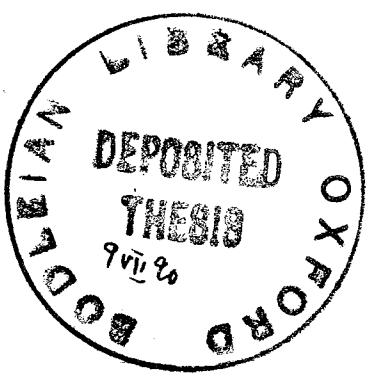
SOME ASPECTS OF THE REGULATION OF RESPIRATION IN MAN

Thesis submitted for the degree of

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David John Pilsbury

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To my father

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Symbols and Abbreviations

$\dot{x}$ - Dot above symbol indicates time derivative

$\bar{x}$ - Dash above symbol indicates mean value.

Respiratory Notations

V - Gas volume.

$\dot{V}$ - Gas volume per unit time.

I - Inspiration.

E - Expiration.

A - Alveolar.

a - Arterial.

[a-v] - Arterio-venous difference.

ET - End-tidal.

F - Fractional concentration of dry gas.

P - Gas pressure (mmHg - torr).

T_I - Duration of inspiration (s).

T_E - Duration of expiration (s).

T_T - Duration of breath (s).

V_T - Tidal volume (L., BTPS).

IC - Inspiratory capacity (L., BTPS).

MBC - Maximal Breathing capacity ($L.min^{-1}$, BTPS).

EEV - End-expiratory volume (L., BTPS).

$\dot{V}O_2$ - Oxygen consumption ($ml.min^{-1}$, STPD).

$\dot{V}O_2r$ - Oxygen consumption by the respiratory muscles ($ml.min^{-1}$, STPD).

$\dot{V}O_2v$ - Oxygen consumption per litre ventilation ($ml.L^{-1}$, STPD).

$\dot{V}CO_2$ - Carbon dioxide elimination ($ml.min^{-1}$, STPD).

$P_{ET}CO_2$ - End-tidal carbon dioxide pressure (mmHg - torr).

$P_{ET}O_2$ - End-tidal oxygen pressure (mmHg - torr).

RQ - Respiratory quotient.

$\ddot{V}_I$ - Inspiratory flow acceleration ($L.min^{-1}min^{-1}$, BTPS).

Tmax - Time to peak inspiratory flow (s).

Tmin - Time to peak expiratory flow (s).

$\dot{V}_I max$ - Peak inspiratory flow ($L.min^{-1}$, BTPS).

$\dot{V}_E max$ - Peak expiratory flow ($L.min^{-1}$, BTPS).

$\bar{\dot{V}}_I/\dot{V}_I max$ - Mean / peak inspiratory flow.

$\bar{\dot{V}}_E/\dot{V}_E max$ - Mean / peak expiratory flow.

STPD - Standard temperature and pressure, dry.

BTPS - Body temperature and pressure, saturated with water vapour.

ATP - Ambient temperature and pressure.

COPD - Chronic obstructive pulmonary disease.

EMG - Electromyelogram.

Statistical Notations

S.D. - Standard deviation.

S.E. - Standard error.

n - Number of observations.

r - Correlation coefficient.

Σ - Summation.

P - Probability.

SOS - Sum of squares.

MSq - Mean square.

VR - Variance ratio.

res - Residual.

DF - Degrees of freedom.

s^2 - Variance.

* - Probability of a significant difference; $0.05 \geq P > 0.01$.

** - Probability of a significant difference; $0.01 \geq P$.

Unit Notations

mm - Millimetre.

m - Metre.

mg - Milligram.

kg - Kilo.

ml - Millilitre.

L - Litre.

ms - Millisecond

s - Second.

min - Minute.

hr - hour.

V - Volt.

W - Watts.

^oC - Temperature in degrees centigrade.

Abstract

The work described in this thesis was undertaken to study the effects of inspiratory flow-resistive loading on gas exchange and breathing pattern in healthy man. The increased oxygen demand of the respiratory muscles accompanying the imposition of loading may lead to problems of "power-sharing" between the respiratory and non-respiratory working muscles, as the supply of oxygen may not be sufficient to meet the demands of both muscle groups and this may lead to the development of fatigue.

The responses of a total of 11 healthy young subjects were studied over a range of ventilations from resting to about 80 $L.min^{-1}$, induced by incremental work tests on a bicycle ergometer or by incremental steps of inspired CO_2. Eight of the subjects were studied during both types of tests. Initially, three different severities of loading were employed, one of which (the most severe) was chosen for the main experiments, this added a resistance of 76 mmH_2O at a flow of 60 $L.min^{-1}$.

The oxygen cost of breathing was significantly increased by loading, during exercise this was evident as a significant increase in total oxygen uptake. However, surprisingly, total oxygen uptake at the highest work levels was little or unaffected by loading. In a separate series of 5 experiments, plasma lactate concentrations were measured during incremental work tests. Above the anaerobic threshold, plasma lactate levels were higher during loading in the subjects in whom oxygen uptake was little or unaffected, indicating an additional energy source.

The breathing pattern responses to hypercapnia and exercise were very similar during both control experiments and those in the presence of loading. Loading was associated with a significant fall in ventilation and CO_2 retention, the result of a significant increase in inspiratory time and reduced mean inspiratory flow,

while expiratory time and mean expiratory flow were unaffected. This suggests that the centrally mechanisms governing expiratory flow are unaffected by imposed changes in inspiratory flow and duration. Loading at the highest levels of ventilation was associated with a different pattern of breathing to that at lower ventilations, inspiratory and expiratory durations not being significantly different from those seen in the unloaded condition.

End-expiratory volume decreased significantly with exercise or hypercapnia and was further decreased by loading.

Increased respiratory drive was associated with a progressive squaring of the flow profile, especially the expiratory portion, evident as a significantly greater initial rate of rise of flow and mean/peak flow ratio.

CHAPTER 1

INTRODUCTION

This chapter is divided into five sections. The first of these introduces the problems to be studied and the hypotheses that are tested, particularly the proposal that respiratory factors may limit exercise. The second section provides a review of the literature directly pertinent to the question of the limitation of exercise by respiratory factors. The third section provides an introduction to the mechanisms and the nature of the response to an increase in the resistance to air flow. The fourth section is a review of the literature concerning the oxygen cost of breathing. The final section describes what is new about the work in this thesis and how it extends previous work in the individual areas studied.

1. Overview

Aims and Objectives

The primary aim of undertaking the work reported in this thesis was to measure and compare the levels of aerobic and anaerobic metabolism, in the presence and absence of an external inspiratory flow-resistive load, when ventilation was raised by exercise or by the addition of carbon dioxide to the inspirate.

The object was to investigate the hypothesis, expounded by Bye et al. (1983), that respiratory factors may limit exercise when limb and respiratory muscle work rates are both high. Bye et

al. cited three respiratory factors as putative sources of exercise limitation: first, that ventilation may be insufficient to maintain an adequate alveolar oxygen level and that oxygen uptake may therefore be limited; secondly, that the supply of oxygen by the available cardiac output may be insufficient to meet the demands of both the respiratory and limb muscles; thirdly, that the respiratory muscles may become fatigued and ventilatory and exercise performance may therefore be reduced.

Secondary aims consisted of investigating and comparing the effect of increasing exercise or hypercapnia level, with and without loading, on a number of respiratory variables.

Primary Line of Investigation

The essential purpose of ventilation is to provide oxygen to, and remove carbon dioxide from, the alveolar air at rates sufficient to maintain their concentrations under a wide range of conditions. The respiratory work involved in the execution of this function is itself a source of oxygen consumption. However, at rest or during the unobstructed hyperpnoea of moderate exercise, the oxygen uptake ($\dot{V}O_2$) of the respiratory muscles is small in comparison with total body oxygen uptake.

During exercise, the oxygen uptake is shared between the active non-respiratory muscles (the limbs and heart), which get the major portion and the respiratory muscles that effect ventilation, which typically require a small fraction. If exercise intensity rises to extremely high levels, oxygen uptake reaches a maximal level ($\dot{V}O_2max$). In normal human subjects, respiratory factors are not considered to determine this value, and therefore not to determine exercise capacity either.

However, Bye et al. (1983) suggested that exercise capacity may be limited if respiratory work rate is increased to high levels during exercise, and that such levels may arise in normal subjects in whom the work of breathing has been artificially increased, in patients with chronic obstructive pulmonary disease and in athletes at very severe exercise intensities.

The mechanism of constraint has been ascribed to three related factors:

1) The mechanical limitation of ventilation.

The oxygen consumed by the respiratory muscles is supplied from the total oxygen uptake. If the oxygen requirement of the respiratory muscles is increased (because respiratory work rate is elevated), there would normally be an increase in ventilation. This increase in ventilation maintains alveolar PO_2 (P_AO_2) level, so it is adequate to provide sufficient oxygen to meet the augmented demand. However, if the ability to increase ventilation is limited by the mechanical limits of the respiratory system pump, alveolar PO_2 levels may fall. If this were the case, the required level of oxygen delivery might not be attained, and performance might thereby be impaired.

2) The high oxygen cost of breathing.

As ventilation rises, the oxygen cost of effecting each litre of ventilation increases (Shephard, 1966). Accordingly, the gain of respiration falls (defined as the increase in oxygen uptake / increase in oxygen cost of breathing). During high intensity exercise, ventilation may reach such high values that a point is reached at which the oxygen cost of breathing per litre ventilation is equivalent to the rise in oxygen uptake

accompanying each litre increase of ventilation; this point defines the critical limit of ventilation. If this limit is exceeded when the peripheral work rate is also high, the supply of oxygen to the active limb muscles may be impaired and performance thus affected.

3) Fatigue of the respiratory muscles.

If the supply of oxygen to the working muscles is insufficient at high respiratory and limb work rates, although ventilation may be maintained in the short term, fatigue of one or both muscle groups may occur. If fatigue occurs and the respiratory muscles therefore fail to generate the required level of force, ventilatory performance will be reduced and P_AO_2 will fall further below that required to meet the demand for gas exchange.

The experiments described in this thesis were undertaken to investigate whether elevating the work of breathing in normal subjects, by the imposition of an inspiratory flow-resistive load, was associated with the respiratory limitation of exercise, and whether this could be ascribed to the factors suggested by Bye et al. (1983).

The Use of Inspiratory Flow-Resistive Loading

In the experiments described in this thesis, high respiratory work rates were produced in normal subjects by the imposition of an external inspiratory flow-resistance (loading). This required subjects to generate additional inspiratory muscle force in order to produce a given level of gas flow (Figure 2.2).

If the functional limits of the respiratory system are being approached during high intensity exercise, the imposition of

loading and the consequent increase in respiratory work rate will exacerbate the situation. This will be the result of both the increased energetic cost of each unit of ventilation, and the reduction in the maximal attainable ventilation, i.e. the oxygen cost of breathing will increase while the ability to satisfy that demand will fall. Loading can thus be used to examine whether the limitation of exercise by respiratory factors occurs as described by Bye et al. (1983).

By measuring total oxygen uptake, oxygen consumption by the respiratory muscles, plasma lactate concentration, the level of ventilation, end-tidal gas compositions, and the pattern of breathing in a group of subjects during exercise and during hypercapnia, with and without loading, the three hypothetical sources of respiratory limitation of exercise described above may be examined.

The major testable hypotheses are:

1) Ventilatory limitation occurs at high respiratory work rates;

2) The oxygen cost of breathing becomes so high at high respiratory work rates that the supply of oxygen to respiratory muscles reduces that to the active limb muscles;

3) The inability to meet the requirement for oxygen at high respiratory and limb work rates augments anaerobiosis.

Secondary Lines of Investigation

Secondary lines of investigation involved the analysis of the effect of the addition of an inspiratory flow-resistance (and also an increase in ventilation from exercise or hypercapnia) on a number of respiratory variables including inspiratory and

expiratory durations, tidal volume, end-expiratory volume, and the shape of the flow profile. These variables will reflect the direct mechanical response to the addition of a flow-resistance (and/or exercise or hypercapnia) governed by neural, mechanical and chemo reflex compensatory mechanisms.

The secondary hypotheses examined are:

1) That these variables are influenced by the prevailing level of metabolism and that their generation may be in accordance with the fulfilment of optimisation criteria;

2) That the effect of loading is different during exercise and during hypercapnia, because the presence of significant work by the limbs affects the energetics and/or mechanics of breathing pattern generation.

By examining the association, if any, between the measures of mechanical performance listed above, and the rate of energy consumption derived from measures of oxygen uptake and plasma lactate concentration, the experiments undertaken in this study may yield data to help answer many of the questions currently posed regarding respiratory muscle physiology. However, the nature of the investigation means that theories concerning the significance and mechanism of associations observed between variables will be speculative.

Summary

The main object of undertaking the work reported in this thesis was to assess whether respiratory factors limit work capacity when both respiratory and limb muscle work rates are high. The total level of energy consumption during exercise, in the presence and absence of an inspiratory flow-resistive load, was estimated from

whole body oxygen uptake and plasma lactate concentrations during incremental work tests. The level of respiratory muscle energy consumption was assessed from measurements of the oxygen cost of breathing and plasma lactate concentration when ventilation was raised by the addition of carbon dioxide to the inspirate.

The effects of loading and/or increasing ventilation on breathing pattern, end-expiratory volume and flow profile were also examined.

2. Respiratory Factors Limiting Exercise

Literature Review

The Limitation of Exercise Capacity by the Mechanical Constraint of Ventilation

Ventilation is the first link in the oxygen transport chain, with the function of maintaining alveolar oxygen sufficiently high to provide adequate oxygenation of the blood. If oxygen uptake increases, it is normally accompanied by an increase in ventilation so as to maintain P_AO_2 and adequate oxygenation of the blood. However, if ventilation is limited mechanically by the ability of the respiratory pump to generate flow, P_AO_2 might fall, and the supply of oxygen and exercise capacity might thereby be impaired.

Normal Subjects

The respiratory system is not usually considered to contribute to the limitation of exercise. There is an enormous reserve capacity and ventilation may briefly increase by more than 50 fold during a Maximal Breathing Capacity (MBC) manoeuvre. This is accompanied by an increase in the oxygen cost of breathing from approximately 1 $ml.min^{-1}$ per litre ventilation at rest to around 10 $ml.min^{-1}$ per litre at levels of ventilation close to MBC (Bartlett et al., 1958; Shephard, 1966).

It is generally agreed that cardiac, not ventilatory, performance limits exercise capacity. Accordingly, Åstrand et al. (1964) showed a high correlation between maximal oxygen uptake and the volume of oxygen delivered to the tissues (the product of maximal cardiac output and the oxygen content of the arterial

blood), and Buick et al. (1980) reported that exercise capacity was increased by the elevation of oxygen transport capacity following the infusion of blood. Further evidence that ventilatory performance does not normally determine work capacity is provided by the observation that, although oxygen uptake reaches a maximum at severe work rates, ventilation typically continues to increase (Åstrand et al., 1960), showing that it is not the limitation of ventilation that limits oxygen uptake.

However, Ouellet et al. (1969) found that, although cardiac performance limited oxygen uptake, there was evidence, albeit conflicting, that the limits of ventilatory performance were approached at high exercise intensities. First, they reported that the highest level of ventilation recorded from three of the four subjects they studied during maximal exercise exceeded their measured MBC (approximately 160 $L.min^{-1}$). Secondly, the ventilatory data of two subjects (one of whom did not exceed his MBC) showed evidence of plateauing as maximal work loads were approached.

If the limitation of ventilation occurs, it is most likely to be the result of reaching the mechanically determined limit of the ability of the respiratory system to generate flow. Flow is not generally considered to approach maximal levels in normal subjects, but there is evidence that it may do so. In normal subjects, flow rates do not approach maximal levels at moderate exercise intensities at normal pressures, but maximal expiratory flow rates may be approached during the latter portion of the maximal effort flow-volume curve during heavy exercise (Olafsson and Hyatt, 1969). Inspiratory flow rates may also approach maximal values during severe exercise, limited by the rate of muscle shortening and the resistance to flow (Grimby et al., 1971;

Olafsson and Hyatt, 1969). Also, Wood and Bryan (1978) reported that normal subjects exercising at elevated ambient pressures (and therefore increased flow-resistance) reached maximal expiratory flow rates and that this was associated with a significant reduction in $\dot{V}O_2max$.

However, other studies have not found $\dot{V}O_2max$ to be significantly reduced at similar increased ambient pressures (Anthonisen et al., 1976; Fagraeus, 1974). Further, it is generally accepted that in normal subjects ventilation is sufficient to maintain P_AO_2 even at the very highest work loads, and in fact, that P_AO_2 typically rises.

Patients With Chronic Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (COPD) were not included in the present study, but reports concerning their responses to exercise are relevant to the present study.

Although ventilation is not generally considered to limit exercise capacity in normal subjects, ventilatory limitation of exercise capacity has been reported in patients with COPD, in whom respiratory work rate is pathologically increased. These patients often reach their MBC during incremental work tests, and this is associated with the limitation of oxygen uptake (Clark et al., 1969; Potter et al., 1971) and the attainment of static maximal expiratory flow rates (Clark et al., 1969; Leaver and Pride, 1971; Potter et al., 1971; Stubbing et al., 1980_b).

The respiratory work rate in these patients may be extremely high. Campbell et al. (1957) suggested that in patients with COPD the oxygen cost of breathing may be as high as 50% of resting total body oxygen uptake at even moderately raised levels of ventilation. Consequently, the oxygen available for use by

muscles other than those concerned with ventilation is markedly reduced.

In some patients, lung function may be so poor and the oxygen cost of breathing so high, that diaphragmatic fatigue occurs at rest (Roussos and Macklem, 1977; Roussos et al., 1979).

Athletes

It was proposed by Bye et al. (1983) that highly fit athletes are a further group who may suffer ventilatory limitation of work capacity. Expiratory flow rates may approach maximal values over most of the course of expiration if exercise intensities are severe (Grimby et al., 1971). As inspiratory flows are also close to maximal values at high exercise intensities (Grimby et al., 1971; Olafsson and Hyatt, 1969) it appears that the ability to generate flow may approach limiting values during severe exercise by highly fit athletes.

However, as stated previously, it is alveolar PO_2 levels that determine whether ventilation is limiting oxygen uptake. The findings of Dempsey et al. (1981, $1982_{a,b}$) may indicate that flow rates do become limiting at high exercise intensities in highly fit athletes, and that this may affect oxygen uptake, although P_AO_2 does not fall. They reported that during heavy exercise, substantial hyperventilation was required to maintain adequate oxygenation, otherwise diffusion limitation led to hypoxaemia. If maximal expiratory flows are approached, ventilation may be elevated by increasing lung volume, though hyperinflation increases respiratory work rate and reduces efficiency (Roussos et al., 1979). However, Dempsey et al. (1981, $1982_{a,b}$) found that some athletes performing high intensity exercise, and therefore approaching the limits of the respiratory system to generate flow,

constrained ventilation at the expense of gas exchange and tolerated the resulting hypoxaemia in preference to increasing ventilation and the work of breathing (those who hyperventilated least showed the greatest hypoxaemia). When air was replaced by a less dense helium-oxygen mixture, which reduced flow-resistance and thereby the work of breathing, ventilation and arterial PO_2 rose.

Thus, arterial PO_2 could have been increased during air breathing if ventilation had risen, and it may be that the rise in ventilation when subjects breathed a less dense gas was due to an increase in the maximal flow possible. However, the findings are also consistent with the suggestion that the prevailing level of respiratory drive was associated with a certain respiratory work rate; lowering the resistance to breathing at a constant respiratory work rate would therefore lead to an increase in the level of ventilation.

The Effect of Loading on Ventilation

The work described above indicates that ventilatory limitation may limit exercise capacity in athletes and in normal subjects breathing dense gases. There is also evidence that exercise capacity may be impaired when the work of breathing is increased by the addition of inspiratory flow-resistive loads.

The addition of an inspiratory flow-resistance will reduce ventilatory performance, first because the increase in resistance reduces the flow accompanying a given level of force generation and secondly, because the addition of an external inspiratory resistance increases expiratory flow rate (Zechman et al., 1957), so escalating the approach of expiratory flow towards maximal values.

Several groups have reported that maximal oxygen uptake and endurance are reduced by the imposition of inspiratory flow-resistive loading (Cerretelli et al., 1969; Craig et al., 1970; Dressendorfer et al., 1977; El-Manshawi et al., 1986). However, the reports of Craig et al. (1970) and Cerretelli et al. (1969) suggest that volitional fatigue occurred before ventilation was limited, i.e. subjects decided to stop exercise before maximal work capacity was reached. In the study of Dressendorfer et al. (1977), maximal work rates were maintained to exhaustion in the presence of loading, and both ventilation and oxygen uptake plateaued at significantly lower levels than in the absence of loading, before the onset of fatigue. These findings are consistent with the limitation of ventilation, and thereby exercise capacity, by the increased work of breathing accompanying the imposition of inspiratory flow-resistive loading. However, Dressendorfer et al. did not report alveolar or end-tidal oxygen partial pressures, so one cannot be sure whether the observed ventilatory plateauing impaired oxygen uptake and was thereby responsible for the reduction of maximal oxygen uptake.

The present study not only examines whether the mechanical limitation of ventilation occurs during exercise when breathing is loaded, but explores the relationship between ventilation, oxygen uptake and end-tidal P_{O_2}. Bye et al. (1983) failed to recognise the importance of P_AO_2 in determining whether ventilation is limiting oxygen uptake, but considered, wrongly, that the mechanical limitation of ventilation is sufficient evidence to indicate that oxygen uptake is being limited.

The examination of the effect of inspiratory flow-resistive loading during an incremental work test further extends previous

work, first, by employing longer durations of exercise than the 1 minute steps of Dressendorfer et al. (1977), and secondly, by measuring flow and breathing pattern variables.

Summary

There is little evidence that ventilatory limitation of oxygen uptake occurs in normal subjects during exercise, but there is some evidence that it may occur in athletes, and in normal subjects when respiratory work rate is artificially increased. The limitation of ventilation appears to be related to the approach towards the mechanical limit of the respiratory pump to generate flow.

The Limitation of Exercise Capacity by the High Oxygen Cost of Breathing

The high oxygen consumption of the respiratory muscles at high ventilatory loads may limit work capacity by reducing the supply of oxygen to the active limb muscles.

The Oxygen Gain of the Respiratory System

At rest, the oxygen consumption of the respiratory muscles is only around 1% of total body oxygen uptake. However as ventilation rises, the oxygen cost of effecting each litre of ventilation also rises, so the oxygen uptake of the respiratory muscles becomes a greater proportion of total oxygen uptake (Shephard, 1966) and the oxygen gain of respiratory work falls.

During high intensity exercise, it is conceivable that ventilation may be elevated to such an extent that it reaches some critical value at which the oxygen gain is unity, and above which any further increase in ventilation would reduce the oxygen available to other tissues. Otis (1954; 1964) suggested that this may occur at levels of ventilation of approximately 150 $L.min^{-1}$, when breathing is unoccluded. Respiratory muscle oxygen uptake does not appear to show any limit with increasing ventilatory work rate, even when ventilation increases up to 200 $L.min^{-1}$ (Bradley and Leith, 1978). It is therefore apparent, that it is possible for the oxygen cost of breathing during high intensity exercise to become so large that the oxygen available for non-respiratory muscles is reduced and exercise capacity is thus impaired.

The suggestion that the oxygen cost of breathing may rise to such high levels as to limit work capacity may be illustrated by considering the situation during heavy exercise, when total oxygen uptake may have risen to around 3000 $ml.min^{-1}$ and ventilation to around 100 $L.min^{-1}$ (Saltin and Åstrand, 1967). At an oxygen cost per litre ventilation of around 3 $ml.min^{-1}$ at this level of ventilation (Shephard, 1966), the oxygen cost of breathing is approximately 300 $ml.min^{-1}$ or 10% of total body oxygen uptake.

The Concept of Power Sharing

The concept described above, in which the respiratory muscles "steal" energy that would otherwise have been available for non-respiratory muscles, signifies that respiratory and non-respiratory muscles share the limited power available when respiratory and non-respiratory work rates are both high. The sharing of power between the two sites of work will be determined by the distribution of cardiac output.

The supply of oxygen to muscles depends on blood flow and the level of extraction of oxygen, indicated by the difference in the oxygen content of arterial and venous blood ($C_{(a-v)}O_2$). An increase in the oxygen uptake of a muscle may theoretically be accomplished by solely increasing $C_{(a-v)}O_2$, or without any change in $C_{(a-v)}O_2$ if muscle blood flow increases. The normal response to an increase in work rate is for both blood flow and $C_{(a-v)}O_2$ to increase.

Robertson et al. ($1977_{a,b}$) have measured the change in respiratory muscle blood flow and $C_{(a-v)}O_2$, in anaesthetised dogs, in response to the elevation of respiratory work rate accompanying unobstructed hyperpnoea or the imposition of an inspiratory resistive load. They reported that the increase in $C_{(a-v)}O_2$ accompanying elevated respiratory work rates quickly reached a maximum. Thereafter, increases in oxygen uptake were satisfied solely by augmenting respiratory muscle blood flow, mostly to the diaphragm. In fact, Robertson et al. (1977_a) reported that the increase in diaphragmatic blood flow failed to demonstrate any plateau during the progressive increase in respiratory work rate (which increased to sixteen times the resting level) accompanying the addition of inspiratory flow-resistive loads of increasing severity. The large increase in respiratory muscle blood flow with the elevation of respiratory work rate confirms the finding of Fixler et al. (1976), who reported that in exercising dogs, by far the largest relative increase in blood flow was to the respiratory muscles, not to the exercising limbs as one might expect.

The finding that respiratory muscle blood flow rises markedly with the elevation of respiratory work rate indicates that, in the presence of significant work rates by non-respiratory muscle

groups, a point might be reached at which the available cardiac output will be insufficient to meet the oxygen requirements of both muscle groups. The mismatch between supply and demand would augment anaerobiosis, which if it is intense, might lead to the fatigue of one or both muscle groups.

The Effect of Loading on Oxygen Uptake

If the potential exists for oxygen supply-demand mismatch when the oxygen cost of breathing is high under unoccluded conditions, it is much more likely to occur when respiratory work rate is elevated by the imposition of loading.

The effects of flow-resistive loading on total body oxygen uptake during incremental work tests have been examined in a number of studies (Cerretelli et al., 1969; Craig et al., 1970; Demedts and Anthonisen, 1973; Dressendorfer et al., 1977; El-Manshawi et al., 1986; Flook and Kelman, 1973). The general finding was that oxygen uptake at a given exercise intensity was slightly, but not significantly, increased by loading. The rise in total oxygen uptake with loading during exercise was probably due to a rise in the oxygen cost of breathing. This suggestion is supported by the reported rise in the oxygen cost of breathing accompanying the imposition of loading (Collet et al., 1985; Eldridge, 1966; Field et al., 1984; McGregor and Becklake, 1961), though the effect of inspiratory flow-resistive loading on the oxygen cost of breathing has only been examined at resting levels of ventilation (Collet et al., 1985; Field et al., 1984).

However, oxygen uptake was unaffected or reduced by the imposition of loading at exercise intensities close to maximal (Cerretelli et al., 1969; Craig et al., 1970; Demedts and Anthonisen, 1973; Dressendorfer et al., 1977; El-Manshawi et al.,

1986). This finding would appear to be irreconcilable with the reported rise in the oxygen cost of breathing accompanying the addition of loading. The fall in ventilation accompanying loading would serve to reduce the oxygen cost of breathing compared with if ventilation were maintained, but it seems unlikely that the relatively small falls in ventilation that occur with loading are sufficient to compensate for the relatively large increase in the oxygen cost of breathing per litre ventilation that accompanies loading.

This situation therefore required further investigation. It was explored in the present study by measuring the oxygen cost of breathing, with and without loading, during progressive hypercapnia at rest, in a group of subjects who had also performed incremental work tests, with and without loading.

Summary

The oxygen cost of maintaining a high level of ventilation is large, especially if breathing is loaded. During exercise, there is a critical level of ventilation above which the supply of oxygen to the respiratory muscles lessens the supply available to the exercising limbs. Normally, the level of ventilation at maximal exercise intensities is well below the critical level. However if ventilation rises to very high levels, or if the level of the critical ventilation is reduced, by loading for example, exercise capacity may be impaired.

If the supply of oxygen to active muscles is insufficient in the presence of high respiratory and limb work rates it may lead to augmented anaerobiosis. Consequently, either or both muscle groups may become fatigued, reducing the capacity for both ventilatory and limb work.

Respiratory Muscle Performance and Fatigue

Respiratory muscle fatigue is defined as the inability to continue generating a given pleural pressure (Roussos and Macklem, 1977). The active respiratory muscles have been reported to be a major site of respiratory fatigue (Bai et al., 1984). The onset of fatigue has been linked to the local level of lactate production (MacDougall, 1977; Tesch et al., 1978) which produces a fall in force production and a rise in perceived exertion (Sjodin and Jacobs, 1981). The effect is probably mediated by the fall in pH accompanying lactacidosis: this interferes with normal calcium binding in the muscle (Fuchs et al., 1970; Nakamura and Schwartz, 1972) so reducing actin-myosin interactions and thereby contractile force.

Ventilatory Fatigue During Ventilatory Work

The diaphragm is particularly resistant to the promotion of anaerobiosis (see below and p. 1.22), but it appears that respiratory fatigue may occur if the ability to perform work is reduced, or if respiratory work rate is raised to high levels. Thus, fatigue may develop at rest, even though lung function is normal, in patients who have suffered respiratory muscle wastage

after being artificially ventilated (Cohen et al., 1982; Lopes et al., 1981).

The effect of high respiratory loads on respiratory muscle performance has been investigated in several studies that have examined the length of time for which various percentages of MBC could be sustained (Bai et al., 1984; Leith and Bradley, 1976; Tenney and Reese, 1968). It was found that the maximum ventilation that could be sustained indefinitely was between 55% and 80% of MBC. However as ventilation rose above this level, the time for which it could be sustained fell. The constraint of ventilatory work capacity was attributed to sustained anaerobiosis leading to fatigue.

The onset of fatigue at levels of ventilation between 55%-80% of MBC was confirmed by the research of Freedman et al. (1983) and Martin et al. (1984), which established that plasma lactate levels were elevated at levels of ventilation greater than 70% of MBC during isocapnic voluntary hyperpnoea.

The respiratory muscles are the most likely site of this increase in anaerobiosis, which probably reflects the energetic consequences of producing the high pleural pressures necessary to effect high levels of ventilation. This proposal is supported by the observation that, during loaded breathing, the elevation of plasma lactate level or onset of fatigue occurs at a lower level of ventilation but at corresponding pleural pressures in the region of 50%-80% of maximal (Jardim et al., 1981; Roussos and Macklem, 1977; Roussos et al., 1979).

Ventilatory Fatigue During Exercise

It used to be generally accepted that, in normal subjects, the level of ventilation at maximal exercise intensity was

considerably below MBC. However, more recent work has indicated that the level of ventilation during high intensity exercise may approach that during a MBC manoeuvre (Jensen et al., 1980; Ouellet et al., 1969), so the work discussed above suggests that ventilatory fatigue might occur during high intensity exercise.

A number of workers have examined whether fatigue of the respiratory muscles occurs during exercise. Olafsson and Hyatt (1969) reported that the estimated mean maximal inspiratory intrapleural pressure during heavy exercise was almost 40% of maximal, i.e. approaching the point at which fatigue would eventually follow. Bye et al. (1984) concluded that diaphragmatic fatigue occurred during high intensity short term exercise in normal young men.

Other workers have appraised the effect of preceding respiratory work on subsequent ventilatory or exercise capacity. Martin et al. (1982_b) reported that ventilatory work preceding running reduced performance, while Loke et al. (1982), Mahler and Loke (1981) and Shephard (1967), all concluded that ventilatory performance was reduced following general exercise.

The most likely reason for the decrement in performance is fatigue of the respiratory muscles. However, Loke et al. (1982) found that marathon running not only reduced post-exercise maximal inspiratory muscle pressure, but also maximal expiratory muscle pressure. Yet expiratory muscle pressures would not be expected to exceed 3% of maximum, even at the highest levels of exercise (Agostoni and Mead, 1964). It would therefore seem unlikely that expiratory muscle fatigue could account for the fall in expiratory muscle performance: it is more likely to be the result of volitional fatigue.

Work Rate, Loading and Augmented Anaerobiosis

There is uncertainty concerning the causes of, and relationship between, lactate production by the respiratory and limb muscles, when respiratory and limb work rates are both high. However, understanding the circumstances that may precipitate anaerobiosis when respiratory and limb work rates are high is important in determining whether respiratory work rate can be raised sufficiently to promote anaerobiosis in exercising normals, as this has not previously been established.

The need for diaphragmatic work rate to rise to very high levels before anaerobiosis is promoted was discussed above, in relation to the high ventilatory work rates necessary to generate significantly increased plasma lactate levels. In vitro studies agree with those performed in vivo: Hollanders (1968) found that only electrical stimulation intense enough to produce tetany in a perfused rat diaphragm preparation would elicit increased lactate production. Rochester and Briscoe (1979) reported that, in an isolated dog diaphragm preparation, venous PO_2 had to drop to 20 torr before significant increases in lactate production occurred. This compares with the 30 torr required to provoke large increases from skeletal muscles.

However, arterial hypoxaemia may occur in exercising normal subjects in whom breathing has been loaded (El-Manshawi et al., 1986), and the combination of hypoxia and the high limb and respiratory work rates may serve to promote anaerobiosis.

The Effect of Loading on Anaerobiosis

There is conflicting evidence as to whether loading increases the level of anaerobic metabolism. Thompson and Sharkey (1966) measured the "oxygen debt" during exercise when ventilation was

loaded (measurements of oxygen debt are commonly understood to reflect the preceding level of anaerobiosis). They reported that the post-exercise oxygen debt was a function of the severity of the added load. Although measurements of oxygen debt are probably a very insensitive index, these results support the proposition that loading elevates the level of anaerobiosis and further, that it does so in proportion to the increase in respiratory work rate. However, Dressendorfer et al. (1977) found that the anaerobic threshold, estimated from the point of inflexion of the work rate - $\dot{V}O_2$ relation, was unaffected by loading. From this they concluded that the level of anaerobic metabolism was unaffected by loading, though the estimated level of the anaerobic threshold is also an insensitive index of the level of anaerobiosis.

In the present study, the role of respiratory muscle fatigue as a factor limiting exercise was investigated by estimating the level of anaerobiosis, from plasma lactate concentrations, both with and without loading. Plasma lactate concentrations were also measured during hypercapnic hyperpnoea and these may be compared with those at similar levels of ventilation during exercise, in the presence and absence of loading.

Summary

The diaphragm is particularly resistant to the promotion of anaerobiosis, ventilation must rise to 70% of maximal before plasma lactate levels are elevated. However, there is evidence that respiratory muscle fatigue may occur during high intensity exercise. As loading increases respiratory work rate it might be expected to augment anaerobiosis. However, previous studies, employing insensitive indexes, have produced conflicting reports of the effect of loading on the level of anaerobiosis.

3. Loading and the Respiratory System.

Although the experiments reported in this thesis were designed primarily to elucidate the effect of loading at high exercise levels, data concerning the general effect of loading at rest, during exercise and during hypercapnia were also collected. Characterisation of the typical response to loading is important in understanding its implications for physiological function in the many situations in which it may arise. This section introduces loading in a wider context, describing the different forms it may take and the nature of the response.

Forms of Loading

Internal Loading

The relationship between drive and ventilation may vary transiently as a result for example, of coughing, sneezing or speech, all of which increase airway resistance. However, these manoeuvres do not usually affect gas exchange markedly. More significant for gas exchange may be longer term changes in resistance arising from the inhalation of irritants, which may affect airway calibre for long periods, but in a reversible manner.

However, the most profound influence upon respiratory function is the increased resistance accompanying pathological changes of the tissue of the lung or airway. Disorders such as COPD may affect flow-resistance in an irreversible manner. Stubbing et al. (1980_b) showed that internal loads may be elevated to such a degree in patients with COPD that exercise may be

limited by the ability to generate ventilation, which is usually held not to be the case in normals.

Pathological loads may be primarily resistive as in asthma, primarily elastic as in patients with fibrotic disease, or a combination of the two as in emphysema. Campbell et al. (1957) found that in patients with emphysema, the oxygen consumption of the respiratory muscles may rise to 50% of total oxygen consumption even when ventilation is only moderately raised to around 20 $L.min^{-1}$.

The internal load of the respiratory system may also appear to be relatively increased at a given level of drive if the ability to generate respiratory muscular force falls. Thus, patients who have been artificially ventilated for prolonged periods may suffer respiratory muscle wastage which reduces the ability to generate force, requiring that patients be slowly weaned from the respirators (Cohen et al., 1982; Lopes et al., 1981; Roussos and Macklem, 1977).

Evaluation of the response to external loading, in a controlled situation, is of great importance in understanding how these patients may be best managed clinically.

External Loading

External loads applied to the airway are frequently experienced outside the laboratory by those who are obliged to wear some form of respiratory apparatus. These range from the sophisticated gas delivery systems used by miners, pilots and firemen, to the simple cloth filters worn in many milling environments to protect against dust. In subjects at rest, the loads presented may be insignificant, but effective loads rise quickly with increasing ventilation (see Cooper, 1961 for discussion). The experimental

investigation of the response to loading is important in determining what are acceptable performance criteria for respiratory apparatus.

Experimental Loading

In the laboratory, the two loads most commonly applied to the airway either resist flow (flow-resistive) or lung expansion (volume-elastic loads). Loads may be added to just one phase of the breathing cycle, or to both.

In the present study, an inspiratory flow-resistive load was employed. Loading was imposed during inspiration because it was predicted that, by loading the more active phase, greater severity of loading would be tolerated and that the control mechanisms would be revealed to a greater extent. Resistive loading was considered the more appropriate, first because it is more commonly encountered naturally than elastic loading and secondly, because there is a substantial body of previous work concerning the effect of flow-resistive loading to which the present work could be related.

The Mechanisms of the Response to Loading

The respiratory system shows many and varied responses to an increased load, whether the generally chronic internal increased load of disease states which is of slow onset, or the acute increased load of elevated levels of ventilation and/or an added external load which is of fast onset. Compensatory mechanisms serve to increase respiratory muscle force development and

minimise the disturbance of ventilation, thereby aiding the maintenance of homeostasis.

In order to understand better the implications of the changes that occur in response to loading, a brief review of the compensatory mechanisms is presented below.

The compensatory mechanisms that come into play with the addition of loading have been classified into two categories on the basis of whether the response is neurally mediated or not. Mead (1979) has called them intrinsic or non-neural responses and extrinsic or neural responses. The precise relative significance of the two mechanisms, especially in man, is unknown, but extrinsic responses are probably responsible for the greater part of the total response, while intrinsic responses are probably responsible for producing the greater part of the immediate or "first breath" response.

The Intrinsic Response

1) Force generation characteristics.

The effect of a given external load on tidal volume is a function of the ratio of the internal resistance and compliance of the respiratory system to the external resistance and compliance of the load (Milic-Emili and Pengelly, 1970).

The inherent nature of the force-length and force-velocity characteristics of the diaphragm, in which respect the diaphragm functionally resembles skeletal muscle, determines that the slowing of the rate of contraction and the increase in initial length that accompany inspiratory loading raise the effective elastance and the effective resistance of the respiratory system.

This increase in the "stiffness" of the lung is accordingly load compensating (Pengelly et al., 1971).

These functional characteristics of diaphragmatic contraction are of considerable benefit for diaphragmatic performance, for they permit combination of sensitivity, allowing control, with rigidity, providing stability.

2) Lung inertia.

The duration of the impeded phase, before loading, also affects load compensation. Zin et al. (1983) calculated that tidal volume was depressed less, in absolute terms, if the duration of inspiration (T_I) before the addition of an inspiratory flow-resistive load, was relatively short. This represented the effect of lung inertia.

3) Inspiratory driving pressure waveform.

Zin et al. (1983) also evaluated the influence of the shape of the inspiratory driving pressure waveform on the response to inspiratory flow-resistive loading. They calculated that load compensation was greater if waveforms exhibited greater upward convexity and lower if they exhibited greater upward concavity.

The Extrinsic Response

Extrinsic responses to loading are those which produce a change in the intensity and/or timing of respiratory drive. The respiratory response to loading depends on these responses as well as on the mechanical characteristics of the chest bellows.

The extrinsic responses may be divided into two categories on the basis of the source of the changes in efferent neural activity; whether it is primarily the result of the imposition of

the load, involving conscious responses and spinal reflexes, or secondary to the fall in alveolar ventilation and therefore a function of the increase in chemo reflex stimulation.

Characterisation of the Extrinsic Response

1) Chemoreceptor influences.

The chemoreceptors are an important potential source of load compensation. The imposition of large external loads generally reduces ventilation and increases PCO_2, and Whitelaw et al. (1975) have reported that in normal conscious humans the intensity of inspiratory drive (measured as mouth pressure at fixed intervals after the onset of inspiration with the airway totally occluded) is approximately doubled by each 8 torr increase in P_aCO_2. The reports of Altose et al. (1976_b; 1979), that mouth occlusion pressure increases linearly with the elevation of P_ACO_2, are in agreement with the findings of Whitelaw et al. (1975). Also, Eldridge and Davis (1959) and Milic-Emili and Tyler (1963) found that although the work rate of the respiratory muscles was independent of loading, it increased linearly with the level of hypercapnic drive.

2) Non-chemo reflex influences.

Altose et al. (1976_b) and Kryger et al. (1975) have reported that at a given P_ACO_2, loading produces an increase in respiratory muscle activity (occlusion pressure), i.e. an increase that is unexplained by changes in chemical drive. Other authors (Campbell et al., $1961_{a,b}$; Freedman and Weinstein, 1965) have demonstrated the existence of a neural response that occurs within one breath followed by a progressive rise in respiratory muscle activity

consequent upon the changes in arterial gas tensions produced by the fall in ventilation accompanying loading.

There are several mechanisms, functioning independently of changes in chemo reflex drive, that may contribute to the extrinsic response to loading. However, most, if not all, appear to be dependent on higher brain functions to some extent. Thus the cerebral cortex probably plays a part in the extrinsic response to loading, both directly (see p. 1.32) and also through its modulation of spinal and supraspinal reflexes.

Some of the possible extrinsic mechanisms of load compensation are introduced below.

a) Pulmonary mechanoreceptors and other vagally mediated responses.

In man, the Breuer-Hering reflex is weak over the normal tidal volume range. Prolongation of T_I is not dependent on vagal influences, but is probably due to a fall in the rate of rise of drive (Lopata et al., 1980). Therefore, the putative change in stretch receptor activity accompanying loading probably plays little or no part in forming the response to loading over most of the tidal volume range. Nevertheless, the Breuer-Hering reflex operates at elevated lung volumes (Guz et al., 1964). Further, although the level of the hypothetical inspiratory "off-switch" in the medulla is not directly affected by loading, it does rise in proportion to P_ACO_2 (Euler and Trippenbach, 1976; Lopata et al., 1977), which is increased by loading. Thus, the Breuer-Hering reflex may play a part in the response to loading in man.

Other vagally mediated reflexes dependent on the extent of lung inflation or deflation have been reported (Guz et al., 1970; McIlroy et al., 1962; Troelstra, 1960), that may have a role in

the response to loading. In addition, irritant and J-receptors may respond to the possible secondary effects of loading such as pulmonary congestion (Camporesi and Sant'Ambrogio, 1971). Although these pathways may be implicated in the response to loading, their importance has yet to be determined.

b) Chest wall proprioceptors.

The intercostal muscles possess a potentially powerful facilitating segmental reflex in the gamma loop system. The reflex has been shown to facilitate intercostal muscle activity in response to loading in animals (Corda et al., 1965) and in man (Newsom Davis and Sears, 1970). However, Shannon and Zechman (1972) reported that increased gamma activity is not important in producing increased respiratory force during loading, but rather acts to stabilise the rib-cage. One may conclude that although this reflex exists, its functional importance in load compensation has yet to be demonstrated. More important may be the cortical projections of these proprioceptors, which may contribute to a higher brain response (see p. 1.33).

c) Facilitatory intercostal-to-phrenic reflex.

Although the diaphragm is itself poorly supplied with muscle spindles, a supraspinal reflex arising from the intercostal muscles that facilitates phrenic activity has been shown to exist in animals (Decima and Euler, 1969; Decima et al., 1967). However, Lopata et al. (1980) found that in conscious man, the rate of rise of diaphragmatic EMG was unaffected or reduced with the addition of loading. This finding suggests that this reflex probably does not play a significant part in the response to loading.

d) Inhibitory reflexes.

Inhibitory as well as facilitatory reflexes are implicated in the response to loading. The sensory organs in the diaphragm are mostly Golgi tendon organs. Their inhibitory effect on respiratory drive when the force of diaphragmatic contraction increases may be an important determinant of inspiratory duration.

An inhibitory intercostal-to-phrenic reflex has also been shown to exist (Remmers, 1970, 1973). Activation of this reflex (by stimulation of mid-thoracic intercostal muscles) produces a shortening of T_I.

These reflexes may be important in limiting diaphragmatic contraction to avoid marked distortion or collapse of the chest.

e) The role of the cortex in the response to loading.

Unlike in conscious subjects, the drive and timing of the first breath after loading in unconscious subjects are reported to be virtually unchanged from that before (Behrakis et al., 1983; Freedman and Campbell, 1970; Nunn and Ezi-Ashi, 1961; Read et al., 1974; Whitelaw et al., 1976). Only in subsequent breaths as chemical drive rises is respiratory muscle activity augmented (Altose et al., 1979; Campbell et al., $1961_{a,b}$).

The finding that load compensation is absent during sleep (Santiago et al., 1981) is further evidence of the dependence of the response on consciousness. However, differences seen in the intercostal muscle EMG in response to elastic loading during different sleep stages (there is less increase in intercostal muscle electrical activity in Rapid Eye Movement (REM) than non-REM sleep; Phillipson et al., 1976) suggest that it is not simply the level of consciousness that determines the influence of higher brain centres on the response to loading.

The importance of cortical involvement in determining the response to loading is further illustrated by the reported effect of psychological state and experience on the response to loading. Newsom Davis and Sears (1970) found that subjects told to resist the imposition of a load showed an enhanced response, while those told to relax before loading showed an attenuated response. Sampson and De Troyer (1982) reported between subject differences in the response to loading that were probably of cortical origin; some subjects fought the imposition of a load, while others showed a more acquiescent response.

It has also been reported that previous experience of loading affects the response (Green et al., 1978), producing a more rapid (Freedman and Weinstein, 1965) and vigorous (Pope et al., 1968) response, while Aitken et al. (1970) demonstrated that the mood state affected the response, and Freedman and Campbell (1970) found that the response to loading was dependent on perceived discomfort.

The level of respiratory drive may also be important in determining the response to loading, separately from the effect of the load. This may be dependent on feedback of the level of motor drive within the central nervous system, for partial curarisation, which increases the motor output required to generate a given force, has been shown to produce overestimation of the magnitude of added loads (Campbell et al., 1980).

f) Afferent inputs.

The afferent information that contributes to the higher brain response probably arises from a variety of sources. One source of information is chest wall proprioceptors, and Bland et al. (1967) have implicated chest wall receptors in the response to loading.

The importance of this pathway is indicated by the finding that load detection is impaired in subjects who have disrupted cortical projections of these receptors, the result of upper spinal cord lesions (Axen and Bergofsky, 1977; Newsom Davis, 1967).

However, Eisele et al. (1968) found chest wall nerve block had no effect on load detection ability or on the response to loading. They concurred with Wiley and Zechman (1966) and Zechman et al. (1967) that chest wall afferents were of little significance.

It may be that one must view chest wall afferents in a wider sense to reconcile these reports, i.e. including diaphragmatic afferents and upper airway receptors. Thus, Zechman et al. (1981) reported an association between the level of diaphragmatic tension and load detection. The involvement of upper airway receptors in the response to loading is implied by the report of Newsom Davis (1967) that the load detection ability of cord-lesioned patients was further depressed by oral anaesthesia. Bartlett et al. (1976) and Hwang et al. (1984) have both found receptors responding to subatmospheric airway pressures.

Until recently, there has been little evidence, in man, that respiratory afferents projected to the cerebral cortex, though it seemed reasonable that they should. However, in 1986 Davenport et al. reported respiratory related cortical potentials evoked in response to inspiratory occlusion in man, suggesting the existence of a cortical pathway for afferents from the respiratory muscles, or lung, or airway.

The specific relevance of respiratory afferents to the loading response is as yet unestablished. It seems likely that one or more of these receptor groups is involved in invoking

cortical activity in response to loading, though their importance has not been explicitly determined. The most likely conclusion is that all these afferents contribute to the response to a greater or lesser extent; the nervous system is accustomed to interpreting redundant information, and if the function of one is reduced the others may assume greater importance.

The Nature of the Response to Loading

The Effect of Loading on Breathing Pattern

The pattern of breathing adopted following the imposition of loading has been recorded periodically since Marey (1865) made the first measurements. The magnitude and the direction of change in the level of a variable with loading depends on the subject, the type and severity of the load and the source and level of respiratory drive, among other factors. However, the general effect on breathing pattern of the addition of a flow-resistive load may be described. The following section introduces the past work that has characterised the form of the response, based upon the study of Zechman et al. (1957), extended and confirmed by other workers.

1) Duration of inspiration.

The most striking feature of the response to imposition of a flow-resistive load is the prolongation of the impeded phase, typically in proportion to the severity of the added load (Zechman et al., 1957).

2) Duration of expiration.

Whether measured spirometrically (Eldridge and Davis, 1959; Milic-Emili and Tyler, 1963; Zechman et al., 1957) or neurologically (Baker et al., 1979), the duration of expiration (T_E), changes little, if at all, with the addition of inspiratory flow-resistive loading.

3) Tidal volume.

Tidal volume (V_T) is unchanged or increased by the imposition of loading, depending on the severity of the load and level of drive (Dressendorfer et al., 1977; El-Manshawi et al., 1986). If V_T does increase, it is usually not sufficient to maintain ventilation at pre-loading levels. However, the increase does constrain the fall in ventilation that would occur if V_T remained at pre-loading levels.

4) Ventilation.

Inspiratory flow-resistive loading produces a greater relative rise in T_I than V_T, while T_E remains relatively constant, so that ventilation falls. As the level of ventilation in the absence of loading rises in response to exercise or CO_2, the addition of loading is associated with a greater absolute reduction of ventilation (Dressendorfer et al., 1977; El-Manshawi et al., 1986; Lopata et al., 1980).

5) Mean inspiratory flow.

The greater proportional increase in T_I than V_T with loading results in a fall in mean inspiratory flow. This variable has been proposed as a good indicator of the level of respiratory

centre output (Milic-Emili, 1982). However, the relationship is dependent on the resistance of the respiratory system.

6) Mean expiratory flow.

Mean expiratory flow is frequently augmented by the addition of inspiratory resistive loading, V_T increasing while T_E remains relatively constant. The fact that a greater volume is expired in a similar time is the result of a combination of mechanical and neurological mechanisms. Mechanical mechanisms include greater potential energy with the increase of tidal volume and a reduction in expiratory braking (England et al., 1982; Murphy et al., 1959; Petit et al., 1960). Neurological mechanisms include a general increase in respiratory drive accompanying inspiratory resistive loading, which leads to recruitment of the abdominal muscles and augmented expiratory activity (Lopata et al., 1983).

7) End-expiratory volume.

As well as increasing mean expiratory flow, the reduced expiratory braking and increased abdominal muscle recruitment accompanying loading are probably responsible for the fall in end-expiratory volume (EEV) that frequently occurs (Martin and De Troyer, 1982; Martin et al., 1982_a).

8) The shape of the flow profile.

The shape of the flow profile at rest and moderately raised levels of ventilation has been compared to a sinusoid, though each phase may more closely resemble a triangle (Zechman et al., 1957), or a quadrilateral (Painter, 1987).

The addition of inspiratory flow-resistive loading typically reduces both the rate of rise and fall of inspiratory flow, and

peak inspiratory flow levels. During expiration, the rate of rise and fall of flow both increase, as does the peak flow level (Zechman et al., 1957).

Loading and Theories of Optimisation

Optimisation of the Shape of the Flow Profile

A number of studies have compared the shape of recorded flow profiles with those generated by models fulfilling various optimisation criteria (see Hämäläinen, 1983 for review). One of the simplest models and a starting point for recent investigators was that formulated by Yamashiro and Grodins (1971). This generated profiles which minimised either respiratory work rate or mean squared volume acceleration. More sophisticated models, such as that produced by Hämäläinen and Viljanen ($1978_{a,b}$) employed a number of optimisation criteria including minimisation of inspiratory mechanical work rate, expiratory mean squared muscle pressure (a function of expiratory braking) and the square of volume acceleration (related to the efficiency of muscular contraction).

The success with which these assorted models predict recorded flow profiles varies. The models that solely minimise inspiratory work rate produce rectangular flow profiles that resemble natural profiles only at high levels of ventilation. The model of Hämäläinen and Viljanen ($1978_{a,b}$), which utilises three criteria, generates profiles that show a gradual change in shape as ventilation rises, from near sinusoid to near rectangle, similar to that evident in recorded profiles.

The change in shape of recorded flow profiles as ventilation is elevated may be evidence that the shape of the flow profile is optimised, as the shape becomes more like that predicted by models that minimise respiratory work rate. However, there may be factors of greater importance than considerations of work rate and energy consumption that determine the shape of the flow profile as ventilation rises. There is evidence that flow limitation occurs during expiration, and possibly inspiration, at very high levels of ventilation (see p. 1.8-14).

The results presented in this thesis demonstrate the effect of loading on the shape of the flow profile, over a wide range of ventilation, during exercise or hypercapnia. The first aim of this examination of the shape of the flow profile is to compare such empirical descriptions with profiles that fulfil optimisation criteria and thereby investigate whether the response to loading is in accordance with optimisation processes. The second aim is the investigation of the relationship between the shape of the flow profile, and mechanical performance and energy consumption (the measurements made in the first series of experiments).

The Optimisation of Breathing Pattern

The shape of the flow profile is not the only variable suggested to be governed by optimisation criteria. Rohrer in 1925, and many authors since have suggested that various aspects of subjects' breathing are governed in accordance with optimisation principles in such a way that the pattern adopted in a particular situation is in some way the most efficient. The variables that have been suggested to be controlled by optimisation systems are listed overleaf.

1) Breathing pattern (particularly respiratory frequency) (Cerretelli et al., 1969; Crossfill and Widdicombe, 1961; Fincham and Priban, 1965; Mead, 1960; Otis, Fenn and Rahn, 1950; Priban and Fincham, 1965; Rohrer, 1925). The suggested criteria for optimisation were minimisation of respiratory work rate or force.

2) Dead-space volume (Widdicombe and Nadel, 1963).
The suggested criteria for optimisation were minimisation of respiratory work rate, or force.

3) End-expiratory volume (Yamashiro and Grodins, 1973).
The suggested criterion for optimisation was the minimisation of the elastic work of breathing.

4) Flow profile (Hämäläinen and Viljanen, $1978_{a,b}$; Ruttiman and Yamamoto, 1972; Yamashiro and Grodins, 1971, 1973). Suggested criteria for optimisation included the minimisation of inspiratory work rate, minimum mean squared inspiratory volume acceleration and expiratory mean squared muscle pressure.

It is probable that some optimisation of function occurs in a highly controlled system such as that regulating ventilation. At rest, when the energy demands of the respiratory system are low, this may not be of great significance, or a central feature in the determination of the values of respiratory variables. However, it might assume much greater significance when respiratory and/or limb work rates are high as in exercise.

4. The Oxygen Cost of Breathing: A Review

The oxygen cost of increasing respiratory work rate has been examined in a number of studies since that by Liljestrand (1918). The method employed in these investigations involves measuring the total body oxygen uptake at rest or during steady state exercise. Respiratory work rate is then raised either by increasing ventilation (voluntarily or as a result of applying some respiratory stimulus) or by the addition of external loads, and total oxygen uptake is remeasured once a new steady state has been established. Assuming that oxygen consumption by tissues other than the respiratory muscles remains constant during the elevation of respiratory work rate, the increased oxygen consumption can be ascribed to the increased metabolism necessary to effect the elevation of respiratory work rate. The oxygen cost of breathing at a given ventilation may then be defined either as the increase in oxygen uptake, or as the increase in oxygen uptake per litre ventilation.

Ventilation has been elevated in a variety of ways in studies of the oxygen cost of breathing: by addition of a dead-space (Campbell et al., 1957, 1959; Cherniack, 1958, 1959; Cournand et al., 1954; Liljestrand, 1918; Milic-Emili and Petit, 1960), by addition of carbon dioxide to the inspirate (Nielsen, 1936), or by isocapnic voluntary hyperventilation (Bradley and Leith, 1978; Fritts et al., 1959). In all these studies, the elevation of ventilation was reported to increase the oxygen cost of breathing, though the extent of the increase appeared to vary depending on whether ventilation was elevated voluntarily (and whether isocapnia was maintained) or by increasing chemo reflex drive.

The oxygen cost of breathing during hypercapnic hyperpnoea and isocapnic voluntary hyperventilation was directly compared by Grollman (1930), and the latter found to be greater.

Normal Values for the Oxygen Cost of Breathing

The energy consumed by the respiratory muscles is almost entirely supplied by aerobic metabolism, as the diaphragm is particularly resistant to the promotion of anaerobic metabolism (Hollanders, 1968; Rochester and Briscoe, 1979; see p. 1.22). The level of energy consumption of the respiratory muscles may therefore be estimated by measuring respiratory muscle oxygen consumption.

The oxygen cost of breathing in normal subjects at low levels of ventilation (less than 20 $L.min^{-1}$) has been calculated to be between 0.25 and 1.87 $ml.min^{-1}$ for each litre of ventilation. The range of values probably reflects both subject and experimental differences.

As ventilation is elevated, the oxygen cost of breathing per litre of ventilation rises: at levels of ventilation of 50-100 $L.min^{-1}$, the oxygen cost of each litre of ventilation has been reported to be between 0.5 and 3.5 $ml.min^{-1}$ (Campbell et al., 1959; Cherniack, 1959; Fritts et al., 1959).

It is apparent from the rise in the oxygen cost of breathing per litre ventilation, that the oxygen gain of ventilation falls as the level of ventilation rises (p. 1.3). It has been reported that during high intensity exercise, the oxygen cost of effecting each litre of ventilation may rise to such high values with the elevation of ventilation, that the critical level of ventilation

may be reached at which the oxygen cost of breathing per litre ventilation is equal to the increase in oxygen uptake per litre rise in ventilation. When ventilation and the oxygen cost of breathing reach these high levels, any further increase in ventilation above the critical value will reduce oxygen available for tissues other than the respiratory muscles. This was reported by Otis (1954, 1964) to occur at approximately 140 $L.min^{-1}$, later estimates by Margaria et al. (1960) and Shephard (1966) confirmed that the threshold was in this region. This level of ventilation is usually only sustainable for 3-4 minutes before the onset of respiratory muscle fatigue induces ventilation to fall (Bai et al., 1984; Leith and Bradley, 1976; Tenney and Reese, 1968). Respiratory muscle oxygen consumption at this level of ventilation has been estimated to be around 5 $ml.min^{-1}$ per litre ventilation compared with approximately 10 $ml.min^{-1}$ at MBC (Bartlett et al., 1958; Shephard, 1966).

Factors Affecting the Oxygen Cost of Breathing

1) Action of the respiratory muscles.

The rise in the oxygen cost of breathing with the elevation of ventilation is due to a number of factors whose significance is unclear.

As ventilation is elevated, there is a general increase in the distortion of the chest wall and abdomen as they move away from their relaxation curves. The level of isometric work resisting even further distortion is also increased (Agostoni and Mognoni, 1966; Macklem et al., 1978). Both factors consume energy but effect no volume change; they therefore do no measurable

mechanical work, but serve to increase the measured oxygen cost of breathing.

The recruitment of other muscle groups such as the accessory muscles, which operate at a lesser mechanical advantage than the diaphragm, may also contribute to the rise in the oxygen cost of breathing with the elevation of ventilation. There may also be an increase in the oxygen uptake by muscles maintaining posture and muscles other than those intimately concerned with effecting ventilation. Thus, Roussos and Macklem (1982) found that the muscles of the arm and trunk were recruited during extreme ventilatory effort.

The Hill equation (Hill, 1938) that defines the energy demands of a contracting muscle, has as variables the tension developed, the duration of contraction and the velocity of shortening. The velocity of shortening will certainly increase as ventilation rises and this may increase the oxygen cost of each litre of ventilation.

The oxygen cost of breathing per litre ventilation may also increase as a function of the force-length relationship, if the respiratory muscles move away from their optimal length with the elevation of ventilation. Thus, changes in both the force-velocity and force-length relations may lead to a fall in efficiency as ventilation rises.

However several studies have reported that the efficiency of breathing is unaffected by the level of ventilation up to 100 $L.min^{-1}$ (Bartlett et al., 1958; Tenney and Reese, 1968), or by mean inspiratory flow (Collet et al., 1985), so the question of whether the efficiency of breathing changes with the level of ventilation is as yet unresolved.

2) Mechanics of the respiratory system.

The oxygen cost of breathing rises with the elevation of ventilation because extra work is required to overcome the increased resistance to flow, and this may be substantial at high levels of ventilation (Otis, 1954). In addition, Stubbing and Jones (1983) have found that the large tidal volumes associated with high levels of ventilation may result in excursions onto the flat portion of the lung and chest wall compliance curve, where greater force is required to effect a given volume change.

Related factors that may contribute to the elevation of the oxygen cost of breathing include an increase in the energy required to overcome the inertia of the tissues and gases as the number of flow reversals is increased, and an increase in the work done in compressing and rarefying gas in the lung (Jaeger and Otis, 1964). In addition, when ventilation is raised by exercise, the increase in pulmonary blood volume reduces the dynamic compliance of the lung (Stubbing et al., 1980_a).

The Effect of Loading on the Oxygen Cost of Breathing

1) Human studies.

It is apparent from the work introduced above that the oxygen cost of breathing at a given ventilation is dependent on a number of factors, the effects of which may be magnified by the imposition of loading. Loading increases the oxygen cost of breathing not only by increasing measurable work rate, but by elevating oxygen consumption by processes that do no measurable work.

A major factor responsible for increasing the oxygen cost of breathing without performing any external work is the increase in the level of isometric work. With the addition of loading there

is an increase in the distorting influences on the chest wall. There is also an increase in muscular activity to resist this distortion, mostly of the intercostal muscles, which performs no measurable mechanical work (Agostoni and Mognoni, 1966; Sampson and De Troyer, 1982). The accessory muscles may also act as fixators for the rib-cage, consuming energy but performing no measurable mechanical work.

To the author's knowledge, there are only two reports in the literature that directly concern the effect of inspiratory flow-resistive loading on the oxygen cost of breathing. Collet et al. (1985) and Field et al. (1984) found that, at resting levels of ventilation, the oxygen uptake of the respiratory muscles was elevated in proportion to the external work rate.

There are several reports that pertain to the present study although they do not involve inspiratory flow-resistive loading. These include that of McGregor and Becklake (1961) who measured the increased oxygen consumption accompanying the imposition of flow-resistive loading common to both inspiration and expiration during hypercapnic hyperpnoea. Also, Eldridge (1966) assessed the effect of a constant inspiratory load of 210 mmH_2O on oxygen uptake when breathing though a 1.3 L dead space (ventilation approximately 20 $L.min^{-1}$). From his data, the oxygen cost of breathing may be calculated to have risen from 1.2 to 4.3 $ml.min^{-1}$ per litre ventilation with the addition of loading.

However, there are no reports of the effect of inspiratory flow-resistive loading on the oxygen cost of breathing at elevated levels of ventilation, in man.

2) Animal studies.

Robertson et al. (1977_a) and Rochester and Bettini (1976) have directly measured respiratory muscle oxygen uptake during inspiratory loading, calculated from the product of respiratory muscle blood flow and the arterio-venous oxygen content difference, i.e. using the Fick principle. Both studies examined the effect of a number of loads of different severity, though in the former this was only at resting levels of ventilation, while in the latter loading was combined with hypercapnia. Both reported that the oxygen uptake of the respiratory muscles rose with the addition of loading, and that it did so in proportion to the magnitude of the added flow-resistance.

The Oxygen Cost of Breathing as an Index of Respiratory Muscle Metabolism

Calculating the Work of Breathing

An alternative to evaluating respiratory muscle energy consumption by measuring the oxygen cost of breathing is to measure the mechanical work performed on the lung, (the product of oesophageal pressure and lung volume change). By introducing theoretical estimations of the mechanical properties of the lung, this variable may be refined to include work done to overcome internal flow-resistance (Otis, Fenn and Rahn, 1950; Otis, 1964).

A number of authors have assessed the mechanical work of breathing. However, the complexity of the relationship between

energy consumption and measurable mechanical work poses a problem for data interpretation. The efficiency of the conversion of energy to work may vary considerably, depending on load and the velocity of contraction amongst other factors (Hill, 1964; Collet et al., 1985).

A further complication in the analysis of measures of mechanical work is that muscles may contract isometrically, producing no measurable work but consuming energy; the rate of energy consumption for isometric contractions is a function of tension and time, in a similar fashion to that described by the Hill equation for isotonic contractions. The intercostal and accessory muscles may perform considerable isometric work when they act as fixators resisting distortion of the chest wall or resisting antagonistic muscle groups (Agostoni et al., 1966; Field et al., 1984), but this force generation would not be included in estimates of mechanical work. Also, the duration of contraction, may markedly affect energy consumption, but estimates of mechanical work take no account of this variable.

A further drawback of measuring the mechanical work of breathing to estimate the energy consumption of the respiratory muscles is that it does not necessarily record all the work done by the diaphragm. Work done in distorting the abdomen by lengthening the antagonist muscles of the abdominal wall, and the work done in post-inspiratory activity to effect expiratory braking are generally not included in measurements of mechanical work, but they may account for up to 15% of the estimated work load (Goldman et al., 1976).

The Effect of Loading

When breathing is loaded, the inadequacy of measuring respiratory work to estimate energy consumption is increased, first, because loading significantly increases the level of isometric work resisting distortion of the rib-cage. Secondly, the increase in the duration of inspiration accompanying loading elevates energy consumption, but does not affect estimates of mechanical work. A strong association between the duration for which tension is maintained and the oxygen consumption has been reported (Field et al., 1984; Collet et al., 1985), suggesting that duration of contraction is a major determinant of energy consumption. Thus, as might be expected from the Hill equation, McGregor and Becklake (1961) found that respiratory force was a better indicator of energy consumption than classical determinations of mechanical work.

It would appear that, although useful for other purposes (see below), the measurement of mechanical work does not provide a good index of the energy consumption of the respiratory muscles.

Respiratory Muscle Efficiency

The deficiencies of calculations of mechanical work listed above probably account for most of the variation in the cited efficiency of respiratory muscles of between 1% and 25% (see Agostoni et al, 1970, for review), where efficiency is calculated as the ratio of the oxygen equivalent of the measured mechanical respiratory work to the estimated respiratory muscle oxygen consumption.

Lloyd and Zacks (1972) reported that the efficiency of limb muscles was approximately 25% during bicycle exercise and 30% during running. As the respiratory and limb muscles are physiologically similar, it is likely that respiratory muscle

efficiency is close to this. The fact that most estimates of respiratory muscle efficiency are much lower supports the proposition that a large fraction of the work done by respiratory muscles is not included in measures of mechanical work.

Measuring the Oxygen Cost of Breathing

The evidence presented above suggests that measurements of the oxygen cost of breathing more accurately reflect respiratory muscle energy consumption than do measurements of mechanical work. This is particularly so when there is a marked increase in the energy consumption of processes not included in assessments of mechanical work, such as those which accompany a substantial increase in the level of ventilation or the addition of loading (Field et al., 1984; McGregor and Becklake, 1961; Robertson et al., $1977_{a,b}$; Rochester and Bettini, 1976).

In animals, the oxygen cost of breathing may be measured directly, using the Fick principle, as the oxygen uptake of the respiratory muscles (see p. 1.47).

In man, the oxygen uptake of the respiratory muscles can so far only be estimated. The method generally employed follows that of Liljestrand (1918) and involves measuring differences in whole body oxygen uptake (p. 1.41).

Validity of Estimates of the Oxygen Cost of Breathing

1) Stability of oxygen uptake.

One of the major problems of estimating the oxygen cost of breathing by the method of Liljestrand (1918), is that oxygen uptake is difficult to measure very accurately. This is the case because the oxygen uptake of the respiratory muscles is generally

small, especially at low levels of ventilation, and the total body oxygen uptake is large and may vary, especially in the face of experimental interference. The stability of resting $\dot{V}O_2$ was assessed by Field et al. (1984). They reported that 10-15 minute time-averaged measurements of total body oxygen consumption varied by only 13.25 $\pm$ 2.2 $ml.hr^{-1}$ (mean $\pm$ S.E.). This figure is of the same order as the oxygen uptake of the respiratory muscles at low levels of ventilation and might therefore obscure the true value of individual determinations of the oxygen cost of breathing. However, by making repeated measurements as in the present study the error is reduced.

2) Factors associated with changes in CO_2 levels.

If isocapnia is not maintained during experiments, the change in intracellular pH may affect the general level of metabolism and thereby the estimated oxygen cost of breathing.

a) Hypercapnia.

There are several reports suggesting that a linear inverse relationship exists between oxygen uptake and PCO_2 or hydrogen ion concentration in resting man and dog (Cain, 1970; Karetsky and Cain, 1970; Mithoeffer and Karetsky, 1968). If this is the case, the oxygen cost of breathing may be underestimated when ventilation is raised hypercapnically, because the general level of metabolism, and thereby total oxygen uptake, may be depressed by the rise in CO_2. The mechanism may be the inhibitory effect of the fall in pH on the activity of rate-limiting enzymes such as phosphofructokinase (Stryer, 1981).

However, Chapler et al. (1980) found no linear inverse relationship between oxygen uptake and PCO_2 or hydrogen ion

concentration in an isolated dog hindlimb preparation, nor did Kowalchuk et al. (1984) in exercising man.

There is also evidence that hypercapnia may increase the general level of metabolism. Pappenheimer (1977) reported that in rats breathing 5% CO_2, oxygen uptake increased by approximately 30%, and this is unlikely to be attributable solely to the increased oxygen cost of breathing. In addition, Kaminski et al. (1982) have reported that the oxygen cost of hypercapnic hyperpnoea in man appeared to be overestimated at low ventilations, though the error was reduced as inspired CO_2 levels and the level of ventilation increased.

The reported rise in total oxygen uptake during hypercapnia may be partly due to the stimulatory effect of increasing intracellular acidosis on the release of calorigenic catecholamines from the sympatho-adrenal system (Morris and Millar, 1962; Rose et al., 1983; Sechzer et al., 1960; Tenney, 1956), although hypercapnia may also elevate the oxygen cost of breathing by causing bronchoconstriction, thereby increasing the work of breathing per litre ventilation (Parker et al. 1963).

It would seem that during hypercapnia, there are two conflicting influences on the general level of cellular metabolism and oxygen uptake, first, a direct depressive effect and secondly, an indirect stimulatory effect. The findings of Kaminski et al. (1982) suggest that, in man, the stimulation of oxygen uptake predominates at low levels of hypercapnia but that this effect declines as the level of hypercapnia increases.

b) Hypocapnia.

The hypocapnia of hyperventilation which increases pH, has been reported to raise the level of metabolism (Karetsky and Cain,

1969; Khambatta and Sullivan, 1973). This may be due to the stimulatory effect of the rise in pH on the activity of rate-limiting enzymes that control glycolysis (see above). This may lead to the overestimation of oxygen uptake at rest, when experimental subjects are prone to hyperventilate. Hypocapnia may also affect oxygen uptake, through its influence on the impedance of the respiratory system (Duane et al., 1979; Newhouse et al. 1964; Tisi et al., 1970).

The CO_2 level effects discussed above will affect the estimated oxygen cost of breathing and they remain as a question mark over the method. However, three considerations should be borne in mind when assessing the accuracy of the method in general and as used in the present study in particular. First, the error of estimation due to changes in oxygen uptake by other than the respiratory muscles will fall as the oxygen cost of breathing increases as a proportion of total oxygen uptake. Secondly, the findings of Kaminski et al. (1982) suggest that the effect of hypercapnia on the general level of metabolism decreases as the level of hypercapnia increases. Thirdly, the difference between the oxygen cost of breathing of unloaded and loaded breathing at the same or similar levels of ventilation, i.e. at similar CO_2 levels, is likely to be estimated more accurately than the absolute oxygen cost of breathing.

3) Temperature factors.

a) Airway effects.

Significant airway cooling may occur during exercise (Deal et al., 1979) and possibly during hypercapnic hyperpnoea if the inspirate

is not warmed. As airway smooth muscle tone increases as airway temperature falls (Souhadra and Souhadra, 1981) cooling of the airway may increase the oxygen cost of breathing. However in the present study, the inspirate was warmed and humidified to minimise airway cooling and reduce subject discomfort.

b) General effects.

The evolution of heat that accompanies the performance of work may itself act to increase the level of metabolism. Robertson et al. (1977_a) and Hales (1973) compared estimates of respiratory muscle oxygen consumption derived from the method of Liljestrand (1918) and calculated from the product of respiratory muscle blood flow and arterio-venous oxygen content difference. They found that respiratory muscle oxygen uptake estimated by measuring the increase in total body oxygen uptake overestimated the oxygen cost of breathing. A significant part of this difference is likely to be attributable to the effect of the increase in temperature accompanying elevated respiratory work rates on general metabolic level. The implication for the present study is that the oxygen cost of breathing may be overestimated at high respiratory and/or limb work rates.

4) Pharmacological effects.

Any increase in work rate or stress will cause the release of circulating catecholamines which have a calorigenic effect and may therefore lead to an overestimation of the oxygen cost of breathing. However, the increase in oxygen uptake from this mechanism should be relatively small in comparison with the increase in oxygen consumption accompanying the performance of work.

5. New Areas Explored in This Thesis

The examination of the testable hypotheses presented at the beginning of this chapter produced much new work pertaining to the suggestion that exercise is limited by respiratory factors at high limb and respiratory muscle work rates. In addition, new work that is of relevance to many different areas of respiratory physiology was produced. The manner in which this work extends what is already known is indicated below.

The various effects of respiratory loading have been extensively examined (see Cherniack and Altose, 1981; Milic-Emili and Zin, 1986 for reviews). However, most previous investigations have been restricted to rest, or to a limited range of ventilation, and exercise has been considered in only a few. The effects of loading over a large range of ventilation induced either by exercise or by CO_2 inhalation have not previously been compared.

Energetics

1) Studies in the absence of loading.

The estimation of the oxygen consumption of, and lactate production by, the respiratory muscles with increasing ventilation in the present study yields much new information. The rise in oxygen consumption accompanying unoccluded hyperpnoea has been investigated in previous studies (see Agostoni et al., 1970 and Shephard, 1955, for reviews), but only in a few has ventilation been elevated to the levels reached in the present study, or been driven by hypercapnia alone. Freedman et al. (1983) and Martin et al. (1984) have conducted studies in which oxygen uptake and

plasma lactate levels were measured at similar or greater levels of ventilation than in the present study. However, the high levels of ventilation were attained by voluntary increases and, although isocapnia was maintained, the reported values of the oxygen cost of breathing during isocapnic voluntary hyperventilation are greater than those when ventilation is driven by an increase in chemical drive (Grollman, 1930; cf. Campbell et al., 1959 and Fritts et al., 1959). In addition, previous workers have not applied estimates of the oxygen cost of breathing during hypercapnic hyperpnoea to evaluate the fraction of oxygen uptake during exercise required by the respiratory muscles.

Past investigations of the energy consumption associated with hyperpnoea have ignored any possible contribution from anaerobic metabolism. Although the measurement of plasma lactate during incremental work tests is not new, measurements when hypercapnic drive increases ventilation have not previously been reported.

2) Studies in the presence of loading.

The effect of loading on total oxygen uptake during exercise has been studied previously by several groups (Cerretelli et al., 1969; Craig et al., 1970; Demedts and Anthonisen, 1973; Dressendorfer et al., 1977; El-Manshawi et al., 1986; Flook and Kelman, 1973). However, measures of gas exchange, ventilation and breathing pattern have not previously been reported as comprehensively as in the present study.

Neither has the effect of inspiratory loading on the oxygen cost of breathing over a range of ventilation been reported previously; this permits estimation of respiratory muscle oxygen consumption during exercise in the presence of loading and

comparison with the oxygen cost of breathing during exercise in the absence of loading.

In investigating the effect of loading on metabolism, the effect of loading on plasma lactate concentrations during incremental work tests has not previously been reported. Further, the effect of loading on venous lactate concentrations during incremental hypercapnia tests has not been assessed before.

Breathing Pattern

1) Studies in the absence of loading.

The effect on breathing pattern of elevating ventilation, whether by exercise or hypercapnia, is well documented (see Cunningham et al., 1986 for review). Notwithstanding this, respiratory drive has rarely been elevated to the levels attained in the present study. Also, there are few reports comparing breathing pattern during exercise and hypercapnia at the same level of ventilation, i.e. isopnoeic comparisons of breathing pattern (Askanazi et al., 1979; Hey et al., 1966; Painter, 1987).

2) Studies in the presence of loading.

The effect of loading on breathing pattern at rest and at elevated levels of ventilation during incremental work tests has been reported by several groups (Axen et al., 1984; Craig et al., 1970; Flook and Kelman, 1973), yet the effect during incremental hypercapnia has been scarcely studied. In the present study the effect in both conditions is studied, i.e. isopnoeic comparison of exercise and hypercapnia induced breathing patterns are made when ventilation is loaded, and may be compared with those in the absence of loading, in the same subjects, at levels of ventilation

exceeding those in most other studies. The further novel aspect of this investigation is the simultaneous recording of breathing pattern and other measures of mechanical performance with measures of energy consumption.

End-Expiratory Volume

The study of breathing pattern, in terms of respiratory phase durations and tidal volume, was extended by estimating changes in EEV. This meant that, where applicable, volume information could be analysed in terms of absolute lung volumes.

1) Studies in the absence of loading

The change of EEV with increasing exercise intensity has been previously reported by several authors. However, only rarely has the work range been as large as in the present study, the most comprehensive recent report being that by Younes and Kivinen (1984).

The effect on EEV of the elevation of ventilation accompanying hypercapnia is the subject of some controversy (cf. Bradley et al., 1974; Cotes et al., 1977; Garfinkel and Fitzgerald, 1978; Garrard and Lane, 1978, Lopata et al., 1983). This may be because ventilation was not greatly elevated in previous investigations. The systematic elevation of drive produced in the experiments reported in this thesis is an attempt to describe the characteristic effect of hypercapnia on EEV.

2) Studies in the presence of loading

The effect on EEV of loading during exercise has not previously been assessed. Past workers have merely reported that EEV at rest falls with inspiratory resistive loading.

The effect of loading on EEV during incremental hypercapnia has also not previously been studied to any significant extent.

Flow Profile

Until recently, the shape of the flow profile has received scant attention (see Hämäläinen, 1983 for review). In the present study 11 variables are used to describe quantitatively the shape of flow profiles and the changes accompanying the elevation of ventilation and/or loading.

The parallel examination of breathing pattern and energetics permits the investigation of the relationship between the shape of the flow profile and energy consumption.

The isopnoeic comparison of flow profiles when driven by exercise or hypercapnia is of considerable interest and has recently been comprehensively studied, in the absence of loading, by Painter (1987). The present study extends this comparison to include loaded breathing. The qualitative assessments of the effect of inspiratory flow-resistive loading, at resting levels of ventilation, reported by Zechman et al. (1957), are to the author's knowledge the only ones reported. The effect of inspiratory flow-resistive loading on flow profile at elevated ventilations has not previously been reported.

CHAPTER 2

METHODS

This chapter describes the subjects, apparatus and methods of data collection used in both experimental series. It is divided into three parts, a brief general introduction to the breathing circuit, a detailed description of each piece of apparatus and how it was employed and finally, an exposition of how experiments were conducted and how the data were collated.

1. The Breathing Circuit

The apparatus used (Figure 2.1) was similar to that of the open breathing circuit described by Ward and Cunningham (1977). The subject, restricted to oral breathing by a nose-clip, inspired and expired through a mouth-piece connected to a Lloyd valve. Gas composition was measured by a mass spectrometer and respiratory variables were displayed on a hot-stylus pen recorder and stored breath-by-breath on a computer.

Inspiratory Line

The inspirate was drawn through a pneumotachograph from a flow delivered in excess of that required by the subject and the pneumotachograph provided breath-by-breath measurement of inspired flows and, by integration, volumes. The gas was supplied from B.O.C. cylinders of oxygen, carbon dioxide and nitrogen, added to air drawn by a vacuum pump from the outside atmosphere. Gas flow from these sources was controlled and indicated by rotameters

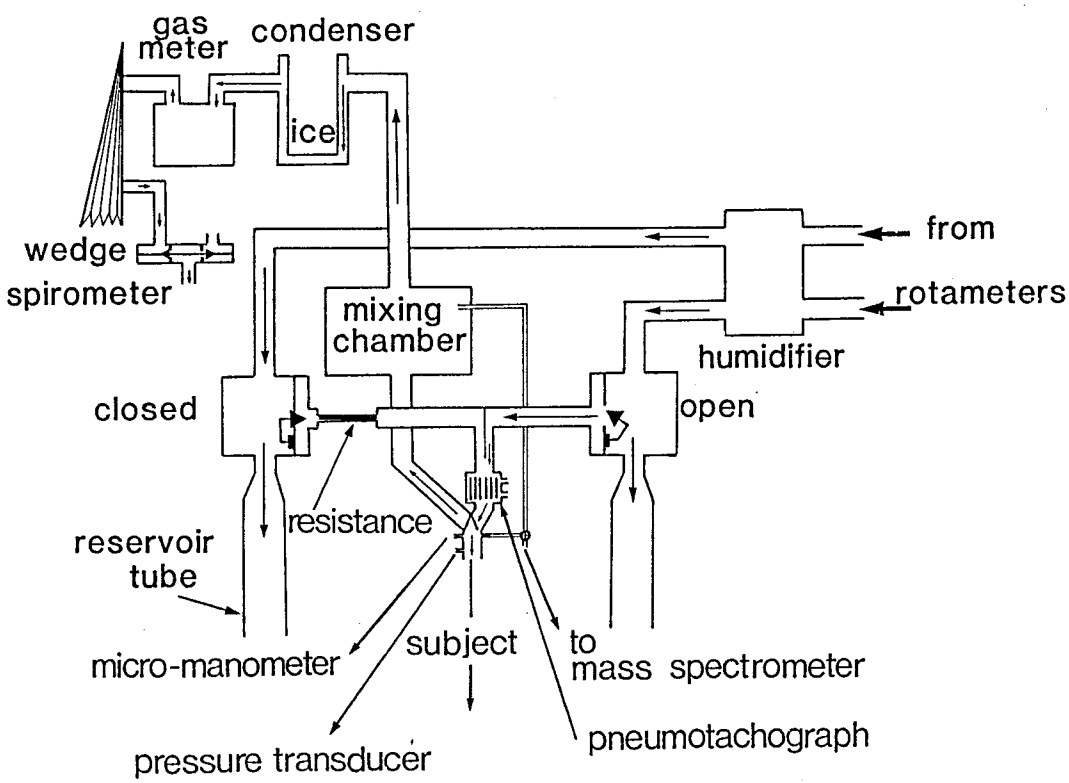


Figure 2.1: Diagrammatic representation of the breathing circuit. Gas of the required composition is supplied, through rotameters, from cylinders or the outside air and reaches the subject via one of the inspired lines after heating and humidification. One of these lines serves as a control, while the other contains a resistance. Excess gas is vented directly to the atmosphere.

(Rotameter Manufacturing Co., Croydon). By adjusting individual flows, gas of any desired composition could be delivered to the subject. Before delivery to the subjects, gas was mixed and passed over water at 40°C to be warmed and humidified.

Expiratory Line

The expirate, separated from the inspirate by a Lloyd valve, passed into an ice-filled condenser. The gas emerging had a lower temperature (10°C), and consequently a lower saturated water vapour pressure. The reduction in water vapour pressure prevented rusting of the dry gas meter which was next in the expired line. The gas meter provided a continuous measure of ventilation, so that the ventilation given by the pneumotachograph and wedge spirometer could be checked. From the gas meter the expirate flowed into a wedge spirometer which had been emptied during the previous inspiration. The wedge spirometer provided a breath-by-breath record of expired volumes.

Timing

Respiratory phase durations were measured by continuously monitoring mouth pressure with a micromanometer; the points of zero pressure signified inspiratory-expiratory transition points. The signals generated from the transition points were used to display respiratory phase durations on the experimental trace and to govern the solenoid-controlled rotary valve which regulated the emptying of the wedge spirometer.

Additional Apparatus

Twin solenoid-controlled rotary valves were used in order to switch between conditions of control and inspiratory loading while

keeping the composition of the inspirate constant (see overleaf). The inspired gas flow was split in two by a "Y" piece, and the two lines were connected to the valves, which worked in a reciprocal manner so that the opening of one occurred simultaneously with the closing of the other. Before the outflows from these valves were joined together upstream of the pneumotachograph, a high resistance was interposed in one line while the other remained unobstructed. It was thus possible to switch between the two inspired lines with different flow-resistances, without interrupting gas flow to the subject.

A further piece of apparatus was a mixing chamber placed on the expiratory side immediately downstream from the Lloyd valve and upstream from the condenser (see p. 2.9). This chamber provided thoroughly mixed expired gas for the measurement of mean expired gas composition using a mass spectrometer sampling catheter positioned in the chamber. The measured mean expired gas composition was used for the calculation of oxygen uptake and carbon dioxide output. It was possible to switch between the catheter sampling from the mixing chamber and a second catheter sampling from the dead space of the Lloyd valve, and so record either mixed expired or tidal gas partial pressures.

In the separate study of flow profiles the pneumotachograph was positioned between the mouthpiece and the Lloyd valve. It was thus common to both inspiration and expiration, and provided a continuous record of gas flow.

Reciprocating Inspiratory Solenoid-Controlled Valves

Each valve consisted of two closely apposed ground glass concentric cylinders (a 100 ml all-glass syringe) with six longitudinal slits of dimensions 1.5 mm x 9 mm, enclosed within a larger plastic cylinder through which gas continually passed (Gardner, 1975). The valve was open when the slits in the glass cylinders were superimposed allowing the subject to inspire from the continuous gas flow through the outer cylinder. The total cross-sectional area for inspired gas flow was 13.5 mm^2.

The inner cylinder (the syringe plunger, the interior of which had been made accessible by sawing off the handle) was connected by string to two solenoids (B.D.C. 7 L/11 Cont. RT6, Benson Brothers, Newmarket). The valve opened and closed when the linear movement of the solenoids (one pulling, the other pushing) was translated into rotation of the inner cylinder. A remote switch controlled opening and closing, the closure of one valve occurring simultaneously with the opening of the other.

After passage through the switching gear excess gas was prevented from immediate dispersion to the atmosphere by reservoir tubes. These consisted of 1.5 m lengths of 0.1 m diameter convoluted tubing. When gas mixtures different from room air were breathed, the reservoir acted as a buffer to ensure that room air was not inspired if inspired flow transiently exceeded the rate of gas delivery from the rotameters.

Flow-Resistances

Three flow-resistances of various degrees of severity were used (lines R2, R3 and R4 of Figure 2.2 describe their flow-

resistance). They consisted of a length of tubing (0.12 m) of diameter 0.015 m, which contained a number of tubes of similar length but of much smaller diameter (0.002 m). Flow-resistance was measured by passing known flows through the resistances and measuring the pressure drop. The pressure-flow relationships for each of the resistances over the 10-200 $L.min^{-1}$ flow range are shown in Figure 2.2, they are non-linear.

Although for convenience breathing was termed "unloaded" when breathing was through the unobstructed circuit, the apparatus itself was a source of flow-resistance.

The resistance to inspiration of the unobstructed breathing circuit (R0 of Figure 2.2) was measured by passing air flows of 10-200 $L.min^{-1}$ down the inspired line to the mouthpiece and measuring the pressure drops. Air flow was measured at ambient temperature and pressure, and was changed 10 $L.min^{-1}$ at a time.

The flow-resistance of the expired line was measured in a similar manner, passing different air flows down the expired line from the mouthpiece to the wedge spirometer. The flow resistance over the 10 - 200 $L.min^{-1}$ range is indicated by line R1 in Figure 2.2.

The measured flow-resistance of the inspired and expired lines are of the same order as previous estimates of adult human airway intrinsic resistance, but small in comparison with the added external resistances used in this study. Assuming a normal value of airway resistance of between 3-12 mm H_2O at 30 $L.min^{-1}$, (Comroe et al., 1962) the external resistances were between 6-25 (R2), 13-50 (R3) and 25-100 (R4) times the intrinsic resistance of the subjects' airway at a flow of 30 $L.min^{-1}$.

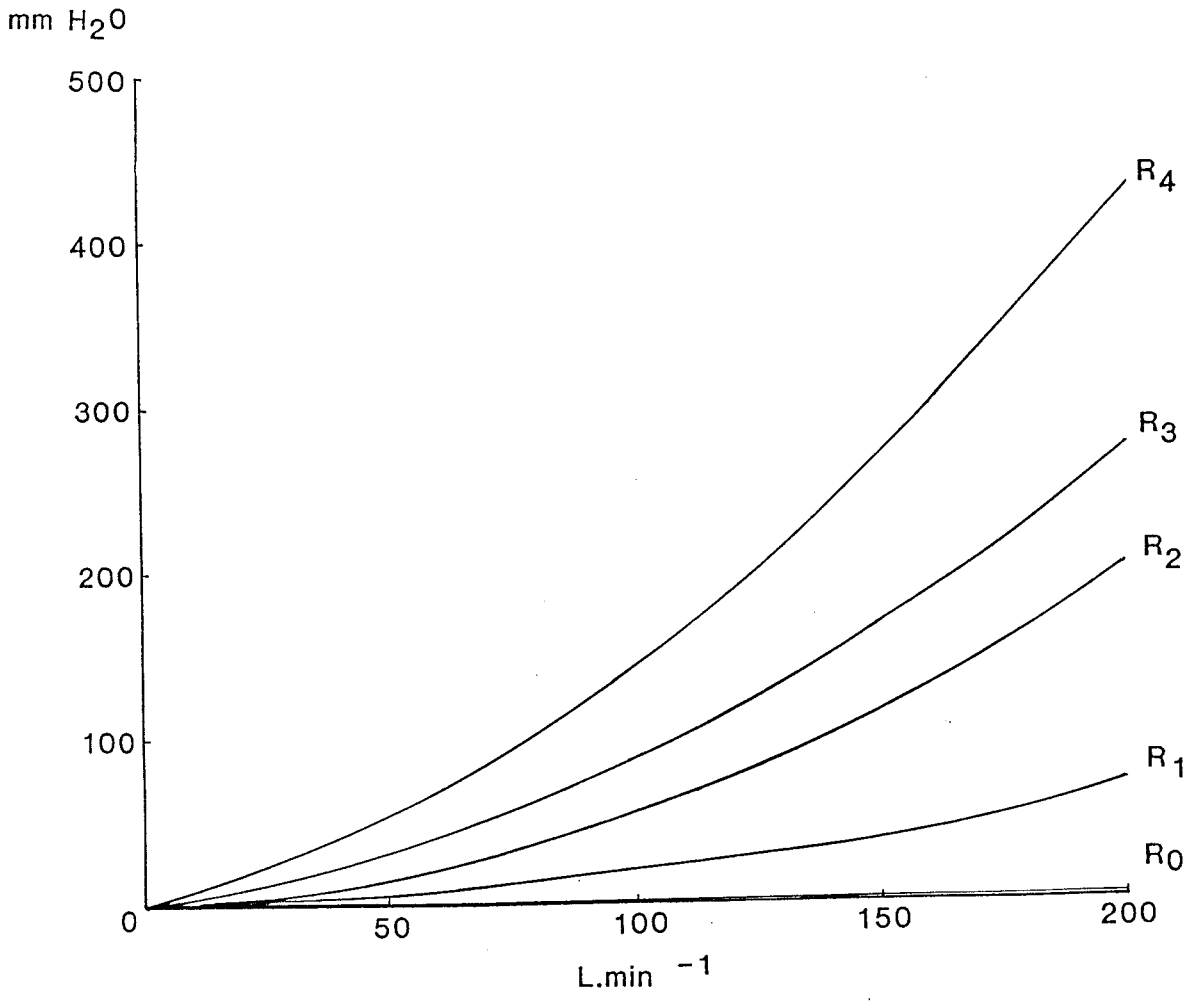


Figure 2.2: Pressure-flow characteristics of the breathing circuit and the added flow-resistances at steady-flows up to 200 $L.min^{-1}$ (ambient temperature and pressure). R0 - inspiratory line; R1 - expiratory line; R2, R3 and R4 - the added flow-resistances.

Pneumotachograph

The pneumotachograph (A. Fleisch, supplied in the U.K. by P.K. Morgan, Chatham, Kent), consists of a cylindrical metal case (of approximately 0.04 m diameter and 0.04 m length) containing metal foil crimped to form a series of thin-walled tubes. The tubes provide a small resistance to flow, which produces a pressure drop along the length of the pneumotachograph. As long as flow through the tubes remains laminar this pressure drop is linearly related to flow (Poiseuille's law, see below). This relationship was examined empirically by passing flows of up to 400 $L.min^{-1}$ through the pneumotachograph; flow was changed incrementally and decrementally in steps of 25 $L.min^{-1}$. The results obtained are shown in Figure 2.3, where it can be seen that the output of the pneumotachograph increased linearly with flow up to 400 $L.min^{-1}$.

Assuming flow to be sinusoidal, mean flow is related to peak flow by a factor of 2/pi. A peak flow of 400 $L.min^{-1}$ will thus correspond to a mean flow of almost 260 $L.min^{-1}$. Assuming the duration of inspiration and expiration to be equal, this is equivalent to a ventilation of almost 130 $L.min^{-1}$. This is well in excess of the levels of ventilation encountered in the present study, so the pneumotachograph calibration is linear throughout. If flow profiles become progressively squarer with increasing ventilation as has been suggested (Hämäläinen, 1983), mean and peak flow are related by a factor less than 2/pi, and so the pneumotachograph calibration is linear to even higher levels of ventilation.

Poiseuille's law for laminar flow through a smooth-walled tube states

$$\text{Flow} = \frac{\pi \, r^4 \, \Delta P}{8 \, \eta \, l}$$

η = viscosity
ΔP = pressure difference
r = radius of tube
l = length of tube

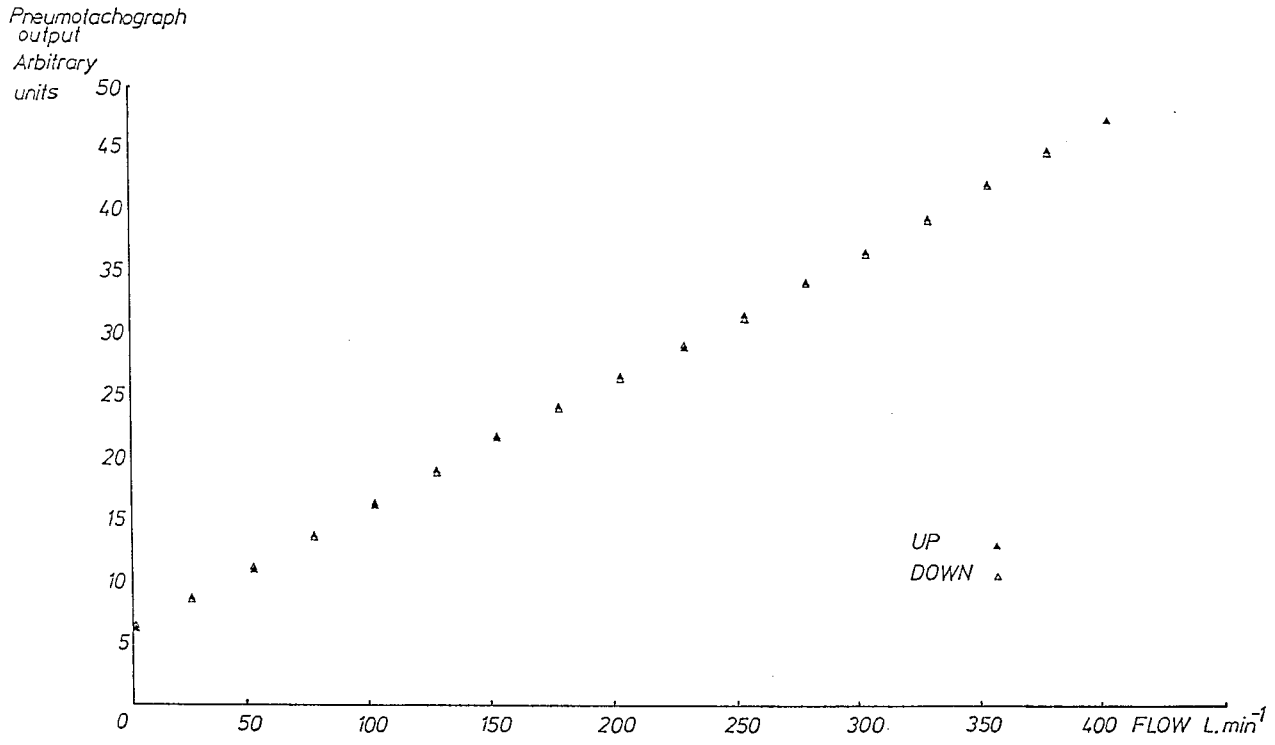


Figure 2.3: The output of the pneumotachograph plotted against steady-flows levels, at 25 $L.min^{-1}$ intervals, up to 400 $L.min^{-1}$. Data were obtained during both rising and falling flow (at ambient temperature and pressure). The relationship is linear up to 400 $L.min^{-1}$.

Theoretically the pressure drop across a pneumotachograph though dependent on viscosity should be independent of the density of the gas passing through it. However, in practice this may not be the case. It is known that as gas emerges from the small tubes that make up the pneumotachograph a small degree of turbulent flow ensues, the end-effect. When flow is turbulent the density of the gas flowing affects the pressure drop recorded.

The effect on measured volume of the changes in gas density and viscosity that accompany changes in gas composition was assessed by Metias (1981). He found that changing inspired gas concentrations from those in air (decreasing F_IO_2 to 10%, and in a second series also increasing F_ICO_2 to 10%) had little effect on recorded inspired volume ($V_{T,I}$). Despite the differences in gas viscosity (1.8%) and density (5.4%) the mean change in recorded $V_{T,I}$ was only 0.1%, S.E. 0.3%. As the present study did not involve an increase in the inspired carbon dioxide fraction of more than approximately 8% (60 torr) the recorded flows and levels of ventilation will display only negligible errors.

The pneumotachograph was used unheated: though heating has the advantage of preventing condensation of water vapour its use may give rise to errors. The recorded pressure drop is a function of gas viscosity, and viscosity is dependent on temperature. Therefore differences in the degree to which gas is heated could have a significant effect on measured tidal volumes. Heating the pneumotachograph could also warm inspired gas to uncomfortably high temperatures.

The pneumotachograph was calibrated before and after experiments to ascertain whether any change in the response characteristics had occurred, e.g. from condensation of water

vapour, or from saliva blocking some of the fine tubes that make up the pneumotachograph.

Pneumotachograph Transducer

The pressure drop across the pneumotachograph was measured using a low pressure differential transducer (10825 PM 15 E Statham, Hatorey, Puerto Rico). The signal from the transducer was proportional to the measured pressure drop and therefore to flow. In flow studies, this signal was relayed directly to the computer and recorded. In the studies of breathing pattern and gas exchange, electronic integration of the signal was performed to give breath-by-breath inspired volumes before being relayed to the computer.

The accuracy of volume measurement by both wedge spirometer and pneumotachograph was investigated by Metias (1981) who connected the breathing circuit to a reciprocating pump at the Lloyd valve and set the pump to "breathe" through the system at a variety of stroke volumes and cycle times (Metias, 1981). The results of this procedure are shown in Figure 2.4. Volumes recorded by pneumotachograph and wedge spirometer are extremely close to the actual volumes "breathed" over the entire frequency and stroke volume range. The normal calibration of the system was performed with the pump volume set to 1 L. and the frequency to 20 cycles min^{-1}.

Lloyd Valve

This is a two-way, low resistance, directional valve with a dead space of 0.05 L. The valve consists of two perspex flaps closed by gravity. Opening is by changes in mouth pressure, requiring 1 mm H_2O to open the inspired flap and 2 mm H_2O the expired. The

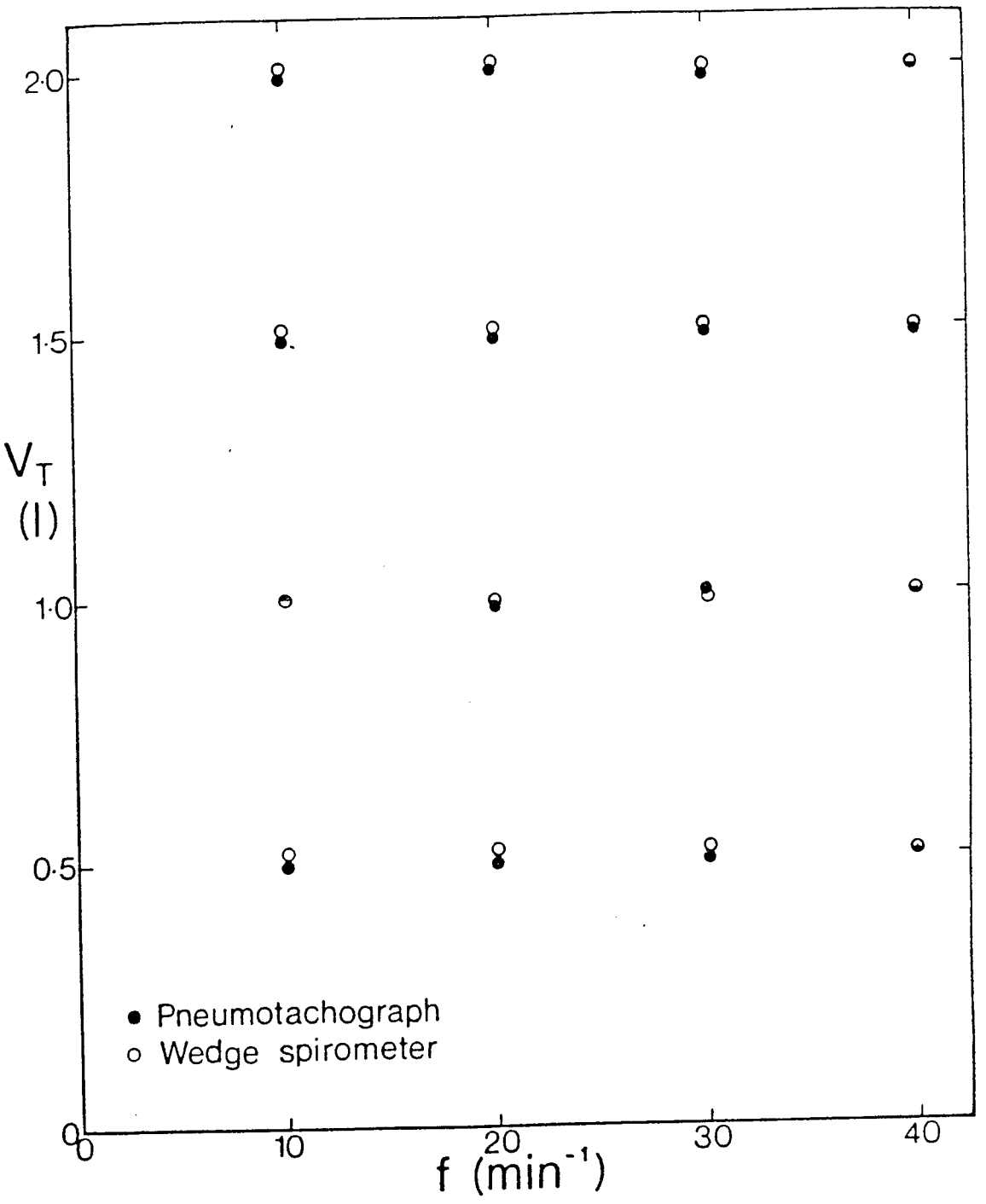


Figure 2.4: Simultaneous measures of "pump-breath" volume from integrated pneumotachograph output and wedge spirometer at a variety of volumes and frequencies. The recorded values agree well over the entire range.

seal between the perspex valve flaps and the metal case was not perfect when the valve was dry. To produce a better seal the valve was therefore lightly wetted before experiments started, the seal was maintained throughout the experiment by subjects' saliva.

Mixing Chamber

The mixing chamber was a perspex box the corners of which were rounded by moulded plastic to prevent stationary pockets of gas forming. The box contained an anaesthetic bag and a perspex baffle. The chamber is diagrammatically represented in Figure 2.5. The volume of the box was 4.25 L., sufficient to contain all single expirations encountered in this study.

Preliminary mixing was effected by the perspex baffle at the entrance to the chamber. The baffle consisted of perspex disks eccentrically aligned on a perspex spindle. Having passed the baffle, gas flowed into the anaesthetic bag. Though the bag was punctured at the distal end by a hole of 0.01 m diameter, the incoming gas tended to inflate the bag rather than pass straight through because of its resistance to flow. The expirate was thoroughly mixed during inflation of the bag.

The bag gradually deflated as expiratory driving pressure fell towards the end of expiration, the weight of the rubber wall of the bag forcing its contents into the box.

The accurate measurement of oxygen uptake was central to the anticipated experiments so a number of tests were conducted to assess the efficiency of mixing and the accuracy with which mean expired gas concentrations could be measured.

The efficiency of mixing was tested initially by injecting boluses of smoke into the chamber, driven both by a reciprocating

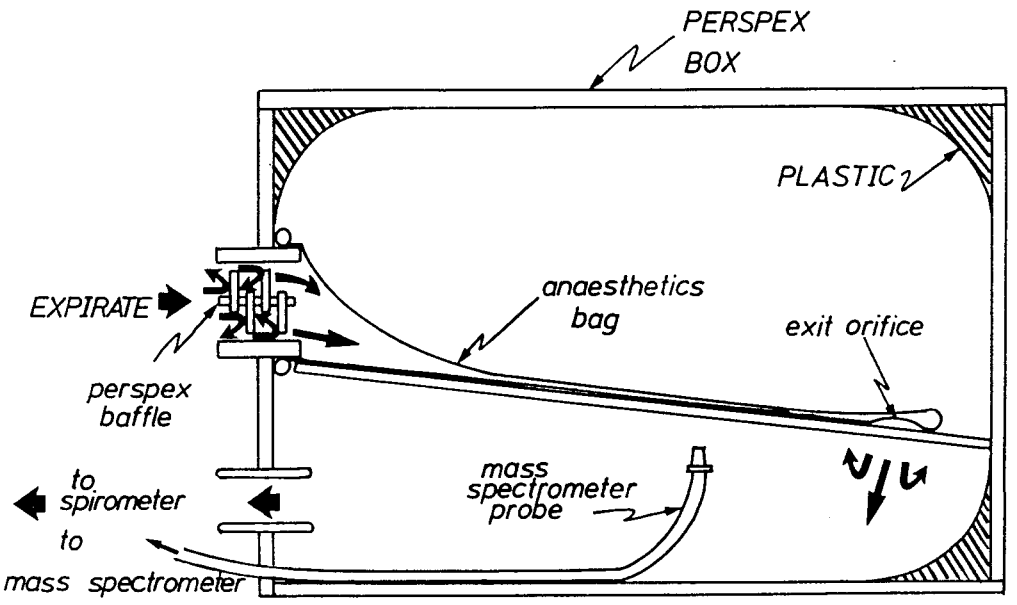


Figure 2.5: Diagrammatic representation of the mixing chamber. Gas mixing is initiated by a perspex baffle and continues during inflation of the anaesthetics bag. Gas may be sampled at any time by connecting the probe to the mass spectrometer.

pump and by exhalation. Assessed subjectively from the uniformity of distribution of smoke, mixing appeared to be good.

A quantitative assessment of the goodness of mixing was obtained from the injection of boluses of carbon dioxide by a reciprocating pump. The uniformity of the distribution of CO_2 was measured by sampling with a mass spectrometer probe from all areas of the chamber. This procedure showed carbon dioxide to be uniformly distributed.

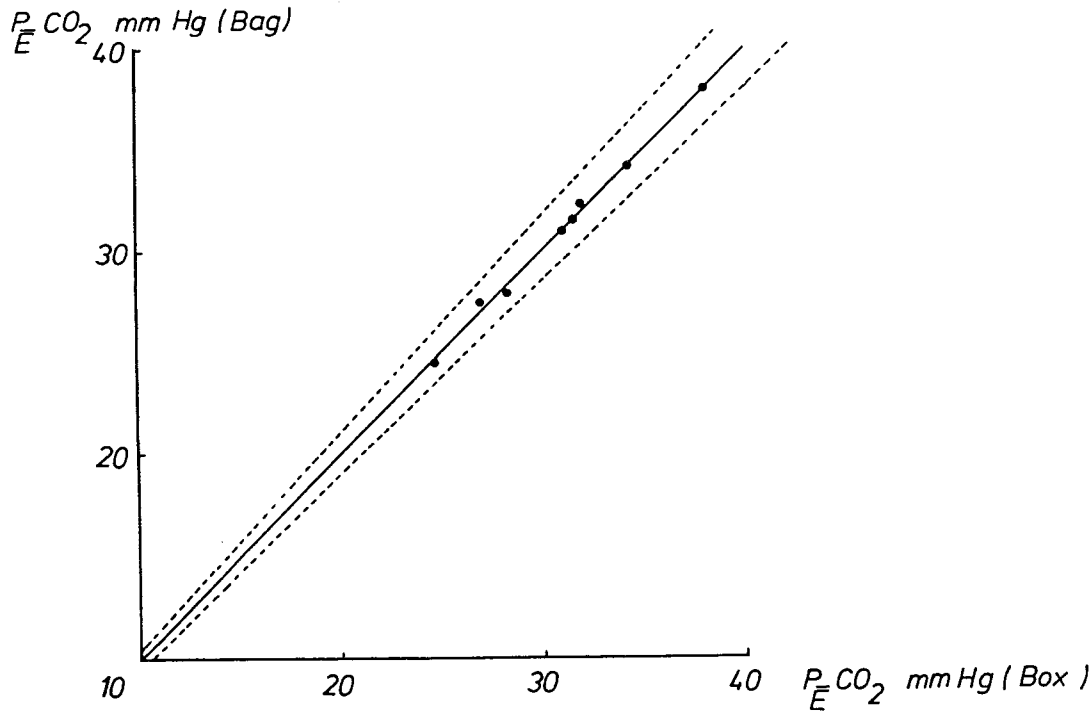
The validity and reliability of determinations of mean expired gas composition and the calculated gas exchange values were assessed by comparing determinations obtained by using the mixing chamber with those obtained from Douglas bags collected sequentially.

First, measurements of mean expired gas concentrations were made during light or moderate exercise in air or hypoxia. Subjects were allowed 4 minutes to achieve a steady state in whatever conditions prevailed. Then a Douglas bag was partially filled by expired gas from the subject. After thorough mixing of its contents the bag was emptied and reconnected to the tap. A wash-out of the bag prior to the gas collection was performed so that any residual gas present in the bag would be of approximately the same composition as the gas to be collected. After bag wash-out, the gas in the chamber was sampled and O_2 and CO_2 compositions recorded for 2 minutes. The tap was then turned so that the expired gas flowed into the Douglas bag. Gas was collected for 2 minutes. A mass spectrometer sampled the contents of the bag to measure the gas tensions. Thus, sequential samples of expired gas were analysed for comparison.

The results of these bag - box comparisons are presented in Figures 2.6a-b and 2.7a-b. If bag and box had given exactly the

Figure 2.6: Comparison of the partial pressures of mixed-expired gas sampled from the mixing chamber and from a Douglas bag (eight determinations). a) Oxygen; r = 0.999, slope = 0.995. b) Carbon dioxide; r = 0.999, slope = 1.003. The full lines indicate the relation of unity, the dotted lines mark the ± 5% error boundaries.

a)


$P_{\bar{E}}CO_2$ mm Hg (Bag)
40
30
20
10
20
30
40
$P_{\bar{E}}CO_2$ mm Hg (Box)

b)

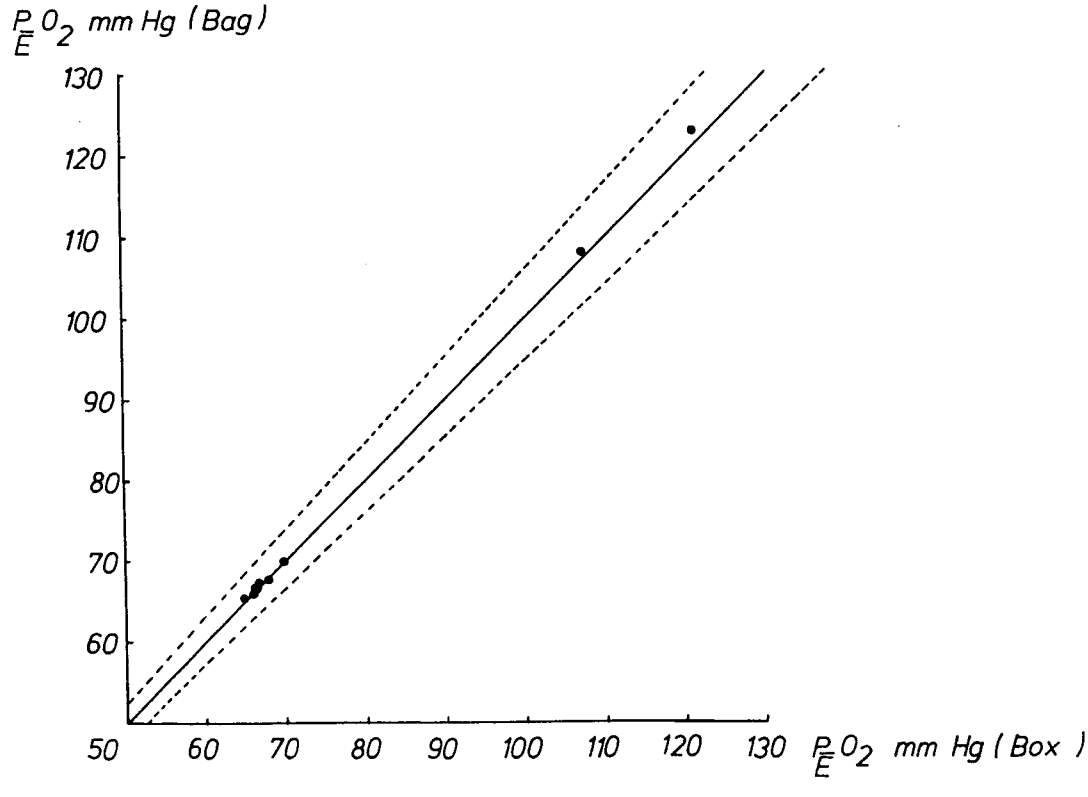
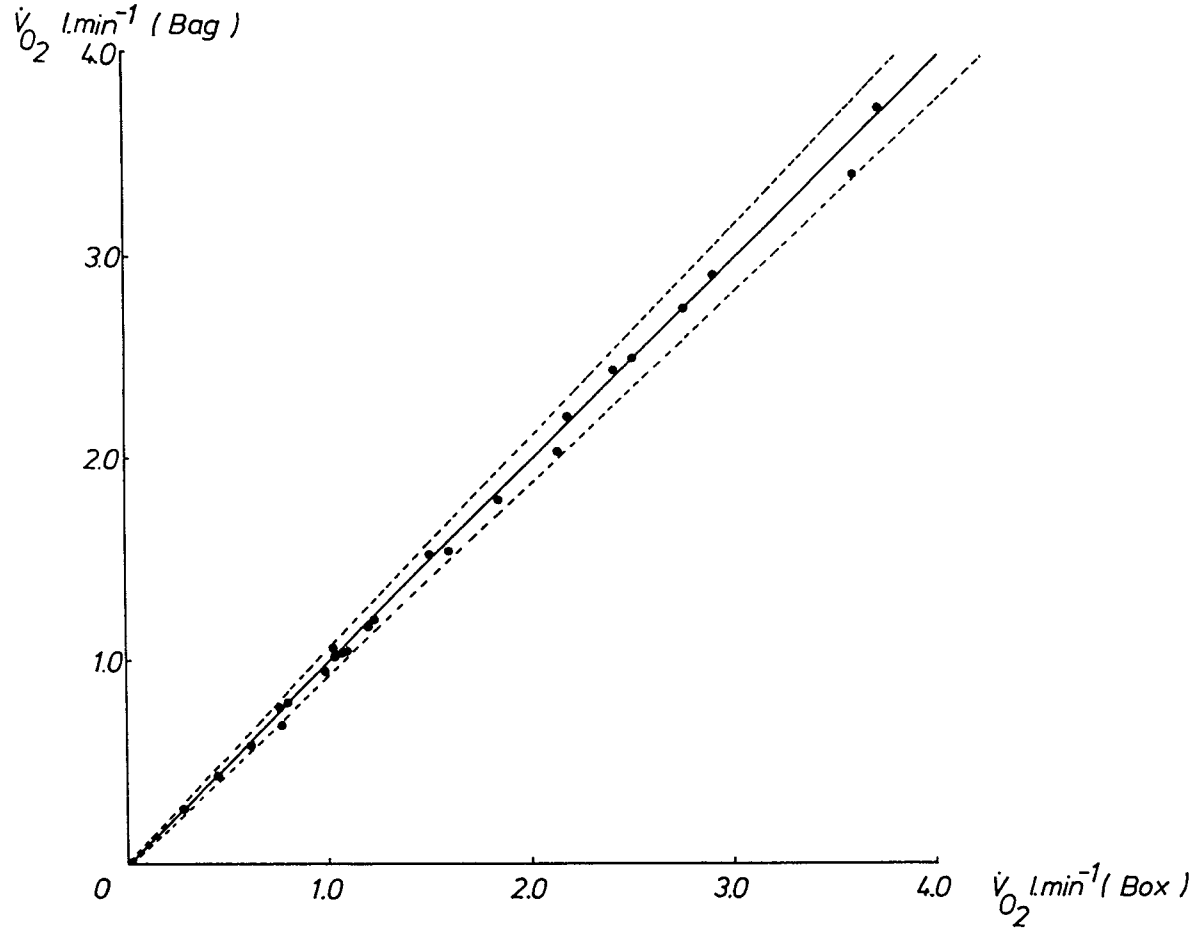
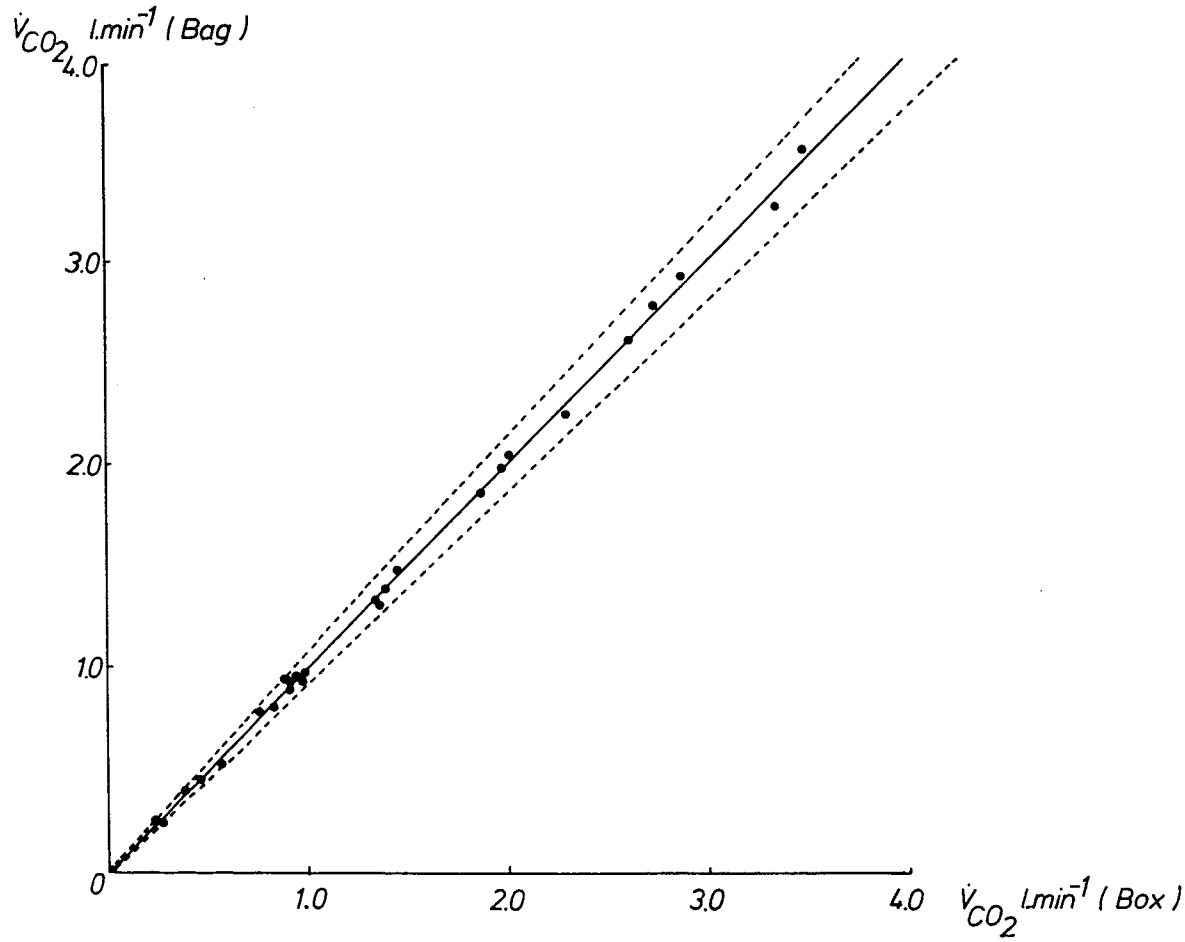

$P_{\bar{E}}O_2$ mm Hg (Bag)
130
120
110
100
90
80
70
60
50
60
70
80
90
100
110
120
130
$P_{\bar{E}}O_2$ mm Hg (Box)

Figure 2.7: Comparison of oxygen uptake and carbon dioxide elimination computed using gas compositions measured from the mixing chamber and from a Douglas bag. These data were obtained during incremental work tests by four subjects. a) Oxygen; r = 0.999, slope = 1.006. b) Carbon dioxide; r = 0.999, slope = 1.025. The full lines indicate the relation of unity, the dotted lines mark the $\pm$ 5% error boundaries.

a)


$\dot{V}_{O_2}$ l.min^{-1} (Bag)
4.0
3.0
2.0
1.0
0
1.0
2.0
3.0
4.0
$\dot{V}_{O_2}$ l.min^{-1} (Box)

b)


$\dot{V}_{CO_2}$ l.min^{-1} (Bag)
4.0
3.0
2.0
1.0
0
1.0
2.0
3.0
4.0
$\dot{V}_{CO_2}$ l.min^{-1} (Box)

same values, the regression coefficient of one upon the other would be unity with a correlation coefficient of unity. The computed line of regression of mean expired oxygen partial pressure (bag upon box) has a slope of 0.995 and a correlation coefficient of 0.999. For mean expired carbon dioxide the bag - box relationship has a slope of 1.006 and a correlation coefficient of 0.999.

Secondly, in a separate study, oxygen uptake ($\dot{V}O_2$) and carbon dioxide elimination ($\dot{V}CO_2$) determinations by bag and box during incremental work tests by four subjects were compared (work rate rising in 50 W steps to 200 W). The least squares error lines of best fit describing the bag-box $\dot{V}O_2$ and $\dot{V}CO_2$ relationships have slopes and correlation coefficients of 1.006 and 0.999 ($\dot{V}O_2$) and 1.025 and 0.999 ($\dot{V}CO_2$) respectively.

The determination of mean expired gas concentrations and thereby $\dot{V}O_2$ and $\dot{V}CO_2$ using the mixing chamber proved to be extremely accurate, the error of measurement never exceeding 5% (see Figures 2.6 and 2.7).

Condenser

This was a "U" shaped metal box insulated with polystyrene, with a central depression filled with ice. When expired gas entered the condenser it was immediately exposed to a large surface of cooled metal which reduced its temperature to about 10°C. The reduction in temperature reduced the saturated water vapour pressure from approximately 44 torr at the mouth to approximately 9 torr.

Gas Meter

The inclusion of a dry gas meter (type C.D., Parkinson-Cowan Ltd., London) in the expired line provided a continuous record of the

expired volume, independent of any other apparatus, which could be used to check the value of the ventilation calculated from the wedge spirometer and pneumotachograph signals.

Each revolution around the analogue volume scale on the meter indicated the passage of 10 litres of gas. A microswitch was fitted to the gas meter; this was momentarily closed on each revolution, completing a circuit that included the hot-stylus pen recorder and thus recorded the passage of every 10 litres of gas on the experimental trace.

The output of the meter was alinear for volumes of less than 10 litres, so the volumes of individual breaths could not be accurately measured; calibration against a Collins bell gasometer (Warren E. Collins Inc., 220 Wood Rd., Braintree, Mass., U.S.A.), at flows of 6, 30, 50 and 100 $L.min^{-1}$, showed that the measurement of large gas volumes was extremely accurate: the error of measurement never exceeded 1%.

Wedge Spirometer

After passing through the dry gas meter, the expired gas flowed into a high compliance wedge spirometer of the bellows type (Cryotech, Wallingford, Oxon.). Gas passing into the spirometer expanded the bellows. The expansion pulled a magnetic rod through a coil inducing an electromotive force (e.m.f.) in the coil. The e.m.f. induced was proportional to the rate of movement of the rod, which was in turn proportional to the rate of flow of gas into the spirometer. Electronic integration of this e.m.f produced a voltage proportional to expired volume.

Electronics

Breath-by-breath measurement of respiratory variables required that the wedge spirometer should be emptied, and that the flow integrators that measured inspired and expired volumes were reset, after each expiration. These functions were achieved by monitoring mouth pressure continuously with a micromanometer (M.D.C. 300, Hilger-IRD Ltd., London). The method and apparatus are represented diagrammatically in Figure 2.8.

The output of the micromanometer passed to a level trigger. At the onset of inspiration when mouth pressure changed from positive to negative the level trigger detected the transition point, giving a high voltage output as pressure passed through zero. This high output voltage continued until the trigger detected the zero pressure point as pressure changed from negative to positive at the onset of expiration, at which point the output voltage was reduced.

The voltage steps were translated into voltage impulses by electronic differentiation. The expiratory impulse occurring at the onset of expiration was used to reset the integrator of the pneumotachograph transducer signal and to interrupt the time-ramp transiently.

The time-ramp was the output signal of a circuit integrating a constant voltage. By virtue of being transiently interrupted by the expiratory impulse and being reset by the inspiratory impulse at the onset of inspiration, the time-ramp when displayed on the pen recorder indicated the respiratory phase durations. The times stored on the computer were not measured from the time-ramp, but using the computer real-time clock, as the time between inspiratory and expiratory volume peaks.

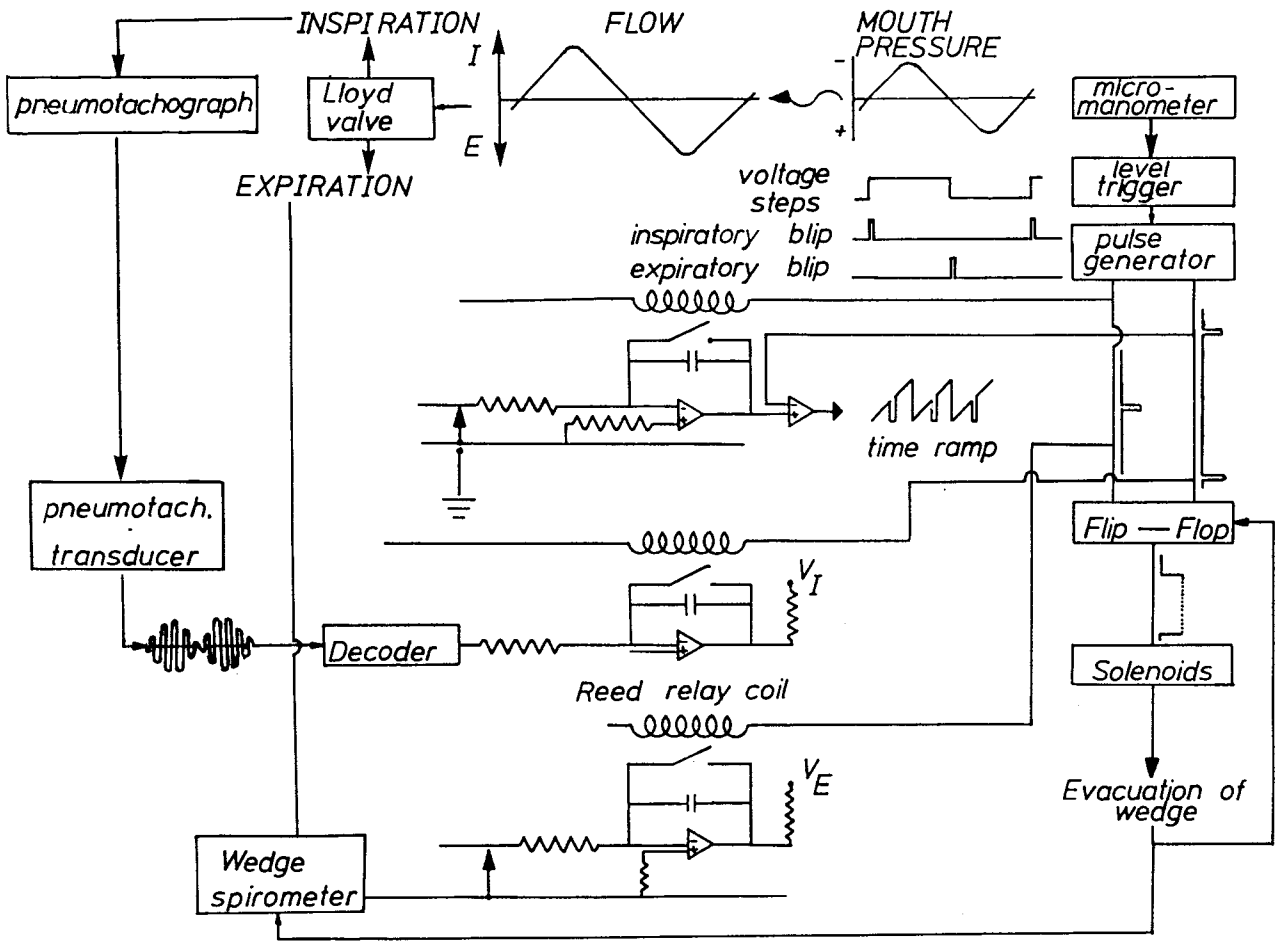


Figure 2.8: Schematic representation of the mechanical and electrical functions of the breathing circuit apparatus. The three electronic circuits illustrated represent the integrators that produce $V_{T,I}$, $V_{T,E}$ and the time ramp.

The main function of the inspiratory impulse was to control the rotary solenoid-controlled valve interposed between the wedge spirometer and a suction pump. The impulse initiated opening of the valve which connected the spirometer to a suction pump and thereby caused the spirometer to be evacuated. The volume to which the spirometer was evacuated was controlled by a microswitch that was tripped when the bellows impinged upon it, closing the valve and so preventing further evacuation.

Mass Spectrometer

1) Operation.

The mass spectrometer (MGA 200, Centronics, New Addington, Croydon) was invaluable in these experiments in providing both tidal and mean expired gas concentrations. Tidal gas was sampled from the portion of the Lloyd valve common to both inspiration and expiration. Mixed expired gas was sampled by a second catheter present within the mixing chamber.

Sample gas flow (20 $ml.min^{-1}$) along the capillaries (1.2 m long, 0.0025 m diameter) was laminar so time-dependent changes in gas concentration at the tip were maintained, aided by Taylorian dispersion within the capillary. Gas travelling down the capillary passed into the sample chamber from where a small portion "leaked" into the ionisation chamber. This molecular leak ensured that molecules of gas entered by diffusion, so that the number of molecules entering was proportional to the partial pressure. Once inside the ionisation chamber the molecules were bombarded by high velocity thermally produced electrons. The ions produced by the collision of these electrons with gas molecules

were accelerated through the quadrupole mass filter by a high voltage.

The quadrupole consisted of four parallel rods arranged in a square. Opposite rods were subject to equal D.C. potentials and adjacent rods were subject to opposite potentials. Oscillating potentials in the radio frequency range were superimposed on this constant potential. As the field oscillated the ions produced were alternately attracted and repelled by the rods. By adjusting the amplitude of oscillation of the A.C. voltage the quadrupole could be made to act as a band-pass mass filter. The oscillation of ions with a high charge/mass (e/m) ratio became unstable in the oscillating field and they crashed into the quadrupole rods. Ions with low e/m ratio once accelerated towards the rods, did not respond quickly when the field reversed and drifted into the rods. By adjusting the D.C./A.C. ratios of the two sets of rods, the width of the pass band of the filter could be made sufficiently narrow to pass only one species of ion.

Pseudo-continuous measurement of up to eight gases was possible by multi plexing. This involved the imposition of a given D.C./A.C. ratio for 2.5 ms, sufficient to permit passage and measurement of the concentration of one ion species. The ratio then changed to permit passage of a different ion species, and so on for up to eight ion species. An electron multiplier measured the number of ions that successfully traversed the quadrupole and updated the measured ion current every 20 ms.

2) Automatic Sensitivity Control.

The ion currents (proportional to partial pressure) were fed to an Automatic Sensitivity Control (A.S.C.) circuit. The A.S.C. consisted of a light emitting diode-controlled negative feedback

circuit which continuously summed the ion currents present and adjusted the gain of the inputs similarly such that they added up to a constant arbitrary value. The output was the ratio of the individual ion currents to the total current, ie. the fractional concentration of each dry gas with respect to all the gases measured. The advantage of using the A.S.C. circuit was that changes in saturated water vapour pressure, or pressure within any part of the system (such as at the capillary tip during respiratory effort) had no effect on output. One drawback of the A.S.C was that all gases of changing concentration had to be measured. However in the present study only four gases of significant concentration were encountered, oxygen, carbon dioxide, nitrogen, and argon.

3) Speed of Response.

The measurement of gas concentrations by the mass spectrometer, though rapid, took place with a constant delay between input at the capillary tip and output from the A.S.C. circuitry. This delay had two components, the first, known as the lag time, was the time for gas presented at the capillary tip to travel down the capillary into the sample chamber. For a step change of gas at the capillary tip no change in output was seen during this time. The second component, known as the analyser response time, was the time taken for a step change of concentration in the sample chamber to be registered at the electron multiplier. This was a function of both the behaviour of the gas molecules within the system and the electronic processes involved in analysis. Output during this phase rose exponentially to the new steady-state value.

The presence of these delays meant that simultaneous gas and volume events were out of phase when relayed to the computer. To restore the correct phase relationship capillary lag and analyser response times were measured. To accomplish this the mass spectrometer probe was fitted with an electrically conducting needle that passed into a tube containing 5% carbon dioxide in air. Two connections were positioned on either side of the needle to complete a circuit including a battery and an oscilloscope. Withdrawal of the needle into room air broke this circuit triggering the time-base of the oscilloscope at the same time as presenting a step change of gas concentration at the catheter tip. This procedure was repeated until an average response was built up. The times determined by this procedure were

Capillary lag time - 200 ms

Analyser response time - 60 ms

(time to reach 90% of new steady-state value)

These times were incorporated into the computer data collection program to bring gas concentration and volume data into phase.

4) Stability.

The long term stability of the mass spectrometer in the face of disturbances not nullified by the A.S.C. circuitry (e.g. temperature of electronic circuitry) was assessed by continuously monitoring output for twelve hours: drift never exceeded 1%.

The mass spectrometer was calibrated before and after experiments in order that any drift of baseline or gain during the experiment would be noted. Calibration was performed with two gas

mixtures. The first, atmospheric air, provided a high oxygen, low carbon dioxide standard. The second, cylinder gas whose exact composition had been determined by Lloyd-Haldane analysis, supplied a low oxygen, high carbon dioxide standard, similar in composition to normal alveolar air. The linearity of response has been reported to be of the order of ± 0.3%, and the drift of the calibration not to exceed 0.5% (I. Scott, 1983).

Estimating Changes in End-Expiratory Volume

It was not feasible to measure end expiratory volume (EEV) directly, but a simple and convenient method was devised to estimate changes (see Figure 2.9). The method assumes that the maximum volume of gas contained in the lungs does not change. Therefore, any change in inspiratory capacity measured from end expiration can be ascribed to a change in EEV.

Subjects were instructed to inspire maximally upon the illumination of a light at end expiration (so the maximal inspiratory effort took place following a spontaneous expiration, not a forced one). Such measurements were made at rest and at each loading condition as ventilation rose. The estimated change in EEV was calculated as the difference between the maximal inspired volume achieved at a given ventilation and that at rest.

Since this method relied heavily on the subjects' cooperation, it was not surprising that the experimental data showed considerable variability.

Plasma Lactate Analysis

Lactate analysis was performed by the fully enzymatic ultraviolet spectrophotometric method (Boehringer Mannheim, GmbH Diagnostica, Lewes, Sussex). The test is fully described by Noll (1974).

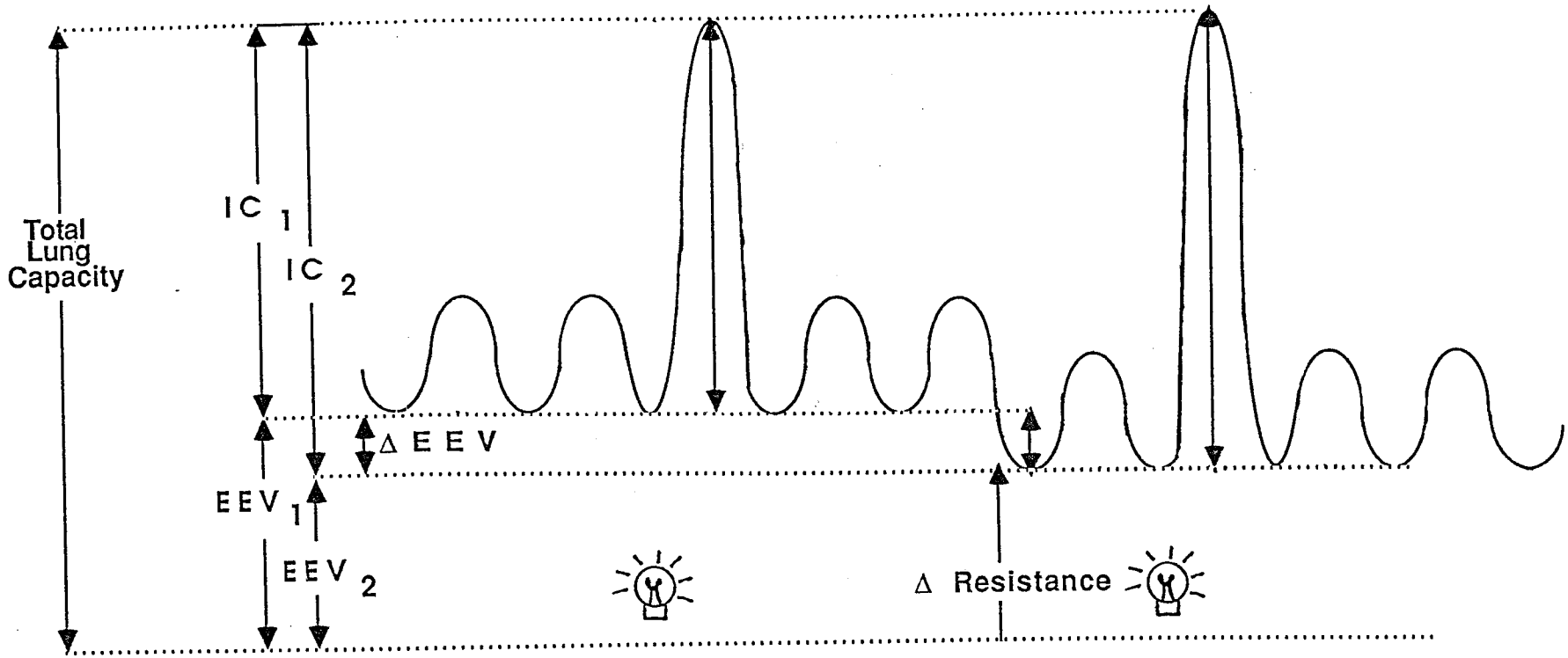


Figure 2.9: Schematic representation of the method of estimating changes in end-expiratory volume (EEV). Inspiratory capacity (IC) was measured before and after changes in loading and exercise or hypercapnia level; subjects were required to make a maximal inspiratory effort following the illumination of a light at end-expiration. Assuming that total lung capacity remains the same, the change in IC could be assumed to reflect the shift in EEV.

Essentially the analysis involved the conversion of lactate to pyruvate by an excess of NAD^+, which was reduced in the process to NADH, a reaction catalysed by lactate dehydrogenase. To push the equilibrium of the reaction completely to the right the pyruvate formed was removed by the addition of L-glutamate which combined with the pyruvate formed to produce L-alanine and oxoglutarate.

Blood samples of 2 ml volume were taken by syringe from an indwelling venous catheter. Care was taken to avoid contact between the sample and experimenters' or subjects' skin both for reasons of safety and because sweat contains considerable amounts of lactate. The sample was immediately transferred to a test tube containing two drops of fluoride/EDTA and thoroughly mixed. Plasma was obtained by centrifugation at 300 revolutions per minute for five minutes. If not immediately analysed for lactate concentration the plasma was transferred to a freezer to be thawed and analysed at a later date.

The plasma samples were analysed by spectrophotometric determination of the amount of NADH (which has an absorption band of 365 nm). This was proportional to the original concentration of lactate.

Bicycle Ergometer

All experiments were performed with the subjects sitting on a bicycle ergometer, the seat height of which was kept constant for each subject. The desired work rate was set and displayed on an analogue scale calibrated from 0 to 400 watts.

The ergometer (Ergotest Universal Ergometry Unit, Jaeger, Vitalograph, Buckingham) employed a dynamo-electrical mechanism to keep work rate independent of pedalling frequency. The flywheel

of the ergometer powered a dynamo which gave an output proportional to the rate of revolution of the flywheel. This voltage was relayed to an electromagnet whose field exerted a braking effect. The circuit was constructed such that as the rate of pedalling and therefore dynamo output increased, the field strength and therefore braking power of the magnet was reduced keeping the work rate constant irrespective of pedalling frequency.

However, the dynamo-electric mechanism did not keep external work rate absolutely constant as it did not compensate for changes in work done in lifting the legs if pedal rate changed. To minimise this factor subjects were asked to chose a pedal rate that was comfortable in the 60-80 revolutions per minute range and to maintain that rate throughout the series of experiments. This procedure proved successful in practice and pedal rate was seen to vary little during or between experiments.

The calibration of the ergometer was checked by measuring the voltage input to the electromagnet at different displayed work rates. Figure 2.10 shows that this relationship was nearly linear, and that the displayed work rate and voltage input were highly correlated (r=0.999), indicating that a unit increase in displayed work produced a unit rise in work performed. The stability of this relationship over time was checked by comparing work rate - $\dot{V}O_2$ data obtained from the same subject at points distant in time (5 months). Figure 2.12 shows the superimposed plots of these sets of data. Similar displayed work rates gave identical or closely similar $\dot{V}O_2$ values in the two experiments.

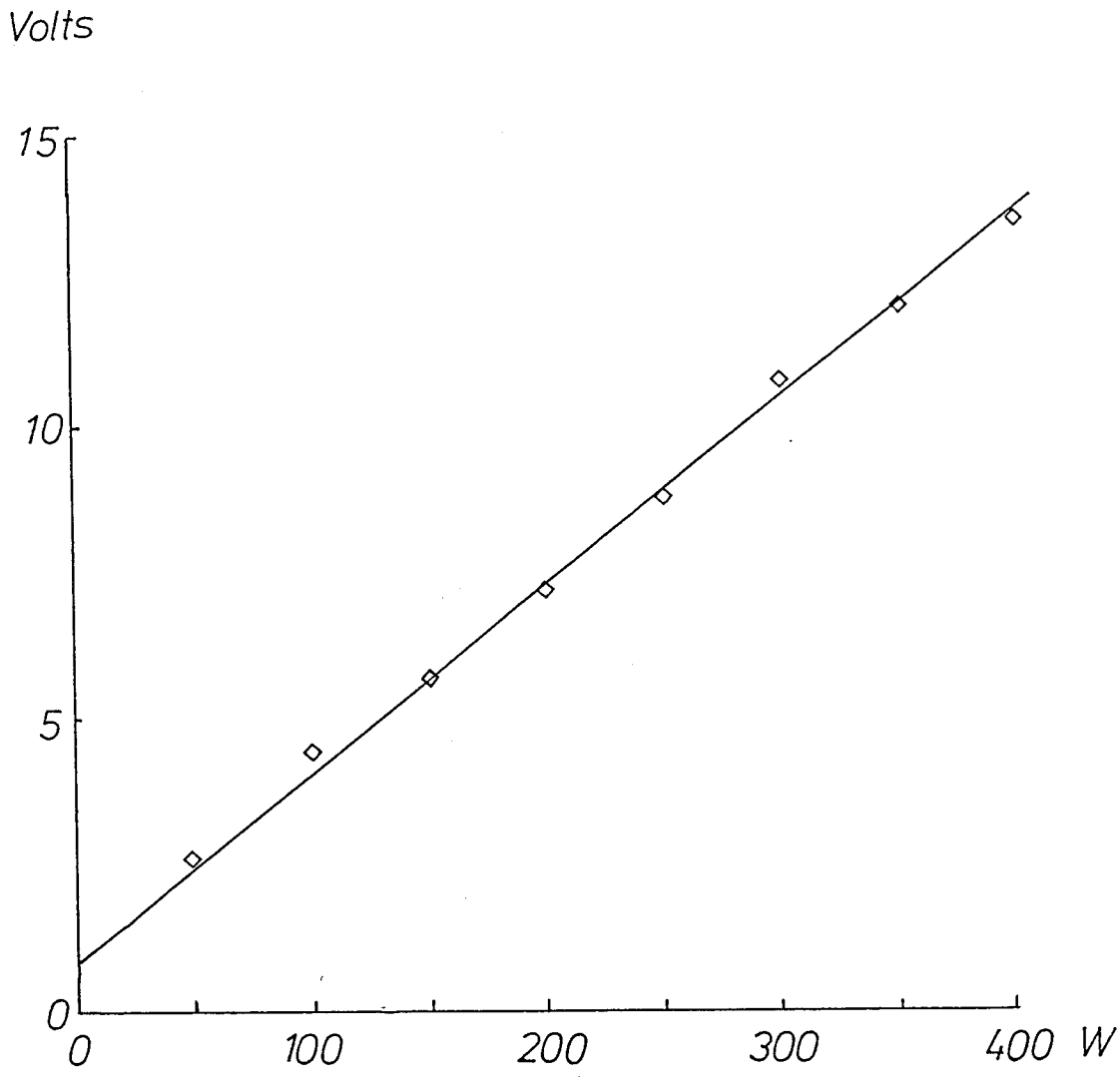


Figure 2.10: The relation between the voltage input to the "braking" electromagnet and the work rate indicator on the bicycle ergometer. The linear nature of the relation signifies that a unit increase in displayed work rate was accompanied by a constant increase in braking and therefore actual work.

Data Collection

The outputs from all measurement devices (volume integrators, gas meter, mass spectrometer, time-ramp, etc.) were relayed to a hot stylus pen recorder (Devices Ltd. (now Ormed Eng. Ltd.), Welwyn Garden City, Herts) and continuously displayed on a paper trace. A time-marker marked each minute of the experiment.

From the pen recorder, signals were relayed to the analogue-to-digital conversion board of an Eclipse S/140 computer (Data General Corporation, Slough) where they underwent digital conversion and could be accessed by the data collection programs. The flow of data is represented diagrammatically in Figure 2.11.

Either of two programs would be running on the computer depending on whether gas exchange or flow data were required; the protocol for the two experimental series was the same. For collection of gas exchange data, the program essentially performed a peak-picking operation, searching continuously for peaks in inspired and expired volume that indicated the end of the respiratory phases (see Appendix A5 for program listing). The peak-picking program consisted of two command loops cycled every 20 ms. Each time round one command loop the computer read the analogue-to-digital interface (the first entry into the loop having set a real time clock). When the first loop calculated that a peak of inspired volume had occurred, the highest previous value was stored along with the time since the onset of inspiration and the gas concentrations at that time (corrected for delays). The program then dropped into the second loop which performed the same process for expiration. Once the program had

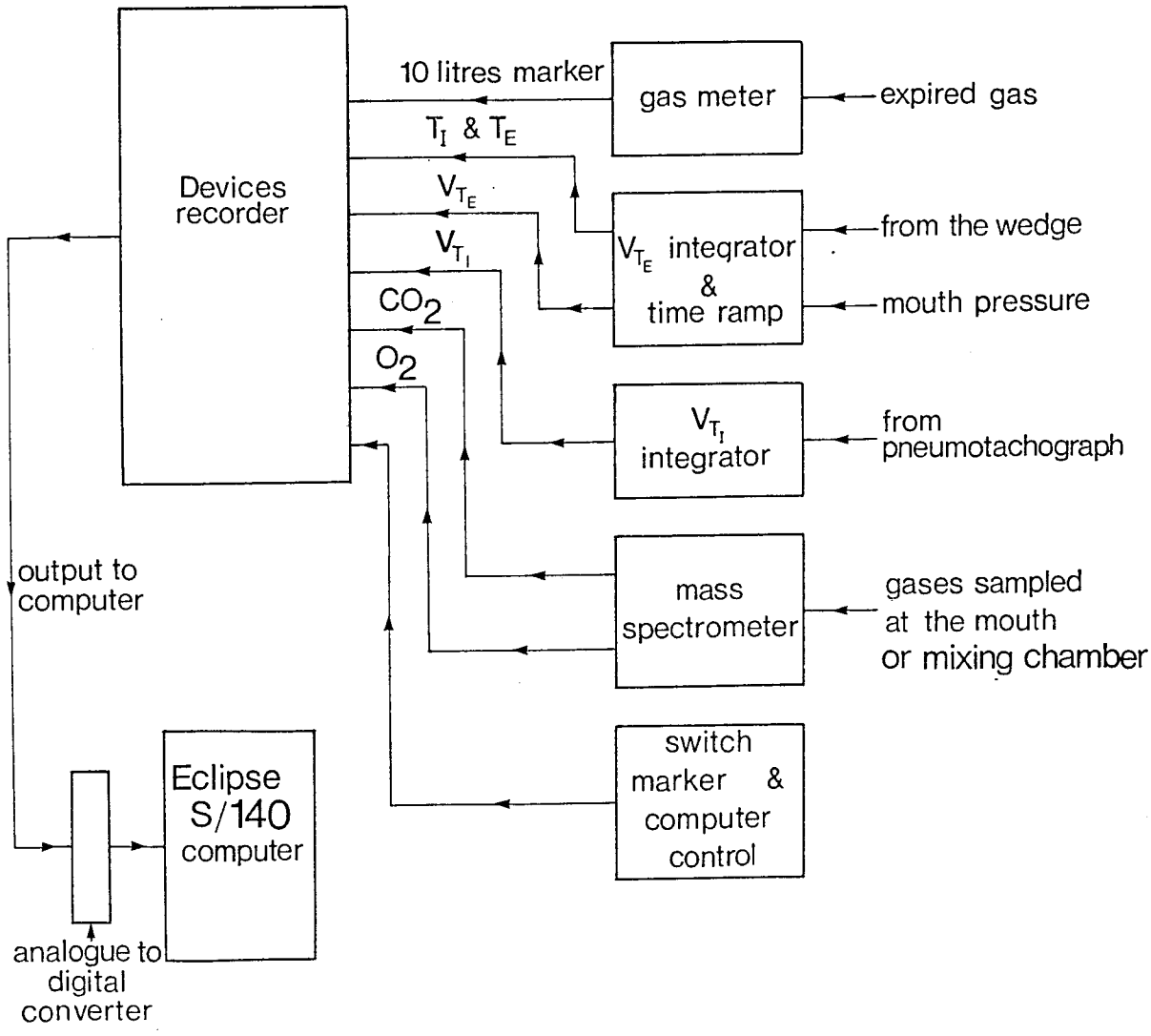


Figure 2.11: Diagram of the flow of data, from the peripheral measuring devices to the hot-stylus pen-recorder for continuous display and thence to the analogue-to-digital converter of a mini computer for real time analysis and storage.

recorded a breath the program set about searching for the next inspired volume peak. At the end of the experimental run the data collected were stored on hard disk for later analysis.

Flow data were collected in 1 minute runs by a program that recorded the pneumotachograph signal every 20 ms (see Appendix A5 for program listing). At the end of each minute of recording the data were transferred to the disk, and the program was then ready to record for another minute.

Subjects

The subjects used in this study were all male volunteers (see table 4.1). Eleven subjects were used in all, of whom eight took part in both exercise and hypercapnic studies of gas exchange. Four also took part in the study of flow profiles. The mean age of the subjects was 21.2, S.E. 0.45 years, mean weight 76.8, S.E. 3.2 kg and mean height 1.80, S.E. 0.03 m. One subject smoked (Subject 640) but only occasionally. All were active, indulging in at least one sporting activity regularly.

Individual fitness was assessed from the ventilatory response to an incremental work test. Subjects' anaerobic thresholds were estimated as the point of onset of alinearity in each individuals' oxygen uptake - ventilation relation.

When possible the subjects were studied during the same period of the day, usually the morning. This was an attempt to minimise the effect of many variables that might have changed with the time at which the study was conducted, including pre-experiment activity, food intake and perceived effort, as well as standardising for the effect of circadian rhythms of other variables (e.g. airway resistance) on measured variables. The subjects were also asked to standardise their intake of

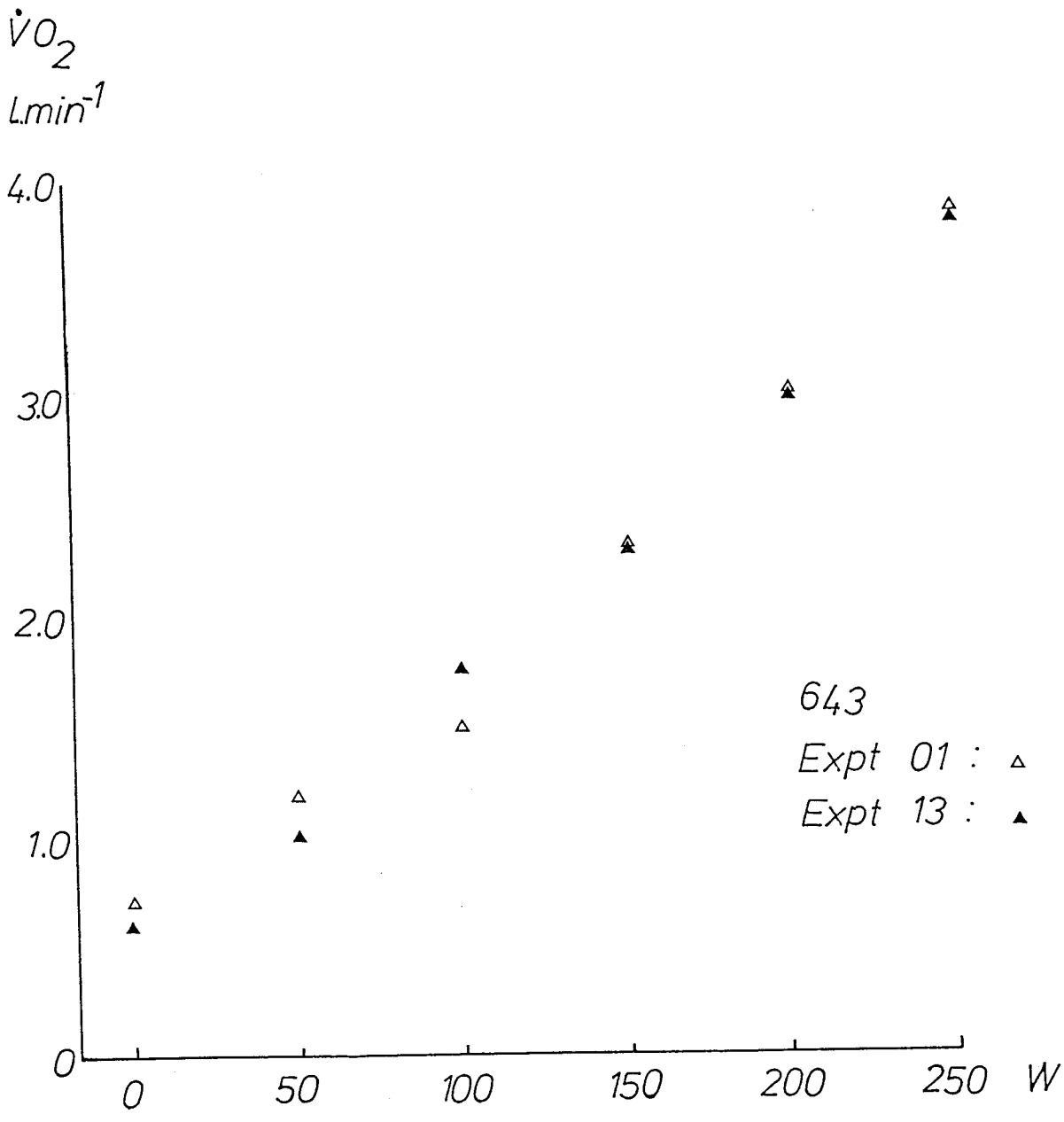


Figure 2.12: Superimposed plots of work rate - $\dot{V}O_2$ relations obtained in a single subject studied twice at an interval of 5 months. The slopes of the lines of regression of the two data sets are 12.6 and 12.8 ml.min^{-1}W^{-1} respectively, a difference of 1.6%. The constancy of readings suggests that the actual vs displayed work rate relation was constant over this period.

respiratory stimulants (caffeine, etc.), preferably by abstinence, for up to two hours before experiments.

In an attempt to minimise the subjects' awareness of breathing generally and of discomfort at higher levels of ventilation, they were asked to indulge in some form of attention focussing-activity. Most preferred to read during experiments at rest, or to listen to the radio during exercise experiments, though not to music which might influence respiratory pattern.

No specific information about the procedures employed was given to the subjects other than that on the consent forms they signed, which were couched in general terms. The stresses to which the subjects were exposed were within the range for which the Oxford Regional Ethics Committee overall approval had been obtained.

Experimental Protocol

Although different computer data collection routines were employed in studies of gas exchange and flow, the basic experimental protocol was the same. Figure 2.13 presents a schematic illustration of the experimental protocol.

The subjects were allowed 10 minutes to settle at the beginning of each experiment. During incremental work tests, the work rate was increased in 50 W steps until the subjects were unable to continue. During hypercapnic experiments, steps of increasing P_ICO_2 were imposed. The initial step was large, 30 torr, but thereafter reduced to 10 and then 5 torr. In this way it was possible to induce approximately equal changes in end-tidal PCO_2.

Four minutes were allowed after each step change for a new steady-state ventilation to be established (Belville et al., 1979;

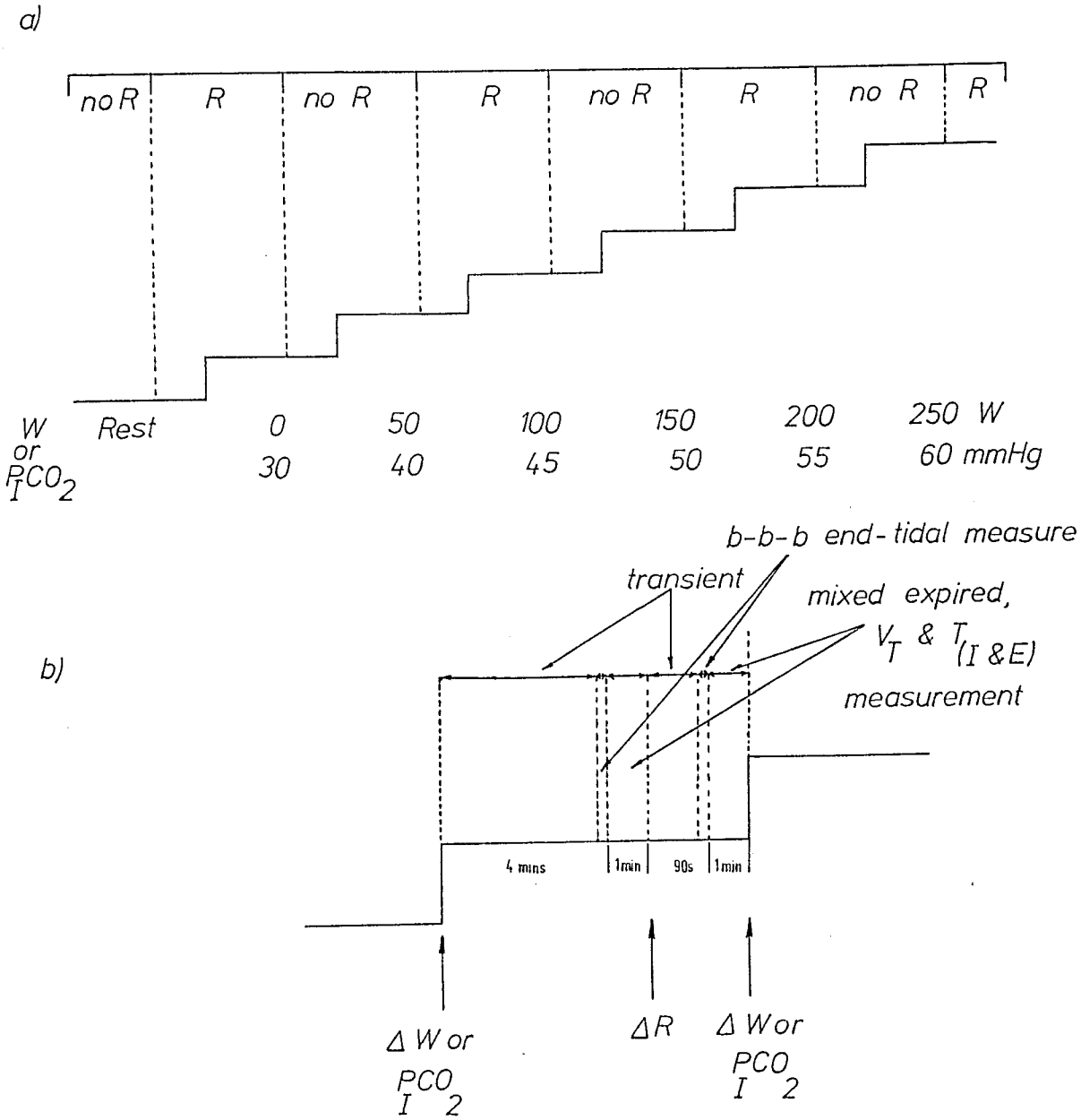


Figure 2.13: Schematic representation of the experimental protocol. Resistance transitions are imposed at each level of work or hypercapnia. Within each stimulus-loading level both breath-by-breath end-tidal and mean expired gas concentrations are recorded, as well as volumes and times.

Whipp et al., 1982). At the end of this time inspired and end-tidal gas partial pressures were recorded. In gas exchange studies the mass spectrometer sampling catheter was then switched to the mixing chamber to record mixed-expired gases for one minute. The catheter was then switched back to measure tidal gases and the inspired line changed from loaded to unloaded or vice versa. Ninety seconds were allowed before new measurements were made, although ventilatory compensation was virtually complete 30 s after the change (see Figure 2.14).

End-tidal gases were again recorded prior to sampling mixed expired gases for one minute (if flow was being studied tidal gas was sampled continuously). The mass spectrometer was then returned to sampling tidal gas from the Lloyd valve and the next step in work or P_ICO_2 instituted.

In some experiments inspiratory capacity was also measured, which allowed estimates of changes in end-expiratory volume to be made. To accomplish this subjects were asked to make two inspiratory capacity manoeuvres at the end of each loading-stimulus condition (p. 2.18).

Experiments Involving Plasma Lactate Analysis

The protocol for these experiments was slightly different. The protocol assumed for the experiments listed above would have provided insufficient time (only 2.5 minutes) for detectable changes in lactate concentrations to occur after loading transitions. Consequently a revised protocol was adopted in which two separate runs were performed, one loaded and the other not, separated in time by at least 2 hours (i.e. 6 - 8 half-times for lactate removal, Ramal and Ström, 1949), to allow lactate levels to return to normal between runs. The run conducted in the

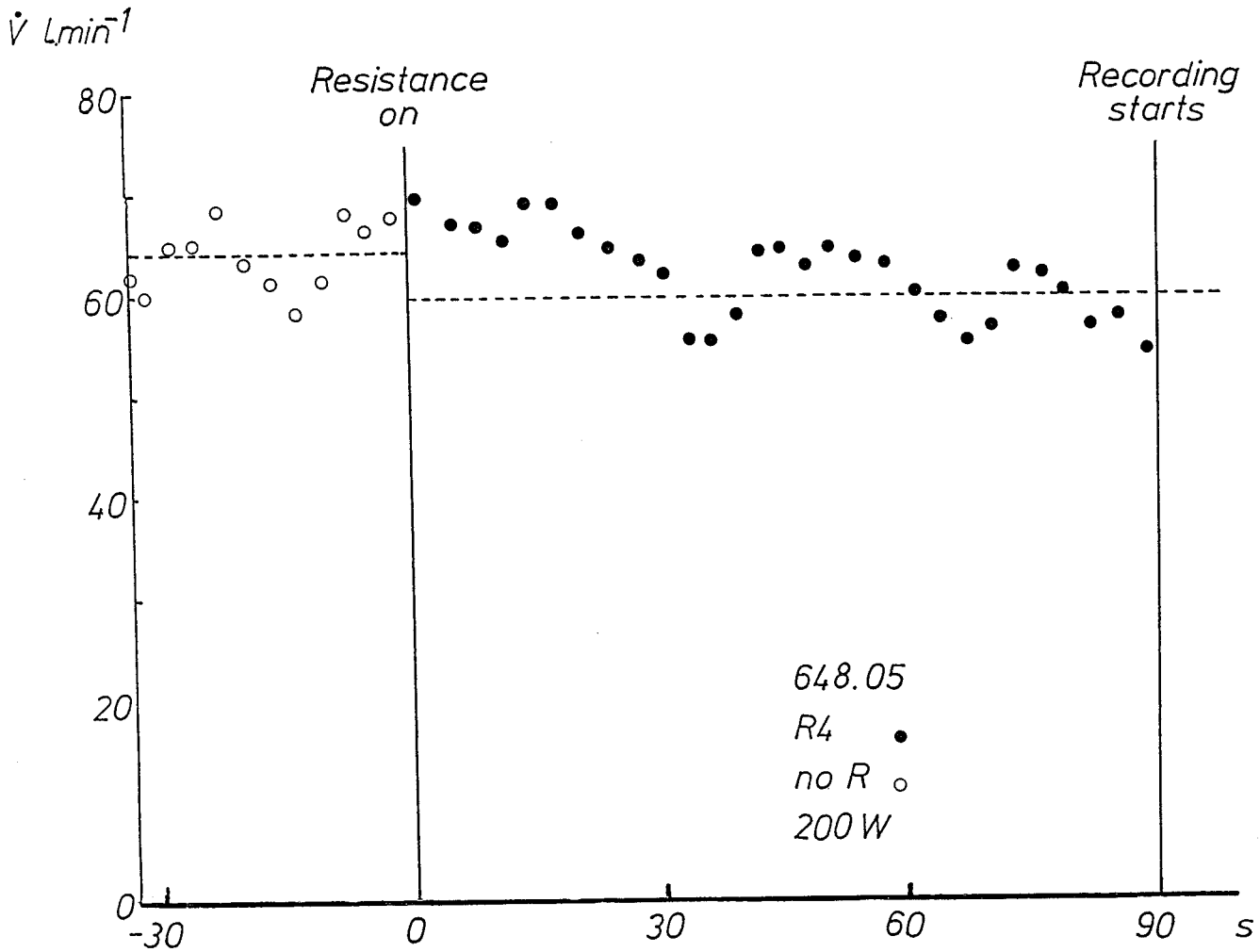


Figure 2.14: Ventilation calculated breath-by-breath is plotted against time for the 30 s preceding and 90 s following the imposition of a resistive load (R4). The pre- and post-switch mean steady-state levels of ventilation are indicated by the dashed lines. Ventilatory compensation is complete after 30 s.

presence of loading was always performed first. This avoided the possibility that residual lactate would elevate plasma concentration and be mistaken for a loading effect.

Other than this change, the protocol was similar to the protocol for the collection of gas exchange data. Work rate or hypercapnia level increased every two minutes, breathing pattern and gas exchange variables being recorded in the last minute. At the end of this time a venous blood sample was taken for analysis.

Data Analysis

1) The study of energetics.

Examples of experimental traces are shown in Figure 2.15. The variables measured and stored by the computer included breath number from the beginning of the run, inspired and expired volumes, the durations of inspiration and expiration and either the partial pressures of gas sampled at the mouth or the mean expired partial pressures of gas sampled from the mixing chamber. In addition the passage of each 10 L. of expired volume was recorded on the experimental trace, and a minute-marker recorded the passage of each minute.

a) Calculation of O_2 uptake and CO_2 elimination.

$\dot{V}O_2$ and $\dot{V}CO_2$ were computed as the difference between inspired and mixed expired concentrations of the two gases multiplied by the expired minute volume.

The inspired volumes were corrected for differences between inspired and expired volumes (when the respiratory exchange ratio

Figure 2.15: Examples of experimental records showing, from above downwards:

1) Time-ramp;

2) $V_{T,I}$;

3) 10 L. marks from dry gas meter;

4) $V_{T,E}$;

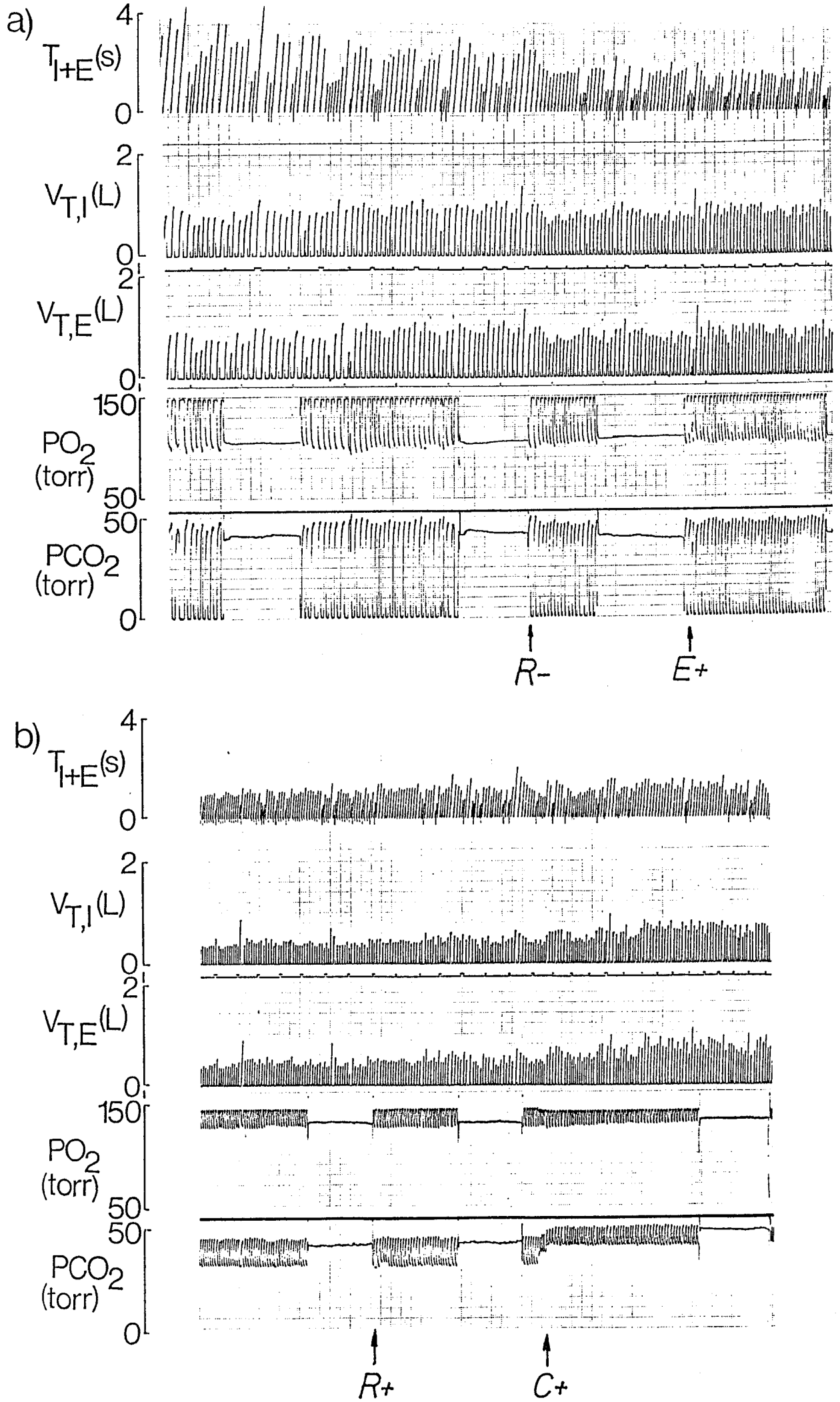
5) Time signal (minute marks);

6) PO_2;

7) PCO_2.

a) Sequence from an incremental work test performed by Subject 640, showing the transition from loaded to unloaded breathing at 100 W (R-), followed by the elevation of work rate to 150 W (E+).

b) Sequence from an incremental hypercapnia test undertaken by Subject 643. The transition from unloaded to loaded breathing at P_ICO_2 30 torr is indicated (R+), as is the subsequent increase in P_ICO_2 to 40 torr (C+).


a)
4
T_{I+E}(s)
0
2
$V_{T,I}$(L)
0
2
$V_{T,E}$(L)
0
150
PO_2
(torr)
50
50
PCO_2
(torr)
0
R-
E+
b)
4
T_{I+E}(s)
0
2
$V_{T,I}$(L)
0
2
$V_{T,E}$(L)
0
150
PO_2
(torr)
50
50
PCO_2
(torr)
0
R+
C+

was different from 1.0) by the ratio of N_2 concentration in expired and inspired gas:

$$\dot{V}O_2 = (F_IO_2 \cdot \frac{F_EN_2}{F_IN_2} - F_EO_2) \cdot \dot{V}_E$$

$$\dot{V}CO_2 = (F_ECO_2 - F_ICO_2 \cdot \frac{F_EN_2}{F_IN_2}) \cdot \dot{V}_E$$

The values of oxygen uptake and carbon dioxide elimination in tables and figures are expressed at STPD (standard temperature and pressure, dry).

b) Calculation of the oxygen cost of breathing.

The oxygen cost of breathing was calculated as the excess oxygen uptake associated with the rise of ventilation during periods of hypercapnia. The assumption underlying the approach is that the only substantial additional O_2 requirement of the body during such periods is that caused by the additional work performed by the respiratory muscles (see p. 1.41).

The experimental protocol thus permitted an estimation of the oxygen cost of breathing over the range of ventilation achieved by CO_2 inhalation in resting subjects both with and without inspiratory loading.

$$\dot{V}O_2 \text{ (breathing)} = \frac{\Delta\dot{V}O_2}{\Delta\dot{V}} \quad \text{ml } O_2 \text{ per litre ventilation}$$

The measurement is known to be difficult and only by making a large number of observations and measurements as in the present study is a reliable value obtained.

2) The study of flow.

Previous reports of the effect of increasing ventilation and/or loading on the inspiratory and expiratory flow profiles are generally restricted to a vague qualitative description of the change. While easy to record, the amount and complexity of information contained in flow profiles as well as the considerable breath-by-breath variability make analysis difficult.

The present study examined the effect of increasing ventilation with and without inspiratory loading on 11 specific variables (see Figure 2.16). These variables were chosen to provide a detailed description of flow profiles. Isopnoeic comparison of variable values, with and without loading, was made possible by partitioning the ventilatory data into 10 litre ventilation "bins".

The 11 variables selected were:

1) Instantaneous inspiratory flow acceleration ($\ddot{v}_I$), the rate of rise of flow over the first 100 ms of inspiration. Over this time the rise in flow is essentially linear and independent of any feedback mechanisms. It is a function of respiratory drive and the resistance of the respiratory system.

2) Time to peak inspiratory flow from the onset of inspiration (Tmax). This variable reflects the shape of the first portion of the profile as it is a function of the rate of rise and the peak level of inspiratory flow.

3) Time to peak expiratory flow from the onset of expiration (Tmin).

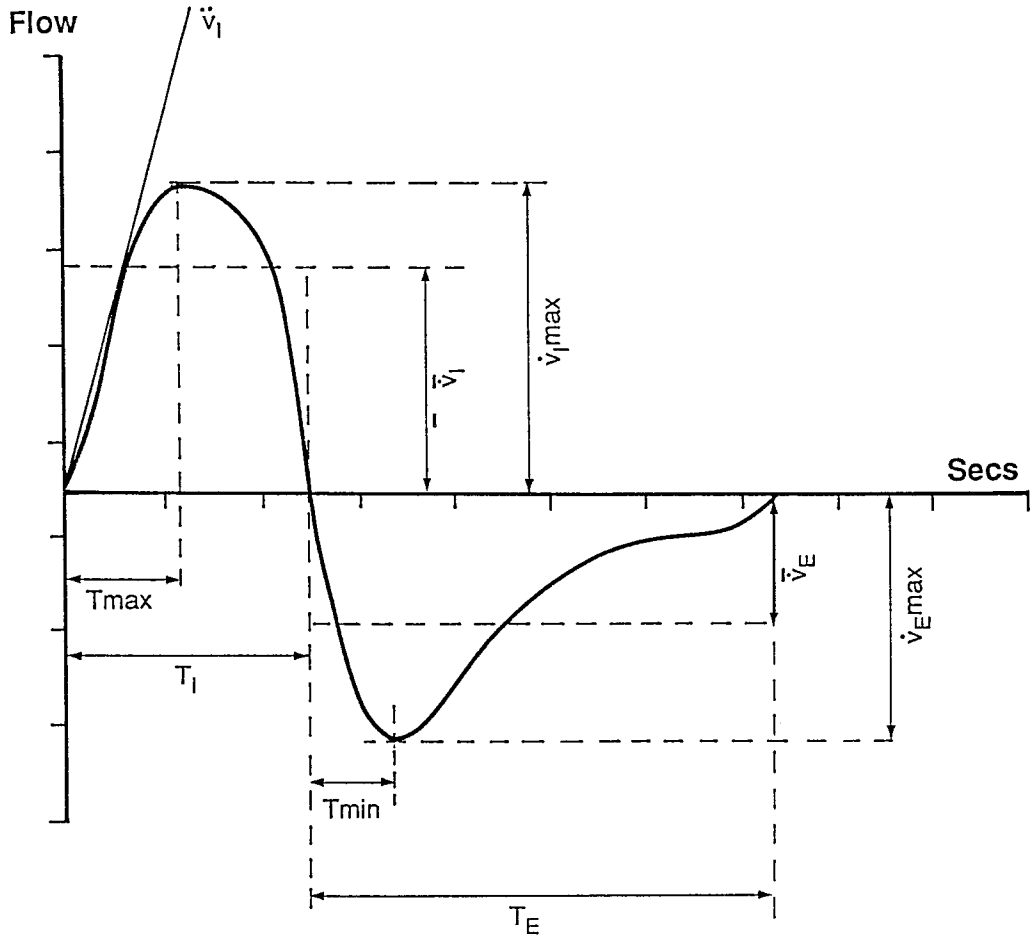


Figure 2.16: Diagrammatic representation of the seven flow variables measured:

1) Inspiratory flow acceleration ($\ddot{v}_I$);

2) Time to peak inspiratory flow (Tmax);

3) Time to peak expiratory flow (Tmin);

4) Peak inspiratory flow ($\dot{v}_I max$);

5) Peak expiratory flow ($\dot{v}_E max$);

6) Mean inspiratory flow ($\bar{\dot{v}}_I$);

7) Mean expiratory flow ($\bar{\dot{v}}_E$).

In addition four variables were generated as ratios:

8) Tmax / T_I;

9) Tmin / T_E;

10) $\bar{\dot{v}}_I$ / $\dot{v}_I max$;

11) $\bar{\dot{v}}_E$ / $\dot{v}_E max$.

4) Peak inspired flow ($\dot{v}_I max$). The absolute level of the maximum inspired flow achieved. This variable describes the upper limit of the profile.

5) Peak expired flow ($\dot{v}_E max$).

6) The fraction of T_I at which Tmax occurs ($Tmax/T_I$). This variable normalises Tmax for changes in T_I and so permits comparison of relative values of Tmax for inspirations of different lengths.

7) The fraction of T_E at which Tmin occurs ($Tmin/T_E$).

8) Mean inspiratory flow ($\bar{\dot{v}}_I$). This variable (V_T/T_I) has been suggested as an index of respiratory drive (Milic-Emili, 1982).

9) Mean expiratory flow ($\bar{\dot{v}}_E$). At rest and at moderately raised levels of ventilation this variable (V_T/T_E) is a function of the passive recoil characteristics of the lung and the prevailing expiratory braking.

10) Mean inspiratory flow as a fraction of peak inspiratory flow ($\dot{v}_I max/\bar{\dot{v}}_I$). This variable is a function of the general shape of the profile. Theoretically, as the shape of the profile tends to squareness this ratio approaches unity, but as the profile tends towards a sine wave the ratio approaches 2/pi.

11) Mean expiratory flow as a fraction of peak expiratory flow ($\dot{v}_E max/\bar{\dot{v}}_E$).

CHAPTER 3

STATISTICAL METHODS

This chapter is divided into two sections. The first section describes the techniques employed in the analysis of gas exchange and breathing pattern data. The second section describes the techniques employed in the analysis of flow profile data. The ways in which these techniques were applied to the experimental data is described at the beginning of the next chapter.

1. The Analysis of Gas Exchange and Breathing Pattern Data

Distribution Variables and Simple Tests of Significance

Breath-by-breath data were collected in runs of 60 s duration during incremental exercise or hypercapnia tests. Each test comprised 6 or 7 work or inspired CO_2 levels, depending on the peak levels attained. Two data collection runs were made at each level, as breathing was alternately loaded and unloaded, so each incremental exercise or hypercapnia test entailed the collection of data in 12 or 14 runs.

Means were calculated by averaging the breath-by-breath data (the data were not edited). For each subject, the distribution (assuming that it is normal) of the run means at a given level of stimulation and in a given loading condition may be described by the mean (of means) and the standard error of the mean (Bailey, 1959, p. 16). These means (of means) and standard errors of the

means (S.E.) are presented for each subject in Appendices A1 and A2, along with and the number of tests that each subject performed. Hereafter, mean may be taken to denote this mean of means.

Pooled means, the average values obtained by pooling the mean data from all subjects, are presented within the Results Chapter.

Analysis of Variance

Introduction

Analysis of variance (ANOVA) is an extension of t-tests that enables the examination of multiple factor effects and interactions between factors. As the experiments undertaken in the present study were factorial in type, i.e. the effect of changing two factors (work or hypercapnia level and loading condition) was examined, ANOVA was well suited to the study and was the main statistical tool employed.

ANOVA involves calculating the total variance of the data, and breaking it down into its component variances. If there is more than one factor which might be affecting the data (for example loading condition, or the level of exercise or hypercapnia), the total variance can be separated into the components due to the different factors. The variance attributable to factors, i.e that between groups, may then be compared with the variance within groups. If it is much bigger, it can be assumed that the factor has a significant effect on the data.

Thus ANOVA separates out the individual effects of different factors so that one obtains data about the significance of the effect of each factor in all the different experimental

conditions. Therefore, as much information is obtained in one multiple factor experiment as in several single factor experiments. In addition, ANOVA indicates the significance of interactions between factors; the extent to which the mean response at a given level of one factor and at a given level of a second factor, is not determined purely by the additive effects of the factors, but by a combination of their effects (see p. 3.7).

Assumptions Implicit in the Analysis of Variance

ANOVA techniques involve two assumptions about the data, first, that they are normally distributed, and secondly, that the variances of the data at each level (of exercise, or hypercapnia, or loading) are the same.

The normality of the data obtained in the present study was not tested statistically. However, examination of the data revealed an approximately normal distribution, and there are a number of reports suggesting that respiratory variables are distributed normally, or may be treated as normally distributed for the purposes of analysis as long as caution is exercised in the interpretation of the results (Kay et al., 1975_a; Marsh, 1982; Painter, 1987; Ward, 1974).

In regard to the homogeneity of variances, some variables did appear to show a correlation between the level of variance and mean. These data were logarithmically transformed in order to produce comparable variances and the ANOVA was then repeated (see p. 4.7).

It should be noted that ANOVA techniques are quite robust in the face of deviations from normality and differences in variance (Armitage, 1971).

Application of Analysis of Variance in the Present Study

The particular ANOVA test applied in this thesis was a two-way (subjects vs. factors) two-factor (exercise or hypercapnia level and loading condition) analysis of variance. The exercise or inspired CO_2 factor had 6 or 7 levels and the loading condition factor had two levels. The individual, or main, effects of these factors were separated out to provide information about their independent action. The main effects examined were those of increasing limb work rate or hypercapnic drive (levels effect), the presence or absence of respiratory loading (resistance effect) and differences between subjects (subjects effect).

1) Main effects.

The main effects mentioned above may be represented as rows and columns in an analysis of variance table, as shown in Table 3.1 (cf. Armitage, 1971, p. 215). The table is complicated by the fact that the rows representing the loading condition are subdivided to demonstrate the differences between subjects.

The analysis involved the calculation of the variance of data grouped by rows and by columns, termed Mean squares (MSq) in the analysis of variance table (see Table 4.3 for example, which is the ANOVA table for oxygen uptake data). They are calculated from the appropriate sum of squares (SOS) divided by the degrees of freedom (DF).

The equations for generating the SOS, using the nomenclature of Table 3.1, are given overleaf. In the interests of clarity these equations are presented as they specifically refer to the main analysis presented in this thesis, of data from 8 subjects, 6 work or hypercapnia levels and 2 resistance states (unloaded and loaded). However the manner in which the equations may be altered

Table 3.1 : Analysis of Variance

General Table of Data for the Main Two-Way Two-Factor Analysis

Row		Column: Work or P_ICO_2 level						
Loading State	Subject	1	2	j	...	5	6	Total
Row 1 (Unloaded)	1	Y_{111}	Y_{121}	Y_{1j1}	...	Y_{151}	Y_{161}	$R_{1,1}$
	2	.	.	Y_{1j2}	...	.	.	$R_{1,2}$
	.	.	.	.	...	.	.	.
	.	.	.	.	...	.	.	.
	k	Y_{11k}	Y_{12k}	Y_{1jk}	...	Y_{15k}	Y_{16k}	$R_{1,k}$
	.	.	.	.	...	.	.	.
	.	.	.	.	...	.	.	.
	8	.	.	Y_{1j8}	...	.	.	$R_{1,8}$
	Total	$C_{1,1}$	$C_{1,2}$	$C_{1,j}$	...		$C_{1,6}$	T_1
Row 2 (Loaded)	1	Y_{211}	Y_{221}	Y_{2j1}	...	Y_{251}	Y_{261}	$R_{2,1}$
	2	.	.	Y_{2j2}	...	.	.	$R_{2,2}$
	.	.	.	.	...	.	.	.
	.	.	.	.	...	.	.	.
	k	Y_{21k}	Y_{22k}	Y_{2jk}	...	Y_{25k}	Y_{26k}	$R_{2,k}$
	.	.	.	.	...	.	.	.
	.	.	.	.	...	.	.	.
	8	.	.	Y_{2j8}	...	.	.	$R_{2,8}$
	Total	$C_{2,1}$	$C_{2,2}$	$C_{2,j}$	...		$C_{2,6}$	T_2

to perform a more general analysis of the same type, is indicated by partly expressing the equations in terms of 1 factor at i levels (i.e. resistance state) and a second factor at j levels (i.e. work or hypercapnia level), whose effects are examined in k subjects (cf. Armitage, 1971, p. 227-232).

y = mean of variable at a given exercise or inspired CO_2 level and loading condition.

$$\text{Total SOS} = \sum_{ijk} y^2_{ijk}$$

The partitioning of the total sum of squares into between and within groups was most easily achieved by using an analogous technique to the short-cut formula for calculating the sum of squares about the mean of a single sample (Armitage, 1971, p. 37). This involved the calculation of a "correction factor" (C.F.) following the formula

$$\text{C.F.} = \sum_{ijk} y_{ijk} \; / \; 2*8*6$$

The application of this technique to the calculation of the sum of squares using the nomenclature of Table 3.1 gives

$$\text{Levels effect SOS (L SOS, 5 DF)} = \frac{\sum_j (C_{1,j} + C_{2,j})^2}{2*8} - \text{C.F.}$$

$$\text{Resistance effect SOS (R SOS, 1 DF)} = \frac{T_1^2 + T_2^2}{8*6} - \text{C.F.}$$

$$\text{Subjects effect SOS (S SOS, 7 DF)} = \frac{\sum_j (R_{1j} + R_{2j})^2}{2*6} - \text{C.F.}$$

In order to assess the significance of differences between group means, the calculated variances were tested against a further unbiased estimate of the true variance of the data, the error variance. In the case of the main effects of work or hypercapnia level and resistance level, the error variance was the mean square of the interaction of the respective main effect with the subjects effect (i.e. LS MSq and RS MSq respectively, see overleaf and Table 4.3). The subjects interaction MSq was used on the assumption that the subjects conformed to a "random effects model" (Armitage, 1971, p. 196), wherein the subjects are assumed to be a random sample from the population of subjects who might have been chosen for the experiment. A significant effect, determined from the ratio of the variance of the main effect to the error variance indicated the presence of a general increase or decrease in the data population while allowing for a variation in the effect amongst subjects.

The subjects effect and interaction effects were similarly tested against the appropriate error variance, the residual mean square.

The assessment of whether the effects were significant proceeded by comparing the calculated variance-ratios, or F-ratios, with the value at the chosen significance limit for the appropriate degrees of freedom in F-ratio tables. If the variance ratio of the analysis exceeded the F-ratio value at the chosen significance limit, the null hypothesis was rejected and the factor examined may be considered to produce a difference.

2) Interaction effects.

In addition to examining the significance of the main effects, the significance of interactions between main effects was evaluated. The significance of all possible two factor interactions were examined; levels * resistance (LR), levels * subjects (LS) and subjects * resistance (SR).

Using the nomenclature of Figure 3.1, the interaction sum of squares were calculated as

Levels * Resistance SOS (LR SOS, 5 DF) =

$$\sum_j \frac{(C_{j,1})^2 + E(C_{j,2})^2}{8} - \text{Levels SOS} - \text{Resistance SOS} - \text{C.F.}$$

Levels * Subjects SOS (LS SOS, 35 DF) =

$$\sum_j \frac{((y_{1j1} + y_{2j1})^2 + \cdots (y_{1j8} + y_{2j8})^2)}{2} - \text{Levels SOS} - \text{Subjects SOS} - \text{C.F.}$$

Resistance * Subjects SOS (RS SOS, 7 DF) =

$$\sum_k \frac{(y_{11k} + \cdots y_{16k})^2 + (y_{21k} + \cdots y_{26k})^2}{6} - \text{Subjects SOS} - \text{Resistance SOS} - \text{C.F.}$$

Residual SOS (35 DF) =

Total SOS - LSOS - RSOS - SSOS - LRSOS - LSSOS - RSSOS - C.F.

Error Mean Square of Differences

The general analysis of variance discussed above examined the separate effects of loading in exercise and in hypercapnia. However, it was also of interest to compare the effects of loading during the two conditions, i.e. the difference between exercise and hypercapnia in the response to loading. The "differences of the differences" test compared the effect of loading at the 6 levels and in the 8 subjects for each of the two stimuli, so a total of 48 (loaded vs. unloaded) comparisons (between exercise and hypercapnia) were made for each variable.

In order to test whether the difference in the effect of loading during exercise and hypercapnia was significant, the summed difference (between the effect of loading during exercise and during hypercapnia) of these 48 comparisons was compared with the standard error of the difference. A significant difference was indicated if reference to normal distribution tables revealed that the difference was greater than the number of standard errors from the mean at the chosen probability level (see Table 4.24).

The variance of the exercise or hypercapnic data was estimated from the residual mean squares of the data samples as

$$s^2 = 2 * \text{no. of comparisons} * \text{ResMSq}$$

and the standard error of the difference was calculated from the pooled variance of the exercise and hypercapnic data as

$$\text{S.E.} = \sqrt{s^2_{EX} + s^2_{CO_2}}$$

(Personal communication, Dr. F.H.C. Marriott, Oxford University Department of Biomathematics).

Regression Analysis of the LR Interaction.

The form of the levels * resistance interaction described the change in the response to the addition of loading as work or hypercapnia level increased. It was therefore of special interest, as it indicated the nature of the response to the substantial increase in respiratory work rate accompanying loading as limb work and/or ventilation increased.

The form of this interaction was analysed by evaluating whether a significant proportion of the variance associated with it was attributable to a linear regression of the effect of loading ($Mean_{R0}$-$Mean_{R4}$ = y) upon limb work rate or inspired CO_2 level (x). The estimate of the variance associated with this linear component, the regression mean square, was equal to the regression SOS since there was only one degree of freedom associated with it.

Using the short-cut method of calculating the sum of squares (p. 3.5), the Corrected sum of $squares_X$ ($CSOS_X$), was calculated as

$$CSOS_X = \Sigma x^2 - \frac{(\Sigma x)^2}{6}$$

the Corrected sum of $squares_{XY}$ ($CSOS_{XY}$), was calculated as

$$CSOS_{XY} = \Sigma(x * y) - \frac{\Sigma x * \Sigma y}{6}$$

the Regression sum of squares (RegSOS) was therefore calculated as

$$RegSOS = \frac{(CSO_{XY})^2}{(CSOS_X)} * \frac{1}{(\frac{1}{n} + \frac{1}{n})}$$

where n was the number of subjects (personal communication, Dr F.H.C. Marriott, Oxford University Department of Biomathematics).

The regression mean square was tested for significance in an F-test against the error variance (the residual mean square of the ANOVA). If the variance ratio was significant, it indicated that the regression mean square accounted for most of the variance attributable to the levels * resistance interaction. If this was the case, the effect of loading increased as a nearly linear function of limb work rate or inspired CO_2 level and a simple difference in slope of the loaded and unloaded relations existed; this of course indicated nothing about the complexity of the mechanisms controlling the variable concerned.

The difference between the levels * resistance sum of squares (which is in effect the total sum of squares in this test), and the regression sum of squares, is the residual sum of squares (ResSOS). Finding the residual sum of squares permits the calculation of the residual mean square of the regression (MSq_{Res}), as the residual sum of squares divided by the degrees of freedom of the (levels * resistance sum of squares) - 1. The residual mean square of the regression is a function of the variance around the regression line, i.e. that variance not accounted for by the extraction of the linear component, and it was also assessed for significance by testing it against the residual mean square of the ANOVA in an F-test. If the alinear component formed a significant part of the interaction variance, a more complex relationship than linearity was suggested. This may be the result of an inherently complex relationship between the two variables and/or a change in the form of the relationship as the independent variable increases.

The results of the regression analysis of the levels * resistance interaction are presented in Table 4.23.

2. The Analysis of Flow Profile Data

In an analogous manner to that for breathing pattern and gas exchange data, preliminary analysis of flow profile data yielded the mean values of a number of one minute data collection runs during incremental exercise or hypercapnia tests. The means for each of these runs were partitioned into 10 $L.min^{-1}$ ventilation bins, subject by subject. Grouping of individual subjects' data in this manner and the calculation of the mean of each 10 $L.min^{-1}$ ventilation bin, over the 10.0-69.9 $L.min^{-1}$ ventilation range, allowed direct isopnoeic comparisons to be made. These data are presented subject by subject in Appendix A4 as means and standard errors of the means.

As in the study of breathing pattern and gas exchange data, analysis of variance was employed to examine flow profile data. The factors evaluated for significance were the effect of the level of ventilation, during exercise or hypercapnia, the loading condition and differences between subjects. Since the analysis was similar to that of the study of gas exchange and breathing pattern, a detailed description of the method is not presented.

CHAPTER 4

RESULTS

This chapter is divided into five sections, the first of which includes a brief description of the experiments and analysis performed. The remaining sections present the experimental results and the outcome of their analysis, commencing with the study of energetics, followed by ventilation and breathing pattern, end-expiratory volume and finally, flow.

1. Description of Experiments and Data Analysis

Overview

The principal aim of this thesis was the investigation of the physiological response to the performance of high levels of exercise when the work of breathing was also high due to the imposition of inspiratory flow-resistive loading. In these circumstances the demand for oxygen by the respiratory and limb muscles may exceed supply, and exercise capacity may thus be impaired.

There were two series of experiments, which both involved the collection of data during exercise or hypercapnia when breathing was loaded and when not. The data collected in the first series concerned energetics and the pattern of breathing, and the data collected in the second series concerned the study of the flow profile.

Great care was taken to keep the experimental protocols of the two series as similar as possible. Generally, protocols differed only in the variables measured in the two series, though some differences arose within the first series. These occurred as it became clear that additional measurements would enhance the investigation and further, that these measurements could not be made routinely. Thus, measurements of inspiratory capacity (IC) and plasma lactate concentration were not made during every experimental run.

First Experimental Series

This series supplied the following data: breath-by-breath inspired and mixed expired gas compositions - from which gas exchange variables were calculated; lactate assay - additional measurements made during one exercise and one hypercapnia run for 5 subjects; breathing pattern variables - measured simultaneously with gas exchange variables; inspiratory capacity - from which the change in end-expiratory level from rest was estimated. Mixed expired gas composition and breathing pattern variables were measured in 60 s data collection runs.

1) Exercise experiments.

The exercise section of the first experimental series involved a total of 11 subjects who each performed a number of incremental work tests (Appendices A1 and A2 give the individual numbers of tests and results). Forty eight tests were performed in the absence of an external flow-resistive load (R0) and in the presence of the severest flow-resistive load employed (R4). A total of 8 further tests were performed by Subjects 642, 643 and 647 in the presence of flow-resistive loads R2 and R3.

During the tests, work rate rose in 50 W steps from rest until subjects were unable to continue. The highest work rate attained by all subjects but one was 250 W; Subject 642 reached only 200 W. Anthropometric data, usual levels of activity and the estimated anaerobic thresholds of the subjects are given in Table 4.1.

2) Hypercapnic experiments.

In this second, hypercapnic, section of the first experimental series, eight of the same subjects performed a number of incremental hypercapnia tests (Appendices A1 and A2 give the individual numbers of tests and results). Forty six tests were performed in the absence of an external flow-resistive load (R0) and in the presence of the severest load employed (R4). A total of 5 further tests were performed by Subjects 642, 643 and 647 in the presence of flow-resistive loads R2 and R3.

For five of the subjects the peak inspired CO_2 that was tolerated was 60 torr, for the remainder it was 55 torr.

Second Experimental Series

The second series of experiments involved the continuous measurement of subjects' air flow at the mouth for 60 s periods during incremental exercise or hypercapnia tests. The experimental protocol was the same as for the first series.

Four of the same subjects who took part in both exercise and hypercapnia runs of the first series took part in this second series (Subjects 632, 634, 639 and 643). A total of 18 exercise and 20 hypercapnic runs were performed (Appendix A4 gives the number of tests performed by each subject and results).

Table 4.1 : Description of Subjects

Subject No.	Age (Years)	Height (Metres)	Weight (kg)	Activities	Estimated A.T. (Watts)
597	24	1.77	72.5	Jogger	100
632	21	1.80	71.1	Jogger	100
634	21	1.83	76.2	College oarsman	100
635	22	1.80	79.4	Touring cyclist	100
639	21	1.80	73.0	Mountaineer	100
640	20	1.86	79.4	College football	150
642	21	1.74	79.4	College oarsman	100
643	21	1.86	76.2	National triathlete	150
644	22	1.84	72.3	Athlete	100
647	20	1.89	82.6	Mountaineer	100
648	25	1.81	81.9	Jogger	150

Anthropometric data and usual levels of activity. The anaerobic threshold (A.T.) was estimated for each subject from the point of alinear rise of the regression of ventilation upon oxygen uptake.

Description of Data

1) Gas exchange and breathing pattern data.

The basic data for each subject consisted of the mean and the standard error of the mean of each variable measured at each work or hypercapnia level. These data are presented subject-by-subject in Appendices A1 and A2. Data concerning measures of inspiratory capacity in each subject may be found in Appendix A3. The subject means were pooled to give level means for each variable, these may be found in tabulated form within the appropriate results section along with the corresponding standard errors of the means (Tables 4.2, 4.5, 4.10, 4.13, 4.15, 4.17, 4.19, 4.21).

2) Flow profile data.

Flow variable data were partitioned into 10 litre ventilation "bins" to allow the calculation of subject means for each ventilatory level over the 10.0-69.9 litre ventilation range. These data are presented subject-by-subject in Appendix A4 as means and standard errors of the means.

Presentation of Data and Analysis

A standard format is used for the presentation of the data and analysis: first exercise data, followed by the effect of loading, and second hypercapnic data, followed by the effect of loading.

A comprehensive guide to the statistical methods employed in the analysis of data was presented in the preceding Statistical Methods chapter. The section below reports in brief how these techniques were applied to the data.

Analysis of Variance

The basic statistical analysis employed for the interpretation of data was an Analysis of Variance (ANOVA). This technique assessed the extent to which the mean of a variable was affected by different factors. In the study of energetics and breathing pattern the factors examined were work or hypercapnia level, loading condition and subjects; these were the main effects. Loading condition and subjects were also two of the main effects examined in the study of flow, but the work or hypercapnia level effect examined in the study of energetics and breathing pattern was replaced by a single ventilatory level effect.

In addition to examining main effects, ANOVA permitted the assessment of the significance of interactions between factors, thereby investigating the extent to which the influence of one factor depended on the level of another. In the present study, the levels of significance of all two-factor interactions (levels * resistance (LR), levels * subjects (LS) and subjects * resistance (SR)) were examined.

Although the data presented concerning gas exchange and breathing pattern are complete, they are not entirely balanced; subjects varied in the highest level of exercise and hypercapnia they tolerated and in the number of tests they were prepared to perform. Symmetry (of the number of subjects, peak work level and

peak inspired CO_2 level) was introduced by basing the analysis on the data of the 8 subjects who performed both exercise and hypercapnia experiments up to common exercise and inspired CO_2 levels of 200 W and 55 torr. The pooled mean levels of ventilation at these levels of exercise and hypercapnia were similar (Table 4.10), which made possible direct comparison of the mechanical and energetic effect of loading in exercise (when there was significant work performance by the limb muscles) and hypercapnia (when the respiratory muscles were the only site of significant work). The results of this analysis are presented in Tables 4.3, 4.6, 4.11, 4.14, 4.16, 4.18 and 4.20.

The analysis of data up to 200 W and inspired CO_2 (P_ICO_2) 55 torr revealed the general form of the response to exercise or hypercapnia, in the presence and absence of loading, relatively uncontaminated by effects specific to the very highest levels. For the particular analysis of the response during putative periods of power-sharing, i.e. when respiratory and limb work were both high, interpretation involved the consideration of data obtained at peak levels, 250 W and P_ICO_2 60 torr. The analysis of these data took two forms: first, the response at these levels was considered in isolation, and compared with that at lower levels, and secondly, ANOVA was employed to examine all the data from the subjects who tolerated these higher levels of exercise and hypercapnia. Generally, the results of these two further analyses of variance (of data from 10 and 5 subjects respectively) were very similar to those of the main analysis, but where the results are different they are mentioned in the text.

The techniques underlying ANOVA assume that the variance of each treatment group (i.e. at each work or hypercapnia level, in the presence or absence of loading) are the same. However, the

variances of ventilation, oxygen uptake and carbon dioxide elimination data were different between levels, and the level of variance and means appeared to be correlated. ANOVA techniques are quite robust in the face of differences in variance, but to verify the findings of the main analysis the data were logarithmically transformed to produce comparable variances and the analysis was repeated. The results of this analysis confirmed the significance (or non-significance) of effects given by the main analysis at the same or similar probability levels.

For the study of flow profiles, the data of four subjects, who had also taken part in the study of gas exchange and breathing pattern, were partitioned into 10 litre ventilation bins to provide 6 ventilatory levels between 10.0 $L.min^{-1}$ and the peak ventilation of 69.9 $L.min^{-1}$. A similar ANOVA to that employed in the study of gas exchange and breathing pattern was then performed on these data.

It should be noted that the demonstration by ANOVA that a factor has a significant effect does not indicate the form of the response, i.e. it does not suggest a linear or progressive increase or decrease. This was evaluated from level means.

Significance Levels

Two levels of significance are indicated throughout this chapter, $P<0.05$, and $P<0.01$; higher levels of significance are indicated by symbol "<<".

2. Energetics

This section presents data concerning the level of gas exchange and extent of anaerobic metabolism, when breathing was either unloaded or loaded, at rest, during exercise and during hypercapnia.

Gas Exchange During Exercise

Oxygen Uptake

1) Exercise effects.

Oxygen uptake ($\dot{V}O_2$) rose in a nearly linear manner with increasing work rate during incremental exercise tests, whether breathing was loaded or not (Figure 4.1 and Table 4.2); the effect of increasing work rate was highly significant ($P<<0.01$, Table 4.3). Work rate and $\dot{V}O_2$ were highly correlated: for the 10 subjects who exercised to 250 W the correlation coefficient, r, was 0.998 and for the eight subjects included in the main ANOVA (data up to 200 W), r was 0.997.

One noticeable feature of the work rate - $\dot{V}O_2$ relation was that the elevation of work rate from 200 W (10 subjects, mean $\dot{V}O_2$ = 2769 $ml.min^{-1}$ $\pm$ 69) to 250 W (10 subjects, mean $\dot{V}O_2$ = 3613 $ml.min^{-1}$ $\pm$ 89) produced a disproportionate rise in oxygen uptake, both when breathing was loaded and when it was not. This was evident as an increase in the slope of the lines of best fit to the relations when data from 250 W were included. In the absence

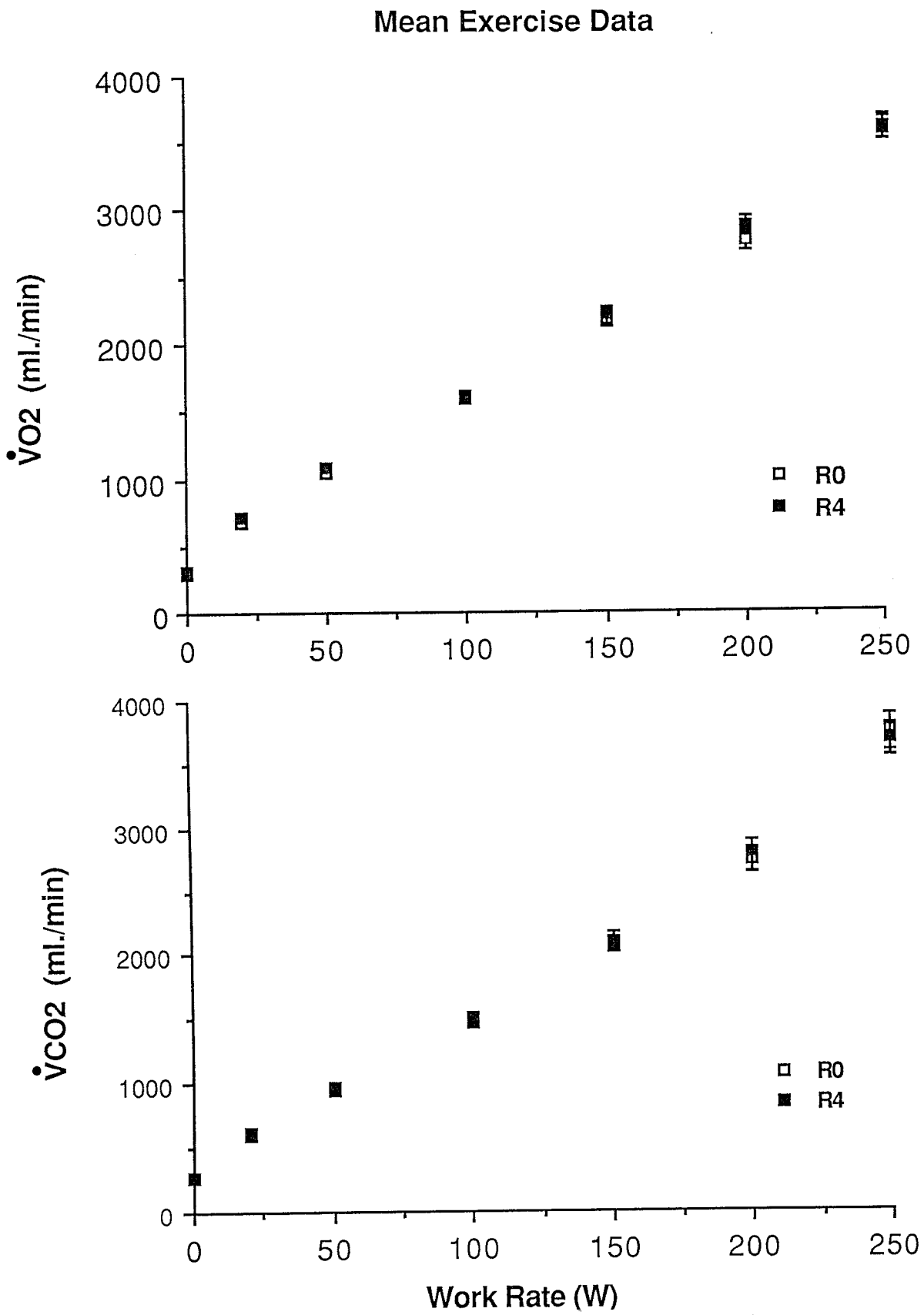


Figure 4.1: Gas Exchange During Exercise - gas exchange variables plotted against work rate at rest and during exercise up to 250 W: a) Oxygen uptake ($\dot{V}O_2$); b) Carbon dioxide elimination ($\dot{V}CO_2$). Data points are the pooled means of 10 subjects $\pm$ standard errors.

Table 4.2 : Oxgen Uptake ($\dot{V}O_2$)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean ($ml.min^{-1}$)	S.E.	Mean ($ml.min^{-1}$)	S.E.
Rest	331.	17.	326.	17.
0 W	708.	22.	732.	18.
50 W	1074.	25.	1109.	21.
100 W	1605.	44.	1644.	48.
150 W	2208.	56.	2243.	61.
200 W	2820.	62.	2866.	336.

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean ($ml.min^{-1}$)	S.E.	Mean ($ml.min^{-1}$)	S.E.
0 torr	331.	17.	326.	17.
30 torr	371.	15.	387.	19.
40 torr	386.	15.	448.	32.
45 torr	418.	26.	497.	35.
50 torr	452.	32.	546.	60.
55 torr	488.	37.	605.	56.

No. of Subjects = 8.

Table 4.3 : Oxygen Uptake

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	$7.18*10^7$	$1.44*10^7$	786.5**
Resistance (R)	1	20112.	20112.	6.8**
Subjects (S)	7	568162.	81165.	36.1**
Interactions				
LR	5	6416.	1283.5	0.6
LS	35	639232.	18263.8	8.1**
SR	7	20752.	2964.6	1.3
Residual (LRS)	35	78608.	2245.9	
Total	95	$7.32*10^7$		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	507120.	101424.	24.7**
Resistance (R)	1	88274.	88274.	14.0**
Subjects (S)	7	511016.	73002.	45.1**
Interactions				
LR	5	43754.	8750.8	5.4**
LS	35	143984.	4113.8	2.5**
SR	7	44272.	6324.6	3.9**
Residual (LRS)	35	56642.	1618.3	
Total	95	1395062.		

** $P<0.01$

* $P<0.05$

No. of subjects = 8

of loading, the slope (units of $ml.min^{-1}W^{-1}$) rose from 11.96 when calculated over the range from rest to 200 W, to 12.56 when calculated over the range from rest to 250 W, and in the presence of loading from 12.33 to 12.68.

There was considerable variation between subjects in the level of oxygen uptake at a given work level (subjects effect significant at $P<0.01$). There were also significant differences between subjects in the response of $\dot{V}O_2$ to increasing exercise intensity (LS interaction effect significant at $P<0.01$).

2) The oxygen cost of unloaded breathing during exercise.

The data obtained concerning the oxygen cost of breathing during hypercapnic hyperpnoea may be used to estimate the oxygen cost of breathing during exercise. The section below shows how this calculation proceeds to estimate the oxygen uptake of the respiratory muscles at the highest exercise levels, though this may also be done at all exercise levels (Table 4.4).

The first method of estimating the oxygen cost of breathing at the ventilation achieved at 200 W (ventilation = 64 $L.min^{-1}$, mean of 8 subjects, Table 4.10) was by calculating the difference between $\dot{V}O_2$ at rest and at 50 torr P_ICO_2 (ventilation = 67.7 $L.min^{-1}$), which gave a value of 121 $ml.min^{-1}$ (Tables 4.2 and 4.10). As $\dot{V}O_2$ at 200 W was 2820 $ml.min^{-1}$ (Table 4.2) the oxygen cost of breathing may be estimated to constitute 4.3% (121/2820 * 100) of total body $\dot{V}O_2$ at 200 W.

One may also use a second method of calculating the oxygen cost of breathing, from the level of ventilation and the oxygen cost of effecting each litre ventilation (see pp. 4.15-4.16). This allows one to calculate the oxygen cost of breathing at any ventilation (Table 4.4), rather than just at those achieved at a

Table 4.4 : Oxygen Uptake During Exercise and the Oxygen Cost of Breathing

	Oxygen Uptake During Exercise			Oxygen Cost of Breathing			Difference
Column.	1.	2.	3.	4.	5.	6.	7.
Work Rate	R0	R4	R4-R0	R0	R4	R4-R0	Column 6 - 3
Rest	331	326	-4	11	13	2	6
0 W	708	732	24	22	32	10	-14
50 W	1074	1109	35	32	56	24	-11
100 W	1605	1644	39	53	99	46	7
150 W	2208	2243	35	79	174	95	60
200 W	2820	2866	46	119	277	158	112

Columns 1 and 2 list the mean pooled oxygen uptake during exercise, in the absence and presence of loading respectively, for the eight subjects of the main analysis (from Table 4.2). Column 3 lists the difference between these values at each work level. Columns 4 and 5 list the estimated oxygen cost of breathing at each work load, in the absence and presence of loading respectively, calculated from the regression equations that describe the relationship between ventilation and the oxygen cost of breathing per litre ventilation during hypercapnic hyperpnoea (Figure 4.3). Column 6 lists the increase in the estimated oxygen cost of breathing with loading at each work level. Column 7 lists the difference between the increase in the estimated oxygen cost of breathing with loading at each work level, and the observed increase in oxygen uptake. Measurements of the oxygen uptake and the oxygen cost of breathing are both presented in ml.min-1 at STP.

given inspired CO_2 level. Using the equation that describes the relation between ventilation and the oxygen cost of breathing per litre ventilation (p. 4.16; see also Figure 4.3), the oxygen cost of breathing per litre at 250 W in the absence of loading (mean ventilation 85.3 $L.min^{-1}$, 10 subjects, Figure 4.7) was estimated as 2.13 $ml.min^{-1}$. The oxygen cost of breathing at this level of ventilation was therefore calculated to be 182 $ml.min^{-1}$ (85.3*2.13), which constituted 5% of total $\dot{V}O_2$ at 250 W (3613 $ml.min^{-1}$), a similar fraction to that at 200 W.

3) Loading effects.

Oxygen uptake also rose in a nearly linear manner with increasing exercise intensity when breathing was loaded. The correlation coefficient of this relationship, r, was 0.998 for the data up to 200 W and 250 W (8 and 10 subjects respectively).

Table 4.2 shows that the addition of loading increased mean $\dot{V}O_2$ at all exercise levels; the effect of loading was significant at $P<0.01$ (Table 4.3).

However, there was no progressive augmentation of $\dot{V}O_2$ above unloaded levels as work rate rose (LR interaction effect non-significant). This absence of a progressive augmentation was also manifest in individual subjects' data, and it was further evident that loading at the highest work rates produced only a slight rise or in some cases a fall in $\dot{V}O_2$.

There was no significant difference between subjects in the effect of loading on $\dot{V}O_2$ (SR interaction non-significant).

4) The oxygen cost of loaded breathing during exercise.

As shown above (p. 4.9), the oxygen cost of breathing at the highest exercise levels may be calculated by two methods.

Applying the first method, which relies on using the $\dot{V}O_2$ at an equivalent hypercapnically induced ventilation, the oxygen cost of breathing at 200 W (8 subjects, 58.5 $L.min^{-1}$ ventilation) was estimated as the difference between $\dot{V}O_2$ at rest and at 50 torr P_ICO_2 (ventilation = 56.0 $L.min^{-1}$), namely 220 $ml.min^{-1}$ (Tables 4.2 and 4.10). Thus by this method, the oxygen cost of breathing may be estimated to constitute 7.8% (220/2866 * 100) of total body $\dot{V}O_2$ at 200 W. This value is almost double that when breathing was unloaded (4.3%) at the same exercise level though total $\dot{V}O_2$ was similar.

Using the second method, which relied on the near linear relation between ventilation and the oxygen cost of breathing per litre ventilation (p. 4.16), the estimated oxygen cost of breathing at 250 W in the presence of loading at a mean ventilation of 74.5 $L.min^{-1}$ (10 subjects, Figure 4.7), was 422 $ml.min^{-1}$ (74.5*5.66). The oxygen cost of breathing was therefore calculated to be 11.7% of total body $\dot{V}O_2$ at 250 W (3621 $ml.min^{-1}$). This was a greater fraction than at 200 W when breathing was loaded and at 250 W when unloaded. Comparing the oxygen cost of breathing at 250 W in the presence of loading (422 $ml.min^{-1}$) with that in the absence of loading (182 $ml.min^{-1}$) reveals that the oxygen cost of breathing at 250 W was more than doubled with the addition of loading, yet total $\dot{V}O_2$ at 250 W was virtually unchanged.

As in the absence of loading, the oxygen uptake required by the respiratory muscles when breathing was loaded at each exercise level up to 200 W was estimated using the near linear relation between ventilation and the oxygen cost of breathing per litre ventilation (Table 4.4).

Carbon Dioxide Elimination

1) Exercise effects.

Carbon dioxide elimination ($\dot{V}CO_2$) initially rose in a nearly linear manner with the elevation of external work rate irrespective of whether breathing was loaded or not, but as work rate increased further this almost linear relationship gave way to one in which $\dot{V}CO_2$ increased disproportionately in response to changes in work rate (Table 4.5 and Figure 4.1). The slope of the relation for unloaded data from rest up to 150 W was 11.91, from rest up to 200 W, 12.04 and from rest up to 250 W, 13.11 (units of $ml.min^{-1}W^{-1}$, 10 subjects). When breathing was loaded, the change in the slope of the relation was from 11.68 to 12.08 and thence to 12.93. The correlation coefficient was high ($r > 0.99$) in all cases.

The results of the ANOVA of $\dot{V}CO_2$ data were generally similar to those of $\dot{V}O_2$ data, showing highly significant exercise level ($P<<0.01$) and significant subject ($P<0.01$) effects (Table 4.6). One difference was the greater variability between subjects in the response of $\dot{V}CO_2$ to increasing exercise intensity, the variance ratio of the LS interaction (significant at $P<.01$) being almost double that of $\dot{V}O_2$ data.

2) Loading effects.

Table 4.5 and Figure 4.1 show that mean $\dot{V}CO_2$ at a given exercise level was little affected by the addition of loading. This observation was corroborated by ANOVA which indicated that loading had no significant effect on mean $\dot{V}CO_2$ at a given exercise level (resistance effect non-significant, Table 4.6). It is further evident from Figure 4.1 that the addition of loading at 250 W was

Table 4.5 : Carbon Dioxide Elimination ($\dot{V}CO_2$)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean ($ml.min^{-1}$)	S.E.	Mean ($ml.min^{-1}$)	S.E.
Rest	293.	15.	291.	14.
0 W	613.	23.	628.	18.
50 W	961.	26.	977.	32.
100 W	1486.	56.	1490.	66.
150 W	2106.	77.	2094.	83.
200 W	2764.	110.	2766.	123.

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean ($ml.min^{-1}$)	S.E.	Mean ($ml.min^{-1}$)	S.E.
0 torr	293.	15.	291.	14.
30 torr	300.	11.	327.	17.
40 torr	305.	13.	339.	27.
45 torr	350.	17.	401.	21.
50 torr	345.	15.	404.	25.
55 torr	356.	20.	445.	36.

No. of Subjects = 8.

Table 4.6 : Carbon Dioxide Elimination

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	$7.01*10^7$	$1.40*10^7$	370.5**
Resistance (R)	1	384.	384.	0.1
Subjects (S)	7	1376256.	196608.	76.8**
Interactions				
LR	5	2336.	436.2	0.18
LS	35	1324336.	37838.2	14.8**
SR	7	37620.	5245.7	2.1
Residual (LRS)	35	89648.	2561.4	
Total	95	$7.29*10^7$		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	147379.	29475.8	10.7**
Resistance (R)	1	44593.	44593.	15.1**
Subjects (S)	7	113138.	16162.	12.1**
Interactions				
LR	5	18947.	3798.4	2.8*
LS	35	96369.	2753.4	2.1**
SR	7	20614.	2944.9	2.20
Residual (LRS)	35	46771.	1336.3	
Total	95	487811.		

** P<0.01

* P<0.05

No. of subjects = 8

associated with a fall in $\dot{V}CO_2$, though a paired t-test revealed that the difference between unloaded and loaded values was not significant. The absence of a significant difference between subjects in the effect of loading on $\dot{V}CO_2$ (SR interaction non-significant) indicated that the lack of any significant resistance effect was a general response amongst all subjects.

Gas Exchange During Hypercapnia

Oxygen Uptake - The Oxygen Cost of Breathing

Measuring differences in whole body oxygen uptake has been the standard method of estimating the oxygen cost of breathing in man since it was done by Liljestrand in 1918 (p. 1.41).

However, there is conflicting evidence as to whether the increase in oxygen consumption accompanying hypercapnia may be ascribed solely to the increased work of breathing, or whether part of the increase may be due to the effect of hypercapnia on the general level of metabolism, in which case the oxygen cost of breathing would be overestimated (see p. 1.52). Nevertheless, the error of estimation declines as respiratory work rate increases and when comparing estimates made at similar levels of hypercapnia (p. 1.53), suggesting that oxygen cost of breathing data are valid as long as they are interpreted with caution and within context.

1) Hypercapnia effects.

During incremental hypercapnia, oxygen uptake rose in a nearly linear manner with increasing ventilation up to 40 $L.min^{-1}$ and at an increasing rate with increasing ventilation above this level (Figure 4.2). Thus in the absence of loading, pooled mean oxygen uptake rose from approximately 330 $ml.min^{-1}$ at 10 $L.min^{-1}$ ventilation to reach nearly 500 $ml.min^{-1}$ at 75 $L.min^{-1}$ ventilation (P_ICO_2 55 torr, Tables 4.2 and 4.10). When breathing was loaded pooled mean oxygen uptake rose, from a similar level to that in the absence of loading at resting levels of ventilation, to reach approximately 600 $ml.min^{-1}$ at 62 $L.min^{-1}$ ventilation (P_ICO_2 55 torr, Tables 4.2 and 4.10). ANOVA indicated that the effect of increasing hypercapnia level was significant at $P<0.01$ (Table 4.3).

There were highly significant differences between subjects in $\dot{V}O_2$ at a given hypercapnia level ($P<0.01$) and further, significant differences in the changes in $\dot{V}O_2$ accompanying incremental hypercapnia (LS interaction significant at $P<0.01$).

2) Loading effects.

Table 4.2 shows that $\dot{V}O_2$ at a given inspired CO_2 level was elevated by the addition of loading and ANOVA indicated that the effect of loading on $\dot{V}O_2$ was significant at $P<0.01$ (Table 4.3).

The presence of a significant LR interaction ($P<0.01$) indicated that the augmentation of $\dot{V}O_2$ with loading increased as inspired CO_2 levels (and therefore ventilation) rose. Regression analysis of the LR interaction (Statistical Methods Chapter, pp. 3.9-3.10) disclosed the existence of a significant linear component ($P<0.01$, Table 4.23), i.e. the rise in $\dot{V}O_2$ accompanying

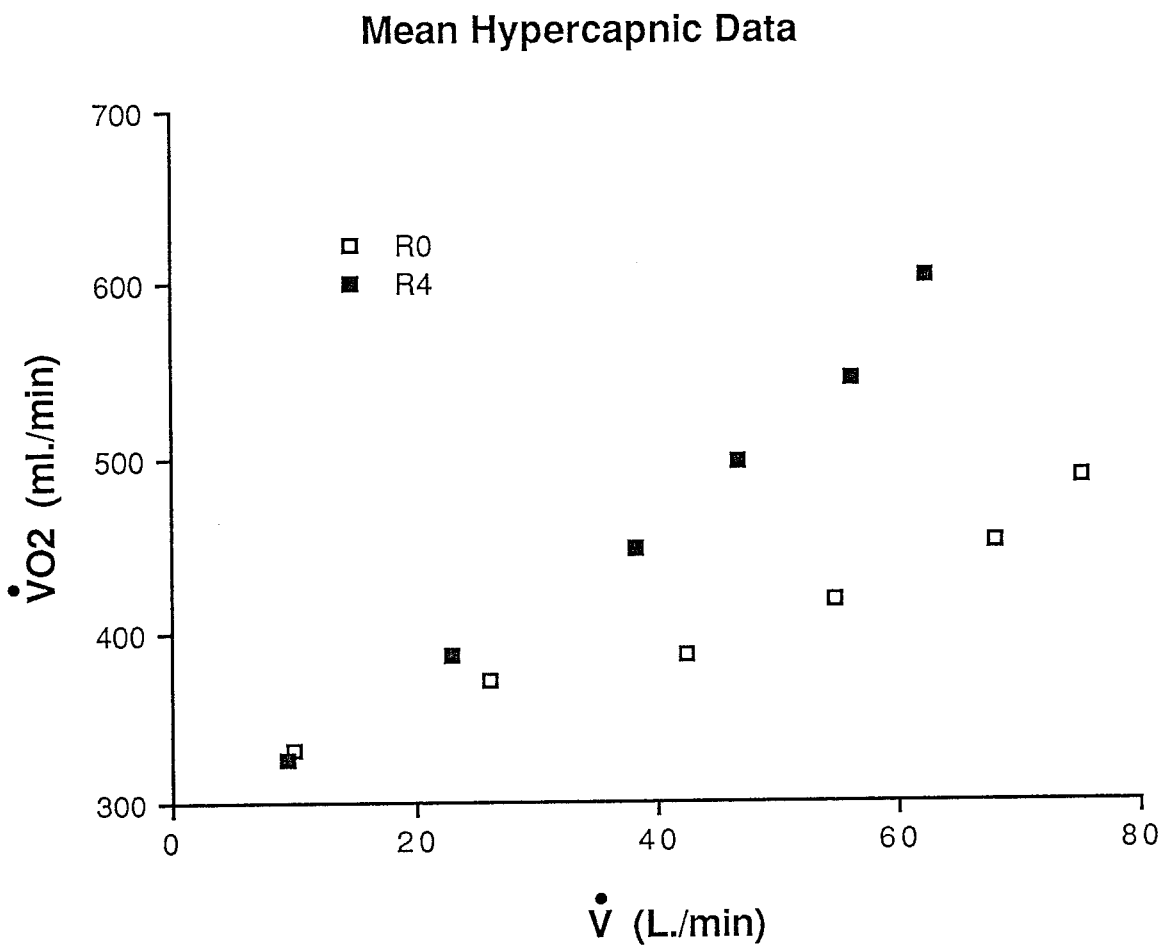


Figure 4.2: The Oxygen Cost of Breathing - the relation between ventilation ($\dot{V}$) and oxygen uptake ($\dot{V}O_2$) with subjects at rest, when ventilation was raised by the addition of carbon dioxide to the inspirate. Data points are the pooled means of eight subjects at inspired carbon dioxide levels of 0, 30, 40, 45, 50 and 55 torr, standard errors are presented in Table 4.2.

N.B. scale is expanded in relation to Figure 4.1.

loading at any inspired CO_2 level increased in a nearly linear fashion with the elevation of inspired CO_2 level.

The presence of a significant SR interaction ($P<0.01$) indicated significant differences between subjects in the effect of loading on $\dot{V}O_2$. This finding may be illustrated by reference to individual subjects' data obtained at 55 torr inspired CO_2 (Appendix A1). While the pooled mean difference in $\dot{V}O_2$ accompanying loading was 117 $ml.min^{-1}$, the mean difference for individual subjects varied from below 10 $ml.min^{-1}$ (Subjects 632 and 634) to above 300 $ml.min^{-1}$ (Subject 635).

Comparison of the effect of loading on $\dot{V}O_2$ during exercise with that during hypercapnia (Statistical Methods Chapter, p. 3.8) revealed significantly greater elevation of oxygen uptake with the addition of loading during hypercapnia than during exercise (Table 4.24).

3) The oxygen cost of breathing per litre ventilation.

Measures of the oxygen cost of breathing were more valuable when considered in relation to the level of ventilation rather than in relation to the inspired CO_2 partial pressure. Therefore the oxygen cost of breathing per unit ventilation at a given ventilation was calculated. This was achieved by dividing the elevation of $\dot{V}O_2$ from that at rest by the observed augmentation of ventilation.

The data concerning the change in the oxygen cost of breathing per litre ventilation ($\dot{V}O_2v$) were grouped in 10 litre ventilation bins and a mean for each bin calculated (Table 4.7). Figure 4.3 shows that the $\dot{V}$ - $\dot{V}O_2v$ relations of both unloaded and loaded pooled mean data from all subjects were well described by fitting lines of regression ($r = 0.82$ and $r = 0.96$ respectively).

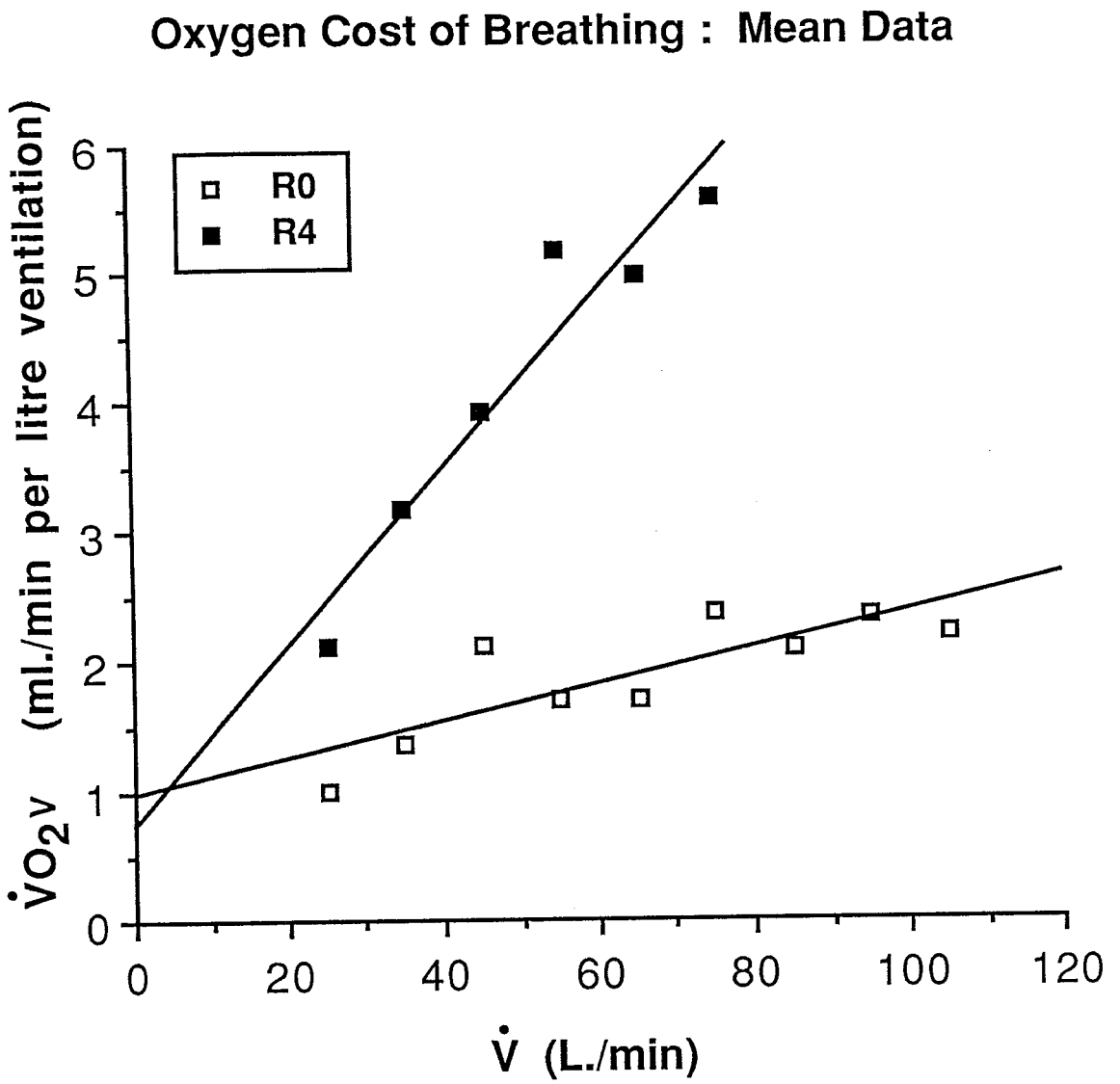


Figure 4.3: The Oxygen Cost of Breathing - the relation between ventilation ($\dot{V}$) and oxygen uptake per litre ventilation ($\dot{V}O_2v$). The data, from eight subjects, were partitioned into 10 litre ventilation bins. Means and standard errors of the means are presented in Table 4.7. The lines represent the best fit lines of regression to the unloaded and loaded relations.

Table 4.7 : The Oxygen Cost of Breathing

Unloaded Condition

Ventilation ($L.min^{-1}$)	Mean $\dot{V}O_2$ $ml.min^{-1}$	S.E.	Mean $\dot{V}O_2v$ $ml.L^{-1}$	S.E.	Number of observations
Rest	315	10.3	-	-	44
20 - 29.9	343	11.4	1.0	1.1	31
30 - 39.9	359	12.5	1.4	0.25	25
40 - 49.9	355	12.7	2.1	0.23	17
50 - 59.9	419	14.9	1.7	0.26	14
60 - 69.9	406	18.4	1.7	0.29	18
70 - 79.9	465	20.3	2.4	0.34	13
80 - 89.9	482	13.7	2.1	0.25	17
90 - 99.9	525	52.9	2.3	0.46	5
100 - 109.9	482	33.7	2.2	0.37	8

Loaded Condition

Ventilation ($L.min^{-1}$)	Mean $\dot{V}O_2$ $ml.min^{-1}$	S.E.	Mean $\dot{V}O_2v$ $ml.L^{-1}$	S.E.	Number of observations
Rest	322	10.1	-	-	44
20 - 29.9	356	5.2	2.1	0.71	35
30 - 39.9	390	11.7	3.2	0.37	28
40 - 49.9	485	15.3	3.9	0.41	19
50 - 59.9	546	25.1	5.2	0.47	27
60 - 69.9	580	31.3	5.0	0.40	20
70 - 79.9	654	38.5	5.6	0.54	20

Mean oxygen uptake ($\dot{V}O_2$) and the oxygen cost of breathing per litre per min. ventilation ($\dot{V}O_2v$) at different ventilatory levels. The data of eight subjects are shown after partitioning into 10 litre ventilation bins; the number of observations contributing to the calculation of each mean is indicated.

In the absence of loading the pooled mean $\dot{V}$ - $\dot{V}O_2v$ relation was best described by the equation:

$$\dot{V}O_2v = 0.96 + 0.014 * \dot{V} \qquad ml.L^{-1}$$

In the presence of loading the relation was best described by the equation:

$$\dot{V}O_2v = 0.72 + 0.069 * \dot{V} \qquad ml.L^{-1}$$

Regressions were also fitted to individual subjects' data (each incremental hypercapnia test contributing 5 or 6 points depending on the peak P_ICO_2 level), the coefficients and intercepts for which are given in Table 4.8.

The finding from the analysis of both mean and individual subjects' data was that the oxygen cost of breathing per litre ventilation at resting levels of ventilation was similar with and without loading; Figure 4.3 indicates that the pooled mean oxygen cost of breathing per litre ventilation at 10 $L.min^{-1}$ was approximately 1 $ml.min^{-1}$. However as ventilation rose, the oxygen cost per litre ventilation rose and the rate of rise was five times greater when breathing was loaded than when unloaded: the slopes of the relations were 0.069 and 0.014 respectively.

At a resting ventilation of 10 $L.min^{-1}$, with a $\dot{V}O_2v$ of 1 $ml.min^{-1}$ per litre ventilation and a total $\dot{V}O_2$ of approximately 330 $ml.min^{-1}$, the oxygen cost of breathing may be calculated to account for approximately 3% (1*10/330 * 100) of total oxygen uptake. When breathing was unloaded, the elevation of ventilation to 65 $L.min^{-1}$ (which was the pooled mean ventilation at 200 W, Table 4.10) was associated with a rise in $\dot{V}O_2v$ to approximately 2 $ml.min^{-1}$ per litre ventilation. The oxygen cost of breathing at

Table 4.8 : The Oxygen Cost of Breathing

Subject No.	Unloaded Slope	Unloaded Intercept ($ml.L^{-1}$)	Loaded Slope	Loaded Intercept ($ml.L^{-1}$)
632	0.004	1.22	0.100	0.37
634	0.022	0.63	0.049	2.80
635	0.031	0.02	0.150	-2.73
639	0.026	0.36	0.082	1.05
642	0.006	0.75	0.050	0.80
643	-0.003	2.99	-0.002	3.83
647	0.001	1.85	0.031	2.79
648	0.015	0.64	0.026	0.85

Coefficients and intercepts of the linear regression of the oxygen cost of breathing per litre ventilation upon ventilation for each of eight subjects. Data from each experimental run was partitioned into 10 litre ventilation bins and the regression calculated using the resulting means.

this level of ventilation could therefore be estimated to account for almost 30% (2*65/((2*65)+330) * 100) of total $\dot{V}O_2$, in the absence of any limb work. When breathing was loaded, the elevation of ventilation to 58 $L.min^{-1}$ (the pooled mean ventilation at 200 W, Table 4.10) was associated with a rise in $\dot{V}O_2v$ to approximately 5 $ml.min^{-1}$ per litre ventilation. In this case the oxygen cost of breathing could be estimated to account for almost 50% of total $\dot{V}O_2$ (5*58/((5*58)+330) * 100) in the absence of significant limb work.

Carbon Dioxide Elimination

1) Hypercapnia effects.

The results of the ANOVA of $\dot{V}CO_2$ data obtained during hypercapnia (Table 4.6) generally resembled those during exercise. However, there were two differences: both the resistance main effect ($P<0.01$) and the LR interaction effect ($P<0.05$) were significant during hypercapnia, indicating that CO_2 elimination was significantly increased following loading and that the increase rose with the level of hypercapnia.

Regression analysis of the LR interaction revealed a significant linear component ($P<0.01$, Table 4.23), i.e. the augmentation of $\dot{V}CO_2$ with loading increased in near proportion to the increase in P_ICO_2.

The finding of a significant resistance effect on $\dot{V}CO_2$ during hypercapnia but not during exercise suggested that the effects of loading during the two conditions were different. The apparent difference in the loading effect in the two conditions was confirmed as being significant by the "difference of differences" test ($P<<0.01$, Table 4.24).

The level of anaerobic metabolism was estimated by measuring plasma lactate concentration in five subjects performing incremental exercise tests and in three of the same subjects during incremental hypercapnia tests.

Interpretation of plasma lactate data was carried out for individual subjects because of the small number of experiments in which plasma lactate concentrations were measured (one per subject), the fact that only single determinations of plasma lactate concentration were made in each loading condition at each work or hypercapnia level, and the discrete responses from subjects (see Figures 4.4-4.6 and Table 4.9). However, this did not preclude general analysis where applicable.

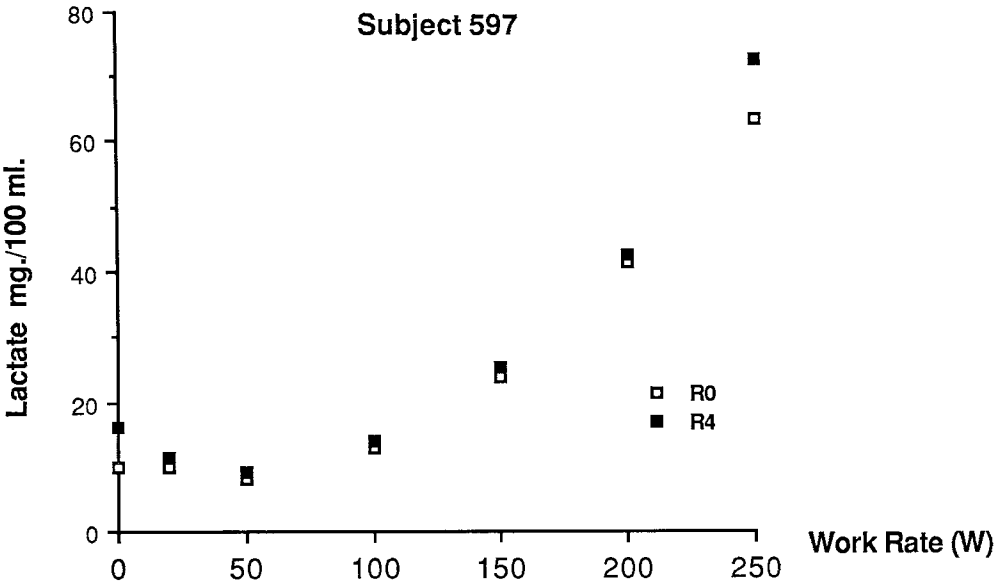
Exercise Data

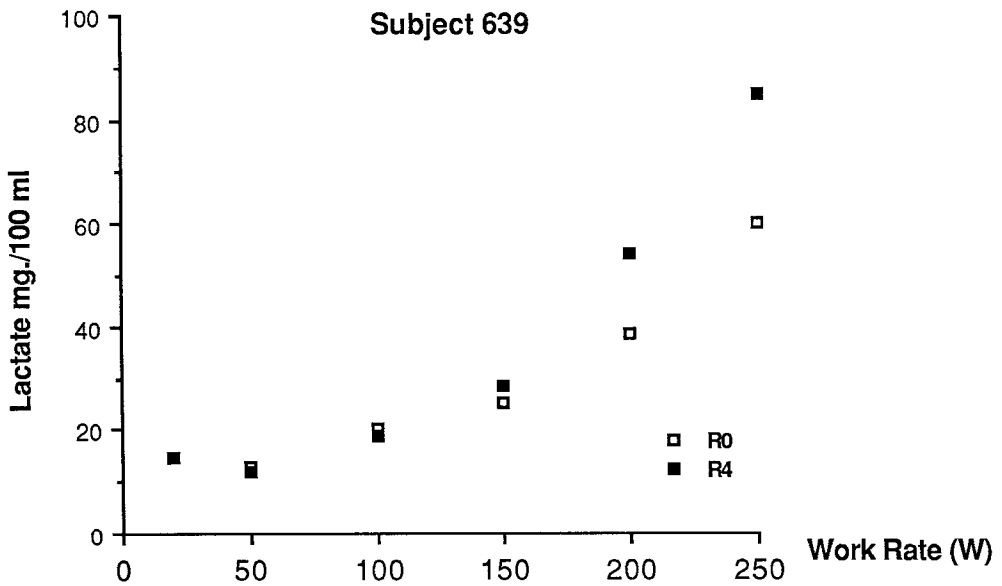
1) Exercise effects.

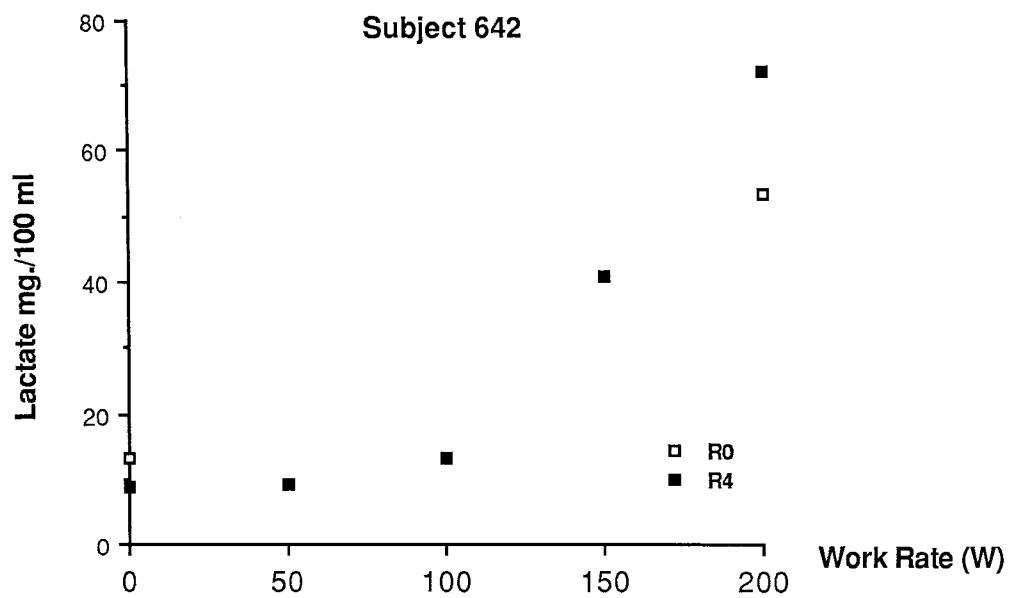
The effect of increasing exercise level on plasma lactate concentration was similar in all subjects. Low exercise intensities had little or no effect, but lactate levels rose markedly as exercise intensity increased further. The point at which plasma lactate concentration rose alinearly was identified as the anaerobic threshold, for four of the five subjects this occurred at 100 W, but for the most physically active subject (643), the threshold occurred at 150 W.

The level of exercise at which the rise in plasma lactate concentration was seen agreed well with the level at which it was estimated to occur from the point of inflection of the $\dot{V}O_2 - \dot{V}$ relation (Figures 4.4-4.5 and Table 4.1).

Figure 4.4: Anaerobic Metabolism During Exercise - plasma lactate concentrations at rest and during incremental work tests, for the three subjects who showed greater lactate concentrations with the addition of loading above the anaerobic threshold. In the absence of loading, venous blood samples could only be obtained from Subject 642 at the highest work level.


Subject 597
Lactate mg./100 ml.
80
60
40
20
0
0
50
100
150
200
250
Work Rate (W)
R0
R4


Subject 639
Lactate mg./100 ml
100
80
60
40
20
0
0
50
100
150
200
250
Work Rate (W)
R0
R4


Subject 642
Lactate mg./100 ml
80
60
40
20
0
0
50
100
150
200
Work Rate (W)
R0
R4

2) Loading effects.

Below the anaerobic threshold there was no apparent change in plasma lactate concentration in response to the addition of loading, nor was the level of the threshold itself affected by loading (Figures 4.4 and 4.5). Above the threshold but below peak exercise level, all subjects showed a higher plasma lactate concentration in presence of loading than when unloaded. However, at the peak exercise level the subjects differed as to the form of the response to loading.

The subjects could be divided into two groups with regard to the change in plasma lactate concentrations accompanying loading at the peak exercise level. The first group (Subjects 597, 639 and 642) exhibited increased plasma lactate levels in response to loading (Figure 4.4). The mean increase for the three subjects was 18.4 mg.100 ml^{-1}, which represented a 30% increase over lactate levels in the absence of loading, and a paired t-test showed the increase to be significant at $P<0.05$.

These subjects were also distinguished by the absence of any increase in $\dot{V}O_2$ with the addition of loading at the highest work level (Table 4.9): In the experiments in which plasma lactate concentrations were measured, oxygen uptakes at the highest work level in the absence of loading were 4250, 3892 and 4072 $ml.min^{-1}$, compared with 4035, 3868 and 3602 $ml.min^{-1}$ when breathing was loaded, i.e. loading was associated with a mean fall of 230 $ml.min^{-1}$. A paired t-test showed this decrease to be insignificant.

In the second group of subjects (643 and 648), lactate levels at highest work level were actually reduced when breathing was loaded compared with those in the absence of loading (Figure 4.5), the mean fall was 7.7 $mg.100ml^{-1}$.

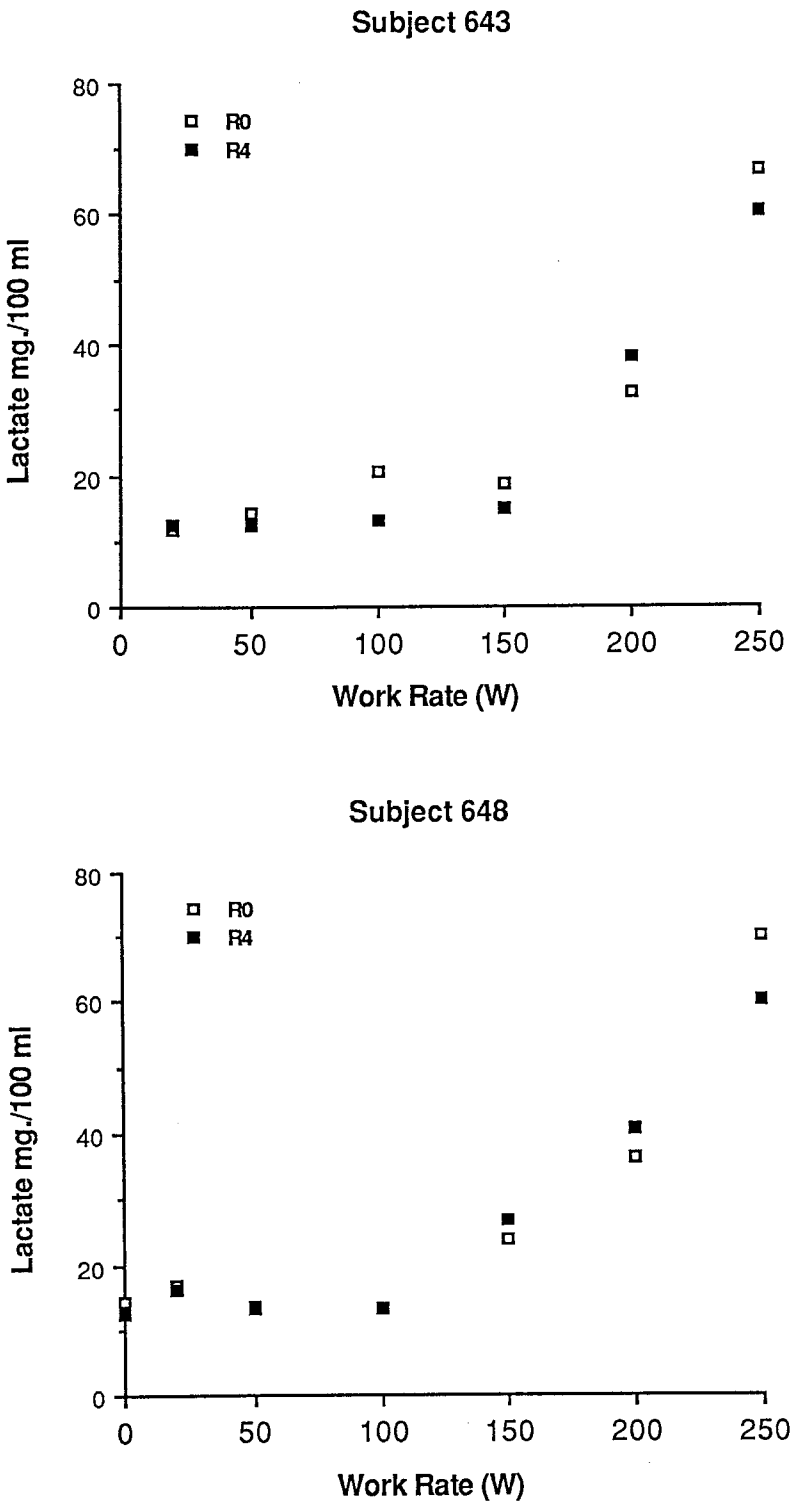


Figure 4.5: Anaerobic Metabolism During Exercise - venous blood lactate concentrations during incremental work tests, for the two subjects who did not show greater lactate levels with the addition of loading at the highest work level.

Table 4.9 : The Energetics of High Work Loads

Subject No.	Work Rate (W)	Total Oxygen Uptake ($ml.min^{-1}$)		Difference in [Lactate] ($mg.100ml^{-1}$)	Oxygen Cost of Breathing ($ml.min^{-1}$)	
		Unloaded	Loaded	(Loaded-Unloaded)	Unloaded	Loaded
597	250	4250	4035	11.8	-	-
639	250	3892	3868	25.2	185	555
642	200	4072	3602	18.3	102	335
643	250	3698	4317	-5.4	283	281
648	250	3573	4054	-10.0	304	372

The difference in plasma lactate concentration at peak work loads, and the corresponding unloaded and loaded oxygen uptakes measured during the experiments in which plasma lactates were measured. The estimated oxygen cost of breathing at the levels of ventilation achieved at peak work loads were estimated using the slopes and intercepts listed in Table 4.7, which describe the linear regression of the oxygen cost of breathing per litre ventilation upon ventilation for each individual.

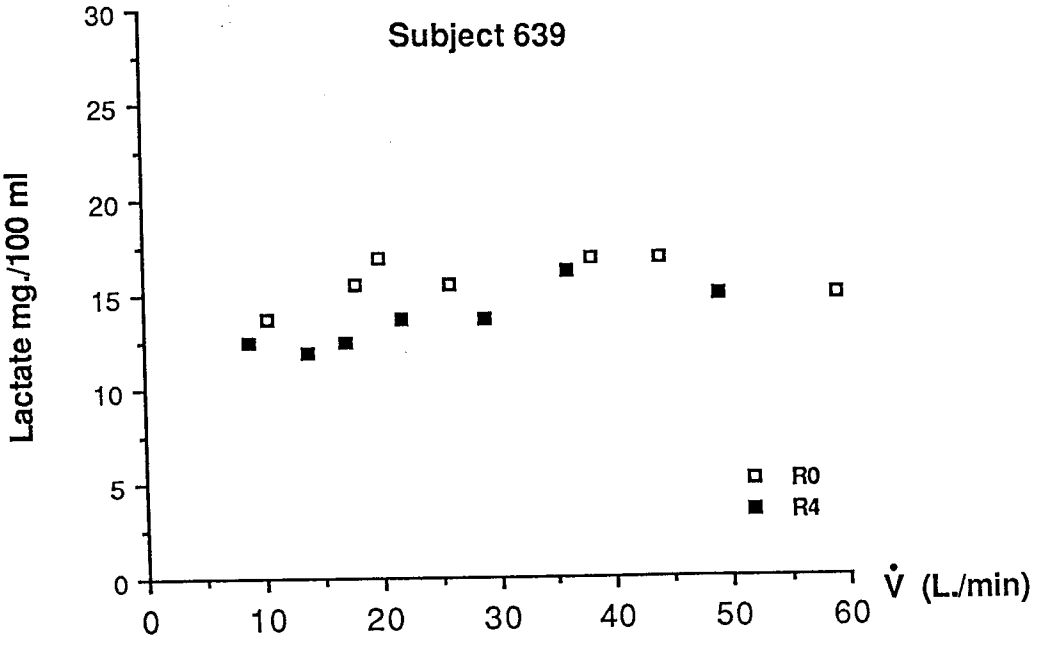
These subjects were further distinguishable by the fact that $\dot{V}O_2$ at the highest work level was increased markedly by the addition of loading; the pooled mean increase was 550 $ml.min^{-1}$ (Table 4.9).

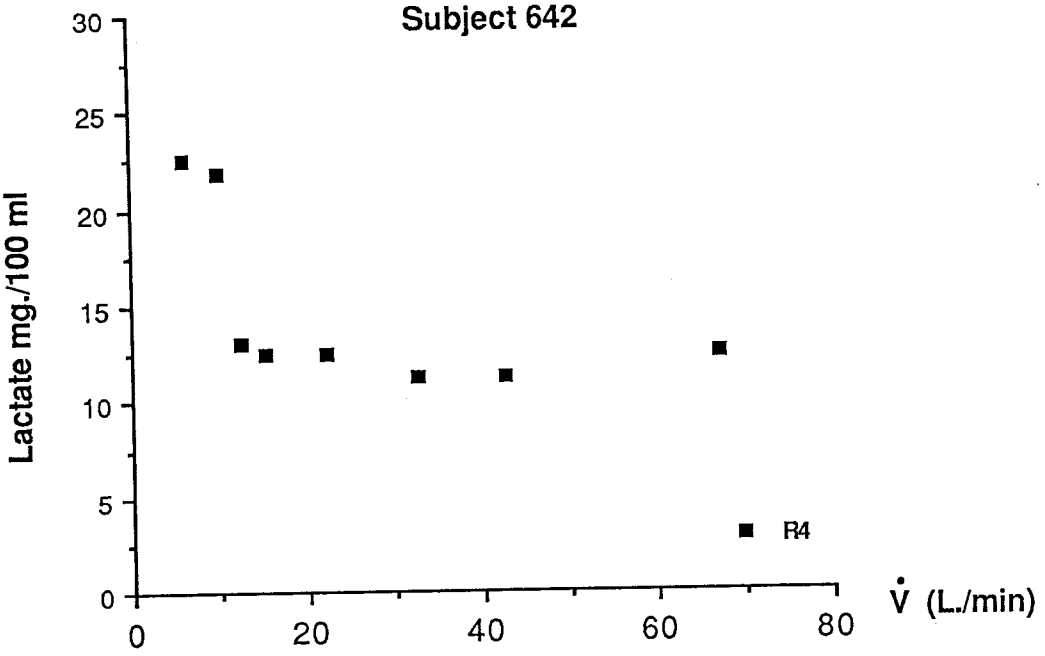
Hypercapnic Data

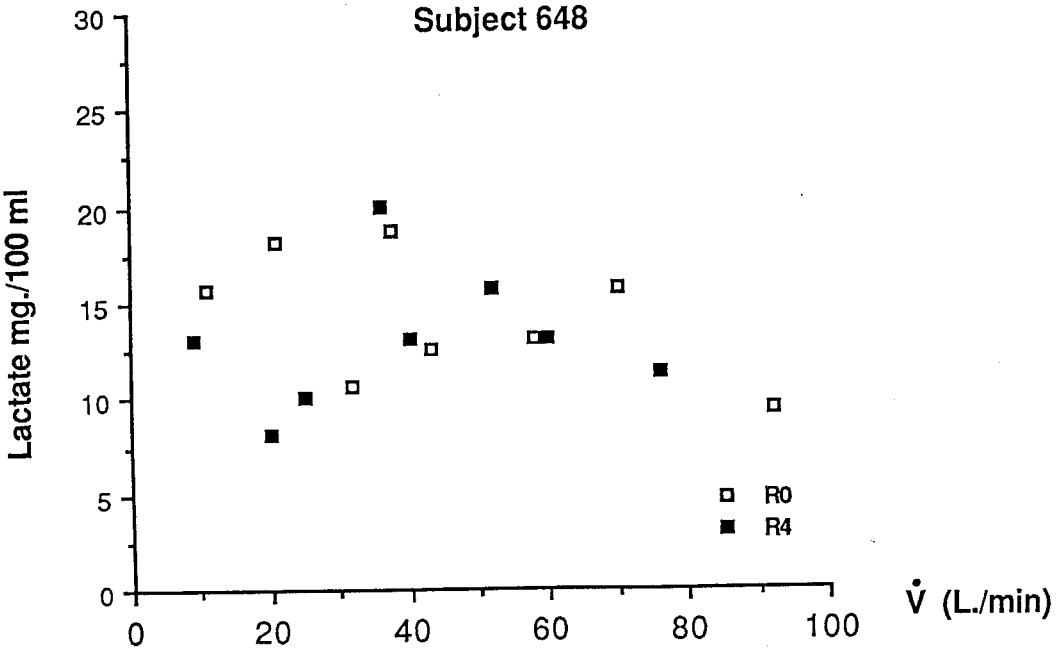
Three of the same subjects in whom plasma lactate measurements were made during exercise (639, 642 and 648; Figures 4.4 and 4.5) had additional measurements made during hypercapnia tests, ventilation being stimulated to levels similar to those achieved at the highest exercise intensities.

The data from these experiments are plotted in Figure 4.6. They show first, that the rise in respiratory work rate accompanying the hypercapnic elevation of ventilation at rest did not augment anaerobiosis when breathing was unloaded, and secondly, loading had no consistent effect on plasma lactate during progressive hypercapnia tests at rest.

Figure 4.6: Anaerobic Metabolism of the Respiratory Muscles- plasma lactate concentrations during incremental hypercapnia. Unfortunately venous blood samples could not be obtained from Subject 642 in the absence of loading. However, if the respiratory muscles were to show augmented anaerobiosis with increasing ventilation, the rise in plasma lactate concentrations would be most evident in the presence of loading when the oxygen cost of breathing is higher, but Subject 642 shows no evidence of a rise in lactate levels with increasing ventilation.


Subject 639
Lactate mg./100 ml
30
25
20
15
10
5
0
0
10
20
30
40
50
60
R0
R4
V̇ (L./min)


Subject 642
Lactate mg./100 ml
30
25
20
15
10
5
0
0
20
40
60
80
R4
V̇ (L./min)


Subject 648
Lactate mg./100 ml
30
25
20
15
10
5
0
0
20
40
60
80
100
R0
R4
V̇ (L./min)

3. Ventilation and Breathing Pattern

This section presents data concerning measures of the mechanical performance of the respiratory system, with and without loading, at rest, during exercise and during hypercapnia.

Ventilation

Loading Effects at Resting Levels of Ventilation

The pooled mean response to the addition of loading was a slight fall in ventilation (4%, Table 4.10). However, one subject (632) showed a mean rise (10%) in ventilation and other subjects sometimes showed a rise (Appendix A1).

Ventilation During Exercise

1) Exercise effects.

Ventilation at a given exercise level was reduced by loading (Figure 4.7, Table 4.10). ANOVA confirmed the well known highly significant exercise effect on ventilatory level ($P<<.01$, Table 4.11). However, there was considerable variation between subjects in the ventilation at a given work level, evident from the ANOVA as the highly significant subjects effect ($P<<.01$). This variation was related to exercise level (LS interaction significant at $P<<0.01$), indicating that subjects showed differences in the extent to which ventilation was increased in response to the increase in exercise level.

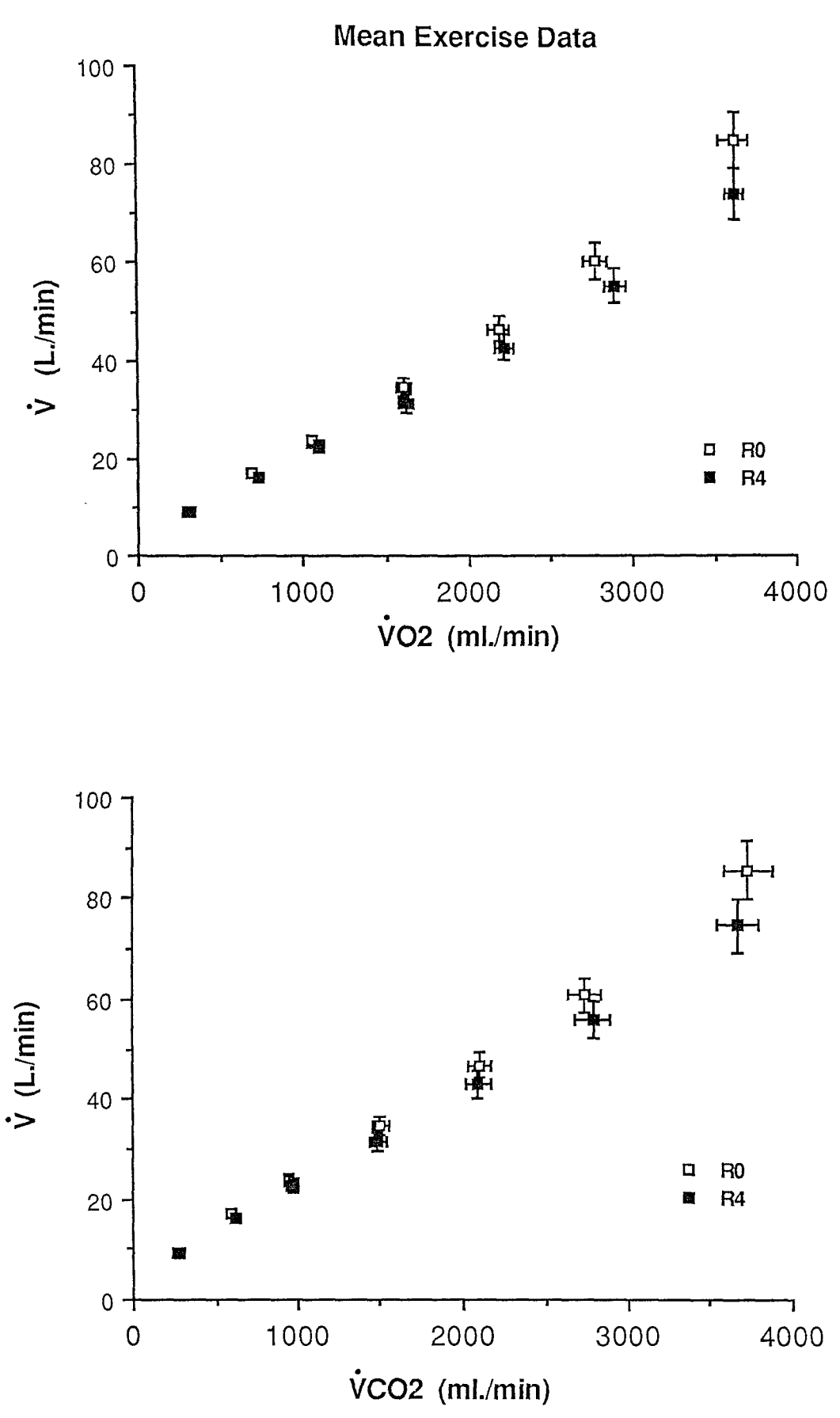


Figure 4.7: The Ventilatory Response to Exercise - the relation between gas exchange variables and ventilation ($\dot{V}$) at rest and during exercise up to 250 W: a) Oxygen uptake ($\dot{V}O_2$); b) Carbon dioxide elimination ($\dot{V}CO_2$). Data points represent the pooled means of 10 subjects $\pm$ standard errors.

Figure 4.7 illustrates the $\dot{V}O_2$ - $\dot{V}$ relation. It is evident that at low to moderate exercise intensities (data up to 150 W, $\dot{V}O_2$ approximately 2200 $ml.min^{-1}$) the relation was nearly linear (unloaded relation; r = 0.999, slope 1.99 * 10^{-2}: loaded relation; r = 0.995, slope 1.756 * 10^{-2}, 10 subjects). However as exercise levels rose further, this initial region of near linearity gave way to a region where the relation was one of increasing slope (data from rest up to 250 W, $\dot{V}O_2$ approximately 3600 $ml.min^{-1}$: unloaded slope 2.25 * 10^{-2}; loaded slope 1.94 * 10^{-2}, 10 subjects).

2) Loading effects.

ANOVA indicated the existence of a highly significant resistance effect ($P<<0.01$, Table 4.11). The change in ventilation with the addition of loading was one of the most significant effects detected in the analysis, being of a similar magnitude to the exercise effect on $\dot{V}$, $\dot{V}O_2$ and $\dot{V}CO_2$.

The finding of a significant LR interaction effect ($P<0.01$) indicated that the extent of the fall in ventilation accompanying the addition of loading was a function of the level of exercise. Regression analysis of the LR interaction revealed the existence of significant linearity ($P<0.01$), i.e. there was a progressive near linear increase in the difference between unloaded and loaded levels of ventilation as exercise intensity rose.

An increasing difference between loaded and unloaded levels of ventilation was generally apparent in the data of the subjects who further increased work rate from 200 to 250 W. The mean fall of ventilation with loading at 250 W (11 $L.min^{-1}$, Figure 4.7) was almost double that at 200 W.

Table 4.10 : Ventilation ($\dot{V}$)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean ($L.min^{-1}$)	S.E.	Mean ($L.min^{-1}$)	S.E.
Rest	10.0	0.51	9.6	0.52
0 W	18.4	0.86	17.0	0.81
50 W	24.8	1.15	23.7	1.39
100 W	36.0	2.02	33.1	2.16
150 W	48.3	3.15	45.2	3.36
200 W	63.9	4.72	58.4	4.44

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean ($L.min^{-1}$)	S.E.	Mean ($L.min^{-1}$)	S.E.
0 torr	10.0	0.51	9.6	0.52
30 torr	26.2	1.48	23.0	1.04
40 torr	42.5	2.56	38.1	2.07
45 torr	54.6	3.32	46.7	2.69
50 torr	67.7	3.85	56.0	2.89
55 torr	75.0	3.83	61.9	3.85

No. of Subjects = 8.

Table 4.11 : Ventilation

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	29301.3	5860.3	111.6**
Resistance (R)	1	138.5	138.5	277.0**
Subjects (S)	7	248.7	35.5	46.1**
Interactions				
LR	5	67.6	13.5	17.6**
LS	35	1838.5	52.5	68.2**
SR	7	3.5	0.5	0.7
Residual (LRS)	35	27.1	0.8	
Total	95	31625.2		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	40160.	8032.	182.8**
Resistance (R)	1	1105.7	1105.7	21.0**
Subjects (S)	7	2505.5	357.9	32.8**
Interactions				
LR	5	489.9	99.8	9.1**
LS	35	1538.	43.9	4.0**
SR	7	368.	52.6	4.8**
Residual (LRS)	35	382.4	10.9	
Total	95	46549.5		

** P<0.01

* P<0.05

No. of Subjects = 8

However, although the addition of loading at 250 W was associated with a greater fall in ventilation than at 200 W, in both absolute and percentage terms, the increase in loaded ventilation accompanying the rise in work rate from 200 W to 250 W was greater than that accompanying the rise from 150 W to 200 W. Thus, there was no lessening of the rate of rise of ventilation as the highest exercise intensities were approached. This was despite the fact that most subjects were experiencing considerable distress and only just managed to complete the protocol. Many cited their subjectively determined inability to generate sufficient ventilation as a major factor in their inability to continue exercising.

The SR interaction effect was not significant, indicating that the addition of resistance had similar effects on ventilation in individual subjects. However, differences between subjects were apparent and examination of individual subjects' data revealed a range of responses (Appendix A1).

The $\dot{V}CO_2$ - $\dot{V}$ relation depicted in Figure 4.7 also shows the disproportionate rise in ventilation with the onset of anaerobiosis that was evident in the $\dot{V}O_2$ - $\dot{V}$ plot.

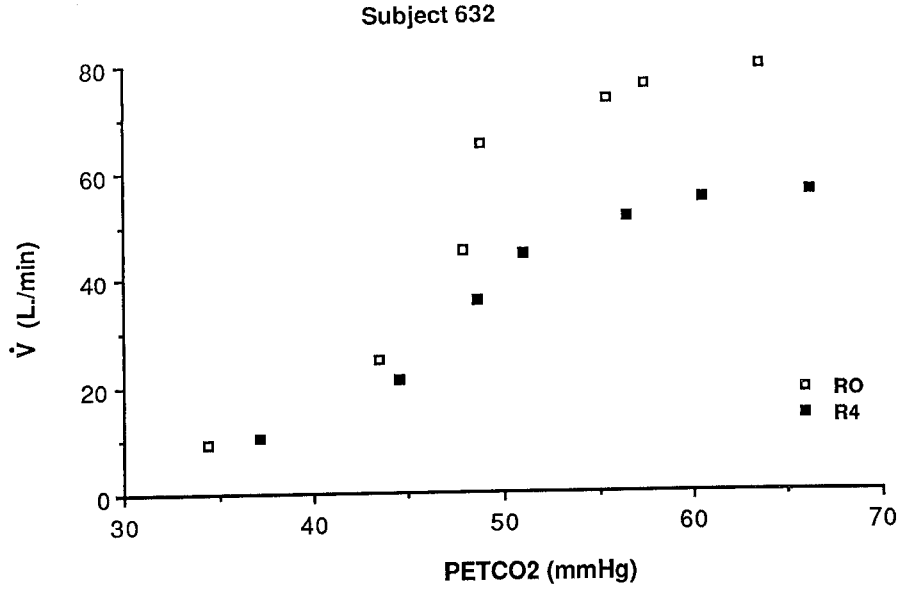
Ventilation During Hypercapnia

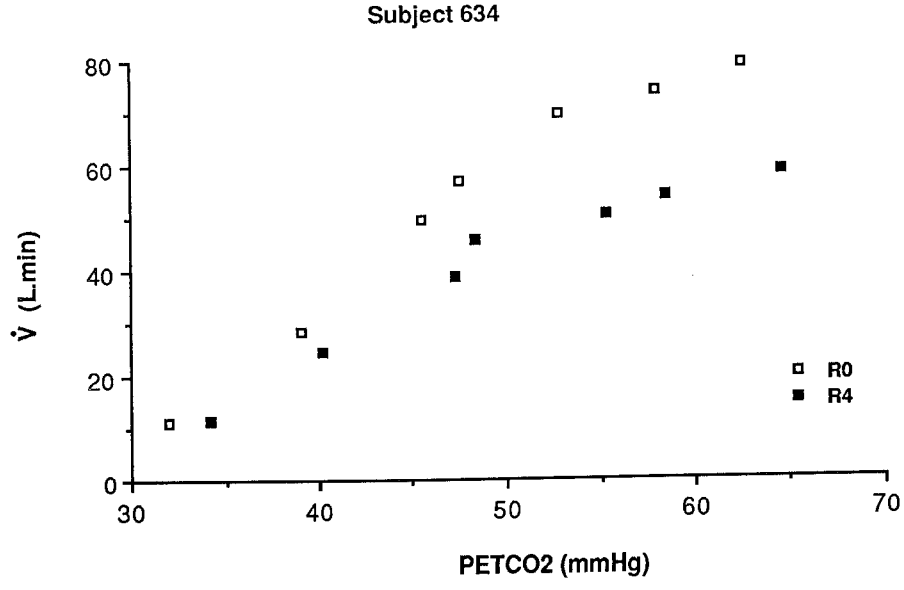
1) Hypercapnia effects.

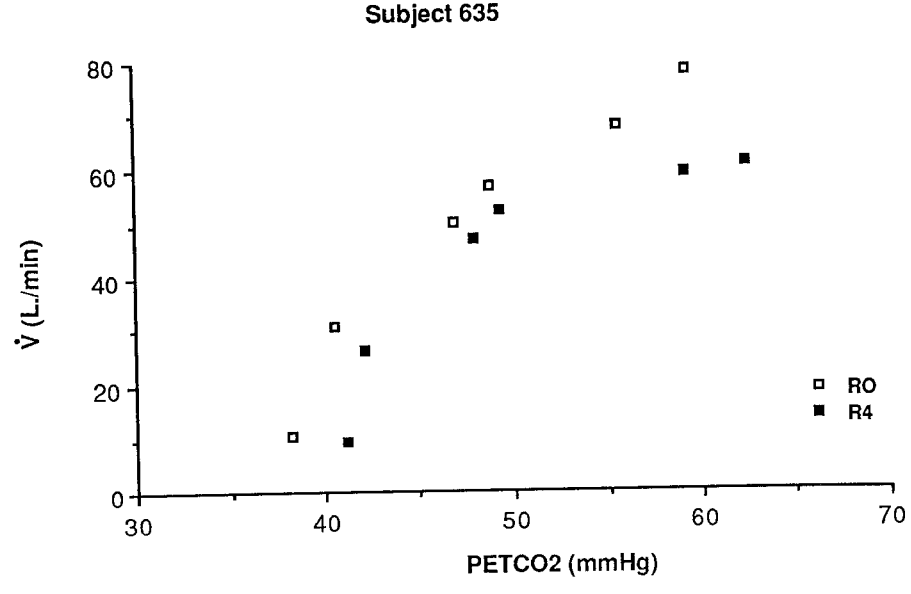
As expected (Lloyd et al., 1958), incremental elevation of inspired CO_2 levels caused marked increases in ventilation (levels effect significant at $P<<0.01$, Table 4.11).

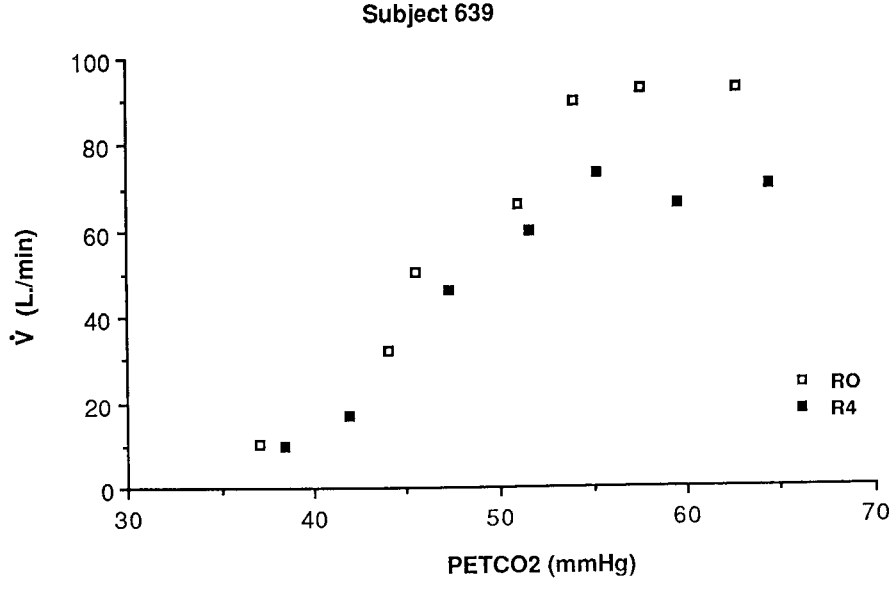
There were significant differences between subjects in the level of ventilation attained at a given inspired CO_2 level (subjects effect significant at $P<<0.01$) and in the extent to

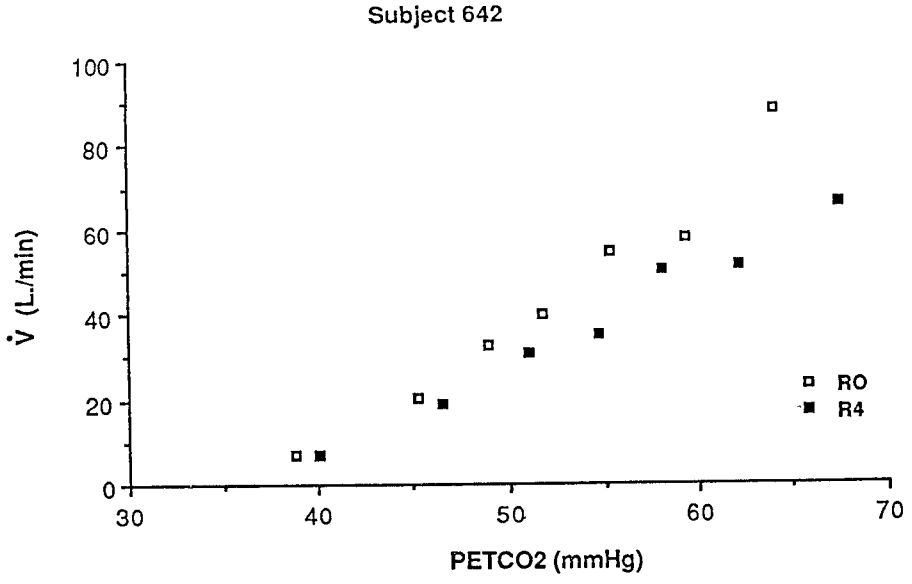
Figures 4.8 and 4.9: The relation between end-tidal carbon dioxide tension ($P_{ET}CO_2$) and ventilation ($\dot{V}$) in eight subjects at inspired carbon dioxide levels of 0, 30, 40, 45, 50 and 55 torr. Data points represent subject means (see Appendix A1). The hypercapnic sensitivities of the subjects are tabulated in Table 4.12.

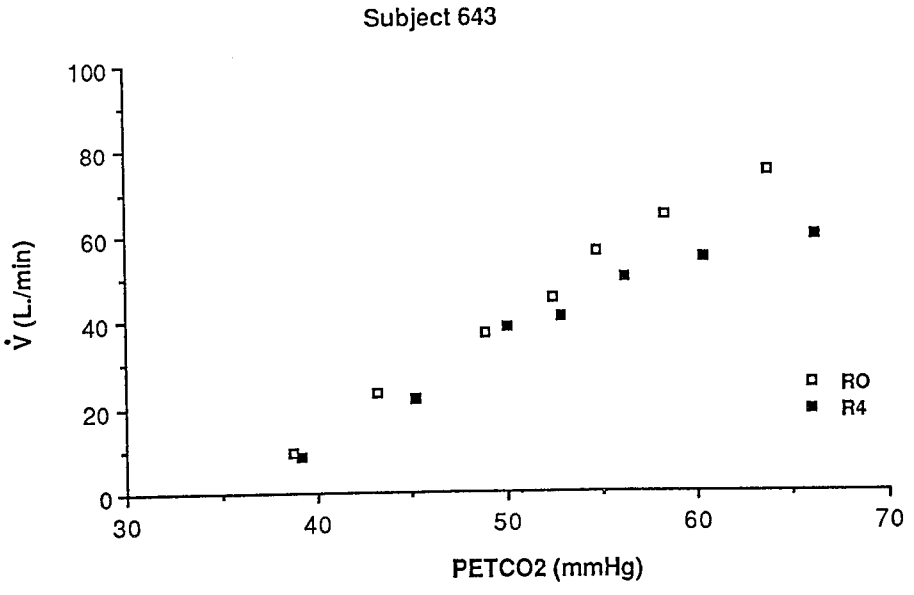

Subject 632
V̇ (L./min)
PETCO2 (mmHg)
RO
R4
0
20
40
60
80
30
40
50
60
70

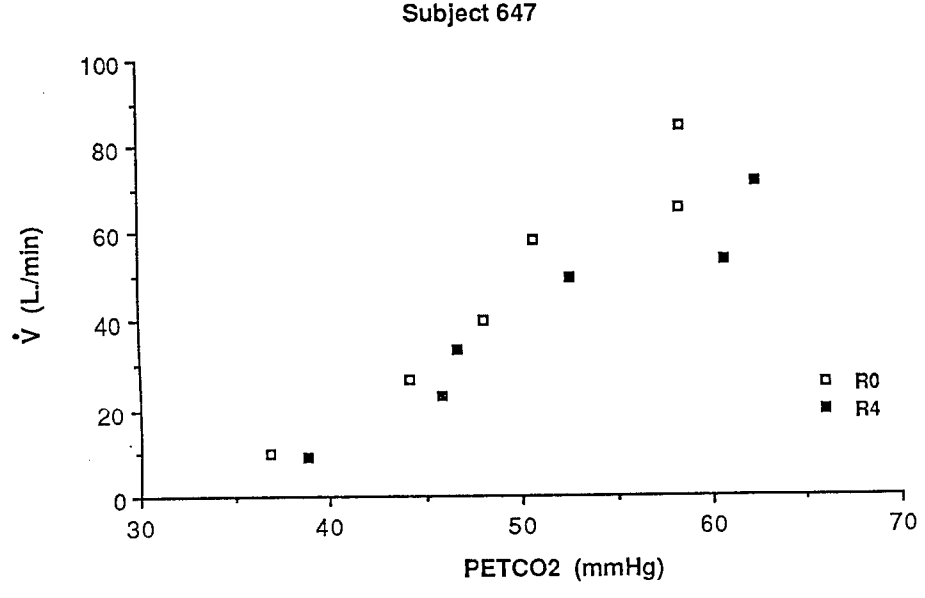

Subject 634
V̇ (L.min)
PETCO2 (mmHg)
R0
R4
0
20
40
60
80
30
40
50
60
70

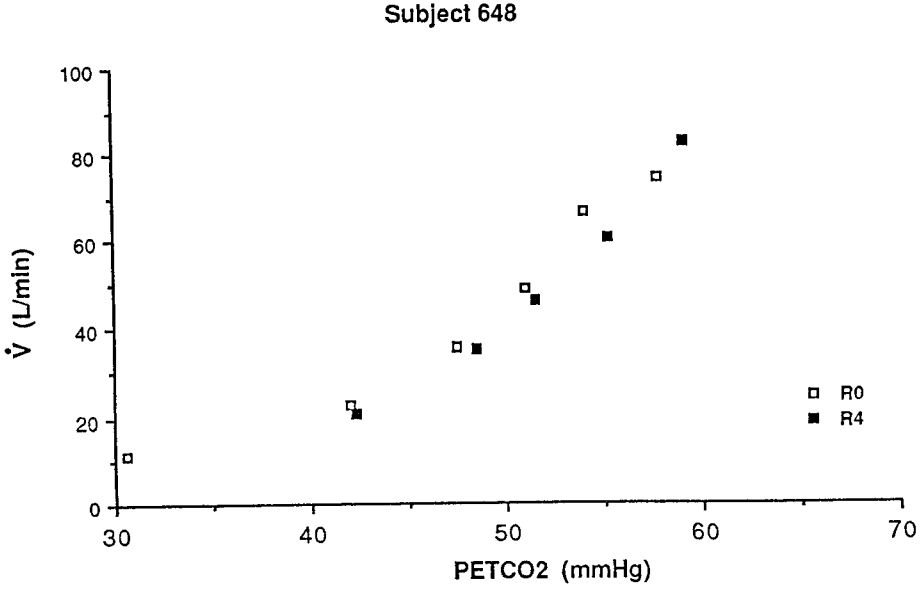

Subject 635
V̇ (L./min)
PETCO2 (mmHg)
RO
R4
0
20
40
60
80
30
40
50
60
70


Subject 639
V̇ (L./min)
PETCO2 (mmHg)
RO
R4
0
20
40
60
80
100
30
40
50
60
70


Subject 642
100
80
60
40
20
0
30
40
50
60
70
V̇ (L./min)
PETCO2 (mmHg)
RO
R4


Subject 643
100
80
60
40
20
0
30
40
50
60
70
V̇ (L./min)
PETCO2 (mmHg)
RO
R4


Subject 647
100
80
60
40
20
0
30
40
50
60
70
V̇ (L./min)
PETCO2 (mmHg)
R0
R4


Subject 648
100
80
60
40
20
0
30
40
50
60
70
V̇ (L/min)
PETCO2 (mmHg)
R0
R4

which ventilation rose as inspired CO_2 levels were increased (LS interaction effect significant at $P<<0.01$).

The $P_{ET}CO_2$ - $\dot{V}$ relation, the slope of which indicates hypercapnic sensitivity, is depicted graphically for each of the subjects in Figures 4.8 and 4.9. The points represent the level means found in the tables of Appendix A1, i.e. the average value of all runs on a subject at a given level of stimulation in each loading condition.

The slopes and intercepts of the best-fit lines of regression to the $P_{ET}CO_2$ - $\dot{V}$ relations of individual subjects are shown in Table 4.12. These were calculated from run means, i.e. 1 minute breath-by-breath averages, in order to represent the true relation most closely. Points below 36 mmHg and therefore likely to be the result of hyperventilation were excluded from the analysis, as were points above 60 mmHg since the rate of rise of ventilation showed a tendency to decline over this region (see Figures 4.8 and 4.9, particularly the data from Subjects 632 and 634).

The pooled mean $P_{ET}CO_2$ - $\dot{V}$ relation, calculated from the average of the level means of all subjects, is represented in Figure 4.10.

2) Loading effects.

The addition of loading during hypercapnia reduced ventilation markedly (resistance effect significant at $P<0.01$, Table 4.11). The extent of the fall was a function of the level of hypercapnia (LR interaction effect significant at $P<0.01$). This was evident as a change in the slope of the $P_{ET}CO_2$ - $\dot{V}$ relation. The linearity of the relation remained little or unaffected, as did the intercept on the abscissa (Figure 4.10).

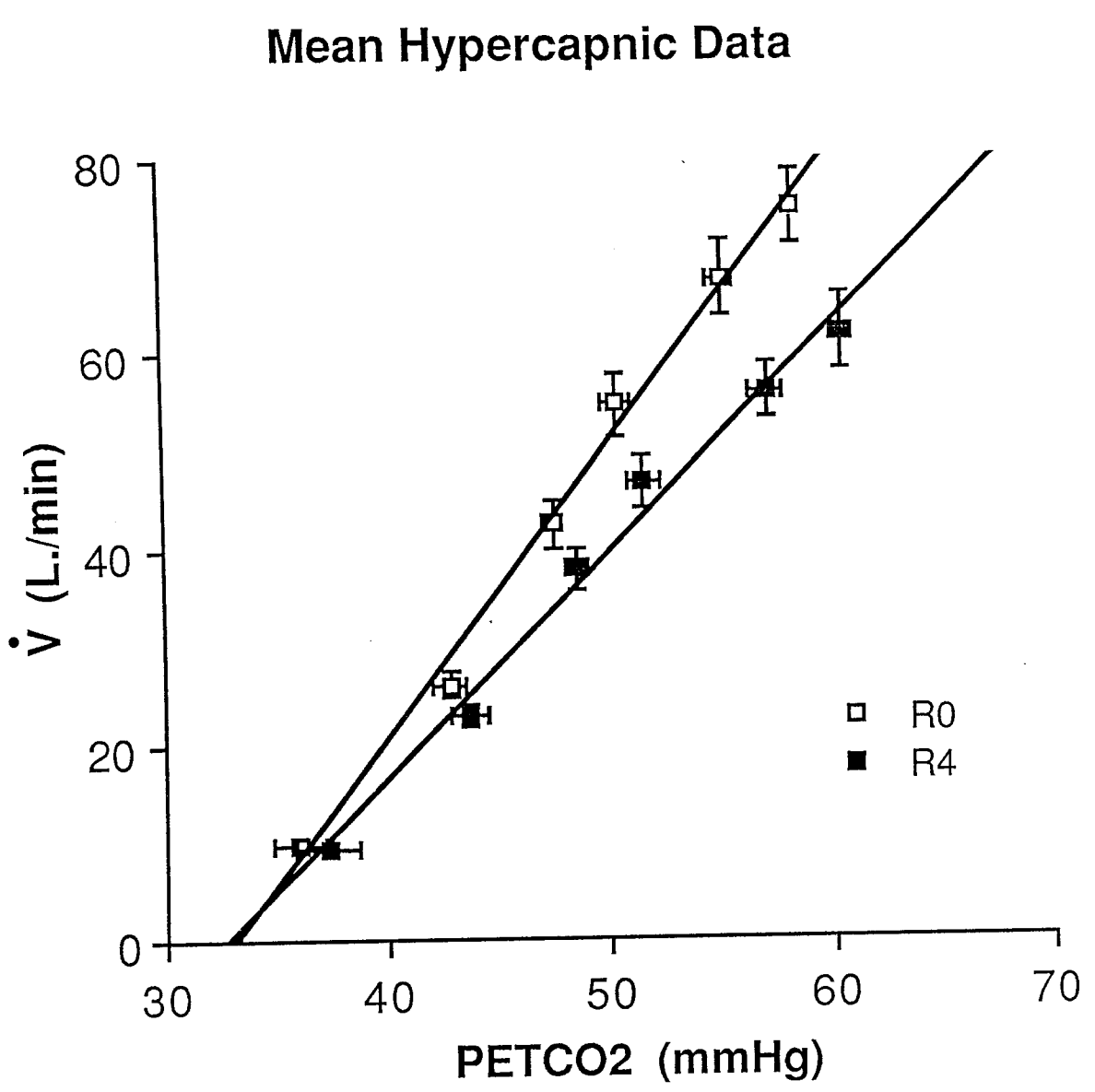


Figure 4.10: Hypercapnic Sensitivity - the pooled mean relation between end-tidal carbon dioxide tension ($P_{ET}CO_2$) and ventilation ($\dot{V}$) at inspired carbon dioxide levels of 0, 30, 40, 45, 50 and 55 torr. Data points represent the pooled means of the eight subjects shown in the previous two figures. The attached bars indicate the standard errors. The lines represent the best fit regressions to the unloaded and loaded relations. The slope of each line, parameter S of Table 4.12, indicates the ventilatory response to hypercapnia; the intercept of the regression on the abscissa is parameter B of Table 4.12.

Regression analysis of the LR interaction revealed a highly significant linear component ($P<0.01$, Table 4.23), indicating that the fall in ventilation accompanying loading increased in a near linear manner as inspired CO_2 levels rose.

The SR interaction was also found to be significant ($P<0.01$), indicating significant differences between subjects in the extent to which loading affected ventilation. This was also evident from the large range of the change in the slope of the $P_{ET}CO_2 - \dot{V}$ relation accompanying loading. Table 4.12 shows that the greatest change (36%) occurred in Subject 639 and the smallest (5%) in Subject 648.

Greater falls of ventilation accompanied loading during hypercapnia than during exercise, over a similar ventilatory range (Table 4.10). Analysis of the difference of differences between the effects of loading in exercise and hypercapnia indicated that this difference was highly significant ($P<<0.01$, Table 4.24).

Breathing Pattern

Duration of Inspiration

1) Exercise effects.

Figure 4.11 depicts graphically the relationship between the duration of inspiration (T_I) and tidal volume (V_T) (and the duration of expiration, T_E, and V_T) during exercise. It may be seen from this figure and Table 4.13, that the pooled mean T_I decreased slightly as V_T increased with increasing exercise level

Table 4.12 : Ventilatory Response to Hypercapnia

	Unloaded		Loaded	
Subject	Slope	Intercept (torr)	Slope	Intercept (torr)
632	3.1	32.2	2.0	32.0
634	3.5	33.2	2.2	31.0
635	2.9	31.8	2.1	31.2
639	4.5	36.7	2.9	32.7
642	3.0	36.5	2.4	36.9
643	3.5	35.6	2.7	34.4
647	3.1	34.3	2.4	34.3
648	3.7	36.3	3.5	36.7

The slopes and intercepts of the $P_{ET}CO_2$ - $\dot{V}$ response lines of each subject are presented. The ventilatory response to carbon dioxide is described by the equation $\dot{V} = S \cdot (P_{ET}CO_2 - B)$, where S, is the slope of the line of regression (units of $L.min^{-1}mmHg^{-1}$) and B, the intercept on the abscissa (LLoyd, Jukes and Cunningham, 1958).

increased. ANOVA indicated a significant exercise effect on T_I ($P<0.01$, Table 4.14), but showed that the form of the response varied markedly between subjects (LS interaction significant at $P<0.01$).

2) Loading effects during exercise.

The effect of loading was to produce a highly significant prolongation of T_I at exercise levels up to 200 W (Figure 4.11; resistance effect significant at $P<<0.01$, Table 4.14). The appearance of almost constant prolongation was confirmed by the non-significant LR interaction effect of data up to 200 W (8 subjects).

However, the ANOVA of data up to 250 W (10 subjects) disclosed the existence of a significant LR interaction ($P<0.01$). The inclusion of the data from the highest work rate revealed the tendency for the prolongation of T_I with loading at higher work rates to be less than that at lower work rates. The fall in the extent to which T_I was prolonged by loading at the highest exercise intensity was of such a degree that T_I approached values measured in the absence of loading. Data from individual subjects showed that in some (632, 644, 647 and 648), unloaded and loaded T_I values were very close at 250 W.

A general difference between subjects in the response to loading, rather than just at the highest work levels, was indicated by the significant ($P<0.01$) SR interaction effect.

In the absence of loading there was only slight evidence of a breakpoint in T_I with increasing exercise intensity such as was reported by Jensen et al. (1980), though in the presence of loading there was clear evidence of a breakpoint at 200 W.

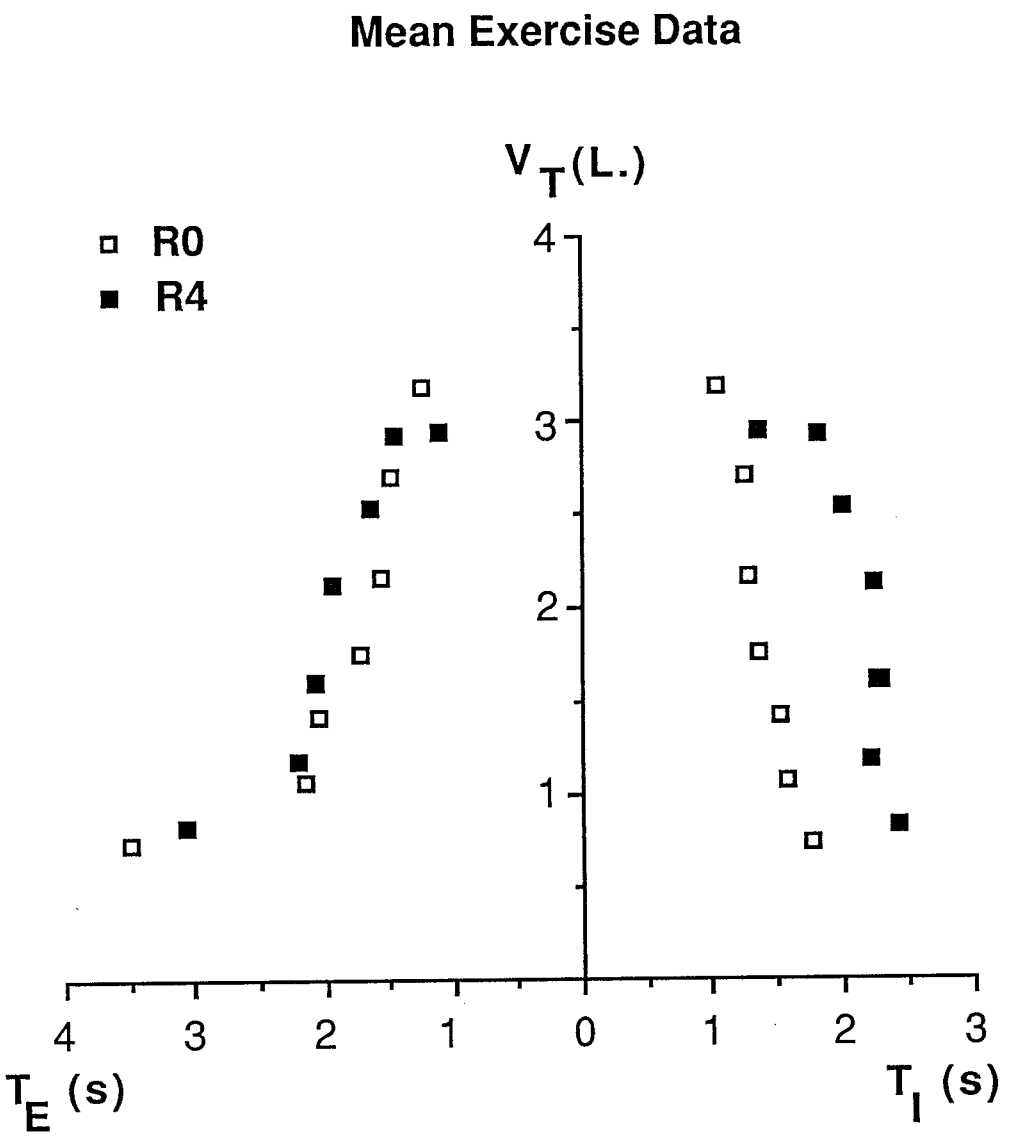


Figure 4.11: The Pattern of Breathing During Exercise - modified Euler plot showing the relation between tidal volume (V_T) and the duration of inspiration (T_I) and the duration of expiration (T_E), at rest and during exercise up to 250 W. As T_E is plotted leftwards from the origin, the horizontal distance between points indicates the duration of the breathing cycle. Data points represent the pooled means of 10 subjects.

3) Hypercapnia effects.

The effect of increasing inspired CO_2 level on T_I is apparent from Figure 4.12 and Table 4.13, where incremental hypercapnia is seen to produce a nearly linear fall, irrespective of whether breathing was loaded or not; the effect of increasing hypercapnia was significant at $P<0.01$ (Table 4.14).

As during exercise, the subjects effect ($P<0.01$) and the LS interaction effect were both significant at $P<0.01$, indicating analogous significant differences between subjects in the change of T_I as ventilation increased.

4) Loading effects during hypercapnia.

As during exercise, the addition of loading significantly prolonged T_I ($P<<0.01$, Table 4.14). However, there was a tendency for T_I during hypercapnia to show less prolongation when breathing was loaded as stimulation increased (Figure 4.12); this observation was confirmed by the significant LR interaction effect ($P<0.05$) given by the main ANOVA (that for the eight subjects who tolerated up to 55 torr P_ICO_2). This finding was different from that in the exercise condition, where the main analysis (of data up to 200 W) indicated the LR effect to be non-significant: the LR effect was found to be significant ($P<0.01$) only if data from the highest attained exercise level were included, at 250 W ventilation was approximately 20 $L.min^{-1}$ higher than at 200 W (Figure 4.7).

This difference in the form of response during hypercapnia and exercise was also disclosed by two further analyses. First, regression analysis of the LR interaction indicated a significant linear component in the hypercapnia data that was not present in the exercise data ($P<0.01$, Table 4.23). Secondly, the difference

Table 4.13 : Duaration of Inspiration (T_I)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean (s)	S.E.	Mean (s)	S.E.
Rest	1.49	0.07	2.19	0.16
0 W	1.57	0.12	2.26	0.17
50 W	1.54	0.11	2.26	0.18
100 W	1.33	0.06	2.10	0.14
150 W	1.26	0.08	1.97	0.13
200 W	1.20	0.10	1.73	0.13

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean (s)	S.E.	Mean (s)	S.E.
0 torr	1.49	0.07	2.19	0.16
30 torr	1.39	0.07	2.07	0.15
40 torr	1.30	0.06	1.82	0.10
45 torr	1.18	0.04	1.67	0.14
50 torr	1.11	0.05	1.54	0.09
55 torr	1.06	0.04	1.46	0.12

No. of Subjects = 8.

Table 4.14 : Duration of Inspiration

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	2.49	0.50	8.3**
Resistance (R)	1	11.25	11.25	86.5**
Subjects (S)	7	7.09	1.01	77.7**
Interactions				
LR	5	0.14	0.03	2.2
LS	35	2.26	0.06	4.6**
SR	7	0.92	0.13	10.0**
Residual (LRS)	35	0.44	0.01	
Total	95	24.59		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	4.17	0.83	18.0**
Resistance (R)	1	6.87	6.87	49.4**
Subjects (S)	7	3.47	0.50	25.0**
Interactions				
LR	5	0.32	0.06	3.2*
LS	35	1.62	0.05	2.3**
SR	7	0.97	0.14	7.0**
Residual (LRS)	35	0.74	0.02	
Total	95	18.16		

** $P<0.01$

* $P<0.05$

No. of Subjects = 8

of the differences test indicated that T_I was lengthened significantly more by loading during exercise than during hypercapnia ($P<<0.01$, Table 4.24).

The finding of a significant SR interaction effect ($P<0.01$, Table 4.14) emphasised that there were significant differences between subjects in the extent to which T_I was lengthened by loading.

Duration of Expiration

1) Exercise effects.

As expected, (e.g. Jensen et al., 1980), the change in T_E as V_T increased with increasing exercise level was much greater than the change in T_I (Figure 4.11; cf. Tables 4.13 and 4.15); the exercise levels effect was highly significant ($P<<0.01$, Table 4.16). However, there were significant differences between subjects in the T_E adopted at a given exercise level ($P<<0.01$) and in the response of T_E to increasing exercise intensity (LS interaction significant at $P<0.01$).

2) Loading effects during exercise.

Figure 4.11 shows that T_E manifested little change in response to inspiratory loading and the extremely small value of the variance ratio confirmed a virtual absence of any loading effect on T_E (resistance effect non-significant, Table 4.16).

However, the finding of a significant SR interaction effect, despite there being no significant resistance effect, confirmed the impression gained from the data of individual subjects, that although there was no common response to loading, individual

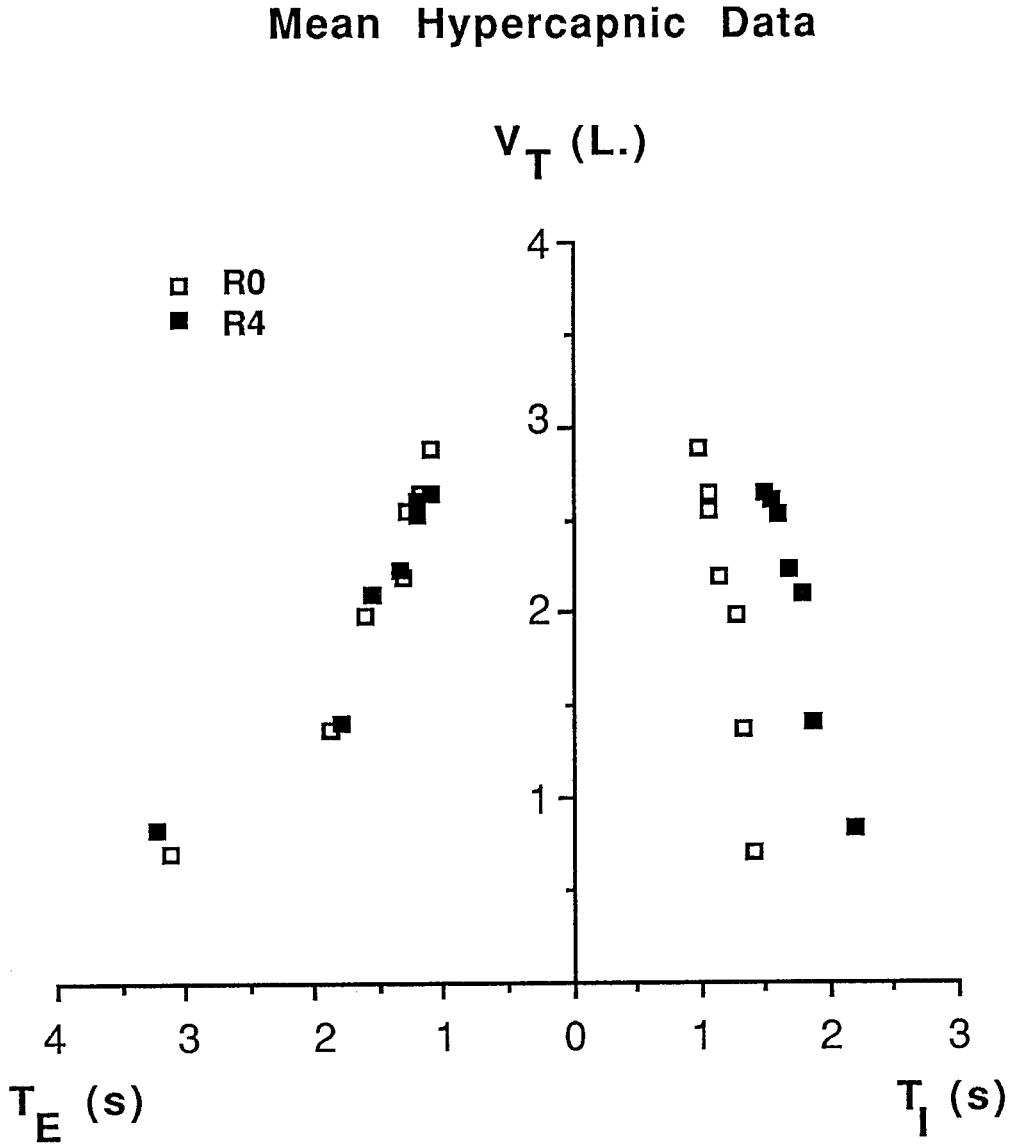


Figure 4.12: The Pattern of Breathing During Hypercapnia- modified Euler plot showing the relation between tidal volume (V_T) and the duration of inspiration (T_I) and the duration of expiration (T_E), at inspired CO_2 levels of 0, 30, 40, 45, 50, 55 and 60 torr. Data points represent the pooled means of five subjects who tolerated inspired carbon dioxide levels up to 60 torr.

subjects did show changes in T_E, some of which were marked (Appendix A1).

3) Hypercapnia effects.

As previously reported by Gardner (1977), there was a highly significant CO_2 levels effect on T_E which represented the progressive reduction of T_E with increasing hypercapnic drive ($P<<0.01$, Table 4.16; Figure 4.12). The existence of significant subjects and LS interaction effects (both of $P<0.01$), similar to the exercise condition, indicated analogous significant differences between subjects in the T_E adopted at a given level and in the change of T_E accompanying increased levels.

The measures of T_E during incremental hypercapnia could be virtually superimposed on those obtained during incremental exercise.

4) Loading effects during hypercapnia.

As during exercise, the addition of loading to breathing during hypercapnia had no significant effect on T_E.

However, the finding of a significant SR effect ($P<0.01$, Table 4.16) indicated disparity between subjects in the response of T_E to the addition of loading.

Analysis of the difference of differences revealed no significant difference in the effects of loading on T_E during exercise and during hypercapnia (Table 4.24).

Table 4.15 : Duration of Expiration (T_E)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean	S.E.	Mean	S.E.
	(s)		(s)	
Rest	3.12	0.22	3.22	0.30
0 W	2.12	0.09	2.18	0.17
50 W	2.06	0.09	2.02	0.19
100 W	1.68	0.07	1.85	0.15
150 W	1.57	0.07	1.60	0.14
200 W	1.41	0.08	1.38	0.13

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean	S.E.	Mean	S.E.
	(s)		(s)	
0 torr	3.12	0.22	3.22	0.30
30 torr	2.01	0.13	1.99	0.17
40 torr	1.67	0.10	1.64	0.11
45 torr	1.46	0.10	1.38	0.08
50 torr	1.43	0.11	1.23	0.05
55 torr	1.27	0.09	1.16	0.05

No. of Subjects = 8.

Table 4.16 : Duration of Expiration

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	31.76	6.35	67.6**
Resistance (R)	1	0.06	0.06	0.3
Subjects (S)	7	11.17	1.60	106.7*
Interactions				
LR	5	0.12	0.02	1.6
LS	35	3.29	0.09	6.3**
SR	7	1.44	0.21	14.0**
Residual (LRS)	35	0.52	0.02	
Total	95	48.36		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	42.41	8.48	51.1**
Resistance (R)	1	0.08	0.08	1.2
Subjects (S)	7	6.69	0.96	48.0**
Interactions				
LR	5	0.20	0.04	2.0
LS	35	5.83	0.17	8.3**
SR	7	0.47	0.07	3.4**
Residual (LRS)	35	0.71	0.02	
Total	95	56.39		

** $P<0.01$

* $P<0.05$

No. of subjects = 8

Tidal Volume

1) Exercise effects.

As previously reported by Hey et al., (1966) and Jensen et al. (1980), the incremental elevation of exercise intensity produced a nearly linear rise in V_T over most of the exercise range (Figure 4.13, Table 4.17); the effect of exercise on V_T was highly significant ($P<<0.01$, Table 4.18).

However, the significant subjects and LS interaction effects (both $P<0.01$), indicated significant differences between the subjects in the change of V_T with increasing exercise intensity.

There was some evidence of a V_T breakpoint in the region $\dot{V}O_2$ = 3000 $ml.min^{-1}$. The level of ventilation at this $\dot{V}O_2$ (Figure 4.7) was similar to the level of ventilation at which Hey et al. (1966) reported tidal volume plateauing.

2) Loading effects during exercise.

Tidal volume was significantly increased with the addition of loading (Figure 4.13; resistance effect $P<0.01$, Table 4.18) and, except at $\dot{V}O_2$ > 3000 $ml.min^{-1}$, the increase of V_T with loading rose almost linearly as exercise intensity increased (LR interaction $P<0.01$, Table 4.18).

However, regression analysis of the form of the LR interaction also betrayed the existence of a significant alinear component ($P<0.05$, Table 4.23). Tidal volume was the only variable for which the LR interaction effect manifested significant alinearity. The source of the alinearity was evident on closer examination of the $\dot{V}O_2$ - V_T relationship at the higher work levels (Figure 4.13); the augmentation of V_T with loading

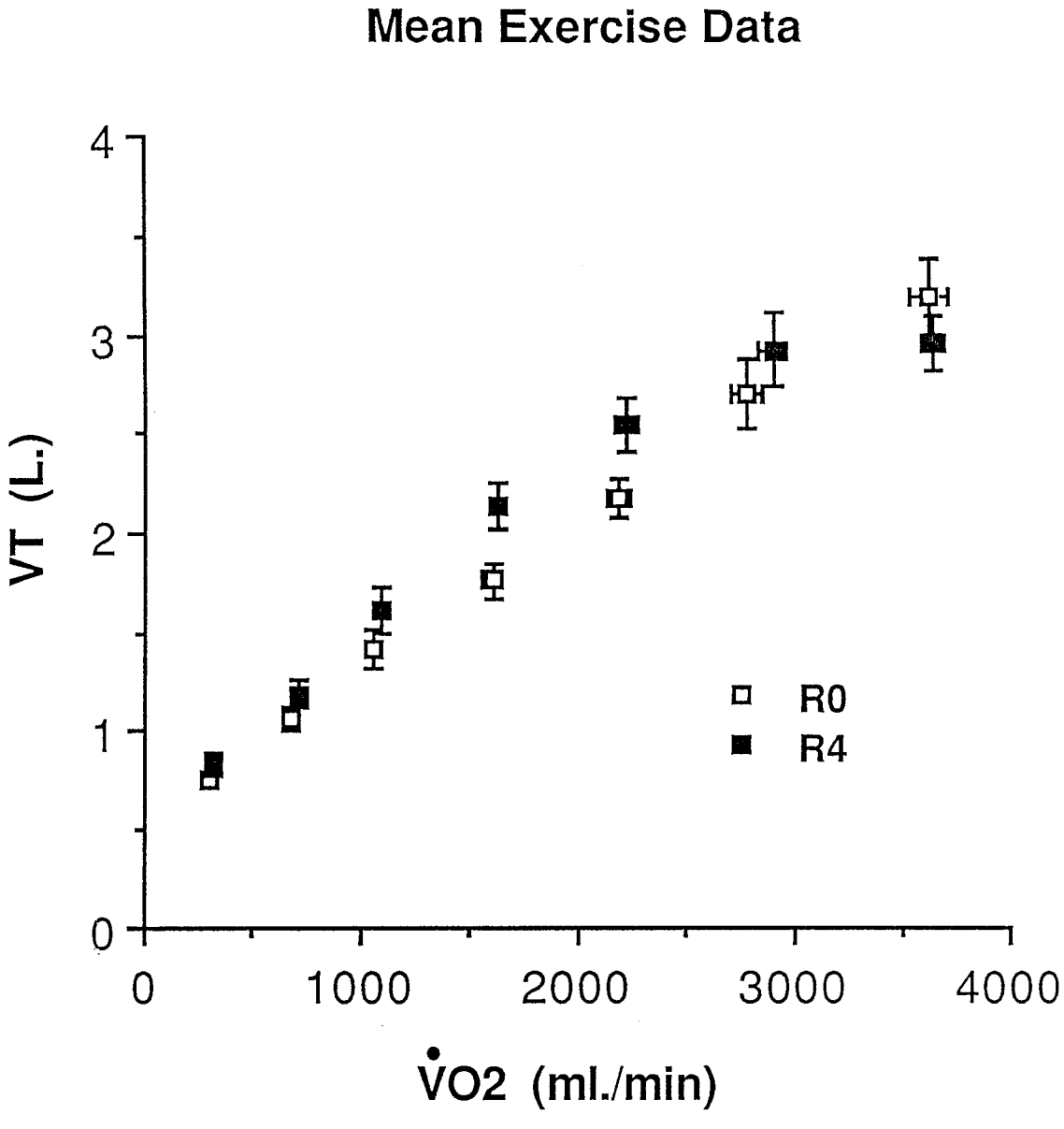


Figure 4.13: The relation between oxygen uptake ($\dot{V}O_2$) and tidal volume (V_T), at rest and during exercise up to 250 Watts. Data points are the pooled means of 10 subjects ± standard errors.

became less marked at 200 W ($\dot{V}O_2$ approximately 2800 ml.min^{-1}), i.e. V_T showed a tendency to plateau at high exercise levels.

The plateauing of V_T in the loaded condition at high exercise levels was more marked at 250 W ($\dot{V}O_2$ approximately 3600 ml.min^{-1}). The attainment of this apparent maximum V_T (at approximately 3 L.) in the presence of loading at the highest exercise level meant that V_T was hardly changed by loading. In fact, the examination of individual subjects' data showed that in four subjects (597, 632, 647 and 648) loading at 250 W was associated with a fall in V_T. Further, in three of the same subjects (not in 648), V_T at 250 W when breathing was loaded was lower than at 200 W, i.e. when breathing was loaded, increasing exercise intensity from the penultimate to the highest level was associated with a fall in V_T.

3) The effect of loading on mean flows.

The variables that determine mean inspiratory and expiratory flows are interrelated, so the section below is limited to a descriptive presentation of the results without consideration of the controlling mechanisms. The physiological interpretation of the data may be found in the discussion (Chapter 5).

Mean inspiratory flows (V_T/T_I) are the slopes of the lines joining the inspiratory points in Figures 4.11 and 4.12 to the origin; these slopes are clearly lessened by loading. During exercise, both V_T and T_I were increased by loading, but T_I was elevated to a proportionately greater extent. During hypercapnia, V_T typically increased slightly with loading while T_I increased markedly, so mean inspiratory flow fell here also.

These findings indicate that two distinct (unloaded and loaded) relations existed between ventilation and mean inspiratory

Table 4.17 : Tidal Volume (V_T)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean (L)	S.E.	Mean (L)	S.E.
Rest	0.77	0.05	0.87	0.08
0 W	1.13	0.06	1.25	0.09
50 W	1.49	0.12	1.67	0.13
100 W	1.80	0.12	2.15	0.15
150 W	2.26	0.14	2.62	0.17
200 W	2.74	0.19	2.95	0.17

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean (L)	S.E.	Mean (L)	S.E.
0 torr	0.77	0.05	0.87	0.08
30 torr	1.48	0.12	1.56	0.14
40 torr	2.09	0.13	2.18	0.13
45 torr	2.39	0.16	2.36	0.15
50 torr	2.80	0.15	2.56	0.13
55 torr	2.90	0.16	2.66	0.14

No. of Subjects = 8.

Table 4.18 : Tidal Volume

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	46.59	9.32	84.7**
Resistance (R)	1	1.17	1.17	20.5**
Subjects (S)	7	6.98	1.00	112.4**
Interactions				
LR	5	0.25	0.05	5.6**
LS	35	3.82	0.11	12.4**
SR	7	0.40	0.06	6.4**
Residual (LRS)	35	0.31	0.01	
Total	95	59.52		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	45.52	9.08	146.5**
Resistance (R)	1	0.03	0.03	0.3
Subjects (S)	7	8.49	1.21	60.5**
Interactions				
LR	5	0.50	0.10	5.0**
LS	35	2.17	0.06	3.1**
SR	7	0.62	0.09	4.5**
Residual (LRS)	35	0.69	0.02	
Total	95	57.92		

** $P<0.01$

* $P<0.05$

No. of subjects = 8

flow. These two relations are depicted for the exercise condition in Figure 4.14.

Mean expiratory flows (V_T/T_E) are the slopes of the lines joining the expiratory points in Figures 4.11 and 4.12 to the origin. It may be seen from these figures that mean expiratory flow during exercise was markedly increased by loading, producing two distinct relations between ventilation and mean flow in an analogous manner to that during inspiration. During hypercapnia, mean expiratory flow was only slightly increased with loading at lower CO_2 levels and was reduced at higher CO_2 levels.

Figure 4.14 shows the loaded and unloaded $\dot{V}$ - mean expiratory flow relations during exercise. Also shown is the loaded $\dot{V}$ - mean expiratory relation after adjustment for the stimulatory effect of the rise in $P_{ET}CO_2$ accompanying loading (using the pooled mean measure of hypercapnic sensitivity illustrated in Figure 4.10), which is shifted to the right by an amount equal to the ventilatory equivalent of the rise in $P_{ET}CO_2$ accompanying loading at each work level. The result of this adjustment was that the mean expiratory flow calculated for a given ventilation in the presence of loading was reduced. This finding was of interest as the adjusted loaded relation was virtually superimposed on the unloaded relation, i.e. a unique relationship was shown to exist between ventilation and mean expiratory flow level independent of loading.

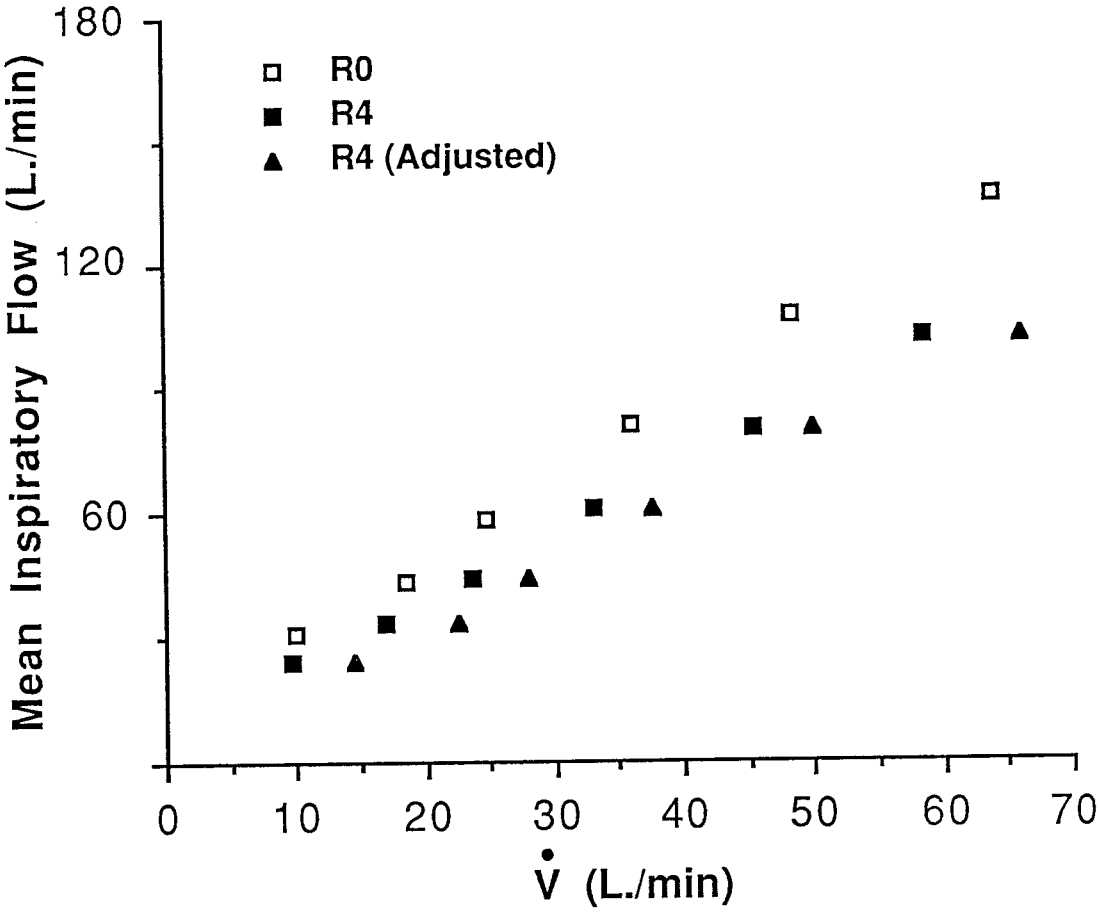
4) Hypercapnia effects.

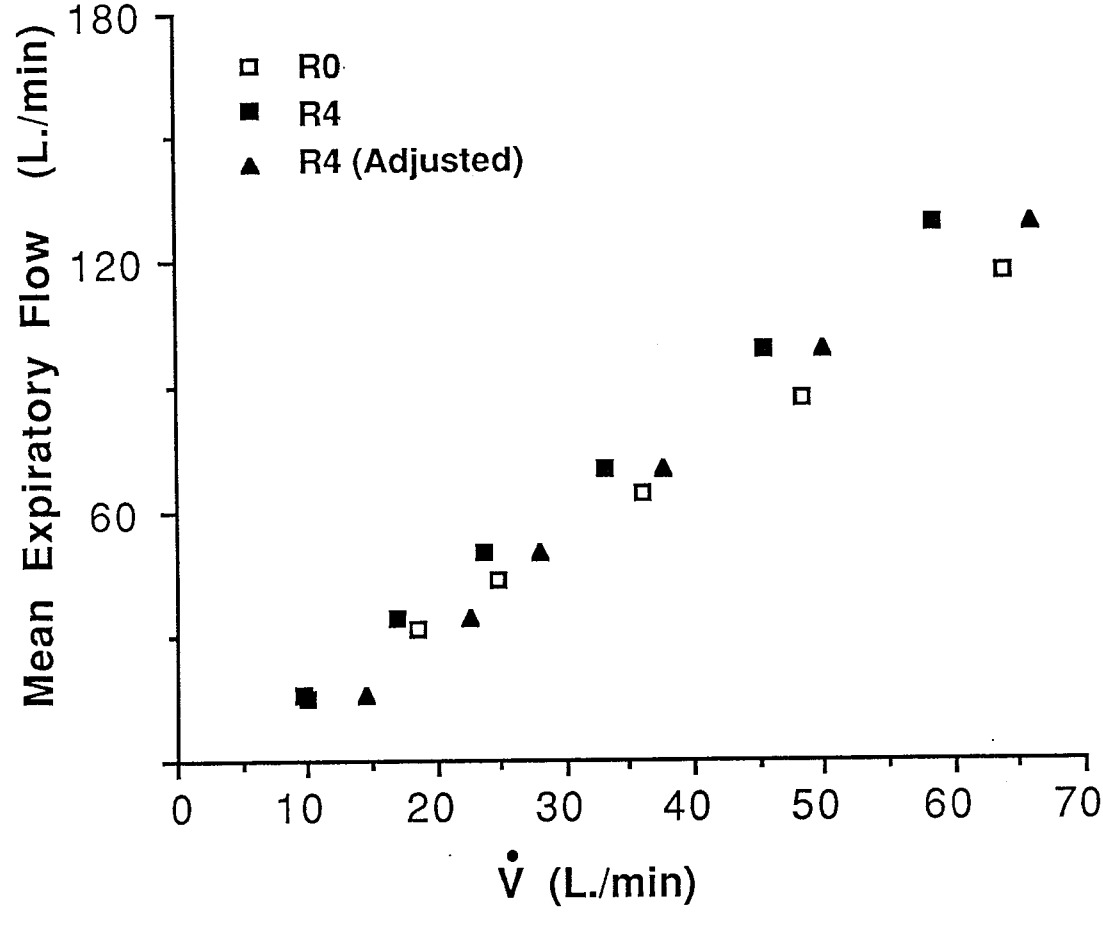
Increments of inspired CO_2 level significantly increased V_T ($P<<0.01$, Table 4.18). However, they did not produce the simple nearly linear rises over most of the ventilatory range seen with increments of exercise intensity, even when V_T was plotted against

Figure 4.14: Mean Flow During Exercise - the relation between ventilation and: a) Mean inspiratory flow; b) Mean expiratory flow; in eight subjects.

Mean flows in the presence of inspiratory loading are shown adjusted for the stimulatory effect of the increase in end-tidal carbon dioxide accompanying loading at each exercise level (triangular symbols). The extent to which each point was shifted to the right was calculated from the mean hypercapnic sensitivity relation in the presence of loading (Figure 4.10).

Mean Exercise Data





$P_{ET}CO_2$ (Figure 4.15), which was linearly related to ventilation (Figure 4.10). Tidal volume rose in near simple proportion to $P_{ET}CO_2$ over the lower $P_{ET}CO_2$ range, but as CO_2 increased towards maximal levels V_T showed a pronounced tendency to plateau. The tidal volume at which this occurred was approximately 2.5 L (cf. Hey et al., 1966).

The significant subjects ($P<<0.01$) and LS interaction ($P<0.01$) effects indicated that there were considerable differences between subjects in both the V_T adopted at a given inspired CO_2 level and in the change of V_T accompanying steps of inspired CO_2.

5) Loading effects during hypercapnia.

ANOVA indicated that the addition of loading during hypercapnia had no significant effect on V_T; this reflected the fact that the direction of change of V_T with the addition of loading varied with the level of hypercapnic drive. Tidal volume was augmented by loading at lower CO_2 levels, but this effect diminished as CO_2 levels rose and the effect was reversed as $P_{ET}CO_2$ increased above 50 torr so that loading was associated with a reduction in V_T at the highest CO_2 levels (Figure 4.15). The effect of loading increased in a nearly linear manner with either reductions or elevations of $P_{ET}CO_2$ from 50 torr (producing positive or negative changes in V_T respectively).

The presence of differences in the effect of loading during exercise and hypercapnia evident from Figures 4.13 and 4.15 was confirmed by the difference of differences test which showed there was significantly greater increase in tidal volume with the addition of loading during exercise ($P<<0.01$, Table 4.24).

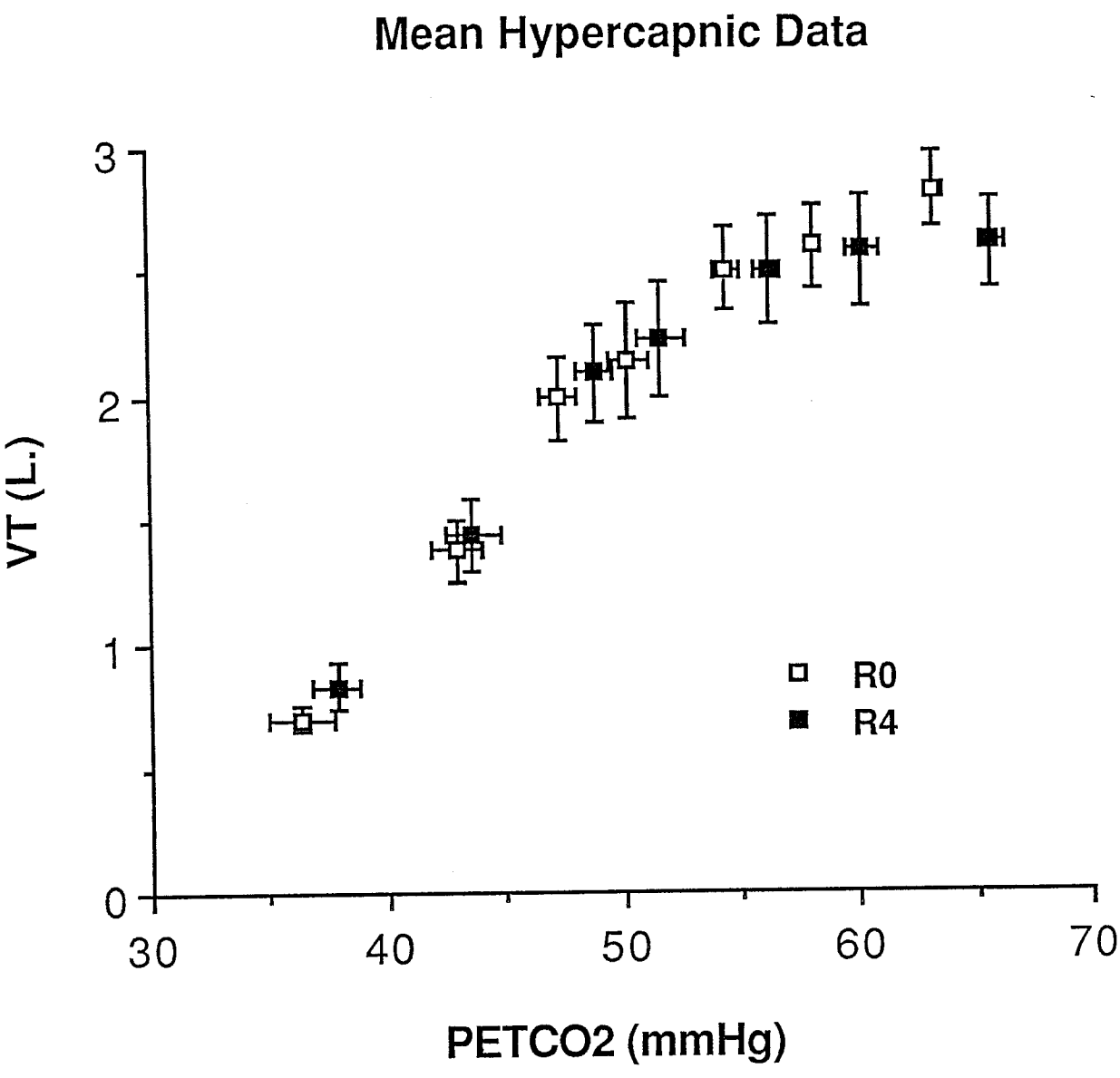


Figure 4.15: The relation between end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) and tidal volume (V_T), at inspired carbon dioxide tensions of 0, 30, 40, 45, 50, 55 and 60 torr. Data points represent the pooled means of the five subjects who tolerated inspired carbon dioxide levels up to 60 torr. $\pm$ standard errors.

End-Tidal Carbon Dioxide Tension

1) Exercise effects.

As expected from the report of Asmussen (1964), $P_{ET}CO_2$ rose with increasing exercise level over the low to moderate exercise range, but fell as work levels increased further (Table 4.19; Figure 4.16; exercise levels effect significant at $P<0.01$, Table 4.20). In two subjects (643 and 644), $P_{ET}CO_2$ at the highest work level was little different from at rest. Pooled mean data (the average of all subjects) and mean data from individual subjects showed that the exercise intensity at which $P_{ET}CO_2$ began to fall was generally a little higher than that at which the anaerobic threshold was estimated to occur.

The variability apparent between subjects in the $P_{ET}CO_2$ level at a given exercise intensity with increasing exercise intensity (Appendix A1) was reflected by the ANOVA as significant subjects and LS interaction effects (both $P<0.01$, Table 4.20).

2) Loading effects during exercise.

The addition of loading was associated with a rise in $P_{ET}CO_2$ (Figure 4.16; resistance effect significant at $P<0.01$, Table 4.20). The increase of $P_{ET}CO_2$ accompanying loading rose as the intensity of exercise increased, but ANOVA indicated that the LR interaction effect was not significant.

There was considerable between-subject variability in the response to loading (SR interaction effect significant at $P<0.01$).

3) Loading effects during hypercapnia.

The addition of loading significantly increased $P_{ET}CO_2$ ($P<0.01$, Table 4.20). As during exercise, the degree of the elevation of

Table 4.19 : End-Tidal Carbon Dioxide Partial Pressure ($P_{ET}CO_2$)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean (torr)	S.E.	Mean (torr)	S.E.
Rest	35.93	1.13	37.22	1.41
0 W	38.75	0.96	40.57	0.94
50 W	41.09	1.24	42.98	1.09
100 W	42.23	1.03	44.41	1.18
150 W	43.17	1.07	45.99	1.30
200 W	42.54	0.92	45.70	1.40

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean (torr)	S.E.	Mean (torr)	S.E.
0 Torr	35.93	1.13	37.22	1.41
30 Torr	42.71	0.74	43.57	0.80
40 Torr	47.37	0.47	48.40	0.53
45 Torr	50.24	0.60	51.48	0.72
50 Torr	55.01	0.58	57.03	0.74
55 Torr	58.25	0.26	60.32	0.49

No. of Subjects = 8.

Table 4.20 : End-Tidal Carbon Dioxide Partial Pressure Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	757.98	151.60	44.72**
Resistance (R)	1	115.25	115.25	34.30**
Subjects (S)	7	717.52	102.50	117.82**
Interactions				
LR	5	9.47	1.89	2.17
LS	35	118.59	3.39	3.90**
SR	7	23.52	3.36	3.86**
Residual (LRS)	35	30.61	0.87	
Total	95	1772.94		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	5577.60	1115.50	218.30**
Resistance (R)	1	48.38	48.38	41.35**
Subjects (S)	7	185.95	26.56	49.19**
Interactions				
LR	5	5.22	1.04	1.93
LS	35	178.80	5.11	9.46**
SR	7	8.19	1.17	2.17
Residual (LRS)	35	19.02	0.54	
Total	95	6023.16		

** $P<0.01$

* $P<0.05$

No. of subjects = 8

$P_{ET}CO_2$ with loading was not significantly different as the level of drive increased (LR interaction not significant).

Unlike during exercise, the ANOVA of hypercapnic data indicated that there were no significant differences between subjects in the change of $P_{ET}CO_2$ accompanying loading (SR interaction effect not significant).

Comparison of the mean change in $P_{ET}CO_2$ accompanying loading during exercise with that during hypercapnia, using the difference of the differences test indicated significantly greater elevation of $P_{ET}CO_2$ with loading during exercise.

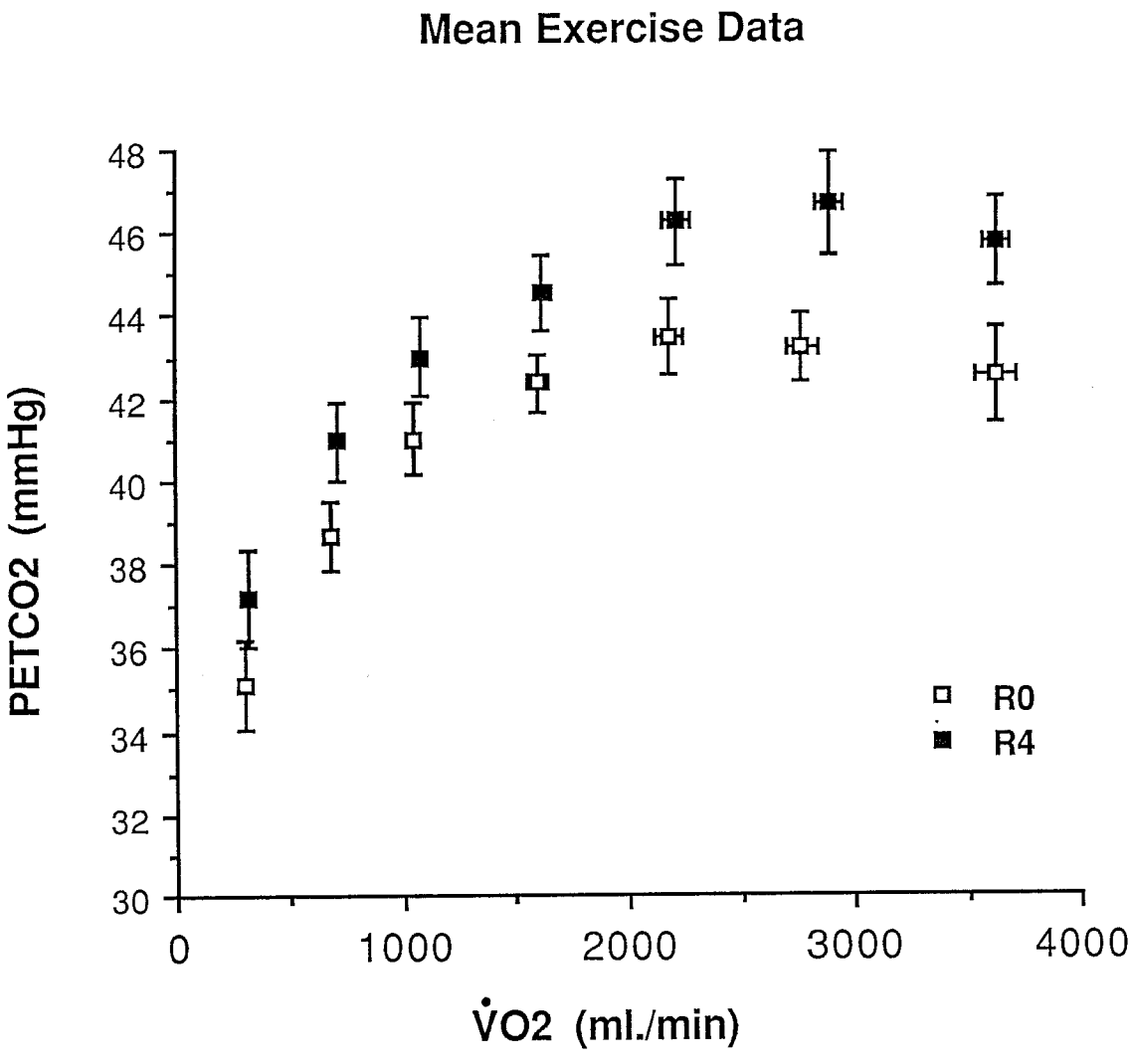


Figure 4.16: The relation between oxygen uptake ($\dot{V}O_2$) and end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), at rest and during exercise up to 250 W. Data points are the pooled means of 10 subjects $\pm$ standard errors.

4. Inspiratory Capacity:

The Estimation of Changes in End-Expiratory Volume

The data presented in this section are the result of 16 runs (8 exercise, 8 hypercapnic) by three subjects (642, 643 and 648). The changes of inspiratory capacity (Table 4.21) are reported as estimated changes in end-expiratory volume (EEV). The data from individual experiments may be found in Appendix A3.

1) Exercise effects.

Figure 4.17 shows that EEV fell as ventilation increased during exercise; the effect of exercise was significant at $P<0.01$ (Table 4.22). However, subjects showed considerable variation in the EEV adopted at a given exercise level and in the exact form of the response of EEV to increasing exercise level, apparent from the highly significant subjects ($P<<0.01$) and LS interaction effects ($P<0.01$). These findings reflected differences between subjects in both the extent of the fall in EEV accompanying the increase of exercise intensity (the range at 200 W was from 0.32 to 1.19 L.) and in the form of the response (Appendix A3). Thus, Subject 647 showed an almost linear fall of EEV with increasing exercise level up to 200 W, Subject 642 showed a progressive near linear fall in EEV as the level of exercise increased from rest, though no further fall above 150 W, and Subject 643 showed a large initial fall in EEV at low exercise levels but little further fall till the highest exercise levels were approached (Appendix A3). The finding of considerable variability in estimations of EEV was probably due in part to the high dependence on the motivation of the subjects. The standard error of four consecutive

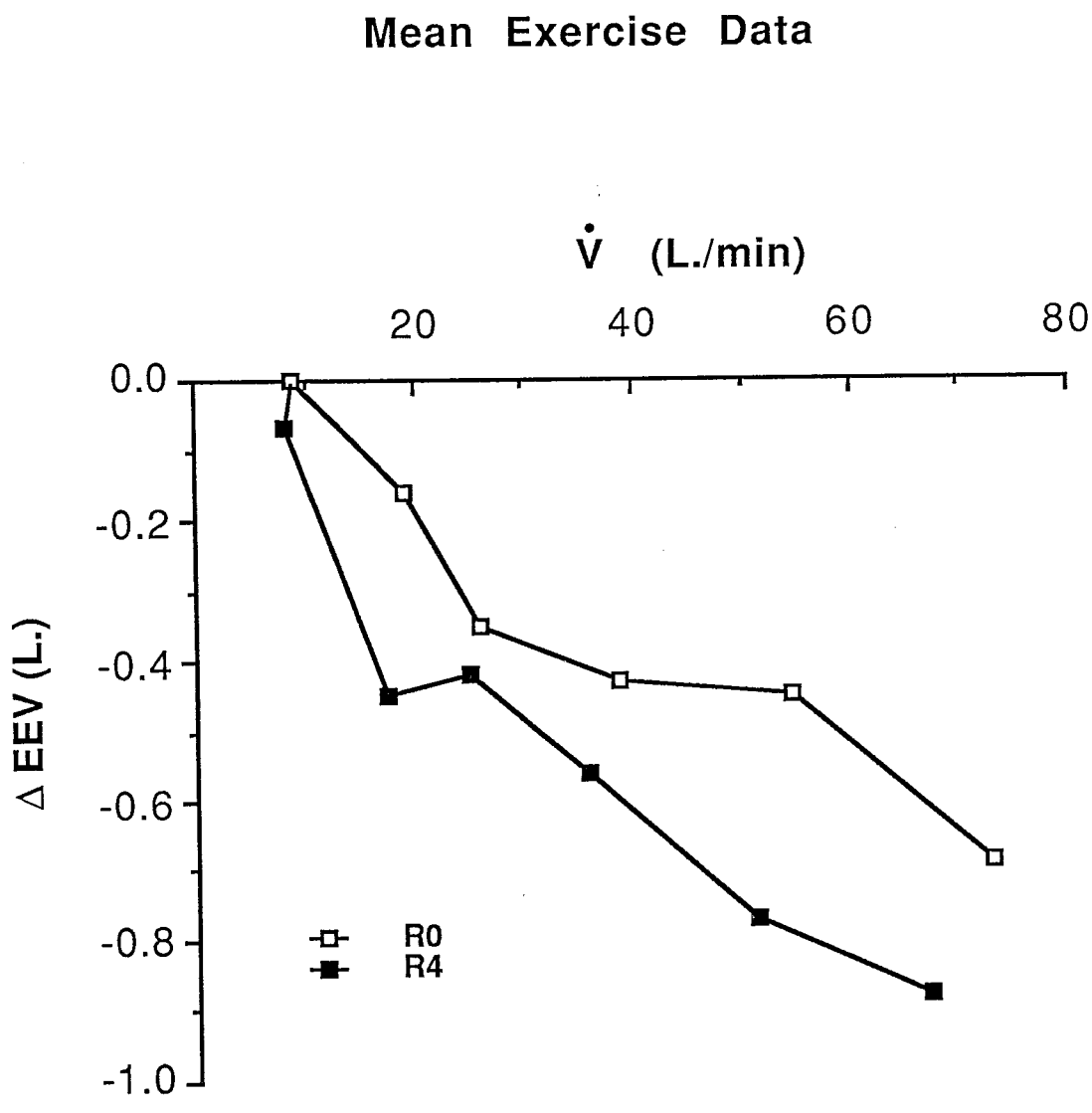


Figure 4.17: The relation between ventilation ($\dot{V}$) and the estimated change in end-expiratory volume (EEV) at rest and during exercise up to 200 W. Data points represent the pooled means of three subjects, standard errors are reported in Table 4.21.

determinations of EEV at rest in one subject was 0.10 L. when breathing was unloaded and 0.08 L. when loaded.

2) Loading effects during exercise.

Loading was typically accompanied by a further fall in EEV at any given exercise level. However, ANOVA indicated that the resistance effect was not significant, despite the fact that the variance ratio exceeded 7. This reflected the relatively small number of subjects (and consequently the few degrees of freedom of the ANOVA) and the highly variable nature of the EEV estimations.

The LR interaction effect was also not significant, indicating that the extent to which the fall in EEV during exercise was augmented by loading was independent of exercise intensity.

3) Hypercapnia effects.

Figure 4.18 shows that the elevation of ventilation consequent upon incremental hypercapnia was associated with a progressive fall in EEV; the effect of increasing hypercapnia was significant at $P<0.01$ (Table 4.22).

The lowest EEV reached during hypercapnia was similar to that during exercise, but the extent of the fall of EEV over the lower ventilatory range (up to 20 $L.min^{-1}$) was noticeably smaller during hypercapnia than during exercise, whether breathing was loaded or not. Conversely, over the 20-60 $L.min^{-1}$ ventilation range the magnitude of the fall was more marked during hypercapnia than during exercise and appeared to be in proportion to the level of ventilation.

The highly significant subjects ($P<<0.01$) and LS interaction

Table 4.21 : Inspiratory Capacity (IC)

Level Means and Standard Errors

Exercise Condition

Work Rate	Unloaded		Loaded	
	Mean (L)	S.E.	Mean (L)	S.E.
Rest	3.01	0.10	3.08	0.25
0 W	3.17	0.17	3.46	0.13
50 W	3.36	0.12	3.43	0.20
100 W	3.44	0.16	3.57	0.23
150 W	3.46	0.21	3.78	0.25
200 W	3.70	0.31	3.89	0.25

Hypercapnia Condition

P_ICO_2	Unloaded		Loaded	
	Mean (L)	S.E.	Mean (L)	S.E.
0 torr	3.21	0.18	3.13	0.20
30 torr	3.22	0.22	3.27	0.17
40 torr	3.29	0.23	3.37	0.23
45 torr	3.50	0.21	3.55	0.26
50 torr	3.77	0.23	3.89	0.36
55 torr	3.80	0.21	3.93	0.22

No. of Subjects = 3.

Table 4.22 : Inspiratory Capacity

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
Work Levels (L)	5	2.29	0.40	10.6**
Resistance (R)	1	0.29	2.97	7.3
Subjects (S)	2	2.52	1.26	201.7**
Interactions				
LR	5	0.09	0.02	1.9
LS	10	0.38	0.04	4.1*
SR	2	0.08	0.04	4.3*
Residual (LRS)	10	0.10	0.01	
Total	35	5.48		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
CO_2 Levels (L)	5	2.66	0.53	24.2**
Resistance (R)	1	0.03	0.03	1.8
Subjects (S)	2	3.51	1.75	350.6**
Interactions				
LR	5	0.40	0.01	1.1
LS	10	0.22	0.02	16.1**
SR	2	0.04	0.18	1.2
Residual (LRS)	10	0.08	0.01	
Total	35	7.65		

** $P<0.01$

* $P<0.05$

No. of subjects = 3

effects ($P<0.01$) reflected the large variation inherent in the data.

4) Loading effects during hypercapnia.

Although mean EEV levels fell with the addition of loading during hypercapnia (Table 4.21), the effect of loading was not significant (Table 4.22). There was greater variation in the form of the EEV response to loading during hypercapnia than during exercise, particularly at low levels of ventilation, when EEV either fell or rose in response to loading depending on the subject and the level of stimulation.

Reference to individual subjects' data indicated that the addition of loading during hypercapnia was generally associated with an almost constant fall in EEV of approximately 0.05 L. This observation was confirmed by the finding of a non-significant LR interaction.

The degree of fall that typically accompanied loading during hypercapnia appeared to be lower than during exercise (cf. Figures 4.17 and 4.18). This observation was confirmed by the analysis of the difference of differences, which showed that loading during hypercapnia had significantly less effect on EEV than during exercise ($P<<0.01$, Table 4.24).

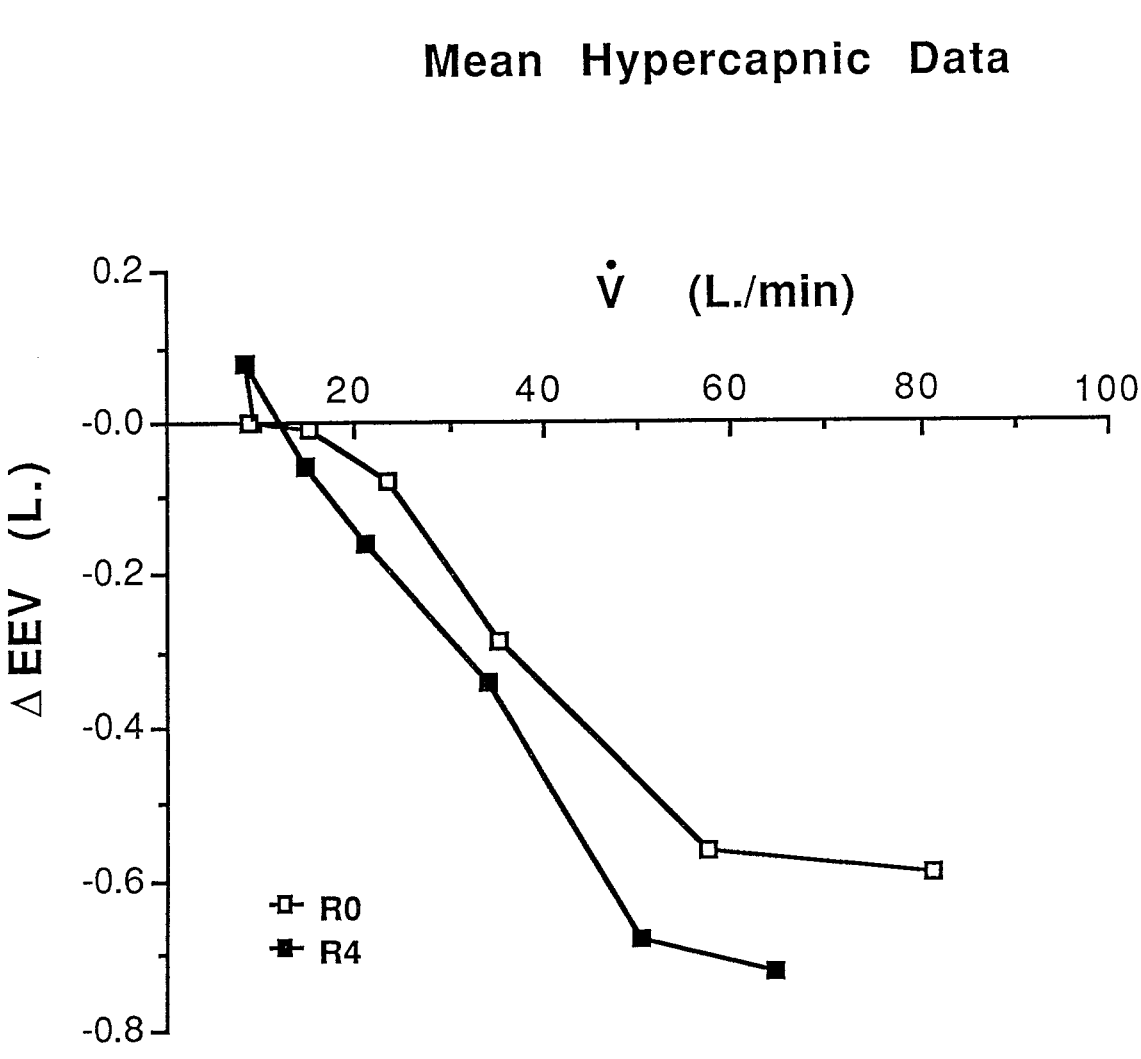


Figure 4.18: The relation between ventilation ($\dot{V}$) and the estimated change in end-expiratory volume (EEV) at inspired carbon dioxide levels of 0, 30, 40, 45, 50 and 55 torr. Data points represent the pooled means of three subjects, standard errors are presented in Table 4.21.

Table 4.23 : Regression Analysis of the Variance Associated With the Levels * Resistance Interaction

Exercise Condition

Variable	Total SOS	Reg MSq	MSq_{Res}	VR_{Reg}	VR_{Res}
T_I	0.135	0.044	0.002	3.53	1.46
T_E	0.125	0.012	0.023	0.78	1.54
V_T	0.246	0.101	0.029	11.22**	3.22*
$\dot{V}_E$	67.67	62.54	1.024	80.84**	1.33
$\dot{V}CO_2$	2336.	518.	363.6	0.20	0.14
$\dot{V}O_2$	267872.	10826.	31922.4	1.95	0.58
$P_{ET}CO_2$	9.47	9.13	0.068	10.44**	0.08
IC	0.089	0.032	0.014	3.2	1.45

Hypercapnia Condition

Variable	Total SOS	Reg MSq	MSq_{Res}	VR_{Reg}	VR_{Res}
T_I	0.321	0.258	0.013	12.29**	0.60
T_E	0.198	0.156	0.008	7.68**	0.41
V_T	0.501	0.250	0.050	12.69**	2.56*
$\dot{V}_E$	498.92	390.44	21.696	37.72**	1.98
$\dot{V}CO_2$	18947.	16240.	541.4	12.15**	0.41
$\dot{V}O_2$	43754.	37830.	1184.8	23.38**	0.73
$P_{ET}CO_2$	5.22	1.32	0.780	2.44	1.44
IC	0.40	0.39	0.004	49.5**	0.50

A linear component (the Reg MSq) was extracted from the Total SOS (the L*R MSq of the ANOVA); both the Reg MSq, and the residual variance of the regression (the MSq_{Res}) are tested against the residual mean square of the ANOVA. If the VR_{Reg} is significant, the regression of the difference between unloaded and loaded values on work or hypercapnia level exhibits significant linearity, if the VR_{Res} is significant, the regression exhibits significant alinearity (Statistical Methods Chapter, p. 3.9). Except for IC, the data was from 8 subjects (IC measurements were only made on three subjects). ** P<.01; * P<.05.

Table 4.24 : Tabulated Data of the Difference of Differences

Variable	Exercise Condition		Hypercapnia Condition	
	Difference (R0-R4)	ResMSq	Difference (R0-R4)	ResMSq
T_I	32.86	0.013	25.69	0.021
T_E	2.30	0.015	2.75	0.020
V_T	10.61	0.009	1.82	0.020
$\dot{V}_E$	115.3	0.774	325.8	10.926
$\dot{V}CO_2$	190.0	2561.37	2069.0	1336.31
$\dot{V}O_2$	1392.	2245.94	2911.	1618.34
$P_{ET}CO_2$	105.17	0.875	6.8	0.543
IC	3.21	0.006	1.05	0.005

Variable	Difference (Ex - CO_2)	Pooled Variance	Standard Error	
T_I	7.17	3.24	1.80	**
T_E	0.45	3.53	1.88	
V_T	8.78	2.75	1.66	**
$\dot{V}_E$	210.	1123.15	33.51	**
$\dot{V}CO_2$	1879.	374177.83	611.70	**
$\dot{V}O_2$	1519.	370970.88	609.07	*
$P_{ET}CO_2$	98.37	136.13	11.66	**
IC	2.16	2.34	0.63	**

The difference between exercise and hypercapnia (Ex - CO_2), in the difference between mean unloaded and loaded values (R0-R4), was assessed for significance using an estimate of the total variance of the two samples, obtained by pooling the residual mean squares (ResMsq) of exercise and hypercapnic data (Statistical Methods Chapter, p. 3.8). Except for IC, the data was from 8 subjects (IC measurements were only made on 3 subjects). ** $P<0.01$; * $P<0.05$.

5. Flow Profile

This section presents the data and analysis concerning the effect of increasing ventilation and/or inspiratory flow-resistive loading on the shape of inspiratory and expiratory flow profiles.

The four subjects who participated in this second experimental series also took part in the study of energetics and the pattern of breathing. Consequently, results may be interpreted with reference to the data presented in previous sections regarding the energetic demand and mechanical performance of the respiratory muscles at a given ventilation during exercise or hypercapnia, with and without loading.

In this series of experiments, eleven variables that describe the shape of the flow profile were measured or calculated. The data concerning two of these variables (mean inspiratory and expiratory flow) were presented in the breathing pattern section (pp. 4.31-4.32). The following section reports the results concerning the nine remaining variables.

The analysis undertaken was an ANOVA which assessed the significance of three factors, level of ventilation (L), presence of inspiratory resistance (R) and subjects (S), and all two-factor interactions (L*R, L*S and S*R). Two extensions of the ANOVA were applied, first, analysis of the difference between exercise and hypercapnia in the effect of loading (see Statistical Methods Chapter p. 3.8) the results of which may be found with in the text, and second, regression analysis of the L*R interaction effect (see Statistical Methods Chapter pp. 3.9-3.10), the results of which are presented in Table 4.34.

Representative examples of flow profiles obtained with and

Figure 4.19: Examples of flow profiles obtained from Subject 643:

At resting levels of ventilation;

a) when breathing was unloaded.

b) when breathing was loaded.

During exercise at 150 W;

c) when breathing was unloaded (ventilation 50 $L.min^{-1}$).

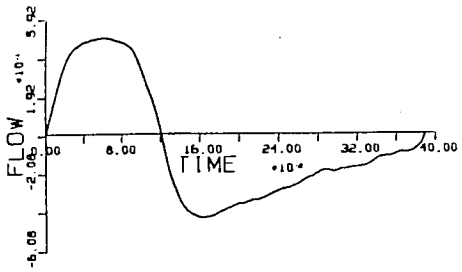
d) when breathing was loaded (ventilation 45 $L.min^{-1}$).

During hypercapnia, at similar ventilations to those at 150 W;

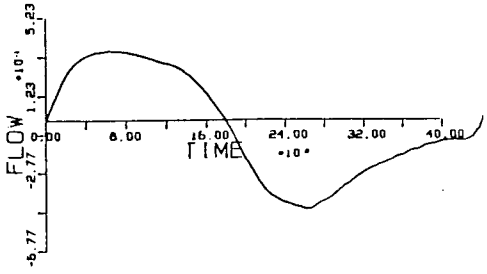
e) when breathing was unloaded.

f) when breathing was loaded.

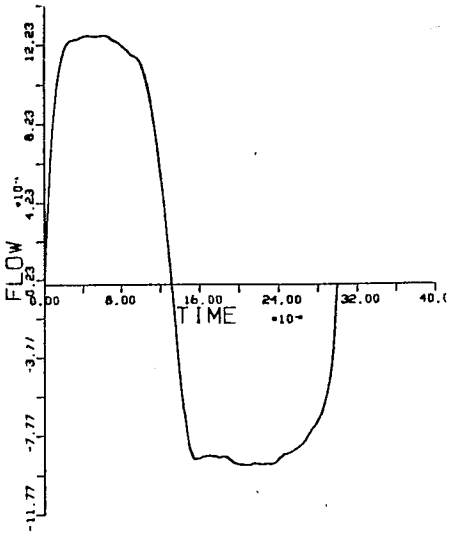
a)


FLOW
TIME
8.00
16.00
24.00
32.00
40.00

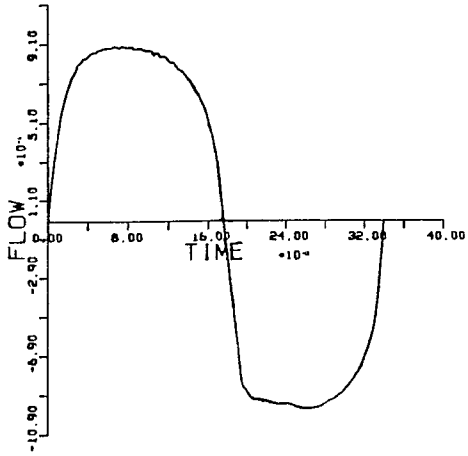
b)


FLOW
TIME
8.00
16.00
24.00
32.00
40.00

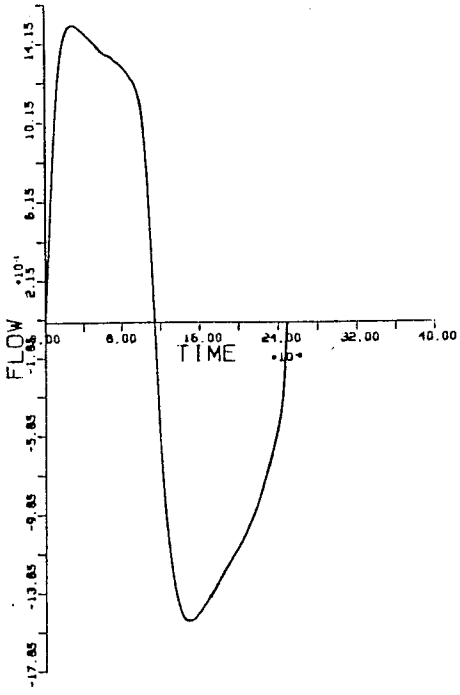
c)


FLOW
TIME
8.00
16.00
24.00
32.00

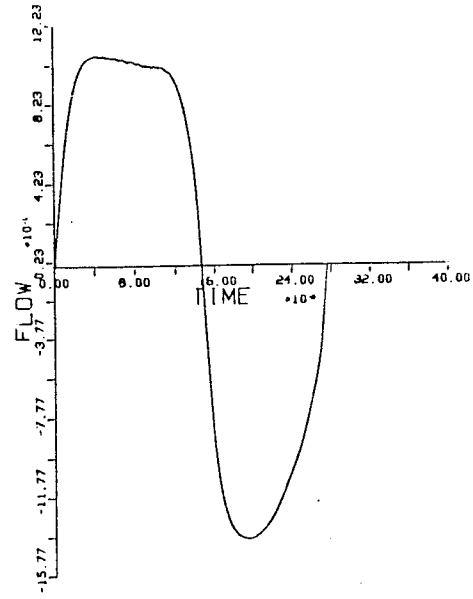
d)


FLOW
TIME
8.00
16.00
24.00
32.00
40.00

e)


FLOW
TIME
8.00
16.00
24.00
32.00
40.00

f)


FLOW
TIME
8.00
16.00
24.00
32.00
40.00

without loading, at rest and at elevated levels of ventilation due to exercise and hypercapnia, are shown in Figure 4.19

Flow variable data are presented in tabulated form in Appendix A4 as subject means with accompanying standard errors of the means at each ventilatory level. The data are presented graphically within the text in Figures 4.20-4.28, and the results of the ANOVA are presented in Tables 4.25-4.33.

Inspiratory Flow Acceleration

1) Ventilatory level effects.

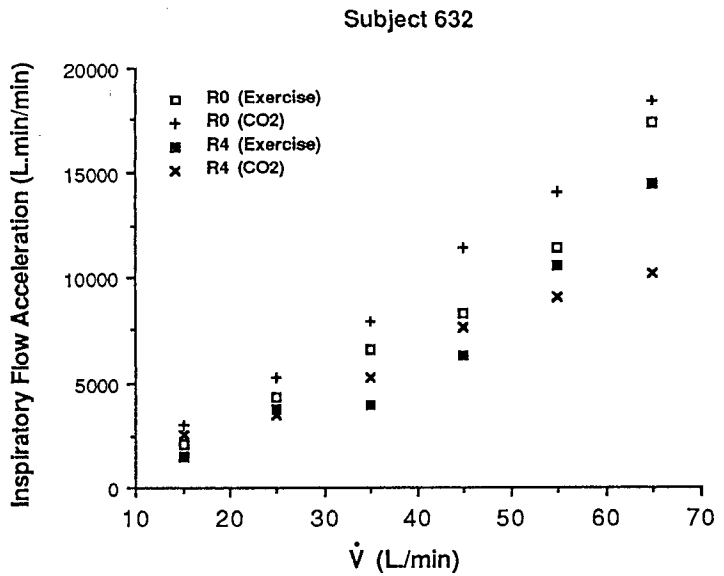
Figure 4.20 shows that inspiratory flow acceleration ($\ddot{V}_I$) increased with the elevation of ventilation, irrespective of whether the elevation of ventilation was due to exercise or hypercapnia or whether breathing was loaded or not; the effect of ventilation was highly significantly at $P<<0.01$ (Table 4.25).

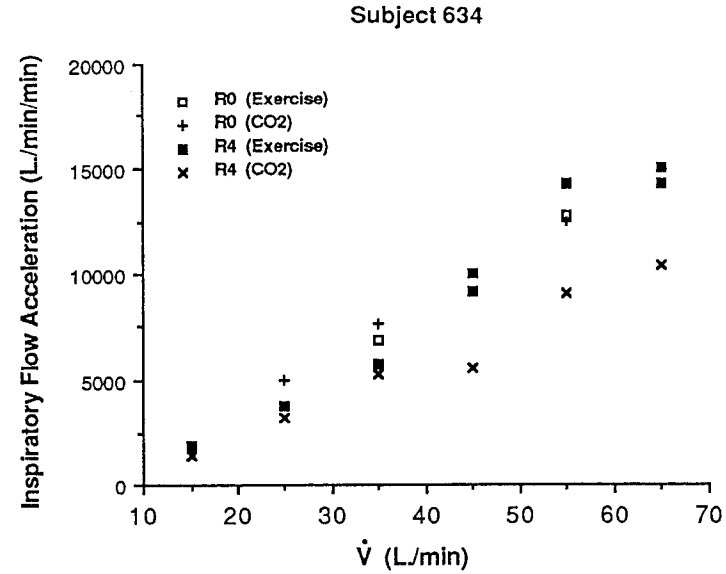
2) Loading effects.

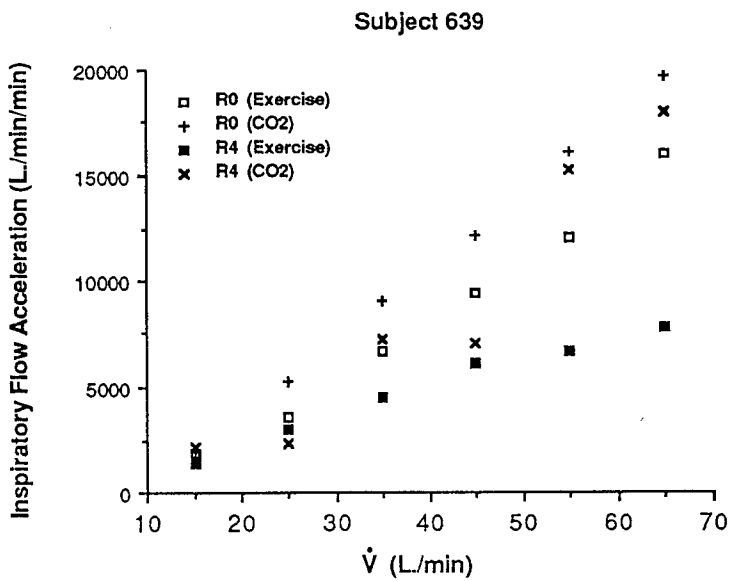
Loading was accompanied by a fall in $\ddot{V}_I$ in all four subjects at almost all ventilatory levels; only in one case was $\ddot{V}_I$ seen to rise with loading (Subject 634 at 50-59.9 $L.min^{-1}$). Unlike during hypercapnia, when ANOVA indicated that loading had a significant effect on $\ddot{V}_I$ ($P<0.01$, Table 4.25), the fall of $\ddot{V}_I$ accompanying loading during exercise was not significant. The absence of a significant effect may be ascribed to the large error variance (cf. hypercapnia effect).

Figure 4.20 shows that $\ddot{V}_I$ was reduced to a greater extent as ventilation rose. This observation was confirmed by the finding of a significant LR effect during both exercise and hypercapnia ($P<0.05$ and $P<0.01$ respectively). Regression analysis of the LR

Figure 4.20: The relation between ventilation ($\dot{V}$) and inspiratory flow acceleration during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Inspiratory Flow Acceleration (L/min/min)
20000
15000
10000
5000
0
10
20
30
40
50
60
70
V̇ (L/min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 634
Inspiratory Flow Acceleration (L/min/min)
20000
15000
10000
5000
0
10
20
30
40
50
60
70
V̇ (L/min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Inspiratory Flow Acceleration (L/min/min)
20000
15000
10000
5000
0
10
20
30
40
50
60
70
V̇ (L/min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

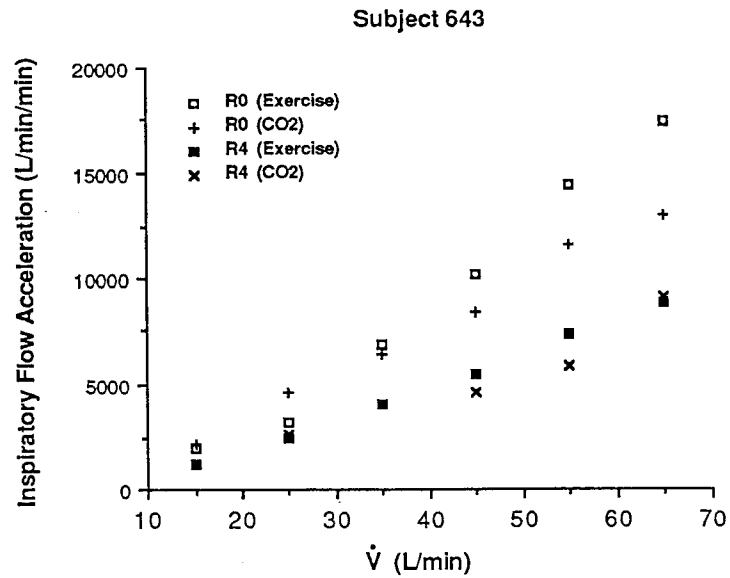

Subject 643
Inspiratory Flow Acceleration (L/min/min)
20000
15000
10000
5000
0
10
20
30
40
50
60
70
V̇ (L/min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.25 : Inspiratory Flow Acceleration ($\ddot{V}_I$)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	$8.65*10^8$	$1.73*10^8$	103.5**
Resistance (R)	1	$6.47*10^7$	$2.41*10^7$	7.0
Subjects (S)	3	$1.86*10^7$	6185984.	3.8*
Interactions				
LR	5	$3.03*10^7$	6052096.	3.8*
LS	15	$2.51*10^7$	1671578.	1.0
SR	3	$2.76*10^7$	9195093.	5.7**
Residual (LRS)	15	$2.41*10^7$	1609318.	
Total	47	$1.06*10^9$		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	$8.49*10^8$	$1.70*10^8$	41.5**
Resistance (R)	1	$1.01*10^8$	$1.01*10^8$	74.7**
Subjects (S)	3	$8.18*10^7$	$2.72*10^7$	26.0**
Interactions				
LR	5	$2.62*10^7$	5249280.	5.0**
LS	15	$6.14*10^7$	4094601.	3.9**
SR	3	4050944	1350315.	1.3
Residual (LRS)	15	$1.57*10^7$	1047757.	
Total	47	$1.14*10^9$		

** P<0.01

* P<0.05

No. of subjects = 4

interaction revealed a significant linear component during exercise and hypercapnia (Table 4.34). However, it is also apparent from Figure 4.20 that sometimes $\dot{V}_I$ in the presence of loading increased notably at high levels of ventilation so as to approach unloaded values (Subjects 632 and 634 in exercise, 639 in hypercapnia).

As for all the measured flow variables except the time to peak inspiratory flow (see below), analysis of the difference of the differences showed no significant difference in the effect of loading during exercise and hypercapnia. In view of the general absence of any difference between the effect of loading during hypercapnia and exercise, data concerning the difference of differences test are not presented in tabulated form.

Time to Peak Inspiratory Flow

1) Ventilatory level effects.

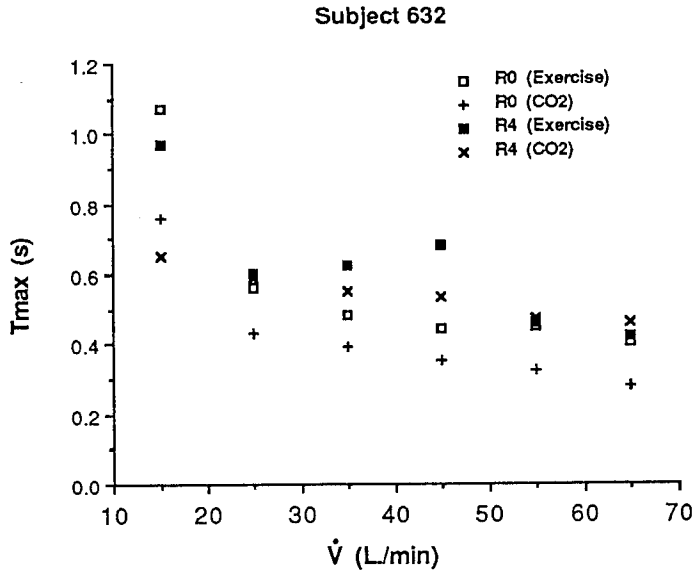
Figure 4.21 shows that the elevation of ventilation was accompanied by a progressive shortening of the time to peak inspiratory flow (Tmax); the effect of ventilation was significant during exercise or hypercapnia ($P<0.01$, Table 4.26).

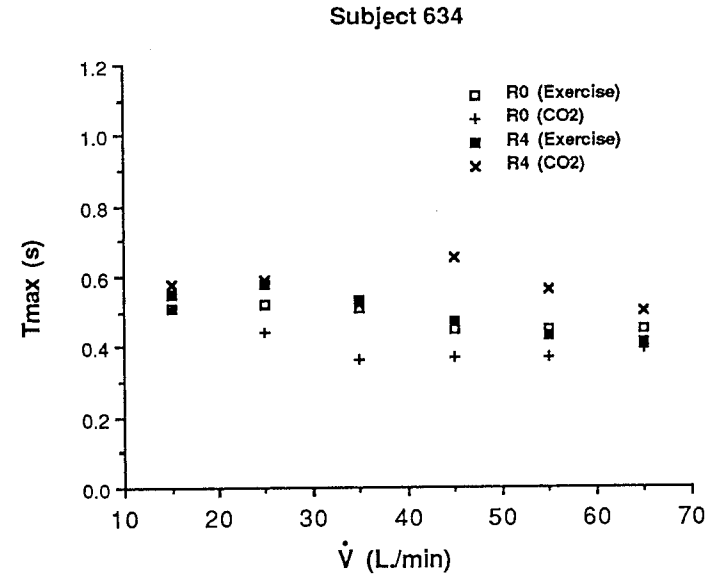
Values obtained during hypercapnia in the absence of loading were markedly shorter than those in any other condition.

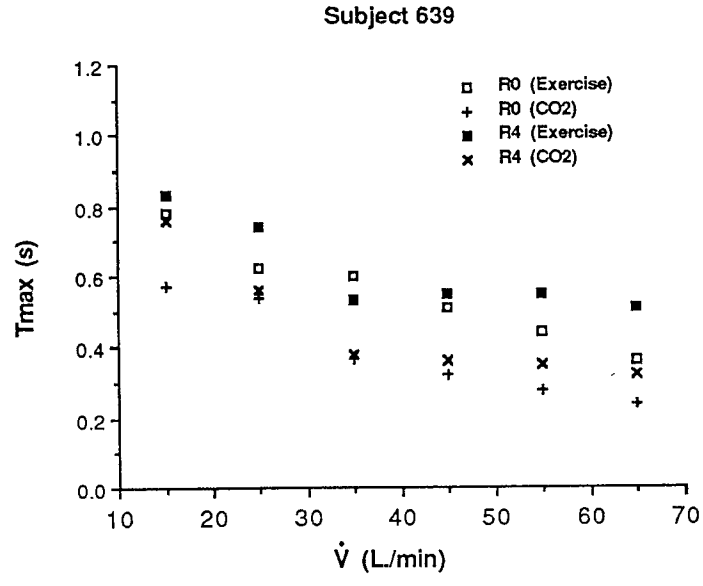
2) Loading effects.

Loading was typically accompanied by a lengthening of Tmax during both exercise and hypercapnia, though the effect only achieved significance during hypercapnia ($P<0.05$, Table 4.26). This apparent difference was confirmed by the analysis of the

Figure 4.21: The relation between ventilation ($\dot{V}$) and the time to peak inspiratory flow (Tmax) during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmax (s)
V̇ (L/min)


Subject 634
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmax (s)
V̇ (L/min)


Subject 639
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmax (s)
V̇ (L/min)

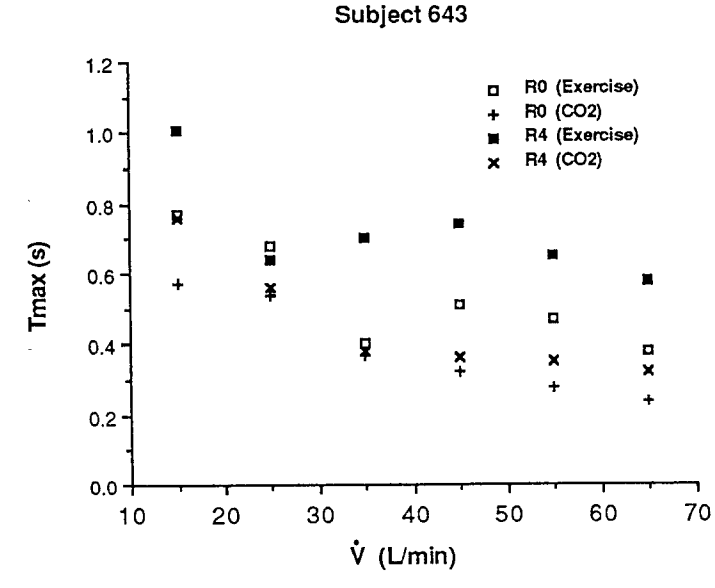

Subject 643
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmax (s)
V̇ (L/min)

Table 4.26 : Time to Peak Inspiratory Flow (Tmax)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.685	0.137	10.1**
Resistance (R)	1	0.078	0.078	4.9
Subjects (S)	3	0.126	0.043	8.3**
Interactions				
LR	5	0.009	0.002	0.4
LS	15	0.204	0.014	2.6*
SR	3	0.048	0.016	3.1
Residual (LRS)	15	0.078	0.005	
Total	47	1.234		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.361	0.072	11.2**
Resistance (R)	1	0.269	0.269	15.2*
Subjects (S)	3	0.034	0.011	3.8*
Interactions				
LR	5	0.014	0.003	0.9
LS	15	0.097	0.006	2.1
SR	3	0.053	0.018	5.8**
Residual (LRS)	15	0.046	0.003	
Total	47	0.873		

** $P<0.01$

* $P<0.05$

No. of subjects = 4

difference of the differences which showed loading had a significantly greater effect on Tmax during hypercapnia ($P<0.01$).

The lengthening of Tmax with loading appeared to be almost constant over the whole ventilatory range, an observation corroborated by the finding of a non-significant LR effect.

Time to Peak Expiratory Flow

1) Ventilatory level effects.

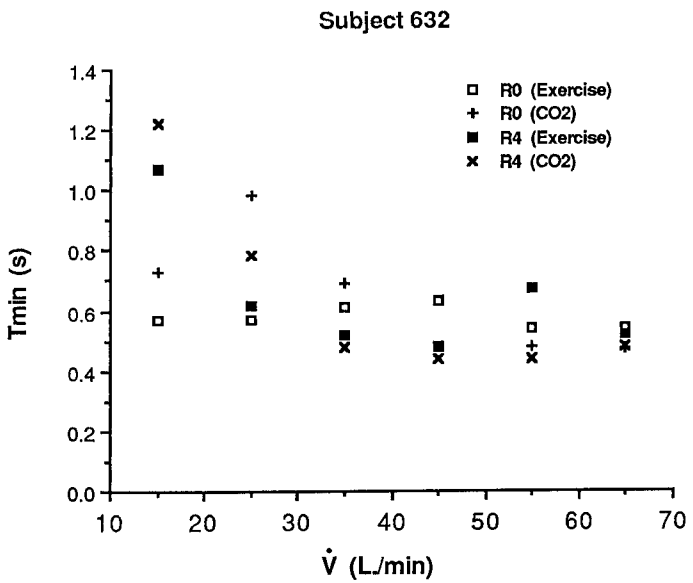
Increasing ventilation was generally accompanied by a shortening of the time to peak expiratory flow (Tmin), i.e the "trough" of the flow profile came earlier, though the response was variable over the low ventilatory range (Figure 4.22; levels effect significant at $P<0.01$, Table 4.27); the variability of the response was most notable during exercise when in the absence of loading Tmin lengthened with the increase of ventilation from resting levels in 3 of the 4 subjects.

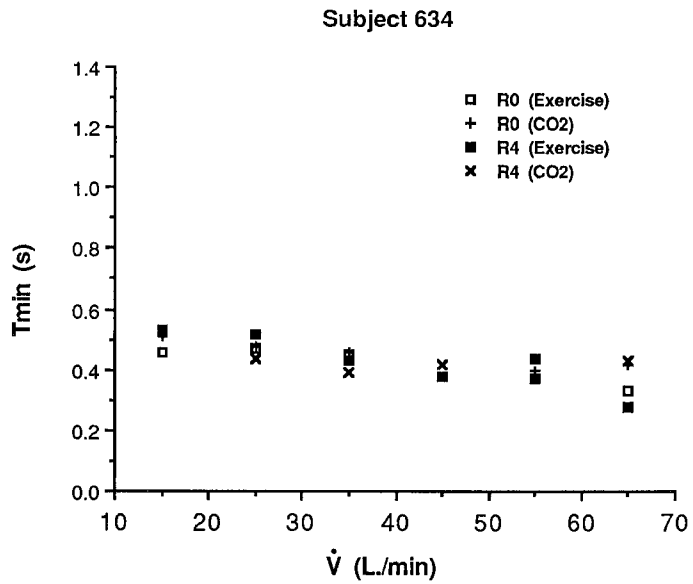
2) Loading effects.

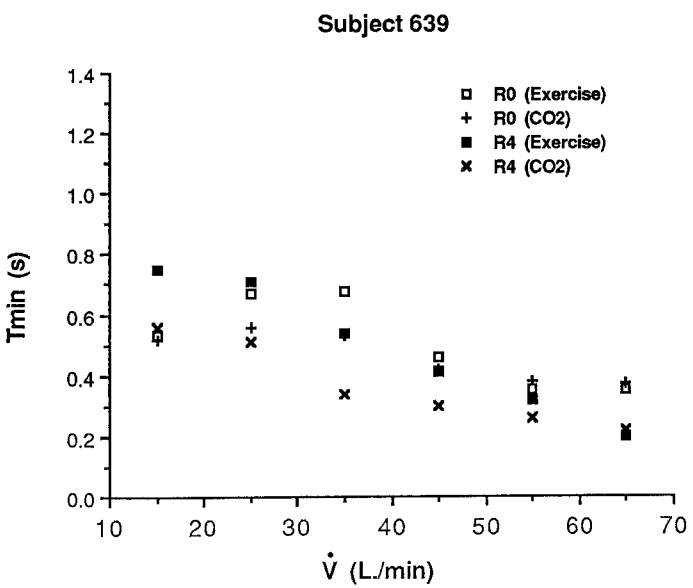
Pooling the data from all four subjects revealed that the addition of loading was associated with a shortening of mean Tmin and Figure 4.22 shows that loaded values were frequently shorter than unloaded. However, the direction of change in Tmin accompanying loading was variable and ANOVA indicated that the resistance effect was not significant.

The finding of a significant LR interaction effect during both exercise and hypercapnia ($P<0.01$ and $P<0.05$ respectively) reflected the tendency for the difference between loaded and unloaded values obtained on pooling all subjects' data to diminish as ventilation increased.

Figure 4.22: The relation between ventilation ($\dot{V}$) and the time to peak expiratory flow (Tmin) during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmin (s)
V̇ (L./min)


Subject 634
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmin (s)
V̇ (L./min)


Subject 639
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmin (s)
V̇ (L./min)

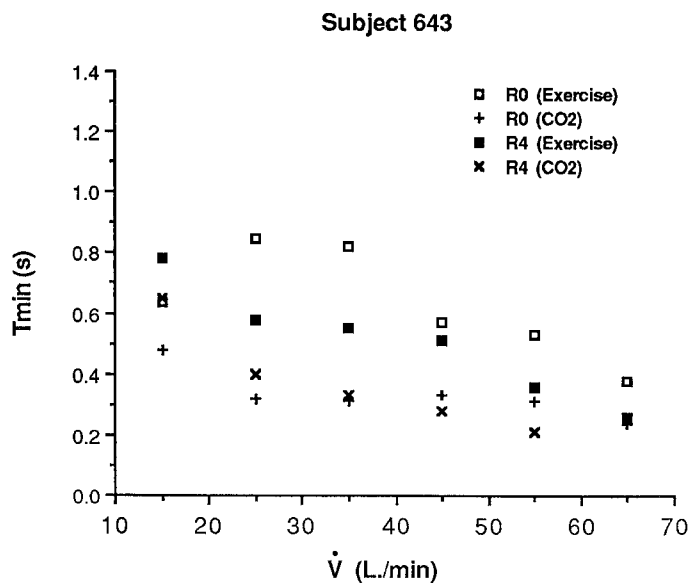

Subject 643
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)
Tmin (s)
V̇ (L./min)

Table 4.27 : Time to Peak Expiratory Flow (Tmin)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.548	0.109	9.0**
Resistance (R)	1	0.004	0.004	0.2
Subjects (S)	3	0.255	0.085	15.2**
Interactions				
LR	5	0.165	0.033	5.9**
LS	15	0.182	0.012	2.2
SR	3	0.058	0.019	3.5*
Residual (LRS)	15	0.084	0.006	
Total	47	1.300		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.569	0.114	7.5**
Resistance (R)	1	0.004	0.004	0.5
Subjects (S)	3	0.578	0.193	27.4**
Interactions				
LR	5	0.103	0.021	2.9*
LS	15	0.227	0.015	2.2
SR	3	0.027	0.009	1.3
Residual (LRS)	15	0.105	0.007	
Total	47	1.613		

** $P<0.01$

* $P<0.05$

No. of subjects = 4

Peak Inspiratory Flow

1) Ventilatory level effects.

Peak inspiratory flow ($\dot{V}_I max$) rose in a nearly linear manner with the elevation of ventilation whether due to exercise or hypercapnia (Figure 4.23); the effect of ventilation was highly significant in exercise and in hypercapnia ($P<<0.01$, Table 4.28).

Although the predominant relationship between ventilation and $\dot{V}_I max$ was one of near linearity, there were in some cases deviations from the prevailing relationship, $\dot{V}_I max$ increasing disproportionately over the higher ventilatory range (Subjects 634 and 639 loaded, Subject 632 unloaded).

2) Loading effects.

The addition of loading produced a marked fall in peak inspiratory flow at a given ventilatory level during exercise or hypercapnia; the effect of loading was significant at $P<0.01$ (Table 4.28).

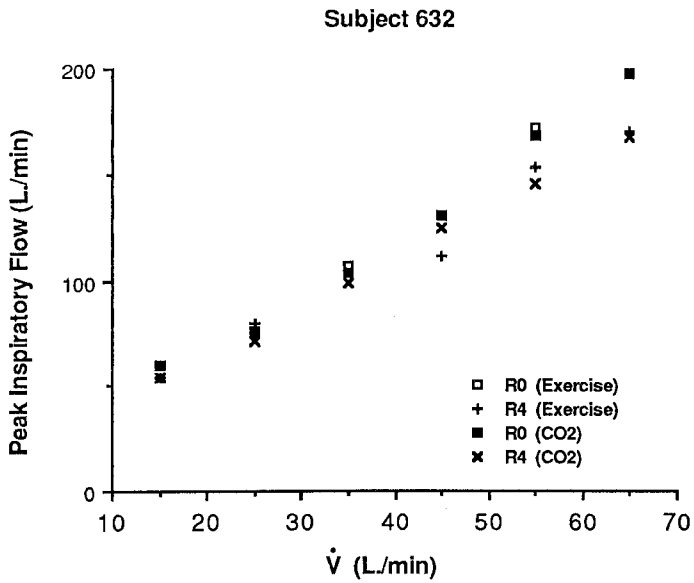
Examination of the pooled mean response revealed that the fall in $\dot{V}_I max$ with loading was augmented slightly with increasing ventilation, though this trend is not obvious in Figure 4.23; the LR interaction effect was not significant.

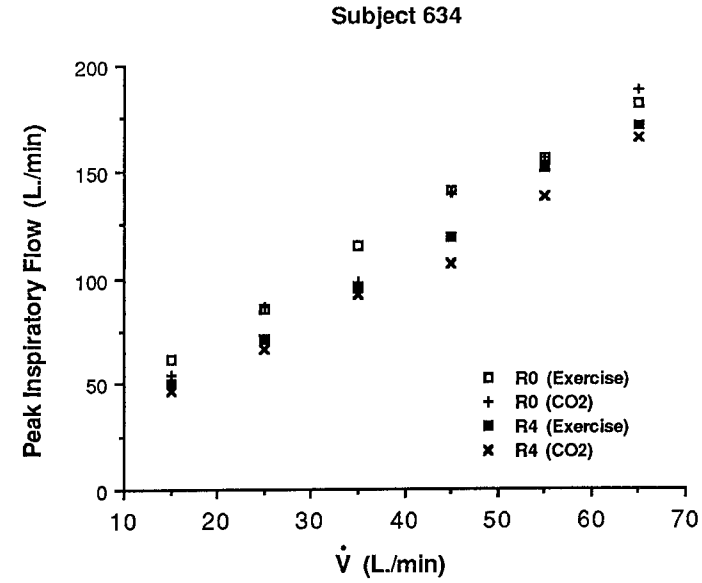
Peak Expiratory Flow

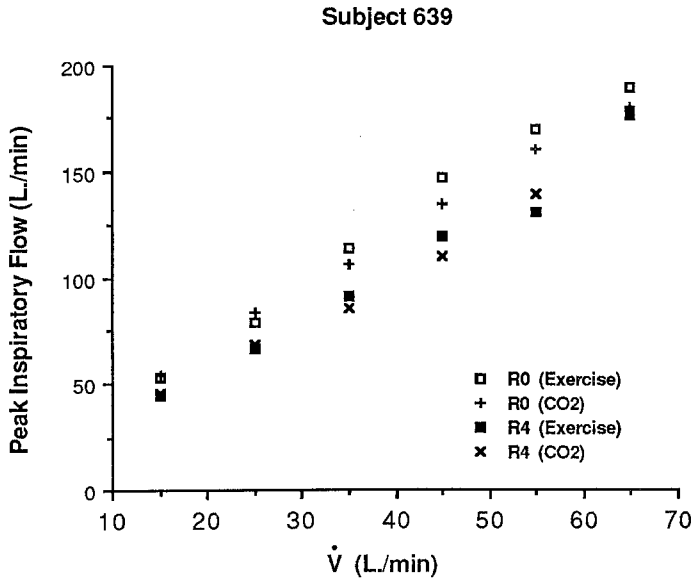
1) Ventilatory level effects.

Peak expiratory flow ($\dot{V}_E max$) increased nearly linearly with increments of ventilation (Figure 4.24); the effect of ventilation during exercise or hypercapnia was highly significant ($P<<0.01$, Table 4.29).

Figure 4.23: The relation between ventilation ($\dot{V}$) and peak inspiratory flow during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Peak Inspiratory Flow (L./min)
200
100
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R4 (Exercise)
R0 (CO2)
R4 (CO2)


Subject 634
Peak Inspiratory Flow (L./min)
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Peak Inspiratory Flow (L./min)
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

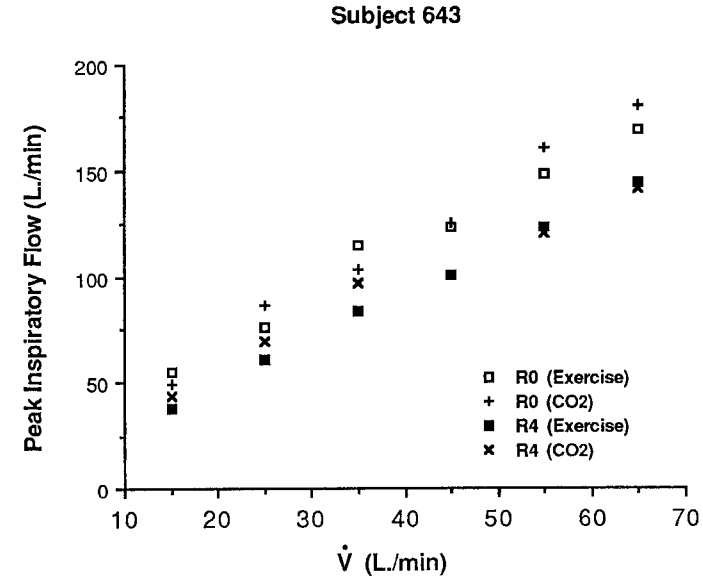

Subject 643
Peak Inspiratory Flow (L./min)
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.28 : Peak Inspiratory Flow ($\dot{V}_{I}max$)

Analysis of variance table

Exercise Condition

Main Effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	86004.	17200.	257.3*
Resistance (R)	1	3703.	3703.	52.6*
Subjects (S)	3	1693.88	564.63	12.7**
Interactions				
LR	5	344.25	68.85	1.6
LS	15	1002.81	66.85	1.5
SR	3	211.25	70.42	1.6
Residual (LRS)	15	668.38	44.56	
Total	47	93627.		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	84445.	16889.	408.8**
Resistance (R)	1	3434.13	3434.13	64.1**
Subjects (S)	3	586.31	195.44	4.2*
Interactions				
LR	5	591.38	118.28	2.5
LS	15	619.75	41.32	0.9
SR	3	160.81	53.60	1.2
Residual (LRS)	15	704.50	46.97	
Total	47	90542.		

** P<0.01

* P<0.05

No. of subjects = 4

However in some cases, deviations from the nearly linear relationship were evident at high levels of ventilation, these were of a similar nature to those in the $\dot{V}$ - $\dot{v}_I$max relation. The most obvious were the disproportionate rises in $\dot{v}_E$max during exercise when ventilation was loaded manifested by Subjects 634, 639 and 643. Conversely, the slope of the loaded $\dot{V}$ - $\dot{v}_E$max relation of Subject 632 fell as the highest levels of ventilation were approached.

2) Loading effects.

The imposition of inspiratory loading increased peak expiratory flow at a given ventilation; the effect of loading was loading was significant at $P<0.05$ in exercise and in hypercapnia (Table 4.29).

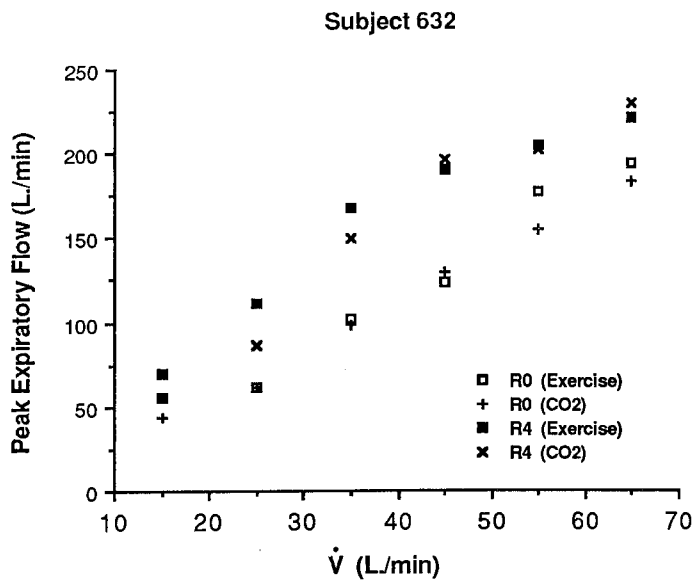
During hypercapnia, the magnitude of the elevation of peak flow with loading was a function of the level of ventilation (LR interaction effect significant at $P<0.01$). Assessed by eye, the response during exercise appeared to be similar, but the ANOVA indicated that the LR effect during exercise was not significant. This was partly due to the fact that the effect was less marked during exercise and partly due to the greater error variance of the exercise data. Regression analysis of the LR interaction indicated a significant linear component in both hypercapnic and exercise data ($P<0.01$ and $P<0.05$ respectively, Table 4.34).

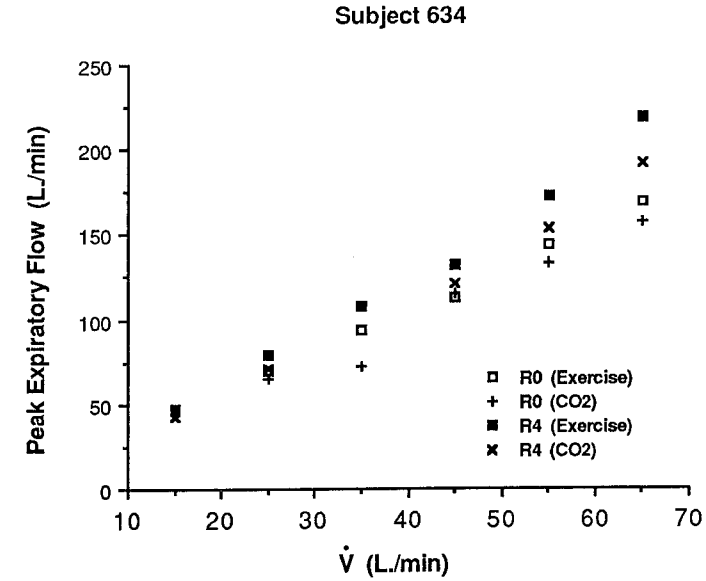
Time to Peak Inspiratory Flow / Inspiratory Time

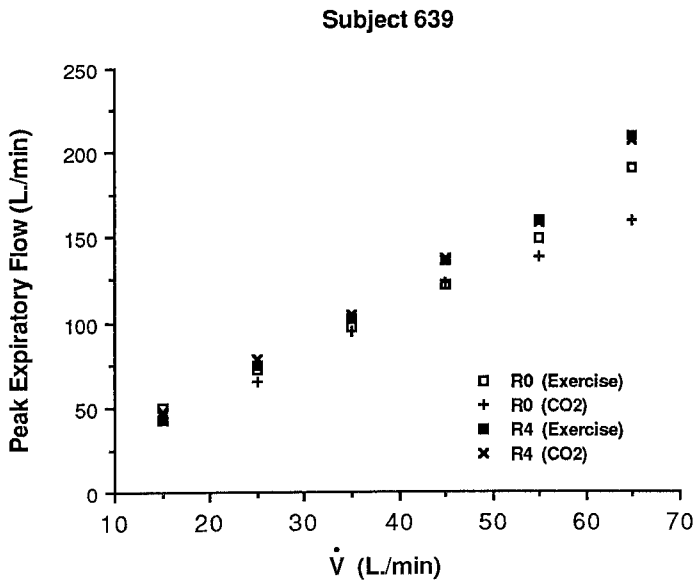
1) Ventilatory level effects.

During exercise, the increase of ventilation was associated with a slight fall in the ratio of the time to peak inspiratory flow to the duration of inspiration ($Tmax/T_I$) in all subjects except 634

Figure 4.24: The relation between ventilation ($\dot{V}$) and peak expiratory flow during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Peak Expiratory Flow (L./min)
250
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 634
Peak Expiratory Flow (L./min)
250
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Peak Expiratory Flow (L./min)
250
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

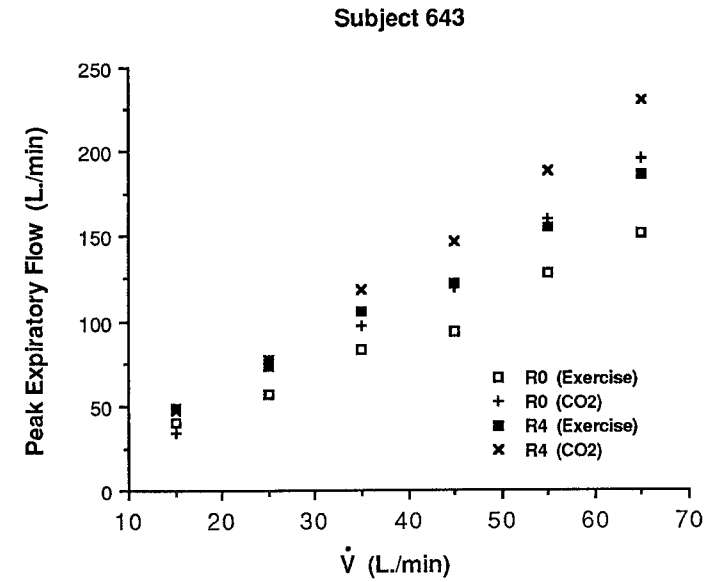

Subject 643
Peak Expiratory Flow (L./min)
250
200
150
100
50
0
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.29 : Peak Expiratory Flow ($\dot{V}_E max$)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	112595.	22519.	215.7**
Resistance (R)	1	6331.9	6331.9	10.5*
Subjects (S)	3	8088.4	2696.1	31.2**
Interactions				
LR	5	1091.00	218.20	2.5
LS	15	1565.88	104.39	1.2
SR	3	1812.50	604.17	7.0**
Residual (LRS)	15	1295.31	86.35	
Total	47	132780.40		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	123952.	24790.57	147.5**
Resistance (R)	1	7039.88	7039.88	17.8*
Subjects (S)	3	4948.13	1649.38	26.1*
Interactions				
LR	5	1602.56	320.51	5.1**
LS	15	2521.75	168.12	2.7*
SR	3	1186.38	395.46	6.3**
Residual (LRS)	15	948.50	63.23	
Total	47	142200.10		

** $P<0.01$

* $P<0.05$

No. of subjects = 4

(Figure 4.25). The fall was more evident over the lower ventilatory range, higher levels of ventilation being associated with little change.

During exercise, the effect of ventilation was significant at $P<0.01$ (Table 4.30). During hypercapnia, the increase of ventilation was associated with a similar fall in $Tmax/T_I$ as during exercise, but of a much lesser degree; the effect of ventilation was not significant.

2) Loading effects.

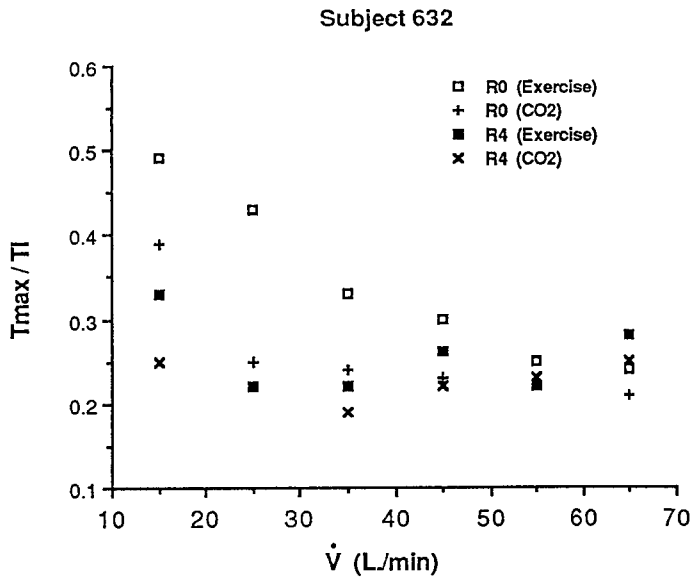
The direction of the change in $Tmax/T_I$ accompanying loading varied depending on the subject and the level of ventilation. Consequently, the ANOVA indicated that loading had no significant effect on $Tmax/T_I$ in either exercise or hypercapnia. The form of the response to loading appeared to be least variable during exercise when $Tmax/T_I$ was frequently seen to be reduced, an observation supported by the finding that the variance ratio of the resistance effect during exercise was greater than during hypercapnia.

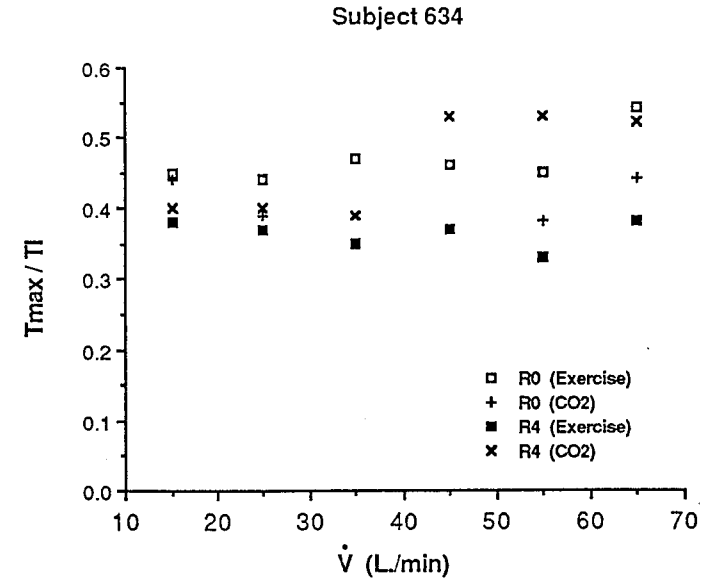
Pooling all the subjects' data revealed that loading at the highest ventilatory level (60-69.9 $L.min^{-1}$) was associated with an increase in $Tmax/T_I$ in 7 cases out of a possible total of 8 (4 subjects during exercise and hypercapnia).

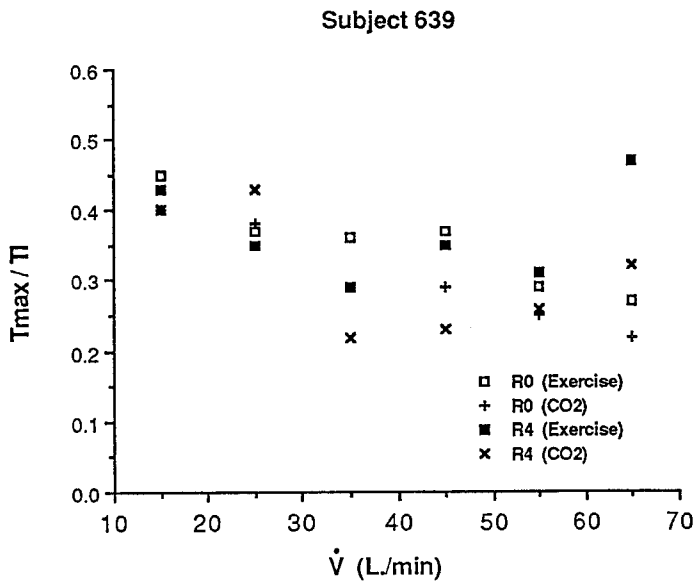
Time to Peak Expiratory Flow / Expiratory Time

This variable ($Tmin/T_E$) showed within-subjects and between-subjects variability in the response to both the effect of increasing ventilation and/or loading (Figure 4.26); the only significant effects were subjects and LS interaction during

Figure 4.25: The relation between ventilation ($\dot{V}$) and the ratio of the time to peak inspiratory flow (Tmax) to the duration of inspiration (T_I) during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Tmax / TI
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 634
Tmax / TI
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Tmax / TI
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

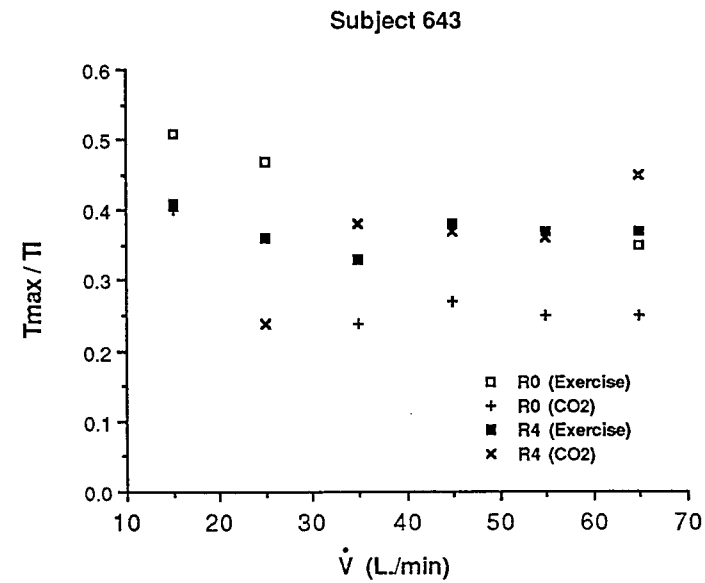

Subject 643
Tmax / TI
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.30 : Time to Peak Inspiratory Flow / Inspiratory Time

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.058	0.011	5.6**
Resistance (R)	1	0.032	0.032	3.6
Subjects (S)	3	0.091	0.030	13.6**
Interactions				
LR	5	0.021	0.004	2.0
LS	15	0.031	0.002	0.9
SR	3	0.026	0.009	4.0*
Residual (LRS)	15	0.033	0.002	
Total	47	0.293		

Hypercapnia Condition

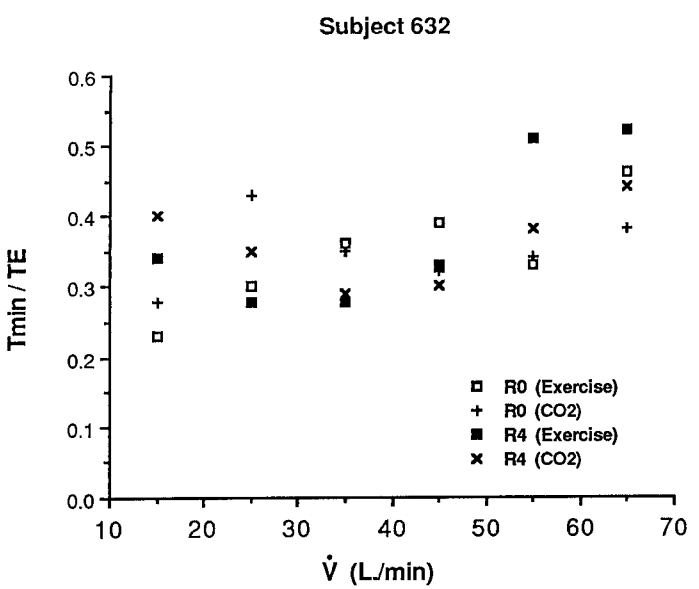
Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.045	0.009	2.3
Resistance (R)	1	0.010	0.010	1.3
Subjects (S)	3	0.215	0.072	29.8**
Interactions				
LR	5	0.031	0.006	2.6
LS	15	0.058	0.004	1.6
SR	3	0.022	0.007	3.1*
Residual (LRS)	15	0.036	0.002	
Total	47	0.418		

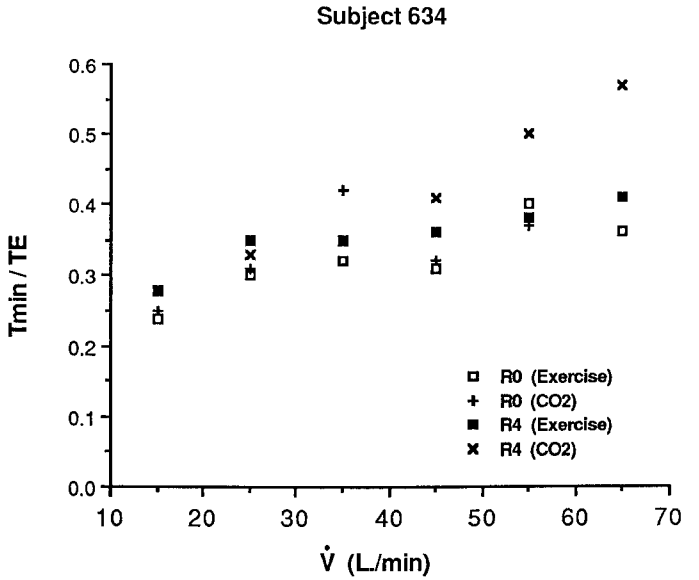
** $P<0.01$

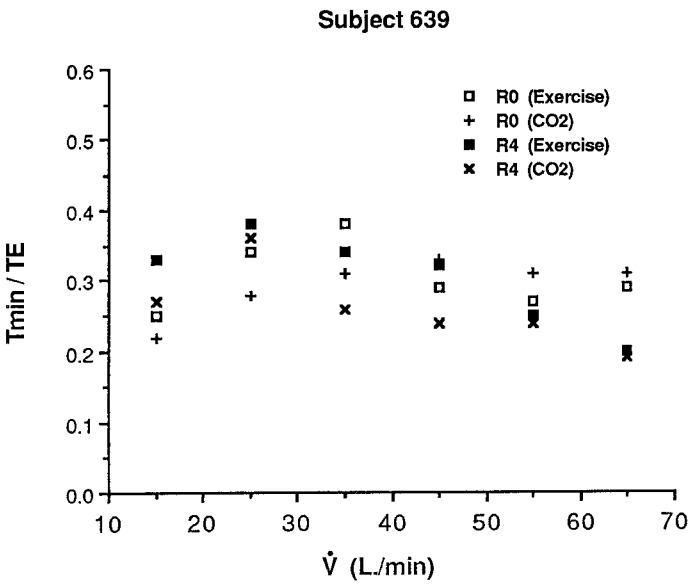
* $P<0.05$

No. of subjects = 4

Figure 4.26: The relation between ventilation ($\dot{V}$) and the ratio of the time to peak expiratory flow (Tmin) to the duration of expiration (T_E) during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Tmin / TE
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 634
Tmin / TE
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Tmin / TE
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

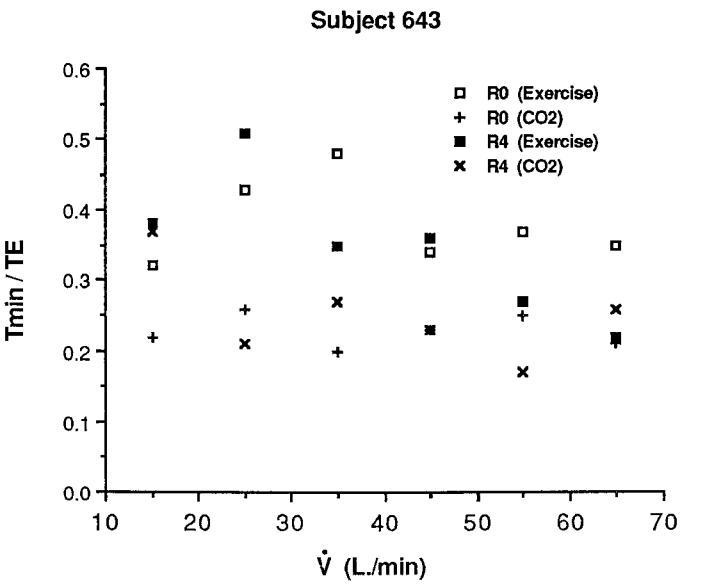

Subject 643
Tmin / TE
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.31 : Time to Peak Expiratory Flow / Expiratory Time (T_{min}/T_E)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.023	0.005	0.5
Resistance (R)	1	0.001	0.001	0.3
Subjects (S)	3	0.029	0.010	3.5*
Interactions				
LR	5	0.021	0.004	1.5
LS	15	0.133	0.009	3.3*
SR	3	0.009	0.003	1.1
Residual (LRS)	15	0.041	0.003	
Total	47	0.256		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.017	0.003	0.7
Resistance (R)	1	0.003	0.003	0.6
Subjects (S)	3	0.150	0.050	15.3**
Interactions				
LR	5	0.017	0.003	1.1
LS	15	0.078	0.005	1.6
SR	3	0.013	0.004	1.4
Residual (LRS)	15	0.049	0.003	
Total	47	0.327		

** $P<0.01$

* $P<0.05$

No. of subjects = 4

exercise ($P<0.05$) and subjects during hypercapnia ($P<0.01$, Table 4.31).

The pooling of all subjects' data revealed that the mean response to the elevation of ventilation, or the addition of loading, was for $Tmin/T_E$ to increase slightly.

Mean Inspiratory Flow / Peak Inspiratory Flow

1) Ventilatory level effects.

The elevation of ventilation, whether by exercise or hypercapnia, was associated with a rise in the ratio of mean to peak inspiratory flow ($\bar{\dot{V}}_I/\dot{V}_I max$, Figure 4.27); the effect of increasing ventilation was significant at $P<0.01$ during exercise and hypercapnia (Table 4.32). Although the form of the response appeared quite similar between subjects, the significant subjects effect ($P<0.01$) indicated that there were significant differences.

2) Loading effects.

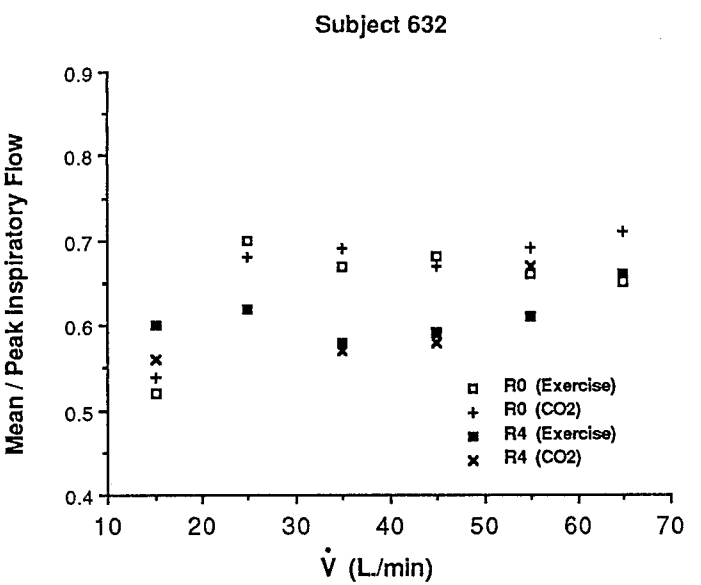
The absence of a common response to loading is evident from Figure 4.27. In some subjects (Subjects 639 and 643), the direction of change in $\bar{\dot{V}}_I/\dot{V}_I max$ with loading depended on the source of drive; the effect of loading was not significant (Table 4.32).

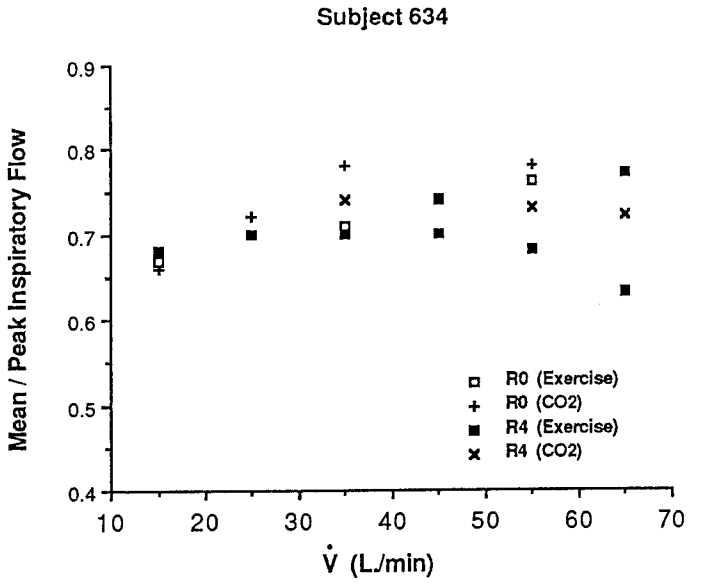
Mean Expiratory Flow / Peak Expiratory Flow

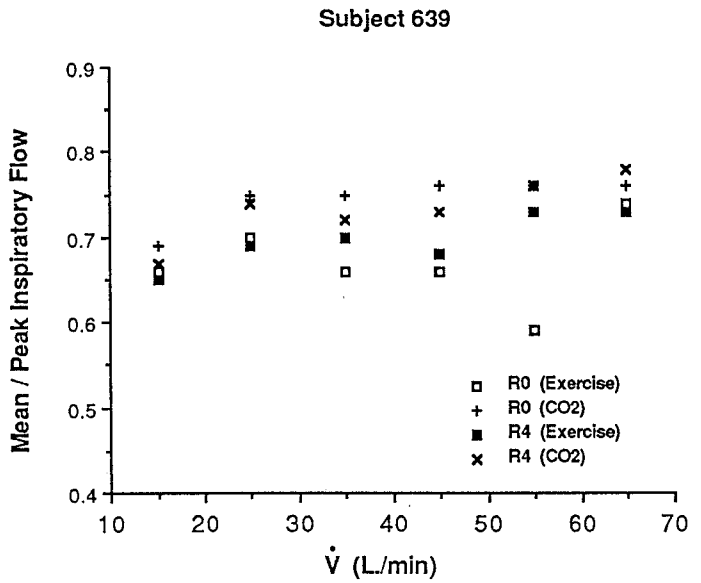
1) Ventilatory level effects.

Figure 4.28 shows that the ratio of mean expiratory flow to peak expiratory flow ($\bar{\dot{V}}_E/\dot{V}_E max$) typically increased with the elevation of ventilation; the effect of ventilation was significant at $P<0.01$ (Table 4.33). The increase of $\bar{\dot{V}}_E/\dot{V}_E max$ with the elevation

Figure 4.27: The relation between ventilation ($\dot{V}$) and the ratio of mean inspiratory flow to peak inspiratory flow during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Mean / Peak Inspiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 634
Mean / Peak Inspiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Mean / Peak Inspiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

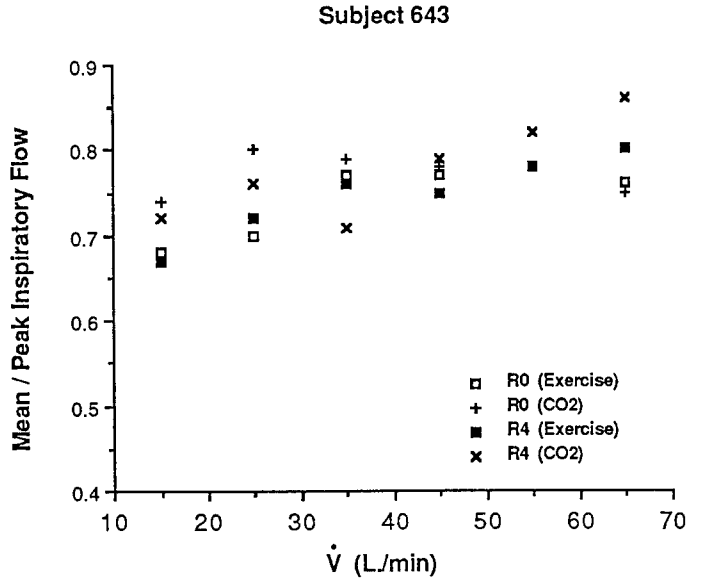

Subject 643
Mean / Peak Inspiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.32 : Mean Inspiratory Flow / Peak Inspiratory Flow ($\bar{\dot{V}}_I/\dot{V}_{I}max$)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.026	0.005	4.7**
Resistance (R)	1	0.002	0.002	0.5
Subjects (S)	3	0.085	0.028	16.1**
Interactions				
LR	5	0.003	0.001	0.4
LS	15	0.017	0.001	0.6
SR	3	0.010	0.003	2.0
Residual (LRS)	15	0.026	0.002	
Total	47	0.169		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.046	0.009	16.0**
Resistance (R)	1	0.005	0.005	3.1
Subjects (S)	3	0.125	0.042	49.3**
Interactions				
LR	5	0.008	0.002	1.8
LS	15	0.009	0.001	0.7
SR	3	0.005	0.002	2.1
Residual (LRS)	15	0.013	0.001	
Total	47	0.210		

** P<0.01

*. P<0.05

No. of subjects = 4

of ventilation occurred markedly in all four subjects over the low to moderate ventilatory range, but at higher levels of ventilation the effect was more variable. As ventilation approached the highest levels, $\bar{v}_E/\dot{v}_E max$ continued to rise in Subject 632 but not in the others. In some cases $\bar{v}_E/\dot{v}_E max$ fell with further increases in ventilation depending on the source of drive (Subject 643) and whether breathing was loaded (Subject 634), or seemed to reach a plateau (Subject 639).

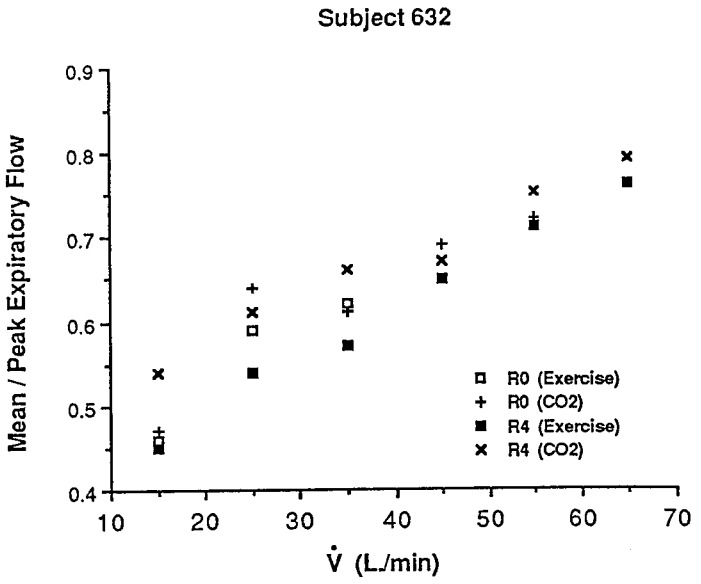
The pooling of all subjects' data indicated that the mean response was for $\bar{v}_E/\dot{v}_E max$ to rise with increasing ventilation up to 40-50 $L.min^{-1}$, but that subsequent increases in ventilation were not accompanied by further notable changes in $\bar{v}_E/\dot{v}_E max$.

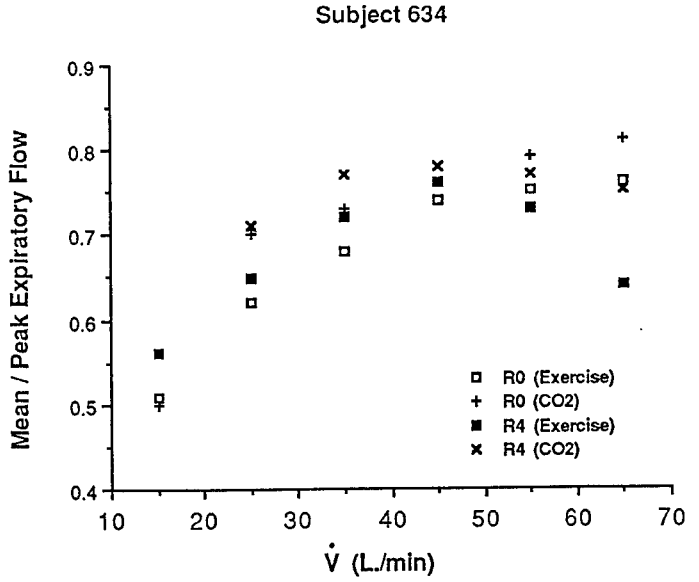
2) Loading effects.

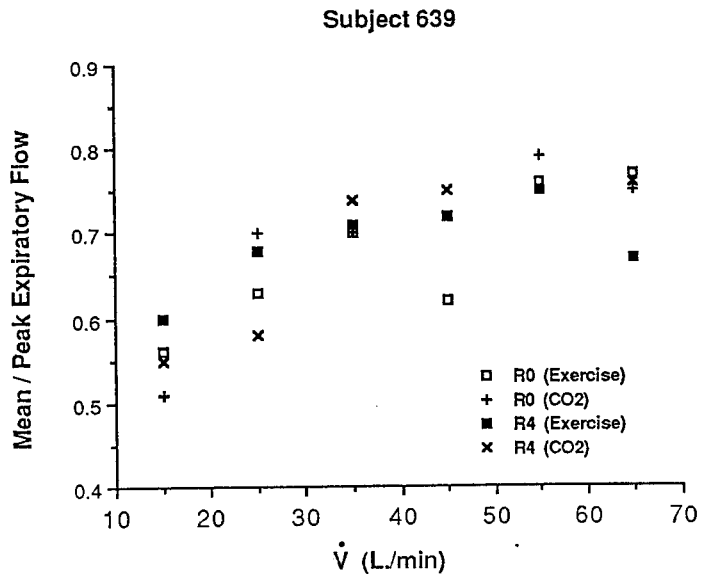
Loading was frequently associated with marked changes in $\bar{v}_E/\dot{v}_E max$, but the direction of change varied with subject, level and source of respiratory drive; the effect of loading was not significant. The data of Subject 634 (Figure 4.28) exemplifies the dependence of the response to loading on the level of ventilation: Loading produced a marked rise in $\bar{v}_E/\dot{v}_E max$ values at levels of ventilation up to 40-50 $L.min^{-1}$, but at levels of ventilation above this loading was associated with equally marked falls in $\bar{v}_E/\dot{v}_E max$ values.

The pooled mean response to loading was similar to that shown by Subject 634. In six of eight instances (during exercise and hypercapnia at four ventilatory levels) loading produced a rise in $\bar{v}_E/\dot{v}_E max$ values at levels of ventilation up to 40-50 $L.min^{-1}$, but at higher levels of ventilation loading was accompanied by a fall in $\bar{v}_E/\dot{v}_E max$. This form of response was reflected by the ANOVA as a significant LR interaction effect ($P<0.05$, Table 4.33).

Figure 4.28: The relation between ventilation ($\dot{V}$) and the ratio of mean expiratory flow to peak expiratory flow during exercise (square symbols) and hypercapnia (cross symbols). The data are represented after partitioning into 10 litre ventilation bins.


Subject 632
Mean / Peak Expiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 634
Mean / Peak Expiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)


Subject 639
Mean / Peak Expiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

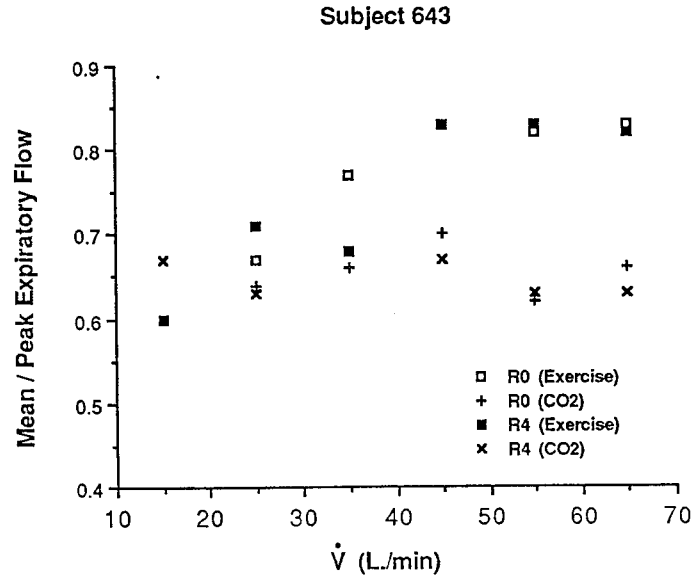

Subject 643
Mean / Peak Expiratory Flow
0.9
0.8
0.7
0.6
0.5
0.4
10
20
30
40
50
60
70
V̇ (L./min)
R0 (Exercise)
R0 (CO2)
R4 (Exercise)
R4 (CO2)

Table 4.33 : Mean Expiratory Flow / Peak Expiratory Flow ($\bar{\dot{V}}_E/\dot{V}_E max$)

Analysis of variance table

Exercise Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.271	0.054	21.3**
Resistance (R)	1	0.001	0.001	0.2
Subjects (S)	3	0.097	0.032	28.4**
Interactions				
LR	5	0.011	0.002	1.9
LS	15	0.038	0.003	2.2
SR	3	0.002	0.001	0.5
Residual (LRS)	15	0.017	0.001	
Total	47	0.436		

Hypercapnia Condition

Main effects	DF	SOS	MSq	VR
$\dot{V}$ Levels (L)	5	0.200	0.040	8.3**
Resistance (R)	1	0.001	0.001	1.5
Subjects (S)	3	0.037	0.012	19.4**
Interactions				
LR	5	0.013	0.003	4.0*
LS	15	0.073	0.005	7.7**
SR	3	0.001	0.001	0.7
Residual (LRS)	15	0.009	0.001	
Total	47	0.333		

** $P<0.01$

* $P<0.05$

No. of subjects = 4

Table 4.34 : Regression Analysis of the Variance Associated With the Levels * Resistance Interaction of Flow Variables

Exercise Condition

Variable	Total SOS	Reg MSq	MSq_{Res}	VR_{Reg}	VR_{Res}
$\ddot{V}_I$	$3.03*10^{7}$	$2.58*10^{7}$	$1.72*10^{5}$	17.10**	0.43
Tmax	$9.79*10^{-3}$	$1.56*10^{-3}$	$2.06*10^{-3}$	0.30	0.40
Tmin	$1.66*10^{-1}$	$6.70*10^{-2}$	$2.45*10^{-2}$	11.95**	4.37*
$\dot{v}_I max$	344.	247.	24.4	5.54*	0.55
$\dot{v}_E max$	1096.	714.	47.1	8.27*	0.55
$Tmax/T_I$	$2.17*10^{-2}$	$9.73*10^{-3}$	0.31	4.20	1.39
$Tmin/T_E$	$2.05*10^{-2}$	$4.24*10^{-3}$	$4.08*10^{-3}$	1.55	1.50
$\bar{\dot{v}}_I/\dot{v}_I max$	$3.46*10^{-3}$	$2.12*10^{-3}$	$1.69*10^{-4}$	1.21	0.09
$\bar{\dot{v}}_E/\dot{v}_E max$	$1.08*10^{-2}$	$1.26*10^{-3}$	$1.19*10^{-3}$	1.11	1.05

Hypercapnia Condition

$\ddot{V}_I$	$2.63*10^{7}$	$2.13*10^{7}$	$1.23*10^{6}$	20.34**	0.94
Tmax	$1.39*10^{-2}$	$7.09*10^{-3}$	$1.69*10^{-3}$	2.33	0.55
Tmin	$1.03*10^{-1}$	$2.70*10^{-2}$	$1.90*10^{-2}$	3.80	1.35
$\dot{v}_I max$	591.	474.	30.5	10.09**	0.63
$\dot{v}_E max$	1603.	1229.	46.8	19.45**	0.74
$Tmax/T_I$	$3.15*10^{-2}$	$3.14*10^{-2}$	$4.21*10^{-5}$	12.99**	0.02
$Tmin/T_E$	$1.72*10^{-2}$	$1.38*10^{-3}$	$3.94*10^{-3}$	0.42	1.21
$\bar{\dot{v}}_I/\dot{v}_I max$	$7.55*10^{-3}$	$6.64*10^{-4}$	$1.67*10^{-3}$	0.79	1.98
$\bar{\dot{v}}_E/\dot{v}_E max$	$1.26*10^{-2}$	$2.61*10^{-3}$	$2.49*10^{-3}$	4.15	3.98*

The Regression mean square (Reg MSq) and the residual mean square of the regression (MSq_{Res}) are tested against the residual mean square of the ANOVA (see p. 3.9 and Table 4.23). If the VR_{Reg} is significant, the regression of the difference between loaded and unloaded values on the level of ventilation exhibits significant linearity; if the VR_{Res} is significant, the regression exhibits significant alinearity. ** $P<0.01$; * $P<0.05$; 4 Subjects.

CHAPTER 5

DISCUSSION

The following chapter is divided into five sections. The first is a general discussion of results relating to gas exchange. The second section concerns results relating to the limitation of exercise by respiratory factors. The third section concerns ventilation and breathing pattern, and the fourth, end-expiratory volume. The final section discusses results relating to the shape of the flow profile.

1. Gas Exchange

This section is concerned with the general effects of loading and increasing exercise or hypercapnia level on oxygen uptake and carbon dioxide elimination. The particular situation at high respiratory and limb work rates, when it has been suggested that there may be respiratory limitation of exercise, is discussed in the following section.

Carbon Dioxide Elimination

Carbon Dioxide Elimination During Exercise

Carbon dioxide elimination ($\dot{V}CO_2$) showed two distinct relations to increasing work load, irrespective of whether breathing was loaded

or not. Over the low to moderate range of exercise intensity (up to 150 W) a linear relation was apparent. However as work rate rose further, a disproportionate rise in $\dot{V}CO_2$ was seen, the slope of the relation increasing with the elevation of work load (Figure 4.1).

The change in the form of the work rate - $\dot{V}CO_2$ relation may be attributed to an increase in the level of anaerobic metabolism. Buffering of the lactic acid produced by anaerobiosis is almost completely accomplished by the bicarbonate system (e.g. Wasserman et al., 1967). The consequent evolution of carbon dioxide from the body is accordingly measured as a rise in $\dot{V}CO_2$.

There was greater variability between subjects in the $\dot{V}CO_2$ response to increasing exercise than in the $\dot{V}O_2$ response. This was reflected in the size of the levels * subjects variance ratios given by the ANOVA (cf. Tables 4.3 and 4.6). This finding is in agreement with the report of Hill (1959), and is probably due mainly to differences between subjects in the level of the anaerobic threshold and the level of anaerobiosis at a given exercise intensity above the anaerobic threshold (Bang, 1936).

Loaded Breathing and Carbon Dioxide Elimination

Loading had no significant effect on $\dot{V}CO_2$ during exercise (Table 4.6), despite the fact that loading increased the level of metabolism, indicated by the slight but significant elevation of $\dot{V}O_2$ (Table 4.3). This finding was illustrated in Figure 4.1 (see also Table 4.5), which showed that generally loading produced only a slight elevation of $\dot{V}CO_2$. The failure of $\dot{V}CO_2$ to rise significantly with the addition of loading suggests that $\dot{V}CO_2$ was not in the steady-state when the measurements were made, 90 s after changes in loading condition. This finding is in agreement

with the report of Courtice et al. (1939) that $\dot{V}CO_2$ is not in the steady-state up to 15 minutes following a change in work level. At the highest exercise intensity the effect of loading was to reduce $\dot{V}CO_2$, this phenomenon did not reflect ventilatory limitation of the ability to effect adequate gas exchange (see pp. 5.13-5.16). However, the finding may indicate that breathing was profoundly constrained when inspiration was loaded at the highest exercise intensities, possibly voluntarily, the subject deciding that tolerating some rise in body CO_2 for the time that ventilation was loaded was preferable to the effort of increasing ventilation (Cain and Otis, 1949).

Oxygen Uptake

Oxygen Uptake During Exercise

As has previously been reported by Demedts and Anthonisen (1973), Dressendorfer et al. (1977) and El-Manshawi et al. (1986), oxygen uptake ($\dot{V}O_2$) rose in a nearly linear fashion with increments in work rate whether breathing was loaded or not (Figure 4.1).

One notable feature of the $\dot{V}O_2$ response to exercise was that elevation of work rate to the highest level was accompanied by a disproportionate rise in $\dot{V}O_2$; a similar phenomenon has been described by Beaver and Wasserman (1968). The disproportionate rise in $\dot{V}O_2$ at high exercise intensities may reflect a reduction in the efficiency of muscular contraction (Gaesser and Brooks, 1975) or the calorigenic effect of the high levels of circulating catecholamines that accompany high intensity exercise (Bertram et al., 1967; Galbo et al., 1975).

1) Validity of estimates of the oxygen cost of breathing.

The similarity of the estimates of the oxygen cost of breathing during unloaded hypercapnic hyperpnoea obtained in the present study (Table 4.7) to those of previous reports (see Agostoni et al., 1970 and Shephard, 1955 for reviews), suggests that the values are at least as accurate as those of previous studies. However as stated in Chapter 1 (p. 1.52), there is evidence that the oxygen cost of breathing during hypercapnic hyperpnoea may be overestimated when calculated from differences in whole body oxygen uptake. In the present study, the relatively high mean pooled oxygen uptake at low inspired CO_2 partial pressures (Figure 4.2) suggests that the oxygen cost of breathing may have been overestimated at low ventilations (Table 4.2: from the present data, the oxygen cost of breathing per litre ventilation at P_ICO_2 30 torr may be calculated to be 2.5 and 4.6 $ml.L^{-1}$, in the presence and absence of loading respectively). However, the estimated oxygen cost of breathing had fallen at the next inspired CO_2 level, 40 torr (1.7 and 4.3 $ml.L^{-1}$ in the presence and absence of loading respectively), suggesting that as ventilation was elevated the error due to the effect, if any, of hypercapnia on the general level of metabolism was reduced. Similar findings have been reported by Kaminski et al. (1982), who estimated the oxygen cost of breathing in man by the whole body method, at inspired CO_2 levels up to 42 torr. They found that the estimated oxygen cost of breathing per litre ventilation was greatest (25 $ml.L^{-1}$) at 14 torr, even though (or possibly because, see below) P_ACO_2 would be increased little and ventilation hardly stimulated,

but that calculated values fell as inspired CO_2 levels rose further.

The results discussed above suggest that estimates of the oxygen cost of breathing by the whole body oxygen uptake method become more accurate with the elevation of respiratory work, as the quantities measured get larger, a suggestion supported by the findings of Robertson et al. (1977_a). They reported that, in dogs, the discrepancy between the oxygen cost of breathing calculated from whole body oxygen uptake, and the directly measured $\dot{V}O_2$ of the respiratory muscles (the product of total respiratory muscle blood flow and arterio-venous O_2 difference) fell with the addition of inspiratory loads of increasing severity, i.e. as the elevation of respiratory muscle oxygen uptake accompanying loading was increased, the error of the estimated oxygen cost of breathing from whole body measures was reduced. The increase in accuracy as the oxygen uptake by the respiratory muscles increases is most probably due to the increase in oxygen uptake by tissues other than the respiratory muscles declining as a fraction of whole body oxygen uptake. In the present study, partitioning the oxygen cost of breathing data into 10 $L.min^{-1}$ ventilation bins and the exclusion from the analysis of data from levels of ventilation below 20 $L.min^{-1}$ (mean pooled ventilation of the 20-29.9 $L.min^{-1}$ bin was 27 $L.min^{-1}$) reduced the error that may arise from the overestimation of the oxygen cost of breathing at low ventilations.

A further point concerning the accuracy of estimates of the oxygen cost of breathing in the present study, is that one of the main aims of undertaking this investigation was to compare estimates of the oxygen cost of breathing in the absence and presence of loading at similar levels of ventilation. It might be

expected that the error due to the effect of hypercapnia on the general level of metabolism would be lower when comparing estimates of the oxygen cost of breathing at similar hypercapnically stimulated levels of ventilation than when estimating the absolute level of the oxygen cost of breathing.

In conclusion, although an element of doubt remains, the findings of the present and previous studies suggest that the whole body oxygen uptake method gives a good estimate of the oxygen cost of hypercapnic hyperpnoea over most of the ventilatory range, but most accurately estimates the oxygen cost at higher ventilations and the increase in the oxygen cost that accompanies loading. However, the validity of applying these values to estimate the oxygen cost of breathing during exercise may be questioned. Doubts concerning the validity of this application of the data are supported by reports that the oxygen cost of breathing, although of the same order, is greater during isocapnic voluntary ventilation than during hypercapnic hyperpnoea, i.e. the different origin of respiratory drive in the two cases is associated with differences in the oxygen cost of breathing (p. 5.32). However, Milic-Emili and Petit (1960) have reported that the relationship between the mechanical work of breathing and ventilation is similar when ventilation is elevated by exercise and when elevated by hypercapnia. Furthermore, in the present study, the close agreement between the increase in oxygen uptake with loading below the anaerobic threshold and the estimated increase in the oxygen cost of breathing (Table 4.4) suggests that the oxygen cost of breathing during exercise and hypercapnia is similar.

2) The oxygen cost of breathing per litre ventilation and the level of ventilation.

The relations between ventilation and the oxygen cost of breathing per litre ventilation in the presence and absence of loading were shown in Figure 4.3. They were well described by linear regressions, so the oxygen cost of breathing at a given ventilation could be calculated using the appropriate regression equations (p. 4.16).

The similarity of unloaded and loaded values at 10 $L.min^{-1}$ reflects the small change in the oxygen cost of breathing with the addition of loading at resting ventilations. However, the slope of the loaded relation was almost five times that of the unloaded relation. Therefore as ventilation was elevated, there was a progressive augmentation of the oxygen cost of breathing with loading compared that in the absence of loading

Probable reasons for the increase in the oxygen cost of breathing per litre ventilation with increasing ventilation, in both the presence and absence of loading, include the increased level of isometric work and distortion of the chest wall and abdomen. There may also be a reduction in the efficiency of muscular contraction with increasing ventilation, as a result of the deleterious effects of high velocity contractions on the ability to generate force (Agostoni and Fenn, 1960) and the fact that at high loads the efficiency of muscular contraction decreases with increasing load (Agostoni et al., 1970). This latter factor is of particular relevance to respiratory muscle function when there is an added external load (see overleaf). However, Collet et al. (1984) have suggested that the efficiency of breathing may be unaffected, or even raised, by increased velocity of shortening. They stated that the oxygen cost of

shortening is small in comparison with the oxygen required for the development and maintenance of tension and that these are reduced with more rapid shortening. They reported that efficiency at resting ventilations remained constant over a range of mean inspiratory flows during resistive breathing. Other workers have measured the effect of increasing ventilation on the efficiency of breathing and reported that the efficiency remained constant up to 100 $L.min^{-1}$ during unobstructed hyperpnoea (Bartlett et al., 1958; Tenney and Reese, 1968). Robertson et al. (1977_b) have measured oxygen uptake by the respiratory muscles in dogs during a ninefold increase in ventilation. They reported that respiratory muscle oxygen uptake increased in a nearly linear manner as the work of breathing increased, i.e. efficiency did not change significantly.

The question of whether the efficiency of breathing changes with increasing ventilation is unresolved and is complicated by the fact that calculated values of efficiency vary widely both between studies (see review by Agostoni et al., 1970) and within studies (Field et al., 1984). Some of the variation between studies may be ascribed to differences in technique, but significant differences also arise because the calculation of respiratory work does not include a time function, because force may be generated without doing measurable work and because the integration of respiratory muscle activity is complex.

3) The oxygen cost of breathing per litre ventilation and loading. The finding that, at rest, the oxygen cost of breathing in the presence of inspiratory flow-resistive loading was close to that in the absence of loading (Figure 4.3), is in agreement with the report of Robertson et al. (1977_a) in dogs. Other workers have also examined the effect of inspiratory flow-resistive loading on

estimates of the oxygen cost of breathing at resting ventilations (Collet et al., 1985; Field et al., 1984), but not at elevated ventilations. Eldridge (1966) reported the effect of a constant inspiratory load of 210 mmH_2O (cf. Figure 2.2) on the oxygen cost of breathing at approximately 25 $L.min^{-1}$ ventilation; the oxygen cost of breathing rose from 1.2 $ml.L^{-1}$ to 4.3 $ml.L^{-1}$. Although the effects of the constant load employed by Eldridge and the flow-dependent loads employed in the present study cannot be directly compared, the increase in the oxygen cost of breathing seen by Eldridge is similar to that at seen at moderate to higher levels of ventilation in the present study (Figure 4.3). The increase in the cost of breathing with loading measured by Eldridge would be expected to be larger than that at 25 $L.min^{-1}$ in the present study because the load was larger: The constant load employed by Eldridge is around twice the peak load at a ventilation of 25 $L.min^{-1}$ in the present study (Figure 4.23 shows that at a ventilation of 25 $L.min^{-1}$, the peak inspiratory flow was approximately 75 $L.min^{-1}$, and Figure 2.2 shows that the pressure required to generate a flow of 75 $L.min^{-1}$ through R4 was approximately 100 mmH_2O).

The elevation of the oxygen cost of breathing with the addition of loading is probably the result of an increase in a number of factors including pressure generation, time of contraction, isometric work and distortion of the chest wall and abdomen (Agostoni and Mognoni, 1966; Macklem et al., 1978).

The efficiency of breathing may have fallen with loading; Robertson et al. (1977_a) reported that the efficiency of breathing ($\dot{V}O_2$ measured using their direct method) decreased from 13% at low added resistances to 4% at high resistance. Conversely, Collet et al. (1985) have reported that the efficiency of breathing at rest

(2%) was unaffected by loading. The difference in the reported results of the two studies might in part reflect differences in the complex integration, recruitment and mechanical function of the respiratory muscles which lead to wide variations in the calculated efficiency of respiratory work. Field et al. (1984) reported that the efficiency of breathing during resistive breathing at rest varied from 0.8% - 7.8%. However, the observation that the reported efficiency of the respiratory muscles is considerably below that reported for the limb muscles (Lloyd and Zacks, 1972), which the respiratory muscles physiologically resemble, suggests that a considerable fraction of respiratory work is not given by measures of mechanical work. Dissimilarities in measured work within and between studies may therefore account for a significant proportion of the differences in calculated efficiency, making it difficult to draw conclusions about the effect of loading on the efficiency of the respiratory muscles.

Exercise, Loading and the Oxygen Cost of Breathing

The addition of inspiratory loading significantly increased $\dot{V}O_2$ at a given exercise intensity, the effect was small but consistent (Figure 4.1). This finding is in accordance with the report of El-Manshawi et al. (1986).

The rise in $\dot{V}O_2$ with the addition of loading was most probably attributable to an increase in the oxygen cost of breathing. This suggestion is supported by the finding that at exercise levels below the anaerobic threshold, i.e. levels up to 100 W, the rise in mean pooled $\dot{V}O_2$ accompanying the addition of loading was close to the increase in the estimated oxygen cost of breathing with the addition of loading (Table 4.4).

However, at higher exercise levels the rise in the estimated oxygen cost of breathing with loading was markedly greater than the observed increase in $\dot{V}O_2$ during exercise (see next section).

2. The Respiratory Limitation of Exercise

This section presents the data concerning the response to loading at higher exercise intensities.

The previous section discussed the finding that at low to moderate work loads, the rise in $\dot{V}O_2$ accompanying loading during exercise was similar to the rise in the estimated oxygen cost of breathing. However, at exercise levels above the anaerobic threshold, the rise in $\dot{V}O_2$ with the addition of loading was smaller than the estimated rise in the oxygen cost of breathing.

For the 10 subjects who exercised to 250 W (these data are different from those of the 8 subjects included the main analysis, which are presented in Table 4.4, but may be compared with them), the estimated increase in the oxygen cost of breathing with the addition of loading at 150 W was 82 $ml.min^{-1}$, but the observed rise in $\dot{V}O_2$ was only 34 $ml.min^{-1}$, while at 200 W the figures were 143 $ml.min^{-1}$ and 117 $ml.min^{-1}$ respectively. However, the disparity the increase in $\dot{V}O_2$ and the increase in the oxygen cost of breathing with the addition of loading was greatest at 250 W when the estimated rise in the oxygen cost of breathing accompanying loading was 252 $ml.min^{-1}$ but the observed rise in $\dot{V}O_2$ during exercise only 7 $ml.min^{-1}$.

The apparent contradiction between the estimated increase in the oxygen cost of breathing with loading and the observed rise in oxygen uptake may indicate that the demand for oxygen by the active limb and respiratory muscles exceeded the possible level of supply.

Bye et al. (1983) hypothesised that a situation might arise when respiratory and limb work were both high, in which the supply

of oxygen by the oxygen transport system was insufficient to meet the demand, leading to the limitation of work capacity, and fatigue of either or both muscle groups. Three possible mechanisms of respiratory limitation of the ability to supply adequate levels of oxygen to the active limb muscles were described in the introduction to this thesis:

1) The mechanical limitation of ventilation;

2) The high oxygen cost of breathing;

3) The fatigue of the respiratory muscles.

The main aim of undertaking the work reported in this thesis was to investigate whether there was any evidence to support the hypothesis that respiratory factors limit exercise, when the work of breathing during exercise was increased by the addition of an inspiratory flow-resistive load. The results of this investigation, as they pertain to the three hypothetical sources of limitation reported by Bye et al. (1983), are discussed below.

The Limitation of Exercise Capacity by the Mechanical Constraint of Ventilation

The limitation of $\dot{V}O_2$ and consequently exercise capacity by inadequate ventilatory performance has been reported in patients with COPD, and has been suggested to occur in athletes and in

normal subjects in whom the work of breathing has been artificially raised (pp. 1.8-1.14.).

Dressendorfer et al. (1977) have reported similar results to the present study, when breathing was loaded during incremental work tests of 1 minute steps. They found that $\dot{V}O_2$ was little affected by loading at sub-maximal exercise levels, but that loading at the highest exercise level was accompanied by a significant reduction of $\dot{V}O_2$. They attributed the reduction in oxygen uptake at the highest exercise level to ventilatory limitation and showed that $\dot{V}O_2$ was significantly increased when breathing 35% O_2 which reduced the ventilatory response to exercise.

In the present study, there was no evidence that oxygen uptake was impaired, or that pulmonary ventilation was being limited, by loading at high exercise levels. Two subjects (632 and 644) did show a tendency towards ventilatory plateauing at 250 W, ventilation failing to rise to the expected extent. However, this was not evident generally and most likely represented profound ventilatory constraint. Further, ventilation is dependent on the ability to generate flow, and the absence of changes in flow variables signifying flow limitation at peak levels of ventilation supports the assertion that there was no limitation of ventilation (see flow section, pp. 5.55-5.67). However, the most convincing evidence that ventilation did not limit oxygen uptake is the finding that the lowest $P_{ET}O_2$ recorded from any of the 11 subjects studied was 95 torr (Subject 643): in no subject did $P_{ET}O_2$ fall below 90 torr, i.e. sufficient to reduce arterial oxygen saturation significantly. Unfortunately Dressendorfer et al. (1977) did not report $P_{ET}O_2$ values, so their

conclusion that they observed ventilatory limitation of oxygen uptake is open to question.

Although there was no evidence of ventilatory limitation, the profound ventilatory constraint associated with the addition of loading at high exercise levels suggests that the limits of ability of the respiratory system to generate ventilation were being approached. Further, although there were no changes in flow variables that might signify the existence of flow limitation, there were changes in some flow variables at high ventilations that might indicate that limiting values were being approached. One such change, shown by Subject 632, was an obvious reduction in the slope of the ventilation - peak expiratory flow relation at high ventilations. Other marked changes, shown by Subjects 634, 639 and 643 during expiration at high ventilatory levels, were disproportionate rises in the ventilation - peak expiratory flow relation. Subjects 634 and 639 also showed large increases in inspiratory flow acceleration coupled with disproportionate increases in peak inspiratory flow at high levels of ventilation.

The observed changes in the ventilation - flow relations may serve to minimise work and/or discomfort when the work of breathing is high and tidal volume is limited (pp. 5.55-5.67).

The shift to a relatively high frequency breathing pattern with the addition of loading at the highest exercise levels (Figure 4.11) may be a further indication that the mechanical limits of the system were being approached, for a shift to a high frequency pattern has previously been reported, in the absence of loading, when approaching the boundary of the maximal effort flow-volume loop (Jensen et al., 1980).

In conclusion, it appears that loading was not associated with the ventilatory limitation of oxygen uptake at high exercise

intensities. However, considerable constraint of ventilation occurred and ventilation at the highest exercise levels may have been approaching the limits of the respiratory pump. This suggestion is consistent with the observed changes in flow variables and the shift in breathing pattern to a relatively high frequency pattern.

The Limitation of Exercise Capacity by the High Oxygen Cost of Breathing

The Oxygen Gain of Breathing

If the oxygen consumption of the respiratory muscles rose to very high levels during loaded exercise, the total demand for oxygen by the active respiratory and limb muscles might exceed supply by the oxygen transport system, with the consequence that performance would be impaired. This hypothesis was examined in the present study by estimating the increase in the oxygen cost of breathing when ventilation was raised hypercapnically, and applying the results to assess the oxygen cost of breathing during exercise.

The results of the present study indicate that the oxygen cost of breathing per unit ventilation increased as ventilation rose (Figure 4.3). Consequently, the more ventilation was elevated, the greater was the reduction of the oxygen gain (the ratio of the increase in oxygen uptake to the increase in the oxygen cost of breathing). The rise in the oxygen cost of breathing occurred irrespective of whether breathing was loaded or not, but the rate of rise was greater when breathing was loaded,

therefore the oxygen gain was reduced to a greater extent at a given ventilation when breathing was loaded.

It would follow that, during exercise, a critical level of ventilation exists above which the increase in oxygen uptake accompanying any further increase ventilation would be entirely consumed by the increased oxygen cost of effecting the ventilation. If this level of ventilation, and thereby level of oxygen uptake by the respiratory muscles, were to be exceeded, it would reduce the supply of oxygen to the active limbs. The critical ventilation during exercise has been estimated to occur in the range of 120 - 150 $L.min^{-1}$ (Otis 1954, 1964; Margaria, 1960; Shephard, 1966), and the oxygen cost of breathing per litre ventilation at these levels of ventilation has been calculated by Shephard (1966) to be approximately 5 $ml.L^{-1}$.

The level of the critical ventilation is considerably higher than the levels of ventilation seen in the present study. However, the increase in oxygen cost of breathing with the addition of loading during exercise would serve to reduce the level of the critical point. The oxygen cost of breathing per litre ventilation at the level of ventilation at 200 W when breathing was loaded (approximately 55 $L.min^{-1}$), was estimated to be 4.7 $ml.L^{-1}$. This was close to the critical value of 5 $ml.L^{-1}$ determined by Shephard (1966), while the estimated oxygen cost of breathing per litre ventilation at the level of ventilation at 250 W (approximately 75 $L.min^{-1}$) was 5.9 $ml.L^{-1}$, which exceeds Shephard's value.

It appears therefore, that the oxygen cost of breathing in the presence of loading at the highest work level was higher than that which Shephard (1966) has suggested determines the useful ceiling of ventilation during exercise. If this was indeed the

case, the maintenance of ventilation may have been associated with a reduction in the oxygen available for limb work, and may thereby have impaired work capacity.

The Oxygen Cost of Breathing as a Fraction of Total $\dot{V}O_2$

In the present study, the oxygen cost of breathing during exercise in the absence of loading was estimated to be approximately 5% of total oxygen uptake at both 200 W and 250 W (p. 4.9). However, when breathing was loaded this value rose to 7.8% at 200 W and to 11.7% at 250 W (p. 4.11).

The oxygen cost of breathing clearly constituted a large fraction of total oxygen consumption during exercise in the presence of loading compared with when breathing was unloaded, suggesting that the supply of oxygen to the active limb and work capacity may have been reduced compared with in the absence of loading.

The Limitation of Exercise Capacity by Respiratory Muscle Fatigue

If the supply of oxygen by the available cardiac output were insufficient to meet the competing demands of respiratory and limb work when both were high, it would lead to augmented anaerobiosis in either or both muscle groups, producing fatigue and further decrements in ventilatory and thence external work performance. This hypothesis was investigated directly in the present study, by measuring plasma lactate concentrations during exercise, in the presence and absence of loading.

The Effect of Loading on Anaerobiosis at Exercise Intensities Below the Anaerobic Threshold

The addition of loading during exercise had no effect on the level of the anaerobic threshold. Also, at exercise levels below the anaerobic threshold, loading did not have any effect on plasma lactate levels (Figures 4.4 and 4.5).

Augmented anaerobiosis in response to loading would not be expected at low to moderate exercise intensities, when the summed demand for oxygen by the limb and respiratory muscles is less than the possible level of supply.

The Effect of Loading on Anaerobiosis at Exercise Intensities Above the Anaerobic Threshold

There was a distinct response to the addition of loading above the anaerobic threshold, though its form varied between subjects and with the level of exercise. Loading at the first exercise level above the anaerobic threshold elevated plasma lactate concentrations above unloaded levels in all subjects (Figures 4.4 and 4.5).

However, there was a divergence between subjects in the effect of loading at the peak exercise level attained. In three subjects (597, 639 and 642) loading was associated with the elevation of plasma lactate concentration, suggesting the presence of augmented anaerobiosis. In the remaining subjects, loading was associated with a slight fall in plasma lactate concentration.

Although it would be hard to dispute that the rise in plasma lactate concentrations in the three subjects was associated with the increased work of breathing, the site of the augmented anaerobiosis is unclear. The respiratory muscles may seem to be the obvious candidate, but there are several reports indicating

that the diaphragm is particularly resistant to the promotion of anaerobiosis (see p. 5.30). Also, while Aubier et al. (1982) reported greater glycogen depletion and higher muscle lactate concentrations in the respiratory muscles of dogs breathing spontaneously than in those being artificially ventilated, presumably attributable to the work of breathing, they also reported greater glycogen depletion of the inactive quadriceps muscle in spontaneously breathing dogs. The latter finding suggests that augmented anaerobiosis took place in the skeletal muscles as well as in the respiratory muscles.

It may be that the increase in plasma lactate concentrations with loading in the present study is primarily attributable to augmented anaerobiosis in the limb muscles. The suggestion that respiratory muscle oxygen uptake is not, or is little, impaired during loading, but that it may become large enough to diminish oxygen uptake by the limb muscles, thereby leading to augmented lactate production, is supported by evidence from studies of respiratory muscle blood flow during loading and exercise. Fixler et al. (1976) showed that in exercising dogs by far the largest percentage increase in blood flow during exercise was to the diaphragm (it being approximately double that to the active limb muscles). Further, Robertson et al. (1977_a) reported that diaphragmatic blood flow rose 26-fold in response to a 15-fold increase in respiratory work rate accompanying the addition of a severe inspiratory flow-resistance, and showed no tendency to plateau.

These findings suggest that respiratory muscle blood flow and therefore respiratory muscle oxygen supply may occur at the expense of limb blood flow and limb muscle oxygen uptake at high respiratory and limb work rates.

Although the augmented anaerobiosis in three subjects was associated with the addition of loading at the highest exercise level, the possibility exists that the augmented anaerobiosis was not directly related to the level of respiratory or limb work, but reflected changes in posture, or the activity of muscles not directly concerned with cycling or breathing such as the arms. Bang (1936) has shown that an exercising subject may produce a rise in plasma lactate at will, by changing his position or modifying his tread on the cycle pedal. However in the present study, the consistent nature of rise in plasma lactate concentration amongst the three subjects suggests that this phenomenon did not contribute significantly to the observed response.

The division of the subjects into two groups, on the basis of the difference in the change of plasma lactate concentrations accompanying loading, appeared to be unrelated to the subjects' hypercapnic sensitivity (parameter S of Table 4.11) or to the change in hypercapnic sensitivity with loading. However, the difference in the effect of loading on plasma lactate concentration was mirrored by differences in the change of oxygen uptake. In the three subjects in whom lactate levels were elevated, oxygen uptake was not markedly changed by loading; the mean response was a slight but insignificant fall. Conversely, in the two subjects in whom lactate levels were reduced, $\dot{V}O_2$ was markedly increased by loading.

The increase of $\dot{V}O_2$ with the addition of loading in two subjects but not in the others may indicate that they were more athletic, with a higher $\dot{V}O_2max$, and could therefore supply a greater proportion of the energetic demand aerobically. The higher anaerobic thresholds (estimated from the point of

alinearity of the plasma lactate measurements or the $\dot{V}$ - $\dot{V}O_2$ relation) for Subjects 643 and 648 than for Subjects 597, 639 and 642 support this suggestion (Figures 4.4 and 4.5, Table 4.1).

Anaerobiosis and the Oxygen Cost of Breathing

The previous section illustrated the fact that the subjects could be divided into two groups on the basis of the change in plasma lactate and in oxygen uptake in response to loading at peak exercise intensities. These two groups were further distinguished by the change in the estimated oxygen cost of breathing at peak work level with the addition of loading (see Table 4.9).

In the first group of subjects, in whom loading was associated with a rise in plasma lactate concentrations, loading produced a mean increase of over 300 $ml.min^{-1}$ in the estimated oxygen cost of breathing at the peak exercise level (Table 4.9). These values were estimated from the individual subjects' $\dot{V}$-oxygen cost of breathing per litre ventilation relations shown in Table 4.8. This marked increase was partly attributable to the fact that ventilation was only slightly reduced by loading, but was also a function of the relatively large increase in the oxygen cost of breathing per litre ventilation accompanying loading in these subjects (Table 4.8 and Appendix A1).

In the second group of subjects, in whom loading was accompanied by a slight reduction in plasma lactate concentration, loading produced a marked fall in ventilation, but only a slight rise in the oxygen cost of breathing per litre ventilation. Consequently, the oxygen cost of breathing was not elevated to such a degree with loading as in the first group; the mean increase accompanying loading was 33 $ml.min^{-1}$.

This difference between the two groups in the change in the oxygen cost of breathing with loading may in part explain the observed difference in the change in plasma lactate concentration with loading. If loading is associated with a large increase in the oxygen cost of breathing, as for the first group, there will be a greater demand on the oxygen supply and increased likelihood that anaerobiosis will be augmented. However, if loading is associated with only a very small rise in the oxygen cost of breathing, the increased demand for energy may be met aerobically.

In order to compare the total energy consumption of the two groups in the presence and absence of loading, the oxygen equivalents of the observed differences in plasma lactate levels were calculated. One may estimate the oxygen equivalent represented by a given plasma lactate concentration and therefore the oxygen uptake that would have been required to furnish the same energy yield aerobically.

First, the data of the three subjects who showed elevation of plasma lactate in response to loading was considered. If one assumes the lactate to be distributed in a body fluid volume of 40 L. (Åstrand and Rodahl, 1977, p. 132), the augmented production of lactate in the presence of loading at the highest exercise level (18.4 $mg.100ml^{-1}$) may be estimated to be 82 millimoles (the molecular weight of lactic acid being 90); it must be acknowledged that this is only a coarse estimate, as lactate will not be evenly distributed after the short time at each work load (Eggleton and Evans, 1930).

The formation of lactate by the donation of hydrogen ions to pyruvate in the lactate dehydrogenase reaction produces a net energy yield of 1.5 moles of adenosine triphosphate (ATP) per mole of lactate (Stryer, 1981). The current estimate of the ATP yield

per molecule of oxygen used in aerobic metabolism with a mixed substrate is 6 (Harper et al., 1977). Therefore, the consumption of 1 mole of oxygen is equivalent to the generation of 4 moles of lactate. Thus, the augmented production of lactate in the presence of loading was equivalent to the consumption of 20.5 millimoles of O_2. As 1 mole of a gas occupies 22.4 L. at STP, 20.5 millimoles may be calculated to occupy 460 ml.

Further assumptions allow one to estimate the rate of energy yield from the production of lactate. Assuming that above the anaerobic threshold lactate output rose in a stepwise fashion in response to increasing (respiratory) work (Chirtel et al., 1984), and that the measured increase in lactate accompanying loading represented the integral of lactate production over the two minutes of work, one may divide the integral by the time of production to produce the rate of lactate production. The equivalent rate of oxygen uptake of the augmented lactate production may therefore be estimated as (460/2 =) 230 $ml.min^{-1}$. This value, representing the oxygen equivalent of the augmented rate of lactate formation in the presence of loading at the peak exercise level at which $\dot{V}O_2$ was unaffected by loading, is close to the mean increase in the oxygen cost of breathing of 300 $ml.min^{-1}$ accompanying loading in this group of subjects (Table 4.9).

The closeness of the mean increase in the oxygen cost of breathing with loading and the oxygen equivalent of the rise in plasma lactate concentrations in the first group of subjects suggests that anaerobiosis was augmented in order to make up the shortfall in the supply of energy by aerobic metabolism and that it furnished at least some of the extra energy required to maintain respiratory and/or limb work.

For the other group of subjects, the oxygen consumption equivalent of the 7.7 $mg.100ml^{-1}$ fall in mean plasma lactate level that accompanied loading was similarly calculated, yielding a value of 96 $ml.min^{-1}$. Subtracting this figure from the difference in $\dot{V}O_2$ between loaded and unloaded conditions at the peak work level (550 $ml.min^{-1}$), gave a net increase with loading of 446 $ml.min^{-1}$. This may be compared with the mean increase in the estimated oxygen cost of breathing of 33 $ml.min^{-1}$. This finding suggests that these subjects were able to meet the small increased oxygen demand accompanying loading by increasing oxygen uptake. The reasons for the disparity between the observed increase in $\dot{V}O_2$ and the estimated increase in the oxygen cost of breathing are unclear.

The Validity of Conclusions Concerning the Level of Anaerobiosis and the Oxygen Cost of Breathing

The findings discussed above suggest that, in some subjects, anaerobiosis may be augmented when respiratory and limb work rates are both high. However, it may be argued that the findings point to other conclusions. First, in view of the finding that $\dot{V}O_2$ at peak exercise intensities was lower in the presence of loading for the three subjects who showed elevated lactate levels, it may be argued that augmented anaerobiosis with loading did not increase the total level of energy consumption above that in the absence of loading, but merely served to make the energy consumption with and without loading the same. Augmented anaerobiosis would not therefore represent an additional source of energy to meet the increased work of breathing with loading. However, the observation that plasma lactate levels were augmented in proportion to the estimated increase in the oxygen cost of

breathing with loading, not the reduction in $\dot{V}O_2$ (Table 4.9), indicates that the augmented anaerobiosis was related to the increased work of breathing with loading, not the total level of oxygen uptake. It therefore seems likely that, in these three subjects, augmented anaerobiosis was important in meeting the extra energy demand when breathing was loaded.

Secondly, although the findings discussed above suggest that augmented anaerobiosis with loading may explain some of the difference between the estimated level of energy consumption and the estimated level of energy demand, adjusting the measured total oxygen uptake values to take account of the oxygen equivalent of the difference in plasma lactate concentrations did not fully account for the increase in the estimated oxygen cost of breathing with loading. However, some of the remaining difference is likely to be attributable to the underestimation of the difference between loaded and unloaded plasma lactate concentrations, and therefore underestimation of the level anaerobic metabolism, as the lactate concentration of blood sampled from the ante cubital vein will be below that in exercising muscles (Bang, 1936).

Thirdly, the conclusions drawn above arose from assumptions that the only significant anaerobic energy source was augmented anaerobiosis, the extent of which could be assessed from the rise increase in plasma lactate concentration. Nevertheless, Margaria (1933) identified the depletion of high energy phosphagens as an alactic energy source, and these have been reported to have a total oxygen equivalent of approximately 1 L. (Karlson and Saltin, 1970). However, it has been reported that this source is fully depleted after 2 - 3 minutes of exercise if $\dot{V}O_2$ is more than 2500 $ml.min^{-1}$ (Karlson and Saltin, 1970). This level of oxygen consumption corresponds to a work rate of between 150 W and 200 W

in the present study. Consequently, this source of energy would be fully depleted before maximal work loads were attained and so would not affect the calculations discussed above.

Fourthly, a further consideration is the possibility that energy was generated from an increase in lactate turnover, without an increase in plasma levels. Depocas et al. (1969) reported that lactate production and removal could both rise during exercise, while plasma concentrations fell. However, the major path for the removal of lactate is by conversion into pyruvate that is metabolised in the citric acid cycle. This process requires oxygen and so would increase $\dot{V}O_2$. Further, although gluconeogenesis in the liver is a major pathway for the removal of lactate (and so to a lesser extent is gluconeogenesis in the kidney), the production of lactate by glycolysis and removal by gluconeogenesis results in a net loss of 4 moles of ATP per mole of glucose (Naimark et al., 1965) so the process would result in a reduction in energy available for the performance of work. The most likely conclusion therefore is that these mechanisms did not significantly contribute to the supply of energy in the present study.

In conclusion, it may be stated that the augmented lactate production at peak exercise levels is in accordance with the supply of oxygen to the active muscle groups by the oxygen transport system being inadequate. Therefore, the results of plasma lactate analysis support the suggestion that, in some subjects, the oxygen cost of breathing during exercise in the presence loading of was so great at peak exercise levels that the demand for oxygen exceeded supply. These findings may be contrasted with the finding that lactate did not rise with the addition of loading at similar ventilations during hypercapnic

hyperpnoea, when there was no competing work by the limb muscles (see p. 5.30).

Anaerobiosis and Performance

The finding of augmented anaerobiosis with loading at the highest exercise intensities suggests that fatigue of the respiratory and/or limb muscles may have been imminent.

There are a number of studies in which fatigue of the respiratory muscles appears to occur during exercise. Loke et al. (1982), Mahler and Loke (1981) and Shephard (1967) have all reported that ventilatory performance was reduced following general exercise. Martin et al. (1982_b) reported that ventilatory work preceding running reduced performance. The reported decrements in post-exercise ventilatory performance may represent ventilatory muscle fatigue. However, caution is required when drawing conclusions from these reports as the fall in performance may have merely reflected reduced effort as a consequence of diminished motivation. Loke et al. (1982) reported that expiratory as well as inspiratory muscle pressure was reduced by marathon running, yet the probable level of expiratory muscle activity entailed would be unlikely to predispose expiratory muscles to fatigue (Agostoni and Mead, 1964).

The fact that augmented anaerobiosis occurred in conjunction with a change in breathing pattern to a relatively high frequency form (p. 5.41-5.42) may be evidence that the respiratory muscles were indeed failing, for similar pattern changes have been reported at the onset of diaphragmatic fatigue from the imposition of very severe inspiratory resistances at resting ventilations (Gallagher et al., 1985), and when respiratory muscle performance is inadequate in patients with chronic obstructive pulmonary

disease in whom internal flow-resistance is pathologically increased (Roussos, 1984). Further, Newsom Davis et al. (1976) reported that the reduction of diaphragmatic force production is associated with rapid shallow breathing and alveolar hypoventilation.

The shift in pattern assumes greater significance when the findings of Buchler et al. (1985) are considered. They reported that increased breathing frequency may lead to limitation of diaphragmatic blood flow, thereby exacerbating the onset of fatigue, particularly if T_I is a large fraction of the total breath duration (T_T), as during inspiratory loading. However, there is evidence that the increase in frequency may represent an attempt to delay the onset or minimise the effect of fatigue. Jones et al. (1985) reported that if the spontaneous fall in T_I seen when breathing at high ventilations against high resistive loads was artificially constrained, endurance time was shorter than when the decrease of T_I was unconstrained. Further, Bellemare and Grassino ($1982_{a,b}$) demonstrated that endurance time was reduced, i.e. the onset of fatigue occurred earlier, when the ratio of T_I to T_T was increased.

The shift in the pattern of breathing with loading at high respiratory and/or limb work rates and the increase in the level of anaerobiosis seen in some subjects may be linked, by cortical mechanisms, to the sensation of breathlessness. Pardy and Bye (1985) have reported that hyperoxia reduces perceived diaphragmatic exertion and it may be that local factors such as the level of lactate are contributing to the sensation. Metabolic by-products may act by stimulating group III fibres which are abundant in the diaphragm (Jammes et al., 1984); electrical stimulation of these fibres has been shown to affect respiratory

pattern (Buchler et al., 1984). As the sensation of breathlessness has been shown to be correlated with the ratio of T_I to T_T (El-Manshawi et al., 1986; Jones et al., 1985; Killian et al., 1985), it might be expected that increasing breathlessness would lead to an increase in breathing frequency.

Anaerobiosis During Hyperpnoea

It was concluded above that the increase in anaerobiosis with loading during exercise was probably a consequence of the inability of the oxygen transport system to meet the competing demands of respiratory and limb muscles for oxygen and other substrates.

The response to loading during exercise may be compared with that when ventilation was raised hypercapnically, permitting the analysis of the effect of solely increasing respiratory work on the level of anaerobiosis, without the competing demands of active limb muscles as during exercise.

During hypercapnia and therefore in the absence of limb work, loading was unaccompanied by augmented plasma lactate concentrations (Figure 4.6), in contrast to the effect of loading during exercise. This is in accordance with previous reports that respiratory work has to be raised to very high levels, or respiratory muscle performance impaired, before lactate production is augmented. Eldridge (1966) found plasma lactate levels were unaffected by a seven-fold increase in respiratory work unless hypoxia was present; Robertson et al. (1977_a) reported the diaphragmatic veno-arterial lactate gradient to be unchanged despite a sixteen-fold increase in respiratory work and the fact that arterial hypoxaemia was present; Hollanders (1968) reported

that only tetanic stimulation of an isolated diaphragm elevated lactate production; lesser intensities had no effect.

Several groups have reported that increasing the level of respiratory work may elevate plasma lactate concentrations, but respiratory work levels had to rise to near maximal before plasma lactate levels were elevated. Martin et al. (1984) and Freedman et al. (1983) both reported that when ventilation was elevated voluntarily it had to rise to 70% of maximal breathing capacity (MBC) before lactate levels were significantly increased, even though isocapnia was maintained; Similarly, Jardim et al. (1981) found increased lactate production during resistive breathing required the generation of mouth pressures that were 80% of maximal.

The conclusion from the studies cited above, that respiratory work must reach high levels in order to promote anaerobiosis, is in accordance with that from studies that have examined the time for which various percentages of MBC could be maintained. The failure to sustain ventilation was taken to indicate the fatigue of the respiratory muscles. Bai et al. (1984), Leith and Bradley (1976) and Tenney and Reese (1968) have reported that maximal sustainable ventilations were 60-80% of MBC. Above this level the time for which ventilation could be sustained fell as the percentage of MBC rose. In a related study, Roussos et al. (1979) demonstrated that airway pressures greater than 60% of maximum could not be sustained indefinitely.

The finding that loading did not lead to augmented anaerobiosis in hypercapnic hyperpnoea, but did so during exercise, lends support to the hypothesis that anaerobiosis is augmented when the demand for oxygen is unable to be met by the available cardiac output when respiratory and limb work are both

high. This suggestion is supported by a number of studies that have shown that lactic acidosis is associated with poor tissue perfusion (Cohen and Iles, 1977; Cohen and Simpson, 1975; Oliva, 1970), and the reported augmentation of plasma lactate concentrations when cardiac output is reduced (Peretz et al., 1964). Further, Aubier et al. (1981, 1982) have shown that the level of respiratory work influences survival chances and muscle lactate concentration of dogs in which cardiac output has been reduced by tamponade (see p. 5.19).

The observation that anaerobiosis was not augmented during hypercapnic hyperpnoea may be contrasted with reports that plasma lactate concentrations are elevated during isocapnic voluntary hyperventilation (Freedman et al., 1983; Martin et al., 1984). This difference may merely indicate that respiratory work rate during hypercapnic hyperpnoea was lower than during isocapnic voluntary ventilation, even when breathing was loaded. However, the difference may also be attributable to a difference in the efficiency of driven breathing and voluntary hyperpnoea. Previous groups have reported that the efficiency of hypercapnically driven breathing is approximately 20% (Milic-Emili and Petit, 1960) while that of normocapnic voluntary hyperventilation has been estimated to be only 1 - 8% (Fritts et al., 1959). If the hypercapnically driven elevation of ventilation in the present study was more efficient than the voluntary increases achieved in the studies of previous groups, it may explain why lactates were not elevated with loading, despite the fact that work rates were probably comparable.

3. Ventilation and Breathing Pattern

This section discusses the changes in ventilation and breathing pattern that occur with increased exercise or hypercapnia in the presence or absence of loading.

Ventilation

Ventilation at Rest

Resting ventilations were generally higher than those commonly quoted in the literature, probably because all measurements were made with subjects sitting on an exercise bicycle. While this excluded postural factors from consideration when interpreting any measured difference between exercise and hypercapnic data, the fact that the subjects were not completely relaxed produced a slight degree of hyperventilation. In two subjects (640 and 648) the level of hyperventilation was sufficient to reduce $P_{ET}CO_2$ below 36 torr, which is the bottom limit of the normal range of $P_{ET}CO_2$ at rest.

Ventilation During Exercise

The onset of sustained anaerobiosis was associated with a disproportionate rise in ventilation. Ventilation was elevated above that adequate for gas exchange by the increase in hydrogen ion concentration accompanying lactacidosis through a reflex mediated by the carotid bodies (Asmussen, 1964).

However, the increase in ventilation was not associated with a fall in $P_{ET}CO_2$ at the anaerobic threshold. In the absence of loading this occurred at the next work load, a finding also reported by Wasserman et al. (1976). In the presence of loading, although $P_{ET}CO_2$ did not rise to such an extent at the next work load above the anaerobic threshold, $P_{ET}CO_2$ did not fall till the peak exercise intensity (250 W).

The point at which $P_{ET}CO_2$ falls has been called the "the threshold of decompensated metabolic acidosis" (Rebuck, 1972) and represents a further relative increase in ventilation at higher exercise levels.

Loading, Ventilation and End-Tidal Carbon Dioxide

The effects of loading when ventilation is elevated by hypercapnia and by exercise have not previously been compared. It was therefore of some interest that, although loading significantly reduced ventilation during exercise and hypercapnia, the effect during hypercapnia was significantly different from that during exercise. Analysis of the difference of the effect of loading during exercise and hypercapnia indicated significantly greater depression of ventilation during hypercapnia (Table 4.24).This may be illustrated by comparing the 13% reduction in ventilation accompanying loading at 250 W, with the 25% reduction at 60 torr P_ICO_2, when unloaded ventilations were similar.

Although ventilation was depressed to a significantly greater extent by loading during hypercapnia, the rise in $P_{ET}CO_2$ with loading during exercise was significantly greater than that during hypercapnia (Table 4.24). The difference is probably attributable to the fact that the relevant part of the metabolic hyperbola is steeper during hypercapnia (see Figure 2 of Cunningham et al.,

1986); a given change in ventilation with the addition of loading during hypercapnia is therefore associated with a smaller change in $P_{ET}CO_2$ than the same change in ventilation during exercise.

Respiratory work rate has been reported to rise as a function of P_ACO_2 (Eldridge and Davis, 1959; Milic-Emili and Tyler, 1963). It may be that the significantly greater rise in $P_{ET}CO_2$ accompanying loading during exercise than that during hypercapnia (Table 4.24) was responsible for some of the observed differences in the effect of loading in the two conditions (p. 5.39, p. 5.45).

Time-Course of the Response to Loading

The breath-by-breath measurement of ventilation following loading indicated that the response was complete within 90 seconds. Though this is true in a restricted sense only, the associated changes in P_ACO_2 and plasma lactate being much slower than the changes in ventilation immediately following loading, the finding is in accordance with previous reports that steady-state values are obtained within the second minute (Bruce et al., 1974; Flook and Kelman, 1973; Tabakin and Hanson, 1960).

Breathing Pattern

A brief introduction to current concepts in the control of the pattern of breathing is presented before the sections concerned with inspiration (T_I - V_T relations) and expiration (T_E - V_T relations) in order that results may considered in physiological perspective.

Inspiration

Current evidence (see Euler, 1986, for review) supports the suggestion that the duration and depth of inspiration are controlled by, first, neural mechanisms that are responsible for the generation and control of the rate of rise of inspiratory activity, and secondly, different neural mechanisms that terminate this activity (the inspiratory off-switch). Normally during the course of inspiration, the neural output to the inspiratory muscles builds up progressively from an abrupt start until its termination (the phrenic ramp), and the slope of the ramp is proportional to drive (Lopata et al., 1977). The rate of increase of inspiratory activity depends on many inputs to the system, both tonic and phasic, from a number of peripheral and central sources, and the time characteristics of the neuronal "leaky integrator". As the trajectory of the phrenic activity often closely resembles the time course of the increase of tidal volume, mean inspiratory flow is a good index of the rate of rise of inspiratory activity under constant loading conditions (Milic-Emili, 1982).

According to the model of Euler and Trippenbach (1976), at least two mechanisms are thought to lead to the activation of the inspiratory off-switch (the threshold of which decays with time over the moderate to high lung volume range): first, vagal lung volume information from pulmonary stretch receptors (PSR); this increases as lung volume increases and excites the inspiratory off-switch, and secondly, respiratory drive. The threshold of the off-switch is increased by chemoreceptor (and other) drives, but reduced by a non-PSR increase in excitability from recurrent feedback from the central inspiratory activity integrator. Respiratory drive rises until the combination of lung volume

information and drive activates the off-switch mechanism and terminates inspiration.

Clark and Euler (1972) mapped the association between V_T and T_I (and T_E) in the absence of loading. They reported that, in man, the intersection of the inspiratory volume profile (the slope of which is mean inspiratory flow) on the inspiratory off-switch threshold revealed two different relations between V_T and T_I. In range 1, V_T increased with the elevation of drive while T_I remained constant, while in range 2, the increase of drive was associated with an increase in V_T and a shortening of T_I. The near hyperbolic nature of range 2 was suggested to represent the influence of lung volume information and features of the central mechanisms.

1) The effect of increasing ventilation.

During exercise or hypercapnia in the absence of loading, T_I fell and V_T rose with the elevation of ventilation (Figures 4.11 and 4.12). This is consistent with these variables being generated as the result of the termination of a ramp of inspiratory drive, as in Euler's model, where the slope of the ramp (mean inspiratory flow, see Figure 4.14) increased in a linear fashion with the elevation of ventilation during exercise (Kao et al., 1979) or hypercapnia (Bruce et al., 1979).

However, the pooled mean V_T - T_I relation did not show two clearly different ranges, as described by Clark and Euler (1972), so the mean results do not neatly fit Euler's model. Nevertheless, the individual data from many subjects showed clear evidence of breakpoints (Appendix A1), and it may be suggested that the absence of such in the pooled mean response was due to the smearing effect of pooling all subjects data (this assertion

is supported by the finding of Gardner, 1975, that breakpoints were not so clear with mean data as with individual data). The breakpoints apparent in individual subjects' data at moderate to high tidal volumes (Appendix A1), of which there was a slight suggestion in the pooled mean response at the highest levels (Figures 4.11 and 4.12), could be evidence of the activation of the inspiratory off-switch by a combination of volume information and drive.

2) The effect of loading.

The addition of loading significantly increased T_I, producing a prolongation of almost constant extent at ventilations up to approximately 45 $L.min^{-1}$.

In man, the Breuer-Hering reflex is weak over the normal tidal volume range (Guz et al., 1964) and the prolongation of T_I with loading is not dependent on vagal feedback as in animals (Davenport et al., 1981; Citterio and Agostoni, 1983; D'Angelo et al., 1976). Thus, Lopata et al. (1980) have reported that, at a given P_ACO_2, the peak level of the diaphragmatic EMG is unaffected, and the rate of rise is unaffected or slightly reduced, by loading.

The prolongation of T_I with loading seen in the present study may be partly attributable to an increase in the time lag between neural drive and mechanical output; a consequence of the rise in resistance to flow (see Milic-Emili and Zin, 1986). In addition, the fall in EEV with loading (pp. 5.52-5.54) probably contributed to both the prolongation of inspiration and the rise in V_T by providing inspiratory activity before the onset of the neural inspiration to which the mechanical effect of the inspiratory activity was added. The close agreement between the fall in EEV

with loading and the rise in V_T supports this hypothesis, even to the extent that the fall in EEV with loading during exercise was greater than that during hypercapnia so mirroring the effect of loading on V_T.

With regard to the response to loading at elevated tidal volumes where the Breuer-Hering reflex is active, it may be significant that pulmonary stretch receptor (PSR) activity is not necessarily increased by a rise in V_T if it occurs in association with a fall in EEV, as the PSR see end-inspiratory volume which may not be much affected.

Other factors that may also have been important in determining the change in breathing pattern with loading include, first, a reduction in the rate of rise of inspiratory activity (see above); although this may be small, Euler's model predicts that it would prolong T_I as it takes longer to reach the threshold, and secondly, a rise in the level of the inspiratory off-switch. Although this threshold is not changed directly by loading, it rises in proportion to P_ACO_2 (Euler and Trippenbach, 1976; Lopata et al., 1977; Trippenbach and Milic-Emili, 1977). The CO_2 retention and consequent rise in $P_{ET}CO_2$ accompanying loading may therefore have been in part responsible for the rise in V_T seen in the present study. This may be so even though the time of measurement was relatively soon after the addition of loading, as Callahan and Read (1974) have reported that changes in arterial PCO_2 may occur rapidly following loading. The finding that during exercise the rise in $P_{ET}CO_2$ with loading was significantly greater than during hypercapnia, and that this was associated with a significantly greater increase in V_T may be further evidence that the CO_2 retention following loading

contributes to the rise in V_T (see p. 5.45, for further discussion).

The observed prolongation of T_I accompanying loading, with the consequent reduction in the velocity of diaphragmatic contraction, is an effective adaptive response, for the prolongation of T_I has been reported to optimise diaphragmatic performance by enhancing the efficiency of muscular contraction (Lopata et al., 1983), presumably as a result of moving down the force-velocity curve. The prolongation of T_I may also be an adaptive behavioural response, as the consequent reduction in peak inspiratory pressure may diminish respiratory sensation (Jones et al., 1985).

The observation that an increase in T_I is associated with a rise in mean inspiratory pressure (Younes and Riddle, 1984), with which respiratory muscle energy consumption is closely correlated (Rochester and Bettini, 1976), suggests that at lower ventilations, mechanical rather than energetic considerations may be more important.

3) Comparison of T_I during exercise and hypercapnia.

In the absence of loading, inspiratory durations at a given ventilation during exercise or hypercapnia were very similar. The general similarity of breathing pattern in steady states with different types of ventilatory stimulation has been reported before (Gardner, 1977; Hey et al., 1966; Jensen et al., 1980; Kay et al., 1975; Petersen and Vejby-Christensen, 1977), although as in the present study, significant differences between subjects have been reported (Clark and Euler, 1972; Gardner, 1977; Jennett et al., 1974).

Analysis of the difference of the effect of loading during exercise and hypercapnia revealed that T_I exhibited a significantly greater prolongation during exercise. This finding may be linked to the greater rise in P_ACO_2 with loading during exercise (see above) though it may also indicate that exercise per se was an important influence on breathing pattern at all intensities, not just when it was near maximal levels. The response to loading during exercise may be affected by the fact that there are competing metabolic demands by the limb and respiratory muscles, and/or by other factors related to the pursuance of exercise: there are reports that the pattern of breathing during exercise is affected by increased body temperature (Petersen and Vejby-Christensen, 1977), vascular pressures (Ekelund and Holmgren, 1967) and afferent impulses from active joints and muscles (Tallarida et al., 1983). A further possibility is that the lesser lengthening with loading during hypercapnia is attributable to tachypnoeic influences originating from CO_2 receptors in the airways (Kiwull-Schöne et al., 1981).

4) The response to loading at high ventilations.

Although loading was typically associated with an almost constant prolongation of T_I over the low to moderate ventilatory range, the prolongation became less pronounced as ventilation approached the maximal measured values (Figure 4.11 and 4.12). In some subjects T_I was only slightly increased by loading at peak ventilations (Subjects 634, 644, 647 and 648 during exercise; 634, 647 and 648 during hypercapnia). This phenomenon was evident in the ANOVA as a significant levels * resistance interaction effect during hypercapnia and exercise up to 250 W. El-Manshawi et al. (1986)

also showed that T_I was barely changed by the addition of loading during high intensity exercise.

Other groups have reported considerable shortening of T_I at the high respiratory work rates associated with high levels of ventilation rather than the addition of flow-resistances. Jensen et al. (1980) reported marked shortening of T_I at high ventilations during CO_2 rebreathing or exercise, and Petersen et al. (1980) saw the same during exercise at near maximal work rates.

The change in breathing pattern at high levels of ventilation in the presence of loading may reflect attempts to minimise the work of breathing and/or the sensation of breathlessness, and it may be that this indicates that the respiratory muscles were beginning to fail or that discomfort was becoming unbearable (p. 5.15, pp. 5.28-5.29).

The change in pattern may be mediated by afferent impulses from chest wall receptors when respiratory force generation is high. Homma (1980) reported that selective stimulation of muscle spindles and Golgi tendon organs by rib-vibration led to a fall in V_T - T_I relation.

Other influences may be suggested as likely to be contributing to the fall in T_I at high ventilations in the presence of loading. During exercise, the increase in temperature during exercise may be a cause of increased breathing frequency (Petersen and Vejby-Christensen, 1977). When considering the effect of a number of respiratory stimulants, Hey et al. (1966) reported that temperature was the only stimulus that affected the $\dot{V}$ - frequency relation. However, it is unlikely that temperature rose much in the short time between measurements being made at 200 W and 250 W. During hypercapnia, the elevation of CO_2 may have a

direct effect on pattern generation, possibly through receptors in the airway (Kiwull-Schöne et al., 1981).

Expiration

In eupnoea and at moderately raised levels of ventilation expiration is largely passive (though the neural control mechanisms are far from passive), driven by the elastic recoil forces built up during inspiration. Expiratory flow is governed by the level of expiratory braking from post-inspiratory activity of the inspiratory muscles and the level of upper and lower airway resistance. With rising ventilation the abdominal muscles are activated, the threshold for activation being governed by postural and higher central influences. Expiratory activity continues within the breath while inspiratory inhibiting influences decay with time until a threshold is crossed, then the central inspiratory activity generator terminates expiration and initiates the next inspiration. The influence of temporal and volume factors on the level of the expiratory threshold is a basic similarity to the control of inspiration, though expiration is different in that the control of its duration is only loosely linked to changes in V_T (Euler, 1986).

1) The general effects of increasing ventilation.

The elevation of ventilation, whether in exercise or in hypercapnia, was associated with a shortening of T_E and an increase of both V_T and mean expiratory flow (the points in Figures 4.11 and 4.12 move up and to the right, and the slopes of the lines connecting these points to the origin increase; see also Figure 4.14). These findings are consistent with the rate of emptying of the lung rising as a result of a reduction in

expiratory braking and airway resistance, and an increase in expiratory muscle activity. The increase in mean expiratory flow may be the result of the increased lung volume and respiratory drive, which have both been reported to reduce resistance to flow and increase expiratory muscle activity, while reducing T_E by subtracting from the central inhibition of inspiration (see Younes and Remmers, 1981, and EEV section pp. 5.50-5.52).

2) The effect of loading.

Inspiratory loading can only affect expiratory variables indirectly and, except at high ventilations (see next section), the addition of loading had no significant effect on T_E. Thus there was no shortening of T_E to "compensate" for the increase in T_I and so keep the breath duration constant as might be intuitively expected, nor a lengthening of T_E as might be expected from the work of Cunningham and Gardner (1977) which showed that (at constant loads) T_E was proportional to the length of the previous inspiration (a volume function) and the level of drive. The timing relationship between T_E and T_I has been shown to be dependent on vagal activity (Knox, 1979) and it may be that the T_I - T_E relation reported by Cunningham and Gardner (1977) does not hold when breathing is loaded because of the change in vagal activity (in this respect it may be significant that Guz and Trenchard, 1971, have presented evidence that the vagus nerves transmit volume-related information over the lower volume ranges as well as at elevated volumes).

The absence of a significant change in spirometrically determined T_E with loading is in accordance with the results of Eldridge and Davis (1959), Milic-Emili and Tyler (1963) and Zechman et al. (1957). The duration of the expiratory burst

recorded from medullary neurones has also been reported to be unchanged by loading (Baker et al., 1979).

The general finding that tidal volume was increased by loading while T_E was little affected (although the effect was only slight and did not occur at all levels during hypercapnia) indicates that mean expiratory flow typically increased (see Figures 4.11, 4.12 and 4.14). This is consistent with the reported rise in expiratory muscle activity with the addition of loading (Martin and De Troyer, 1982; Martin et al. 1982; see EEV section pp. 5.52-5.54).

2) The effect of loading at high levels of ventilation.

Although loading had no significant effect on T_E generally, at the very highest work load T_E shortened markedly in most subjects during exercise and in some subjects during hypercapnia (see particularly the data of Subjects 634 and 648 in Appendix A1). This phenomenon was similar to the change seen in T_I with loading at the highest work load.

Craig et al. (1970) have reported that T_E approached a reproducible minimum as exhaustion was approached during exercise whether breathing was loaded or not. The fall in T_E in the present study at the highest work load is in accordance with the suggestion that minimal values were assumed as the limit of performance was approached. The significance of the shift to a relatively higher frequency breathing pattern at high work loads, of which the shortening of T_E was a part, was discussed above (p. 5.41-5.42).

Mean Flow

In inspiration, loading was associated with a fall in mean inspiratory flow (the slopes of the lines joining the inspiratory points to the origin in Figures 4.11 and 4.12) during both exercise and hypercapnia. Thus, two relations (unloaded and loaded) existed between ventilation and mean inspiratory flow; this finding is illustrated for the exercise condition in Figure 4.14.

In expiration, mean flow was little affected by the addition of loading during hypercapnia. However, mean expiratory flow during exercise was markedly increased by loading. Therefore during exercise, two relations existed between ventilation and mean expiratory flow, analogous to the two ventilation - mean inspiratory flow relationships (Figure 4.14). However, if mean expiratory flow during exercise was adjusted for the stimulatory effect of the rise in $P_{ET}CO_2$ accompanying loading, a unique relationship was shown to exist between ventilation and mean expiratory flow, though no such relationship existed for mean inspiratory flow (Figure 4.14).

This finding may be at least partially attributable to the greater rise in $P_{ET}CO_2$ during exercise (Table 4.19) which would be expected to increase respiratory drive and therefore mean inspiratory flow (p. 5.37).

The apparent constancy of the ventilation - mean expiratory flow relation when the resistance to breathing is increased agrees with the work of Remmers and Bartlett (1977) which suggested that expiratory air flow is continuously controlled by neuromechanical feedback loops which has been called tracking (p. 5.52).

The Tidal Volume Response to Loading at High Levels of Ventilation

Although loading during exercise was generally associated with an elevation of V_T (see above), at the highest exercise level loading reduced V_T (Figure 4.13). The imposition of loading during hypercapnia was similarly associated with notable falls in V_T at high ventilations (Figure 4.15). In some subjects, the fall in V_T when breathing was loaded at the highest ventilations, was sufficient to reduce V_T below that at lesser ventilations (e.g. Subject 632, see Appendix A1).

Two aspects of the observed tidal volume response to increasing ventilation, and to the addition of loading, have previously been reported by others in response to high unoccluded ventilations or loading during exercise. Firstly, the failure of V_T to rise at high ventilatory levels when drive is further increased has been reported by Hey et al. (1966), Lind and Hesser (1984), Petersen et al. (1980) and Younes and Kivinen (1984). All reported plateauing of V_T at 2.5 L. during maximal or high intensity exercise. Mertz et al. (1975) have also reported that V_T peaked at 2.5 L. during exercise, then fell as ventilation was increased further by CO_2 rebreathing. Gallagher et al. (1987) reported ventilatory plateauing at approximately 3 L. during maximal exercise and sub-maximal exercise with hypercapnia. Jensen et al. (1980) have reported that V_T plateaued at a higher level of approximately 4 L. during CO_2 rebreathing, while during exercise V_T peaked at this level but fell as ventilation was increased further.

Secondly, there are several reports that V_T is reduced by the addition of loading at high exercise intensities (Dressendorfer et al., 1977; El-Manshawi et al., 1986; D'Urzo et al., 1987).

The shift to higher frequency breathing and the failure of tidal volume to rise as high ventilations were approached was discussed above (p. 5.41) and it was suggested that it indicated that the respiratory muscles were failing. Otis, Fenn and Rahn (1950) reported that a shift to higher frequency breathing increases respiratory work, so the change cannot simply reflect minimisation of work.

The suggestion that the change in pattern may have been an attempt to reduce the sensation of breathlessness may be directly linked to the reduction of tidal volume. The reduction of V_T would lessen peak inspiratory pressure, and breathlessness is reported to be directly related to the fraction of maximum inspiratory pressure that peak inspiratory pressure attains (Jones et al., 1985; Killian et al., 1985). This is in accordance with subjects' reports that severe breathlessness was the reason they stopped exercising. If the ability to continue exercising was dependent on the severity of breathlessness, it would be likely that minimising the sensation of breathlessness would be a significant factor in the determination of breathing pattern at high exercise intensities. The report of Petersen et al. (1980) may be cited as evidence against this suggestion. In their study of (unloaded) breathing pattern during high intensity exercise, subjects who showed a high frequency - low tidal volume pattern reported extreme fatigue in the working legs but not breathlessness. However, constraints by mechanical factors, to which breathlessness is linked, are likely to be implicated in the determination of the observed pattern. Thus, Jensen et al. (1980) have shown that, although the limits of the maximal effort flow-volume loop are rarely reached at elevated ventilations, the approach towards limiting values was associated with changes in

breathing pattern as mechanical factors interfered with the central regulation of ventilation. In addition, the large tidal volumes at high levels of ventilation were probably associated with excursions onto the flat portion of the pressure-volume curve where volume change for a given increase in respiratory force is reduced, and this is likely to have affected breathing pattern.

In view of the proposal that mean inspiratory flow is an index of respiratory drive (Milic-Emili, 1982), the change to a higher frequency pattern accompanying loading, with the increase in mean inspired flow it involves, may be suggested to reflect the demands of increasing drive when V_T is constrained, or even reduced.

Exercise and End-Expiratory Volume

The findings that end-expiratory volume (EEV) was significantly reduced by exercise and was reduced to a greater extent as the intensity of exercise increased, agree with those of previous studies that have reported that EEV falls in proportion to work rate (Asmussen and Christensen, 1939; Grimby et al., 1968; Lind and Hesser, 1984; Linnarson, 1974).

Other studies, examining the effect of low to moderate exercise levels, have reported that EEV falls, but not significantly (Chiang et al., 1965; Hanson et al., 1962; Kagawa and Kerr, 1970; Stubbing et al., 1980_a), while Younes and Kivinen (1984) have reported that EEV falls significantly with the onset of exercise but does not fall further as exercise intensity increases. These differences from the findings of the present study may be due to the larger exercise range and/or the more sophisticated form of analysis of the present study.

The fall of EEV during exercise can be mainly ascribed to recruitment of the abdominal musculature. The abdominal muscles are the most powerful expiratory muscles and have a major action during expulsive acts such as coughing, vomiting and defaecation (Agostoni and Campbell, 1970). Grimby et al. (1968) reported that the onset of exercise was associated with a reduction in end-expiratory abdominal diameter while the rib-cage volume remained generally similar to resting levels, suggesting that abdominal muscle activity was augmented.

The recruitment of the abdominal musculature is primarily dependent on the increase of drive with exercise, though Linnarson

(1974) has suggested that a simple mechanical coupling between the legs and the muscles of the trunk may also contribute to the initial changes in EEV.

The reduction in expiratory braking during exercise (England et al., 1982; Murphy et al., 1959; Petit et al., 1960) probably also contributed to the fall of EEV.

Hypercapnia and End-Expiratory Volume

A number of groups have previously examined the effect of hypercapnia on EEV, but the various reports disagree on both the direction and extent of the change. Some groups have reported that EEV falls during CO_2 rebreathing (Cotes et al. 1977; Garrard and Lane, 1978; Grassino et al., 1973; Lopata et al., 1983; Pengelly et al., 1979), though Bradley et al. (1974) reported that EEV was unchanged, while Garfinkel and Fitzgerald (1978) reported that EEV was increased by breathing 4% CO_2.

In the present study, all subjects showed marked falls in EEV as ventilation was increased above 20 $L.min^{-1}$; in fact EEV commonly fell as ventilation was increased from rest, but one subject (643) showed elevated EEV levels at ventilations up to this level.

Hypercapnia has been shown to increase abdominal muscle activity (Campbell and Green, 1953; Grimby et al., 1976) and it seems probable that the typical response to the elevation of ventilation accompanying hypercapnia is for EEV to fall.

Campbell (1952) reported that subjects showed considerable variability in the level of ventilation at which abdominal muscle recruitment occurred in hypercapnia. If subjects do have different ventilatory thresholds for the recruitment of the abdominal musculature it may explain some of the dissimilarities

between studies and between subjects in the present study. The reason for the variability may be differences in the preferred method of regulating expiratory airflow by "tracking" flow and "triggering" the next inspiration (Remmers and Bartlett, 1977). Gautier et al. (1973) have proposed that these mechanisms determine EEV.

Respiratory Muscle Performance and End-Expiratory Volume

The fall in EEV may have a number of advantages for respiratory muscle performance. First, the more expiratory reserve volume is encroached upon, the smaller is the incursion into inspiratory reserve volume when maintaining or increasing tidal volume, and so the excursion onto the flatter portion of the pressure - volume is reduced. A further benefit of a fall in EEV is the assistance of diaphragmatic function by optimising its performance (see above). The fall of EEV with increasing ventilation serves to augment the efficiency of diaphragmatic function by increasing its resting length and radius of curvature (Martin et al., 1982). This both prevents undue diaphragmatic shortening and increases its mechanical advantage (Evanich et al., 1973; Marshall, 1967; Pengelly et al., 1971). In addition, the recruitment of the abdominal musculature and fall in EEV means that the abdominal wall has a true inspiratory action at end-expiration, as it moves out under passive recoil pressures with the relaxation of the abdominal muscles (Agostoni and Torri, 1967).

Loading and End-Expiratory Volume

Loading was not associated with a statistically significant fall in EEV, despite the fact that marked changes were apparent. The absence of significance can be attributed to the relatively small

number of subjects and the high variability of EEV estimations (the standard error of four estimations of EEV at rest was 0.10 L. when breathing was unloaded and 0.08 L. when loaded).

The effect of loading on EEV was somewhat variable at resting or slightly elevated ventilations, but EEV was typically reduced by 0.10 - 0.15 L. during exercise and by 0.05 L. during hypercapnia over most of the ventilatory range. This difference between the effect of loading during exercise and during hypercapnia was found to be statistically significant (Table 4.24).

Several groups have previously reported that EEV (Campbell et al., 1961; Martin et al. 1982_a; Zechman et al., 1976) or the volume of the abdominal compartment (Lopata et al., 1983; Martin and De Troyer, 1982; Mengeot et al., 1985) falls with the addition of an inspiratory flow resistance, though most have examined only the effect at rest. To the author's knowledge the only study to assess the effect of loading at elevated ventilations is that by Lopata et al. (1983). They reported that the end-expiratory dimensions of both the rib-cage and abdomen were reduced to a greater extent by loading during hypercapnia than by CO_2 rebreathing alone. The effect of loading during CO_2 rebreathing reported by Lopata et al. therefore agrees with the effect of loading during steady-state CO_2 inhalation reported in the present study.

The fall of EEV with loading may be attributed to the increase of abdominal muscle activity. Martin and De Troyer (1982) and Martin et al. (1982_a) recorded earlier and increased EMG activity of the abdominal muscles with the addition of inspiratory loading while Mengeot et al. (1985) and Lopata et al. (1983) have reported increased abdominal pressures accompanying

inspiratory loading, consistent with abdominal muscle recruitment. Such a fall may have a number of beneficial effects on diaphragmatic performance (see above).

The implication of the work discussed above is that EEV level is an important determinant of the ability of the diaphragm to generate tension. In addition to the possibility that the observed changes in EEV optimise force generation, they may also minimise work and/or the oxygen cost of breathing. Yamashiro and Grodins (1973) showed that theoretically predicted EEVs that minimised the work of breathing with increasing ventilation were close to those obtained empirically. Roussos et al. (1979) reported that endurance time was reduced, when breathing through a resistance, if end-expiratory volume was voluntarily increased to 50% of inspiratory capacity. They ascribed this effect to reduced muscle strength, increased work of breathing and reduced energy supply (the latter as a consequence of the increased resistance to diaphragmatic blood flow) when EEV was increased. Collet and Engel (1986) have shown that increased EEV reduces the efficiency of breathing. The significance of EEV level for the efficiency of respiratory muscle function was reported by Lopata et al. (1985) who showed that load compensation was reduced in patients who were hyperinflated as a results of chronic obstructive pulmonary disease. It appeared that the shortened diaphragm of hyperinflated patients provided little additional contractile support to effect load compensation.

5. Flow Profile

The current interest in flow profiles has developed from the hypothesis that flow profiles are generated in accordance with optimisation principles. Though there was earlier work by Bretschger (1925) and Rohrer (1925), Otis, Fenn and Rahn in 1950 produced one of the pioneering investigations of the role of optimisation in the control of the pattern of breathing, presenting evidence that breathing frequency was regulated to minimise respiratory work. In their study, they recognised the importance of the shape of the flow profile in determining the work of breathing, but as an approximation assumed the shape of the flow profile to be sinusoidal. Yamashiro and Grodins (1971) extended this work by considering the shape of the flow profile to be a further variable for optimisation.

Yamashiro and Grodins (1971) reported that optimal airflow patterns that minimised respiratory work rate were square waves. In human subjects at rest, inspiratory flow profiles are far from square but more resemble a sinusoid, or a quadrilateral (Painter, 1987). However, a number of studies have reported increasing "squareness" at elevated ventilations (Lafortuna et al., 1984; Morrow and Vosteen, 1953; Proctor and Hardy, 1949; Silverman et al., 1951). Subsequent studies that have developed optimisation models predict increasing squareness with the elevation of respiratory work (see Hämäläinen, 1983 for review), and it may be that the change in shape seen in profiles recorded from subjects represents an optimisation process.

In the present study, the effects of increased ventilation in exercise or hypercapnia, with and without loading, on 11 variables used to describe the shape of the flow profile were

examined. The discussion below considers how the shape of the flow profile varied as ventilation was elevated, and to what extent the shape of the flow profile reflected mechanical and/or energetic demands, as determined by findings of the oxygen cost of breathing and mechanical performance of the respiratory system.

Inspiratory Flow Acceleration

The nearly linear rise in $\ddot{V}_I$ with increasing ventilation shown in Figure 4.20 may be attributed to the augmented rate of rise of inspiratory activity, and therefore of the driving inspiratory pressure waveform, within each breath. This is consistent with the report of Altose et al. ($1979_{a,b}$) that occlusion pressure rose in a near linear manner with the progressive hypercapnia accompanying rebreathing.

The fall in EEV that accompanies the elevation of ventilation (see pp. 5.50-5.52) may also contribute to the increase of $\ddot{V}_I$, first, by optimising the efficiency of diaphragmatic contraction and secondly, by the facilitatory effect of the passive recoil of the lung and chest wall at the start of inspiration.

The observation that $\ddot{V}_I$ was little affected by loading at resting levels of ventilation is in accordance with the results reported by Zechman et al. (1957), from which it was evident that loads of increasing severity did not affect the slope of the flow profile at the beginning of inspiration.

The findings that $\ddot{V}_I$ was significantly reduced by loading, and that the extent of the fall increased in a nearly linear manner as the level of ventilation rose (Table 4.25), are probably due to the direct effect of the increased resistance to

air flow accompanying loading. Thus, loading would reduce the rate of rise of flow during inspiration for a given rate of rise of inspiratory activity. However, Lopata et al. (1980) have reported that the rate of rise of inspiratory activity within a breath falls with loading, and this may also be a significant factor in the reduction of $\ddot{V}_I$ with loading.

A fall in the rate of rise of inspiratory activity will lead to a reduction in the velocity of muscular contraction, and this may be energetically favourable (Agostoni et al., 1970). It may be, therefore, that this neuronal response represents an optimisation process.

Although when breathing was loaded, $\ddot{V}_I$ typically rose in a nearly linear manner with the elevation of ventilation, at high ventilations there were instances of substantial departures from the prevailing nearly linear relation, $\ddot{V}_I$ increasing out of proportion to the increase of ventilation. This disproportionate rise in $\ddot{V}_I$ was seen during both exercise and hypercapnia.

High acceleratory flows in the presence of loading during heavy exercise have also been reported by Silverman et al. (1951). The generation of high acceleratory flows is associated with a substantial elevation of the effective load, suggesting that, in some subjects, a considerable augmentation of drive took place at high ventilations. This augmentation was most likely of conscious origin, and possibly due to the distress caused by the constraint of air flow. Generally, the avoidance of rapid accelerations is energetically favourable, since the loss of efficiency is minimised. However, it may be that high accelerative flows minimise respiratory work and the oxygen consumption of the respiratory muscles when respiratory work rates are very high. This point is illustrated by the finding of

Yamashiro and Grodins (1971), that rectangular flow profiles minimise the work of breathing, and follows from the fact that the volumes accelerated are small, and therefore the inertial work may be relatively low, yet peak pressure is minimised. High accelerative flows may become optimal if the production of large tidal volumes is limited by the high pressures, and therefore, high rates of energy consumption involved (Collet et al., 1985; McGregor and Becklake, 1961; Field et al., 1984 have shown driving pressure and the oxygen cost of breathing to be correlated). It may also be that the generation of high accelerative flows is an optimisation process related to the reported fall in the efficiency of muscular contraction with increasing load at higher loads (Agostoni et al., 1970). Hämäläinen (1983) reported that flow profiles predicted in accordance with optimisation criteria showed an elevated $\ddot{V}_I$ and $\dot{V}_I max$, and reduced Tmax when a factor was included that modelled this decrease in efficiency.

A further possibility is that discomfort is minimised by minimising peak pressure generation (Freedman and Campbell, 1970; Otis, Fenn and Rahn, 1950).

Time to Peak Inspiratory Flow

The suggestion that the optimisation of flow profiles involves a squaring of their shape implies that peak flows will occur earlier. ANOVA indicated that during hypercapnic hyperpnoea, peak flows occurred significantly earlier than at resting levels of ventilation. A tendency for peak flows to occur earlier than at rest was also present in exercise data, though the effect did not achieve significance (Table 4.26).

Lafortuna et al. (1984) also saw reductions in Tmax with the increase of ventilation accompanying exercise and maximal voluntary hyperventilation.

The increase in respiratory drive during exercise and hypercapnia was probably responsible for the fall in Tmax as ventilation was elevated.

The finding that Tmax rose with inspiratory loading at resting levels of ventilation (Figure 4.21) is in agreement with the findings of Zechman et al. (1957).

The prolongation of Tmax with loading may be due mainly to the fall in the rate of rise of inspiratory activity (Lopata et al., 1980). This may be an optimisation process to avoid the deleterious effects of rapid contractions on muscular efficiency which are particularly pronounced when loads are high. However, the fall in EEV accompanying loading (p. 5.52-5.54) may also have contributed to the prolongation of Tmax. Hämäläinen (1983) has reported that introducing a reduced EEV into his model made predicted flow profiles more triangular, thereby increasing Tmax.

Tmax was the only variable to show a significant difference in the response to loading between exercise and hypercapnia, there being significantly greater prolongation of Tmax with loading during hypercapnia. This finding reflected the combined effect of two non-significant differences in the effect of loading; the reduction of $\dot{V}_I$ was larger in hypercapnia than exercise, but the reduction in peak inspiratory flow was smaller, so the time to reach the peak inspiratory flow level was significantly greater.

The difference in the effect of loading on Tmax during exercise and hypercapnia may be due to energetic considerations during loaded exercise, the total work rate being considerable

when both the limb and respiratory muscle work rates are high. However, a number of alternative reasons for the difference may be suggested: neural, hormonal and temperature factors associated with the pursuance of exercise (p. 5.41); the different sources of respiratory drive; the influence of high CO_2 levels through another receptor mediated response such as airway receptors; the deleterious effect of hypercapnia on the rate at which the respiratory muscles can generate force (Agostoni et al., 1970).

Time to Peak Expiratory Flow

The general tendency for increasing ventilation to be accompanied by a fall in Tmin (this decline was marked as ventilation increased over the moderate ventilatory range, Figure 4.22) may represent the start of, or a substantial increase of, abdominal muscle activity (p. 5.50-5.52).

The addition of loading had no significant effect on Tmin. It may be that Tmin remained relatively constant with the addition of loading because peak expiratory flow and expiratory flow acceleration rose to the same relative extent.

Peak Inspiratory flow

In the absence of marked changes in mean/peak inspiratory flow ratio (see below) or T_I (see p. 5.37), the nearly linear increase of $\dot{v}_I max$ accompanying the elevation of ventilation (Figure 4.23) reflects the progressive increase of inspired volume (the area under the inspiratory flow profile).

However at high ventilations, there were instances of marked deviation from the predominantly nearly linear relationship, $\dot{v}_I max$ rising disproportionately. This change in the form of the $\dot{V}$ - $\dot{v}_I max$ relationship often occurred in conjunction with the

disproportionate rise in $\ddot{V}_I$ seen in some subjects. In view of the high energetic cost of generating excessive flows, the disproportionate rises in these flow variables probably represented conscious augmentation of respiratory effort. They may also be related to optimisation processes related to the efficiency of muscular contraction at high loads (see $\ddot{V}_I$ section, pp. 5.56-5.58).

The fall in EEV accompanying the elevation of ventilation may also have contributed to the production of high peak inspiratory flows. Hämäläinen (1983) reported that predicted inspiratory peak flow levels generated in accordance with optimisation criteria increased markedly when the EEV boundary condition of his model was reduced.

The finding that loading significantly decreased $\dot{V}_I max$ (Table 4.28) was in accordance with the reported reduction in the rate of rise of inspiratory activity (Lopata et al., 1980). The fall in $\dot{V}_I max$ would reduce peak pressure generation and thereby constrain the rise in oxygen consumption by the respiratory muscles. It may therefore represent an optimisation process.

Peak Expiratory Flow

Although peak expiratory flow ($\dot{V}_E max$) exhibited a predominantly nearly linear relation to the level of ventilation, there were instances of marked deviation at high ventilations during both loaded and unloaded breathing (Figure 4.24). In two subjects (634 and 639), the extra augmentation of expiratory peak flows at high ventilations in the loaded state was associated with the disproportionate elevation of inspiratory peak flows. These disproportionate rises in peak flow levels may represent the conscious augmentation of respiratory drive and/or optimisation

processes related to the efficiency of muscular contraction at high loads (see $\dot{V}_I$ section, pp. 5.56-5.58).

The finding that $\dot{V}_E max$ was increased to a greater extent with loading as the level of ventilation was elevated (though the effect only achieved significance during hypercapnia, Table 4.29), may have been related to the observation that the elevation of ventilation over the low to moderate range (up to 50 $L.min^{-1}$) was associated with large changes in the mean/peak expiratory flow ratio. This latter finding indicated that the shape of the expiratory profile became more square as ventilation increased over this range. Therefore, the expiratory volume (the area under the expiratory flow profile) could be increased as ventilation rose (p. 5.37) in association with only a relatively small increase in peak expiratory flow, but a marked rise in mean flow. However, at higher ventilations (greater than 50 $L.min^{-1}$), the mean/peak flow ratio was relatively constant, and high, indicating the shape of the flow profile already tended to squareness. Therefore, increasing the area under the expiratory flow profile was associated with increasing height of the "square" to which the flow profile approximated, i.e. raising peak expiratory flow.

Time to Peak Inspiratory Flow / Inspiratory Time

$Tmax/T_I$ commonly fell with increasing ventilation: as T_I only fell slightly with the elevation of ventilation (see p. 5.37), this reflected the earlier occurrence of peak inspiratory flow.

Although loading frequently had a marked effect on $Tmax/T_I$, the direction of change varied. However, loading at the highest ventilatory level (60.0-69.9 $L.min^{-1}$) was accompanied by an increase in $Tmax/T_I$ in 7 of 8 comparisons, frequently to a

greater value than that at the penultimate ventilatory level (50.0-59.9 $L.min^{-1}$). This rise in $Tmax/T_I$ with loading indicated a greater relative rise in Tmax than in T_I, as the increase of Tmax with loading remained relatively constant or fell as the highest ventilatory levels were approached. This revealed that, at the highest levels of ventilation, T_I was prolonged to a lesser extent by loading than at lower levels ventilation.

Time to Peak Expiratory Flow / Expiratory Time

The one notable feature of the response of this variable ($Tmin/T_E$) to loading was that changes were commonly similar to changes in Tmin, reflecting the observation that loading did not significantly affect T_E (see p. 5.44).

Mean / Peak Inspiratory Flow

The ratio of mean to peak inspiratory flow ($\bar{\dot{V}}_I/\dot{V}_I max$) indicated the general shape of the flow profile, the ratio being 1 for a square wave and 0.64 (2/pi) for a sine wave. Thus, increases in this variable indicate a squaring of the inspiratory flow profile. ANOVA indicated a significant ventilatory levels effect on $\bar{\dot{V}}_I/\dot{V}_I max$ during exercise and hypercapnia, revealing that the elevation of ventilation significantly increased the squareness of inspiratory flow profiles.

The effect of the elevation of ventilation on $\bar{\dot{V}}_I/\dot{V}_I max$ during exercise and hypercapnia were very similar (although values were noticeably higher during unloaded hypercapnia), $\bar{\dot{V}}_I/\dot{V}_I max$ rising steadily from approximately 0.60-0.65 at low ventilations to around 0.70-0.75 at high ventilations. Lafortuna et al. (1984) have reported similar observations during exercise,

$\bar{\dot{V}}_I/\dot{V}_I max$ rising from a mean value of 0.70 at rest to 0.79 during exercise at 200 W.

The findings that the addition of loading had no significant effect on $\bar{\dot{V}}_I/\dot{V}_I max$, and that the response to loading at high ventilations showed considerable variation between subjects, indicate that loading was not associated with a simple squaring of the inspiratory flow profile at low or at high respiratory work rates. This suggests that the shape of the flow profile at high respiratory work rates was not determined solely by the requirement to minimise respiratory work.

Mean / Peak Expiratory Flow

The effect of increasing ventilation and/or loading on $\bar{\dot{V}}_E/\dot{V}_E max$ has rarely been reported, since previous workers have concentrated on inspiratory variables. However, it was expected that this variable would show profound changes with increasing respiratory work, as the shape of the expiratory flow profile at rest (peak flow attained quickly, followed by a slow decline), is far removed from the square shape that would minimise respiratory work during an active expiration.

The elevation of ventilation significantly increased $\bar{\dot{V}}_E/\dot{V}_E max$, and the rise was very marked over the low to moderate ventilatory range (up to 50 $L.min^{-1}$). However, in three subjects (634, 639 and 643) there was little evidence of any further increase in this variable as the level of ventilation increased further. The rise in $\bar{\dot{V}}_E/\dot{V}_E max$ at ventilations up to 50 $L.min^{-1}$ may indicate that expiratory work was being minimised, as it represented a significant increase in the squareness of the expiratory flow profile.

Loading had no significant effect on $\bar{\dot{V}}_E/\dot{V}_E max$. Examination of the pooled mean response revealed that at low ventilations loading was associated with an increase of $\bar{\dot{V}}_E/\dot{V}_E max$, the magnitude of which decreased as ventilation was elevated. The effect was reversed at approximately 40 $L.min^{-1}$, and $\bar{\dot{V}}_E/\dot{V}_E max$ was depressed by loading at greater levels of ventilation.

The falls in $\bar{\dot{V}}_E/\dot{V}_E max$ seen in subjects at high levels of ventilation were the result of large rises in $\dot{V}_E max$. These rises may represent the conscious augmentation of respiratory drive. Alternatively, they may be due to the reduction in the efficiency of muscular contraction that has been reported to accompany the elevation of respiratory work rate when the load is already high (Agostoni et al., 1970, see pp. 5.56-5.58). The fact that the fall in $\bar{\dot{V}}_E/\dot{V}_E max$ with the addition of loading at high levels of ventilation reduces the squareness of the expiratory flow profile suggests that factors other than the simple minimisation of expiratory work are important in determining the shape of the expiratory flow profile when breathing is loaded.

In conclusion it may be stated that the elevation of ventilation was associated with significant changes in a number of variables that described the shape of inspiratory and expiratory flow profiles. Several variables increased in a nearly linear manner with increments of ventilation ($\bar{\dot{V}}_I$, $\dot{V}_I max$, $\dot{V}_E max$ and $\bar{\dot{V}}_I/\dot{V}_I max$) while others showed significant falls (Tmax, $Tmax/T_I$ and Tmin). The general effect of these changes was to increase the "squareness" of the profile. This is consistent with the operation of a controller optimising the shape of flow profiles, as theoretically a square profile minimises respiratory work.

Loading was associated with significant changes in a number of flow variables ($\ddot{v}_I$, Tmax, $\dot{v}_I max$, $\dot{v}_E max$). The nearly linear relation to ventilation shown by some variables when breathing was unloaded also existed when breathing was loaded, though with a changed slope ($\ddot{v}_I$ and $\dot{v}_I max$ decreased, $\dot{v}_E max$ increased). The response to loading of the variables $\ddot{v}_I$, Tmin, $\dot{v}_E max$ and $\bar{\dot{v}}_E/\dot{v}_E max$ depended on the level of ventilation.

At low to moderate ventilations, the changes in the expiratory variables with loading appeared to be associated with a simple squaring of the expiratory flow profile, though the inspiratory flow profile did not show a similar simple tendency towards squareness with the addition of loading.

The approach towards peak ventilatory levels was associated with disproportionate increases in $\ddot{v}_I$, $\dot{v}_I max$ and $\dot{v}_E max$ in some subjects, depending on the stimulus to ventilation. The disproportionate increases in the inspiratory flow variables led to pronounced asymmetry of the inspiratory profile and tended to reduce its squareness. The disproportionate rise of some inspiratory and expiratory variables possibly represented the conscious augmentation of respiratory drive and/or may have been related to optimisation processes related to a reduction in the efficiency of muscular contraction at high respiratory work rates.

One might expect that the effect of loading would be significantly different in exercise and hypercapnia, there being only significant levels of respiratory work during hypercapnia but significant limb work as well during exercise. However, only one variable (Tmax) showed statistically significant differences, the increase in Tmax with loading during hypercapnia being greater than during exercise.

The findings reported in the present study suggest that optimisation of the shape of the flow profile may occur, but that the criterion for optimisation is not simply the minimisation of mechanical work. This was particularly apparent from the difference between the shape of the inspiratory profile at high work rates and the shape of the flow profile that theoretically minimises respiratory work rate.

SUMMARY

Chapter 1: Introduction

Work that is suggested to be evidence of the limitation of exercise by respiratory factors is introduced. Three main testable hypotheses are generated; the way in which these are examined by increasing inspiratory flow-resistance is indicated.

Chapter 2: Methods

The apparatus used for the measurement of respiratory variables, for loading and unloading inspiration, and for measuring mixed expired gas composition (to calculate $\dot{V}O_2$ and $\dot{V}CO_2$) is described, along with the method of estimating changes in EEV.

Chapter 3: Statistical Methods

The techniques employed in the analysis of data are described.

Chapter 4: Results

The results of incremental exercise or hypercapnia tests, with and without loading, on a total of 11 subjects are presented.

Energetics During exercise, $\dot{V}O_2$ was increased slightly, but significantly, with loading. The oxygen cost of breathing estimated during hypercapnic hyperpnoea was also significantly increased with loading. Over the low to moderate exercise range, the rise in oxygen uptake with loading during exercise, and the estimated increase in the oxygen cost of breathing were similar.

At high exercise levels, the estimated increase in the oxygen cost of breathing with loading was much larger than the observed increase in oxygen uptake.

Analysis of blood samples taken during exercise revealed that loading was associated with a rise in plasma lactate concentration

in those subjects in whom $\dot{V}O_2$ was unaffected. Plasma lactate levels were unchanged during hypercapnic hyperpnoea, with or without loading.

Ventilation and Breathing Pattern

In exercise and in hypercapnia, loading produced a progressively greater reduction in ventilation as the unloaded level of ventilation increased.

Although loading was associated with an almost constant lengthening of T_I at low and moderate levels of ventilation (this was greatest in exercise), there was evidence of a breakpoint at higher levels; the tendency for T_I not to increase so markedly with loading at high levels of ventilation was associated with tidal volume plateauing. T_E was unaffected by loading.

End-Expiratory volume

EEV fell progressively with increasing ventilation from exercise or hypercapnia. The addition of loading was associated with a further fall in EEV, which was greatest during exercise.

Flow Profile

Increasing ventilation was associated with a near linear rise in $\ddot{V}_I$, $\dot{V}_I max$, $\dot{V}_E max$ and $\bar{\dot{V}}_I/\dot{V}_I max$, suggesting increasing squareness of the profile. Loading was associated with changes in $\ddot{V}_I$, Tmax, $\dot{V}_I max$, $\dot{V}_E max$, which at low to moderate levels of ventilation were associated with a simple squaring of the expiratory profile.

Chapter 5: Discussion

Respiratory Factors Limiting Exercise

1) Mechanical limitation of ventilation: Although loading at the highest exercise levels appeared to be associated with approaching the limit of the ability of the respiratory system to generate ventilation (a suggestion supported by changes in

breathing pattern and flow variables), the finding that P_AO_2 did not fall below 95 torr indicates that loading did not produce ventilatory limitation of $\dot{V}O_2$.

2) The high oxygen cost of breathing: When breathing was loaded, the estimated oxygen cost of breathing at the highest ventilations may have exceeded the level which determines the limit of useful ventilation during exercise, and may therefore indicate that the supply of oxygen to the active limb muscles was impaired.

3) Fatigue of the respiratory muscles: Loading at the highest exercise levels was associated with a rise in anaerobiosis in those subjects in whom $\dot{V}O_2$ was little affected, if this were sustained it might lead to fatigue of the respiratory and/or limb muscles.

Breathing Pattern and End-Expiratory Volume

The changes in breathing pattern with loading were generally consistent with Euler's model. It appeared that in large part the increase in T_I and V_T that typically accompanied loading could be ascribed to the effect of the associated changes in EEV, and CO_2 retention. The relatively high frequency pattern at high levels of ventilation when breathing was loaded, particularly during exercise, may be evidence that the respiratory muscles were beginning to fail.

The Shape of the Flow Profile

The increasing squareness of the flow profile as ventilation increased may have represented the effect of optimisation processes, though the criterion for optimisation was not simply minimisation of mechanical work. The addition of loading was associated with a squaring of the expiratory profile which may have similarly represented the effect of optimisation process.

Potential Further Research

The work reported in this thesis could be fruitfully extended in a number of ways, a few possibilities are presented below.

First, it would be of interest to examine, in man, to what extent the rise in $\dot{V}O_2$ during hypercapnia may be due to the effect of CO_2 on the general level of metabolism rather than the level of respiratory work. As Pappenheimer (1977) showed in rats, this could involve comparing increases in $\dot{V}O_2$ accompanying the elevation of ventilation by hypercapnia and hypoxia.

Secondly, the findings of the present study suggest that EEV is important in determining the breathing pattern response to loading. This hypothesis could be comprehensively examined, ideally by measuring changes in EEV directly using a whole-body plethysmograph.

Thirdly, it would be interesting to investigate further the relationship between respiratory work rate, plasma lactate concentration and breathing pattern in exercising man. Perhaps the most interesting aspect of this would be the isolation of the site or sites of the augmented anaerobiosis accompanying loading during exercise.

Fourthly, further work might include a more comprehensive examination of the relationship between ventilation, oxygen uptake and P_AO_2 at high ventilatory work rates (especially considering the confusion of some workers in this field), producing the increase in respiratory work rate either by an increase in ventilation alone or in association with an added load.

Finally, the examination of the shape of the flow profile, with and without loading, might be extended to include comparisons during hypoxia, voluntary hyperventilation, and at raised body temperatures.

REFERENCES

Agostoni, E., and Campbell, E.J.M.(1970). The abdominal muscles. In The Respiratory Muscles: Mechanics and Neural Control. Ed. E.J.M. Campbell, E. Agostoni and J.N. Davis. London. Lloyd-Luke pp. 175-180.

Agostoni, E. and Fenn, W.O.(1960). Velocity of muscle shortening as a limiting factor in respiratory airflow. J.Appl.Physiol. 15: 349-353.

Agostoni, E., Campbell, E.J.M., and Freedman, S.(1970). Energetics. In The Respiratory Muscles: Mechanics and Neural Control. Ed. E.J.M. Campbell, E. Agostoni and J.N. Davis. London. Lloyd-Luke. pp. 115-137.

Agostoni, E., and Mead, J.(1964). Statics of the respiratory system. In Handbook of Physiology. Section 3. Respiration. Ed. W.O. Fenn and H. Rahn. Washington DC. American Physiological Society. pp. 387-409.

Agostoni, E., and Mognoni, P.(1966). Deformation of the chest wall during breathing efforts. J.Appl.Physiol. 21: 1827-1832.

Agostoni, E., Mognoni, P., Torri, G., and Miserocchi, G.(1966). Forces deforming the rib cage. Respir.Physiol. 2: 105-117.

Agostoni, E., and Torri, G.(1967). An analysis of chest wall motions at high values of ventilation. Respir.Physiol. 3: 318-332.

Aitken, R.C.B., Zeally, A.K., and Rosenthal, S.V.(1970). Some psychological considerations of breathlessness.

In Breathing. Hering-Breuer Centenary Symposium. Ed. R. Porter. London. Churchill. pp. 253-266.

Altose, M.D., Kelsen, S.G., and Cherniack, N.S.(1979). Respiratory responses to changes in airflow resistance in conscious man.

Respir.Physiol. 36: 249-260.

Altose, M.D., Kelsen, S.G., Stanley, N.N., Cherniack, N.S., and Fishman, A.P. (1976_a). Effects of hypercapnia and flow resistive loading on tracheal pressure during airway occlusion.

J.Appl.Physiol. 40: 345-351.

Altose, M.D., Kelsen, S.G., Stanley, N.N., Levinson, R.S., Cherniack, N.S., and Fishman, A.P.(1976_b). Effects of hypercapnia on mouth pressure during airway occlusion in conscious man.

J.Appl.Physiol. 40: 338-344.

Anthonisen, N.R., Utz, G., Kryger, M.H., and Urbanetti, J.S.(1976). Exercise tolerance at 4 and 6 Ata.

Undersea Biomed.Res. 3: 95-102.

Armitage, P.(1971). Statistical Methods in Medical Research. Oxford. Blackwell.

Askanazi, J., Silverberg, P.A., Foster, R.J., Hyman, A.I., Milic-Emili, J., and Kinney, J.M.(1980). Effects of respiratory apparatus on breathing pattern.

J.Appl.Physiol. 48: 577-580.

Asmussen, E.(1964). Muscular Exercise.

In Handbook of Physiology. Section 3. Respiration. Ed. W.O. Fenn and H. Rahn. Washington DC. American Physiological Society. pp. 939-978.

Asmussen, E., and Christensen, E.H.(1939). Die Mittelkapazitat der Lungen bei erhohtem O_2-Bedarf.

Skand.Arch.Physiol. 82: 210-211.

Åstrand, I., Åstrand P.-O., Christensen, E.H., and Hedman, R.(1960). Circulatory and respiratory adaptation to severe muscular work.

Acta.Physiol.Scand. 50: 254-258.

Åstrand P.-O., Cuddy, T.E., Saltin, B., and Stenberg, J.(1964). Cardiac output during submaximal and maximal work.

J.Appl.Physiol. 19: 268-274.

Åstrand P.-O., and Rodahl, K.(1977). Textbook of Work Physiology.

New York. McGraw-Hill. pp. 131-140.

Aubier, M., Trippenbach, T., and Roussos, Ch.(1981). Respiratory muscle fatigue during cardiogenic shock.

J.Appl.Physiol. 51: 499-508.

Aubier, M., Vires, N., Syllie, G., Mozes, R., and Roussos, Ch.(1982). Respiratory muscle contribution to lactic acidosis in low cardiac output.

Am.Rev.Respir.Dis. 126: 648-652.

Axen, K., and Bergofsky, E.H.(1977). Thoracic reflexes stabilizing loaded ventilation in normal and cord injured man.

J.Appl.Physiol. 43: 339-346

Axen, K., Haas, F., Gaudino, D., and Hass, J.P.(1984). Effect of mechanical loading on breathing pattern in women.

J.Appl.Physiol. 56: 175-181.

Bai, T.R., Rabinovitch, B.J., and Pardy, R.L.(1984). Near maximal voluntary hyperpnea and ventilatory muscle function.

J.Appl.Physiol. 57: 1742-1748.

Bailey, N.T.J.(1959). Statistical Methods in Biology. London. English Universities Press.

Baker, J.P., Frazier, D.T., Hanley, M., and Zechman, F.W.(1979). Behaviour of expiratory neurones in response to mechanical and chemical loading.

Respir.Physiol. 36: 337-351.

Bang, O.(1936). The lactate content of the blood during and after muscular exercise in man.

Skand.Arch.Physiol. Suppl. 10: 51-82.

Bartlett, D., Sant'Ambrogio, G., and Wise, J.C.M.(1976). Transduction properties of tracheal stretch receptors.

J.Physiol. 258: 421-432.

Bartlett, R.G., Brubach, H.F., Specht, H.(1958). Oxygen cost of breathing.

J.Appl.Physiol. 12: 413-424.

Beaver, W.L., and Wasserman, K.(1968). Transients at start and end of exercise.

J.Appl.Physiol. 25: 390-399.

Behrakis, P.K., Higgs, B.D., Baydur, A., Zin, A., and Milic-Emili, J.(1983). Active inspiratory impedance in halothane anaesthetised humans.

J.Appl.Physiol. 54: 1477-1481.

Bellemare, F., and Grassino, A.(1982_a). Effect of pressure and timing on contraction of human diaphragm.

J.Appl.Physiol. 53: 1190-1195.

Bellemare, F., and Grassino, A.(1982_b). Evaluation of human diaphragm fatigue.

J.Appl.Physiol. 53: 1196-1206.

Belville, J.W., Whipp, B.J., Kaufman, R.D., Swanson, G.D., Aoleh, K.A., and Wiberg, D.M.(1979). Central and peripheral chemoreflex gain in normal and carotid body resected subjects.

J.Appl.Physiol. 46: 843-860.

Bertram, F.W., Wasserman, K., and Van Kessel, A.L.(1967). Gas exchange following lactate and pyruvate injections.

J.Appl.Physiol. 23: 190-197.

Bland, S., Lazerou, G. Dyck, and Cherniack, R.M.(1967). The influence of the chest wall on respiratory rate and depth.

Respir.Physiol. 3: 47-54.

Bradley, G.W., Euler, C., Martilla, I., and Roos, B.(1974). Transient and steady state effects of CO_2 on mechanisms determining rate and depth of breathing.

Acta.Physiol.Scand. 92: 351-363.

Bradley, M.E., and Leith, D.E.(1978). Ventilatory muscle training and the oxygen cost of sustained hyperpnea.

J.Appl.Physiol. 45: 885-892.

Bretschger, H.J.(1925). The curve of velocity of human respiratory air (pneumotachogram).

Arch.Ges.Physiol. 210: 134-148.

Bruce, E.N., von Euler, C., and Yamashiro, S.M.(1979). Reflex and central chemoceptive control of the time course of inspiratory activity.

In Central Nervous Control Mechanisms in Breathing Ed. C. von Euler and H. Lagercrantz. Oxford. Pergamon. pp. 177-184.

Bruce, E.N., Smith, J.D., and Grodins F.S.(1974). Chemical and reflex drives to breathing during resistance loading in cats.

J.Appl.Physiol. 37: 176-182.

Buchler, Y., Jammes, Y., Delpierre, S., Rasidakis, A., and Roussos, Ch.(1984). Effect of peripheral phrenic nerve stimulation on motor phrenic output.

Bull.Eur.Physiopathol.Respir. 20: 1A.

Buchler, Y., Magder, S., and Roussos, C.(1985). Effects of diaphragmatic frequency and duty cycle on diaphragmatic blood flow.

J.Appl.Physiol. 58: 265-273.

Buick, F.J., Gledhill, N., Froese, A.B., Spriet, L., and Meyers, E.C.(1980). Effect of induced erythrocythemia on aerobic work capacity.

J.Appl.Physiol. 45: 636-642.

Bye, P.T.P., Esau, S.A., Walley, K.R., Macklem, P.T. and Pardy, R.L.(1984). Ventilatory muscles during exercise in air and oxygen in normal man.

J.Appl.Physiol. 56: 464-471.

Bye, P.T.P., Farkas, G.A., and Roussos, Ch.(1983). Respiratory factors limiting exercise.

Ann.Rev.Physiol. 45: 439-451.

Cain, S.M.(1970). Increased oxygen uptake with passive hyperventilation of dogs.

J.Appl.Physiol. 28: 4-7.

Cain, C.C., and Otis, A.B.(1949). Some physiological effects resulting from added resistance to respiration.

J.Aviation.Med. 20: 149-160.

Callahan, D., and Read, D.J.C.(1974). The role of arterial chemorecptors in the breath-by-breath augmentation of respiratory effort in rabbits during airway occlusion or elastic loading.

J.Physiol. 241: 33-44.

Campbell, E.J.M.(1952). An electromyographic study of the role of the abdominal muscles in breathing.

J.Physiol. 117: 222-223.

Campbell, E.J.M., Dickinson, C.J., Dinnick, O.P., and Howell, J.B.L.(1961_a). The immediate effects of threshold loads on the breathing of men and dogs.

Clin.Sci. 21: 309-320.

Campbell, E.J.M., Dinnick, O.P, and Howell, J.B.L.(1961_b). The immediate effects of elastic loads on the breathing of man.

J.Physiol. 156: 260-273.

Campbell, E.J.M., Gandevia, S.C., Killian, K.J., Mahutte, C.K., and Rigg, J.R.A.(1980). Changes in the perception of inspiratory resistive loads during partial curarization.

J.Physiol. 309: 93-100.

Campbell, E.J.M., and Green, J.H.(1953). The variations in intraabdominal pressure and the activity of the abdominal muscles during breathing; a study in man.

J.Physiol. 122: 282-290.

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

J.Appl.Physiol. 11: 303-308.

Campbell, E.J.M., Westlake, E.K., and Cherniack, R.M.(1959). The oxygen consumption and efficiency of the respiratory muscles of young male subjects.

Clin.Sci. 18: 55-65.

Camporesi, E., and Sant'Ambrogio, G.(1971). Influences on the respiratory rhythm originating from the lungs and the chest wall.

Pflügers Arch. 324: 311-318.

Cerretelli, P., Sikand, R.S., and Fahri, L.E.(1969). Effect of increased airway resistance on ventilation and gas exchange during exercise.

J.Appl.Physiol. 27: 597-600.

Chapler, C.K., Stainsby, W.N., and Gladden, L.B.(1980). Effect of changes in blood flow, norepinephrine, and pH on oxygen uptake by resting skeletal muscle.

Can.J.Physiol.Pharmacol. 58: 93-96.

Cherniack, R.M.(1958). The oxygen consumption and efficiency of the respiratory muscles of young male subjects.

Clin.Sci. 18: 55-64.

Cherniack, R.M.(1959). The oxygen consumption and efficiency of the respiratory muscles in health and emphysema.

J.Clin.Invest. 38: 494-499.

Cherniack, N.S., and Altose, M.D.(1981). Respiratory responses to ventilatory loading.

In The Regulation of Breathing: Lung Biology in Health and Disease Vol. 17, Pt.II. Ed. T.F. Hornbein. New York. Marcel Dekker. pp. 905-964.

Chiang, S.T., Steigbigel, N.H., and Lyons, H.A.(1965). Pulmonary compliance and non-elastic resistance during treadmill exercise.

J.Appl.Physiol. 20:1194-1198.

Chirtel, S.J., Barbee, R.W., and Stainsby, W.N.(1984). Net O_2, CO_2, lactate and acid exchange by muscle during progressive working contractions.

J.Appl.Physiol. 56: 161-165.

Citterio, G., and Agostoni, E.(1983). Inspiratory facilitation and inhibition from pulmonary stretch receptors in rabbits.

Respir.Physiol. 53: 307-323.

Clark, F.J., and von Euler, C.(1972). On the regulation of depth and rate of breathing.

J.Physiol. 222: 267-295.

Clark, T.J.H., Freedman, S., Campbell, E.J.M., and Winn, R.R.(1969). The ventilatory capacity of patients with chronic airways obstruction.

Clin.Sci. 36: 307-316.

Cohen, R.D., and Iles, R.A.(1977). Lactic acidosis: A clinically significant aspect of shock.

Clin.Sci.Mol.Med. 53: 405-410.

Cohen, R.D., and Simpson, B.R.(1975). Lactate metabolism.

Anaesthesiology 43: 661-673.

Cohen, C., Zagelbaum, G., Gross, D., Roussos, C., and Macklem, P.T.(1982). Clinical manifestations of inspiratory muscle fatigue.

Am.J.Med. 73: 308-316.

Collet, P.W., and Engel, L.A.(1986). Influence of lung volume on oxygen cost of resistive breathing.

J.Appl.Physiol. 61: 16-24.

Collet, P.W., Perry, C., and Engel, L.A.(1985). Pressure-time product, flow, and oxygen cost of resistive breathing.

J.Appl.Physiol. 58: 1263-1272.

Comroe, H., Forster, R.E., Dubois, A.B., Briscoe, W.A., and Carlsen, E.(1962). The Lung. Chicago. YBMP Inc.

Cooper, E.A.(1961). Behaviour of respiratory apparatus.

National Coal Board Medical Service Report.

Corda, M., Eklund, G., and Euler, C.(1965). External intercostal and phrenic alpha motor responses to changes in respiratory load.

Acta.Physiol.Scand. 63: 391-400.

Cotes, J.E., Saunders, M.J., and Sen Gupta, J.(1977). Functional residual capacity in man during altered chemical drive to respiration.

J.Physiol. 264: 42P-43P

Cournand, A., Richards, D.W., Bader, R.A., Bader, M.E., and Fishman, A.P.(1954). The oxygen cost of breathing.

Trans.Ass.Amer.Physns. 67: 162-173.

Courtice, F.C., Douglas, C.G., and Priestly, J.G.(1939). Adrenaline and muscular exercise.

Proc.Roy.Soc. 127: 288-297.

Craig, F.N., Blevins, W.V., and Cummings, E.G.(1970). Exhausting work limited by external resistance and inhalation of carbon dioxide.

J.Appl.Physiol. 29: 847-851.

Crossfill, M.L., and Widdicombe, I.G.(1961). Physical characteristics of the chest and lungs and the work of breathing in different mammalian species.

J.Physiol. 158: 1-14.

Cunningham, D.J.C., and Gardner, W.N.(1977). A quantitative description of the pattern of breathing during steady state CO_2 inhalation in man with special emphasis on expiration.

J.Physiol. 272: 613-632.

Cunningham, D.J.C., Robbins, P.A., and Wolff, C.B.(1986). Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH.

In Handbook of Physiology. The respiratory system. II. Bethesda. American Physiological Society. pp. 475-528.

D'Angelo, E., Misserocchi, G., and Agostoni, E.(1976). Effect of rib-cage or abdomen compression at iso-lung volume on breathing pattern.

Respir.Physiol. 28: 161-177.

Davenport, P.W., Frazier, D.T., and Zechman, F.W.(1981). The effect of the resistive loading of inspiration and expiration on pulmonary stretch receptor discharge.

Respir.Physiol. 43: 299-314.

Davenport, P.W., Friedman, W.A., Thompson, F.J., and Franzen, O.(1986). Respiratory-related cortical potentials evoked by inspiratory occlusion in humans.

J.Appl.Physiol. 60: 1843-1848.

Deal, E.C., McFadden, E.R., Ingram, R.H., and Jaeger, J.J.(1979). Esophageal temperature during exercise in asthmatic and non-asthmatic subjects.

J.Appl.Physiol. 46: 484-490.

Decima, E.E., and Euler, C.(1969). Excitability of phrenic motor neurones to afferent input from lower intercostal nerves in the spinal cat.

Acta.Physiol.Scand. 75: 580-591.

Decima, E.E., Euler, C., and Thoden, U.(1967). Spinal intercostal-to-phrenic reflexes.

Acta.Physiol.Scand. 75: 568-579.

Demedts, M., and Anthonisen, N.R.(1973). Effects of increased external airway resistance during steady-state exercise.

J.Appl.Physiol. 35: 361-316.

Dempsey, J.A., Hanson, P.E., and Mastenbrook, S.M.(1981). Arterial hypoxaemia during exercise in highly trained runners.

Fed.Proc. 40: 396.

Dempsey, J.A., Hanson, P.E., Pegelow, D., and Claremont, A.(1982). Limitations to exercise capacity and endurance: Pulmonary system.

Can.J.Appl.Sport. 7: 4-13.

Dempsey, J.A., Hanson, P.E., Pegelow, D., and Fregosi, R.(1982). Mechanical vs. chemical determinants of hyperventilation in heavy exercise.

Med.Sci.Sports.Exer. 14: 131.

Dempsey, J.A., Thompson, J.M., Forster, H.V., Cerny, F.C., and Chosy, L.W.(1975). HbO_2 in man during prolonged work in chronic hypoxia.

J.Appl.Physiol. 38: 1022-1029.

Depocas, F., Minaire, Y., and Chatonnet J.(1969). Rates of formation of and oxidation of lactic acid in dogs at rest and during moderate exercise.

Can.J.Physiol.Pharmacol. 43: 603-610.

Dressendorfer, R.H., Wade, C.E., and Bernauer, E.M.(1977). Combined effects of breathing resistance and hyperoxia on aerobic work tolerance.

J.Appl.Physiol. 42: 444-448.

Duane, S.F., Weir, E.K., Stewart, R.M., and Niewoeher, D.E.(1979). Distal airway responses to changes in oxygen and carbon dioxide tensions.

Respir.Physiol. 38, 303-311.

D'Urzo, A.D., Chapman, K.R., and Rebuck, A.S.(1987). Effect of inspiratory resistive loading on control of ventilation during progressive exercise.

J.Appl.Physiol. 62: 134-140.

Eggleton, M.G., and Evans, R.C.(1930). The lactic acid content of the blood after muscular contraction under experimental conditions.

J.Physiol. 70: 269-293.

Eisele, J., Trenchard, D., Burki, N., and Guz, A.(1968). The effect of chest wall block on respiratory sensation and control in man.

Clin.Sci. 35: 23-33.

Ekelund, L.G. and Holmgren, A.(1967). Central haemodynamics during exercise.

Circ.Res. Suppl. 20: 1-33.

Eldridge, F.(1966). Anaerobic metabolism of the respiratory muscles.

J.Appl.Physiol. 21: 853-857.

Eldridge, F., and Davis, J.M.(1959). Effect of mechanical factors on respiratory work and the ventilatory response to CO_2.

J.Appl.Physiol. 14: 721-726.

El-Manshawi, A., Killian, K.J., Summers, E., and Jones, N.L.(1986). Breathlessness during exercise with and without resistive loading.

J.Appl.Physiol. 61: 896-905.

England, S.J., Bartlett, D., and Daubenspeck, J.A.(1982). Influence of human vocal cord movements on airflow and resistance during eupnoea.

J.Appl.Physiol. 52: 773-779.

Euler, C.(1986). Brain stem mechanisms for generation and control of breathing pattern

In Handbook of Physiology. The respiratory system. II. Bethesda. American Physiological Society. pp. 1-67.

Euler, C., and Trippenbach, T.(1976). Excitability changes of the inspiratory "off-switch" mechanism tested by electrical stimulation in the nucleus parabrachialis in the cat.

Acta.Physiol.Scand. 97: 175-188.

Evanich, M.J., Franco, M.J., and Lourenco, R.V.(1973). Force output of the diaphragm as a function of phrenic nerve firing rate and lung volume.

J.Appl.Physiol. 35: 208-212.

Fagraeus, L.(1974). Maximal work performance at raised air and helium-oxygen pressures.

Acta.Physiol.Scand. 91: 545-556.

Field, S., Sanci, S., and Grassino, A.(1984). Respiratory muscle oxygen consumption estimated by the diaphragm pressure-time index.

J.Appl.Physiol. 57:44-51.

Fincham, W.F., and Priban, I.P.(1965). Autonomic control of respiration.

Proc.2nd.IAFC.Symp. The theory of self-adaptive control systems. pp. 57-63.

Fixler, D.E., Atkins, J.M., Mitchell, J.H., and Horwitz, L.D.(1976). Blood flow to respiratory, cardiac and limb muscles in dogs during graded exercise.

Am.J.Physiol. 231: 1515-1519.

Flook, V., and Kelman, G.R.(1973). Submaximal exercise with increased inspiratory resistance to breathing.

J.Appl.Physiol. 35: 379-384.

Freedman, S., and Campbell, E.J.M.(1970). The ability of normal subjects to tolerate added inspiratory loads.

Respir.Physiol. 10: 213-235.

Freedman, S., Cooke, N.T., and Moxham, J.(1983). Production of lactic acid by the respiratory muscles.

Thorax 38: 50-54.

Freedman, S., and Weinstein, S.A.(1965). Effects of external elastic and threshold loading on breathing in man.

J.Appl. Physiol. 20: 469-474.

Fritts, H.W., Jr., Filler, J., Fishman, A.P., and Cournand, A.(1959). The efficiency of ventilation during voluntary hyperpnea. Studies in normal subjects and in dypsnoeic patients with either chronic pulmonary emphysema or obesity.

J.Clin.Invest. 38: 1339-1348.

Fuchs, F., Reddy, V., and Briggs, F.N.(1970). The interaction of cations with the calcium binding site of troponin.

Biochim.Biophys.Acta. 221: 407-409.

Gaesser, G.A., and Brooks, G.A.(1975). Muscular efficiency during steady-state exercise: The effect of speed and work rate.

J.Appl.Physiol. 38: 1132-1139.

Galbo, H., Holst, J.J., and Christensen, N.J.(1975). Glucagon and plasma catecholamine responses to graded and prolonged exercise in man.

J.Appl.Physiol. 38: 70-76.

Gallagher, C.G., Browne, E., and Younes, M.(1987). Breathing pattern during maximal exercise and during sub-maximal exercise with hypercapnia.

J.Appl.Physiol. 63: 238-244.

Gallagher, C.G., Hof, V.I., and Younes, M.(1985). Effect of inspiratory muscle fatigue on breathing pattern.

J.Appl.Physiol. 59: 1152-1158.

Gardner, W.N.(1975). Some factors affecting respiration in man.

D.Phil. Thesis. University of Oxford.

Gardner, W.N.(1977). The relation between VT and inspiratory and expiratory times during steady state carbon dioxide inhalation in man.

J.Physiol. 272: 591-611.

Garfinkel, F., and Fitzgerald, R.S.(1978). The effect of hyperoxia, hypoxia and hypercapnia on FRC and occlusion pressure in human subjects.

Respir.Physiol. 33: 241-250.

Garrard, C.S., and Lane, D.J.(1978). The pattern of stimulated breathing in man during non-elastic expiratory loading.

J.Physiol. 279: 17-29.

Gautier, H.(1973). Respiratory responses of the anaesthetised rabbit to vagotomy and thoracic dorsal rhizotomy.

Respir.Physiol. 17: 238-247.

Goldman, M.D., Grimby, G., and Mead, J.(1976). Mechanical work of breathing derived from rib-cage and abdominal V-P partitioning.

J.Appl.Physiol. 41: 752-763.

Grassino, A., Lewinson, G.E., and Tyler, J.M.(1973). Effects of hyperinflation of the thorax on the mechanics of breathing.

J.Appl.Physiol. 35: 336-342.

Green, M., Mead, J., and Sears, T.(1978). Muscle activity during chest wall restriction and positive pressure breathing in man.

Respir.Physiol. 35: 383-400.

Grimby, G., Bunn, J., and Mead, J.(1968). Relative contribution of rib-cage and abdomen to ventilation during exercise.

J.Appl.Physiol. 24: 159-166.

Grimby, G., Goldman, M., and Mead, J.(1976). Respiratory muscle action inferred form rib cage and abdominal V-P partitioning.

J.Appl.Physiol. 41: 739-751.

Grimby, G., Saltin, B., and Wilhelmsen, L.(1971). Pulmonary flow-volume and pressure-volume relationships during sub-maximal and maximal exercise in young well-trained men.

Bull.Eur.Physiopathol.Respir. 7: 157-168.

Grollman, A.(1930). Physiological variations in the cardiac output of man; the effect of breathing carbon dioxide and of voluntary forced ventilation on the cardiac output of man.

Am.J.Physiol. 94: 287-299.

Guz, A., Noble, M.I.M., Eisele, J.H., and Trenchard, D.(1970). The role of vagal inflation reflexes in man and other animals.

In Breathing. Hering-Breuer Centenary Symposium. Ed. R.F. Porter. London. Churchill. pp. 17-39.

Guz, A., Noble, M.I.M., Trenchard, D., Cochrane, H.L., and Markey, A.R.(1964). Studies on the vagus nerve in man: their role in respiratory and circulatory control.

Clin.Sci. 27: 293-300.

Guz, A., and Trenchard, D.(1971). Pulmonary stretch receptor activity in man: a comparison with dog and cat.

J.Physiol. 213: 329-343.

Hales, J.R.S.(1973). Effects of heat stress on blood flow in respiratory and non-respiratory muscles in the sheep.

Pflügers Arch. 345: 123-130.

Hämäläinen, R.P.(1983). Optimisation of respiratory airflow.

In Modelling and Control of Breathing. Ed. B.J. Whipp and D.M. Wiberg. New York. Elsevier. pp. 181-188.

Hämäläinen, R.P., and Viljanen, A.A.(1978_a). A hierarchical goal-seeking model of the control of breathing. I: Model description.

Biol.Cybernetics. 29: 151-158.

Hämäläinen, R.P., and Viljanen, A.A.(1978_b). A hierarchical goal-seeking model of the control of breathing. II: Model performance.

Biol.Cybernetics. 29: 159-166.

Hanson, J.S., Tabakin, B.S., and Caldwell, E.J.(1962). Response of lung volumes and ventilation to posture change and upright exercise.

J.Appl.Physiol. 17: 783-786.

Harper, H.A., Rodwell, V.W., and Mayes, P.A.(1977). Review of Physiological Chemistry. 16th ed. Los Altos. California. Lange Medical Publications, p. 256.

Hey, E.N., Lloyd, B.B., Cunningham, D.J.C., Jukes, M.G.M., and Bolton, D.P.G.(1966). Effects of various respiratory stimuli on the depth and frequency of breathing in man.

Respir.Physiol. 1: 193-205.

Hill, A.V.(1938). The heat of shortening and dynamic constants of muscle.

Proc.Roy.Soc. 126: 136-195.

Hill, A.V.(1964). The effect of load on the heat of shortening muscle.

Proc.R.Soc. 159: 297-318.

Hill, J.R.(1959). The oxygen consumption of the new born and adult mammals, its dependence on the oxygen tension in the inspired air and on environmental temperatures.

J.Physiol. 149: 346-373.

Hollanders, F.D.(1968). The production of lactic acid by the perfused rat diaphragm.

Comp.Biochem.Physiol. 26: 907-916.

Hwang, J.C., St. John, W.C., and Bartlett, D.(1984). Receptors corresponding to changes in upper airway pressure.

Respir.Physiol. 55: 355-366.

Jaeger, M.J., and Otis, A.B.(1964). Effects of compressibility of alveolar gas on dynamics and work of breathing.

J.Appl.Physiol. 19: 83.

Jammes, Y., Buchler, B., Delpiere, S., Grimand, C., Rasichakis, A., and Roussos, C.(1984). Investigation of the presence of small afferent fibres in the cat phrenic nerve and of their possible functional role.

Bull.Eur.Physiopathol.Respir. 20: 4A

Jardim, J., Farkas, G., Prefaut, C., Thomas, D., Macklem, P.T., and Roussos, Ch.(1981). The failing inspiratory muscles under normoxic and hypoxic conditions.

Am.Rev.Resp.Dis. 124: 274-279.

Jennet, S., Russel, T., and Warnock, K.A.(1974). The duration of inspiration during changing states of ventilation in man.

J.Physiol. 238: 54P-55P.

Jensen, J.I., Lyager, S., and Pedersen, O.F.(1980). The relationship between maximal ventilation, breathing pattern and mechanical limitation of ventilation.

J.Physiol. 309: 521-532.

Jones, G.L., Killian, K.J., Summers, E., and Jones, N.L.(1985). Inspiratory muscle forces and endurance in maximum resistive loading.

J.Appl.Physiol. 58: 1608-1615.

Kagawa, J., and Kerr, H.D.(1970). Effects of brief graded exercise on specific airway conductance in normal subjects.

J.Appl.Physiol. 28: 138-144.

Kaminski, R.P., Forster, H.V., Klein, J.P., Pan, L.G., Bisgard, G.E., and Hamilton, L.H.(1982). Effect of elevated P_ICO_2 on metabolic rate in humans and ponies.

J.Appl.Physiol. 52: 1623-1628.

Kao, F.F., Mei, S.S., and Kalia, M.(1979). Interaction between neurogenic exercise drive and chemical drive.

In Central Nervous Control Mechanisms in Breathing Ed. C. von Euler and H. Lagercrantz. Oxford. Pergamon. p. 75-89.

Karetsky, M.S., and Cain, S.M.(1969). Oxygen uptake stimulation following Na-L-lactate infusion in anaesthetized dogs.

Am.J.Physiol. 216: 1486-1490.

Karetsky, M.S., and Cain, S.M.(1970). Effect of carbon dioxide on oxygen uptake during hyperventilation in normal man.

J.Appl.Physiol. 28: 8-12.

Karlson, J., and Saltin, B.(1970). Lactate, ATP and CP in working muscles during exhaustive exercise in man.

J.Appl.Physiol. 29: 598-602.

Kay, J.D.S., Petersen, E.S., and Vejby-Christhensen.(1975_a). Breathing in man during steady-state exercise on the bicycle at two pedalling frequencies, and during treadmill walking.

J.Physiol. 251: 645-656.

Kay, J.D.S., Petersen, E.S., and Vejby-Christhensen.(1975_b). Mean breath by breath pattern of breathing in man during steady state exercise.

J.Physiol. 251: 657-659.

Khambatta, H.J., and Sullivan, S.F.(1973). Effects of respiratory alkalosis on oxygen consumption and oxygenation.

Anaesthesiology. 38: 53-58.

Killian, K.J., Summers, E., Basalygo, M., and Campbell, E.J.M.(1985). Effect of frequency on perceived magnitude of added loads to breathing.

J.Appl.Physiol. 58: 1616-1621.

Kiwull-Schöne, H., Ward, S.A., and Kiwull, P.(1981). The involvement of expiratory termination in vagally mediated facilitation of ventilatory CO_2 responsiveness during hyperoxia.

Pflügers Arch. 390: 63-69.

Knox, C.K.(1979). Reflex and central mechanisms controlling expiratory duration.

In Central Nervous Control Mechanisms in Breathing Ed. C. von Euler and H. Lagercrantz. Oxford. Pergamon. p. 203-216.

Kowalchuk, J.M., Heigenhauser, G.J.F., and Jones, N.L.(1984). Effect of pH on metabolic and cardiorespiratory responses during progressive exercise.

J.Appl.Physiol. 57: 1558-1563.

Kryger, M.H., Yacoub, O., and Anthonisen, N.R.(1975). Effect of inspiratory resistance on occlusion pressure in hypoxia and hypercapnia.

Respir.Physiol. 24: 241-248.

Lafortuna, C.L., Minetti, A.E., and Mognoni, P.(1984). Inspiratory flow pattern in humans.

J.Appl.Physiol. 57: 1111-1119.

Leaver, D.G., and Pride, N.B.(1971). Flow-volume curves and expiratory pressures during exercise in patients with chronic airways obstruction.

Scand.J.Respir.Dis Suppl. 77: 23-27.

Leith, D.E., and Bradley, M.(1976). Ventilatory muscle strength and endurance training.

J.Appl.Physiol. 41: 508-516.

Liljestrand, G.(1918). Untersuchungen uber die atmungsarbeit.

Skand.Arch.Physiol. 35: 199-293.

Lind, F., and Hesser, C.M.(1984). Breathing pattern and lung volumes during exercise.

Acta.Physiol.Scand. 120: 123-129.

Linnarson, D.(1974). Dynamics of pulmonary gas exchange and heart rate changes at start and end of exercise.

Acta.Physiol.Scand. 415: 1-68.

Lloyd, B.B., Jukes, M.G.M., and Cunningham, D.J.C.(1958). The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man.

Q.J.Exp.Physiol. 43: 214-227.

Lloyd, B.B. and Zachs, R.M.(1972). Mechanical efficiency in man.

J.Physiol. 224: 57P.

Loke, J., Mahler, D.A., and Virgulto, J.A.(1982). Respiratory muscle fatigue after marathon running.

J.Appl.Physiol. 52: 821-824.

Lopata, M., Onal, E., and Cromydas, G.(1985). Respiratory load compensation in chronic airway obstruction.

J.Appl.Physiol. 59: 1947-1954.

Lopata, M., Evanich, M.J., and Lourenco, R.V.(1977). Quantification of diaphragmatic EMG response to CO_2 rebreathing in humans.

J.Appl.Physiol. 43: 262-270.

Lopata, M., Onal, E., Evanich, M.J., and Lourenco, R.V.(1980). Respiratory neuromuscular response to CO_2 rebreathing with inspiratory flow resistance in humans.

Respir.Physiol. 39: 95-110.

Lopata, M., Onal, E., and Ginzburg, A.S.(1983). Respiratory muscle function during CO_2 rebreathing with inspiratory flow resistive loading.

J.Appl.Physiol. 54: 475-482.

Lopes, J.M., Muller, N.L., and Bryan, C.A.(1981). Synergistic behaviour inspiratory muscles and diaphragmatic fatigue in the new born.

J.Appl.Physiol. 57: 547-551.

McGregor, M., and Becklake, M.R.(1961). The relationship of oxygen cost of breathing to respiratory mechanical work and respiratory force.

J.Clin.Invest. 40: 971-980.

McIlroy, M.B., Butler, J., and Finley, T.(1962). Effects of chest compression on reflex ventilatory drive and pulmonary function.

J.Appl.Physiol. 17: 701-705.

Macdougal, J.D.(1977). The anaerobic threshold: Its significance for the endurance athlete.

Can.J.Appl.Sport.Sci. 2: 137-140.

Macklem, P.T., Gross, D., Grassino, A., and Roussos, C.(1978). Partitioning of inspiratory pressure swings between diaphragm and intercostal/accessory muscles.

J.Appl.Physiol. 44: 200-208.

Mahler, D.A., and Loke, J.(1981). Lung function after marathon running at warm and cold ambient temperatures.

Am.Rev.Resp.Dis. 124: 124: 154-157.

Marey, E.(1865). Pneumographia: Etude graphique des mouvements respiratoires et des influences qui les modifent.

J.Anat. (Paris) 2: 425-453.

Margaria, R., Edwards, H.T., and Dill, D.B.(1933). The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction.

Am.J.Physiol. 106: 689-715.

Magaria, R., Milic-Emili, G., Petit, J.M., and Cavagna G.(1960). Mechanical work of breathing during muscular exercise.

J.Appl.Physiol. 15: 354-357.

Marsh, J.(1982). Some factors affecting respiration in man.

D.Phil. Thesis. University of Oxford.

Marshall, R.(1962). The relationship between stimulus and work of breathing at different lung volumes.

J.Appl.Physiol. 17: 917-921.

Martin, J., Aubier, M., and Engel, L.A.(1982_a). Effects of inspiratory loading on respiratory muscle activity during expiration.

Am.Rev.Respir.Dis. 125: 352-358.

Martin, B.J., Chen, H-I., and Kolka, M.A.(1984). Anaerobic metabolism of the respiratory muscles during exercise.

Med.Sci.Sports Exer. 16: 82-86.

Martin, J.G., and De Troyer, A.(1982). The behaviour of the abdominal muscles during inspiratory mechanical loading.

Respir.Physiol. 50: 63-73.

Martin, B., Heintzelman, M., and Chen H.(1982_b). Exercise performance after ventilatory work.

J.Appl.Physiol. 52: 1581-1585.

Mead, J.(1960). Control of respiratory frequency.

J.Appl.Physiol. 15: 325-336.

Mead, J.(1979). Responses to loaded breathing.

Bull.Physiopathol.Respir. 15 (Suppl.): 61-71.

Mengeot, P.M., Bates, J.H.T., and Martin, J.G.(1985). Effect of mechanical loading on displacements of chest wall during breathing in humans.

J.Appl.Physiol. 58: 477-484.

Mertz, J., Paulev, P-E., and Pedersen, S.S.(1975). Breathing at supramaximal ventilations during rebreathing and steady state exercise.

Acta.Physiol.Scand. 95: 63A-64A.

Metias, E.F.(1981). Some factors affecting respiration in man.

D.Phil Thesis. University of Oxford.

Milic-Emili, J.(1982). Recent advances in clinical assessment of control of breathing.

Lung. 160: 1-17.

Milic-Emili, J., and Pengelly, L.D.(1970). Ventilatory effects of mechanical loading.

In The Respiratory Muscles: Mechanics and Neural Control. Ed. E.J.M. Campbell, E. Agostoni and J.N. Davis. London. Lloyd-Luke. pp. 271-290.

Milic-Emili, G., and Petit, J.M.(1960). Mechanical efficiency of breathing.

J.Appl.Physiol. 15: 359-362.

Milic-Emili, J., and Tyler, J.M.(1963). Relation between work output of the respiratory muscles and end-tidal CO_2 tension.

J.Appl.Physiol. 18: 497-504.

Milic-Emili, J.E., and Zin, W.A.(1986). Breathing responses to imposed mechanical loads.

In Handbook of Physiology. The respiratory system. II. Bethesda. American Physiological Society. pp. 751-769.

Mithoefer, J.M. and Karetsky, M.S.(1968). Comparative effects of organic and mineral acid on acid-base balance and gas exchange.

J.Lab.Clin.Med. 72: 924-932.

Morris, M.E., and Millar, R.A.(1962). Blood pH/plasma catecholamine relationships; non-respiratory acidosis.

Brit.J.Anaesthesia 34: 682-689.

Morrow, P.E., and Vosteen, R.E.(1953). Pneumotachographic studies in man and dog incorporating a portable wireless transducer.

J.Appl.Physiol. 5: 348-360.

Murphy, A.J., Koepke, G.H., Smith, E.M., and Dickinson, D.(1959). Sequence of action of the diaphragm and intercostal muscles during respiration. II. Expiration.

Arch.Phys.Med.Rehabil. 40: 337-342.

Naimark, A., Jones, N.L., and Lal, S.(1965). The effect of hypoxia on gas exchange and arterial lactate and pyruvate concentrations during moderate exercise.

Clin.Sci.Mol.Med. 28: 1-13.

Nakamura, Y., and Schwartz S.(1972). The influence of hydrogen ion concentration on calcium binding and release by skeletal muscle sarcoplasmic reticulum.

J.Gen.Physiol. 59: 22-3.

Newhouse, M.T., Becklake, M.T., Macklem, P.T., and McGregor, M.(1964). Effect of alterations in end-tidal CO_2 tension on flow resistance.

J.Appl.Physiol. 19: 745-749.

Newsom Davis, J.(1967). Contribution of somatic receptors in the chest wall to detection of added inspiratory airway resistance.

Clin.Sci. 33: 249-260.

Newsom Davis, J., Goldman, M., Loh, L., and Casson, M.(1976). Diaphragm function and alveolar hyperventilation.

Q.J.Med. 45: 87-100.

Newsom Davis, J., and Sears, T.A.(1970). The proprioceptive reflex control of the intercostal muscles during their voluntary activation.

J.Physiol. 209: 711-738.

Nielson, M.(1936). Die Respirationsarbeit bei Koperruhe und bei Muskel Arbeit.

Skand.Arch.Physiol. 74: 299-316.

Noll, F.(1974). Lactate determination with LDH, GPT and NAD.

In Methods of Enzymatic Analysis Ed. H. Bergmeyer. New York. Academic Press Inc. p. 1475 ff.

Nunn, J.F., and Ezi-Ashi, T.I.(1961). The respiratory effects of resistance to breathing in anaesthetised man.

Anaesthesiology 22: 174-185.

Olafsson, S., and Hyatt, R.E.(1969). Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects.

J.Clin.Invest. 48: 564-573.

Oliva, P.B.(1970). Lactic acidosis.

Am.J.Med. 48: 209-225.

Otis, A.B.(1954). The work of breathing.

Physiol.Rev. 34, 449-458.

Otis, A.B.(1964). The work of breathing.

In Handbook of Physiology. Section 3, Respiration. Ed. W.O. Fenn and H. Rahn. Washington D.C. American Physiological Society. pp. 463-476.

Otis, A.B., Fenn, W.O., and Rahn, H.(1950). The mechanics of breathing.

J.Appl.Physiol. 2, 592-607.

Ouellet, Y., Poh, S.C., Becklake, M.R.(1969). Circulatory factors limiting maximal exercise capacity.

J.Appl.Physiol. 27: 874-880.

Painter, R.(1987). Some factors affecting respiration in man.

D.Phil. Thesis. University of Oxford.

Pappenheimer, J.R.(1977). Sleep and respiration in rats during hypoxia.

J.Physiol. 266: 191-197.

Pardy, R.L., and Bye, P.T.P.(1985). Diaphragmatic fatigue in normoxia and hyperoxia.

J.Appl.Physiol. 58: 738-742.

Parker, J.C., Peters, R.M., and Barnett, T.B.(1963). Carbon dioxide and the work of breathing.

J.Clin.Invest. 42: 1362-1372.

Pengelly, L.D., Alderson, A.M., and Milic-Emili, J.(1971). Mechanics of the diaphragm.

J.Appl.Physiol. 30: 797-805.

Pengelly, L.D., Tarshis, A.M., and Rebuck, A.S.(1979). Contribution of rib cage and abdomen-diaphragm to tidal volume during CO_2 rebreathing.

J.Appl.Physiol. 46: 709-715.

Peretz, D.I., McGregor, H., and Dossetor, J.B.(1964). Lactic acidosis: Some physiological and clinical considerations.

Can.Med.Assoc.J. 90: 673-675.

Petersen, E.S., Davis, J.A., Wasserman, K., and Whipp, B.J.(1980). Changes in breathing pattern at maximal work rates in man.

Clin.Respir.Physiol. 16: 276P

Petersen E.S., and Vejby-Christensen, H.(1977). Effects of body temperature on ventilatory response to hypoxia and breathing pattern in man.

J.Appl.Physiol. 42: 492-500.

Petit, J.M., Milic-Emili, J., and Delhez, L.(1960). Role of the diaphragm in breathing in conscious normal man: an electromyographic study.

J.Appl.Physiol. 15: 1101-1106.

Phillipson, E.A., Murphy, E., Kozar, L.F.(1976). Regulation of respiration in sleeping dogs.

J.Appl.Physiol. 40: 688-693.

Pope, H., Holloway, R., and Campbell, E.J.M.(1968). The effects of elastic and resistive loading of inspiration on the breathing of conscious man.

Respir.Physiol. 4: 363-372.

Potter, W.A., Olafsson, S., and Hyatt, R.E.(1971). Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease.

J.Clin.Invest. 50: 910-919.

Priban, I.P., and Fincham, W.F.(1965). Self adaptive control and the respiratory system.

Nature. 208: 339-343.

Proctor, D.F., and Hardy, J.B.(1949). Studies of respiratory airflow.

Bull.Johns Hopkins Hosp. 85: 253-280.

Ramal, K., and Strȍm, G.(1949). The rate of lactate utilisation in man during work and at rest.

Act.Physiol.Scand. 17: Fasc.4, Excerptum.

Read, D.J.C., Freedman, S., and Kafer, E.R.(1974). Pressures developed by loaded inspiratory muscles in conscious and anaesthetised man.

J.Appl.Physiol. 37: 207-218.

Rebuck, A.S., Jones, N.L., Campbell, E.J.M.(1972). Ventilatory response to exercise and CO2 rebreathing in normal subjects,

Clin.Sci.Mol.Med. 43: 861-867.

Remmers, J.E.(1970). Inhibition of inspiratory activity by intercostal muscle afferents.

Respir.Physiol. 10: 358-383.

Remmers, J.E.(1973). Extra-segmental reflexes derived from intercostal afferents: Phrenic and laryngeal responses.

J.Physiol. 233: 45-62.

Remmers, J.E., and Bartlett, D.(1977). Reflex control of expiratory airflow and duration.

J.Appl.Physiol. 42: 80-87.

Robertson, C.H., Forster, G.H., and Johnson, R.L.(1977_a). The relationship of respiratory failure to the oxygen consumption of, lactate production by, and distribution of blood flow among respiratory muscles during increasing inspiratory resistance.

J.Clin.Invest. 59: 31-42.

Robertson, C.H., Pagel, A.M., and Johnson, R.L.(1977_b). The distribution of blood flow, oxygen consumption and work output among respiratory muscles during unobstructed hyperventilation.

J.Clin.Invest. 59: 43-50.

Rochester, D.F. and Bettini, G.(1976). Diaphragmatic blood flow and energy expenditure in the dog.

J.Clin.Invest. 57: 661-672.

Rochester, D.F., and Briscoe, A.M.(1979). Metabolism of the working diaphragm.

Am.Rev.Respir.Dis. 119: 101-106.

Rohrer, F.(1925). Physiologie der atembewegung.

In Nandbuch der Normalen und Pathologischen Physiologie. Berlin. Springer. pp. 70-127.

Rose, C.E., Althaus, J.A., Kaiser, D.L., Miller, E.D., and Carey, R.M.(1983). Acute hypoxemia and hypercapnia: increase in plasma catecholamines in conscious dogs.

Am.J.Physiol. 245: H924-H929.

Roussos, C.(1984). Ventilatory muscle fatigue governs breathing frequency.

Bull.Eur.Physiopathol.Respir. 20: 445-451.

Roussos, C., Fixley, M., Gross, D., and Macklem, P.T.(1979). Fatigue of inspiratory muscles and their synergic behaviour.

J.Appl.Physiol. 46: 897-904.

Roussos, Ch.S., and Macklem, P.T.(1977). Diaphragmatic fatigue in man.

J.Appl.Physiol. 43: 189-197.

Roussos, C., and Macklem, P.T.(1982). The respiratory muscles.

N.Eng.J.Med. 307: 786-797.

Ruttiman, U.E., and Yamamoto, W.S.(1972). Respiratory airflow profiles that satisfy power and force criteria of optimality.

Ann.Biomed.Engrn. 1: 146-159.

Saltin, B. and Åstrand, P.-O.(1967). Maximal oxygen uptake in athletes.

J.Appl.Physiol. 23: 353-360.

Sampson, M.G., and De Troyer, A.(1982). Role of intercostal muscles in the rib cage distortions produced by inspiratory loads.

J.Appl.Physiol. 52: 517-523.

Santiago, T.V., Sinha, A.K., and Edelman, N.H.(1981). Respiratory flow-resistive load compensation during sleep.

Am.Rev.Respir.Dis. 123, 382-387.

Scott, I.(1983). Towards lung volume measurement by a rebreathing technique.

D.Phil. Thesis. Univ. of Oxford.

Sechzer, P.H., Egbert, L.D., Linde, H.W., Cooper, D.Y., Dripps, R.D., and Price, H.L.(1960). Effect of CO_2 inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man,

J.Appl.Physiol. 15: 454-458.

Shannon, R., and Zechman, F.W.(1972). The reflex and mechanical response of the inspiratory muscles to an increased airflow resistance.

Respir.Physiol. 16: 51-69.

Shephard, R.J.(1955). The immediate metabolic effects of breathing carbon dioxide mixtures.

J.Physiol. 129: 393-407.

Shephard, R.J.(1966). The oxygen cost of breathing during vigorous exercise.

Quart.J.Exp.Physiol. 51: 336-350.

Shephard, R.J.(1967). The maximum sustained voluntary ventilation in exercise.

Clin.Sci. 32: 167-176.

Silverman, L., Lee, G., Plotkin, T., Sawyers, L.A., and Yancey, A.R.(1951). Airflow measurements with and without respiratory resistance at several work rates.

Arch.Industr.Hyg.Occupat.Med. 3: 461-478.

Sjodin, B., and Jacobs, I.(1981). Onset of blood lactate accumulation and marathon running performance.

Int.J.Sports.Med. 2: 23-26.

Souhrada, M., and Souhrada, J.F.(1981). The direct effect of temperature on airway smooth muscle.

Respir.Physiol. 44, 311-323.

Stryer, L.(1981). Biochemistry.

San Francisco. Freeman and Co.

Stubbing, D.G., and Jones, N.L.(1983). The thorax in exercise.

In The Thorax: The Vital Pump. Ed C. Roussos and P.T. Macklem. Little Brown Publ.

Stubbing, D.G., Pengelly, L.D., Morse, J.L.C., and Jones, N.L.(1980_a). Pulmonary mechanics during exercise in normal males.

J.Appl.Physiol. 49: 506-510.

Stubbing, D.G., Pengelly, L.D., Morse, J.L.C., and Jones, N.L.(1980_b). Pulmonary mechanics during exercise in subjects with chronic airflow obstruction.

J.Appl.Physiol. 49: 511-515.

Tabakin, B.S., and Hanson, J.S.(1960). Response to ventilatory obstruction during steady state exercise.

J.Appl.Physiol. 15: 579-582.

Tallarida, G., Baldoni, F., Peruzzi, G., Raimondi, G., Massaro, M., Abate, A., and Sangiorgi, M.(1983). Different patterns of respiratory reflexes originating in exercising muscle.

J.Appl.Physiol. 55: 84-91.

Tenney, S.M.(1956). Sympatho-adrenal stimulation by carbon dioxide and the inhibitory effect of carbonic acid on epinephrine response.

Am.J.Physiol. 187: 341-346.

Tenney, S.M., and Reese, R.E.(1968). The ability to sustain great breathing efforts.

Respir.Physiol. 5, 187-201.

Tesch, P., Sjodin, B., Thorstensson, A., and Karlsson, J.(1978). Muscle fatigue and its relation to lactate accumulation and LDH activity.

Acta.Physiol.Scand. 103: 413-420.

Thompson, S.H., and Sharkey, B.J.(1966). Physiological cost and air flow resistance of respiratory protective devices.

Ergonomics 9: 495-499.

Tisi, G.M., Wolfe, W.G., and Fallat, R.G.(1970). Effects of O2 and CO2 on airway smooth muscle following pulmonary vascular occlusion.

J.Appl.Physiol. 28: 570-573.

Trippenbach, T., and Milic-Emili, J.(1977). Temperature and CO2 effect on phrenic activity and tracheal occlusion pressure.

J.Appl.Physiol. 43: 449-454.

Troelstra, H.J.(1960). De invloed van afferente vagus in pulsen op ademniveau en frequentie

M.D. Thesis. University of Groningen.

Ward, S.A.(1974). Some factors affecting respiration in man.

D.Phil. Thesis. University of Oxford.

Ward, S.A., and Cunningham, D.J.C.(1977). The relation between hypoxia and CO_2 induced reflex alternation of breathing in man.

Respir.Physiol. 29, 363-378.

Wasserman, K., Van Kessel, A.L., and Burton, G.G.(1967). Interaction of physiological mechanisms during exercise.

J.Appl.Physiol. 22: 71-85

Wasserman, K., Whipp, B.J., Koyal, S.N., and Cleary, M.G.(1976). Effect of carotid body resection on ventilatory and acid base control during exercise.

J.Appl.Physiol. 39: 354

Whipp, B.J., Ward, S.A., Lamara, N., Davis, J.A., and Wasserman, K.(1982). Parameters of ventilatory and gas exchange dynamics during exercise.

J.Appl.Physiol. 52: 1506-1513.

Whitelaw, W.A., Derenne, J.Ph., Couture, J., and Milic-Emili, J.(1976). Adaptation of anaesthetised men to breathing through an inspiratory resistor.

J.Appl.Physiol. 41: 285-291.

Whitelaw, W.A., Derennne, J.-P., and Milic-Emili, J.(1975). Occlusion pressure as a measure of respiratory centre output in conscious man.

Respir.Physiol. 23: 181-199.

Widdicombe, J.G., and Nadel, J.A.(1963). Airway volume, airway resistance, and work and force of breathing: theory.

J.Appl.Physiol. 18: 863-868.

Wiley, R.L., and Zechman, F.W.(1966). Perception of added airflow resistance in humans.

Respir.Physiol. 2: 73-87.

Wood, L.D.H., and Bryan, A.C.(1978). Exercise ventilatory mechanics at increased ambient temperature.

J.Appl.Physiol. 44: 231-237.

Yamashiro, S.M., and Grodins, F.S.(1971). Optimal regulation of respiratory airflow.

J.Appl.Physiol. 30: 597-602.

Yamashiro, S.M., and Grodins, F.S.(1973). Respiratory cycle optimization in exercise.

J.Appl.Physiol. 35: 522-525.

Younes, M., and Kivinen, G.(1984). Respiratory mechanics and breathing pattern during and following maximal exercise.

J.Appl.Physiol. 57: 1773-1782.

Younes, M., and Remmers, J.E.(1981). Control of tidal volume and respiratory frequency.

In The Regulation of Breathing: Lung Biology in Health and Disease Vol. 17, Pt.II. Ed. T.F. Hornbein. New York. Marcel Dekker Inc. pp. 621-671.

Younes, M., and Riddle, W.(1984). Relation between respiratory neural output and tidal volume.

J.Appl.Physiol. 56: 1110-1119.

Zechman, F.W., Frazier, D.T., and Lally, D.A.(1976). Respiratory volume-time relationships during resistive loading in the cat.

J.Appl.Physiol. 40: 177-183.

Zechman, F.W., Hall, F.G., and Hull, W.E.(1957). Effects of graded resistance to tracheal airflow in man.

J.Appl.Physiol. 10: 356-362.

Zechman, F.W., O'Neill, R., and Shannon, R.(1967). Effect of low cervical spinal cord lesions on detection of increased airflow resistance in man.

Physiologist 10: 356.

Zechman, F.W., Wiley, R.L., and Davenport, P.W.(1981). Ability of healthy men to discriminate between added inspiratory resistive and elastic loads.

Respir.Physiol. 45: 111-120.

Zin, W.A., Rossi, A., and Milic-Emili, J.(1983). Model analysis of respiratory responses to inspiratory resistive loads.

J.Appl.Physiol. 55: 1565-1573.

APPENDIX

This appendix is divided into five sections, the contents of each being listed below.

A1. Data concerning the effect of exercise or hypercapnia on breathing pattern and gas exchange, in the absence of an external flow-resistive load (R0) and in the presence of the most severe load employed (R4).

A2. Data concerning the effect of exercise or hypercapnia on breathing pattern and gas exchange, in the presence of external flow-resistive loads of lesser severity than R4; either relatively low (R2) and relatively high (R3).

A3. Data concerning the effect of exercise or hypercapnia on inspiratory capacity, in the absence of an external flow resistive load (R0) and in the presence of the most severe load employed (R4). Results are also presented in terms of the estimated change in end-expiratory volume (EEV).

A4. Data concerning the effect of exercise or hypercapnia on the shape of the flow profile, in the absence of an external flow resistive load (R0) and in the presence of the most severe external load employed (R4).

A5. Printouts of the computer programs that were employed to collect, analyse and display data.

Appendix A1

A total of 48 exercise and 46 hypercapnic runs were performed in the absence of an external flow-resistance (R0) and in the presence of the most severe flow-resistive load employed (R4). The number of tests undertaken by each subject in each condition (n) may be found at the head of each data page.

During incremental exercise tests, work rate rose in 50 W steps until subjects were unable to continue. All subjects managed to complete the experimental protocol up to 200 W, and all but one up to 250 W. During incremental hypercapnia tests, inspired CO_2 level was raised to 30, 40, 45, 50 and 55 torr in all subjects. In addition, some subjects tolerated inspired CO_2 levels of 60 torr.

Data are presented as mean and standard error of the mean at a given exercise or inspired CO_2 level, these were obtained for each subject by averaging the results from all the tests they performed.

The units in which the data are presented are:

T_I and T_E .. seconds;

V_T .. .. .. litres (BTPS);

$\dot{V}$ .. .. .. litres per minute (BTPS);

$\dot{V}CO_2$ and $\dot{V}O_2$ .. millilitres per minute (STPD);

$P_{ET}CO_2$ .. .. millimetres of mercury.

Subject No. 597 : Exercise data : n=1

Work Rate	Variable	Resistance : R0 Mean	Resistance : R4 Mean
Rest	T_I	2.49	3.04
	T_E	4.90	2.09
	$\dot{V}_T$	.58	.60
	$\dot{V}_E$	4.7	6.5
	$\dot{V}CO_2$	166.	229.
	$\dot{V}O_2$	189.	263.
	$P_{ET}CO_2$	33.20	35.55
0 Watts	T_I	1.34	2.01
	T_E	1.92	2.02
	$\dot{V}_T$	.72	.96
	$\dot{V}_E$	13.2	14.3
	$\dot{V}CO_2$	503.	577.
	$\dot{V}O_2$	577.	672.
	$P_{ET}CO_2$	37.98	38.89
50 Watts	T_I	1.54	2.53
	T_E	2.17	2.15
	$\dot{V}_T$	1.32	1.51
	$\dot{V}_E$	20.5	19.4
	$\dot{V}CO_2$	863.	881.
	$\dot{V}O_2$	971.	1021.
	$P_{ET}CO_2$	40.42	40.91
100 Watts	T_I	1.23	2.36
	T_E	1.60	1.71
	$\dot{V}_T$	1.62	1.96
	$\dot{V}_E$	34.3	28.9
	$\dot{V}CO_2$	1521.	1417.
	$\dot{V}O_2$	1582.	1544.
	$P_{ET}CO_2$	42.11	44.77
150 Watts	T_I	1.06	2.43
	T_E	1.31	1.59
	$\dot{V}_T$	2.12	2.79
	$\dot{V}_E$	53.8	41.6
	$\dot{V}CO_2$	2315.	2174.
	$\dot{V}O_2$	2294.	2285.
	$P_{ET}CO_2$	42.56	47.06
200 Watts	T_I	1.55	2.51
	T_E	1.80	1.67
	$\dot{V}_T$	3.24	3.80
	$\dot{V}_E$	57.9	54.2
	$\dot{V}CO_2$	2858.	2949.
	$\dot{V}O_2$	2830.	3062.
	$P_{ET}CO_2$	44.90	49.69
250 Watts	T_I	1.34	1.40
	T_E	1.54	.97
	$\dot{V}_T$	3.91	3.01
	$\dot{V}_E$	81.4	76.8
	$\dot{V}CO_2$	4250.	4035.
	$\dot{V}O_2$	4014.	3884.
	$P_{ET}CO_2$	48.75	47.86

Subject No. 632 : Exercise data : n=5

Resistance : R0

Work Rate	Variable	Mean	S.E.
Rest	T_I	1.47	.05
	T_E	3.76	.32
	$\dot{V}_T$	.82	.06
	$\dot{V}_E$	9.4	.39
	$\dot{V}CO_2$	288.	25.
	$\dot{V}O_2$	330.	20.
	$P_{ET}CO_2$	34.40	.75
0 Watts	T_I	2.17	.18
	T_E	2.38	.18
	$\dot{V}_T$	1.16	.06
	$\dot{V}_E$	15.2	.94
	$\dot{V}CO_2$	507.	34.
	$\dot{V}O_2$	655.	56.
	$P_{ET}CO_2$	38.56	.78
50 Watts	T_I	1.78	.22
	T_E	2.36	.28
	$\dot{V}_T$	1.46	.17
	$\dot{V}_E$	21.1	.39
	$\dot{V}CO_2$	887.	55.
	$\dot{V}O_2$	990.	60.
	$P_{ET}CO_2$	40.07	.65
100 Watts	T_I	1.59	.11
	T_E	1.74	.08
	$\dot{V}_T$	1.70	.05
	$\dot{V}_E$	30.7	.62
	$\dot{V}CO_2$	1252.	79.
	$\dot{V}O_2$	1454.	89.
	$P_{ET}CO_2$	41.44	.79
150 Watts	T_I	1.71	.14
	T_E	1.85	.16
	$\dot{V}_T$	2.37	.17
	$\dot{V}_E$	39.9	.95
	$\dot{V}CO_2$	1826.	130.
	$\dot{V}O_2$	1948.	103.
	$P_{ET}CO_2$	42.04	1.24
200 Watts	T_I	1.77	.13
	T_E	1.69	.07
	$\dot{V}_T$	3.17	.12
	$\dot{V}_E$	55.1	1.89
	$\dot{V}CO_2$	2693.	150.
	$\dot{V}O_2$	2734.	169.
	$P_{ET}CO_2$	42.13	1.29
250 Watts	T_I	1.27	.04
	T_E	1.29	.06
	$\dot{V}_T$	3.49	.06
	$\dot{V}_E$	81.7	2.12
	$\dot{V}CO_2$	3688.	159.
	$\dot{V}O_2$	3590.	90.
	$P_{ET}CO_2$	38.50	.98

Resistance : R4

Work Rate	Variable	Mean	S.E.
Rest	T_I	2.60	.11
	T_E	4.13	.23
	$\dot{V}_T$	1.16	.05
	$\dot{V}_E$	10.3	.43
	$\dot{V}CO_2$	323.	17.
	$\dot{V}O_2$	336	14.
	$P_{ET}CO_2$	37.13	.59
0 Watts	T_I	3.04	.12
	T_E	3.12	.17
	$\dot{V}_T$	1.64	.16
	$\dot{V}_E$	16.0	1.45
	$\dot{V}CO_2$	649.	44.
	$\dot{V}O_2$	747.	56.
	$P_{ET}CO_2$	40.54	.34
50 Watts	T_I	3.25	.31
	T_E	3.07	.22
	$\dot{V}_T$	2.03	.13
	$\dot{V}_E$	19.3	.60
	$\dot{V}CO_2$	861.	60.
	$\dot{V}O_2$	1022.	89.
	$P_{ET}CO_2$	42.38	.33
100 Watts	T_I	2.80	.29
	T_E	2.51	.20
	$\dot{V}_T$	2.34	.19
	$\dot{V}_E$	26.5	1.14
	$\dot{V}CO_2$	1282.	77.
	$\dot{V}O_2$	1510.	96.
	$P_{ET}CO_2$	43.58	1.02
150 Watts	T_I	2.63	.17
	T_E	2.24	.31
	$\dot{V}_T$	3.13	.13
	$\dot{V}_E$	38.6	1.28
	$\dot{V}CO_2$	1942.	112.
	$\dot{V}O_2$	2028.	99.
	$P_{ET}CO_2$	45.56	.79
200 Watts	T_I	2.31	.16
	T_E	1.76	.33
	$\dot{V}_T$	3.36	.09
	$\dot{V}_E$	49.6	1.82
	$\dot{V}CO_2$	2569.	130.
	$\dot{V}O_2$	2615.	149.
	$P_{ET}CO_2$	44.56	.07
250 Watts	T_I	1.57	.28
	T_E	1.65	.33
	$\dot{V}_T$	3.14	.10
	$\dot{V}_E$	58.6	1.01
	$\dot{V}CO_2$	3702.	137
	$\dot{V}O_2$	3638.	97.
	$P_{ET}CO_2$	44.55	1.12

Subject No. 634 : Exercise data : n=8

Work Rate	Variable	Resistance : R0 Mean	S.E.	Work Rate	Variable	Resistance : R4 Mean	S.E.
Rest	T_I	1.10	.03	Rest	T_I	1.50	.06
	T_E	2.37	.10		T_E	2.14	.08
	$\dot{V}_T$	.65	.02		$\dot{V}_T$	.69	.01
	$\dot{V}_E$	11.3	.27		$\dot{V}_E$	11.4	.24
	$\dot{V}CO_2$	337.	12.		$\dot{V}CO_2$	320.	15.
	$\dot{V}O_2$	385.	10.		$\dot{V}O_2$	392.	20.
	$P_{ET}CO_2$	32.01	.71		$P_{ET}CO_2$	34.21	.41
0 Watts	T_I	1.14	.05	0 Watts	T_I	1.54	.04
	T_E	1.90	.07		T_E	1.76	.05
	$\dot{V}_T$	1.01	.03		$\dot{V}_T$	1.02	.02
	$\dot{V}_E$	20.1	.42		$\dot{V}_E$	18.6	.03
	$\dot{V}CO_2$	688.	34.		$\dot{V}CO_2$	666.	23.
	$\dot{V}O_2$	803.	49.		$\dot{V}O_2$	788.	6.
	$P_{ET}CO_2$	35.01	.21		$P_{ET}CO_2$	36.65	.31
50 Watts	T_I	1.12	.04	50 Watts	T_I	1.54	.06
	T_E	1.63	.03		T_E	1.54	.05
	$\dot{V}_T$	1.16	.04		$\dot{V}_T$	1.19	.03
	$\dot{V}_E$	25.3	.63		$\dot{V}_E$	23.1	.53
	$\dot{V}CO_2$	954.	22.		$\dot{V}CO_2$	932.	42.
	$\dot{V}O_2$	1048.	8.		$\dot{V}O_2$	1084.	6.
	$P_{ET}CO_2$	36.15	.62		$P_{ET}CO_2$	37.50	.21
100 Watts	T_I	1.07	.03	100 Watts	T_I	1.59	.06
	T_E	1.48	.03		T_E	1.40	.04
	$\dot{V}_T$	1.43	.04		$\dot{V}_T$	1.52	.04
	$\dot{V}_E$	33.6	.60		$\dot{V}_E$	30.4	.60
	$\dot{V}CO_2$	1348.	76.		$\dot{V}CO_2$	1380.	72.
	$\dot{V}O_2$	1471.	52.		$\dot{V}O_2$	1536.	28.
	$P_{ET}CO_2$	37.56	.16		$P_{ET}CO_2$	38.50	.36
150 Watts	T_I	1.01	.02	150 Watts	T_I	1.53	.07
	T_E	1.30	.02		T_E	1.22	.03
	$\dot{V}_T$	1.61	.06		$\dot{V}_T$	1.78	.07
	$\dot{V}_E$	41.8	1.42		$\dot{V}_E$	38.8	.94
	$\dot{V}CO_2$	1879.	142.		$\dot{V}CO_2$	1911.	137.
	$\dot{V}O_2$	2030.	95.		$\dot{V}O_2$	2122.	54.
	$P_{ET}CO_2$	37.18	.43		$P_{ET}CO_2$	40.18	.52
200 Watts	T_I	.94	.02	200 Watts	T_I	1.35	.06
	T_E	1.16	.02		T_E	1.04	.03
	$\dot{V}_T$	1.80	.05		$\dot{V}_T$	1.89	.07
	$\dot{V}_E$	51.5	1.57		$\dot{V}_E$	47.4	1.41
	$\dot{V}CO_2$	2461.	125.		$\dot{V}CO_2$	2347	142.
	$\dot{V}O_2$	2629.	12.		$\dot{V}O_2$	2567.	14.
	$P_{ET}CO_2$	38.08	.74		$P_{ET}CO_2$	40.53	.88
250 Watts	T_I	.81	.04	250 Watts	T_I	1.13	.07
	T_E	.96	.03		T_E	.88	.06
	$\dot{V}_T$	2.00	.06		$\dot{V}_T$	2.07	.16
	$\dot{V}_E$	67.9	1.37		$\dot{V}_E$	61.8	2.64
	$\dot{V}O_2$	3311.	82.		$\dot{V}CO_2$	3081.	117.
	$\dot{V}O_2$	3423.	78.		$\dot{V}O_2$	3359.	88.
	$P_{ET}CO_2$	37.15	.91		$P_{ET}CO_2$	39.65	1.01

Subject No. 635 : Exercise data : n=4

Work Rate	Variable	Resistance : R0 Mean	S.E.	Work Rate	Variable	Resistance : R4 Mean	S.E.
Rest	T_I	1.67	.12	Rest	T_I	3.02	.14
	T_E	4.10	.19		T_E	4.56	.26
	$\dot{V}_T$	1.01	.05		$\dot{V}_T$	1.19	.06
	$\dot{V}_E$	10.4	.27		$\dot{V}_E$	9.4	.28
	$\dot{V}CO_2$	372.	37.		$\dot{V}CO_2$	347.	29.
	$\dot{V}O_2$	423.	35.		$\dot{V}O_2$	403.	26.
	$P_{ET}CO_2$	38.19	.62		$P_{ET}CO_2$	41.13	.42
0 Watts	T_I	1.25	.04	0 Watts	T_I	2.16	.31
	T_E	2.49	.09		T_E	2.76	.11
	$\dot{V}_T$	1.01	.05		$\dot{V}_T$	1.12	.06
	$\dot{V}_E$	16.0	.37		$\dot{V}_E$	13.6	.38
	$\dot{V}CO_2$	543.	28.		$\dot{V}CO_2$	555.	25.
	$\dot{V}O_2$	667.	42.		$\dot{V}O_2$	709.	34.
	$P_{ET}CO_2$	41.55	.71		$P_{ET}CO_2$	42.86	.30
50 Watts	T_I	1.41	.10	50 Watts	T_I	2.24	.16
	T_E	2.23	.18		T_E	2.57	.07
	$\dot{V}_T$	1.27	.06		$\dot{V}_T$	1.53	.01
	$\dot{V}_E$	21.1	.83		$\dot{V}_E$	19.1	.96
	$\dot{V}CO_2$	838.	40.		$\dot{V}CO_2$	856.	37.
	$\dot{V}O_2$	1016.	31.		$\dot{V}O_2$	1065.	47.
	$P_{ET}CO_2$	41.25	.22		$P_{ET}CO_2$	45.56	.43
100 Watts	T_I	1.42	.09	100 Watts	T_I	2.36	.03
	T_E	2.06	.15		T_E	2.54	.10
	$\dot{V}_T$	1.72	.07		$\dot{V}_T$	2.10	.06
	$\dot{V}_E$	29.7	.64		$\dot{V}_E$	25.7	.52
	$\dot{V}CO_2$	1403.	146.		$\dot{V}CO_2$	1235.	34.
	$\dot{V}O_2$	1618.	115.		$\dot{V}O_2$	1485.	40.
	$P_{ET}CO_2$	42.11	.39		$P_{ET}CO_2$	43.44	.29
150 Watts	T_I	1.30	.06	150 Watts	T_I	2.22	.05
	T_E	1.87	.08		T_E	2.20	.07
	$\dot{V}_T$	2.00	.06		$\dot{V}_T$	2.50	.05
	$\dot{V}_E$	37.9	1.20		$\dot{V}_E$	33.9	.92
	$\dot{V}CO_2$	1966.	258.		$\dot{V}CO_2$	1742.	38.
	$\dot{V}O_2$	2218.	197.		$\dot{V}O_2$	2031.	56.
	$P_{ET}CO_2$	45.47	.75		$P_{ET}CO_2$	51.63	.66
200 Watts	T_I	1.21	.09	200 Watts	T_I	2.03	.13
	T_E	1.70	.04		T_E	2.06	.15
	$\dot{V}_T$	2.30	.09		$\dot{V}_T$	2.94	.18
	$\dot{V}_E$	47.5	.60		$\dot{V}_E$	43.1	.85
	$\dot{V}CO_2$	2328.	96.		$\dot{V}CO_2$	2314.	30.
	$\dot{V}O_2$	2579.	37.		$\dot{V}O_2$	2678.	65.
	$P_{ET}CO_2$	43.13	.92		$P_{ET}CO_2$	51.96	.98
250 Watts	T_I	1.06	.03	250 Watts	T_I	1.68	.05
	T_E	1.59	.04		T_E	1.64	.06
	$\dot{V}_T$	2.84	.09		$\dot{V}_T$	3.24	.08
	$\dot{V}_E$	64.3	3.03		$\dot{V}_E$	58.5	2.28
	$\dot{V}O_2$	2994.	69.		$\dot{V}CO_2$	3024	98.
	$\dot{V}O_2$	3441	102.		$\dot{V}O_2$	3440.	122.
	$P_{ET}CO_2$	42.33	.98		$P_{ET}CO_2$	49.89	1.12

Subject No. 639 : Exercise data : n=7

Work Rate	Variable	Resistance : R0 Mean	S.E.	Work Rate	Variable	Resistance : R4 Mean	S.E.
Rest	T_I	1.62	.07	Rest	T_I	2.14	.13
	T_E	2.94	.25		T_E	2.94	.24
	$\dot{V}_T$	.79	.04		$\dot{V}_T$	.95	.05
	$\dot{V}_E$	10.4	.30		$\dot{V}_E$	9.7	.59
	$\dot{V}CO_2$	265.	32.		$\dot{V}CO_2$	272.	27.
	$\dot{V}O_2$	302.	25.		$\dot{V}O_2$	295.	29.
	$P_{ET}CO_2$	37.71	.30		$P_{ET}CO_2$	38.41	.52
0 Watts	T_I	1.59	.09	0 Watts	T_I	2.26	.10
	T_E	2.19	.06		T_E	2.16	.12
	$\dot{V}_T$	1.04	.04		$\dot{V}_T$	1.10	.04
	$\dot{V}_E$	16.5	.50		$\dot{V}_E$	14.9	.78
	$\dot{V}CO_2$	577.	38.		$\dot{V}CO_2$	558.	35.
	$\dot{V}O_2$	633.	35.		$\dot{V}O_2$	630.	32.
	$P_{ET}CO_2$	38.58	1.11		$P_{ET}CO_2$	41.03	.06
50 Watts	T_I	1.57	.05	50 Watts	T_I	2.21	.06
	T_E	2.05	.08		T_E	1.92	.05
	$\dot{V}_T$	1.36	.03		$\dot{V}_T$	1.51	.05
	$\dot{V}_E$	22.5	.74		$\dot{V}_E$	21.9	.52
	$\dot{V}CO_2$	958.	25.		$\dot{V}CO_2$	1016.	27.
	$\dot{V}O_2$	1033.	23.		$\dot{V}O_2$	1110.	21.
	$P_{ET}CO_2$	41.82	.56		$P_{ET}CO_2$	44.18	.24
100 Watts	T_I	1.42	.03	100 Watts	T_I	2.08	.05
	T_E	1.71	.11		T_E	1.74	.07
	$\dot{V}_T$	1.63	.06		$\dot{V}_T$	1.91	.05
	$\dot{V}_E$	31.3	1.18		$\dot{V}_E$	30.0	.78
	$\dot{V}CO_2$	1551.	47.		$\dot{V}CO_2$	1626.	41.
	$\dot{V}O_2$	1595.	26.		$\dot{V}O_2$	1700.	46.
	$P_{ET}CO_2$	43.49	.68		$P_{ET}CO_2$	47.23	.22
150 Watts	T_I	1.38	.08	150 Watts	T_I	2.13	.15
	T_E	1.59	.10		T_E	1.71	.09
	$\dot{V}_T$	2.13	.07		$\dot{V}_T$	2.34	.19
	$\dot{V}_E$	43.0	1.84		$\dot{V}_E$	36.6	1.62
	$\dot{V}CO_2$	2210.	62.		$\dot{V}CO_2$	2263.	39.
	$\dot{V}O_2$	2211.	78.		$\dot{V}O_2$	2377.	28.
	$P_{ET}CO_2$	44.72	.40		$P_{ET}CO_2$	48.13	.66
200 Watts	T_I	1.38	.10	200 Watts	T_I	2.08	.14
	T_E	1.47	.09		T_E	1.45	.06
	$\dot{V}_T$	2.71	.07		$\dot{V}_T$	3.00	.18
	$\dot{V}_E$	57.0	3.30		$\dot{V}_E$	51.0	3.41
	$\dot{V}CO_2$	2807.	156.		$\dot{V}CO_2$	3051.	109.
	$\dot{V}O_2$	2844.	143.		$\dot{V}O_2$	3034.	149.
	$P_{ET}CO_2$	45.52	.87		$P_{ET}CO_2$	48.39	.85
250 Watts	T_I	1.28	.16	250 Watts	T_I	1.51	.02
	T_E	1.10	.09		T_E	1.00	.10
	$\dot{V}_T$	3.08	.15		$\dot{V}_T$	3.16	.07
	$\dot{V}_E$	77.6	4.92		$\dot{V}_E$	75.6	1.23
	$\dot{V}CO_2$	3744.	154.		$\dot{V}CO_2$	3757.	169.
	$\dot{V}O_2$	3495.	179.		$\dot{V}O_2$	3536.	188.
	$P_{ET}CO_2$	41.74	1.43		$P_{ET}CO_2$	46.23	1.39

Subject No. 640 : Exercise data : n=3

Work Rate	Variable	Resistance : R0 Mean	S.E.	Work Rate	Variable	Resistance : R4 Mean	S.E.
Rest	T_I	2.38	.46	Rest	T_I	3.26	.46
	T_E	3.30	.47		T_E	3.58	.95
	$\dot{V}_T$	.78	.12		$\dot{V}_T$	.83	.14
	$\dot{V}_E$	8.2	.44		$\dot{V}_E$	7.3	.37
	$\dot{V}CO_2$	273.	28.		$\dot{V}CO_2$	223.	36.
	$\dot{V}O_2$	313.	31.		$\dot{V}O_2$	274.	18.
	$P_{ET}CO_2$	30.57	2.88		$P_{ET}CO_2$	41.13	3.01
0 Watts	T_I	1.85	.35	0 Watts	T_I	2.17	.38
	T_E	2.30	.32		T_E	2.25	.36
	$\dot{V}_T$	.91	.18		$\dot{V}_T$	.92	.17
	$\dot{V}_E$	12.8	.66		$\dot{V}_E$	12.2	.45
	$\dot{V}CO_2$	467.	57.		$\dot{V}CO_2$	493.	45.
	$\dot{V}O_2$	522.	29.		$\dot{V}O_2$	540.	36.
	$P_{ET}CO_2$	37.64	1.19		$P_{ET}CO_2$	45.77	.78
50 Watts	T_I	1.53	.32	50 Watts	T_I	2.33	.69
	T_E	1.89	.38		T_E	2.16	.58
	$\dot{V}_T$	1.05	.23		$\dot{V}_T$	1.23	.33
	$\dot{V}_E$	18.2	.68		$\dot{V}_E$	16.5	.44
	$\dot{V}CO_2$	836.	41.		$\dot{V}CO_2$	881.	38.
	$\dot{V}O_2$	900.	49.		$\dot{V}O_2$	939.	31.
	$P_{ET}CO_2$	44.55	1.23		$P_{ET}CO_2$	47.11	1.09
100 Watts	T_I	1.57	.06	100 Watts	T_I	3.31	.36
	T_E	1.96	.14		T_E	2.63	.22
	$\dot{V}_T$	1.65	.10		$\dot{V}_T$	2.30	.26
	$\dot{V}_E$	28.1	.51		$\dot{V}_E$	23.2	.58
	$\dot{V}CO_2$	1468.	52.		$\dot{V}CO_2$	1489.	43.
	$\dot{V}O_2$	1481.	38.		$\dot{V}O_2$	1541	46.
	$P_{ET}CO_2$	46.10	.82		$P_{ET}CO_2$	48.31	.72
150 Watts	T_I	1.71	.18	150 Watts	T_I	2.60	.15
	T_E	1.98	.08		T_E	2.21	.08
	$\dot{V}_T$	2.17	.16		$\dot{V}_T$	2.58	.12
	$\dot{V}_E$	35.3	1.87		$\dot{V}_E$	32.2	.32
	$\dot{V}CO_2$	1793.	55.		$\dot{V}CO_2$	1841.	59.
	$\dot{V}O_2$	1831.	61.		$\dot{V}O_2$	1894.	53.
	$P_{ET}CO_2$	47.75	.47		$P_{ET}CO_2$	48.57	.63
200 Watts	T_I	1.44	.11	200 Watts	T_I	2.08	.06
	T_E	1.70	.07		T_E	1.99	.07
	$\dot{V}_T$	2.45	.10		$\dot{V}_T$	2.79	.08
	$\dot{V}_E$	46.8	2.61		$\dot{V}_E$	41.1	.87
	$\dot{V}CO_2$	2365.	93.		$\dot{V}CO_2$	2716.	113.
	$\dot{V}O_2$	2316.	102.		$\dot{V}O_2$	2800.	125.
	$P_{ET}CO_2$	46.02	1.14		$P_{ET}CO_2$	50.66	.89
250 Watts	T_I	1.23	.11	250 Watts	T_I	1.72	.12
	T_E	1.70	.10		T_E	1.49	.06
	$\dot{V}_T$	3.02	.03		$\dot{V}_T$	3.07	.06
	$\dot{V}_E$	68.9	4.62		$\dot{V}_E$	57.3	2.04
	$\dot{V}CO_2$	3302.	147.		$\dot{V}CO_2$	3423.	132.
	$\dot{V}O_2$	3127.	75.		$\dot{V}O_2$	3388.	85.
	$P_{ET}CO_2$	47.59	1.02		$P_{ET}CO_2$	50.10	.97

Subject No. 642 : Exercise data : n=7

Resistance : R0

Work Rate	Variable	Mean	S.E.
Rest	T_I	1.56	.06
	T_E	3.00	.20
	$\dot{V}_T$	.54	.05
	$\dot{V}_E$	7.1	.59
	$\dot{V}CO_2$	277.	27.
	$\dot{V}CO_2$	297.	19.
	$P_{ET}CO_2$	38.83	.71
0 Watts	T_I	1.68	.04
	T_E	1.89	.07
	$\dot{V}_T$	1.12	.12
	$\dot{V}_E$	18.9	.93
	$\dot{V}CO_2$	647.	32.
	$\dot{V}O_2$	695.	24.
	$P_{ET}CO_2$	40.74	1.51
50 Watts	T_I	1.45	.03
	T_E	1.85	.05
	$\dot{V}_T$	1.40	.12
	$\dot{V}_E$	25.4	2.03
	$\dot{V}CO_2$	1034.	35.
	$\dot{V}O_2$	1118.	26.
	$P_{ET}CO_2$	47.72	.47
100 Watts	T_I	1.33	.03
	T_E	1.64	.06
	$\dot{V}_T$	1.96	.18
	$\dot{V}_E$	39.5	3.15
	$\dot{V}CO_2$	1636.	50.
	$\dot{V}O_2$	1702.	39.
	$P_{ET}CO_2$	47.37	.56
150 Watts	T_I	1.18	.02
	T_E	1.43	.03
	$\dot{V}_T$	2.59	.21
	$\dot{V}_E$	59.3	3.79
	$\dot{V}CO_2$	2442.	79.
	$\dot{V}O_2$	2412.	56.
	$P_{ET}CO_2$	46.83	.87
200 Watts	T_I	0.98	.01
	T_E	1.13	.02
	$\dot{V}_T$	2.89	.99
	$\dot{V}_E$	82.3	1.72
	$\dot{V}CO_2$	3277.	137.
	$\dot{V}O_2$	3075.	101.
	$P_{ET}CO_2$	43.47	.80

Resistance : R4

Work Rate	Variable	Mean	S.E.
Rest	T_I	2.02	.07
	T_E	3.23	.27
	$\dot{V}_T$	.60	.59
	$\dot{V}_E$	6.9	.39
	$\dot{V}CO_2$	281.	19.
	$\dot{V}O_2$	314.	17.
	$P_{ET}CO_2$	40.14	.78
0 Watts	T_I	2.11	.11
	T_E	1.79	.55
	$\dot{V}_T$	1.06	.12
	$\dot{V}_E$	16.3	2.07
	$\dot{V}CO_2$	597.	19.
	$\dot{V}O_2$	695.	20.
	$P_{ET}CO_2$	42.28	.97
50 Watts	T_I	2.00	.08
	T_E	1.65	.06
	$\dot{V}_T$	1.50	.13
	$\dot{V}_E$	24.6	2.52
	$\dot{V}CO_2$	1022.	36.
	$\dot{V}O_2$	1124.	28.
	$P_{ET}CO_2$	46.59	.39
100 Watts	T_I	1.81	.04
	T_E	1.52	.03
	$\dot{V}_T$	2.07	.20
	$\dot{V}_E$	37.2	3.78
	$\dot{V}CO_2$	1661.	61.
	$\dot{V}O_2$	1767.	66.
	$P_{ET}CO_2$	49.17	.50
150 Watts	T_I	1.69	.04
	T_E	1.32	.04
	$\dot{V}_T$	2.88	.32
	$\dot{V}_E$	57.4	6.03
	$\dot{V}CO_2$	2398.	63.
	$\dot{V}O_2$	2436.	52.
	$P_{ET}CO_2$	47.74	1.06
200 Watts	T_I	1.34	.05
	T_E	1.16	.17
	$\dot{V}_T$	3.09	.15
	$\dot{V}_E$	74.2	.55
	$\dot{V}CO_2$	3213.	120.
	$\dot{V}O_2$	3094.	104.
	$P_{ET}CO_2$	44.00	1.03

Subject No. 643 : Exercise data : n=3

Resistance : R0				Resistance : R4			
Work Rate	Variable	Mean	S.E.	Work Rate	Variable	Mean	S.E.
Rest	T_I	1.26	.08	Rest	T_I	2.04	.15
	T_E	3.42	.62		T_E	3.63	.69
	$\dot{V}_T$	.73	.05		$\dot{V}_T$	.78	.05
	$\dot{V}_E$	9.3	.93		$\dot{V}_E$	8.3	.68
	$\dot{V}CO_2$	245.	26.		$\dot{V}CO_2$	229.	17.
	$\dot{V}O_2$	281.	30.		$\dot{V}O_2$	275.	26.
	P_ETCO_2	38.77	4.03		P_ETCO_2	39.12	3.66
0 Watts	T_I	1.36	.11	0 Watts	T_I	2.22	.20
	T_E	1.82	.23		T_E	1.98	.15
	$\dot{V}_T$	.99	.06		$\dot{V}_T$	1.18	.08
	$\dot{V}_E$	18.6	.52		$\dot{V}_E$	16.9	.75
	$\dot{V}CO_2$	613	85.		$\dot{V}CO_2$	655	46.
	$\dot{V}O_2$	690.	29.		$\dot{V}O_2$	756.	24.
	P_ETCO_2	40.90	1.23		P_ETCO_2	43.19	.39
50 Watts	T_I	1.48	.06	50 Watts	T_I	2.09	.11
	T_E	2.25	.28		T_E	1.69	.12
	$\dot{V}_T$	1.56	.21		$\dot{V}_T$	1.52	.08
	$\dot{V}_E$	25.3	.10		$\dot{V}_E$	24.1	.36
	$\dot{V}CO_2$	975.	25.		$\dot{V}CO_2$	995.	17.
	$\dot{V}O_2$	1100.	51.		$\dot{V}O_2$	1130.	32.
	P_ETCO_2	42.97	1.44		P_ETCO_2	45.06	.59
100 Watts	T_I	1.20	.05	100 Watts	T_I	1.84	.03
	T_E	1.49	.05		T_E	1.67	.09
	$\dot{V}_T$	1.66	.06		$\dot{V}_T$	1.97	.03
	$\dot{V}_E$	37.0	.60		$\dot{V}_E$	33.7	.55
	$\dot{V}CO_2$	1464.	46.		$\dot{V}CO_2$	1458.	25.
	$\dot{V}O_2$	1553.	47.		$\dot{V}O_2$	1613.	15.
	P_ETCO_2	44.05	1.10		P_ETCO_2	46.21	.55
150 Watts	T_I	1.13	.01	150 Watts	T_I	1.73	.08
	T_E	1.37	.03		T_E	1.38	.03
	$\dot{V}_T$	2.05	.04		$\dot{V}_T$	2.35	.07
	$\dot{V}_E$	49.2	.88		$\dot{V}_E$	45.3	.72
	$\dot{V}CO_2$	2056.	66.		$\dot{V}CO_2$	2007.	64.
	$\dot{V}O_2$	2209.	74.		$\dot{V}O_2$	2222.	64.
	P_ETCO_2	44.80	.95		P_ETCO_2	47.50	.58
200 Watts	T_I	1.02	.02	200 Watts	T_I	1.54	.06
	T_E	1.24	.02		T_E	1.26	.01
	$\dot{V}_T$	2.39	.13		$\dot{V}_T$	2.75	.04
	$\dot{V}_E$	63.4	2.10		$\dot{V}_E$	59.0	.87
	$\dot{V}CO_2$	2660.	142.		$\dot{V}CO_2$	2628.	79.
	$\dot{V}O_2$	2806.	131.		$\dot{V}O_2$	2861.	88.
	P_ETCO_2	45.53	.57		P_ETCO_2	48.66	.83
250 Watts	T_I	.92	.02	250 Watts	T_I	1.46	.03
	T_E	1.08	.03		T_E	.99	.10
	$\dot{V}_T$	2.90	.12		$\dot{V}_T$	3.08	.11
	$\dot{V}_E$	87.1	4.18		$\dot{V}_E$	75.5	2.61
	$\dot{V}CO_2$	3714.	190.		$\dot{V}CO_2$	3540.	184.
	$\dot{V}O_2$	3596.	166.		$\dot{V}O_2$	3662.	207.
	P_ETCO_2	44.93	.84		P_ETCO_2	48.89	1.25

Subject No. 644 : Exercise data : n=2

Resistance : R0			Resistance : R4		
Work rate	Variable	Mean	Work Rate	Variable	Mean
Rest	T_I	2.48	Rest	T_I	2.31
	T_E	4.72		T_E	2.44
	$\dot{V}_T$	.53		$\dot{V}_T$	.62
	$\dot{V}_E$	4.4		$\dot{V}_E$	7.8
	$\dot{V}CO_2$	145.		$\dot{V}CO_2$	285.
	$\dot{V}O_2$	166.		$\dot{V}O_2$	296.
	P_ETCO_2	39.10		P_ETCO_2	37.26
0 Watts	T_I	1.75	0 Watts	T_I	2.12
	T_E	2.34		T_E	2.15
	$\dot{V}_T$	1.16		$\dot{V}_T$	1.14
	$\dot{V}_E$	17.0		$\dot{V}_E$	16.3
	$\dot{V}CO_2$	734.		$\dot{V}CO_2$	726.
	$\dot{V}O_2$	783.		$\dot{V}O_2$	826.
	P_ETCO_2	42.11		P_ETCO_2	42.76
50 Watts	T_I	1.38	50 Watts	T_I	1.77
	T_E	1.78		T_E	1.95
	$\dot{V}_T$	1.29		$\dot{V}_T$	1.46
	$\dot{V}_E$	24.5		$\dot{V}_E$	23.5
	$\dot{V}CO_2$	1099.		$\dot{V}CO_2$	1125.
	$\dot{V}O_2$	1180.		$\dot{V}O_2$	1202.
	P_ETCO_2	44.22		P_ETCO_2	44.61
100 Watts	T_I	1.40	100 Watts	T_I	1.77
	T_E	1.85		T_E	1.71
	$\dot{V}_T$	1.89		$\dot{V}_T$	1.94
	$\dot{V}_E$	34.9		$\dot{V}_E$	33.4
	$\dot{V}CO_2$	1727.		$\dot{V}CO_2$	1683.
	$\dot{V}O_2$	1812.		$\dot{V}O_2$	1728.
	P_ETCO_2	44.87		P_ETCO_2	46.24
150 Watts	T_I	1.08	150 Watts	T_I	1.13
	T_E	1.27		T_E	1.14
	$\dot{V}_T$	1.98		$\dot{V}_T$	1.92
	$\dot{V}_E$	50.6		$\dot{V}_E$	50.7
	$\dot{V}CO_2$	2447.		$\dot{V}CO_2$	2497.
	$\dot{V}O_2$	2423.		$\dot{V}O_2$	2456.
	P_ETCO_2	45.57		P_ETCO_2	46.68
200 Watts	T_I	.87	200 Watts	T_I	1.07
	T_E	1.04		T_E	.85
	$\dot{V}_T$	2.30		$\dot{V}_T$	2.17
	$\dot{V}_E$	72.3		$\dot{V}_E$	67.8
	$\dot{V}CO_2$	3284.		$\dot{V}CO_2$	3272.
	$\dot{V}O_2$	3057.		$\dot{V}O_2$	3160.
	P_ETCO_2	44.05		P_ETCO_2	44.69
250 Watts	T_I	.76	250 Watts	T_I	.98
	T_E	.98		T_E	.80
	$\dot{V}_T$	2.75		$\dot{V}_T$	2.29
	$\dot{V}_E$	94.8		$\dot{V}_E$	77.2
	$\dot{V}CO_2$	4255.		$\dot{V}CO_2$	4003.
	$\dot{V}O_2$	3927.		$\dot{V}O_2$	3724.
	P_ETCO_2	41.93		P_ETCO_2	44.16

Subject No. 647 : Exercise data : n=3

Resistance : R0				Resistance : R4			
Work Rate	Variable	Mean	S.E.	Work Rate	Variable	Mean	S.E.
Rest	T_I	1.52	.06	Rest	T_I	1.98	.10
	T_E	2.40	.13		T_E	2.63	.10
	$\dot{V}_T$	.67	.04		$\dot{V}_T$	.72	.03
	$\dot{V}_E$	10.2	.34		$\dot{V}_E$	9.4	.36
	$\dot{V}CO_2$	279.	22.		$\dot{V}CO_2$	258.	15.
	$\dot{V}O_2$	316.	23.		$\dot{V}O_2$	295.	19.
	$P_{ET}CO_2$	36.86	1.11		$P_{ET}CO_2$	38.78	1.03
0 Watts	T_I	1.41	.02	0 Watts	T_I	1.94	.08
	T_E	2.08	.03		T_E	1.95	.09
	$\dot{V}_T$	1.12	.08		$\dot{V}_T$	1.26	.04
	$\dot{V}_E$	19.2	1.16		$\dot{V}_E$	19.4	1.40
	$\dot{V}CO_2$	648.	64.		$\dot{V}CO_2$	673.	62.
	$\dot{V}O_2$	723.	55.		$\dot{V}O_2$	768.	55.
	$P_{ET}CO_2$	40.24	1.03		$P_{ET}CO_2$	41.62	.83
50 Watts	T_I	1.36	.08	50 Watts	T_I	1.98	.07
	T_E	1.85	.03		T_E	1.75	.02
	$\dot{V}_T$	1.47	.08		$\dot{V}_T$	1.67	.09
	$\dot{V}_E$	27.4	.76		$\dot{V}_E$	26.8	1.19
	$\dot{V}CO_2$	967.	57.		$\dot{V}CO_2$	1003.	47.
	$\dot{V}O_2$	1073.	49.		$\dot{V}O_2$	1108.	28.
	$P_{ET}CO_2$	41.17	.93		$P_{ET}CO_2$	42.90	.83
100 Watts	T_I	1.14	.07	100 Watts	T_I	1.97	.05
	T_E	1.53	.03		T_E	1.60	.04
	$\dot{V}_T$	1.76	.02		$\dot{V}_T$	2.21	.06
	$\dot{V}_E$	39.5	1.30		$\dot{V}_E$	37.2	.65
	$\dot{V}CO_2$	1486.	80.		$\dot{V}CO_2$	1518.	36.
	$\dot{V}O_2$	1604.	65.		$\dot{V}O_2$	1661.	33.
	$P_{ET}CO_2$	41.83	.83		$P_{ET}CO_2$	45.39	.82
150 Watts	T_I	1.15	.01	150 Watts	T_I	1.81	.08
	T_E	1.49	.04		T_E	1.36	.09
	$\dot{V}_T$	2.43	.03		$\dot{V}_T$	2.72	.09
	$\dot{V}_E$	55.2	.31		$\dot{V}_E$	51.5	1.12
	$\dot{V}CO_2$	2129.	81.		$\dot{V}CO_2$	2120.	56.
	$\dot{V}O_2$	2246.	42.		$\dot{V}O_2$	2269.	35.
	$P_{ET}CO_2$	42.83	.47		$P_{ET}CO_2$	45.54	.68
200 Watts	T_I	1.30	.05	200 Watts	T_I	1.77	.10
	T_E	1.51	.04		T_E	1.31	.11
	$\dot{V}_T$	3.45	.08		$\dot{V}_T$	3.52	.23
	$\dot{V}_E$	73.7	.88		$\dot{V}_E$	68.7	.22
	$\dot{V}CO_2$	2788.	135.		$\dot{V}CO_2$	2911.	137.
	$\dot{V}O_2$	2863.	91.		$\dot{V}O_2$	2992.	124.
	$P_{ET}CO_2$	42.82	1.05		$P_{ET}CO_2$	46.62	.90
250 Watts	T_I	1.04	.04	250 Watts	T_I	1.12	.08
	T_E	1.17	.03		T_E	.76	.05
	$\dot{V}_T$	3.90	.20		$\dot{V}_T$	3.12	.31
	$\dot{V}_E$	106.1	2.13		$\dot{V}_E$	99.6	5.11
	$\dot{V}CO_2$	3612.	180.		$\dot{V}CO_2$	3850.	397.
	$\dot{V}O_2$	3534.	88.		$\dot{V}O_2$	3817.	243.
	$P_{ET}CO_2$	42.47	2.07		$P_{ET}CO_2$	44.45	3.49

Subject No. 648 : Exercise data : n=5

Resistance : R0

Work Rate	Variable	Mean	S.E.
Rest	T_I	1.69	.16
	T_E	3.00	.46
	$\dot{V}_T$	.92	.10
	$\dot{V}_E$	11.8	.67
	$\dot{V}CO_2$	277.	33.
	$\dot{V}O_2$	312.	31.
	$P_{ET}CO_2$	30.64	1.69
0 Watts	T_I	1.94	.08
	T_E	2.19	.19
	$\dot{V}_T$	1.55	.10
	$\dot{V}_E$	22.6	2.23
	$\dot{V}CO_2$	678.	38.
	$\dot{V}O_2$	797.	34.
	$P_{ET}CO_2$	34.39	1.98
50 Watts	T_I	2.12	.23
	T_E	2.29	.18
	$\dot{V}_T$	2.25	.18
	$\dot{V}_E$	30.6	3.06
	$\dot{V}CO_2$	1073.	64.
	$\dot{V}O_2$	1214.	55.
	$P_{ET}CO_2$	37.59	1.14
100 Watts	T_I	1.50	.14
	T_E	1.79	.19
	$\dot{V}_T$	2.54	.13
	$\dot{V}_E$	46.4	3.60
	$\dot{V}CO_2$	1750.	80.
	$\dot{V}O_2$	1842.	72.
	$P_{ET}CO_2$	40.01	1.88
150 Watts	T_I	1.23	.13
	T_E	1.64	.20
	$\dot{V}_T$	2.87	.26
	$\dot{V}_E$	60.0	2.70
	$\dot{V}CO_2$	2341.	88.
	$\dot{V}O_2$	2388	119.
	$P_{ET}CO_2$	41.49	1.51
200 Watts	T_I	1.00	.08
	T_E	1.38	.17
	$\dot{V}_T$	3.19	.27
	$\dot{V}_E$	80.4	5.45
	$\dot{V}CO_2$	3097.	98.
	$\dot{V}O_2$	3031.	149.
	$P_{ET}CO_2$	39.65	1.50
250 Watts	T_I	.81	.01
	T_E	1.08	.08
	$\dot{V}_T$	3.87	.16
	$\dot{V}_E$	122.8	1.60
	$\dot{V}CO_2$	4370.	255.
	$\dot{V}O_2$	3983.	149.
	$P_{ET}CO_2$	40.01	.20

Resistance : R4

Work Rate	Variable	Mean	S.E.
Rest	T_I	2.18	.16
	T_E	2.48	.32
	$\dot{V}_T$	.87	.11
	$\dot{V}_E$	11.2	1.18
	$\dot{V}CO_2$	295.	43.
	$\dot{V}O_2$	300.	33.
	$P_{ET}CO_2$	28.80	2.42
0 Watts	T_I	2.78	.26
	T_E	1.95	.13
	$\dot{V}_T$	1.60	.14
	$\dot{V}_E$	20.3	1.51
	$\dot{V}CO_2$	671.	42.
	$\dot{V}O_2$	759.	17.
	$P_{ET}CO_2$	36.36	2.88
50 Watts	T_I	2.73	.24
	T_E	1.94	.22
	$\dot{V}_T$	2.41	.14
	$\dot{V}_E$	31.0	3.45
	$\dot{V}CO_2$	1132.	54.
	$\dot{V}CO_2$	1226.	58.
	$P_{ET}CO_2$	39.64	2.75
100 Watts	T_I	2.38	.15
	T_E	1.79	.10
	$\dot{V}_T$	3.04	.21
	$\dot{V}_E$	43.7	2.83
	$\dot{V}CO_2$	1765.	75.
	$\dot{V}O_2$	1880.	75.
	$P_{ET}CO_2$	41.79	.93
150 Watts	T_I	1.98	.12
	T_E	1.39	.17
	$\dot{V}_T$	3.27	.21
	$\dot{V}_E$	58.2	2.88
	$\dot{V}CO_2$	2368.	87.
	$\dot{V}O_2$	2456.	108.
	$P_{ET}CO_2$	41.63	1.51
200 Watts	T_I	1.40	.15
	T_E	1.03	.06
	$\dot{V}_T$	3.02	.33
	$\dot{V}_E$	74.5	3.77
	$\dot{V}CO_2$	3092.	116.
	$\dot{V}O_2$	3088.	123.
	$P_{ET}CO_2$	40.85	1.66
250 Watts	T_I	1.12	.08
	T_E	.80	.07
	$\dot{V}_T$	3.34	.32
	$\dot{V}_E$	104.4	7.01
	$\dot{V}CO_2$	4256.	175.
	$\dot{V}O_2$	3761.	97.
	$P_{ET}CO_2$	41.87	1.91

Subject No. 632 : Hypercapnia data : n=5

Resistance : R0

P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.47	.05
	T_E	3.76	.32
	$\dot{V}_T$	.82	.06
	$\dot{V}_E$	9.4	.39
	$\dot{V}CO_2$	288.	25.
	$\dot{V}O_2$	330.	20.
	$P_{ET}CO_2$	34.40	.75
30 torr	T_I	1.69	.07
	T_E	2.40	.08
	$\dot{V}_T$	1.70	.12
	$\dot{V}_E$	25.0	1.70
	$\dot{V}CO_2$	252.	21.
	$\dot{V}O_2$	395.	47.
	$P_{ET}CO_2$	43.50	.43
40 torr	T_I	1.57	.04
	T_E	1.75	.09
	$\dot{V}_T$	2.48	.09
	$\dot{V}_E$	44.9	1.50
	$\dot{V}CO_2$	274.	39.
	$\dot{V}O_2$	374.	21.
	$P_{ET}CO_2$	47.88	.21
45 torr	T_I	1.22	.07
	T_E	1.34	.07
	$\dot{V}_T$	2.77	.05
	$\dot{V}_E$	64.9	2.71
	$\dot{V}CO_2$	433.	37.
	$\dot{V}O_2$	371.	24.
	$P_{ET}CO_2$	48.83	.60
50 torr	T_I	1.19	.08
	T_E	1.25	.04
	$\dot{V}_T$	2.96	.02
	$\dot{V}_E$	72.8	2.53
	$\dot{V}CO_2$	293.	138.
	$\dot{V}O_2$	436.	24.
	$P_{ET}CO_2$	55.50	.53
55 torr	T_I	1.21	.08
	T_E	1.19	.06
	$\dot{V}_T$	3.03	.03
	$\dot{V}_E$	75.7	2.90
	$\dot{V}CO_2$	338.	60.
	$\dot{V}O_2$	488.	56.
	$P_{ET}CO_2$	57.50	.96
60 torr	T_I	1.09	.06
	T_E	1.14	.03
	$\dot{V}_T$	2.93	.17
	$\dot{V}_E$	78.7	3.32
	$\dot{V}CO_2$	297.	44.
	$\dot{V}O_2$	376.	56.
	$P_{ET}CO_2$	63.55	.45

Resistance : R4

P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	2.60	.11
	T_E	4.13	.23
	$\dot{V}_T$	1.16	.06
	$\dot{V}_E$	10.3	.43
	$\dot{V}CO_2$	323.	17.
	$\dot{V}O_2$	336.	14.
	$P_{ET}CO_2$	37.13	.59
30 torr	T_I	2.83	.11
	T_E	2.50	.15
	$\dot{V}_T$	1.87	.19
	$\dot{V}_E$	21.1	1.60
	$\dot{V}CO_2$	297.	24.
	$\dot{V}O_2$	361.	31.
	$P_{ET}CO_2$	44.50	.29
40 torr	T_I	2.37	.21
	T_E	2.11	.19
	$\dot{V}_T$	2.68	.12
	$\dot{V}_E$	35.9	2.40
	$\dot{V}CO_2$	312.	25.
	$\dot{V}O_2$	476.	43.
	$P_{ET}CO_2$	48.67	.33
45 torr	T_I	2.56	.19
	T_E	1.47	.06
	$\dot{V}_T$	2.98	.10
	$\dot{V}_E$	44.3	3.11
	$\dot{V}CO_2$	414.	90.
	$\dot{V}O_2$	538.	47.
	$P_{ET}CO_2$	51.00	.71
50 torr	T_I	2.11	.03
	T_E	1.28	.10
	$\dot{V}_T$	2.88	.02
	$\dot{V}_E$	51.0	2.18
	$\dot{V}CO_2$	310.	109.
	$\dot{V}O_2$	489.	49.
	$P_{ET}CO_2$	56.51	.47
55 torr	T_I	2.09	.18
	T_E	1.25	.13
	$\dot{V}_T$	3.03	.01
	$\dot{V}_E$	54.5	5.02
	$\dot{V}CO_2$	251.	87.
	$\dot{V}O_2$	493.	79.
	$P_{ET}CO_2$	60.52	.71
60 torr	T_I	1.94	.04
	T_E	1.17	.03
	$\dot{V}_T$	2.87	.06
	$\dot{V}_E$	55.4	1.72
	$\dot{V}CO_2$	266.	23.
	$\dot{V}O_2$	590.	46.
	$P_{ET}CO_2$	66.17	1.18

Subject No. 634 : Hypercapnia data : n=8

Resistance : R0				Resistance : R4			
P_ICO_2	Variable	Mean	S.E.	P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.10	.03	0 torr	T_I	1.50	.06
	T_E	2.37	.10		T_E	2.14	.08
	$\dot{V}_T$	.65	.02		$\dot{V}_T$	.69	.01
	$\dot{V}_E$	11.3	.27		$\dot{V}_E$	11.4	.24
	$\dot{V}CO_2$	337.	12.		$\dot{V}CO_2$	320.	15.
	$\dot{V}O_2$	385.	10.		$\dot{V}O_2$	392.	20.
	$P_{ET}CO_2$	32.00	.71		$P_{ET}CO_2$	34.21	.41
30 torr	T_I	1.08	.02	30 torr	T_I	1.59	.08
	T_E	1.52	.03		T_E	1.39	.05
	$\dot{V}_T$	1.23	.02		$\dot{V}_T$	1.22	.06
	$\dot{V}_E$	28.4	.63		$\dot{V}_E$	24.6	.81
	$\dot{V}CO_2$	341.	22.		$\dot{V}CO_2$	402.	48.
	$\dot{V}O_2$	422.	27.		$\dot{V}O_2$	436.	44.
	$P_{ET}CO_2$	39.00	.67		$P_{ET}CO_2$	40.18	.78
40 torr	T_I	1.00	.04	40 torr	T_I	1.41	.09
	T_E	1.17	.07		T_E	1.14	.06
	$\dot{V}_T$	1.79	.05		$\dot{V}_T$	1.66	.09
	$\dot{V}_E$	49.6	1.82		$\dot{V}_E$	39.0	1.27
	$\dot{V}CO_2$	297.	24.		$\dot{V}CO_2$	403.	58.
	$\dot{V}O_2$	410.	45.		$\dot{V}O_2$	540.	44.
	$P_{ET}CO_2$	45.51	.51		$P_{ET}CO_2$	47.25	.41
45 torr	T_I	.97	.03	45 torr	T_I	1.25	.06
	T_E	1.17	.05		T_E	1.01	.04
	$\dot{V}_T$	2.04	.03		$\dot{V}_T$	1.72	.08
	$\dot{V}_E$	57.1	1.97		$\dot{V}_E$	45.6	1.27
	$\dot{V}CO_2$	328.	37.		$\dot{V}CO_2$	449.	90.
	$\dot{V}O_2$	470.	33.		$\dot{V}O_2$	553.	64.
	$P_{ET}CO_2$	47.52	.78		$P_{ET}CO_2$	48.30	.79
50 torr	T_I	.91	.02	50 torr	T_I	1.27	.06
	T_E	1.06	.04		T_E	.97	.04
	$\dot{V}_T$	2.29	.05		$\dot{V}_T$	1.88	.06
	$\dot{V}_E$	69.8	2.24		$\dot{V}_E$	50.2	1.13
	$\dot{V}CO_2$	306.	24.		$\dot{V}CO_2$	451.	59.
	$\dot{V}O_2$	533.	31.		$\dot{V}O_2$	683.	40.
	$P_{ET}CO_2$	52.75	.66		$P_{ET}CO_2$	55.25	.67
55 torr	T_I	.95	.10	55 torr	T_I	.99	.12
	T_E	.98	.07		T_E	1.08	.24
	$\dot{V}_T$	2.38	.16		$\dot{V}_T$	1.86	.22
	$\dot{V}_E$	73.9	1.29		$\dot{V}_E$	54.0	2.49
	$\dot{V}CO_2$	380.	43.		$\dot{V}CO_2$	565.	79.
	$\dot{V}O_2$	668.	91.		$\dot{V}O_2$	758.	85.
	$P_{ET}CO_2$	57.89	.99		$P_{ET}CO_2$	58.41	.66
60 torr	T_I	.88	.03	60 torr	T_I	1.07	.07
	T_E	.96	.05		T_E	.91	.06
	$\dot{V}_T$	2.42	.09		$\dot{V}_T$	1.93	.09
	$\dot{V}_E$	78.8	3.03		$\dot{V}_E$	58.5	1.10
	$\dot{V}CO_2$	377.	55.		$\dot{V}CO_2$	743.	59.
	$\dot{V}O_2$	580.	43.		$\dot{V}O_2$	819.	78.
	$P_{ET}CO_2$	62.44	.52		$P_{ET}CO_2$	64.56	.77

Subject No. 635 : Hypercapnia data : n=4

	Resistance : R0			Resistance : R4		
P_ICO_2	Variable	Mean	S.E.	P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.67	.12	0 torr	T_I	3.02	.14
	T_E	4.10	.19		T_E	4.56	.26
	$\dot{V}_T$	1.00	.05		$\dot{V}_T$	1.19	.06
	$\dot{V}_E$	10.4	.27		$\dot{V}_E$	9.4	.28
	$\dot{V}CO_2$	372.	37.		$\dot{V}CO_2$	347.	29.
	$\dot{V}O_2$	423.	35.		$\dot{V}O_2$	403.	26.
	$P_{ET}CO_2$	38.19	.62		$P_{ET}CO_2$	41.13	.42
30 torr	T_I	1.59	.13	30 torr	T_I	2.50	.16
	T_E	2.52	.28		T_E	2.76	.18
	$\dot{V}_T$	2.12	.16		$\dot{V}_T$	2.33	.16
	$\dot{V}_E$	30.9	2.81		$\dot{V}_E$	26.6	1.91
	$\dot{V}CO_2$	315.	38.		$\dot{V}CO_2$	344.	35.
	$\dot{V}O_2$	434.	39.		$\dot{V}O_2$	461.	42.
	$P_{ET}CO_2$	40.50	.48		$P_{ET}CO_2$	42.13	.78
40 torr	T_I	1.27	.05	40 torr	T_I	1.63	.19
	T_E	1.91	.09		T_E	1.68	.14
	$\dot{V}_T$	2.66	.11		$\dot{V}_T$	2.59	.08
	$\dot{V}_E$	50.2	2.69		$\dot{V}_E$	47.1	3.18
	$\dot{V}CO_2$	318.	45.		$\dot{V}CO_2$	413.	34.
	$\dot{V}O_2$	461.	15.		$\dot{V}O_2$	596.	51.
	$P_{ET}CO_2$	46.85	.55		$P_{ET}CO_2$	47.85	.67
45 torr	T_I	1.20	.04	45 torr	T_I	1.48	.09
	T_E	1.85	.04		T_E	1.43	.08
	$\dot{V}_T$	2.89	.06		$\dot{V}_T$	2.41	.15
	$\dot{V}_E$	56.8	2.01		$\dot{V}_E$	52.6	5.21
	$\dot{V}CO_2$	320.	38.		$\dot{V}CO_2$	477.	52.
	$\dot{V}O_2$	491.	43.		$\dot{V}O_2$	680.	43.
	$P_{ET}CO_2$	48.72	.81		$P_{ET}CO_2$	49.30	.39
50 torr	T_I	1.08	.11	50 torr	T_I	1.27	.25
	T_E	1.78	.12		T_E	1.27	.20
	$\dot{V}_T$	3.23	.12		$\dot{V}_T$	2.51	.19
	$\dot{V}_E$	67.8	4.92		$\dot{V}_E$	59.4	5.53
	$\dot{V}CO_2$	421.	33.		$\dot{V}CO_2$	536.	86.
	$\dot{V}O_2$	624.	45.		$\dot{V}O_2$	895.	76.
	$P_{ET}CO_2$	55.50	.57		$P_{ET}CO_2$	59.01	.41
55 torr	T_I	.95	.05	55 torr	T_I	1.20	.09
	T_E	1.51	.06		T_E	1.25	.11
	$\dot{V}_T$	3.20	.07		$\dot{V}_T$	2.50	.05
	$\dot{V}_E$	78.1	2.99		$\dot{V}_E$	61.3	4.42
	$\dot{V}CO_2$	447.	69.		$\dot{V}CO_2$	555.	95.
	$\dot{V}O_2$	582.	49.		$\dot{V}O_2$	905.	103.
	$P_{ET}CO_2$	59.21	.63		$P_{ET}CO_2$	62.30	1.18

Subject No. 639 : Hypercapnia data : n=8

Resistance : R0				Resistance : R4			
P_ICO_2	Variable	Mean	S.E.	P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.62	.07	0 torr	T_I	2.14	.13
	T_E	2.94	.25		T_E	2.94	.24
	$\dot{V}_T$	.79	.04		$\dot{V}_T$	.95	.05
	$\dot{V}_E$	10.4	.30		$\dot{V}_E$	9.7	.59
	$\dot{V}CO_2$	265.	34.		$\dot{V}CO_2$	272.	54.
	$\dot{V}O_2$	302.	51.		$\dot{V}O_2$	295.	58.
	P_ETCO_2	37.71	.30		P_ETCO_2	38.41	.52
30 torr	T_I	1.33	.04	30 torr	T_I	1.99	.10
	T_E	1.69	.06		T_E	1.75	.10
	$\dot{V}_T$	1.63	.08		$\dot{V}_T$	1.69	.05
	$\dot{V}_E$	32.3	2.28		$\dot{V}_E$	27.1	.19
	$\dot{V}CO_2$	329.	27.		$\dot{V}CO_2$	366.	36.
	$\dot{V}O_2$	365.	29.		$\dot{V}O_2$	438.	35.
	P_ETCO_2	44.01	.33		P_ETCO_2	41.89	.64
40 torr	T_I	1.27	.05	40 torr	T_I	1.73	.18
	T_E	1.40	.09		T_E	1.37	.14
	$\dot{V}_T$	2.25	.08		$\dot{V}_T$	2.38	.08
	$\dot{V}_E$	50.5	3.17		$\dot{V}_E$	46.0	3.48
	$\dot{V}CO_2$	368.	22.		$\dot{V}CO_2$	394.	11.
	$\dot{V}O_2$	409.	32.		$\dot{V}O_2$	461.	21.
	P_ETCO_2	45.59	.43		P_ETCO_2	47.19	.38
45 torr	T_I	1.10	.05	45 torr	T_I	1.39	.16
	T_E	1.22	.10		T_E	1.10	.07
	$\dot{V}_T$	2.55	.12		$\dot{V}_T$	2.49	.12
	$\dot{V}_E$	66.0	3.85		$\dot{V}_E$	59.9	3.95
	$\dot{V}CO_2$	370.	28.		$\dot{V}CO_2$	458.	52.
	$\dot{V}O_2$	429.	40.		$\dot{V}O_2$	537.	37.
	P_ETCO_2	50.97	.88		P_ETCO_2	51.54	.13
50 torr	T_I	.94	.08	50 torr	T_I	1.49	.12
	T_E	.98	.09		T_E	1.05	.09
	$\dot{V}_T$	2.86	.07		$\dot{V}_T$	3.10	.11
	$\dot{V}_E$	89.4	7.44		$\dot{V}_E$	73.2	4.83
	$\dot{V}CO_2$	355.	29.		$\dot{V}CO_2$	398.	43.
	$\dot{V}O_2$	428.	28.		$\dot{V}O_2$	566.	37.
	P_ETCO_2	53.87	.21		P_ETCO_2	55.17	.45
55 torr	T_I	.89	.05	55 torr	T_I	1.70	.08
	T_E	.99	.07		T_E	1.10	.04
	$\dot{V}_T$	2.89	.09		$\dot{V}_T$	3.08	1.11
	$\dot{V}_E$	92.3	3.08		$\dot{V}_E$	66.2	3.22
	$\dot{V}CO_2$	404.	43.		$\dot{V}CO_2$	448.	56.
	$\dot{V}O_2$	523.	56.		$\dot{V}O_2$	661.	34.
	P_ETCO_2	57.48	.66		P_ETCO_2	59.49	.79
60 torr	T_I	.84	.05	60 torr	T_I	1.53	.07
	T_E	.98	.02		T_E	.98	.04
	$\dot{V}_T$	2.80	.08		$\dot{V}_T$	2.94	.98
	$\dot{V}_E$	92.6	3.13		$\dot{V}_E$	70.3	2.98
	$\dot{V}CO_2$	389.	56.		$\dot{V}CO_2$	454.	54.
	$\dot{V}O_2$	513.	65.		$\dot{V}O_2$	720.	76.
	P_ETCO_2	62.49	.48		P_ETCO_2	64.34	.67

Subject No. 642 : Hypercapnia data : n=9

		Resistance : R0			Resistance : R4	
P_ICO_2	Variable	Mean	S.E.	Mean	S.E.	
0 torr	T_I	1.56	.06	2.02	.07	
	T_E	3.00	.20	3.23	.27	
	$\dot{V}T$	.54	.05	.60	.06	
	$\dot{V}E$	7.1	.58	6.9	.39	
	$\dot{V}CO_2$	277.	27.	281.	19.	
	$\dot{V}O_2$	297.	19.	314.	17.	
	$P_{ET}CO_2$	38.83	.71	40.14	.78	
30 torr	T_I	1.40	.03	1.85	.03	
	T_E	1.90	.04	1.98	.22	
	$\dot{V}T$	1.11	.07	1.19	.09	
	$\dot{V}E$	20.2	1.20	18.7	1.21	
	$\dot{V}CO_2$	298.	6.	319.	9.	
	$\dot{V}O_2$	326.	18.	326.	16.	
	$P_{ET}CO_2$	45.28	.51	46.56	.89	
40 torr	T_I	1.25	.04	1.76	.05	
	T_E	1.59	.07	1.52	.06	
	$\dot{V}T$	1.55	.09	1.68	.68	
	$\dot{V}E$	32.7	2.21	30.8	1.61	
	$\dot{V}CO_2$	286.	15.	313.	12.	
	$\dot{V}O_2$	332.	15.	376.	19.	
	$P_{ET}CO_2$	48.94	.50	51.02	.44	
45 torr	T_I	1.09	.02	1.66	.13	
	T_E	1.21	.08	1.39	.14	
	$\dot{V}T$	1.52	.07	1.77	.18	
	$\dot{V}E$	39.7	2.98	34.8	1.23	
	$\dot{V}CO_2$	312.	21.	342.	18.	
	$\dot{V}O_2$	336.	49.	411.	56.	
	$P_{ET}CO_2$	51.83	.56	54.71	.66	
50 torr	T_I	1.12	.04	1.55	.05	
	T_E	1.60	.07	1.28	.08	
	$\dot{V}T$	2.19	.09	2.35	.09	
	$\dot{V}E$	54.2	3.50	49.9	3.52	
	$\dot{V}CO_2$	322.	19.	344.	19.	
	$\dot{V}O_2$	371.	21.	423.	16.	
	$P_{ET}CO_2$	55.40	.43	58.09	.36	
55 torr	T_I	1.05	.10	1.58	.06	
	T_E	1.16	.11	1.27	.05	
	$\dot{V}T$	2.13	.18	2.42	.12	
	$\dot{V}E$	57.7	1.14	51.0	3.12	
	$\dot{V}CO_2$	302.	17.	362.	61.	
	$\dot{V}O_2$	353.	52.	443.	28.	
	$P_{ET}CO_2$	59.39	.52	62.23	1.16	
60 torr	T_I	1.03	.06	1.37	.54	
	T_E	1.03	.06	1.16	.68	
	$\dot{V}T$	3.33	.39	2.77	.12	
	$\dot{V}E$	87.6	10.40	65.8	3.81	
	$\dot{V}CO_2$	374.	29.	485.	60.	
	$\dot{V}O_2$	429.	39.	581.	37.	
	$P_{ET}CO_2$	64.14	.62	67.46	.93	

Subject No. 643 : Hypercapnia data : n=4

Resistance : R0				Resistance : R4			
P_ICO_2	Variable	Mean	S.E.	P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.26	.08	0 torr	T_I	2.04	.15
	T_E	3.42	.62		T_E	3.63	.69
	$\dot{V}_T$	.73	.05		$\dot{V}_T$	.78	.05
	$\dot{V}_E$	9.3	.93		$\dot{V}_E$	8.3	.68
	$\dot{V}CO_2$	245.	26.		$\dot{V}CO_2$	229.	17.
	$\dot{V}O_2$	281.	30.		$\dot{V}O_2$	275.	26.
	$P_{ET}CO_2$	38.77	4.03		$P_{ET}CO_2$	39.12	3.66
30 torr	T_I	1.22	.07	30 torr	T_I	1.66	.02
	T_E	1.78	.13		T_E	1.39	.05
	$\dot{V}_T$	1.17	.10		$\dot{V}_T$	1.10	.06
	$\dot{V}_E$	23.3	1.78		$\dot{V}_E$	21.6	.19
	$\dot{V}CO_2$	301.	28.		$\dot{V}CO_2$	327.	29.
	$\dot{V}O_2$	358.	23.		$\dot{V}O_2$	379.	26.
	$P_{ET}CO_2$	43.19	1.00		$P_{ET}CO_2$	45.20	1.41
40 torr	T_I	1.25	.04	40 torr	T_I	1.72	.07
	T_E	1.79	.08		T_E	1.68	.11
	$\dot{V}_T$	1.87	.21		$\dot{V}_T$	2.16	.10
	$\dot{V}_E$	36.9	5.10		$\dot{V}_E$	38.2	3.34
	$\dot{V}CO_2$	345.	31.		$\dot{V}CO_2$	396.	27.
	$\dot{V}O_2$	408.	33.		$\dot{V}O_2$	451.	23.
	$P_{ET}CO_2$	48.87	.80		$P_{ET}CO_2$	50.04	1.21
45 torr	T_I	1.26	.10	45 torr	T_I	1.60	.12
	T_E	1.61	.15		T_E	1.66	.48
	$\dot{V}_T$	2.13	.39		$\dot{V}_T$	2.20	.44
	$\dot{V}_E$	44.6	9.13		$\dot{V}_E$	40.5	8.65
	$\dot{V}CO_2$	411.	29.		$\dot{V}CO_2$	399.	31.
	$\dot{V}O_2$	530.	35.		$\dot{V}O_2$	454.	20.
	$P_{ET}CO_2$	52.38	.69		$P_{ET}CO_2$	52.89	.76
50 torr	T_I	1.17	.04	50 torr	T_I	1.56	.20
	T_E	1.47	.05		T_E	1.41	.05
	$\dot{V}_T$	2.46	.19		$\dot{V}_T$	2.46	.18
	$\dot{V}_E$	55.8	5.62		$\dot{V}_E$	49.7	4.04
	$\dot{V}CO_2$	390.	30.		$\dot{V}CO_2$	424.	40.
	$\dot{V}O_2$	481.	32.		$\dot{V}O_2$	497.	23.
	$P_{ET}CO_2$	54.73	.95		$P_{ET}CO_2$	56.19	1.31
55 torr	T_I	1.17	.08	55 torr	T_I	1.59	.05
	T_E	1.47	.07		T_E	1.35	.06
	$\dot{V}_T$	2.82	.22		$\dot{V}_T$	2.65	.37
	$\dot{V}_E$	64.0	7.74		$\dot{V}_E$	54.1	7.98
	$\dot{V}CO_2$	372.	8.		$\dot{V}CO_2$	429.	34.
	$\dot{V}O_2$	492.	8.		$\dot{V}O_2$	500.	16.
	$P_{ET}CO_2$	58.33	1.17		$P_{ET}CO_2$	60.28	1.44
60 torr	T_I	1.07	.04	60 torr	T_I	1.48	.03
	T_E	1.28	.07		T_E	1.26	.04
	$\dot{V}_T$	2.92	.14		$\dot{V}_T$	2.72	.21
	$\dot{V}_E$	74.5	7.08		$\dot{V}_E$	59.6	4.87
	$\dot{V}CO_2$	399.	11.		$\dot{V}CO_2$	470.	55.
	$\dot{V}O_2$	500.	23.		$\dot{V}O_2$	587.	16.
	$P_{ET}CO_2$	63.72	.29		$P_{ET}CO_2$	66.14	1.29

Subject No. 647 : Hypercapnia data : n=2

Resistance : R0			Resistance : R4		
P_ICO_2	Variable	Mean	P_ICO_2	Variable	Mean
0 torr	T_I	1.52	0 torr	T_I	1.98
	T_E	2.40		T_E	2.63
	$\dot{V}_T$	.67		$\dot{V}_T$	.72
	$\dot{V}_E$	10.2		$\dot{V}_E$	9.4
	$\dot{V}CO_2$	279.		$\dot{V}CO_2$	258.
	$\dot{V}O_2$	316.		$\dot{V}O_2$	295.
	$P_{ET}CO_2$	36.86		$P_{ET}CO_2$	38.78
30 torr	T_I	1.33	30 torr	T_I	2.02
	T_E	1.87		T_E	1.94
	$\dot{V}_T$	1.43		$\dot{V}_T$	1.53
	$\dot{V}_E$	26.8		$\dot{V}_E$	23.2
	$\dot{V}CO_2$	297.		$\dot{V}CO_2$	316.
	$\dot{V}O_2$	351.		$\dot{V}O_2$	370.
	$P_{ET}CO_2$	44.17		$P_{ET}CO_2$	45.81
40 torr	T_I	1.38	40 torr	T_I	2.01
	T_E	1.65		T_E	1.62
	$\dot{V}_T$	2.01		$\dot{V}_T$	2.01
	$\dot{V}_E$	39.8		$\dot{V}_E$	33.2
	$\dot{V}CO_2$	268.		$\dot{V}CO_2$	199.
	$\dot{V}O_2$	354.		$\dot{V}O_2$	339.
	$P_{ET}CO_2$	48.03		$P_{ET}CO_2$	46.67
45 torr	T_I	1.35	45 torr	T_I	1.77
	T_E	1.36		T_E	1.38
	$\dot{V}_T$	2.64		$\dot{V}_T$	2.60
	$\dot{V}_E$	58.5		$\dot{V}_E$	49.5
	$\dot{V}CO_2$	316.		$\dot{V}CO_2$	340.
	$\dot{V}O_2$	336.		$\dot{V}O_2$	420.
	$P_{ET}CO_2$	50.70		$P_{ET}CO_2$	52.60
50 torr	T_I	1.40	50 torr	T_I	1.57
	T_E	1.65		T_E	1.27
	$\dot{V}_T$	3.34		$\dot{V}_T$	2.55
	$\dot{V}_E$	65.7		$\dot{V}_E$	53.9
	$\dot{V}CO_2$	329.		$\dot{V}CO_2$	363.
	$\dot{V}O_2$	346.		$\dot{V}O_2$	371.
	$P_{ET}CO_2$	58.31		$P_{ET}CO_2$	60.80
55 torr	T_I	1.18	55 torr	T_I	1.32
	T_E	1.22		T_E	1.00
	$\dot{V}_T$	3.38		$\dot{V}_T$	2.78
	$\dot{V}_E$	84.5		$\dot{V}_E$	71.9
	$\dot{V}CO_2$	275.		$\dot{V}CO_2$	496.
	$\dot{V}O_2$	399.		$\dot{V}O_2$	534.
	$P_{ET}CO_2$	58.44		$P_{ET}CO_2$	60.24

Subject No. 648 : Hypercapnia data : n=6

	Resistance : R0			Resistance : R4		
P_ICO_2	Variable	Mean	S.E.	P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.69	.16	0 torr	T_I	2.18	.16
	T_E	3.00	.46		T_E	2.48	.32
	$\dot{V}_T$	.92	.10		$\dot{V}_T$	.87	.11
	$\dot{V}_E$	11.8	.67		$\dot{V}_E$	11.2	1.18
	$\dot{V}CO_2$	277.	33.		$\dot{V}CO_2$	295.	43.
	$\dot{V}O_2$	312.	31.		$\dot{V}O_2$	300.	33.
	$P_{ET}CO_2$	30.64	1.69		$P_{ET}CO_2$	28.80	2.42
30 torr	T_I	1.51	.14	30 torr	T_I	2.14	.13
	T_E	2.38	.04		T_E	2.21	.03
	$\dot{V}_T$	1.47	.10		$\dot{V}_T$	1.52	.11
	$\dot{V}_E$	22.6	.97		$\dot{V}_E$	21.0	.93
	$\dot{V}CO_2$	265.	21.		$\dot{V}CO_2$	245.	9.
	$\dot{V}O_2$	317.	18.		$\dot{V}O_2$	322.	18.
	$P_{ET}CO_2$	41.99	.72		$P_{ET}CO_2$	42.30	.61
40 torr	T_I	1.44	.10	40 torr	T_I	1.94	.10
	T_E	2.09	.16		T_E	1.97	.06
	$\dot{V}_T$	2.07	.19		$\dot{V}_T$	2.25	.10
	$\dot{V}_E$	35.2	2.01		$\dot{V}_E$	34.5	1.78
	$\dot{V}CO_2$	282.	18.		$\dot{V}CO_2$	285.	13.
	$\dot{V}O_2$	341.	22.		$\dot{V}O_2$	345.	20.
	$P_{ET}CO_2$	47.40	.38		$P_{ET}CO_2$	48.46	.36
45 torr	T_I	1.27	.06	45 torr	T_I	1.68	.10
	T_E	1.88	.22		T_E	1.63	.13
	$\dot{V}_T$	2.56	.22		$\dot{V}_T$	2.54	.12
	$\dot{V}_E$	48.8	4.03		$\dot{V}_E$	46.0	4.72
	$\dot{V}CO_2$	308.	15.		$\dot{V}CO_2$	325.	20.
	$\dot{V}O_2$	381.	23.		$\dot{V}O_2$	386.	19.
	$P_{ET}CO_2$	50.95	.74		$P_{ET}CO_2$	51.47	.33
50 torr	T_I	1.10	.06	50 torr	T_I	1.46	.10
	T_E	1.66	.10		T_E	1.30	.08
	$\dot{V}_T$	3.04	.15		$\dot{V}_T$	2.77	.18
	$\dot{V}_E$	66.0	5.13		$\dot{V}_E$	60.4	4.95
	$\dot{V}CO_2$	343.	28.		$\dot{V}CO_2$	407.	47.
	$\dot{V}O_2$	393.	34.		$\dot{V}O_2$	445.	28.
	$P_{ET}CO_2$	53.98	.53		$P_{ET}CO_2$	55.23	.54
55 torr	T_I	1.08	.11	55 torr	T_I	1.23	.24
	T_E	1.62	.19		T_E	.95	.23
	$\dot{V}_T$	3.33	.29		$\dot{V}_T$	2.99	.31
	$\dot{V}_E$	74.0	5.22		$\dot{V}_E$	82.3	9.96
	$\dot{V}CO_2$	330.	46.		$\dot{V}CO_2$	451.	94.
	$\dot{V}O_2$	396.	50.		$\dot{V}O_2$	542.	88.
	$P_{ET}CO_2$	57.77	.50		$P_{ET}CO_2$	59.10	.94

Appendix A2

Eight exercise and five hypercapnic tests were undertaken, by three subjects, in the presence of two flow-resistances (R2 and R3) of lower severity than R4.

The experimental protocol was the same as for the main series of experiments and the data is presented similarly, in the same units, as the mean and standard error of the mean for each subject at each work or inspired CO_2 level. The number of tests performed by each subject (n) is indicated at the top of each page.

Subject No. 642 : Exercise data : n=3

Resistance : R2

Work Rate	Variable	Mean	S.E.
Rest	T_I	1.54	.06
	T_E	4.02	.59
	$\dot{V}_T$	.89	.08
	$\dot{V}_E$	8.6	.50
	$\dot{V}O_2$	267.	13.
	$\dot{V}CO_2$	293.	12.
	$P_{ET}CO_2$	41.97	.78
0 Watts	T_I	1.43	.03
	T_E	2.00	.11
	$\dot{V}_T$	.77	.01
	$\dot{V}_E$	15.6	.86
	$\dot{V}O_2$	594.	68.
	$\dot{V}CO_2$	634.	33.
	$P_{ET}CO_2$	44.83	.65
50 Watts	T_I	1.35	.01
	T_E	1.67	.04
	$\dot{V}_T$	1.11	.01
	$\dot{V}_E$	25.2	.44
	$\dot{V}O_2$	1033.	28.
	$\dot{V}CO_2$	1089.	10.
	$P_{ET}CO_2$	46.31	.51
100 Watts	T_I	1.26	.02
	T_E	1.39	.05
	$\dot{V}_T$	1.47	.04
	$\dot{V}_E$	38.0	1.07
	$\dot{V}O_2$	1590.	74.
	$\dot{V}CO_2$	1630.	40.
	$P_{ET}CO_2$	47.38	.78
150 Watts	T_I	1.23	.04
	T_E	1.25	.05
	$\dot{V}_T$	1.97	.09
	$\dot{V}_E$	54.6	1.11
	$\dot{V}O_2$	2286.	97.
	$\dot{V}CO_2$	2321.	49.
	$P_{ET}CO_2$	46.05	.74
200 Watts	T_I	1.09	.06
	T_E	1.01	.01
	$\dot{V}_T$	2.42	.11
	$\dot{V}_E$	79.3	2.38
	$\dot{V}O_2$	3017.	135.
	$\dot{V}CO_2$	2908.	19.
	$P_{ET}CO_2$	42.77	.83

Resistance : R3

Work Rate	Variable	Mean	S.E.
Rest	T_I	1.61	.05
	T_E	3.55	.57
	$\dot{V}_T$	.65	.08
	$\dot{V}_E$	7.5	.08
	$\dot{V}O_2$	265.	25.
	$\dot{V}CO_2$	286.	17.
	$P_{ET}CO_2$	42.15	.93
0 Watts	T_I	1.71	.06
	T_E	1.86	.09
	$\dot{V}_T$	.87	.03
	$\dot{V}_E$	14.7	.29
	$\dot{V}O_2$	552.	35.
	$\dot{V}CO_2$	644.	30.
	$P_{ET}CO_2$	44.74	.45
50 Watts	T_I	1.57	.01
	T_E	1.54	.13
	$\dot{V}_T$	1.30	.04
	$\dot{V}_E$	25.1	.81
	$\dot{V}O_2$	1048.	51.
	$\dot{V}CO_2$	1125.	31.
	$P_{ET}CO_2$	46.50	1.21
100 Watts	T_I	1.41	.04
	T_E	1.36	.11
	$\dot{V}_T$	1.72	.06
	$\dot{V}_E$	37.2	1.16
	$\dot{V}O_2$	1594.	54.
	$\dot{V}CO_2$	1629.	31.
	$P_{ET}CO_2$	48.41	1.50
150 Watts	T_I	1.36	.05
	T_E	1.17	.09
	$\dot{V}_T$	2.34	.15
	$\dot{V}_E$	55.6	2.05
	$\dot{V}O_2$	2332.	26.
	$\dot{V}CO_2$	2436.	52.
	$P_{ET}CO_2$	46.85	1.13
200 Watts	T_I	1.20	.11
	T_E	1.93	.03
	$\dot{V}_T$	2.88	.15
	$\dot{V}_E$	81.1	4.06
	$\dot{V}O_2$	3150.	90.
	$\dot{V}CO_2$	3003.	52.
	$P_{ET}CO_2$	44.00	1.03

Subject No. 643 : Exercise data : n=3

Resistance : R2			Resistance : R3		
Work Rate	Variable	Mean	Work Rate	Variable	Mean
Rest	T_I	1.42	Rest	T_I	1.83
	T_E	3.09		T_E	3.41
	$\dot{V}_T$	.73		$\dot{V}_T$	.74
	$\dot{V}_E$	9.7		$\dot{V}_E$	8.5
	$\dot{V}CO_2$	298.		$\dot{V}CO_2$	266.
	$\dot{V}O_2$	306.		$\dot{V}O_2$	300.
	P_ETCO_2	40.59		P_ETCO_2	39.97
0 Watts	T_I	1.37	0 Watts	T_I	1.97
	T_E	2.06		T_E	2.65
	$\dot{V}_T$	.93		$\dot{V}_T$	1.13
	$\dot{V}_E$	16.3		$\dot{V}_E$	14.6
	$\dot{V}CO_2$	568.		$\dot{V}CO_2$	534.
	$\dot{V}O_2$	625.		$\dot{V}O_2$	627.
	P_ETCO_2	42.04		P_ETCO_2	41.88
50 Watts	T_I	1.48	50 Watts	T_I	1.74
	T_E	2.39		T_E	2.10
	$\dot{V}_T$	1.41		$\dot{V}_T$	1.45
	$\dot{V}_E$	21.9		$\dot{V}_E$	22.7
	$\dot{V}CO_2$	855.		$\dot{V}CO_2$	905.
	$\dot{V}O_2$	971.		$\dot{V}O_2$	1029.
	P_ETCO_2	44.11		P_ETCO_2	43.17
100 Watts	T_I	1.68	100 Watts	T_I	1.93
	T_E	2.11		T_E	2.07
	$\dot{V}_T$	2.01		$\dot{V}_T$	2.15
	$\dot{V}_E$	31.9		$\dot{V}_E$	32.2
	$\dot{V}CO_2$	1349.		$\dot{V}CO_2$	1394.
	$\dot{V}O_2$	1478.		$\dot{V}O_2$	1601.
	P_ETCO_2	46.65		P_ETCO_2	45.84
150 Watts	T_I	1.47	150 Watts	T_I	1.73
	T_E	1.67		T_E	1.38
	$\dot{V}_T$	2.34		$\dot{V}_T$	2.34
	$\dot{V}_E$	44.7		$\dot{V}_E$	43.2
	$\dot{V}CO_2$	1876.		$\dot{V}CO_2$	1791.
	$\dot{V}O_2$	2115.		$\dot{V}O_2$	2049.
	P_ETCO_2	45.44		P_ETCO_2	45.35
200 Watts	T_I	1.46	200 Watts	T_I	1.66
	T_E	1.49		T_E	1.54
	$\dot{V}_T$	2.65		$\dot{V}_T$	2.82
	$\dot{V}_E$	53.7		$\dot{V}_E$	52.8
	$\dot{V}CO_2$	2357.		$\dot{V}CO_2$	2407.
	$\dot{V}O_2$	2602.		$\dot{V}O_2$	2521.
	P_ETCO_2	47.76		P_ETCO_2	47.82
250 Watts	T_I	1.43	250 Watts	T_I	1.50
	T_E	1.27		T_E	1.36
	$\dot{V}_T$	3.18		$\dot{V}_T$	3.15
	$\dot{V}_E$	70.6		$\dot{V}_E$	66.2
	$\dot{V}CO_2$	3264.		$\dot{V}CO_2$	3047.
	$\dot{V}O_2$	3357.		$\dot{V}O_2$	3211.
	P_ETCO_2	48.23		P_ETCO_2	47.59

Subject No. 647 : Exercise data : n=2

Resistance : R2			Resistance : R3		
Work Rate	Variable	Mean	Work Rate	Variable	Mean
Rest	T_I	1.64	Rest	T_I	2.02
	T_E	2.40		T_E	3.69
	$\dot{V}_T$	.67		$\dot{V}_T$	.57
	$\dot{V}_E$	6.3		$\dot{V}_E$	9.4
	$P_{ET}CO_2$	37.12		$P_{ET}CO_2$	38.30
0 Watts	T_I	2.17	0 Watts	T_I	2.24
	T_E	2.71		T_E	2.41
	$\dot{V}_T$	1.23		$\dot{V}_T$	1.23
	$\dot{V}_E$	15.1		$\dot{V}_E$	15.9
	$P_{ET}CO_2$	40.77		$P_{ET}CO_2$	41.02
50 Watts	T_I	1.92	50 Watts	T_I	1.90
	T_E	2.01		T_E	1.72
	$\dot{V}_T$	1.59		$\dot{V}_T$	1.49
	$\dot{V}_E$	24.2		$\dot{V}_E$	24.7
	$P_{ET}CO_2$	41.29		$P_{ET}CO_2$	41.33
100 Watts	T_I	1.75	100 Watts	T_I	1.89
	T_E	1.75		T_E	1.74
	$\dot{V}_T$	2.09		$\dot{V}_T$	2.11
	$\dot{V}_E$	35.9		$\dot{V}_E$	34.8
	$P_{ET}CO_2$	44.78		$P_{ET}CO_2$	45.02
150 Watts	T_I	1.53	150 Watts	T_I	1.72
	T_E	1.47		T_E	1.44
	$\dot{V}_T$	2.48		$\dot{V}_T$	2.65
	$\dot{V}_E$	49.5		$\dot{V}_E$	50.3
	$P_{ET}CO_2$	43.20		$P_{ET}CO_2$	43.19
200 Watts	T_I	1.35	200 Watts	T_I	1.58
	T_E	1.34		T_E	1.25
	$\dot{V}_T$	2.83		$\dot{V}_T$	3.32
	$\dot{V}_E$	63.0		$\dot{V}_E$	68.7
	$P_{ET}CO_2$	44.76		$P_{ET}CO_2$	44.90
250 Watts	T_I	1.04	250 Watts	T_I	1.12
	T_E	1.17		T_E	.76
	$\dot{V}_T$	3.90		$\dot{V}_T$	3.12
	$\dot{V}_E$	86.9		$\dot{V}_E$	77.0
	$P_{ET}CO_2$	43.18		$P_{ET}CO_2$	43.98

Subject No. 642 : Hypercapnia data : n=3

Resistance : R2

P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.54	.09
	T_E	4.02	.59
	$\dot{V}_T$	.89	.08
	$\dot{V}_E$	8.6	.50
	$\dot{V}CO_2$	263.	13.
	$\dot{V}O_2$	293.	12.
	$P_{ET}CO_2$	41.97	.78
30 torr	T_I	1.43	.01
	T_E	1.82	.07
	$\dot{V}_T$	1.31	.13
	$\dot{V}_E$	24.1	3.11
	$\dot{V}CO_2$	334.	47.
	$\dot{V}O_2$	364.	30.
	$P_{ET}CO_2$	46.81	1.47
40 torr	T_I	1.32	.10
	T_E	1.32	.18
	$\dot{V}_T$	1.80	.10
	$\dot{V}_E$	40.8	5.63
	$\dot{V}CO_2$	311.	15.
	$\dot{V}O_2$	359.	11.
	$P_{ET}CO_2$	49.86	1.30
50 torr	T_I	1.30	.05
	T_E	1.84	.09
	$\dot{V}_T$	2.89	.08
	$\dot{V}_E$	55.3	2.96
	$\dot{V}CO_2$	309.	31.
	$\dot{V}O_2$	397.	28.
	$P_{ET}CO_2$	56.96	.63
60 torr	T_I	1.16	.06
	T_E	1.00	.08
	$\dot{V}_T$	2.65	.41
	$\dot{V}_E$	73.6	5.40
	$\dot{V}CO_2$	317.	35.
	$\dot{V}O_2$	431.	45.
	$P_{ET}CO_2$	64.71	.88

Resistance : R3

P_ICO_2	Variable	Mean	S.E.
0 torr	T_I	1.61	.05
	T_E	3.55	.57
	$\dot{V}_T$	.65	.08
	$\dot{V}_E$	7.5	.08
	$\dot{V}CO_2$	265.	25.
	$\dot{V}O_2$	286.	17.
	$P_{ET}CO_2$	42.15	.93
30 torr	T_I	1.60	.03
	T_E	1.73	.07
	$\dot{V}_T$	1.20	.15
	$\dot{V}_E$	21.7	3.44
	$\dot{V}CO_2$	298.	37.
	$\dot{V}O_2$	338.	46.
	$P_{ET}CO_2$	46.85	1.73
40 torr	T_I	1.50	.06
	T_E	1.49	.20
	$\dot{V}_T$	1.61	.11
	$\dot{V}_E$	32.4	4.80
	$\dot{V}CO_2$	293.	25.
	$\dot{V}O_2$	345.	28.
	$P_{ET}CO_2$	51.26	1.10
50 torr	T_I	1.32	.04
	T_E	1.79	.08
	$\dot{V}_T$	2.93	.10
	$\dot{V}_E$	56.6	3.12
	$\dot{V}CO_2$	380.	29.
	$\dot{V}O_2$	450.	17.
	$P_{ET}CO_2$	58.34	.56
60 torr	T_I	1.32	.32
	T_E	1.79	.52
	$\dot{V}_T$	2.93	.21
	$\dot{V}_E$	56.8	6.81
	$\dot{V}CO_2$	347.	54.
	$\dot{V}O_2$	482.	69.
	$P_{ET}CO_2$	66.03	1.20

Subject No. 643 : Hypercapnia data : n=2

Resistance : R2

P_ICO_2	Variable	Mean
0 torr	T_I	1.42
	T_E	3.09
	V_T	.73
	$\dot{V}_E$	9.7
	$\dot{V}CO_2$	298.
	$\dot{V}O_2$	306.
	$P_{ET}CO_2$	40.59
30 torr	T_I	1.48
	T_E	1.78
	V_T	1.44
	$\dot{V}_E$	25.0
	$\dot{V}CO_2$	344.
	$\dot{V}O_2$	343.
	$P_{ET}CO_2$	46.10
40 torr	T_I	1.90
	T_E	2.22
	V_T	2.36
	$\dot{V}_E$	34.4
	$\dot{V}CO_2$	358.
	$\dot{V}O_2$	442.
	$P_{ET}CO_2$	51.71
50 torr	T_I	1.43
	T_E	1.50
	V_T	3.01
	$\dot{V}_E$	60.4
	$\dot{V}CO_2$	384.
	$\dot{V}O_2$	414.
	$P_{ET}CO_2$	57.18

Resistance : R3

P_ICO_2	Variable	Mean
0 torr	T_I	1.83
	T_E	3.41
	V_T	.74
	$\dot{V}_E$	8.3
	$\dot{V}CO_2$	266.
	$\dot{V}O_2$	300.
	$P_{ET}CO_2$	39.97
30 torr	T_I	1.79
	T_E	2.10
	V_T	1.71
	$\dot{V}_E$	26.3
	$\dot{V}CO_2$	406.
	$\dot{V}O_2$	475.
	$P_{ET}CO_2$	47.93
40 torr	T_I	1.71
	T_E	1.69
	V_T	2.17
	$\dot{V}_E$	38.3
	$\dot{V}CO_2$	383.
	$\dot{V}O_2$	438.
	$P_{ET}CO_2$	53.05
50 torr	T_I	1.63
	T_E	1.50
	V_T	2.81
	$\dot{V}_E$	53.9
	$\dot{V}CO_2$	375.
	$\dot{V}O_2$	494.
	$P_{ET}CO_2$	57.75

Appendix A3

This appendix presents data concerning measures of inspiratory capacity made during eight incremental exercise tests and eight incremental hypercapnia tests, by three subjects, in the absence of an external flow-resistance (R0) and in the presence of the severest load employed (R4).

Measurements of inspiratory capacity (measured in litres, BTPS) are presented both as means for each subject and as pooled means (the average of all subjects' data), at each exercise or inspired CO_2 level.

The difference between inspiratory capacity at rest and at a given exercise or inspired CO_2 level estimates the change in end-expiratory volume (EEV). These values are presented as pooled means, in association with the pooled mean ventilation (units of litres per minute), during these experiments, at each exercise or inspired CO_2 level.

Exercise Condition

Work Rate

Subject	Rest		0 W		50 W		100 W		150 W		200 W	
No.	R0	R4	R0	R4	R0	R4	R0	R4	R0	R4	R0	R4
642	3.09	3.36	3.29	3.58	3.35	3.59	3.58	3.73	3.60	3.95	3.41	3.86
643	2.81	2.59	2.93	3.21	3.16	3.04	3.11	3.13	3.06	3.28	3.37	3.56
647	3.13	3.29	3.38	3.60	3.57	3.66	3.62	3.86	3.73	4.12	4.32	4.34
Mean	3.01	3.08	3.17	3.46	3.36	3.43	3.44	3.57	3.45	3.78	3.70	3.89
ΔEEV		-.07	-.16	-.45	-.35	-.42	-.43	-.56	-.45	-.77	-.69	-.88
$\dot{V}$	8.9	8.2	18.9	17.5	26.0	25.2	38.7	36.0	54.6	51.4	73.1	67.3

Hypercapnia Condition

Inspired CO_2 Level

Subject	Rest		20 torr		30 torr		40 torr		50 torr		55 torr	
No.	R0	R4	R0	R4	R0	R4	R0	R4	R0	R4	R0	R4
642	3.12	3.20	3.23	3.21	3.31	3.44	3.56	3.70	3.90	4.13	3.93	4.20
643	2.94	2.76	2.84	3.01	2.89	2.94	3.11	3.05	3.33	3.18	3.40	3.59
647	3.57	3.44	3.60	3.60	3.66	3.73	3.83	3.91	4.08	4.36	4.08	4.09
Mean	3.21	3.13	3.22	3.27	3.29	3.37	3.50	3.55	3.77	3.89	3.80	3.93
ΔEEV		.08	-.01	-.06	-.08	-.16	-.29	-.34	-.56	-.68	-.59	-.72
$\dot{V}$	9.3	8.4	15.0	14.5	23.5	21.1	35.5	34.1	57.5	50.5	81.4	64.7

Appendix A4

This appendix contains data concerning the shape of the flow profile, from 18 incremental exercise tests and 20 incremental hypercapnia tests, performed by four subjects, in the absence of a flow-resistive load (unloaded) and in the presence of the severest load employed R4 (loaded).

Each subjects' data was grouped in 10 litre per minute ventilation ranges, the mean and standard error of the mean of each ventilatory level is presented subject by subject. The number of tests performed by each subject is shown at the foot of each page, the numbers of observations (n) contributing to the calculation of each mean and standard error are shown within the tables.

The variables measured and units of measurement are listed below:

$\dot{V}$	- Ventilation	- $L.min^{-1}$ (BTPS).
$\ddot{v}_I$	- Inspiratory flow acceleration	- $L.min^{-1}min^{-1}$ (BTPS).
Tmax	- Time to peak inspiratory flow	- s.
Tmin	- Time to peak expiratory flow	- s.
$\dot{v}_I max$	- Peak inspiratory flow	- $L.min^{-1}$ (BTPS).
$\dot{v}_E max$	- Peak expiratory flow	- $L.min^{-1}$ (BTPS).
$Tmax/T_I$	- Tmax / Duration of inspiration.	
$Tmin/T_E$	- Tmin / Duration of expiration.	
$\bar{\dot{v}}_I/\dot{v}_I max$	- Mean / Peak inspiratory flow.	
$\bar{\dot{v}}_E/\dot{v}_E max$	- Mean / Peak expiratory flow.	

Subject 632 : Exercise Flow Data

Unloaded Data

$\dot{V}$	n	$\bar{V}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\bar{\dot{V}}_I}{\dot{V}_I max}$	$\frac{\bar{\dot{V}}_E}{\dot{V}_E max}$
		2058	1.07	0.57	59.8	55.2	0.49	0.23	0.52	0.46
10-19.9	5	251	.21	.05	3.7	5.0	.05	.02	.05	.02
		4341	0.56	0.57	75.4	61.9	0.43	0.30	0.70	0.59
20-29.9	4	281	.04	.02	4.5	3.5	.01	.01	.02	.02
		6567	0.48	0.61	106.4	101.8	0.33	0.36	0.67	0.62
30-39.9	7	564	.03	.03	7.2	8.5	.03	.02	.03	.03
		8280	0.44	0.63	130.0	122.7	0.30	0.39	0.68	0.65
40-49.9	3	605	.02	.03	8.5	5.9	.05	.02	.03	.02
		11402	0.45	0.54	171.5	177.1	0.25	0.33	0.66	0.71
50-59.9	4	1020	.02	.05	9.5	6.4	.03	.01	.05	.01
		17403	0.40	0.54	205.4	193.7	0.24	0.46	0.65	0.76
60-69.9	3	1840	.09	.04	12.0	15.3	.04	.01	.06	.03

Loaded Data

		1513	0.97	1.07	54.3	69.6	0.33	0.34	0.60	0.45
10-19.9	6	156	.14	.14	2.7	8.4	.03	.03	.02	.02
		3474	0.60	0.62	79.5	111.9	0.22	0.28	0.62	0.54
20-29.9	3	536	.07	.02	3.7	12.1	.01	.01	.04	.03
		3954	0.62	0.52	102.9	166.8	0.22	0.28	0.58	0.57
30-39.9	4	384	.02	.11	6.3	8.7	.02	.05	.04	.05
		6366	0.68	0.48	111.2	189.5	0.26	0.33	0.59	0.65
40-49.9	4	719	.07	.13	6.2	6.9	.03	.02	.01	.08
		10605	0.46	0.67	152.5	204.3	0.22	0.51	0.61	0.71
50-59.9	5	1266	.04	.13	8.2	7.9	.01	.09	.01	.04
		14398	0.42	0.52	169.8	220.4	0.28	0.52	0.66	0.76
60-69.9	3	1384	.04	.09	8.3	8.1	.04	.04	.01	.05

No. of tests = 4

Subject 634 : Exercise Flow Data

Unloaded Data

$\dot{V}$	n	$\bar{\dot{V}}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\bar{\dot{V}}_I}{\dot{V}_I max}$	$\frac{\bar{\dot{V}}_E}{\dot{V}_E max}$
		1853	0.51	0.46	61.7	46.9	0.45	0.24	0.67	0.51
10-19.9	5	48	.02	.03	3.5	2.3	.01	.02	.02	.02
		3769	0.52	0.47	85.6	70.0	0.44	0.30	0.70	0.62
20-29.9	4	282	.02	.02	2.7	2.9	.02	.02	.01	.01
		6865	0.51	0.45	114.5	93.4	0.47	0.32	0.71	0.68
30-39.9	4	544	.02	.03	2.8	3.3	.02	.02	.01	.01
		10010	0.45	0.38	140.4	113.1	0.46	0.31	0.74	0.74
40-49.9	3	564	.02	.02	3.0	4.7	.02	.01	.01	.01
		12720	0.45	0.44	155.6	143.6	0.45	0.40	0.76	0.75
50-59.9	4	1620	.03	.04	4.4	10.2	.09	.03	.01	.01
		14985	0.45	0.33	181.3	168.6	0.54	0.36	0.77	0.76
60-69.9	5	2299	.06	.02	7.3	16.7	.06	.02	.05	.04

Loaded Data

		1755	0.55	0.53	50.5	47.1	0.38	0.28	0.68	0.56
10-19.9	7	278	.04	.05	4.9	6.0	.02	.02	.02	.03
		3746	0.58	0.52	70.8	78.9	0.37	0.35	0.70	0.65
20-29.9	5	264	.07	.04	4.5	5.9	.01	.03	.01	.02
		5777	0.53	0.43	95.1	107.4	0.35	0.35	0.70	0.72
30-39.9	6	445	.09	.05	5.6	6.6	.03	.02	.02	.16
		9184	0.47	0.38	118.1	131.8	0.37	0.36	0.70	0.76
40-49.9	7	914	.06	.02	8.1	3.2	.05	.02	.01	.09
		14265	0.43	0.37	151.1	172.2	0.33	0.38	0.68	0.73
50-59.9	7	2275	.09	.02	10.8	4.8	.05	.03	.02	.01
		14220	0.41	0.28	170.3	218.6	0.38	0.41	0.63	0.64
60-69.9	3	1981	.08	.02	9.5	6.9	.06	.02	.02	.01

No. of tests = 5

Subject 639 : Exercise Flow Data

Unloaded Data

$\dot{V}$	n	$\bar{V}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\bar{\dot{V}}_I}{\dot{V}_I max}$	$\frac{\bar{\dot{V}}_E}{\dot{V}_E max}$
10-19.9	8	1928	0.78	0.53	53.3	49.5	0.45	0.25	0.66	0.56
		212	.08	.06	4.5	3.2	.04	.03	.01	.02
20-29.9	6	3563	0.62	0.67	78.9	71.7	0.37	0.34	0.70	0.63
		337	.06	.04	4.3	5.1	.03	.02	.05	.01
30-39.9	5	6674	0.60	0.68	113.4	97.2	0.36	0.38	0.66	0.63
		564	.05	.04	4.3	5.1	.03	.02	.05	.01
40-49.9	5	9422	0.51	0.46	146.8	151.9	0.37	0.29	0.66	0.62
		504	.09	.09	5.7	27.3	.08	.04	.04	.06
50-59.9	3	12075	0.44	0.35	169.8	148.9	0.29	0.27	0.59	0.76
		1215	.02	.05	5.3	11.1	.09	.04	.01	.02
60-69.9	5	16080	0.36	0.35	189.5	190.4	0.27	0.29	0.74	0.77
		2340	.09	.05	11.5	7.9	.07	.05	.03	.02

Loaded Data

10-19.9	9	1425	0.83	0.75	44.6	43.1	0.43	0.33	0.65	0.60
		209	.06	.08	3.9	3.7	.03	.03	.01	.02
20-29.9	6	3045	0.74	0.71	66.5	74.8	0.35	0.38	0.69	0.68
		273	.08	.03	3.8	5.0	.03	.01	.02	.01
30-39.9	5	4499	0.53	0.54	90.9	101.9	0.29	0.34	0.70	0.71
		488	.03	.04	4.5	8.7	.02	.02	.02	.02
40-49.9	3	6105	0.55	0.41	119.1	135.8	0.35	0.32	0.68	0.72
		495	.07	.07	13.9	8.8	.03	.07	.01	.03
50-59.9	6	6720	0.55	0.32	131.2	159.5	0.31	0.25	0.68	0.75
		717	.09	.02	8.9	5.7	.02	.05	.02	.04
60-69.9	4	7831	0.51	0.20	176.1	208.3	0.47	0.20	0.73	0.67
		811	.07	.02	9.9	7.2	.03	.03	.03	.03

No. of tests = 5

Subject 643 : Exercise Flow Data

Unloaded Data

$\dot{V}$	n	$\bar{\dot{V}}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\bar{\dot{V}}_I}{\dot{V}_I max}$	$\frac{\bar{\dot{V}}_E}{\dot{V}_E max}$
		1980	0.77	0.64	55.4	40.5	0.51	0.32	0.68	0.60
10-19.9	5	87	.03	.03	3.2	4.2	.01	.01	.02	.03
		3210	0.68	0.85	76.3	56.3	0.47	0.43	0.70	0.67
20-29.9	3	311	.03	.03	3.5	6.2	.02	.03	.01	.03
		6913	0.40	0.82	114.5	83.1	0.33	0.48	0.77	0.77
30-39.9	5	539	.03	.03	4.9	7.2	.03	.04	.01	.02
		10194	0.51	0.57	123.2	94.1	0.38	0.34	0.77	0.83
40-49.9	4	632	.02	.02	7.0	8.9	.07	.05	.01	.01
		14400	0.47	0.53	148.3	127.5	0.37	0.37	0.78	0.82
50-59.9	3	1283	.03	.06	7.8	17.2	.06	.05	.01	.01
		17475	0.38	0.38	168.9	151.6	0.35	0.35	0.76	0.83
60-69.9	6	1444	.05	.03	10.8	18.4	.03	.05	.03	.04

Loaded Data

		1218	1.01	0.78	37.9	48.5	0.41	0.38	0.67	0.60
10-19.9	5	183	.03	.05	3.1	2.4	.02	.02	.02	.02
		2470	0.64	0.58	60.9	73.4	0.36	0.51	0.72	0.71
20-29.9	4	257	.03	.05	4.8	3.8	.03	.04	.02	.01
		4094	0.70	0.55	83.3	105.1	0.33	0.35	0.76	0.68
30-39.9	4	438	.04	.05	7.8	5.1	.03	.03	.02	.01
		5514	0.74	0.51	100.2	121.5	0.38	0.36	0.75	0.83
40-49.9	3	634	.04	.02	9.5	6.4	.05	.02	.01	.01
		7384	0.65	0.36	123.3	155.0	0.37	0.27	0.78	0.83
50-59.9	4	1060	.08	.02	10.7	8.0	.04	.01	.02	.09
		8860	0.58	0.26	144.2	186.6	0.37	0.22	0.80	0.82
60-69.9	5	1339	.07	.02	11.8	8.2	.05	.02	.02	.08

No. of tests = 4

Subject 632 : Hypercapnic Flow Data

Unloaded Data

$\dot{V}$	n	$\bar{V}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\bar{\dot{V}}_I}{\dot{V}_I max}$	$\frac{\bar{\dot{V}}_E}{\dot{V}_E max}$
10-19.9	7	2995	0.76	0.73	59.7	44.3	0.39	0.28	0.54	0.47
		503	.26	.13	4.6	4.0	.07	.05	.08	.04
20-29.9	7	5298	0.43	0.98	75.6	61.1	0.25	0.43	0.68	0.64
		316	.04	.05	3.3	4.1	.03	.02	.01	.01
30-39.9	3	7896	0.39	0.69	103.7	98.7	0.24	0.35	0.69	0.61
		517	.06	.04	4.8	5.1	.03	.02	.02	.03
40-49.9	6	11380	0.35	0.48	129.6	128.7	0.23	0.32	0.67	0.69
		610	.07	.05	2.8	6.5	.05	.04	.02	.03
50-59.9	4	14060	0.32	0.48	167.9	153.7	0.22	0.34	0.69	0.72
		732	.05	.03	3.8	2.2	.02	.03	.09	.04
60-69.9	6	18441	0.28	0.47	197.2	182.7	0.21	0.38	0.71	0.76
		802	.01	.03	4.1	2.5	.01	.02	.02	.02

Loaded Data

10-19.9	8	2588	0.65	1.22	53.6	56.1	0.25	0.40	0.56	0.54
		408	.11	.22	2.3	4.6	.05	.04	.03	.04
20-29.9	6	3451	0.59	0.78	71.4	86.7	0.22	0.35	0.62	0.61
		318	.07	.08	6.5	2.7	.03	.06	.02	.02
30-39.9	5	5330	0.55	0.48	98.5	148.9	0.19	0.29	0.57	0.66
		387	.03	.05	3.1	6.7	.01	.02	.02	.02
40-49.9	6	7620	0.53	0.44	124.7	195.2	0.22	0.30	0.79	0.67
		796	.04	.06	3.9	3.1	.02	.03	.02	.01
50-59.9	7	9060	0.47	0.44	145.8	201.3	0.23	0.38	0.67	0.75
		824	.05	.03	3.4	4.1	.03	.03	.02	.09
60-69.9	3	10186	0.46	0.48	167.1	228.6	0.25	0.44	0.66	0.72
		935	.07	.02	4.7	7.6	.04	.12	.05	.04

No. of tests = 5

Subject 634 : Hypercapnic Flow Data

Unloaded Data

$\dot{V}$	n	$\ddot{V}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\dot{V}_I}{\dot{V}_I max}$	$\frac{\dot{V}_E}{\dot{V}_E max}$
10-19.9	7	1673	0.51	0.51	54.4	43.8	0.44	0.25	0.66	0.50
		236	.02	.04	2.7	1.8	.02	.02	.01	.03
20-29.9	7	5001	0.44	0.48	86.1	65.2	0.39	0.31	0.72	0.70
		388	.01	.03	2.7	2.1	.01	.01	.01	.02
30-39.9	4	7662	0.36	0.46	97.3	71.7	0.35	0.42	0.78	0.73
		583	.02	.03	3.8	4.2	.02	.02	.02	.02
40-49.9	5	10032	0.37	0.38	139.2	114.6	0.37	0.32	0.74	0.76
		710	.03	.01	8.3	5.9	.01	.01	.02	.02
50-59.9	6	12492	0.37	0.40	155.8	132.3	0.38	0.37	0.78	0.79
		966	.04	.05	3.7	4.9	.03	.05	.02	.01
60-69.9	4	15004	0.39	0.42	187.5	156.1	0.44	0.41	0.77	0.81
		1202	.02	.04	7.9	2.4	.01	.05	.03	.01

Loaded Data

10-19.9	5	1391	0.58	0.53	46.0	42.1	0.40	0.28	0.68	0.56
		256	.04	.06	4.4	4.0	.02	.02	.04	.05
20-29.9	8	3216	0.59	0.44	66.4	71.4	0.40	0.33	0.70	0.71
		352	.05	.01	1.9	2.4	.03	.01	.01	.02
30-39.9	7	5304	0.52	0.39	91.7	107.6	0.39	0.35	0.74	0.77
		576	.02	.05	4.5	3.7	.03	.04	.01	.02
40-49.9	4	5592	0.65	0.42	106.2	120.5	0.53	0.41	0.74	0.78
		886	.01	.03	2.9	2.7	.06	.03	.02	.02
50-59.9	7	9059	0.56	0.44	137.3	152.5	0.53	0.41	0.74	0.78
		1075	.05	.02	5.2	4.6	.04	.02	.02	.01
60-69.9	4	10334	0.50	0.43	165.2	190.6	0.52	0.57	0.72	0.75
		1348	.07	.02	5.7	4.3	.04	.03	.03	.01

No. of tests = 5

Subject 639 : Hypercapnic Flow Data

Unloaded Data

$\dot{V}$	n	$\bar{V}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\dot{V}_I}{\dot{V}_I max}$	$\frac{\dot{V}_E}{\dot{V}_E max}$
10-19.9	9	1974	0.57	0.52	54.3	42.9	0.40	0.22	0.69	0.51
		553	.01	.04	4.1	7.0	.03	.03	.03	.04
20-29.9	3	5292	0.54	0.56	83.6	64.9	0.38	0.28	0.75	0.70
		483	.02	.03	9.9	5.8	.04	.04	.02	.02
30-39.9	6	9028	0.37	0.53	106.1	94.7	0.29	0.31	0.75	0.70
		480	.01	.07	7.2	1.8	.02	.02	.01	.03
40-49.9	7	12201	0.32	0.42	134.3	123.6	0.29	0.33	0.76	0.72
		2739	.01	.01	5.1	3.5	.05	.06	.03	.01
50-59.9	6	16108	0.28	0.38	159.8	138.7	0.25	0.31	0.76	0.79
		1144	.02	.05	6.8	5.9	.01	.03	.02	.02
60-69.9	3	19701	0.24	0.37	180.2	160.3	0.22	0.31	0.76	0.75
		2739	.03	.02	7.2	8.7	.03	.01	.01	.02

Loaded Data

10-19.9	7	2168	0.76	0.56	45.9	47.6	0.40	0.27	0.67	0.55
		725	.03	.10	6.1	7.9	.03	.08	.05	.08
20-29.9	7	2328	0.56	0.51	68.3	78.3	0.43	0.36	0.74	0.58
		249	.06	.04	3.4	6.9	.02	.04	.04	.02
30-39.9	6	7248	0.38	0.34	85.1	103.9	0.22	0.26	0.72	0.74
		717	.09	.03	7.2	6.1	.03	.02	.04	.02
40-49.9	3	7070	0.36	0.30	109.9	137.4	0.23	0.24	0.73	0.75
		809	.08	.03	8.8	7.1	.03	.03	.04	.02
50-59.9	4	15326	0.35	0.26	139.3	158.6	0.26	0.24	0.76	0.75
		4234	.07	.05	14.6	8.1	.07	.03	.06	.01
60-69.9	5	17987	0.32	0.22	176.8	207.5	0.32	0.19	0.78	0.76
		4818	.04	.02	11.3	8.6	.02	.02	.03	.01

No. of tests = 5

Subject 643 : Hypercapnic Flow Data

Unloaded Data

$\dot{V}$	n	$\dot{V}_I$	Tmax	Tmin	$\dot{V}_I max$	$\dot{V}_E max$	$\frac{Tmax}{T_I}$	$\frac{Tmin}{T_E}$	$\frac{\dot{V}_I}{\dot{V}_I max}$	$\frac{\dot{V}_E}{\dot{V}_E max}$
10-19.9	4	2130	0.50	0.48	49.0	34.4	0.40	0.22	0.74	0.60
		177	.02	.02	3.0	4.6	.02	.03	.06	.02
20-29.9	6	4638	0.35	0.32	86.3	76.8	0.36	0.26	0.80	0.64
		393	.03	.02	4.7	5.2	.01	.03	.02	.02
30-39.9	6	6450	0.28	0.31	103.5	96.8	0.24	0.20	0.79	0.66
		639	.02	.03	5.9	6.0	.02	.04	.09	.03
40-49.9	4	8400	0.26	0.33	125.2	120.1	0.27	0.23	0.78	0.70
		632	.03	.02	6.2	6.9	.05	.07	.06	.02
50-59.9	6	11580	0.28	0.31	160.3	160.5	0.25	0.25	0.78	0.62
		1237	.03	.02	6.9	3.9	.05	.06	.06	.02
60-69.9	5	13020	0.27	0.24	180.5	195.2	0.25	0.21	0.75	0.66
		1510	.02	.03	8.4	5.1	.03	.03	.05	.04

Loaded Data

10-19.9	3	1272	0.71	0.65	43.9	47.2	0.41	0.37	0.72	0.67
		101	.09	.04	2.3	3.4	.03	.01	.05	.04
20-29.9	6	2628	0.56	0.40	68.9	76.8	0.24	0.21	0.76	0.63
		297	.08	.05	3.8	5.9	.04	.05	.04	.05
30-39.9	5	4092	0.53	0.33	96.4	117.9	0.38	0.27	0.71	0.68
		408	.05	.05	5.5	7.7	.06	.07	.02	.04
40-49.9	7	4590	0.57	0.28	100.9	147.4	0.37	0.23	0.79	0.67
		545	.03	.06	2.9	5.1	.03	.02	.02	.02
50-59.9	6	5880	0.53	0.21	120.7	188.7	0.36	0.17	0.82	0.63
		531	.04	.04	3.7	6.9	.03	.03	.02	.05
60-69.9	5	9140	0.54	0.26	141.1	230.3	0.45	0.26	0.86	0.63
		1038	.02	.03	4.8	8.8	.06	.05	.04	.03

No. of tests = 5

Appendix A5

This appendix contains printouts of the computer programs that were employed to collect, analyse and display data:

Program 1: Breathing pattern and gas exchange data collection program. This program consisted of six subroutines: Subroutine P4S1 - define filename; P4S2 - set data channels; P4S3 - data collection; P4S4 - data calibration; P4S5 - writing data to file; P4S6 - program status report.

Program 2: Flow data collection program. This program recorded the pneumotachograph transducer output (proportional to instantaneous level of flow at the mouth) every 20 ms for 1 minute.

Program 3: Flow data calibration program. This program converted the data produced by Program 2 (in arbitrary units) into real flow data, in units of $L.min^{-1}$, by use of calibration factors calculated from steady flow values.

Program 4: Program to calculate the mean and standard deviation of flow profile variables for each 1 minute data collection run.

Program 5: Program to graphically display flow data.

Program 6: Analysis of variance program. The example program shown was for the analysis of data from six (exercise or hypercapnia) levels, two resistance conditions and eight subjects. The results of the computation were variance ratios for the main effects (levels, resistance and subjects) and the interaction effects, levels * resistance, levels * subjects, and subjects * resistance.

①

```
C                  **********
C                  PROGRAM F4
C                  **********
C
C
C       THIS PROGRAM  READS DATA FROM  UP  TO  SEVEN
C       A-D INPUT CHANNELS.  PERFORMS A PEAK PICKING
C       OPERATION ON TWO OF THOSE CHANNELS (VOLUMES)
C       AND STORES  THE  RESULTING  'BREATHS'  IN  AN
C       INTEGER ARRAY  (ISTOR).  CALIBRATIONS,  FILE
C       WRITING, STATUS  REPORTS  ETC  CAN  THEN  BE
C       INVOKED.
C
C       THE PROGRAM CALLS SIX SUBROUTINES:- P4S1,
C       P4S2, P4S3, P4S4, P4S5 AND P4S6.
C
        COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEORI,
     1  ISTOR(12000),IA(5),IB(5),IC(5),ID(5)
     2  ,IF(1),IR(1),IDR(9),IAR(8),IORBA(16),IFLNM(5)
        DIMENSION IPREV(2,99),CAL(8),N(10)
C       THESE FLAGS ENABLE THE SUBROUTINES TO BE
C       CALLED ONLY IN A LOGICAL ORDER
        CALL DSTRT(IER)
        IFL1=0
        IFL2=0
        IFL3=0
        IFL4=0
        IFL5=0
        IFL6=0
        IFL7=0
        GOTO 70
100     ACCEPT "INPUT SELECTION NO'. . . . . ",ISEL
        IF (ISEL.LT.1.OR.ISEL.GT.6) GOTO 70
        IF ((IFL1.NE.1.OR.IFL2.NE.1).AND.ISEL.GE.3) GOTO 100
        IF (IFL3.NE.1.AND.ISEL.GE.4) GOTO 100
        IF ((IFL3.NE.1.OR.IFL4.NE.1).AND.ISEL.EQ.5) GOTO 100
        IF (IFL7.EQ.1) TYPE"CALIBRATION MUST BE STORED. "
        IF (IFL7.EQ.1) GOTO 50
        GOTO (10,20,30,40,50,60),ISEL
10      IFL1=1
        CALL P4S1(ISN,IEN,IRUN,IPREV)
        GOTO 100
20      IFL2=1
        CALL P4S2(ILIMIT,IDELAY,ITST,JUMP)
        GOTO 100
30      IFL3=1
        CALL P4S3(ITST,NB,JUMP,ILIMIT,IDELAY,IRUN)
        IF(IFL4.EQ.1) TYPE"SELECTION 5 WILL STORE THE DATA"
        GOTO 100
40      IFL4=1
        CALL P4S4(CAL,N,NB,IFL7,JUMP)
        GOTO 100
50      IFL5=1
        CALL P4S5(IFL7,JUMP,CAL,NB,IPREV,IRUN)
        GOTO 100
60      IFL6=1
        CALL P4S6(ISN,IEN,IRUN,IPREV,CAL,N,JUMP)
        GOTO 100
70      TYPE   "1.....EXPT STARTING ROUTINE"
        TYPE   "2.....SETTING A-D CHANNELS"
        TYPE   "3.....DATA ACQUISITION LOOP"
        TYPE   "4.....CALIBRATION UPDATE"
        TYPE   "5.....FILE WRITING ROUTINE"
        TYPE   "6.....STATUS REPORT ROUTINE"
        TYPE   "7.....LIST THESE COMMANDS"
        GOTO 100
        END
```

```
        SUBROUTINE P4S1(ISN,IEN,IRUN,IPREV)
C
C       THIS SUBROUTINE SETS UP THE USER DEFINED SUBJECT,
C       EXPERIMENT AND RUN NUMBERS.  IT ALSO ACCEPTS THE
C       ROOT FOR THE OUTPUT FILE NAME.
C
        COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEORI,
     1  ISTOR(12000),IA(5),IB(5),IC(5),ID(5)
     2  ,IC(1),IR(1),IDR(9),IAR(8),IORBA(16),IFLNM(5)
        DIMENSION IPREV(2,99)
        DO 10 I=1,2
          DO 20 J=1,99
20        IPREV(I,J)=0
10      CONTINUE
        TYPE
        ACCEPT"SUBJECT NUMBER      . . . . . ",ISN
        ACCEPT"EXPERIMENT NUMBER   . . . . . ",IEN
        ACCEPT"STARTING RUN NUMBER . . . . . ",IRUN
        WRITE(10,910)
910     FORMAT(32H FILENAME (10CHRS)   . . . . . ,Z)
900     FORMAT(10S2)
        READ (11,900) IFLNM
        TYPE
        RETURN
        END
```

```
        SUBROUTINE P4S2(ILIMIT,IDELAY,ITST,JUMP)
C
C       THIS SUBROUTINE ASSIGNS THE A-D CHANNELS
C
        COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEORI,
     1  ISTOR(12000),IA(5),IB(5),IC(5),ID(5)
     2,IC(1),IR(1),IDR(9),IAR(8),IORBA(16),IFLNM(5)
        TYPE
        ACCEPT"VOL LIMIT/GAS DELAY  ...",ILIMIT,IDELAY
        ACCEPT"CONTROL CHANNEL  . . . . . ",IDR(2)
        ACCEPT"VTI CHANNEL      . . . . . ",IDR(3)
        ACCEPT"VTE CHANNEL      . . . . . ",IDR(4)
        ACCEPT"CO2 CHANNEL      . . . . . ",IDR(5)
        ACCEPT"O2  CHANNEL      . . . . . ",IDR(6)
        ACCEPT"RESPITRACE   1 FOR YES. . ",JUMP
        IF (JUMP.NE.1) JUMP=8
        IF (JUMP.EQ.8) GOTO 10
        JUMP=12
        ACCEPT"RESPITRACE THRX CHANNEL. ",IDR(7)
        ACCEPT"RESPITRACE ABD CHANNEL. ",IDR(8)
10      TYPE
        RETURN
        END
```

```
        SUBROUTINE P4S3(ITST,NB,JUMP,ILIMIT,IDELAY,IRUN)
C
C             VERSION III.  J.M.  16/3/82
C       THIS SUBROUTINE READS 5/7 A-D CHANNELS IN
C       EACH OF TWO LOOPS, RETURNING UNCALIBRATED
C       DATA IN THE ARRAY ISTOR.  THIS ROUTINE IS
C       DERIVED FROM NOVA PROGRAM MGH SAVE 3.
C             THE PROGRAM OPERATES BY PICKING PEAKS
C       ON THE VTI OR VTE SIGNALS IN THE APPROPRIATE
C       PHASE AND DEFINING TI AND TE BY THESE PEAKS.
C       END-TIDAL GASES ARE READ AFTER ALLOWING FOR THE
C       MASS SPECTROMETER DELAY.  RESPITRACE DATA CAN
C       ALSO BE OBTAINED.
C
C
C       ISTOR  ;DATA STORAGE ARRAY
C       IAR    ;A-D INPUT ARRAY
C       IAMAX  ;PEAK PICKING ARRAY (VTI OR VTE)
C       IAZERO ;ZERO ARRAY (VTI OR VTE)
C       IPTI   ;TI STORED AT THE LAST A-D INPUT
C       IPTE   ;TE STORED AT THE LAST A-D INPUT
C       IDELAY ;MASS SPECTROMETER DELAY
C       ILIMIT ;PEAK PICKING DEFINER
C       JT/JA  ;RESPITRACE PEAKS (OPTIONAL)
C       LT/LA  ;RESPITRACE TROUGHS (OPTIONAL)
C
        COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEORI,
     1  ISTOR(12000),IAMAX(5),IAZERO(5),
     2  IPTI(5),IPTE(5),IMASK(1),IADOUT(1),
     3  IDR(9),IAR(8),IORBA(16),IFLNM(5)
        EXTERNAL NTIME,IDS21
        DIMENSION JT(2),JA(2),LT(2),LA(2),ISUM(2)
        INONE=20
        IDR(1)=100005K
        IF(JUMP.EQ.12) IDR(1)=100007K     ;SELECTS CHANNELS
        IDATA1=0
        IMASK(1)=177777K
        TYPE
        IE=1
        C=0
        DO 2 I=1,3
          CALL DQITW(IORBA,IDS21,8,IDATA1,IDR,IAR,IER)
          C=C+IAR(1)/16
2       CONTINUE
        IAR(1)=C/3
        DO 13 I=1,5
          IAMAX(I)=-50                    ;INITIALISATION
          IAZERO(I)=1
13      CONTINUE
C       K IS THE LOOP COUNTER,  INCREMENTED IN STEPS OF JUMP
        K=-1*JUMP
        WRITE(10,901) IRUN
        PAUSE START IN INSP.
        WRITE(10,902)
901     FORMAT('1H RUN NUMBER,I3,4H    ',Z)
902     FORMAT('1H PROGRAM RUNNING')
        CALL DINT(DIN)
        CALL DUCLK(1,NTIME,IER)
        ITI=0
        ITE=0
        IF(JUMP.NE.12) GOTO 17
        JT(1)=IAR(6)/16
        JA(1)=IAR(7)/16
        ISUM(1)=JT(1)+JA(1)
17      ITIME=0
C
C       IDLE LOOP STARTS HERE
```

```
15      CALL DQITW(IORBA,IDS21,8,IDATA1,IDR,IAR,IER)
        IFLG=0
        IAMAX(5)=-100
        IAR(1)=IAR(1)/16
        ITEMP=ITIME-ITI-ITE
        ITIME=ITEMP
16      IF(IAR(1).LT.-300) GOTO 150       ;EXIT CONDITION
        IF(IAR(1).GT.0) GOTO 11           ;START CONDITION
        GOTO 17
C
C       INSPIRATION LOOP STARTS HERE
C
11      IVTI=0
        INONE=8
        IEORI=1
        JT(2)=0
        JA(2)=0
        DO 20 I=1,3
C         READ A-D CHANNELS 3 TIMES AND SUM
          CALL DQITW(IORBA,IDS21,8,IDATA1,IDR,IAR,IER)
          IVTI=IVTI+IAR(2)/16
          IF(JUMP.NE.12) GOTO 20
          JT(2)=JT(2)+IAR(6)/16
          JA(2)=JA(2)+IAR(7)/16
20      CONTINUE
        IF(JUMP.NE.12)GOTO 21
C       CHECK FOR RESPATRACE MAXIMUM
        ISUM(2)=(JT(2)/3)+(JA(2)/3)
        IF (ISUM(2).LE.ISUM(1)) GOTO 21
        ISUM(1)=ISUM(2)
        JT(1)=JT(2)/3
        JA(1)=JA(2)/3
21      CONTINUE
C
        ITI=ITIME
        IVTE2=IAR(5)/16
        IVTI=IVTI/3
C       NOW COMES THE TEST FOR THE END OF INSPIRATION
        IF(IAMAX(5).GT.IVTI+ILIMIT) GOTO 40
        IF(IFLG.EQ.1) GOTO 35
        IF(ITI.LT.IDELAY) GOTO 35
C       READING THE END-TIDAL GASES
        IECO2=IAR(4)/16
        IEO2=IAR(5)/16
        IFLG=1
35      DO 30 I=2,5
          IAMAX(I-1)=IAMAX(I)             ;
          IAZERO(I-1)=IAZERO(I)           ;STEP DOWN THE ARRAYS
          IPTI(I-1)=IPTI(I)               ;
30      CONTINUE
        IAMAX(5)=IVTI                     ;
        IAZERO(5)=IVTE2                   ;STORE CURRENT VALUE
        IPTI(5)=ITI                       ;
C       END OF INSPIRATION LOOP
        GOTO 16
C
```

```
C       I/E TRANSITION
C
40      DO 50 I=2,5
          IAMAX(I-1)=IAMAX(I)              !
          IAZERO(I-1)=IAZERO(I)            !STEP DOWN ARRAYS
          IPTI(I-1)=IPTI(I)                !
50      CONTINUE
C       STORE THE INSPIRATORY VALUES
        LT(1)=JT(1)
        LA(1)=JA(1)
        IAMAX(5)=IVTI
        IAZERO(5)=IVTEZ
        IPTI(5)=ITI
C       FIND THE TRUE PEAK
        DO 60 I=2,5
          II=I-1
          IF(IAMAX(I-1).GT.IAMAX(I))GOTO 70
60      CONTINUE
C       STORE THE INSPIRATORY VARIABLES
70      IVTI=IAMAX(II)
        ITI=IPTI(II)
        IVTEZ=IAZERO(II)
        IAMAX(5)=-100
        IFLG=0
   75 IVTE=0
        INONE=3
        IEORI=0
        LT(2)=0
        LA(2)=0
C
C       EXPIRATION LOOP STARTS HERE AND
C       IS THE  CONVERSE OF INSPIRATION
C
        DO 80 I=1,3
          CALL DOITW(IORBA,IDS21,8,IDATA1,IDR,IAR,IER)
          IVTE=IVTE+IAR(3)/16
          IF(JUMP.NE.12) GOTO 80
          LT(2)=LT(2)+IAR(6)/16
          LA(2)=LA(2)+IAR(7)/16
80      CONTINUE
        IF(JUMP.NE.12) GOTO 81
        ISUM(2)=(LT(2)/3)+(LA(2)/3)
        IF (ISUM(2).GE.ISUM(1)) GOTO 81
        ISUM(1)=ISUM(2)
        LT(1)=LT(2)/3
        LA(1)=LA(2)/3
81      ITE=ITIME-ITI
        IVTE=IVTE/3
        IVTIZ=IAR(2)/16
        IF(IAMAX(5).GT.IVTE+ILIMIT) GOTO 110
        IF(IFLG.EQ.1) GOTO 100
        IF(ITE.LT.IDELAY) GOTO 100
        IICO2=IAR(4)/16
        IIO2=IAR(5)/16
        IFLG=1
100     DO 90 I=2,5
          IAMAX(I-1)=IAMAX(I)
          IAZERO(I-1)=IAZERO(I)
          IPTE(I-1)=IPTE(I)
90      CONTINUE
        IAMAX(5)=IVTE
        IAZERO(5)=IVTIZ
        IPTE(5)=ITE
C       END OF EXPIRATION LOOP
        GOTO 75
C


C       E/I TRANSITION
C
110     DO 120 I=2,5
          IAMAX(I-1)=IAMAX(I)
          IAZERO(I-1)=IAZERO(I)
          IPTE(I-1)=IPTE(I)
120     CONTINUE
        IAMAX(5)=IVTE
        IAZERO(5)=IVTIZ
        IPTE(5)=ITE
        DO 130 I=2,5
          IE=I-1
          IF(IAMAX(I-1).GT.IAMAX(I)) GOTO 140
130     CONTINUE
140     IVTE=IAMAX(IE)
        IVTIZ=IAZERO(IE)
        ITE=IPTE(IE)
        K=K+JUMP                           !INCREASE BREATHCOUNT
C       STORE PREVIOUS DATA
        ISTOR(1+K)=IVTI-IVTIZ
        ISTOR(2+K)=ITI
        ISTOR(3+K)=IICO2
        ISTOR(4+K)=IIO2
        ISTOR(5+K)=IVTE-IVTEZ
        ISTOR(6+K)=ITE
        ISTOR(7+K)=IECO2
        ISTOR(8+K)=IEO2
        IF(JUMP.NE.12) GOTO 15
        ISTOR(K+9)=IIPTI
        ISTOR(K+10)=IIPT2
        ISTOR(K+11)=IEPT1
        ISTOR(K+12)=IEPT2
        IIPTI=0
        IIPT2=0
        IEPT1=0
        IEPT2=0
        JT(1)=LT(1)
        JA(1)=LA(1)
C       RETURN TO INSPIRATION LOOP
        GOTO 15
C
C       LOOP EXIT
150     KD=K/JUMP
        CALL DICLR
        CALL RUCLK
        KC=(12000/JUMP)-KD
        TYPE"BR  USED..",KD,"     BR  LEFT..",KC
        TYPE
        NB=KD
        RETURN
        END
```

```
        SUBROUTINE P4S4(CAL,N,N8,IFL7,JUMP)
C
C       THIS SUBROUTINES CALCULATES SCALE FACTORS
C       AND INTERCEPTS FOR THE VOLUME AND GAS DATA
C       ACCORDING TO USER SUPPLIED STANDARD VALUES.
C       THE OPTION OF USING THESE FACTORS, OR INPUTTING
C       ONES OWN IS THEN OFFERED.
C
        COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEORI,
     1  ISTOR(12000),IAMAX(5),IAZERO(5),
     2  IPTI(5),IFTE(5),IMASK(1),IADOUT(1),
     3  IDR(9),IAR(8),IORBA(16),IFLNM(5)
        DIMENSION CAL(8),N(10)
          REAL MVTI,MTI,MVTE,MTE,MLOCO2,MHIO2,MHICO2,MLOO2
        TYPE
        ACCEPT"TYPE 0 TO INPUT OWN CALIBRATION..",IFL7
        IF(IFL7.EQ.0) GOTO 1000
        WRITE(10,901)
901     FORMAT(" <7>** STANDARD **<7>")
12      ACCEPT "NO. OF CALIB. POINTS TO BE DISPLAYED-N1 TO N2 ",N1,N2
        DO 15 J=N1,N2
          KA=(J-1)*JUMP+1
          KB=KA+(JUMP-1)
          IF (JUMP.EQ.12) GOTO 25
          WRITE(10,20)J,(ISTOR(K),K=KA,KB)
20      FORMAT(1H ,I4,8(",",I4))
        GOTO 15
25      WRITE(10,21)J,(ISTOR(K),K=KA,KB)
21      FORMAT(1H ,I4,12(",",I4))
15      CONTINUE
        ACCEPT "TYPE 1 FOR FURTHER BREATHS ",IAGAIN
        IF(IAGAIN.EQ.1) GOTO 12
        SVTI=0.0
        STI=0.0
        SVTE=0.0
        STE=0.0
        SLOCO2=0.0
        SHICO2=0.0
        SLOO2=0.0
        SHIO2=0.0
        ACCEPT "NO. OF POINTS TO BE USED IN CALIB."
        ACCEPT "OF VOL. AND TIMES.....N1 TO N2 ",N1,N2
        ACCEPT "OF CO2 LOW STANDARD....N3 TO N4 ",N3,N4
        ACCEPT "OF O2 HIGH STANDARD...N5 TO N6 ",N5,N6
        ACCEPT "OF CO2 HIGH STANDARD..N7 TO N8 ",N7,N8
        ACCEPT "OF O2 LOW STANDARD....N9 TO N10 ",N9,N10
        DO 30 J=N1,N2
          KA=(J-1)*JUMP+1
          KB=KA+1
          KE=KA+4
          KF=KA+5
C         SUMMING VOLUMES AND TIMES
          SVTI=SVTI+ISTOR(KA)
          STI=STI+ISTOR(KB)
          SVTE=SVTE+ISTOR(KE)
          STE=STE+ISTOR(KF)
30      CONTINUE
C       SUMMING THE GASES
        DO 40 J=N3,N4
        KC=(J-1)*JUMP+3
        SLOCO2=SLOCO2+ISTOR(KC)
40      CONTINUE
        DO 50 J=N5,N6
        KD=(J-1)*JUMP+4
        SHIO2=SHIO2+ISTOR(KD)
50      CONTINUE
        DO 60 J=N7,N8
        KG=(J-1)*JUMP+7
        SHICO2=SHICO2+ISTOR(KG)
60      CONTINUE
        DO 70 J=N9,N10
        KH=(J-1)*JUMP+8
        SLOO2=SLOO2+ISTOR(KH)
70      CONTINUE
C       OBTAINING THE MEANS
        MVTI=SVTI/(N2-N1+1)
        MTI=STI/(N2-N1+1)
        MVTE=SVTE/(N2-N1+1)
        MTE=STE/(N2-N1+1)
        MLOCO2=SLOCO2/(N4-N3+1)
        MHIO2=SHIO2/(N6-N5+1)
        MHICO2=SHICO2/(N8-N7+1)
        MLOO2=SLOO2/(N10-N9+1)
        ACCEPT "VOLUME STANDARD.............. ",VST
        ACCEPT "CO2 HI STAND.   CO2 LO STAND. ",CO2HI,CO2LO
        ACCEPT "O2 HI STAND.    O2 LO STAND.. ",O2HI,O2LO
C       CALCULATING THE SCALE FACTORS
        SFVTI=VST/MVTI
        SFTI=MTI/1000
        SFVTE=VST/MVTE
        SFTE=MTE/1000
        SFCO2=(CO2HI-CO2LO)/(MHICO2-MLOCO2)
        SFO2=(O2HI-O2LO)/(MHIO2-MLOO2)
        TYPE "SFVTI=   ",SFVTI
        TYPE "SFTI=    ",SFTI
        TYPE "SFVTE=   ",SFVTE
        TYPE "SFTE=    ",SFTE
        TYPE "SFCO2=   ",SFCO2
        TYPE "SFO2=    ",SFO2
        CCO2=CO2HI-SFCO2*MHICO2
        CO2= O2HI-SFO2*MHIO2
        TYPE "INT. CO2= ",CCO2
        TYPE "INT. O2=  ",CO2
        ACCEPT"CALIB' TO BE USED?  1 FOR YES..",IFL7
        IF(IFL7.EQ.1) GOTO 100
        IFL7=0
        GOTO 110
100     CAL(1)=SFVTI
        CAL(2)=SFTI
        CAL(3)=SFVTE
        CAL(4)=SFTE
        CAL(5)=SFCO2
        CAL(6)=SFO2
        CAL(7)=CCO2
        CAL(8)=CO2
        N(1)=N1
        N(2)=N2
        N(3)=N3
        N(4)=N4
        N(5)=N5
        N(6)=N6
        N(7)=N7
        N(8)=N8
        N(9)=N9
        N(10)=N10
        TYPE  "CALIBRATION ARRAY UPDATED"
        GOTO 110
1000    ACCEPT"SFVTI  ....",CAL(1)
        ACCEPT"SFTI   ....",CAL(2)
        ACCEPT"SFVTE  ....",CAL(3)
        ACCEPT"SFTE   ....",CAL(4)
        ACCEPT"SFCO2  ....",CAL(5)
        ACCEPT"SFO2   ....",CAL(6)
        ACCEPT"CCO2   ....",CAL(7)
        ACCEPT"CO2    ....",CAL(8)
        DO 1010 I=1,10
          N(I)=0
1010    CONTINUE
110     TYPE
        RETURN
        END
```

```
      SUBROUTINE P4S5(IFL7,JUMP,CAL,NB,IPREV,IRUN)
C
C     THIS SUBROUTINE WRITES THE CALIBRATED DATA TO A
C     STANDARD FORMAT FILE. UPDATES THE RUN NUMBER AND
C     IPREV ARRAY AND CLEARS IFL7 IF IT WAS NOT=0.
C
      COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEOR1,
     1 ISTOR(12000),IA(5),IB(5),IC(5),ID(5)
     2 ,IP(1),IR(1),IDR(9),IAR(8),IORBA(16),IFLNM(5)
      DIMENSION CAL(10),IPREV(2,99)
      TYPE
      CALL RESET
      IRUNT=IRUN
      K=0
      IF(IRUNT.LT.10) GOTO 20
      K=K+1
      IRUNT=IRUNT-10
      GOTO 10
      GENERATE THE OUTPUT FILENAME
      IFLNM(4)=(256*(K+48)+IRUNT+48)
      IFLNM(5)=(256*(69))+67
      IF(JUMP.EQ.12) IFLNM(5)=(256*(82))+67
      CALL FOPEN(1,IFLNM)
      WRITE(1,910) IFLNM
      FORMAT(1H ,5S2)
      WRITE(1,920) NB,IRUN
      FORMAT(1H ,I6,",",I3)
      RAT10=1.0
      IF (IFL7.EQ.1) GOTO 29
      K=0
      K=K-JUMP
      K1=0
      SVTI=0
      SVTE=0
      K1=K1+1
      K=K+JUMP
      SVTI=SVTI+(ISTOR(K+1)*CAL(1))
      SVTE=SVTE+(ISTOR(K+5)*CAL(3))
      IF(K1.GE.NB) GOTO 22
      GOTO 21
      RAT10=SVTE/SVTI
      K=0
      K=K-JUMP
      K1=0
      TCUM=0.0
      K1=K1+1
      K=K+JUMP
      CALCULATE OF THE CALIBRATED VALUES
      VTI=ISTOR(K+1)*CAL(1)
      VTI=VTI*RAT10
      IF(VTI.LT.0.0) VTI=0.0
      K4=K+2
      TI=FLOAT(ISTOR(K4))
      TI=TI/1000.
      IF(TI.LT.0.0) TI=0.0
      VTE=ISTOR(K+5)*CAL(3)
      IF(VTE.LT.0.0) VTE=0.0
      K4=K+6
      TE=FLOAT(ISTOR(K4))
      TE=TE/1000.
      IF(TE.LT.0.0) TE=0.0
      P1CO2=(ISTOR(K+3)*CAL(5))+CAL(7)
      P1O2=(ISTOR(K+4)*CAL(6))+CAL(8)
      PECO2=(ISTOR(K+7)*CAL(5))+CAL(7)
      PEO2=(ISTOR(K+8)*CAL(6))+CAL(8)
      TCUM=TCUM+((TI+TE)/60)
      IF(JUMP.NE.12) GOTO 40
      JT=ISTOR(K+9)
      JA=ISTOR(K+11)
      LT=ISTOR(K+10)
      LA=ISTOR(K+12)

      WRITE TO FILE

      WRITE(1,930) K1,VTI,TI,P1CO2,P1O2,VTE,TE,PECO2,PEO2,JT,LT,JA,LA,TCUM
930   FORMAT(1H ,I4,",",2(F4.2,","F5.2,","F4.1,",",F5.1,",")
     1,4(I4,","),F5.2)
      GOTO 50
40    WRITE(1,940) K1,VTI,TI,P1CO2,P1O2,VTE,TE,PECO2,PEO2,TCUM
940   FORMAT(1H ,I4,",",2(F6.3,",",F6.3,",",F5.1,",",F5.1,","),F7.2)
50    IF(K1.GE.NB) GOTO 60
      GOTO 30
60    IPREV(1,IRUN)=NB
      IPREV(2,IRUN)=0
      IF(IFL7.EQ.1) IPREV(2,IRUN)=1
      IFL7=0
      IRUN=IRUN+1
      CALL RESET
      TYPE"FILE OUTPUT DONE"
      TYPE
      RETURN
      END



      SUBROUTINE P4S6(ISN,IEN,IRUN,IPREV,CAL,N,JUMP)
C
C     THIS SUBROUTINE OUTPUTS ALL INFORMATION ON THE
C     CURRENT PROGRAM RUN TO THE TELETYPE.
C
      COMMON ITIME,IIPT1,IIPT2,IEPT1,IEPT2,INONE,IEOR1,
     1 ISTOR(12000),IA(5),IB(5),IC(5),ID(5)
     2 ,IP(1),IR(1),IDR(9),IAR(8),IORBA(16),IFLNM(5)
      DIMENSION IPREV(2,99),N(10),CAL(8),IDAT(3)
      TYPE
      TYPE  "  ****  STATUS  REPORT  ****  "
      CALL DATE(IDAT,IERR)
      CALL FGTIME(14,15,16)
      WRITE (10,900) IDAT(2),IDAT(1),IDAT(3),14,15,16
900   FORMAT (6H  DATE,3(3,7H    TIME,3(3
      WRITE (10,910) ISN,IEN,IRUN
910   FORMAT (6H EXPT ,I3,1H-,I2,17H         NEXT RUN -,I2)
      WRITE (10,920) IFLNM
920   FORMAT (17H OUTPUT FILENAME -,5S2)
      TYPE  "CALIBRATION FIGURES"
      TYPE  "SCALE FACTOR  VTI..... ",CAL(1),"   BREATHS ",N(1),N(2)
      TYPE  "SCALE FACTOR  TI ..... ",CAL(2),"   BREATHS ",N(1),N(2)
      TYPE  "SCALE FACTOR  VTE..... ",CAL(3),"   BREATHS ",N(1),N(2)
      TYPE  "SCALE FACTOR  TE ..... ",CAL(4),"   BREATHS ",N(1),N(2)
      TYPE  "SCALE FACTOR  CO2..... ",CAL(5),"   BREATHS ",N(3),N(4)
      TYPE  "INTERCEPT     CO2..... ",CAL(7),"   BREATHS ",N(5),N(6)
      TYPE  "SCALE FACTOR  O2 ..... ",CAL(6),"   BREATHS ",N(7),N(8)
      TYPE  "INTERCEPT     O2 ..... ",CAL(8),"   BREATHS ",N(9),N(10)
      TYPE  "ASSIGNED CHANNELS"
      TYPE  "CONTROL   CHANNEL ",IDR(2)
      TYPE  "VTI       CHANNEL ",IDR(3)
      TYPE  "VTE       CHANNEL ",IDR(4)
      TYPE  "CO2       CHANNEL ",IDR(5)
      TYPE  "O2        CHANNEL ",IDR(6)
      IF(JUMP.NE.12) GOTO 10
      TYPE  "THRX      CHANNEL ",IDR(7)
      TYPE  "ABD       CHANNEL ",IDR(8)
10    TYPE  "PREVIOUS RUNS"
      TYPE  "    USED    CALIB"
      J=IRUN-1
      DO 20 I=1,J
        WRITE (10,930) IPREV(1,I),IPREV(2,I)
20    CONTINUE
930   FORMAT(5H     ,I4,6H       ,I1)
      TYPE
      RETURN
      END
```

②

```
C     DATA COLLECTION PROGRAM
C
      COMMON ITIME,IFL(5200),IDR(2),IAR(3)
      COMMON IFLNM(5),NPTS,IORBA(16)
C     OPEN A TO D ROUTE
      CALL DSTRT(IER)
      IDR(1)=100003K
C     SET CHANNEL FOR RECORDING FROM
      ACCEPT "FLOW CHANNEL ..",IDR(2)
151   CALL RUN
      IF (NPTS .GT. 0) GOTO 151
      STOP
      END

      SUBROUTINE RUN
C
      COMMON ITIME,IFL(5200),IDR(2),IAR(3)
      COMMON IFLNM(5),NPTS,IORBA(16)
      EXTERNAL NTIME,IDS21
      IDATA1=0
      NP=1
      NA=1
C     SETTING RECORDINGS TO EVERY 20 MS
      JF=20
      TYPE
      ACCEPT "NPTS = ",NPTS
      PAUSE START IN EXPIRATION
      TYPE "RUNNING"
C     DEFINE USER CLOCK
      CALL DUCLK(1,NTIME,IER)
      ITIME=0
C     RECORD A TO D SIGNAL
45    CALL DOITW(IORBA,IDS21,8,IDATA1,IDR,IAR,IER)
      IFL(NP)=IAR(1)/16
C     RESET CLOCK EVERY 30 S SO NO INTEGER OVERFLOW
      IF (ITIME .LT. 30000) GOTO 15
      IRT=ITIME
      ITIME=0
      IDIF=IRT-30000
      NA=1
C     JF IS RESET TO ALLOW FOR TIME WHEN
C     CLOCK IS RESET
      JF=JF-IDIF
      IF (JF .LT. 0) JF=JF+20
15    NP=NP+1
      IF (NP .GT. NPTS) GOTO 85
      NA=NA+1
C     IF TIME IS MULTIPLE OF 20 MS, RECORD A TO D
55    IF (ITIME .GE. 20*(NA-2)+JF)  GOTO 45
      GOTO 55
C     RESET USER CLOCK
85    CALL RUCLK
      TYPE"RUN COMPLETE"
C     WRITE DATA TO FILE
      IFIL=0
      ACCEPT "TYPE 1 TO WRITE TO FILE ",IFIL
      IF (IFIL .NE. 1) GOTO 30
25    WRITE(10,100)
100   FORMAT(13H FILENAME ....,2)
      READ(11,200)IFLNM
200   FORMAT(10S2)
      CALL RESET
      CALL FOPEN(1,IFLNM)
300   FORMAT(1X,I6)
      DO 30 J=1,NPTS
      WRITE(1,300)IFL(J)
30    CONTINUE
      RETURN
      END
```

③

```
C     PROGRAM TO CALIBRATE FLOW FILES
C     NB : ASSUMES LINEAR CALIBRATION
C     DN - A TO D VALUES
C     FN - CALCULATED FLOW VALUES
C     IFLNM - FILE WITH UNCALIBRATED DATA
C     IFLNMC - FILE WITH CALIBRATED DATA
      COMMON DN(3000),FN(3000),IFLNM(6),IFLNMC(5)
      COMMON IFLSP(100,6)
      ACCEPT"NO.  OF FILES",NF
      DO 101 I1=1,NF
      WRITE(10,100)
      READ(11,200) IFLNM
      DO 102 L=1,6
      IFLSP(I1,L)=IFLNM(L)
102   CONTINUE
101   CONTINUE
      ACCEPT"TYPE NO.  OF PTS.  ",NPTS
      ACCEPT"TYPE A TO D VALUE AT ZERO FLOW ",DO
C     BLOWING GAS IS ACCEPTED AS +VE,BUT CONVERTED TO -VE
C     IT DOESNT MATTER IF I OR E IS UP - FFRO SORTS THIS OUT
      ACCEPT"TYPE CALIBRATION GAS FLOW ",F1
      F1=-F1
      ACCEPT"TYPE A TO D VALUE AT THIS FLOW ",D1
      TYPE
100   FORMAT(13H FILENAME ....,2)
200   FORMAT(12S2)
      DO 103 I1=1,NF
      DO 104 J=1,6
      IFLNM(J)=IFLSP(I1,J)
104   CONTINUE
      WRITE(10,105) IFLNM
105   FORMAT(6S2)
      CALL RESET
      CALL OPEN(1,IFLNM,2,ERROR)
      DO 10 I=1,NPTS
      READ(1,300)DN(I)
      FN(I)=F1*(DN(I)-DO)/(D1-DO)
10    CONTINUE
300   FORMAT(1X,I6)
      DO 106 K=1,4
      IFLNMC(K)=IFLNM(K)
106   CONTINUE
      IFLNMC(5)=(256*(70))+67
      CALL RESET
      CALL OPEN(1,IFLNMC,2,ERROR)
      J1=0
21    J1=J1+1
      FN(J1)=FN(J1)
      WRITE(1,400) FN(J1)
      IF(J1.NPTS) GOTO 22
      21
22    CALL RESET
      (1X,F8.2)
       END
```

④

```
C       PROGRAM TO CALCULATE PARAMETERS FOR FLOW PROFILES FROM UP TO 10 FILES
        COMMON IFLNM(60),FL(2600),T(2600),NBEG(50)
        COMMON TP(400),FLP(400),SD(10)
        COMMON IFLNM1(6),AV(10),
        COMMON NEBEG(50),P(10,180),UP(10),RL(10)
        COMMON BIN(10),V(10),IFLSP(36,6),IFLNM2(6)
        J9=0
        TYPE"BIN SIZE"
        DO 67 I9=1,10
        TYPE I9
        ACCEPT"BIN ",BIN(I9)
67      CONTINUE
        ACCEPT"NO OF FILES TO BE COMPARED",NFC
        ACCEPT"NO. OF FILES",NF
        K9=NF/NFC
        N7=NFC*6
        DO 27 I3=1,NF
        READ(1,28) IFLNM2
28      FORMAT(12S2)
        L9=0
        DO 29 I4=1,6
        IFLSP(I3,I4)=IFLNM2(I4)
29      CONTINUE
27      CONTINUE
        K1=0
26      L5=1
        K5=0
        L6=6
        DO 42 L7=1,NFC
        L9=L9+1
        J7=0
        DO 41 L8=L5,L6
        J7=J7+1
        IFLNM(L8)=IFLSP(L9,J7)
41      CONTINUE
        L5=L5+6
        L6=L6+6
42      CONTINUE
        DO 81 N8=N7,60
        IFLNM(N8)=0
81      CONTINUE
        WRITE(10,38) IFLNM
38      FORMAT(1H ,60S2)
        NPTS=2600
        NCAL=0
C       ACCEPT"TYPE 1 IF USING CALIBRATED DATA ",NCAL
        NCAL=1
        ZER=0.0
        IF (NCAL .EQ. 1) GOTO 425
        TYPE "ASSUME 1 IS UP "
C       ACCEPT "TYPE ZERO FLOW VALUE ",ZER
425     T(1)=3.0
        T(2)=23.0
        T(3)=42.0
        DO 30 I=4,NPTS
        T(I)=T(I-1)+20.0
30      CONTINUE

C       ACCEPT "TYPE +1 IF FLOW VALUES ARE I UP/ E DOWN ",CH
        CH=1
        IF (CH .NE. 1) CH=-1
C       ACCEPT"TYPE NO. OF FLOW FILES (10 IS MAX) ",IFILE
        DO 170 IW=1,10
        DO 140 I=1,180
        P(IW,I)=0.0
140     CONTINUE
170     CONTINUE
        DO 180 I=1,180
        P(6,I)=-1000.0
        P(7,I)=1000.0
180     CONTINUE
        IP=1
C       DO 60 I=1,IFILE
C       WRITE(10,100)
C       READ(11,200)IFLNM1
C       IL=IP+4
C       IQ=1
C       DO 110 J=IP,IL
C       IFLNM(J)=IFLNM1(IQ)
C       IQ=IQ+1
C110    CONTINUE
C       IP=IP+5
C60     CONTINUE
C100    FORMAT(13H FILENAE ...,Z)
C200    FORMAT(1P=1
        IWR=0
C  ACCEPT"TYPE 1 TO TYPE OUT PMETERS ",IWR
         CALL RES       TYPE
        IZ=1 1JK=1,NFC
        IL=IP+5
      QQ=1
        DO 130 IA=IP,IL
        IFLNM1(IQ)=IFLNM(IA)
        IQ=IQ+1
130     CONTINUE
        IP=IP+6
        CALL OPEN(1,IFLNM1,2,ERROR)
        TYPE"OPENED FILE ",IJK
        FILMAX=-1000.0
        FILMIN=1000.0
        DO 50 I=1,NPTS
        IF (NCAL .EQ. 1) GOTO 435
        READ(1,300)FL(I)
        GOTO 445
435     READ(1,400)FL(I)
445     FL(I)=(CH*FL(I))-K5
        IF (FILMAX .LT. FL(I)) FILMAX=FL(I)
        IF (FILMIN .GT. FL(I)) FILMIN=FL(I)
50      CONTINUE
300     FORMAT(1X,I6)
        CALL RESET
400     FORMAT(F8.2)
        TYPE

        J=0
        JE=0
        INSP=0
        IF (FL(1) .GT. ZER) INSP=1
        NBEG(1)=0
        DO 20 I=1,NPTS
        IF (FL(I) .GE. (ZER+(FILMAX-ZER)*0.2)) GOTO 35
        IF (INSP .EQ. 0) GOTO 20
        IF (FL(I) .GT. (FILMIN*0.2)) GOTO 20
        IF (NBEG(1) .NE. 0) GOTO 456
        INSP=0
        GOTO 20
456     JE=JE+1
        ISE=1
505     ISE=ISE-1
        IF (ISE .NE. 0) GOTO 515
        INSP=0
        JE=JE-1
        GOTO 20
515     IF (FL(ISE) .LT. ZER) GOTO 505
        ISE=ISE+1
        JKE=JE-1
        IF (JKE .EQ. 0) GOTO 525
        IF (NEBEG(JKE) .NE. ISE) GOTO 525
        JE=JE-1
        INSP=0
        GOTO 20
525     NEBEG(JE)=ISE
        INSP=0
        GOTO 20
35      IF (INSP .EQ. 1) GOTO 20
        J=J+1
        IS=I
25      IS=IS-1
        IF (IS .NE. 0) GOTO 65
        INSP=1
        J=J-1
        GOTO 20
65      IF (FL(IS) .GE. ZER) GOTO 25
        IS=IS+1
        JK=J-1
        IF (JK .EQ. 0) GOTO 165
        IF (NBEG(JK) .NE. IS) GOTO 165
        J=J-1
        INSP=1
        GOTO 20
165     NBEG(J)=IS
        INSP=1
20      CONTINUE
        NB=J-1
        TP(1)=0.0
        FLP(1)=ZER
        TYPE
        IF (IWR .NE. 1) GOTO 85
        TYPE   "BREATH  TI      TE      TT      TMAX    TMIN    MAX     MIN     IPK
85      DO 70 I=1,NB
        NS=NBEG(I)
        NE=NBEG(I+1)
        NCH=NEBEG(I)
        DT=FL(NS)-ZER)*20.0/(FL(NS)-FL(NS-1))
        DO 80 JL=2,400
        TP(JL)=(JL-2)*20.0+DT
        FLP(JL)=FL(LS+JL-2)
        K=JL
        IF (JL .EQ. 400) TYPE"MORE THAN 400 PTS IN BREATH"
        IF ((NS+JL-1) .EQ. NE) GOTO 45
80      CONTINUE
45      DTE=(ZER-FLP(K))*20.0/(FL(NS+K-1)-FLP(K))
        KK=K+1
        TP(KK)=TP(K)+DTE
        KCH=NCH-NS+1
        P(1,I2)=TP(KCH)+20.0*(FLP(KCH)-ZER)/(FLP(KCH)-FLP(KCH+1))
        P(2,I2)=TP(KK)-P(1,I2)
        P(3,I2)=TP(KK)
        FLP(KK)=ZER
        DO 90 M=1,KK
        IF (P(6,I2) .GE. FLP(M)) GOTO 95
        P(6,I2)=FLP(M)
        P(4,I2)=TP(M)
95      IF (P(7,I2) .LE. FLP(M)) GOTO 90
        P(7,I2)=FLP(M)
        P(5,I2)=TP(M)-P(1,I2)
90      CONTINUE
        P(7,I2)=-P(7,I2)
        P(8,I2)=P(4,I2)/P(1,I2)
        P(9,I2)=P(5,I2/P(2,I2)
        IST=KCH+2
        IEND=KK-2
        DO 40 M=IST,IEND
        P(10,I2)=P(10,I2)+FLP(M)
40      CONTINUE
        P(10,I2)=P(10,I2)*20.0
        TA=(ZER-FLP(KCH+1))*20.0/(FLP(KCH)-FLP(KCH+1))
        P(10,I2)=P(10,I2)+(FLP(KCH+1))*(20.0+TA)/2.0+(FLP(KK-1))*(20.0+DTE)/2.0
        P(10,I2)=-P(10,I2)*0.001/60.0
        DO 340 M=1,10
        V(M)=P(M,I2)
340     CONTINUE
        IF (IWR .NE. 1) GOTO 215
        WRITE(10,900)I,V(1),V(2),V(3),V(4),V(5),V(6),V(7),V(8),V(9),V(10)
215     IZ=IZ+1
70      CONTINUE
900     FORMAT(1X,I3,3X,3(F6.1,2X),F5.1,2X,F6.1,2(2X,F5.2),3(2X,F4.2))
        TYPE
120     CONTINUE
        IZ=IZ-1
        TYPE"TOTAL NO. OF BREATHS = ",IZ
        TTT=0.0
        TVOL=0.0
        DO 320 I=1,IZ
        TVOL=TVOL+P(10,I)
        TTT=TTT+P(3,I)
```

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320     CONTINUE
        TTT=TTT*0.001/60.0
        TYPE"TOTAL TIME = ",TTT,"MINUTES"
        VENT=IVOL/TTT
        TYPE
        TYPE"VENTILATION = ",VENT,"L/MIN"
        TYPE
        TYPE
        DO 160 I=1,10
        AV(I)=0.0
160     CONTINUE
        DO 150 J=1,10
        DO 150 I=1$Z
        AV(J)=AV(J)+P(J,I)
150     CONTINUE
190     CONTINUE
        TOT=IZ
        DO 210 I=1,10
        AV(I)=AV(I)/TOT
210     CONTINUE
        TYPE"MEANS"
        WRITE(10,500)AV(1),AV(2),AV(3),AV(4),AV(5),AV(6),AV(7),AV(8),AV(9),AV(10
        TYPE
500     FORMAT(7X,3(F6.1,2X),F5.1,2X,F6.1,2(2X,F5.2),3(2X,F4.2))
        TYPE
        DO 220 J=1,10
        SUMDIF=0.0
        DO 230 K=1,IZ
        SUMDIF=SUMDIF+(P(J,K)-AV(J))*(P(J,K)-AV(J))
230     CONTINUE
        SD(J)=SQRT(SUMDIF/FLOAT(IZ-1))
220     CONTINUE
        DO 240 J=1,10
        UP(J)=AV(J)+2.0*SD(J)
        RL(J)=AV(J)-2.0*SD(J)
240     CONTINUE
        TYPE"MEAN+2SDS"
        WRITE(10,500)UP(1),UP(2),UP(3),UP(4),UP(5),UP(6),UP(7),UP(8),UP(9),UP(10
        TYPE"MEAN-2SDS"
        WRITE(10,500)RL(1),RL(2),RL(3),RL(4),RL(5),RL(6),RL(7),RL(8),RL(9),RL(10
        TYPE
        TYPE"SDS"
        WRITE(10,500)SD(1),SD(2),SD(3),SD(4),SD(5),SD(6),SD(7),SD(8),SD(9),SD(10
        DIFV=30
        SFLOI=0
        SFLOE=0
        M7=NSEG(1)
        M8=NSEG(NB+1)
901     DO 888 63= M7,M8
        IF(FL(K3).GT.0) SFLOI=SFLOI+FL(K3)
        IF(FL(K3).LT.0) SFLOE=SFLOE+FL(K3)
888     CONTINUE
        SFLOI=SFLOI/(3000*TTT)
        SFLOE=SFLOE/(3000*TTT)
        TYPE SFLOI
        TYPE SFLOE
        DIFV1=DIFV
        DIFV=SFLOI+SFLOE
        TYPE DIFV
        TYPE DIFV1
        IF(DIFV.LT.0) K5=K5-1
        IF(DIFV.LT.0) GOTO 42
        DO 889 K4=1,2600
        FL(K4)=FL(K4)-1
889     CONTINUE
        K5=K5+1
        GOTO 901
        TYPE
        J9=J9+1
        IF(J9.GE.K9) GOTO 34
        GOO 26
34      CONTINUE
        END
```

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        COMMON IFLNM(105),IPAR(3),T(2600),Y(2600)
        COMMON IFLNM1(5)
        COMMON IA1(50),IA2(50),IB1(50),IB2(50),IC1(50),IC2(50),ID1(50),ID2(50)
        COMMON IE1(50),IE2(50),IF1(50),IF2(50),IG1(50),IG2(50)
        ACCEPT "TYPE NO. OF POINTS IN FILES ",NPTS
        ISY=0
        IPLOTS=0
        ACCEPT"TYPE T AXIS LENGTH ", TAX
        TSF=52000.0/TAX
        DO 60 L=1,50
        IA1(L)=" "
        IA2(L)=" "
        IB1(L)=" "
        IB2(L)=" "
        IC1(L)=" "
        IC2(L)=" "
        ID1(L)=" "
        ID2(L)=" "
        IE1(L)=" "
        IE2(L)=" "
        IF1(L)=" "
        IF2(L)=" "
        IG1(L)=" "
        IG2(L)=" "
80      CONTINUE
        TYPE"FLOW FILES"
        TYPE"UP TO 21 FILES ALLOWED"
        ACCEPT"TYPE NO. OF FILES ",IFILE
        NFILE=(IFILE/3)+1
        DO 70 I=1,NFILE
        WRITE(10,500)
500     FORMAT(15H WRITE HEADINGS)
        GOTO (11,12,13,14,15,16,17),I
11      READ(11,600)IA1
        READ(11,600)IA2
        GOTO 70
12      READ(11,600)IB1
        READ(11,600)IB2
        GOTO 70
13      READ(11,600)IC1
        READ(11,600)IC2
        GOTO 70
14      READ(11,600)ID1
        READ(11,600)ID2
        GOTO 70
15      READ(11,600)IE1
        READ(11,600)IE2
        GOTO 70
16      READ(11,600)IF1
        READ(11,600)IF2
17      READ(11,600)IG1
        READ(11,600)IG2
70      CONTINUE
        TYPE
600     FORMAT(50A2)
100     FORMAT(13H FILENAME ...,Z)
200     FORMAT(10A2)
        T(1)=3.0
        T(2)=23.0
        T(3)=42.0
        DO 10 I=4,NPTS
        T(I)=T(I-1)+20.0
10      CONTINUE
        IP=1
        DO 60 I=1,IFILE
        WRITE(10,100)
        READ(11,200)IFLNM1
        IL=IP+4
        IQ=1
        DO 110 J=IP,IL
        IFLNM(J)=IFLNM1(IQ)
        IQ=IQ+1
110     CONTINUE
        IP=IP+5
60      CONTINUE
        IF=1
        DO 20 IJ=1,NFILE
        DO 40 I=1,3
        IL=IP+4
        IQ=1
        DO 130 IW=IP,IL
        IP=ID#(IQ)+IFLNM(IW)
130     CONTINUE
        IP=IP+5
        CALL RESET
        CALL OPEN(1,IFLNM1,2,ERROR)
        NF=3*IJ+I-3
        TYPE"OPENED FILE ",NF
        DO 50 J=1,NPTS
        READ(1,400)Y(J)
50      CONTINUE
400     FORMAT(F8.2)
        TYPE"READ FILE"
        AVFLOWI=0
        AVFLOWE=0
        ICOUNT1=0
        ICOUNT2=0
        DO 875 I9=1,2600
        IF(Y(I9).GT.0 ) AVFLOWI=AVFLOWI+Y(I9)
        IF(Y(I9).GT.0) ICOUNT1=ICOUNT1+1
        IF(Y(I9).LE.0 ) AVFLOWE=AVFLOWE+Y(I9)
        IF(Y(I9).LE.0) ICOUNT2=ICOUNT2+1
875     CONTINUE
        AVFLOWI=AVFLOWI/ICOUNT1
        AVFLOWE=AVFLOWE/ICOUNTE
        TYPE AVFLOWI
        TYPE AVFLOWE
        FMAX=-1000.0
        FMIN=10000.0
        DO 30 K=1,NPTS
      IF (FMAX .LT. Y(K)) FMAX=Y(K)
       IF (FMIN .GT. Y(K)) FMIN=Y(K)
30      CONTINUE
        TYPE "MAX = ",FMAX
        TYPE "MIN = ",FMIN
        FSF=(FMAX-FMIN)/5.0
        TYPE"FSF = ",FSF
        TYPE
        CALL RESET
        CALL FOPEN(1,"$DPO")
        CALL FOPEN(2,"$IP1")
        IPAR(1)=1
        IPAR(2)=2
        IPAR(3)=1
        IF (IPLOTS .GT. 0) GOTO 85
        CALL PLOTS(IPAR)
85      IF (I .NE. 1) GOTO 145
        ISY=ISY+1
        CALL PLOT(1.5,1.0,-3)
        GOTO (21,22,23,24,25,26,27),ISY
21      CALL SYMBOL(0.0,0.0,0.3,IA1,0.0,50)
        CALL SYMBOL(0.0,-1.0,0.3,IA2,0.0,50)
        GOTO 95
22      CALL SYMBOL(0.0,0.0,0.3,IB1,0.0,50)
        CALL SYMBOL(0.0,0.6,0.3,IB2,0.0,50)
        GOTO 95

23      CALL SYMBOL(0.0,0.0,0.3,IC1,0.0,50)
        CALL SYMBOL(0.0,-1.0,0.3,IC2,0.0,50)
        GOTO 95
24      CALL SYMBOL(0.0,0.0,0.3,ID1,0.0,50)
        CALL SYMBOL(0.0,-1.0,0.3,ID2,0.0,50)
        GOTO 95
25      CALL SYMBOL(0.0,0.0,0.3,IE1,0.0,50)
        CALL SYMBOL(0.0,-1.0,0.3,IE2,0.0,50)
        GOTO 95
26      CALL SYMBOL(0.0,0.0,0.3,IF1,0.0,50)
        CALL SYMBOL(0.0,-1.0,0.3,IF2,0.0,50)
        GOTO 95
27      CALL SYMBOL(0.0,0.0,0.3,IG1,0.0,50)
        CALL SYMBOL(0.0,-1.0,0.3,IG2,0.0,50)
95      CALL PLOT(0.0,0.0,-3)
145     IPLOTS=IPLOTS+1

        CALL LOCREF(0.0,0.1 0.1.0)
        CALL PLOT(0.0,23.0,-3)
155     CALL LOCREF(0.0,FMIN,TSF,FSF)
        CALL AXIS(0.0,FMIN,5.0,90.0,FMIN,FSF,4HFLOW,-4)
        CALL AXIS(0.0,0.0,TAX,0.0,0.0,TSF,4HTIME,4)
        CALL LINE(T,Y,NPTS,0,0,0,TSF,0.0,FSF)
        CALL PLOT(52000.0,FMIN,-3)
        CALL LOCREF(0.0,0.0,1.0,1.0)
        YDOWN=-10.0
        IF (I .EQ. 3) YDOWN=-4.5
        BTAX=-TAX
        IF (I .EQ. 3) BTAX=5.0
        CALL PLOT(BTAX,YDOWN,-3)
      IF (IFILE .EQ. NF) GOTO 125
40      CONTINUE
20      CONTINUE
125     CALL PLOT(0.0,0.0,999)
        END
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      COMMON D(8,7),R(8,7),SUMD(6),SUMR(6),S(8),RMEAND(7),RMEANR(7)
      DIMENSION IFLNM(12)
      DIMENSION SUMX(7),SUMY(7)
      TYPE 100
100   FORMAT(9H FILENAME)
      READ(5,200) IFLNM
      OPEN(UNIT=1,TYPE='OLD',NAME=IFLNM)
200   FORMAT(12A2)
      DO 5 I=1,8
      READ(1,*)A,B,C,D,E,F
      D(I,1)=A/10
      D(I,2)=B/10
      D(I,3)=C/10
      D(I,4)=D/10
      D(I,5)=E/10
      D(I,6)=F/10
5     CONTINUE
      TYPE*,'UNLOADED DATA COLLECTION COMPLETE'
      DO 6 I=1,8
      READ(1,*) A,B,C,D,E,F
      R(I,1)=A/10
      R(I,2)=B/10
      R(I,3)=C/10
      R(I,4)=D/10
      R(I,5)=E/10
      R(I,6)=F/10
6     CONTINUE
      CLOSE(UNIT=1)
      DO 13 I=1,6
      SUMD(I)=0
      SUMR(I)=0
13    CONTINUE
      DO 10 J=1,6
      DO 11 I=1,8
      SUMD(J)=SUMD(J)+D(I,J)
      SUMR(J)=SUMR(J)+R(I,J)
11    CONTINUE
10    CONTINUE
      TYPE*, SUMD
      TYPE*, SUMR
      T=0
      DO 14 I=1,6
      T=T+SUMD(I)+SUMR(I)
14    CONTINUE
      T=T*10
      TYPE*,'T=',T
      CF=(T*T)/((8*6)+(8*6))
      CF=CF
      TYPE*,'CF = ',CF
      ELEV=0
      DO 15 I=1,6
      ELEV=ELEV+((SUMD(I)+SUMR(I))*(SUMD(I)+SUMR(I)))
15    CONTINUE
      ELEV=ELEV*100
      ELEV=ELEV/(8*2)-CF
      TYPE*,'LEVELS EFFECT = ',ELEV
      RSUMD=0
      RSUMR=0
      DO 16 I=1,6
      RSUMD=RSUMD+(SUMD(I))
      RSUMR=RSUMR+(SUMR(I))
16    CONTINUE
      RSUMD=RSUMD*RSUMD
      RSUMR=RSUMR*RSUMR
      RSUM=(RSUMD+RSUMR)*100/48-CF
      TYPE*,'RESISTANCE EFFECT',RSUM
      DO 4 I=1,8
      S(I)=0
4     CONTINUE
      DO 17 I=1,8
      DO 18 J=1,6
      S(I)=S(I)+(D(I,J)+R(I,J))
18    CONTINUE
17    CONTINUE
      DO 19 I=1,8
      S(I)=S(I)*S(I)
      S(I)=S(I)*100
19    CONTINUE
      TYPE*,S
      SS=0
      DO 20 I=1,8
      SS=SS+S(I)
20    CONTINUE
      SS=SS/12-CF
      TYPE*,'SUBJECTS EFFECT = ',SS
C     INTERACTION LR
      SUMLR=0
      DO 3 I=1,8
      SUMLR=SUMLR+((SUMD(I)*SUMD(I))+(SUMR(I)*SUMR(I)))
3     CONTINUE
      SUMLR=SUMLR*100/8-CF-ELEV-RSUM
      TYPE*,'INTERACTION LR',SUMLR
      SUMLS=0
C     INTERACTION LS
      DO 1 J=1,6
      DO 2 I=1,8
      SUMLS=SUMLS+(D(I,J)+R(I,J))**2
2     CONTINUE
1     CONTINUE
      SUMLS=SUMLS*100/2-CF-ELEV-SS
      TYPE*,'INTERACTION LS',SUMLS
C     INTERACTION RS
      SUMRS=0
      SUMRSR=0
      SSUM=0
      DO 21 I=1,8
      SUMRS=0
      SUMRSR=0
      DO 22 J=1,6
      SUMRS=SUMRS+(D(I,J))
      SUMRSR=SUMRSR+(R(I,J))
22    CONTINUE
      SUMRS=SUMRS*SUMRS
      SUMRSR=SUMRSR*SUMRSR
      SSUM=SSUM+(SUMRS+SUMRSR)
21    CONTINUE
      SSUM=SSUM*100/6-CF-RSUM-SS
      TYPE*,'INTERACTION RS',SSUM
C     CALCULATION OF MEANS AND SD'S
      DO 23 I=1,7
      DO 24 J=1,6
      RMEAND(I)=RMEAND(I)+D(J,I)*10
      RMEANR(I)=RMEANR(I)+R(J,I)*10
24    CONTINUE
23    CONTINUE
      DO 25 I=1,7
      RMEAND(I)=RMEAND(I)/8
      RMEANR(I)=RMEANR(I)/8
25    CONTINUE
      DO 26 I=1,7
      TYPE*,'MEAN UNLOADED = ',RMEAND(I)
      TYPE*,'MEAN LOADED   = ',RMEANR(I)
26    CONTINUE
      DO 30 I=1,7
      SUMX(I)=0
      SUMY(I)=0
30    CONTINUE
      DO 27 I=1,7
      DO 28 J=1,6
      SUMX(I)=SUMX(I)+(D(J,I)*10-RMEAND(I))**2
      SUMY(I)=SUMY(I)+(R(J,I)*10-RMEANR(I))**2
28    CONTINUE
27    CONTINUE
      DO 29 I=1,7
      SUMX(I)=SUMX(I)/7
      SUMY(I)=SUMY(I)/7
      TYPE*, 'VAR. UNLOADED',I,' = ',SUMX(I)
      TYPE*, 'VAR. LOADED  ',I,' = ',SUMY(I)
      SUMX(I)=SQRT(SUMX(I))
      SUMY(I)=SQRT(SUMY(I))
      TYPE*,'SD UNLOADED',I,' = ',SUMX(I)
      TYPE*,'SD UNLOADED',I,' = ',SUMY(I)
29    CONTINUE
      TSUM=0
      DO 32 I=1,8
      DO 31 J=1,6
      TSUM=TSUM+(10*D(I,J))**2+(10*R(I,J))**2
31    CONTINUE
32    CONTINUE
      TSUM=TSUM-CF
      TYPE*,'TOTAL SS = ',TSUM
      RSS=TSUM-ELEV-RSUM-SS-SUMLR-SUMLS-SSUM
      TYPE*,'RESIDUAL SS = ',RSS
      STOP
      END
```