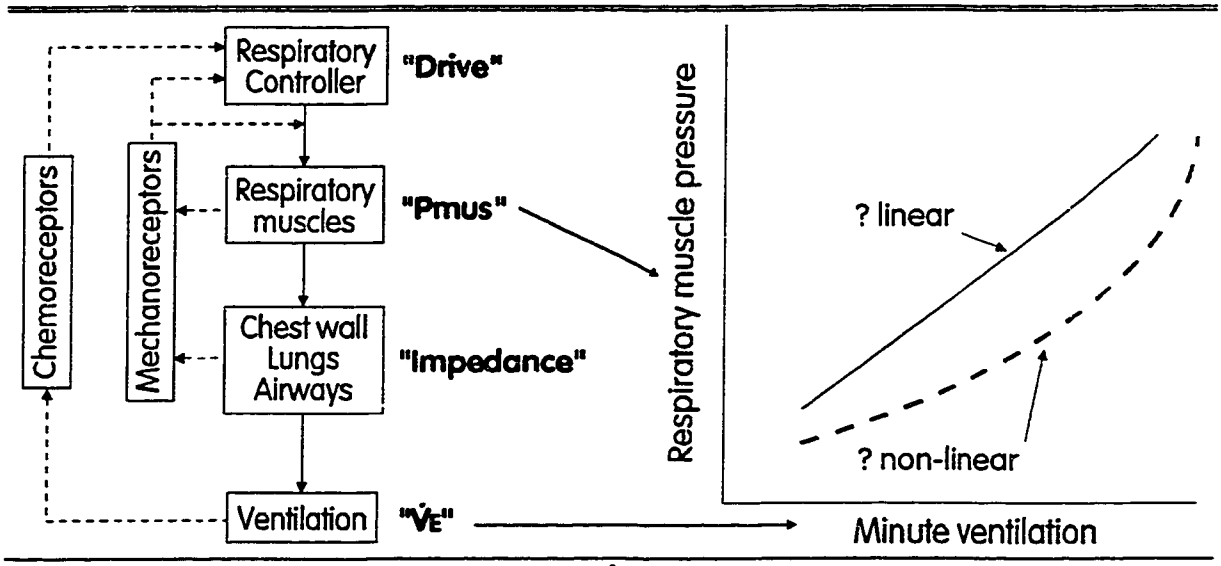

Figure 1.11. Respiratory control system: $\dot{V}_E$ - P_{mus} relationships.

excitatory and inhibitory information that originates from a respiratory-active, supraspinal neuronal complex, and eventually terminates in the respiratory muscles *via* spinal efferents. The specific information designed for each of the respiratory muscles, or fasciculi inside each muscle is different in both pattern and content, from those that are intended for other muscles or fasciculi. Other nervous structures that are also involved include the spinal afferents from the respiratory muscles, chest wall, lungs and airways as well as afferents involved in posture, phonation and other non-respiratory acts.

The "respiratory control system" therefore is best characterized as all the central nervous system components that are involved in determining the ultimate amplitude and pattern of the command signal to the respiratory muscles. Due to the complexities of the number of structures that are involved in the generation of the "drive" signal, it is not possible to measure the true output of the respiratory control system. Indirect estimates of respiratory motor output (flow, volume, pressure, EMG's) however are only useful in the context in which they are interpreted, as these signals themselves represent only the result of the effect of motor output on the respiratory pump. The mechanical properties (resistance, compliance) of the respiratory pump (chest wall, lungs and airways) represent the overall load on the respiratory muscles or the impedance to airflow. The relationship between the respiratory muscle pressure and minute ventilation (pressure *vs.* flow) can be used to gauge the nature of this impedance and its role in the regulation of ventilation and the command signal to the respiratory muscles (right panel, figure 1.11).

It has been suggested that the relationship between respiratory motor output (measured as mouth occlusion pressure, *see below*) and flow (mean inspiratory flow) becomes curvilinear with increasing exercise levels. The finding that respiratory motor output increases at a faster rate than flow has been attributed to the non-linear increase in respiratory impedance during exercise. However, the

measurement of pressure across the respiratory system at the start of inspiration will vary with the rate of rise of the overall drive to the respiratory muscles and will also be dependent on the impedance of the pump itself (time constants between applied pressure and flow) which it purportedly is used to estimate.

The pressure generated by the respiratory muscles (P_{mus}) throughout each breath and patterns of respiratory muscle recruitment represent a valid estimate of the "integrated" output of the respiratory controller. Both at rest and at low levels of ventilation, the diaphragm is the main muscle of inspiration [GRIMBY *ET AL*, 1976; LEVINE *ET AL*, 1988] and expiration is a passive process resulting from the elastic recoil of the respiratory system. During exercise however, all the respiratory muscles are recruited so that diaphragmatic contribution to overall ventilation become less and less as exercise continues [JOHNSON *ET AL*, 1993; MADOR *ET AL*, 1993]. As ventilation continues to increase with increasing exercise intensity, the increase in expiratory flow is achieved by increasing expiratory muscle recruitment, chiefly the abdominals. While it is well known that with increasing exercise intensities, both inspiratory and expiratory muscles are actively recruited, there is very little information on the differential contribution of inspiratory *vs.* expiratory muscles to the progressively increasing ventilatory need during heavy exercise.

1.5.1.1. Pressure-volume relationships in the respiratory system

The act of breathing is the result of net forces generated by the respiratory muscles acting on the respiratory system which tend to displace (i.e. cause a change in volume) it from its pre-inspiratory position. The direction of airflow (inspiratory or expiratory) therefore depends on the balance between the exerted respiratory muscle pressure (P_{mus}) and the elastic recoil pressure (P_{el}) of the respiratory system. P_{mus} may be positive (inspiratory) or negative depending on the pattern of respiratory muscle activation and P_{el} may be positive or negative depending on whether lung volume is above or below the resting end-expiratory position (*see below*). Inspiratory

flow results if P_{mus} exceeds P_{el} and flow will be expiratory when respiratory system elastic recoil exceeds P_{mus} (i.e. $P_{mus} < P_{el}$).

As described earlier (figure 1.4), in the resting position and with the absence of respiratory muscle activity, the volume of air in the lungs (FRC) is determined by the balance of forces between the inwardly directed elastic recoil of the lungs (P_L) which equals the outwardly directed elastic recoil of the chest-wall (P_W). At a lung volume above FRC (~55% VC) chest wall recoil equals zero (relaxation volume for the chest wall) and all the recoil pressure in the respiratory system (P_{RS}) is due to the inward recoil of the lungs. At higher lung volumes however (> 85% VC) elastic recoil of both the lungs and the chest wall are in the same direction and therefore additive. The respiratory system however becomes stiffer at these high lung volumes mostly due to the increasing lung stiffness. At very low lung volumes (i.e. < FRC) the inward recoil of the lung is minimal and the most of the elastic recoil of the respiratory system is outward due to the recoil of the chest wall. It is therefore evident that the upper limit of lung volume is determined by lung stiffness, and the lower limit, by chest wall stiffness.

The P - V relationship of the respiratory system therefore defines the possible maximal end-inspiratory lung volume and minimal end-expiratory lung volume within each breath (V_T), given a pattern of respiratory muscle activation (peak and minimum P_{mus}). This dependence of the V_T limits on the pattern of P_{mus} and P - V relationship of the respiratory system is valid only if the system expands along its relaxation configuration. Otherwise, some of the pressure exerted is lost in distorting the chest wall, as is shown to occur during exercise [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976], resulting in an increase in the elastic work of breathing. This elastic work of breathing can be minimized only if the increases in V_T are within 20% - 80% VC, as the P_{RS} - V relationship is linear and the respiratory system is considered "compliant" in this range. Inspiratory muscle activity causes an increase in lung volume above

FRC and during resting breathing, expiration is a passive process due to elastic recoil of the lungs. Increasing expiratory muscle activity, as occurs during exercise, results in lung volumes below FRC. This results in the elastic recoil of the chest wall (and the respiratory system) tending to bring the operational lung volume towards FRC, as expiratory muscle activity tapers off. This is one of the mechanisms by which increasing expiratory muscle activity aids the inspiratory muscles in the expansion of the lungs, at the start of inspiration.

1.5.1.2. Assessment of respiratory motor output.

Figure 1.11 outlines how the command signal from the respiratory controller gets transformed into tension (pressure) developed by the respiratory muscles which move the respiratory pump to cause airflow. Due to the complexities of the number of structures involved both in the shaping of this command signal and its final transformation to airflow, any single variable used as an indirect index of the true output of the system, would be incomplete. The best measure for any given situation depends on the question under study and sometimes one measurement to characterize the nature of the output will not suffice [DERENNE *ET AL*, 1978; WHITELAW AND DERENNE, 1993]. One of the signals used has been the electromyogram (EMG), a measure of the electrical field strength of a given muscle. EMG's provide an adequate picture of the temporal course of the spread of the electrical activity within the muscle, but this activity cannot be standardized in any absolute manner for comparison with other muscles. The use of EMG as a measure of respiratory motor output therefore assumes that the electrical activity of the muscle in question, forms the same proportion of the total output each time. As the diaphragm is the main muscle of inspiration, diaphragmatic EMG's have been used in the past to characterize output [BYE *ET AL*, 1984; HUSSAIN *ET AL*, 1985]. With the recruitment of other respiratory muscles however, e.g. during exercise, diaphragm activity has been shown to assume a progressively smaller proportion of global respiratory output

[JOHNSON *ET AL*, 1993; MADOR *ET AL*, 1993]. The contribution of numerous muscles to minute ventilation during exercise therefore, makes multiple EMG measurements and their interpretation very complicated.

Measurement of the result of action of the command signal on the respiratory system (changes in flow, volume and pressure) is another common approach used in the assessment of respiratory motor output. For example, the ultimate output of the respiratory pump can be measured and analyzed in terms of inspired minute ventilation ($\dot{V}_I$) and its components, tidal volume (V_T) and breathing frequency (f_b). Since f_b is the reciprocal of the total breath duration (T_T), $\dot{V}_I = V_T \cdot 1/T_T$; or $\dot{V}_I = V_T/T_I \cdot T_I/T_T$, where V_T/T_I is mean inspiratory flow and T_I/T_T is the index of proportion of total time the inspiratory muscles are active and is called the inspiratory duty cycle. This latter ratio, while representing an important timing mechanism for inspiratory muscle activity, is only an approximation, as graded inspiratory muscle relaxation continues into early expiration *(see below)*. Thus minute ventilation can be measured as the product of the "drive" to breathe (V_T/T_I) and the "timing" mechanism (T_I/T_T) for the start and stop of inspiratory muscle activity [VON EULER *ET AL*, 1970; CLARK AND VON EULER, 1972; GRUNSTEIN *ET AL*, 1973]. However, the efficiency with which inspiratory muscle activity is transformed into flow and volume, is dependent on lung mechanics and the mechanical advantage of the individual muscles as well as the synergism of action of the various groups of muscles contributing to inspiratory flow [DERENNE *ET AL*, 1978].

Another common index of respiratory drive is the measurement of pressures developed by the inspiratory muscles. In the transformation of the drive signal into inspiratory muscle pressure, two main steps i.e., the transformation of electrical activity into muscle tension and the transformation of the tension into pressure applied to the respiratory system are important and have to be accounted for. First, the transformation of electrical impulses into muscle tension depends on the force-length properties of muscles involved and this in turn is dependent on initial length of

the muscle and the degree of shortening during contractions. Second, for a given stimulus, muscle tension developed also depends on velocity of shortening of these fibres. Thus the pressure generating capacity of contracting inspiratory muscles is less at a higher lung volume and falls with increasing flow rates [RAHN *ET AL*, 1946; AGOSTONI AND FENN, 1960; HYATT AND FLATH, 1966; PENGELLY *ET AL*, 1971]. These intrinsic pressure-volume and pressure-flow relationships of the respiratory muscles are further influenced by the mechanical properties of the respiratory pump, and therefore differ between individuals. Flow and volume, if used as indices of respiratory motor output should therefore be normalized for the size of the subject being studied [WHITELAW AND DERENNE, 1993]. In addition, the use of dynamic pleural pressure swings during inspiration as an index of inspiratory drive is not valid, as there is not only shortening of muscles occurring as inspiration proceeds, but also a progressive decrease in the magnitude of pressure for given level of activation as inspiratory flow increases, due to the force-velocity properties of the inspiratory muscles. Furthermore, based on degree of inflation, afferent information from the lungs and chest wall, has a confounding effect on central inspiratory drive, which one is trying to assess. Generally, the transformation of muscle tension into pressure is based on its geometric configuration. For a curved structure such as the diaphragm for example, this relation can be approximated according to Laplace's law, which relates pressure developed across a curved surface to the tension developed in its walls. For the other respiratory muscles however, the mechanisms underlying the transformation of tension into pressure are unclear, but will ultimately depend on the geometric configuration and the mechanical advantage of each muscle. Their pressure-tension relationships therefore will be affected by changes in lung/chest wall volume and respiratory system geometry.

A non-invasive measure of the pressure developed at the mouth by the muscles during the first 100 ms of inspiration against an occluded airway is called the

mouth occlusion pressure ($Pm_{0.1}$) and is by far the commonest method used in the assessment of respiratory drive. With an occlusion, the inspiratory effort causes no flow and therefore no change in volume, but generates a negative pressure wave that can be used as an index of respiratory drive. This constancy of volume with no flow involves no shortening of the inspiratory muscles, or any velocity of contraction. The pressure developed is independent of the resistance and compliance of the respiratory system, and the lack of lung expansion with an essentially isometric contraction results in no vagal stretch-receptor afferent activity. $Pm_{0.1}$, measured instantaneously in "open-loop" (i.e. infinite impedance) condition, thus represented respiratory motor output that was unaffected by mechanical afferent feedback.

The use of $Pm_{0.1}$ as an index of global respiratory output and the interpretation of changes in that index in humans, are however based on the following considerations. **a)** The shape of the driving pressure signal throughout inspiration can definitely influence the relationship of $Pm_{0.1}$ to other variables such as flow and volume. It has been shown in relaxed or anaesthetized subjects, that the driving pressure waveform is well regulated, i.e. breath-by-breath variations are minimal within the individual and species [ALTOSE *ET AL*, 1975; YOUNES AND REMMERS, 1981; MILIC-EMILI AND ZIN, 1986]. While the measurement of the driving pressure signal with an isometric contraction of the inspiratory muscles against an occlusion is possible only in an anesthetized subject, it has been possible to calculate its shape using the flow and volume signals and reasonable modelling assumptions [RIDDLE AND YOUNES, 1981; YOUNES AND RIDDLE, 1981]. **b)** For $Pm_{0.1}$ to reflect global respiratory center output, it should bear a constant relationship with the driving pressure waveform throughout inspiration and thus any changes in shape after the first 100 ms would result in $Pm_{0.1}$ becoming unreliable as an index. For example, while the ratio between $Pm_{0.1}$ and $Pm_{0.2}$ has been found to be constant in anesthetized subjects with significant increases in ventilatory stimulation [DERENNE *ET AL*, 1976], it is possible that changes in

shape after 200 ms would still result in an unreliability of $Pm_{0.1}$ as an index of global output in awake humans. **c)** It has been shown repeatedly that the shape of the driving pressure waveform changes significantly in anesthetized humans subjected to a load [DERENNE *ET AL*, 1986], in patients with COPD [SERGEYSELS *ET AL*, 1981], in normal subjects with an applied pressure assist at rest [GALLAGHER *ET AL*, 1989], or with an inspiratory resistive load [IMHOF *ET AL*, 1986] and during exercise [GALLAGHER AND YOUNES, 1989]. It is evident from figure 1.12 (left panel) that changes in shape of the driving pressure waveform especially in early inspiration can impact significantly on the measure of $Pm_{0.1}$ (difference between "a" and "b"). It is therefore imperative that possible changes in shape of driving pressure waveform throughout inspiration have to be considered in the interpretation of $Pm_{0.1}$ as an index of respiratory motor output.

Figure 1.12 [WHITELAW AND DERENNE, 1993] summarizes the above considerations as well as other complexities involved in the interpretation of $Pm_{0.1}$. An additional confounding feature in the interpretation of $Pm_{0.1}$ as an index of inspiratory motor output, is the fact that expiratory activity can contribute to $Pm_{0.1}$. In many instances, such as exercise [HENKE *ET AL*, 1988] or CO_2 inhalation [GRASSINO *ET AL*, 1981], expiratory muscle recruitment forces end-expiratory lung volume (EELV) below the resting lung

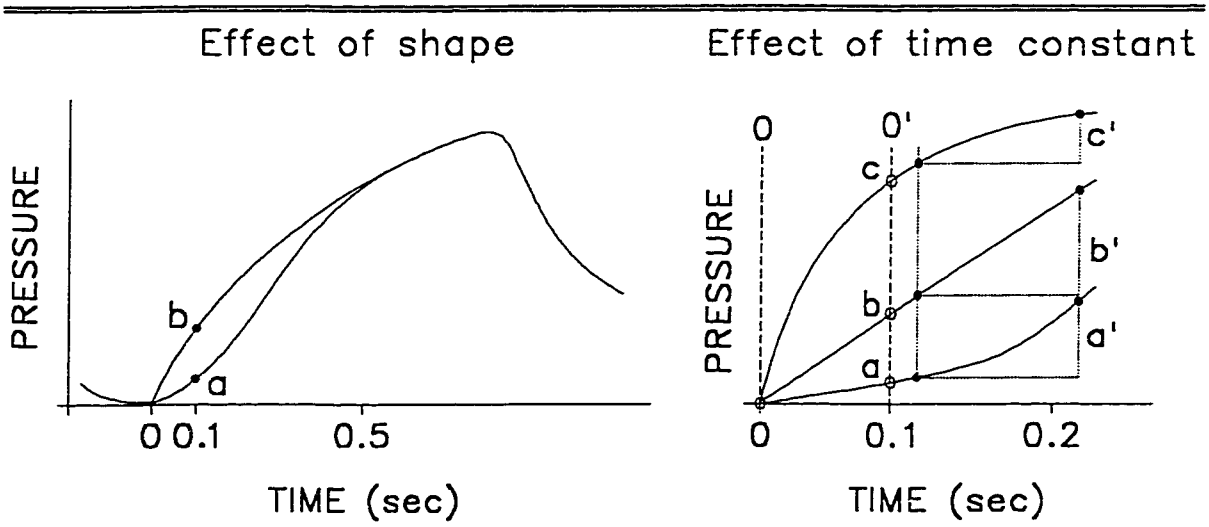

Figure 1.12. Considerations in the measurement and interpretation of $Pm_{0.1}$. [WHITELAW AND DERENNE, 1993].

volume (FRC) and expiratory muscle relaxation at the start of inspiration can therefore contribute to the bulk of $Pm_{0.1}$. It is therefore important to recognize that any change in EELV as occurring during exercise, makes the use of $Pm_{0.1}$ as an index of exclusive inspiratory neural output quite unreliable.

Furthermore, the measurement of $Pm_{0.1}$ assumes a constant relationship between transduction of pressure changes into volume and flow changes, i.e., any change in the phase relationship between the driving pressure waveform and flow and/or volume would necessarily impact on the measurement of $Pm_{0.1}$ and thus its interpretation. The right panel in figure 1.12 illustrates the effect of the change in respiratory system time constant (τ = resistance · compliance) on the measurement of $Pm_{0.1}$. Any change (e.g. from 0 to 0', figure 1.12) in the normal delay between pressure and flow (which is the basis of the 100 ms into inspiration) would therefore result in the under- (a *.vs.* a') or over-estimation (c *.vs.* c') of $Pm_{0.1}$ based on the original shape of the driving pressure waveform. Such changes in τ, in addition to changes in shape have been shown to occur with increased levels of ventilation, as during exercise [GALLAGHER AND YOUNES, 1989].

1.5.1.3. Respiratory muscle pressure (P_{mus}) as an index of motor output.

Another measure of respiratory center output used in the studies presented in this thesis, is respiratory muscle pressure or P_{mus} calculated throughout the respiratory cycle. P_{mus} by definition, represents the net dynamic pressure resulting from the contraction of all the respiratory muscles and not that of any single muscle (e.g. the diaphragm, the only muscle whose independent output can be measured) or group (inspiratory *vs.* expiratory). The measurement of P_{mus} treats the respiratory system as a simple visco-elastic structure with essentially one or two components and involves the addition of active pressures across the respiratory system thus:

$$P_{mus} = P_{el} + P_{res} + P_{in} \qquad \textbf{(1.5)}$$

where P_{el}, P_{res} and P_{in} are the pressures used to overcome the elastic, resistive and inertial properties of the respiratory system (lungs + chest wall) respectively. With inertial losses being negligible in the respiratory system, equation 1.5 suggests inspiratory flow will begin (i.e. P_{res} will be +ve) when P_{mus} exceeds P_{el} and vice versa. This method of calculating P_{mus} variables is based on previously described techniques [CAMPBELL, 1958; MEAD AND AGOSTONI, 1964] and is described in detail in chapter 2. Briefly, it involves the use (and measurement) of lung and chest wall properties (resistance and elastance etc.) and instantaneous flow and volume information throughout the breathing cycle and is an useful index of respiratory motor output. However, the overall transduction of respiratory neural output into pressure development by any respiratory muscle (or group) depends on the length of contracting muscle which varies with lung volume [RAHN *ET AL*, 1946] and of its velocity of shortening which varies with the flow rate [PENGELLY *ET AL*, 1971]. The interpretation of P_{mus} as an index of respiratory motor output should therefore involve the consideration of the above constraints. Inspiratory P_{mus} however, can be expressed as a fraction of the volume-matched, flow-velocity corrected capacity of all the inspiratory muscles (P_{capI}) at any lung volume. This index, i.e. P_{musI}/P_{capI} (%)is another useful index of inspiratory motor output as it reflects the load on all the inspiratory muscles. It has been used in the studies described in this thesis.

While inspiring from FRC, breathing is predominantly an inspiratory active event, when inspiratory flow begins as soon as the inspiratory muscles (chiefly the diaphragm) exert an inflationary pressure (i.e. P_{mus} becomes +ve). As shown in figure 1.12, the driving pressure (P_{mus}) increases in a ramp-like fashion and declines slowly. Peak P_{mus} occurs while flow is still inspiratory and expiration begins as soon as P_{mus} starts to decline. P_{mus} remains positive through the initial part of expiration, and this persistence of inspiratory P_{mus} during early expiration is called post-inspiratory inspiratory activity (PIIA). The measurement of P_{mus} throughout the

breathing cycle thus enables the assessment of the individual components of P_{mus} as well as PIIA. While there is no expiratory muscle activity at rest, expiratory P_{mus} (i.e. P_{mus} = -ve) becomes increasingly a greater component of net P_{mus} throughout the respiratory cycle, whenever ventilation is increased. With the dramatic increase in ventilatory requirements, increase in expiratory flow (with a progressive shortening of expiratory duration) is achieved by a combination of both increasing expiratory muscle activity as well as a progressive fall in PIIA.

1.5.1.4. Patterns of Respiratory muscle recruitment during exercise.

While there has been a considerable focus on the regulation of exercise hyperpnea in humans, there is only little information available regarding the mechanisms underlying respiratory muscle recruitment appropriate to the level of hyperpnea of exercise. Furthermore, direct evidence of respiratory muscle recruitment patterns during exercise are only available from chronically instrumented animal models. A variety of quantitative techniques have been employed, such as indwelling electrode EMG of respiratory active and accessory respiratory muscles, microsphere measurement of respiratory muscle blood flow and sonomicrometric measurements of changes in respiratory muscle length. In humans however, indirect techniques have been employed. These include body surface measurements to monitor rib-cage *vs.* abdominal compartmental activity as well as esophageal and gastric pressure measurements to quantify respiratory muscle function.

The results of several animal (in dogs, ponies and horses) studies reveal that thoracic and abdominal expiratory muscle activity is normally present during inspiration and this is viewed as assisting inspiratory active muscles [KOTERBA *ET AL*, 1988; DETROYER *ET AL*, 1989; SMITH *ET AL*, 1989; BRICE *ET AL*, 1990]. Furthermore, these studies also showed that electrical activity of both inspiratory and expiratory active muscles at rest was often delayed in comparison to mechanical effects (flow) and this suggested that initial changes in airflow (i.e. pressure) in each phase was achieved

passively by the relaxation of antagonistically active muscles. It was also shown that these animals breathe *around*, rather than *from* a relaxation lung volume. During exercise however, both the pattern and intensity (pressure) of respiratory muscle recruitment were shown to be closely related to both the amplitude and the onset of myo-electrical activity. Furthermore, it was shown that accessory muscles were recruited tonically and/or phasically to stabilize the rib-cage or affect head or neck locomotion, all of which serve to assist the primary respiratory muscles.

It has been shown that with either spontaneous or electrically induced exercise in decerebrate cats, there was a simultaneous activation of both locomotory and respiratory muscles at exercise onset. This was associated with an increase in both diaphragmatic and intercostal expiratory muscle activity, while intercostal inspiratory activity decreased [DiMarco *et al*, 1983]. This suggested that the primary input to the respiratory muscles was linked to the descending neural outflow associated with locomotion. More recently, Ainsworth *et al* [1989a] have also demonstrated that with the increases in both $\dot{V}CO_2$ and $\dot{V}E$ during exercise, there was a proportional increase in both inspiratory (diaphragmatic) and expiratory (both thoracic and abdominal) muscle mean electrical activity (MEA) and that with exercise, electrical events no longer lagged behind mechanical events, but preceded them. Additionally, the degree of expiratory muscle recruitment increased with the degree of exercise, for example, expiratory MEA increased significantly when the dogs were trotting as compared to when they were walking.

The above study also showed that with exercise, there was evidence of phasic abdominal expiratory muscle (and not thoracic expiratory muscles) activity coincidental with footplant. In contrast, with hypercapnic hyperpnea induced at rest [Ainsworth *et al*, 1989b], such phasic activity was not demonstrable in any expiratory muscle group, suggesting that abdominal expiratory activity during exercise subserved an additional postural/locomotory function in these dogs. Furthermore,

tonic expiratory muscle activity as evidenced by baseline offsets of both EMG and the pressure signals suggested that the end expiratory lung volume (thus the initial length of contraction of the inspiratory muscles and therefore their efficiency) was actively regulated during exercise in these animals. Such tonic expiratory muscle activity was also conspicuously absent with induced hypercapnic hyperpnea at rest [AINSWORTH *ET AL*, 1989B]. These results have been further confirmed by other researchers [GUTTING *ET AL*, 1991], who showed that in exercising ponies, MEA of both inspiratory and expiratory active muscles increased linearly with increasing exercise intensity and that abdominal expiratory muscle activity demonstrated a phasic coordination with footplant. These studies therefore demonstrate that, at least in these animals, abdominal expiratory activity which becomes significant during exercise, also subserves to maintain (or determine) end expiratory lung volume and may act in conjunction with postural and locomotory mechanisms during exercise. While the above studies provide significant qualitative insight into the recruitment of respiratory active muscles during exercise, data from studies involved in the measurement of respiratory and limb muscle blood flow in maximally exercising ponies [MANOHAR, 1986; 1990] clearly demonstrate that perfusion of the respiratory muscles increased significantly (on a per gram basis) with exercise and that increasing respiratory muscle recruitment accounted for nearly 15% of exercise cardiac output. All of the above studies clearly show that with exercise, both the degree of recruitment and the metabolic requirements of all the respiratory active muscles increase significantly.

As stated earlier, indirect evidence of increased respiratory muscle recruitment in humans is available as a result of many studies in this area. The diaphragm in the human remains the only respiratory muscle whose individual activity can be studied both qualitatively and quantitatively. Using both EMG and trans-diaphragmatic pressures, BYE *ET AL* [1980] demonstrated that diaphragmatic activity increased in proportion to the increase in minute ventilation during

submaximal exercise. At rest, the diaphragm is the main muscle of inspiration in humans and expiratory flow is as a result of passive relaxation of the respiratory system. The results of respiratory induction plethysmography (measurement of rib-cage and abdominal dimensions) suggest however, that rib-cage expansion contributes a greater portion of the increase in tidal volume during exercise, than at rest [GRIMBY *ET AL*, 1976]. The increase in rib-cage activity during exercise is also supported by the fact that gastric pressure falls at the start of inspiration [BYE *ET AL*, 1980]. This is in contrast to resting conditions when gastric pressure increases throughout inspiration, when the diaphragm is the sole inspiratory active muscle.

However, recent evidence suggests that the increase in diaphragmatic activity is not always in proportion to the level of exercise hyperpnea. For example, it has been shown that with exhaustive exercise eventually resulting in diaphragmatic fatigue, the "time-integral" of P_{DI} tends to plateau (or even decrease) while both $\dot{V}_{CO_2}$ and esophageal pressure (an index of intra-thoracic pressure) continue to increase significantly. This suggests that the diaphragm contributed less and less to the total pressure output as exercise proceeded [JOHNSON *ET AL*, 1992]. This has also led to the suggestion that during exhaustive endurance exercise, the diaphragm might be "spared" from further fatiguing contractions by the accessory inspiratory muscles. It has also been suggested that this inhibition of diaphragmatic contractions may be as a result of phrenic afferent activity triggered by local metabolic changes characteristic of "impending" diaphragmatic fatigue [JAMMES *ET AL*, 1986]. Other studies also confirm increasing inspiratory/intercostal muscle and/or reduced diaphragmatic pressures [LEVINE *ET AL*, 1988] during exercise. A recent report [ALIVERTI *ET AL*, 1997] however demonstrated that with increasing exercise intensity, there was significant increases in both velocity of diaphragmatic shortening as well as diaphragmatic work, despite only modest increase in trans-diaphragmatic pressure. This suggests that during

moderate exercise intensities, the diaphragm behaved essentially as a "flow" generator rather than as a "pressure" generator.

Several studies provide evidence of increasing inspiratory-accessory and expiratory muscle recruitment with increasing exercise intensity [GRIMBY *ET AL*, 1976; ALIVERTI *ET AL*, 1997]. However, both the pattern and magnitude of respiratory muscle recruitment have been shown to depend upon posture and the mode of exercise (cycle ergometry *.vs.* treadmill running) [HENKE *ET AL*, 1988]. During maximal incremental exercise, it has been shown [LEBLANC *ET AL*, 1988] that both peak inspiratory and expiratory esophageal pressures increase significantly, suggesting increasing inspiratory and expiratory muscle activity with exercise. Furthermore, the data from KEARON *ET AL* [1991] demonstrate that with constant work rate exercise of moderate-to-severe intensity, there was an increase in both peak and end expiratory esophageal pressures, while inspiratory pressures tended to plateau. This suggested that with increasing exercise intensity, expiratory pressures assumed a greater fraction of the total respiratory muscle pressures. Although the measurement of pressures does not provide information on any specific pattern of respiratory muscle recruitment, it indirectly and qualitatively provides information on the degree of respiratory muscle activity during increasing exercise levels.

The abdominal expiratory muscles have been shown to be active whenever ventilation is increased, (e.g. CO_2, exercise). For example, it has been demonstrated with the aid of intramuscular wire electrodes, that the abdominal expiratory muscles become tonically and phasically active even with low intensity bicycle ergometry (at $\dot{V}E$ levels of 15 - 20 $L \cdot min^{-1}$) [DEMPSEY *ET AL*, 1990A]. Furthermore, the fall in EELV that accompanies this increase in expiratory muscle activity has been documented with minor increases in $\dot{V}E$ above resting levels [YOUNES AND KIVINEN, 1984; HENKE *ET AL*, 1988]. This fall in EELV has also been shown to precede the increase in EILV with low intensity exercise [BABB AND RODARTE, 1991]. Marked tonic activation of the abdominal

muscles (as shown by tonic increase in gastric pressure) has been documented when exercise intensity was increased (e.g. walking to running) [GRILLNER *ET AL*, 1978; HENKE *ET AL*, 1988]. It has been proposed [GRILLNER *ET AL*, 1978] therefore, that this increase in abdominal muscle tone may be actively linked to locomotor activity and may serve to offf-load some of the shock on the vertebral column caused by the impact of the footplant .

A combination of the increase in expiratory muscle activity and the reduction in upper airway resistance during exercise, serves to increase expiratory flow and progressively reduce EELV, despite the progressively shortening expiratory duration that occurs at increasing exercise intensities. This significant fall in EELV with the increasing $\dot{V}_E$ levels of exercise is in contrast to what happens with hypercapnia at rest, when EELV changes very little even when $\dot{V}_E$ is increased significantly from eupneic values [HENKE *ET AL*, 1988]. This fall in EELV due to increased abdominal muscle recruitment specifically associated with exercise is considered beneficial, as it ensures that the diaphragm and other inspiratory muscles are allowed to operate on a more efficient part of their length-tension relationships [GRIMBY *ET AL*, 1976; HENKE *ET AL*, 1988; LEVINE *ET AL*, 1988[, when the need for increasing inspiratory muscle pressure approaches maximal levels [LEBLANC *ET AL*, 1988; JOHNSON *ET AL*, 1992]. The shift of the operating lung volume below FRC also allows for lung expansion on a relatively linear part of the P - V relationship of the respiratory system. Furthermore, a reduction in EELV protects against high EILV's, thus preventing a significant increase in the elastic work of breathing, when V_T needs to increase with increasing exercise intensity. Increasing expiratory muscle recruitment during exercise therefore serves to significantly off-load some of the work of the inspiratory muscles, by improving their efficiency.

In healthy young adults, it has also been shown that the maximal expiratory intra-pleural pressures exerted at different intensity levels of exercise, including

maximal exercise, do not usually exceed the capacity for "effective" pressure generation. This "protective" effect against ineffective pressure generation is evident in a normal "untrained" human at maximal exercise and persists even if an additional ventilatory stimulus ($\uparrow CO_2$, $\downarrow O_2$) is superimposed at maximal exercise [JOHNSON *ET AL*, 1992A]. This suggests that significant inhibitory influences are at play in preventing over-recruitment of, and ineffective pressure generation by, the expiratory muscles. Similar inhibitory reflexes which are effective in preventing fatiguing contractions or excessive stretch have been demonstrated with the diaphragm and other intercostal inspiratory muscles [JAMMES *ET AL*, 1986].

1.5.1.5. The relationship between P_{mus} and $\dot{V}_E$ during exercise.

The right panel of figure 1.11 illustrates the possible relationships between P_{mus} and $\dot{V}_E$ during exercise. As described earlier, the slope of this relationship is an index of the net impedance (load) faced by the respiratory muscles. This relationship between the respiratory neural ("drive") and mechanical ("minute ventilation") outputs during exercise, has been the focus of many studies in the past [LIND AND HESSER 1984; HUSSAIN *ET AL*, 1985], which have employed $P_{m_{0.1}}$ as an index of drive and V_T/T_I (mean inspiratory flow) as an index of minute ventilation. These studies showed a curvilinear relationship that was as a result of $P_{m_{0.1}}$ increasing at a faster rate than V_T/T_I during exercise. This was attributed to a non-linear increase in respiratory impedance during exercise and it has therefore been suggested [HUSSAIN *ET AL*, 1985], that mechanical impedance is a significant determinant of the exercise ventilatory response *(also see below)*. Other studies suggest however that this relationship may be linear during exercise [WANKE *ET AL*, 1991].

As discussed in section 1.5.1.2., the use of, and the interpretation of changes in, $P_{m_{0.1}}$ as an index of respiratory motor output during exercise is questionable because of the changes in shape of the driving pressure waveform and the changes in operating lung volume that result from antagonistic muscle actions. However, it

has also been demonstrated that both electrical (EMG) and mechanical (pressure output) indices increase in a proportional and linear fashion appropriate to the increasing hyperpnea in exercising animals [AINSWORTH *ET AL*, 1989A; 1989B; 1996]. A more recent analysis by ALIVERTI *ET AL* [1997] suggests that with increasing exercise intensity, the drive to breathe increases proportionally to all respiratory active muscles. The transduction of this drive into either pressure (force) or flow (velocity) however, by individual (e.g. the diaphragm) or groups of muscles (e.g. the abdominals), is further dependent on their individual mechanical advantages.

1.5.2. Respiratory muscle load and exercise ventilatory regulation.

For a given pattern of respiratory muscle contraction, both minute ventilation and its pattern are determined by the mechanical properties (resistance and/or elastance) of the respiratory system. At any given level of exercise, both the levels of $\dot{V}_E$ and V_T have a significant impact on blood-gas tensions and acid-base homoeostasis, which further impact limb muscle performance. It has therefore been hypothesized that the intrinsic respiratory load in normal humans may constrain ventilation, thereby contributing to the fatigue of the exercising muscles. Furthermore, it has been argued that while arterial P_{CO_2} during exercise is less (i.e. hyperventilation) than that at rest, exercise $\dot{V}_E$ would be considerably greater (with significant improvement in arterial blood-gas status and acid-base homoeostasis), if the intrinsic impedance was less.

1.5.2.1. Ventilatory responses to altered impedance during exercise.

Many studies in the control of ventilation and its pattern, have used the technique of altering the load against which the respiratory muscles have to operate. As the alterations in respiratory mechanics due to disease processes usually result in an increase in load, both resistive and/or elastic loads have been employed to study the response of the normal system to a change in load. The effects of an increase in external resistance on exercise ventilation have been studied extensively [GEE *ET AL*,

1968; DEMEDTS AND ANTHONISEN, 1973; D'URZO *ET AL*, 1987] and external resistive loading has been shown to decrease $\dot{V}E$ while increasing respiratory pressure, especially during heavy exercise [D'URZO *ET AL*, 1987; RAMONATXO *ET AL*, 1991]. While these studies clearly demonstrate that an increase in external load definitely constrains $\dot{V}E$, they do not provide any insight into the importance of the intrinsic load in ventilatory regulation in general, and the role of the respiratory muscles in the ventilatory response to exercise.

Unloading the respiratory muscles however, can provide information about the role of the intrinsic impedance in ventilatory regulation during exercise. Two very different techniques have been employed in the past to unload the respiratory muscles during exercise: **1)** The use of a heliox mixture (79% He + 21% O_2) as the inspirate results in a significant fall in flow turbulence which results in a reduction in airway resistance during exercise; **2)** Flow-proportional mouth pressure assist, when mouth pressure is made positive on inspiration and negative with expiration, resulting in the unloading of the respiratory muscles throughout the respiratory cycle.

Figure 1.13 illustrates the possible ventilatory responses to an alteration in respiratory impedance during exercise. A linear relationship (solid line) between the

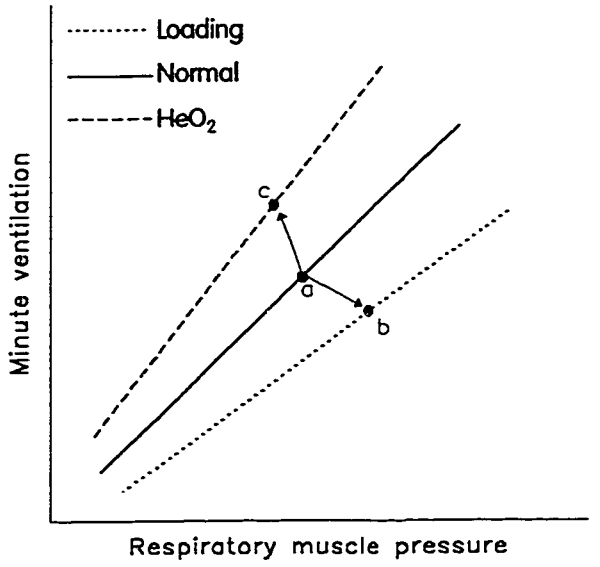

Figure 1.13. Exercise $\dot{V}E$ and P_{mus} responses to an alteration of load.

minute ventilation and respiratory muscle output has been used to simplify the interpretation of the response to changes in load. The slope of this relationship then can be used as an index of impedance. An increase in load (dotted line) has been shown to result in the response a → b, when $\dot{V}_E$ is downregulated and P_{mus} was increased. A reduction in the load with HeO_2 breathing during moderately high levels of exercise has however been shown to result in a significant increase in $\dot{V}_E$ while respiratory muscle activity was downregulated slightly (i.e. a → c). These results suggest that the intrinsic load (always present and is reduced with HeO_2 breathing) is a significant influence on exercise ventilation, i.e. the normal respiratory impedance constrains exercise $\dot{V}_E$ [HUSSAIN *ET AL*, 1985]. However, GALLAGHER AND YOUNES [1989] have argued that since the degree of reduction in resistance by HeO_2 breathing during heavy exercise is small (< 1 $cmH_2O \cdot L^{-1} \cdot s$) and the estimated consequent increase in $\dot{V}_E$ (without the downregulation of P_{mus}) was also small (Δ < 10%), the observed significant increase in $\dot{V}_E$ (Δ ~ 30%) and the uncorrected hypocapnia with HeO_2 breathing during exercise, was not due to a reduction in respiratory impedance *per se* but due to other factors *(see below)*.

It has been possible in recent years to unload the respiratory muscles to a much greater extent than with HeO_2 breathing during exercise. Using a specially designed loading/unloading device [YOUNES *ET AL*, 1987], it is possible to apply a flow-proportional pressure assist so that mouth pressure is positive during inspiration and negative during expiration such that respiratory muscles are unloaded throughout the respiratory cycle. Using this or similar devices, many recent studies have attempted to reduce the normal respiratory load [POON *ET AL*, 1987; YOUNES *ET AL*, 1987; GALLAGHER AND YOUNES, 1989] and it has been shown that during mild or moderately heavy exercise, flow-proportional mouth pressure assist has no significant effect on $\dot{V}_E$, while P_{mus} was reduced in some studies. However, these studies do not provide any insight into the role of intrinsic load in ventilatory regulation with the high $\dot{V}_E$

levels (when the effects of HeO_2 are marked) observed during heavy exercise. This apparatus has been modified for use during heavy exercise and has been tested to be effective in unloading the respiratory muscles in normal humans, even at the highest levels of $\dot{V}E$ (> 150 L · min^{-1}) [KRISHNAN, 1992].

1.5.2.2. The hyperventilatory response to HeO_2 breathing during exercise.

The substitution of a normoxic helium-oxygen mixture (79% He + 21% O_2) for room air during exercise has been shown to result in an immediate and sustained hyperventilation and hypocapnia which persists as long as the HeO_2 mixture is being breathed [NATTIE AND TENNEY, 1970; WARD *ET AL*, 1982; BRICE AND WELSH, 1983; DEMPSEY *ET AL*, 1984; HUSSAIN *ET AL*, 1985; POWERS *ET AL*, 1986]. While the specific mechanisms underlying this phenomenon are not clear, the increase in $\dot{V}E$ with HeO_2 breathing has been attributed predominantly to the physical properties of the gas mixture. By virtue of its higher kinematic viscosity (viscosity · $density^{-1}$, 3x that of Air), HeO_2 significantly reduces airflow turbulence in the large central airways, where airflow is turbulent even at rest [MURPHY *ET AL*, 1969]. While HeO_2 breathing at rest has only a minimal effect on $\dot{V}E$ and its pattern, the effects are much greater and more significant during exercise, as airflow turbulence increases markedly during exercise even in the airways where flow is usually laminar. Therefore, in addition to a reduction in total respiratory resistance, the distribution of airflow resistance within different airway segments (large *.vs.* small) is also altered by HeO_2 breathing during exercise [DRAZEN *ET AL*, 1976; WOOD *ET AL*, 1976].

It has been suggested that the hyperventilatory response to HeO_2 is as result of a reduction in respiratory impedance, i.e. the pressures which the respiratory muscles have to generate for a given level of $\dot{V}E$ is less with HeO_2 breathing [HUSSAIN *ET AL*, 1985]. However, flow-proportional mouth pressure assist of the respiratory muscles (resistive unloading) has been shown to have little effect of $\dot{V}E$ and P_{CO_2} during moderate exercise [GALLAGHER AND YOUNES, 1989]. Furthermore, it has been

shown that the hyperventilatory response to HeO_2 in ponies, is unaffected by diaphragmatic deafferentation [FORSTER *ET AL*, 1994].

It therefore appears, that while respiratory muscle output during exercise is reduced when the normal load is reduced (either with HeO_2 or pressure-assist), there are fundamental differences in ventilatory regulation during exercise, between the two techniques. For example, it is not clear why, the hyperventilatory response to HeO_2 shown to occur even at sub-θan levels of exercise [WARD *ET AL*, 1982], is not attenuated by the fall in P_{a,CO_2} that results. As suggested earlier, if $\dot{V}E$ regulation during steady-state exercise was a result of precise humoral control based on maintaining stability of P_{a,CO_2}, the precise reasons why the $\dot{V}E$ control system is disrupted at these levels of exercise, are not apparent. Indeed, with HeO_2 breathing during supra-θan exercise, the ventilatory response is further compounded by: **1)** the requirement for the ventilatory compensation for the metabolic acidosis and **2)** other stimuli such as increasing body temperature or circulating catecholamines etc. (see section 1.4.2.). Helium breathing has also been reported to have several systemic effects [RAYMOND *ET AL*, 1972; RAYMOND *ET AL*, 1974], and it is possible that the hyperventilatory response to HeO_2 breathing is related to an interaction between the systemic stimulus and the exercise stimulus [GALLAGHER AND YOUNES, 1989].

1.5.3. Possible role of airway afferents in the hyperventilatory response to HeO_2 unloading .

Both in animals and in humans, several studies that have examined the breath-by-breath ventilatory and respiratory motor output responses to HeO_2, show that these changes are evident in the first breath of HeO_2 as the inspirate [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985; PAN *ET AL*, 1987; MAILLARD *ET AL*, 1990; FORSTER *ET AL*, 1994]. In humans, HUSSAIN *ET AL* [1985] showed a significant fall in the rate of rise of diaphragmatic EMG, within the first breath of switching to HeO_2 as the inspirate. FORSTER *ET AL* [1994] have also demonstrated a significant fall in both the rate of rise

and the duration of diaphragmatic EMG within three breaths of HeO_2 in exercising ponies. This immediate and rapid fall in diaphragm EMG suggests the involvement of a possible airway mechanoreceptor based reflex response to switching to HeO_2 (from air breathing) as the inspirate. Due to its higher thermal conductivity (~8x that of air), HeO_2 breathing results in increased heat exchange from the airways [VARENE AND KAYS, 1985], thus possibly altering the temperature profiles in the large airways [MCFADDEN *ET AL*, 1985]. It is not clear whether the altered activation of temperature sensitive airway receptors might play a role in sustaining the hyperventilatory response to HeO_2 breathing during exercise.

It has been suggested that the hyperventilatory response to HeO_2 might be the result of an airway reflex [HUSSAIN *ET AL*, 1985] consequent to an altered activation of irritant and/or other airway receptors [WARD *ET AL*, 1982]. The mucosal lining of both the larynx and the tracheo-bronchial tree is rich in a variety of receptors (sensitive to flow, pressure, temperature and/or CO_2) that have been shown to influence ventilatory control in both humans and animals [SANT'AMBROGIO, 1982; SANT'AMBROGIO *ET AL*, 1983; COLERIDGE AND COLERIDGE, 1986]. Laryngeal receptors have been shown to respond to changes in transmural pressure, flow, changes in intra-luminal P_{CO_2} and/or the respiratory activity of the upper airway musculature [BOUSHEY *ET AL*, 1974; SANT'AMBROGIO *ET AL*, 1983]. The "flow" receptors in particular have been shown to respond to small changes in flow and/or temperature [BOUSHEY *ET AL*, 1974; JAMMES *ET AL*, 1987]. Both intra- and extra-thoracic slow-adapting stretch receptors (SAR) have been shown to respond to changes in transmural pressure, but while those inside the thorax respond to changes in both flow and volume, extra-thoracic tracheal SAR's respond primarily to airflow and its rate of change [SANT'AMBROGIO AND MORTOLA, 1977]. Tracheo-laryngeal afferents in the superior laryngeal nerve that respond predominantly to airway thermal changes have been described. Furthermore, the activity in these afferents has been shown to increase markedly with cold HeO_2

compared to that with cold air, presumably due to the higher thermal conductivity and specific heat of HeO_2 [JAMMES *ET AL*, 1987]. Due to its unique physical properties (↑kinematic viscosity, ↑thermal conductivity), HeO_2 breathing might activate any or all of these receptors. It is therefore possible that both the transient and sustained ventilatory and respiratory neuromuscular adaptations to HeO_2 breathing during exercise, might be as a result of airway reflexes that are triggered by the altered activation of one (or more) of these receptors. Those airway mucosal receptors that are accessible for local anesthesia have been shown to significantly influence ventilatory control and respiratory drive in animals [SANT'AMBROGIO, 1982].

1.5.4. The role of airway afferents in the ventilatory and breathing pattern responses to exercise and during added dead space.

As reviewed earlier, vagally mediated afferent information from the upper airways and the tracheobronchial tree, has been shown to play an important role in ventilatory and breathing pattern control in animals [SANT'AMBROGIO, 1982; WIDDICOMBE, 1986]. In humans, it has been shown that lung inflation in the resting tidal volume range has no effect on ventilation, suggesting that slowly adapting stretch receptor activity if present, is minimal [WIDDICOMBE, 1961]. While it is has been shown that volume-related vagal afferent activity is present at rest [GUZ AND TRENCHARD, 1971], vagal blockade has been shown to have no effect on resting ventilation either in conscious or anesthetized subjects [GUZ *ET AL*, 1964; 1966]. Other studies however suggest that airway afferent blockade (by local anesthetic aerosols) in humans results in an alteration of breathing pattern at rest [SAVOY *ET AL*, 1982], inspiratory motor output [POLACHEK *ET AL*, 1980], or resting pulmonary function [CHAUDHARY AND SPIER, 1979; KUNA *ET AL*, 1988]. Breathing pattern at low exercise levels has been shown to slower and deeper in heart-lung transplantation recipients (with pulmonary denervation) [SCIURBA *ET AL*, 1988], but the response at higher exercise levels was similar to that seen in both normal subjects and patients with cardio-pulmonary disease (but with intact

pulmonary innervation) [GALLAGHER *ET AL*, 1986; GOWDA *ET AL*, 1990]. This suggests that vagal afferent input may influence exercise breathing pattern in humans, at least at low levels of ventilation. In exercising animals (e.g., dogs, ponies), it has been shown that pulmonary denervation [FLYNN *ET AL*, 1985] or vagal cooling [AINSWORTH *ET AL*, 1992] results in slower and deeper breathing pattern, but exercise ventilation is not affected. It has also been shown that with airway afferent blockade, the sensation of breathlessness after exercise was significantly reduced in both normal subjects [WINNING *ET AL*, 1985] and patients with cardio-pulmonary disease [GUZ *ET AL*, 1970; ENRIGHT *ET AL*, 1980]. Furthermore, WINNING *ET AL* [1985] have shown that in normal subjects aerosol airway anesthesia resulted in an increase in minute ventilation and a slower and deeper breathing pattern during exercise. These results were interpreted to mean that airway stretch receptors were active and may play a significant role in ventilatory and breathing pattern control during exercise in humans. These results also suggested that the alteration in stretch receptor activity may have played a role in the genesis of the perceived breathlessness during exercise. In asthmatics for example, there was an increase in exercise minute ventilation and a reduction in exercise induced bronchoconstriction associated with a significant attenuation of dyspnea after aerosol airway anesthesia [ENRIGHT *ET AL*, 1980]. All the above evidence suggests that airway afferent activity may play a significant role in exercise ventilatory and breathing pattern regulation.

A number of investigators have examined the effects of an added external deadspace (V_D) on ventilatory control. Both at rest and at any metabolic rate during exercise, added V_D results in an increase in minute ventilation ($\dot{V}_I$) and P_{CO_2} [JONES *ET AL*, 1971, FENNER *ET AL*, 1972; WARD AND WHIPP, 1980; MCPARLAND *ET AL*, 1991, SYABBALO *ET AL*, 1993; SIDNEY AND POON, 1995]. Figure 1.14 summarizes the results from the study of SYABBALO *ET AL* [1993], who examined the mechanisms underlying the ventilatory response to an added V_D (940 ml) during exercise. Panels A and B show that

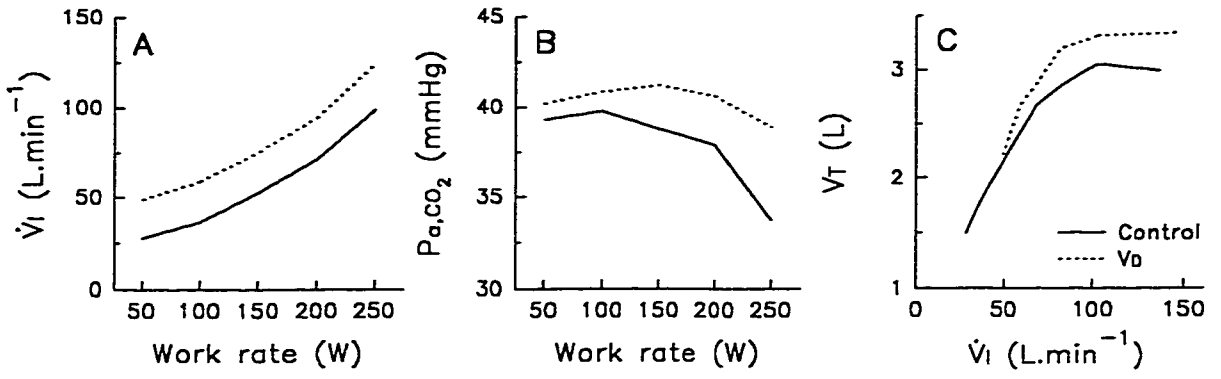

Figure 1.14. Ventilatory response to added dead space during exercise (normoxia). [SYABBALO *ET AL*, 1993].

average $\dot{V}_I$ and estimated P_{a,CO_2} data (n = 9) were higher with an added V_D (dotted line) throughout incremental exercise in these subjects. The increase in $\dot{V}_I$ has been attributed to the increase in P_{CO_2}, but as $\Delta\dot{V}_I/\Delta P_{CO_2}$ with added V_D was higher than that with pure CO_2 load in some studies [GOODE *ET AL*, 1969; SHINDOH *ET AL*, 1988], but not others [WARD AND WHIPP, 1980], it appears the increased P_{CO_2} is not the sole mechanism involved.

This hyperpnea has also been attributed to: **1)** the increased ratio of the physiological deadspace to tidal volume ratio (V_D/V_T), **2)** the transient increase in P_{A,CO_2} that occurs before $\dot{V}_I$ reaches a new steady state or **3)** the alteration of the temporal characteristics of the CO_2 signal reaching the arterial chemoreceptors [FENNER *ET AL*, 1968; GOODE *ET AL*, 1969; CUNNINGHAM *ET AL*, 1973]. While the phenomenon of increased ventilation with added V_D has been studied extensively, the effects on breathing pattern (i.e., V_T - f_b relationships) had not been presented before the study done by MCPARLAND *ET AL* [1991]. However, it has been noticed and reported that the increased $\dot{V}_I$ with added V_D during exercise was achieved mostly by an increase in V_T [JONES *ET AL*, 1971; FENNER *ET AL*, 1972; KELMAN AND WATSON, 1973; SACKNER *ET AL*, 1980]. The study of MCPARLAND *ET AL* [1991] first revealed that at matched levels of $\dot{V}_I$ during exercise, the breathing pattern with an added V_D during exercise was "slower and

deeper" (i.e., $\uparrow V_T$, $\downarrow f_b$). As panel C in figure 1.14 shows, subsequent studies [SYABBALO *ET AL*, 1993] have confirmed these results.

The mechanisms underlying the ventilatory and breathing pattern adaptations to added V_D during exercise have been reviewed extensively by MCPARLAND *ET AL* [1991]. Using a process of elimination, they reasoned that while the breathing pattern changes observed in earlier studies with added V_D could be possibly attributed to: **a)** entrainment of breathing frequency to pedalling rhythm, a phenomenon elicited by a constant pedalling frequency [KELMAN AND WATSON, 1973; WARD *ET AL*, 1980] or, **b)** the hypoxic conditions under which the response to added V_D was studied [GOODE *ET AL*, 1969; CUNNINGHAM *ET AL*, 1973]. However, the persistence of a slower and deeper breathing pattern when the above factors were all accounted for, suggested that this breathing pattern response to added V_D, was due to other factors. Furthermore, the absence of any breathing pattern changes with inhaled CO_2 during exercise [GALLAGHER *ET AL*, 1987], even with higher P_{CO_2} levels (> 50 mmHg) than with added V_D, suggests that the breathing pattern response was not related to the increase in mean P_{CO_2} *per se*. Accordingly, it was suggested that the breathing pattern response to added V_D during exercise was probably as a result of the alteration of the temporal profile of P_{CO_2}. That the altered P_{CO_2} time profile with added V_D is the possible signal is indirectly supported by the evidence that $\dot{V}_I$ increased when the alveolar P_{CO_2} time profile seen with added V_D was simulated without tube breathing [CUNNINGHAM *ET AL*, 1973]. Based on the evidence regarding CO_2 chemoreception, the breathing pattern adaptations to added V_D, may be as a result of the altered P_{CO_2} temporal profile sensed by: **1)** arterial chemoreceptors; **2)** airway/pulmonary chemoreceptors and **3)** central chemoreceptors.

It has been shown that the cyclical changes in alveolar P_{O_2} and P_{CO_2} caused by breathing, are transmitted (after minor damping) to the systemic arterial blood, including that which perfuses the carotid chemoreceptors [CUNNINGHAM *ET AL*, 1986]

and the P_{CO_2} oscillations have been shown to cause oscillations in the carotid body afferent input which appear to have respiratory periodicity [FITZGERALD AND LAHIRI, 1986]. Furthermore, these oscillations in carotid body activity have been shown to influence, respiratory motor output independent of mean carotid body discharge [CROSS *ET AL*, 1979; CROSS AND SEMPLE, 1987], or respiratory timing [BAND *ET AL*, 1969]. However, the hypothesis that the carotid chemoreceptors are activated by the oscillations in the temporal P_{CO_2} profile assumes, that these oscillations are large enough and do occur at higher breathing frequencies as found during exercise. A recent study [CROSS *ET AL*, 1995] has demonstrated pH_a oscillations in man at breathing frequencies similar to those found during exercise. All the above evidence, combined with that from the study of MARSH AND NYE [1982], who showed that the ventilatory response to added V_D in cats disappeared after carotid sinus denervation, suggests that the arterial chemoreceptors in man may be involved in the mediation of the ventilatory and breathing pattern adaptations to added V_D.

Recent studies that have used hyperoxia to silence the carotid bodies both at rest [SIDNEY AND POON, 1995] and during exercise [SYABBALO *ET AL*, 1993], suggest that carotid bodies may not be wholly responsible for the respiratory adaptations to added V_D. As reviewed elsewhere [SYABBALO *ET AL*, 1993], hyperoxia has been shown to abolish: **1)** the fast component of the carotid chemoreceptor response to CO_2

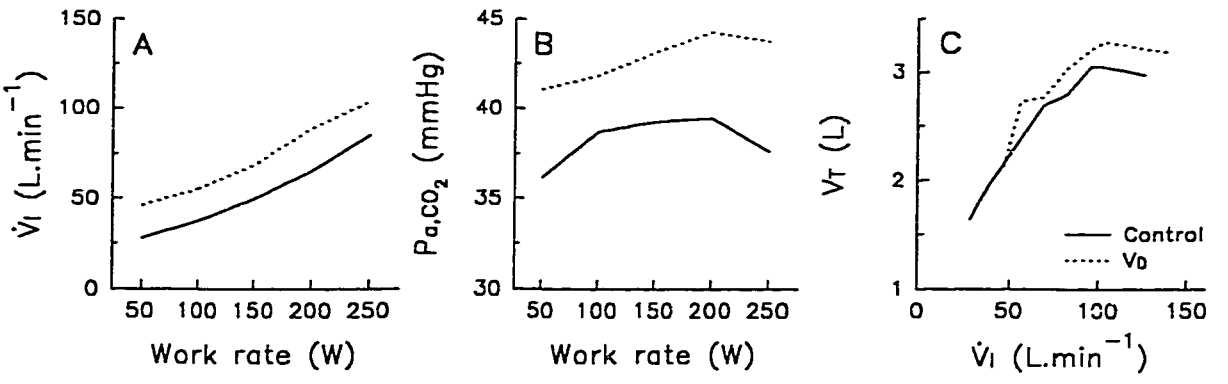

Figure 1.15. Ventilatory response to added dead space during exercise (hyperoxia). [SYABBALO *ET AL*, 1993].

[MILLER *ET AL*, 1974; WARD AND BELLVILLE, 1983]; **2)** ventilatory stimulation by norepinephrine infusion [JOEL AND WHITE, 1968; HEISTAD *ET AL*, 1972] and **3)** ventilatory stimulation by potassium infusion [PATERSON AND NYE, 1991]. Therefore, hyperoxia has been used in several studies to effectively inhibit peripheral chemoreceptor afferent input in humans.

Figure 1.15 summarizes the effects of added V_D in nine healthy humans (mean data from the study of SYABBALO *ET AL* [1993] are shown) during incremental maximal exercise under hyperoxic ($F_IO_2 = 1$) conditions. In comparison to data from the same subjects during normoxia (Figure 1.14), $\dot{V}_I$ at any work rate was reduced (and significantly so at higher work rates) with hyperoxia, presumably because of the removal of the chemoreceptor afferent stimulus to breathing. This reduction in $\dot{V}_I$ resulted in a higher P_aCO_2 with hyperoxia throughout exercise (compared to air breathing values). However, with added V_D, both $\dot{V}_I$ and P_aCO_2 were significantly higher at all work rates during exercise (Panels A and B), even when the subject was breathing 100% O_2, suggesting that arterial chemoreceptors were not involved in the mediation of this response. Furthermore, the slower and deeper breathing pattern response at matched levels of ventilation persisted with hyperoxia (Panel C), suggesting that the arterial chemoreceptors were neither instrumental nor important for the altered breathing pattern observed with added V_D. The authors concluded that while the study excluded a major role for the arterial chemoreceptors in the mediation of the ventilatory adaptations to added V_D during exercise, there was no evidence to exclude the roles of airway/pulmonary chemoreceptors or central chemoreceptors in the mediation of this response. It was also possible that the adaptations to added V_D are part of an overall homoeostatic and optimization response by the respiratory controller in order to reduce respiratory work and improve gas exchange, on the face of an increased ventilatory (mechanical) load faced by the respiratory system [POON, 1987; SIDNEY AND POON, 1995]. The specific

findings that the ventilatory and breathing pattern responses to added VD do not depend on carotid chemosensitivity [SYABBALO *ET AL*, 1993; SIDNEY AND POON, 1995] and the demonstration of the short latency breathing pattern responses to step changes in airway P_{CO_2} in humans [CUNNINGHAM *ET AL*, 1977], suggests that airway receptors may play a major role in the mediation of these responses.

Animal studies have shown that vagal afferents from a variety of upper and lower airway receptors that respond to changes in intra-luminal P_{CO_2}, play a significant role in ventilation and breathing pattern regulation [BOUSHEY AND RICHARDSON, 1973; BARTOLI *ET AL*, 1974; BARTLETT AND SANT'AMBROGIO, 1976; COLERIDGE *ET AL*, 1978; ANDERSON *ET AL*, 1990; BARTLETT *ET AL*, 1992; BRANFORD *ET AL*, 1993]. Some receptors in the larynx are stimulated and some inhibited by intra-laryngeal CO_2 [ANDERSON *ET AL*, 1990; BRANFORD *ET AL*, 1993]. Some studies showed that hypercapnia stimulates laryngeal "irritant" receptors [ANDERSON *ET AL*, 1990; BRANFORD *ET AL*, 1993], while others showed that rapidly adapting (irritant) receptors in the tracheo-bronchial tree are stimulated by hypocapnia [COLERIDGE *ET AL*, 1978]. Slowly adapting (stretch) receptors on the other hand, are inhibited by increases in airway P_{CO_2}, the effects being prominent at or below (~30 mmHg) normocapnic levels [COLERIDGE *ET AL*, 1978], but have been shown to persist up to airway P_{CO_2} levels of 60 mmHg [GREEN *ET AL*, 1986]. It has also been shown that the stretch receptors are affected preferentially by increases in bronchial luminal CO_2 and not by increases in mean arterial P_{CO_2} [BARTOLI *ET AL*, 1974; BARTLETT AND SANT'AMBROGIO, 1976], suggesting that the site of hypercapnia appears functionally closer to the airway lumen than to the smooth muscle layer [MISEROCCHI *ET AL*, 1973]. Furthermore, aerosol airway anesthesia has been shown to be effective against stretch receptor activity in both animal and human studies [DAIN *ET AL*, 1975; CROSS *ET AL*, 1976; CAMPORESI *ET AL*, 1979; FAHIM AND JAIN, 1979; SAVOY *ET AL*, 1982; EASTON *ET AL*, 1985; WINNING *ET AL*, 1985]. The effect of anesthesia on the ventilatory response to inhaled CO_2 in humans has been attributed to the blockade of airway

stretch receptor activity [CROSS *ET AL*, 1976; WINNING *ET AL*, 1985; SULLIVAN *ET AL*, 1987; MADOR, 1993]. A vagal pulmonary CO_2 chemoreflex has been shown to influence breathing pattern in dogs [BARTOLI *ET AL*, 1974]. Using small or large particle anesthetic aerosols (thus determining the site of deposition [LIPPMANN AND ALBERT, 1969; BRAIN AND VALBERG, 1979]), it has been shown that the site of pulmonary CO_2 chemosensitivity in humans is more centrally (tracheo-bronchial tree) located than at the peripheral (alveolar) level [GUZ *ET AL*, 1985; MADOR, 1993]. All of the above evidence clearly suggests an increased airway/pulmonary receptor chemosensitivity to the alterations in both the mean levels of, and the breath-by-breath temporal profiles of CO_2 caused by added V_D. Furthermore, the effect of aerosol airway anesthesia on the ventilatory response to added V_D at rest [SHINDOH *ET AL*, 1988], definitely supports this hypothesis.

1.5.5. Effect of locomotor-respiratory coupling on the ventilatory and breathing pattern responses during bicycle ergometry.

Ventilatory control is the result of central integration of a number of chemical and neuro-mechanical stimuli and exercise is an unique situation when limb movements and breathing movements are no longer independently controlled but, when one exerts a significance influence on the outcome of the other. A number of studies have shown that both feed-forward and feed-back neural mechanisms play a major role in the concomitant increase in ventilation in proportion to the degree of limb movements [AGOSTONI AND D'ANGELO, 1976; DIMARCO *ET AL*, 1983, WHIPP, 1983; CASEY *ET AL*, 1987]. It is also generally accepted that significant interactions exist between exercise and breathing rhythms in humans. The physiological importance of this locomotor - respiratory coupling (LRC) has been examined from the perspectives of both biomechanical advantages of LRC and the independent impact of locomotion on respiratory muscle activity, in the absence of significant LRC. Entrainment, a synchronization of limb movement and breathing pattern, is the most

commonly recognized form of LRC and has been reported extensively in humans [ASMUSSEN, 1964; BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983; YONGE AND PETERSEN, 1983; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; LORING *ET AL*, 1990], quadrupeds [BRAMBLE AND CARRIER, 1983; LAFORTUNA *ET AL*, 1996], birds [BUTLER AND WOAKES, 1980], and in other mammals [BRAMBLE AND JENKINS, 1993].

LRC has been well documented in cursorial mammals (e.g. dogs, horses) and as such the degree of LRC appears to be a function of both gait and the duration of exercise [ATTENBURROW, 1982; BRAMBLE AND CARRIER, 1983; ART *ET AL*, 1991]. While cantering or galloping horses show a significant coupling of breathing and limb rhythm, even under conditions of ventilatory stimulation by CO_2 breathing during exercise [GILLESPIE *ET AL*, 1991], systematic LRC is seldom found in these animals during walking or trotting [ART *ET AL*, 1991; LAFORTUNA AND SAIBENE, 1991]. Exercise breathing pattern in dogs has been shown to be significantly influenced by high frequency panting (used for thermo-regulation) and as a result, the reported findings of LRC (1:1 and 1:2, breathing:limb frequency ratios) in galloping or trotting dogs [BRAMBLE AND CARRIER, 1983; BRAMBLE AND JENKINS, 1993], have been disputed [AINSWORTH *ET AL*, 1989; 1995].

The specific incidence of LRC in exercising quadrupeds has been a significant part of the studies into the biomechanical implications/advantages of LRC on energy expenditure optimization, i.e., a greater ventilatory efficiency if both limb and breathing muscular activity were coordinated [BRAMBLE AND CARRIER, 1983]. With motion, it has been suggested that the forces acting on the trunk and thorax, *viz.* **a)** acceleration/deceleration of visceral contents ("visceral piston"); **b)** concussive forces from limb impact transmitted that result in thoracic pressure and/or volume changes and **c)** abdominal compressive forces that result from lumbo-sacral flexion and extension, are all biomechanically relevant in the generation of airflow during exercise [BRAMBLE, 1989; YOUNG *ET AL*, 1992]. However, conclusive evidence about the

specific quantitative contribution of these biomechanical forces to airflow during exercise in these animals is lacking. Additionally, the importance and the effectiveness of both the visceral piston [YOUNG *ET AL*, 1992] and the role of limb impact on thoracic motion [FREVERT *ET AL*, 1990] have been questioned recently. While the effects of these biomechanical forces seem important in ventilatory energetics, it is clear that it is respiratory muscle action that predominantly contributes to the generation of airflow during exercise in these animals, with or without LRC [DEMPSEY *ET AL*, 1996]. The recent studies of AINSWORTH *ET AL* [1989, 1994, 1995] in both horses and dogs, have confirmed that while LRC may or may not be present, respiratory muscle (diaphragm intercostals and abdominals) activity is significantly associated with the generation of airflow during exercise and that the contribution of passive mechanical forces to changes in intra-thoracic pressures (and to air-flow) was trivial.

In humans, significant entrainment has been documented during different forms of exercise, *viz.* running, cycling and rowing [BECHBACHE AND DUFFIN, 1977; KOHL *ET AL*, 1981; PATERSON *ET AL*, 1986; SZAL AND SCHOENE, 1987; MAHLER *ET AL*, 1991]. While several studies have examined the phenomenon of entrainment closely, conclusive data on the nature of the stimulus that triggers entrainment has been elusive. However, the degree of entrainment has been shown to be influenced by the degree of familiarity (experience) with the given exercise modality [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983; GARLANDO *ET AL*, 1985; MAHLER *ET AL*, 1991; BERNASCONI AND KOHL, 1993] and the type of exercise [BECHBACHE AND DUFFIN, 1977; PATERSON *ET AL*, 1987; BERNASCONI AND KOHL, 1993]. Many studies have suggested that the degree of entrainment increases with increasing exercise intensity [KAY *ET AL*, 1975; JASINSKAS *ET AL*, 1980; SZAL AND SCHOENE, 1989; CARETTI *ET AL*, 1992; BERNASCONI AND KOHL, 1993], or when breathing is paced with auditory cues, e.g., with a metronome [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; PATERSON *ET AL*, 1986; YONGE AND PETERSON, 1987]. While physical fitness has been shown to influence

spontaneous cycling rhythm ("preferred cadence selection") [MARSH AND MARTIN, 1997], it does not seem to apparently affect the degree of LRC [GARLANDO *ET AL*, 1985]. Furthermore, it appears that at comparable exercise intensities, the degree of LRC is higher during running than cycling [BECHBACHE AND DUFFIN, 1977, BERNASCONI AND KOHL, 1993], perhaps because humans (as bipedal mammals) find running a more natural form of movement [BRAMBLE AND CARRIER, 1983; BRAMBLE, 1983].

However, it has been difficult to assess the importance of the passive biomechanical forces in ventilatory control and respiratory muscle energetics during exercise in humans. The contribution of the visceral piston (hepatic/diaphragmatic combination) to thoracic expansion in humans has been questioned [TENNEY AND LEITER, 1994]. However, the low incidence of entrainment in subjects performing upper body exercise (compared to that present during treadmill running) has been intrepreted to mean that both the greater involvement of active muscles with whole-body exercise and the piston-like activity of visceral contents may significantly influence LRC in exercising humans [PATERSON *ET AL*, 1986; MACDONALD *ET AL*, 1992]. Furthermore, it has also been shown that the concussive forces that result from leg impact (footfall) during running, contribute but to a trivial proportion of the tidal volume change at the mouth, suggesting that passive biomechanical forces do not influence airflow in exercising humans [BANZETT *ET AL*, 1991]. Elite rowers have been shown to switch from 1:1 to 2:1 breath/stroke ratio with increasing exercise intensity [MAHLER *ET AL*, 1991; STEINACKER *ET AL*, 1993], presumably due to a tidal volume limit imposed by abdominal compression that impaired diaphragmatic excursions [CUNNINGHAM *ET AL*, 1975] as also due to increased inspiratory elastic work [STEINACKER *ET AL*, 1993]. However, in these subjects it was shown that the increasing expiratory flow-limitation (as a result of increased frequency of breathing) posed a new mechanical constraint for increasing ventilation. Furthermore, it has been shown that while both significant entrainment and the increasing inspiratory and expiratory

mechanical constraints on ventilation were apparent during rowing at high intensity, inspiratory "phase-coupling" (onset of inspiration) with rowing was quite irregular, suggesting that despite the increase in biomechanical constraints, there was no apparent optimization/regulation of the onset of either inspiration or expiration in these subjects [MAHLER *ET AL*, 1991].

While the bulk of available evidence suggests that some synchronization of limb and breathing rhythms is present in exercising humans [BECHBACHE AND DUFFIN, 1977; ; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; LORING *ET AL*, 1990; MAHLER *ET AL*, 1991; BERNASCONI AND KOHL, 1993], some studies have suggested otherwise [KAY *ET AL*, 1975], and the differing results among the studies have been attributed [PATERSON *ET AL*, 1986] to differences in experimental design, the type of exercise and more importantly, the criteria used to quantify LRC. Most of the above study designs promoted LRC during exercise, e.g., by paced breathing [BECHBACHE AND DUFFIN, 1977; GARLANDO *ET AL*, 1985; BERNASCONI AND KOHL, 1993], enforced pedalling rates [JASINSKAS *ET AL*, 1980; PATERSON *ET AL*, 1986] (including those that advised a "comfortable and constant" rate [KOHL *ET AL*, 1981]), presumably to study its effect on exercise ventilatory control [TAKANO, 1988; CARETTI *ET AL*, 1992, HUNTER *ET AL*, 1997] or oxygen uptake [GARLANDO *ET AL*, 1985; BERNASCONI AND KOHL, 1993] during bicycle ergometry. However, there are no conclusive data regarding the effects of spontaneous LRC in humans (if and when present) on the above variables throughout maximal incremental exercise. While it is acceptable that these exercise designs (sub-maximal exercise [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; GARLANDO *ET AL*, 1985; CARETTI *ET AL*, 1992; BERNASCONI AND KOHL, 1993], sub-anaerobic exercise [TAKANO, 1988], constant work rate exercise [KOHL *ET AL*, 1981; PATERSON *ET AL*, 1986; HUNTER *ET AL*, 1997) were used to study the role of LRC in exercise ventilatory control in the steady-state [GARLANDO *ET AL*, 1985; HAGAN *ET AL*, 1992], in order to avoid the confounding influence of progressive metabolic acidosis on exercise

ventilation [WHIPP, 1983], there are also no objective data available on the importance of LRC (if any) in ventilatory control at higher exercise levels. It is also not clear, whether LRC (if and when present) has a significant influence on breathing pattern during cycle ergometry. At matched metabolic rates during exercise, it has been shown that breathing frequency increases in proportion to limb frequency in both animals [BAYLY *ET AL*, 1989] and humans during treadmill running [LORING *ET AL*, 1990]. LORING *ET AL* [1990] further showed that limb rhythm had a significant influence on breathing frequency, even in the absence of significant entrainment. Furthermore, the question of whether spontaneous LRC (entrainment, inspiratory and/or expiratory phase-coupling in the absence of enforced pedalling rates) has any influence on breathing pattern in naive and healthy humans performing maximal incremental bicycle ergometry, has not been fully resolved and merits closer study.

1.6. Summary.

This chapter provided a general overview of some of the well understood mechanisms involved in the control of exercise ventilation (and its pattern) in humans. The possible roles of the various chemical and non-chemical determinants of exercise $\dot{V}_E$ were also described in the previous sections. As suggested earlier, there is abundant information available on the chemoreceptor(s) based control of exercise $\dot{V}_E$ and their role in the regulation of breathing pattern, arterial blood gases and acid-base homoestasis throughout exercise of varying intensities [WHIPP, 1983; DEMPSEY *ET AL*, 1994; WARD, 1994]. As figure 1.10 reveals, there is only limited information available on the roles of some of the elements involved in the neuro-mechanical feedback control of exercise $\dot{V}_E$ in humans. The studies described in this thesis will therefore attempt to address some of these less-understood issues in the control of exercise $\dot{V}_E$ and its pattern.

It has long been known that while at rest the diaphragm is the main muscle of inspiration, the increase in $\dot{V}_E$ during exercise is possible due to an increasing

recruitment of all the respiratory active muscles [GRIMBY *ET AL*, 1976]. It has also been suggested however that there is a divergence between the neuromuscular output ($Pm_{0.1}$, an index of the drive to breathe) and mechanical output (flow), possibly due to an non-linear increase in respiratory impedance during exercise [LIND AND HESSER, 1984; HUSSAIN *ET AL*, 1985]. Chapter 2 of this thesis will examine the evolution of inspiratory and expiratory muscle pressures and the dynamic relationship between Total P_{mus} (neuromuscular output) and $\dot{V}_E$ (mechanical output) throughout constant work rate heavy exercise. The role of the intrinsic load faced by the respiratory muscles in ventilatory regulation during heavy exercise will be examined in chapter 3. While it has been shown that a reduction in respiratory load does not affect $\dot{V}_E$ during light to moderate exercise [GALLAGHER AND YOUNES, 1989], the reduction in airflow resistance with HeO_2 breathing has been shown to result in an uncorrected tachypneic hyperventilation, in many studies. It has also been suggested that this immediate response to HeO_2 breathing may be due to its exclusive effect on airflow dynamics and may be mediated (and sustained) by airway reflexes [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985]. Chapter 4 will therefore examine the role of airway receptors in the mediation of the hyperventilatory response to HeO_2 breathing during constant work rate exercise in humans.

The addition of an external deadspace has been shown to result in an increase in $\dot{V}_E$ and P_{a,CO_2} both at rest and during exercise in most humans. [WARD AND WHIPP, 1980]. Furthermore, it has been demonstrated that at matched ventilatory levels during moderately heavy exercise, added V_D results in a "slower and deeper" breathing pattern [MCPARLAND *ET AL*, 1991]. It has however been shown that these ventilatory adaptations to added V_D during exercise are not due *per se* to an increase in mean P_{a,CO_2} [GALLAGHER *ET AL*, 1987], but possibly as a result of P_{CO_2} oscillations in the airways and/or in the arterial blood. Furthermore, these responses have been shown to persist with hyperoxia [SYABBALO *ET AL*, 1993], suggesting that the peripheral

chemoreceptors do not play a major role in this response. The effect of airway anesthesia on the ventilatory response both during exercise [WINNING *ET AL*, 1985] and with added V_D [SHINDOH *ET AL*, 1988], suggests that airway receptors in humans may be involved in exercise $\dot{V}_E$ regulation. Therefore, the possible role of airway reflexes (from chemosensitive airway receptors) in the regulation of $\dot{V}_E$ and breathing pattern in humans during incremental exercise with and without added V_D, will be examined in chapter 5.

It is currently accepted that both feedback and feedforward neural mechanisms may play a major role in the concomitant increase of $\dot{V}_E$ in proportion to limb movements during exercise [AGOSTONI AND D'ANGELO, 1976; DIMARCO *ET AL*, 1983; WHIPP, 1983; CASEY *ET AL*, 1987]. Several studies have also demonstrated that significant interactions between exercise and breathing rhythms exist in humans. Entrainment of the breathing frequency, the most common form of locomotor-respiratory coupling (LRC) has been reported extensively in humans [BECHBACHE AND DUFFIN, 1977; LORING *ET AL*, 1990], quadrupeds [BRAMBLE AND CARRIER, 1983; LAFORTUNA *ET AL*, 1996], birds [BUTLER AND WAKES, 1980] and in other mammals [BRAMBLE AND JENKINS, 1993]. While the incidence of LRC in exercising humans has been extensively examined, there is little or no information on whether humans exhibit spontaneous LRC while pedalling freely (i.e., without an imposed pedalling frequency) and if so, whether the LRC has any effect on exercise performance or specifically, on breathing pattern during incremental cycle ergometry. The studies described in chapter 6 will examine whether LRC occurs spontaneously in untrained normal humans performing incremental bicycle ergometry, using three ranges of pedalling frequency. The result of these studies (i.e. the presence and/or the lack of effect of spontaneously occurring LRC on exercise variables and breathing pattern) would therefore provide more information on the validity of incremental bicycle ergometry, which is the most common technique employed in cardio-pulmonary exercise testing.

2. THE RELATIONSHIP BETWEEN RESPIRATORY MUSCLE PRESSURES AND MINUTE VENTILATION DURING HEAVY EXERCISE.

2.1. Introduction.

The pattern of respiratory muscle recruitment and the individual contribution of the different respiratory muscle groups to ventilation at rest and during exercise, have been the focus of many studies in the past. At rest, inspiration is predominantly as a result of diaphragmatic contraction [GRIMBY *ET AL*, 1976; LEVINE *ET AL*, 1988], while expiration is a passive process determined by the interaction of inspiratory muscle pressure decay ("expiratory braking") and the elastic characteristics of the respiratory system [MEAD AND AGOSTONI, 1964; AGOSTONI AND CITTERIO, 1979; SHEE *ET AL*, 1985]. It is well documented that during mild and moderate exercise, other inspiratory-accessory and expiratory (abdominals) muscles are recruited to meet the increasing flow requirements [GRIMBY *ET AL*, 1976; HENKE *ET AL*, 1988; LEVINE *ET AL*, 1988]. Furthermore, it has been shown that during heavy endurance exercise (> 80% maximal oxygen uptake), inspiratory-accessory muscles contribute more to the increase in inspiratory air flow, while diaphragmatic pressures plateau [JOHNSON *ET AL*, 1993; MADOR *ET AL*, 1993].

A recent report [ALIVERTI *ET AL*, 1997] however has shown that while trans-diaphragmatic pressure increased only modestly with increasing exercise intensity, the dramatic increases in both the velocity of diaphragm shortening and diaphragmatic work suggest that the diaphragm during exercise behaves essentially as a flow generator rather than a pressure generator. The authors also suggested that while there is an immediate increase in central drive to all respiratory muscle

groups in the transition between quiet breathing and exercise, this drive increases equally and proportionally to all muscle groups with increasing exercise intensity thereafter. The translation of this drive (into force or velocity of shortening) however depends on the load on the specific muscle groups. For example, the increase in abdominal pressures serves to off-load the diaphragm thus enabling a dramatic increase in its velocity of shortening (flow), with only modest increases in its force (pressure). Increasing expiratory muscle recruitment during exercise has been inferred from the measurement of rib-cage and abdominal volume displacements [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976; HENKE *ET AL*, 1988], changes in end-expiratory lung volume [LIND AND HESSER, 1984; JOHNSON *ET AL*, 1993], expiratory pleural [LEBLANC *ET AL*, 1988; KEARON *ET AL*, 1991] and/or gastric pressures [BYE *ET AL*, 1984]. Recent studies in humans also indicate that while inspiratory pleural pressures plateau, expiratory pleural pressures continue to increase throughout heavy endurance exercise [KEARON *ET AL*, 1991]. More recently, SLIWINSKI *ET AL* [1996] have shown that during heavy exercise after induced global inspiratory muscle fatigue, increasing tonic and phasic abdominal muscle pressures contribute in maintaining tidal volume despite reduced diaphragmatic and rib-cage inspiratory muscle activity. In addition to increasing airflow, expiratory muscle activity during exercise reduces end-expiratory lung volume [HENKE *ET AL*, 1988]. The resultant increase in outward elastic recoil of the respiratory system combined with the relaxation of the abdominal muscles at end expiration contribute significantly to lung inflation [GRIMBY *ET AL*, 1976]. Furthermore, the gradual relaxation of abdominal muscle contraction well into inspiration has been interpreted as assisting in diaphragmatic output, while stabilizing the rib-cage thus reducing distortion [ALIVERTI *ET AL*, 1997].

During moderate prolonged exercise (e.g. < 50% of maximal work rate, $\dot{W}max$), minute ventilation ($\dot{V}E$) increases initially, but stabilizes soon thereafter [KEARON *ET AL*, 1991]. $\dot{V}E$ however, continues to increase throughout constant work-rate

heavy exercise (CWHE, > 70% $\dot{W}_{max}$) [KEARON *ET AL*, 1991; JOHNSON *ET AL*, 1993], resulting in an ever-increasing load on all the respiratory muscles. A variety of indices, **1)** Rib cage-abdominal pressure-volume relationships [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976; HENKE *ET AL*, 1988; LEVINE *ET AL*, 1988; ALIVERTI *ET AL*, 1997], **2)** EMG [BYE *ET AL*, 1984]) and **3)** pressure [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976; BYE *ET AL*, 1984; HENKE *ET AL*, 1988; LEBLANC *ET AL*, 1988; LEVINE *ET AL*, 1988;; KEARON *ET AL*, 1991; JOHNSON *ET AL*, 1993; ALIVERTI *ET AL*, 1997] have been used in the past to assess patterns of respiratory muscle activity during exercise.

While the above indices provide for qualitative assessment, quantitative measures of net respiratory muscle pressure (P_{mus}) throughout the breathing cycle during heavy exercise, have been relatively scarce. The measurement of P_{mus} throughout the respiratory cycle however provides information on the relative contributions of all the inspiratory (not just the diaphragm) and expiratory muscles to the ventilatory output of heavy exercise. P_{mus} measurements throughout the respiratory cycle also allow for the assessment of post-inspiratory inspiratory activity (PIIA), by which inspiratory P_{mus} (P_{musI}) "brakes" the start of expiration [AGOSTONI AND CITTERIO, 1979; SHEE *ET AL*, 1985]. Data from animal studies also suggest that diaphragmatic PIIA remains the same or increases during exercise [AINSWORTH *ET AL*, 1996], or with hypercapnic ventilatory stimulation [OLIVEN *ET AL*, 1985; SMITH *ET AL*, 1989].

2.1.1. Study objectives.

This study was designed to address the following issues: **1)** What is the relationship between the ventilatory output and net respiratory muscle pressure (Total P_{mus}) throughout the breathing cycle, in humans performing CWHE to exhaustion? **2)** What is the relative contribution of inspiratory and expiratory pressures to minute ventilation during CWHE in humans? **3)** What happens to post-inspiratory activity of the inspiratory muscles in humans during CWHE ?

Previous studies that have examined the relationship between minute ventilation and pressure (measured as $P_{m0.1}$, mouth pressure at 100 ms into inspiration [LIND AND HESSER, 1984; HUSSAIN *ET AL*, 1985], or P_{es}, esophageal pressure [WANKE *ET AL*, 1991]), or their rates of change [WANKE *ET AL*, 1991] (dP/dt) during exercise, have produced conflicting results. It has been suggested that the non-linear relationship between $\dot{V}_E$ and $P_{m0.1}$ during exercise [LIND AND HESSER, 1984; HUSSAIN *ET AL*, 1985], was due to the non-linear increase in respiratory impedance during exercise [HUSSAIN *ET AL*, 1985]. As discussed elsewhere [WHITELAW AND DERENNE, 1993] and as shown in figure 1.12 in previous chapter, while $P_{m0.1}$ is an useful non-invasive index of inspiratory muscle output, its interpretation during exercise is confounded by **a)** the changes in end-expiratory lung volume, **b)** the changes in the shape of the inspiratory P_{mus} waveform [GALLAGHER AND YOUNES, 1989; WHITELAW AND DERENNE, 1993] and **c)** the varying temporal difference between the start of neural and mechanical inspirations [GALLAGHER AND YOUNES, 1989]. Furthermore, occluded airway pressure measured at the start of inspiration does not necessarily reflect the complex interactions between inspiratory (I) and expiratory (E) forces throughout the breathing cycle, that ultimately contribute to air flow with each breath. The relation between $\dot{V}_E$ and P_{mus} has therefore been measured throughout the respiratory cycle (Total P_{mus} and its components) in subjects performing heavy exercise in this study.

Inspiratory muscle pressure (P_{musI}) at any time during exercise can be expressed in terms of the dynamic capacity (P_{capI}) of the muscles to generate that pressure. While the demand on all the inspiratory muscles increases during heavy exercise ($\uparrow P_{musI}$), the capacity to generate that pressure decreases ($\downarrow P_{capI}$) with increases in lung volume [LEBLANC *ET AL*, 1988; JOHNSON *ET AL*, 1992] and inspiratory flow rate [AGOSTONI AND FENN, 1960; LEBLANC *ET AL*, 1988; JOHNSON *ET AL*, 1992]. P_{musI} in this study has therefore been measured as a fraction of volume-matched, flow-corrected P_{capI}, as an index of inspiratory muscle load during CWHE.

2.2. Methods.

2.2.1. Subjects.

Six healthy males (average age, 25 years) with no previous history of cardio-pulmonary or neuro-muscular disorders were recruited and gave informed consent in writing. On a preliminary visit to the laboratory, each subject had a physical examination, an electrocardiogram and pulmonary function assessment. Absolute lung volumes were measured in a body-box (Cardio-Pulmonary Instruments, Houston). The subjects were physically active and well motivated to perform exhausting exercise; subjects 1, 3 and 5 exercised regularly (cycling, swimming, weight-training etc., 3 - 4 times/wk); subjects 2 and 4 took part in recreational exercise (cycling, tennis etc.) and subject 6 exercised infrequently. They were specifically advised to avoid any strenuous physical activity on the day of the test and to refrain from food and caffeinated drinks for 2 hours before exercise testing.

2.2.2. Equipment.

Exercise tests were performed on an electrically braked cycle ergometer (Godart 18070). Subjects wore nose-clips and breathed through a mouth-piece. Inspiratory and expiratory flows ($\dot{V}$) were measured separately using two pneumotachograph-transducer (Fleisch #3-Validyne MP45, ± 2 cmH_2O) assemblies on either side of a two-way non-rebreathing valve (Vacumed K271). The response of this system was linear over the range of flows measured and the resistance of the inspiratory and expiratory limbs of the breathing circuit was less than 1.0 $cmH_2O \cdot L^{-1} \cdot s$ at flow rates upto 6 $L \cdot s^{-1}$. The individual flow signals (I and E) were monitored on a breath-by-breath basis for zero drift [GOWDA *ET AL*, 1990] and were integrated electronically (Gould), to provide biphasic $\dot{V}$ and volume (V) throughout exercise. The expiratory pneumotachograph was heated. Respired gases (O_2 and CO_2) were monitored by a mass-spectrometer calibrated with two standard gas mixtures of known composition. Electrocardiogram (ECG) and heart rate (HR) were recorded

continuously using standard chest leads. Intra-pleural pressure (P_{pl}) was measured with an esophageal balloon-catheter system connected to a pressure transducer, using standard techniques [MILIC-EMILI *ET AL*, 1964]. The balloon, with known characteristics (Zero volume < 1.5 ml, cutoff frequency > 10 Hz) was carefully positioned in the esophagus where the best P_{pl} signal was obtained (most negative at end expiration and with the least cardiogenic artifacts). An occlusion test [BAYDUR *ET AL*, 1982] was used to check the position and the volume of the balloon before and after exercise. Both P_{pl} and mouth pressure (P_m) were measured with Validyne (MP45) transducers and calibrated against a water manometer at the start of each test. All signals ($\dot{V}$, V, P_{pl}, P_m, ECG, HR, O_2 and CO_2) were recorded continuously on an 8-channel strip-chart recorder (Gould 8000), sampled (at 100 Hz) and digitized. Minute by minute exercise data were then analyzed on the microcomputer.

2.2.3. Chest wall mechanics.

Static elastic recoil of the chest wall ($P_{w,el}$, Figure 2.1) and inspiratory muscle strength (P_{maxI}) were measured in all subjects, on a separate occasion. Care was taken to make the measurements in a position identical to that assumed on the cycle ergometer during exercise. Two methods were used to measure $P_{w,el}$ (see below)

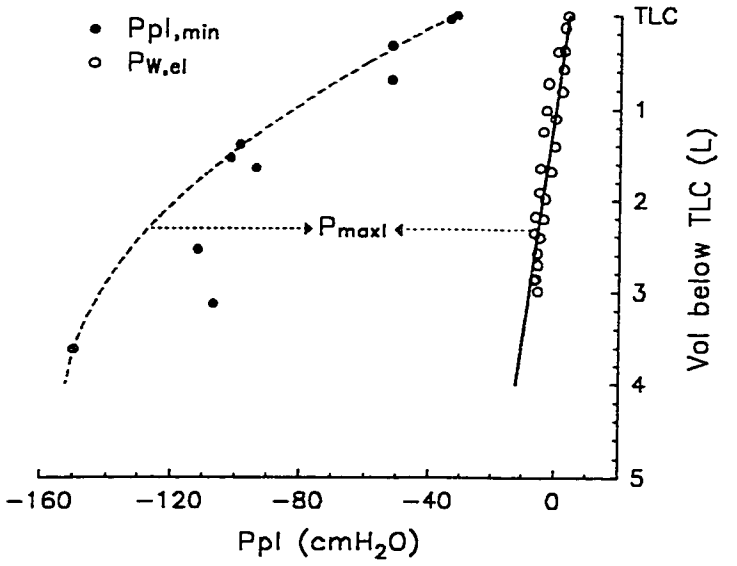

Figure 2.1. Assessment of chest wall elastic recoil and inspiratory strength.

and reproducible measurements of static chest wall elastic recoil were available from only one method, in each subject.

Relaxation technique [RAHN *ET AL*, 1946]: The subjects were trained to relax against an occluded airway after full inspiration to total lung capacity (TLC). The occlusion was then released in a step-wise fashion when the subject expired passively through a flow-resistor (I.D. = 3 mm). Relaxation pressures (P_{pl}) were obtained during occlusion steps, at various lung volumes below TLC. That the subject was relaxed at each volume step was confirmed by observing the P_{pl} signal for a steady plateau (without artifacts). The maneuver was repeated several times and only the relaxed, reproducible data were used to construct the chest wall P - V relation (Figure 2.1).

Weighted spirometry: A modification of the weighted spirometry technique [CHERNIACK AND BROWN, 1965; ESTENNE *ET AL*, 1983] was employed. A special loading-unloading device [YOUNES *ET AL*, 1987; KRISHNAN, 1992] was used to apply static positive airway pressures and was connected to a closed breathing system that had a regulated 100% O_2 supply and a CO_2 absorber on the expiratory limb. All the subjects were encouraged to breathe normally and relax their respiratory muscles at end expiration. The subject was seated comfortably and breathed on the apparatus for 3 - 5 minutes until the inspired O_2 concentration stabilized at 21% and end-expiratory lung volume (EELV) was stable. With the subject thus relaxed, static airway pressures (1 - 8 cmH_2O) were applied at 2 minute intervals. The changes in both the baseline EELV (ΔV) and P_{pl} at end expiration (ΔP_{pl}) were measured at each pressure step. That the subject was relaxed was confirmed by the breath-by-breath reproducibility (during several breaths) of the end-expiratory P_{pl} values at each pressure step. The chest wall P - V relation was then constructed using P_{pl} measured at functional residual capacity (FRC) and the slope of the ΔV - ΔP_{pl} relation.

Inspiratory muscle strength: The subject was instructed to exert maximal inspiratory efforts against an occluded airway, at various lung volumes from TLC down to

residual volume. The most negative P_{pl} ($P_{pl,min}$) was measured during these efforts. P_{pl} displayed on an oscilloscope served as visual feedback to the subject to maximize his efforts. Lung volume at each step was corrected for decompression and a curve of $P_{pl,min}$ - V was then constructed in each subject.

2.2.4. Exercise testing.

Maximal incremental exercise (MIE): At least 3 - 5 days before CWHE, each subject performed an incremental exercise test to volitional maximum. Exercise began at 50 watts after 2 minutes of breathing on the mouth piece, at rest. The work-load was then raised incrementally (25 W/min) until the subject was unable to continue exercise. Peak oxygen uptake ($\dot{V}o_{2max}$) was calculated from the minute of the last completed work-load ($\dot{W}_{max}$).

Constant work heavy exercise (CWHE): While seated on the cycle ergometer, each subject was first trained to make inspiratory capacity (IC) maneuvers. This was followed by 2 minutes of quiet breathing and a short warm-up exercise (50 watts for 2 minutes). The subject was then alerted and the work load was abruptly raised to the pre-determined level (~80% $\dot{W}_{max}$). The subject pedaled at 50 - 70 rpm against this work load using speedometer feedback, until exhaustion. At the end of every 2 minutes during CWHE, each subject was instructed to inhale to TLC and hold his breath with glottis open, for 1 second (IC maneuver). The validity of these IC maneuvers (full inspiration to TLC) was ensured by one investigator who monitored both lung volume and reproducible P_{pl} ($P_{pl,IC}$) throughout each exercise test.

2.3. Data analysis.

For each minute of exercise, the computer marked all valid breaths (except those interrupted by swallowing, cough and after IC maneuvers, < 5 - 6 /min). The onset and end of inspiratory and expiratory $\dot{V}$ were identified. The computer then calculated inspiratory (T_I), expiratory (T_E) and total breath (T_T) durations, for each breath. Tidal volume (V_T) was obtained by digital integration of expiratory flow, to

calculate $\dot{V}_E$. For each minute of exercise, the computer was then used to derive (by interpolation) the average time course of all signals ($\dot{V}$, Ppl etc.) at 1% intervals of T_I and T_E. The techniques employed in the assessment of the net dynamic pressure generated by all the respiratory muscles (P_{mus}) with each breath is now described.

2.3.1. Methods of assessment of respiratory muscle pressure (P_{mus}).

Figure 2.1 graphically illustrates the static P - V relationships of the chest-wall ($P_{W,el}$, relaxation configuration) and the most negative P_{pl} ($P_{pl,min}$) that could be generated by maximal occluded inspiratory efforts in one subject. At any lung volume, with inspiratory muscle activity, the horizontal distance between these curves represents the static volume-matched inspiratory muscle strength (P_{maxI}). Thus:

$$P_{maxI} = P_{W,el} - P_{pl,min} \qquad \textbf{(2.1)}$$

The time course of the net dynamic pressure that results from the contraction of all the respiratory muscles throughout each breath was then calculated using previously described techniques [CAMPBELL, 1958; MEAD AND AGOSTONI, 1964; YOUNES AND KIVINEN, 1984; GALLAGHER AND YOUNES, 1989]. These techniques treat respiratory muscle pressure (P_{mus}) as if it were used to overcome the visco-elastic properties of the respiratory system with each breath. Therefore:

$$P_{mus} = P_{el} + P_{res} + P_{in} \qquad \textbf{(2.2)}$$

where P_{el}, P_{res}, and P_{in} are the pressures used to overcome the elastic, resistive and inertial properties of the respiratory system (airways, lungs and chest wall) respectively. Inspiratory P_{mus} is arbitrarily assigned a positive value and expiratory P_{mus} is negative. Since the inertial pressure losses in the respiratory system are usually very small, equation 2.2 can be re-written as:

$$P_{res} = P_{mus} - P_{el} \qquad \textbf{(2.3)}$$

Thus inspiratory flow (i.e. P_{res} is +ve) will begin (or continue) if and only if P_{mus} exceeds the recoil pressure of the respiratory system and expiratory flow will begin (or continue) if and only if P_{mus} is less than P_{el}. In the static condition (and in the absence

of respiratory muscle contraction, e.g. at FRC), P_{pl} which represents the pressure across the lungs (and airways), is equal (but opposite) to the elastic recoil of the chest wall (Figure 1.4), i.e. $P_{pl} = P_{w,el}$. Furthermore in the presence of respiratory muscle contraction in the static condition (i.e. no flow), P_{pl} will deviate from $P_{w,el}$ by an amount that is equal to the pressure generated by the respiratory muscles (P_{mus}). Therefore,

$$P_{pl} = P_{w,el} - P_{mus} \text{ or } P_{mus} = P_{w,el} - P_{pl} \quad \textbf{(2.4)}$$

Under dynamic conditions (i.e. with flow) however, $P_{w,el} - P_{pl}$ will underestimate P_{mus}, as part of the pressure in the chest wall is used to overcome flow resistance elements of the chest wall (Rw) and will thus not manifest in P_{pl}. Therefore,

$$P_{mus} = P_{w,el} - P_{pl} + P_{w,res} \quad \textbf{(2.5)}$$

where $P_{w,res}$ is the pressure used to overcome the flow resistance of the chest wall.

Figure 2.2 describes both the static and dynamic P - V relationships in a minute during exercise in one subject. In the left panel, the distance between the $P_{w,el}$ and $P_{pl,min}$ curves represents the potential for inspiratory muscle pressure generation. The loops representing dynamic pressure development across the lungs (P_{pl}) and the chest wall (Pw) are also shown. The hatched portions of these loops

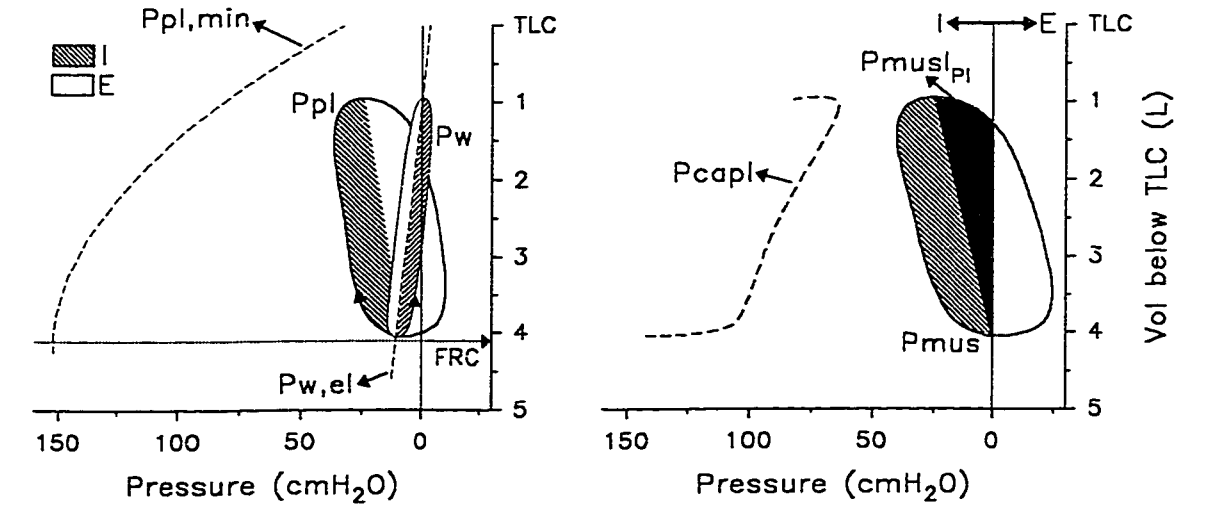

Figure 2.2. Dynamic Pressure - Volume relationships in the respiratory system.

represent inspiratory (I) flow and the open portions represent expiratory (E) flow. Pressure changes throughout each breath occur in the clock-wise direction across the lungs, while those across the chest-wall occur in the anti-clockwise direction. The P_{mus} loop during this breath is shown in the right-panel and at any lung volume within each breath represents the sum of the pressures across the lungs (P_{pl}) and chest wall ($P_W = P_{W,el} + P_{W,res}$). Inspiratory P_{mus} (P_{musI}) is all of the loop to the left of the zero pressure line and it is evident that inspiratory muscle activity continues into the first part of expiration (post-inspiratory P_{musI}, $P_{musI_{pI}}$ is shown as the dark shaded region of the P_{musI} loop). Also shown in the right panel of figure 2.2 is the dynamic capacity of the inspiratory muscles to generate pressure (P_{capI}, see below).

Figure 2.3 illustrates an example of how breath-by-breath P_{mus} data during exercise could be calculated using the instantaneous $\dot{V}$, V and P_{pl} values on the computer. As $P_{W,el} = V \cdot E_{lW}$ and $P_{W,res} = \dot{V} \cdot R_W$, equation 2.5 becomes:

$$P_{mus} = V \cdot E_{lW} - P_{pl} + \dot{V} \cdot R_W \qquad \textbf{(2.6)}$$

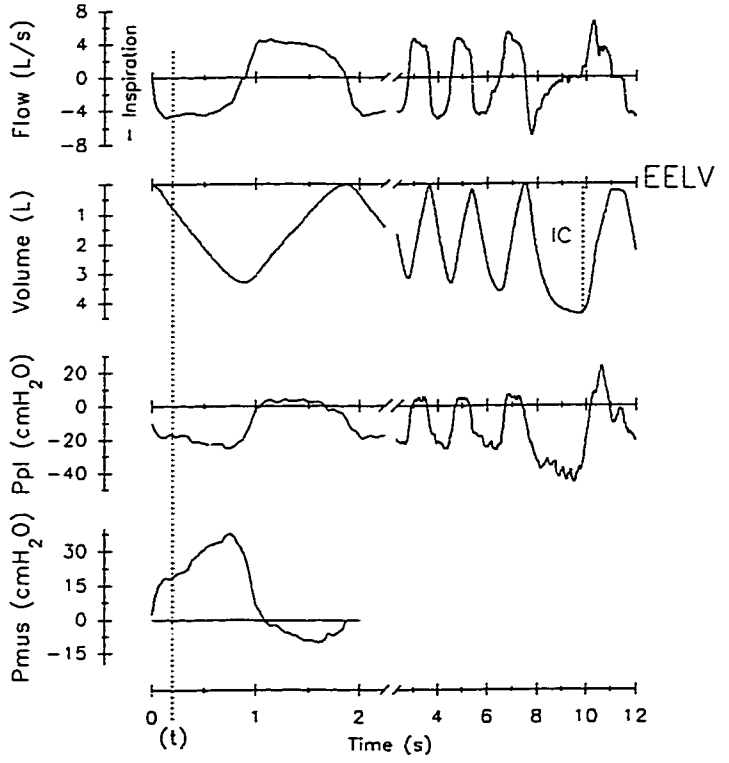

Figure 2.3. Method of assessment of respiratory muscle pressure (P_{mus}).

where Elw represent chest wall elastance. A value of 1.0 $cmH_2O \cdot L^{-1} \cdot s$ was used for Rw, as this is the normal value of Rw for subjects of this age and as there is very little variation between results of different studies [ARONSSON *ET AL*, 1977; BARNAS *ET AL*, 1989; BARNAS *ET AL*, 1992]. Figure 2.3 illustrates breath-by-breath $\dot{V}$, V and P_{pl} data during exercise in one subject. The volume was measured in relation to end-expiratory lung volume (EELV) that was assessed from the IC measured for that minute of exercise (EELV = TLC - IC). Using equation 2.6. it is therefore possible to calculate instantaneous P_{mus} during a single breath (as shown in figure 2.3) or for a range of breaths during any minute of exercise in each subject, using the instantaneous values of $\dot{V}$, V and P_{pl}, given measured Elw and normal values for Rw. It is also evident from figure 2.3 that P_{mus} and its components are constantly changing throughout the respiratory cycle.

The method used to calculate inspiratory and expiratory P_{mus} variables for

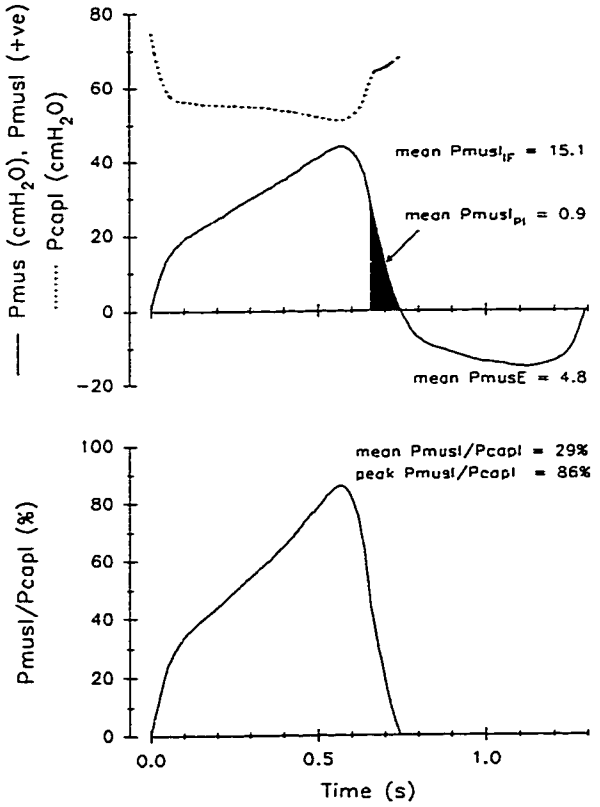

Figure 2.4. Method of assessment of different P_{mus} variables.

each minute of CWHE is illustrated in Figure 2.4. Mean inspiratory P_{mus} (P_{musI}) was calculated as the area of the positive segment of the P_{mus} waveform averaged over the total breath duration (T_T).

$$\text{mean } P_{musI} = \frac{1}{T_T}\int P_{musI} \qquad \textbf{(2.7)}$$

Inspiratory pressure (P_{musI}) throughout each breath was subdivided into its component parts: P_{musI} during mechanical inspiration (during inspiratory flow, $P_{musI_{IF}}$) and P_{musI} persisting during the initial part of expiration (post-inspiratory inspiratory activity ($P_{musI_{PI}}$), shaded area - Figure 2.4). Mean $P_{musI_{IF}}$ was then calculated as:

$$\text{mean } P_{musI_{IF}} = \frac{1}{T_T}\int P_{musI_{IF}} \qquad \textbf{(2.8)}$$

and mean $P_{musI_{PI}}$ calculated as:

$$\text{mean } P_{musI_{PI}} = \frac{1}{T_T}\int P_{musI_{PI}} \qquad \textbf{(2.9)}$$

Mean expiratory (negative) P_{mus} (P_{musE}) was similarly averaged over T_T, thus:

$$\text{mean } P_{musE} = \frac{1}{T_T}\int P_{musE} \qquad \textbf{(2.10)}$$

The net pressure generated by all the respiratory muscles, averaged over the respiratory cycle (Total P_{mus}) is the "sum" of average inspiratory and expiratory (absolute value) muscle pressures, therefore,

$$\text{Total } P_{mus} = \text{mean } P_{musI} - \text{mean } P_{musE} \qquad \textbf{(2.11)}$$

P_{musI} at each point in time was expressed as a fraction of that subject's capacity (P_{capI}) to generate P_{musI} at the same lung volume and flow rate. Firstly, to calculate inspiratory muscle strength corrected for lung volume, the measured $P_{W,el}$ and $P_{pl,min}$ data for each subject were analyzed graphically. Only maximal inspiratory efforts were taken into account and a 2^{nd}-order polynomial was used to fit the outer envelope of the $P_{pl,min}$ - V relation (Figure 2.1). All submaximal efforts therefore lay within this curve and these measurements were discarded. In each

subject, static volume-matched inspiratory muscle strength (P_{maxI}) on a breath-by-breath basis was then derived digitally, as the horizontal distance between the $P_{W,el}$ and $P_{pl,min}$ curves at each lung volume increment (Equation 2.1 and left panel figure 2.3), at all points when P_{mus} was inspiratory (right panel, figure 2.3).

The dynamic force generating capacity of the inspiratory muscles however has been shown to decline with increasing velocities of muscle shortening [AGOSTONI AND FENN, 1960] and this has been shown to correlate with increases in flow rates [ROCHESTER AND FARKAS, 1995]. It has also been shown that at any given lung volume, P_{maxI} ($P_{W,el}$ - $P_{pl,min}$, left panel, figure 2.3) falls by ~5%, for every 1 $L \cdot s^{-1}$ increase in flow rate [LEBLANC *ET AL*, 1988; JOHNSON *ET AL*, 1992]. Each subject's capacity (P_{capI}, right panel figure 2.3) to generate P_{musI} at any lung volume and for a given flow rate was therefore calculated as:

$$P_{capI} = P_{maxI} \cdot (1 - 0.05 \cdot \text{inspiratory flow rate}) \qquad \textbf{(2.12)}$$

The top panel of figure 2.4 shows P_{capI} throughout inspiration in one subject. As also shown in lower panel, P_{musI} was then represented as a fraction (%) of P_{capI} at the same lung volume and flow rate, at each point in time during which P_{mus} was positive, for each breath. Like the other P_{mus} variables, mean P_{musI}/P_{capI} (%) values were averaged over T_T.

$$\text{mean } P_{musI}/P_{capI}\ (\%) = \frac{1}{T_T}\int P_{musI}/P_{capI}\ (\%) \qquad \textbf{(2.13)}$$

The tension · time index of the diaphragm (TT_{DI}) has been defined [BELLEMARE AND GRASSINO, 1982], as the product of ratio of mean diaphragmatic pressure (mean P_{DI}) to maximal diaphragmatic pressure (P_{DImax}) and the inspiratory duty cycle (T_I/T_T):

$$\frac{\text{mean } P_{DI}}{P_{DImax}} \times \frac{T_I}{T_T} \qquad \textbf{(2.14)}$$

Mean P_{musI}/P_{capI} (%) therefore represents the tension · time index of all the inspiratory muscles as it is the product of mean inspiratory muscle pressure (P_{musI})

expressed as fraction of maximal inspiratory pressure (P_{capI} at the same volume and flow rate) and the inspiratory duty-cycle (t = neural inspiration, including post-inspiratory inspiratory activity) thus:

$$\frac{\text{mean } P_{musI}}{P_{capI}} \times \frac{t}{T_T} \approx \frac{1}{T_T} \times \int_0^t \frac{P_{musI}}{P_{capI}} \qquad \textbf{(2.15)}$$

2.3.2. Statistical Analyses.

For all the ventilatory and P_{mus} variables, statistical comparisons between the 3rd minute of CWHE and end exercise values were made using a paired t test and a $P < 0.05$ was accepted as significant. The relationships between the ventilatory output ($\dot{V}_E$) and respiratory muscle output (P_{mus}) variables were examined graphically and analyzed with regression analyses. Both a straight-line and a 2nd-order polynomial function were used to fit each of the data sets in each subject, in order to determine whether any of the $\dot{V}_E$ - Pmus relationships were linear or curvilinear. A *f*-test (ANOVA) was then used to determine whether the beta coefficients of the quadratic equation provided a significantly better fit than a linear equation. Data are presented as means ± S.E.M. unless indicated otherwise.

2.4. Results.

2.4.1. Exercise and ventilatory variables.

Table 2.1. summarizes subjects' exercise performance data. The subjects were moderately fit (108 ± 5% pred. $\dot{V}O_{2max}$ [JONES, 1988]) and completed all exercise tests to exhaustion. The subjects exercised (CWHE) for 14 minutes on average at a mean work-rate of 260 watts (81 ± 2% $\dot{W}_{max}$). Although dyspnea at end exercise was described as "moderate" or "heavy", exercise cessation was attributed to leg fatigue by each subject. Table 2.2. summarizes the average changes (Δ%) in metabolic rate, heart rate (fc), breathing frequency (f_b) and other ventilatory variables, from 3 minutes to end of CWHE. Consistent with data from previous studies of CWHE [KEARON *ET AL*, 1991; JOHNSON *ET AL*, 1993], $\dot{V}_E$, $\dot{V}O_2$ and fc increased significantly

Table 2.1. Subject characteristics and exercise performance data.

			MIE		CWHE		
Subj.	Age	Height	Peak $\dot{V}O_2$		Workload		Duration
	yrs	m	$ml \cdot Kg^{-1} \cdot min^{-1}$	%pred	watts	% $\dot{W}max$	min
1.	25	1.70	54	119	310	83	12.9
2.	26	1.75	49	118	190	76	9.8
3.	23	1.84	54	120	290	89	17.5
4.	27	1.81	47	103	280	80	9.8
5.	23	1.80	42	91	280	80	12.5
6.	25	1.87	41	96	210	76	21.4
mean	24.8	1.80	48	108	260	81	14.0

throughout exercise. End exercise $\dot{V}O_2$, fc and $\dot{V}E$ values were similar to those at the end of MIE (data in parentheses, Table 2.2; mean ± S.E.M., $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.005$).

The temporal courses of $\dot{V}E$, end-tidal CO_2 ($P_{ET}CO_2$) and lung volumes during CWHE are illustrated in figure 2.5. Group mean (± S.E.M, n = 6) data at 10%

Table 2.2. Exercise ventilatory variables.

Variable	3rd minute	End exercise	Δ%
$\dot{V}O_2$ ($L \cdot min^{-1}$)	3.16 ± 0.3 (84)	3.63 ± 0.2 (97)	16 ± 5†
fc ($\cdot min^{-1}$)	149 ± 2 (86)	180 ± 3 (103)	20 ± 1‡
$\dot{V}E$ ($L \cdot min^{-1}$)	87.8 ± 6.7 (60)	141.6 ± 15.5 (95)	60 ± 9‡
V_T (L)	2.61 ± 0.1	2.56 ± 0.2	-3 ± 5
fb ($\cdot min^{-1}$)	33.5 ± 2.2	55.4 ± 5.3	64 ± 6‡
TI/TT	0.50 ± 0.01	0.50 ± 0.01	0.3 ± 3
$P_{ET}CO_2$ (mmHg)	40.0 ± 0.8	29.2 ± 1.0	-27 ± 2‡
EELV (%TLC)	44.8 ± 2.6	46.9 ± 1.1	6.5 ± 6.9
EILV (%TLC)	84.5 ± 1.8	85.5 ± 2.5	1.4 ± 4.0

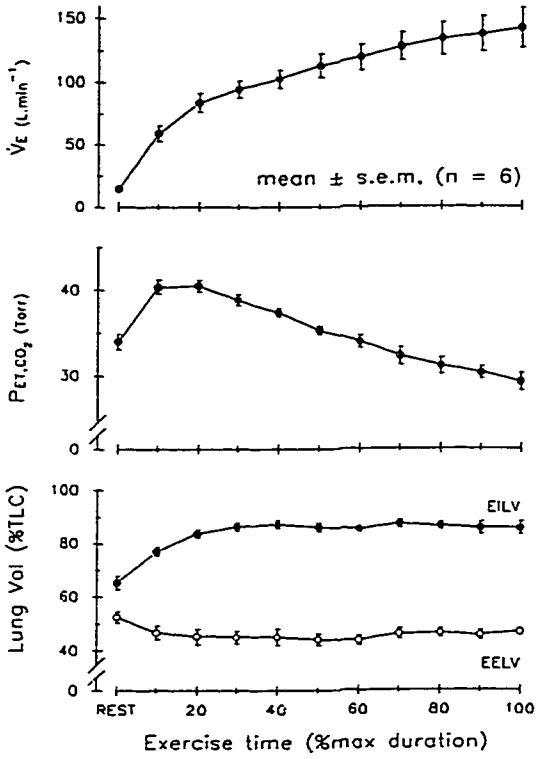

Figure 2.5. Ventilatory and lung volume responses during CWHE.

increments of exercise time are shown. $\dot{V}E$ increased rapidly at the start of exercise and continued to increase throughout CWHE. All the increase in $\dot{V}E$ ($\Delta = 60 \pm 9\%$, $P < 0.005$) from 3 minutes to end exercise was due to a significant increase in breathing frequency ($\Delta = 64 \pm 6\%$, $P < 0.005$). After an initial increase at the start of exercise, VT did not increase any further during CWHE; VT decreased slightly with increasing exercise time in 3 subjects similar to previous reports [KEARON *ET AL*, 1991], but this fall from 3 minutes to end of CWHE (ΔVT, Table 2.2) was not statistically significant. The $\dot{V}E$ drift of CWHE was associated with a progressive fall in P_{ETCO_2}, which fell significantly from 40.0 ± 0.8 mmHg at 3 minutes to 29.2 ± 1.0 mmHg at end exercise ($P < 0.005$).

2.4.2. Respiratory mechanical variables.

Figure 2.5 also describes the average time course of the limits of exercise VT throughout CWHE. End-expiratory lung volume was derived from measured IC's (EELV = TLC - IC). TLC was assumed to remain constant during CWHE, as it has been

shown that TLC remains unchanged during both incremental and endurance exercise in normal subjects [MARON *ET AL*, 1979; YOUNES AND KIVINEN, 1984]. The IC measurements were validated by the reproducibility of P_{pl} values at the end of a full inspiration ($P_{pl,IC}$). $P_{pl,IC}$ did not change significantly during CWHE; -38 ± 4 cmH_2O at rest, -40 ± 5 cmH_2O at 50% exercise duration and -37 ± 4 cmH_2O at end exercise. End-inspiratory lung volume (EILV) was derived as a sum of V_T and EELV. As figure 2.5 illustrates, most of the changes in the limits of exercise V_T occurred at the start of heavy exercise; after the first 3 minutes, both EE- and EILV remained essentially stable throughout CWHE. EELV decreased significantly at the start of exercise; EELV fell from 3.52 ± 0.26 L (53 ± 2 %TLC) at rest to 3.01 ± 0.27 L (45 ± 3 %TLC) at 3 minutes ($P <$ 0.05). EILV increased significantly at the start of exercise; from 4.38 ± 0.36 L (65 ± 3 %TLC) at rest to 5.62 ± 0.26 L (84 ± 2 %TLC) at 3 minutes ($P < 0.05$), but did not change significantly thereafter.

Table 2.3 summarizes (mean ± S.E.M., $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.005$) the changes in respiratory mechanical variables from 3 minutes to end of exercise. With the significant (and ~equal) increases in both inspiratory and expiratory flows during

Table 2.3. Respiratory mechanics during heavy exercise.

Variable	3rd minute	End exercise	Δ
Mean flow (Insp, $L \cdot s^{-1}$)	2.92 ± 0.24	4.69 ± 0.50	1.77 ± 0.31‡
Mean flow (Exp, $L \cdot s^{-1}$)	2.95 ± 0.25	4.75 ± 0.54	1.80 ± 0.37‡
Peak $P_{pl,Insp}$ (cmH_2O)	-24.1 ± 2.2	-30.3 ± 3.4	6.2 ± 2.2†
Mean $P_{pl,Insp}$ (cmH_2O)	-19.7 ± 1.8	-25.9 ± 3.0	6.2 ± 1.8†
Peak $P_{pl,Exp}$ (cmH_2O)	2.7 ± 1.3	14.0 ± 1.5	11.3 ± 1.8‡
$R_{L,Insp}$ ($cmH_2O \cdot L^{-1} \cdot s$)	1.97 ± 0.36	2.26 ± 0.24	0.29 ± 0.27
$R_{L,Exp}$ ($cmH_2O \cdot L^{-1} \cdot s$)	3.16 ± 0.23	3.89 ± 0.35	0.74 ± 0.28†
C_{dyn} ($L \cdot cmH_2O^{-1}$)	0.18 ± 0.02	0.23 ± 0.04	0.05 ± 0.02

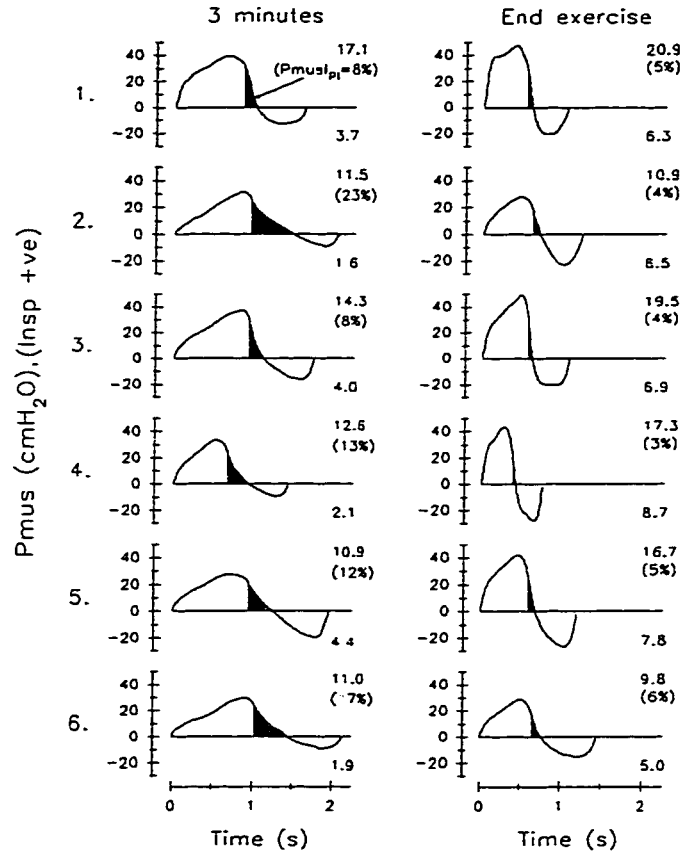

Figure 2.6. P_{mus} waveforms at 3 minutes and at end of CWHE.

CWHE, intra-pleural pressure (both peak and mean values) during inspiration increased significantly. However, there was a greater increase in peak expiratory intra-pleural pressure ($P_{pl,Exp}$) and this increase (> 4x) was significant ($P < 0.005$).

Inspiratory and expiratory lung resistances (R_L) at 1.0 liter above EELV, were calculated using the subtraction technique of MEAD AND WHITTENBERGER [1953]. Elastic pressure at 1.0 L above EELV was calculated by adding $1/C_{dyn}$ to the value of trans-pulmonary pressure (P_{TP}) at end expiration. This value was then subtracted from P_{TP} at 1.0 L during inspiration and expiration to obtain resistive pressure losses during inspiration and expiration ($P_{res,I}$ and $P_{res,E}$ respectively). $R_{L,Insp}$ and $R_{L,Exp}$ were then calculated from these values and the corresponding inspiratory and expiratory flow rates. Both $R_{L,Insp}$ and $R_{L,Exp}$ increased from 3 minutes to end of CWHE, and as shown in earlier studies [GALLAGHER AND YOUNES, 1989], $R_{L,Exp}$ was greater than $R_{L,Insp}$ in 5 of 6

subjects during CWHE. The increase in $R_{L,Exp}$ from 3 minutes to end of CWHE was significant ($P = 0.048$). Table 2.3 also shows that while dynamic lung compliance (C_{dyn}) increased slightly (24%) from 3 minutes to end of CWHE in 5 of 6 subjects, these changes were small and not statistically significant.

2.4.3. P_{mus} variables.

Figure 2.6 illustrates the P_{mus} waveforms at 3 minutes and at end exercise in each subject. P_{musI} is positive and P_{musE} is negative. Subject numbers are shown alongside each row. Mean P_{musI} and P_{musE} values are indicated in each panel and the fractional contribution of post-inspiratory inspiratory activity ($P_{musI_{PI}}$, shaded segment) to total P_{musI} is given in parentheses.

Table 2.4 summarizes all average P_{mus} data at 3 minutes and at end

Table 2.4. Respiratory muscle pressure (P_{mus}) during heavy exercise.

Variable	3rd minute	End exercise	Δ%
Peak P_{musI} (cmH_2O)	33.0 ± 1.8	39.8 ± 3.8	21 ± 10
Peak P_{musE} (cmH_2O)	-12.8 ± 1.9	-22.3 ± 1.9	90 ± 28†
Mean P_{musI} (cmH_2O)	12.9 ± 1.0	15.8 ± 1.9	22 ± 10
Mean P_{musE} (cmH_2O)	-3.0 ± 0.5	-6.9 ± 0.5	168 ± 48‡
Total P_{mus} (cmH_2O)	15.9 ± 1.3	22.7 ± 2.1	43 ± 9‡
Peak P_{musI}/P_{capI} (%)	50.2 ± 5.0	71.4 ± 11.1	44 ± 18
Mean P_{musI}/P_{capI} (%)	17.8 ± 2.0	25.4 ± 4.3	42 ± 16†
Mean $P_{musI_{IF}}$ (cmH_2O)	11.2 ± 1.1	15.2 ± 1.8	35 ± 10†
	(86)	(96)	
Mean $P_{musI_{PI}}$ (cmH_2O)	1.7 ± 0.2	0.7 ± 0.1	-54 ± 10†
	(14)	(4)	
$TP_{musI_{PI}}$ (%TE)	33.5 ± 4.4	15.3 ± 0.8	-49 ± 9†
$TP_{musI_{PI}}$ (%TT)	16.9 ± 2.6	7.6 ± 0.4	-48 ± 10†

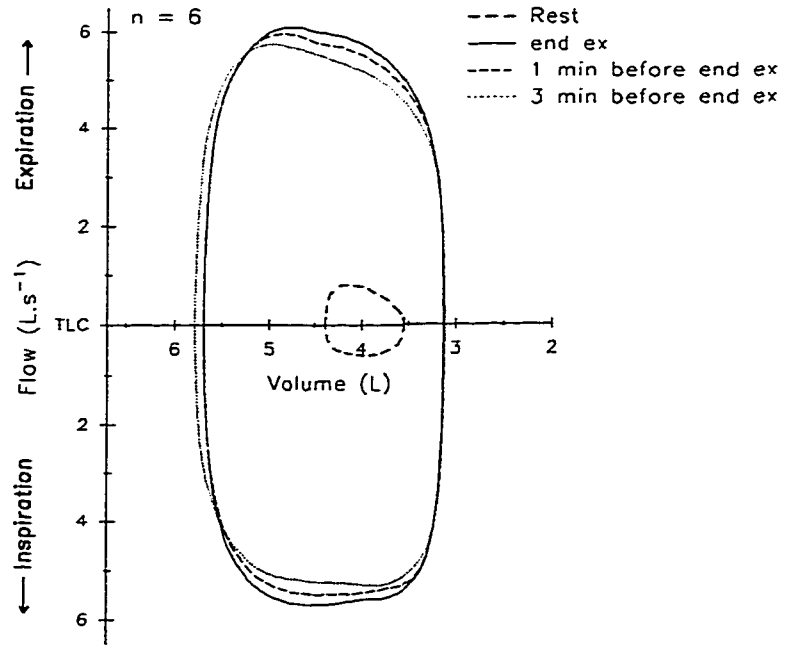

Figure 2.7. Flow - volume relationships during CWHE.

exercise. Four out of 6 subjects showed an increase in both peak and mean P_{musI} from 3 minutes to end exercise; however subjects 2 and 6 showed little or no change in peak P_{musI} and a slight fall in mean P_{musI} from 3 minutes to end exercise. These 2 subjects (#2 and #6, figure 2.6) displayed substantial $P_{musI_{PI}}$ at 3 minutes (23% and 17% of total P_{musI} respectively), but not at the end of CWHE. While $P_{musI_{PI}}$ fell significantly from 14% of net P_{musI} at 3 minutes to 4% of net P_{musI} at end exercise, P_{musI} associated with inspiratory flow ($P_{musI_{IF}}$) increased significantly from 11.2 ± 1.1 cmH_2O at 3 minutes to 15.2 ± 1.8 cmH_2O at end exercise.

Figure 2.6 also shows that with the increasing $\dot{V}_E$ levels of CWHE, the shape of P_{musI} changed significantly, i.e. the P_{musI} waveform became increasingly concave towards the time axis. The ratio (%) of P_{musI} at 50% of the rising duration of positive P_{mus}, to peak P_{musI}, was calculated as an index of the shape of P_{musI}. This index increased significantly ($P < 0.01$) from 62 ± 3% at 3 minutes to 74 ± 3% at end exercise. While there was some variation in the increase in P_{musI} among subjects, figure 2.6 shows that both peak and mean expiratory pressures (P_{musE}) increased

consistently from 3 minutes to end exercise in all subjects. Mean P_{musE} increased significantly from 3.0 ± 0.5 cmH_2O at 3 minutes to 6.9 ± 0.5 cmH_2O at end exercise (Δ = 168 ± 48%, $P < 0.005$; Table 2.4). This resulted in a doubling of the mean P_{musE}/mean P_{musI} ratio from 3 minutes (23%) to end exercise (46%).

It was further questioned whether the relatively greater increase in expiratory muscle pressures in these subjects, was "excess pressure" resulting from expiratory flow-limitation during CWHE. As maximal flow-volume ($\dot{V}$ - V) measurements were not included in the study protocol, tidal $\dot{V}$ - V data from the last minutes of exercise were analyzed in each subject. Figure 2.7 shows the group average $\dot{V}$ - V loops at rest and during exercise, positioned on the x-axis (V) in relation to group mean TLC (6.69 L). Data from 3 minutes before (dotted line), 1 minute before (dashed line) end exercise and at end exercise (solid line) show that both inspiratory and expiratory flows at the same lung volume continued to increase till end exercise This suggests that expiratory flow-limitation did not occur during CWHE, on average. This is also supported by the observation (Figure 2.5) that EELV did not change over the last 3 minutes of CWHE. Because it was still possible that individual subjects might have

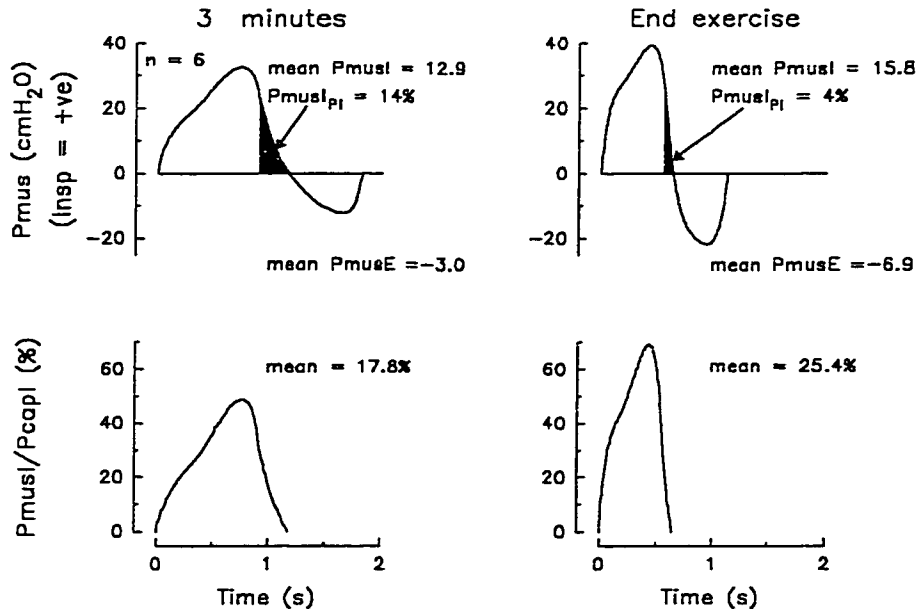

Figure 2.8. Average P_{mus} variables at 3 minutes and at end of CWHE.

had flow-limitation, flow-volume data in each subject was examined. Five of 6 subjects continued to increase expiratory flow rates over the last few minutes of exercise, but 1 subject did not do so over the last minute of exercise. Expiratory flow-limitation therefore, while possible in him, was unlikely in the other 5 subjects.

Figure 2.8 illustrates the average (n = 6) P_{mus} data at 3 minutes and at end exercise. P_{musI} is positive and P_{musE} negative. As in figure 2.6, group mean P_{musI}, mean P_{musE} and $P_{musI_{PI}}$ (%P_{musI}) are given in each panel. Both peak and mean P_{musI} increased from 3 minutes to end exercise, but these increases (>20%) failed to reach statistical significance ($P = 0.07$). P_{musE} increased significantly from 3 minutes to end exercise; in relative terms this increase ($\Delta = 168 \pm 48\%$) was significantly greater than that observed with mean P_{musI}. However, as table 2.4 reveals, the increase in P_{musI} in absolute terms (~4 cmH_2O) is identical to the increase in $P_{musI_{IF}}$ (P_{musI} associated with inspiratory flow). The increase in mean P_{musI} from 3 minutes to end of CWHE was smaller due to the significant fall in $P_{musI_{PI}}$ during CWHE (also see below). $P_{musI_{PI}}$ fell significantly from 3 minutes to end of CWHE.

Average P_{musI}/P_{capI} (%) throughout inspiration at 3 minutes and at end exercise is also shown in figure 2.8. The subjects generated a wide range of P_{musI}/P_{capI} (%) values; Peak P_{musI}/P_{capI} (%) ranged from 25% - 80% and increased from 3 minutes (50 ± 5%) to end exercise (71 ± 11%). This increase however ($\Delta = 44 \pm 18\%$, Table 2.4.), failed to reach statistical significance ($P = 0.055$). As described earlier, mean P_{musI}/P_{capI} (%) averaged over the respiratory cycle is the tension · time index of all the inspiratory muscles. This index increased significantly from 17.8 ± 2.0 % at 3 minutes to 25.4 ± 4.3 % at end exercise ($P < 0.05$, Table 2.4.).

The decrease in post-inspiratory inspiratory activity with increasing minute ventilatory levels throughout CWHE is summarized in figure 2.9. Group mean duration of post-inspiratory inspiratory activity ($T_{PmusI_{PI}}$) at matched $\dot{V}_E$ levels during CWHE are shown as a fraction of T_E and T_T. $T_{PmusI_{PI}}$ fell progressively with increasing

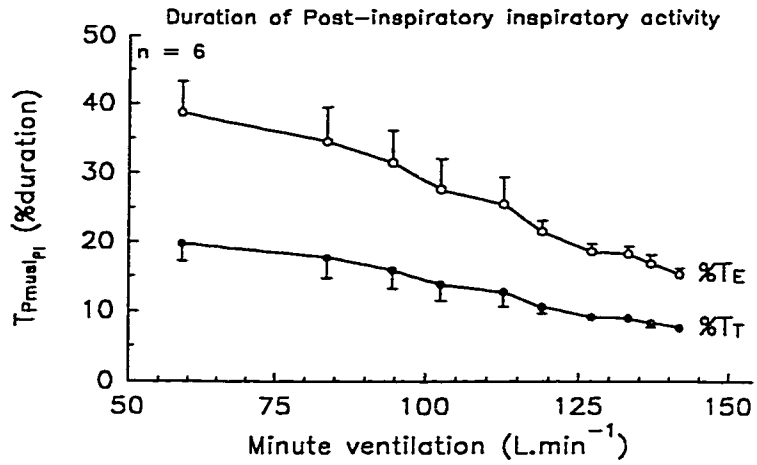

Figure 2.9. Post-inspiratory inspiratory activity during CWHE.

$\dot{V}_E$ levels throughout CWHE; the values at end exercise were less than half of those at the start of exercise. $T_{Pmusl_{PI}}$ decreased significantly ($P < 0.05$, Table 2.4) from 3 minutes (33.5 ± 4.4 %TE, 16.9 ± 2.6 %TT) to end exercise values (15.3 ± 0.8 %TE, 7.6 ± 0.4 %TT). While the post-inspiratory activity of the inspiratory muscles was significant throughout CWHE, post-expiratory activity of the expiratory muscles (P_{musE} persisting during the period of inspiratory flow) was negligible in these subjects ($T_{PmusE_{PE}}$, 1.3 ± 0.8 %TI at 3 minutes and 0.2 ± 0.2 %TI at end exercise). $P_{musE_{PE}}$ similarly was negligible during CWHE (0.6 ± 0.5 %mean P_{musE} at 3 minutes and 0.03 ± 0.03 %mean P_{musE} at end exercise).

2.4.4. $\dot{V}_E$ - P_{mus} regression analyses.

The results of regression analyses between $\dot{V}_E$ and the various P_{mus} variables in each subject during CWHE are presented in figures 2.10, 2.11 and 2.12. Table 2.5 summarizes the results of linear regressions ($P_{mus} = m \cdot \dot{V}_E + b$, where m and b are the slopes and intercepts respectively) in each subject during CWHE. The asterisks (*) indicate whether the correlation of the specific variable with $\dot{V}_E$ in that subject, improved significantly with a 2nd - order regression.

In the figures, subject numbers are in the top left corner and the individual correlation coefficients (r) are given in the lower right corner of each panel. Figure

Table 2.5. $\dot{V}_E$ - P_{mus} regressions summary

Variable	Coeff.	Subjects 1	2	3	4	5	6
Mean P_{musI}	m	0.135	0.092	0.036	0.072	0.065	0.065
	b	3.486	3.559	10.84	4.902	6.156	6.985
	r	0.974*	0.873	0.500	0.911*	0.932	0.654
Mean P_{musE}	m	-0.083	-0.076	-0.045	-0.051	-0.045	-0.051
	b	3.924	2.508	0.517	3.128	0.551	2.038
	r	0.928	0.841	0.819	0.908*	0.914	0.875
Total P_{mus}	m	0.219	0.168	0.081	0.122	0.109	0.116
	b	-0.439	1.062	10.35	1.779	5.711	4.947
	r	0.979	0.975	0.812	0.991	0.952	0.904*
Mean P_{musI}/P_{capI} (%)	m	0.253	0.150	0.125	0.177	0.112	0.155
	b	-4.172	3.393	11.533	2.820	3.079	3.369
	r	0.976	0.843	0.686	0.969*	0.927	0.792

2.10 illustrates mean P_{musI} - $\dot{V}_E$ (top panels) and mean P_{musE} - $\dot{V}_E$ (bottom panels) relationships in each subject. Except in subject #4, it is evident that both mean P_{musI} and mean P_{musE} increase in a linear fashion with increasing $\dot{V}_E$ levels during CWHE. However, the correlation coefficient for a linear regression of mean P_{musI} and mean P_{musE} with $\dot{V}_E$ in this subject (#4) was significantly high ($r = 0.91$, $P < 0.05$, in both cases). While both mean P_{musI} and mean P_{musE} increased linearly with increasing $\dot{V}_E$ throughout CWHE, there was considerable variation in both the slopes (range = 0.065 - 0.135 $cmH_2O \cdot L^{-1} \cdot min$) and correlation coefficients (range = 0.50 - 0.97) of the mean $\dot{V}_E$ - P_{musI} relation. However, the $\dot{V}_E$ - P_{musE} relationship during CWHE in these subjects was more consistent, with less variable slopes (range = 0.051 - 0.083 $cmH_2O \cdot L^{-1} \cdot min$) and correlation coefficients (range = 0.82 - 0.93).

In contrast to the variability observed in both the $\dot{V}_E$ - mean P_{musI} and $\dot{V}_E$ - mean P_{musE} relations, the relationship between the net respiratory muscle pressure throughout the breathing cycle (Total P_{mus}) and $\dot{V}_E$ was highly linear in all subjects

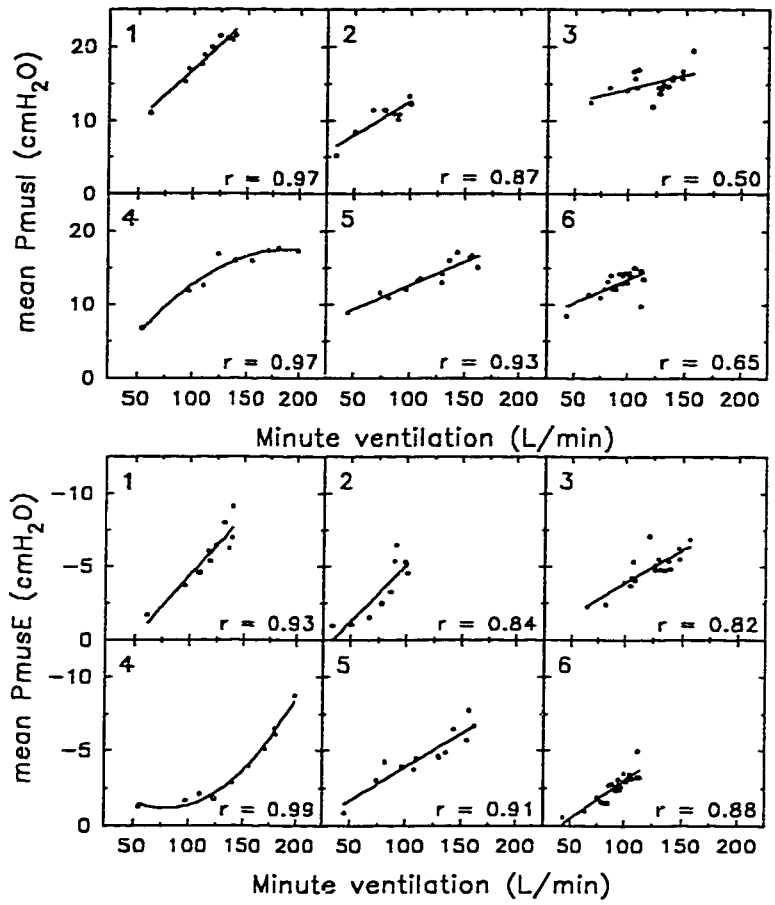

Figure 2.10. $\dot{V}_E$ - P_{musI} and $\dot{V}_E$ - P_{musE} relationships during CWHE.

(Figure 2.11). In each subject, the $\dot{V}_E$ - Total P_{mus} correlation coefficient was significantly greater than the individual's $\dot{V}_E$ - P_{musI} or $\dot{V}_E$ - P_{musE} correlation coefficients. The slopes of this relation averaged 0.136 ± 0.020 $cmH_2O \cdot L^{-1} \cdot min$ (range = 0.081 - 0.219, table 2.5.). In one subject (#6) however, this relationship improved slightly with 2^{nd}-order regression (r = 0.92). Total P_{mus} increased significantly ($P < 0.005$) from 3 minutes to end exercise ($\Delta = 43 \pm 9\%$, Table 2.4.).

Figure 2.12. illustrates the relationship between the inspiratory muscle tension · time index (mean P_{musI}/P_{capI} (%)) and $\dot{V}_E$ and reveals that the $\dot{V}_E$ - mean P_{musI}/P_{capI} (%) relation was linear during CWHE, in each subject. Subjects generated a wide range (6.2% - 35.8%) of mean P_{musI}/P_{capI} (%) values during exercise. Figure 2.12 also reveals that for all $\dot{V}_E$ values above 75 $L \cdot min^{-1}$, mean P_{musI}/P_{capI} (%) was greater

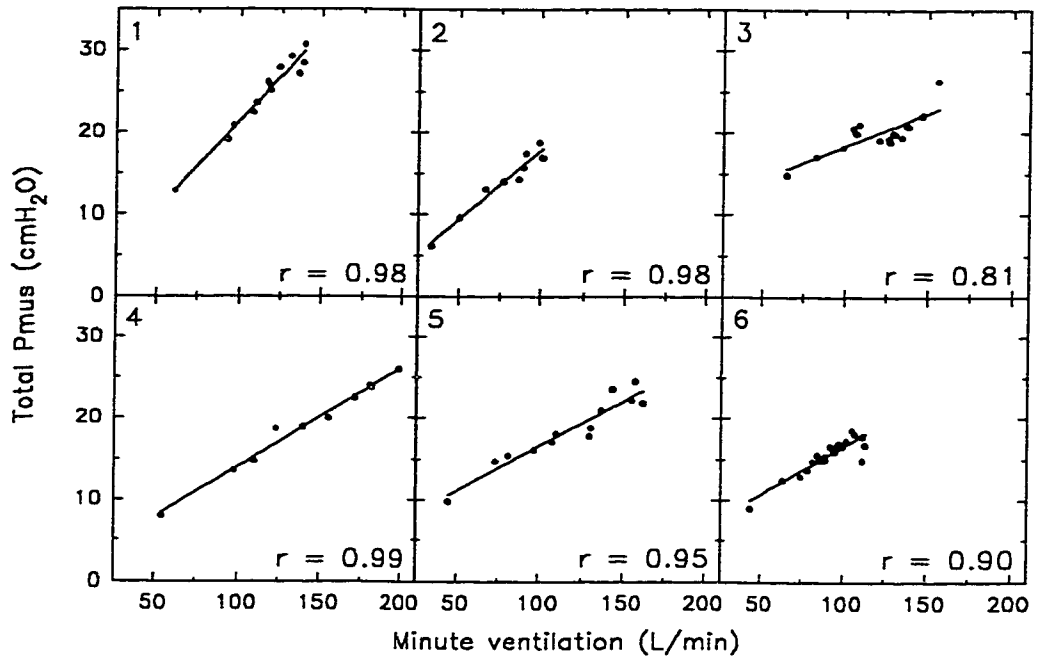

Figure 2.11. $\dot{V}_E$ - Total P_{mus} relationships during CWHE.

than 15% in these subjects. In subject #4, the correlation coefficient for a 2nd order fit to the data (which improved on the linear fit slightly, see Table 2.5.) was 0.98.

2.5. Discussion.

This study was designed to examine the relationship between ventilatory

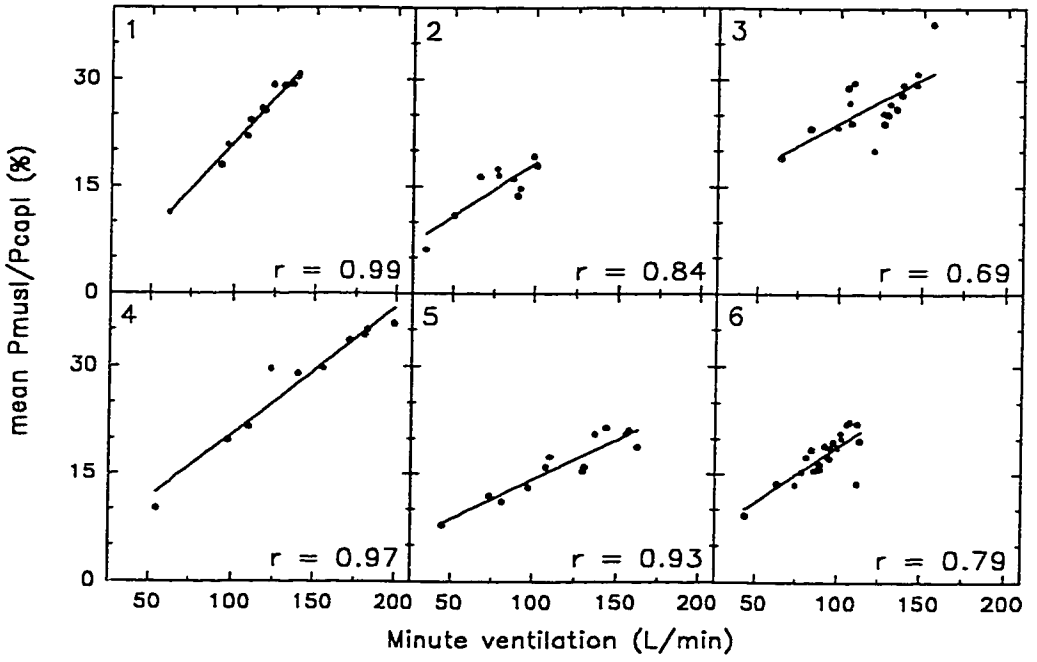

Figure 2.12. $\dot{V}_E$ - mean P_{musl}/P_{capl} (%) relationships during CWHE.

output and respiratory muscle output during constant work heavy exercise in normal humans. Net respiratory muscle pressure (P_{mus} and its components) measured throughout the breath was used as the index of output of all the inspiratory and expiratory muscles. The study showed that: **1)** Both inspiratory and expiratory muscle pressures increased to meet the increasing ventilatory demands of CWHE; **2)** The relationship between the ventilatory output and the net pressure output of respiratory muscles (Total P_{mus} and its components) is significantly linear during CWHE; **3)** The ventilatory increase of CWHE is associated with a relatively greater increase in expiratory than inspiratory muscle pressures; **4)** Post-inspiratory (expiratory) activity of the inspiratory muscles in humans diminishes significantly with the increasing ventilatory demands of CWHE.

2.5.1. Critique of methods.

This study examined the changes in net respiratory muscle pressure (P_{mus}) that mediate the progressive increase in $\dot{V}_E$ during sustained heavy exercise. The validity of our findings depends on the accuracy with which the components of P_{mus} (Equation 2.5) are measured. Esophageal pressure measured with a balloon-catheter system has been found to be an excellent index of intra-pleural pressure [MILIC-EMILI *ET AL*, 1964], and has therefore been used in many studies [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976; BYE *ET AL*, 1984; LEBLANC *ET AL*, 1988; WANKE *ET AL*, 1991; KEARON *ET AL*, 1991]. The P_{pl} measurement was validated before and after exercise with the occlusion technique [BAYDUR *ET AL*, 1982]. The raw P_{pl} signal however contains noise from cardiogenic oscillations but since this noise is unrelated to the breathing cycle, it disappeared with the digital averaging of the P_{pl} data from numerous breaths (25 - 50) in each minute of exercise.

In contrast to data from a previous study [GALLAGHER AND YOUNES, 1989], chest wall recoil pressure ($P_{W,el}$) was measured in each subject, to improve the accuracy with which P_{mus} was calculated. Subjects were adequately trained and the two

techniques used (see methods) ensured that a reliable and reproducible measure of $P_{W,el}$ was available in each subject, from at least one technique (in 3 subjects in each). Because reliable measures of $P_{W,el}$ were not available from both techniques in any subject, it was not possible to compare the efficacy of any one technique with that of the other. However, ESTENNE *ET AL* [1983] have shown a good correlation between the two techniques in $P_{W,el}$ data measured in the same subject. Furthermore, the $P_{W,el}$ - V relationship has been shown to be predominantly linear within the range of lung volume limits [RAHN *ET AL*, 1946] as seen in our study (EELV > 40% TLC and EILV < 90% TLC). Measurement of static $P_{W,el}$ does not however account for the forces involved in chest wall distortion [GOLDMAN *ET AL*, 1976] and therefore static $P_{W,el}$ underestimates the pressure needed to expand the chest wall during exercise. Chest wall distortion during exercise is a complex phenomenon that occurs when the increasing contribution of accessory rib-cage and abdominal muscles to increasing ventilation, results in the P - V characteristics of the chest wall (therefore its geometry) deviating significantly from its relaxation configuration [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976]. With the significant increases in $\dot{V}_E$ throughout CWHE in our study, the pressure losses due to chest wall distortion are likely to increase from 3 minutes to end exercise. Although distortive forces are present to a varying degree throughout the respiratory cycle, chest wall distortion is most marked at tidal volume extremes [GOLDMAN *ET AL*, 1976] (corresponding to peak pressures). Since the limits of tidal volume (EE- and EILV) changed very little from 3 minutes to end exercise, it is probable that the pressure losses due to distortion, while not measured under these conditions, were similar, i.e., changes in pressure (Δ) due to chest wall distortion would have been small compared to the changes in Total P_{mus}.

Chest wall resistance (R_W) has been shown to be dependent on both tidal volume and breathing frequency in the normal range of breathing [BARNAS *ET AL*, 1989; 1992]. With increased frequencies (0.5 - 2 Hz) however, R_W tends to fall, with most of

the changes (Δ = ~40%) occurring at the transition from 0.5 to 1 Hz [BARNAS *ET AL*, 1989]. Rw would therefore have decreased from 3 minutes ($f_b = 34 \cdot min^{-1}$) to end exercise ($f_b = 55 \cdot min^{-1}$) by ~0.4 $cmH_2O \cdot L^{-1} \cdot s$, resulting in $P_{W,res}$ (Equation 2.5.) being overestimated by < 1 cmH_2O. At end exercise, this amounts to mean P_{musI} and mean P_{musE} being overestimated by ~6% and ~16% respectively. P_{mus} (Equation 2.5.) is therefore a valid index of respiratory muscle output during exercise. P_{musI} was further expressed at each point in time as a fraction (%) of the capacity (P_{capI}) of all the inspiratory muscles to generate pressure at that lung volume and flow-rate. This index (P_{musI}/P_{capI}) averaged over the respiratory cycle is the tension · time index [BELLEMARE AND GRASSINO, 1982] of all the inspiratory muscles.

2.5.2. Respiratory muscle output during heavy exercise.

A variety of techniques have been used to assess both the qualitative and quantitative contribution of different respiratory muscle groups to ventilation, both at rest and during the increased ventilatory needs of exercise. These include: **1)** Measurement of thoraco-abdominal P - V relationships [GOLDMAN *ET AL*, 1976; GRIMBY *ET AL*, 1976; LEVINE *ET AL*, 1988; ALIVERTI *ET AL*, 1997] which provide qualitative information about the diaphragm, the abdominal expiratory muscles and the intercostal/accessory inspiratory and expiratory muscles; **2)** Pressure measurements (mouth [LIND AND HESSER, 1984; HUSSAIN *ET AL*, 1985], esophageal [LEBLANC *ET AL*, 1988; KEARON *ET AL*, 1991], trans-diaphragmatic [JOHNSON *ET AL*, 1993] and gastric [BYE *ET AL*, HENKE *ET AL*, 1988; LEVINE *ET AL*, 1988; ALIVERTI *ET AL*, 1997] pressures); **3)** Direct assessment of patterns of respiratory muscle recruitment with EMG measurements [ABE *ET AL*, 1996]. At rest, the diaphragm is the main muscle of inspiration in humans [GRIMBY *ET AL*, 1976; LEVINE *ET AL*, 1988] and using thoraco-abdominal pressure volume relationships, both GRIMBY *ET AL* [1976] and more recently ALIVERTI *ET AL* [1997] have documented increasing contribution of both inspiratory-accessory and expiratory muscles to the $\dot{V}E$ increase during exercise. Similar analyses by HENKE *ET AL* [1988]

confirm the increasing recruitment of abdominal expiratory muscles during exercise in humans. However, both the pattern and the magnitude of respiratory muscle activity have been shown to depend on posture and the mode of exercise (cycle ergometry .vs. treadmill running) [HENKE *ET AL*, 1988].

Studies that have used esophageal [KEARON *ET AL*, 1991; LEBLANC *ET AL*, 1988], and/or trans-diaphragmatic pressure [BYE *ET AL*, 1984; LEVINE *ET AL*, 1988; JOHNSON *ET AL*, 1993] measurements, clearly document increasing peak inspiratory and expiratory pressures. These indicate progressively increasing inspiratory and expiratory muscle activity during exercise. P_{pl} has been used commonly as an index of net respiratory muscle pressure (P_{mus}). However as Equation 2.5 shows, P_{pl} measurement by itself underestimates respiratory muscle output, as it does not account for static ($P_{w,el}$) and dynamic ($P_{w,res}$) pressure losses across the chest wall. Despite these limitations, P_{pl} measurement during exercise serves as a qualitative index of respiratory muscle output. During incremental exercise, LEBLANC *ET AL* [1988] have shown progressive increases in peak inspiratory and expiratory P_{pl} which indicate progressive increases in inspiratory and expiratory muscle pressures. In subjects performing CWHE at 80% $\dot{V}O_{2max}$, BYE *ET AL* [1984] have reported a significant increase in expiratory abdominal and pleural pressures. More recently, KEARON *ET AL* [1991] have shown that with increasing exercise time during CWHE at > 80% $\dot{W}_{max}$, there was a progressive increase in peak- and end- expiratory pressures (P_{pl}), while inspiratory pressures tended to plateau. In another recent report, JOHNSON *ET AL* [1993] who studied subjects performing CWHE to exhaustion at 2 different exercise intensities (85% and 95% VO_{2max}), reported a significant increase in the time-integral of esophageal pressure throughout exercise with the increases in $\dot{V}E$ and inspiratory flow. In contrast, the time-integral of trans-diaphragmatic pressure began to plateau early in exercise, which they interpreted as indicating that the diaphragm was contributing less and the "inspiratory-accessory" muscles more, to the hyperventilatory response to heavy

exercise. However this does not necessarily reflect the recruitment patterns of different muscle groups, as their relative shortening and velocities of shortening were not taken into account. For example, it has recently been shown [ALIVERTI *ET AL*, 1997] that during short duration constant load exercise, while trans-diaphragmatic pressure increased only modestly with increasing exercise intensity (0% → 70% $\dot{W}_{max}$), the dramatic increases in both the velocity of diaphragm shortening and diaphragmatic work suggest that the diaphragm during exercise behaves essentially as a flow generator rather than a pressure generator. Findings from other studies confirm increased inspiratory/intercostal muscle and/or reduced diaphragmatic pressures [LEVINE *ET AL*, 1988] during exercise. JOHNSON *ET AL* [1993] had also reported that the subjects in whom the relative contribution of the diaphragm (P_{DI}) was decreased or minimal for most of the duration of heavy exercise, showed less post-exercise diaphragmatic fatigue. Similar findings have been reported in subjects performing cycle ergometer CWHE (at 80% $\dot{V}O_{2max}$) to exhaustion [MADOR *ET AL*, 1993].

Electromyography and measurement of length changes in the various respiratory muscles can provide more direct information on the patterns of respiratory muscle recruitment. It has been shown that with CO_2 augmented ventilation, abdominal expiratory muscle activity in humans (as measured by EMG) increases significantly in proportion to level of CO_2 stimulation [ABE *ET AL*, 1996], and the authors interpreted this increase in expiratory muscle activity and its persistence in early inspiration, as contributing to inspiratory flow under these augmented ventilatory conditions. EMG data from specific inspiratory and/or expiratory muscles in animals clearly indicate increased respiratory muscle recruitment whenever $\dot{V}_E$ is increased, either as a result of chemical stimulation [SMITH *ET AL*, 1989] or during exercise [AINSWORTH *ET AL*, 1989; 1996]. All of the above evidence suggests that increasing inspiratory-accessory and expiratory muscle activity contribute significantly to the ventilatory response to exercise.

The quantitative assessment of respiratory muscle activity throughout the breathing cycle during heavy exercise in humans in this study is comparable to that of YOUNES AND KIVINEN [1984]. Mean P_{musI}, P_{musE} and $\dot{V}_E$ data (14.0 cmH_2O, 3.0 cmH_2O and 80.7 $L \cdot min^{-1}$) at end of maximal incremental exercise to exhaustion in their study, were very similar to those at 3 minutes in the present study (Tables 2.2. and 2.4.). Consistent with previous studies (outlined above), the present results show significant inspiratory, and less so, expiratory muscle pressures in early exercise. However, as exercise proceeds, there were differences in temporal course of P_{musI} and P_{musE}. While mean P_{musI} associated with inspiratory flow (mean $P_{musI_{IF}}$) increased significantly from 3 minutes to end exercise and this increase in absolute terms was similar to that of mean P_{musE} (Table 2.4.), post-inspiratory P_{musI} ($P_{musI_{PI}}$) decreased throughout CWHE. In relative terms therefore these subjects showed a greater increase in P_{musE} than P_{musI} from early to end exercise. While both the increase in P_{musE} and reduction in $P_{musI_{PI}}$ served to augment expiratory flow, increasing expiratory muscle activity served to possibly determine optimal EELV during exercise, thus aiding the diaphragm and the other inspiratory muscles to operate on a more efficient range of their length-tension relationships as well as allow for a greater tidal volume in the linear P - V range of the respiratory system [GRIMBY *ET AL*, 1976; HENKE *ET AL*, 1988; LEVINE *ET AL*, 1988]. The progressive and significant increase in P_{musE} can therefore be interpreted as "sparing" the inspiratory muscles, as the expiratory muscles take on a greater proportion of P_{mus} (from 19% of Total P_{mus} at 3 minutes to 30% Total P_{mus} at end exercise). These findings are in concurrence with those of a recent study [SLIWINSKI *ET AL*, 1996], which showed that during exercise after induced global inspiratory muscle fatigue, progressively increasing expiratory muscle activity significantly contributed to the maintenance of the pressure generation capacity of the diaphragm and rib-cage inspiratory muscles.

Each of the 3 measures of respiratory muscle pressure (P_{pl}, P_{DI} and P_{mus}) may be expressed as a fraction of the subjects' capacity (P_{cap}) to generate pressure. P_{cap} varies with muscle length (lung volume) and velocity of shortening (flow rates). Studies that have examined inspiratory muscle function (as inspiratory P_{pl} or P_{DI}) during incremental [LEBLANC *ET AL*, 1988] or endurance exercise [KEARON *ET AL*, 1991] clearly document the increasing demand on the inspiratory muscles while their dynamic capacity to generate pressure decreases progressively with increasing exercise intensity. In the present study, the ratio P_{musI}/P_{capI} (%) was calculated as a volume-matched, flow-corrected index of inspiratory muscle contraction throughout the breath and as figure 2.8 showed, P_{musI}/P_{capI} (%) varied throughout the breathing cycle. Tension · time indices, that relate the force and duration of muscle contraction, have been used to assess endurance of the respiratory muscles; a value of 0.26 for the rib-cage muscles [ZOCCHI *ET AL*, 1993] and 0.15 for the diaphragm [BELLEMARE AND GRASSINO, 1982] have been suggested. In the present study, P_{musI}/P_{capI} (%) averaged over the respiratory cycle is the tension · time index of all the inspiratory muscles (also see equations 2.13 and 2.14). Mean P_{musI}/P_{capI} (%) varied between subjects (Figure 2.13.) but averaged 17.8% at 3 minutes and 25.4% at end exercise (Table 2.4.). However this does not by itself imply that the inspiratory muscles were fatiguing during heavy exercise, as there is very unlikely to be an invariant index above which fatigue always occurs. Recent studies using bilateral supra-maximal phrenic nerve stimulation however [JOHNSON *ET AL*, 1993; MADOR *ET AL*, 1993], have shown that at the end of exhausting exercise, the pressure generating capacity of the diaphragm is significantly compromised. More recently, it has been shown [FULLER *ET AL*, 1996] that expiratory muscle endurance is significantly compromised after submaximal exercise to exhaustion. However, while fatigue has been likely to have occurred, there is good evidence that it does not limit exercise tolerance in humans [MARCINIUK *ET AL*, 1994; SLIWINSKI *ET AL*, 1996].

2.5.3. The relationship between $\dot{V}_E$ and P_{mus} during CWHE.

Perhaps the most important finding of this study is that a linear relationship exists between ventilatory output ($\dot{V}_E$) and respiratory muscle output (P_{mus} and its components) during heavy exercise in humans. This indicates that in addition to an efficient partition of work between inspiratory and expiratory muscle groups, increases in net respiratory muscle pressure throughout each breathing cycle (Total P_{mus}) and its components (mean P_{musI} and P_{musE}) are precisely tuned to the ventilatory need of the exercising individual. The relationship between ventilation (mechanical output) and indices of respiratory neural output (Drive) during exercise has been examined in the past. Occluded mouth pressure at 100 ms into inspiration ($P_{m0.1}$) has been commonly used as an index of drive and previous studies [LIND AND HESSER, 1984; HUSSAIN *ET AL*, 1985] that have examined the $\dot{V}_E$ - $P_{m0.1}$ relationship have shown that $P_{m0.1}$ increased at faster rate than $\dot{V}_E$ in humans during exercise. This non-linear $\dot{V}_E$ - $P_{m0.1}$ relation has been attributed to non-linear increases in "effective impedance" of the respiratory system [HUSSAIN *ET AL*, 1985]. Other studies of this relationship however, have shown that other indices of drive (e.g. dP/dt or esophageal pressure · time product [WANKE *ET AL*, 1991]) increase linearly with the increases in ventilation during exercise. Limited data from animals performing exercise also suggest that both the electrical (EMG) and mechanical (pressure) activity of inspiratory and expiratory muscles increase proportionately with exercise hyperpnea [AINSWORH *ET AL*, 1989; 1996]. Furthermore, the recent analysis of ALIVERTI *ET AL* [1997] clearly demonstrates that while there is a dramatic increase in drive to all the respiratory muscles in the transition between rest and start of exercise, this drive increases equally and proportionally to all the respiratory muscle groups as exercise intensity is increased. However the authors suggest, that the transduction of this drive into a specific force · velocity expression by the individual muscle groups, depends entirely on their mechanical advantage.

As discussed in detail elsewhere [WHITELAW AND DERENNE, 1993], $Pm_{0.1}$ measurements during exercise may not accurately reflect inspiratory drive and/or respiratory muscle output, because of **1)** the increased elastic recoil due to reduction in EELV below FRC; **2)** the changes in the shape of P_{musI} (Figures 2.6 and 2.7) during exercise [GALLAGHER AND YOUNES, 1989; WHITELAW AND DERENNE, 1993] and **3)** the variability of the time difference between the onset of neural inspiration and $Pm_{0.1}$ measurement [GALLAGHER AND YOUNES, 1989; WHITELAW AND DERENNE, 1993]. The non-linear relationship between $\dot{V}_E$ and $Pm_{0.1}$ therefore may not necessarily reflect a true non-linear increase in respiratory impedance during exercise. The relationship between $\dot{V}_E$ and P_{mus} throughout the respiratory cycle has therefore been examined, over a wide range of $\dot{V}_E$ levels in this study and the results show that a strong linear relationship exists between the ventilatory and respiratory muscle output during heavy exercise. The correlation coefficients of the $\dot{V}_E$ - Total P_{mus} relationship (Figure 2.12) was higher than that of both the $\dot{V}_E$ - mean P_{musI} or $\dot{V}_E$ - mean P_{musE} relations in each subject, suggesting the net pressure generated by all the respiratory muscles (not inspiratory or expiratory alone) throughout each breath is determined by the ventilatory need of the individual during heavy exercise. Furthermore, except in subject #4 (Figure 2.10), the increases in mean P_{musI} and mean P_{musE} were significantly related in a linear fashion to the hyperpnea of CWHE. The linear relationship between $\dot{V}_E$ and mean P_{musI}/P_{capI} (%) in all these subjects also indicates that the dynamic load on the inspiratory muscles increases as a linear function of ventilatory output during heavy endurance exercise.

2.5.4. Post-inspiratory (expiratory) inspiratory activity during CWHE.

This study also provides new evidence on the persistence of inspiratory muscle activity in the first part of expiration (post-inspiratory inspiratory activity, P_{musIpI}) in humans performing heavy exercise. Resting breathing in humans is predominantly an inspiratory event from a respiratory muscle point of view and

expiration is a result of passive relaxation and slowly decaying P_{musI} which persists during and "brakes" expiration [AGOSTONI AND CITTERIO, 1979; SHEE *ET AL*, 1985]. With the substantial increase in breathing frequency during CWHE, both the magnitude and the rate of rise of inspiratory P_{musI} are increased significantly. As figures 2.5. and 2.6 also reveal, the rate of decay of P_{musI} from peak values is also significantly increased and this decay rate has been determined to depend on breathing frequency in humans [AGOSTONI AND CITTERIO, 1979]. $P_{musI_{PI}}$ persists at the high $\dot{V}_E$ levels throughout exercise however, as a smaller fraction of T_E. As figure 2.9 and table 2.4 showed, both the duration of post-inspiratory inspiratory activity (PIIA) and its magnitude at end exercise are ~50% of values at the start of exercise. Animal studies that have examined PIIA however, have shown that the both the duration and the magnitude of changes in PIIA depend on the nature of the ventilatory stimulus. In exercising dogs for example, the duration of PIIA remains the same while there is progressive shortening of T_E, resulting in a relative increase in PIIA [AINSWORTH *ET AL*, 1989]. Hypoxia and hypercapnia have been shown to reduce PIIA in some [OLIVEN *ET AL*, 1985] studies, but increase PIIA in others [SMITH *ET AL*, 1989]. The combination of increased expiratory pressures with a progressively decreasing $P_{musI_{PI}}$ in these subjects served to augment expiratory flow which increased throughout heavy exercise.

In conclusion, this study has shown that the relationship between minute ventilation and net respiratory muscle pressure throughout the respiratory cycle (and its components) during heavy exercise in humans, is linear. The study also showed that the hyperventilatory response during CWHE is associated with a progressive increase in both inspiratory and expiratory muscle pressures. While inspiratory muscle load increased significantly, post-inspiratory inspiratory muscle activity progressively diminished during CWHE, thus resulting in a relatively greater contribution by the expiratory muscles to Total P_{mus} throughout each breath.

3. THE ROLE OF INTRINSIC RESPIRATORY MUSCLE LOAD ON VENTILATORY REGULATION DURING HEAVY EXERCISE.

3.1. Introduction.

Minute ventilation ($\dot{V}_E$) and breathing pattern are determined by the intensity and pattern of respiratory muscle contraction (i.e. respiratory muscle output) and the mechanical properties of the respiratory system. The relation between respiratory muscle pressure (P_{mus}) and $\dot{V}_E$ is illustrated schematically in figure 3.1; the solid line indicates that increases in P_{mus} cause $\dot{V}_E$ to increase. Consistent with data from the previous chapter but not all [HUSSAIN *ET AL*, 1985] previous studies, a linear model has been used to illustrate the P_{mus} - $\dot{V}_E$ relation in figure 3.1. A linear model is used here to facilitate discussion of concepts raised in this chapter but the concepts and questions addressed here do not depend on the linearity (or otherwise) of this

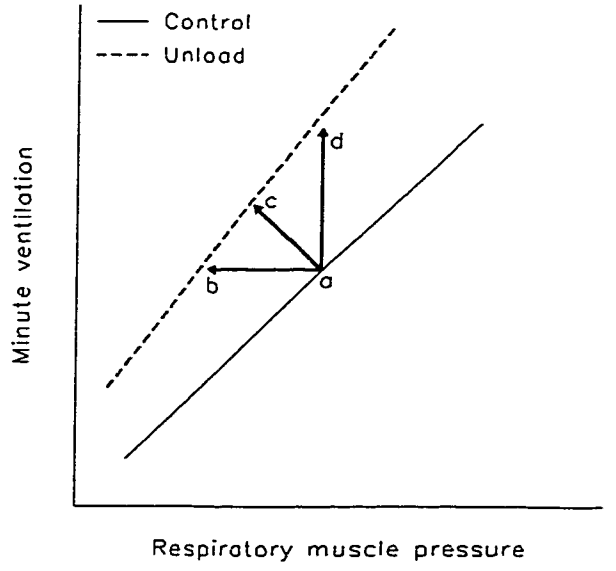

Figure 3.1. The effect of reducing respiratory impedance on $\dot{V}_E$ regulation during CWHE (Theory).

relation. The term "respiratory impedance" will be used in this chapter as a descriptive term to denote the relation between respiratory muscle pressure generated by the subject (P_{mus}) and minute ventilation ($\dot{V}_E$). "Reducing respiratory impedance" is merely a short-hand way of stating that the "relation between P_{mus} and $\dot{V}_E$ was altered such that one gets a higher $\dot{V}_E$ for a given P_{mus} or the same $\dot{V}_E$ for a lower P_{mus}".

The possible effects of reducing respiratory impedance are shown by the dashed line of figure 3.1. Compared to point "a" in the Control (normal impedance) situation, reducing impedance must alter $\dot{V}_E$ and/or P_{mus} and the three possible effects of reducing respiratory impedance are shown by arrows in Figure 3.1. If P_{mus} remained unchanged, $\dot{V}_E$ would rise (point "d"). Alternatively, a lesser rise in $\dot{V}_E$ would occur if P_{mus} fell slightly (point "c"). $\dot{V}_E$ would not rise at all if the fall in impedance was accompanied by a similar fall in P_{mus} (point "b"). Which of these (or other) responses to unloading is adopted, clearly has implications for the mechanisms (or goals) of ventilatory regulation during exercise. If P_{mus} falls so that $\dot{V}_E$ remains the same (a $\rightarrow$ b), this would suggest that, regardless of the underlying mechanisms, the respiratory control system adjusts respiratory motor output so as to provide the appropriate $\dot{V}_E$ and therefore blood gases. If P_{mus} remains unchanged and $\dot{V}_E$ rises (a $\rightarrow$ d), this would indicate that regulation of $\dot{V}_E$ and blood gases is not the primary goal of the respiratory controller.

There is little information about the effects of normal respiratory impedance on regulation of $\dot{V}_E$ and P_{mus} during exercise. Increasing the normal impedance by external loading has been shown to decrease $\dot{V}_E$ and increase respiratory motor output especially during heavy exercise [D'URZO *ET AL*, 1987; RAMONATXO *ET AL*, 1991]. However such studies of "added loading" do not necessarily provide insight into the importance of the normal load. Recently a number of studies have attempted to reduce the normal respiratory load by applying pressure assist at the mouth [YOUNES

ET AL, 1987; POON *ET AL*, 1987; GALLAGHER AND YOUNES, 1989]. They found little change in $\dot{V}_E$ and a fall in P_{mus} during mild and moderate exercise. However, these studies provide little insight into the role of the normal load at high levels of $\dot{V}_E$ during heavy exercise.

3.2. Study objectives.

This study was designed to test the hypothesis that the load on the respiratory muscles ("intrinsic respiratory impedance") is an important determinant of the ventilatory response to heavy exercise in normal humans. Therefore the effects of reducing respiratory impedance, on $\dot{V}_E$ and respiratory muscle output (P_{mus}) during endurance exercise was examined in this study. An unloading device [YOUNES *ET AL*, 1987] was used to apply a flow-proportional mouth pressure assist during both inspiration (I) and expiration (E), throughout heavy exercise. This device was adapted, modified and tested for optimal performance during heavy endurance exercise and the results have been published previously [KRISHNAN, 1992]. Heavy endurance exercise was studied because high (and progressively increasing) levels of $\dot{V}_E$ are observed for most of its duration. A manuscript from this study has also been published [KRISHNAN *ET AL*, 1996].

3.3. Methods.

3.3.1. Subjects.

Seven healthy males (age 20 - 30 years) who had normal physical examination and pulmonary function were studied. The subjects were physically active, motivated, took part in some form of regular exercise and had no history of respiratory, cardiovascular or neuromuscular disorders. They were also free from any recent upper respiratory illness. All subjects gave informed consent to the procedures but none was aware of the specific goals of the study. They were instructed to refrain from heavy physical activity on the day before testing and to avoid food and caffeinated drinks for two hours before testing.

3.3.2. Exercise testing.

Peak O_2 uptake ($\dot{V}O_{2,max}$) and peak work-rate ($\dot{W}max$) were measured in all subjects using an incremental cycle ergometer (25 watts per minute) exercise protocol to exhaustion. Three days after the incremental exercise test each subject performed constant work-rate heavy exercise (CWHE at ~80% of $\dot{W}max$) to exhaustion enabling him to become familiarized with the endurance exercise protocol. The Control and Unload endurance exercise studies were then conducted at least 3 - 5 days after the pilot CWHE test.

3.3.3. Chest wall mechanics.

Using similar techniques as described in chapter 2, static chest wall recoil pressure ($P_{W,el}$) and inspiratory muscle strength (P_{max}) were measured in 5 subjects in whom pleural pressure (P_{pl}) was measured during exercise. All measurements were made in the posture identical to that assumed on the cycle ergometer. Two

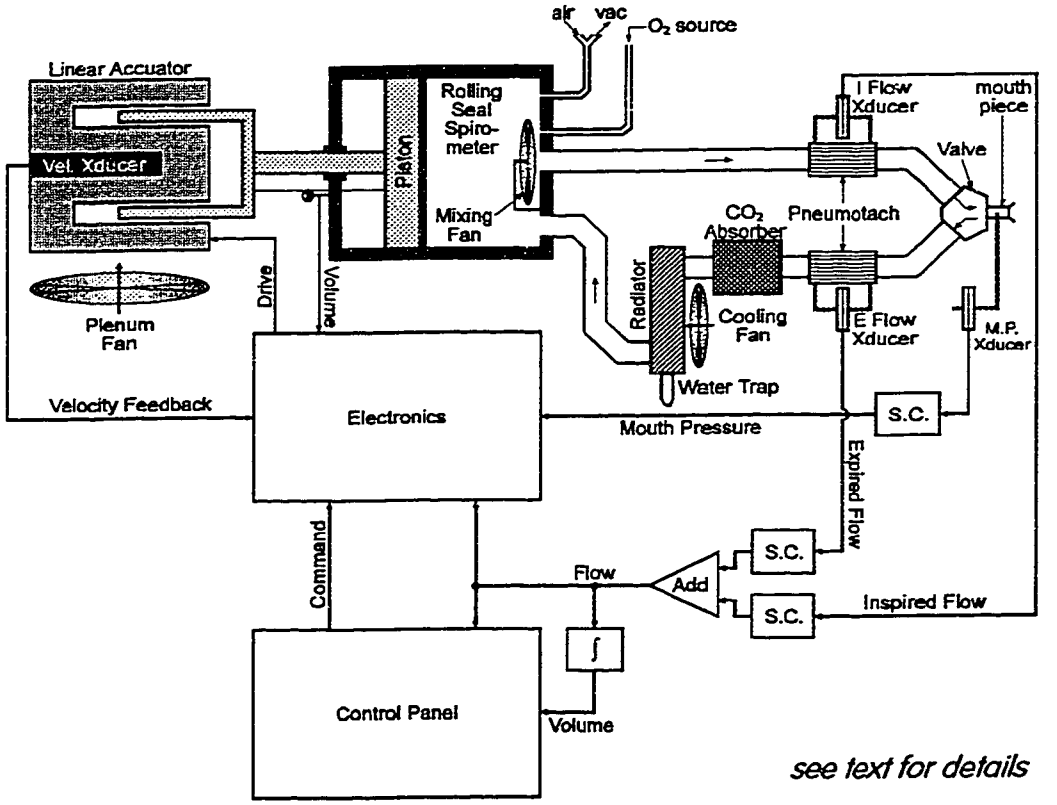

Figure 3.2. The modified loading/unloading device [KRISHNAN, 1992].

techniques were used to measure $P_{W,el}$ and reliable measurements were available for each subject, from only one technique.

3.3.4. Equipment.

Exercise was performed on an electrically braked cycle ergometer (Godart). The subjects wore nose-clips and breathed through a mouth-piece into a closed breathing circuit (Figure 3.2) consisting of a two-way valve (Vacumed, K271), the inspiratory and expiratory sides of which were connected to a special feedback controlled loading/unloading device, that has been described in detail elsewhere [YOUNES *ET AL*, 1987; KRISHNAN, 1992]. Briefly, it consists of a rolling-seal spirometer system driven by a linear motor piston which develops a force (and hence pressure inside the spirometer) in proportion to a command signal (CS). A control panel allows for appropriate signal conditioning (S.C., amplification, rectification etc.) and phase selection (inspiration and/or expiration) of the CS. The CS in this study was airflow ($\dot{V}$) and mouth pressure (P_m) was made positive during inspiration and negative during expiration in proportion to respiratory flow such that flow-proportional pressure assist

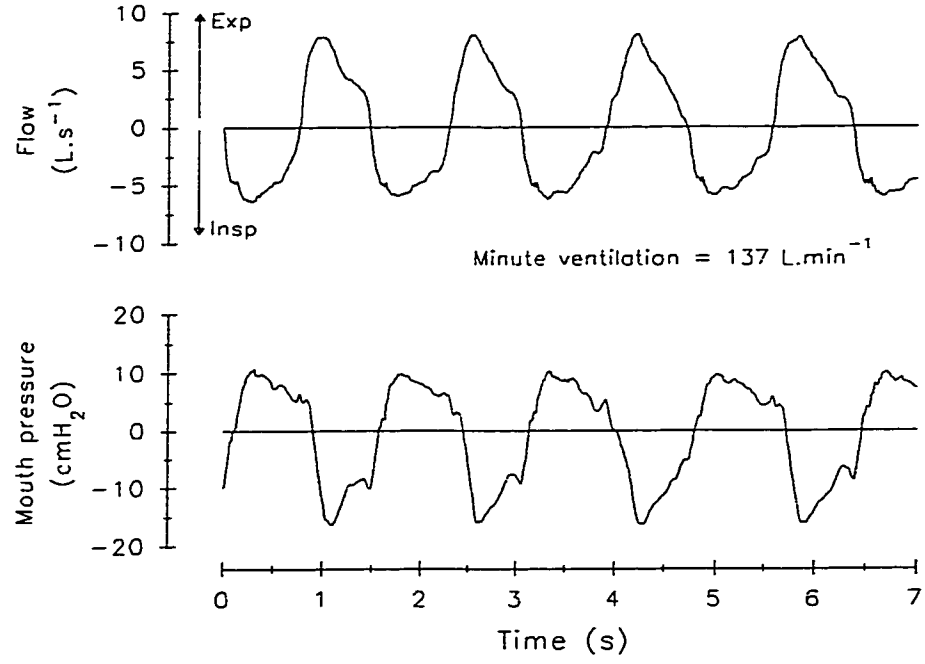

Figure 3.3. Flow-proportional mouth pressure assist during heavy exercise.

(unloading) of the respiratory muscles occurred throughout the respiratory cycle. An example of flow-proportional pressure assist during heavy exercise in shown in Figure 3.3. As evident from the figure, even at these high $\dot{V}_E$ levels (> 130 L · min^{-1}) the shape of the breath-by-breath P_m signal is based clearly on the command signal ("flow"). The magnitude of the breath-by-breath assist ($P_m/\dot{V}$ ratio, $cmH_2O \cdot L^{-1} \cdot s$) throughout exercise was continuously adjustable with a 10-turn potentiometer on the control panel.

The setup of the unloading device was, with minor exceptions, as previously described for unloading during incremental exercise [YOUNES *ET AL*, 1987; GALLAGHER AND YOUNES, 1989]. The device itself was part of the closed breathing circuit with provisions for O_2 inflow and expiratory CO_2 re-absorption. All tubing (except for a short segment of flexible tubing near the mouth-piece to allow for minimal subject movement) consisted of 2" ID rigid pipes. Inspired O_2 and end-tidal CO_2 concentrations (F_{I,O_2}, F_{ET,CO_2}, %) were monitored breath-by-breath by a mass-spectrometer (AIRSPEC, MGA-2000) calibrated with standard gas mixtures. To replace consumed O_2, 100% O_2 was added to the spirometer where it mixed rapidly with the chamber gases with the help of a mixing fan. O_2 flow was measured with a pneumotachograph-transducer (Fleisch #00 - Validyne MP45, ± 2 cmH_2O) system calibrated with a 60-ml precision syringe (at 30 - 60 ml · s^{-1}) before each test. F_{I,O_2} was carefully regulated throughout exercise at ~21% by one investigator monitoring both O_2 flow and F_{I,O_2}. Integrated O_2 flow ($O_{2,vol}$) was measured at ATPD (ambient and dry) conditions throughout exercise.

Inspiratory and expiratory flow signals, measured separately with two pneumotachograph-transducer (Fleisch #3-Validyne MP45, ± 2 cmH_2O) assemblies on either side of the breathing valve (Valve, figure 3.2), were added and integrated electronically to provide flow and volume throughout the breathing cycle. The individual flow signals were calibrated with a 4-litre precision syringe before each test

and were monitored during exercise, for any zero drift [GOWDA *ET AL*, 1990]. Both P_m and $\dot{V}$ were feedback signals to the unloading device and were filtered at 50 Hz to prevent any oscillations.

Two minor modifications of the previously described system [YOUNES *ET AL*, 1987] were used to facilitate exercise to exhaustion and unloading at the high work-rates and $\dot{V}_E$ levels of this study. During preliminary experiments a progressive rise in inspired gas temperature and accumulation of water in the apparatus was observed as this was a closed breathing system. The former was uncomfortable for the subjects and the latter impaired the mechanical efficiency of the unloading device. Therefore a cooling system with a water trap (radiator) was added distal to the CO_2 absorber, to cool the expirate and prevent condensation in the spirometer. Thus inspired gas temperature (measured during each test) was only 1 - 2 °C greater than room temperature and condensation in the spirometer did not occur. Secondly, the magnitude of resistive unloading ($P_m/\dot{V}$ ratio) falls below that desired at high $\dot{V}_E$ and breathing frequencies (f_b) because of the mechanical properties of the system. Therefore the actual resistive unload ($P_m/\dot{V}$ ratio) was continuously monitored by an analog divider circuit during unloaded exercise and, if the unload fell below the required level, the command signal to the linear motor was increased. For a detailed description of all the modifications made to the original unloading device and the results of testing it with or without resistive unloading under heavy exercise conditions, the reader is referred to the author's M.Sc thesis [KRISHNAN, 1992].

P_{pl} during exercise was measured (in 5 subjects) with a latex balloon-catheter system connected to a pressure transducer (Validyne MP45, $\pm$ 140 cmH_2O). Using standard techniques [MILIC-EMILI *ET AL*, 1964; WANG *ET AL*, 1991] the balloon was positioned in the same location in the mid-oesophagus before exercise in both the Control and Unload tests. P_m and P_{pl} transducers were calibrated with a water manometer. ECG was recorded with standard chest leads. $\dot{V}$, V, $O_{2,vol}$, F_{I,O_2}, F_{ET,CO_2},

P_m, P_{pl} and ECG were recorded on an 8-channel strip-chart recorder (Gould) and stored on a computer disk for later analysis. All transducers and measuring equipment were calibrated before and rechecked after each test.

3.3.5. Protocol.

The subjects breathed into the closed breathing circuit connected to the unloading device on both Control and Unload exercise days (separated by at least 3 days). Three subjects performed the Control test first and four performed the Unload test first. In the Control test there was no pressure assist and P_m was slightly negative during inspiration and positive during expiration in proportion to $\dot{V}$, as dictated by the resistance of the breathing circuit (~0.3 $cmH_2O \cdot L^{-1} \cdot s$). With unloading, P_m was made positive during inspiration and negative during expiration in proportion to $\dot{V}$ resulting in resistive unloading throughout the breathing cycle (Figure 3.3). The magnitude of the pressure assist delivered was on average 1.7 $cmH_2O \cdot L^{-1} \cdot s$. Because equipment resistance (present in the Control studies) was also removed, the net "negative resistance" (resistive assist) applied at the mouth was 2.0 $cmH_2O \cdot L^{-1} \cdot s$. Each subject was familiarized with the sensation of pressure assist, which was delivered for a few breaths, before exercise. The 5 subjects in whom Ppl was measured were trained to make inspiratory capacity (IC) maneuvers.

After a period of quiet breathing, warm-up exercise began at 50 watts. The subject was then alerted and the work-load was raised rapidly to the pre-determined level (~80% $\dot{W}_{max}$). The subject pedaled at 50 - 70 rpm at this work-load until he was unable to continue exercising. The noise generated by both the linear motor plenum fan and the radiator fan helped to drown out any sounds from the spirometer piston on both the Control and Unload test days. At the end of every 2 minutes during exercise the subject was instructed to inhale to TLC and hold his breath with glottis open for 1 second. Both the volume and Ppl signal were monitored so as to ensure a maximal effort during this IC maneuver. Endurance time

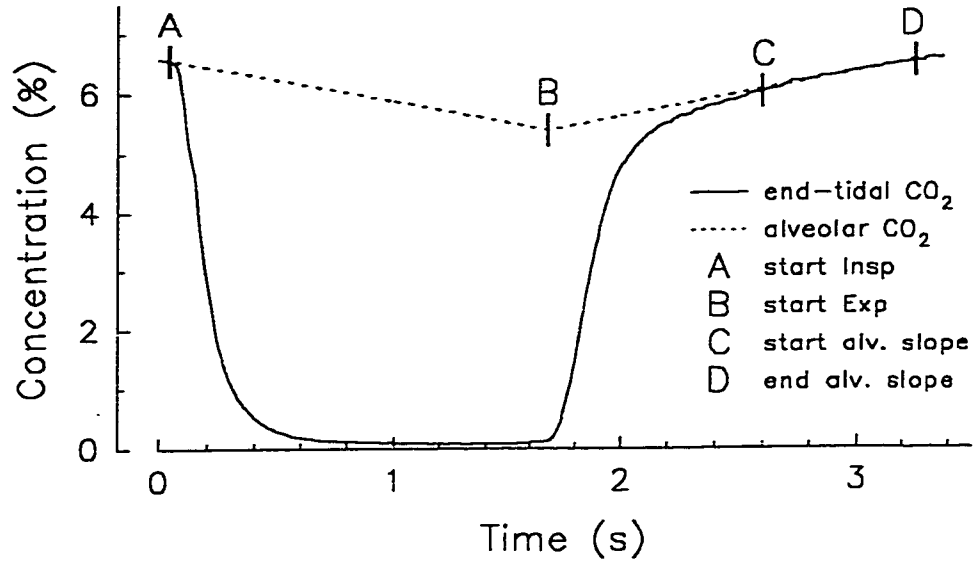

Figure 3.4. Assessment of time-weighted mean alveolar P_{CO_2} ($P_{\bar{A},CO_2}$).

was recorded on a stop-watch as the time between the commencement of heavy exercise and exercise cessation.

3.3.6. Data analysis.

Integrated O_2 flow ($O_{2,vol}$) was measured from the paper trace record for each minute of exercise. $\dot{V}O_2$ was calculated from the measured O_2 flow required to maintain a stable F_{I,O_2} (21%) in the closed breathing system thus:

$$\dot{V}O_{2,ATPD} = \int O_{2,flow} - (\Delta F_{I,O_2} \cdot k) \qquad (3.1)$$

where $\int O_{2,flow}$ was cumulative O_2 flow ($O_{2,vol,ATPD}$), $\Delta F_{I,O_2}$ was the small change in O_2 concentration over the period of measurement (< 0.5%) and k was the calibration factor used to convert $\Delta F_{I,O_2}$ to O_2 volume. $\dot{V}O_{2,ATPD}$ was converted to Standard temperature and Pressure, Dry (STPD) values. This method of calculating $\dot{V}O_2$ has been described in detail previously [GALLAGHER AND YOUNES, 1989].

The methods of assessment of exercise ventilatory variables, respiratory mechanics, lung volumes, P_{mus} and inspiratory muscle strength (P_{maxI}) were described in detail in chapter 2, and will therefore not be elaborated in this section. Figure 3.4 illustrates the average time course of end-tidal and mean alveolar P_{CO_2} in

one minute during exercise. As time-weighted mean alveolar P_{CO_2} ($P_{\bar{A},CO_2}$) has been shown to accurate estimate of P_{a,CO_2} during exercise [ROBBINS *ET AL*, 1990], it was estimated in all subjects, for each minute of exercise, using the average CO_2 profile of numerous (10 - 50) breaths, using established techniques [DUBOIS *ET AL*, 1952; WARD AND WHIPP, 1980]. Briefly, this technique uses the computer to measure the slope of alveolar gas (between "C" and "D" in figure 3.4) and estimate $P_{\bar{A},CO_2}$ values at the start of expiration ("B"). $P_{\bar{A},CO_2}$ is then calculated as the time-weighted average of P_{A,CO_2} (from "A" at the start of inspiration, through "B" and then on to "C" and "D").

3.3.6.1. Statistical analyses.

Since the subjects had varying exercise durations, group mean variables from the Control and Unload tests at multiple common exercise time points were compared, using a repeated measures ANOVA design. As the shortest exercise duration was 7.2 min, data from the 1st to 7th minutes of exercise, 50% Control duration, matched time at end exercise (data from the shorter test was compared with iso-time data from the other) and end exercise were included in the ANOVA. Ventilatory ($\dot{V}_E$, V_T, f_b, $P_{\bar{A},CO_2}$) and metabolic (heart rate (f_c), $\dot{V}_{O_2}$) data were available in all subjects ($n = 7$) while P_{mus} and lung mechanics data were measured only in five subjects. Fractional differences between the 2 tests (Unload - Control) are calculated as a percentage of Control values ($\Delta\%$). Endurance time (figure 3.5) during the Control and Unload tests were compared by Student's paired t testing. A P value of < 0.05 was accepted as significant. All data are presented as mean $\pm$ S.E.M.

3.4. Results.

3.4.1. Exercise ventilatory variables.

All subjects completed both the incremental and endurance exercise tests to exhaustion. $\dot{V}_{O_2}$, $\dot{W}_{max}$, f_c and $\dot{V}_E$ at the end of maximal incremental exercise were 3.77 ± 0.2 L · min^{-1} (48 ± 2 ml · Kg^{-1} · min^{-1}), 325 ± 16 watts, 178 ± 4 min^{-1} and 144.7 ± 13.1 L · min^{-1} respectively. These values are within normal limits for their age [JONES,

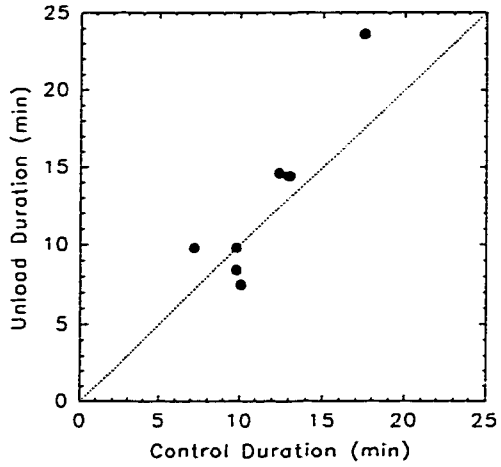

Figure 3.5. Endurance time (Control and Unload).

1988]. The constant work-rate during the Control and Unload endurance exercise tests averaged 257 ± 16 W, representing ~80% $\dot{W}_{max}$. At the end of endurance exercise the subjects stated on questioning that the applied pressure assist did not interfere with their breathing and in general it felt easier to breathe with unloading. Exercise cessation on both the Control and Unload exercise days was usually attributed to increasing leg pain/discomfort, by the subjects. The magnitude [BORG, 1982] of dyspnea and leg discomfort at the end of unloaded exercise (6 ± 1 and 7 ± 1 respectively) were not significantly different from those at the end of Control exercise (7 ± 1 and 7 ± 1 respectively).

Figure 3.5 compares exercise duration in the Control test with that in the unload test in each subject (closed circles). The line of identity (dashed line) is also shown and reveals that the average exercise duration during the Unload test (12.6 ± 2.1 min) was not significantly different than the duration of Control exercise (11.4 ± 1.2 min). Given the hypothesis that unloading the respiratory muscles would improve exercise performance (Type I error = 5%, one-tailed *t* test), the probability (β) of a Type II error was calculated. With the observed within-subject variability in endurance time with unloading, the power (1 - β) of detecting a small (25%) but significant increase in exercise duration was over 88% [FREIMAN *ET AL*, 1978; LACHIN, 1981].

The temporal course of $\dot{V}_E$ during Control exercise is compared with that during the Unload test, in each subject, in figure 3.6. All the subjects showed a rapid rise in $\dot{V}_E$ at the start of heavy exercise and a slow progressive increase throughout exercise (except subject #3 who showed a fall at end exercise). This resulted in the subjects reaching high ventilatory levels early in exercise (> 100 L · min^{-1} at 50% Control duration) in both tests. The time course of $\dot{V}_E$ in the Control and Unload test was almost identical in subjects 1, 2, 5 and 6. Subjects 3, 4 and 7 however had a marginally higher $\dot{V}_E$ with unloading at certain times during the course of CWHE.

Average exercise variables at 2 matched times from the Control and Unload exercise tests (at 50% Control duration and at matched times at end exercise) are presented in Table 3.1. The subjects were exercising at over 85% of peak $\dot{V}O_2$ through most of endurance exercise in both tests. End endurance exercise $\dot{V}O_2$ was slightly less than that at the end of maximal incremental exercise, while fc values were similar (Table 3.1). Repeated measures ANOVA revealed no significant differences between the Control and Unload tests in any of the above variables at either 50% Control duration or at matched time at end exercise.

The average temporal courses of $\dot{V}O_2$, $P\bar{A}CO_2$, fc and $\dot{V}_E$ in the Control and

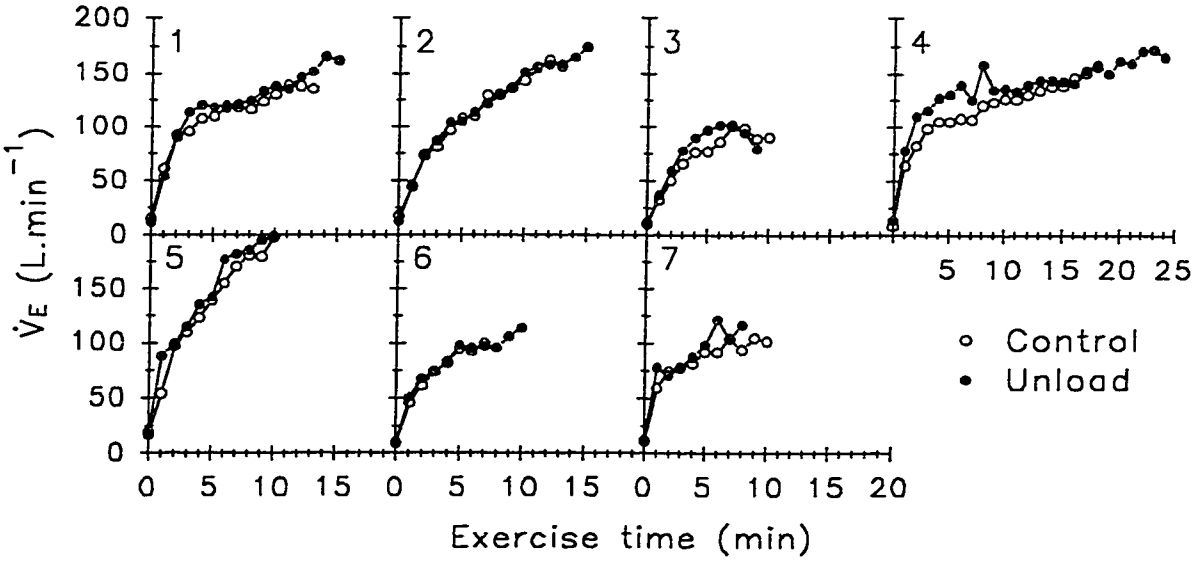

Figure 3.6. Minute ventilation during CWHE (Control and Unload).

Table 3.1. Metabolic and ventilatory variables.

	50% Control Duration			Matched time at End Exercise		
	Control	Unload	Δ%	Control	Unload	Δ%
$\dot{V}_E$ (L · min^{-1})	110 ± 10	114 ± 8	5 ± 4	133 ± 15	137 ± 15	4 ± 4
V_T (L)	2.80 ± 0.1	3.05 ± 0.2	8 ± 6	2.64 ± 0.2	2.88 ± 0.2	10 ± 5
fb (min^{-1})	39 ± 4	39 ± 4	0.5 ± 11	51 ± 6	49 ± 6	4 ± 6
$\dot{V}_{O_2}$ (L · min^{-1})	3.33 ± 0.25	3.23 ± 0.24	-3 ± 3	3.46 ± 0.30	3.29 ± 0.30	-5 ± 4
TI/TT	0.51 ± 0.01	0.49 ± 0.01	-2 ± 1	0.51 ± 0.00	0.51 ± 0.01	0.8 ± 1
fc (min^{-1})	169 ± 3	168 ± 5	-0.4 ± 1	181 ± 4	181 ± 4	0.4 ± 1
$P\bar{A}.co_2$ (mmHg)	31.4 ± 1.3	31.3 ± 1.4	-0.3 ± 3	27.0 ± 2.0	27.3 ± 1.7	2 ± 3

Unload exercise tests are presented in Figure 3.7. Exercise iso-time data are presented as group mean ± S.E.M (n = 7) and the results of tests of significance (*, $P < 0.05$, ANOVA) are also shown. The rapid increase in $\dot{V}_{O_2}$ early in exercise followed by a slow progressive increase throughout exercise, was similar in both tests. There was no difference in the progressive increase in fc and the fall in $P\bar{A}.co_2$ throughout

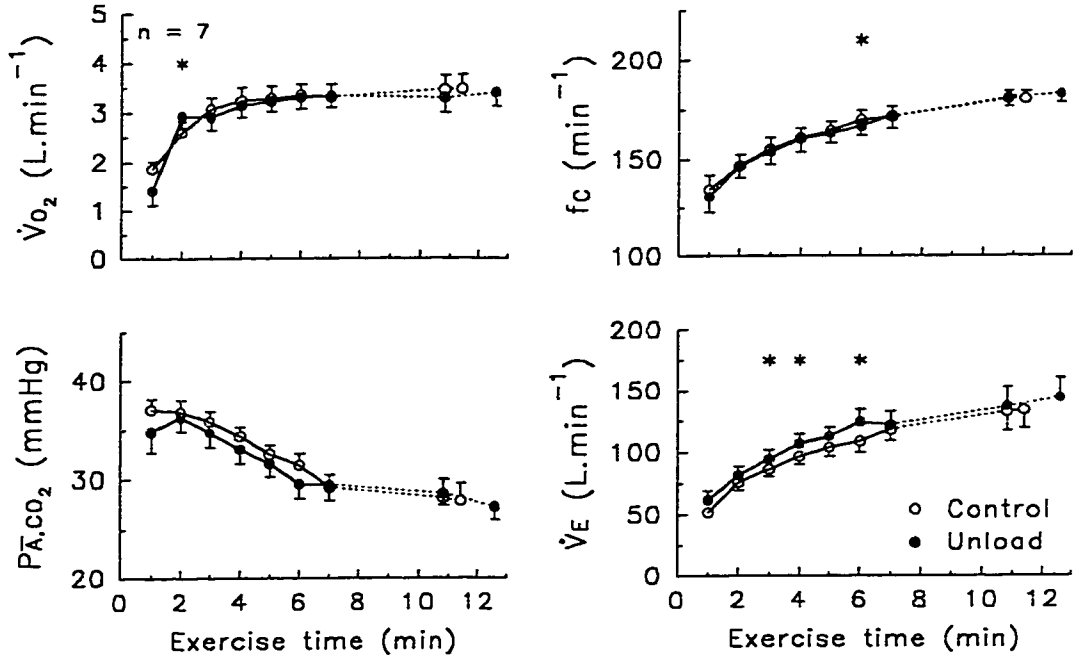

Figure 3.7. Metabolic and ventilatory variables (Control and Unload CWHE).

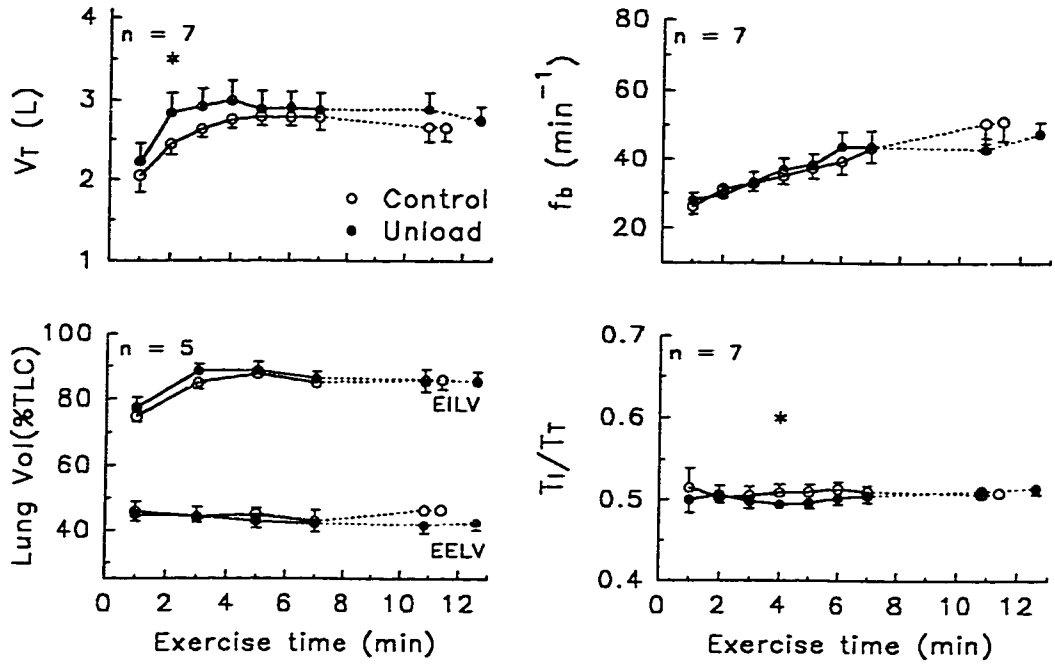

Figure 3.8. Breathing pattern during CWHE (Control and Unload).

exercise between the Control and Unload exercise tests. $\dot{V}_E$ with unloading was slightly higher during the 3rd, 4th and 6th minutes of exercise, but there was no significant difference in $\dot{V}_E$ at any other time between the two tests.

The average time courses of V_T, f_b, T_I/T_T (n = 7) and lung volume (%TLC, n = 5) are summarized in figure 3.8 and reveal no significant differences between the Control and Unload exercise tests. Most of the initial hyperpnea (in both tests) was due to an augmentation of V_T which soon reached a plateau and fell slightly towards end exercise; this is consistent with data from previous studies [DEMPSEY *ET AL*, 1990; SYABBALO *ET AL*, 1994]. As average V_T with unloading was slightly higher throughout exercise with little change in T_I, mean inspiratory flow (V_T/T_I) was slightly and significantly greater with unloading during the 4th, 5th and 6th minute of exercise. There was no significant difference in V_T/T_I between the Control and Unload tests at any other time during CWHE. Almost all the changes in V_T with time were due to changes in EILV, as EELV showed little change after the first minute of exercise. Reproducible IC's during exercise and measured TLC at rest were used to calculate

EELV (EELV = TLC - IC). P_{pl} at end inspiration ($P_{pl,IC}$) was used to validate full inspiration to TLC during exercise. There were neither any changes in $P_{pl,IC}$ with increasing exercise time nor any differences between the Control and Unload tests.

As there was little increase in $\dot{V}_E$ with unloading (especially at the higher $\dot{V}_E$ levels), it was speculated whether the airways had reached their capacity to generate flow; i.e. whether expiratory flow limitation prevented further increases in $\dot{V}_E$ with unloading. As maximal flow-volume ($\dot{V}$ - V) envelopes were not measured as part of the protocol, tidal $\dot{V}$ - V loops from matched times during exercise were analyzed. Figure 3.9 shows average data from 5 periods during CWHE from both the Control and Unload tests; 50% Control duration (thin solid line), 3 minutes (dashed line) and 1 minute before matched time at end exercise (dashed and dotted line), matched time at end exercise (thick solid line) and at end exercise (dotted line). The loops are positioned on the abscissa (V) in relation to group mean TLC (6.64 L). As end-expiratory lung volume (measured in 5 subjects) did not change significantly after the start of heavy exercise (Figure 3.8), EELV in the other two subjects was estimated from

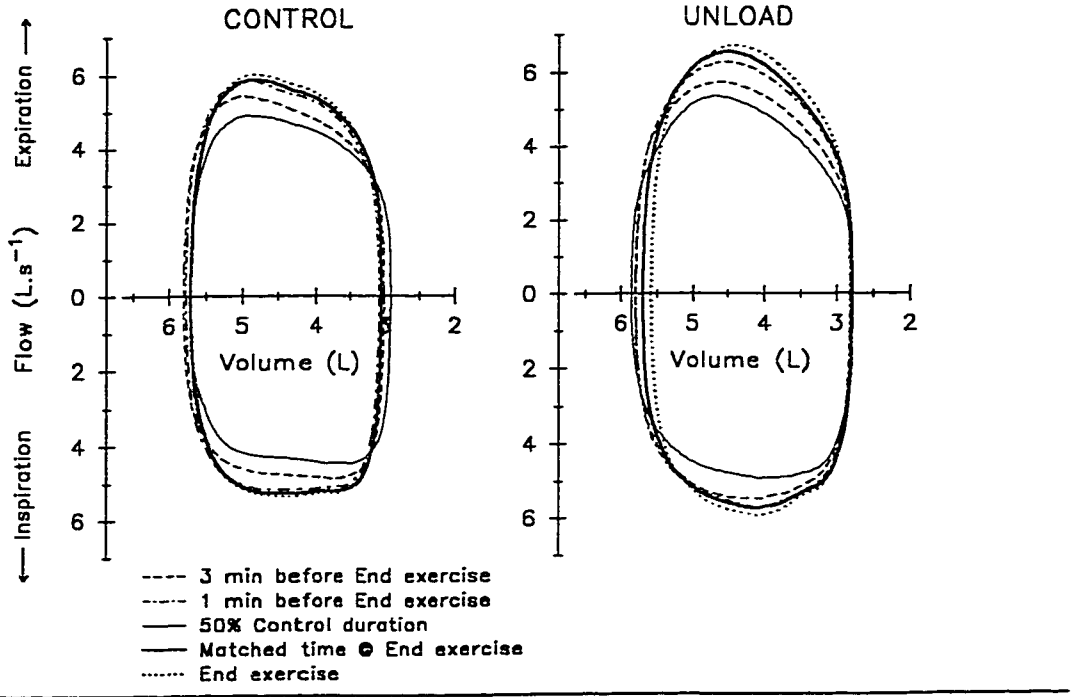

Figure 3.9. Flow-Volume profiles during CWHE (Control and Unload).

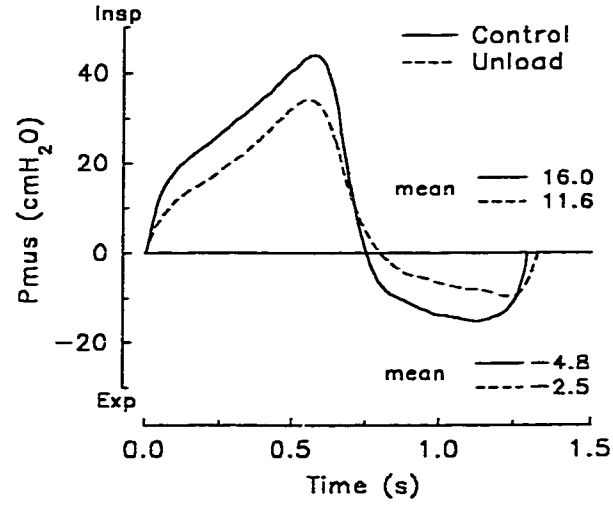

Figure 3.10. Respiratory muscle pressure (P_{mus}, Control and Unload).

the group average (n = 5) EELV. Figure 3.9 reveals that both inspiratory and expiratory flows at matched lung volumes continued to increase throughout and until end exercise in both the Control and Unload tests. It is therefore unlikely that expiratory flow limitation was the cause of the lack of increase in $\dot{V}_E$.

3.4.2. Respiratory mechanical variables.

Figure 3.10 illustrates typical respiratory muscle pressure (P_{mus}) waveforms during exercise in both the Control and Unload tests. Data shown are from the same subject (#4) as in figure 3.3, from exercise iso-time (15th minute) in the Control and Unload exercise tests. P_{musI} is positive and P_{musE} negative and the waveforms have

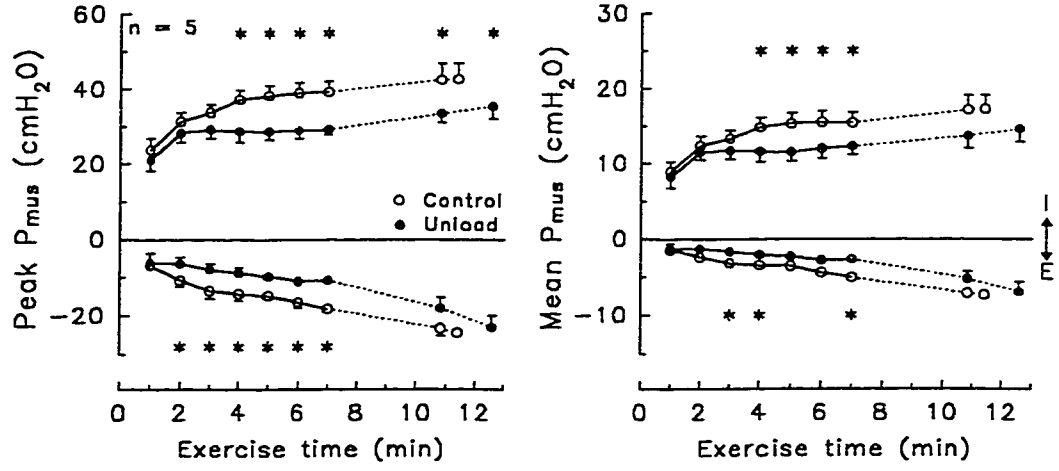

Figure 3.11. P_{musI} and P_{musE} during CWHE (Control and Unload).

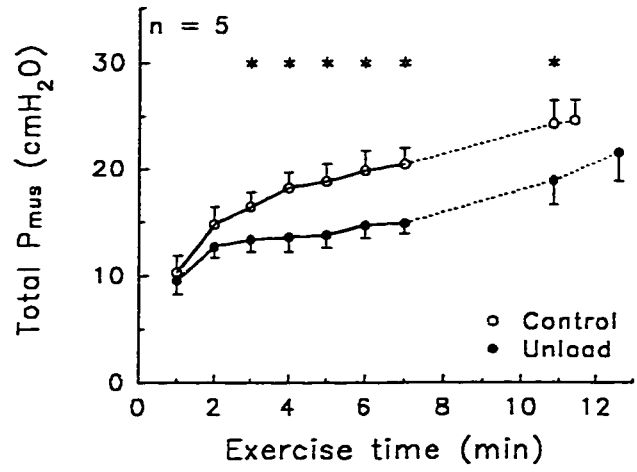

Figure 3.12. Total P_{mus} during CWHE (Control and Unload).

been time-aligned at the start of neural inspiration (+ve zero crossing). Figure 3.10 clearly highlights a net reduction in pressure generated by both the inspiratory and expiratory muscles at the high $\dot{V}_E$ levels of CWHE ($\dot{V}_E$ > 130 L · min^{-1}, see figure 3.3) in this subject. Figure 3.11 summarizes the average (n = 5) time course of P_{mus} in these subjects and reveals that with unloading, there were sustained and significant reductions in both inspiratory and expiratory peak and mean P_{mus} throughout exercise. The significant reduction in net respiratory neuromuscular output throughout the breath (Total P_{mus} = mean P_{musI} - mean P_{musE}) as a result of the applied pressure assist throughout CWHE is shown in figure 3.12.

As indicated earlier, P_{musI} was represented a fraction (%) of volume-matched inspiratory muscle strength (P_{maxI}), on a breath-by-breath basis throughout CWHE. At exercise iso-time, both peak and mean P_{musI}/P_{maxI} (%) were significantly reduced with unloading. In addition, the ratio of the difference between peak P_{musE} and peak P_{musI} values (ΔP_{mus}) and the time difference (ΔT) was calculated as index of the rate of rise of P_{mus}. Unloading significantly reduced $\Delta P_{mus}/\Delta T$ at matched time at end exercise (by 29%). Table 3.2 summarizes all the P_{mus} and other respiratory mechanical variables at 2 iso-times (50% Control duration, matched time at end exercise, * $P < 0.05$, ** $P < 0.005$) during CWHE.

Table 3.2. Respiratory mechanical variables.

	50% Control Duration			Matched time at End Exercise		
	Control	Unload	Δ%	Control	Unload	Δ%
Peak P_{musI} (cmH_2O)	38.5 ± 2.5	29.0 ± 2.1	-24** ± 4	41.8 ± 4.0	33.4 ± 2.5	-19* ± 5
Mean P_{musI} (cmH_2O)	15.0 ± 1.4	11.9 ± 1.3	-21** ± 3	17.0 ± 1.8	13.6 ± 1.6	-18 ± 6
Peak P_{musE} (cmH_2O)	16.1 ± 1.5	9.4 ± 1.0	-41** ± 6	22.7 ± 1.9	18.1 ± 2.8	-20 ± 10
Mean P_{musE} (cmH_2O)	4.2 ± 0.6	2.2 ± 0.3	-44* ± 9	7.0 ± 0.6	5.3 ± 1.0	-26 ± 11
Total P_{mus} (cmH_2O)	19.2 ± 1.8	14.1 ± 1.3	-26** ± 2	24.0 ± 2.1	18.9 ± 2.3	-21* ± 6
Peak P_{musI}/P_{maxI} (%)	50.4 ± 3.5	38.3 ± 4.5	-25** ± 6	54.6 ± 7.7	41.6 ± 3.7	-20* ± 8
Mean P_{musI}/P_{maxI} (%)	17.8 ± 1.9	14.0 ± 1.5	-21** ± 5	20.0 ± 2.9	15.5 ± 1.6	-19 ± 7
$\Delta P_{mus}/\Delta t$ ($cmH_2O \cdot s^{-1}$)	74.0 ± 8.5	50.1 ± 3.2	-27 ± 13	113.0 ± 19.3	83.9 ± 21.2	-29** ± 7
R_L ($cmH_2O \cdot L^{-1} \cdot s$)	2.60 ± 0.3	3.34 ± 0.3	32** ± 11	3.13 ± 0.23	3.69 ± 0.41	16 ± 5
C_{dyn} ($L \cdot cmH_2O^{-1}$)	0.18 ± 0.03	0.19 ± 0.04	8 ± 12	0.26 ± 0.06	0.24 ± 0.04	-3 ± 9

The effects of unloading on lung mechanics during exercise are seen in Figure 3.13. Iso-volume pulmonary resistance (R_L, both at 0.5 and 1.0 liter above EELV) was greater with unloading (~0.5 $cmH_2O \cdot L^{-1} \cdot s$) compared to Control values, throughout CWHE. The R_L data at 1.0 liter above EELV are given in both figure 3.13 and in table 3.2. Figure 3.13 also reveals that there was no difference in the average time course of dynamic lung compliance (C_{dyn}) between the Control and Unload exercise tests. C_{dyn} fell slightly at the start of heavy exercise but eventually increased to values similar to those at the start of exercise. These changes however, were not significant.

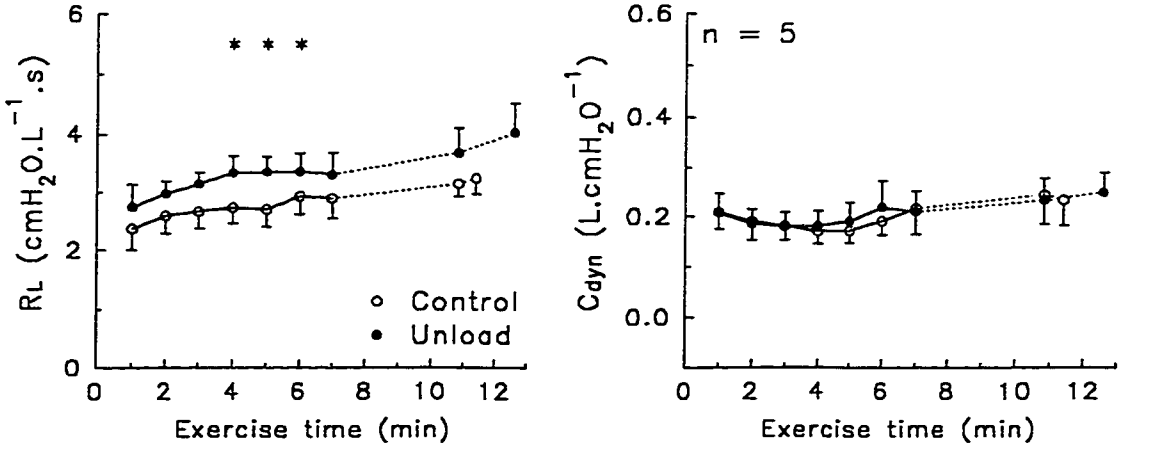

Figure 3.13. Respiratory mechanics during CWHE (Control and Unload).

3.5. Discussion.

3.5.1. The effect of respiratory muscle unloading on $\dot{V}_E$ during CWHE.

This study examined the importance of normal respiratory impedance in the regulation of $\dot{V}_E$ and breathing pattern during CWHE. The progressive rise in $\dot{V}o_2$, fc, and fb, fall in $P\bar{A},co_2$ and little change in V_T with increasing exercise duration are consistent with data from previous studies [MARTIN *ET AL*, 1981; POOLE *ET AL*, 1988; DEMPSEY *ET AL*, 1990; SYABBALO *ET AL*, 1994]. The most striking feature of these results is the extent to which the normal ventilatory response of CWHE was largely unaffected by unloading. Minute ventilation at a given exercise time was similar during the Control and Unload exercise tests for most subjects (Figure 3.6). However, $\dot{V}_E$ during unloading was slightly greater for some subjects but there was little difference for the group as a whole. Of note, those subjects (e.g. subjects 2 and 5, Figure 3.6) with the greatest rate of rise in $\dot{V}_E$ (and the highest $\dot{V}_E$ at end exercise) had essentially no change in $\dot{V}_E$ with unloading. There were small differences in $\dot{V}_E$ for the group as a whole early in exercise but unloading had no significant effect on $\dot{V}_E$ later in exercise; mean $\dot{V}_E$ at matched times at end exercise averaged 133 and 137 $L \cdot min^{-1}$ respectively for the Control and Unload tests. Thus the results suggest that respiratory muscle unloading does not affect the regulation of $\dot{V}_E$ during heavy exercise. Consistent with the lack of change in $\dot{V}_E$, there was no difference in $P\bar{A},co_2$ at any time during or at end exercise.

3.5.2. The effect of respiratory muscle unloading on P_{mus} during CWHE.

Changes in external respiratory load (i.e. applied at the mouth) may be accompanied by changes in internal load [SEKIZAWA *ET AL*, 1988; GALLAGHER AND YOUNES, 1989]. An increase in pulmonary resistance with flow-related pressure unloading during moderate exercise has been reported in an earlier study [GALLAGHER AND YOUNES, 1989]. It was of concern that such an increase in internal resistance might offset the effects of the external unload in this study, i.e. respiratory muscle unloading

might not occur. As figure 3.13 (left panel) reveals, while pulmonary resistance did increase with unloading, a significant fall in P_{mus} with unloading was however documented (Figure 3.12).

What are the limitations of using P_{mus} as an index of respiratory motor output in this setting? As discussed in chapter 2, the measurement of relaxed chest wall recoil ($P_{W,el}$) at rest underestimates the pressure needed to expand the chest wall during exercise because it does not include forces involved in chest wall distortion during exercise [GOLDMAN *ET AL*, 1976]. Because intra-thoracic pressure was less negative during inspiration with unloading, it is likely that chest wall distortion was less or similar. Therefore differences, if any, in chest wall distortion cannot account for the difference in P_{mus} between the Control and Unload studies. The relation between motor output and P_{mus} however is dependent on the length-tension and force-velocity properties of respiratory muscles [YOUNES AND RIDDLE, 1981, YOUNES, 1991]. The former are proportional to lung volume and the latter on inspiratory and expiratory flow rates. Because unloading had no significant effect on either end-expiratory and end-inspiratory lung volumes or mean inspiratory and expiratory flow

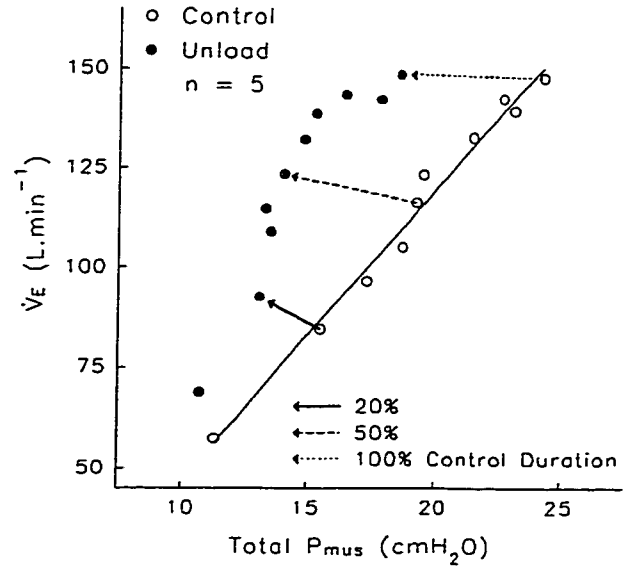

Figure 3.14. The effect of reducing respiratory impedance on $\dot{V}_E$ regulation during CWHE (Results).

rates, at the higher $\dot{V}_E$ levels of CWHE, the relationship between motor output and P_{mus} should also be unaffected. Therefore the fall in Total P_{mus} in this study (Figure 3.12), implies a reduction in net respiratory motor output.

3.5.3. The role of respiratory impedance on $\dot{V}_E$ regulation during CWHE.

As proposed in figure 3.1, this study attempts to examine the effects of reduction in respiratory impedance on the relation between respiratory muscle and ventilatory outputs during CWHE. Figure 3.14 summarizes the results of this study in 5 subjects in whom P_{mus} was measured. Data shown are from matched times in both the Control and Unload CWHE tests. In the Control study, it is evident that the relationship between Total P_{mus} and $\dot{V}_E$ during CWHE is linear ($r = 0.99$) and these results are consistent from those in the previous study (chapter 2). With a reduction in respiratory impedance (Unload) however, the control system responds slightly differently between moderate and high $\dot{V}_E$ levels; in early exercise (20% of Control duration, Control $\dot{V}_E$ ~85 $L \cdot min^{-1}$, "solid arrow") there is a small increase in $\dot{V}_E$ with unloading (Unload $\dot{V}_E$ ~92 $L \cdot min^{-1}$) and a fall in Total Pmus. At the higher $\dot{V}_E$ levels (> 100 $L \cdot min^{-1}$) during CWHE (at 50% of Control duration, "dashed arrow" and at matched time at end exercise, "dotted arrow"), the respiratory controller, in response to a reduction in respiratory impedance, maintains $\dot{V}_E$ constant and Pmus falls markedly. While this strategy is beneficial to respiratory muscle energetics (↓ work), it is unclear why the control system does not permit any further increase in $\dot{V}_E$ (within ventilatory limits) so as to provide greater respiratory compensation for the metabolic acidosis that usually occurs at these exercise intensities during cycle exercise [POOLE *ET AL*, 1988]. The lack of significant change in $\dot{V}_E$ or $P\bar{A},CO_2$ despite substantial respiratory muscle unloading provides strong evidence that the normal respiratory impedance does not constrain or limit the ventilatory response to exercise in normal humans. However the normal respiratory load is an important determinant of respiratory muscle output during heavy exercise; changes in load are accompanied

by changes in P_{mus} so that $\dot{V}_E$ shows little or no change (figure 3.14). The mechanisms responsible for the change in P_{mus} when the load changes are unclear but mechanoreceptor or chemoreceptor input is probably important.

This study was not designed to explore the mechanisms of exercise hyperpnea but it may provide some insight regarding this issue. The "central command" theory [ELDRIDGE *ET AL*, 1981] proposes that the increase in respiratory motor output during exercise is proportional to the neural output to the limb muscles. If this were the sole determinant of the hyperpneic response to exercise, reducing respiratory impedance would have resulted in little/no change in P_{mus} and a large increase in $\dot{V}_E$ (i.e. pathway a $\rightarrow$ d of Figure 3.1). The present data indicate that, while central command may be important, it may not be the sole determinant of respiratory motor output during exercise.

As discussed in chapter 1, the breathing pattern (f_b, T_I, T_E, V_T) and lung volumes (EELV and EILV) used at any given level of $\dot{V}_E$ have major implications for the energy cost of breathing, gas exchange and cardiovascular function. Because breathing pattern and lung volumes were largely unaffected by unloading, the current data suggest that the normal respiratory impedance is not a major determinant of breathing pattern and lung volumes during CWHE. However this has been shown not to be the case, when respiratory impedance is increased above normal [ABBRECHT *ET AL*, 1991].

This study indicates that the pressure which the respiratory muscles have to generate does not determine or constrain $\dot{V}_E$ during exercise. It did not address the importance of airway mechanics, which is a different issue. A number of studies substituted helium for nitrogen as the carrier gas in the inspirate, thus reducing turbulent airflow and airway resistance during exercise. These studies noted a significant increase in $\dot{V}_E$, especially during heavy exercise [SPITLER *ET AL*, 1980; BRICE AND WELSH, 1983; HUSSAIN *ET AL*, 1985]. Helium increases the maximum flow-volume

curve and thus decreases expiratory flow-limitation when it is present. It is likely that the hyperventilation related to HeO_2 breathing is due to its effects on airway mechanics. This may indicate that airway mechanics (e.g. expiratory flow limitation) may constrain $\dot{V}E$ during heavy exercise. This is supported by the finding that the ventilatory response to inhaled CO_2 falls markedly during heavy exercise at levels of $\dot{V}E$ where expiratory flow-limitation develops [CLARK *ET AL*, 1980; JOHNSON *ET AL*, 1992].

Because inspiratory muscles are subjected to heavy loads during CWHE, it has been suggested that respiratory muscle function contributes to exercise limitation [BYE *ET AL*, 1983]. It has recently been shown that diaphragm fatigue develops during CWHE at work rates and levels of $\dot{V}E$ similar to those in this study [JOHNSON *ET AL*, 1993; MADOR *ET AL*, 1993]. However, whether this contributes to exercise limitation is unclear. The development of diaphragmatic fatigue during exercise depends on the pressure/work which the diaphragm generates as well as the "metabolic environment" during heavy exercise [BABCOCK ET AL, 1995]. Unloading reduced inspiratory muscle pressure by approximately 25% in this study. Because metabolic rate and $P\bar{A},CO_2$ were essentially unaffected by unloading, it is likely that acid-base status was also unaffected. Therefore, if inspiratory muscle fatigue was present during control exercise in this study, it was probably significantly less with unloading. Therefore the lack of improvement in endurance time with unloading indicates that respiratory muscle function does not contribute to limitation of CWHE in moderately fit normal humans, during cycle exercise. This conclusion is also supported by a recent study which applied unloading for part of CWHE [MARCINIUK *ET AL*, 1994]. It is also supported by the demonstration that the $\dot{V}E$ and breathing pattern of maximal exercise can generally be sustained for at least 15 minutes (i.e. greater than the average exercise duration in this study) in normal humans [AARON *ET AL*, 1992B]; the levels of $\dot{V}E$ in the latter study were comparable to those in this study.

The reduction in P_{mus} with unloading should be associated with a fall in respiratory muscle oxygen consumption ($\dot{V}O_{2,RM}$) [ROCHESTER AND BETTINI, 1976]. Based on the data of AARON *ET AL*, [1992A], $\dot{V}O_{2,RM}$ during control exercise in this study should be ~0.32 L · min^{-1}, near end exercise. Therefore a reduction in Total P_{mus} of 26% at 50% Control duration and of 21% at end exercise would be expected to decrease $\dot{V}O_{2,RM}$ by 83 ml · min^{-1} or less. Such a small change is within the day to day variability of measuring total body $\dot{V}O_2$ and it may therefore have been missed in this study. There was a reduction in $\dot{V}O_2$ with unloading at matched time at end exercise (Table 3.1) but this was not statistically significant.

In conclusion, the results of this study indicate that the normal respiratory impedance has only a minor role in the regulation of $\dot{V}E$ during heavy endurance exercise, in moderately fit normal humans. In response to a reduction in impedance at the high $\dot{V}E$ levels during heavy endurance exercise, they adopt pathway "a $\rightarrow$ b " shown in figure 3.1, i.e., keep $\dot{V}E$ constant while down-regulating respiratory motor output. Furthermore this study also shows that respiratory muscle function does not limit endurance exercise performance in moderately fit normal humans during cycle exercise.

4. THE HYPERVENTILATORY RESPONSE TO HELIUM-OXYGEN BREATHING DURING EXERCISE - ROLE OF AIRWAY AFFERENTS.

4.1. Introduction.

The substitution of a normoxic helium-oxygen mixture (HeO_2) for room air (AIR) during exercise causes an increase in minute ventilation ($\dot{V}_I$) that is evident in the first breath [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985; FORSTER *ET AL*, 1994]. However, the mechanisms underlying the hyperventilatory response to HeO_2 breathing during exercise are unclear. Because of its reduced density, HeO_2 reduces turbulence and therefore flow resistance in the airways, especially in the upper airways [MURPHY *ET AL*, 1969]. It has also been suggested that the respiratory adaptations to HeO_2 breathing may indicate a reflex effect [HUSSAIN *ET AL*, 1985]. Furthermore, WARD *ET AL* [1982] have suggested that the altered activation of irritant or other airway receptors might contribute to the hyperventilation with HeO_2. Information arising from numerous receptors (sensitive to changes in flow, pressure, temperature and CO_2 tension) in the larynx [SANT'AMBROGIO *ET AL*, 1983] and the tracheo-bronchial tree [SANT'AMBROGIO, 1982], has been shown to influence ventilatory control, both in humans and animals [SANT'AMBROGIO, 1982]. Both topical [EASTON *ET AL*, 1985; KUNA *ET AL*, 1988] and inhaled aerosol anesthesia [EASTON *ET AL*, 1985; MADOR, 1993] have been used effectively in humans for reversible blockade of these vagally mediated afferents. It was therefore possible that airway anesthesia (Anesthesia) might affect the transient and sustained $\dot{V}_I$ response to HeO_2 breathing during exercise in normal humans. As the reduction in turbulent flow with HeO_2 breathing during exercise is most marked in the upper (extra-thoracic) and major intra-thoracic airways [MURPHY

ET AL, 1969], two methods of Anesthesia administration [EASTON *ET AL*, 1985; KUNA *ET AL*, 1988; MADOR, 1993] were combined, to target these sites.

It was also important to exclude the effects of external tubing resistance on the hyperventilatory response to HeO_2. When used as the breathing mixture, HeO_2 reduces both internal airway resistance as well as the resistance of the external tubing. It has been shown that with AIR breathing, an increase in external resistance causes a decrease in $\dot{V}_I$ during exercise [D'URZO *ET AL*, 1987]. It is therefore possible that the $\dot{V}_I$ response to HeO_2 breathing is a consequence of the change in external resistive load, rather than the change in internal load. The external equipment resistance was therefore matched for both AIR and HeO_2 breathing in this study [DEWEESE *ET AL*, 1984].

4.2. Methods.

4.2.1. Subjects.

Eleven active males (age 25 ± 2 years, mean ± SEM) with no history of cardio-respiratory or other diseases, and no known hypersensitivity to local anesthetics were studied. Informed consent in writing was obtained after each subject underwent a physical examination and a 12-lead electrocardiogram. The study was approved by the institutional ethics committee for human experimentation. All subjects reported to the laboratory at least 2 hours in the post-prandial state and were specifically instructed not to undertake any strenuous exercise on the days of exercise testing.

4.2.2. Study Design.

This study was designed to examine whether airway anesthesia (Anesthesia) affected the transient and sustained hyperventilatory response to HeO_2 breathing during exercise. Each subject was therefore tested on *five* separate days: *day 1,* to establish the effectiveness and duration of Anesthesia; *day 2,* maximal incremental exercise to exhaustion to measure peak work rate ($\dot{W}_{max}$); *days 3, 4 and 5,* constant work-rate exercise (CWE) breathing AIR and HeO_2. The subjects performed CWE after

either Saline inhalation *(days 3 and 5, Control studies)*, or after airway anesthesia administration *(day 4, Anesthesia)*.

4.2.3. Administration of airway anesthesia.

Each subject gargled 5 ml of 4% Lidocaine solution for 2 - 3 minutes attempting to get the solution as far back in the oro-pharynx as possible, without swallowing. In order to achieve good laryngeal anesthesia, cotton pledgets (held by laryngeal forceps) soaked in 4% Lidocaine were then applied directly to the piriform recess, for 1 minute on each side. This technique has been validated in animals to provide effective blockade of the internal branch of the superior laryngeal nerve and thus block sensory feedback from the larynx [KUNA *ET AL*, 1988]. The subject then inhaled 200 mg of nebulized Lidocaine (5 ml of 4% solution for ophthalmic injection USP, with no preservatives) with a fixed breathing pattern (a 5s inspiration to total lung capacity, breath hold for 5s and a slow (~5s) relaxed expiration, that has been shown to promote uniform deposition of hetero-disperse aerosols throughout the tracheo-bronchial tree [PAVIA AND THOMSON, 1976; BRAIN AND WALBERG, 1979; PHIPPS *ET AL*, 1989]. Lidocaine was nebulized only during inspiration to maximize aerosol delivery and the process was completed in ~6 minutes. This combined method of upper and lower airways Anesthesia administration had been used previously in the laboratory and had been found to provide reliable airway anesthesia for over 15 minutes.

All aerosols used in the study (Lidocaine, Saline) were generated by Devilbiss-646 (Somerset, PA) jet nebulizers, run by a regulated compressed air source (35 psi) at a flow rate of 7 - 8 L · min^{-1}. Particle size information was obtained from the manufacturer who determined that operating under identical conditions to that in our laboratory, these nebulizers produced a hetero-disperse normal saline aerosol with a mass median aero-dynamic diameter [BRAIN AND WALBERG, 1979] of 5 μm (range of particle size, 2 - 8 μm). Both the size and distribution of the aerosol and the breathing pattern were chosen to maximize deposition in the larynx and in the

central airways (trachea, hilum and the large bronchi) [PAVIA AND THOMSON, 1976; PHIPPS *ET AL*, 1989]. Particles of this size seldom deposit in the peripheral bronchioles or alveoli [PAVIA AND THOMSON, 1976; BRAIN AND WALBERG, 1979].

4.2.4. Assessment of airway anesthesia.

On *day 1* (no exercise) the presence of effective Anesthesia for over 15 minutes was confirmed in each subject in the following manner. Before Anesthesia was administered, the baseline subjective responses such as sensation (baseline score = 5), response to blunt pharyngeal probing (5), gag reflex (5) and difficulty in swallowing (0) were graded on a $0 \rightarrow 5$ (least $\rightarrow$ most) scale, in each subject. The *single breath vital capacity* inhalation (at 1 $L \cdot s^{-1}$) maneuver [STOCKWELL *ET AL*, 1993] was then used to assess the subjects' cough threshold for nebulized citric acid solutions of doubling concentration (0%, 1%, 2%, 4%....32%). At the end of every 2 minutes after Anesthesia was administered using the technique described above, each subject was asked to grade these same sensations on the same scale as before. At the end of every 5 minutes after Anesthesia administration, each subject underwent a nebulized citric acid inhalation challenge [STOCKWELL *ET AL*, 1993] at the previously determined threshold concentration.

4.2.5. Exercise protocol.

On *Day 2*, each subject performed maximal incremental exercise to exhaustion breathing AIR, to measure peak work rate ($\dot{W}_{max}$, 325 ± 16 W). On *Days 3, 4 and 5*, each subject performed constant work rate exercise (CWE) at ~69 ± 2% $\dot{W}_{max}$ (range 160 - 290 W, 64% - 77% $\dot{W}_{max}$) for 13 minutes. The CWE protocol on all occasions consisted of a brief warm up exercise at 75 W (range 19% - 30% $\dot{W}_{max}$) for 1 minute, after which the work rate was abruptly increased to the pre-determined level for each subject. The inspirate was AIR during both the warm up period and for the first 5 minutes of CWE (AIR-1), at the end of which the inspirate was abruptly switched (during expiration) to HeO_2. The subject breathed HeO_2 for the next 3

minutes and the inspirate was then switched back (during expiration) to AIR. Each subject continued exercise breathing AIR for the next 5 minutes (AIR-2) or until exhaustion (whichever came first). On *days 3 and 5 (Control studies)*, the subjects inhaled nebulized normal saline (5 ml of 0.9% solution, no preservatives) just before the start of CWE (Saline-1, Saline-2), using the same inhalation pattern as that used with Anesthesia administration. On *day 4*, Anesthesia was administered just before the start of CWE, in an identical fashion as described earlier. An identical CWE protocol was used on all three (Saline-1, Saline-2, Anesthesia) occasions. One subject completed the first minute of exercise in the AIR-2 period on all three occasions and another subject stopped exercise immediately after the start of the AIR-2 period on the Anesthesia *(Day 4)* test day. However, 9 of the 11 subjects completed the 13 minutes of CWE (AIR-1, HeO_2, AIR-2) on all the three exercise days.

4.2.6. Exercise equipment and measurements.

Both the incremental and constant work-rate exercise tests were conducted on an electrically braked cycle ergometer (GODART, Bilthoven, Holland). The breathing apparatus consisted of a 2-way non-rebreathing "Y" valve (Hans-Rudolph 2700, Kansas MO, dead space, 115 ml) connected by short tubing (1¼" I.D.) to inspiratory and expiratory pneumotachographs (Fleisch #3), each of which was connected to a 2-way (switching) valve. These silent valves were used to manually switch the inspiratory and expiratory limbs from AIR to HeO_2 and *vice versa*, without any disturbance to the exercising subject. As it was possible that the hyperventilatory effects of HeO_2 breathing may in part be due to its unloading of the external tubing resistance, care was taken to match the flow resistance of the breathing circuit for both AIR and HeO_2 before the study, using methods employed by DEWEESE *ET AL* [1984], for resting measurements. By adding appropriate fixed resistances to the HeO_2 ports of the switching valves (on both the inspiratory and expiratory limbs), it was possible to match the flow resistances of both the inspiratory and expiratory limbs of

the breathing circuit for AIR and HeO_2. Table 4.1 summarizes the flow ranges through which the resistances of the inspiratory and expiratory limbs of the breathing circuit (in both AIR and HeO_2) were matched. Both AIR and HeO_2 were warmed and humidified and delivered from large meteorological balloon reservoirs, which were concealed from the subjects' direct view. With the aid of inspiratory and expiratory flow sensors, it was possible to switch the inspirate from AIR to HeO_2 (and back again) at the appropriate phase of the breathing cycle and exercise periods. None of the subjects was aware of any of these switches made during exercise.

Inspiratory (I) and expiratory (E) flows, measured by two pneumotachograph-transducer (Fleisch #3, Validyne MP45 $\pm$ 2 cmH_2O) assemblies on either side of the breathing valve, were added electronically to provide flow and volume throughout the breathing cycle. The inspiratory and expiratory pneumotachographs were calibrated (at 4 $L \cdot s^{-1}$) with both AIR and HeO_2 before the start of each test, and checked immediately after the end of each exercise test. Measurements were also made in both AIR and HeO_2, at flow rates of 2 and 8 $L \cdot s^{-1}$, in order to confirm the matching of the flow resistance of the breathing circuit for AIR and HeO_2 through those flow ranges. The individual flow signals (I) and (E) were monitored on a breath-by-breath basis throughout exercise for any zero drift [GOWDA *ET AL*, 1990].

A mass spectrometer (AIRSPEC, MGA 2000) was used to measure gases at

Table 4.1. Flow resistance of the breathing apparatus.

Flow ($L \cdot s^{-1}$)	Inspiratory resistance ($cmH_2O \cdot L^{-1} \cdot s$)		Expiratory resistance ($cmH_2O \cdot L^{-1} \cdot s$)	
	AIR	HeO_2	AIR	HeO_2
2	0.79	0.78	0.75	0.74
4	0.87	0.87	0.77	0.76
6	1.06	1.09	0.98	0.98
8	1.18	1.20	0.98	0.98

the mouth. Pilot studies revealed that when the mass spectrometer was calibrated with an AIR standard gas mixture (carrier, N_2), the measurements of CO_2 in HeO_2 were inaccurate, probably due to the physical properties of HeO_2. For accurate CO_2 measurements therefore, the mass spectrometer was calibrated at the start of each gas period (AIR-1, HeO_2, AIR-2) during CWE, with the gas standard (carrier N_2 or He) appropriate for the inspirate being used (AIR or HeO_2). A pulse oximeter (NELLCOR) was used to record both finger-tip O_2 saturation (SaO_2) and a standard 3-lead ECG during exercise.

4.3. Data analysis.

Inspiratory and expiratory flow ($\dot{V}$), volume (V), CO_2, SaO_2, and ECG were recorded continuously on an 8-channel strip chart recorder (GOULD) and digitzed. Data analysis was performed on a computer which measured inspiratory (T_I), expiratory (T_E) and total (T_T) breath durations and tidal volume (V_T) for all valid breaths during exercise (those interrupted by cough and/or swallowing were identified and discarded). Inspired minute ventilation ($\dot{V}_I$) was derived from averaged V_T and breathing frequency (f_b). Appropriate flow correction factors based on calibrations before and after exercise, were used to correct $\dot{V}_I$ during the HeO_2 periods. As the mass spectrometer was being calibrated (with the appropriate gas standard) during the first 15s of the minute immediately after the gas transitions (HeO_2, AIR-2), the CO_2 data during these periods were unavailable for analysis. However all other variables were analyzed during these periods. All the other data were collected on a breath by breath basis throughout exercise and were then used in data analysis. As described in the previous chapter, time-weighted mean alveolar P_{CO_2} ($P_{\bar{A},CO_2}$) was estimated from the averaged breath by breath airway P_{CO_2} signal, for each minute of exercise using established techniques [DUBOIS *ET AL*, 1952; WARD AND WHIPP, 1980]. $P_{\bar{A},CO_2}$ has been shown to accurately estimate arterial P_{CO_2} during exercise [ROBBINS *ET AL*, 1990].

4.3.1. Statistical analysis.

Data from the two Saline tests (Saline-1, Saline-2, NS) were averaged (Saline) in each subject for comparison with Anesthesia data. To study "steady-state" effects, data from the last minute of AIR-1 was averaged with data from the first minute of AIR-2 for comparison with the average data from the second minute of HeO_2. A paired *t*- test (2-tailed) was used to detect differences between AIR and HeO_2, as well as between Saline and Anesthesia. To study the effects of Anesthesia on the breath by breath effects of HeO_2, $\dot{V}_I$ data from the last 10 breaths in AIR-1, first 6 breaths in HeO_2, and average $\dot{V}_I$ data from the 2nd minute of HeO_2 were analyzed with a 2-factor (gas, Anesthesia) repeated measures ANOVA design. Significant breath by breath effects of HeO_2 on $\dot{V}_I$ (in both the Saline and Anesthesia tests) were then compared to AIR in a Dunnett's comparison procedure (Control group, AIR-1). A $P < 0.05$ was accepted as significant.

4.4. Results.

4.4.1. Evidence of Anesthesia.

On the initial assessment day *(day 1),* subjects reported significant numbness in the mouth and oro-pharynx and a noticeable difficulty in swallowing, immediately after Anesthesia administration. The cough response to inhaled citric acid aerosol was abolished for over 15 minutes in all subjects and it took longer (> 20 mins) for subjective sensations to return to baseline levels. After a brief warm down period at the end of CWE on *day 4* (Anesthesia), all subjects reported significant residual Anesthesia as shown by their grading (0 $\rightarrow$ 5, least $\rightarrow$ most) of the subjective sensations in the mouth (2.8 $\pm$ 0.2), in the throat (2.5 $\pm$ 0.2), increased tolerance to blunt pharyngeal probing (2.2 $\pm$ 0.3), gag reflex (2.5 $\pm$ 0.4) as well as persistent difficulty in swallowing (2.5 $\pm$ 0.2). These results are also consistent with those from other studies from this laboratory, in which the subjects showed presence of significant residual Anesthesia after exercise.

4.4.2. Effect of Anesthesia on the hyperventilatory response to HeO_2.

Figure 4.1 shows group mean (± S.E.M.) $\dot{V}_I$, V_T, f_b and $P_{\bar{A}}CO_2$ data during warm up exercise (0) and during the AIR-1, HeO_2 and AIR-2 periods during CWE. Each point represents all valid data averaged over one minute. As shown in chapter 3 and in previous reports during CWE [DEMPSEY *ET AL*, 1990], $\dot{V}_I$ increased rapidly in the first 3 - 4 minutes at the start of CWE, and continued to increase slowly throughout CWE. Most of the increase in $\dot{V}_I$ was as a result of an increase in f_b, as V_T leveled off after the initial increase in the first 2 minutes of CWE. There was a significant increase in $\dot{V}_I$ and a fall in $P_{\bar{A}}CO_2$ after the switch to HeO_2 as the inspirate, and this hyperventilation persisted throughout the HeO_2 period. On switching back to AIR (AIR-2) however, there was a fall in $\dot{V}_I$ and an increase in $P_{\bar{A}}CO_2$, after which $\dot{V}_I$ increased (and $P_{\bar{A}}CO_2$

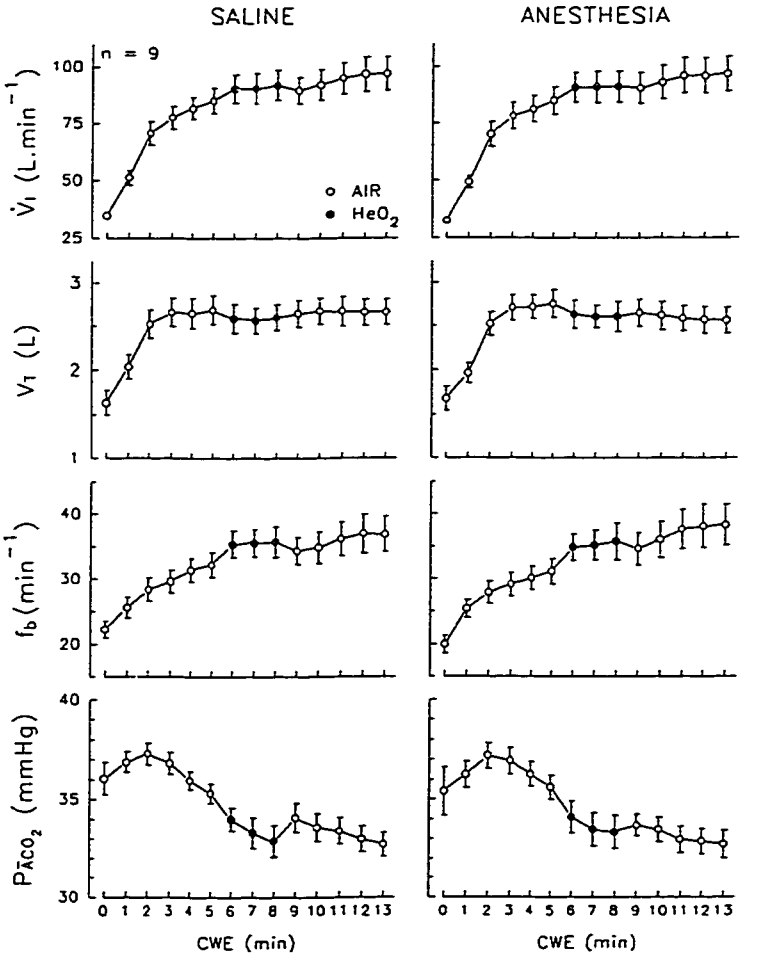

Figure 4.1. Effect of Anesthesia on the hyperventilatory response to HeO_2.

Table 4.2. Variables during constant work exercise.

	Saline			Airway Anesthesia			Effect of AA
	AIR	HeO_2	Δ	AIR	HeO_2	Δ	
$\dot{V}_I$ ($L \cdot min^{-1}$)	89.6 ± 5.4	93.6 ± 6.6	4.0 ± 1.6*	90.0 ± 6.1	94.0 ± 6.9	4.0 ± 1.3*	NS
V_T (L)	2.66 ± 0.14	2.58 ± 0.13	-0.08 ± 0.12	2.69 ± 0.13	2.60 ± 0.11	-0.09 ± 0.05	NS
f_b (min^{-1})	34.0 ± 1.9	36.4 ± 2.0	2.3 ± 0.6†	33.9 ± 2.2	36.3 ± 2.3	2.3 ± 0.6†	NS
T_I/T_T	0.49 ± 0.00	0.48 ± 0.00	-0.01 ± 0.00*	0.49 ± 0.00	0.48 ± 0.00	-0.01 ± 0.00*	NS
$P_{\bar{A}}CO_2$ (mmHg)	34.4 ± 0.6	32.9 ± 0.8	-1.5 ± 0.4†	34.4 ± 0.6	32.9 ± 0.9	-1.4 ± 0.4†	NS
f_C (min^{-1})	155 ± 4	156 ± 5	1.0 ± 0.3*	153 ± 4	154 ± 4	1.0 ± 1.0	NS
SaO_2 (%)	96.6 ± 0.4	96.9 ± 0.5	0.3 ± 0.1†	96.6 ± 0.3	97.0 ± 0.3	0.4 ± 0.1*	NS

fell) gradually until end exercise. The magnitudes of increase in $\dot{V}_I$ (~4 $L \cdot min^{-1}$) and fall in $P_{\bar{A}}CO_2$ (~1.5 mmHg) with HeO_2 breathing, though small, were significant (*$P < 0.05$, †$P < 0.01$ respectively, 2-tailed *t*- test) in both the Saline and Anesthesia tests and these data are summarized in table 4.2. This modest increase in $\dot{V}_I$ with HeO_2 breathing was due to a significant increase in f_b, as HeO_2 breathing did not alter V_T significantly. HeO_2 breathing also resulted in a small but significant fall in the inspiratory duty cycle (T_I/T_T) and a small but significant increase in SaO_2. However, as both figure 4.1 and table 4.2 reveal, Anesthesia had no overall effect on the hyperventilatory response to HeO_2 breathing during CWE.

4.4.3. Effect of Anesthesia on the $\dot{V}_I$ transients with HeO_2.

The effect of Anesthesia on the immediate increase in $\dot{V}_I$ on switching to HeO_2 is shown in figure 4.2. The averaged data from the last 10 breaths in AIR-1 period (Saline *.vs.* Anesthesia, NS) represent the baseline (0, closed square) values. Data are shown as the increase in $\dot{V}_I$ ($\Delta\dot{V}_I$) in the first 6 breaths of HeO_2 and in the 2nd minute of HeO_2 breathing. It can be seen that in the Saline test, $\dot{V}_I$ increased immediately with HeO_2 breathing (*, $P < 0.05$, compared to AIR values) and almost all the increase

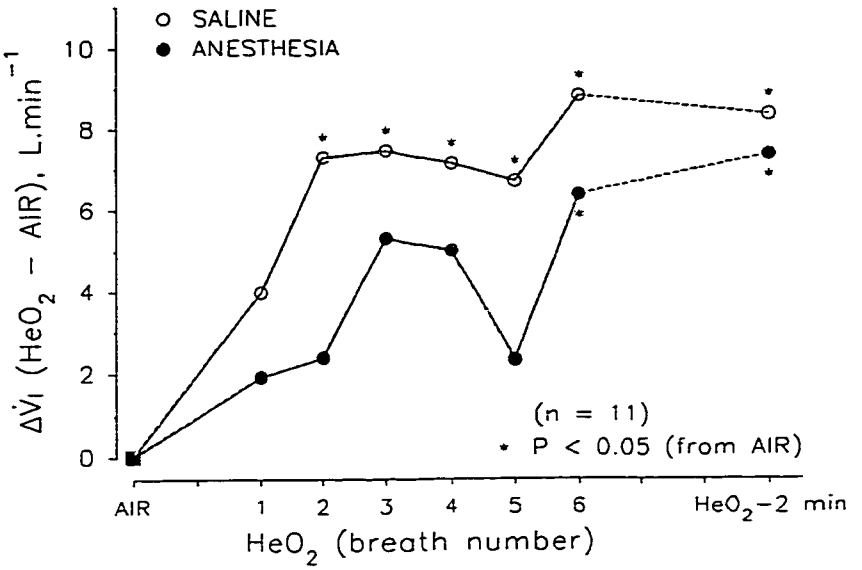

Figure 4.2. Effect of Anesthesia on the $\dot{V}_I$ transients with HeO_2.

in $\dot{V}_I$ had occurred with the 2nd breath of HeO_2. With Anesthesia however, there was a noticeable attenuation of this transient increase in $\dot{V}_I$ in the first 5 - 6 breaths of HeO_2, but this effect was not present in the 2nd minute of HeO_2.

Figure 4.3 summarizes the effects of Anesthesia on the transient increase in $\dot{V}_I$ in the 2nd breath of HeO_2 and in the 2nd minute of HeO_2 in all subjects (open circles). $\Delta\dot{V}_I$ (HeO_2 - AIR) data in the Saline test is compared with that in the

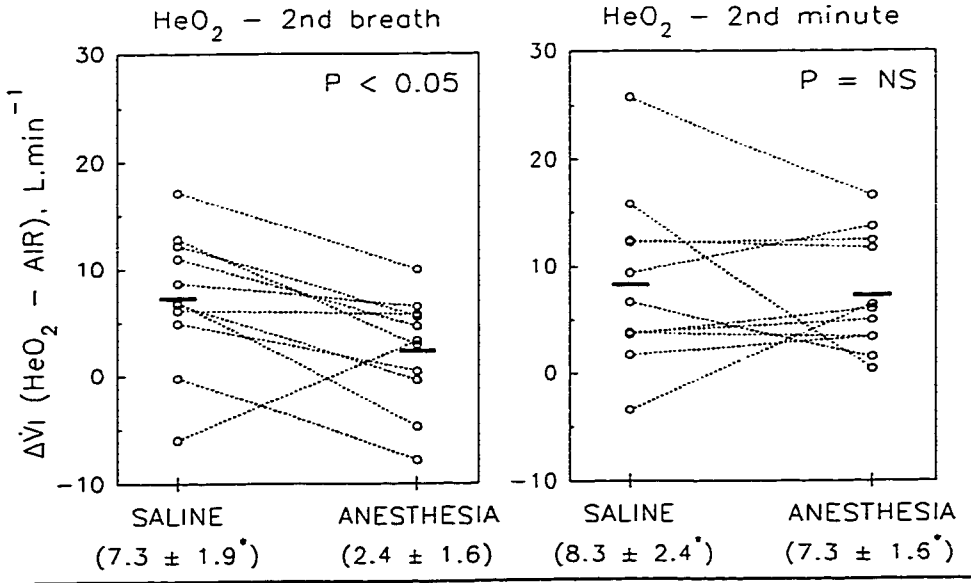

Figure 4.3. A comparison of the effect of Anesthesia on the transient and steady-state ventilatory responses to HeO_2.

Anesthesia test in each subject. Group mean data (thick lines) in each case are also shown as mean ± S.E.M. * indicate whether the increase in $\dot{V}_I$ ($\Delta\dot{V}_I$) was significantly different from zero. Ten of the 11 subjects had a smaller increase in $\dot{V}_I$ in the 2nd breath of HeO_2 after Anesthesia than with Saline and this difference was statistically significant ($P < 0.05$, ANOVA). This effect of Anesthesia however did not continue into the steady-state (2nd minute) of HeO_2 breathing.

4.5. Discussion.

The major findings of this study are: **1)** the immediate, but not the sustained, hyperventilation due to HeO_2 is attenuated by airway anesthesia; **2)** HeO_2 causes hyperventilation even when the reduction in tubing resistance due to HeO_2 is prevented; therefore the HeO_2 hyperventilation is not simply due to a change in external resistive load.

4.5.1. Previous Studies.

It has been shown that the substitution of HeO_2 for AIR results in an immediate and sustained increase in $\dot{V}_I$ [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985; FORSTER *ET AL*, 1994]. The magnitude of the HeO_2 induced hyperventilation during exercise however, varies significantly between different studies but is greatest at high levels of $\dot{V}_I$ [BRICE AND WELCH, 1983; DEMPSEY *ET AL*, 1984; POWERS *ET AL*, 1986]. As emphasized by WARD *ET AL* [1982] and PAN *ET AL* [1987], this increase in $\dot{V}_I$ is attenuated by the resulting fall in arterial P_{CO_2}. The increase in $\dot{V}_I$ with HeO_2 has been attributed predominantly to its physical properties; because of its lower density than AIR, HeO_2 reduces turbulence in airways, primarily large airways, where airflow is turbulent [MURPHY *ET AL*, 1969]. This changes the distribution of resistance among different parts of the airways and reduces total airway resistance [MAIO AND FARHI, 1967] and results in respiratory muscle unloading, i.e. respiratory muscles have to generate less pressure for a given $\dot{V}_I$ [MAIO AND FARHI, 1967; HUSSAIN *ET AL*, 1985]. However, as shown earlier (chapter 3) and in previous studies [GALLAGHER AND YOUNES, 1989], respiratory muscle unloading

by pressure-assist at the mouth [YOUNES *ET AL*, 1987] causes little or no increase in $\dot{V}_I$ during heavy exercise. Therefore, as reviewed elsewhere [DEMPSEY *ET AL*, 1996; CHAPTER 3 in this thesis], the hyperventilation with HeO_2 is probably not a consequence of respiratory muscle unloading *per se*. This is supported by the finding that the $\dot{V}_I$ response to HeO_2 is unaffected by diaphragm deafferentation [FORSTER *ET AL*, 1994]. The hyperventilation may therefore be related to the airway effects of HeO_2 [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985; FORSTER *ET AL*, 1994; DEMPSEY *ET AL*, 1996]. For example, the average rate of rise of the diaphragm EMG has been shown to fall immediately when HeO_2 is substituted for room air in exercising ponies and humans [HUSSAIN *ET AL*, 1985; FORSTER *ET AL*, 1994]. It has therefore been suggested that the respiratory responses to HeO_2 may involve "a reflex effect" [HUSSAIN *ET AL*, 1985]. WARD *ET AL* [1982] have suggested that changing from AIR to HeO_2 may activate irritant or other airway receptors and this might contribute to the $\dot{V}_I$ response to HeO_2 breathing.

4.5.2. Airway anesthesia and the ventilatory response to HeO_2.

The methods of Anesthesia used in this study were chosen to cause anesthesia of the large airways where the effects of HeO_2 on turbulent airflow are greatest [MURPHY *ET AL*, 1969]. The method of aerosol anesthesia employed in this study has been shown to cause deposition of most of the anesthetic in the upper airways (oro-, hypo-pharynx, larynx) and in the central intra-thoracic airways (trachea, hilum and large bronchi) [PAVIA AND THOMSON, 1976; BRAIN AND VALBERG, 1979; PHIPPS *ET AL*, 1989]. Aerosols of the particle size (5 μm) as used in our study, seldom deposit in the peripheral lung regions or in the alveoli [PAVIA AND THOMSON, 1976; BRAIN AND VALBERG, 1979]. This method has been already shown to cause large airway anesthesia in previous studies in resting [EASTON *ET AL*, 1985; MADOR *ET AL*, 1993] or exercising [KRISHNAN *ET AL*, 1997] humans. Additionally, the method of topical laryngeal anesthesia administration used in this study, has been shown to block

afferents in the superior laryngeal nerve [KUNA *ET AL*, 1988]. The technique of laryngeal anesthesia differed somewhat between this study and that of KUNA *ET AL* [1988]. Pledgets soaked in 4% Lidocaine were held in each piriform recess for one minute in this study and for two minutes in their study. Also, 10% Cocaine was dropped onto the epiglottis and vocal cords in their study. Could the persistence of the HeO_2 induced sustained hyperventilation with Anesthesia in this study, be due to the shorter duration of Lidocaine application or because Cocaine was not used ? While this possibility cannot be completely excluded, it is unlikely to have happened as the presence of residual Anesthesia was demonstrable after exercise. Anesthesia of both the upper and lower (central) airways was shown to persist for over 15 minutes as evidenced by the loss of gag reflex and the cough response to inhaled citric acid respectively, in all our subjects. It has been shown in previous studies that that this method of Anesthesia administration results in persistence of upper and lower airway anesthesia during and after exercise [KRISHNAN *ET AL*, 1997].

Anesthesia caused the attenuation of the transient $\dot{V}_I$ response to HeO_2 but did not affect the steady-state $\dot{V}_I$ response. The attenuation of the transient $\dot{V}_I$ response supports the notion that the respiratory adaptations to HeO_2 are related to its airway effects [MURPHY *ET AL*, 1969]. It also supports the hypothesis that airway reflexes are involved [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985].

While this study indicates that airway receptors are involved in the immediate $\dot{V}_I$ response to HeO_2, it provides no information as to which receptors may be involved. There are a large number of receptors in the pharynx, larynx and tracheo-bronchial tree, whose activation could be altered by HeO_2. For example, the activation of tracheal and bronchial irritant receptors, which respond to flow, might be altered by HeO_2 [SANT'AMBROGIO, 1982]. Because of their dynamic properties, tracheo-bronchial stretch receptor activation is influenced by flow rate [SANT'AMBROGIO AND MORTOLA, 1977]. The larynx has a rich supply of submucosal and mucosal

receptors, some of which are sensitive to pressure and flow [SANT'AMBROGIO *ET AL*, 1983]. Activation of these receptors may have been altered by HeO_2 breathing. For example, JAMMES *ET AL* [1987] noted greater activation of laryngeal receptors by HeO_2 than by air, but this occurred at 18 °C, a temperature which is lower than the normal laryngeal temperature. Because of its non-invasive nature, this study provides no information as to which, *if any*, of these specific receptors were activated (or inhibited) by HeO_2.

While the transient $\dot{V}_I$ response to HeO_2 was attenuated by Anesthesia, the steady-state response was unaffected. The reasons for this are unclear. This suggests that, while the initial $\dot{V}_I$ response to HeO_2 is at least partly dependent on airway receptors, activation of these receptors is not necessary for the sustained response. It has recently been shown that increasing inspiratory flow rate in mechanically ventilated subjects causes a tachypneic hyperventilation, that is not sensitive to airway anesthesia [GEORGOPOULOS *ET AL*, 1996]. It is possible therefore that the initial HeO_2 induced increase in inspiratory flow rate in this study, activates mechanisms not sensitive to Anesthesia, that cause the sustained tachypneic hyperventilation and override the resulting hypocapnia. It should be noted however, that the HeO_2 induced transient increase in $\dot{V}_I$ in our subjects was attenuated, not abolished by Anesthesia. It is further possible that the attenuated initial increase in flow rate was enough to trigger the sustained hyperventilation. This hypothesis is speculative but merits further study.

It is conceivable that the effect of Anesthesia on the transient but not the sustained hyperventilatory response to HeO_2, was due to a time-dependent reduction in the intensity of Anesthesia during exercise. However the chances of that having occurred in this study are remote, as there was evidence of residual Anesthesia at end exercise in these subjects. These results are similar to those from another study [KRISHNAN *ET AL*, 1997], where the subjects had evidence of significant

residual Anesthesia after exercise. Furthermore, it was ascertained on an initial occasion, that each subject in this study had evidence of airway anesthesia for at least the duration of exercise (i.e. 15 min).

4.5.3. Possible mechanisms underlying HeO_2 hyperventilation.

HeO_2 increases the maximum expiratory flow-volume curve [MINK AND WOOD, 1980]. Therefore, for the same $\dot{V}_I$ and breathing pattern, HeO_2 reduces flow limitation when it is present during AIR breathing. The presence of flow limitation however, was not assessed in the current study. It is possible that the $\dot{V}_I$ response to HeO_2 may be related to its effect of reducing expiratory flow limitation [DEMPSEY *ET AL*, 1996]. This is supported by the observation that the $\dot{V}_I$ response to inhaled CO_2 during heavy exercise falls, at levels of $\dot{V}_I$ where expiratory flow limitation develops [CLARK *ET AL*, 1980].

Ventilatory control during HeO_2 breathing may be further influenced by its effects on gas exchange. Some [CHRISTOPHERSON AND HLASTALA, 1982], but not all [NEMERY *ET AL*, 1983] studies have found that a decrease in carrier gas density increases the alveolar-arterial P_{O_2} gradient. This, if itself, would cause a small fall in arterial P_{O_2}, if nothing else changed. However, this could not have contributed to the HeO_2 induced increase in $\dot{V}_I$ in this study because there was a small but significant increase in SaO_2 with HeO_2 breathing (Table 4.2).

4.5.4. Equipment Resistance and Helium Hyperventilation.

HeO_2 reduces external tubing resistance, as well as internal airway resistance. Previous studies of helium breathing during exercise however had not matched equipment resistance for AIR and HeO_2, although DEWEESE *ET AL* [1984] had matched external resistance in their studies with HeO_2 at rest. FORSTER *ET AL* [1994] noted a 47% fall in external resistance with HeO_2 breathing, compared to room air breathing. This fall was almost the same as the fall in pulmonary resistance in their studies. Increasing the resistive load at the mouth causes a reduction in $\dot{V}_I$ during

exercise during room air breathing [D'URZO *ET AL*, 1987]. It was therefore possible that the HeO_2 induced hyperventilation demonstrated in previous studies was related to the reduction in external resistive load, not the change in internal load. Therefore care was taken to match external tubing resistance during HeO_2 to that during room air breathing (table 3.1). Despite this, HeO_2 breathing resulted in a significant hyperventilation. Therefore the hyperventilation with HeO_2 is not simply due to a change in tubing resistance, although this may have accentuated the hyperventilation in previous studies.

In conclusion, this study indicates that the transient, but not the sustained, hyperventilation with HeO_2 is dependent on airway afferents sensitive to topical anesthesia. The hyperventilation with HeO_2 breathing is not simply due to a change in external equipment resistance.

5. VENTILATORY RESPONSE TO DEAD SPACE LOADING AND DURING MAXIMAL INCREMENTAL EXERCISE - ROLE OF AIRWAY AFFERENTS.

5.1. Introduction.

5.1.1. Hypotheses.

This study tested the hypotheses that **1)** airway receptors sensitive to topical anesthesia influence minute ventilation ($\dot{V}_I$) and breathing pattern in exercising humans and **2)** the respiratory adaptations to added external dead space (V_D) during exercise, are mediated by airway reflexes. The rationale of the study was as follows.

5.1.2. Background.

Vagally mediated afferent information arising from a variety of receptors in the larynx [BARTLETT *ET AL*, 1992] and tracheo-bronchial tree [SANT'AMBROGIO, 1982] has been shown to significantly influence resting ventilation and breathing pattern in animals. An increase in $\dot{V}_I$ and an alteration in breathing pattern after airway anesthesia has been documented in exercising humans [WINNING *ET AL*, 1985]. However, in animals performing exercise, neither pulmonary denervation [FLYNN *ET AL*, 1985], nor vagal cooling [AINSWORTH *ET AL*, 1992], have had any effects on $\dot{V}_I$, although breathing pattern was altered. This study was therefore designed to re-examine the role of airway receptors in the control of exercise ventilation and breathing pattern in humans. A technique of airway anesthesia (Anesthesia) that has been shown to reliably alter airway reflexes, has been employed in this study.

An added external V_D has been shown to increase $\dot{V}_I$ both at rest [WARD AND WHIPP, 1980] and during exercise [MCPARLAND *ET AL*, 1991; SYABBALO *ET AL*, 1993]. Furthermore, at moderate and high $\dot{V}_I$ levels during exercise, the breathing pattern

with added V_D becomes slower and deeper [McParland *et al*, 1991; Syabbalo *et al*, 1993]. Both the $\dot{V}_I$ and the breathing pattern responses to added V_D may be viewed as homeostatic responses, as both act to attenuate the alterations in blood gases caused by the added V_D. However, the mechanisms underlying the respiratory adaptations to added V_D are unclear. They have been shown to be not due to an increase in mean alveolar/arterial P_{CO_2} *per se*, because the slower and deeper breathing pattern response does not occur with CO_2 inhalation during exercise [Gallagher *et al*, 1987]. As reviewed elsewhere [McParland *et al*, 1991], the respiratory adaptations to added V_D are probably due to alteration of the intra-breath time profile of P_{CO_2}, that is sensed by the carotid, airway/pulmonary and/or central chemoreceptors. Carotid chemoreceptors however are unlikely to play a major role, as the $\dot{V}_I$ and breathing pattern responses to added V_D have been shown to persist when the carotid bodies are silenced by hyperoxia [Syabbalo *et al*, 1993]. The breathing pattern responses to airway CO_2 transients [Cunningham *et al*, 1977] as well as the evidence that airway anesthesia significantly alters the ventilatory response to CO_2 inhalation [Mador, 1993], support the notion that airway chemoreceptors may be significantly involved in the mediation of this response. Furthermore, it has been shown that the ventilatory response to added external V_D at rest, was significantly attenuated after airway anesthesia [Shindoh *et al*, 1988]. This study was therefore designed to examine the effects of airway anesthesia on the respiratory adaptations to added V_D during exercise in humans.

5.2. Methods.

5.2.1. Subjects.

Twelve healthy males (24.3 ± 5.6 years, mean ± SD) with normal pulmonary function, with no history of cardiopulmonary or neuromuscular disease and no known hypersensitivity to local anaesthetics, were studied. Each subject gave informed consent to the procedures in writing after a physical examination and a 12-

lead electrocardiogram and the study was approved by the institutional ethics committee for human experimentation. All tests were conducted under identical conditions (except for the added V_D and/or Anesthesia) in an air-conditioned laboratory with the subjects at least 2 hours in the post-prandial state. None of the subjects was aware of the specific focus of the study (i.e. exercise breathing pattern).

5.2.2. Study design.

This study was designed to examine the role of airway receptors in ventilation and breathing pattern control during maximal incremental exercise (MIE) and in the ventilatory adaptations to V_D loading during exercise. Each subject therefore performed cycle ergometer exercise on 4 separate days, 2 days each after inhaling Saline or Anesthesia before the start of exercise. MIE was performed with (V_D) or without added V_D (Control) and the 4 tests (Saline Control, Anesthesia Control, Saline V_D, Anesthesia V_D) were administered in a random order to each subject.

Initial testing in each subject involved measurement of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), followed by the assessment of the cough threshold for inhaled citric acid aerosol. The intensity and duration of Anesthesia was also recorded in each subject on this initial visit, to ensure adequate Anesthesia throughout MIE on the exercise test days. All aerosols used in this study (Saline, Citric acid and Lidocaine) were generated by Devilbiss-646 (Somerset, PA) jet nebulizers run by a regulated compressed air source (35 psi) at a flow rate of 7 - 8 $L \cdot min^{-1}$. As described in the previous chapter, both the size and distribution of the aerosol droplets (Mass Median Aerodynamic Diameter = 5 μm, range = 2 - 8 μm) and the pattern of breathing were chosen to maximize deposition in the larynx and throughout the tracheo-bronchial tree [PAVIA AND THOMSON, 1976, BRAIN AND VALBERG, 1979]. The techniques of administration of Anesthesia and its assessment in this study were identical to those described in the previous chapter (Chapter 4) and will therefore not be discussed in detail here.

5.2.3. Experimental technique.

The exercise breathing apparatus (Both added V_D and Control) was similar to those used in previous studies from this laboratory [McParland *et al*, 1991; Syabbalo *et al*, 1993] and was concealed so that the subjects were unaware of any particular arrangement (Control or V_D) during any exercise test. A piece of flexible tubing (940 ml, 1¼" I.D.) added between the mouthpiece and the two-way non-rebreathing valve (Hans-Rudolph, dead space = 115 ml) served as the added V_D for the dead space exercise studies (Added V_D < 20% VC). In the studies involving subjects #2 and #6, a 650 ml V_D was used because of their smaller vital capacities (FVC < 5 L). The total resistance (which was carefully matched in both the Control and V_D tests) of the inspiratory limb of the breathing circuit (including the Fleisch #3 pneumotachograph and Hans-Rudolph valve) was 1.34 $cmH_2O \cdot L^{-1} \cdot s$ at a flow rate of 10 $L \cdot s^{-1}$.

After one minute of quiet breathing, exercise commenced on an electrically braked cycle ergometer (GODART, Bilthoven, Holland) with the subjects pedalling at 50 - 70 rpm with speedometer feedback. The work-rate in each subject thereafter was increased by 25 watts each minute to the limit of his tolerance. Inspiratory (I) and expiratory (E) flow signals were measured by Fleisch #3 pneumotachographs and Validyne MP45 ± 2 cmH_2O (Northridge, CA) pressure transducers and the biphasic flow signal (I + E) was integrated electronically (GOULD, Ballainvilliers, France) to provide volume. A manual solenoid tap alternating between the mouth and the baffled mixing chamber (on the expiratory limb) enabled a calibrated (with standard gas mixtures) mass spectrometer (AIRSPEC MGA 2000, Kent, UK) to sample O_2 and CO_2 concentrations from both sites. A pulse-oximeter (NELLCOR, Pleasonton, CA) was used to monitor both finger tip O_2 saturation (SaO_2) and a 3-lead pre-cordial ECG. All the above signals were recorded continuously on an 8-channel strip-chart recorder (GOULD) and were sampled (at 100 Hz) for digital storage and off-line analysis of

minute-by-minute data. All the measuring equipment was calibrated before each exercise test and checked immediately afterwards.

Subjects performed MIE on four different days, each separated from the other by 2 - 3 days and in a random order: **1)** After Saline inhalation without added V_D *(Saline Control)*, **2)** After Saline inhalation with added V_D *(Saline V_D)*, **3)** after Anesthesia without added V_D *(Anesthesia Control)* and **4)** after Anesthesia with added V_D *(Anesthesia V_D)*. The presence of residual Anesthesia was assessed in each subject after a brief warm-down period (~2 mins) at the end of MIE, using techniques described in the previous chapter.

5.2.4. Data analysis.

After manually discarding those breaths (n < 5 /min) interrupted by a swallow or a cough, all valid breaths in each minute of exercise were identified by the computer which measured inspiratory (T_I) and expiratory (T_E) durations, tidal volume (V_T) and breathing frequency (f_b) to derive inspiratory minute ventilation ($\dot{V}_I$). Oxygen uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$) were calculated using standard formulae. The lactate-threshold ($\dot{V}O_{2,LT}$) during exercise in each test, was derived using the "V - slope" method [BEAVER *ET AL*, 1986], from the $\dot{V}O_2$ - $\dot{V}CO_2$ relationships during MIE. Mean alveolar P_{CO_2} ($P_{\bar{A},CO_2}$) was estimated from time-weighted mean CO_2 profiles using previously described techniques [WHIPP AND WARD, 1980; WHIPP *ET AL*, 1990] as it has been shown to be an accurate estimate of arterial P_{CO_2} during exercise [ROBBINS *ET AL*, 1990]. Physiological dead-space fraction (V_D/V_T) of each breath was then calculated using the Bohr equation.

5.2.4.1. Statistical analysis.

Results during the *Saline Control, Saline V_D, Anesthesia Control* and *Anesthesia V_D* tests were compared at rest, at matched work rates and at end exercise. Breathing pattern during exercise in all tests was examined as $\dot{V}_I$ - V_T relationships at matched levels of $\dot{V}_I$ (20% - 90% of maximum $\dot{V}_I$ in the *Saline Control*

test, $\dot{V}_{I,max}$). Statistical analysis of all variables was performed using analysis of variance with repeated measures and post-hoc pair-wise multiple comparisons (Tukey's HSD). All data are presented as means ± SD and significant effects are reported as $P < 0.05$ even when P values were much smaller then this.

5.3. Results.

5.3.1. Evidence of Anesthesia.

The presence of adequate Anesthesia for over 15 minutes was assessed in each subject, using the techniques described in the previous chapter. In addition, after the warm-down period at end exercise on both the *Anesthesia Control* and *Anesthesia VD* test days, all subjects reported significant residual Anesthesia as shown by their grading (0 → 5, least → most) of subjective sensation in the mouth (2.7 ± 0.9, 3.0 ± 0.8; *Anesthesia Control, Anesthesia VD* respectively), in the throat (2.4 ± 0.8, 2.1 ± 0.6), increased tolerance to blunt pharyngeal probing (2.0 ± 1.0, 2.3 ± 0.9), gag reflex (1.9 ± 1.0, 2.3 ± 1.1), as well as persistent difficulty in swallowing (2.3 ± 0.6, 2.8 ± 0.7). On the *Anesthesia Control* and *Anesthesia VD* test days, the cough response to inhaled citric acid was abolished after end exercise on both occasions in 8 subjects, absent on one occasion in 3 subjects, and elicitable on both occasions in 1 subject. However, on the *Saline Control* and *Saline VD* test days, the cough response to inhaled citric acid at threshold concentration, was readily and reproducibly elicited after exercise on both occasions in 10 subjects, on one occasion in 1 subject and not elicitable in 1 subject. This difference in the cough response to inhaled citric acid challenge ~2 minutes after end exercise between the Saline and Anesthesia test days was statistically significant (χ^2, $P < 0.025$, McNemar's test of symmetry).

5.3.2. Exercise performance.

Each subject completed all four exercise tests to voluntary maximum. Consistent with data from previous studies [McParland *et al*, 1991; Syabbalo *et al*, 1993], added VD had no effect on maximal exercise capacity. In addition, Anesthesia

Table 5.1. Variables at end exercise.

	Saline		Anesthesia (AA)		Effect of AA
	Control	V_D	Control	V_D	(ANOVA)
Duration (min)	11.45 ± 1.71	10.85 ± 1.46	11.21 ± 1.51	10.73 ± 1.50	NS
$\dot{W}_{max}$ (W)	314.6 ± 40.5	302.1 ± 32.8	312.5 ± 42.0	297.9 ± 40.5	NS
$\dot{V}_I$ ($L \cdot min^{-1}$)	139.4 ± 21.2	151.5 ± 22.7*	141.8 ± 26.0	151.1 ± 23.1*	NS
V_T (L)	3.02 ± 0.60	3.20 ± 0.57*	3.02 ± 0.57	3.17 ± 0.61	NS
f_b (min^{-1})	47.5 ± 10.3	48.5 ± 9.9	48.0 ± 10.1	49.3 ± 11.6	NS
T_I/T_T	0.50 ± 0.02	0.50 ± 0.02	0.51 ± 0.02	0.49 ± 0.02	NS
$P_{\bar{A}}CO_2$ (mmHg)	35.5 ± 2.6	45.0 ± 4.7*	35.2 ± 2.7	45.0 ± 3.6*	NS
V_D/V_T (%)	9.3 ± 4.9	43.1 ± 5.0*	9.6 ± 4.3	43.9 ± 5.4*	NS
$\dot{V}O_2$ ($L \cdot min^{-1}$)	3.73 ± 0.66	3.47 ± 0.59	3.75 ± 0.50	3.51 ± 0.69	NS
fc (min^{-1})	179 ± 12	175 ± 11	178 ± 11	176 ± 12	NS
SaO_2 (%)	93.3 ± 3.4	92.8 ± 2.1	94.0 ± 6.0	91.5 ± 3.9*	NS

had no effect on maximal exercise performance; ANOVA revealed no differences in either exercise duration or the completed maximal exercise work-rate ($\dot{W}_{max}$) among the four exercise tests. Table 5.1 summarizes (mean ± SD, n = 12) the effects of both added V_D (*$P < 0.05$, ANOVA) and Anesthesia (P = NS) on ventilatory and other variables at end exercise. As shown in table 5.1, both Anesthesia and added V_D did not have any effect on the time course of $\dot{V}O_2$, $\dot{V}CO_2$ or fc during MIE. Furthermore, $\dot{V}O_{2,LT}$ was not significantly different among the 4 MIE tests: $\dot{V}O_{2,LT}$ = 1.94 ± 0.41, 1.85 ± 0.38, 1.83 ± 0.43 and 1.86 ± 0.43 L ± min^{-1} in the *Saline Control, Anesthesia Control, Saline V_D and Anesthesia V_D* tests respectively.

5.3.3. Effect of Anesthesia on Exercise ventilation and breathing pattern.

Figure 5.1. summarizes the effect of Anesthesia on the ventilatory response during MIE in the Control tests (*Saline Control* - open circles, *Anesthesia Control* -

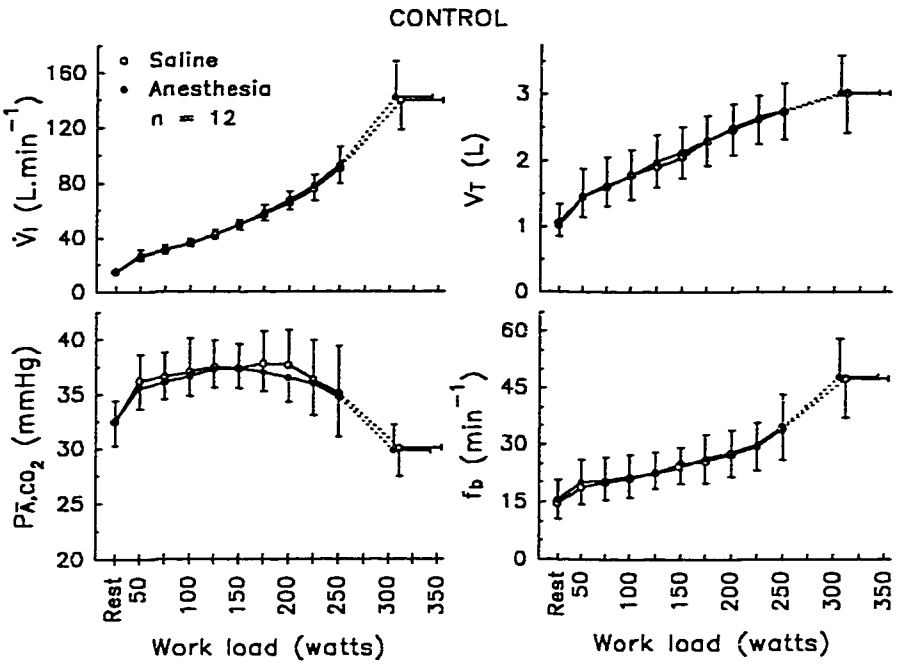

Figure 5.1. Effect of Anesthesia on exercise ventilatory variables.

closed circles). Group mean (± SD, n = 12) $\dot{V}_I$, V_T, f_b and $P_{\bar{A}}CO_2$ data at rest, at matched common work-rates (50w → 250w) and at end exercise are shown. It is evident from figure 5.1 that Anesthesia had no effect on the ventilatory response or the time course of any other variable during (figure 5.1) or at the end of (Table 1) Control (i.e. with no added V_D) exercise in these subjects. Given the variability in $\dot{V}_I$ at 150 W in this study for example, the probability of missing (Type II error, [FREIMAN *ET AL*, 1978; LACHIN, 1981]) a 5 L · min^{-1} change in $\dot{V}_I$ due to effect of Anesthesia was less than 1%.

The effect of Anesthesia on the breathing pattern response (examined as the $\dot{V}_I$ - V_T relationship) during MIE in each subject in the Control tests (*Saline Control* - dotted line, *Anesthesia Control* - solid line) is described in figure 5.2. Subject number is shown at the top left corner of each panel. It is evident that Anesthesia had no effect of breathing pattern in any of these individuals during MIE. The increase in $\dot{V}_I$ through most of MIE was achieved with increases in both V_T and f_b, except towards

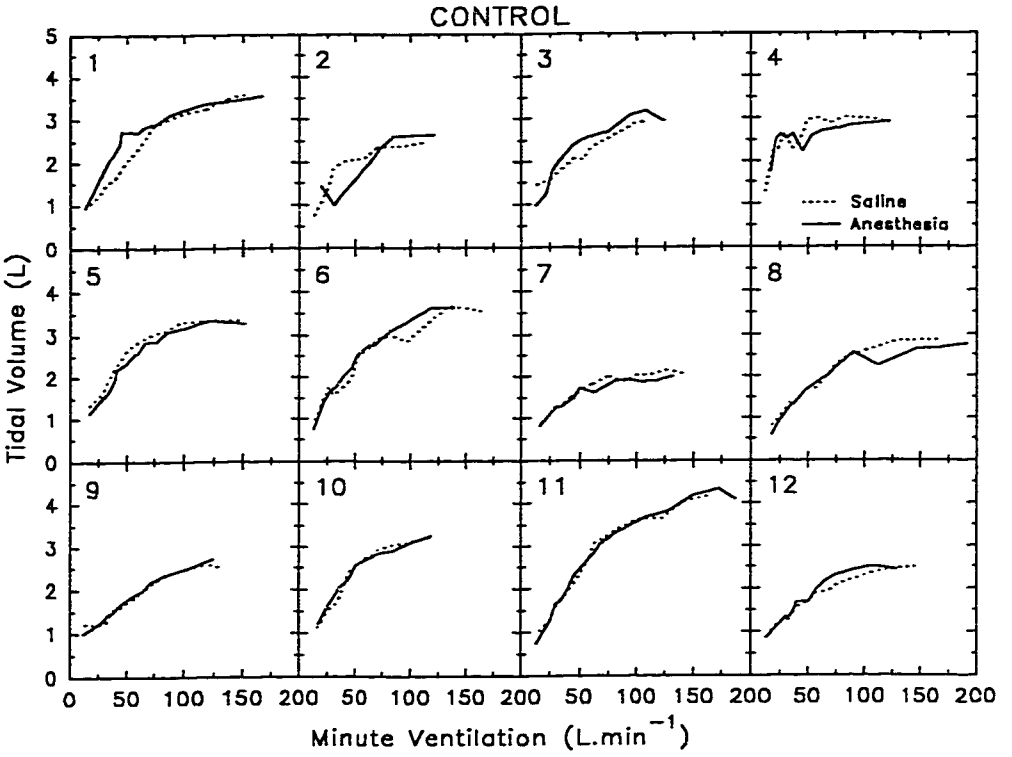

Figure 5.2. Effect of Anesthesia on individual exercise breathing patterns.

end exercise, when VT tended to plateau, or even fall in some subjects (e.g. in subjects 3, 5, 6 and 11).

Figure 5.3. summarizes the average breathing pattern response in the Control (*Saline Control* - dotted line, *Anesthesia Control* - solid line) tests. Group mean

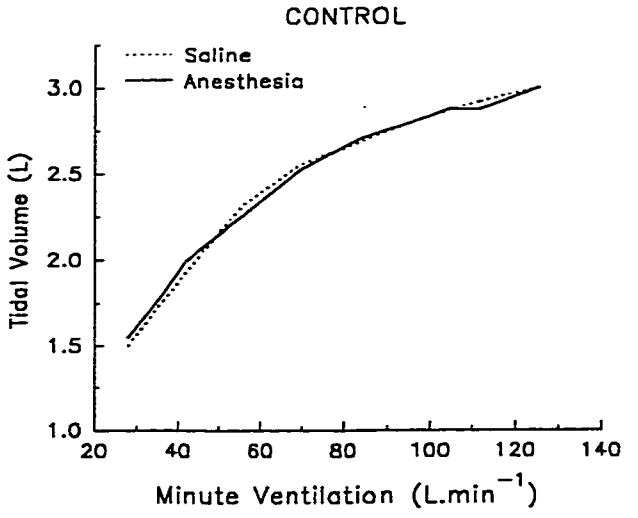

Figure 5.3. Effect of Anesthesia on breathing pattern during exercise (Group).

responses of V_T at matched levels of $\dot{V}_I$ (20% to 90% $\dot{V}_{I,max}$ - the maximum $\dot{V}_I$ in *Saline Control* test) reveal the breathing pattern response at matched $\dot{V}_I$ levels are identical in two Control (no added V_D) tests. Table 5.2. summarizes the Group mean breathing pattern at 3 matched ventilatory levels (50%, 70% and 90% $\dot{V}_{I,max}$) during MIE in all tests. Given the variability in V_T at 90% of matched $\dot{V}_I$ in the *Saline Control* and *Anesthesia Control* tests, the chances of missing (Type II error) a 150 ml (5% of V_T) change in V_T due to effect of Anesthesia was also less than 1%.

5.3.4. Effect of Anesthesia on the ventilatory and breathing pattern responses to added V_D during MIE.

The effects of added V_D on $\dot{V}_I$, V_T, f_b and $P_{\bar{A}}CO_2$ during exercise are shown in figures 5.4 and 5.5. Figure 5.4. reveals that added V_D caused a significant increase (*$P < 0.05$, ANOVA, Effect of V_D) in $\dot{V}_I$ at all work-rates, whether the subjects inhaled Saline or Anesthesia before exercise. The increase in $\dot{V}_I$ during MIE was due to significant increases in V_T (figure 5.5) with lesser increases in f_b; breathing frequency was only slightly higher throughout MIE with V_D loading and significantly so at the higher work-rates (*, $P < 0.05$, ANOVA, figure 5.5). Furthermore, V_D loading had no

Table 5.2. Breathing pattern at 3 matched ventilatory levels.

		Saline		Anesthesia (AA)		Effect of AA
% $\dot{V}_{I,max}$	Variable	Control	V_D	Control	V_D	(ANOVA)
	$\dot{V}_I$ ($L \cdot min^{-1}$)	69.7 ± 10.6	69.7 ± 10.6	69.7 ± 10.6	69.7 ± 10.6	
50 %	V_T (L)	2.56 ± 0.50	2.65 ± 0.42	2.53 ± 0.50	2.68 ± 0.42	NS
	f_b (min^{-1})	27.9 ± 5.6	26.8 ± 4.8	28.3 ± 5.9	26.4 ± 4.5	NS
	$\dot{V}_I$ ($L \cdot min^{-1}$)	97.6 ± 14.9	97.6 ± 14.9	97.6 ± 14.9	97.6 ± 14.9	
70%	V_T (L)	2.82 ± 0.49	3.05 ± 0.45*	2.82 ± 0.54	3.02 ± 0.48*	NS
	f_b (min^{-1})	35.2 ± 7.0	32.3 ± 5.2*	35.6 ± 8.4	32.8 ± 6.0*	NS
	$\dot{V}_I$ ($L \cdot min^{-1}$)	125.5 ± 19.1	125.5 ± 19.1	125.5 ± 19.1	125.5 ± 19.1	
90%	V_T (L)	3.00 ± 0.57	3.24 ± 0.53*	3.00 ± 0.59	3.19 ± 0.55*	NS
	f_b (min^{-1})	42.7 ± 8.6	39.3 ± 6.7*	43.1 ± 10.3	40.3 ± 8.6*	NS

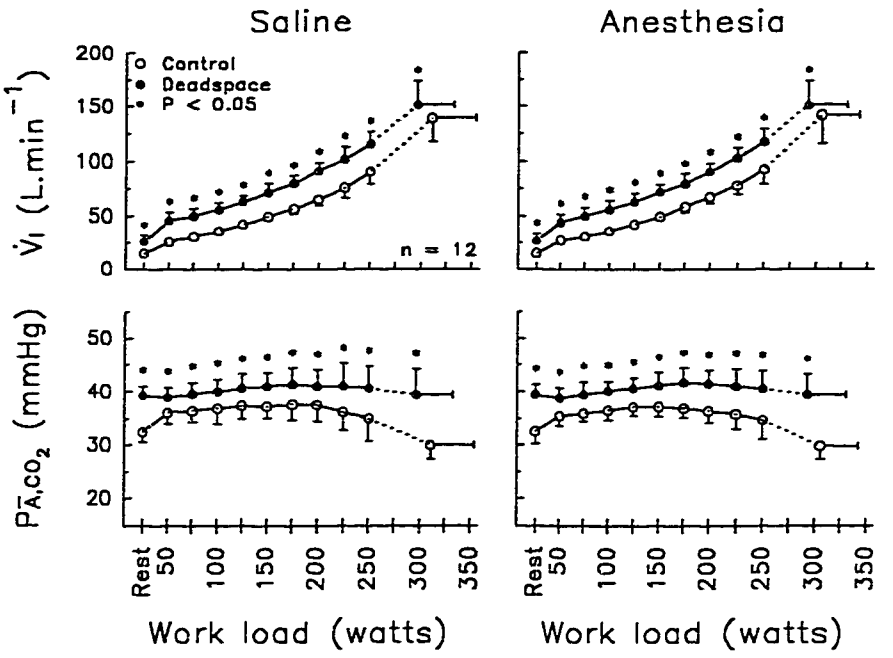

Figure 5.4. Effect of Anesthesia on the ventilatory response to added VD.

effect on TI/TT either at rest or at any other time during MIE. VD loading resulted in a slight fall (*$P < 0.05$, Anesthesia VD test, Table 5.1) in SaO_2 (%) at end exercise.

As shown in earlier studies, [WARD AND WHIPP, 1980; MCPARLAND *ET AL*, 1991; SYABBALO *ET AL*, 1993], added VD resulted in significantly higher $P_{\bar{A},CO_2}$ levels both at

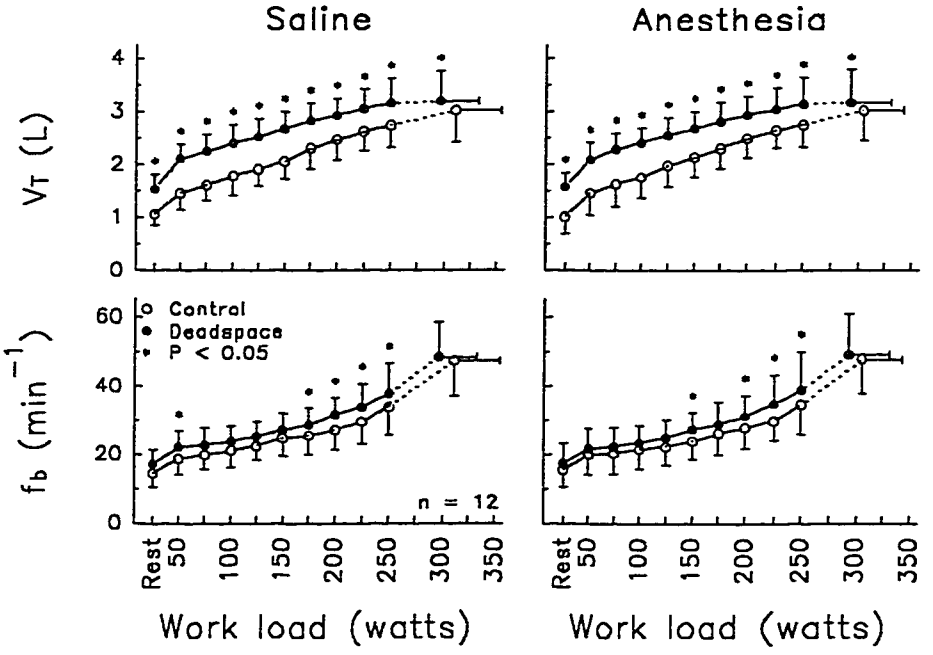

Figure 5.5. Effect of Anesthesia on the breathing pattern response to added VD.

rest and at all work-rates during MIE, compared to the Control tests. At end exercise the increase in $P_{\bar{A}}CO_2$ with added V_D was of the order of ~10 mmHg (Table 5.1). However, it is clearly evident from Figures 5.4 and 5.5, that Anesthesia had no effect on the ventilatory responses to added V_D both during MIE and at end of MIE (Table 5.1), in these subjects. The probability (Type II error) of missing a 5 L · min^{-1} difference in the $\dot{V}_I$ response to added V_D at 150 W, due to an effect of Anesthesia, was less than 5%.

The breathing pattern response to added V_D in the Saline and Anesthesia tests are described in left and right panels respectively of figure 5.6. Average $\dot{V}_I$ - V_T relationships at matched ventilatory levels (30% → 90% maximum $\dot{V}_I$ in *Saline Control* test) reveal that, compared to Control exercise, V_T at any given level of $\dot{V}_I$ was higher with added V_D and significantly (*, $P < 0.05$, ANOVA, Figure 5.6) so at the higher $\dot{V}_I$ levels. However as figure 5.6 illustrates, the "slower and deeper" (↓f_b, ↑V_T) breathing pattern response to added V_D at matched $\dot{V}_I$ levels during exercise, persisted after airway anesthesia. The difference (Δ = V_D - Control) in V_T between the *Saline V_D* and *Saline Control* tests was not significantly different from that between the

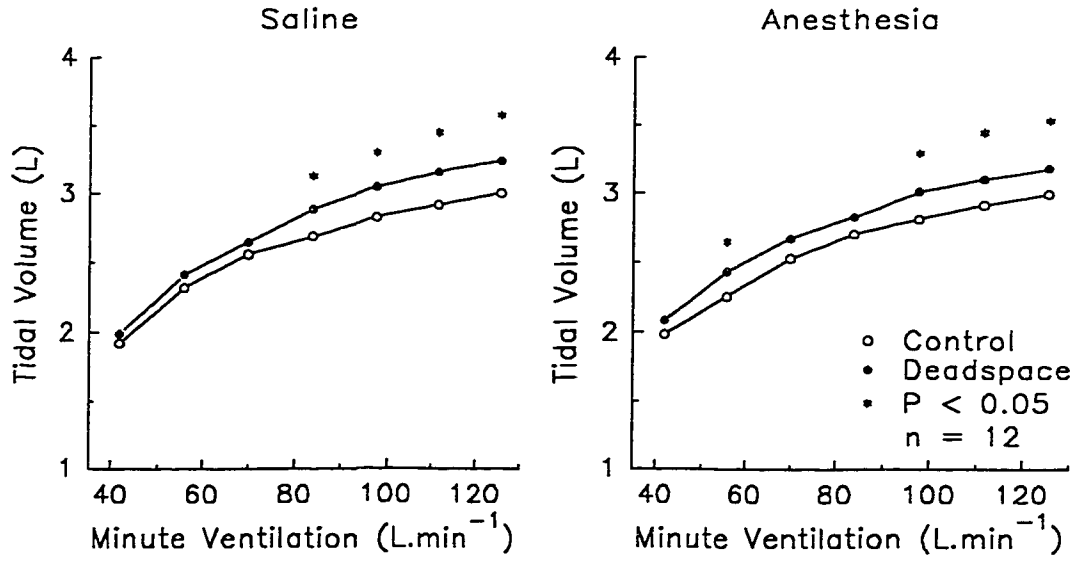

Figure 5.6. Effect of Anesthesia on breathing pattern response to added V_D at matched $\dot{V}_I$ levels.

Anesthesia VD and *Anesthesia Control* tests. Changes in breathing pattern produced by added V_D at 3 matched ventilatory levels are also summarized in table 5.2 and reveal that Anesthesia did not affect the slower and deeper breathing pattern response to added V_D both at moderate and high levels of $\dot{V}_I$ during MIE. The probability (Type II error) of missing a 150 ml difference in the V_T response to added V_D at the highest (125.5 $L \cdot min^{-1}$) matched level of $\dot{V}_I$, due to an effect of Anesthesia, was less than 1%. The probability of missing a 100 ml difference in V_T was less than 7%.

5.4. Discussion.

The two major findings of this study are that: **1)** Airway anesthesia did not affect the ventilatory and breathing pattern responses during maximal incremental exercise; **2)** Airway anesthesia did not alter the respiratory adaptations to V_D loading during exercise.

5.4.1. Critique of methods.

As all the exercise tests were randomized and conducted under identical conditions for each subject at the same time of day, the within-subject variability of ventilatory and breathing pattern responses was small. The subjects were naive to the specific focus of the study (exercise breathing pattern) and entrainment of breathing frequency to pedaling rhythm was avoided with the subject choosing his pedaling rate in the range of 50 - 70 rpm [McParland *et al*, 1991; Syabbalo *et al*, 1993]. The technique of airway anesthesia that was employed, has been shown to reliably affect airway reflexes in humans [Kuna *et al*, 1988; Mador, 1993]. In addition to ensuring on an initial occasion that each subject had effective Anesthesia for the duration of exercise, the persistence of residual Anesthesia was confirmed after exercise, in all subjects in the study.

The method of airway anesthesia used has been shown to block vagal afferent activity from the larynx [Kuna *et al*, 1988], and the tracheo-bronchial tree

[CAMPORESI *ET AL*, 1979], that are sensitive to a variety (transmural pressure, flow, temperature, CO_2 and irritant) of stimuli. While CO_2 sensitivity varies among receptor (rapidly adapting and slow adapting) types, it has been shown that stretch receptors are functionally accessible to airway luminal CO_2 and are inhibited in the range of airway P_{CO_2} as observed in this study [SANT'AMBROGIO, 1982]. Slow-adapting stretch receptors have been shown to be inhibited by increases in airway P_{CO_2}, the effects being prominent at or below (~30 mmHg) normocapnic levels [COLERIDGE *ET AL*, 1978], but these effects have been shown to persist with airway P_{CO_2} levels of upto 60 mmHg [GREEN *ET AL*, 1986]. Furthermore, it has been shown that stretch receptor activity is affected preferentially by an increase in bronchial luminal P_{CO_2} and not by increases in mean arterial P_{CO_2} [BARTLETT AND SANT'AMBROGIO, 1976], suggesting that site of effect of hypercapnia appears functionally closer to the airway lumen than to the smooth muscle layer [MISEROCCHI *ET AL*, 1973]. Both animal [DAIN *ET AL*, 1975; CROSS *ET AL*, 1976; CAMPORESI *ET AL*, 1979; KUNA *ET AL*, 1988] and human studies [CROSS *ET AL*, 1976; SAVOY *ET AL*, 1982; EASTON *ET AL*, 1985; SULLIVAN *ET AL*, 1987; MADOR, 1993], indicate that aerosol airway anesthesia can be effective in inhibiting stretch receptor activity. Human studies employing aerosol airway anesthesia have clarified the role of airway receptors in ventilation and breathing pattern responses to inhaled CO_2 [MADOR, 1993]. Both the technique of Anesthesia administration and the aerosol particle size chosen in this study, were designed to target upper and large airways and major divisions in the tracheo-bronchial tree, the preferential sites of aerosol deposition [PAVIA AND THOMSON, 1976; BRAIN AND VALBERG, 1979]. More recently, MADOR [1993], using small *.vs.* large particle anesthetic aerosols, has demonstrated that the site of pulmonary CO_2 chemosensitivity in humans is more centrally (tracheo-bronchial tree) located than at the peripheral (alveolar) level.

5.4.2. Airway receptors and exercise ventilatory control.

As reviewed elsewhere [SANT'AMBROGIO, 1982; MCPARLAND *ET AL*, 1991], various animal studies have shown that airway receptors may play an important role in ventilation and breathing pattern control. Many studies in the past have focused on effects of airway anesthesia on breathing pattern at rest [SAVOY *et al*, 1979] or on pulmonary function [KUNA *ET AL*, 1988]. Studies in exercising animals have shown that pulmonary denervation [FLYNN *ET AL*, 1995] or vagal cooling [AINSWORTH *ET AL*, 1992] resulted in an increased V_T and a reduced f_b. While both vagotomy and vagal cooling have been shown to alter breathing pattern, they have had no effect on $\dot{V}_I$ during exercise in animals [FLYNN *ET AL*, 1985; AINSWORTH *ET AL*, 1992]. The effects of airway anesthesia (with aerosolized Bupivacaine) on ventilatory control during exercise in normal humans, has been examined by WINNING *ET AL* [1985]. In their study, it was shown that after Bupivacaine inhalation "$\dot{V}_E$ was increased (mean difference, 7.7%) but this just failed to reach significance ($P > 0.05$) while end-tidal P_{CO_2} decreased" significantly. However, in contrast to these results, there was no change in $\dot{V}_I$ at any point during exercise after airway anesthesia in this study (figure 5.1). This finding was not likely to be due to a loss of Anesthesia, as residual and significant Anesthesia was documented in these subjects after end exercise. Furthermore, it was shown that the probability of missing a small (5 $L \cdot min^{-1}$) change in $\dot{V}_I$ due to an effect of Anesthesia was less than 1%. Central effects of absorbed anesthetic are unlikely to important in this study, as serum levels measured after aerosol inhalation of ~400 mg of lidocaine, have been shown to be less than 1 μg/ml, a concentration that is not consistent with any known systemic effects [SULLIVAN *ET AL*, 1987]. Although bupivacaine is ~4x more potent than lidocaine as a local anesthetic (on a per weight basis), the discrepancy between the present results and those of WINNING *ET AL* [1985], may probably not only be due to the type of local anesthetic aerosol used, but also due to differences in study design. In the previous

study [WINNING *ET AL*, 1985], the test order (Saline, Anesthesia) was not randomized and both exercise tests to exhaustion were conducted on the same day with 3 hours of rest in-between. Increased intra-subject variability in exercise V_T in that study was also likely as the authors documented significant variability in resting V_T after bupivacaine inhalation but not after saline inhalation; at rest and at low $\dot{V}_I$ levels during exercise, V_T has been shown to be quite variable in a given subject [MCPARLAND *ET AL*, 1991]. Furthermore, the breathing pattern in the previous study was also likely to be influenced by the entrainment of the breathing frequency to limb rhythm [BECHBACHE AND DUFFIN, 1977], in some of the subjects performing treadmill exercise (instead of bicycle ergometry). The present finding (the lack of effect of Anesthesia on $\dot{V}_I$ regulation during exercise) along with the demonstration that a reduction of the load on the respiratory muscles has no significant effect on exercise $\dot{V}_I$ (chapter 3), indicates that afferent feedback from the airways and/or the chest wall has no significant influence on control of $\dot{V}_I$ or its pattern during exercise in humans.

5.4.3. Airway receptors and respiratory adaptations to V_D loading.

The respiratory adaptations to added V_D have been shown to be not due to an increase (with added V_D) in mean alveolar/arterial P_{CO_2} *per se*, because the breathing pattern response did not occur when P_{CO_2} was increased by CO_2 inhalation during exercise [GALLAGHER *ET AL*, 1987]. As reviewed elsewhere [MCPARLAND *ET AL*, 1991], these responses are probably a consequence of an alteration in the P_{CO_2} time profile, sensed by carotid chemoreceptors, airway/pulmonary receptors or the central chemoreceptors. V_D loading has been shown to alter the temporal profile of arterial P_{CO_2} (P_{a,CO_2}) and the resultant temporal alteration of carotid afferent input may affect/alter respiratory timing [BAND *ET AL*, 1969; CROSS AND SEMPLE, 1987]. However, carotid chemoreceptors are unlikely to play a major role as the $\dot{V}_I$ and breathing pattern responses to added V_D during both rest [SIDNEY AND POON, 1995] and during exercise [SYABBALO *ET AL*, 1993] have been shown to persist when the carotid bodies

were silenced by hyperoxia. The evidence that transient changes in airway CO_2 in man may affect respiratory timing [CUNNINGHAM *ET AL*, 1977] and $\dot{V}_I$ [MILLER *ET AL*, 1974] suggests that the site of reception of the altered CO_2 time profile may possibly reside in the airways. This study therefore examined the possible role of airway receptors in mediating the respiratory adaptations to added V_D.

Similar to the results of previous studies [WARD AND WHIPP, 1980; MCPARLAND *ET AL*, 1991; SYABBALO *ET AL*, 1993], V_D loading in this study resulted in a higher $\dot{V}_I$ and P_{CO_2} at all work rates during and at the end of incremental exercise. The increased $\dot{V}_I$ at maximal exercise with added V_D indicates that there is normally a significant ventilatory reserve at maximal exercise, i.e. respiratory function does not limit maximal exercise in normal humans. Also consistent with previous studies [MCPARLAND *ET AL*, 1991; SYABBALO *ET AL*, 1993], breathing pattern during exercise in this study, was slower and deeper with added V_D (Table 5.2 and Figure 5.6). The present study also shows that these respiratory adaptations to added V_D were unaffected by airway anesthesia. Furthermore, the probability (Type II error) of missing a partial inhibition of the response to added V_D was shown to be small. In contrast, SHINDOH *ET AL* [88] have shown that airway anesthesia resulted in a marked reduction in the $\dot{V}_I$ response to added V_D at rest. The reasons for the discrepancy between the study of SHINDOH *ET AL* [1988] and this study are unclear. It is however unlikely to be due to the fact that SHINDOH *ET AL* [1988] did not study exercise because, if anything, exercise as a stimulus, only accentuates the respiratory responses to added V_D. It is possible however, that the altered $\dot{V}_I$ response to added V_D in the study of SHINDOH *ET AL* [1988] may have been partly due to the repeated inhalation of 10% citric acid (to test the cough reflex) on the Anesthesia but not on the Saline test days. Citric acid inhalation occurred before assessment of the $\dot{V}_I$ response to added V_D in their study. During the setup of this study and other previous studies [STOCKWELL *ET AL*, 1993] in this laboratory, it has been noted that the taste of citric acid may be perceived even when

local anesthesia abolishes citric-acid induced cough. Discomfort from the repeatedly inhaled citric acid aerosol may have therefore influenced the $\dot{V}_I$ response to added V_D in the study of SHINDOH *ET AL* [1988] .

Although the results of this study and those from another previous study [SYABBBALO *ET AL*, 1993] exclude a major role of both airway receptors and carotid chemoreceptors in the respiratory adaptations to V_D loading, they do not lend support to any specific mechanisms. For example, it has been shown that respiratory oscillations in arterial P_{CO_2} cause medullary CSF pH oscillations in cats [MILLHORN *ET AL*, 1984]. Although the amplitude of these pH changes is small (20% of arterial pH oscillations), it is possible that they are detected and that they contribute to the responses to added V_D. More recently, arterial pH oscillations have been recorded in humans, at breathing frequencies similar to those found during exercise [CROSS *ET AL*, 1995]. Furthermore, the slower and deeper breathing pattern adopted with V_D loading should be beneficial in reducing respiratory muscle work and mean respiratory muscle tension [MCPARLAND *ET AL*, 1991], and in improving gas exchange by a partial offset of the increased V_D/V_T due to V_D loading. The breathing pattern adaptation to V_D loading therefore may not be as a result of altered stimulation of one particular receptor (airway, peripheral or central chemoreceptor) but might be an optimization response to minimize changes in gas exchange and/or the energy cost of breathing [POON, 1987].

In conclusion, this study provides evidence that in humans, airway receptors do not play a major role in the control of $\dot{V}_I$ or breathing pattern during exercise. The lack of effect of airway anesthesia on the ventilatory and breathing pattern adaptations to V_D loading during exercise suggests that airway reflexes do not play a major role in the respiratory adaptations to added V_D.

6. THE ROLE OF LOCOMOTOR - RESPIRATORY COUPLING (LRC) ON VENTILATORY AND BREATHING PATTERN REGULATION DURING BICYCLE ERGOMETRY.

6.1. Introduction.

The ventilatory and breathing pattern responses during exercise are considered to be as a result of a central integration of several chemical and neuro-mechanical stimuli [WHIPP, 1983]. While neural mechanisms are thought to play a major role in ventilatory control in the dynamic state at the start of exercise [DIMARCO *ET AL*, 1983; WHIPP, 1983; CASEY *ET AL*, 1987] and humoral mechanisms prevail in exercise ventilatory control in the steady state [WHIPP, 1983], it has been shown that other factors may also be important in these responses [JEYARANJAN *ET AL*, 1989].

6.1.1. Background.

Both feedback and feed-foward neural mechanisms have been shown to be capable of increasing ventilation in proportion to the degree of movements in the limbs [AGOSTONI AND D'ANGELO, 1976; DIMARCO *ET AL*, 1983; WHIPP, 1983; CASEY *ET AL*, 1987] and it has therefore been suggested that significant interactions between exercise and breathing rhythms exist in humans. Furthermore, limb frequency has been shown to significantly influence ventilatory control in cats [AGOSTONI AND D'ANGELO, 1976; ISCOE AND POLOSA, 1976; DIMARCO *ET AL*, 1983]. This form of synchronization between limb and breathing frequencies (Locomotor-Respiratory Coupling, LRC) has been demonstrated in quadrupeds [LAFORTUNA *ET AL*, 1996], birds [BUTLER AND WOAKES, 1980] and in many mammals [BRAMBLE AND CARRIER, 1983] including humans [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983;

GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; LORING *ET AL*, 1990]. LRC in humans has been observed during walking [HILL *ET AL*, 1988, LORING *ET AL*, 1990], running [BRAMBLE, 1983; BERNASCONI AND KOHL, 1993], rowing [MAHLER *ET AL*, 1991], arm-cranking [PATERSON *ET AL*, 1986] and bicycle ergometry [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; BERNASCONI AND KOHL, 1993]. It has been suggested that the degree of LRC varies with the type [PATERSON *ET AL*, 1986; BERNASCONI AND KOHL, 1993], subjects' familiarity/training in the form [BECHBACHE AND DUFFIN, 1977; KOHL *ET AL*, 1981; PATERSON *ET AL*, 1986; BERNASCONI AND KOHL, 1993], the intensity [KAY *ET AL*, 1975; BERNASCONI AND KOHL, 1993] of exercise and whether breathing is paced with auditory cues such as metronomes [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; BERNASCONI AND KOHL, 1993]. It has also been shown that at comparable exercise intensities, humans exhibit greater degree of LRC during running than with cycling [BERNASCONI AND KOHL, 1993], perhaps because running is a more natural movement in bipedal mammals [BRAMBLE, 1983; BRAMBLE AND CARRIER, 1983].

While the bulk of available evidence suggests that some synchronization of limb and breathing rhythms is present in exercising humans [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; LORING *ET AL*, 1990; MAHLER *ET AL*, 1991; BERNASCONI AND KOHL, 1993], some studies have suggested otherwise [KAY *ET AL*, 1975]. The differing results among the studies have been attributed [PATERSON *ET AL*, 1986] to differences in experimental design, the type of exercise and more importantly, the criteria used to quantify LRC. Most of the above study designs promoted LRC during exercise for example, by paced breathing [BECHBACHE AND DUFFIN, 1977; GARLANDO *ET AL*, 1985; BERNASCONI AND KOHL, 1993], enforced pedalling rates [JASINSKAS *ET AL*, 1980; PATERSON *ET AL*, 1986] (including those that advised a "comfortable and constant" rate [KOHL *ET AL*, 1981]), presumably to study its effect on exercise ventilatory control [TAKANO, 1988; CARETTI *ET*

AL, 1992, HUNTER *ET AL*, 1997] or oxygen uptake [GARLANDO *ET AL*, 1985; BERNASCONI AND KOHL, 1993] during bicycle ergometry. However, there are no conclusive data regarding the effects of spontaneous LRC in humans (if and when present) on the above variables throughout maximal incremental exercise. In order to avoid the confounding influence of progressive metabolic acidosis on exercise ventilation [WHIPP, 1983], different exercise designs, *viz.*, sub-maximal exercise [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; GARLANDO *ET AL*, 1985; CARETTI *ET AL*, 1992; BERNASCONI AND KOHL, 1993], sub-anaerobic threshold exercise [TAKANO, 1988], constant-work rate exercise [KOHL *ET AL*, 1981; PATERSON *ET AL*, 1986; HUNTER *ET AL*, 1997] have been used to study the role of LRC in exercise ventilatory control in the steady-state [GARLANDO *ET AL*, 1985; HAGAN *ET AL*, 1992]. There are however no objective data available on the importance of LRC (if any) in ventilatory control at higher exercise levels.

This study was therefore designed to examine whether humans exhibit spontaneous and significant LRC throughout maximal incremental bicycle ergometry while pedalling freely within three different ranges of pedal frequencies. The study also closely examined whether LRC (if present) had any significant impact on ventilation and breathing pattern control during incremental exercise in humans.

6.2. Methods.

6.2.1. Subjects.

Seven healthy males (mean age, 24.3 years; range 18 - 29 years) with no evidence of cardio-pulmonary or neuro-muscular disease, were recruited for the study. Each subject underwent a physical examination, an electrocardiogram and pulmonary function assessment and gave written, informed consent to the procedures. The study was approved by the institutional ethics committee for human experimentation. All the subjects were physically active and of above average fitness (maximal O_2 uptake, $\dot{V}O_{2,max}$ = 121 ± 7 %pred, mean ± S.E.M.; range = 97% - 151%). Three subjects (subjects 1, 2 and 7) were active cyclists, while the others engaged in

recreational cycling as a part of their weekly physical activities. All the subjects were naive about the specific focus of the study (i.e. the effect of pedalling rate on breathing pattern) and they were instructed to refrain from any strenuous physical activity and caffeinated drinks before each exercise test.

6.2.2. Exercise studies.

Subjects performed incremental exercise to volitional maximum, listening to non-rhythmic music with headphones. Exercise began at 50 watts after 2 minutes of breathing at rest and the work rate was incremented by 25 watts each minute, until the subject was unable to continue exercise. Each subject performed maximal incremental exercise using 3 pedalling speed ranges ("LOW", 30 - 50 rpm; "MEDIUM", 50 - 70 rpm; "HIGH", 70 - 90 rpm) on 3 different days, at approximately the same time of day each time. The order of presentation of the pedalling speeds was randomized and the exercise tests were separated from each other by at least 2 days.

6.2.3. Equipment.

All exercise tests were performed on an electrically braked cycle ergometer (Godart 18070) which is designed to maintain work load independent of pedal frequency, within the range of 40 - 90 rpm. The subject was instructed to pedal at a comfortable rate anywhere within a given range (of 20 rpm) marked on an analog speedometer display. By adjusting the gain on the amplifier controlling the speedometer unbeknownst to the subject, it was possible for this marked range to represent 3 different actual pedaling ranges (LOW, MEDIUM, HIGH) on 3 different occasions. The actual pedalling frequency (f_{ped}) was measured with the aid of a small permanent magnet mounted on the right pedal arm that triggered a magnetic sensor mounted on the bicycle frame. The sensor and the magnet were so arranged such that when the right pedal arm was in the trailing horizontal position, a signal representing the start of the pedal cycle (0°) was recorded. The study was thus designed to blind each subject from his true pedalling frequency.

All subjects wore nose-clips and breathed through a mouthpiece. Inspiratory (I) and expiratory (E) flows were measured separately using two pneumotachograph - transducer (Fleisch #3 - Validyne MP45, ± 2 cmH_2O) assemblies on either side of a two-way non-rebreathing valve (Hans-Rudolph #2700, dead space 115 ml). The individual flow signals (I and E) were monitored (and corrected) on a breath-by-breath basis throughout exercise for zero drift [GOWDA *ET AL*, 1990] and the biphasic (I + E) flow signal was integrated to provide volume. The response of the system was linear and the total resistance of the inspiratory limb of the breathing apparatus (including the Fleisch #3 pneumotachograph and the Hans-Rudolph valve) was 1.34 $cmH_2O \cdot L^{-1} \cdot s$ at 10 $L \cdot s^{-1}$ flow. A manual solenoid tap alternating (every 30s) between the mouthpiece and a baffled mixing chamber (on the expiratory limb) enabled the sampling of both end-tidal and mixed expired gases respectively. Gas concentrations (O_2 and CO_2) from the two sites were measured by a mass spectrometer (MGA 2000, Airspec, Kent, UK), calibrated with a standard gas mixture of known composition. A 3-lead precordial ECG and finger tip O_2 saturation (SaO_2, %) were monitored by a pulse oximeter (Nellcor, Pleasonton, CA).

6.3. Data analysis.

All the signals (biphasic flow [I + E], volume, O_2, CO_2, SaO_2, ECG and the pedal signal) were recorded continuously on an eight-channel strip-chart recorder (Gould) and were sampled (at 100 Hz) for digital storage and off-line data analysis on a microcomputer. The computer measured inspiratory (T_I), expiratory (T_E), total (T_T) breath durations and tidal volume (V_T) for all valid breaths during exercise. Those breaths that were interrupted by cough or swallowing (< 5 /min) were discarded. Inspired minute ventilation ($\dot{V}_I$) was derived from averaged V_T (digital integration of flow) and breathing frequency ($f_b = 60/T_T$) for each minute of exercise. Oxygen uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$) for each minute were calculated using standard formulae and the "V-slope" method [BEAVER *ET AL*, 1986] was used derive the lactate

threshold ($\dot{V}O_{2,LT}$) from the $\dot{V}O_2$ - $\dot{V}CO_2$ relationship during exercise. Using previously described techniques [WHIPP AND WARD, 1980; WHIPP *ET AL*, 1990], mean alveolar P_{CO_2} ($P_{\bar{A},CO_2}$) was estimated from the time-weighted mean CO_2 profiles, since $P_{\bar{A},CO_2}$ has been shown to provide an excellent estimate of arterial P_{CO_2} during exercise in normal humans [ROBBINS *ET AL*, 1990; WHIPP *ET AL*, 1990]. Heart rate (fc) at each work load was counted from the ECG waveforms.

6.3.1. Assessment of significant LRC during exercise.

Figure 6.1 describes the method of assessment of LRC during exercise. Flow (upper panel) and R-pedal signal (lower panel) data from 4 consecutive breaths are shown. Inspiratory flow was negative and the f_{ped}/f_b ratios for each of the 4 breaths are indicated in the top most row. By transforming the interval between two consecutive pedal signals as 360°, it was possible for the computer to locate the R-pedal position (in degrees) at the start of both inspiration (dashed arrows) and expiration (thin arrows) for each breath during exercise. These data (starting angle

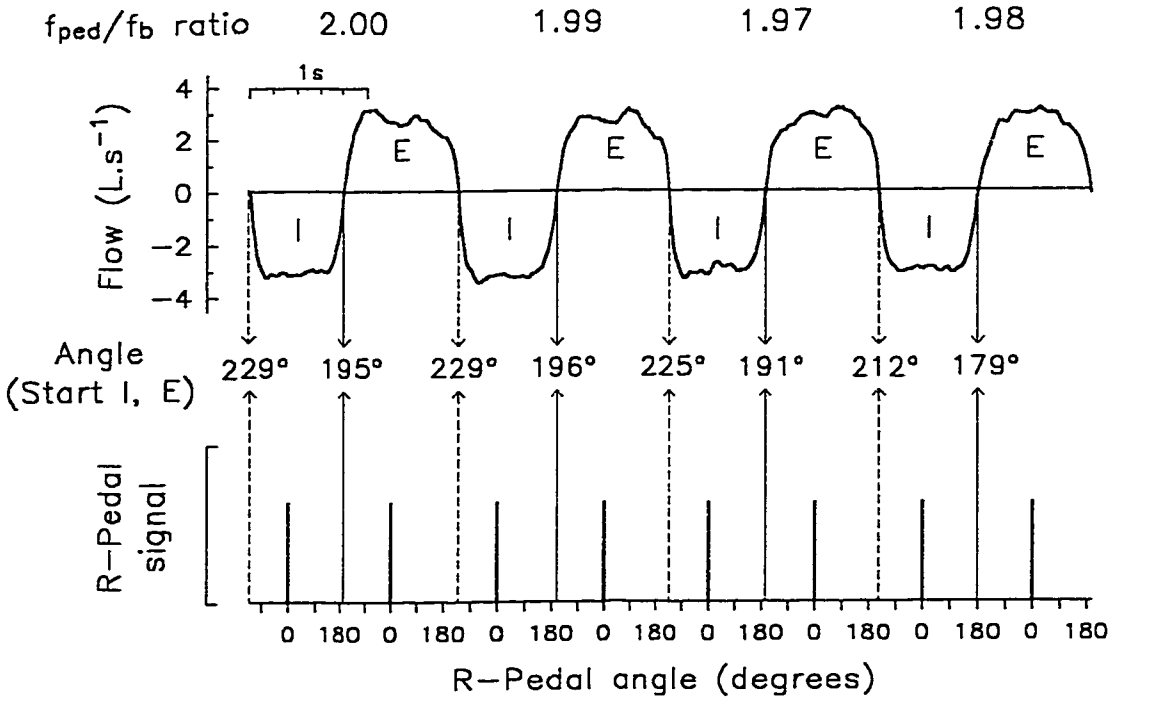

Figure 6.1. Methods of assessment of LRC during exercise.

for I and E) are also indicated for the 4 breaths in the row between the two panels. f_{ped}/f_b ratios and starting angles of inspiration and expiration for each valid breath throughout exercise were then analyzed for the presence of significant LRC in each subject. These data samples (f_{ped}/f_b ratios, starting angle - I, starting angle - E, from all valid breaths) in each subject (and in each exercise test) were then tested against an uniform distribution, with a one sample Kolmogorov-Smirnoff (K-S) test.

Figure 6.2 describes the distributions of the f_{ped}/f_b ratios, starting angle - I and starting angle - E, from the three exercise tests (LOW, MEDIUM AND HIGH) in one subject (subject #1) who demonstrated significant LRC during exercise. Significant LRC in any exercise test was deemed to have occurred if any (or all) of following 3 conditions were present: **1)** *Entrainment of breathing frequency to pedalling frequency* - A significant proportion of f_{ped}/f_b ratios from breaths throughout exercise tended to aggregate around integers or half integers (n = 0.5, 1, 1.5, 2.0.. and so on), i.e. the distribution of the f_b/f_{ped} ratios from all breaths throughout exercise in the n ±

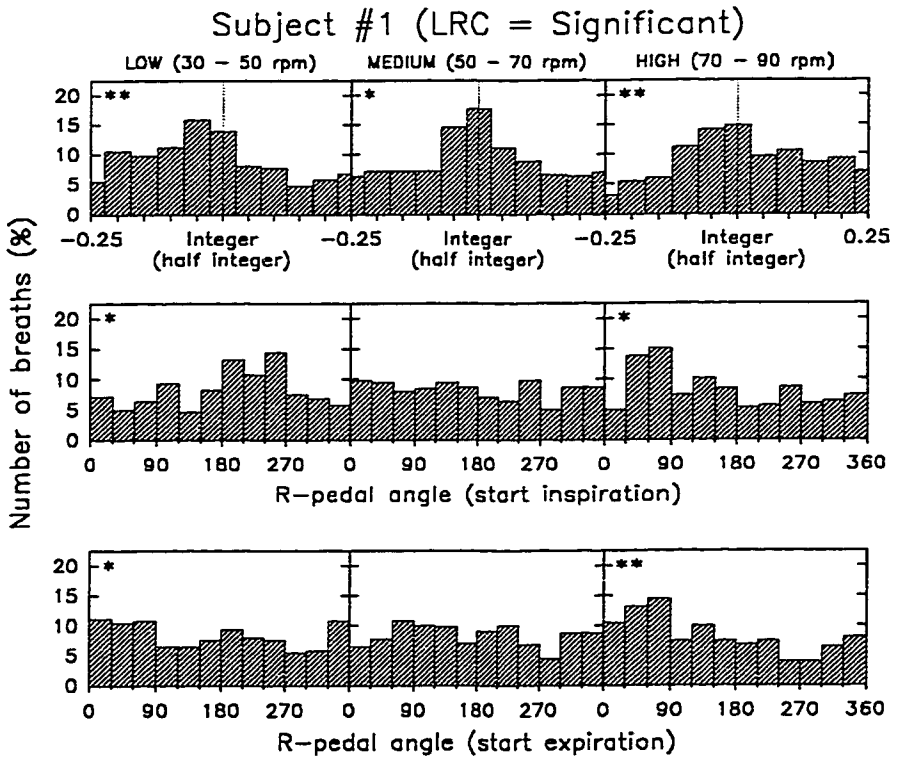

Figure 6.2. An example of significant LRC during exercise.

0.25 interval was *not* uniform (top panel, figure 6.2); **2)** *Inspiratory Phase Coupling* - a significant proportion of breaths in which inspiration tended to start at a specific pedal position, i.e. the distribution of the R-pedal angle at the start of inspiration from all breaths throughout exercise in 0° - 360° interval was *not* uniform (middle panel, figure 6.2); **3)** *Expiratory Phase Coupling* - a significant proportion of breaths in which expiration tended to start at a specific pedal position, i.e. the distribution of the R-pedal angle at the start of expiration from all breaths throughout exercise in 0° - 360° interval was *not* uniform (lower panel, figure 6.2). A P value < 0.05 was deemed as significant. A Bonferroni correction for multiple significances (7 subjects x 3 tests = 21 levels) was also applied and if the P value was < 0.0025 (~0.05/21), it was recorded.

6.3.2. Statistical Analysis.

Ventilatory and exercise variables from the 3 exercise tests (LOW, MEDIUM AND HIGH) were compared at all common work rates (50w → 275w) and at end exercise using a repeated measures ANOVA design. If statistically significant differences existed among tests, a *post-hoc* Student Newman-Keuls test for multiple comparisons was then used to investigate for significant differences at specific work rates. Breathing pattern during exercise in each subject was examined as $\dot{V}_I$ - V_T relationships at matched levels of $\dot{V}_I$ (0 - 100% of the lowest maximum $\dot{V}_I$ in the 3 tests, $\dot{V}_{I,max}$). A repeated measures ANOVA design was then used to look for differences in breathing pattern at matched $\dot{V}_I$ levels (0 - 100% $\dot{V}_{I,max}$ at 10% increments) among the 3 tests. A $P < 0.05$ was accepted as significant. All data are shown as mean ± S.E.M., unless stated otherwise.

6.4. Results.

Table 6.1 summarizes the average exercise performance data from the LOW, MEDIUM AND HIGH exercise tests in the 7 subjects. As shown clearly, pedalling rates had no significant effect on exercise duration (T_{LIM}), maximal work rate completed ($\dot{W}_{max}$), maximal oxygen uptake ($\dot{V}O_{2,max}$), lactate threshold ($\dot{V}O_{2,LT}$) and the degree

Table 6.1. Exercise performance summary.

Variable	LOW	MEDIUM	HIGH	ANOVA
T_{LIM} (min)	11.8 ± 0.5	12.0 ± 0.5	12.0 ± 0.4	NS
$\dot{W}_{max}$ (Watts)	321 ± 13	332 ± 12	329 ± 12	NS
$\dot{V}O_{2,max}$ ($L \cdot min^{-1}$)	3.71 ± 0.18	3.73 ± 0.16	3.85 ± 0.17	NS
$\dot{V}O_{2,max}$ (%pred)	120 ± 6	121 ± 7	125 ± 6	NS
$\dot{V}O_{2,LT}$ ($L \cdot min^{-1}$)	2.14 ± 0.16	2.06 ± 0.11	2.30 ± 0.14	NS
Dyspnea (Borg)	7.6 ± 0.3	7.9 ± 0.7	7.9 ± 0.6	NS†
Leg fatigue (Borg)	8.3 ± 0.4	8.3 ± 0.5	8.1 ± 0.5	NS†

of dyspnea or leg fatigue [BORG, 1982] at end exercise in these subjects. Both the dyspnea and leg fatigue scores were compared using non-parametric methods (†,Friedman's ANOVA).

6.4.1. LRC during exercise.

Figure 6.3 describes f_{ped}/f_b (pedal/breath) ratios from all valid breaths throughout exercise from subject #1 (left panel) who demonstrated significant LRC

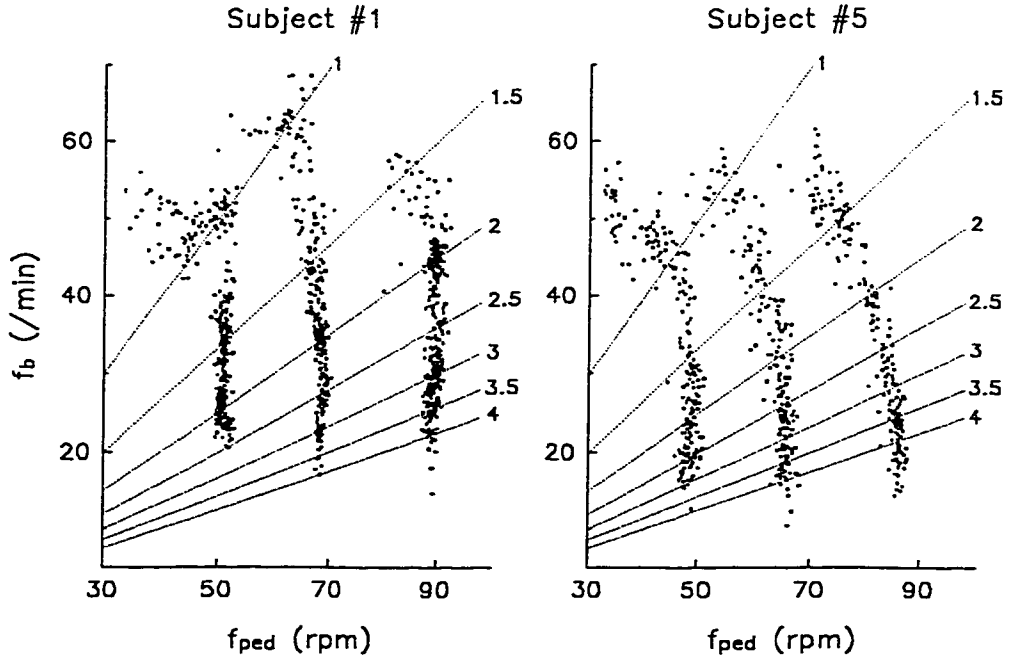

Figure 6.3. Integer (half-integer) f_{ped}/f_b ratios during exercise.

and subject #5 (right panel) in whom LRC was not apparent. The integer and half-integer ratio ranges (1:1, 1:1.5,..., 1:4) are also shown as iso-pleths in each panel. It is evident from figure 6.3 that in subject #1, the f_{ped}/f_b ratios tended to aggregate around integers or half-integers. As already shown on figure 6.2, this subject had significant entrainment of breathing frequencies to pedalling frequency during exercise in all the 3 tests. Figure 6.3 also reveals that $f_b:f_{ped}$ ratios in this subject ranged from 1:2 to 1:1 in the LOW test (30 - 50 rpm), from 1:3 to 1:2 in the MEDIUM test (50 - 70 rpm) and from 1:4 to 1:2 in the HIGH (70 - 90 rpm) test. This subject also showed a preponderance of 1:2 ($f_b:f_{ped}$) ratios in all three tests. f_{ped}/f_b ratios in subject #5 on the other hand, tended to be more randomly distributed and this subject therefore did not have significant entrainment of breathing frequencies to pedalling frequency throughout exercise in any of the three tests.

The results of analysis of all the valid breaths in subject #1 during exercise were summarized in figure 6.2 as an example of a subject who demonstrated

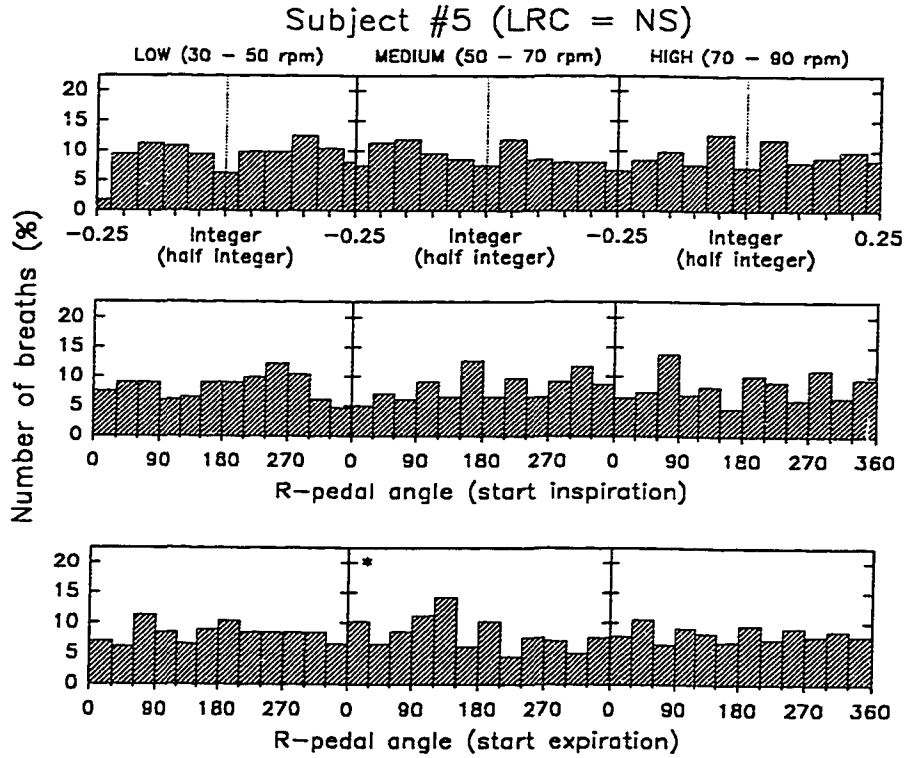

Figure 6.4. An example of insignificant (or absent) LRC during exercise.

significant LRC during exercise. In addition to significant entrainment of breathing frequencies to pedalling frequency in all three exercise tests, this subject also demonstrated significant inspiratory (middle panel, figure 6.2) and expiratory phase coupling (lower panel, figure 6.2), in both the LOW and HIGH tests. Figure 6.4 is an example of similar data from subject #5, who did not demonstrate significant LRC (except for some expiratory phase coupling in the MEDIUM test) during exercise in the three tests. Table 6.2 summarizes the results of analysis of all valid breaths during exercise in all three tests, in each subject. Significant LRC (integer f_{ped}/f_b ratios, inspiratory and expiratory phase coupling) data from all the three tests are given. It is evident that LRC in some form was present predominantly in subjects #1 and #2 and to a lesser extent in subjects #3 and #6, while the other subjects show little (subject #5) or no (subjects #4 and #7) LRC during exercise in any of the three tests.

6.4.2. Exercise variables and breathing pattern.

Figure 6.5 describes the time course of group mean $\dot{V}_I$, V_T, f_b and $P_{\bar{A},CO_2}$ data

Table 6.2. LRC during exercise (subject summary).

		Subjects						
LRC	TEST	1	2	3	4	5	6	7
Integer f_b/f_{ped} ratios	LOW	**					*	
	MEDIUM	*	**					
	HIGH	**					*	
Inspiratory Phase-coupling	LOW	*						
	MEDIUM		**	**				
	HIGH	*	**					
Expiratory Phase-coupling	LOW	*						
	MEDIUM		**	*		*		
	HIGH	**	**				**	

at matched work rates (50w → 275w) and at end exercise, in the three (LOW, MEDIUM and HIGH) tests. These comparisons reveal that pedalling rates had little effect on these variables during exercise. $\dot{V}_I$ at the start of exercise in the HIGH test was significantly higher than that in the LOW test at 50 W (+, ANOVA) and higher than that in both the LOW and MEDIUM tests at 75 W and 100 W (*, ANOVA). However, the time course of $\dot{V}_I$ at the higher work rates during exercise and end exercise was similar in all the three tests. As figure 6.5 also reveals, this increase in $\dot{V}_I$ at the start of the exercise in the HIGH test could be attributed to increases in both V_T and f_b. However, there were no significant differences in the courses of V_T, f_b, and $P_{\bar{A},CO_2}$ during exercise among the three tests.

The time course of group mean $\dot{V}O_2$, $\dot{V}CO_2$, heart rate and f_{ped} data at matched work rates (50w → 275w) and at end exercise in the three (LOW, MEDIUM and HIGH) tests, is shown in figure 6.6. During exercise at the lower work rates, both

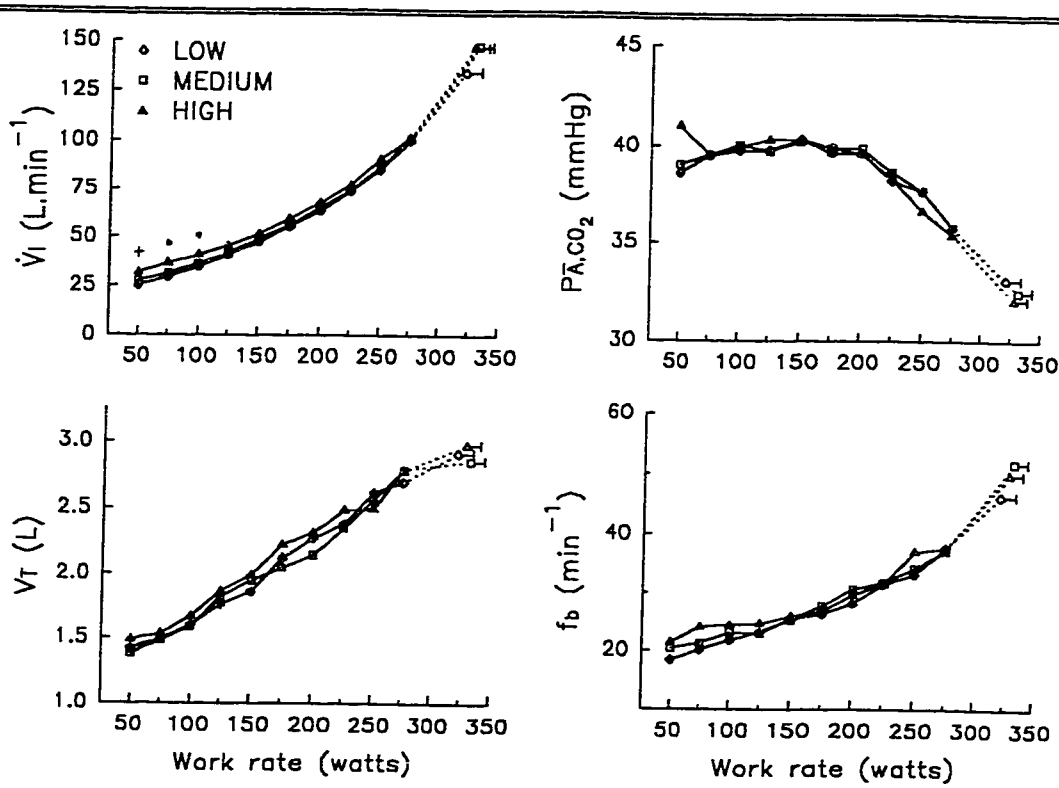

Figure 6.5. Effect of pedaling frequency on ventilatory variables during exercise.

$\dot{V}O_2$ (50w → 100w) and $\dot{V}CO_2$ (50w → 125w) in the HIGH test were significantly (*, ANOVA) higher than that in the LOW and MEDIUM tests. The subsequent time course of these variables during and till end of exercise was however not significantly different among the three tests.

It was possible however, that the increase in metabolic rate ($\dot{V}O_2$, $\dot{V}CO_2$) with the increased pedalling frequency, was due to differences in external work load applied by the bicycle ergometer. Using the corrections (as specified by the ergometer manufacturer) for work load variations based on actual pedalling frequencies (also shown in figure 6.6), it was established that the actual external work load applied was identical throughout exercise, at all pedalling ranges. Furthermore, as figure 6.6 also shows, the heart rate response throughout exercise was identical in the three tests. It is therefore likely that the increased $\dot{V}O_2$ and $\dot{V}CO_2$ in the HIGH test was not due to discrepancies in external work load due to the different pedalling

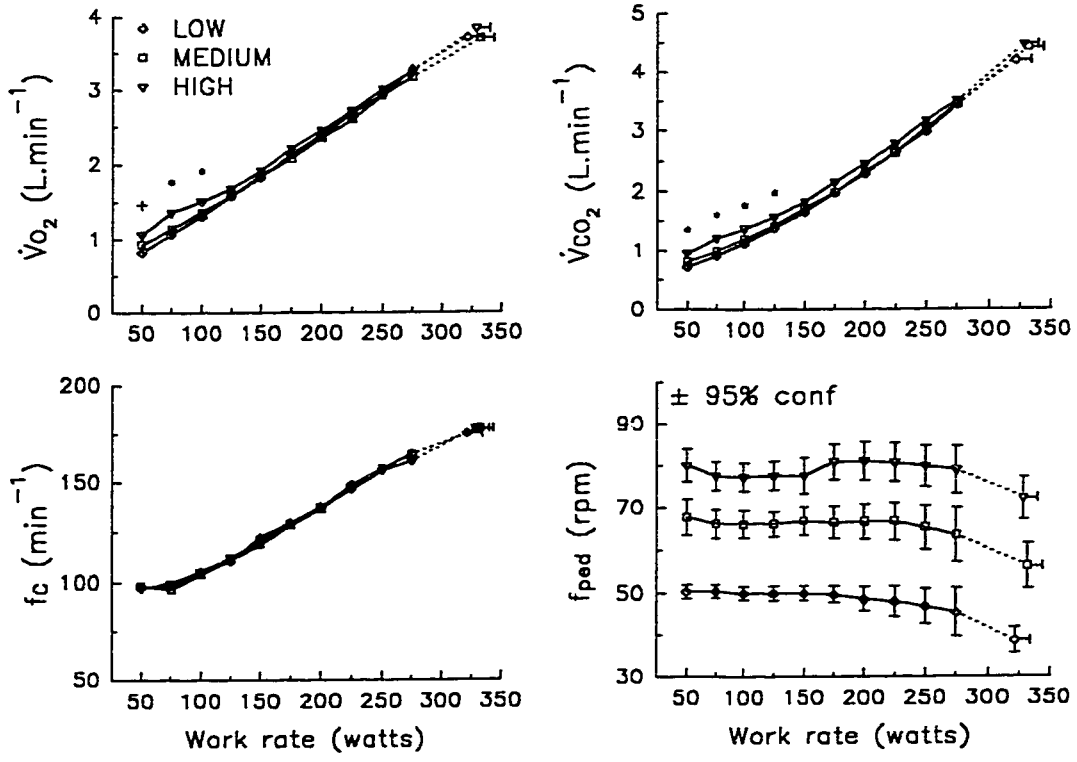

Figure 6.6. Effect of pedaling frequency on metabolic variables during exercise.

Table 6.3. Exercise variables summary (200 Watts).

Variable	LOW	MEDIUM	HIGH	ANOVA
$\dot{V}O_2$ ($L \cdot min^{-1}$)	2.39 ± 0.01	2.35 ± 0.02	2.45 ± 0.02	NS
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	2.29 ± 0.02	2.31 ± 0.02	2.46 ± 0.02	NS
$\dot{V}I$ ($L \cdot min^{-1}$)	63.8 ± 1.0	65.3 ± 0.8	68.1 ± 0.8	NS
$\dot{V}I/\dot{V}O_2$	26.7 ± 0.8	27.3 ± 1.0	27.8 ± 0.6	NS
$\dot{V}I/\dot{V}CO_2$	27.8 ± 0.5	28.0 ± 0.6	27.7 ± 0.7	NS
$P\bar{A},CO_2$ (mmHg)	39.7 ± 0.6	39.9 ± 0.8	39.6 ± 0.6	NS
SaO_2 (%)	98.0 ± 0.1	97.9 ± 0.1	98.1 ± 0.1	NS
fc (min^{-1})	137 ± 2	137 ± 2	138 ± 2	NS
V_T (L)	2.27 ± 0.02	2.15 ± 0.03	2.32 ± 0.03	NS
T_I (s)	0.99 ± 0.02	0.91 ± 0.02	0.95 ± 0.02	NS
T_E (s)	1.17 ± 0.02	1.07 ± 0.02	1.10 ± 0.02	NS
T_I/T_T	0.457 ± 0.002	0.459 ± 0.002	0.463 ± 0.002	NS
f_b (min^{-1})	28.1 ± 0.5	30.6 ± 0.4	29.6 ± 0.4	NS
f_{ped} (rpm)	48.7 ± 2.8†	66.7 ± 4.0†	81.1 ± 4.6†	

rates, but due to increased metabolic demands as a result of increased limb muscle work at the higher pedalling rates *(SEE DISCUSSION)*. The increased $\dot{V}I$ in the HIGH test therefore reflected the increased metabolic requirements as the temporal courses of the ventilatory equivalent for oxygen ($\dot{V}I/\dot{V}O_2$) and CO_2 ($\dot{V}I/\dot{V}CO_2$) were identical in the three tests. In addition, pedalling rates had no significant effect on these variables during exercise in any of three tests.

The actual pedalling frequencies used by these subjects (mean ± 95% conf.) during the three tests are also summarized in figure 6.6. While it was possible for the subjects to maintain their pedalling rates in the higher part of each range through most of exercise (< 225w) in all three tests, the pedalling rates tended to drop towards and at end exercise. However as figure 6.6 reveals, all the subjects

managed to keep their pedalling rates in the appropriate ranges throughout the LOW (30 - 50 rpm), MEDIUM (50 - 70 rpm) and HIGH (70 - 90 rpm) tests. Table 3 describes all the mean (± S.E.M.) exercise and ventilatory variables at 200 watts and reveals that pedalling frequency (†, ± 95% conf.) had no effect on any of these variables.

Breathing pattern responses ($\dot{V}_I$ - V_T relationships) during exercise in each subject and for the group as a whole in all the three tests are shown in figure 6.7. Data shown are at matched ventilatory levels (at 10% increments of $\dot{V}_{I,max}$) and reveal that on average, pedalling frequencies had little or no effect on breathing pattern in any of the exercise tests. It was shown earlier (Table 6.2) that subjects #1 and #2 demonstrated significant LRC during exercise in all the three pedalling range tests (LOW, MEDIUM and HIGH). Figure 6.2 however reveals that except in subject #2, LRC (when present) did not significantly alter breathing pattern during exercise in any other subject. Even in subject #2, the effect of LRC is seen only in the LOW test, when it caused a slower and deeper breathing pattern at $\dot{V}_I$ levels below 100 L/min. There was however no discernible effect of LRC on breathing pattern neither at higher $\dot{V}_I$ levels in LOW test, nor in the MEDIUM or HIGH tests in this subject. Table 6.4 summarizes the group mean breathing pattern responses at two matched ventilatory

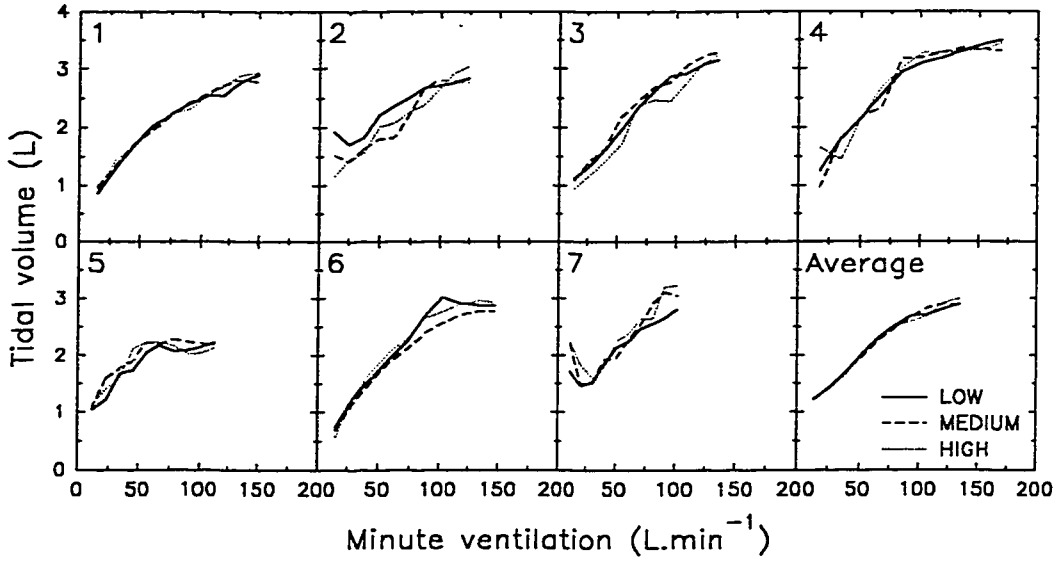

Figure 6.7. Effect of pedaling frequency on breathing pattern during exercise.

Table 6.4. Breathing pattern at matched ventilatory levels.

$\%\dot{V}_{I,max}$ ($\dot{V}_I$, $L \cdot min^{-1}$)	Variable	LOW	MEDIUM	HIGH	ANOVA
50% (66.9 ± 1.7)	V_T (L)	2.33 ± 0.04	2.28 ± 0.06	2.36 ± 0.04	NS
	f_b (min^{-1})	28.7 ± 0.5	29.6 ± 0.6	28.4 ± 0.5	NS
	T_I (s)	0.98 ± 0.02	0.95 ± 0.02	0.10 ± 0.02	NS
	T_E (s)	1.14 ± 0.02	1.11 ± 0.02	1.16 ± 0.03	NS
	T_I/T_T	0.46 ± 0.00	0.46 ± 0.00	0.46 ± 0.00	NS
90% (120.3 ± 3.0)	V_T (L)	2.82 ± 0.06	2.90 ± 0.05	2.92 ± 0.06	NS
	f_b (min^{-1})	42.8 ± 0.7	41.9 ± 1.0	41.6 ± 1.0	NS
	T_I (s)	0.69 ± 0.02	0.73 ± 0.02	0.74 ± 0.03	NS
	T_E (s)	0.73 ± 0.01	0.76 ± 0.02	0.76 ± 0.02	NS
	T_I/T_T	0.49 ± 0.00	0.49 ± 0.00	0.49 ± 0.00	NS

levels (50% and 90% $\dot{V}_{I,max}$). It is evident that LRC had little or no effect on either the breathing pattern (V_T, f_b) or the timing components of ventilation (T_I, T_E or T_I/T_T), at matched ventilatory levels during exercise.

6.5. Discussion.

A synchronization of limb and breathing rhythms (Locomotor-Respiratory Coupling, LRC) during exercise, has been documented in birds [BUTLER AND WOAKES, 1980] and mammals [BRAMBLE AND CARRIER, 1983; LAFORTUNA *ET AL*, 1996], including humans [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; LORING *ET AL*, 1990]. While the ventilatory and breathing pattern responses during exercise in horses [LAFORTUNA *ET AL*, 1996] and other mammals [BRAMBLE AND CARRIER, 1983] have been shown to be significantly influenced by rigid LRC, there is very little objective data on the effects of LRC (as and when it occurs) on breathing pattern in humans performing bicycle exercise. This study was designed to examine whether LRC was present in normal

humans performing incremental bicycle exercise to exhaustion and if so, whether it has a significant impact on exercise performance, ventilatory control and on breathing pattern. The results of the study reveal that in humans performing incremental bicycle exercise while pedalling freely anywhere within a given range: **1)** Spontaneous LRC occurs intermittently in some, but not all subjects during exercise; **2)** LRC, even if present, has no significant impact on the temporal course of exercise and ventilatory variables and **3)** At matched ventilatory levels during exercise, LRC has no significant effect on breathing pattern.

6.5.1. LRC during exercise - Critique of methods.

A number of studies have explored the possibility of a co-ordination of exercise and breathing rhythms in humans, and the results from some studies suggest that some relationship exists [BECHBACHE AND DUFFIN 1973; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981; BRAMBLE, 1983; PAINTER AND YONGE, 1984; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; LORING *ET AL*, 1990; MAHLER *ET AL*, 1991; BERNASCONI AND KOHL, 1993], while other studies refute such relationship [KAY *ET AL*, 1975]. However, it is currently accepted that LRC in some form may be present intermittently during exercise in humans and that the degree of LRC during running is significantly greater than that observed during cycling [BRAMBLE, 1983; BRAMBLE AND CARRIER, 1983; BERNASCONI AND KOHL, 1993]. Furthermore, LRC during exercise is thought to influenced by the intensity of exercise [KAY *ET AL*, 1975; BERNASCONI AND KOHL, 1993], subjects' training and familiarity with the mode of exercise [BECHBACHE AND DUFFIN 1977; KOHL *ET AL*, 1981; PATERSON *ET AL*, 1986; BERNASCONI AND KOHL, 1993]. Therefore the considerable disagreement about the presence or absence of significant LRC during exercise, generally appears to be dependent on the methods and the subjects used in the assessment of presence of significant LRC. While the primary intention of the present study was not to cause or prevent LRC during exercise it was desirable to reliably document LRC in normal healthy subjects, as and when it occurred, and study its

effects on a number of exercise variables such as, breathing pattern. To this end, it was ensured that these subjects were completely unaware of any of the specific goals of study, other than the fact their "exercise performance" was being assessed and that each subject was told clearly to perform maximal exercise until exhaustion, on each occasion. The different exercise tests were performed by the subjects under identical conditions. Each subject wore headphones and exercised while listening to non-rhythmic music thus eliminating extraneous auditory stimuli (including the sounds of the bicycle ergometer) as these stimuli (e.g. paced breathing or pedalling to a metronome beat) have been shown repeatedly [BECHBACHE AND DUFFIN 1977; JASINSKAS *ET AL*, 1980; PAINTER AND YONGE; 1984; GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986; BERNASCONI AND KOHL, 1993] to promote significant LRC during exercise. For the same reason, visual cues such as numeric pedal rate displays were also avoided and each subject had visible to him the same pedalling range, marked (but not numbered) on an analog speedometer. While no single pedalling rate was enforced, the subjects were clearly instructed before the start of the study, to pedal freely anywhere within the given range. As figure 6.6 reveals the subjects were able to maintain the rates of pedalling within the specified range for each test, in all tests.

The variety of techniques employed in the evaluation of both the degree and the significance of LRC during exercise and the lack of uniformity among these techniques, makes quantitative comparisons between the results from different studies a formidable task. Furthermore, the criteria used in the definition of LRC during exercise also are quite varied. Commonly used criteria include the presence of integer or half-integer ($\pm$ 0.05) f_{ped}/f_b ratios [KAY *ET AL*, 1975; KOHL *ET AL*, 1981; GARLANDO *ET AL*, 1985] and/or the presence of phase-coupling between inspiration (and/or expiration) and limb position [KOHL *ET AL*, 1981; BERNASCONI AND KOHL, 1993], cross-correlation between breathing period and limb rhythm periods [BECHBACHE AND DUFFIN, 1977; JASINSKAS *ET AL*, 1980; PAINTER AND YONGE, 1984], as well as Fourier analysis

of limb frequency and the ventilation frequency signals [PATERSON *ET AL*, 1986]. Most, if not all of the above study protocols were designed to quantitatively study LRC *per se* and the results indicate that LRC in some form does exist during bicycle exercise in humans. Subjects in all the above studies were either instructed to adopt a constant pedal frequency, or the pedalling rhythm was reinforced with a metronome and/or visual digital speedometer feedback.

Using cross-correlation analysis on the pedalling and breathing frequencies, BECHBACHE AND DUFFIN [1977] showed that significant LRC could be detected in a majority of subjects during a 3 min period of constant work-rate exercise at 60%$\dot{V}O_{2,max}$. Using similar techniques, JASINSKAS *ET AL* [1980] further showed that statistically significant LRC was present during periods (3 min) of constant-work rate exercise (at ~40% and > 70% $\dot{V}O_{2,max}$) and the degree of LRC was not affected by either the imposed work rate or whether the "maintained" pedal rate was reinforced with the help of a metronome or a digital speedometer display. However, it has been suggested that both the cross-correlation technique and the subsequent Fourier analysis may be invalid in the reliable assessment of LRC, as the former does not recognize breath-by-breath phase-coupling and the latter may record spurious LRC due to the duplication of breath counts at displacements equal to the pedal period [YONGE, 1982; PATERSON *ET AL*, 1986]. It has therefore been suggested that the techniques employed in the reliable detection of LRC require a method of analysis which involves phase relationships between breath and pedal signals on a breath-by-breath basis [YONGE, 1982; PAINTER AND YONGE, 1984], as employed in this study.

Using defined (n = 20 [KOHL *ET AL*, 1981], n > 150 [BERNASCONI AND KOHL, 1993]) or arbitrary [GARLANDO *ET AL*, 1985] breath ranges, previous studies have shown that LRC during bicycle exercise occurs significantly both across subjects [BECHBACHE AND DUFFIN 1977; JASINSKAS *ET AL*, 1980; KOHL *ET AL*, 1981] and across a range of breaths [GARLANDO *ET AL*, 1985; PATERSON *ET AL*, 1986]. These studies have used either integer f_{ped}/f_b ratios

and/or inspiratory/expiratory phase-coupling to quantify LRC during exercise. However, the χ^2 analysis used in these studies to identify either the number of breaths [KOHL *ET AL*, 1981 GARLANDO *ET AL*, 1985], or the number of subjects [KOHL *ET AL*, 1981], as a proportion of the total number (%), demands that the proportion of random and chance occurrences be specified before the test. It has been argued that 20% of such significant occurrences can be ascribed to random chance alone [PATERSON *ET AL*, 1986]. Using Fourier analysis to assess pedal:ventilation frequency ratios from all breaths and subsequent statistical comparisons to all possible random events, PATERSON *ET AL* [1986] have shown that during bicycle exercise with a constant "preferred" pedalling rate, LRC in the form of integer f_{ped}/f_b ratios occurs approximately 25% of the exercise time on average (13% - 62%, range). This study also showed that the range of pedal:ventilation ratios (1:2, 1:3, 2:3, 2:5, 1:4) observed occurred in a non-systematic fashion.

While the basic technique of assessment of LRC used in this study is similar in some aspects to the ones from previous studies [KOHL *ET AL*, 1981; BERNASCONI AND KOHL, 1993], the methods used to explore whether significant LRC occurred during bicycle exercise in humans are slightly different. For example, $f_{ped}:f_b$ ratios and inspiratory/expiratory pedal angle data from all breaths (not specific breath ranges) during exercise, were used and it was tested whether the distribution of these data (histograms) were significantly different from that of a random one (uniform). In the case of $f_{ped}:f_b$ ratios, the statistical testing (Kolmogorov-Smirnoff test) demonstrated whether these ratios were significantly distributed in a non-random fashion in the integer/half-integer ($\pm$ 0.25) interval (figure 6.2). The exact range of $f_{ped}:f_b$ ratios during exercise was further examined individually in each subject (figure 6.4). To assess significant inspiratory/expiratory phase-coupling, it was tested whether the pedal angles from all breaths during exercise are distributed in a non-random fashion in the 0° - 360° interval (bin size = 30°). While it is conceivable that these

criteria are not as stringent as those used in previous studies, significant LRC, even as defined by the above conditions, occurs only infrequently in some subjects in an intermittent manner (Table 6.3).

6.5.2. Effect of pedaling frequency on the ventilatory and metabolic responses during exercise.

This study examined the effects of pedalling frequency on the ventilatory response to maximal incremental exercise. It has long been suggested that the metabolic and ventilatory responses to exercise may be significantly influenced by limb movements [GUELI AND SHEPHERD, 1976; HAGBERG *ET AL*, 1981; MCMURRAY AND AHLBORN, 1982; GARLANDO *ET AL*, 1985; MCMURRAY AND SMITH, 1985; TAKANO, 1988; CARETTI *ET AL*, 1992; HAGAN *ET AL*, 1992], and that neurogenic (in addition to humoral) mechanisms may play a significant role in the control of exercise ventilation [AGOSTONI AND D'ANGELO, 1976; ISCOE AND POLOSA, 1976; DIMARCO *ET AL*, 1983; WHIPP, 1983]. These conclusions have mainly been as a result of studies showing that breathing frequency is significantly influenced by exercise rhythm, independent of metabolic rates [MCMURRAY AND AHLBORN, 1982; MCMURRAY AND SMITH, 1985; TAKANO, 1988; LORING *ET AL*, 1990]. Furthermore, it has been shown that at the same metabolic rate, ventilation and breathing frequency are higher during exercise using increased limb movements, either with a higher pedalling rate [TAKANO, 1988], or with running as compared to walking [MCMURRAY AND AHLBORN, 1982; MCMURRAY AND SMITH, 1985]. However, it is not clear how exercise rhythm may have influenced breathing rhythm and therefore the pattern of ventilation, as these studies importantly did not show any evidence of LRC during exercise.

The results of this study reveal that the $\dot{V}_I$, $\dot{V}O_2$ and $\dot{V}CO_2$ responses at work rates at the start of exercise ($\leq$ 100 w) in the HIGH test, were significantly higher than those in MEDIUM and LOW tests (Figures 6.5 & 6.6). However, pedalling rates had no effect on the temporal courses of any of the above variables at higher work rates, as

exercise progressed. As stated in the RESULTS section, the increased $\dot{V}O_2$ and $\dot{V}CO_2$ responses at the lower work rates in the HIGH test was not due to any discrepancies in the external work load applied by the ergometer, but possibly due to an increase in internal aerobic demands. It has been suggested that at the same work load, increases in pedalling forces, joint moments and muscle stresses imposed by the higher rates of pedalling, may actually result in an increase in muscle energy expenditure and therefore a decrease in efficiency, caused by an increase in internal viscous friction [GASSER AND BROOKS, 1975], and due a greater recruitment of fast-twitch fibres [GASSER AND BROOKS, 1975; CITTERIO AND AGOSTONI, 1984] or slow twitch fibres [SUZUKI, 1979]. This increase in internal muscle work with increasing pedalling rates has also been shown to assume a significant proportion of external work at lower power outputs [KANEKO *ET AL*, 1979]. It is therefore possible that the increased $\dot{V}O_2$ and $\dot{V}CO_2$ at the lower work rates in the HIGH test in this study, was due to an increase in internal work due to the increase in pedalling rates. However, the increased pedalling rates had no effect on the heart rate response at any work load in all the three tests in this study (figure 6.5).

The present results also show that the $\dot{V}I$ response at the lower work rates was significantly higher with the higher pedalling rates in the HIGH test. These results are similar to those of another study [TAKANO *ET AL*, 1988], which showed that the $\dot{V}I$ response at matched submaximal metabolic rates, was significantly higher at 60 rpm than that at 30 rpm. It was also shown that the increased $\dot{V}I$ with pedalling at 60 rpm was also accompanied by a fall in end-tidal PCO_2 and the authors [TAKANO *ET AL*, 1988] concluded that the increased $\dot{V}I$ response at the higher pedalling rates represented the result of an added neurogenic respiratory stimulus (central/peripheral) possibly related to increased limb movements. Similar results from other studies [MCMURRAY AND AHLBORN, 1982; MCMURRAY AND SMITH, 1985;] which showed an increased $\dot{V}I$ response to increased limb frequencies (running *vs* walking)

and a fall in P_{CO_2} also lend support to idea that $\dot{V}_I$ response to exercise may be influenced significantly by neurogenic mechanisms. However, the lack of any significant effect of pedalling frequencies on $P_{\bar{A},CO_2}$ during exercise in our study (figure 6.5) and the identical time courses of $\dot{V}_I/\dot{V}O_2$ and $\dot{V}_I/\dot{V}CO_2$ in all the three tests suggest that the increase in $\dot{V}_I$ at the lower work rates in the HIGH test, reflects a response to the increase in the metabolic demand with the higher rates of pedalling at these work rates and not to an increase in limb-activity based neurogenic mechanisms. A recent abstract [HUNTER *ET AL*, 1997] also confirms that during moderate and heavy exercise, the increase in $\dot{V}_I$ with the increase in pedalling rates, correlated significantly with humoral factors such as $[K^+]_a$ and lactate, both of which were significantly greater at the higher rates of pedalling.

The observation that trained cyclists prefer a higher pedalling rate than untrained or naive subjects, has led to a number of studies in the area of preferred/economical cadences and the effect of limb rhythm on the ventilatory and metabolic responses during ergometer exercise [GUELI AND SHEPHERD, 1976; MCKAY AND BANISTER, 1976; SEABURY *ET AL*, 1977; HAGBERG *ET AL*, 1981; COAST AND WELCH, 1985; COAST *ET AL*, 1986; HAGAN *ET AL*, 1992; MARSH AND MARTIN, 1997]. In 10 healthy young men performing submaximal exercise (at 60%$\dot{V}O_{2,max}$) using 5 different pedalling rates, GUELI AND SHEPHERD [1976] showed that while minute ventilation and breathing frequency were noticeably related to pedalling rates, $\dot{V}O_2$, heart-rate and $\dot{V}_I/\dot{V}O_2$ were significantly influenced by the rate of pedalling. Specifically, this study showed that pedalling at 60 rpm resulted in the lowest $\dot{V}O_2$ and fc values, than when the pedalling rates were lower (50 rpm) or higher (70, 85 and 100 rpm). In another study of elite cyclists performing bicycle exercise (5 min bouts) at 80%$\dot{V}O_{2,max}$, a pedalling rate of 80 rpm was shown to be energetically more efficient as it was associated with a significantly lower heart rate, lower ratings of perceived exertion and most importantly of all, significantly lower blood lactate levels [HAGBERG *ET AL*, 1981]. These

data have also been confirmed to be true during prolonged heavy exercise [COAST *ET AL*, 1986; HAGAN *ET AL*, 1992]. It has also been shown that the optimal "economical" pedal rate increases linearly with increases in power outputs in trained cyclists performing progressive exercise using different cadences [SEABURY *ET AL*, 1977; COAST AND WELCH, 1985]. A more recent study [MARSH AND MARTIN, 1997] has shown that the aerobic demand increases as cycling cadence increases, in both trained (cyclists and non-cyclists) and untrained subjects. This study also showed that cycling experience had no effect on preferred cadence levels and that the latter was more significantly related to the level of training. In all cases, this study showed that the most economical cadence was always lower than that of the preferred cadence and that in untrained subjects, preferred cadence had a tendency to drop as power output increased. The authors interpreted these results as suggesting that while in trained subjects, aerobic demands may not play a major role in the selection of preferred pedalling rates, it was an important factor in cadence selection, in untrained subjects.

In the present study, a progressive decline in preferred pedalling rates with increases in work load was shown to occur in subjects who were healthy but not elite cyclists. These results are similar to those from the untrained subjects in the previous study [MARSH AND MARTIN, 1997] and suggest that increasing metabolic demand is an important determinant of the pedalling frequency that the subjects preferred and were able to sustain till end of exercise. However, the increase in $\dot{V}O_2$ and $\dot{V}CO_2$ at the lower work rates in the HIGH test in the present study suggests, that metabolic demands do not play a major role in preferred cadence selection (in the 70 - 90 rpm range) at these power outputs in these subjects. Furthermore, this study also showed that pedalling rates have no significant effect on the time course of metabolic and ventilatory variables during or at the end of incremental exercise (Table 6.1) and these results are different from previous studies [GUELI AND SHEPHERD, 1976; MCKAY AND BANISTER, 1976; SEABURY *ET AL*, 1977; HAGBERG *ET AL*, 1981; COAST AND WELCH, 1985; COAST *ET*

AL, 1986; HAGAN *ET AL*, 1992; MARSH AND MARTIN, 1997] that suggest that there exists a relationship between pedalling rates and the metabolic needs of the exercising individual. Furthermore, the lack of any difference in $\dot{V}O_2$, $\dot{V}CO_2$ at the higher work rates among the 3 tests and the identical $\dot{V}I/\dot{V}O_2$, $\dot{V}I/\dot{V}CO_2$ and fc responses throughout exercise in all tests in this study, suggests that the ventilatory response to incremental exercise is significantly determined by aerobic demands and is not influenced by pedalling frequency.

6.5.2. Effect of pedaling frequency on breathing pattern during exercise.

Perhaps the most significant finding of this study is that at matched ventilatory levels during incremental exercise, neither pedalling frequencies nor LRC have any effect on the pattern of breathing (Figure 6.7). The maximal ventilation in a subject during exercise is determined by the ability to generate maximal inspiratory/expiratory flows which are ultimately limited by the maximal flow-volume relationships in the respiratory system [OGILVIE *ET AL*, 1955; OLAFSSON AND HYATT, 1969; JENSEN *ET AL*, 1980]. Furthermore, the choice of breathing pattern at any ventilatory level is determined by the mechanical constraints in the respiratory system. VT can theoretically equal VC (vital capacity) at least at low $\dot{V}I$ levels. However, as $\dot{V}I$ increases (and therefore mean inspiratory and expiratory flows increase) the maximum possible VT falls [BERNSTEIN *ET AL*, 1952; JENSEN *ET AL*, 1980; MCPARLAND *ET AL*, 1991]. This is because breathing with a sufficiently high VT must involve lung volumes associated with lower maximal inspiratory and expiratory flows, than does breathing with a small VT [MCPARLAND *ET AL*, 1991]. It has also been shown that at any given lung volume, there exists a unique VT - f_b combination ("breathing pattern") that can be employed to generate the appropriate maximal $\dot{V}I$ that is energetically efficient as well as that is necessary for the metabolic and gas exchange requirements [YAMASHIRO AND GRODINS, 1973]. Exercise breathing pattern in humans has been shown to be further dependent on the mode and intensity of exercise [SYABBALO *ET AL*,

1994] and on added stimuli (e.g. added dead space [McParland *et al*, 1991]). Furthermore, it has long been suggested that f_b during exercise may be influenced by frequency of limb movements [Agostoni and D'Angelo, 1976; Iscoe and Polosa, 1976; DiMarco *et al*, 1983; Loring *et al*, 1990], but the question of whether LRC influences breathing pattern during bicycle exercise, has however not been resolved.

In many exercise studies that did not explicitly look for LRC, breathing pattern has been shown to be influenced by limb rhythm, independent of metabolic rate. For example, the study of McMurray and Ahlborn [1982] revealed that breathing frequency and ventilation at a given metabolic rate were greater during running than walking. The authors suggested that breathing pattern was linked to limb-based neural mechanisms. However, both the increase in f_b and the fall in V_T with running in their study could represent an optimization of breathing pattern due to changes in operating lung volume, which has been shown to be reduced more with running compared with cycling or walking [Henke *et al*, 1988]. Furthermore it was not clear from the above study [McMurray and Ahlborn, 1982], whether the change in ventilation and breathing pattern with running was influenced by LRC, as they did not present any evidence for the latter. A similar study [McMurray and Smith, 1985] also showed that at a constant metabolic rate and at similar ventilatory levels, V_T fell and f_b increased significantly as stride frequency increased (walk $\rightarrow$ slow run $\rightarrow$ fast run), suggesting that limb frequency significantly influenced exercise breathing pattern. However, this study also did not provide any information on the presence or absence of LRC in their subjects as it was not assessed.

More recently, Loring *et al* [1990] have observed significant increases in f_b with increased limb movements in humans during treadmill exercise. While changes in minute ventilation could explain the increases in f_b in their study, it is unlikely because both the magnitude of increase in f_b and the estimated metabolic rate remained constant as limb frequency increased. These authors further showed that only half

their subjects demonstrated significant LRC (measured as breath to step ratios) and that predominantly at the higher metabolic rate. In their study, breathing frequency was shown to be influenced by both stepping frequency and metabolic responses in the presence of significant LRC. However, these authors also showed that some subjects showed a marked influence of stepping frequency on breathing frequency, in the complete absence of LRC. These authors concluded that a "loose but definite coupling exists" between limb and breathing frequencies and that limb frequency does influence breathing pattern significantly even in absence of such coupling (LRC).

While the above studies reveal a possible influence of limb frequency on breathing pattern during treadmill exercise, they do not provide any information on the effect of LRC or limb frequency on breathing pattern during bicycle exercise. In a study involving both bicycle and treadmill submaximal exercise, KAY *ET AL* [1975] showed that significant LRC did not occur and that frequency of limb movement had no effect on breathing pattern or respiratory timing variables. During cycle exercise at 50% $\dot{V}O_{2,max}$ at 3 pedalling ranges, CARETTI *ET AL* [1992] have show that LRC does not occur and that pedalling frequency had no effect on breathing pattern or respiratory timing variables. However, these authors showed that increasing stride frequencies on a treadmill had a significant effect on all the ventilatory and breathing pattern variables. However, the increases in metabolic rates that occurred with the increases in stride frequency, makes the assessment of the specific role of limb frequency on these changes, quite difficult. During incremental bicycle work below the anaerobic threshold, it has been shown that at matched levels of $\dot{V}CO_2$, both minute ventilation and f_b were found to be greater at 60 rpm than at 30 rpm [TAKANO, 1988]. These authors also showed the effects of pedalling frequency on f_b were predominantly due to changes in T_E and not in T_I.

The results of this study suggest however, that at matched moderate and high power outputs during maximal incremental exercise, pedalling rates have no effect

$\dot{V}_I$, V_T and f_b (figure 6.5). The increase in frequency during (Table 6.3) and throughout (figure 5) exercise was achieved by progressively decreasing T_I and T_E both of which were unaffected by changes in pedalling frequency. Furthermore, table 6.4 and figure 6.7 reveal that on average, breathing pattern and respiratory timing variables at matched ventilatory levels are not significantly influenced by pedalling frequency, or by LRC.

It is conceivable however, that LRC may have had some influence on the breathing pattern of individual subjects. For example, subject #2 demonstrated significant LRC in all tests and the changes in his V_T ($\downarrow$) and f_b ($\uparrow$) with increasing pedalling frequency, suggest that LRC may have had a significant influence on his breathing pattern, at least at $\dot{V}_I$ levels below 100 $L \cdot min^{-1}$. However, neither pedalling rates nor LRC had any effect on the breathing pattern of Subject #1, who demonstrated significant LRC throughout exercise (Figures 6.2 and 6.3). Figure 6.7 also showed that except for Subject #2, neither LRC nor the pedalling frequency had any major effect on the pattern of breathing at matched ventilatory levels in any other subject or the group as a whole ("Average", Figure 6.7).

In conclusion, the results of the present study show that in normal healthy humans performing maximal incremental exercise to exhaustion on a bicycle ergometer, spontaneously chosen pedalling frequencies have no significant effect on ventilatory and metabolic variables, both during and at end exercise. In addition, this study shows that locomotor-respiratory coupling (LRC) occurs intermittently and infrequently in normal humans performing cycle ergometer exercise, while pedalling freely within a given range. Furthermore, the results of the study reveal that at matched ventilatory levels during exercise, neither pedalling frequency nor LRC have any effect on breathing pattern. The changes in minute ventilation (and its pattern) and the other variables during incremental exercise seem therefore determined by metabolic and gas exchange requirements and not influenced significantly by either

limb-movement based neurogenic influences or the presence (or absence) of locomotor respiratory coupling.

7. GENERAL PERSPECTIVE.

The phenomenon of whole-body muscular exercise is exceptional in its demands on the ventilatory controller, as the nature of these demands are not only multifaceted but also ever changing depending on the type, duration and the intensity of exercise. The ventilatory response even to short-term heavy exercise, needs to be appropriate to the need for CO_2 elimination by the lungs which is primarily based on the rate of CO_2 production in the exercising muscles. Additionally, as the CO_2 load on the lungs increases dramatically during heavy exercise due to the additional load imposed by metabolic acid buffering (which also increases circulating $[H^+]$), ventilation needs to increase further to compensate for these metabolic processes. Furthermore, the precise and significant increase in ventilation to match increasing gas exchange requirements and acid-base homoeostasis of heavy exercise has to be achieved on the face of dramatic increases in the work done by the respiratory muscles on the respiratory pump (chest wall, lungs and the airways). The controller therefore needs both feed-back and feed-forward information dynamically throughout exercise, that enables it to achieve all of the above requirements appropriately. It also needs to take into account that the ultimate ventilatory output is based critically on the structural limits on the healthy respiratory pump to increase its volume (and gas flow rates) which are further based on the functional efficiency of working respiratory muscles, which are potentially fatiguable.

Figure 7.1. [DEMPSEY *ET AL*, 1995] summarizes the possible role of the various components of the ventilatory control system that appear to be involved in the regulation of ventilation (and its pattern) during exercise. In this chapter, the

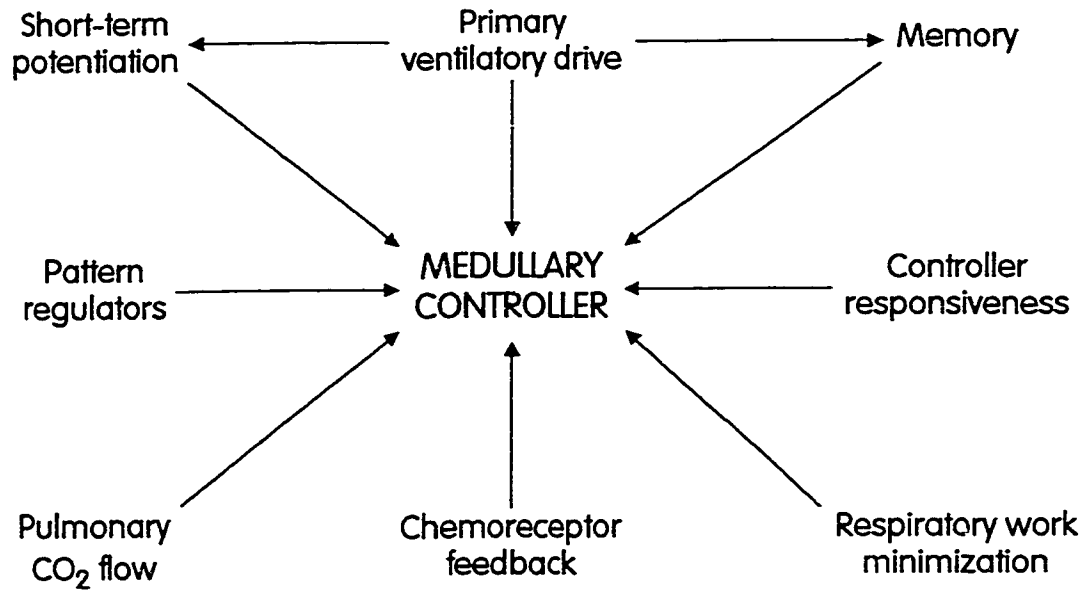

Figure 7.1. A synthesis of various possible component control systems responses involved in exercise ventilatory regulation. [DEMPSEY *ET AL*, 1995].

results and conclusions of the various studies described in this thesis that provide further insight into the role of some of these components will be briefly discussed from the perspective of their overall relevance in exercise ventilatory control.

As reviewed in chapter 1 of this thesis (overview) and as figure 7.1. shows, exercise ventilatory control is as a result of the integrated response of the medullary controller to a variety of stimuli rather than one "primary" stimulus. Studies that focused on the neural regulation of exercise ventilation however, have recognized early on that the rapidity of the ventilatory and circulatory responses at the onset of exercise, could not be accounted for any known humoral mechanisms [KROGH AND LINDHARD, 1913]. Furthermore, the demonstration by electrical/chemical stimulation in decorticate animals that locomotion and respiration were linked [DIMARCO *ET AL*, 1983; ELDRIDGE *ET AL*, 1985] and that the ventilatory response was proportional to degree of locomotion, whether it was spontaneous or fictive, in both paralyzed and non-paralyzed animals [ELDRIDGE *ET AL*, 1985], suggested that the ventilatory response was consistent with a "central command" rather than due to feedback regulation. While

these studies demonstrated a strong "feed-forward" primary cortical stimulus to breathe that arises in parallel to locomotory stimuli, it is not possible to conclude that other mechanisms are any less important, given that the increase in metabolic rates in these decorticate animal preparations were minimal. However, the increased ventilation and heart rate at matched metabolic rates (or exercise intensities) that have been shown to occur in partially curarized exercising humans, suggest that there was an increased drive ("central command") to breathe that was associated with the increased drive to the weakened muscles [ASMÜSSEN *ET AL*, 1965; GOODWIN *ET AL*, 1972; GALBO *ET AL*, 1987]. The lack of difference between the ventilatory response during spontaneous exercise and that during electrically induced exercise suggests however, that central command may be insignificant or absent in humans during exercise [ASMÜSSEN *ET AL*, 1943; ADAMS *ET AL*, 1984; BRICE *ET AL*, 1988]. The lack of any increase in $\dot{V}_E$ in response to a significant reduction in respiratory impedance during heavy exercise (chapter 3) also suggests that while central command may be important, it is not the sole determinant of exercise hyperpnea or the motor output to the respiratory muscles.

The studies described in this thesis, however, do not add any information to the possible role of other cortical phenomena ("short-term potentiation" and "memory") outlined in figure 7.1. The phenomenon of short-term potentiation or "respiratory after-discharge" occurs when respiratory motor activity has been shown to increase gradually after an initial increase in response to the primary stimulus (neural or humoral) and decreases gradually after the stimulus is removed [ELDRIDGE *ET AL*, 1974; VIS AND FOLGERING, 1981; MILLHORN *ET AL*, 1982]. It is currently accepted that the primary drive to breathe (neural or humoural) that mediates ϕ_1 hyperpnea (chapter 1) also activates short-term potentiation that may then contribute significantly in the mediation of ϕ_2 hyperpnea. It has also been suggested that exercise ventilatory control may be influenced by memory processes, i.e., based on previous experiences

(effective and successful patterns of ventilation), the process of learning ("adaptive feed-forward control") may further influence the ventilatory (and breathing pattern) response to a given form (or intensity) of exercise [SOMJEN, 1992, DEMPSEY *ET AL*, 1995]. The ventilatory response during exercise has also been shown to be influenced by the degree of responsiveness of the medullary controller (figure 7.1.) Reviews of numerous studies that have examined the effects of chronic changes in $[H^+]$ [JONES *ET AL*, 1977; OREN *ET AL*, 1981; 1982], chronic hypoxia [BISGARD AND NEUBAUER, 1995] and/or neuro-chemical modulators [DEMPSEY *ET AL*, 1986; TATSUMI *ET AL*, 1995] suggest that these may influence the ultimate gain or the responsiveness of the medullary controller to the primary exercise hyperpneic drive. The studies described in this thesis, however, do not provide any additional information in this area.

It is believed that spinal, lung, chest wall, respiratory muscle, limb muscle and thermal afferents are important determinants of ventilation and breathing pattern during exercise and may also be involved in the optimization/minimization of the work done by the respiratory muscles. In healthy humans, it has also been suggested that, given the intensity of exercise, the ultimate ventilatory and breathing pattern responses are directed so as to maximize gas exchange and minimize respiratory muscle work within the mechanical constraints in the respiratory pump. The results of the study described in chapter 2 of this thesis suggest that the ventilatory increase throughout constant work-rate heavy exercise (CWHE) was achieved by a significant increase in both inspiratory and expiratory muscle pressures. This study also showed that this $\dot{V}E$ increase during CWHE was associated with a relatively greater increase in expiratory than inspiratory muscle pressures, despite the absence of significant expiratory flow-limitation in these subjects. These results are similar to many previous studies that have documented progressively increasing inspiratory and expiratory muscle activity with increasing exercise *(see section 2.5.2).* Several studies have also shown that with increasing

exercise intensities, inspiratory pressures tend to plateau, while expiratory pressure continue to increase. Furthermore, it has been also shown that while diaphragmatic pressures plateau, "accessory-inspiratory" muscle activity contributes significantly to the hyperventilatory response of heavy exercise. However, the measurement of pressure generated by these muscles alone does not provide any information on the pattern of respiratory muscle recruitment during heavy exercise, as changes in muscle length and the velocities of contractions are not accounted for. For example, a recent report [ALIVERTI *ET AL*, 1997] suggests that the diaphragm during exercise functions predominantly as a "flow generator" rather than as a pressure generator. This conclusion was based on the evidence that with increasing exercise intensity, there was only a modest increase in trans-diaphragmatic pressure while diaphragmatic velocity of shortening increased significantly. This study also demonstrated that abdominal (expiratory) muscle activity was present even with light exercise ("unloaded cycling") and increased significantly with increasing exercise intensity. It was also evident from the abdominal pressure-volume loops, that abdominal pressure persisted throughout inspiration, and this persistent and gradually decaying abdominal muscle activity during inspiration was interpreted to minimize diaphragmatic pressure, and to reduce the expiratory action of the abdominal muscles on the lower rib-cage, thus minimizing rib-cage distortion. However, no such post-expiratory expiratory pressures were documented at the high levels of ventilation (>80 $L \cdot min^{-1}$) during heavy exercise in the present study reported in this thesis.

It was also shown (chapter 2) that inspiratory muscle activity persists during the initial part of expiration (Post-inspiratory Inspiratory activity, PIIA) in humans performing heavy exercise. PIIA, documented in both animals and humans, is a phenomenon by which decaying inspiratory muscle activity aids in the "braking" of passive expiration under resting condition. PIIA however, has been shown to vary

depending on the nature of ventilatory stimulation and between studies *(see section 2.5.4)*. PIIA in the present study was also shown to diminish progressively with the increasing $\dot{V}_E$ levels of CWHE, suggesting that this, combined with the significant increase in expiratory muscle pressures, served to augment expiratory flow throughout CWHE.

The results of the present studies further show that with the increasing $\dot{V}_E$ levels of CWHE, there was a proportional and significant increase on the dynamic load (P_{musl}/P_{capl} (%)) on all the inspiratory muscles. As figure 2.4. and table 2.4. both confirm, peak P_{musl}/P_{capl} (%) values during CWHE were well over 50%, suggesting that inspiratory muscles were operating at well over half their dynamic capacity to generate effective pressure throughout heavy exercise. Additionally, mean P_{musl}/P_{capl} (%), the tension · time index of all the inspiratory muscles [BELLEMARE AND GRASSINO, 1982; ZOCCHI *ET AL*, 1993], was over 15% at $\dot{V}_E$ levels over 50 L · min^{-1}, suggesting that the inspiratory muscles were possibly performing at the limit of their endurance through most of CWHE. While this finding does not provide direct evidence of fatiguing contractions of the inspiratory muscles, and while it is unlikely that there is an invariant index above which inspiratory muscle fatigue always occurs, it is very clear that the ventilatory load on the inspiratory muscles is very high during heavy exercise. These findings receive further support from the evidence that respiratory muscle blood flow in both animals and humans, increases significantly with increasing levels of $\dot{V}_E$, and can account for a significant proportion (10% - 15%) of cardiac output [MANOHAR, 1986; 1990; HARMS *ET AL*, 1998]. The evidence that the pressure generating capacity of the diaphragm was significantly compromised after intense exercise in healthy humans [JOHNSON *ET AL*, 1993; MADOR *ET AL*, 1993], also provides support to the notion that the load on the respiratory muscles increases significantly with increasing $\dot{V}_E$ levels during heavy exercise. While both the increase in expiratory muscle pressures and the diminishing PIIA served to increase expiratory

flow during CWHE, increasing expiratory pressures also served to possibly determine optimal end expiratory lung volume (therefore the initial length of the inspiratory muscles). This may aid the diaphragm and the other inspiratory muscles to operate on a more efficient range of their length-tension relationships as well as allow for a greater tidal volume in the linear pressure-volume range of the respiratory system [GRIMBY *ET AL*, 1976; LEVINE *ET AL*, 1988]. As shown in the present study, the expiratory muscles took on a greater proportion of Total P_{mus} as CWHE progressed, thus "sparing" the inspiratory muscles of some work. This also serves to optimize operating lung volumes and thus breathing pattern, all of which is directed towards an possible improvement in inspiratory muscle efficiency.

The most important finding from the study described in chapter 2 of this thesis is that, a linear relationship exists between the ventilatory requirements ($\dot{V}_E$) and the net respiratory muscle output (Total P_{mus}) of the individual during heavy exercise. This suggests that with the increasing $\dot{V}_E$ levels of heavy exercise, there is not only an efficient partitioning of work between inspiratory and expiratory muscle groups, but also the net pressure (or respiratory muscle work) generated in each breathing cycle is precisely tuned to the ventilatory need throughout CWHE. These data are supported by findings in both animals [AINSWORTH *ET AL*, 1989; 1996] and in humans [ALIVERTI *ET AL*, 1997], that respiratory muscle activity during exercise increases proportionally with the increase in $\dot{V}_E$ during exercise. The linear relationship between P_{mus} and $\dot{V}_E$ through a wide range of $\dot{V}_E$ also suggests that respiratory system "impedance" ($P_{mus}/\dot{V}_E$, the slope of the relationship) in healthy humans is unchanging and well regulated during heavy endurance exercise. All the above data clearly suggest that respiratory muscle output and efficiency are significant determinants of the ventilatory and breathing pattern responses to heavy exercise.

While the above results suggest that the load on the respiratory muscles may possibly constrain the ventilatory response to exercise, the results of the study

described in chapter 3 on the other hand, suggest otherwise. It was shown in chapter 3 that in healthy humans, significant reduction in respiratory muscle work (by unloading) had no effect on $\dot{V}_E$, breathing pattern, gas exchange or exercise endurance while respiratory muscle pressures were significantly reduced. This suggests that, in response to a reduction in respiratory impedance, the medullary controller regulates $\dot{V}_E$, while reducing respiratory muscle energy needs (with a reduction in pressure). The lack of increase in $\dot{V}_E$ however does not provide for greater compensation of the metabolic acidosis that occurs at these exercise intensities. While both this study and the previous study (chapter 2) revealed respiratory muscle work increased significantly with increase in $\dot{V}_E$ during CWHE, there was no improvement in exercise tolerance when respiratory muscles were unloaded. While it is not clear whether respiratory muscle fatigue was occurring during heavy exercise, respiratory muscle function does not appear to limit endurance exercise performance in normal humans [MARCINIUK *ET AL*, 1994].

However, recent studies in elite cyclists suggest that respiratory muscle work at maximal exercise is a significant determinant of limb muscle blood flow. An increase in respiratory load results in a reduction in leg blood flow, while unloading increases it [HARMS *ET AL*, 1997]. It has long been speculated that the increased blood flow to the respiratory muscles is as a result of a "steal" (re-distribution) from the working limb muscles and this may contribute to earlier fatigue in the working limb muscles. It has been shown recently that in elite cyclists performing maximal exercise, while respiratory muscle unloading resulted in a significant reduction in $\dot{V}o_2$ (due to a reduction in cardiac output (CO) and stroke volume), there was a relative increase in blood flow to the legs (from 77% to 85% of CO). This suggests that the reduction in respiratory muscle work resulted in a redistribution of total CO between the muscles of the legs and the respiratory system [HARMS *ET AL*, 1998]. This study has also shown that at maximal exercise in highly fit subjects, the respiratory muscles

receive ~15% of total CO (without respiratory muscle unloading). Recent data from this group of researchers also suggests that increased leg blood flow consequent to respiratory muscle unloading results in an increase in both power output at maximal exercise and also exercise endurance time [HARMS *ET AL*, 1998; WETTER *ET AL*, 1998]. At least in highly fit humans performing maximal exercise, the load on the respiratory muscles and therefore respiratory muscle work, may be a significant determinant of limb muscle endurance. All the above data also suggest that at any exercise level, the ultimate ventilatory output of the exercise is influenced significantly by mechanisms that operate to meet gas-exchange and acid-base homoeostatic requirements while optimizing work of breathing and improving respiratory muscle efficiency.

The lack of effect of respiratory muscle unloading by applied pressure assist on ventilation and breathing pattern responses during heavy exercise is in contrast to the significant hyperventilatory response that results when one breathes a HeO_2 mixture during exercise (Chapter 4). Due to its lower density (than air), HeO_2 significantly reduces airflow turbulence and the degree of reduction in respiratory impedance with HeO_2 therefore depends on the degree of reduction in airflow turbulence. Virtually every study has documented a significant increase in $\dot{V}_E$ with HeO_2 and this hyperventilatory response to HeO_2 breathing had led to the suggestion that the native respiratory impedance is a significant determinant of the exercise ventilatory response [HUSSAIN *ET AL*, 1985]. However, GALLAGHER AND YOUNES [1989] have argued that since the degree of respiratory muscle unloading achieved with HeO_2 breathing was trivial compared to that with mouth pressure assist, the increase in $\dot{V}_E$ with HeO_2 was not consequent to respiratory muscle unloading *per se*. Furthermore, the immediate fall in diaphragmatic EMG (EMG_{DI}) that occurs within the first 3-4 breaths of HeO_2 (a possible compensatory change in neural drive to the diaphragm due to unloading), does not persist; EMG_{DI} values return to control (air breathing)

values with prolonged HeO_2 breathing in both animals and humans [HUSSAIN *ET AL*, 1985; FORSTER *ET AL*, 1994]. This has led to the suggestion that factors other the reduction of load affect neural drive during HeO_2 breathing [GALLAGHER AND YOUNES, 1989]. The persistence of these effects even on switching to room-air breathing suggests that HeO_2 breathing may have a secondary "stimulating" effect on the neural drive that may sustain the hypocapnic hyperpnea.

As discussed in chapter 4 of this thesis, it has been shown that the respiratory responses to HeO_2 breathing are immediate and occur within the first few breaths. Several studies that have examined the breath-by-breath effects in both humans and animals show that both the hyperventilation ($\dot{V}E$, PCO_2) and the fall in rate of rise of diaphragmatic EMG were apparent within the first few breaths of HeO_2 [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985; MAILLARD *ET AL*, 1990; FORSTER *ET AL*, 1994]. This has led to the suggestion that the respiratory adaptations to HeO_2 breathing may indicate a reflex effect [WARD *ET AL*, 1982; HUSSAIN *ET AL*, 1985]. The immediate "startle-like" behavioural and ventilatory responses in ponies to a reduction in load with HeO_2 breathing, also indicates that a mechano-receptor based reflex may mediate the immediate response to change in load. Furthermore, as these responses have been shown not to be dependent on either chest wall [PUDDY *ET AL*, 1992] or diaphragmatic/hilar afferents [FORSTER *ET AL*, 1994], it is possible that the hyperventilatory and neuromuscular adaptations to the reduction in resistive load with HeO_2 are mediated by airway reflexes. However, as the results of the study described in chapter 4 of this thesis reveal, airway receptors appear to be involved significantly only in mediating the transient ventilatory responses and not the sustained hyperventilation that is seen when HeO_2 is substituted for room air. The results therefore suggest that the while the initial hyperventilatory response to HeO_2 is partly dependent on airway receptors, activation of these receptors is not necessary for the maintenance of the sustained hyperventilatory response. It is also possible that the transient increase in flow rate

induced by HeO_2 breathing activates other mechanisms that sustain the increased ventilation and are not dependent on airway receptors. These possibilities are in keeping with those of WARD *ET AL* [1982] who had speculated that at least during sub-anaerobic threshold steady-state exercise, the initial alteration of airway flow dynamics induced by HeO_2 breathing may have induced an excitatory influence of ventilation, whose magnitude was effective against any chemoreceptor based feedback that tend to reduce ventilatory drive. The present studies show that this is true even at higher exercise intensities.

By virtue of its effect on turbulent flow, HeO_2 breathing reduces and changes the distribution of flow resistance among different parts of the airways. This is in contrast to the results of studies with flow-proportional mouth pressure assist, in which total pulmonary resistance has been shown to increase slightly (figure 3.12) [GALLAGHER AND YOUNES, 1989]. The hyperventilatory response to HeO_2 breathing may be directly related to its effect on airway mechanics and/or related to the increase in the maximum flow-volume envelope. Recent studies that have examined the ventilatory response to inhaled CO_2 or HeO_2 during exercise in healthy older subjects suggest that the increased slope of the ventilatory response with HeO_2 breathing was due mainly to its effect on the maximal flow-volume envelope [BABB, 1997A; 1997B]. The results of these studies also suggest that at least during maximal exercise in some healthy older subjects, mechanical ventilatory constraints might exist that influence the exercise ventilatory response.

It is not clear why the hypocapnic hyperventilatory response to HeO_2 breathing during steady-state exercise is not corrected by chemoreceptor based feedback mechanisms. While the bulk of the evidence suggests that chemoreceptor based feedback mechanisms are overridden with HeO_2 breathing during exercise, evidence from carotid body denervated animals reveals that the hyperventilatory response to HeO_2 breathing is clearly tempered by chemoreceptor input [PAN *ET AL*,

1987]. It is therefore currently accepted that by error feedback, the carotid bodies essentially operate to "fine-tune" and/or minimize the hyperventilatory influences which would otherwise disrupt arterial blood gases and pH_a.

It has been suggested that the hyperventilatory response to heavy exercise is a consequence of increased carotid chemoreceptor stimulation caused by the lactacidosis ($\uparrow[H^+]$) that occurs at these exercise intensities [DEMPSEY AND RANKIN, 1967; DEJOURS, 1974; WHIPP, 1981]. Other stimuli *viz.* increasing plasma K^+, catecholamines and or hypoxia [$\downarrow P_{O_2}$] have been shown to influence the ventilatory response to exercise both in an independent or synergistic fashion [EULER AND HELLNER, 1952; ASMUSSEN, 1967; CUNNINGHAM *ET AL*, 1968; HAGGENDAL *ET AL*, 1970; WEIL *ET AL*, 1972; HUGHES *ET AL*, 1982; BURGER *ET AL*, 1988; PATERSON *ET AL*, 1990; PATERSON, 1992; BISGARD AND NEUBAUER, 1995; ROE *ET AL*, 1997]. Support for the evidence that the carotid chemoreceptors mediate the hyperventilatory response to heavy exercise is available from studies employing hyperoxia. This has been shown to attenuate both the $\dot{V}_E$ and the lactacidosis response during heavy exercise resulting in an increase in both P_{a,CO_2} and pH_a [ASMUSSEN AND NIELSEN, 1958; CUNNINGHAM *ET AL*, 1986; FITZGERALD AND LAHIRI, 1986]. Furthermore, hyperoxia has been shown to specifically suppress the ventilatory responses to hypercapnia [MILLER *ET AL*, 1974; WARD AND BELLVILLE, 1983], norepinephrine infusion [JOEL AND WHITE, 1968; HEISTAD *ET AL*, 1972], and to K^+ infusion [PATERSON AND NYE, 1991]. It is not known whether hyperoxia *per se* has any influence on the plasma levels of H^+, K^+ and or catecholamines and therefore the specific role of the carotid chemoreceptors in the ventilatory response during hyperoxic exercise remains uncertain.

The normal hyperventilatory response in subjects in whom exercise induced lactacidosis was attenuated either as a result of dietary manipulation [HUGHES *ET AL*, 1982; GREEN *ET AL*, 1983; HAGENHAUSER *ET AL*, 1983] or due to congenital conditions (McArdle's disease) [HAGBERG *ET AL*, 1982; PATERSON *ET AL*, 1990], further brings into

question the exact role of carotid chemoreceptors in the mediation of the ventilatory response to heavy exercise. There is mixed evidence regarding the role of the carotid chemoreceptors in the ventilatory response to experimentally induced acidemia in animals both at rest [BAINTON, 1978; KAEHNY AND JACKSON, 1979; NATTIE, 1983] and during exercise [ERICKSON *ET AL*, 1991]. This suggests that at least the carotid chemoreceptors are not totally responsible for the ventilatory response to exogenously induced acidosis. It is also possible that the rapid changes in cerebral extracellular fluid pH may explain the bulk of the increase in ventilation to experimentally induced acidosis [TEPPEMA *ET AL*, 1983]. Furthermore, the data from carotid body denervated ponies, which are hypercapnic at rest and which show a significant hyperventilatory and an exaggerated hypocapnic response to heavy exercise, suggests that the hypocapnia in normal ponies influences the carotid chemoreceptors more significantly than the previously described stimulants ($[H^+]$, $[K^+]$) [PAN *ET AL*, 1986; FORSTER *ET AL*, 1990]. The augmented hyperventilatory response in the carotid chemoreceptor denervated ponies also indicates that the chemoreceptors may have an inhibitory influence on breathing during heavy exercise. All the above data indicate that while there are many stimuli that are clearly involved in the determination of the magnitude of the peripheral chemoreceptor input to the respiratory controller, the chemoreceptors themselves appear to be able to play both a stimulatory and inhibitory role in fine-tuning the ventilatory response to exercise.

While it has been shown that airway receptors may be involved in the mediation of the transient ventilatory response to an abrupt reduction in respiratory load (chapter 4), the data from the studies described in chapter 5 suggest that they do not play a significant role in determining the ventilatory and breathing pattern response both during exercise and to added external dead space in normal humans. The influence of sensory feedback from the lungs and airways on the regulation of ventilation and breathing pattern has been examined in many studies.

While vagal afferent input has been shown to affect breathing pattern and the patterns of respiratory muscle recruitment, minute ventilation is usually unaffected in vagally denervated exercising animals [FLYNN *ET AL*, 1985; CLIFFORD *ET* AL, 1986; AINSWORTH *ET AL*, 1992]. Vagally mediated, volume feedback from the lungs (Hering-Breuer reflex) is considered to be weak in humans [WIDDICOMBE, 1961], but has been shown to influence breathing pattern at rest in anesthetized humans [POLACHEK *ET AL*, 1980]. Furthermore, the altered breathing pattern at low levels of $\dot{V}_E$ during exercise in post heart-lung transplantation subjects as compared to subjects with heart transplantation alone (i.e., with intact pulmonary innervation) [SCUIRBA *ET AL*, 1988] suggests, that vagal afferent input might influence exercise breathing pattern in humans at least at the lower $\dot{V}_E$ levels.

The addition of an external deadspace has been shown to increase $\dot{V}_E$ both at rest and during exercise [WARD AND WHIPP, 1980] and causes a slower and deeper breathing pattern at matched ventilatory levels during exercise [MACPARLAND *ET AL*, 1991; SYABBALO *ET AL*, 1993]. The absence (or significant reduction) of this breathing pattern in response to inhaled CO_2 alone [GALLAGHER, 1987], has led to the suggestion that it is not the increase in P_{CO_2} *per se* but an alteration of the breath-by-breath temporal P_{CO_2} profile that might be responsible [MCPARLAND *ET AL*, 1991]. However, as shown in chapter 5 and by the studies of SYABBALO *ET AL*, [1993], it appears that neither the airway receptors nor the carotid chemoreceptors are significantly involved in the mediation of this breathing pattern response to added dead space. As discussed in chapter 5, while it is possible that the central chemoreceptors may be involved, the respiratory adaptations to dead space loading during exercise may not be as a result of altered stimulation of any one receptor (airway, peripheral and/or central chemoreceptors) but might be the result of an optimization process to minimize changes in gas exchange and/or the energy cost of breathing [POON, 1987].

As both feed-forward and feed back neural influences have been shown to play a major role in the increase in ventilation in proportion to the intensity of limb movements during exercise, it has frequently been suggested that significant interactions exist between exercise and breathing rhythms in humans. This form of synchronization between limb and breathing frequencies (Locomotor-Respiratory Coupling, LRC) has been demonstrated in humans, animals and birds *(see section 6.1.2.)*. It has been also shown that at comparable exercise intensities, humans exhibit a greater degree of LRC during running than with cycling and it has been suggested that this is due to running being a more natural form of movement in bi-pedal mammals [BRAMBLE, 1983; BRAMBLE AND CARRIER, 1983]. While many studies have examined the phenomenon of LRC in humans and its effect on exercise variables, there have not been many studies that have examined the effect of spontaneously occurring LRC on breathing pattern during cycle ergometry. The studies of LORING *ET AL*, [1990] have shown that breathing frequency increased in relation to limb frequency at a given metabolic rate during treadmill exercise and these authors also showed that breathing frequency was influenced by limb frequency even in the absence of LRC. As discussed earlier *(see section 1.5.5.)*, a number of different locomotory-respiratory interactions have been documented during exercise that may influence the efficiency of either activity. It has been suggested that alveolar ventilation during maximal exercise in thoroughbred horses may be constrained by both LRC and increasing ventilatory work to maintain normocapnia [ART *ET AL*, 1990; 1991; BUTLER *ET AL*, 1993]. While the biomechanical forces resulting from LRC appear to contribute to airflow in variable amounts in both humans and animals, it has been clearly shown that it is increasing respiratory muscle activity that contributes to the majority of airflow that is necessary during exercise [AINSWORTH *ET AL*, 1989A; 1995].

Chapter 6 examined the phenomenon of spontaneous LRC during bicycle ergometry in healthy subjects and showed that while LRC in some form (significant

pedal:breath ratios, inspiratory and/or expiratory phase coupling) is present in some subjects during exercise, it had no effect on the metabolic and ventilatory responses during heavy exercise. It was shown further, that at matched ventilatory levels throughout exercise with subjects pedalling at their own chosen rate within a given range, LRC had no effect on breathing pattern. These results are significant as incremental bicycle ergometry is an effective and a widely used technique in cardiopulmonary exercise testing and the interpretation of the ventilation and breathing pattern responses in both health and disease requires that the phenomenon of spontaneously occurring LRC must be accounted for.

In conclusion, as figure 7.1. suggests, no single factor (neural or humoral) can be implicated in the mediation of exercise hyperpnea. As proposed by YAMAMOTO [1977], exercise ventilatory regulation probably represents the final synthesis of various redundant feed-forward and feedback stimuli and is ultimately directed towards appropriate gas exchange and acid-base homoestasis while minimizing both the effort and O_2 cost of breathing. The results of the studies described in this thesis clearly suggest that in active, healthy, young humans, the respiratory pump is ideally built (overbuilt ?) to meet the ventilatory and gas exchange requirements of even short-term high intensity exercise.

8. BIBLIOGRAPHY

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