Doctor of Philosophy

The Control of Breathing During Exercise in Rowers

by

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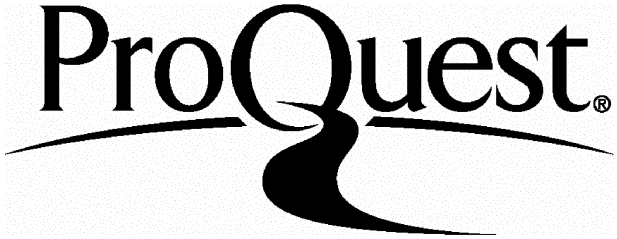

ACKNOWLEDGEMENTS:

This thesis is now bound. There have been many occasions over the last four years when I thought this moment was an impossible dream; a juicy morsel dangled in front of poor hapless students as some diabolical form of torture. It is a testament to the support I have received throughout this ordeal that I have finally reached the end of this chapter of my life.

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Finally, thanks to James Dowie for introducing me to the only proper way to travel around London and to Kawasaki Heavy Engineering, for building 750 cc. of throbbing, growling meanness and exhilaration.

FORMAL DECLARATION.

I declare that I have written this thesis presented to University of London for the degree of Doctor of Philosophy. All the studies reported in this thesis are my own.

For my mother and father.

ABSTRACT

The ventilatory response to exercise is well described in the literature, starting with an abrupt increase in ventilation coincident with the start of exercise. This is superseded some 20-40 seconds later by a more gradual rise, reaching steady-state some 3 to 5 min after the start of exercise.

Despite considerable research throughout the last century, the mechanisms responsible for the control of breathing during exercise remain controversial. In 1963 Dejours published his neurohumoral hypothesis, whereby the initial increase is a response to neural stimuli and later increase is a response to humorally mediated stimuli.

In this thesis I have addressed the following questions:

1. Highly trained athletes are reported to exhibit a large initial ventilatory response to the onset of exercise. Does the ventilatory response to exercise of highly trained sportsmen follow a similar profile to those reported in the literature for normal individuals?

2. Is exercise hyperpnoea a response to a neural and a humoral stimulus?

3. Is it possible to separate the ventilatory responses to the two stimuli by changing arterial Pco_2?

In addition I have addressed the following questions:

- Does pedal frequency affect a subject's exercise responses?

- Does the act of prior hyperventilation directly affect a subject's initial ventilatory response to the onset of exercise?

- Does lowering arterial Pco_2 affect postural sway - a control mechanism with a subcortical CNS component?

The results reported in this thesis support the view that CO_2 plays a major part in the control of the ventilatory response to moderate intensity exercise. They raise questions concerning the origin of the stimulus responsible for the initial increase in ventilation seen on commencing exercise or following a step-increase in workload, and they highlight the effect of forewarning on the initial ventilatory and pulmonary gas exchange response to an increase in exercise intensity.

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LIST OF ABBREVIATIONS AND UNITS:

$\dot{V}_E$	Minute ventilation (BTPS)	$l.min^{-1}$
V_T	Tidal volume (BTPS)	l
f_{BR}	Frequency of breathing	min^{-1}
T_I	Inspiratory time	sec
T_E	Expiratory time	sec
T_{TOT}	Total breath time	sec
P_{I,O_2}	Inspired oxygen tension	mmHg
P_{I,CO_2}	Inspired carbon dioxide tension	mmHg
Pa,O_2	Arterial oxygen tension	mmHg
Pa,CO_2	Arterial carbon dioxide tension	mmHg
P_{A,CO_2}	Alveolar carbon dioxide tension	mmHg
P_{ET,O_2}	End-tidal oxygen tension	mmHg
P_{ET,CO_2}	End-tidal carbon dioxide tension	mmHg
PE,O_2	Mixed expired oxygen tension	mmHg
PE,CO_2	Mixed expired carbon dioxide tension	mmHg
$\dot{V}o_2$	Oxygen consumption (STPD)	$l.min^{-1}$
$\dot{V}co_2$	Carbon dioxide production (STPD	$l.min^{-1}$
RER	Respiratory exchange ratio	
f_C	Heart rate	min^{-1}
$\dot{Q}$	Cardiac output	$l.min^{-1}$
$\dot{Q}_P$	Pulmonary bloodflow	$l.min^{-1}$
$\dot{Q},CO_2$	CO_2 flux	$l.min^{-1}$
f_{PED}	Pedal frequency	min^{-1}
τ	Time constant	Sec
t_D	Time delay	Sec
$\Sigma(Res^2)$	Sum of the square of the residuals	varies
N.S.	Statistical significance at the $p < 0.05$ level not achieved.	

CHAPTER 1

BRIEF REVIEW: THE DETERMINANTS OF EXERCISE HYPERPNOEA.

Chapter 1

INTRODUCTION

Exercise is characteristically associated with, among other things, a rise in minute ventilation, the size of which is related to the work rate. As the major function of ventilation is the maintenance of arterial blood gas homeostasis, it would be logical for the rise in ventilation to simply be a response to the change in oxygen (O_2) uptake and carbon dioxide (CO_2) output by the active muscles consequent to their increased metabolic rate.

However, the control of exercise hyperpnoea is rather more complicated than that: during steady-state moderate exercise in man, i.e. at a work rate below the lactate threshold (Wasserman et al., 1973) arterial blood gas tensions do not differ appreciably from resting levels (Hansen et al., 1967; Jones, 1975; Rasmussen et al., 1975; Whipp, 1981).

It is difficult to envisage how mean levels of the partial pressures of O_2 (P_{O_2}) and/or CO_2 (P_{CO_2}) could be the stimulus for exercise hyperpnoea. Coupling between ventilation ($\dot{V}E$) and pulmonary gas exchange is suggestive of humoral control. The response to such a humoral would presumably show a time-lag in response to a change in work rate, due to the time taken for blood leaving the active muscles to reach the sensing site(s). Experimental evidence shows, however, that hyperpnoea accompanies the start of exercise (Whipp et al., 1971; Paulev, 1971; Jensen et al., 1972) and can even precede it if a preparatory warning is given (Torelli & Brandi, 1961; Tobin et al., 1986).

Consideration has also to be given to the large body of evidence suggesting that other (i.e. non-chemoreceptor) sensors may be involved in the control of breathing during exercise. These are located at sites ranging from the exercising skeletal muscle (Kao, 1963; Kao et al., 1963, 1965; Torelli & Brandi, 1961) to the higher centres of the brain (Krogh & Lindhard, 1913; Eldridge et al., 1981; Torelli & Brandi, 1965).

Therefore, the control of breathing during exercise is a complicated process, involving a large number of inputs from a wide range of sources, with some interaction between different control mechanisms. Before discussing the current evidence for each proposed control mechanism, it is necessary to outline the relationship between alveolar gas exchange and minute ventilation, to discuss how the pattern of breathing varies at different intensities of exercise, and how minute ventilation changes in response to a change in workload.

THE DETERMINANTS OF EXERCISE HYPERPNOEA

The maintenance of arterial blood gas partial pressures and pH within normal limits is of vital importance to survival. P_{O_2} and P_{CO_2} in the blood are dependent on the rates of addition and removal of CO_2 and O_2 from the blood: active tissues utilise O_2 during metabolism and produce CO_2 as a waste product. To maintain homeostasis mixed venous blood is reoxygenated in the lungs, and CO_2 cleared.

By definition, these rates of gas exchange are described by the net movement of gases in the lungs: the rates of oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$) by the body. As both O_2 and CO_2 are transported to the lungs by the blood, both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are described by variants of the Fick equation:

$$\dot{V}_{O_2} = \dot{Q}_p.[(a\text{-}v)O_2], \text{ and} \qquad (1)$$

$$\dot{V}_{CO_2} = \dot{Q}_p.[(v\text{-}a)CO_2] \qquad (2)$$

where $\dot{Q}_p$ is pulmonary blood flow and $(a\text{-}v)O_2$ and $(v\text{-}a)CO_2$ are the arteriovenous differences in oxygen and carbon dioxide contents respectively. In the "ideal" lung (one in which there is no ventilation-perfusion inequality, diffusion limitation or right-to-left shunt), ventilation at rest and during exercise at sea level is sufficient for maintaining alveolar, and therefore arterial P_{O_2} and P_{CO_2} (PaO_2 and $PaCO_2$). That is, alveolar P_{CO_2} (P_{A,CO_2}) is dependent on alveolar ventilation ($\dot{V}_A$) and V_{CO_2} according to the following equation:

$$P_ACO_2 = 863.\dot{V}_{CO_2}\,[STPD]/V_A[BTPS] \qquad (3)$$

where 863 is the conversion factor for changing values given as standard temperature (273 K), pressure (dry; 760 mmHg) to body temperature (37° C) and pressure (saturated with water vapour). Thus, if P_{A,CO_2} (and therefore Pa,CO_2) is to be kept constant, $\dot{V}_A$

must be proportional to $\dot{V}CO_2$. Consequently the slope of the $\dot{V}A$:$\dot{V}CO_2$ relationship increases as the level at which Pa,CO_2 is maintained falls.

$\dot{V}A$ is dependent on total minute ventilation ($\dot{V}E$). However, $\dot{V}E$ ventilates the whole lung, including those parts which are not involved in gas exchange, e.g. the mouth, trachea, bronchi and those areas of the lung not well perfused by the pulmonary circulation. The space encompassed by these regions is called the physiological dead space (VD) and that proportion of the $\dot{V}E$ which ventilates the dead space is called the dead space ventilation ($\dot{V}D$). Therefore:

$$\dot{V}A = \dot{V}E - \dot{V}D \qquad (4)$$

this relationship is further complicated by the fact that $\dot{V}E$ and $\dot{V}D$ are dependent on the frequency of breathing (fBR) and tidal volume (VT) and physiological dead space (VD) respectively. Equation 4 can therefore be rewritten as:

$$\dot{V}A = \dot{V}E(1-VD/VT) \qquad (5)$$

By substituting equation 5 into equation 3, it is possible to obtain an equation relating $\dot{V}co_2$ to $\dot{V}E$:

$$\dot{V}E = 863.\dot{V}co_2/PaCO_2.(1-VD/VT) \qquad (6)$$

where VD/VT is the physiological dead space fraction of the breath. As this equation demonstrates, if Pa,CO_2 is to be maintained, VE must increase in proportion to the increase in $\dot{V}co_2$. By convention, work rate is measured as metabolic rate, or $\dot{V}o_2$. The relationship between $\dot{V}o_2$ and $\dot{V}co_2$ is governed by the respiratory exchange ratio (RER) which in the steady-state is confluent with the respiratory quotient (RQ):

$$\dot{V}co_2 = \dot{V}o_2/RQ \qquad (7)$$

RQ is dependent on the type of substrate being oxidised: oxidation of carbohydrates has a RQ of 1.00, while β-oxidation of fatty acids has a RQ of about 0.7.

THE TIME COURSE OF EXERCISE HYPERPNOEA.

Although it is true to say that during steady-state exercise $\dot{V}E$ varies in proportion to $\dot{V}co_2$ (Wasserman, 1967), exercising at a constant work rate is an artificial occurrence restricted to the exercise laboratory. During normal everyday life, exercise work rate constantly varies as different tasks are performed. It is therefore important to determine how VE changes with time in response to a change in exercise work rate (i.e. the non steady-state response).

The profile of the changes in ventilation on transition from rest to moderate-intensity exercise can be separated into 3 stages:

Initial Increase: The onset of exercise is associated with by an abrupt rise in $\dot{V}E$, characteristically to a plateau, lasting approximately 20 seconds (D'Angelo & Torelli, 1971; Dejours, 1963, 1964; Jensen et al., 1971; Jensen, 1972; Torelli & Brandi, 1964; Whipp et al., 1982). This abrupt increase was first reported by Krogh and Lindhard in 1913. The abrupt increase in $\dot{V}E$ characteristically occurs in synchrony with the onset of exercise (Jensen et al., 1972; Whipp et al., 1982). but can precede exercise if the subject is given a preparatory warning (Torelli & Brandi, 1961; Tobin et al.,1986). The rapidity of the initial ventilatory response to exercise led Dejours (1964) to propose in his neurohumoral hypothesis that it must be under neural control.

Some authors have reported the magnitude of this initial increase in $\dot{V}E$ to be independent of work rate (Dejours, 1964; Jensen et al., 1972; Craig et al., 1963), while others have demonstrated a workload-dependant effect (Krogh & Lindhard, 1913; Jensen et al., 1971; Asmussen & Nielsen, 1948; Asmussen, 1973; Cummin et al., 1986; Pearce & Milhorn, 1977).

Dynamic work rate forcing techniques and computer analysis have determined an initial response is present even against a background of mild exercise (e.g. unloaded cycling; Asmussen, 1973; Broman & Weigertz, 1971; Fujihara et al., 1973a; Whipp et al., 1982),

although considerably reduced in magnitude. Karlsson et al. (1975) and Weiler-Ravell et al. (1983) reported that if exercise was started in the supine position, the initial stage of the exercise hyperpnoea was greatly attenuated.

The initial increase in $\dot{V}E$ on transition from rest to exercise is accompanied by an abrupt rise in both $\dot{V}o_2$ and $\dot{V}co_2$ Wasserman et al., 1967; Whipp et al., 1982). Furthermore, the magnitudes of the increases in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ are in proportion, resulting in a constancy of RER and the end-tidal partial pressures of carbon dioxide (P_{ET},CO_2) and oxygen (P_{ET},O_2. Casaburi et al., 1978a; Whipp et al., 1982; Whipp & Ward, 1982; Wasserman et al., 1974; Linnarson, 1974; Pearce & Milhorn, 1977).

As the initial ventilatory response to exercise is therefore not associated with hyperventilation, and mixed venous gas tensions are still at resting levels during the initial increases in $\dot{V}E$ and pulmonary gas exchange, the sudden increase in $\dot{V}o_2$ and $\dot{V}co_2$ must be due to a proportional rise in pulmonary blood flow (Qp). Whipp & Ward (1982) termed this initial stage the "Phase 1", or cardiodynamic, response.

More recently, Casaburi et al. (1989b) have measured a rise in Pco_2 and a fall in Po_2 in the pulmonary artery within 6 seconds of starting exercise. This they attributed to a shunting of blood from the visceral circulation into the systemic circulation by the initial effort at the start of exercise. This casts doubt on the "cardiodynamic" nature of the initial increase in $\dot{V}E$, as proposed by Whipp & Ward (1982).

Later Increase: The onset of the later increase is signalled by mixed venous blood of altered gas composition entering the pulmonary circulation (Whipp & Ward, 1982; Whipp et al., 1982 Dejours, 1964), resulting in an increase in the rates of O_2 and CO_2 transfer across the alveolar surface, with an accompanying rise in P_{ET},CO_2, and fall in P_{ET},O_2 and RER. Dejours (1964) proposed that the later increase in $\dot{V}E$ was under humoral control and Whipp & Ward (1982) termed this Phase of the ventilatory and pulmonary gas exchange responses "Phase 2".

Square wave, ramp, impulse and sinusoidal work-rate forcing techniques have determined that the Phase 2 the ventilatory response is adequately described by simple first-order kinetics with a time constant of around 60-70 seconds (Whipp et al., 1982; Wasserman & Whipp, 1983; Broman & Weigertz, 1971; Fujihara et al., 1973b; Miyamoto & Niizeki, 1992; Casaburi et al., 1977).

The time course of the Phase 2 ventilatory response has been compared to those of $\dot{V}O_2$ and $\dot{V}CO_2$. These have shown that the rise in ventilation most closely follows the rise in $\dot{V}CO_2$ (Whipp et al., 1983 report time constants of 50-60 seconds for $\dot{V}CO_2$ and 35-40 seconds for $\dot{V}O_2$). Young & Woolcock (1978) have reported a transient fall in PaO_2 during the later rise in $\dot{V}E$. This has been attributed to the difference in the time constants for the later rises in $\dot{V}E$ and $\dot{V}O_2$ (Lamarra et al., 1989).

There is considerable evidence to suggest that the carotid chemoreceptors are responsible for the control of exercise hyperpnoea during the Phase 2 response: Wasserman et al. (1975) reported the rise in $\dot{V}E$ to the steady-state be slower in patients who had had their carotid bodies surgically resected than in normal individuals.

The time constant of the Phase 2 ventilatory response is affected by changes in the inspired partial pressures of O_2: Griffiths et al. (1986) studied the time constants of $\dot{V}E$, $\dot{V}CO_2$ and $\dot{V}O_2$ during cycle ergometry at inspired oxygen fractions (FI,O_2) varying between 12% and 100%, and reported that while the time constant for $\dot{V}O_2$ was not significantly affected, the time constants of both $\dot{V}CO_2$ and $\dot{V}E$ were reduced in hypoxia (which increases carotid body discharge) and increased in hyperoxia (which significantly reduces carotid body discharge: time constant for $\dot{V}E$ = 40 seconds at FI,O_2 = 12%, 112 seconds at FI,O_2 = 100%). Ward et al. (1987) investigated the effects of hyperoxia (FI,O_2 = 12%), normoxia and hyperoxia (FI,O_2 = 100%) on the ventilatory dynamics for moderate-intensity cycle ergometry. The time constants obtained were 40, 58 and 92 seconds respectively.

The time course of the Phase 2 response can be reduced by induction of metabolic acidosis induced by ingestion of ammonium chloride (Oren et al., 1982) and intravenous infusion of dopamine (Boetger & Ward, 1986), both of which are known to stimulate the carotid chemoreceptors. Conversely, induction of metabolic alkalosis by ingestion of sodium bicarbonate slows the time course of the Phase 2 response (Oren et al., 1982).

Ward et al. (1983) investigated the effect of body CO_2 stores on ventilatory responses to 100 Watts cycle ergometry, reducing pre-exercise P_{ET},CO_2 to 25 Torr by volitional hyperventilation. They reported that the half-times of the Phase 2 rises in $\dot{V}_E$ and $\dot{V}_{CO_2}$ were considerably slowed following volitional hyperventilation (Normal $t½$ = 48 and 43 seconds respectively vs. 76 and 71 seconds respectively following hyperventilation), whereas the half-time for $\dot{V}_{O_2}$ was only slightly prolonged (Normal $t½$ = 31 seconds; 39 seconds after hyperventilation).

Carotid chemoreceptor activity would not appear to be the sole mediator of the Phase 2 response: Griffiths et al. (1986) reported the time constant for the Phase 2 ventilatory response to be greater at F_I,O_2 = 1.00 than at F_I,O_2 = 0.30, despite there being no discernible peripheral chemosensitivity at F_I,O_2 = 0.30. A similar effect has been reported in subjects whose carotid bodies have been surgically resected (Whipp et al. 1994).

Steady-state: The ventilatory response to moderate intensity exercise becomes constant by the fifth or sixth minute (i.e. 4 x τ. Whipp et al., 1982). The magnitude of the response is proportional to both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, with $\dot{V}_{CO_2}$ showing the closer correlation with $\dot{V}_E$ (Wasserman et al., 1967), providing more circumstantial evidence for a CO_2-dependent control mechanism.

Oren et al. (1981) investigated the ventilatory response to steady-state exercise during induced chronic metabolic acidosis and alkalosis, and demonstrated that while arterialised venous P_{CO_2} was maintained at normal levels, the ventilatory response to exercise was raised during exercise with acidosis and lowered during exercise with alkalosis. However,

Forster et al. (1986) questioned the view that Pa,CO_2 is maintained at a constant level during exercise, demonstrating the presence of small transient changes in Pa,CO_2 during both the onset and the end of exercise. Despite this demonstration, these authors showed that during steady-state exercise Pa,CO_2 did not vary by more than 1-3 Torr.

At work rates which engender lactic acidosis, i.e. work rates above the lactate threshold (θ_L), Ventilation faces the additional challenge of having to compensate for the metabolic acidosis. That is it not only has to clear metabolic CO_2 from the lungs, but it also has to drive Pa,CO_2 down to constrain the fall in pH. At these workloads there is partial buffering of lactate by bicarbonate. This results in an additional CO_2 load to be cleared from the lung. RER therefore rapidly rises above 1.0.

Recent evidence, however, would suggest other factors may be responsible for this increase in $\dot{V}E$: Paterson et al. (1990) studied the ventilatory response to exercise in patients with McArdle's syndrome. These patients suffer from a congenital deficiency of the enzyme myophosphorylase, rendering them incapable of muscle glycogenolysis. As a result, they do not produce lactate during exhaustive exercise, and characteristically demonstrate a respiratory alkalosis. These patients still show a rise in the $\dot{V}E/\dot{V}co_2$ ratio during severe exercise which, due to the lack of metabolic acidosis, is accompanied by a rise in arterial pH. It has been suggested, however (Riley et al., 1993), that this hyperventilation is a result of pain in the exercising limbs rather than a result of the exercise *per se*.

THE PATTERN OF BREATHING DURING EXERCISE.

The increases in VE which accompany a rise in work rate may be achieved by the varying of a number of factors, the most obvious of which are increases in VT and *f*BR. These effects can, however, be achieved in different ways: VT can be increased by a decrease in end-expiratory lung volume (EELV) and/or an increase in end-inspiratory lung volume (EILV). The frequency of breathing may be increased as a result of a fall in the duration of inspiration (TI) and/or expiration (TE). The dominant effect can be determined by studying the ratio of TI/TTOT (TTOT = 60/*f*BR). Changes in any of these variables may result in a change in the mean inspiratory and expiratory flow rates (VT/TI and VT/TE respectively).

The pattern of breathing seen in response to exercise can be separated into three ranges (Gardner, 1977). it should be stressed that these ranges refer to patterns of breathing and are not directly related to the ventilatory response to exercise. Any association between exercise work rate and pattern of breathing mentioned in the subsequent section is a consequence of changes in the ventilatory response to exercise with changing work rate, rather than the work rate *per se*.

Range 1 occurs at low work rates, i.e. when $\dot{V}E$ is only marginally elevated above normal resting levels, and is characterised by an increase in $\dot{V}E$ almost entirely due to an increase in VT, with no consistent change in *f*BR (Gardner, 1977; Lind, 1984; Lind & Hesser, 1984). The increase in VT is mostly due to a fall in EELV, with little or no increase in EILV (Ward et al., 1979; Lind, 1984; Lind & Hesser, 1984; Babb & Rodarte, 1991).

Range 2 covers light to moderately severe exercise, and is characterised by both an increase in both *f*BR and VT. Both TI and TE fall in proportion with the increase in VT, but TE falls more rapidly than TI, resulting in an increase in TI/TTOT (Gardner, 1977; Lind, 1984; Lind & Hesser, 1984).

Range 3, which is seen during severe exercise, is characterised by a sharp rise in f_{BR} while V_T remains constant or falls slightly (Jensen et al., 1980). Again the rise in f_{BR} is accompanied by a rise in T_I/T_{TOT}, as T_E changes more rapidly than T_I. The maximum V_T which occurs during exercise has been reported to be about 50% of an individual's vital capacity (VC), with a frequency of about 50 breaths min^{-1} (Åstrand & Rodahl, 1986) although Clark et al. (1983) reported f_{BR} at maximal exercise to be 62 min^{-1} in a group of elite oarsmen while running and Steinacker et al. (1993) reported f_{BR} to be approximately 50 min^{-1} at maximal exercise in a group of national standard oarsmen while rowing. $\dot{V}_E$ at that time was approximately 170 $l.min^{-1}$, approximately 90% of the oarsmen's' maximal voluntary ventilation.

It would appear, from this data, that breathing during maximal exercise is not subject to any mechanical limitation. This has been studied by Jensen et al. (1980), who compared tidal flow-volume loops at maximal exercise with resting maximal effort flow-volume loops (MEFV). They demonstrated that during maximal exercise, expiratory flows commonly attain and even surpass those achieved during the MEFV manoeuvres, suggesting that breathing pattern at maximal exercise may be determined by pulmonary mechanics as well as the ventilatory drive. Jensen et al. (1980) also used the MEFV loops obtained to calculate the lowest possible values for T_I and T_E theoretically attainable at each V_T, and determined that both T_I and V_E at maximal exercise approach these values.

These results have been challenged by Stubbing et al. (1986) who used whole-body plethysmography during exercise to measure lung volumes. Although they also reported that tidal flow:volume loops during maximal exercise approached the resting MEFV envelope, they were unable to report any cases in which the MEFV loop was surpassed. They suggested that such cases could be due to incorrect placement of the exercise loop on the volume axis.

RESPIRATORY CONTROL DURING EXERCISE

The study of exercise hyperpnoea has identified a number of possible control signals, ranging in site from the active muscles to the higher centres of the brain, and in mechanism from intrinsic neural pathways to detection of changes in the humoral environment. Despite considerable research, no one control mechanism has been identified as the primary source for the control of exercise hyperpnoea. The evidence for and against each proposed site for the control of breathing during exercise will be discussed in the proceeding section, starting with the active muscles, proceeding through the humorally mediated mechanisms before finishing with the purely higher centres of the brain.

Muscle Afferents:

Evidence of a role for neural activity stemming from the muscles has arisen from a number of sources: Jeager-Denavit et al. (1973) demonstrated that passive movement of the knees through an angle of 90° in paraplegics with complete spinal cord lesions at T12 failed to elicit the hyperpnoea during the first movement seen in normal subjects. Both Duncan et al. (1981) and Poole et al. (1988) looked at the ventilatory response to isometric forearm contractions with occlusion of the circulation to the exercising muscles. Both groups reported that $\dot{V}E$ increased with time during the contractions and attributed the increase to activation of nerve endings in the exercising muscles.

Duncan et al. (1981) also compared the results seen in normal individuals with those seen in two patients suffering from a loss of sensation in the exercising muscles (One patient suffered from a partial Brown-Sequard lesion resulting in an almost complete left hemisection at the T5 level, the other suffered from a congenital sensory neuropathy). These patients showed no rise in ventilation during muscle contraction, which they attributed to the lack of afferent muscle nerve supply. The only caution cited by Duncan et

al. (1981) came from the fact that hypnosis reduced the exercise hyperpnoea, which they interpreted to suggest that the hyperpnoea may be in response to pain.

Bennett (1984) investigated the importance of muscle afferents by inducing leg exercise in dogs by electrically stimulating the peripheral ends of cut sciatic nerves. They demonstrated hyperpnoea, but it was accompanied by hypercapnia, whereas exercise hyperpnoea in dogs is characteristically normocapnic or hypocapnic. They suggested that the hyperpnoea seen in this situation was in response to the hypercapnia, rather than in response to the exercise itself, the hyperpnoeic exercise response having been abolished by the removal of the muscle afferent nerve supply.

The type of muscle afferent activity responsible for exercise hyperpnoea has also been investigated: Jammes et al. (1981) demonstrated that high frequency mechanical vibration of the tendons of the biceps or triceps, a potent stimulator of muscle spindle afferents, induced an increase in $\dot{V}E$ on the first or second breath following the start of the vibration. Takano (1988) showed that cycle ergometry at 60 rpm elicited a larger increase in ventilation than the same work rate at 30 rpm. This he attributed to the faster muscle movement necessary when cycling at 60 rpm.

McCloskey and Mitchell (1972) demonstrated that when the group III and group IV muscle afferent activity was abolished the exercise hyperpnoea was largely attenuated, as were the associated cardiovascular responses. Tibes et al. (1977) demonstrated that the non steady-state changes in VE during Phase 2 hyperpnoea correlated most closely with the changes in K^+ concentration in the venous effluent, which they postulated was stimulating the small diameter group III and group IV fibres.

The evidence for a role for muscle afferents in the control of exercise hyperpnoea is, however, by no means conclusive: Adams et al. (1984b) found no difference between the onset of the ventilatory responses to electrically stimulated leg exercise in normal subjects and paraplegic patients; both showing a rapid rise in $\dot{V}E$ by the second breath after the start

of the exercise. Similarly Brice et al. (1988) demonstrated a normal ventilatory response to two levels of electrically induced leg exercise in paraplegics with complete spinal cord lesions between T4 and T11.

Cross et al. (1982a) demonstrated that these effects were not due to chronic adaptation of the respiratory control system in response to the loss of sensory information from the lower limbs by comparing the exercise response to electrically stimulated phasic hind limb contractions in the dog before and after spinal cord transection. They showed there was no change in steady-state exercise hyperpnoea for a given workload following transection of the spinal cord, although $\dot{V}_I$ and $\dot{V}_{CO_2}$ both rose more slowly. This was attributed to attenuation of the pressor response to exercise following spinal cord transection and the resulting reduction in venous return.

Finally, Fernandes et al. (1990) demonstrated that epidural anaesthesia administered at L3-L4 in man had no effect on the steady-state ventilatory response to dynamic exercise (Epidural anaesthesia blocks afferent neural impulses from the exercising limbs). This provides yet further evidence against a role for muscle afferents in the control of exercise hyperpnoea.

Cardiopulmonary Coupling:

As mentioned earlier, Phase 1 of the ventilatory response to exercise is characterised by a rapid increase in $\dot{V}_E$ in virtual synchrony with the start of exercise. Krogh and Lindhard (1913) hypothesised that this had to be associated with an abrupt rise in pulmonary blood flow (Q_P) as $\dot{V}_{O_2}$ also showed an abrupt rise. More recent studies (e.g. Cummin et al. 1986a), have also supported these results, and have also shown that $\dot{Q}_P$ rises in proportion with $\dot{V}_E$, with the rise in both $\dot{Q}_P$ and $\dot{V}_E$ being almost entirely due to rises in f_C and f_{BR} respectively.

Based on this proportionality, Wasserman et al. (1974) suggested that the link between cardiac output and ventilation may be causal rather than coincident. There is considerable evidence to support such a hypothesis: Karlsson et al. (1975) and Weiller-Ravell et al. (1983) have demonstrated that the abrupt increases in $\dot{V}_I$ and $\dot{V}_{O_2}$ (i.e. the increment in $\dot{V}_{O_2}$ is essentially proportional to the increase in $\dot{Q}_P$) associated with Phase 1 were attenuated when exercise was performed in the supine position. However, the proportionality of the responses was maintained. Huszczuk et al. (1981) were able to demonstrate in dogs a good correlation between right ventricle moving average pressure, varied by inflating a balloon in the right ventricle outflow, and $\dot{V}_E$.

Green and Sheldon (1983) bypassed the heart in dogs and artificially varied $\dot{Q}_P$. $\dot{V}_E$ varied in proportion with $\dot{Q}_P$ when Pa,CO_2 was maintained at constant levels. When Pa,CO_2 was raised, the intercept of the $\dot{V}_E/\dot{Q}_P$ relationship rose, but the gradient remained constant. In a similar experiment, Huszczuk et al. (1982) used a partial cardiopulmonary bypass to vary blood flow through the heart and lungs in dogs during steady-state exercise, and were able to demonstrate a progressive hypopnoea as bloodflow through the heart and lung $\dot{V}_E$ was reduced, even to the extent of inducing apnoea.

Lloyd (1984) used dogs to investigate the effect of an abrupt increase in pressure in the pulmonary artery and right ventricle on $\dot{V}_E$, and were able to demonstrate a vagally mediated rise in f_{BR} due mostly to a fall in T_E.

Jones et al. (1982) reported a strong correlation between changes right ventricular pressure (induced either by pharmacological intervention or by inflating a balloon in the right ventricle) and changes in $\dot{V}_E$ in the anaesthetised dog. This led them to believe that the sensors responsible for the link between $\dot{Q}_p$ and $\dot{V}_E$ were located in the right ventricle.

There is also a large body of evidence which is not consistent with such a hypothesis: Cummin et al. (1986b) investigated the effect of changing $\dot{Q}$ by postural manoeuvres and lower body positive pressure on $\dot{V}_E$, but were unable to demonstrate a consistent effect.

Jones et al. (1981) induced increases in $\dot{Q}$ in patients with demand-type pacemakers, but could find no evidence of a rise in $\dot{V}E$ for 20 seconds following the increase in $\dot{Q}$, despite a rise in P_{ET,CO_2} of a mean of 2.5 Torr. Huszczuk et al. (1990) reported calves fitted with artificial hearts to display a normal ventilatory response to exercise despite $\dot{Q}$ being constrained during exercise at resting levels. Similar results have been reported in humans (Marconi et al., 1991).

Adams et al. (1987), investigating the early responses to voluntary and electrically induced exercise, were unable to demonstrate any proportionality in the rises in $\dot{Q}$ and $\dot{V}I$ for either form of exercise, as evidenced by the slight fall in P_{ET,CO_2} measured in both cases. Although the changes in $\dot{Q}$ were similar for both forms of exercise, voluntary exercise induced a larger initial rise in $\dot{V}I$ than did electrically induced exercise.

Favier et al. (1983a) used the β-adrenoceptor antagonist propranolol to reduce the initial rise in $\dot{Q}$, and demonstrated that it had no effect on $\dot{V}E$, V_T or fBR. Banner et al. (1988) investigated the early cardiorespiratory responses to exercise in patients who had undergone heart or heart-lung transplantation (i.e. who lacked any cardiac and/or pulmonary innervation) and demonstrated a normal ventilatory response to exercise in the absence of an initial rise in $\dot{Q}$. As such, the evidence available seems to favour the abrupt rises in $\dot{V}E$ and $\dot{Q}_P$ seen at the start of exercise as being coincidental rather than interlinked.

Catecholamines:

Another potential mechanism for the humorally mediated control of exercise hyperpnoea is the plasma concentrations of adrenaline and noradrenaline. Both of these have been shown to rise during exercise (Bannister & Griffiths, 1972; Flandrois et al., 1977), are known to stimulate the carotid chemoreceptors (Joels & White, 1968; McCloskey, 1975; Milsom & Sadig, 1983; Nye et al., 1994) and increase $\dot{V}E$ in humans (Cunningham et al., 1958).

Galbo et al. (1987), investigating the effects of partial neuromuscular blockade on exercise hyperpnoea in man, demonstrated that $\dot{V}E$, plasma adrenaline and noradrenaline were all significantly higher for a given $\dot{V}O_2$ during neuromuscular blockade, and all returned to their normal levels as the extent of the blockade reduced with time. In contrast, Favier et al. (1983a) was unable to demonstrate any reduction in Phase 1 hyperpnoea on administration of the β-adrenoceptor antagonist propranolol in dogs.

However, the concentrations of circulating catecholamines do not appear to increase at work rates below the anaerobic threshold (Banister & Griffiths, 1972; Haggendal et al., 1970; Flandrois et al.), casting doubt on their importance in the control of ventilation during moderate-intensity exercise. Furthermore, β-adrenergic blockade with propranolol has been shown to have no effect on the $\dot{V}E:\dot{V}co_2$ relationship during steady-state moderate intensity exercise (Petersen et al., 1983). β-adrenergic blockade has been shown to increase the kinetics of the Phase 2 response (Conway & Petersen, 1987), but the constancy of PET,CO_2 values during this Phase would suggest that the ventilatory effects were secondary to changes in the kinetics of the circulatory response to exercise.

Peripheral Chemoreceptors:

As mentioned in the introduction, during Phase 2 the rise in $\dot{V}E$ correlates well with the rise in $\dot{V}CO_2$. It has been suggested that this is causal rather than coincidental, thus centring considerable research on the central chemoreceptors of the medulla in the brain and the peripheral chemoreceptors situated in the carotid bodies and the aortic arch. In man, the role of chemoreceptors in the aortic arch is minimal, as patients who have undergone carotid body resection (CBR) show very little response to hypoxia (Lugliani et al., 1971; Wade et al., 1970; Swanson et al., 1978; Wasserman et al., 1975b). The evidence for and against a role for the central chemoreceptors will be discussed in the following section.

One region of the hyperpnoeic response to exercise possibly under the influence of the carotid bodies is Phase 2. As mentioned earlier, hypoxia and hyperoxia speed up and slow down Phase 2 dynamics respectively (Ward et al., 1987; Griffiths et al., 1986; Weill & Swanson, 1990). In addition, Wasserman et al. (1975) reported that the duration of Phase 2 for the CBR subjects was roughly twice that for the normal subjects at moderate levels of exercise, and was accompanied by a transient increase in P_{ET,CO_2}. Further circumstantial evidence for a role for the carotid bodies comes from the fact that Phase 2 is characteristically associated with a transient fall in Pa,O_2, which would tend to increase any carotid body response present. It is generally accepted that carotid body discharge contributes to the kinetics of Phase 2, but is not the only determinant.

It also generally accepted that the carotid bodies are of importance in the determination of exercise hyperpnoea at work above the lactate threshold. Wasserman et al. (1975) demonstrated that the abrupt rise in slope of the $\dot{V}_E/\dot{V}_{CO_2}$ relationship which occurs in normal individuals above the lactate threshold is greatly attenuated in subjects who have undergone bilateral carotid body resection, while Whipp et al. (1980) detected considerable metabolic acidosis at high work intensities in such subjects.

Factors Affecting Carotid Body Discharge 1: Muscle Metabolites.

The sharp rise in the $\dot{V}_E/\dot{V}_{CO_2}$ relationship coincides with a sharp rise in the arterial plasma lactate concentration ($[La^-]_a$), except in ramp workload forcings where the lactate threshold is associated with an "isocapnic buffering" region prior to the increase in the $\dot{V}_E/\dot{V}_{CO_2}$ relationship (Whipp et al., 1989). The resultant acidosis is responsible for an additional ventilatory stimulus, with the consequent reduction in Pa,CO_2 constraining the fall in arterial pH.

Arterial plasma potassium ($[K^+]_a$) has been shown to rise on transition from rest to exercise (Kilburn, 1966; Linton et al., 1984; Struthers et al., 1988; Medbo & Sejersted, 1990), partly as a result of haemoconcentration (Tibes et al., 1974; van Beaumont et al., 1973;

Okuno, 1992) and partly as a result of efflux from the exercising muscles (Fenn & Cobb, 1936; Kilburn, 1965; Medbo & Sejersted, 1990). The magnitude of the ventilatory response to moderate intensity exercise is roughly in proportion to the rise in $[K^+]_a$ (Paterson et al., 1990; Newsted et al., 1990; Yoshida et al., 1990; Busse et al., 1991) and the kinetics of the rise in $[K^+]_a$ and the Phase 2 response for $\dot{V}E$ are similar (Band et al., 1982; Conway et al., 1988; Paterson et al., 1989; Newstead et al., 1990).

Increases in $[K^+]_a$ of a similar size to those seen in exercise have been shown to stimulate $\dot{V}E$ via a direct effect on the carotid chemoreceptors (Band et al., 1985; Linton & Band, 1986; Burger et al., 1986, 1988; Band & Linton, 1986, 1987; Nye et al., 1994), leading to the theory that $[K^+]_a$ is an important mediator of exercise hyperpnoea.

Patterson et al. (1990) has also demonstrated an increase in the$\dot{V}E/\dot{V}CO_2$ relationship at near maximal workloads in patients with McArdle's Syndrome. These patients are unable to produce lactate, due to a congenital deficiency of the enzyme myophosphorylase, and therefore demonstrate respiratory alkalosis on exercise. The pattern of the rise in $\dot{V}E$ closely matched by the rise in arterial potassium ion concentration ($[K^+]_a$), leading the authors to suggest that this was the signal responsible for the rise in $\dot{V}E$. Yoshida et al. (1990) studied the changes in $\dot{V}E$ and $[K^+]_a$ during incremental exercise and during recovery in normal subjects. They were able to demonstrate a linear relationship between $\dot{V}E$ and $[K^+]_a$ during both exercise and recovery, although for recovery the relationship was shifted to the left.

There is also evidence to suggest that changes in $[K^+]_a$ do not have a role to play in the control of breathing during moderate intensity exercise. As has already been mentioned, β-adrenergic blockade has no effect on the steady-state ventilatory response (Petersen et al., 1983), despite β-adrenergic blockade inhibiting K^+ uptake (Struthers et al., 1983) and enhancing exercise-induced hyperkalaemia (Carlsson et al., 1978; Lim et al., 1981; Paterson et al., 1991).

Factors Affecting Carotid Body Discharge 2: Arterial P_{CO_2} Oscillations.

Although $\dot{V}_E$ is closely matched to $\dot{V}_{CO_2}$ during light and moderate exercise, as discussed earlier, mean arterial P_{CO_2} remains at resting levels in. Thus it appears that there is no change in signal amplitude to be detected. The possibility that Pa,CO_2 may show breath-by-breath oscillations while being maintained at a constant mean value was first put forward by Yamamoto (1960), and more recent studies have suggested that the Phase, amplitude and slope of these oscillations may provide a signal for the feed-forward control of exercise hyperpnoea.

A possible role for the timing of the CO_2 oscillations at the carotid body with respect to the respiratory cycle has been identified by a number of authors (e.g. Cross et al., 1979; Nye et al., 1981, Black et al., 1971; Eldridge, 1976), and is based on the fact that the insertion of a chemical stimulus of constant amplitude and direction at varying times of the respiratory cycle induces a larger response in late than in early inspiration, while the response is absent or in the opposite direction during expiration.

Cross et al. (1979) investigated the effect on arterial pH oscillations (easier to measure than the corresponding oscillations in Pa,CO_2) and integrated phrenic nerve activity of altering V_T and the timing of the onset of inspiration with respect to phrenic nerve output in paralysed artificially ventilated dogs. Changing V_T caused small transient changes in mean blood gas composition, resulting in a rapid ventilatory response mostly occurring by a change in T_E, although some change was seen in T_I and peak phrenic nerve output. Changing the Phase relationship between the respiratory and blood gas cycles also resulted in a rapid corrective response predominantly due to changes in T_E. Denervation of the carotid bifurcation abolished both of these effects, although in the case of the change in mean arterial blood gas composition, a delayed response was seen, attributed to central chemoreceptor activation and mediated mostly by a change in peak phrenic nerve output with a less pronounced effect on T_I and T_E.

Cross et al. (1982b) studied the possible role of arterial pH oscillations in the control of breathing during electrically induced exercise in the anaesthetised dog. They concluded that the Phase shift seen on starting exercise was in the wrong direction to account for a rise in $\dot{V}_I$ and the amplitude of the oscillations reduced with rising f_{BR}. A linear relationship was seen, however, between $\dot{V}_I$ and the maximum rate of fall of pH on the downstroke of the pH oscillation (i.e. the maximum rate of rise in Pa,CO_2, $\delta Pa,CO_2/\delta t\uparrow$ max) during the first ten breaths of exercise. $\delta Pa,CO_2/\delta t\uparrow$ max is dependent on the rate of supply of CO_2 to the lungs, as is $\dot{V}co_2$ which makes it an attractive signal for the control of exercise hyperpnoea.

Allen and Jones (1984) investigated the relationship between another variant of $\delta Pa,CO_2/\delta t\uparrow$, the rate of rise of alveolar PCO_2 ($\delta P_ACO_2/\delta t\uparrow$), and $\dot{V}_E$ following a step change in exercise work rate in humans, and again demonstrated a linear relationship in the first few breaths after the change in exercise work rate. This relationship was closer than that for $\dot{V}co_2$ and $\dot{V}_E$. Cross et al. (1990) have demonstrated in the cat that in isoxic normocapnia a rise in amplitude of the Pa,CO_2 oscillation produced a rise in both the amplitude and mean carotid chemoreceptor discharge.

Cross et al. (1986), attempting to determine the relationship between carotid sinus nerve discharge frequency and arterial pH oscillations in the anaesthetised, paralysed and artificially ventilated cat were unable to demonstrate any simple proportionality: the trough of the discharge frequency coincided with the pH peak and the maximum discharge frequency coincided with the maximum rate of fall of pH on the downstroke of the pH oscillation. They concluded that there was a large rate of change component to the discharge pattern.

Murphy et al. (1987) raised doubts about the importance of arterial PCO_2 oscillations in the control of breathing during exercise, reporting that in renal patients arterial pH oscillations disappeared above a f_{BR} of 20 min^{-1}. However, pH oscillations have been recorded at frequencies in excess of 30 min^{-1} in the cat (Cross et al., 1979) and conscious humans (Cross et al., 1995).

To conclude, the carotid bodies are of importance in the control of breathing at high workloads, and have an effect on the kinetics of Phase 2. It is possible that the carotid bodies are important in the breath-by-breath control of breathing at rest, and in Phase 1, but evidence for these possible roles is at the moment equivocal, and further research is needed.

Central Chemoreceptors:

The ventilatory response to changes in Pa,CO_2 has been demonstrated by Haldane and Priestley (1905). Studies using cerebro-spinal fluid (CSF) perfusion to vary CSF P_{CO_2} and/or pH demonstrated that this response was in fact a response to a change in CSF pH (Leusen, 1950, 1954a,b), while studies into the ventilatory response to electrical stimulation of the brain located the relevant chemoreceptors on the ventral surface of the medulla (Loeschcke & Koepchen, 158a,b,c; Loeschcke et al., 1958; Loeschcke & Katasaros, 1959). More recently, Eldridge et al. (1984) have demonstrated that central chemoreceptor activity is dependent on changes in the pH of the medullary extracellular fluid, rather than changes in CSF pH, and that the response is curvilinear in the cat.

Due to the correlation between $\dot{V}E$ and $\dot{V}CO_2$ during light and moderate intensity exercise, a possible role for the central chemoreceptors in the control of exercise hyperpnoea has been investigated. However, as Pa,CO_2, and hence CSF pH, remain constant during exercise in man and actually fall in most other mammals, there appears to be no error signal for the chemoreceptors to respond to.

One possible mechanism by which the central chemoreceptors might play a role in exercise hyperpnoea would be if their CO_2 response characteristics changed at the onset of exercise. There is some evidence for this being the case, with Poon and Greene (1985) and Cummin et al. (1986c) reporting that the ventilatory response to inhaled CO_2 was more marked during exercise; Cummin et al. (1986c) also demonstrated that the CO_2 sensitivity rose with increasing exercise work rate. On the other hand, both Casey et al. (1987) and Duffin &

McAvoy (1988) were unable to find any evidence for a change in central chemoreceptor threshold with exercise, Duffin & McAvoy (1988) reporting a CO_2 threshold value of around 45 mmHg. This would tend to disprove any role for the central chemoreceptors in the control of breathing during exercise.

Further evidence against a role for the central chemoreceptors in the control of exercise hyperpnoea comes from the study of patients with congenital central hypoventilation syndrome (CCHS). These patients do not increase their level of ventilation in response to hypercapnia or hypoxia (Paton et al., 1989; Shea et al., 1993b), but exhibit a normal ventilatory response to exercise (Paton et al., 1993; Shea et al., 1993a).

Central Command:

Zuntz and Geppert (1886) were the first to suggest that there may be areas in the brain above the medullary respiratory centres which increase respiratory centre activity in conjunction with activating skeletal muscle. Since then, evidence has slowly accrued in favour of this view: Favier et al. (1983a) investigated the effects of propranolol, morphine sulphate and phenobarbital on Phase 1 of exercise hyperpnoea in dogs, and reported that only phenobarbital, an hypnotic, reduced the amplitude of Phase 1, the other drugs having no effect. Adams et al. (1987b) demonstrated that electrically stimulated leg exercise induced a smaller rise in $\dot{V}_I$ during the first five breaths of the on-transient than a similar work rate of voluntary exercise.

Brice et al. (1988) compared Phase 2 kinetics for electrically stimulated and voluntary exercise in man and could find no difference, suggesting that central command was not important during this Phase of the hyperpnoeic response, while Galbo et al. (1987) reported that partial neuromuscular blockade induced a higher level of ventilation for a given $\dot{V}_{O_2}$. This they attributed to the higher level of central command required to exercise under the neuromuscular blockade. It should be noted that this study increased central command

whereas the three papers previously quoted were designed to reduce/abolish it. As such, it is possible that the rise in central command elicited by the neuromuscular blockade was sufficient to override the control mechanisms usually responsible for exercise hyperpnoea.

Perhaps the best evidence of a role for central command in controlling exercise hyperpnoea comes from the work of Eldridge et al. (1985). They studied the cardiorespiratory effects of stimulation of the hypothalamic motor centre in decerebrate cats. Stimulation of the hypothalamic motor centre by either electrical stimulation or the drug picrotoxin resulted in co-ordinated walking or running movements against a treadmill which were accompanied by a rise in $\dot{V}E$, the amplitude of which was related to the work rate of the exercise. Electrical stimulation demonstrated that the ventilatory response slightly preceded the onset of exercise, and a normal ventilatory response could be elicited during 'fictive locomotion', i.e. during stimulation after the motor nerves have been cut, so removing all locomotion. Under these conditions, the increase in ventilation could only be in response to the rise in central command produced by stimulation. It should be noted, however, that 'fictive locomotion' is associated with a pronounced hypocapnia (Eldridge et al., 1985)

It has also been postulated that the higher centres of the brain contain an intrinsic pathway which potentiates the hyperpnoeic response to a constant stimulus. This mechanism was termed afterdischarge by Eldridge (1974). It was first demonstrated by Gesell et al. (1942) who reported that following carotid nerve stimulation, ventilation took 44 seconds to return to normal, despite considerable hypocapnia from the excess ventilation. Eldridge and Milhorn (1980) investigated the response to different patterns of carotid sinus nerve stimulation in the paralysed vagotomised cat, using phrenic nerve discharge as a measure of respiratory drive. They demonstrated that on stimulation during expiration there was no direct effect on phrenic activity, but there were signs of gradual potentiation. This was more obvious when the carotid sinus nerve was stimulated on alternate breaths, with a marked rise in the phrenic nerve activity of the unstimulated breaths.

Short-term potentiation has been postulated as the control mechanism during Phase 3 of exercise, and as being responsible for the kinetics of the off-transient being longer than those of the on-transient, and dependent on the work rate and duration of the preceding work.

CONCLUSION: INTEGRATION OF CONTROL

As the above treatise demonstrates, the control of breathing during exercise is dependent on a complex sequence of events, originating in the numerous receptors which provide an input for the control of breathing. It is important to note that different circumstances will result in the stimulation of different receptors. One could hypothesise that, for example, a strong isometric contraction may activate intramuscular receptors and any central command pathways, while the contraction will occlude blood supply to the muscles, so greatly attenuating any signal from receptors sensitive to changes in blood gas composition or muscle metabolites. Conversely, it is possible that electrically stimulated low-intensity leg exercise in paraplegics at altitude would result in a marked hypoxic stimulus, activating the peripheral chemoreceptors, while the muscle afferent and central command inputs would be negligible.

Despite the wide range of hyperpnoeic stimuli which occur during exercise, the rise in ventilation tends to follow a set pattern as described above. There are some exceptions; Cross et al. (1979) reported that prior to carotid bifurcation denervation, the withholding of two breaths in anaesthetised, paralysed and artificially ventilated dogs produced a rise in $\dot{V}E$ due mostly to a fall in TE, whereas following denervation the rise in $\dot{V}E$ occurred later and was characterised by a rise in phrenic nerve activity.

In contrast, Gallagher et al. (1987) demonstrated that in man the pattern of breathing at a given level of ventilation was similar regardless of whether it was in response to exercise alone, or a mixture of exercise and hypercapnia. In a similar experiment, Mekjavic et al. (1987) could find no difference in the pattern of breathing elicited by exercise or exercise with hypoxia. This would suggest that there is a convergence of inputs at the level of the respiratory centre, resulting in the production of the ventilatory drive.

Such a statement begs the question as to how the various inputs interact to produce a single drive. Evidence does not favour a simple additive mechanism: studies into the ventilatory

responses of paraplegics (Adams et al. 1984a,b; Brice et al. 1988a), spinal denervation of dogs (Cross et al. 1982) and individuals with no muscle afferent nerve supply (Duncan et al 1981) could not demonstrate a reduction in exercise hyperpnoea. Similar results have been reported by studies investigating the removal of central command (Adams et al. 1984a, 1987; Brice et al. 1988b; Fernandes 1990) and carotid body resection (Whipp et al. 1980; Wasserman et al. 1975; Honda 1985), although the studies involving carotid body resection did demonstrate a change in the time-course of the ventilatory response, also confirmed by studies investigating the effects of hypoxia and hyperoxia on the kinetics of exercise hyperpnoea (Griffiths et al. 1986; Ward et al. 1987).

These results can, however, be explained by an occlusive control system, in which the level of exercise hyperpnoea is under the control of the strongest signal arising from the various receptors. Under such circumstances, it is possible for there to be no change in ventilation following the attenuation/ablation of an input, if that input is not dominant at that time. Should the input under investigation be dominant, the reduction in ventilation may still only be small if the next input be only slightly less strong than the dominant one. Such a model also provides an explanation for the results of studies which increase the activity of a specific signal, e.g. tendon stretch receptors (Jammes et al. 1981) or central command (Galbo 1987; Eldridge et al. 1985), induces a rise in ventilation. Under such circumstances, the increase in signal strength is sufficient to make it the dominant signal.

There is also evidence of signal interaction at a different level, as evidenced by the increase in gain of the central chemoreceptors seen during exercise. The increase in gain has been shown to be dependent on the work rate of the exercise (Cummin et al. 1986c), possibly due to modification of the receptor signal strength, by other input(s) to the respiratory centre, or by modification of receptor activity itself. Flenley and Warren (1983) and Weill and Swanson (1990) both report that hypoxic exercise attenuates the response to hypercapnia, Flenley and Warren (1983) suggesting that this is due to an increase in carotid body sensitivity to arterial P_{CO_2} oscillations.

The last level of integration occurs between the respiratory centre and the lung, and is responsible for determining the interaction between rate and depth of breathing by which the rise in ventilation is attained. An important input at this level arises from the lung and airway receptors: Favier et al. (1982) and Clifford et al. (1986) demonstrated that pulmonary denervation in dogs did not affect the ventilatory response to exercise, but did increase V_T and decrease f_{BR}. Eldridge et al (1985) reported a similar response following vagotomy in the cat, and Flynn et al. (1985) demonstrated a change in breathing pattern in ponies following hilar nerve denervation with no change in $\dot{V}_E$.

In conclusion, it is apparent that the control of breathing during exercise in multifactorial in origin, with a number of different levels of signal interaction resulting in a hyperpnoeic stimulus. This stimulus is then modified inputs from the lungs to determine the pattern by which ventilation will be achieved.

CHAPTER 2:

METHODOLOGY AND APPARATUS.

INTRODUCTION:

One of the basic tenets of research is that the techniques used are both valid and reproducible. Included in this is the assumption that the equipment used is reliable and accurate. Furthermore, it is essential the techniques used in any experiment do not themselves adversely affect the results by exerting a direct influence over the relevant variables. It therefore seems sensible to include at this stage of the thesis a section with the express purpose of putting the reader's mind at rest on these matters.

Approval was sought from the joint UCL/UCH committee on the ethics of human research Middlesex hospital clinical investigations panel and granted (Application No. 2599). All subjects were required to fill in a health questionnaire and sign an informed consent form prior to performing each study.

SUBJECTS:

The main thrust of this thesis is an investigation into the ventilatory responses to an increase in exercise intensity, against a background of rest or mild exercise. It would therefore seem advisable to study a group of subjects who are reported to have a large initial ventilatory response to exercise and a high capacity for work under the anaerobic threshold. These criteria are filled by highly trained athletes (Krogh & Lindhard, 1913; Åstrand & Rodahl, 1986).

An enthusiastic source of subjects was found in oarsmen, initially from University College Boat Club and later from University of London Boat Club and Vesta Boat Club. These oarsmen were all competitive at levels ranging from Senior III to international level, training at least five times a week. Use of these subjects also naturally restricted other factors which are known to affect the respiratory system; none of the subjects smoked or was clinically obese and they were between eighteen and thirty five years old (the kinetics of the later ventilatory response have been shown to slow with increasing age; Babcock et al., 1994).

It was expedient to exclude oarswomen from the study as it is well known that CO_2 sensitivity for women changes during the menstrual cycle (White et al., 1983). In addition, amenorrhoea is known to occur in a significant number of competitive oarswomen. Although in the majority of studies each subject was used as their own control and all tests were performed on the same day, interpretation of the results is inevitably easier without these added complications.

There is one caveat in using highly trained athletes as subjects in experiments: there is an abundance of literature reporting that the movements associated with a mode of exercise can significantly influence the subject's pattern of breathing (phase locking: Mahler et al., 1991a, b). This is discussed in detail in Chapter 3; suffice it to say here that phase locking is usually seen in highly trained individuals , but only in modes of exercise with which they

regularly train. It is unusual to find evidence of phase locking in a subject performing an exercise with which he is not familiar.

Not all the subjects used in this thesis were oarsmen. Other trained subjects were used in some of the experiments, drawn from the workforces of the Departments of Physiology and Medicine at University College London and University College Hospital respectively. These subjects were identified in the Methods section of each Chapter and care was taken to ensure that their responses to the exercise protocols did not differ significantly from those of the oarsmen.

In addition, the subjects used in Chapter 6 were all sedentary. This was unfortunate and was due to the time when the tests were performed; May and June 1994. This period of the year is probably the busiest for a collegiate oarsmen, with college examinations coinciding with the regatta season. Availability of specialist equipment used in this study (The Mills-McIntyre Postural Swaymeter) forced us to use what subjects were available, including some women. This study did not involve exercise and care was taken to ensure that the ventilatory responses seen in these subjects were similar to those seen in oarsmen (reported in Chapter 2).

APPARATUS:

Exercise testing was performed using a custom-built set-up, consisting of a number of different pieces of equipment. These are described below. Data from the equipment was analysed by a custom-written computer program and the information saved to disc for later analysis. This program is explained in Appendix A, validated in Appendix B and listed in Appendix C. In addition, data were saved on magnetic tape as a backup. The following pieces of equipment were used:

LÖDE CYCLE ERGOMETER:

This is an electrically braked cycle ergometer, workload range from 0 to 400 W. One of the characteristics of electrically braked cycle ergometers is that the desired workload is relatively unaffected by pedal frequency, unlike friction braked cycle ergometers, where the workload increases in proportion to the pedal frequency. There will inevitably be some increase in workload associated with an increase in pedal frequency with electrically braked cycle ergometers like this, due to the internal resistance of the machine. So long as the changes in pedal frequency are small the associated changes in workload will not be significant.

One problem with an electrically braked cycle ergometer is its calibration. We were unable to calibrate the cycle ergometer used in this study, due to the inherent difficulties involved. This does limit the validity of the results obtained, except that each subject was used as his own control in two tests, each using the same workload and there was no significant difference between the steady-state cardiorespiratory responses of the two tests. It would therefore seem safe to say that although the absolute workload may not be known with any certainty, any deviation from the reported value was consistent.

A cycle ergometer was preferred over a treadmill mostly on grounds of the size and availability of equipment, but also because respiratory-locomotor coupling would appear to be more common when running than when cycling (See Chapter 1 for details). This was also the reason that a rowing ergometer was not used: respiratory-locomotor coupling is associated with the mode of exercise most commonly used and does not appear to transfer between exercise modes (Again, see Chapter 1 for details).

During those tests where subjects were required to maintain a constant pedal frequency, feedback was via a speedometer rather than a metronome, as used in some studies. This is as a result of the findings of Bechbache & Duffin (1977), who reported a 33% rise in respiratory-locomotor coupling when a metronome was used to maintain pedal frequency instead of a speedometer. Haas et al. (1986) reported that movement (tapping a finger) in time to a metronome or music significantly reduced the coefficient of variation of breath interval (T_{TOT}) and produced significant correlation between breath and beat intervals. They suggested that the musical signal acted as a zeitgerber, subsequently reinforced by movement. From their results and those of Steinacker et al. (1992), the converse could also be true.

Following complaints from the subjects, the cycle ergometer was fitted with drop handlebars and a racing saddle. This did improve the seating position of the subject, but there was still considerable room for further improvement. However any further improvements would have involved major changes to the structure of the ergometer.

f_{PED} was monitored on a breath-by-breath basis using a frequency-voltage converter (Maplin Technologies No. YQ67X).

MOUTHPIECE AND VALVEBOX:

During the tests subjects breathed through a Hans Rudolph mouthpiece (No. 9013) connected to a Hans Rudolph 2,700 series 2-way non-rebreathing valve. Dead space of this apparatus was 103 ml. Subjects wore a noseclip (Hans Rudolph No. 9015) throughout. Pressure difference across the apparatus at a flow of 300 $l.min^{-1}$ was 2.1 cmH_2O on inspiration and 2.4 cmH_2O on expiration.

Measuring expired gases via a mouthpiece is not without its disadvantages: it has been shown by some investigators that, compared to normal resting breathing, $\dot{V}E$ and VT may be increased by as much as 30% by the act of breathing through a mouthpiece while fBR is relatively unaffected (Weissman et al., 1984; Askazani et al., 1980 and Maxwell et al., 1985) all report that use of a mouthpiece and noseclip result in an increase in VT and $\dot{V}E$. Gilbert et al. (1972), on the other hand, report VT as increasing, fBR as decreasing and $\dot{V}E$ remaining relatively constant with breathing using a mouthpiece and noseclip compared to impedance plethysmography.

Impedance plethysmography might well have given more accurate results, but I am not aware of it having been validated for use in hyperventilation during exercise. Furthermore, one was not available throughout the entire length of the study.

2X FLEISCH NO. 4 HEADS IN CONJUNCTION WITH 2X GOULD PNEUMOTACHOGRAPHS:

Inspiratory and expiratory flow were measured separately using two heated Fleisch flow transducer heads (No. 4) connected to two Godart pneumotachographs (Gould). The Fleisch head consists of a metal tube (internal diameter = 42 mm) into which is inserted a metal gauze. Gas flow through the head creates a pressure differential across the gauze, proportional to the flow rate (assuming a fixed gas concentration). The pressure difference

is then fed to the pneumotachograph via two thin-gauge polythene tubes. It is listed in its specifications as accurate to 600 $l.min^{-1}$ for $\dot{V}E$ and 5 l for VT.

The Godart Gould pneumotachograph is a fast responding (0% to 90 % response time = 15 msec) differential pressure transducer, the flow range of which is governed by the choice of Fleisch head (preferred head produces maximal pressure of 6 $cm.H_2O$), with an output range of -5 to +5 V. Drift < 10 mV/hour (assuming constant ambient temperature) and accuracy = ± 1 %.

One of the problems with using a Fleisch head is that the voltage output is not linear over the entire physiological range, but rather is curvilinear, as shown in *Fig.2.1*. Under normal circumstances, this problem would be rectified by changing the Fleisch head for a smaller one, but the range of flows occurring during a test made this impracticable (especially for the tests reported in Chapter 7: $\dot{V}E$ typically varied between 10 l/min and 140 l/min, but higher and lower values were occasionally recorded). To circumvent this problem, the pneumotachographs were calibrated at four flows. As can be seen from the results of Appendix A, this was highly successful.

By integrating the expiratory flow, **VT** could be measured on a breath-by-breath basis, in conjunction with **TI**, **TE** and **TTOT**. From these values (and the barometric pressure and saturated water vapour pressure) $\dot{V}E$ could be calculated, both as **BTPS** and **STPD** (for calculation of $\dot{V}o_2$ and $\dot{V}co_2$). For further details of these calculations, please refer to appendices A, B and C.

It should be noted that only one Fleisch head was available for approximately half of this project. During that time programs EXTEST 1 and EXTEST 2 were used for testing. EXTEST 3 was used with two Fleisch heads.

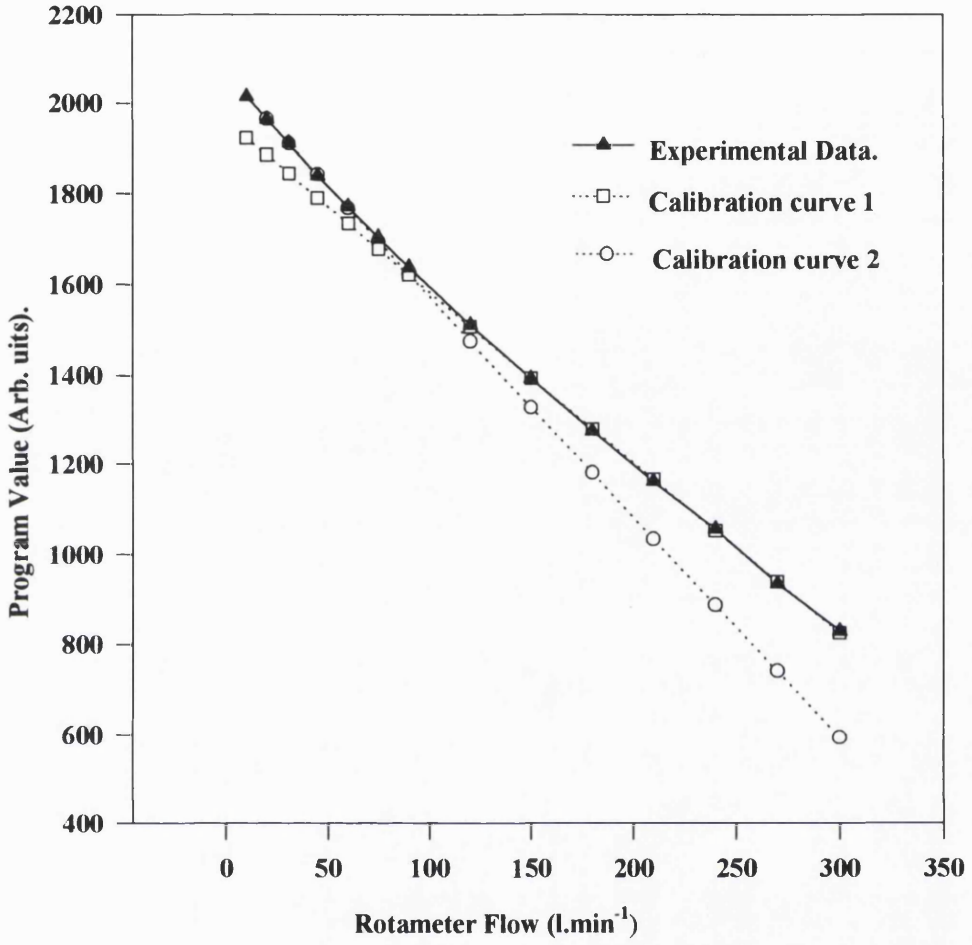


Figure 2.1: Response characteristics of one of the Fleisch heads used in this project. Output voltage is expressed as analogue to digital converter number. -10 V = 0, 0 V = 2040 and +10 V = 4080.

AIRSPEC 2.600 SERIES MASS SPECTROMETER:

This is a quadropole mass spectrometer, incorporating a sophisticated range of analysis software. The mass range of the instrument was 2 to 200 amu with a sensitivity of 10 ppm. The linearity was < 1% over the calibrated range, drift was < 1%.24 Hr^{-1}. Sample flow rate was 37 $ml.min^{-1}$, delay was 340 msec and 0% to 90% response time was < 80 msec (Airspec manual).

The software incorporates a multiplexer, allowing the simultaneous analysis of more than one gas and a normalisation feature which corrects for any changes in sample inlet pressure. This, in conjunction with the fast response characteristics of the analyser makes it ideal for the monitoring of tidal changes in P_{O_2} and P_{CO_2} for the calculation of $\mathbf{P_{ET,O_2}}$ and $\mathbf{P_{ET,CO_2}}$.

It should be noted that the airspec mass spectrometer was not available for the tests described in Chapter 3, but was used in all subsequent tests.

CALIBRATION GASES:

All gas analysers were subjected to a two-point calibration using air (BOC; 20.93 % O_2, 0.33 % CO_2) and a special gas (BOC; 12.66 % O_2, 6.03 % CO_2). O_2 and CO_2 gas concentrations were determined using the Lloyd technique.

MIXING BOX:

Expired gases were passed via elephant tubing (Internal diameter = 40 mm, volume = approx. 0.5 l) to a mixing box (Airspec 2,400), the volume of which was 10 l. This allowed the measuring of $\mathbf{P\bar{E}O_2}$ and $\mathbf{P\bar{E}CO_2}$.

MEDISHIELD MS2 MASS SPECTROMETER:

This is another quadropole mass spectrometer and so operates on the same principle as the Airspec 2 600 described above. It was used to measure $\mathbf{P\bar{E},O_2}$ from the end of the mixing box, used in the calculation of $\dot{V}_{O_2}$. Being older, however, the supporting software is not as sophisticated: It would only monitor one gas at a time (mass range = 1 to 50 amu) and had

no capability to correct for drift or changes in probe pressure. It had a delay of < 250 msec and a 0% to 90% response time of < 50 msec. Drift was 3 $\%.Hr^{-1}$, but tended to be less if switched on for at least an hour prior to performing a test.
Sampling rate is 15 to 40 $ml.min^{-1}$. Accuracy = ± 0.2 %. This mass spectrometer was calibrated with the 2 gases described above.

BECKMAN LB-2 CO_2 ANALYSER:

This is a non-dispersive infra-red CO_2 analyser, typical sample rate = 500 $ml.min^{-1}$. 0 % to 90 % response time < 130 msec, it is accurate to 0.01 % and drift is typically 0.5 % over 8 hours. It was used to measure $\bar{PE}CO_2$ from the end of the mixing box, used in the calculation of $\dot{V}o_2$ and $\dot{V}co_2$.

FLOWPAST SYSTEM:

In some studies it was necessary to maintain P_{ET},CO_2 close to normal levels during hyperventilation. This was achieved by adding CO_2 to the inspirate by way of a flowpast system. The flowpast system consisted of a pneumatic pump, the exhaust of which was connected to a long tube. A second tube joined this at right angles and connected to the inspiratory side of the valvebox. If required, CO_2 could be added to the inlet of the pump (thereby allowing good mixing) from a gas cylinder. The flow from the pump was approx. 75 $l.min^{-1}$. The exit from the system was put outside a window, thereby reducing the possibility of a build up of CO_2 in the ambient room air.

A-I LIFE TRACE 12 ECG MONITOR:

This is a three-lead electrocardiograph (ECG) monitor with a worst case patient fault current of less than 2 μA. It provides an on-line display of the ECG trace as a moving picture on an oscilloscope and the heart rate on a digital display. Heart rate is calculated by counting the number of QRS complexes in a given time (not listed in technical specifications). A slew-rate limiter is used to eliminate fast artefacts and a 2-pole low-pass filter is used to eliminate 50 Hz and skeletal muscle noise.

DATA ACQUISITION:

Data from the analysers described above was saved on magnetic tape using a RACAL DS-7 magnetic tape recorder; tape speed 1 3/4".sec^{-1}. The data was also analysed by a custom-written exercise testing program using an IBM Pc (DSC turbo) incorporating an analogue to digital converter (Amplicon Pc26a).

The exercise testing program went through three major metamorphoses (EXTEST 1 to 3) and these are presented in appendices 2.1 to 2.3. The programs are also presented in flow diagram form in appendices 3.1 to 3.3 and are validated in Appendix 1.

Data generated by the exercise test programs was saved to disc in a format compatible with Microsoft EXCEL 4.0, and data manipulation and statistics were performed using EXCEL 4.0 spreadsheets and analysis tools.

The equipment set-up used is shown in *Fig. 2.2.*

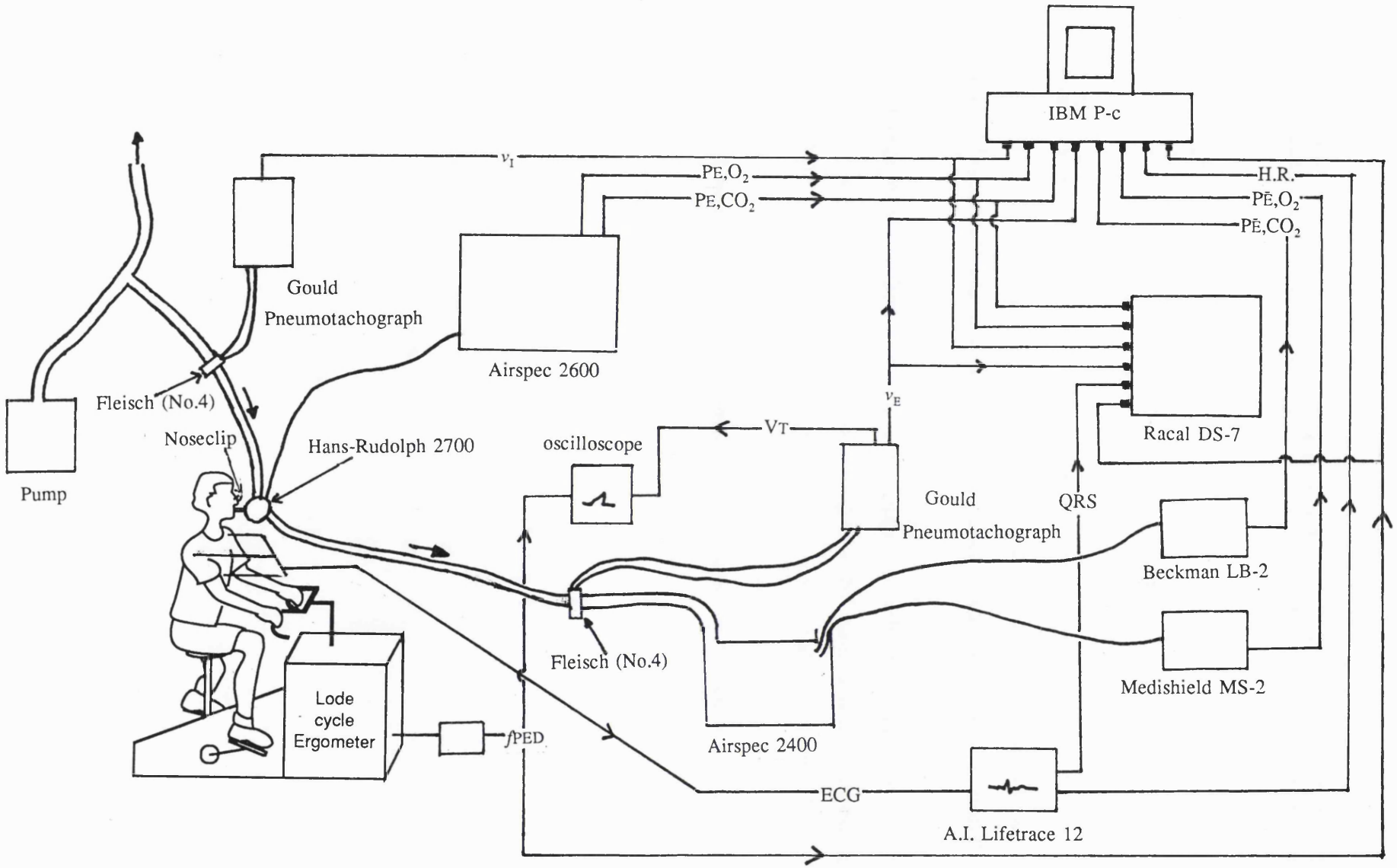


Figure 2.2: Representation of the equipment used in the majority of tests.

PROTOCOLS:

There are some general points pertaining to the protocols used in this thesis:

Every test started with a period of rest to allow subjects to acclimatise to the apparatus. This also made it possible to detect subjects who were sufficiently apprehensive about the study to hyperventilate spontaneously at rest. If this occurred, the test was abandoned.

All changes occurring during the tests were signalled by verbal command. It was surmised that the subjects would be more used to reacting to verbal commands than, for example, a flashing light, so reducing the surreal nature of the experimental procedures. The mode of command does not affect the ventilatory response to the start of exercise (Jensen et al, 1971), but as a precaution, the commands were given by the same person in a well modulated voice.

CONCLUSIONS:

The apparatus, although having some unusual elements, was appropriate for the intended purpose. The use of the MS-2 mass spectrometer to measure $P\bar{E}O_2$ may seem a little excessive, but it was the only O_2 analyser available.

The validation of the values produced by the EXTEST 3 program compare well with those from the spirometer (see Appendix A). One can therefore only conclude that the equipment used was capable of accurately monitoring the changes in pulmonary gas flow and concentrations encountered during this project, and that the data acquisition programs were capable of performing the necessary calculations.

CHAPTER 3

THE EFFECT OF PEDAL FREQUENCY ON EXERCISE RESPONSE

INTRODUCTION:

A central tool in the study of the control of breathing during exercise is the exercise test itself: it is important that the subjects are presented with a consistent, reproducible stimulus if the results obtained are to be collated as a group, or if valid comparisons are to be made with results obtained with a different population group or using a different test protocol. The choice of which mode of exercise to choose for a study is subject to a number of constraints, including the availability of equipment, reproducibility of workloads, ease of use, subjects' familiarity with the mode of exercise and the hypothesis to be tested by the study itself. These constraints have resulted in cycle ergometry and treadmill running emerging as the two most commonly used modes of exercise, although other modes of exercise have been used, e.g. rowing ergometer, ski-walking on a treadmill, arm cranking. These, however, involve a greater degree of co-ordination from the subject which may affect the results adversely.

A further consideration when deciding on the appropriate mode of exercise is whether the mode of exercise itself exerts an effect on the particular exercise responses being investigated. An example of this can be seen with one of the more common uses of exercise testing: determination of a subject's $\dot{V}O_{2,max}$. A number of authors have reported that cycle ergometry elicits a lower value of $\dot{V}O_{2,max}$ than does treadmill running (e.g. Davis & Kasch, 1975; McArdle et al., 1973; Faulkner et al., 1971), although Hermansen & Saltin (1969) and Åstrand & Rodahl (1986) both report no difference in $\dot{V}O_{2,max}$ measured using these two modes of exercise. This difference in results may be partly due to differing levels of familiarity with cycling between the subject groups. Further evidence for this comes from Withers et al. (1981) who reported that trained cyclists achieved a 4.5% higher value for $\dot{V}O_{2,max}$ when exercising on a cycle ergometer than on a treadmill, while in trained runners this trend was reversed, with treadmill running eliciting a 10.4% higher value for $\dot{V}O_{2,max}$ than cycle ergometry.

Exercise responses can also be affected by the mode of exercise employed. It is well established that at similar submaximal workloads arm cranking elicits a higher heart rate than cycle ergometry (Åstrand & Rodahl, 1986), while Weiler-Ravell et al. (1983) reported that the initial responses for both heart rate and $\dot{V}E$ were attenuated when exercise was performed in the supine position rather than upright. There is evidence that changes in stride frequency, e.g. when comparing walking and running at equivalent metabolic loads, can affect a subject's ventilatory response (Berry et al., 1989; Caretti et al., 1992 and McMurray & Ahlborn, 1982), although this is not a universal finding (McMurray & Smith, 1985). The change in ventilatory response is associated with an increase in fBR, with running resulting in a lower P_{ET,CO_2} and higher RER than walking (Caretti et al., 1992; McMurray & Ahlborn, 1982; McMurray & Smith, 1985).

One likely reason for this influence of stride frequency over the ventilatory response to exercise is that runners breathe in time with their stride pattern (Bramble & Carrier, 1983; Bechbache & Duffin, 1977; McMurray & Ahlborn, 1982; McMurray & Smith, 1985). Bramble & Carrier (1983) reported this phenomenon to be more common in highly trained endurance runners than untrained individuals, respiratory-locomotor coupling occurring as early as the fourth stride of running in highly trained subjects. Furthermore, they reported that breathing was coupled to stride pattern, not the other way round.

The ventilatory response to rowing has been investigated by Mahler et al. (1991a, b) and again experienced rowers demonstrate a high level of coupling between respiratory events and certain parts of the rowing stroke, with the incidence of coupling rising with experience. Steinacker et al. (1993) also reported considerable respiratory-locomotor coupling in a group of highly trained oarsmen. They reported that while at low and moderate workloads breathing pattern was constrained by the stroke frequency, at high workloads it was possible for stroke frequency to be driven up by fBR.

Respiratory-locomotor coupling is also common in trained cyclists (Kohl et al., 1981), the incidence falling with decreasing experience. There is also evidence that pedal frequency directly influences a subject's exercise responses, with the metabolic cost of cycling increasing with increasing pedal frequency (Hagan et al., 1992; Casaburi et al., 1978b; Gaesser & Brooks, 1975; Takano, 1988), although Sipple & Gilbert (1966) were unable to find any effect attributable to pedal frequency. Takano also reported pedal frequency as directly influencing $\dot{V}_E$, although Casaburi et al. (1978) could find no evidence of this.

It would therefore appear that trained subjects phase couple their breathing to their movements within their sport. Whether this coupling is transferable between exercise modes remains to be seen. Berry et al. (1989) was unable to demonstrate any difference in the ventilatory response to exercise in runners cycling at 60 vs. "90 RPM" or in cyclists walking/running at equivalent metabolic loads.

Steinacker et al. (1986) compared rowers' and cyclists' exercise responses on both modes of exercise and reported rowers as achieving a higher $\dot{V}o_{2,max}$ than cyclists on the rowing ergometer and vice versa. Szal et al. (1989) reported rowers as having a higher ventilatory response to both maximal and submaximal exercise when rowing than when cycling.

PURPOSE OF EXPERIMENT:

The purpose of the experiment was to investigate:

(i) Whether changes in pedal frequency would affect the metabolic cost of cycling at a given workload;

(ii) Whether, having made allowances for any changes in the metabolic cost of pedalling, changes in pedal frequency affect the ventilatory response to exercise.

(iii) Does the act of pedalling directly affect the timing of respiratory events, and therefore exert a direct influence over a subject's pattern of breathing that may compromise the validity of the results.

Preliminary findings of this study have appeared in abstract form (Howell & Cross, 1993b)

METHODOLOGY:

SUBJECTS:

Six subjects took part in this study; their anthropometric data are presented in *Table 3.1.* All subjects exercised regularly; three were members of the college rowing club, one was a club-level fell runner, one was a squash player and one was a circuit training instructor.

SUBJECT	AGE	HEIGHT	WEIGHT	SPORT
A	19	1.8	84.2	ROWER
B	26	1.87	75.8	ROWER
C	22	1.9	75	ROWER
D	29	1.76	66	FELL RUNNER
E	24	1.74	76	CIRCUIT TRAINER
F	49	1.77	71.8	SQUASH PLAYER

Table 3.1: Anthropometric data for the subjects used in Chapter 3.

PROTOCOLS:

Each subject was scheduled to perform eight submaximal exercise tests. These tests all had the same basic protocol, starting with 3 min of rest. This allowed the determination of the subjects' basal level of activity prior to the start of the exercise period, and also allowed the subjects to get used to breathing through a mouthpiece while wearing a nose clip. This period was followed by a continuous incremental submaximal exercise test consisting of four 3 min stages at workloads of 50, 100, 150 and 200 W. The start of exercise was signalled by a verbal command ("Start exercising now"), as were the changes in exercise intensity ("Workload going up/down now").

In three of the eight tests, subjects were allowed to choose their own pedal frequency (Collectively, "FREE" tests; individually, "FR1", "FR2" and "FR3" tests), while in the

other five, subjects were asked to pedal at a fixed pedal frequency of 30, 50, 60, 70 or 90 rpm. The free tests were the first, fifth and eighth tests to be performed in all subjects. The order of the other tests were randomised between subjects to minimise any possible learning or training effect.

In addition to the repetition of the "FREE" tests, subject A performed 2 tests at "60 RPM", subject E performed 2 tests at both "90 RPM" and "30 RPM" and subject D performed 2 tests at 70 rpm.

APPARATUS:

The apparatus was used as described in the previous Chapter, with the exception of the Airspec 2600 mass spectrometer. This was not available at the time. As a result, there are no data for P_{ET,O_2} or P_{ET,CO_2}. Data acquisition program EXTEST 1 (See Appendix A) was used in this study. As a result, data for $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and RER were available only every 20 sec.

DATA ANALYSIS:

Resting values: The mean values of $\dot{V}_E$ (BTPS), f_{BR}, V_T, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and f_C were calculated for the last minute of the pre-exercise resting period.

Initial Responses: The traditional view of the initial ventilatory response to exercise (an abrupt increase to a plateau) would suggest that a more accurate measurement of the magnitude of the initial response would be the mean response over the first 15-30 sec of exercise (Dejours, 1963; Whipp & Ward, 1982, Whipp et al., 1982). However the results discussed subsequently in Chapter 5 demonstrate that this method is not appropriate for $\dot{V}_E$ for this highly trained subject population. The initial responses for $\dot{V}_E$ to the start of

exercise was taken as the maximum value over the first three breaths following the start of exercise. Results from the same breath were taken as the initial response for VT and f_{BR}.

The initial response for f_C was determined on a test-by-test basis, as it was not always apparent. Characteristically, the initial response presented as a notch in the otherwise smooth monoexponential rise in heart rate seen at the start of exercise.

The initial responses to the transitions from rest to 50 W were interpolated over 1 sec intervals and time aligned and the mean responses for all subjects then determined.

Steady-state response: Steady-state values for each parameter at each workload were calculated as the mean value over the last 30 sec of each stage. Linear regression through the analysed data at 200 W for each tests was used to determine whether the subject was truly in steady-state at that time.

Respiratory-Locomotor Coupling: To detect any unconsciously occurring co-ordination between pedalling and breathing, the number of pedal revolutions in each breath was calculated (After Kohl et al., 1981). The number of complete pedal revolutions was discarded and the remaining incomplete revolution (expressed as a decimal) occurring in each breath was then allocated to one of the five ranges below:

RANGE 1: Remaining portion = 0 to 0.099 and 0.9 to 0.99
RANGE 2: Remaining portion = 0.1 to 0.19 and 0.8 to 0.89
RANGE 3: Remaining portion = 0.2 to 0.29 and 0.7 to 0.79
RANGE 4: Remaining portion = 0.3 to 0.39 and 0.6 to 0.69
RANGE 5: Remaining portion = 0.4 to 0.59

For example, if f_{BR} for a breath was 17.3 min^{-1} and mean f_{PED} during that breath was 88.3 min^{-1} then f_{PED}/f_{BR} = 5.104. The incomplete portion of the pedal cycle = 0.104 and the breath would be allocated to RANGE 2. The time bin over which the breaths were analysed

was either the entire exercise period of the test, or the 30 sec of exercise used for the calculation of steady-state values for a particular workload.

There are limitations to the strength of this method of analysis, most notably in that the time bin covered by each of the ranges is inversely related to the pedal frequency. Also, it could be argued that each pedal revolution contains two end-points: top dead centre for both the left and the right foot. It could therefore be argued that breaths falling into RANGE 5 should be considered as significant as well. This is, however, debatable, as Bramble & Carrier (1983) report that runners who tightly couple breathing and gait are "footed", and use even coupling ratios.

The cross-correlation technique, used by Bechbache & Duffin (1977) was not used following publication of its limitations (Yonge, 1994).

Pattern of breathing: As a simplification of the method used by Kay et al. (1975a, b) and Takano (1988), mean inspiratory and expiratory times (TI & TE respectively) were calculated for four ranges of tidal volume for each exercise test. These were:

RANGE A: 0.75 l to 1.249 l
RANGE B: 1.25 l to 1.749 l
RANGE C: 1.75 l to 2.249 l
RANGE D: 2.25 l to 2.749 l

The strength of this analysis could have been increased by expressing VT as a percentage of vital capacity rather than as absolute values. Unfortunately vital capacity was not measured. This was an oversight. Once it had been realised the subjects were not available for testing.

Statistical analysis: Any significant difference ($p < 0.05$) between resting values for the different tests and the effect of pedal frequency on the magnitude of the initial response was determined using a single factor ANOVA.

The influence of workload and pedal frequency on the cardiorespiratory and metabolic responses to exercise and the influence of pedal frequency on subjects' patterns of breathing were determined using a two-factor ANOVA with repeated measures and multiple regression techniques.

The relative proportion of breaths falling into RANGE 1 was compared with a random distribution (i.e. 20%) using the X^2-test to test for a significantly high incidence, indicative of respiratory-locomotor coupling.

RESULTS:

All subjects performed the "30 RPM", "60 RPM", "90 RPM" and 2 FREE tests. Subjects A and E did not perform the 50 rpm test and subject E did not perform the 70 rpm test. As a result, statistical comparisons were made between the "30 RPM", "60 RPM", "90 RPM" and the third "FREE" tests unless otherwise stated.

RESTING VALUES:

The resting values of $\dot{V}_E$ (BTPS), f_{BR}, V_T, $\dot{V}_{O_2}$ (STPD), $\dot{V}_{CO_2}$ (STPD) and f_C were calculated and compared using a one-factor ANOVA. The group means, standard errors and *p*-values are presented in *Table 3.2*. As was expected, there was no significant difference between the resting values of the four tests.

	30 RPM	60 RPM	90 RPM	FREE
f_C	67.4 ± 6.0	65.0 ± 5.1	69.7 ± 7.6	63.2 ± 4.1
$\dot{V}_E$	12.59 ± 1.19	12.08 ± 0.87	12.58 ± 1.25	12.84 ± 0.41
V_T	1.33 ± 0.2	1.05 ± 0.01	1.13 ± 0.21	0.98 ± 0.07
f_{BR}	11.8 ± 1.7	12.3 ± 1.2	12.3 ± 1.1	14.1 ± 1.3
$\dot{V}_{O_2}$	0.48 ± 0.03	0.44 ± 0.02	0.51 ± 0.01	0.44 ± 0.02
$\dot{V}_{CO_2}$	0.37 ± 0.04	0.34 ± 0.03	0.37 ± 0.04	0.34 ± 0.01

Table 3.2: Group mean (± S.E.) resting values before the start of each test (n = 6).

When resting f_{BR} was compared between rowers and non-rowers, the rowers had a significantly lower f_{BR} ($p < 0.05$, see *Table 3.3*), despite having a significantly higher resting $\dot{V}_E$.

SUBJECT	A	B	C	D	E	F
f_C	87	68	75	51	58	59
$\dot{V}_E$	16.4	12.2	12.0	12.2	10.8	11.5
VT	1.32	1.50	1.15	0.74	0.98	0.89
f_{BR}	13.5	8.3	10.5	17.2	13.2	13.3

Table 3.3: Mean resting values of f_C, $\dot{V}_E$, VT and f_{BR} for each subject.

EXERCISE:

Pedal frequency: f_{PED} was maintained close to its target levels (See *Table 3.4*) for most of the fixed frequency tests. The exception was the onset of exercise; commonly associated with a slight overshoot (See *Fig. 3.1*). During the "FR2" and "FR3" tests, f_{PED} rose with increasing workload. There did appear to be a learning effect: f_{PED} was significantly lower in "FR3" than in "FR2" (See *Table 3.4*).

	30 RPM	60 RPM	90 RPM	FR2	FR3
50 W	30.8 ± 0.2	60.2 ± 0.3	91.4 ± 0.9	78.8 ± 10.1	69.2 ± 7.9
100 W	30.8 ± 0.3	60.0 ± 0.3	91.1 ± 0.3	86.1 ± 11.7	74.4 ± 6.1
150 W	31.0 ± 0.4	60.5 ± 0.2	91.3 ± 0.6	93.3 ± 13.8	78.2 ± 5.7
200 W	30.7 ± 0.4	60.6 ± 0.2	90.0 ± 0.8	99.4 ± 16.4	81.9 ± 5.8

Table 3.4: Mean (± S.E.) f_{PED} during the steady-state at each workload.

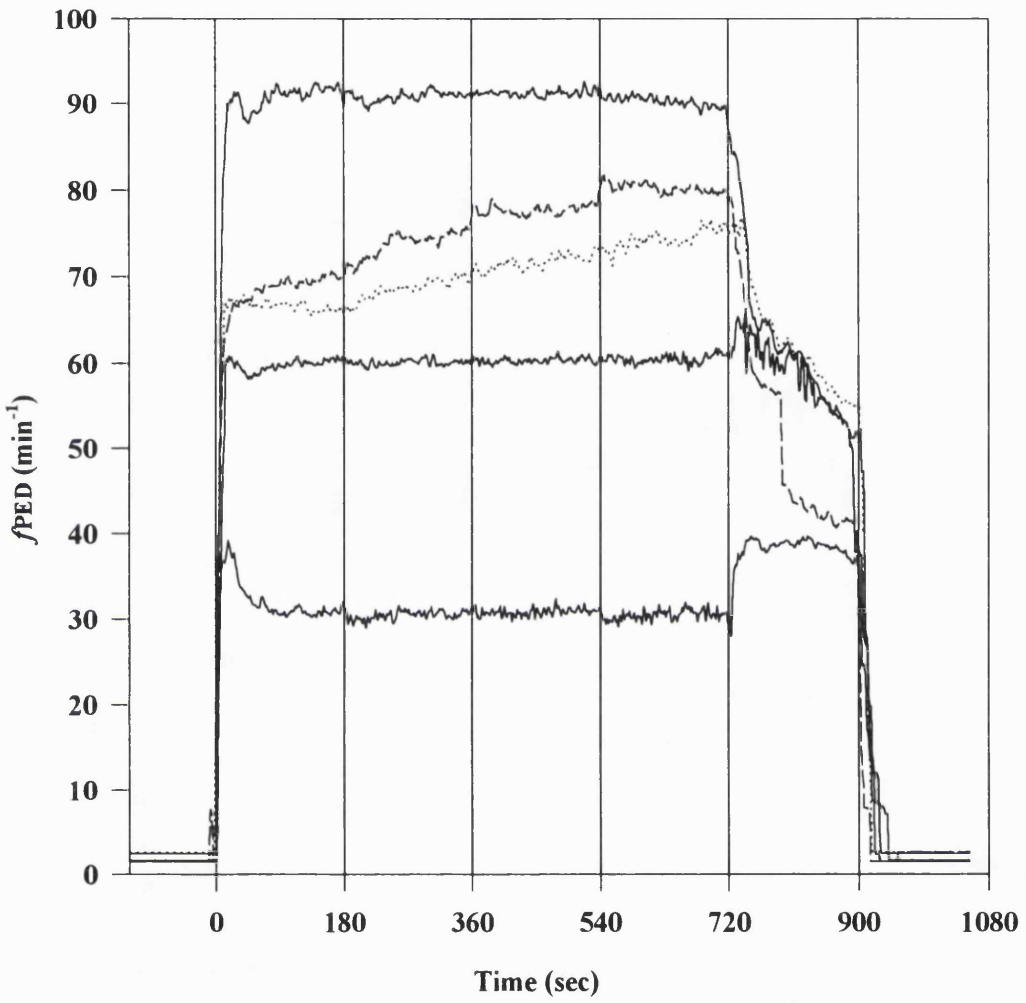


Figure 3.1: Mean interpolated *f*PED for "30 RPM", "60 RPM", "90 RPM", "FR2" and "FR3" tests. Minor differences in timing for changes in workload has resulted in blurring of non steady-state responses. Time 0 represents the onset of exercise. The "30 RPM", "60 RPM" and "90 RPM" tests are obvious from the scale. "FR2" test is the dotted line while "FR3" test is the dashed line.

Minute ventilation: An example of the breath-by-breath changes in $\dot{V}E$ during the "30 RPM", "60 RPM", "90 RPM" and "FR2" tests for one subject are presented in *Fig.3.2* and the mean interpolated responses are presented in *Fig. 3.3*.

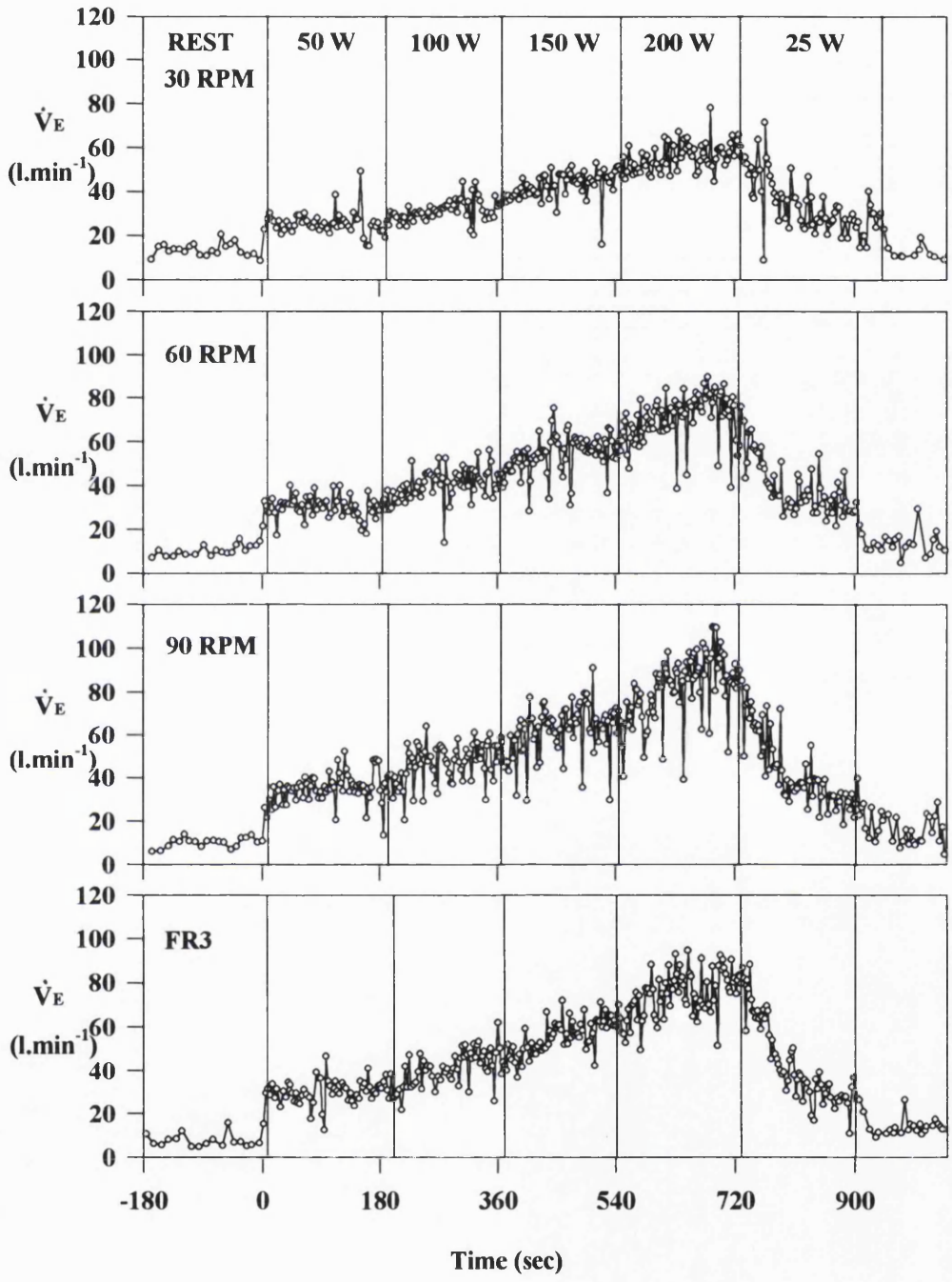


Figure 3.2: Breath-by-breath data for $\dot{V}_E$ from the "30 RPM", "60 RPM", "90 RPM" and "FR2" tests performed by subject B. Graphs are temporally aligned, lines denote changes in exercise intensity. Each stage lasted approx. 3 min.

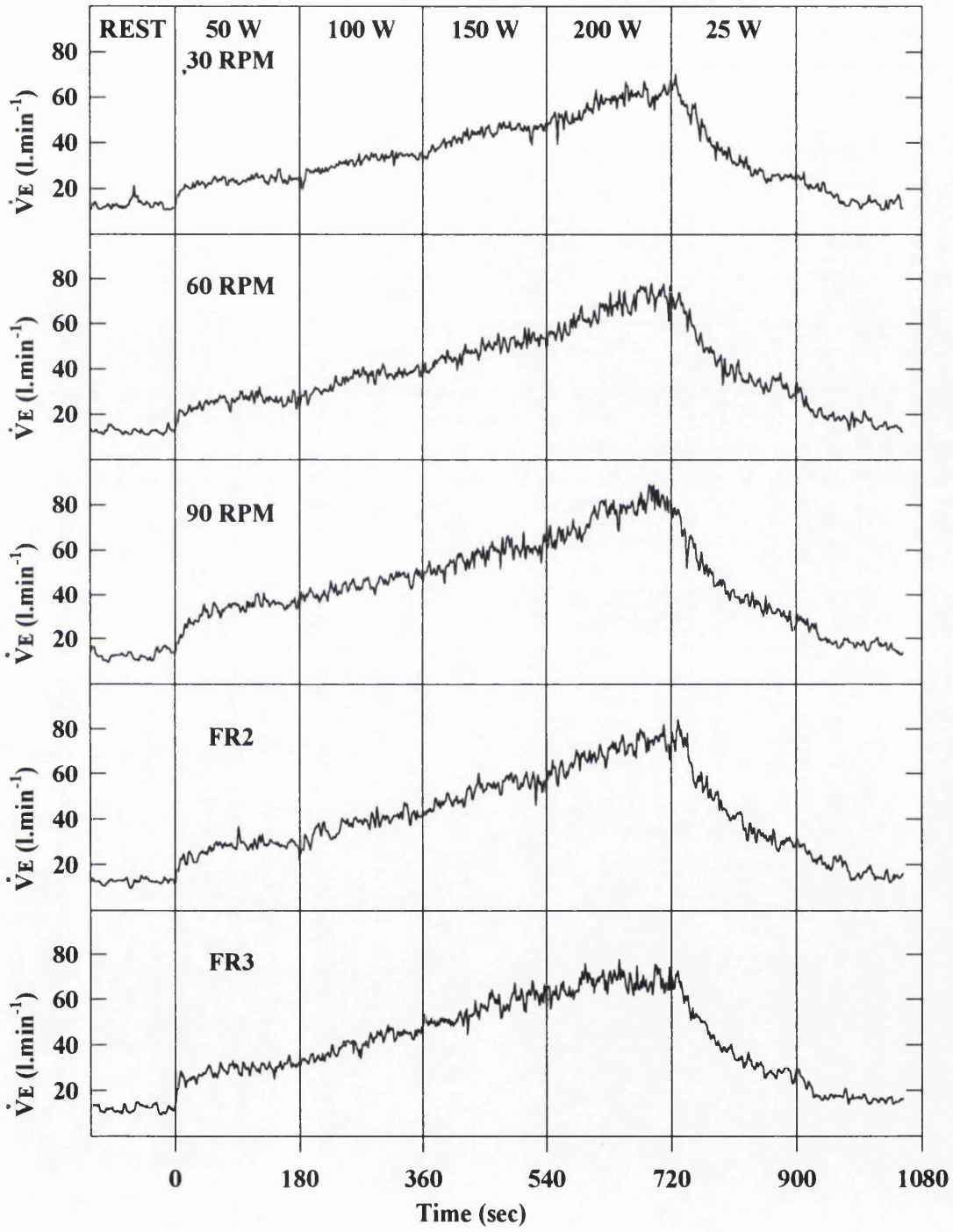


Figure 3.3: Mean interpolated data for $\dot{V}E$ from "30 RPM", "60 RPM", "90 RPM", "FR2" and "FR3" tests. Graphs are temporally aligned. Each stage lasted approx. 3 min. Minor differences in timing for changes in workload has resulted in blurring of non steady-state responses. Time 0 represents the onset of exercise.

Initial ventilatory response to the onset of exercise: $\dot{V}E$ increased abruptly in conjunction with the start of exercise (see *Table 3.5*, *Figs. 3.4 & 3.5*). Analysis using a single factor ANOVA with repeated measures demonstrated that the magnitude of the initial ventilatory response was not significantly affected by pedal frequency, but post-hoc analysis with paired t-tests revealed significant differences between the initial ventilatory responses seen in the "30 RPM" and "60 RPM" tests and also between the "30 RPM" and "FR3" tests.

	30 RPM	60 RPM	90 RPM	FREE
$\dot{V}E$	22.3 ± 1.8	26.8 ± 2.1	22.8 ± 1.1	26.7 ± 1.4

Table 3.5: Initial ventilatory responses to the start of exercise for $\dot{V}E$. Values are means ± S.E. (n = 6)

Steady-state responses: Linear regression was performed on data from the last 30 sec of each 200 W exercise stage. In none of the tests did the slope of the line differ significantly from zero, demonstrating that all subjects were in a true steady-state.

Analysis of the steady-state ventilatory responses to the different exercise intensities and fixed pedal frequency by two-factor ANOVA with repeated measures demonstrated that both workload and f_{PED} have a highly significant effect on $\dot{V}E$ (Workload: $p < 0.0005$; pedal frequency: $p < 0.0005$. See *Table 3.6*), but there was no significant interaction between the two.

Multiple regression analysis produced the equation:

$$\dot{V}E\ (BTPS) = -0.361 + (0.279 \times W) + (0.235 \times f_{PED})\ (r^2 = 0.924)$$

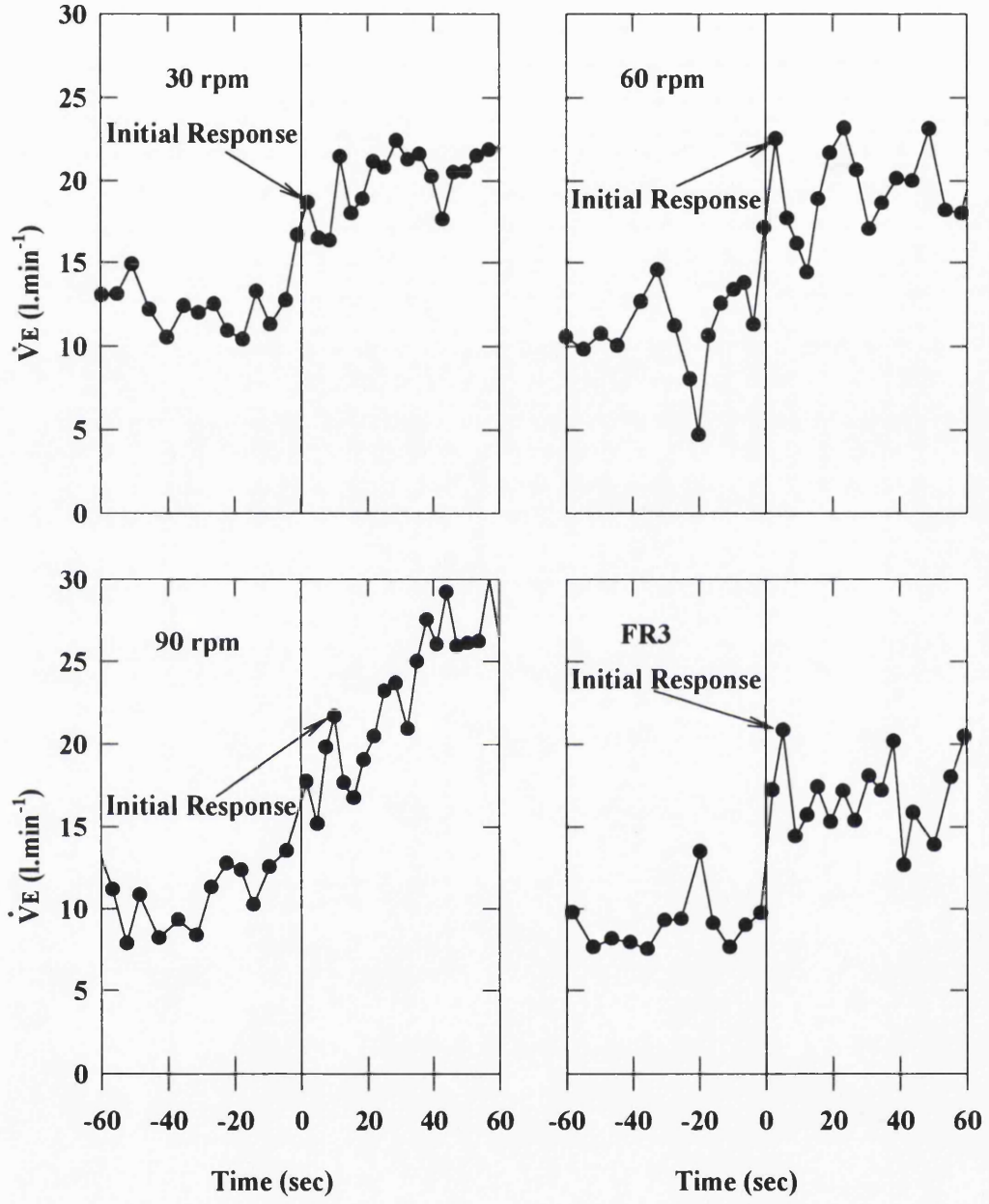


Figure 3.4: Breath-by-breath changes in $\dot{V}_E$ seen in subject F on transition from rest to 50 W exercise in the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests. Time 0 represents the onset of exercise. Arrows mark initial ventilatory response to exercise.

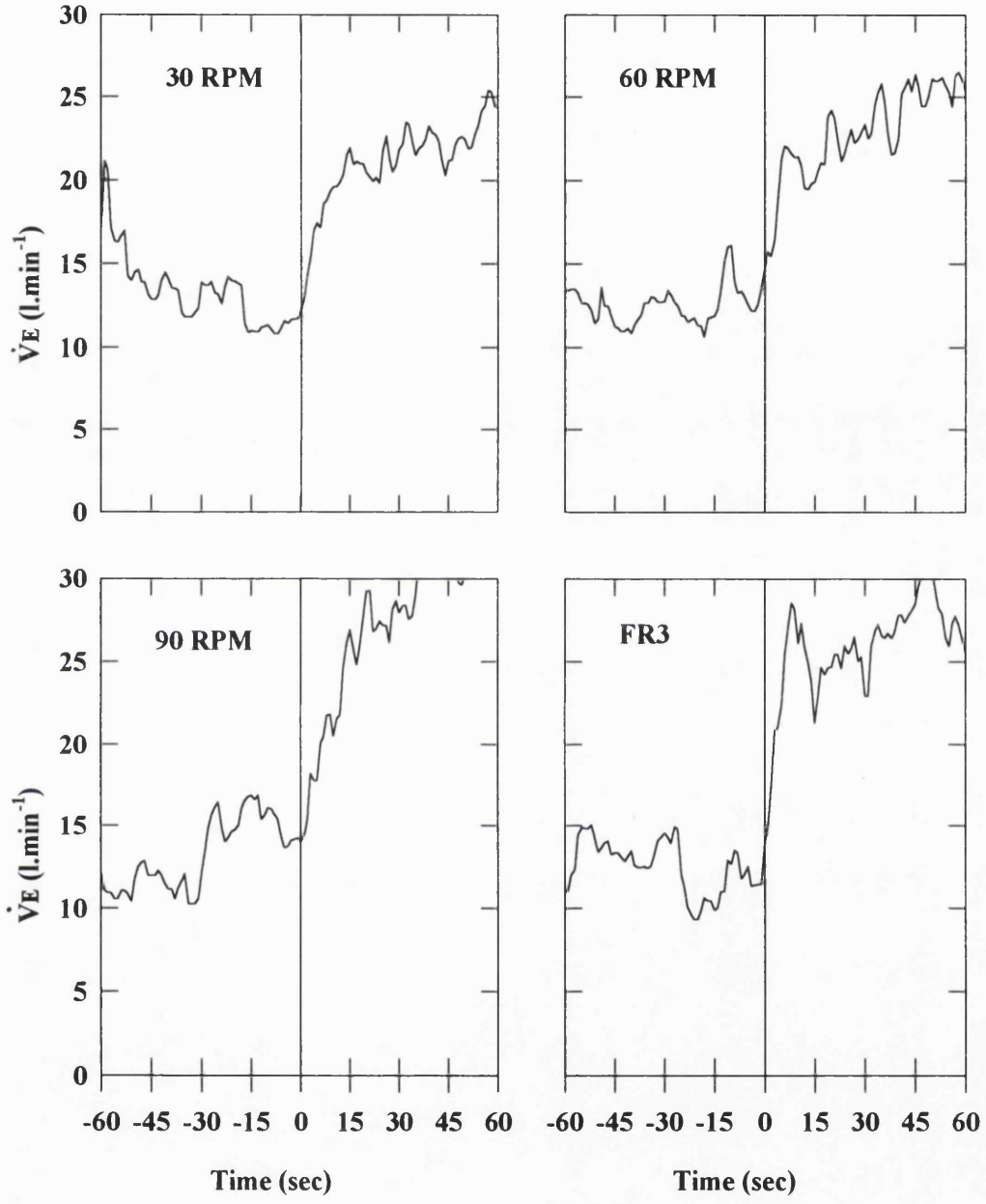


Figure 3.5: Mean interpolated changes in $\dot{V}E$ on transition from rest to 50 W exercise in the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests. Time 0 represents the onset of exercise.

	30 RPM	60 RPM	90 RPM	FR3
50 W	24.6 ± 1.1	27.3 ± 1.4	36.2 ± 0.9	30.3 ± 1.8
100 W	34.9 ± 0.6	38.6 ± 1.9	47.2 ± 1.8	43.0 ± 1.6
150 W	47.0 ± 1.3	52.0 ± 1.9	61.0 ± 2.1	59.2 ± 2.9
200 W	62.2 ± 1.4	71.6 ± 2.31	80.7 ± 3.5	80.0 ± 4.4

Table 3.6: Mean (± S.E.) steady-state ventilatory responses to 50, 100, 150 and 200 W exercise at different pedal frequencies (n = 6).

By taking the mean pedal frequency over each analysis period in the free pedal frequency tests it is possible to perform a similar multiple regression analysis as above. This generated similar results to those seen in the fixed pedal frequency tests:

$$\dot{V}E\ (BTPS) = -8.07 + (0.313 \times W) + (0.302 \times fPED)\ (r^2 = 0.969)$$

As some of the subjects did not perform all three of the "FREE" tests, it is not possible to assume equal variances for both the free and the fixed pedal frequency data; however, the constants in the same equation are of a similar order of magnitude although the intercepts are rather different.

$\dot{V}o_2$, $\dot{V}co_2$ and RER: Steady-state responses: Steady-state RER did not exceed 1.0 in any of the 200 W workloads (See *Table 3.9*) in the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests, except for the "60 RPM" test performed by subject D. This demonstrates that all subjects were still below their θ_{AN} at this workload.

Analyses of the steady-state values of $\dot{V}o_2$ and $\dot{V}co_2$ in response to exercise at different workloads were performed using a two-factor ANOVA with repeated measures. Both pedal frequency and workload had a significant effect on $\dot{V}o_2$ ($\dot{V}o_2$: Workload: $p < 0.0005$; $fPED$: $p < 0.0005$. See *Table 3.7*) and $\dot{V}co_2$ ($\dot{V}co_2$: Workload: $p < 0.0005$; $fPED$: $p <$

0.0005. See *Table 3.8*), but without any significant interaction. Multiple regression analyses of the steady-state responses generated the following relationships:

$$\dot{V}o_2 = 0.123 + (0.0113 \times W) + (0.0096 \times fPED)\ (r = 0.89), \text{ and}$$

$$\dot{V}co_2 = -0.317 + (0.0121 \times W) + (0.0096 \times fPED)\ (r = 0.91).$$

	30 RPM	60 RPM	90 RPM	FR3
50 W	0.96 ± 0.04	1.13 ± 0.11	1.77 ± 0.08	1.17 ± 0.13
100 W	1.60 ± 0.1	1.70 ± 0.09	2.21 ± 0.12	1.86 ± 0.10
150 W	2.22 ± 0.12	2.20 ± 0.18	2.85 ± 0.16	2.47 ± 0.08
200 W	2.87 ± 0.15	2.68 ± 0.20	3.40 ± 0.20	3.09 ± 0.15

Table 3.7: Mean (± S.E.) steady-state values of $\dot{V}o_2$ at 50, 100, 150 and 200 W exercise performed at different pedal frequencies (n = 6).

	30 RPM	60 RPM	90 RPM	FR3
50 W	0.71 ± 0.03	0.83 ± 0.08	1.30 ± 0.07	0.90 ± 0.1
100 W	1.21 ± 0.06	1.39 ± 0.10	1.84 ± 0.10	1.53 ± 0.07
150 W	1.80 ± 0.07	1.94 ± 0.20	2.50 ± 0.12	2.25 ± 0.05
200 W	2.44 ± 0.10	2.51 ± 0.27	3.09 ± 0.15	2.95 ± 0.12

Table 3.8: Mean (± S.E.) steady-state values of $\dot{V}co_2$ at 50, 100, 150 and 200 W exercise performed at different pedal frequencies (n = 6).

	30 RPM	60 RPM	90 RPM	FR3
50 W	0.747 ± 0.03	0.744 ± 0.02	0.740 ± 0.03	0.77 ± 0.03
100 W	0.764 ± 0.03	0.814 ± 0.04	0.858 ± 0.01	0.826 ± 0.02
150 W	0.820 ± 0.04	0.880 ± 0.05	0.880 ± 0.02	0.912 ± 0.02
200 W	0.858 ± 0.05	0.924 ± 0.06	0.914 ± 0.02	0.959 ± 0.02

Table 3.9: Mean (± S.E.) steady-state values of RER at 50, 100, 150 and 200 W exercise performed at different pedal frequencies (n = 6).

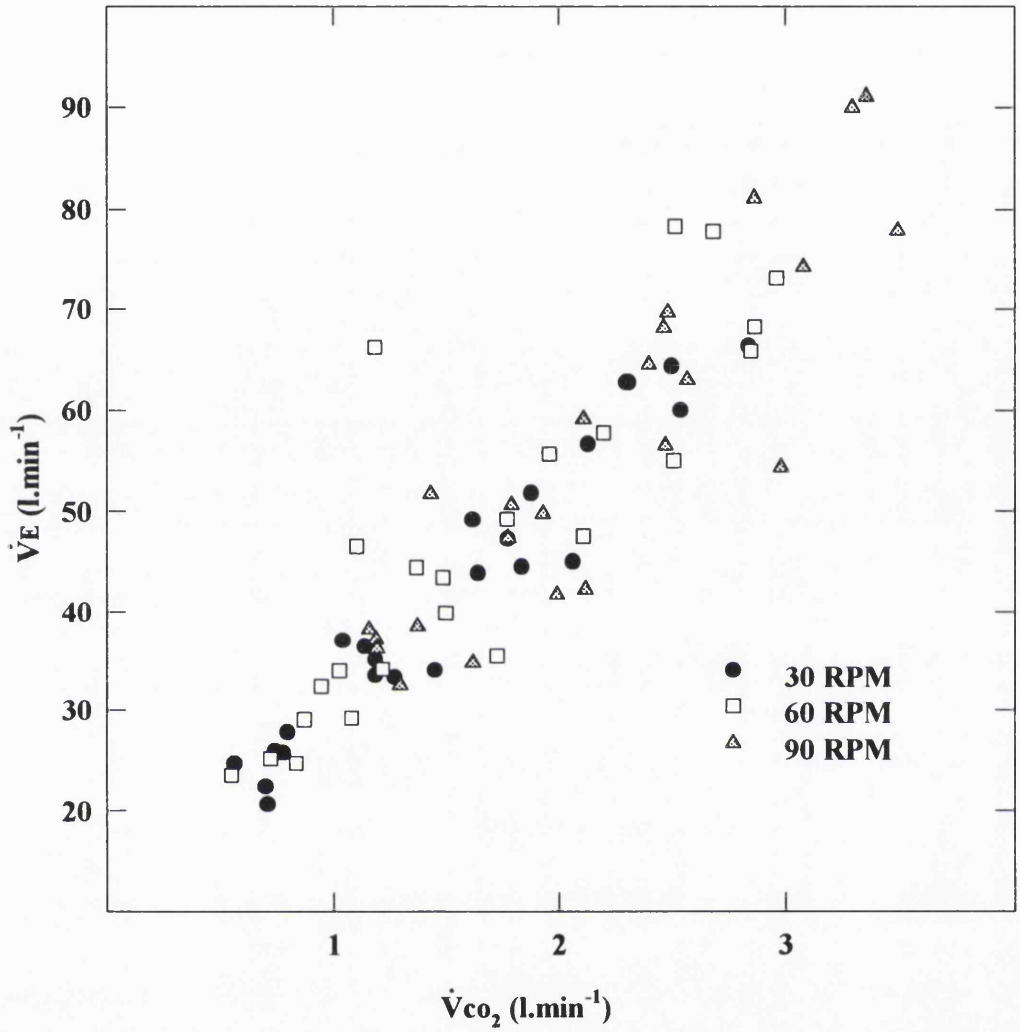


Figure 3.6: Relationship between $\dot{V}E$ and $\dot{V}co_2$ during the steady-state response at each workload.

The effect of *f*PED on the relationship between $\dot{V}E$ and $\dot{V}co_2$ (See *Fig. 3.6*) was determined using multiple regression analysis. This yielded the equation:

$$\dot{V}E = 11.35 + (19.3 \times \dot{V}co_2) + (0.05 \times fPED). \ (r = 0.91)$$

The influence of f_{PED} on the ventilatory response to exercise in this case was indirect; a result of the increase in V_{CO_2}. The direct influence of f_{PED} on the ventilatory response to exercise was not significant (S.E. of slope = 0.04).

HEART RATE:

The changes in f_C throughout the "30 RPM", "60 RPM", "90 RPM" and "FREE" tests performed by subject D are presented in *Fig. 3.7.*

Initial response to the onset of exercise: Analysis using a one-factor ANOVA demonstrated that the initial f_C response to exercise was unaffected by changes in f_{PED} (Initial f_C response: "30 RPM" vs. "60 RPM" vs. "90 RPM": *N.S.* See *Figs. 3.8 & 3.9* and *Table 3.10*).

	30 RPM	60 RPM	90 RPM	FREE
Initial Response	83 ± 5	86 ± 5	90 ± 7	91 ± 4
50 W	85 ± 6	86 ± 4	105 ± 5	91 ± 3
100 W	98 ± 6	101 ± 4	117 ± 5	106 ± 2
150 W	115 ± 5	117 ± 4	131 ± 5	122 ± 1
200 W	130 ± 6	134 ± 5	147 ± 6	140 ± 2

Table 3.10: Changes in f_C in response to exercise at 30, 60, 90 and free pedal frequencies (n = 6).

Steady-state responses: Subjects' steady-state f_C at the different workloads during the three fixed pedal frequency tests were analysed using two-factor ANOVA with replication. Both workload and pedal frequency significantly affected the heart rate response to cycle ergometer exercise (f_C: Workload: $p < 0.0005$. f_{PED}: $p < 0.0005$. See *Table 3.10*), although there is no significant interaction between the two. Multiple regression analysis of the steady-state responses generated the following relationship:

$$f_C = 58.37 + (0.301 \times W) + (0.299 \times f_{PED}) \quad (r = 0.84)$$

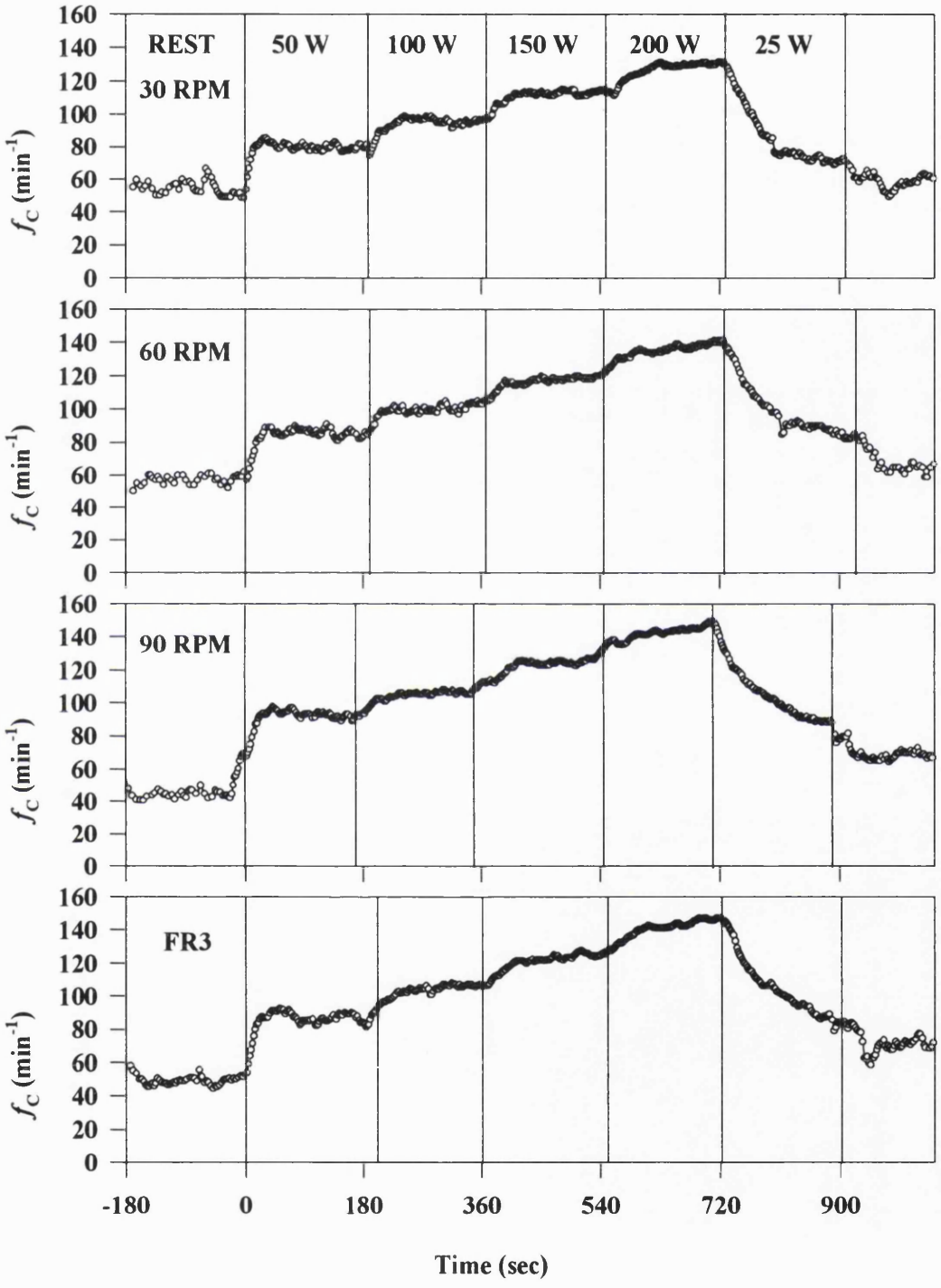


Figure 3.7: Breath-by-breath changes in f_C throughout "30 RPM", "60 RPM", "90 RPM" and "FR3" tests performed by subject D. Graphs are temporally aligned, lines denote changes in workload, each stage lasted approx. 3 min.

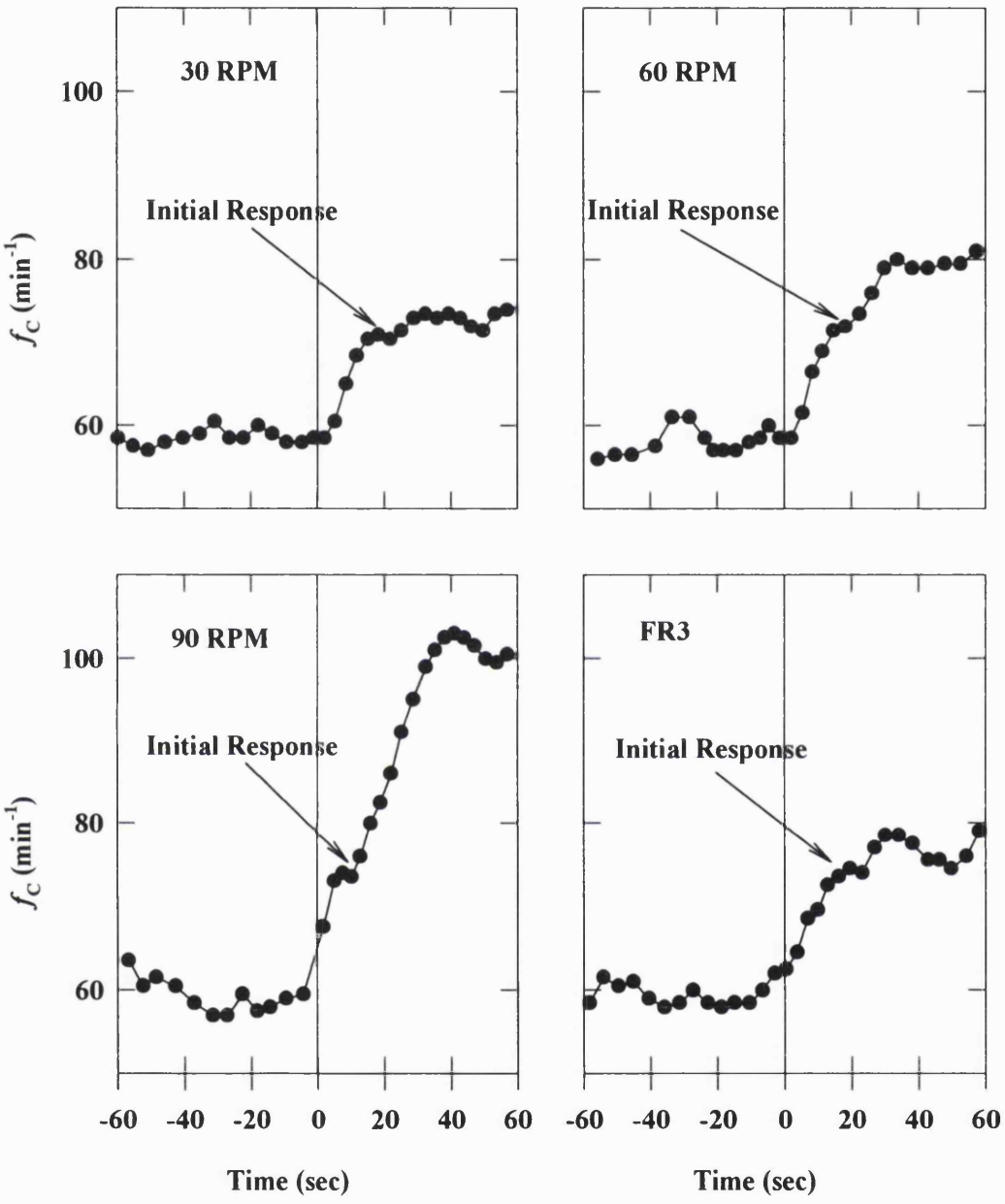


Figure 3.8: Early changes in f_C in response to 50 W exercise in the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests performed by subject F. Exercise started at time 0, arrows denote initial responses to exercise.

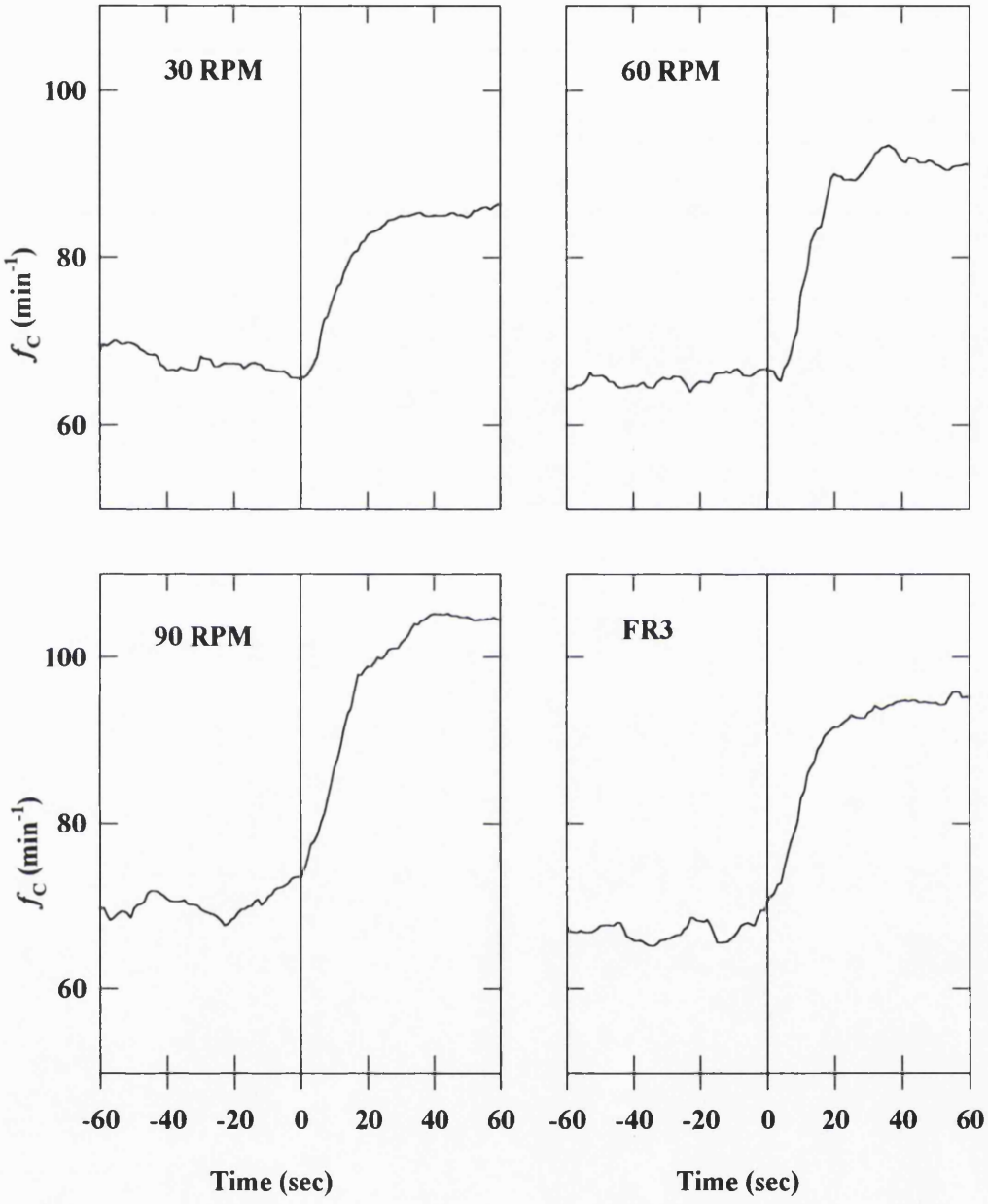


Figure 3.9: Mean interpolated changes in f_C on transition from rest to 50 W exercise in the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests. Time 0 represents the onset of exercise.

***f*BR & VT:** An example of the breath-by-breath changes in VT and *f*BR throughout the 30, 60, 90 and "FR3" tests for one subject can be seen in *Figs. 3.10 & 3.11* respectively. The mean responses obtained from the interpolated data are presented in *Figs. 3.12 & 3.13* respectively.

Initial responses to the onset of exercise: Analysis by single factor ANOVA demonstrated that pedal frequency had no significant effect on the magnitude of the initial responses to the onset of exercise for either *f*BR or VT (See *Fig. 3.14*). The initial ventilatory response was predominantly due to an increase in *f*BR (*f*BR = 175 ± 11% of resting value) with a small increase in VT (VT = 115 ± 6% of resting value; see *Table 3.11*).

	30 RPM	60 RPM	90 RPM	FR3
VT	1.22 ± 0.16	1.9 ± 0.63	1.12 ± 0.17	1.36 ± 0.17
*f*BR	19.0 ± 1.3	20.3 ± 4.7	22.4 ± 3.0	21.0 ± 2.4

Table 3.11: Initial responses to the start of exercise for VT and *f*BR. Values are means ± S.E. (n = 6).

Steady-state responses to exercise: Given the effect of *f*PED on the steady-state ventilatory responses to exercise at different workloads, it should come as no surprise that *f*PED and workload had a significant ($p < 0.05$) effect on both steady-state *f*BR and steady-state VT (See *Tables 3.12 and 3.13*).

	30 RPM	60 RPM	90 RPM	FR3
50 W	1.36 ± 0.1	1.42 ± 0.09	1.57 ± 0.1	1.45 ± 0.05
100 W	1.67 ± 0.13	1.77 ± 0.14	1.86 ± 0.13	1.91 ± 0.13
150 W	2.07 ± 0.14	2.1 ± 0.17	2.23 ± 0.13	2.32 ± 0.12
200 W	2.35 ± 0.18	2.67 ± 0.19	2.61 ± 0.12	2.74 ± 0.12

Table 3.12: Mean (± S.E.) steady-state values of VT at 50, 100, 150 and 200 W exercise performed at different pedal frequencies (n = 6).

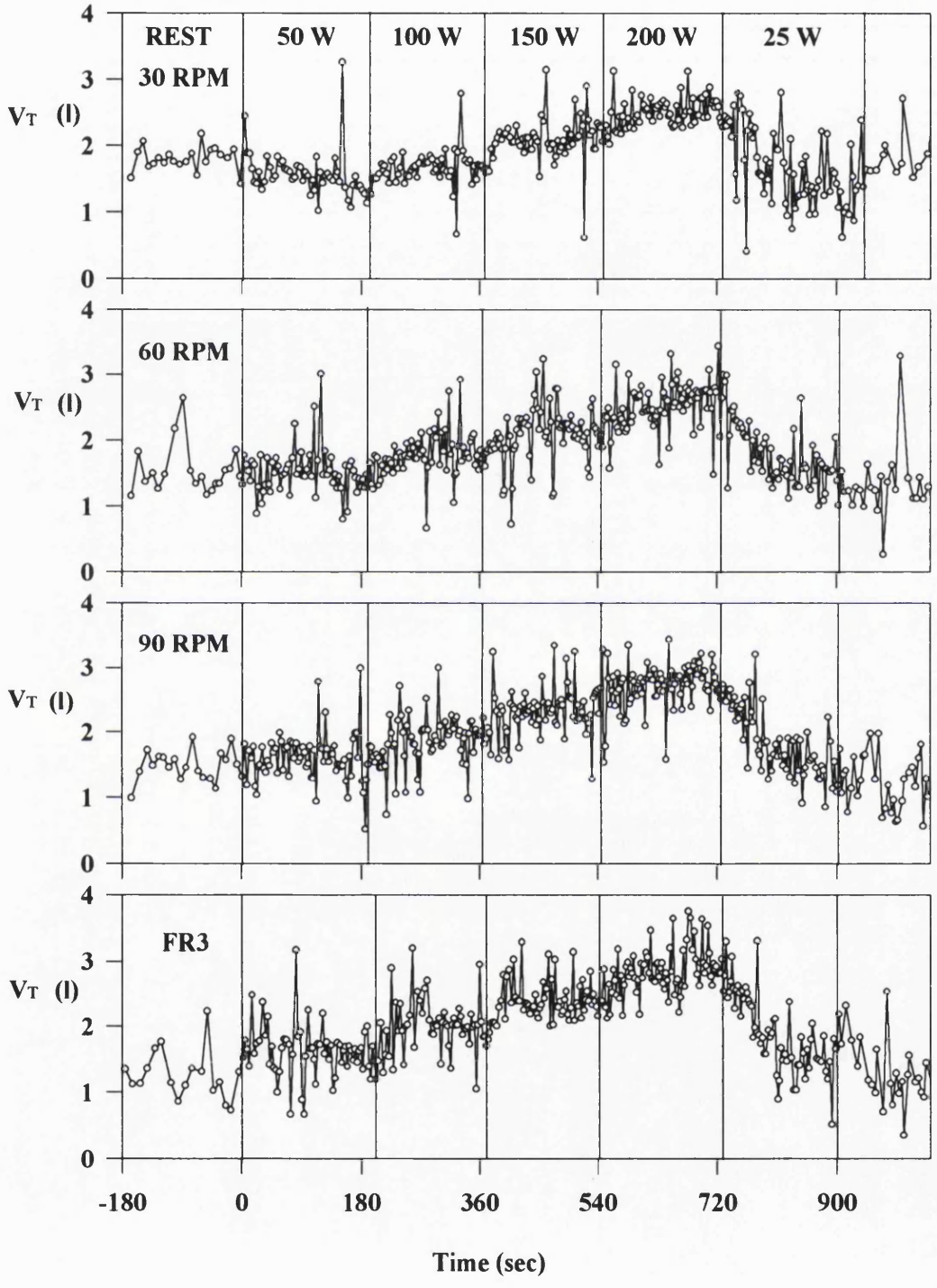


Figure 3.10: Breath-by-breath changes in VT throughout "30 RPM", "60 RPM", "90 RPM" and "FR3" tests performed by subject B. Graphs are temporally aligned, lines denote changes in workload, each stage lasted approx. 3 min.

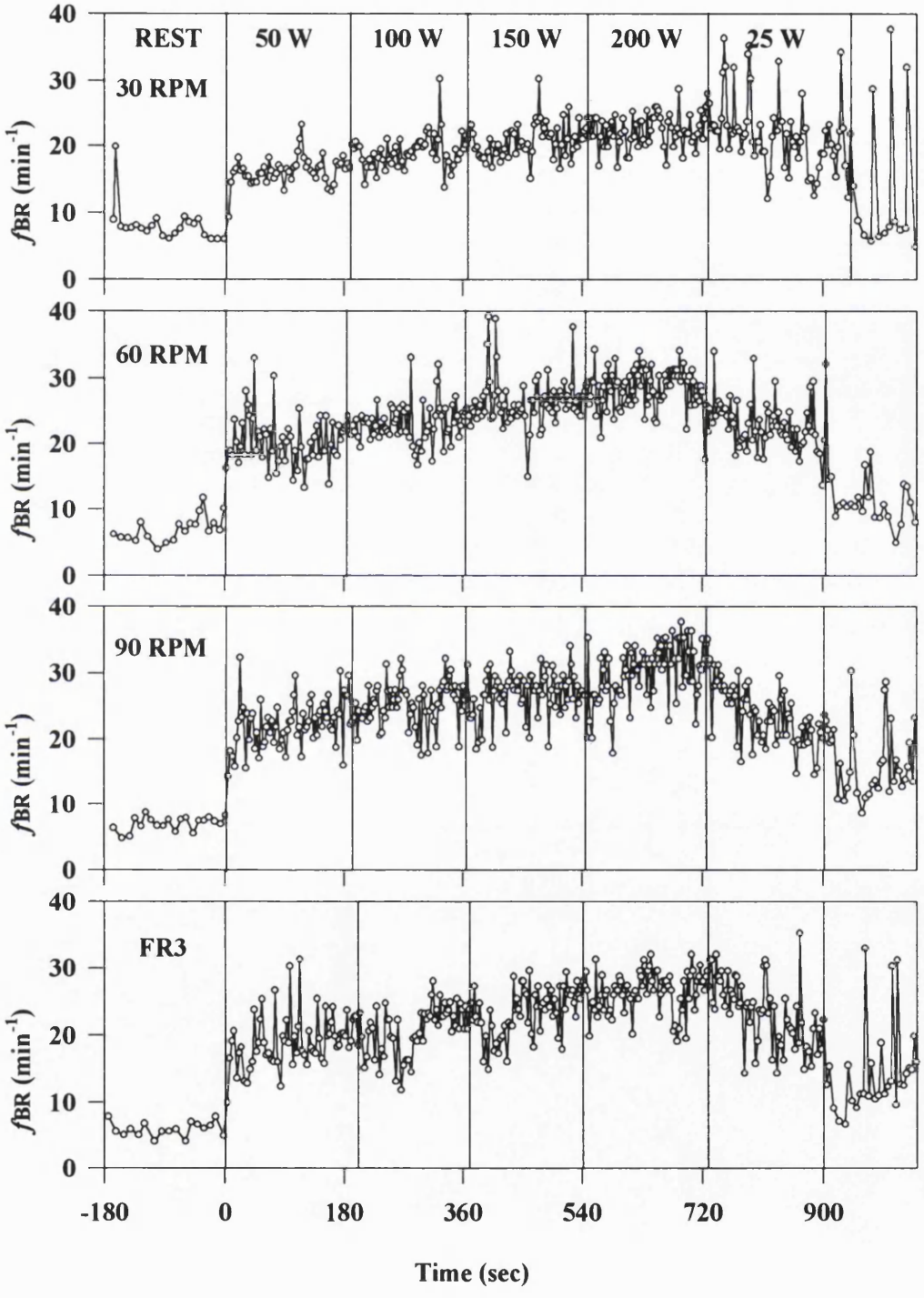


Figure 3.11: Breath-by-breath changes in f_{BR} throughout "30 RPM", "60 RPM", "90 RPM" and "FR3" tests performed by subject B. Graphs are temporally aligned, lines denote changes in workload.

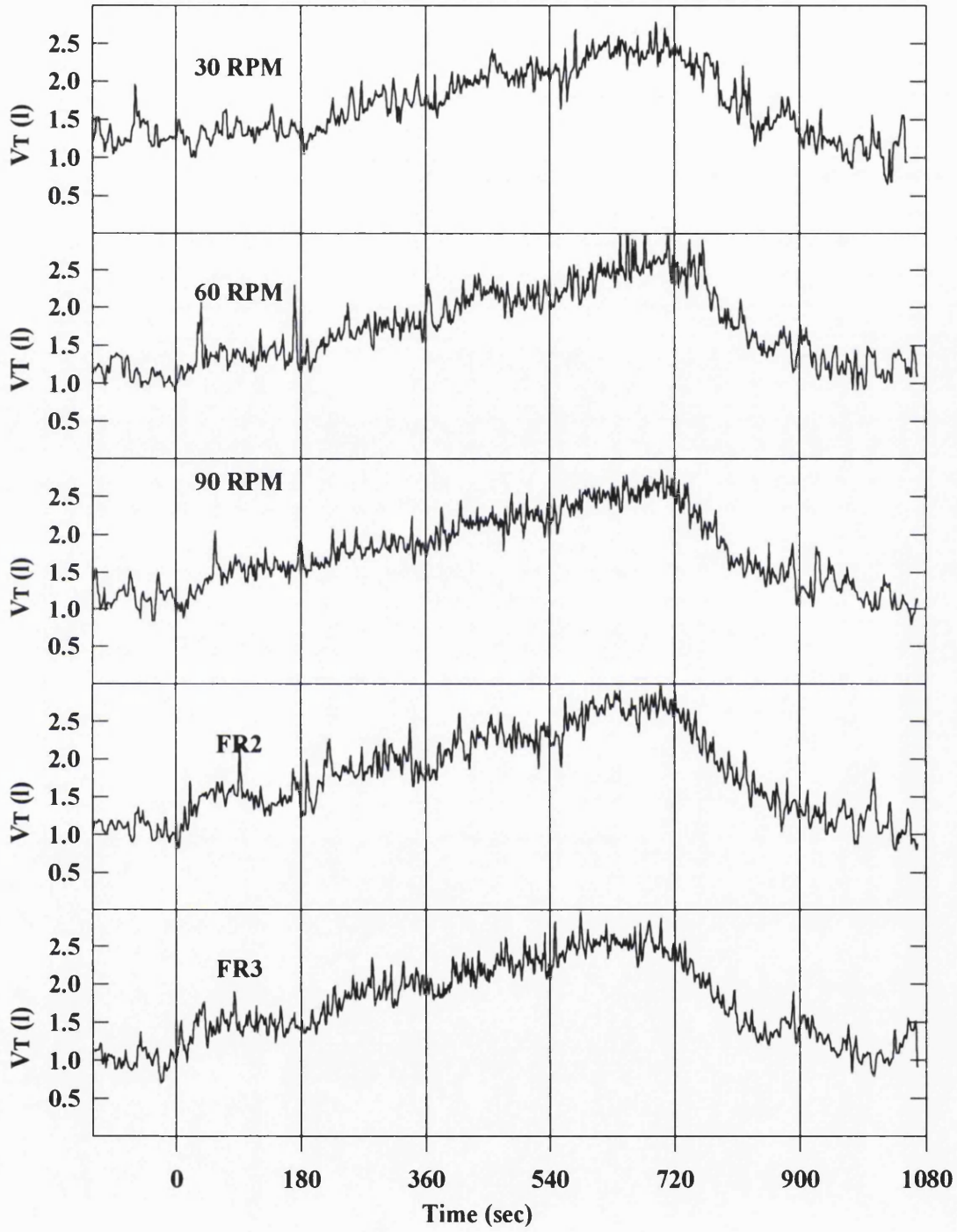


Figure 3.12: Mean interpolated changes in VT throughout the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests. Graphs are temporally aligned. Each stage lasted approx. 3 min. Minor differences in timing for changes in workload has resulted in blurring of non steady-state responses. Time 0 represents the onset of exercise.

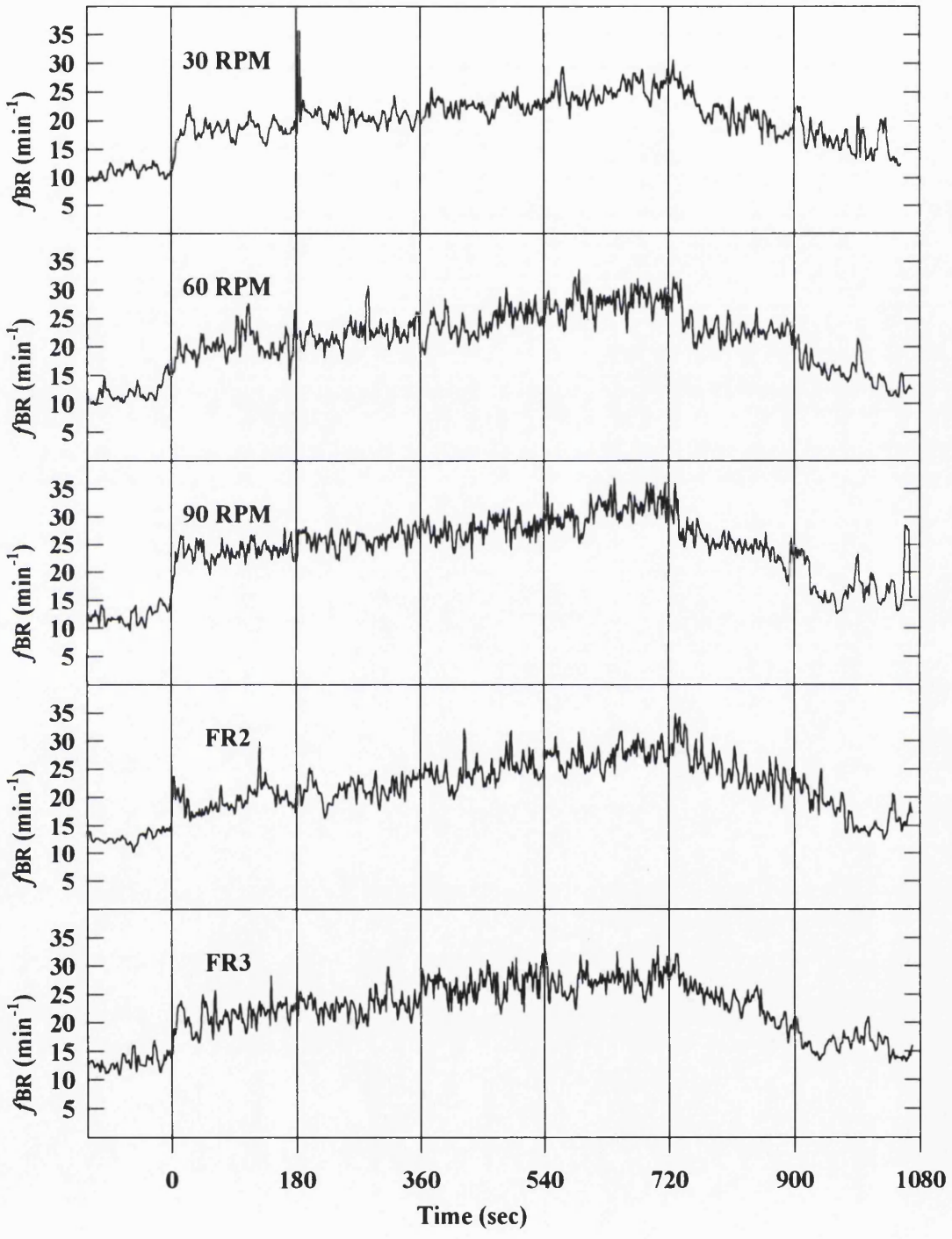


Figure 3.13: Mean interpolated changes in f_{BR} throughout the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests. Graphs are temporally aligned. Each stage lasted approx. 3 min. Minor differences in timing for changes in workload has resulted in blurring of non steady-state responses. Time 0 represents the onset of exercise.

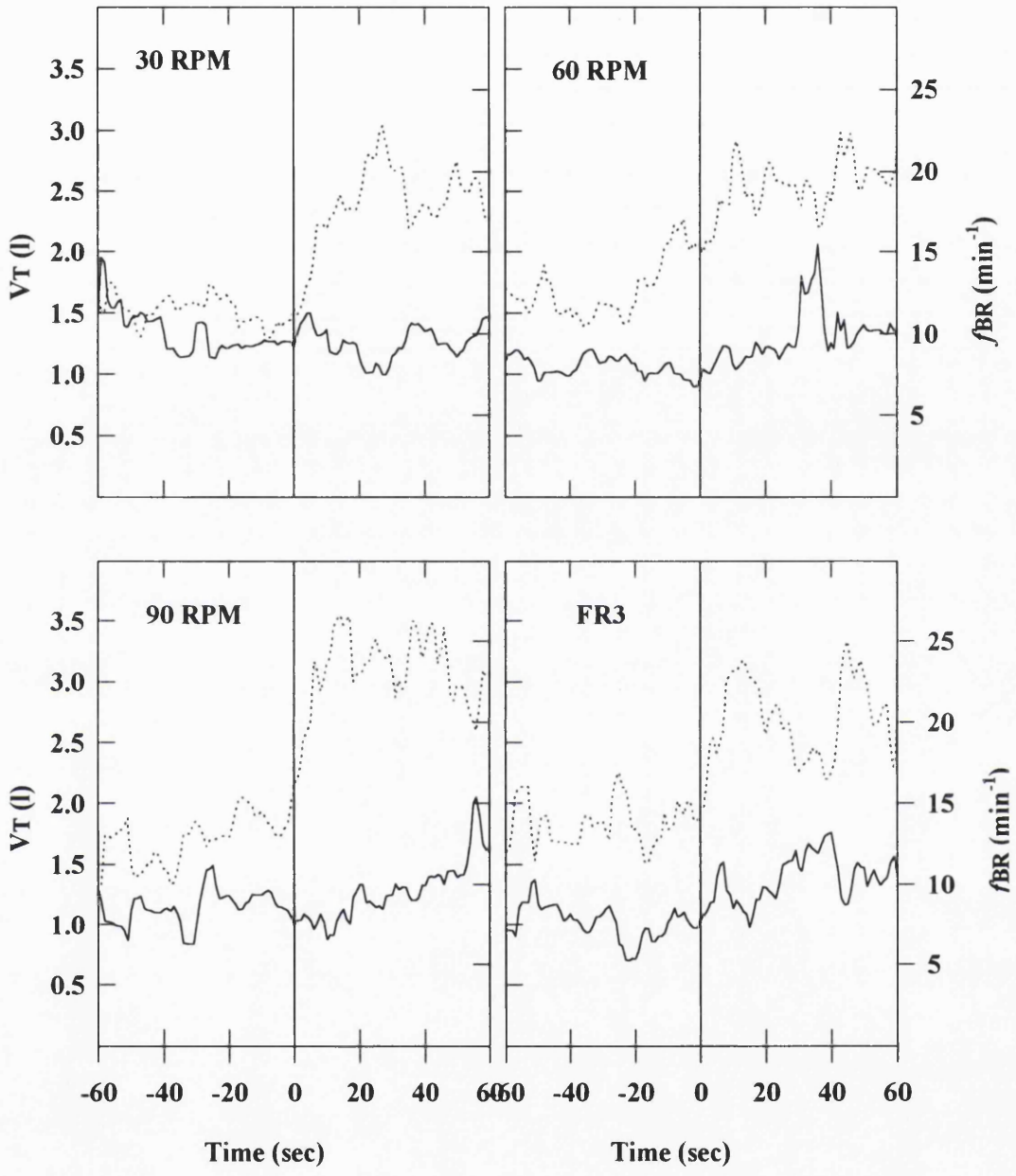


Figure 3.14: Mean interpolated changes in f_{BR} (¨) & VT (-)on transition from rest to 50 W exercise in the "30 RPM", "60 RPM", "90 RPM" and "FR3" tests.

	30 RPM	60 RPM	90 RPM	FR3
50 W	19.26 ± 1.76	22.69 ± 2.02	24.34 ± 2.25	21.49 ± 1.72
100 W	22.12 ± 2.01	23.21 ± 2.25	26.73 ± 2.62	23.72 ± 2.39
150 W	23.68 ± 1.76	26.1 ± 2.34	28.67 ± 3.02	26.75 ± 2.82
200 W	27.61 ± 2.13	28.24 ± 2.1	31.84 ± 2.72	30.4 ± 3.15

Table 3.13: Mean (± S.E.) steady-state values of f_{BR} at 50, 100, 150 and 200 W exercise performed at different pedal frequencies (n = 6).

Is there any evidence of respiratory-locomotor coupling? Breath-by-breath results of the ratio between pedal frequency and respiratory frequency were analysed as described in the Methods section. Those tests which showed a significantly high number of breaths falling into RANGE 1 can be seen in *Table 3.14* and *Figs. 3.15* and *3.16*.

As can be seen, only one of the subjects, subject D, consistently showed any evidence of respiratory-locomotor coupling, the other five subjects showing evidence of respiratory-locomotor coupling in, at most, only one of their tests.

The regularity of the subjects' patterns of breathing during the steady-state was also determined, regularly breathing subjects being identified as having a coefficient of variation for f_{BR} of less than 10% (After Kohl et al., 1981). Only one subject (Subject F, the squash player) satisfies this criterion (See *Table 3.15*).

To determine whether respiratory-locomotor coupling was affected by workload, the incidence of respiratory-locomotor coupling was determined at 50 W and 200 W for each test. The results of these analyses are shown in *Tables 3.16* and *3.17*:

SUBJECT	A	B	C	D	E	F	TOTAL
30 RPM	N.S.	N.S.	$p<0.01$	$p<0.01$	$p<0.01$	N.S.	3/6
50 RPM		N.S.		N.S.		N.S.	0/3
60 RPM	$p<0.01$	N.S.	N.S.	$p<0.01$	N.S.	N.S.	2/6
70 RPM	N.S.	$p<0.01$	N.S.	$p<0.01$		N.S.	2/5
90 RPM	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	0/6
FR 2	N.S.	N.S.		$p<0.01$	N.S.	N.S.	1/5
FR 3	N.S.	N.S.	N.S.	$p<0.01$	N.S.	N.S.	1/6
TOTAL	1/6	1/7	1/5	5/7	1/5	0/7	

Table 3.14: Results of X^2 tests on incidence of breaths falling into RANGE 1(See Methods section). Shaded squares represent missing tests.

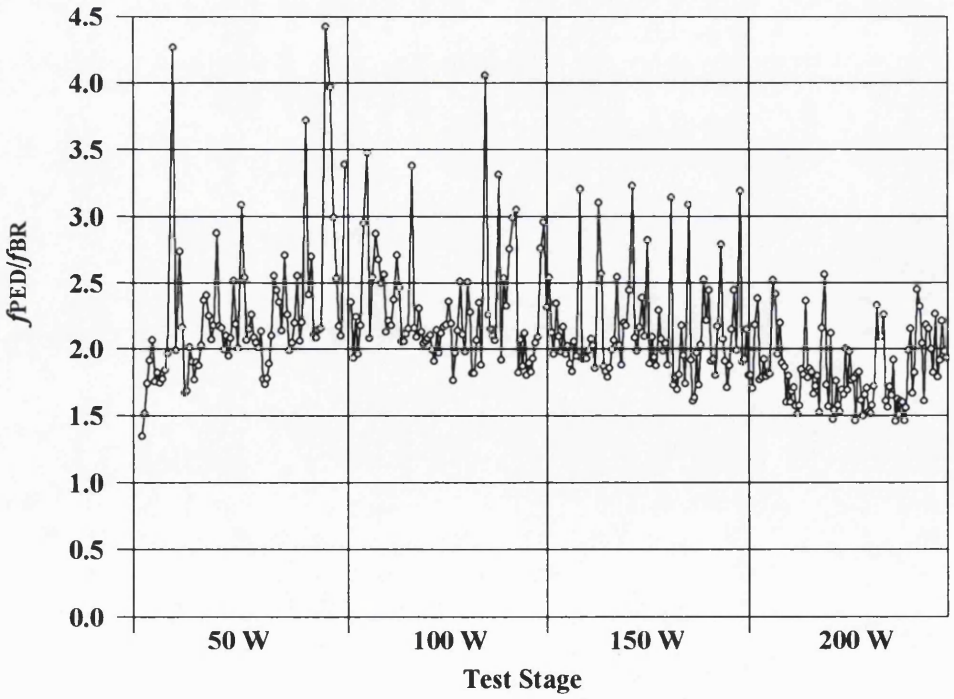


Figure 3.15: Breath-by-breath values of f_{BR}:f_{PED} ratios for the 60 test performed by subject D. Lines denote changes in workload, each stage lasted approx. 3 min.

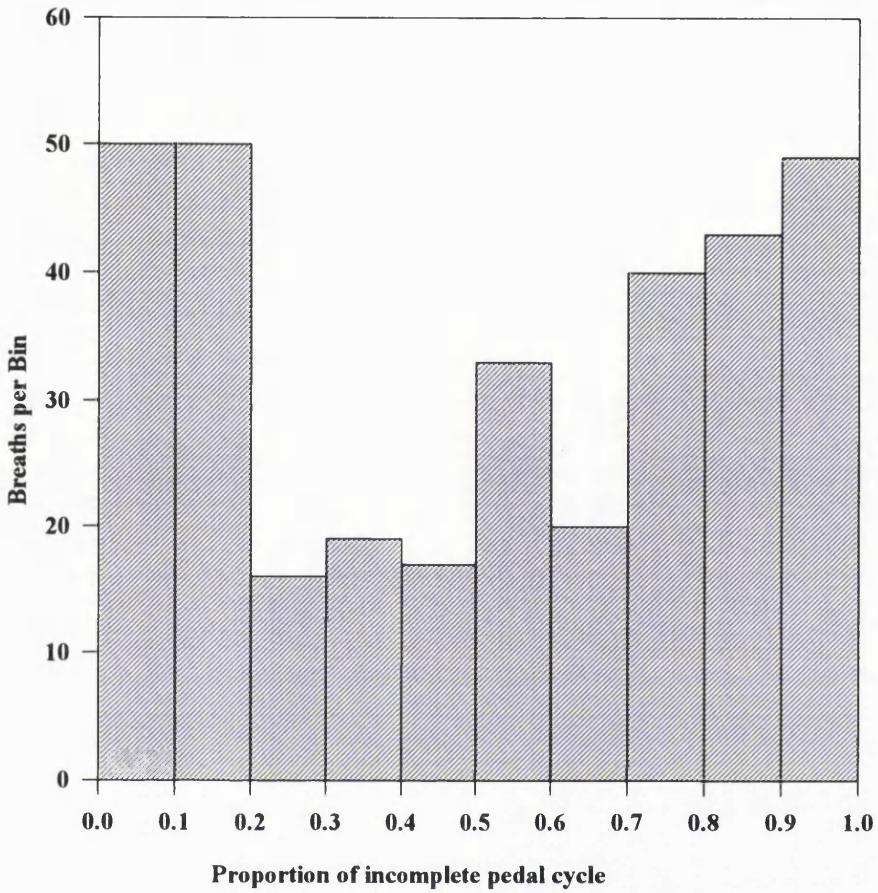


Figure 3.16: Breath-by-breath results from *Fig. 3.15* sorted into bins by their incomplete pedal cycles (see Methods section for details).

	A	B	C	D	E	F
50 W	23.0	15.2	14.2	13.9	30.8	8.4
100 W	18.3	14.6	11.2	10.9	27.1	7.6
150 W	17.2	13.2	16.2	11.0	23.8	5.6
200 W	15.5	11.4	19.9	12.4	22.9	5.5

Table 3.15: Combined coefficients of variation (%) of f_{BR} (min^{-1}) during steady-state measurements at each workload of "30 RPM", "60 RPM", "90 RPM" & "FR3" tests.

As can be seen, there is no evidence of increased respiratory-locomotor coupling at the higher workload; in fact, when these results are compared to those in *Table 3.14*, it is

apparent that the incidence of tests with a significant number of breaths in RANGE 1 is considerably reduced when only these steady-state values are analysed.

	A	B	C	D	E	F
30 RPM	N.S.	N.S.	$p<0.01$	N.S.	N.S.	N.S.
60 RPM	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
90 RPM	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
FR 3	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Table 3.16: Results of X^2 analysis of incidence of breaths in Range 1 over 1 min of 50 W stage.

	A	B	C	D	E	F
30 RPM	N.S.	N.S.	$p<0.01$	$p<0.01$	N.S.	N.S.
60 RPM	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
90 RPM	N.S.	N.S.	$p<0.05$	N.S.	N.S.	N.S.
FR 3	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Table 3.17: Results of X^2 analysis of incidence of breaths in Range 1 over 1 min of 200 W stage.

Effect of pedal frequency on the pattern of breathing: The effect of f_{PED} on the relationships between V_T and T_I and V_T and T_E were analysed by comparing mean values of T_I (or T_E) from each fixed f_{PED} test at four values of V_T using a 2-factor ANOVA with repeated measures (See *Table 3.18* and *Fig. 3.17*). This demonstrated that pedal frequency had a significant effect ($p < 0.005$ for T_I; $p < 0.05$ for T_E) on pattern of breathing. The effect of f_{PED} on both T_I and T_E was more pronounced for the transition between 60 and 90 rpm than for the transition between 30 and 60 rpm: There was no significant difference in the pattern of breathing for the "30 RPM" and "60 RPM" tests, while there was a difference between the "60 RPM" and the "90 RPM" tests ($p < 0.05$ for both T_I and T_E).

	V_T	RANGE A	RANGE B	RANGE C	RANGE D
30 RPM	T_I	1.10 ± 0.86	1.11 ± 0.1	1.05 ± 0.07	1.23 ± 0.18
	T_E	1.65 ± 0.11	1.79 ± 0.19	1.7 ± 0.15	1.78 ± 0.13
60 RPM	T_I	1.01 ± 0.17	1.06 ± 0.1	1.01 ± 0.1	1.02 ± 0.09
	T_E	1.61 ± 0.13	1.74 ± 0.17	1.69 ± 0.18	1.67 ± 0.13
90 RPM	T_I	0.88 ± 0.08	0.93 ± 0.1	0.91 ± 0.06	0.85 ± 0.03
	T_E	1.38 ± 0.1	1.51 ± 0.14	1.51 ± 0.14	1.47 ± 0.12

Table 3.18: Effect of changes in f_{PED} on mean (± S.E.) values of T_I and T_E over 4 ranges of V_T. For definition of ranges see Methods section.

REPEAT TESTS:

The effect of repeat testing on the cardiorespiratory and metabolic responses to exercise were equivocal. f_{BR} was significantly higher in the second test performed at a f_{PED} of "30 RPM" and "90 RPM" by subject E. In the second "90 RPM" test this was accompanied by an increase in $\dot{V}_E$. $\dot{V}_E$ was also higher in the second 70 rpm test performed by subject D, although this was due to an increase in V_T. The cardiorespiratory responses to exercise were similar in both "60 RPM" tests performed by subject A.

DISCUSSION:

EFFICACY OF TEST PROTOCOL:

There was no significant difference between the subjects' cardiorespiratory and metabolic values during the REST periods of each test. Had any change been present, it would have seriously compromised the analysis of the results obtained.

The rowers tested here breathed slower and deeper than the non-rowers. Both groups of subjects were trained individuals, therefore this cannot be attributed to a different level of fitness between the two groups, as suggested by Åstrand & Rodahl (1986). This will be discussed in Chapter 9. Additionally, the rowers as a group had a higher resting heart rate ($p < 0.05$) than the non-rowers.

A true steady-state response was obtained for VE in all 200 W workloads, as determined by linear regression. This demonstrates that 3 min was a sufficiently long period of time for the steady-state to be reached. Given the monoexponential nature of the rise in $\dot{V}E$ and the standard value of the time constant of the response of 50 to 70 sec, it would appear that 3 min was insufficient time to attain steady-state ($4x\ \tau$ = 98% of the response). The faster than expected ventilatory kinetics are compatible with the results of Hagberg et al. (1980), who reported the half times of the changes in $\dot{V}E$, $\dot{V}o_2$, $\dot{V}co_2$ and fC to be shortened by training.

Implicit in the attainment of the steady-state response is that all workloads were below θ_{AN}. Although direct measurement of $\dot{V}o_{2,max}$ or θ_{AN} were not performed on each subject, the fact that steady-state RER was below 1.0 in all but one of the 200 W exercise stages would also provide strong support for all workloads being below the θ_{AN}. It should be noted that the one test in which RER exceeded 1.0 at 200 W was the "60 RPM" test performed by subject D. In this instance, an RER greater than 1.0 was net considered indicative of

exceeding θ_{AN} as his steady-state $\dot{V}o_2$ at 200 W was higher in the "90 RPM" test, when RER was below 1.0 than in the "60 RPM" test.

In 11 of the fixed fPED tests, linear regression analysis highlighted a small but significant rise in fC during the last 30 sec of the 200 W exercise period. This may have been due to a number of confounding influences, but the prime candidates were the relatively short duration of the exercise stage and an increase in core temperature. Any rise in $\dot{V}$E during this period was not significant, presumably due to its greater signal to noise ratio. There was also a significant rise in fC over the last 30 sec of the 200 W exercise period in all the free fPED tests. This highlights the fact that the workload itself was not constant throughout the stage, due to the gradual increase in fPED. To account for this, mean data recorded over the last 30 sec of each exercise stage will be referred to as "Quasi Steady-state".

INITIAL RESPONSES TO EXERCISE:

$\dot{V}$E: The profile of the initial ventilatory response to exercise in a similar subject group to this one is discussed at length in Chapter 5. The results obtained demonstrate the magnitude of the initial ventilatory response to exercise to be affected by fPED. This would agree with the results of Dejours (1967), that the initial ventilatory response to exercise increased with increasing speed of limb movement.

The analysis is complicated to some extent, as exercise was started with the flywheel of the cycle ergometer stationary. The acceleration of the flywheel to the desired speed will in itself entail a transient rise in workload to overcome the inertia of the flywheel. This "excess" work at the start of exercise was kept to a minimum by raising the applied workload from 0 W to 50 W over the first 5 pedal revolutions; however raising the pedal frequency from stationary to "90 RPM" will inevitably take more energy than raising it to "30 RPM".

There are a number of reports in the literature to the effect that the magnitude of the initial ventilatory response increases with increasing exercise intensity (Pearce & Milhorn, 1977; Krogh & Lindhard, 1913: Asmussen, 1973). Miyamura et al. (1992) have reported that varying the speed of limb movement does have an effect on the magnitude of the initial ventilatory response to exercise, presumably via a change in the activity of muscle spindles or joint receptors. Increasing pedal frequency must inevitably involve faster limb movements, so this would be expected to exert some control on the magnitude of the initial ventilatory response to exercise. There is no evidence of this in our results.

VT & *f*BR: The initial ventilatory response to exercise was predominantly achieved by an increase in *f*BR with a small accompanying increase in VT. This is in agreement with the results of Pearce & Millhorn (1977) and Cummin et al. (1986). It should be stated, however, that the pattern by which the increase in VE was achieved was variable between subjects and within subjects where repeat tests were performed. This variability may explain the lack of any statistically significant effect of *f*PED on either *f*BR or VT, despite the significant effect of *f*PED on $\dot{V}E$. This would agree with the findings of Priban (1963) that VE shows less variation than either of its 2 components. Repeat testing may allow a *f*PED-dependent response to be elucidated.

***f*C:** The initial *f*C response to exercise does not follow the pattern described by Whipp et al., (1982), but has a similar profile to that described by Linnarsson (1974). This comprises a notch in an otherwise smooth monoexponential increase in *f*C to the steady-state. This will be discussed in more detail in Chapter 5, but it is beyond the scope of any of the studies described in this thesis to propose a possible unifying mechanism which can account for both profiles of response described in the literature. The results obtained in this study demonstrate that changes in *f*PED do not affect the magnitude of the initial *f*C response to exercise. This would suggest that either the control mechanisms responsible for the initial ventilatory and *f*C responses to exercise do not interact, or that the increased stimulus is only manifested in the ventilatory response to exercise. This may be achieved either by a

saturation of the *f*C response, or some inhibition of the *f*C response by another pathway, possibly control of arterial blood pressure.

QUASI STEADY-STATE RESPONSES TO EXERCISE:

$\dot{V}_E$, $\dot{V}_{O_2}$ & $\dot{V}_{CO_2}$: The ventilatory response to exercise at a given workload increased significantly with increasing *f*PED. These results agree with those of Casaburi et al. (1978b), Takano (1988) and McMurray & Smith (1985). Sipple & Gilbert (1966), however, were unable to report any change in ventilatory response to a given workload when pedal frequency was increased.

Increasing *f*PED was also associated with an increase in both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. This is in agreement with the results of Takano (1988), Casaburi et al. (1978), Hagan et al. (1992) and Gaesser & Brooks (1975), but in contrast to the findings of Sipple & Gilbert (1966) and Kay et al. (1975). Gaesser & Brooks (1975) attributed the increase in $\dot{V}_{O_2}$ with increasing pedal frequency to a fall in muscular efficiency. The change in efficiency does not appear to be due to a change in motor unit recruitment pattern (Gollnick et al., 1974), rather the recruitment of additional muscle groups (Ericson, 1986).

Analysis of the relationship between $\dot{V}_{CO_2}$ and $\dot{V}_E$ demonstrated that the increase in $\dot{V}_E$ associated with increasing *f*PED was in proportion with the accompanying increase in $\dot{V}_{CO_2}$. These results are in agreement with those obtained by Casaburi et al. (1978) using a sinusoidally varying pedal frequency protocol. They reported that $\dot{V}_{CO_2}$ increased with increasing *f*PED, $\dot{V}_E$ increasing in proportion with $\dot{V}_{CO_2}$ and maintaining a relatively constant P_{ET,CO_2}. These results support the hypothesis of Whipp & Ward (1982) that CO_2 flux to the lung is the prime controller of the hyperpnoea of moderate-intensity exercise. Indirect support for this view also comes from the results of Berry et al. (1989), Kay et al. (1975) and Caretti et al. (1992). They were unable to demonstrate a change in $\dot{V}_E$ attributable to a change in pedal frequency when cycling at equivalent metabolic loads.

Takano (1988) also reported an increase in $\dot{V}co_2$ with increasing pedal frequency, but the accompanying increase in VE was disproportionately large and resulted in a fall in P_{ET},CO_2.

Studies into the effect of stride frequency on ventilatory control would suggest that $\dot{V}E$ increases independently of $\dot{V}co_2$ when running compared to walking (Berry et al., 1989; Caretti et al., 1992 and McMurray & Ahlborn, 1982). This resulted in a lower P_{ET},CO_2 when running compared to walking (McMurray & Ahlborn, 1982; Berry et al., 1989; not measured in Caretti et al., 1992). Hanson et al. (1982) report that the predominant response of highly trained runners throughout a prolonged (60-80 min) bout of treadmill running is a tachypneic respiratory alkalosis, again suggesting that running induces a dissociation between ventilation and its metabolic requirements.

McMurray & Smith (1985) found no difference in $\dot{V}E$ when slow-walking, fast-walking and running at equivalent metabolic loads, and suggested that this may be due to their subjects being untrained, as opposed to the subjects of McMurray & Ahlborn (1982), 80% of whom were trained runners. Despite this lack of variation in $\dot{V}E$ with changing stride frequency, they were still able to report a significant fall in P_{ET},CO_2 when running as opposed to either fast or slow walking.

Given the change in absolute values of $\dot{V}E$ at each workload with changing f_{PED}, analysis of the effect of f_{PED} on VT and f_{BR} would be meaningless.

Is there any evidence of respiratory-locomotor coupling? There was little evidence to suggest a relationship between frequency of movement (i.e. f_{PED}) and f_{BR} in any of these subjects with the exception of subject D. Subject D was a competitive fell runner.

Bramble & Carrier (1983) reported that competitive runners strongly entrain their breathing to their gait while running, but it is debatable from these results whether this entrainment is transferable to a different mode of exercise. Indeed, if respiratory-locomotor coupling is

transferable from one exercise mode to another, the three college rowers should also show strong evidence of respiratory-locomotor coupling (Mahler et al. 1991a,b).

It is possible that the technique used in this study was not sufficiently sensitive to detect respiratory-locomotor coupling in the subjects used: Kohl et al. (1981) reported 25%-33% of their irregularly breathing non-cyclists showed a significant level of integer pedal: breathing ratios, while this proportion rose to 50%-63% in regularly breathing non-cyclists. When using the same criterion as Kohl et al. (1981) for identifying regularly breathing cyclists (i.e. coefficient of variation for f_{BR} < 10%), only 1 subject (Subject F) was classified as regularly breathing.

Kohl et al. (1981), also compared the timing of inspiration and expiration with EMG signals from the left and right M. vastus medialis in cyclists and non-cyclists. The beginning of expiration was strongly associated with mid-contraction of either leg for all groups, while the majority of the cyclists also coupled the beginning of inspiration to the onset of contraction of either leg. This was not seen in the non-cyclists. This is a much more sensitive and powerful technique for detecting phase locking of breathing to movement and not using it here was an oversight. Given the irregularity of breathing seen in the majority of these subjects, however, it is debatable as to whether its use would have significantly changed the conclusions of this study.

Bechbache & Duffin (1977), using their cross-correlation technique, reported 20% of their volunteers as showing entrainment when exercising at 50 rpm with speed kept constant with a speedometer. In a later paper, Bechbache et al. (1979) reported entrainment of breathing to exercise rhythm occurred in 28% of subjects when presented with two respiratory stimulators by rebreathing hyperoxic air while performing light (25 W) exercise on a cycle ergometer. The incidence of respiratory-locomotor coupling seen in this experiment (1 subject out of 6, i.e. 16%; 9 tests out of 36, i.e. 25%) is therefore similar to that reported in other studies.

Respiratory-locomotor coupling is not an uncommon finding during exercise: Bramble and Carrier (1983) reported young hares as coupling their respiratory rate to their gait with a 1:1 ratio at high running speeds, while utilising a 1:2 respiratory:gait ratio at lower speeds. Further studies demonstrated that dogs and horses also exhibit respiratory-locomotor coupling, normally at a 1:1 ratio. This has been attributed to the biomechanical constraints of quadrupedal locomotion making non-coupled ventilation energetically undesirable. Iscoe & Polosa (1976), however, demonstrated phase locking in anaesthetised paralysed cats between repetitive stimulation of muscle and somatic afferents, and phrenic nerve activity. This they considered evidence of a reflex capable of phase locking respiratory and locomotor activity.

Studies of respiratory-locomotor coupling in man while walking/running by Bramble & Carrier (1983) and Bechbache & Duffin (1977) have yielded conflicting results: Bechbache & Duffin (1977) cross-correlated respiratory and stride frequencies while walking and running and demonstrated entrainment in 53% of their subjects while walking. This proportion rose to 80% when running; Bramble & Carrier (1983) compared the timing of footfalls and breathing signals in experienced runners, conditioned runners and subjects with little or no running experience. They reported that while inexperienced runners exhibit little or no synchronisation between gait and breathing, locomotor-respiratory coupling increased in the runners with increasing experience, with marathon runners phase locking during the first four or five strides of a run. Furthermore, they report that experienced runners often change coupling patterns during a run and that if stride frequency is perturbed (e.g. by running up or downhill), ventilation closely tracks the change in stride frequency. This suggests that respiratory frequency is under the influence of gait, not the other way round.

Mahler et al. (1991a), investigating the ventilatory responses to rowing ergometry in untrained individuals, college standard and international standard oarswomen, reported an increase in the incidence of respiratory-locomotor coupling with increasing experience. This included switching from a 1:1 respiration:stroke ratio at moderate workloads to a 2:1 ratio

at maximal effort. In a later study (Mahler et al., 1991b), they reported an increase in respiratory-locomotor coupling in novice college oarswomen over the course of a year's training. It would therefore appear that respiratory-locomotor coupling is a learned response, rather than an innate response which might predispose to improved performance.

McMurray & Smith (1985) reported an inverse relationship between VT and stride frequency when comparing slow walking to running ($r = 0.608$) at equivalent metabolic loads, but was unable to find any difference in f_{BR} between slow and fast walking. This led them to suggest there may be a threshold for gait exerting an effect over pattern of breathing when walking and running. This may be the reason for 50% of the "30 RPM" tests showing significant levels of entrainment, a higher incidence than for any of the other pedal frequencies, as at a given workload, the force applied to the pedals must increase with a reduction in pedal frequency.

Further analysis of the data obtained in this study would appear to refute this, for cycling at least: The incidence of breaths falling in RANGE 1 throughout the tests was not appreciably greater in the 50 W stage than in the 200 W stage. It is unlikely that 200 W was too low a workload to traverse this putative threshold as the mean (± S.E.) quasi steady-state RER was 0.92 ± 0.07 for the subject group. This would imply that there was little scope for increasing workload without exceeding the ventilatory anaerobic threshold, whereupon a true steady-state response in unattainable.

EFFECT OF f_{PED} ON THE SUBJECTS' PATTERNS OF BREATHING.

Analysis of the VT-TI-TE relationship for each fixed f_{PED} test at 4 values of VT by a 2 factor ANOVA with repeated measures demonstrated that for a given VT, changes in f_{PED} can affect both TI and TE. There was a consistent fall in TI with increasing f_{PED}. The VT-TE relationships for "30 RPM" and "60 RPM" exercise were similar but TE was significantly reduced at "90 RPM".

These results do not agree with the literature: Berry et al. (1989) reported no difference in the pattern of breathing elicited at 60 and 90 rpm by cycling at equivalent metabolic loads in trained runners and cyclists. Kay et al. (1975a,b) were unable to find any difference in the relationship between VT and its relation to TI or TE when comparing exercise at two pedal frequencies; when comparing cycle ergometer exercise with treadmill running or when comparing cycle ergometer exercise with and without hypercapnia. Bechbache et al. (1979) reported that thirteen out of eighteen subjects who rebreathed hyperoxic air during cycle ergometer exercise showed the same pattern of breathing as when rebreathing hyperoxic air at rest; the five who didn't showed entrainment to the exercise rhythm, i.e. had constant values of TI and TE irrespective of VT. Takano (1988) reported a fall in TE at higher levels of VT when cycling at 60 rpm as opposed to 30 rpm, but no change in TI.

The difference between these results and those reported here could be due to the different pedal frequencies used: Kay et al. (1975a,b) used frequencies of 50 and 70 rpm; Bechbache et al. (1979) used 50 rpm and Takano (1988) used 30 and 60 rpm. Caretti et al. (1992) were able to demonstrate a rise in fBR when pedal frequency was increased from 70 rpm. to 90 rpm, despite being unable to demonstrate any difference in $\dot{V}E$. Interestingly, they were unable to find any difference in fBR or $\dot{V}E$ when comparing exercise at 50 rpm and 70 rpm.

There is little agreement between studies into the effect of stride frequency on pattern of breathing either: Kay et al. (1975) looked at the relationship between TI, TE and VT and were unable to find any clear influence of stride rate. Caretti et al. (1992), McMurray & Smith (1985), Berry et al. (1989) and McMurray & Ahlborn (1982) all report an increase in respiratory frequency when running compared to walking. Caretti et al. (1992) report, however, that although the increases in respiratory and stride frequencies were equivalent, individual results did not show a high degree of entrainment; McMurray & Ahlborn (1982) found a weak but significant correlation between the changes in stride frequency and fBR ($r=0.650$, $P<0.05$). Berry et al. (1989) reported that the increase in fBR was due to a fall in TI with TE remaining constant.

CONCLUSIONS:

From the results of this study, it would be inadvisable to directly compare results obtained from exercise performed at different pedal frequencies. This effectively rules out allowing subjects to choose their own pedal frequencies during a test. Although there is evidence of entrainment of respiratory frequency to the exercise rhythm in only one of the subjects, variations in pedal frequency do affect the metabolic cost of the exercise, resulting in a change in the resultant ventilatory and heart rate responses. Furthermore, pedal frequency influences the pattern of breathing at higher rates.

Given these findings, the next question has to be "What is the best frequency to use?" An overview of the literature will show that the most common frequency is 60 rpm (e.g. Stanley et al., 1985; Lind & Hesser, 1984; Babb & Rodarte, 1991). This value seems to have arisen from studies to determine the optimum pedal frequency for maximal exercise testing (Hermansen & Saltin, 1969; McArdle et al., 1973). Whether this value is entirely appropriate for all exercise testing performed using a cycle ergometer is, however, debatable: Åstrand & Rodahl (1986) recommend a pedal frequency of 40-50 rpm for submaximal exercise, While Withers et al. (1981) used a pedal frequency of 80 rpm to test endurance-trained cyclists. Hagberg et al. (1981) report that the preferred pedal frequency of competitive cyclists at 80% $Vo_{2,max}$ ranged from between 72 and 102 rpm. During a submaximal exercise test, trained cyclists adopted a mean pedal frequency ranging from 83 rpm. at 50 W to 87 rpm. at 200 W; while at the same workloads non-cyclists adopted pedal frequencies ranging from 50 rpm. to 68 rpm (Kohl et al., 1981).

The pedal frequencies chosen by the six subjects used in this study vary from 71 ± 18 at 50 W to 82 ± 6 at 200 W. It would therefore seem appropriate to choose a value within this range. To accommodate exercise at both low (< 75 W) and moderate (75 to 250 W) workloads, the target pedal frequency for all the studies described below was set at 75 rpm.

CHAPTER 4:

THE VENTILATORY CONSEQUENCES OF HYPOCAPNIC HYPERVENTILATION

INTRODUCTION:

The main part of this thesis is concerned with the effect of depletion of body CO_2 stores on the initial ventilatory response to an increase in workload, imposed against a background of either rest or mild exercise. As discussed in the introduction to this thesis, the mechanisms responsible for the control of exercise hyperpnoea have yet to be fully described, but the evidence available would suggest that Pa,CO_2 is tightly regulated. The proportionality of the Phase 1 response to exercise for $\dot{V}E$, $\dot{V}co_2$ and $\dot{V}o_2$, as defined by the relative constancy of RER, PET,CO_2 and PET,O_2 during this Phase, has given rise to the theory of cardiodynamic hyperpnoea (Wasserman et al., 1974). The evidence currently available (e.g. Jones et al., 1981; Marconi et al., 1991, Huszczuk et al. 1990) would suggest that this is responsible for the initial increase in VE seen at the start of exercise.

The Phase 2 response for $\dot{V}E$, however, does appear to be intricately linked to the rate at which CO_2 appears at the lung: evidence from step (Wasserman & Whipp, 1983; Pearce & Milhorn, 1977; Casaburi et al., 1989; Whipp et al., 1983), ramp (Miyamoto & Niizeki, 1992; Fujihara et al., 1973a, b) and sinusoidal workload forcings (Casaburi et al., 1977; Bakker et al., 1980) demonstrate a remarkable conformity between the Phase 2 kinetics of $\dot{V}E$ and $\dot{V}co_2$, with the rise in $\dot{V}co_2$ slightly preceding that of $\dot{V}E$ (Casaburi et al., 1977). The kinetics of $\dot{V}o_2$, on the other hand, are much faster, giving rise to a transient hypoxaemia (Whipp, 1986).

The steady-state ventilatory response to moderate intensity exercise is also closely linked to $\dot{V}co_2$; dietary manipulation of RER, either by varying substrate availability or by inducing metabolic acidaemia/alkalaemia will change the $\dot{V}E:\dot{V}o_2$ ratio while leaving the $\dot{V}E:\dot{V}co_2$ ratio relatively unaffected (Oren et al., 1981).

Not everyone shares the view that the ventilatory response to exercise is humorally mediated: Kao et al., (1954, 1955) demonstrated that in dogs it is possible to explain almost the entire ventilatory response to exercise in terms of a neurogenic stimulus originating in

the limbs, while Eldridge (1985) has demonstrated a sustained increase in $\dot{V}E$ associated directly with the neural mechanism that induces fictive locomotion in the decerebrate cat. Furthermore, exercise is typically associated with isocapnia in man, leaving no obvious error signal for the chemoreceptors to respond to.

To determine whether or not CO_2 has a role to play in mediating the normal ventilatory response to exercise in man, Pa,CO_2 can be lowered prior to the start of exercise by hyperventilation (These results are described in Chapters 5, 7 and 8). A working knowledge of the short and medium-term effects of hyperventilation on a subject's ventilation is therefore essential.

Hyperventilation can be performed volitionally (i.e. actively) or passively using a mechanical ventilator. In this study volitional hyperventilation was used for a number of reasons, but a major consideration was the desire to use similar methods of hyperventilation both at rest and during mild exercise. As the level of hyperventilation needed during mild exercise was approximately 100 l/min, truly passive hyperventilation would have been unfeasible. Equally there was a concern that the transition from passive hyperventilation to active post-hyperventilation would involve a distinct change in state of the subject. This change may in itself adversely affect the initial ventilatory responses to the exercise.

Active hyperventilation is not without its disadvantages: It is apparent that ventilation remains elevated above pre-hyperventilation levels for some time after the cessation of hyperventilation. This gradual decline in ventilation has been termed "afterdischarge" or "short-term potentiation" (Eldridge, 1973). It has been characterised in anaesthetised (Eldridge, 1973; Engwall et al., 1994; Lawson & Long, 1983) and awake (Engwall et al., 1991, 1994) animals and in awake man (Georgopulous et al., 1990; Tawadrous & Eldridge, 1974; Fregosi, 1991; Swanson et al., 1976; Gleeson & Sweer, 1993).

It is important that $\dot{V}E$ has recovered sufficiently from the hyperventilation when exercise is started that the initial ventilatory response to exercise is not engulfed in the afterdischarge resulting from the prior hyperventilation. To that end, the time course of the afterdischarge associated with the levels of hyperventilation and hypocapnia to be used in this thesis must be characterised. The number of studies that quantify the effects of afterdischarge following volitional hyperventilation in awake humans is, however, small (Swanson et al., 1976; Tawadrous & Eldridge, 1974). Equally, if the onset of the Phase 2 response is to be significantly delayed, P_{ET},CO_2 must still be well below normal levels (Ward et al., 1983). It is therefore propitious to characterise the after-effects of volitional hyperventilation in our subject group to determine the optimum delay between the end of hyperventilation and the start of exercise.

PURPOSE OF EXPERIMENT

The purpose of this experiment is:

(i) to identify the optimum delay between the cessation of hyperventilation and the start of exercise (or the increase in exercise intensity); and

(ii) to determine whether the act of hyperventilation modifies breathing in a manner which may affect the subject's ventilatory response to exercise in a way which would invalidate its use in the experiments described in Chapters 5 to 8.

METHODOLOGY:

SUBJECTS:

Seven subjects performed protocol "A", five performed protocol "B" and seven performed protocol "C" (These are described below). Their anthropometric data are described in *Table 4.1* below.

SUBJECT	TESTS	AGE	HEIGHT	WEIGHT	SPORT
1	A & B	23	1.91	90.5	ROWER
Q	A, B & C	19	1.89	85	ROWER
3	A & B	26	2.02	95	ROWER
5	A & B	27	1.83	86	ROWER
2	A & B	20	1.96	83	ROWER
C	A & C	23	1.90	75	ROWER
D	A & C	30	1.76	66	FELL RUNNER
H	C	22	1.85	77.5	ROWER
W	C	24	1.89	85	ROWER
T	C	17	1.84	82.5	ROWER
U	C	25	1.8	77	CYCLIST
4	C	28	1.72	68	ROWER

Table 4.1: Anthropometric data of subjects tested for this Chapter.

APPARATUS:

The apparatus used in these tests was as described in Chapter 2. Data acquisition program EXTEST 2 (See Appendices A to C) was used for protocol "C" and protocol "A" tests performed by subjects C and D . Program EXTEST 3 was used for the remainder of the tests (see Appendices A to C for details).

TEST PROTOCOLS.

A: Resting Hyperventilation: Subjects were asked to breathe normally for three minutes while resting measurements were taken. At 2½ min an oscilloscope which was visible to the subject was switched on displaying a dot which rose in proportion to the subject's V_T. At the end of exhalation the dot reset to its original height. At 3 min the subject was asked to increase in depth of breathing such that the dot rose to between two and three times the height seen during normal breathing without changing f_{BR} (roughly detectable as the number of breaths per sweep of the screen). This level of hyperventilation was maintained for 4 minutes or until P_{ET,CO_2} fell to between 20 and 25 mmHg, which ever was sooner. Once one of these endpoints was reached, the oscilloscope was switched off and the subject was asked to breathe normally. The test was terminated 4 min following the end of hyperventilation. Following the test subjects were asked to report any sensations they felt during the test.

It should be noted at this stage that the decision to achieve the increase in $\dot{V}_E$ associated with the hyperventilation by increasing V_T and not f_{BR} was based on the premise that the purpose of the hyperventilation was to lower Pa,CO_2, which necessitates an increase in $\dot{V}_A$. Increasing V_T is a more efficacious method of achieving this objective than increasing f_{BR}, as it will inevitably result in a decrease in the V_D/V_T ratio. In addition, Folgering & Durlinger (1983) reported afterdischarge to be less following V_T-mediated hyperventilation compared with f_{BR}-mediated hyperventilation to similar levels of $\dot{V}_E$.

The minimum P_{ET,CO_2} at which hyperventilation should be continued was determined by a pilot study: below 17 mmHg hyperventilation was increasingly associated with sensations of extreme dizziness, loss of peripheral vision and incipient unconsciousness. Furthermore, Macefield & Burke (1991) have reported muscle tetany when P_{ET,CO_2} fell below 16 mmHg.

B: Eucapnic Resting Hyperventilation. This test differs from test "A" only in that during the hyperventilation period CO_2 was added into the inspirate in sufficient quantities to maintain P_{ET},CO_2 close to normal resting values. The hyperventilation period was approximately the same as that in test "A".

C: Hyperventilation During Exercise. Subjects sat on the exercise bicycle for 1 min, whereupon the subject exercised at 50 W. After 2½ min of exercise the oscilloscope was switched on and at 4 min of exercise the subject was asked to increase V_T by a factor of three without changing f_{BR} or f_{PED}. Hyperventilation was maintained for 4 min or until P_{ET},CO_2 fell below 25 mmHg, whereupon the subject was told to breathe normally while continuing to exercise. 4 min after the end of hyperventilation the subject was told to stop exercising. After 1 min of recovery the test was stopped.

DATA ANALYSIS:

Resting Values: Resting values for each subjects were taken as the mean values over the 30 sec between 30 sec and 1 min prior to the start of hyperventilation.

Hyperventilation: Values during hyperventilation for each subject are the mean values for the last five breaths of the hyperventilation period.

Post-hyperventilation: Each subject's responses were calculated at 30 sec, 1 min, 2 min, 3 min and 4 min post-hyperventilation for protocols "A" and "B," and 15 sec, 30 sec, 1 min, 2 min and 3 min post-hyperventilation for protocol "C." Each value was the mean of the three nearest breaths to the desired time.

Afterdischarge: The best-fit function through each subject's responses was calculated using the "SOLVER" function in Microsoft EXCEL 4.0. The model used ("MODEL 1") was of the form:

$$\dot{V}E_{(t)} = \dot{V}E_{MIN} + \left[\left(\dot{V}E_{MAX} - \dot{V}E_{MIN}\right) * e^{-t/\tau}\right]$$

where $\dot{V}E_{(t)}$ is the value of VE at time t ($l.min^{-1}$), $\dot{V}E_{max}$ is the value of $\dot{V}E$ after the abrupt fall seen immediately after the cessation of hyperventilation ($l.min^{-1}$), $\dot{V}E_{min}$ is the minimum value of $\dot{V}E$ seen following hyperventilation ($l.min^{-1}$. See Appendix D for more details). This was the resting value for protocol "B." For protocols "A" and "C" $\dot{V}E_{min}$ was taken to be the nadir of the fall in $\dot{V}E$ resulting from the hypocapnia, i.e. a value below the normal level of ventilation. t is time (sec) and τ is the time constant of the fall in $\dot{V}E$ (sec). The model is illustrated in *Fig. 4.1* with data from protocol "B". The line of best fit is defined as that which results in the lowest value for the sum of the square of the residuals.

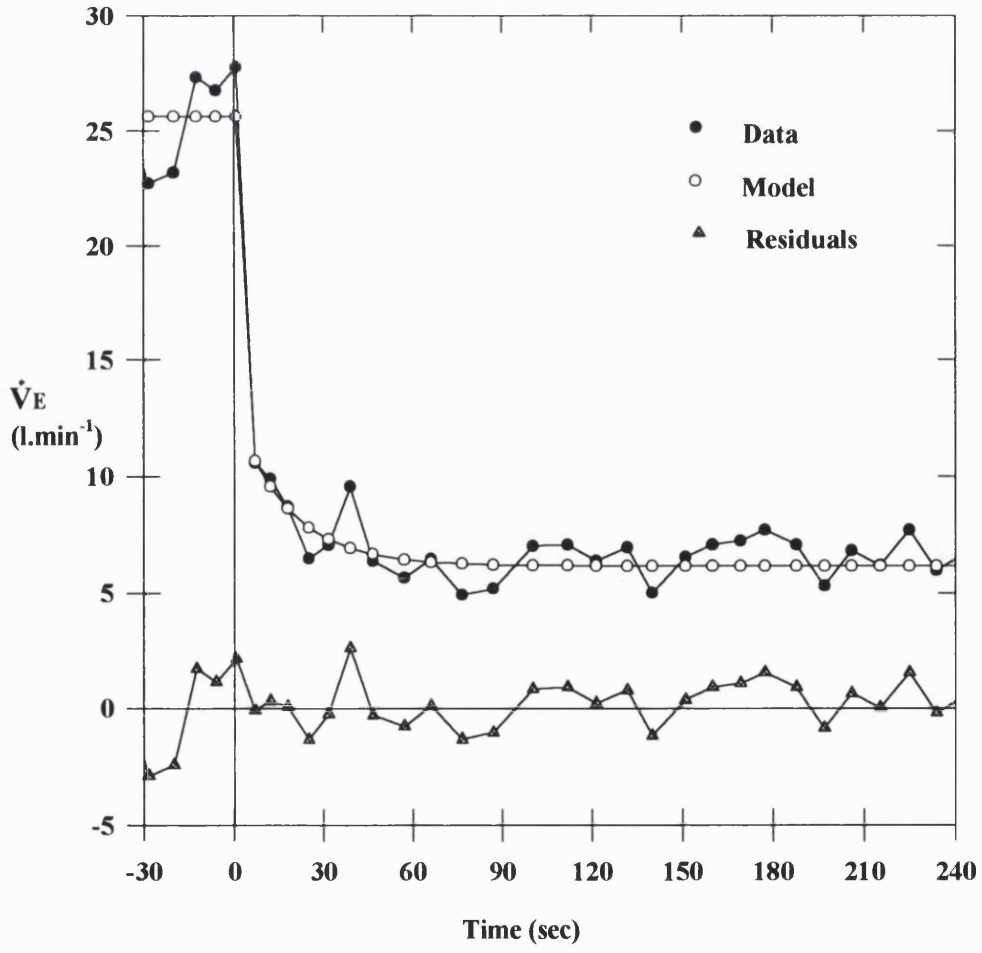


Figure 4.1: Example of modelling of the fall in VE following active hyperventilation using MODEL 1. $\dot{V}E_{max}$ = 12.78 $l.min^{-1}$, $\dot{V}E_{min}$ = 6.17 $l.min^{-1}$, τ = 18.2 sec. Time 0 represents the end of hyperventilation, data are from protocol "B".

Group averaging of responses: Breath-by-breath data for each subject were interpolated in 1 sec intervals from 1 min prior to the end of hyperventilation to the end of the test for protocol "A". For protocol "B" each subjects breath-by-breath data were interpolated in 1 sec intervals from 1 min prior to the onset of 50 W exercise to the start of hyperventilation and from 1 min prior to the end of hyperventilation to the end of 50 W exercise. Interpolated data were then time-aligned and averaged to provide mean responses for the subject group.

Statistical tests: Comparison of data from the same protocol was performed using paired t-tests, comparison between protocols "A" and "B" was performed using non-paired t-tests assuming equal variance.

RESULTS:

COMPARISON OF PROTOCOLS "A" AND "B":

The original traces for both protocols and the corresponding breath-by-breath results for subject 2 are presented in *Figs. 4.2* and *4.3*.

RESTING VALUES:

The resting values for the two protocols are presented in *Table 4.2.* There were no significant differences between resting in the 2 protocols.

	A	B
f_C	68 ± 6	69 ± 6
$\dot{V}_E$	9.61 ± 0.56	10.74 ± 2.14
V_T	1.09 ± 0.14	1.32 ± 0.19
f_{BR}	10.6 ± 1.2	10.2 ± 1.3
P_{ET,CO_2}	43 ± 1	39 ± 2
P_{ET,O_2}	103 ± 2	105 ± 4
$\dot{V}_{O_2}$	0.37 ± 0.03	0.36 ± 0.05
$\dot{V}_{CO_2}$	0.31 ± 0.02	0.25 ± 0.04
RER	0.86 ± 0.05	0.82 ± 0.05

Table 4.2: Mean (± SE) resting data for protocols "A" and "B". n = 7 for protocol "A", n = 5 for protocol "B".

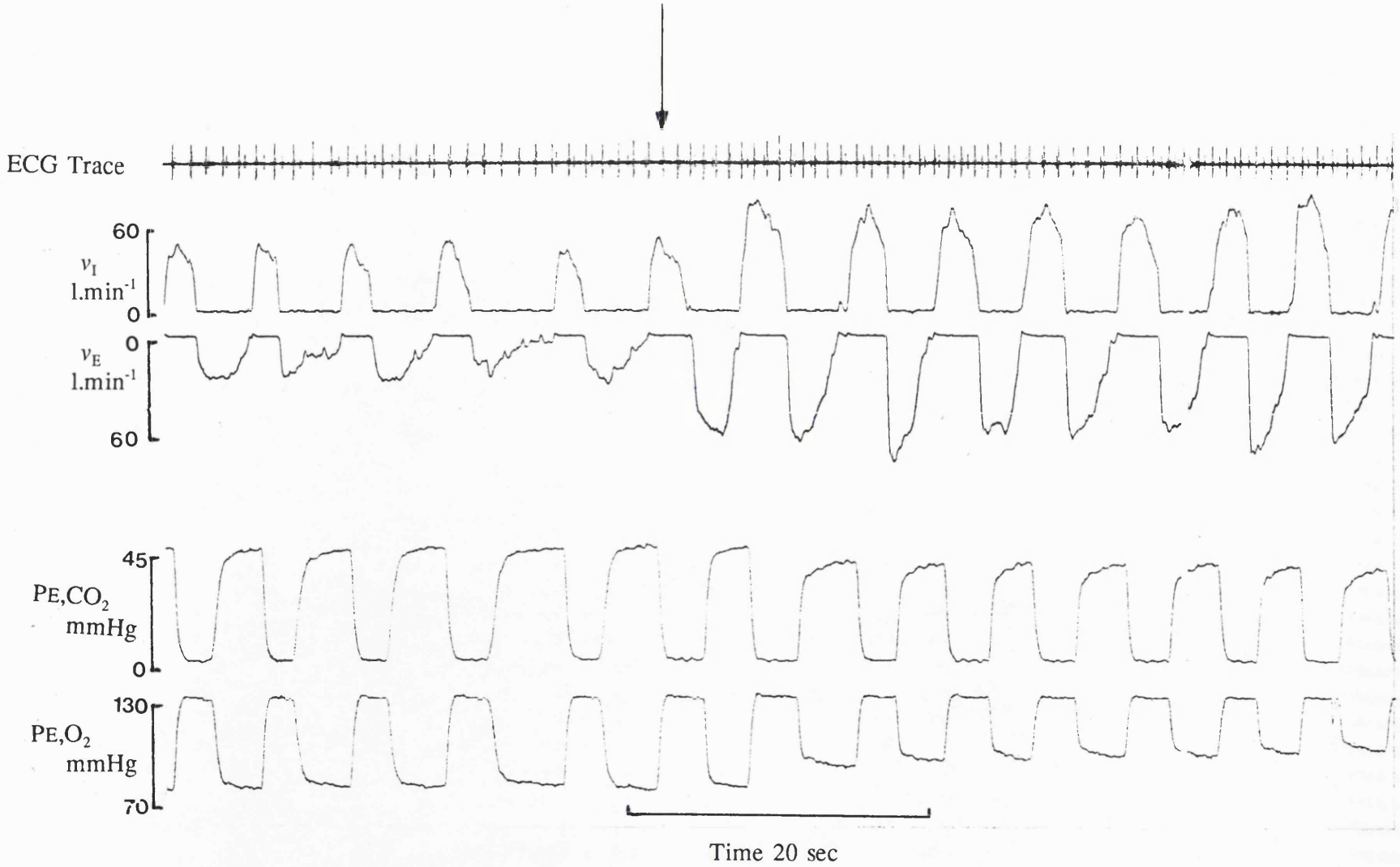


Figure 4.2a: Trace of QRS complexes, v_I, v_E, P_{E,CO_2} and P_{E,O_2} at the start of hyperventilation (arrowed) in protocol "A" performed by subject 2.

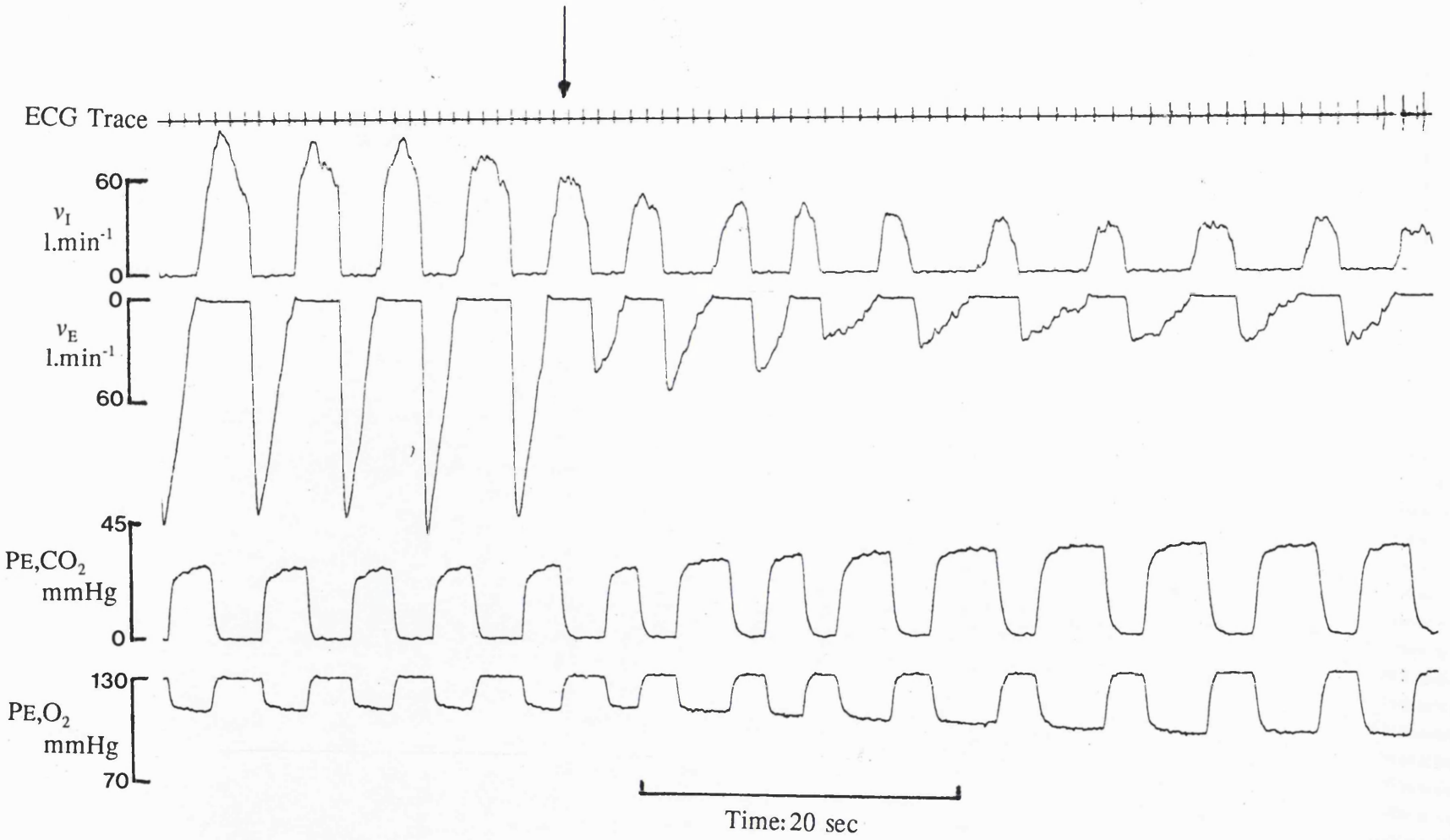


Figure 4.2b: Trace of QRS complexes, v_I, v_E, P_{E,CO_2} and P_{E,O_2} at the end of hyperventilation (arrowed) in protocol "A" performed by subject "2".

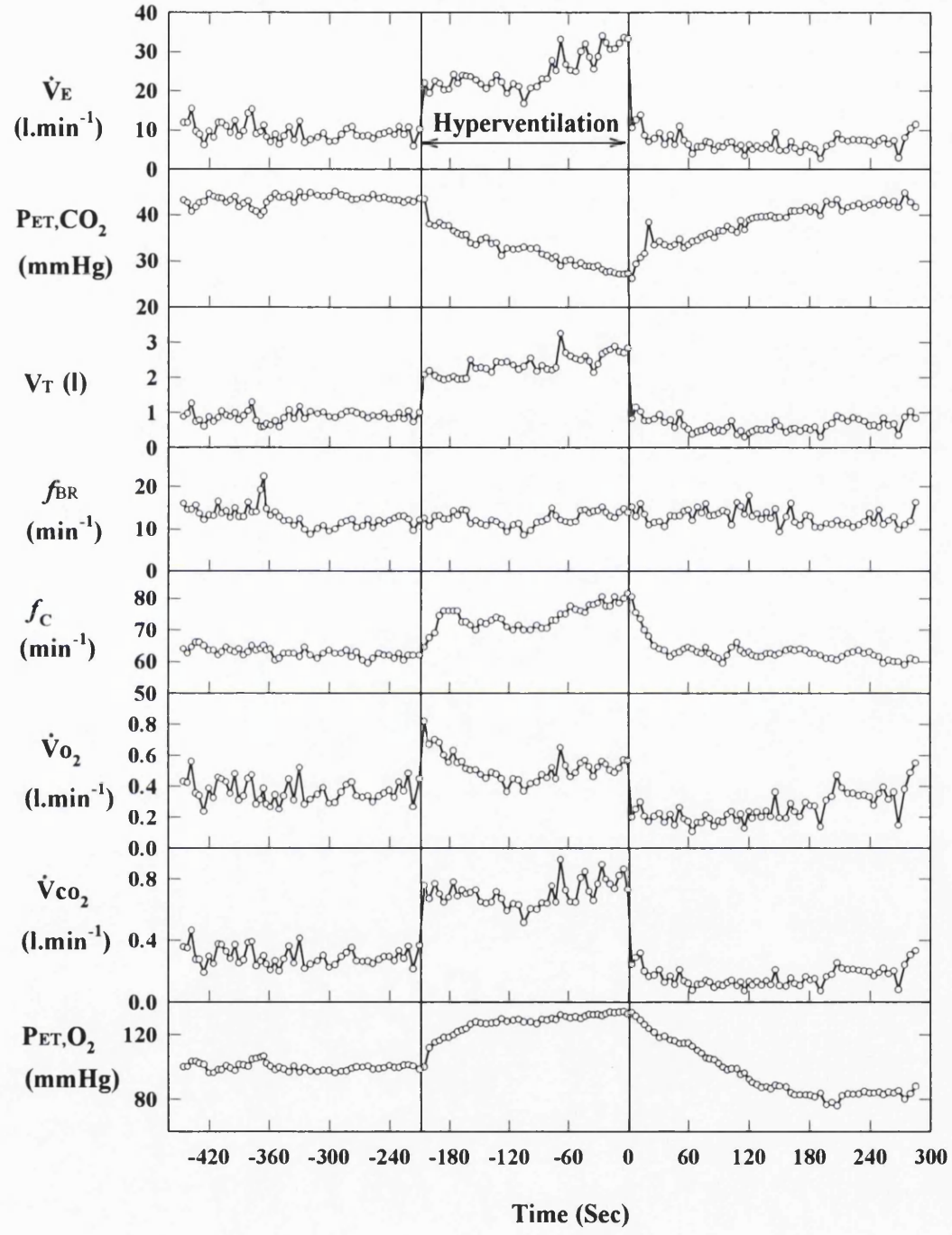


Figure 4.2c: Breath-by-breath values for $\dot{V}E$, PET,CO_2, VT, fBR, f_C, $\dot{V}o_2$, $\dot{V}co_2$ and PET,O_2 (Respectively from top to bottom) throughout protocol "A" performed by subject 2. Time 0 represents the end of hyperventilation.

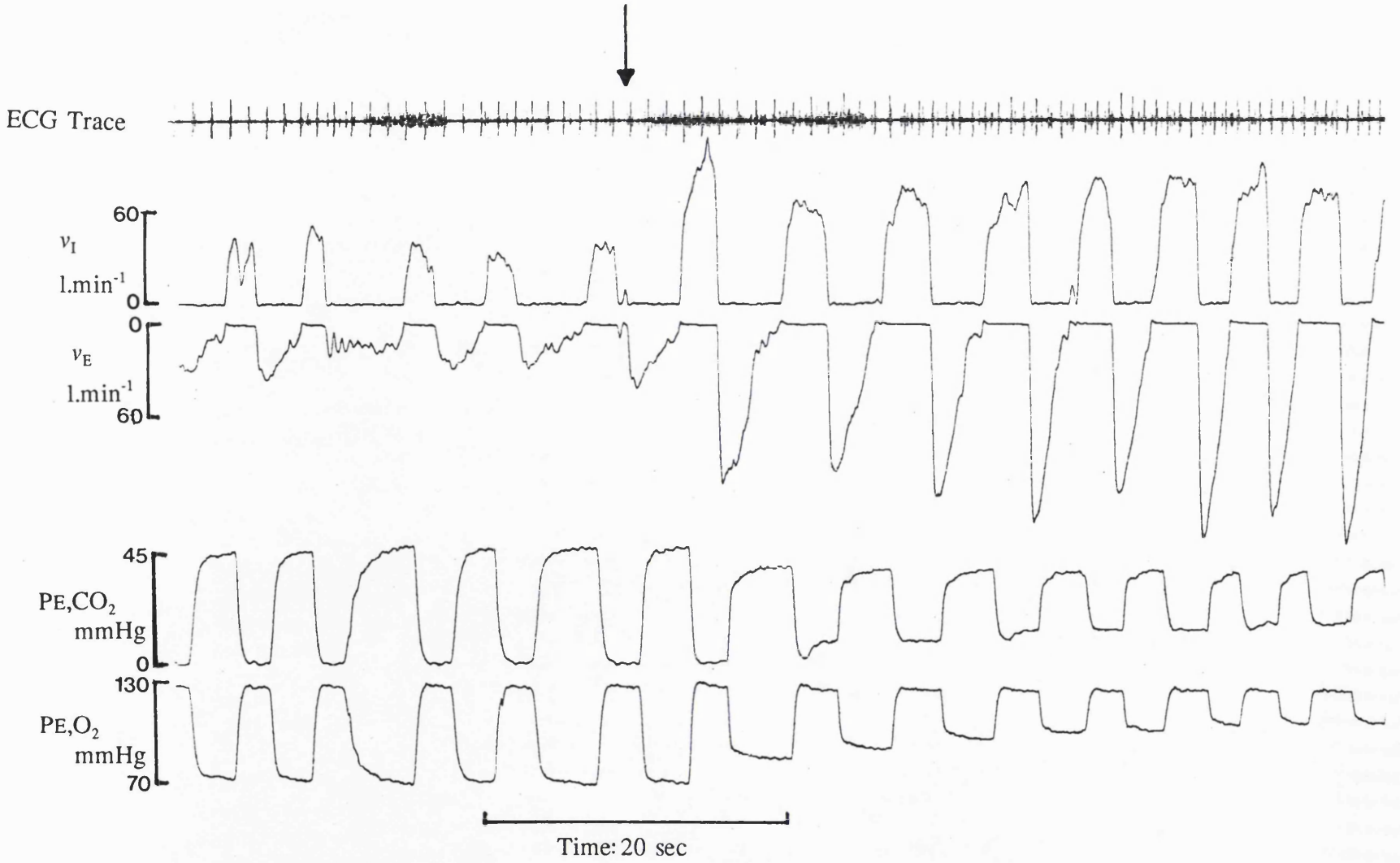


Figure 4.3a: Trace of QRS complexes, v_I, v_E, P_{E,CO_2} and P_{E,O_2} at the start of hyperventilation (arrowed) in protocol "B" performed by subject 2. Note rise in P_{E,CO_2} baseline following start of hyperventilation due to addition of CO_2 to inspirate.

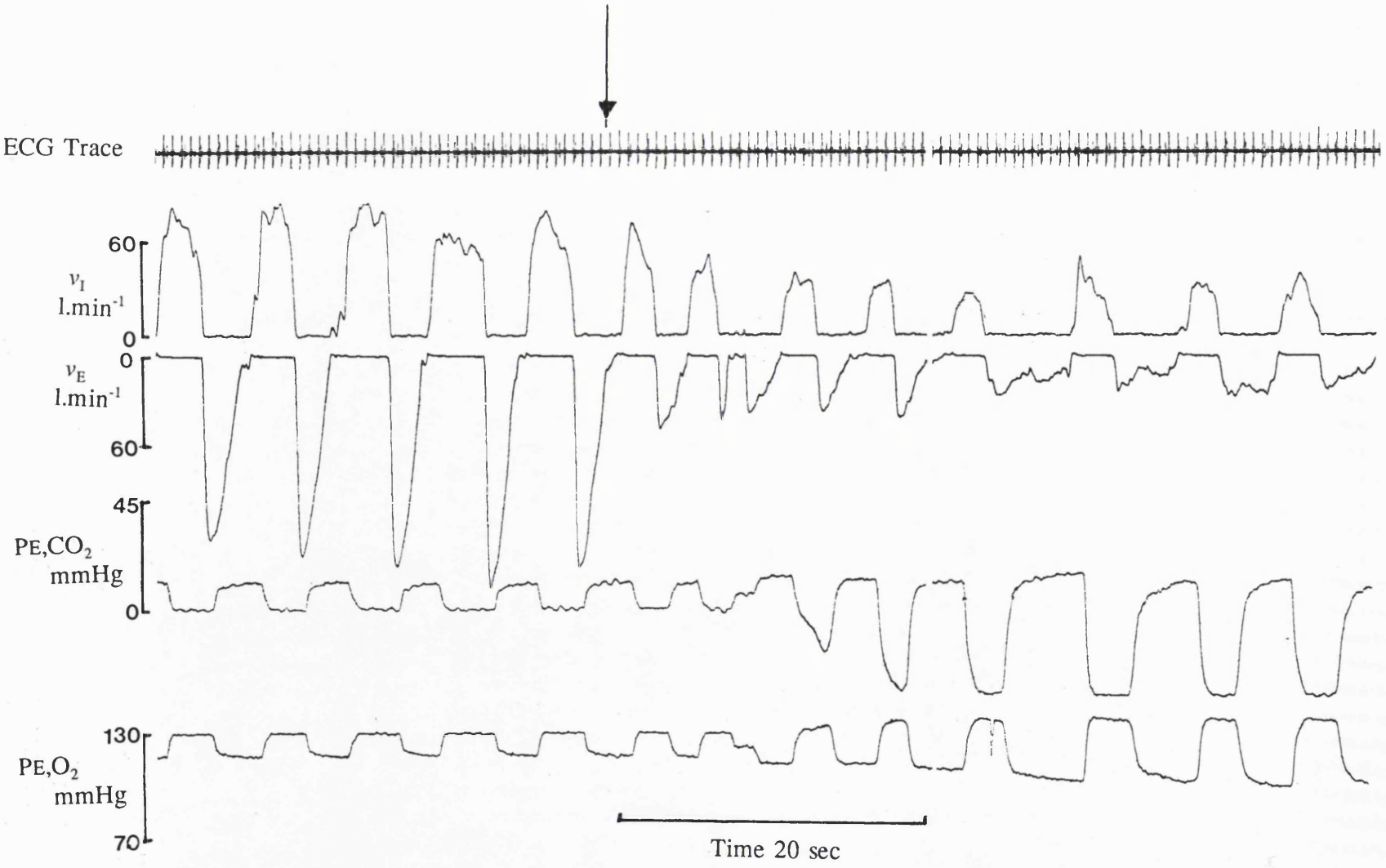


Figure 4.3b: Trace of QRS complexes, v_I, v_E, P_{E,CO_2} and P_{E,O_2} at the end of hyperventilation (arrowed) in protocol "B" performed by subject 2.

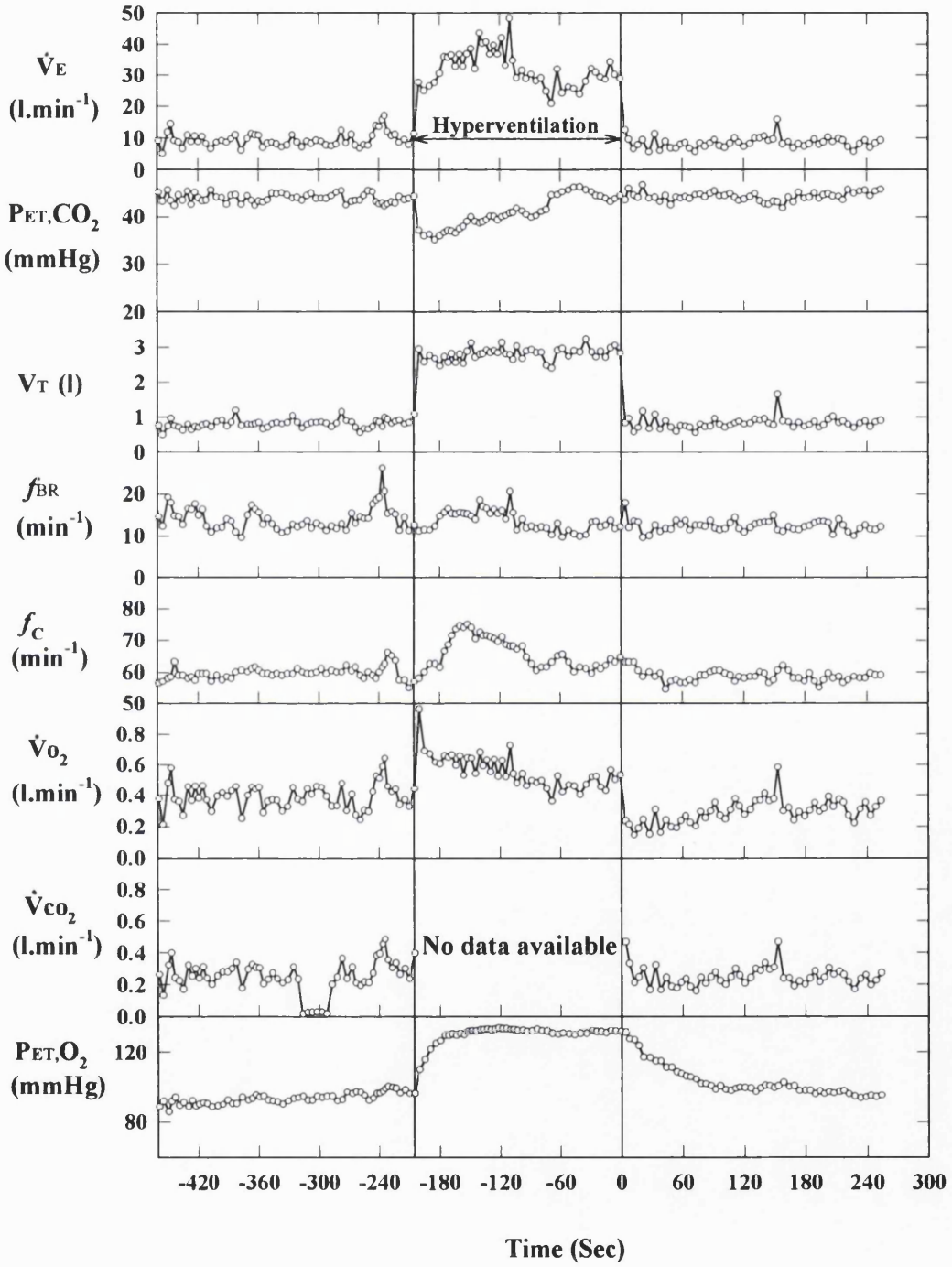


Figure 4.3c: Breath-by-breath values for $\dot{V}E$, PET,CO_2, VT, fBR, f_C, $\dot{V}o_2$, $\dot{V}co_2$ and PET,O_2 (Respectively from top to bottom) throughout protocol "B" performed by subject 2.Time 0 represents the end of hyperventilation.

HYPERVENTILATION:

During the hyperventilation period, $\dot{V}E$ increased by a factor of 3.6 ± 0.3 in protocol "A" and 3.2 ± 0.3 in protocol "B" ("A" vs. "B"; *N.S.* See *Figs. 4.2c* and *4.3c*). This increase was achieved in by an increase in VT of 2.92 ± 0.29 in protocol "A" and 2.96 ± 0.37 in protocol "B" ("A" vs. "B"; *N.S.* See *Figs. 4.2* and *4.3c*).with an increase in f_{BR} of 1.28 ± 0.12 in protocol "A" and 1.08 ± 0.08 in protocol "B" (See *Table 4.3.* A vs. "B".; *N.S.*). In Protocol "A" P_{ET,CO_2} had fallen below 25 mmHg in four of the subjects by the end of the hyperventilation period (See *Figs. 4.2c* and *4.8a*). The highest level of P_{ET,CO_2} among the remaining three subjects was, however, 27 mmHg, demonstrating that the level of hyperventilation needs to be raised slightly to ensure that all subjects reduce their P_{ET,CO_2} to below 25 mmHg in the time available. In Protocol "B" P_{ET,CO_2} was well maintained close to pre-hyperventilation values in all subjects (See *Table 4.3* and *Figs. 4.3c* and *4.8a*). P_{ET,O_2} rose rapidly following the start of hyperventilation in both protocols (See *Table 4.3*; "A" vs. "B": *N.S.* See *Figs. 4.2, 4.3c* and *4.8b*). Given the already high level of haemoglobin saturation, this is unlikely to be of physiological significance.

	A	B
f_C	87 ± 6*	74 ± 4*
$\dot{V}E$	34.52 ± 4.74*	33.79 ± 6.68*
VT	2.91 ± 0.26*	3.67 ± 0.35*
f_{BR}	13.7 ± 2.3	10.8 ± 1.3
P_{ET,CO_2}	26 ± 1*#	40 ± 2
P_{ET,O_2}	135 ± 1*#	131 ± 2*
$\dot{V}o_2$	0.58 ± 0.08	
$\dot{V}co_2$	0.79 ± 0.12*	
RER	1.37 ± 0.12*	

Table 4.3: Mean (± SE) hyperventilation data for protocols "A" and "B". n = 7 for protocol "A", n = 5 for protocol "B". * denotes value significantly ($p < 0.05$) different from rest, # denotes significant ($p < 0.05$) difference between values for protocols "A" and "B".

Data for $\dot{V}O_2$, $\dot{V}CO_2$ and RER were available during the hyperventilation period for protocol "A" only. In protocol "A" $\dot{V}O_2$ increased abruptly at the beginning of hyperventilation (See *Fig. 4.2c*). This increase was transient. $\dot{V}O_2$ did not return to resting levels, but was increased by a factor of 1.51 ± 0.01 above resting levels at the end of hyperventilation (See *Table 4.3*). $\dot{V}CO_2$ also increased abruptly at the onset of hyperventilation and this increase was also transient (See *Fig. 4.2c*). The rate of decline of $\dot{V}CO_2$ was, however, slower than for $\dot{V}O_2$; $\dot{V}CO_2$ was increased by a factor of 2.08 ± 0.45 over resting levels. This difference between the effects of volitional hyperventilation on $\dot{V}O_2$ and $\dot{V}CO_2$ was reflected in the significant increase in RER during hyperventilation.

f_C: f_C increased to similar levels during hyperventilation for the two protocols (See *Table 4.3* and *Figs 4.2c* and *4.3c*). f_C did not increase abruptly at the onset of hyperventilation but increased more gradually to a steady-state.

POST HYPERVENTILATION:

$\dot{V}E$: The profile of the fall in $\dot{V}E$ following the cessation of hyperventilation was similar to that described by Tawadrous & Eldridge (1974) for hypocapnic hyperventilation and Swanson et al. (1976) for eucapnic hyperventilation. There was an initial abrupt fall in $\dot{V}E$ followed by a more gradual fall either to or below baseline values, depending on the level of P_{ET,CO_2} (See *Figs. 4.2c, 4.3c* and *4.4*).

In protocol "A", $\dot{V}E$ did not fall below normal resting levels following the cessation of volitional hyperventilation in 2 subjects(subjects Q and 1), but remained elevated (See *Figs. 4.10* and *4.11*). They were not included in any further analysis. For the remaining subjects, $\dot{V}E$ fell to below pre-hyperventilation levels within 30 sec of ceasing hyperventilation (See *Table 4.4* and *Fig. 4.4*) and continued to fall, reaching a nadir between 1 and 2 min post-hyperventilation (See *Table 4.4*). After this $\dot{V}E$ gradually increased, but did not return to resting levels by 4 min post-hyperventilation (See *Table 4.4* and *Fig. 4.4*).

	30 SEC	1 MIN	2 MIN	3 MIN	4 MIN
f_C	71 ± 7	67 ± 6	68 ± 5	70 ± 5	67 ± 6
$\dot{V}E$	7.92 ± 0.86*	5.8 ± 0.91*#	6.52 ± 0.72*	6.81 ± 0.69*#	8.23 ± 0.69*
VT	0.78 ± 0.14#	0.72 ± 0.11*#	0.89 ± 0.25	0.92 ± 0.23	1.01 ± 0.14
fBR	12.3 ± 1.3	10.7 ± 2.2	10.0 ± 1.3	10.0 ± 1.1	909 ± 1.0
P_{ET,CO_2}	32 ± 1*#	34 ± 1	37 ± 1	39 ± 1	40 ± 1
P_{ET,O_2}	119 ± 1*	109 ± 5	95 ± 5	90 ± 8	93 ± 5
$\dot{V}o_2$	0.21 ± 0.03*	0.19 ± 0.02*	0.22 ± 0.02*	0.28 ± 0.03*	0.36 ± 0.05
$\dot{V}co_2$	0.17 ± 0.03*	0.14 ± 0.02	0.14 ± 0.03*#	0.17 ± 0.03*#	0.23 ± 0.03*#
RER	0.8 ± 0.07	0.71 ± 0.05*	0.62 ± 0.08*	0.61 ± 0.09*	0.66 ± 0.07*

Table 4.4: Mean (± SE) values at 30 sec, 1 min, 2 min, 3 min and 4 min after the cessation of hyperventilation in protocol "A". n = 5. * denotes values are significantly ($p < 0.05$) different from normal resting values. # denotes a significant ($p < 0.05$) difference between values in protocols "A" and "B".

The time constant of the fall in $\dot{V}E$ following hyperventilation, obtained using MODEL 1 (See Methods section and Appendix D), was 19.0 ± 3.8 sec.

In protocol "B". $\dot{V}E$ fell to resting levels within 30 sec of ceasing hyperventilation (See *Table 4.5* and *Fig. 4.4*) in three of the five subjects, the other two taking until 2 min post-hyperventilation to fully recover. These were not the same subjects those mentioned in the preceding paragraph. Modelling the fall in $\dot{V}E$ following hyperventilation using MODEL 1 (described in the Methods section and in Appendix D) yielded similar time constants for the fall in $\dot{V}E$ in protocol "A" (τ = 15.2 ± 5.2 sec for protocol "B".; "A" vs. "B".; *N.S.*).

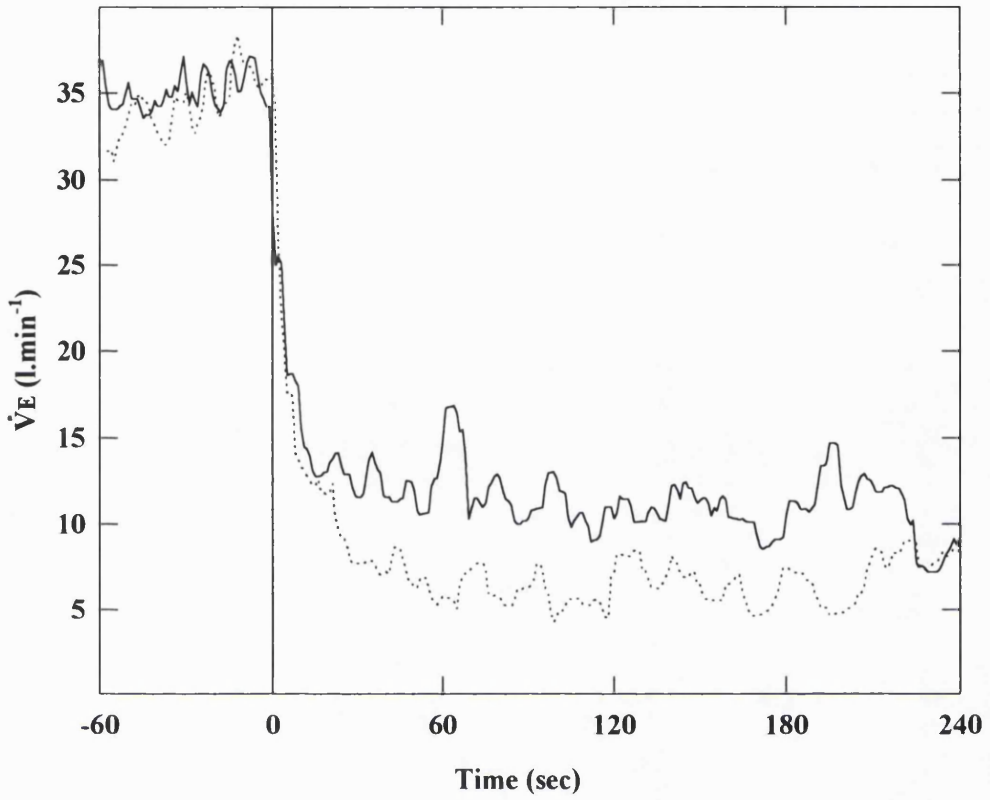


Figure 4.4: Group mean changes in $\dot{V}E$ over the last min of hyperventilation and the subsequent 4 min of rest in protocols "A" (dotted line) and "B" (solid line). Time 0 represents the end of hyperventilation. Individual data were interpolated over 1 sec intervals, time-aligned and averaged. n = 5 for both protocols.

	30 SEC	1 MIN	2 MIN	3 MIN	4 MIN
f_C	67 ± 4	69 ± 5	68 ± 4	67 ± 4	66 ± 3
$\dot{V}E$	12.39 ± 2.6	12.19 ± 2.8	10.73 ± 1.99	10.35 ± 1.5	10.88 ± 1.85
VT	1.28 ± 0.2	1.52 ± 0.32	1.32 ± 0.19	1.3 ± 0.15	1.31 ± 0.2
f_{BR}	11.3 ± 1.3	9.8 ± 1.1	9.9 ± 0.99	10.7 ± 1.4	10.4 ± 1.5
P_{ET,CO_2}	38 ± 3	36 ± 3	38 ± 3	38 ± 2	38 ±3
P_{ET,O_2}	118 ± 4*	115 ± 4*	110 ± 4*	109 ± 3	109 ± 6
$\dot{V}O_2$	0.28 ± 0.08	0.31 ± 0.09	0.32 ± 0.02*	0.34 ± 0.05*	0.34 ± 0.03*
$\dot{V}CO_2$	0.27 ± 0.08	0.27 ± 0.09	0.27 ± 0.01	0.29 ± 0.03	0.28 ± 0.02
RER	1.11 ± 0.15*	0.98 ± 0.11	0.87 ± 0.04	0.9 ±0.06	0.85 ±0.12

Table 4.5: Mean (± SE) values at 30 sec, 1 min, 2 min, 3 min and 4 min after the cessation of hyperventilation in protocol "B". n = 6. * denotes values are significantly ($p < 0.05$) different from normal resting values. $^{\#}$ denotes a significant ($p < 0.05$) difference between values in protocols "A" and "B" (See *Table 4.3*).

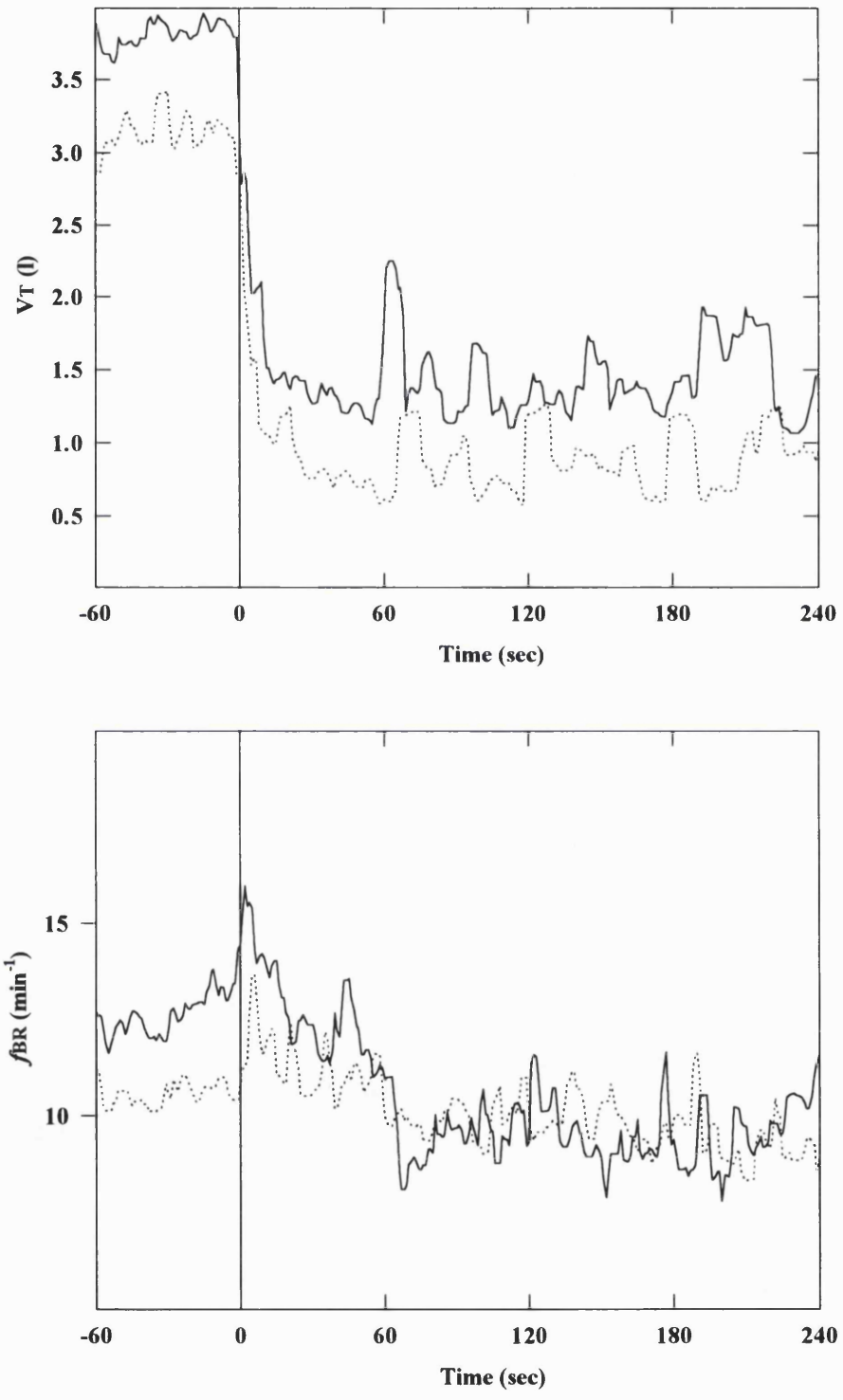


Figure 4.5: Group mean changes in VT (*a*) and *f*BR (*b*) over the last min of hyperventilation and the subsequent 4 min of rest in protocols "A" (dotted line) and "B" (solid line). Time 0 represents the end of hyperventilation. Individual data were interpolated over 1 sec intervals, time-aligned and averaged. n = 5 for both protocols.

$\dot{V}o_2$, $\dot{V}co_2$ and RER: In protocol "A" $\dot{V}o_2$ and $\dot{V}co_2$ decreased abruptly following the cessation of hyperventilation (See *Figs. 4.6a & 4.6b*). This was followed by a more gradual decline similar in profile to that described above for VE (See *Table 4.4*). $\dot{V}o_2$ was similar to resting values by 30 sec after the end of hyperventilation but continued to fall before increasing again. $\dot{V}co_2$ also fell to below resting levels but did not fully recover by the end of the test. RER decreased steadilly following the end of hyperventilation (See *Table 4.4 and Fig. 4.6c*), falling below normal resting levels. This reflected the different effects of hyperventilation on body O_2 and CO_2 stores. It was still below resting levels at the end of the test.

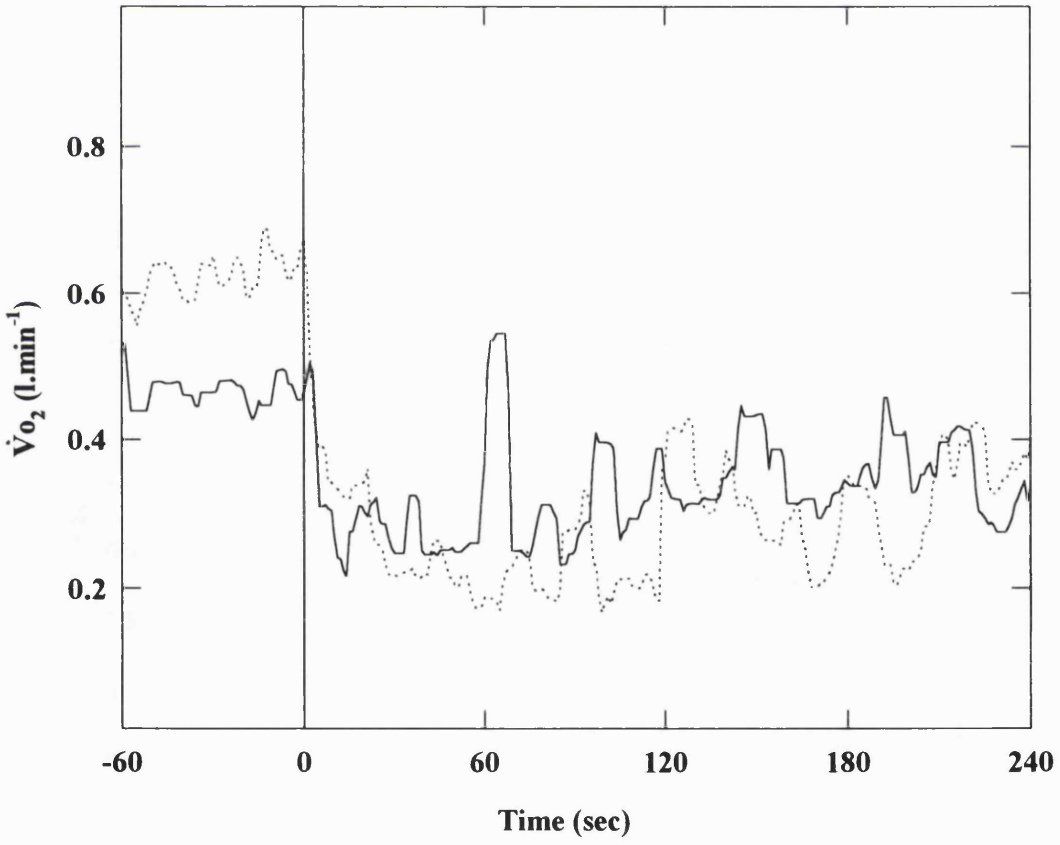


Figure 4.6a: Group mean changes in $\dot{V}o_2$ over the last min of hyperventilation and the subsequent 4 min of rest in protocols "A" (dotted line) and "B" (solid line). Time 0 represents the end of hyperventilation. Individual data were interpolated over 1 sec intervals, time-aligned and averaged. n = 4 for protocol "B"., n = 5 for protocol "B".

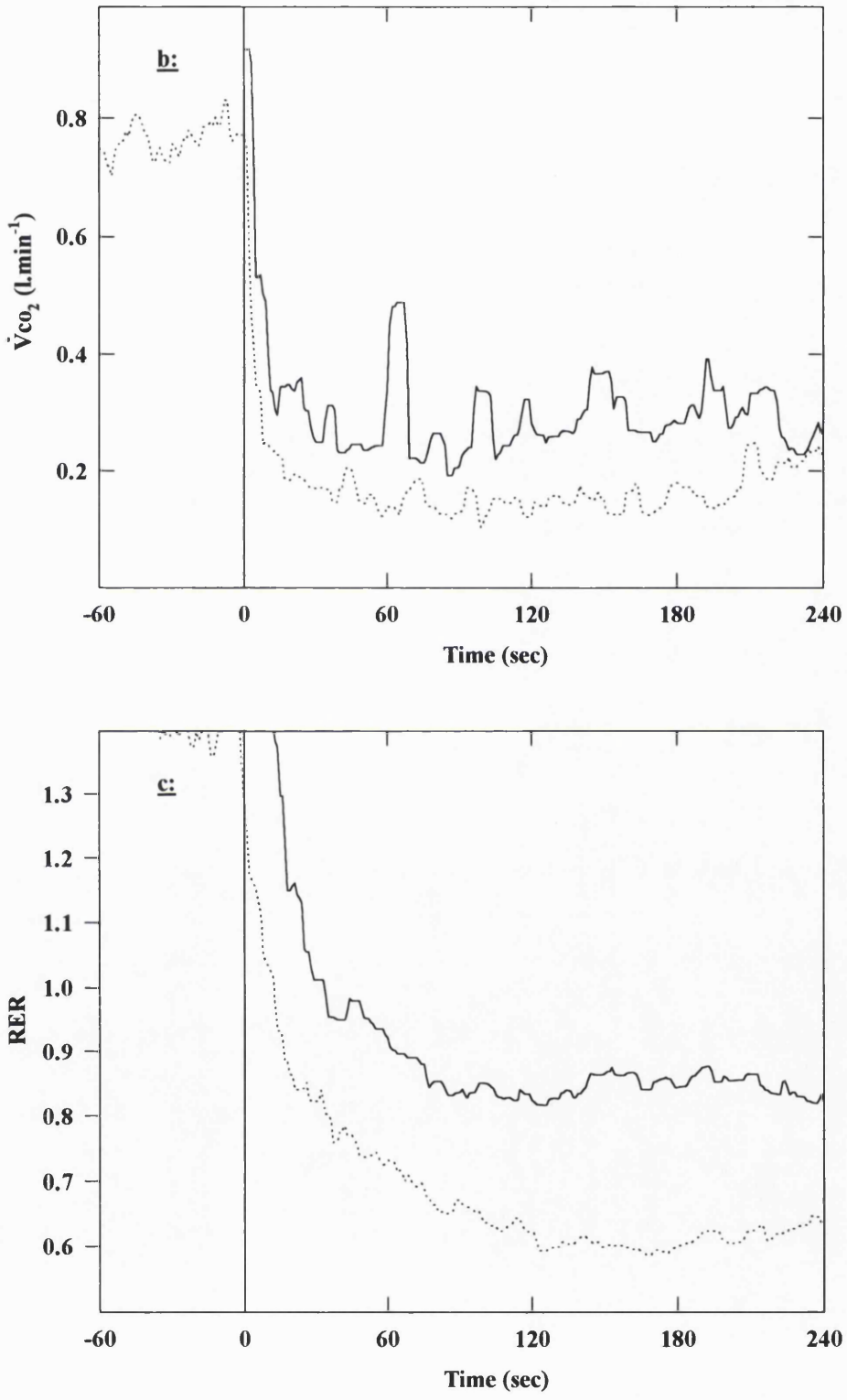


Figure 4.6b & c: Group mean changes in $\dot{V}co_2$ (*b*) and RER (*c*) over the last min of hyperventilation and the subsequent 4 min of rest in protocols "A" (dotted line) and "B" (solid line). Time 0 represents the end of hyperventilation. Individual data were interpolated over 1 sec intervals, time-aligned and averaged. n = 5 for protocol "A", n = 4 for protocol "B".

In protocol "B" $\dot{V}O_2$ and $\dot{V}CO_2$ decreased abruptly following the cessation of hyperventilation. Both variables had returned to resting levels within 30 sec of the end of hyperventilation and remained similar to resting levels for the remainder of the test (See *Table 4.4*). RER decreased rapidly following the end of hyperventilation and was similar to resting levels within 30 sec of the end of hyperventilation (See *Table 4.4*).

f_C: Following the end of hyperventilation, f_C fell rapidly to resting levels (See *Tables 4.4* and *4.5* and *Figs. 4.2c, 4.*3c and *4.*7).

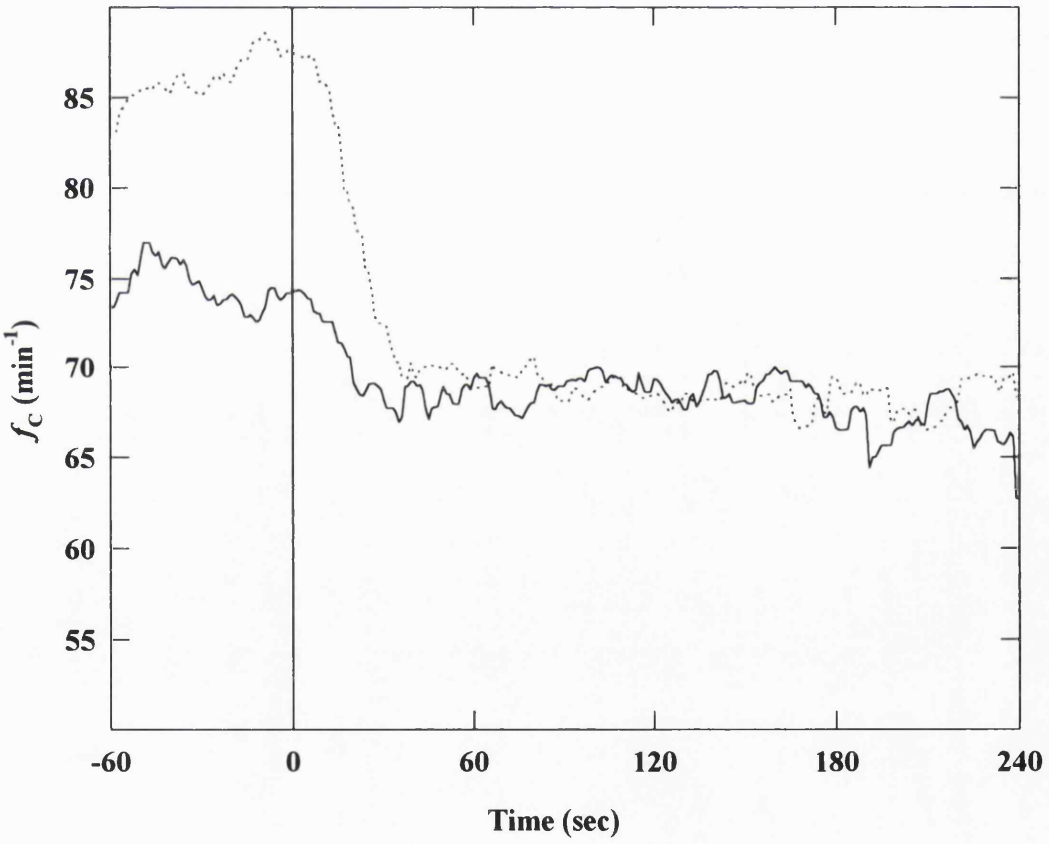


Figure 4.7: Group mean changes in f_C over the last min of hyperventilation and the subsequent 4 min of rest in protocols "A" (dotted line) and "B" (solid line). Time 0 represents the end of hyperventilation. Individual data were interpolated over 1 sec intervals, time-aligned and averaged. n = 5 for both protocols.

P_{ET,O_2} and P_{ET,CO_2}: P_{ET,CO_2} rose following the end of hyperventilation in protocol "A" (See *Fig. 4.*8a) but did not return to resting levels by the end of the test (See *Table 4.4*). In protocol "B"., P_{ET,CO_2} fell slightly following the end of hyperventilation, reflecting the excess ventilation associated with the afterdischarge (See *Fig. 4.8a*). Once $\dot{V}_E$ had fallen to resting levels, P_{ET,CO_2} rapidly returned to resting levels for the remainder of the test (See *Table 4.5*).

P_{ET,O_2} decreased following hyperventilation in protocol A, reaching a nadir of 82 ± 8 mmHg at 175 ± 19 sec after the end of hyperventilation (See *Table 4.4* and *Fig. 4.8b*). P_{ET,O_2} fell following the cessation of hyperventilation in protocol "B"., but remained above resting levels for the duration of the test (See *Table 4.5*)

Pattern of breathing following hyperventilation: Following eucapnic hyperventilation (Protocol "B".), the fall in V_E seen was almost entirely mediated by changes in V_T, f_{BR} remaining remarkably constant throughout the tests (See *Fig. 4.3b & c, 4.5a & b* and *Table 4.5*). This pattern was also seen in three subjects following hypocapnic hyperventilation (Protocol "A"). The remaining 2 subjects adopted a more variable pattern of breathing following the end of hyperventilation, with marked variation in V_T, T_I and T_E (See *Fig. 4.9*). The pattern of breathing adopted by the other two subjects was, however, similar to that described by Corfield et al. (1995), Apnoea following hyperventilation was not seen in any of the subjects tested; defined by Bainton & Mitchell (1966) as the loss of a single breath.

Chronic Hyperventilation: As mentioned above, two subjects (1 & Q) continued to hyperventilate (albeit at a much lower level that occurred during volitional hyperventilation) throughout the post-hyperventilation period (See *Fig. 4.10 & 4.11*). There is no obvious explanation for this and it will be discussed in the relevant section below.

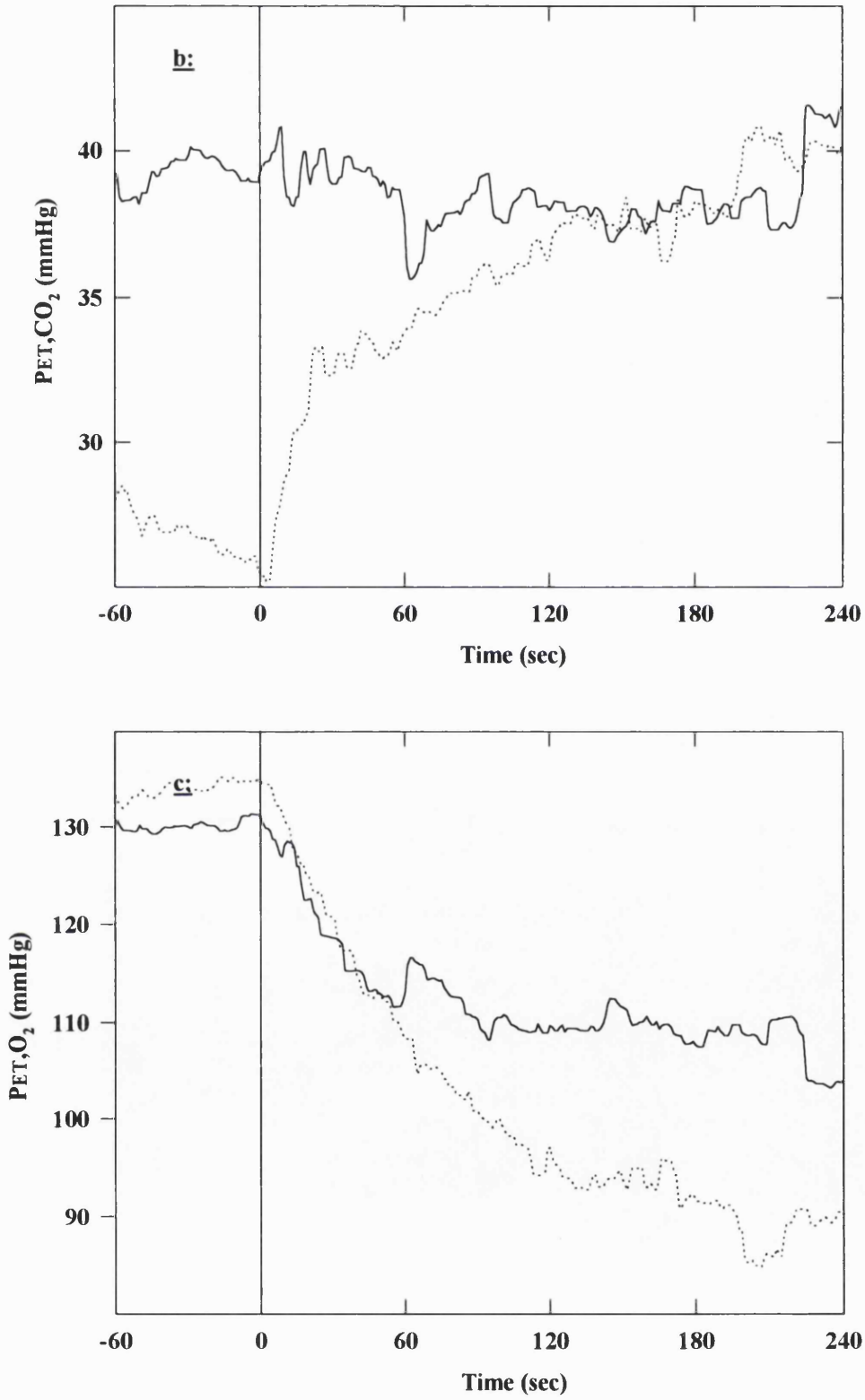


Figure 4.8a & b: Group mean changes in P_{ET,CO_2} (*a*) and P_{ET,O_2} (*b*) over the last min of hyperventilation and the subsequent 4 min of rest in protocols "A" (dotted line) and "B" (solid line). Time 0 represents the end of hyperventilation. Individual data were interpolated over 1 sec intervals, time-aligned and averaged. n = 5 for both protocols.

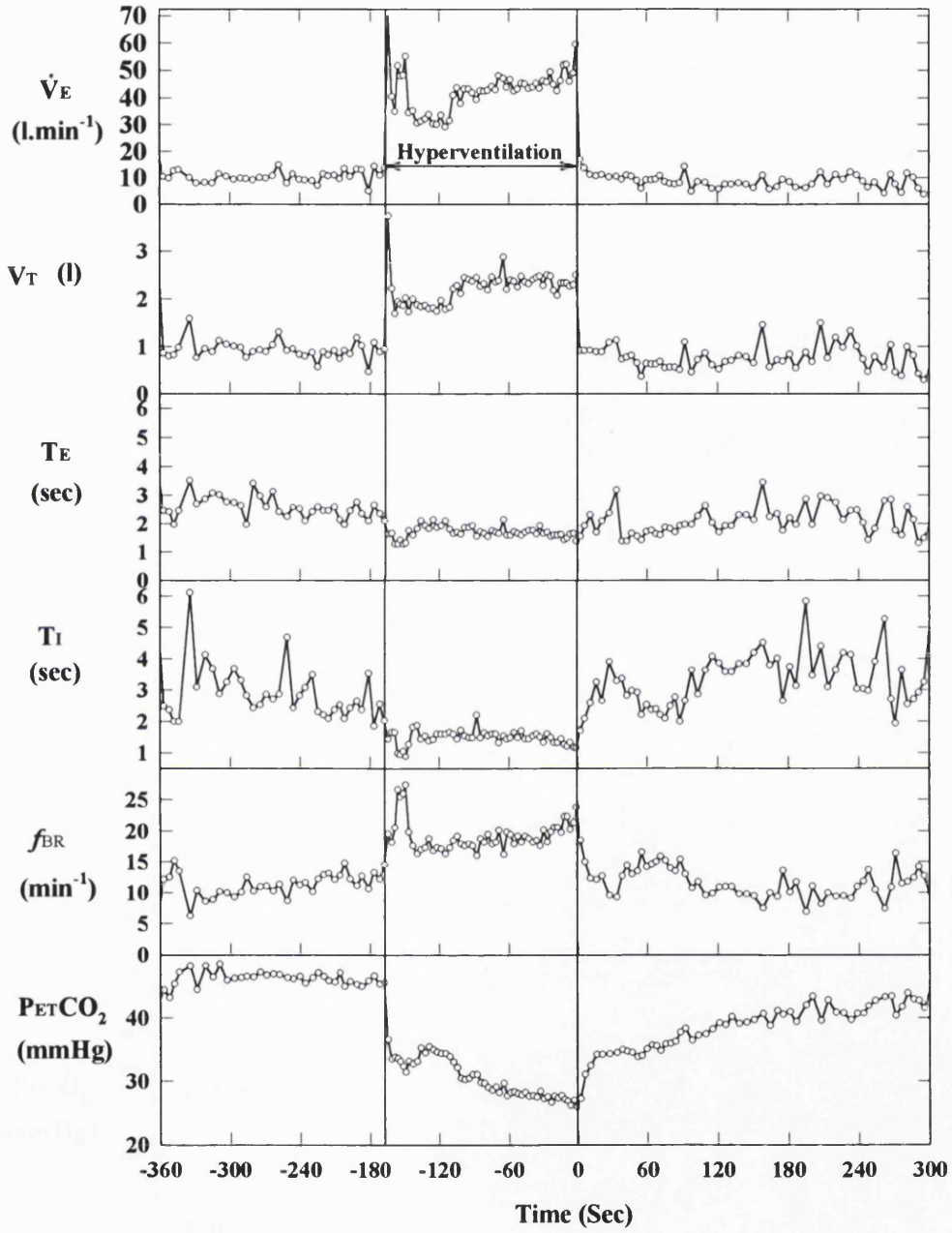


Figure 4.9: Breath-by-breath values for $\dot{V}E$, VT, TE, TI, fBR and P_{ET},CO_2 (respectively from top to bottom) throughout protocol "A" performed by subject C. Time 0 represents the end of hyperventilation. Note the increased variability of VT, TI, TE and fBR during recovery from hyperventilation. As only $\dot{V}E$ was monitored in this test, end-expiratory pauses are included in TI.

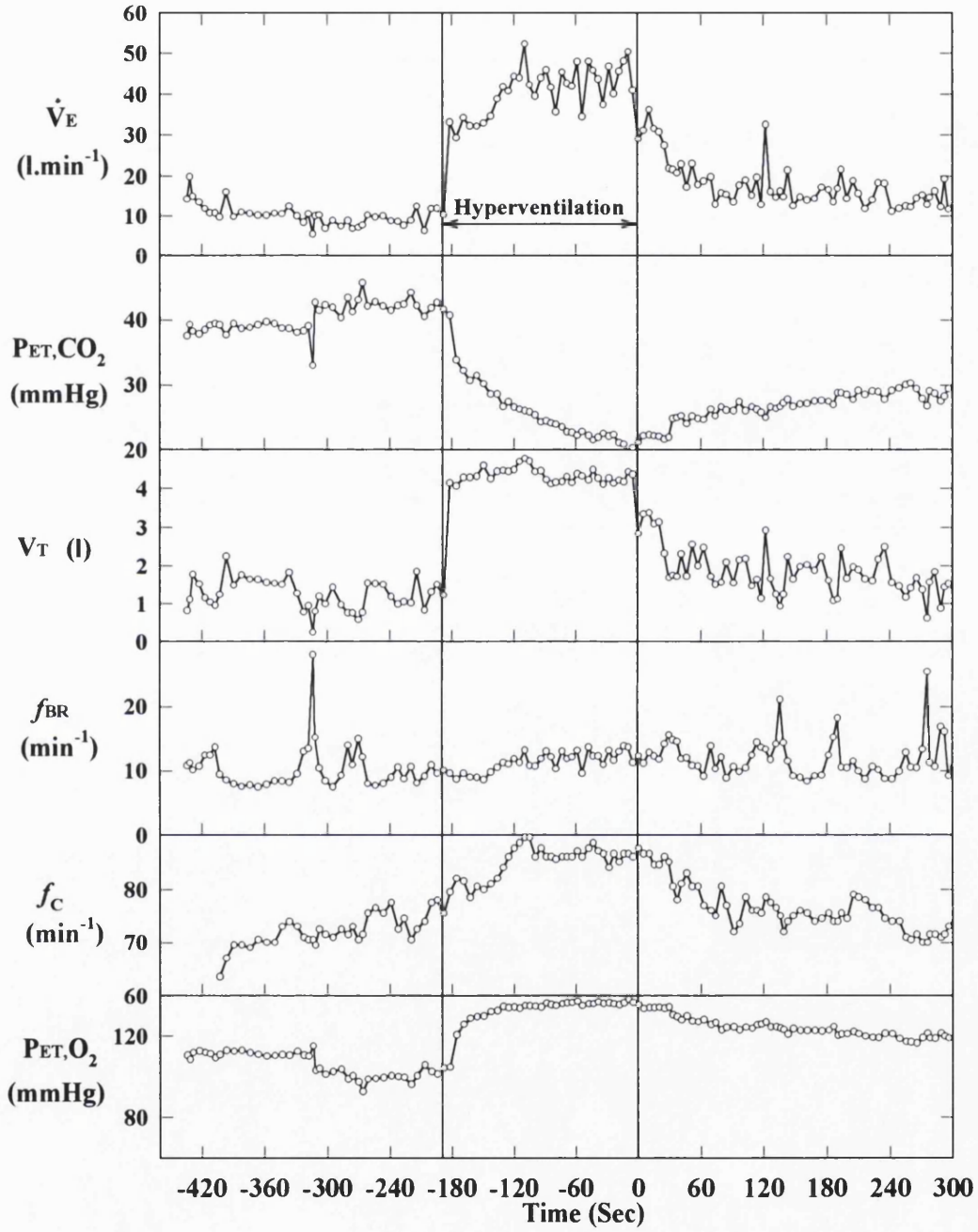


Figure 4.10: Breath-by-breath values for $\dot{V}_E$, P_{ET,CO_2}, V_T, f_{BR}, f_C, V_{O_2}, V_{CO_2} and P_{ET,O_2} (Respectively from top to bottom) throughout protocol "A" performed by subject 1. Hyperventilation ended at time 0. Note that $\dot{V}_E$ does not fall below normal resting levels.

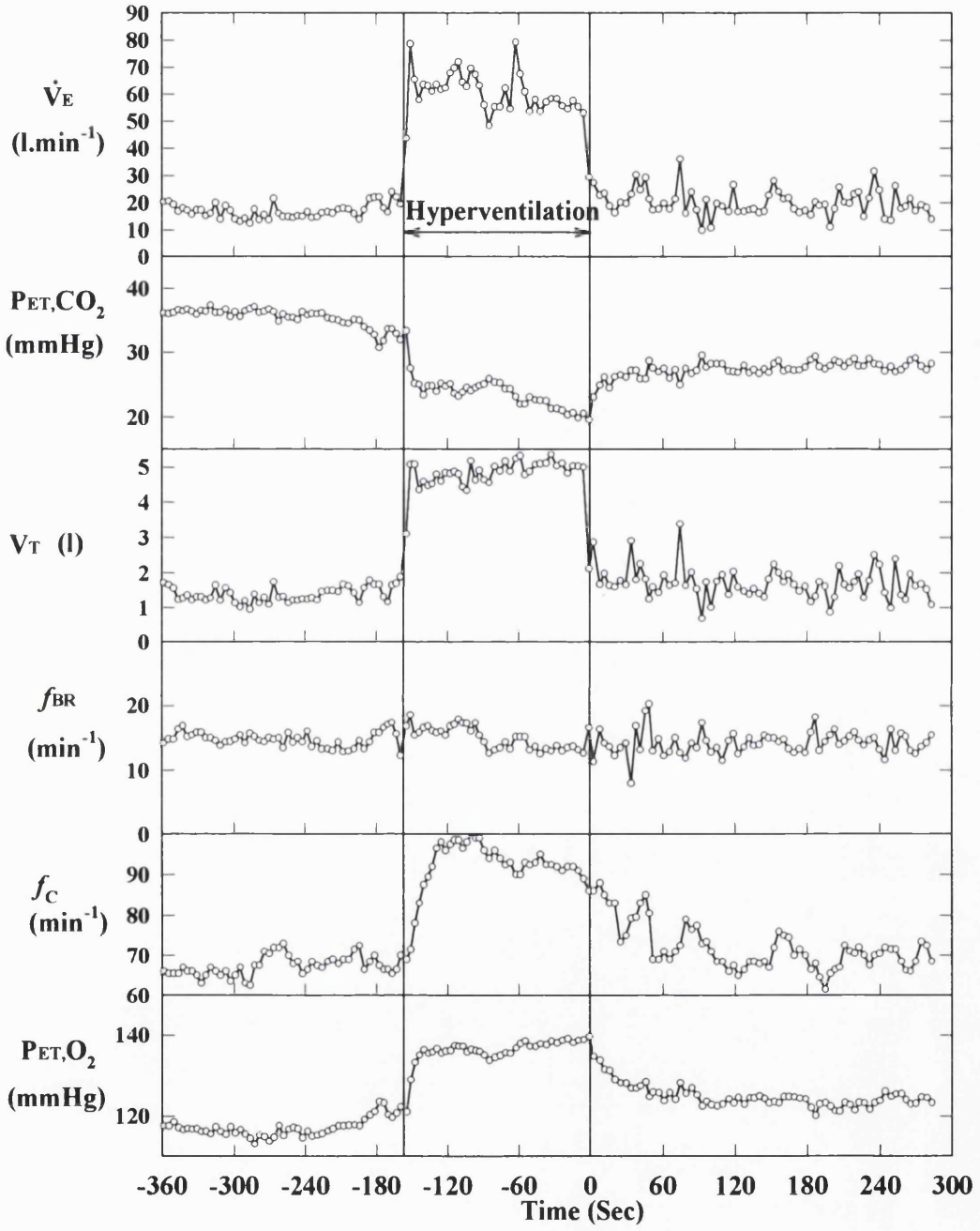


Figure 4.11: Breath-by-breath values for $\dot{V}E$, PET,CO_2, VT, fBR, f_C, Vo_2, Vco_2 and PET,O_2 (Respectively from top to bottom) throughout protocol "A" performed by subject Q. Hyperventilation ended at time 0. Again, note incomplete recovery from hyperventilation.

PROTOCOL C:

Resting values and cardiorespiratory responses to 50 W exercise were comparable to those reported in Chapter 3 and elsewhere in this thesis. The results from a representative test can be seen in *Fig. 4.12a* to *d.*

RESTING VALUES:

Mean (± SE) resting data for protocol "C" are presented in *Table.4.6.* These values are similar to the resting values reported in the other Chapters of the thesis.

	REST
f_C	72 ± 9
$\dot{V}E$	13.06 ± 0.78
VT	1.0 ± 0.06
f_{BR}	14.23 ± 1.79
P_{ET,CO_2}	41 ± 1
P_{ET,CO_2}	103 ± 2
$\dot{V}_{O_2}$	0.47 ± 0.02
$\dot{V}_{CO_2}$	0.38 ± 0.02
RER	0.8 ± 0.05

Table 4.6: Mean (± SE) data for the rest period in Protocol "C". n = 7

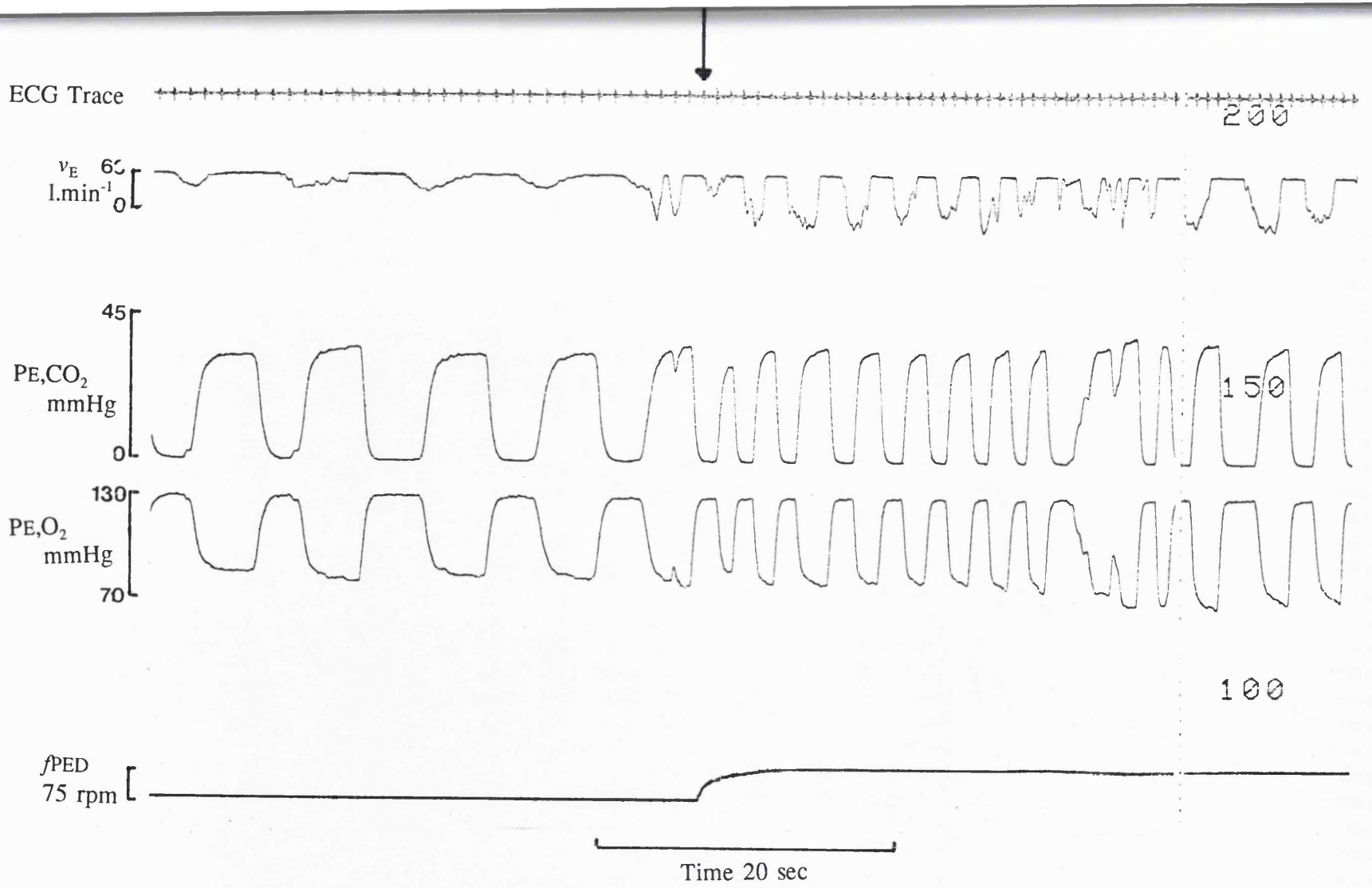


Figure 4.12a: Trace showing the start of 50 W exercise (arrowed) in Protocol "C" performed by subject T.

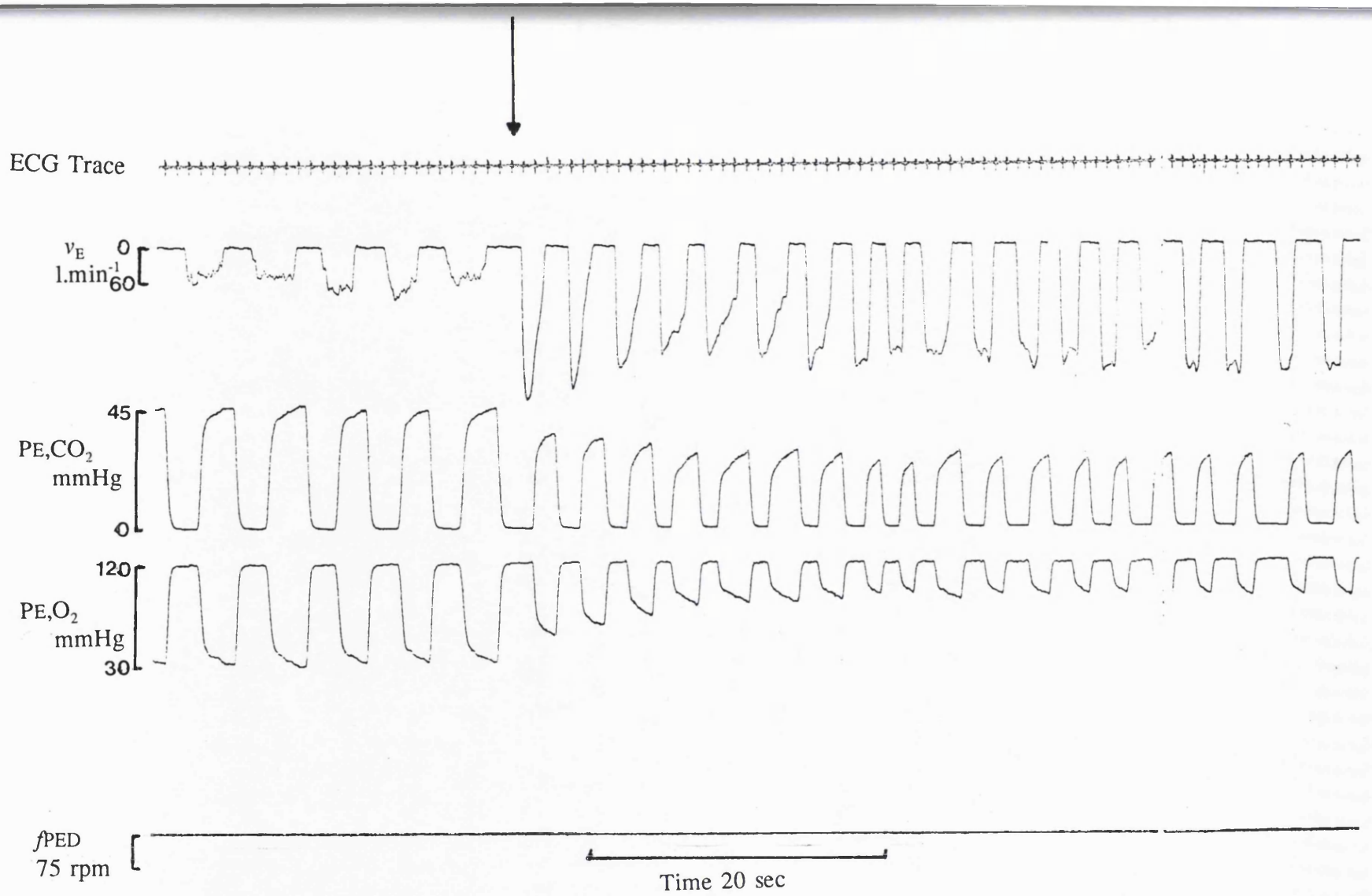


Figure 4.12b: Trace showing the start of hyperventilation (arrowed) in Protocol "C" performed by subject T.

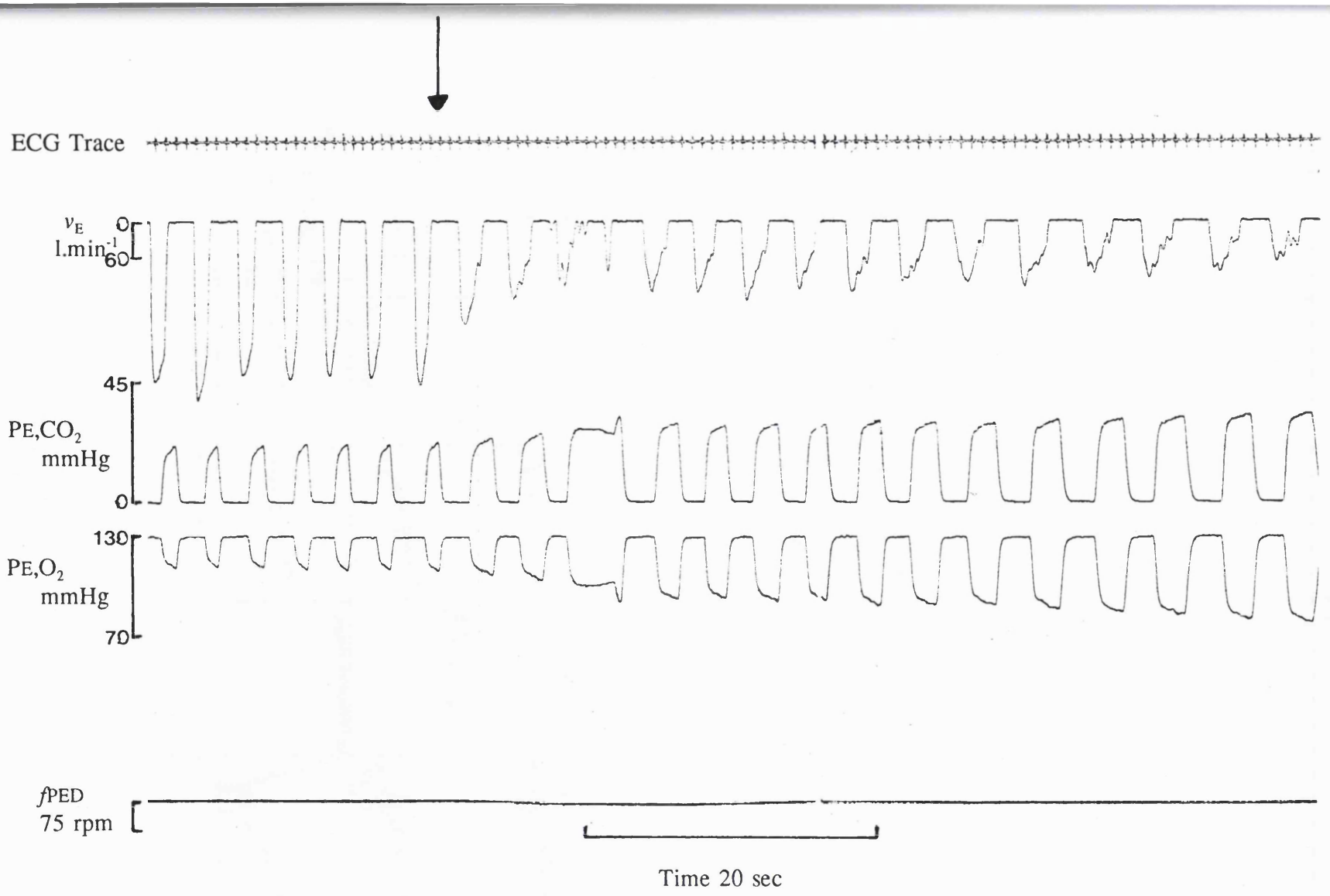


Figure 4.12c: Trace showing the end of hyperventilation (arrowed) in Protocol "C" performed by subject T.

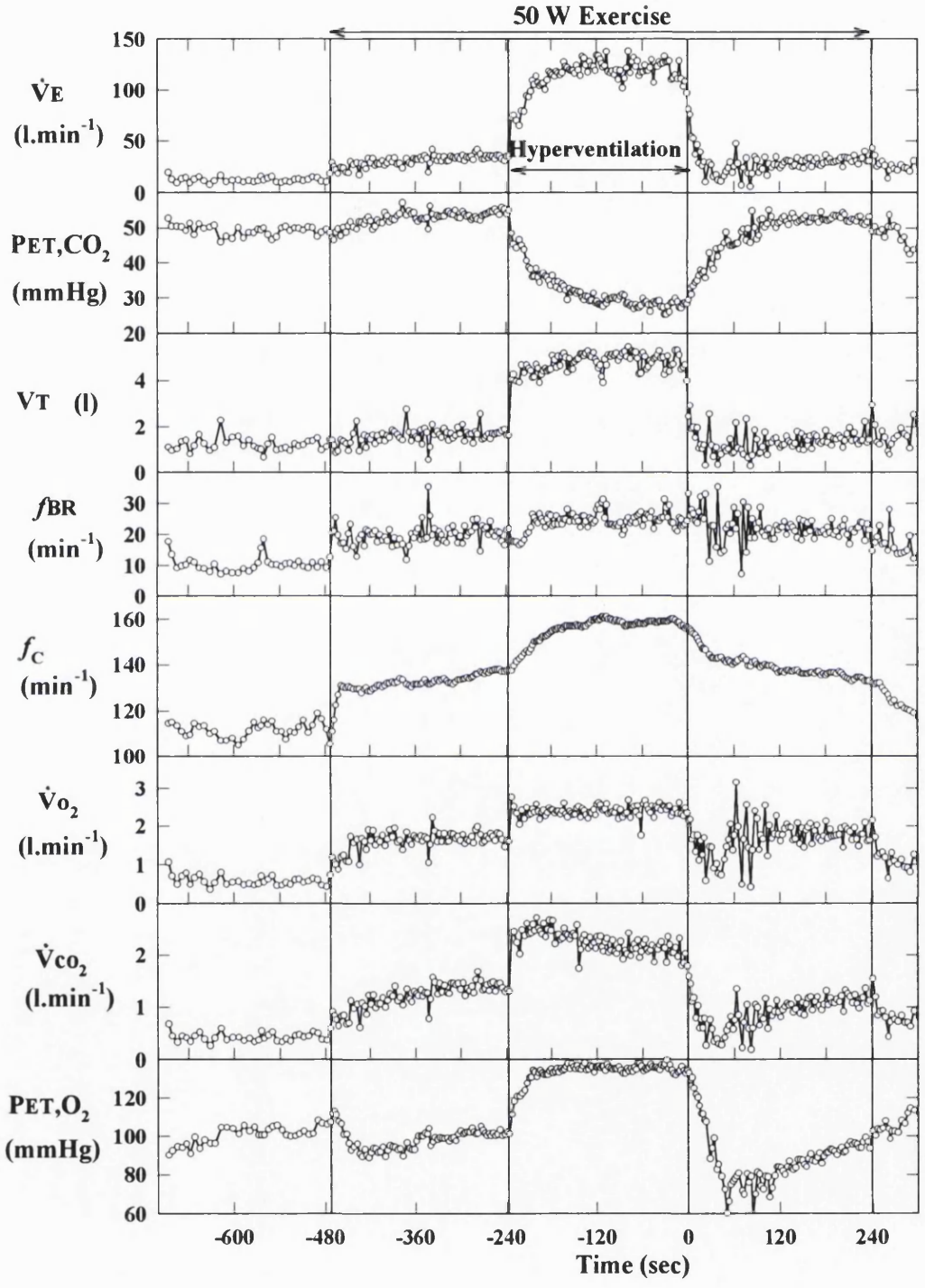


Figure 4.12d: Breath-by-breath values for $\dot{V}_E$, P_{ET,CO_2}, f_C, $\dot{V}o_2$, $\dot{V}co_2$, P_{ET,O_2}, V_T and f_{BR} (Respectively from top to bottom) throughout protocol "C" performed by subject T. Time 0 represents the end of hyperventilation.

50 W EXERCISE:

The initial cardiorespiratory and pulmonary gas exchange responses to the transition from rest to 50 W exercise are presented in *Table 4.7* and *Figs.4.13* to *4.15*.

	INITIAL RESPONSES
f_C	No data
$\dot{V}E$	34.0 ± 2.84
VT	1.51 ± 0.23
f_{BR}	23.72 ± 2.38
P_{ET,CO_2}	42 ± 1
P_{ET,O_2}	106 ± 3
$\dot{V}_{O_2}$	1.37 ± 0.12
$\dot{V}_{CO_2}$	1.11 ± 0.12
RER	0.82 ± 0.05

Table 4.7: Mean (± SE) initial responses to the onset of 50 W exercise in Protocol "C". n = 7

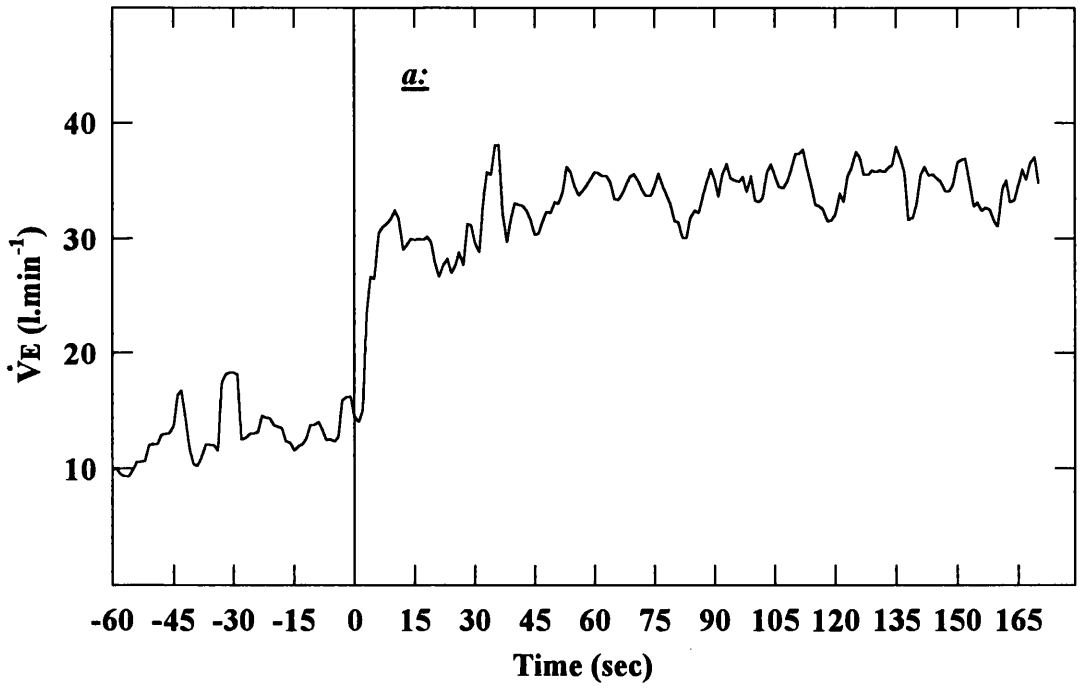


Figure 4.13a: Mean changes in $\dot{V}E$ during 1 min prior to and 3 min after the onset of 50 W exercise. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 7.

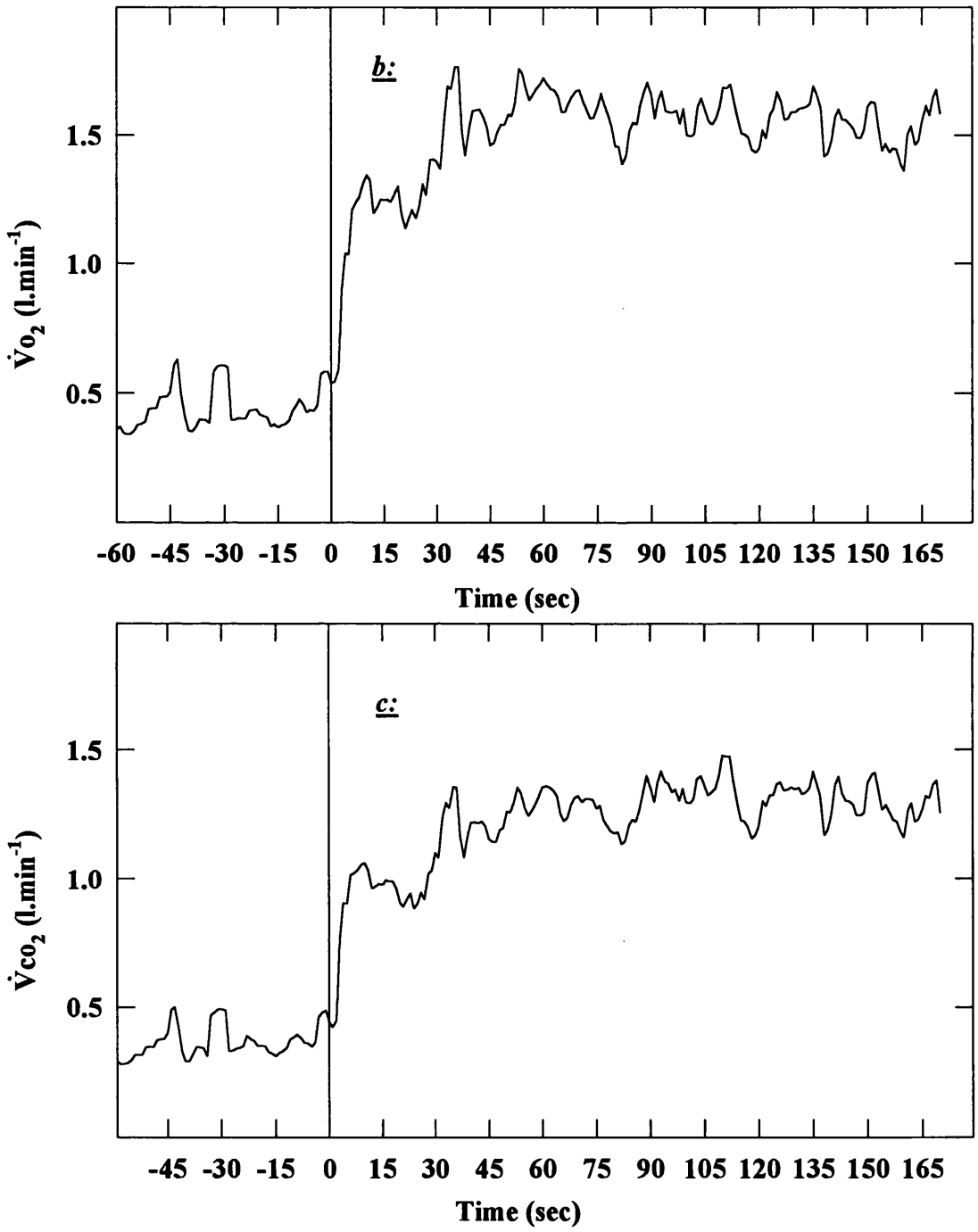


Figure 4.13b & c: Mean changes in $\dot{V}o_2$ and $\dot{V}co_2$ during 1 min prior to and 3 min after the onset of 50 W exercise in protocol "C". Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 7.

Modelling the respiratory and pulmonary gas exchange responses to the onset of 50 W exercise was not possible in these tests due to the similarity between the initial and steady-state responses (See *Tables 4.7* and *4.8* and *Fig. 4.13*). It was apparent from the interpolated data that the initial ventilatory and pulmonary gas exchange responses to the onset of 50 W exercise was transient in nature (See *Fig. 4.13*). This is in agreement with the results obtained in Chapter 7 and 8 for $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ and in Chapter 3 for $\dot{V}E$.

The initial increase in VE was due to an increase in VT (VT increased by a factor of 2.51 ± 0.21 over resting values. Initial response vs. rest: $p < 0\ 05$) with a smaller rise in fBR (fBR increased by a factor of 1.28 ± 0.12 over resting values (See *Figs. 4.14b & c* and *Tables 4.6* and *4.7*. Initial response vs. rest: $p < 0.05$).

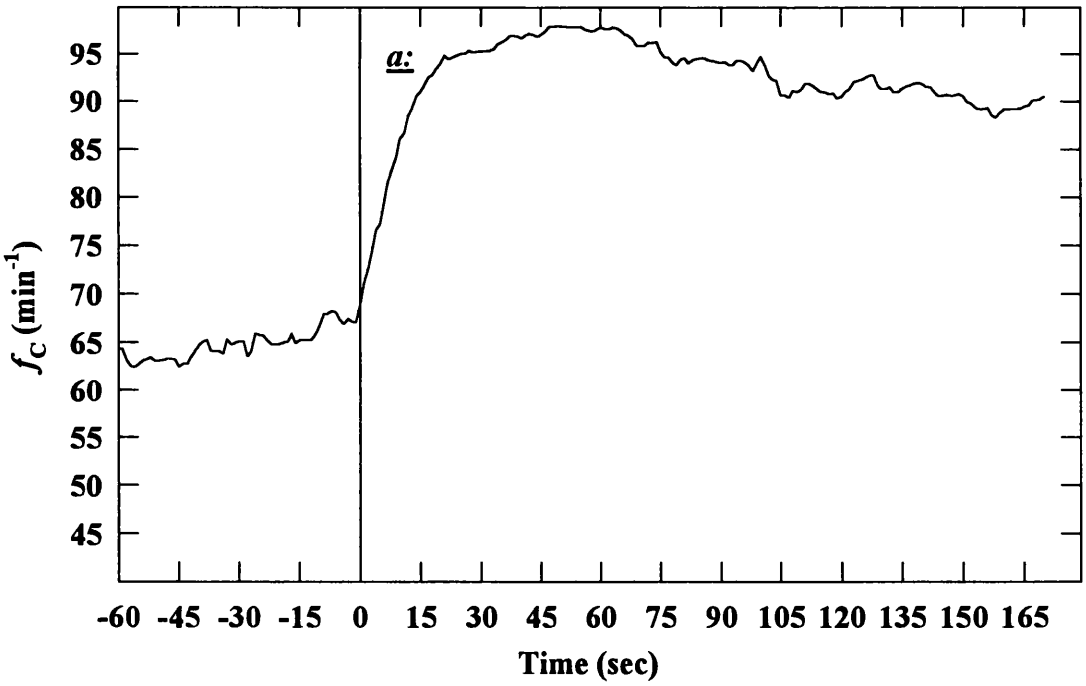


Figure 4.14a: Mean changes in f_C during 1 min prior to and 3 min after the onset of 50 W exercise in protocol "C". Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 7.

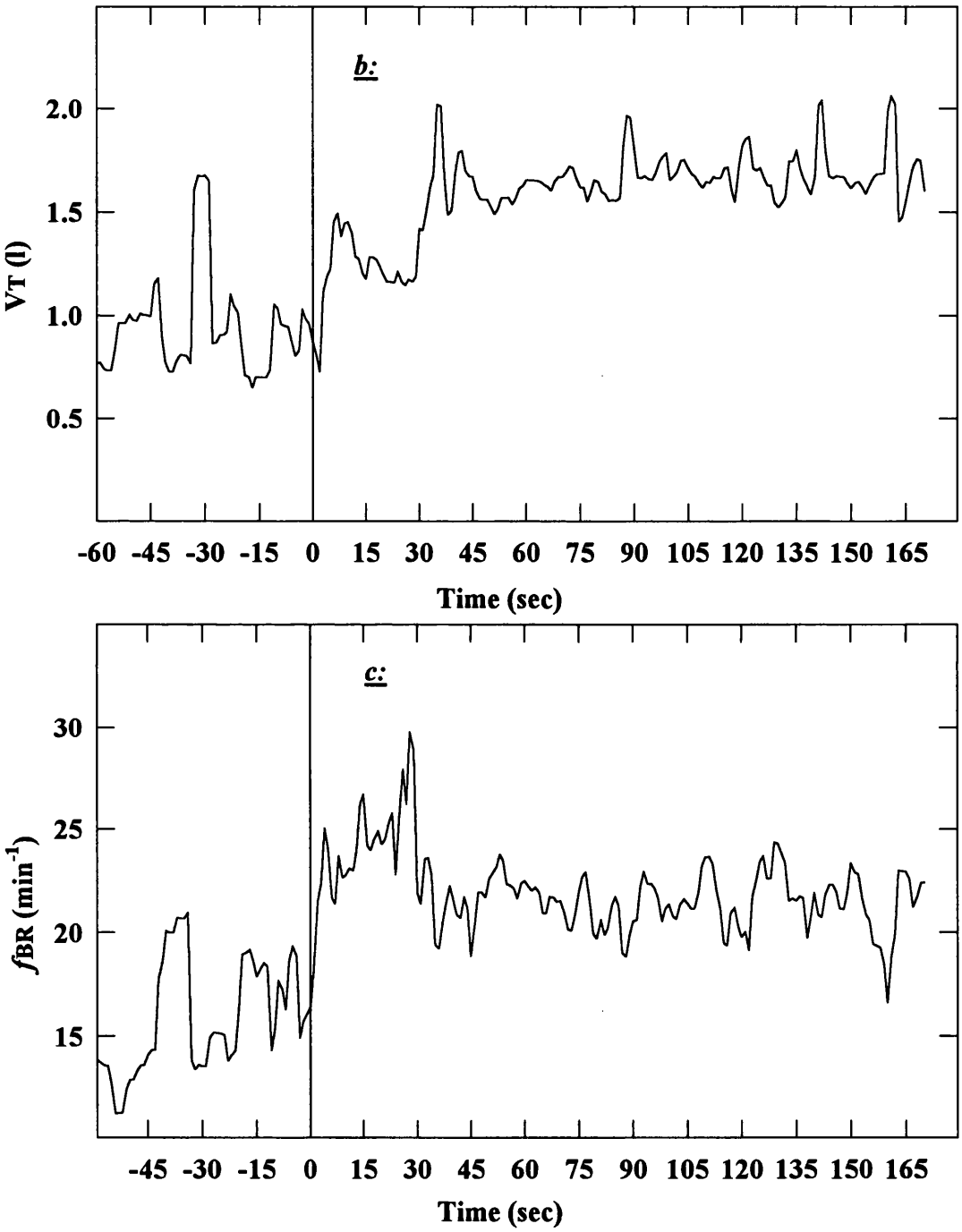


Figure 4.14b & c: Mean changes in VT and f_{BR} during 1 min prior to and 3 min after the onset of 50 W exercise in protocol "C". Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 7.

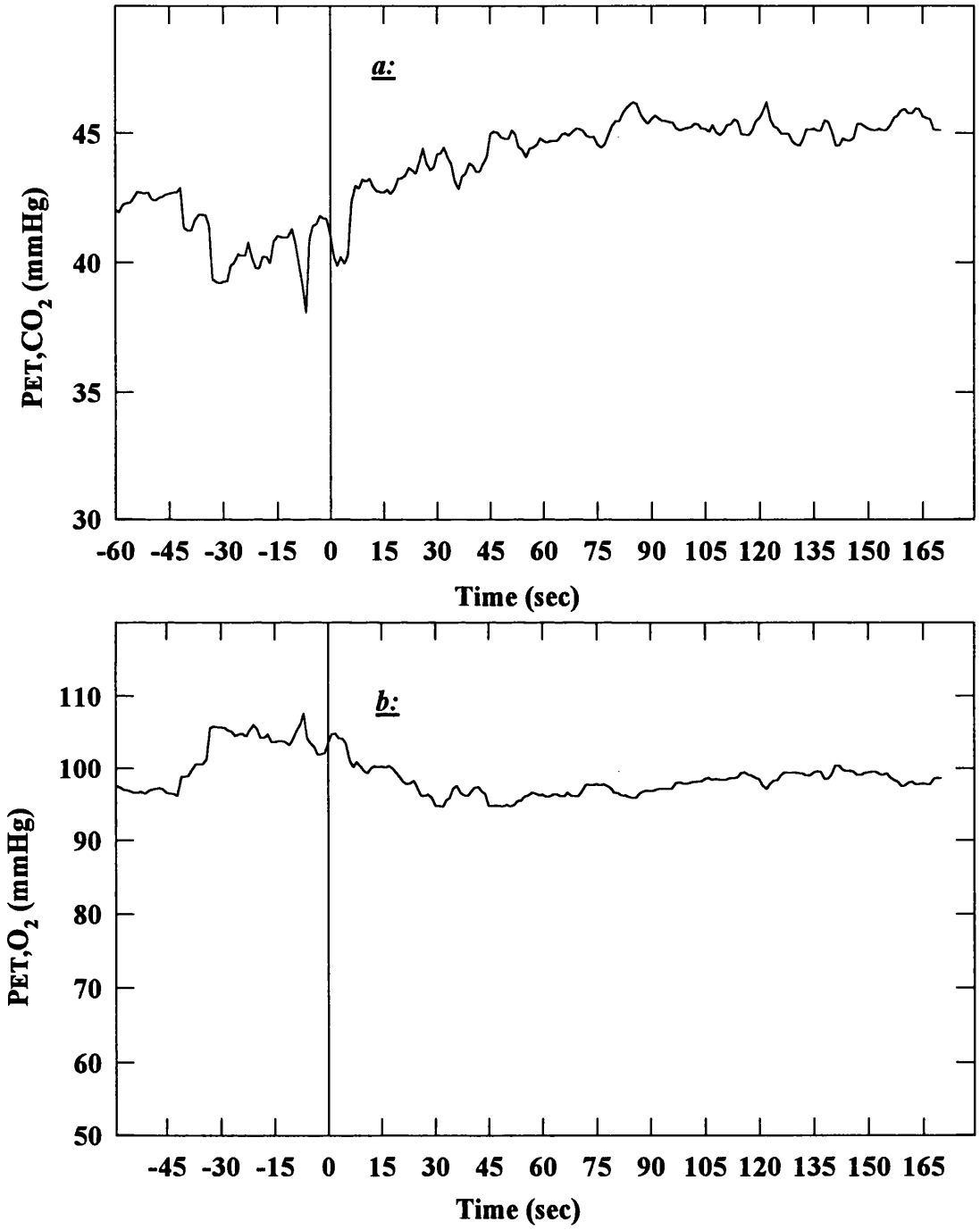


Figure 4.15a & b: Mean changes in P_{ET,CO_2} and P_{ET,O_2} during 1 min prior to and 3 min after the onset of 50 W exercise in protocol "C". Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 7.

There was no evidence of an initial response for f_C to 50 W exercise in any of the tests, as described by Whipp et al., 1982 (See *Fig. 4.14a*). This is in broad agreement with the results obtained in Chapters 5, 7 and 8.

The relative constancy of P_{ET,CO_2}, P_{ET,O_2} and RER during the initial ventilatory response to the onset of exercise (See *Fig. 4.15a, b & c* and *Tables 4.6* and *4.7*) indicated that the initial increase in $\dot{V}_E$ was not associated with hyperventilation.

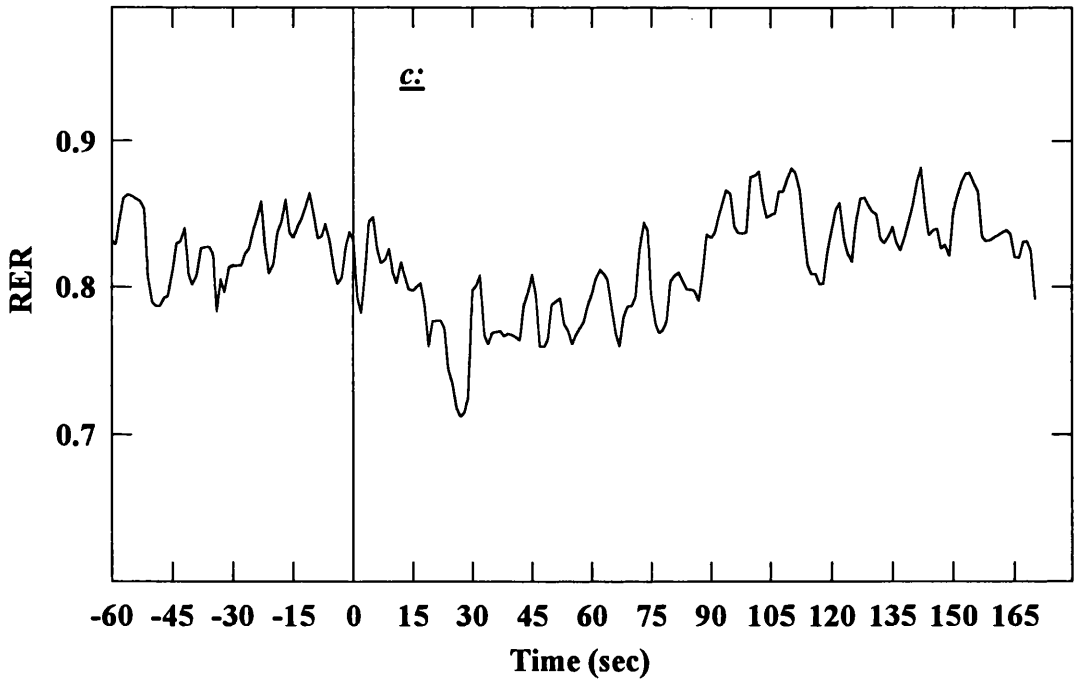


Figure 4.15c: Mean changes in RER during 1 min prior to and 3 min after the onset of 50 W exercise in protocol "C". Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 7.

The steady-state cardiorespiratory and pulmonary gas exchange responses to 50 W exercise are presented in *Table 4.8*.

	S/S 50 W EXERCISE
f_C	98 ± 8
$\dot{V}E$	33.93 ± 2.08
VT	1.73 ± 0.13
f_{BR}	20.94 ± 1.61
P_{ET,CO_2}	46 ± 2
P_{ET,O_2}	101 ± 3
$\dot{V}_{O_2}$	1.53 ± 0.05
$\dot{V}_{CO_2}$	1.28 ± 0.07
RER	0.84 ± 0.03

Table 4.8: Mean (± SE) steady-state cardiorespiratory responses to 50 W exercise. n = 7

HYPERVENTILATION:

The results of hyperventilation on the cardiorespiratory and pulmonary gas exchange responses to 50 W exercise are presented in *Table 4.9*. Hyperventilation lasted for 223 ± 10 sec. During the hyperventilation period VE increased over normal 50 W values by a factor of 3.1± 0.25 (See *Tables 4.8* and *4.9*). VT was increased by a factor of 2.51 ± 0.21 and f_{BR} was increased by a factor of 1.28 ± 0.12 to achieve this.

	HYPER
f_C	117 ± 9*
$\dot{V}E$	106.6 ± 9.3*
VT	4.21 ± 0.23*
f_{BR}	25.7 ± 1.5
P_{ET,CO_2}	46 ± 1*
P_{ET,O_2}	126 ± 2*
$\dot{V}_{O_2}$	2.46 ± 0.17*
$\dot{V}_{CO_2}$	2.31 ± 0.1*
RER	0.97 ± 0.07*

Table 4.9: Mean (± SE) cardiorespiratory responses to 50 W exercise. n = 7. * denotes values are significantly ($p < 0.05$) different from steady-state 50 W data.

fPED increased during the hyperventilation period to 79 ± 4 rpm (fPED during steady-state 50 W exercise = 74 ± 3 rpm. 50 W exercise vs. Hyperventilation: $p < 0.05$). This was despite the subjects being constantly requested to reduce their fPED.

$\dot{V}O_2$ and $\dot{V}CO_2$ both increased abruptly with the onset of hyperventilation (See *Fig. 4.12d*). Thereafter, $\dot{V}O_2$ remained relatively constant for the duration of the hyperventilation period. $\dot{V}CO_2$ and RER fell gradually over the course of the hyperventilation period. f_C rose to a new steady-state over the first 2 min of the hyperventilation period (See *Fig. 4.12d*).

P_{ET},O_2 increased rapidly to a plateau which was then maintained throughout the hyperventilation period (See *Fig 4.12d*). P_{ET},CO_2 fell more gradually over the period. Despite the high level of ventilation, P_{ET},CO_2 fell below 25 mmHg in only three of the seven tests by the end of the hyperventilation period. With the exception of one test, however, P_{ET},CO_2 was not much above this level by the end of hyperventilation.

POST HYPERVENTILATION:

Following hyperventilation, $\dot{V}E$ fell rapidly in all subjects except 1 (Subject 4), who continued to hyperventilate for the remainder of the exercise period. His results were therefore not included in the analysis. The mean cardiorespiratory and pulmonary gas exchange responses to 50 W exercise following the cessation of hyperventilation are presented in *Table 4.10*. fPED rapidly returned to the target value in all subjects following the end of hyperventilation (See *Fig. 4.16*)

$\dot{V}E$: $\dot{V}E$ was below normal 50 W levels in 4 of the 6 subjects analysed by 15 sec after the end of hyperventilation. Mean $\dot{V}E$ was not significantly lower than pre-hyperventilation levels 15 sec after the end of hyperventilation, but was by 30 sec (See *Table 4.10* and *Fig. 4.17a*). Modelling the fall in $\dot{V}E$ following the end of hyperventilation yielded a time constant for the decline in $\dot{V}E$ of 10.9 ± 3.5 sec. VE was still below pre-hyperventilation

values 1 and 2 min post-hyperventilation, but had recovered by 4 min post hyperventilation (See *Table 4.10* and *Fig. 4.17a*).

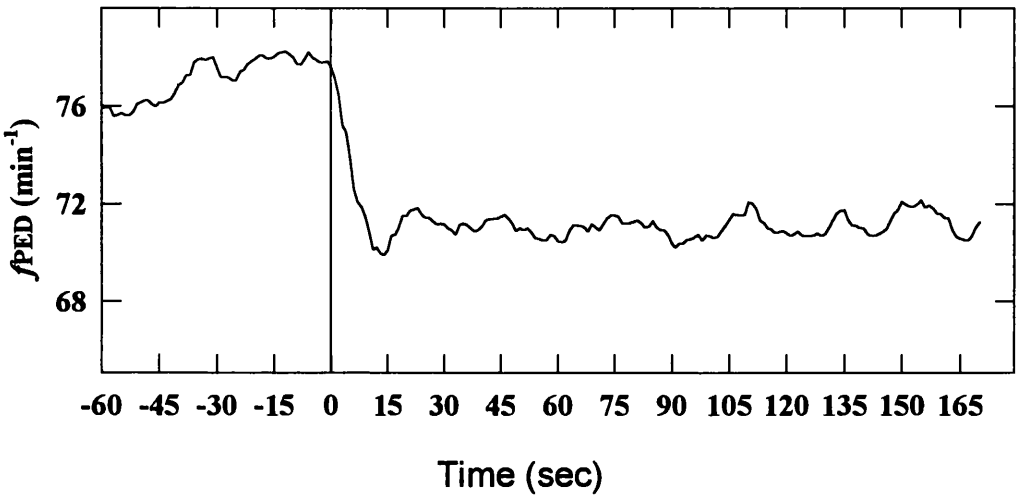


Figure 4.16: Mean changes in f_{PED} during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the onset of exercise, n = 6.

	15 SEC	30 SEC	1 MIN	2 MIN	3 MIN
f_C	109 ± 8*	105 ± 8*	103 ± 8*	101 ± 8*	100 ± 7*
$\dot{V}E$	30.46 ± 6.9	20.94 ± 6.05*	22.32 ± 4.65*	28.23 ± 3.6*	33.3 ± 2.72
VT	1.69 ± 0.3	1.65 ± 0.28	1.49 ± 0.28	1.73 ± 0.24	1.78 ± 0.2
f_{BR}	23.7 ± 2.4	16.6 ± 1.2*	21.1 ± 2.9	19.4 ± 1.6	21.2 ± 2.1
P_{ET,CO_2}	36 ± 2*	40 ± 2*	43 ± 1	44 ± 2	46 ± 2
P_{ET,O_2}	105 ± 4	90 ± 6	80 ± 6*	92 ± 5*	96 ± 4*
$\dot{V}_{O_2}$	1.51 ± 0.22	1.34 ± 0.15	1.6 ± 0.11	1.68 ± 0.1	1.64 ± 0.06
$\dot{V}_{CO_2}$	0.99 ± 0.18*	0.85 ± 0.21*	0.89 ± 0.15*	1.11 ± 0.11*	1.27 ± 0.08
RER	0.639 ± 0.04*	0.595 ± 0.07*	0.547 ± 0.07*	0.663 ± 0.05*	0.737 ± 0.04*

Table 4.10: Mean (± SE) cardiorespiratory and pulmonary gas exchange values at 15 sec, 30 sec, 1 min, 2 min and 3 min after the cessation of hyperventilation. n = 6. * denotes value is significantly ($p < 0.05$) different from steady-state 50 W values.

Changes in VT and *f*BR were variable following hyperventilation, both within subjects and between subjects. In general, the changes in $\dot{V}E$ were mediated by changes in both VT and *f*BR (See *Table 4.10* and *Figs. 4.12d* and *4.17b & c*).

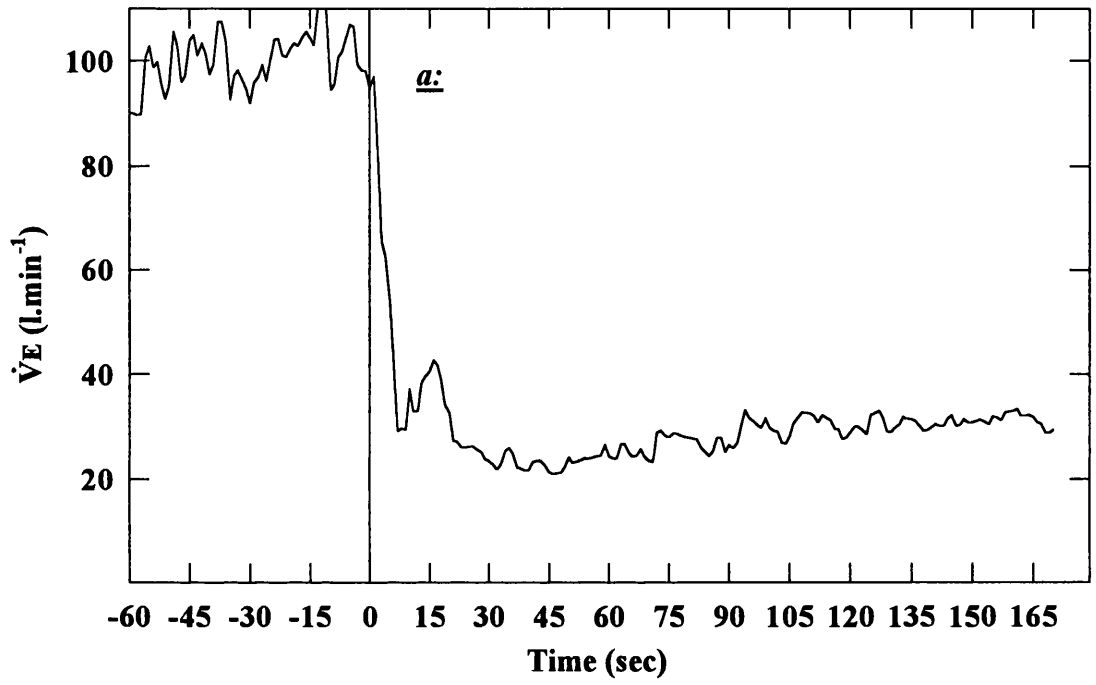


Figure 4.17a: Mean changes in $\dot{V}E$ during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the end of hyperventilation, n = 6.

$\dot{V}o_2$, $\dot{V}co_2$ and RER: $\dot{V}o_2$ fell abruptly following the end of hyperventilation (See *Figs. 4.12d* and *4.18a*). $\dot{V}o_2$ was at similar values to those recorded during steady-state 50 W exercise by 15 sec after the end of hyperventilation but continued to decrease, being significantly below 50 W levels at 30 sec after the end of hyperventilation (See *Table 4.10*, *Figs. 4.12d* and *4.18a*). By 1 min after the end of hyperventilation $\dot{V}o_2$ had recovered, returning to steady-state 50 W levels.

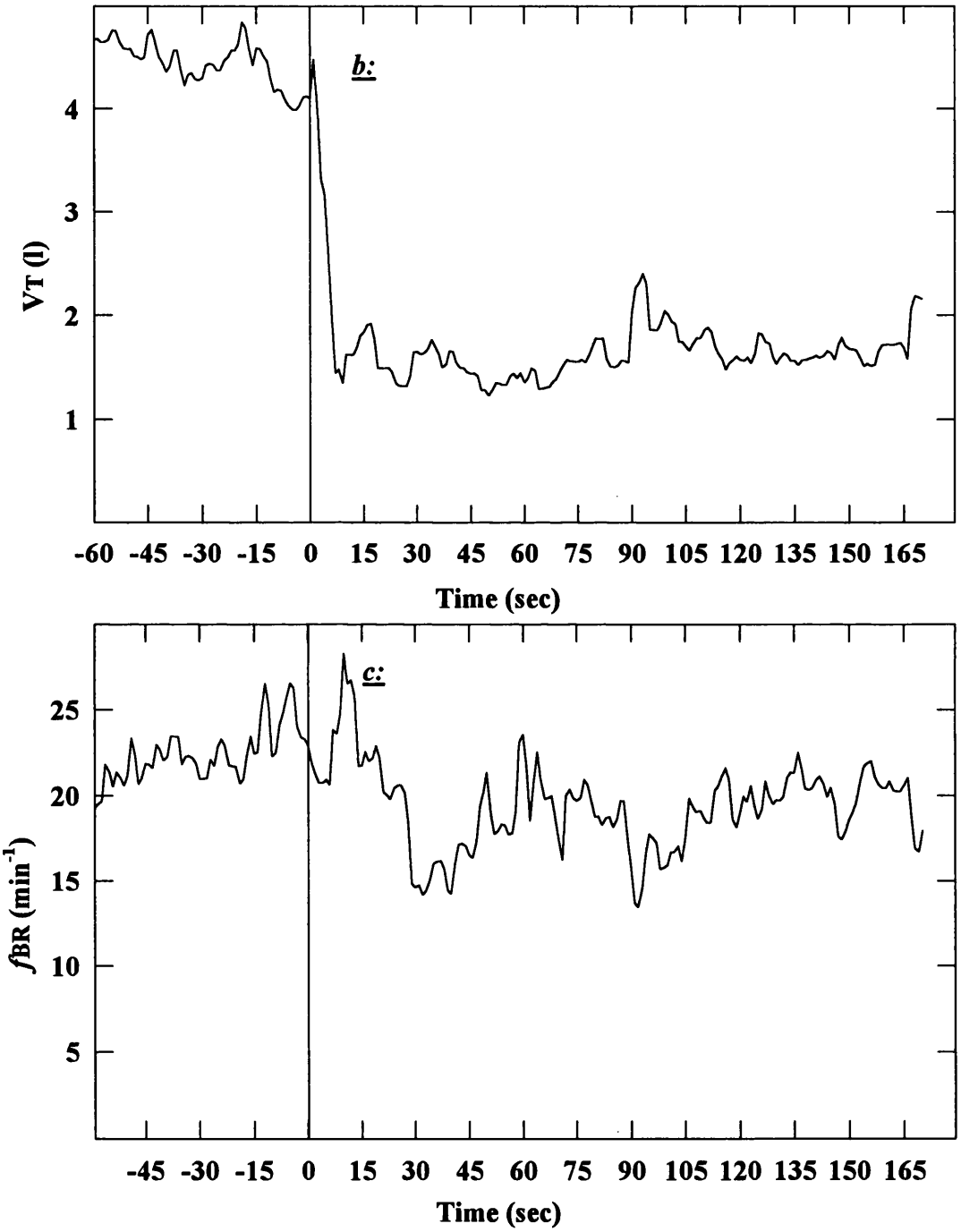


Figure 4.17b & c: Mean changes in VT and *f*BR during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the end of hyperventilation, n = 6.

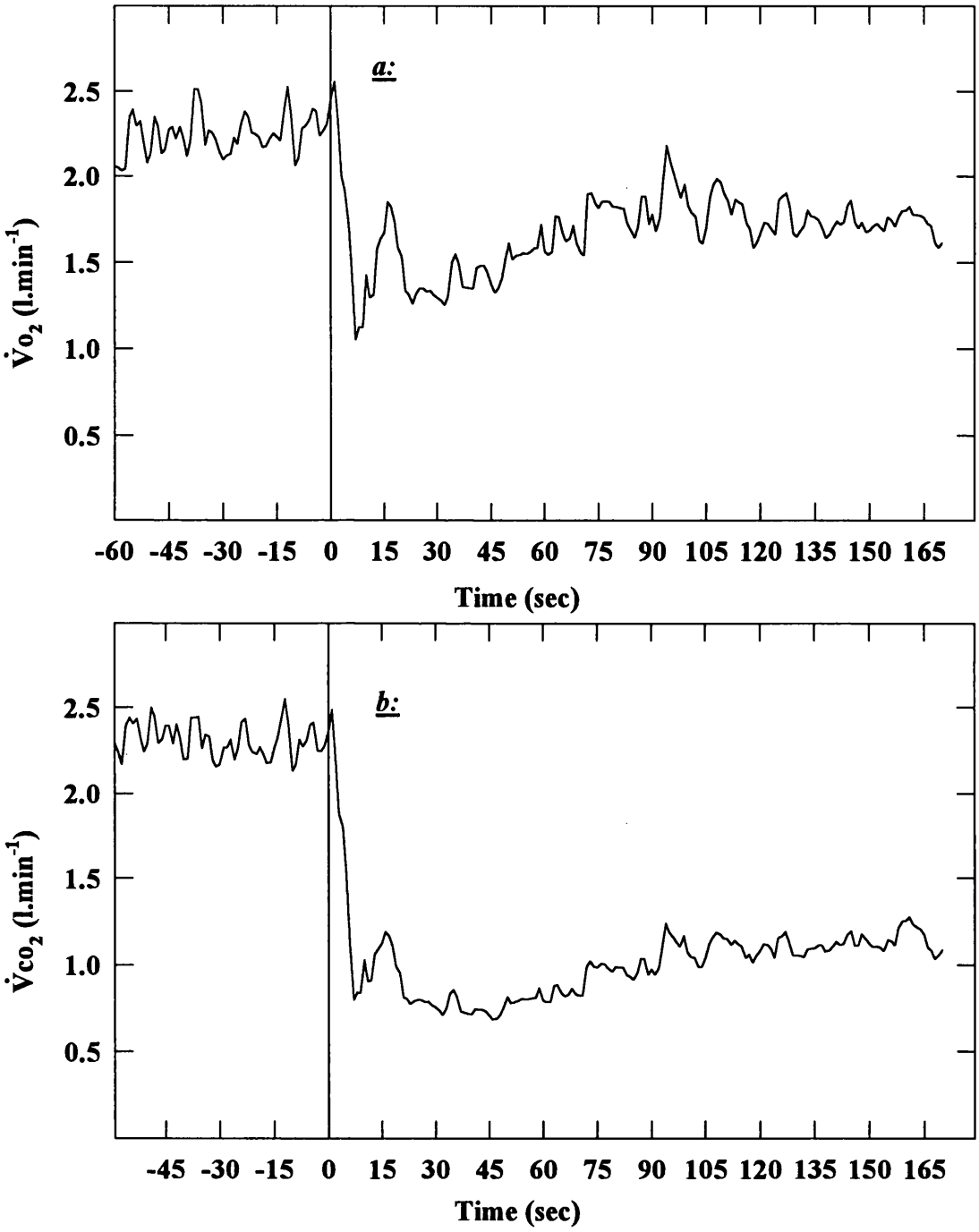


Figure 4.18a & b: Mean changes in $\dot{V}o_2$ and $\dot{V}co_2$ during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents end of hyperventilation, n = 6.

$\dot{V}co_2$ fell abruptly following the end of hyperventilation (See *Figs. 4.12d* and *4.18b*). The magnitude of the fall was greater than that seen for $\dot{V}o_2$ (See *Table 4.10*). $\dot{V}co_2$ was significantly below steady-state 50 W levels by 15 sec after the end of hyperventilation and remained so until 3 min after the end of hyperventilation (See *Table 4.10* and *Fig. 4.18b*).

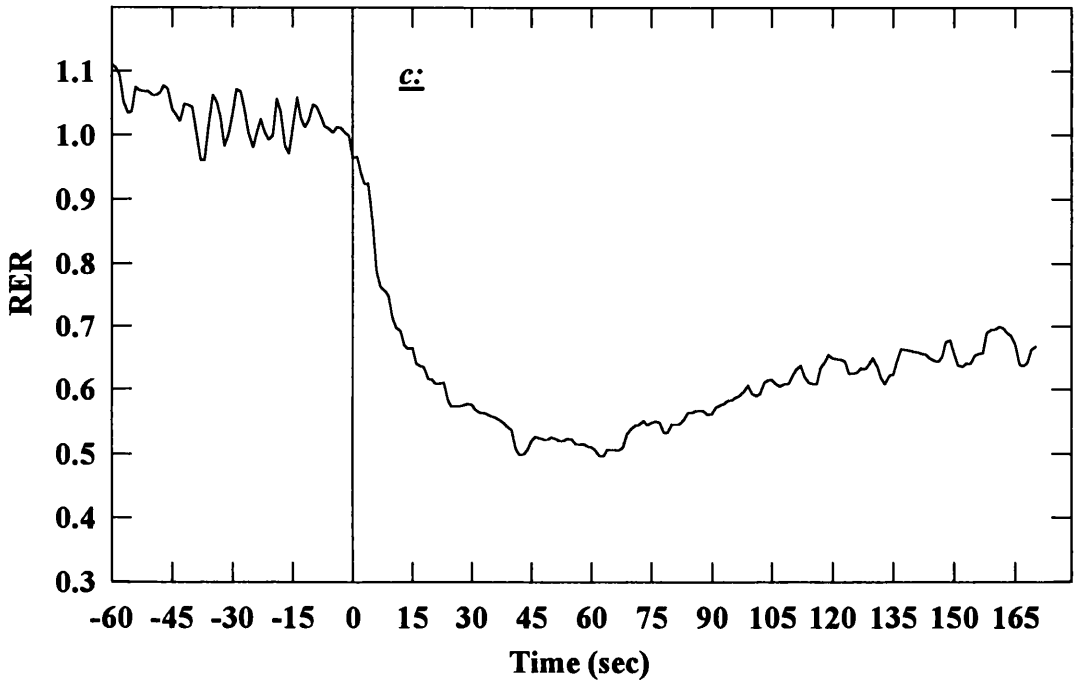


Figure 4.18c: Mean changes in RER during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the end of hyperventilation, n = 6.

The different time courses for the recovery of $\dot{V}o_2$ and $\dot{V}co_2$ from the effects of the hyperventilation were reflected in the RER (See *Fig. 4.18c*). RER fell rapidly following the end of hyperventilation. It was significantly below steady-state 50 W levels for the duration of the exercise period (See *Table 4.10* and *Fig. 4.18c*).

fc: f_C decreased gradually following the end of hyperventilation (See *Figs. 4.12d* and *4.19a*) and returned to steady-state 50 W levels by 3 min after the end of hyperventilation (See *Table 4.10* and *Fig. 4.19a*).

PET,CO_2 and PET,O_2: PET,CO_2 initially rose rapidly in all subjects such that 54% ± 9% of the reduction in PET,CO_2 achieved by the hyperventilation had been recouped within 15 sec of ceasing hyperventilation (See *Table 4.10* and *Figs. 4.12d* and *4.19b*). 30 sec after the end of hyperventilation, PET,CO_2 was no longer significantly lower than pre-hyperventilation levels (See *Table 4.10* and *Figs. 4.12d* and *4.19b*).

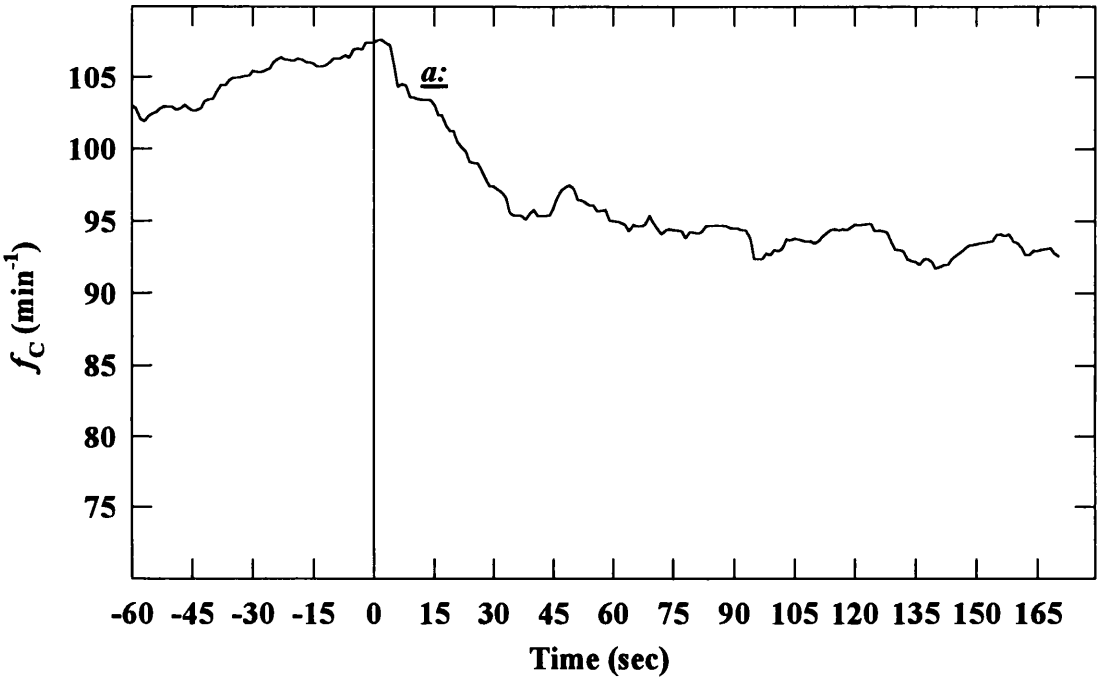


Figure 4.19a: Mean changes in f_C during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the end of hyperventilation, n = 6.

PET,O_2 decreased rapidly following the end of hyperventilation, reflecting the dissociation between $\dot{V}E$ and its metabolic requirements (See *Table 4.10* and *Figs. 4.12d* and *4.19c*). PET,O_2 had fallen to steady-state 50 W values at 15 sec after the end of hyperventilation, but continued to fall before rising again. The nadir of this response was reached 55 ± 8 sec after the end of hyperventilation with a fall in PET,O_2 to 72 ± 7 mmHg. PET,O_2 had not returned to steady-state 50 W levels by the end of exercise (See *Table 4.10* and *Figs. 4.12d* and *4.19c*).

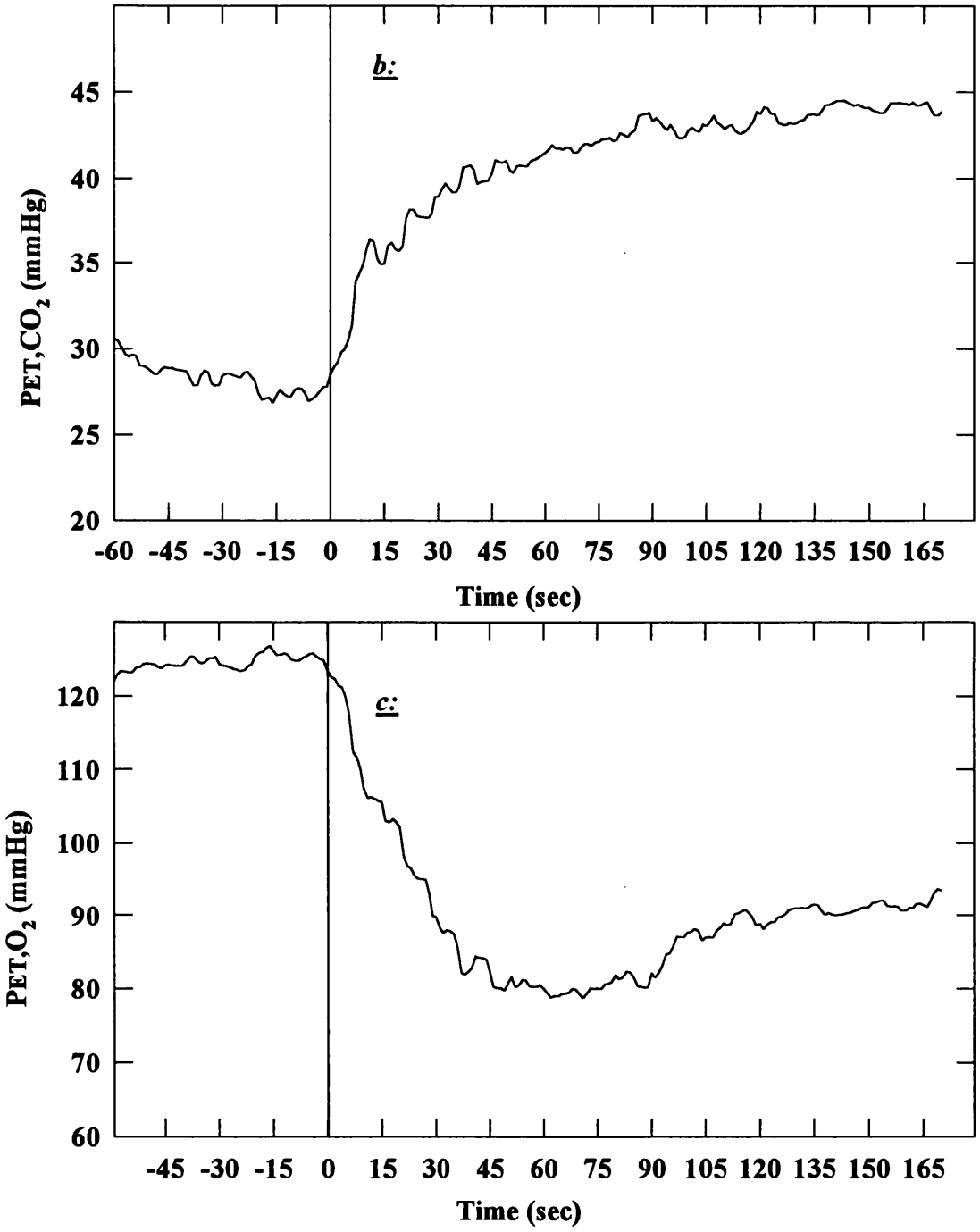


Figure 4.19b & c: Mean changes in P_{ET,CO_2} and P_{ET,O_2} during the 1 min prior to and 3 min after the end of hyperventilation. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. Time 0 represents the end of hyperventilation, n = 6.

DISCUSSION:

SINGLE VS. REPETITIVE TESTING:

Repetitive testing of subjects followed by interpolation and time-averaging of the data has the benefit of reducing the effective noise variance of the underlying respiratory and pulmonary gas exchange responses. In this study, however, repetitive testing of subjects was avoided on the grounds that the incidence of apnoeas following volitional hyperventilation has been reported to increase with increasing repetitions (Bainton & Mitchell, 1966).

EFFICACY OF HYPERVENTILATION:

Hyperventilation was well maintained in all tests. The target P_{ET,CO_2} was achieved in all of the Protocol "A" tests within the allotted 4 min. With the exception of a period of uncertainty at the beginning of hyperventilation in each test, P_{ET,CO_2} was maintained close to pre-hyperventilation values in Protocol "B". The target P_{ET,CO_2} was less well achieved in Protocol "C", but was close to target levels by the end of hyperventilation in all except 1 of the tests. In retrospect, reducing P_{ET,CO_2} to 25 mmHg or below was not indicative of a similar level of hypocapnia to that protocol "A": the slope of the plateau portion of the P_{CO_2} profile steepens on exercise, resulting in a 4-6 mmHg increase in P_{ET,CO_2} without a change in Pa,CO_2 (Jones et al., 1979, Whipp et al., 1989). However, as the rise in P_{ET,CO_2} following hyperventilation in protocol "C" was so rapid, the slightly lower Pa,CO_2 was probably of benefit to the protocol, given the purpose of the hyperventilation. The subjects did not complain of any ill-effects.

The desired pattern of breathing was well maintained in Protocols "A" and "B", with no significant change in f_{BR} during hyperventilation when compared to pre-hyperventilation levels. The increase in f_{BR} during hyperventilation in Protocol "C" was unfortunate but

unavoidable: it would have been impossible to achieve the necessary increases in VE purely by a rise in VT. It should be noted, however, that the rise in *f*BR during hyperventilation was small (See *Table 4.9*) and the majority of the hyperventilation was achieved by increases in VT.

The strategy of achieving the desired increase in $\dot{V}E$ by an increase in VT while regulating *f*BR at pre-hyperventilation levels was based on the findings of Folgering & Durlinger (1983). They reported afterdischarge to be reduced following hyperventilation achieved solely by an increase in VT compared to a similar level of hyperventilation achieved with no regulation of breathing pattern. Given the purpose of hyperventilation in the following studies, to deplete body CO_2 prior to a change in workload, the more rapid the fall in $\dot{V}E$ the sooner after the end of hyperventilation the change in workload can occur and therefore the recovery of body CO_2 stores following hyperventilation will be less.

The minimum P_{ET},CO_2 during hyperventilation was limited to 20 mmHg, with a target level of 20-25 mmHg. Macefield & Burke (1991) reported an increase in axonal excitability following hyperventilation sufficient to achieve a 20 mmHg fall in P_A,CO_2. This resulted in paraesthesiae of the hands, face and trunk. A further fall in P_A,CO_2 of 4 mmHg resulted in twitching of facial muscles and the muscles of the hand. The latter symptoms are not conducive to relaxation in the subject, so the lower threshold for P_{ET},CO_2 was set such that the occurrence of spontaneous muscle activity would be avoided.

THE EFFECT OF HYPERVENTILATION ON METABOLIC RATE:

Previous studies have reported whole body V_{O_2} to rise in a curvilinear manner when $\dot{V}E$ was increased either voluntarily, by an added dead space or by adding CO_2 to the inspirate (Bartlett et al., 1973; Bradley & Lieth, 1978; Campbell et al., 1957; McKerrow & Otis, 1956; Milic-Emili & Petit, 1957; Otis, 1954). The O_2-cost of breathing reported in the literature ranges from 0.25 to 10 ml O_2/min per l/min $\dot{V}E$ (Bartlett et al., 1973; Bradley &

Lieth, 1978; Campbell et al., 1957; McKerrow & Otis, 1956; Milic-Emili & Petit, 1957; Otis, 1954). The O_2 cost of breathing measured in Protocol "A" was approximately 10 ml O_2/min per l/min $\dot{V}E$ and in Protocol "C" was approximately 14 ml O_2.min per l/min $\dot{V}E$. These values are larger than those reported in the literature (Bartlett et al., 1973; Bradley & Lieth, 1978; Campbell et al., 1957; McKerrow & Otis, 1956; Milic-Emili & Petit, 1957; Otis, 1954). The reason for this is most likely to be the pattern of breathing chosen for increasing $\dot{V}E$ during hyperventilation.

One weakness of the experimental protocol was the lack of monitoring of P_I,CO_2 in protocol "B." This precluded the monitoring of changes in $\dot{V}co_2$ during the hyperventilation period for these tests. In protocol "A," however, $\dot{V}co_2$ rose at the start of the hyperventilation period and remained elevated above resting levels until the end of hyperventilation, indicating the falling body CO_2 stores. $\dot{V}o_2$ increased abruptly on starting hyperventilation with both protocols, but fell rapidly after the initial rise (see *Figs 4.2c* and *4.3c*). This initial increase is a result of changes in the body's O_2 stores, while the transient nature of this increase compared to that of $\dot{V}co_2$ is a manifestation of the difference in size between the O_2 and CO_2 stores in the body.

Another complication in analysis of the O_2-cost of hyperventilation in Protocol "C" was the associated increase in *f*PED. This fact is in itself of interest as it would suggest that the increase in *f*BR was causing as increase in *f*PED. This possibility has previously been reported by Steinaker et al. (1993) as occurring during high intensity exercise in oarsmen while rowing. The results obtained here allow no more than a suggestion that this might be the case during cycling as well. The influence of the increase in *f*PED on $\dot{V}o_2$ during hyperventilation was likely to be negligible: the regression equation derived from the data reported in Chapter 3 would suggest that the increase in *f*PED which occurred during hyperventilation would have resulted in an increase in $\dot{V}o_2$ of around 0.04 $l.min^{-1}$.

EFFECT OF HYPERVENTILATION ON f_C:

Hyperventilation was associated with an increase in f_C in all tests. (See *Tables 4.3* and *4.9*). A proportion of this increase was no doubt associated with the increase in $\dot{V}O_2$ reported above, but may also be influenced by the act of hyperventilation *per se*. Cummin et al. (1986b) reported a rise in heart rate (and cardiac output) with a similar hyperventilation protocol to that used here. By contrast, a similar level of hyperventilation achieved by increasing fBR rather than VT resulted in a stroke volume-mediated increase in cardiac output. This, they hypothesised, may have been due to a combination of the mechanical effects of the rhythmical changes in thoracic pressure on central venous flow and stimulation of a cardiac accelerator response to lung inflation. Boutellier & Farhi (1986) reported similar results for VT-mediated hyperventilation, but no increase in cardiac output when VE was increased by raising fBR. It should be noted, however, that Matalon et al. (1982) failed to find any increase in either heart rate or cardiac output on hyperventilation, despite a similar protocol to that of Cummin et al. (1986b).

EFFECT OF HYPERVENTILATION ON CO_2 STORES:

Hyperventilation in Protocols "A" and "C" resulted in a fall in PET,CO_2. The CO_2 dissociation curve of tissue fluid has been shown to be curvilinear in form (Haldane & Priestley, 1935; Riley & Cournand, 1949), but it is effectively linear over the physiological range (McHardy et al., 1967; McHardy, 1967) with a slope of 3-4 ml CO_2/mmHg/l body fluid. The dynamics of CO_2 depletion following a change in ventilation is not, however, constant throughout the body (Farhi & Rahn, 1960; Vance & Fowler, 1960; Sullivan et al., 1966; Cherniack et al., 1966; Irving et al., 1983; Barstow et al., 1992), but rather is better described by a multicompartment model (Farhi & Rahn, 1960) The major cause of the differences in the rates of change in CO_2 stores following a change in $\dot{V}E$ would appear to be differences in the rates of perfusion of tissue compartments (Farhi & Rahn, 1960; Vance & Fowler, 1960). Farhi & Rahn (1960) proposed a model to describe changes in CO_2

stores following a change in the rate of CO_2 elimination at the lung. The body was divided into a number of compartments, each consisting of a single organ. The rate of change of CO_2 stored in each compartment was a function of the size of its CO_2 store and its rate of perfusion.

The use of [^{13}C] bicarbonate has resulted in a modification of this model (Irving et al., 1983; Barstow et al., 1990, 1992), such that CO_2 stores may be divided into 3 pools; a central pool in communication with 2 peripheral pools with fast and slow exchange kinetics. Both the fast and slow pools may exchange CO_2 with the central pool, but cannot exchange CO_2 with each other directly (Irving et al., 1983; Barstow et al., 1990, 1992).

The rate constants reported by Irving et al. (1983) would suggest that the duration of hyperventilation used here would have little effect on CO_2 stored in the slow peripheral pool while resulting in a depletion of the central and fast peripheral pools. Using rebreathing as a method of reducing CO_2 excretion at the mouth, Fowle & Campbell (1964) reported the rate of rise in CO_2 in the bag to be constant for the first 4 min of rebreathing at rest. This would also suggest that the slow peripheral compartment has little influence over CO_2 washout kinetics for hyperventilation of the duration used in Protocol "A".

The relevance of this is determined by the physiological correlates of the 3 CO_2 pools at rest, as hypothesised by Irving et al. (1983). They postulated that the central CO_2 store represented the blood, the fast peripheral store represented metabolically active tissues, e.g. the heart, liver, kidneys, brain and intestines, and the slow peripheral compartment represented poorly perfused tissues, e.g. resting muscle and bone. This would suggest that muscle CO_2 stores were unaffected by the level and duration of hyperventilation used in this study and in the studies described in Chapters 5 and 6.

CO_2 stored in the body increases on transition from rest to exercise (Yano, 1986; Clode et al. 1967; Jones & Jurowski, 1979; Farhi & Rahn, 1960; Barstow et al., 1990, 1992; Hughson & Inman, 1985). This is manifested as a dissociation between $\dot{V}o_2$ and $\dot{V}co_2$

measured at the mouth during the on-transient in response to the transition from rest to exercise. The quantity of CO_2 stored in the central compartment increases on transition from rest to exercise (Hughson & Inman, 1985; Barstow et al., 1990, 1992). The CO_2 storage capacity during exercise reported in the literature range from 0.65 to 1.83 ml CO_2/Kg tissue/mmHg. As such, if Pco_2 is to remain within the physiological range, the increase in the central CO_2 compartment must be associated with an increase in the size of the central CO_2 compartment (Barstow et al., 1992). The results obtained by Hughson & Inman (1985) and Barstow et al. (1990, 1992) would suggest that the transition from rest to exercise is associated with the movement of skeletal muscle from the slow peripheral pool to the central pool. Furthermore, CO_2 storage capacity does not increase on transition from light to moderate exercise (Barstow et al., 1990; Hughson & Inman, 1985).

The effect of hyperventilation during exercise on body CO_2 stores is therefore different to hyperventilation at rest. Hyperventilation of the severity and duration as occurred in Protocol "C" would be expected to result in depletion of the central and fast peripheral CO_2 pools. Whereas muscle CO_2 stores are unlikely to be affected by the hyperventilation which occurred in Protocol "A", the hyperventilation which occurred in Protocol "C" would be likely to significantly deplete muscle CO_2 stores. This would be likely to modify the effect of hyperventilation on the kinetics of the Phase 2 response for $\dot{V}co_2$ to an increase in workload performed against a background of rest (See Chapter 5) and mild exercise (See Chapter 7).

CHANGES IN $\dot{V}_E$ FOLLOWING HYPERVENTILATION:

The purpose of hyperventilation in Chapters 5, 7 and 8 was to deplete CO_2 stores prior to a change in workload, imposed against either a background of rest or mild exercise. The effects of hyperventilation of the duration and severity used in these studies on CO_2 stores has been discussed in the previous section. To measure the initial ventilatory response to the increase in workload it was necessary to allow $\dot{V}E$ to fall to close to pre-

hyperventilation levels by the change in workload. The fall in $\dot{V}E$ measured in Protocols "A", "B" and "C" were well described by the monoexponential decay described in the Methods section and by Tawadrous & Eldridge (1974).

The values for τ reported here are similar to those reported by Swanson et al. (1976) and Georgopoulos et al. (1990) in awake man, but are longer than those reported by Engwall et al. (1991) and contrary to the findings of Engwall et al. (1994): they reported a shortening of the timecourse of afterdischarge with increasing hypocapnia in the awake goat. This may be related to the fact that hyperventilation was volitional in this study, while it was reflexly achieved by carotid body stimulation in the goats, or it may be a species-related difference.

A similar value for τ to that measured following hyperventilation at rest was measured following hyperventilation during mild exercise. This would support the view that afterdischarge is present following active hyperventilation during exercise in man, as reported by Fregosi (1991). The time constants for the decay of the afterdischarge reported by Fregosi (1991; $\tau = 28.6 \pm 6.7$ sec) were, however, considerably longer than those found in this study ($\tau = 10.9 \pm 3.5$ sec). There are a number of possible explanations for this difference, including the different methods of measuring $\tau(\dot{V}E)$ used and the different methods by which the hyperventilation was achieved. It could also be that the degree of hypocapnia (which was much greater in this study than that of Fregosi, 1991) may exert an influence over the time course of the afterdischarge. This has been shown in the awake resting goat (Engwall et al., 1994), but further research is needed before this can be considered the explanation of the difference between the results reported here and those of Fregosi (1991). Cummin et al. (1991) did not model the fall in $\dot{V}E$, but reported that $\dot{V}E$ fell below pre-hyperventilation values by 20 sec post-hyperventilation; a similar time course to that reported here.

Folgering & Durlinger (1983) reported τ for afterdischarge at rest following hyperventilation with fBR maintained at pre-hyperventilation levels to be virtually zero in sedentary subjects. This was not the case for any of the highly trained subjects tested in this

study but was the case for some of the sedentary subjects tested in the study described in Chapter 6. It would therefore seem likely that this discrepancy between the results obtained here and those of Folgering & Durlinger (1983) was the level of fitness of the subjects tested. It is not possible to determine the mechanism responsible from these results.

Another method of removing the unwanted effects of afterdischarge would have been to perform the hyperventilation passively. There is, however, a danger of apnoea occurring when the ventilator is disconnected (Leevers et al., 1993). Although this is not a universal finding in man (Fink, 1961; Datta et al., 1993; Skatrud & Dempsey, 1983), it has also been reported in awake animals (Horner et al., 1994; Mitchell et al., 1966). Bainton & Mitchell (1966) reported an increase in the incidence of apnoeic periods following mechanical hyperventilation in their subjects with increasing numbers of studies, suggesting a learning process.

Apnoea is a contraindication for starting exercise for three reasons. Firstly, apnoea is a different state for the subject compared to spontaneous breathing, however low the level of ventilation may be. This may exert an unwanted effect over the initial ventilatory response to exercise. Secondly, apnoea occurs as a result of a complete suppression of the ventilatory drive. It is therefore impossible to determine the extent to which the ventilatory drive is inhibited by the prior hyperventilation, other than the duration of the apnoea This is a circular argument, as the duration of the apnoea can only be determined by waiting until it is finished, whereupon there is no apnoea. Thirdly, it would be difficult to determine whether the end of an apnoeic period in conjunction with the start of exercise was coincidental or causal.

Active hyperventilation, on the other hand is rarely associated with apnoea (Gleeson & Sweer, 1993; Gardner & Meah, 1987; Plum et al., 1962; Mills 1946; Fink, 1961; Bainton & Mitchell, 1966; Tawadrous & Eldridge, 1974), even in the face of profound hypocapnia. More recently Gardner & Meah (1994) and Corfield et al. (1995) have reported apnoeas in normal, awake subjects following volitional hypocapnic hyperventilation, but these apnoeas

are mostly short (< 15 sec). The more striking finding of both groups is the increase in variability in breathing pattern seen during hypocapnia, especially in TE. Corfield et al. (1995) report that this variability abruptly ceases, usually when P_{ET,CO_2} returns to normal values.

CHRONIC HYPERVENTILATION:

As reported in the Results section, $\dot{V}_E$ failed to fall to close to pre-hyperventilatiion levels after the end of volitional hyperventilation (2 in Protocol "A" and 1 in Protocol "C"). Their responses to hypocapnic hyperventilation are similar to those described by Gardner & Meah (1987) for sufferers of chronic hyperventilation syndrome, but their responses to eucapnic hyperventilation were perfectly normal. Furthermore, the psychological abnormalities associated with chronic hyperventilation syndrome are not compatible with being a highly successful oarsman (One of the subjects was of national level, the other 2 of international standard). Mills (1946) reported post-hyperventilation hyperpnoea in some subjects, but concluded that the hyperpnoea was the result of the same cortical activity responsible for the original hyperventilation.

It is possible that the cause of the chronic hyperventilation was also responsible for the presence of afterdischarge following hyperventilation in this highly trained subject population following a protocol which has been reported to significantly reduce the timecourse of afterdischarge (Folgering & Durlinger, 1983). Hyperventilation in asleep man and anaesthetised animals is usually followed by apnoea (Eldridge, 1973; Datta et al., 1991; Skatrud & Dempsey, 1983), whereas hyperventilation during wakefulness in not (Skatrud & Dempsey, 1983; Datta et al., 1991; Gleeson & Sweer, 1993; Fregosi, 1991; Swanson et al., 1976). This phenomenon has led to the suggestion that there is a "Wakefulness drive to breathe" (Fink, 1961). It is possible that this "Wakefulness drive to breathe" is greater in highly trained individuals than in sedentary subjects, thus resulting in an enhanced afterdischarge compared to sedentary subjects (Folgering & Durlinger, 1983; see also

results reported in Chapter 6 for sedentary subjects), even to the extent of chronic hyperventilation following volitional hyperventilation.

Another possible cause for this abnormal response to hypocapnic hyperventilation came to light from the post-test debriefing: both subjects stated that they felt that they would pass out if the hyperventilation was continued for much longer. This may have resulted in a feeling of anxiety in the subjects; a phenomenon well known to cause abnormal hyperventilation in normal subjects. The sensations of impending unconsciousness may have been the result of a fall in systemic blood pressure. Boothby (1928) reported marked differences in the changes in blood pressure both during and following hyperventilation in 2 subjects. It may have been that the 3 subjects who continued to hyperventilate spontaneously were more prone to the systemic effects of active hyperventilation than the other subjects tested, with the consequence that their recovery following the cessation of the hyperventilation was incomplete.

VENTILATORY AND PULMONARY GAS EXCHANGE RESPONSES TO THE ONSET OF 50 W EXERCISE:

The initial ventilatory and pulmonary gas exchange responses to the onset of 50 W exercise in Protocol "C" were characterised by an abrupt, but transient, increase in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$. These results are not in agreement with the majority of the literature, which describe the profile of the initial ventilatory and pulmonary gas exchange responses to the transition from rest to exercise as an abrupt increase to a plateau (eg. Whipp et al., 1982; Dejours, 1964). The implications and possible mechanisms responsible for this difference in response will be discussed in detail in Chapter 7.

IDEAL TIME TO START EXERCISE:

Hyperventilation at rest: From these results, it would appear that there is considerable freedom as to when exercise is started. The overriding factor is that $\dot{V}E$ has fallen to near normal resting values. From the results reported here for $\dot{V}E$, it would appear that the ideal time to start exercise would be no sooner than 30 sec (To allow for the effects of afterdischarge). Gardner & Meah (1994) and Corfield et al. (1995) reported apnoeas to occur after 1 min of recovery from the hyperventilation. On the basis of these results, exercise should commence no later than 1 min after the end of the hyperventilation period (To avoid the occurrence of apnoeas). If, however, the kinetics of the afterdischarge are such that it takes more than 1 min for $\dot{V}E$ to reach normal resting levels, prolonging the delay between ceasing hyperventilation and starting exercise is unlikely to compromise the results obtained.

The other important criterion for the ideal time to start exercise is that P_{ET},CO_2 is still low. Following the cessation of hyperventilation, P_{ET},CO_2 rose rapidly over the first 30 sec in protocol "A" (See *Fig. 4.3*), thereafter rising more slowly. Between 30 sec and 1 min post-hyperventilation, however, P_{ET},CO_2 was still well below pre-hyperventilation levels (See *Fig. 4.3*). In fact, P_{ET},CO_2 did not return to pre-hyperventilation levels by the end of the test (4 min post-hyperventilation). It would therefore appear that ensuring that $\dot{V}E$ has fallen sufficiently following hyperventilation is the major criterion governing when to start exercise, and that there is no difficulty in ensuring that P_{ET},CO_2 is still low at that time.

Hyperventilation during exercise: The timecourse of the fall in $\dot{V}E$ described in these results (and those of Cummin et al., 1991) would suggest that, for the majority of subjects, it would be inadvisable to increase the exercise intensity within 15 sec of the end of the hyperventilation period.

Cummin et al. (1991) also highlight another possible confounding factor for analysis of the effects of increasing exercise intensity following hyperventilation: one of the consequences of the fall in $\dot{V}E$ seen following the cessation of hyperventilation was a fall in P_{ET,O_2}. In these results the nadir occurred 55 ± 8 sec after the end of hyperventilation with a fall in P_{ET,O_2} to 72 ± 7 mmHg. P_{ET,CO_2} then gradually increased, reaching pre-exercise values by 4 min post-hyperventilation. Cummin et al. (1991) report P_{ET,O_2} as falling to 48 mmHg during this period in one subject, a value somewhat lower than those reported here (minimum value recorded = 60 mmHg, reached in three subjects). Such low levels of P_{ET,O_2} are highly likely to act as a ventilatory stimulus via the carotid bodies and in one test an abrupt increase in $\dot{V}E$ is clearly visible approximately 10 sec after the nadir in P_{ET,O_2} is reached. It is therefore essential that the workload is increased as far in advance of the predicted nadir in P_{ET,O_2} as possible to avoid compromising the analysis of the test results.

CONCLUSIONS:

Hyperventilation at Rest: The results of this Chapter would suggest that exercise may be started once the effects of afterdischarge have ended, i.e. once $\dot{V}E$ has returned to near pre-hyperventilation levels. This is unlikely to occur until at least 30 sec after volitional hyperventilation has ceased. In most subjects, exercise should be started within 1 min of ceasing hyperventilation to avoid the unwanted complications of periodic breathing and/or apnoea. It is, however, acceptable to prolong the delay between the end of hyperventilation and the start of exercise in some cases to up to 2 min.

Hyperventilation During Exercise: The above data would suggest that the ideal time to increase the exercise intensity would be between 15 and 30 sec post-hyperventilation. This would result in both $\dot{V}E$ and P_{ET},CO_2 being below pre-hyperventilation levels, while reducing the risk of contamination of the data as a result of a developing. It would therefore be advisable to increase exercise intensity as soon as $\dot{V}E$ falls close to pre-hyperventilation values. This has the advantage that Pa,CO_2 will be lower but the disadvantage that $\dot{V}E$ is unlikely to be below pre-hyperventilation levels.

CHAPTER 5:

EFFECT OF PRIOR HYPERVENTILATION ON THE VENTILATORY RESPONSE TO MODERATE INTENSITY EXERCISE.

INTRODUCTION

The ventilatory response to a square-wave exercise stimulus of moderate intensity against a background of rest is well described in the literature, consisting of an initial abrupt increase in $\dot{V}E$ to a plateau (Phase 1), followed some fifteen to thirty seconds later by a further slower increase (Phase 2) to the steady-state level (Phase 3, *Fig. 5.1*, see Whipp & Ward, 1982 for further explanation). Despite considerable research dating back over 100 years, the exact mechanisms responsible for the genesis and control of these responses remain elusive.

These have been discussed at some length in the introduction to this thesis. The 2 theories which have been at the forefront of recent research into the control of the exercise hyperpnoea are Dejour's neurohumoral hypothesis (1963) and Whipp & Ward's cardiodynamic hyperpnoea (1982). Dejours suggested that the initial increase in $\dot{V}E$ seen in conjunction with the onset of exercise was too fast to be humorally mediated and attributed it to an increase in neurogenic drive to the respiratory centres. As such, this drive was present throughout exercise and its cessation was responsible for the abrupt fall in $\dot{V}E$ seen on transition from exercise to rest. The second, slower rise he attributed to an increase in some blood-borne respiratory stimulus.

The origin of the neural stimulus responsible for the initial ventilatory response to exercise has been the subject of considerable debate. Research has centred on two main areas, peripheral stimuli from the joints and muscle spindles or metaboreceptors from the exercising muscles (Krogh & Lindhard, 1917; Cross et al., 1982a; Concu, 1988; Morikawa et al., 1989) and central stimuli from the motor cortex or the hypothalamus (Eldridge et al., 1985; Bennett, 1984; Favier et al., 1983; Tobin et al., 1986). There is no doubt that stimulation of any of these neural pathways can increase ventilation, but the question of whether they are responsible for the control of the Phase 1 ventilatory response to exercise still remains unresolved, since the response is still present in the absence of spinal cord transmission (Adams et al., 1984) and under anaesthesia, when the conscious drive is removed (Cross et al., 1982a).

Whipp & Ward (1982) suggested that $\dot{V}E$ was controlled by CO_2 flow to the lung. The Phase 1 response was mediated entirely by increased $\dot{Q}_P$, while the Phase 2 response resulted from the arrival at the lungs of venous blood with changed gas tensions (from the exercising muscles) and a further increase in $\dot{Q}_P$. They cited the constancy of arterial Pco_2 and the close relationship between $\dot{V}E$ and $\dot{V}co_2$ as evidence of this link. The proportionality of changes in $\dot{V}E$ and $\dot{V}co_2$ seen in response to impulse (Bennett et al., 1981; Lamarra et al., 1987b; Miyamoto et al., 1983), square-wave (Pearce & Milhorn, 1977; Casaburi et al., 1989a; Wasserman & Whipp, 1983; Whipp et al., 1982; Miyamoto et al., 1982), ramp (Miyamoto & Niizeki, 1992, Whipp et al., 1989) and sinusoidal (Casaburi et al., 1977, 1978; Miyamoto et al., 1983) forcings adds credence to their proposal.

The difference between these 2 theories lies in the mechanism responsible for the control of the initial ventilatory response to exercise: is it under neural or humoral control? One method of answering this question would be to reduce the rate of CO_2 flow to the lungs at this time (by reducing $PaCO_2$ prior to the onset of exercise with hyperventilation) and see its effect on the initial ventilatory response to exercise. This experiment has been performed before (Krogh & Lindhard, 1913; Asmussen, 1973; Lefrançois & Dejours, 1968; Ward et al., 1983; Gardner & McConnell, 1988; Cerretelli et al., 1994), but with variable results. All these authors used normal subjects in their studies. It is purported that athletes have a larger initial ventilatory response to exercise than normal sedentary individuals. The effect of reducing CO_2 stores prior to the onset of exercise should therefore be more obvious in athletes than in sedentary subjects.

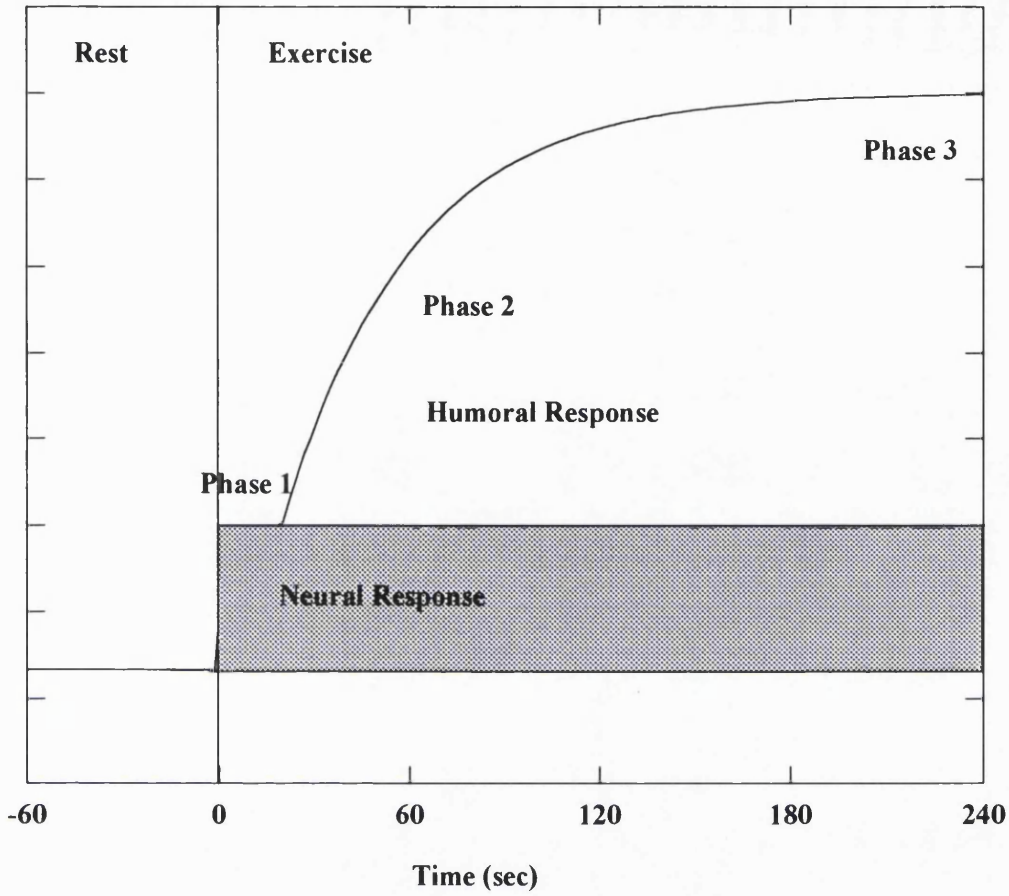


Figure 5.1: Illustration of the different phases of ventilatory or pulmonary gas exchange responses seen following the transition from rest to moderate intensity exercise. The neurohumoral theory of Dejours (1963) implies the initial responses are a result of a neurogenic stimulus present throughout exercise (shaded area) while the later responses are under the control of some blood-borne stimulus. Whipp & Ward (1982) suggested that Phase 1 was a cardiodynamic phase and Phase 2 was a result of a further increase in $\dot{Q}_P$ combined with changes in the gas tensions of venous blood arriving at the lungs.

PURPOSE OF THE EXPERIMENT:

The purpose of the experiment was to see whether reducing Pa,CO_2 and/or reducing CO_2 flow to the lung prior to the start of exercise would affect the characteristics of the phase 1 and 2 responses.

According to the neurohumoral theory first proposed by Dejours (1963), this should delay the onset of the Phase 2 response while leaving the Phase 1 response relatively untouched (except, of course, that it will be longer in duration).

Whipp & Ward (1982) would predict that the initial ventilatory response to exercise be reduced in proportion with the depletion of blood CO_2 stores. The changes in the profile of the later rise in $\dot{V}E$ and $\dot{V}co_2$ would be complex, depending on how the prior hyperventilation had affected the various compartments of the body's CO_2 stores, and hence the rate and extent to which metabolically produced CO_2 was diverted from excretion at the lungs to replenishment of body CO_2 stores.

Preliminary findings of this study have been already been published in abstract form (Howell & Cross, 1994a, 1996)

METHODOLOGY:

SUBJECTS:

Eight subjects performed tests "N1" and "H1", while a further six subjects performed tests "N2", "H2" and "H3". All were male. Their anthropometric data are presented in *Table 5.1.* All fourteen trained regularly, eleven trained at least six times per week. Incremental exercise tests were not performed on these subjects to determine their $Vo_{2,max}$ or $\varnothing_{AN}$.

SUBJECT	AGE	HEIGHT	WEIGHT	SPORT
C	23	1.9	75	ROWER
D	30	1.76	66	FELL RUNNER
F	50	1.77	71.8	SQUASH PLAYER
G	19	1.83	75	ROWER
H	22	1.85	77.5	ROWER
I	22	1.75	68.5	HOCKEY PLAYER
J	21	1.71	78	ROWER
K	21	1.77	77	ROWER
L	20	1.91	81	ROWER
M	20	1.83	71	ROWER
N	38	1.93	97.5	ROWER
O	24	1.98	82	ROWER
6	22	1.9	90	CYCLIST
X	29	1.85	78	ROWER

Table 5.1: Anthropometric data for subjects of this study. Subjects L and below performed tests "N2", "H2" and "H3", others performed tests "N1" and "H1".

Ten were club, college or university oarsmen, one represented his college at hockey, one played squash regularly and one cycled to and from college each day. None of the subjects smoked and all refrained from eating and drinking for at least one hour before the tests were performed. Subjects C, D and F had previously been used in the study described in Chapter 3.

PROTOCOLS:

The tests for each subject were performed on the same day, separated by a rest period of approximately twenty minutes. The "N" test was always performed first, but for those subjects who performed the "H2" and "H3" tests, the order of these was randomised between subjects.

Normal ("N1" and "N2") Tests: The subjects sat quietly on the cycle ergometer for 4 min with the flywheel stationary. At the end of this time the subjects were told "Start pedalling ....now", whereupon they exercised at 150 W @ 75 rpm for 4 min. The workload was increased gradually over the first 5 sec of exercise to account for the extra work associated with accelerating the flywheel ("N1" tests). In a subset of tests ("N2" tests), the flywheel was set spinning prior to the start of exercise. This removed any influence of the extra work associated with overcoming the inertia of the flywheel on the subjects' exercise responses. Most tests ended with approximately 3 min rest.

Hyperventilation Without Added CO_2 ("H1" and "H2" Tests): The test started with 4 min rest ("REST" stage). In the last 30 sec of this period an oscilloscope was switched on, on which a dot deflected throughout expiration in proportion to the tidal volume. Subjects were then asked to hyperventilate by increasing V_T to thrice their normal resting level (this could be monitored via the dot on the oscilloscope), while keeping their frequency of breathing constant (i.e. the number of deflections per sweep of the oscilloscope). Hyperventilation was maintained at this level until P_{ET},CO_2 fell to between 20 and 25 mmHg. This took on average 2 min ("HYPER" period). Once this end-point had been reached, subjects were asked to breathe normally and the oscilloscope was switched off ("POST-HYPER" period).

Within 1 min of ceasing hyperventilation, subjects were asked to start exercising in the same manner as in the "N1" and "N2" tests ("EXERCISE" period). Subjects then exercised at 150 W @ 75 rpm for 4 min ("H1" tests). Again, in a subset of tests ("H2" tests) the wheel was set spinning prior to the start of exercise to remove any extra work associated with overcoming the inertia of the flywheel.

Hyperventilation With Added CO_2 ("H3" Test): Subjects sat at rest on the cycle ergometer for 4 min. In the last 30 sec of this stage the oscilloscope was switched on and subjects were asked to hyperventilate according to the protocol described for "H1" and "H2" tests. During the hyperventilation period, however, P_{ET},CO_2 was maintained close to its normal resting value by adding CO_2 to the inspirate (Ward et al., 1983). After 2 min of hyperventilation subjects were told to breathe normally. Within 1 min of ceasing hyperventilation subjects were asked to start exercising at 150 W @ 75 rpm. for 4 min. This was followed by 2 min rest. In all these tests, exercise was started with the flywheel spinning and the workload being increased abruptly at the start of the exercise period. Exercise was always started with a verbal command.

APPARATUS:

The apparatus was used as described in Chapter 2. Data acquisition program EXTEST 2 (see Appendix A) was used for tests "N1" and "H1" and EXTEST 3 (see Appendix A) was used for tests "N2", "H2" and "H3".

DATA ANALYSIS:

Resting Values: Resting measurements of each of the cardiorespiratory variables were taken as the mean response seen over the last 30 sec of the resting period, assuming there were no dramatic changes in breathing pattern, eg. associated with the acts of swallowing or coughing. If this occurred, the analysis period was taken as close to the start of the proceeding stage as possible without including this unwanted data.

Hyperventilation Period: The response to hyperventilation was taken as the mean values of the last five breaths of the hyperventilation period.

Post-Hyperventilation Period: This was taken as the mean response of the five breaths prior to the start of exercise to avoid any adverse influence on the results from afterdischarge associated with the act of hyperventilation.

Modelling: All modelling was performed in Microsoft EXCEL 4.0 using the "Solver" function. The time courses of the cardiorespiratory and pulmonary gas exchange responses to a square wave exercise stimulus against a background of rest are well described in the literature. They consist of an initial fast response (Early response) followed by a slower, delayed response (Later response) to the steady-state. The latter is well described by a single order exponential equation of the form:

$$y_{(t)} = y_R + \left[\left(y_{S/S} - y_R\right) * \left(1 - e^{-(t-t_D)/\tau}\right)\right]$$

where $y_{(t)}$ is the value of the variable at time t, y_R is the resting value of the variable, $y_{S/S}$ is the steady-state response to exercise, t is the time in sec from the start of the test, t_D is the delay time in sec and τ is the time constant of the response. t_D was taken as the time when the model data intercepted with normal resting levels. This is consistent with the model 3 of Whipp et al. (1982) and model 2 of Casaburi et al. (1989a).

The model of the later response was combined with two models of the early response. "MODEL 2" (see *Fig. 5.2* and Appendix E) defined the early response as the mean $\dot{V}E$ from the start of exercise to the onset of the later response. This corresponds to the traditional view of the initial response (Whipp & Ward, 1982; Whipp et al., 1982) described in the introduction to this Chapter.

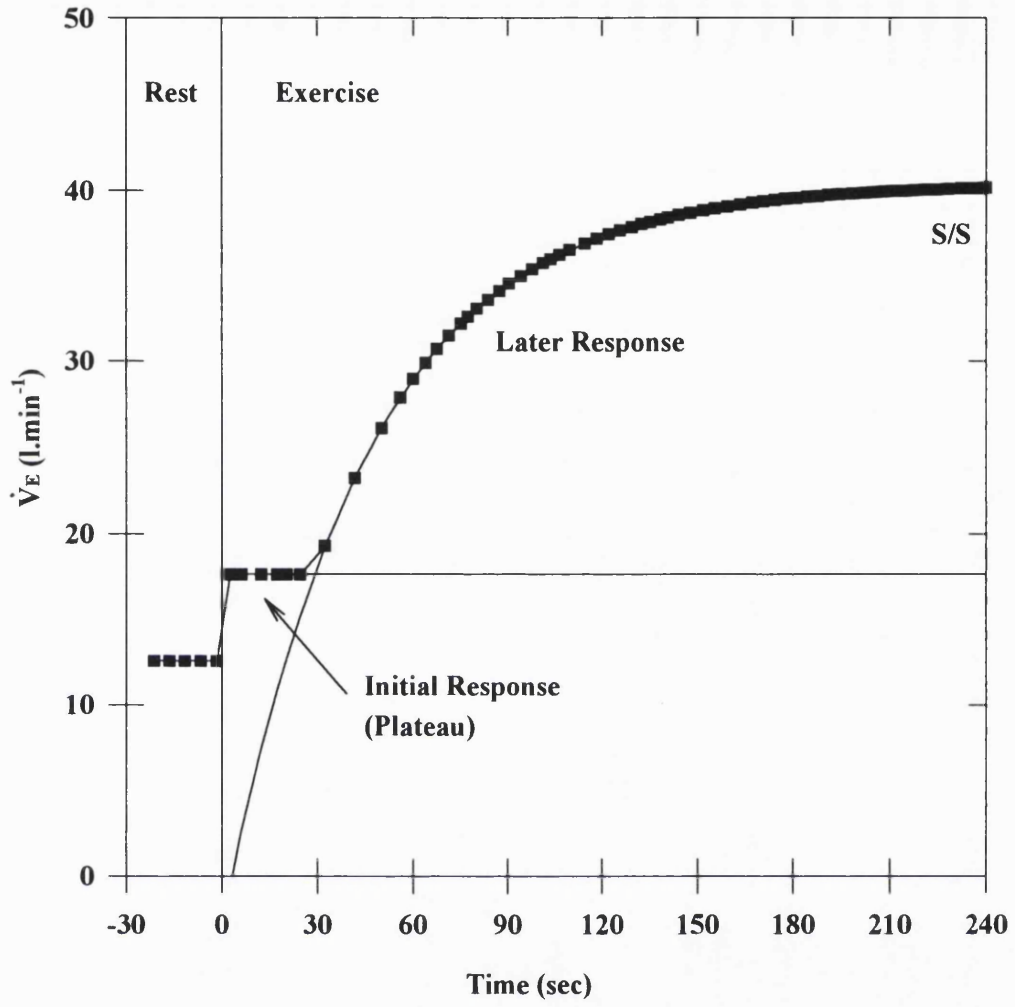


Figure 5.2: Example of the use of MODEL 2, here modelling $\dot{V}_E$ ($l.min^{-1}$, BTPS). Time 0 represents the start of exercise. Squares mark model data, lines extrapolate the algorithms of the initial and later responses. Intersection of the lines corresponds to the onset of the later response. Initial response = 18 $l.min^{-1}$; t_D = 30 sec; τ = 45 sec, S/S = 40 $l.min^{-1}$. See text for symbols.

The profile of the changes in $\dot{V}_E$ seen over the first 20 sec of exercise in a high proportion of the tests performed in this study were not well described by the traditional model above.

Instead of an abrupt increase to a plateau, $\dot{V}_E$ increased abruptly, but then fell to a plateau until the onset of the later, more gradual response. This profile of response has been described before in the literature (Krogh & Lindhard, 1913; Cummin et al., 1986b) and the ramifications of these results will be discussed later in this Chapter.

To account for this transient overshoot, the early ventilatory response was separated into 2 parts: the initial increase was defined as the maximum $\dot{V}E$ achieved over the first three breaths of exercise, while the plateau response was defined as the mean $\dot{V}E$ from the fourth breath of exercise to the onset of the later response (MODEL 3, see *Fig. 5.3* and Appendix F).

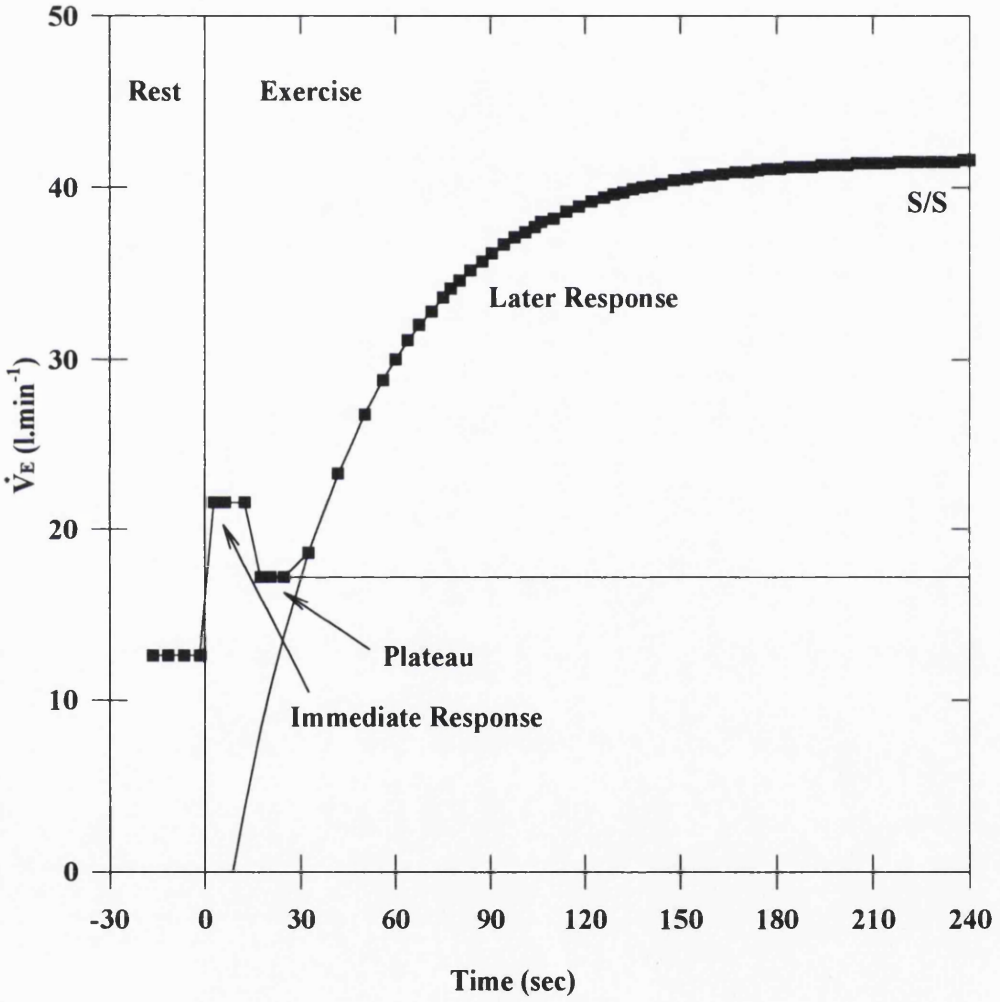


Figure 5.3: Example of the use of MODEL 3, here modelling $\dot{V}E$ (BTPS). Time 0 represents the start of exercise. Squares mark model data, lines extapolate the algorithms of the initial and later responses. Intersection of the lines corresponds to the onset of the later response. Initial response = 21.6 $l.min^{-1}$; Plateau response = 17.5 l.min-1; t_D = 23 sec; τ = 40 sec, S/S = 42 $l.min^{-1}$. See text for symbols.

To determine the best fit function to the data, the method of least squares was used ($\Sigma(Res^2)$). The entire response was modelled simultaneously; "Solver" being able to vary the value of the initial response, the descriptors of the monoexponential rise and the plateau value to attain the profile which best fit the experimental data.

In order to determine whether the difference between the initial rise and the subsequent plateau was significant, it was compared to the 95% confidence interval for the exercise period. This was calculated from the standard deviation of the residuals over the entire response. Lamarra et al. (1987) reported that the variability of the data varies between subjects, but does not change on transition from one workload to another, or between the two steady states.

Interpolation of Data: Breath-by-breath data for each subject were interpolated over 1 sec intervals. The individual results were then time-aligned and averaged to produce a population mean response.

Initial Heart-Rate Response: None of the tests generated a classic initial response for f_C (Whipp et al., 1982). However, in some tests there was evidence of an early response (See Results section and *Fig. 5.9*). This took the form of a notch in the otherwise smooth transition to the steady-state.

Onset of the Phase 2 Response: The onset of the Phase 2 response (Whipp & Ward, 1982; Whipp et al., 1982) was taken as the mean time (i) for the onset of the second rise in V_{O_2}, (ii) the increase in O_2 Pulse, (iii) RER started to fall and (iv) P_{ET,O_2} started to fall.

Steady-State Responses: The steady-state (or Phase 3) responses to 150 W exercise were taken as the mean values of each of the cardiorespiratory variables over the last 30 sec of exercise.

Statistical comparisons between the responses seen in the "N" and "H1" and "H2" tests were performed using paired t-tests. Where data from the "N2", "H2" and "H3" tests were compared, a single-factor ANOVA was used with post-hoc analysis by paired t-test where significance was indicated.

RESULTS:

A representative example of the breath-by-breath changes in $\dot{V}E$ (BTPS), P_{ET,CO_2}, VT, f_{BR}, f_C, $\dot{V}_{O_2}$ (STPD), $\dot{V}_{CO_2}$ (STPD), and P_{ET,O_2} throughout tests "N1" and "H1", "N2" and "H2" and "N2" and "H3" are presented in *Figs. 5.4, 5.5* and *5.6*. The cardiorespiratory responses to exercise were similar in tests "N1" and "N2" and "H1" and "H2". The results of the "N1" and "N2" tests were combined to form "N" tests and the results of the "H1" and "H2" tests were combined to form "H" tests. "N1" tests were considered separately if comparison with the results of the "H3" tests was warranted.

RESTING VALUES:

There was no significant difference between the resting values recorded at the start of the "N" and "H" tests for f_C, $\dot{V}E$, VT, f_{BR}, P_{ET,CO_2}, P_{ET,O_2}, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and RER (see *Table 5.2*). The resting values for the "H3" tests were not significantly different from those obtained in the "N2 and "H2" tests.

	N1	H1	N2	H2	H3
f_C	69 ± 3	71 ± 2	64 ± 5	62 ± 2	63 ± 3
$\dot{V}E$	12.4 ± 0.5	11.7 ± 0.9	13.0 ± 1.5	12.3 ± 1.2	12.0 ± 1.4
VT	0.88 ± 0.06	0.78 ± 0.09	1.05 ± 0.95	0.94 ± 0.11	0.97 ± 0.13
f_{BR}	14.9 ± 1.3	16.8 ± 2.1	15.6 ± 2.2	17.0 ± 2.3	16.1 ± 2.7
P_{ET,CO_2}	40 ± 1	39 ± 1	37 ± 2	37 ± 2	37 ± 1
P_{ET,O_2}	104 ± 2	104 ± 3	111 ± 3	108 ± 3	106 ± 3
$\dot{V}_{O_2}$	0.43 ± 0.02	0.4 ± 0.01	0.37 ± 0.02	0.24 ± 0.04	0.39 ± 0.02
$\dot{V}_{CO_2}$	0.34 ± 0.03	0.31 ± 0.02	0.34 ± 0.03	0.3 ± 0.02	0.28 ± 0.02
RER	0.8 ± 0.05	0.82 ± 0.08	0.89 ± 0.08	0.74 ± 0.06	0.85 ± 0.11

Table 5.2: Mean (± S.E.) resting results for all test protocols. See text for symbols and units. n = 8 for protocols "N1" and "H1". n = 6 for the remaining 3 protocols.

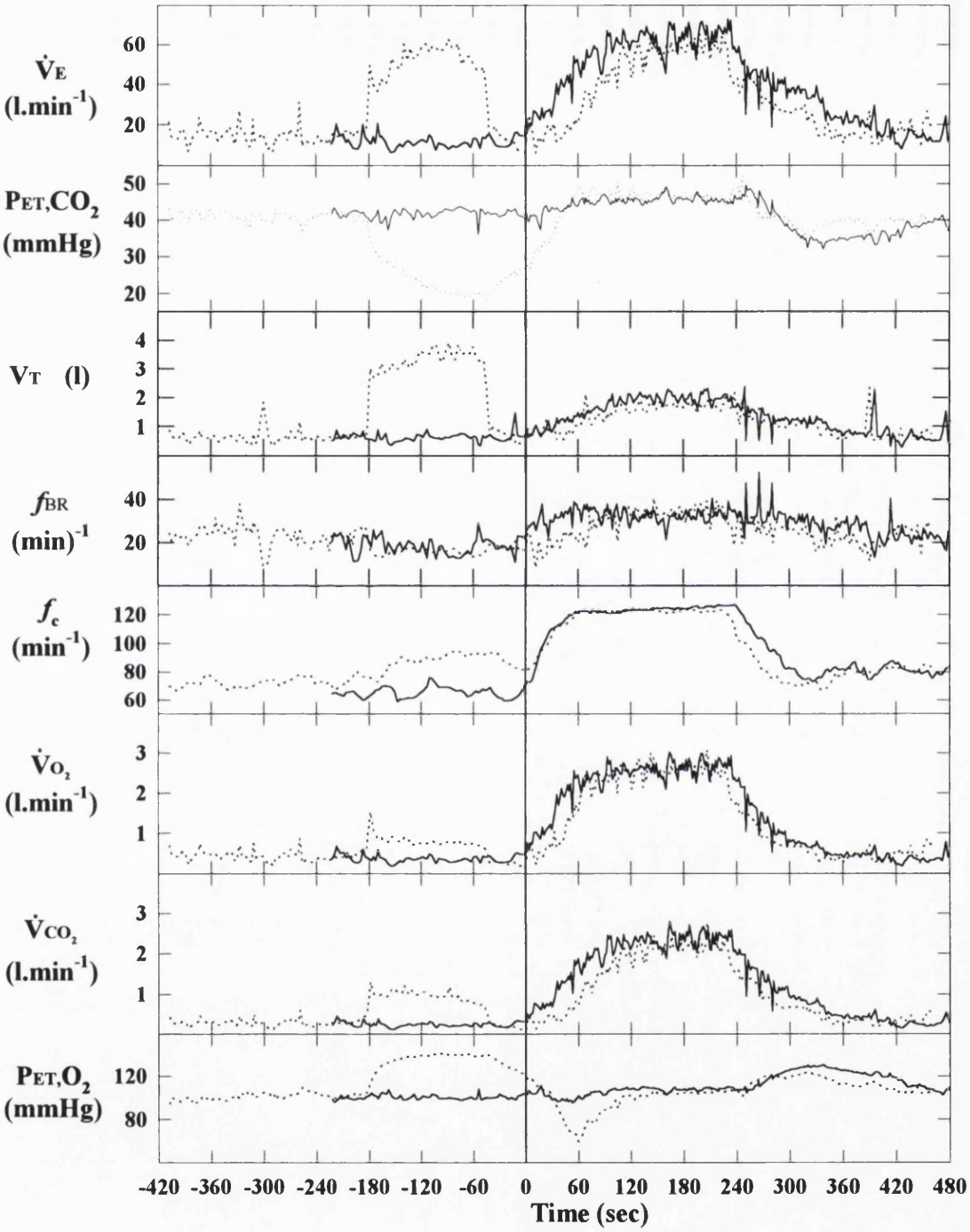


Figure 5.4: Breath-by-breath changes in $\dot{V}_E$ (BTPS), P_{ET,CO_2}, V_T, f_{BR}, f_C, $\dot{V}_{O_2}$ (STPD), $\dot{V}_{CO_2}$ (STPD), and P_{ET,O_2} (From top to bottom respectively) during tests "N1" (solid line) and "H1" (dashed line) for subject D. Time zero represents the start of exercise.

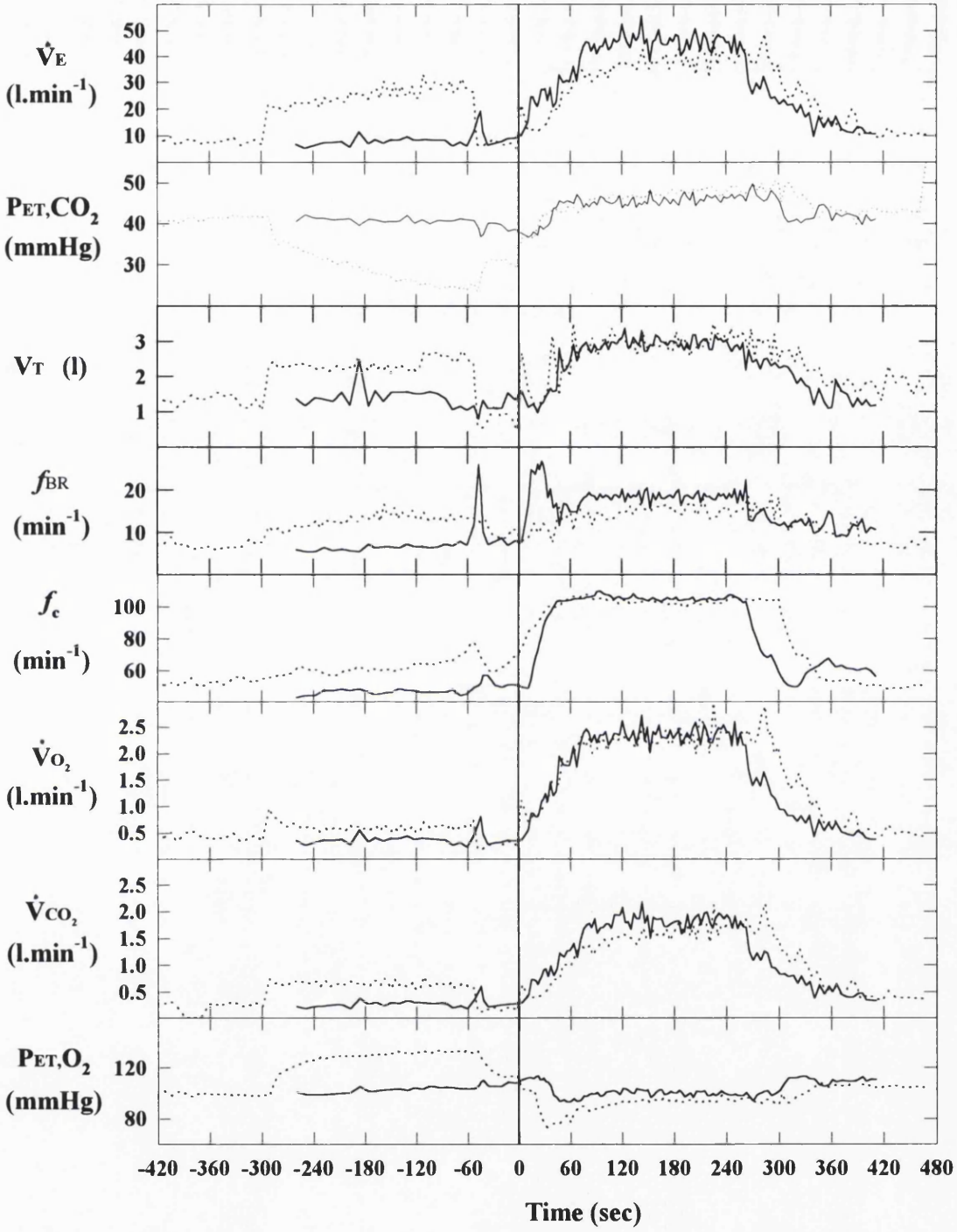


Figure 5.5: Breath-by-breath changes in $\dot{V}_E$ (BTPS), P_{ET,CO_2}, V_T, f_{BR}, f_C, $\dot{V}_{O_2}$ (STPD), $\dot{V}_{CO_2}$ (STPD), and P_{ET,O_2} (From top to bottom respectively) during tests "N2" (solid line) and "H2" (dashed line) for subject M. Time 0 represents the start of exercise.

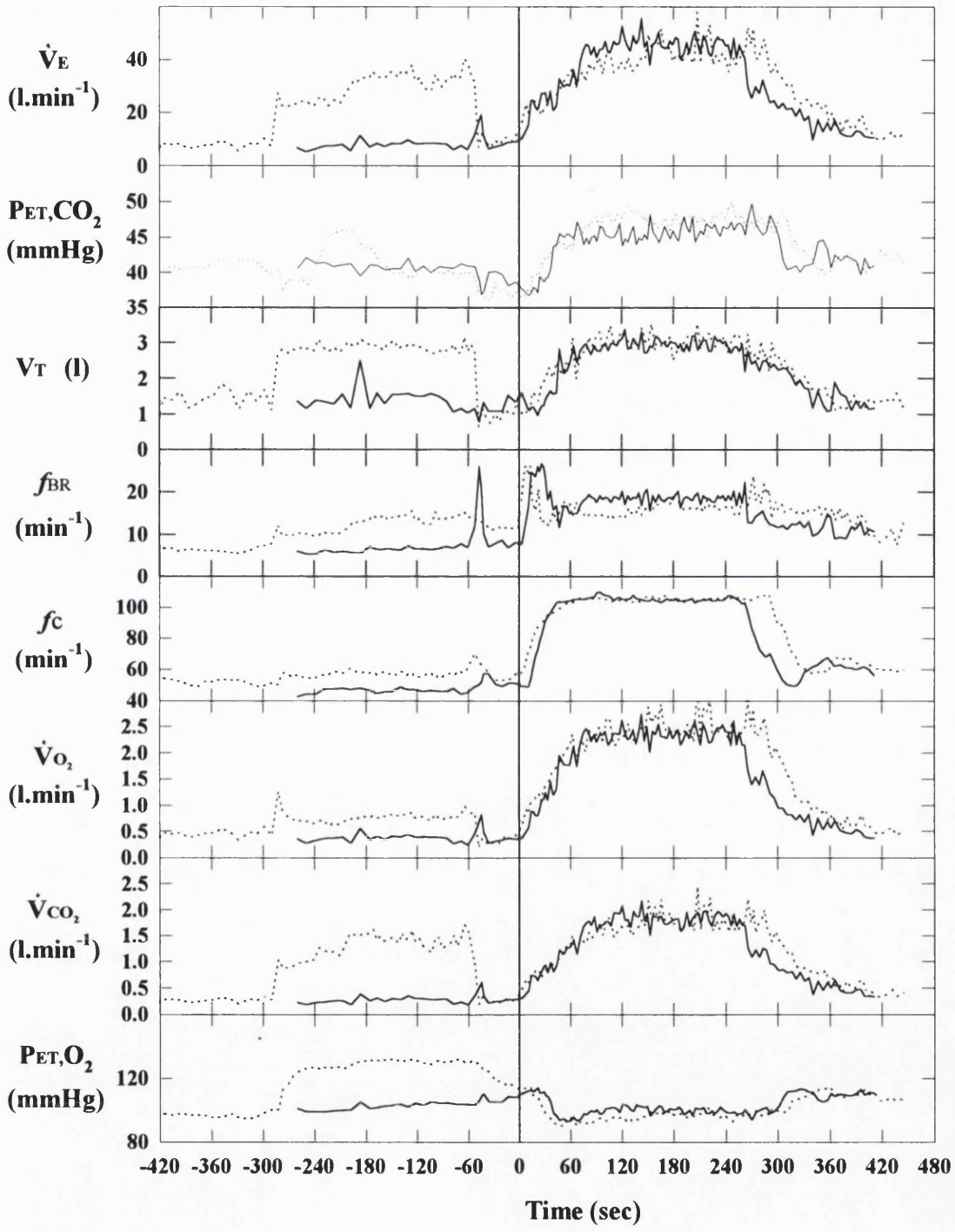


Figure 5.6: Breath-by-breath changes in $\dot{V}_E$ (BTPS), $P_{ET,CO}$, V_T, f_{BR}, f_C, $\dot{V}_{O_2}$ (STPD), $\dot{V}_{CO_2}$ (STPD), and P_{ET,O_2} (From top to bottom respectively) during tests "N2" (solid line) and "H3" (dashed line) for subject M. Time zero represents the start of exercise.

HYPERVENTILATION:

The hyperventilation period lasted for 126 ± 5, 199 ± 10 and 189 ± 13 sec in tests "H1", "H2" and "H3" respectively ("H2" vs. "H3" = *N.S.*). During the hyperventilation period, VE increased by a factor of 3.8, 2.7 and 2.5 over normal resting values in tests "H1", "H2" and "H3" respectively ("H2" vs. "H3" = *N.S.*, see *Table 5.3*). This increase was achieved by an increase in VT ("H2" vs. "H3" = *N.S.*), while *f*BR did not change significantly from normal resting values.

	H1	H2	H3
*f*C	91 ± 4*	81 ± 3*	71 ± 4*
$\dot{V}E$	44.2 ± 3.8*	32.8 ± 2.5*	30.4 ± 2.3*
VT	3.17 ± 0.16*	2.11 ± 0.21*	2.04 ± 0.27*
*f*BR	15.8 ± 1.9	19.3 ± 2.1	18.6 ± 1.4
P_{ET,CO_2}	22 ± 1*	23 ± 1*	38 ± 2*
P_{ET,O_2}	133 ± 3*	134 ± 1*	130 ± 1*
$\dot{V}o_2$	0.65 ± 0.06*	0.53 ± 0.05*	0.59 ± 0.11*
$\dot{V}co_2$	0.91 ± 0.07*	0.80 ± 0.04*	
RER	1.29 ± 0.29	1.54 ± 0.26	

Table 5.3: Mean (± S.E.) responses at the end of the hyperventilation period. Shading denotes missing data, * denotes values significantly ($p < 0.05$) different from rest. See text for symbols and units. n = 8 for protocol "H1", n = 6 for remaining 2 protocols.

As a result of the hyperventilation, P_{ET,CO_2} fell in the "H1" and "H2" tests. In the "H3" tests there were transient changes in P_{ET,CO_2} at the start of hyperventilation due to mismatching of P_{I,CO_2} to requirements. Thereafter P_{ET,CO_2} was maintained close to normal resting values.

$\dot{V}o_2$ increased abruptly but transiently at the start of hyperventilation in all tests. This increase typically lasted for three to four breaths and was attributed to changes in lung O_2 stores (see *Fig. 5.4*). Vo_2 then fell to a steady-state level slightly but significantly above normal resting levels. This was attributed to the increased work of breathing associated with the hyperventilation.

f_C increased significantly in all hyperventilation periods. This increase was due to the act of hyperventilation, rather than any change in $PaCO_2$ ("H2" vs. "H3" = *N.S.*). These results are consistent with those reported in Chapter 4.

POST-HYPERVENTILATION:

The post-hyperventilation period prior to exercise lasted for 50 ± 10 sec in the "H1" test, 55 ± 7 sec in the "H2" test and 62 ± 7 sec in the "H3" test ("H2" vs. "H3" = *N.S.*). This is approaching the limits of the preferred duration for this period described in Chapter 4. By the end of this period, V_E was not significantly different from normal resting values in the "H1", "H2" or "H3" tests (see *Table 5.4*). The change in $\dot{V}_E$ following hyperventilation was achieved by a fall in V_T; f_{BR} remaining constant or, in some cases, increasing slightly. This is in agreement with the results reported in Chapter 4.

P_{ET},CO_2 had partially recovered following hyperventilation in the "H1" and "H2" tests, but was still well below normal resting levels at the start of exercise. In the "H3" test, P_{ET},CO_2 was similar to normal resting values. P_{ET},O_2, having increased during the hyperventilation period, fell gradually post-hyperventilation, but was still above normal resting levels at the start of exercise ("H2" vs. "H3" = *N.S.*).

Both $\dot{V}o_2$ and $\dot{V}co_2$ had returned to close to normal resting levels by the end of the post-hyperventilation period in the "H1"and "H2" tests, while $\dot{V}o_2$ (but not $\dot{V}co_2$) was still elevated above normal resting levels in the "H3" test.

f_C fell following hyperventilation, but was still significantly above normal resting levels by the end of the post-hyperventilation period ("H2" vs. "H3" = *N.S.*).

	H1	H2	H3
f_C	87 ± 3	71 ± 1	68 ± 4
$\dot{V}_E$	14.3 ± 2.2	11.5 ± 2.4	13.5 ± 0.9
V_T	0.89 ± 0.16	0.75 ± 0.13	0.94 ± 0.05
f_{BR}	17.5 ± 1.7	20.3 ± 5.0	16.9 ± 1.6
P_{ET,CO_2}	27 ± 1	23 ± 1	37 ± 1
P_{ET,O_2}	121 ± 3	115 ± 4	113 ± 2
$\dot{V}_{O_2}$	0.36 ± 0.05	0.35 ± 0.04	0.43 ± 0.03
$\dot{V}_{CO_2}$	0.33 ± 0.05	0.33 ± 0.03	0.35 ± 0.01
RER	0.94 ± 0.18	0.77 ± 0.08	0.99 ± 0.14

Table 5.4: Mean (± S.E.) values of cardiorespiratory variables prior to the start of exercise in tests "H1", "H2" and "H3". See text for symbols and units. n = 8 for test "H1", n = 6 for test "H2" and "H3".

The pattern of recovery from the hyperventilation seen here is, therefore, similar to that reported in Chapter 4.

RESPONSES TO EXERCISE:

$\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ increased abruptly in conjunction with the start of exercise in all tests. This was followed by a plateau period before the onset of a second, more gradual increase to the steady-state.

The RER data obtained from these tests demonstrate that subject I exceeded his $\varnothing_{AN}$ during these tests. His results were therefore excluded from the analysis. The ventilatory response of subject G was too variable to model. This variability of response was also present in his pulmonary gas exchange responses to exercise. His results were also excluded from the analysis.

In addition, analysis of changes in f_C were not possible for 2 subjects (Subjects F and C) due to excessive noise in their ECG trace, no data was obtained for P_{ET,O_2} in the tests performed by subjects H and K and no data was obtained for $\dot{V}_{O_2}$ in the "H1" tests performed by subjects F and C due to technical difficulties.

Choice of Models: Ventilatory and pulmonary gas exchange responses were modelled with both MODEL 2 and MODEL 3, described in the Methods section. The sum of the squares of the residuals generated by MODEL 3 were significantly smaller than those generated by MODEL 2 for the ventilatory response to exercise in both the "N" and "H" tests (See *Table 5.5*). In addition, the difference between $\dot{V}E$ over the first 3 breaths of exercise and the subsequent plateau value could not be accounted for by noise in the signal for 5 of the "N" tests and 10 of the "H" tests. Based on these findings, MODEL 3 was used in preference to MODEL 2 for modelling the ventilatory response to exercise.

The sum of the squares of the residuals generated by MODEL 3 were also significantly smaller than those generated by MODEL 2 for the pulmonary gas exchange responses to exercise in both the "N" and "H" tests (See *Table 5.5*). The difference between the initial increases in $\dot{V}o_2$ and $\dot{V}co_2$ and the subsequent plateau values were studied with respect to signal noise. The differences could be explained in terms of signal noise for all except 3 of the "H" tests for Vo_2 and 2 of the "N" and 3 of the "H" tests for $\dot{V}co_2$. These findings do not favour either MODEL 2 or MODEL 3. MODEL 2 was used for modelling the pulmonary gas exchange responses on the grounds that it was the simpler of the 2 models.

		MODEL 3		MODEL 2	
		N	H	N	H
$\dot{V}E$	$\Sigma(Res^2)$	1825 ± 412*	1235 ± 205*	1958 ± 435	1445 ± 249
	I vs. Pl	4/12	9/12		
$\dot{V}o_2$	$\Sigma(Res^2)$	3.02 ± 0.49	3.6 ± 0.58*	3.29 ± 0.6	3.6 ± 0.58
	I vs. Pl	0/12	3/10		
$\dot{V}co_2$	$\Sigma(Res^2)$	2.56 ± 0.48*	1.81 ± 0.27*	2.72 ± 0.52	1.9 ± 0.28
	I vs. Pl	2/12	3/12		

Table 5.5: Data used to determine which model provided the better description of the experimental data. Values are sample mean ± S.E. for $\Sigma(Res^2)$ (* denotes values are significantly ($p<0.05$) different) and sample ratio for whether the immediate increase was significantly ($p<0.05$) greater than the plateau value (I vs. Pl). See text for symbols and units. n = 12 for VE, n = 13 for Vo_2 and Vco_2..

		Initial Response		Later Responses		
		Immediate	Plateau	Delay	τ	S/S
$\dot{V}_E$	"N"	29.4 ± 2.4	23.4 ± 1.5*	27.5 ± 3.2*	45.6 ± 5.6	52.7 ± 3.3
	"H"	29.6 ± 3.1	18.9 ± 1.8	38.9 ± 2.9	47.6 ± 4.8	49.4 ± 3.3
$\dot{V}o_2$	"N"		1.01 ± 0.08	18.6 ± 1.2	26.9 ± 3.5	2.34 ± 0.11
	"H"		0.8 ± 0.06	22.7 ± 3.3	26.8 ± 2.8	2.34 ± 0.1
$\dot{V}co_2$	"N"		0.78 ± 0.06*	24.4 ± 2.0*	47.5 ± 4.7	2.17 ± 0.14
	"H"		0.57 ± 0.05	36.5 ± 2.6	47.8 ± 4.0	2.09 ± 0.15

Table 5.6: Results of the modelling of ventilatory and pulmonary gas exchange responses to exercise with and without prior hyperventilation. * signifies results significantly ($p<0.05$) different between the 2 protocols. For symbols and units see text. Shading denotes data not available. n = 12 for VE, n = 13 for Vo_2 and Vco_2.

		Initial Response		Later Responses		
		Immediate	Plateau	Delay	τ	S/S
$\dot{V}_E$	N2	28.6 ± 3.9	21.6 ± 1.2	23.7 ± 3.7	35.9 ± 6.1	47.1 ± 2.0
	H3	24.4 ± 2.3	23.2 ± 1.2	32.4 ± 39.4	39.4 ± 7.4	45.8 ± 1.7
$\dot{V}o_2$	N2		0.88 ± 0.09	18.8 ± 1.5	26.0 ± 4.9	2.04 ± 0.1
	H3		0.64 ± 0.07	12.6 ± 1.85	29.1 ± 4.81	2.1 ± 0.1
$\dot{V}co_2$	N2		0.7 ± 0.04	21.9 ± 2.8	45.2 ± 7.01	1.82 ± 0.05
	H3		0.6 ± 0.08	20.0 ± 2.8	47.1 ± 8.2	1.83 ± 0.06

Table 5.7: Results of the modelling of the ventilatory and pulmonary gas exchange responses to exercise in tests "N2" and "H3". n = 6. See text for symbols and units. Shading denotes data not available.

Initial Responses to Exercise: $\dot{V}o_2$ and $\dot{V}co_2$ increased abruptly to a plateau in conjunction with the onset of exercise (See *Figs. 5.4, 5.5 & 5.6*). This pattern of response was modelled by MODEL 2. The magnitude of the plateau for $\dot{V}o_2$ was unaffected by either the act of hyperventilation ("N2" vs. "H3" = *N.S.* See *Fig. 5.7a*) or by hypocapnia consequent to hyperventilation ("N" vs. "H" = *N.S.* See *Fig 5.7b*). The magnitude of the plateau for $\dot{V}co_2$ was also unaffected by the act of hyperventilation (See *Fig. 5.8a*), but was significantly reduced in the "H" tests (See *Fig 5.8b*).

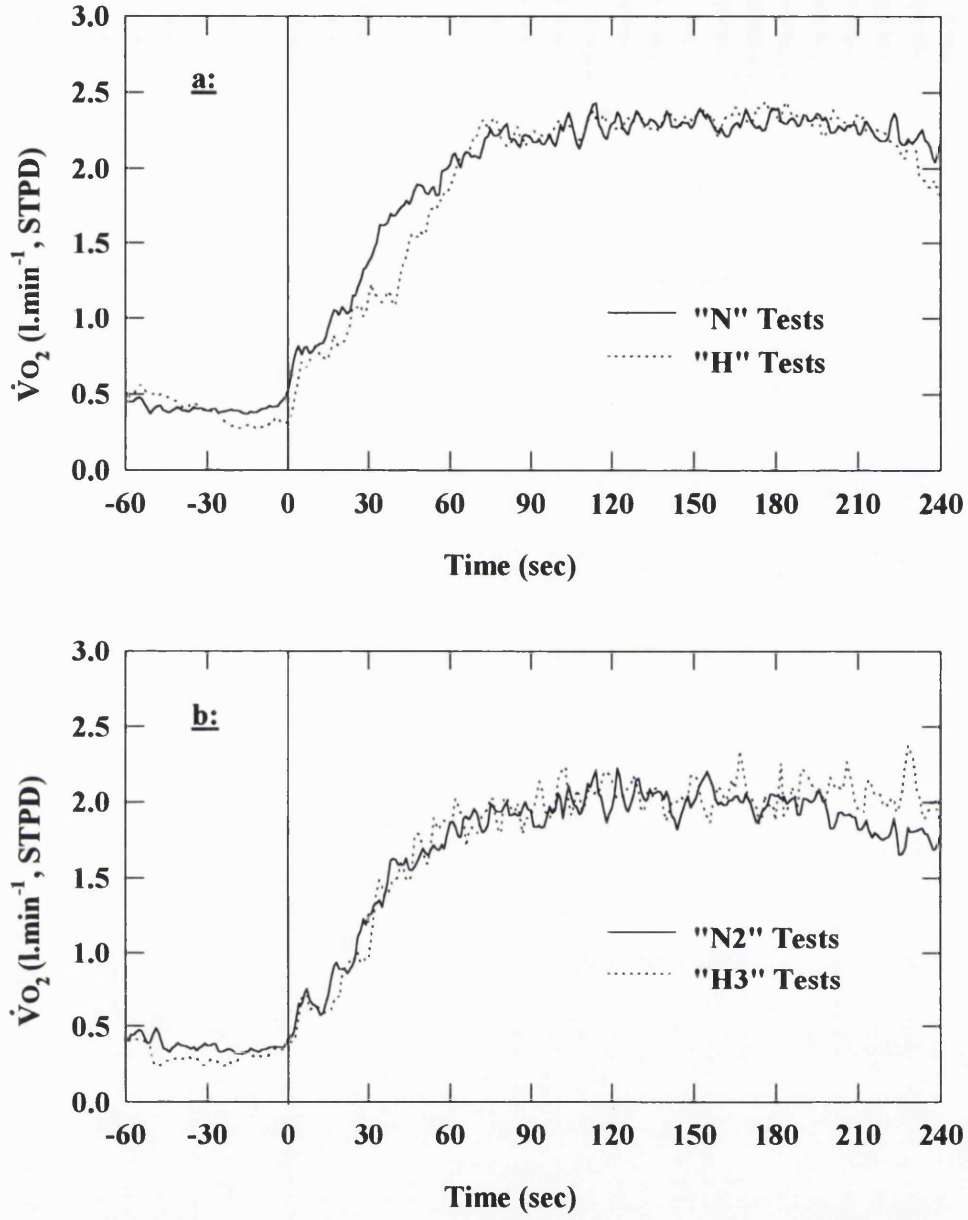


Figure 5.7a: Mean changes in $\dot{V}o_2$ in response to exercise in tests "N" and "H". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.
b: Mean changes in $\dot{V}o_2$ in response to exercise in tests "N2" and "H3". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

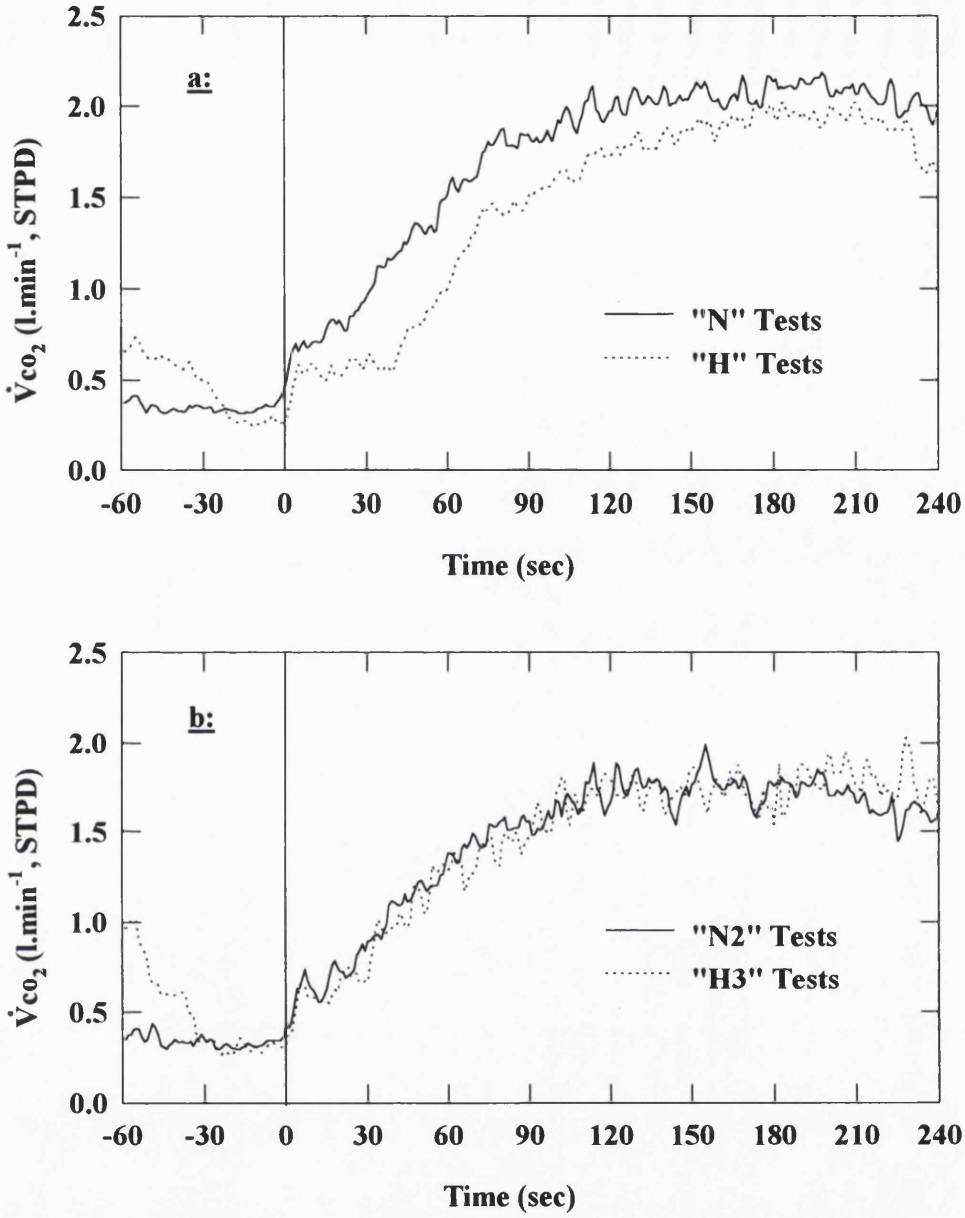


Figure 5.8a: Mean changes in $\dot{V}co_2$ in response to exercise in tests "N" and "H". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.
b: Mean changes in $\dot{V}co_2$ in response to exercise in tests "N2" and "H3". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

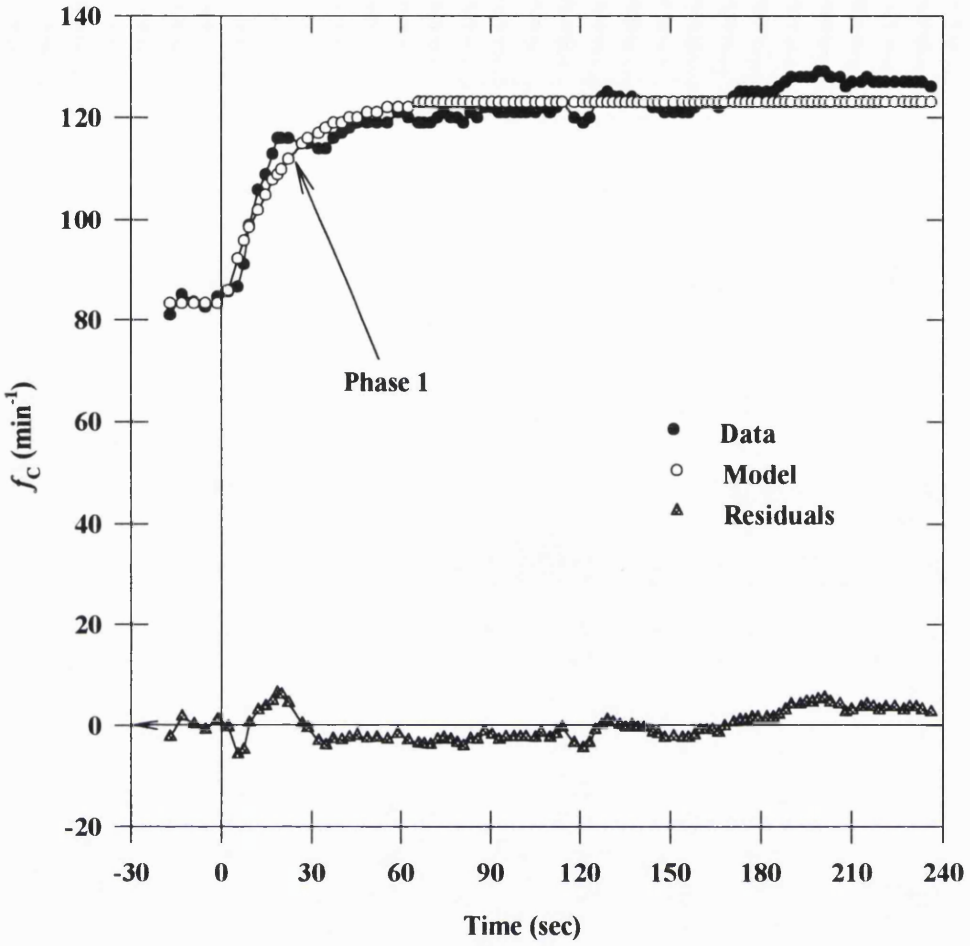


Figure 5.9: Modelling of breath-by-breath f_C response to exercise in test "N" performed by subject G. Note initial response (arrowed), also evident from the plot of the residuals. Exercise started at time 0. Initial response = 116 bpm, t_D = -1.0 sec, τ = 16.9 sec, S/S = 124 l.min^{-1}, $\Sigma(Res^2)$ = 852.

f_C increased rapidly, but not abruptly, in all tests at the start of exercise. In 5 out of 9 of the "N" tests, 4 out of 7 of the "H" tests and 2 out of 6 of the "H3" tests, a notch was visible in the rise in f_C (see *Fig. 5.9*, but not in *Figs. 5.6, 5.7 or 5.8*) approximately 16 sec after the onset of exercise (See *Table 5.8*). Where this was present, it was taken as an initial response to exercise. The magnitude and timing of this peak was similar for both "N" and "H" tests (See *Fig. 5.10a* and *Table 5.8*), despite f_C being significantly higher prior to the start of exercise in the "H" tests. The magnitude of the peak was not affected by the act of hyperventilation (See *Fig. 5.10b*).

	Early Response		Later Responses		
	Value	Time	Onset	τ	S/S
"N"	106.8 ± 4.7	16.8 ± 1.0	1.1 ± 0.9	24.8 ± 3.8	123.5 ± 4.3
"H"	106.7 ± 5.1	15.3 ± 2.3	-1.9 ± 2.0	32.2 ± 5.6	122.9 ± 4.6

Table 5.8: Mean (± S.E.) changes in f_C as determined by modelling (Later Responses) and by visual inspection of the data (Early Response). See text for symbols and units. n = 11

$\dot{V}_E$ also increased abruptly in conjunction with the start of exercise, but then typically fell to a plateau before rising again (See *Figs. 5.6, 5.7 and 5.8*). This pattern of response was modelled using MODEL 3 (See *Fig 5.11a*). The magnitude of the initial increase in $\dot{V}_E$ was constant throughout the protocols (See *Figs. 5.12a and b*), but the magnitude of the plateau was significantly reduced by prior hypocapnic hyperventilation ("N" vs. "H": $p<0.05$).

A caveat: if the ventilatory response to exercise was modelled using MODEL 2, the magnitude of the initial response seen in the "H" tests was significantly lower than that seen in the "N" tests (See *Table 5.9* and *Fig. 5.11b*). Use of this less sophisticated model would significantly corrupt the description of the effect of prior hyperventilation on the ventilatory response to exercise.

	N1	H1	N2	H2	H3
Plateau	24.4 ± 0.1	20.4 ± 2.1	24.5 ± 1.0	20.8 ± 2.0	22.3 ± 2.2

Table 5.9: Mean (± S.E.) initial responses for the different protocols as defined by MODEL 2. See text for discussion.

Changes in V_T and f_{BR} associated with the onset of exercise were variable. In general, an abrupt increase in f_{BR} was responsible for the majority of the initial increase in $\dot{V}_E$ in the "N" tests, whilst an increase in V_T was responsible for the majority of the increase in $\dot{V}_E$ in the "H" tests (See *Fig. 5.5*). These patterns were not seen in all subjects tested.

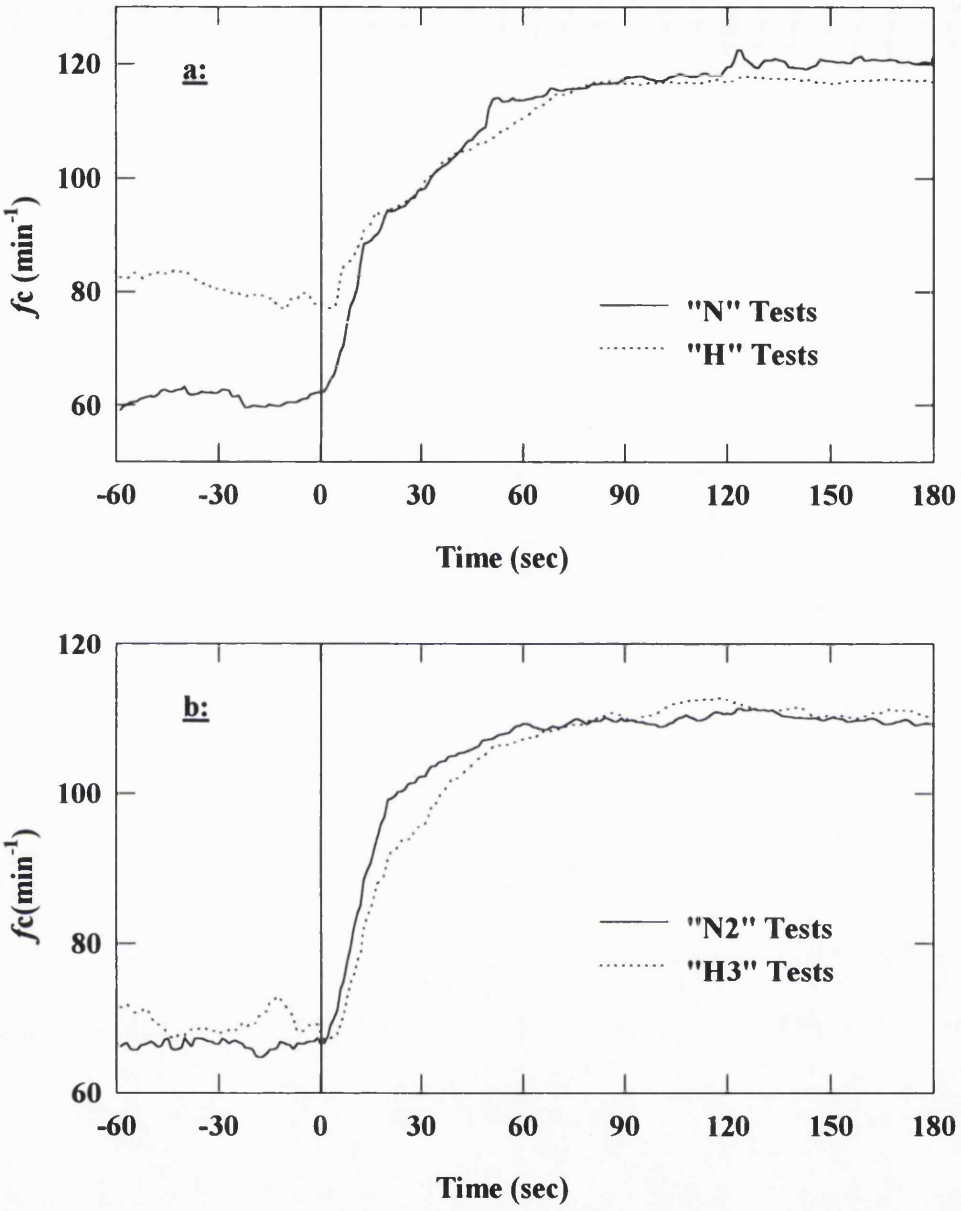


Figure 5.10a: Mean changes in *f*C in response to exercise in tests "N" and "H". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.
b: Mean changes in *f*C in response to exercise in tests "N2" and "H3". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

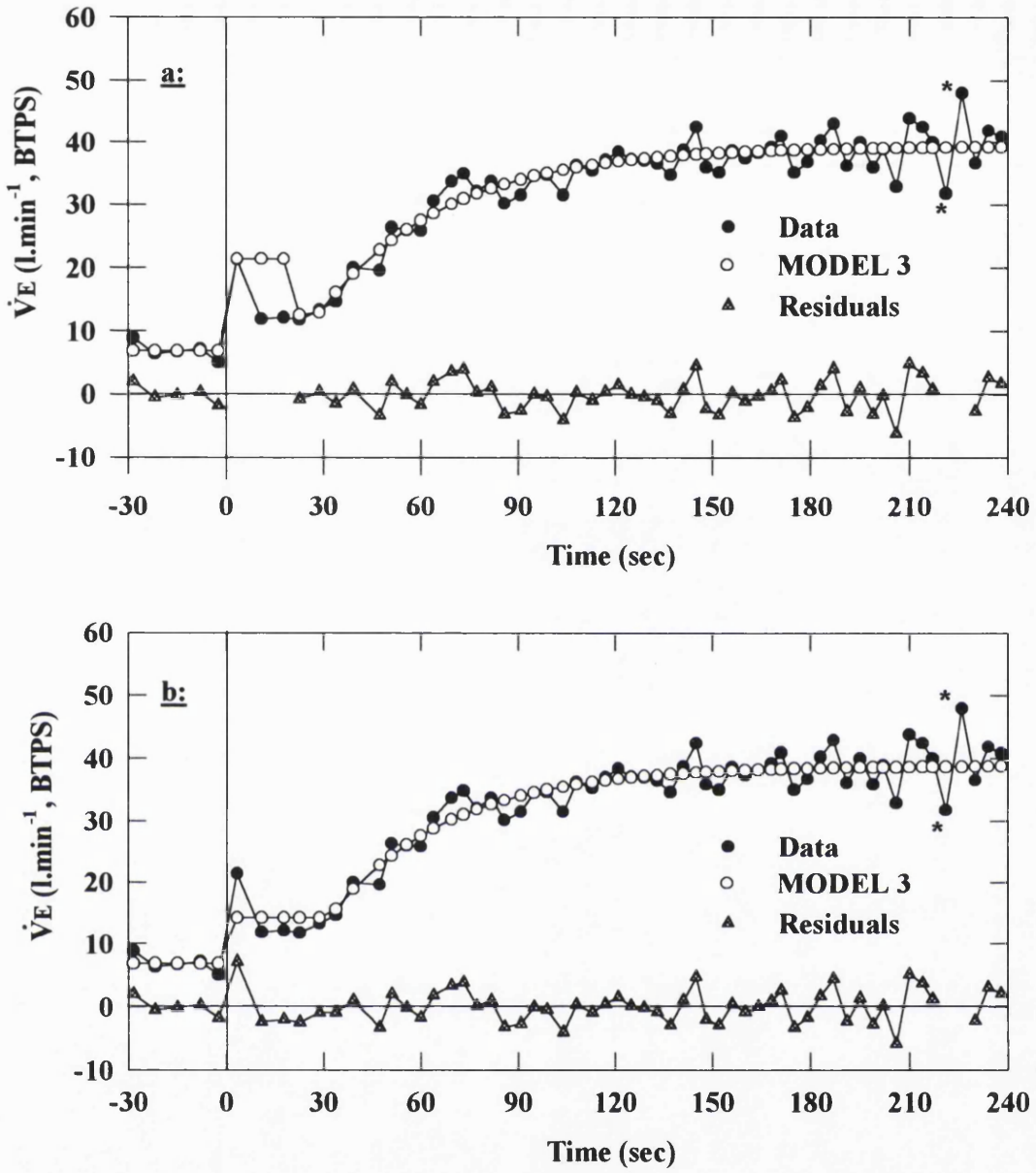


Figure 5.11a: Modelling of ventilatory responses to exercise in test "H" performed by subject M using MODEL 3. Pattern of residuals and $\Sigma(Res^2)$ shows that MODEL 3 describes the data well. Time 0 represents the start of exercise. Initial increase = 21.4 $l.min^{-1}$, plateau = 13.0 $l.min^{-1}$, t_D = 20.6 sec, τ = 38.8 sec, S/S = 40.4 $l.min^{-1}$, $\Sigma(res^2)$ = 313. See text for symbols. * denotes data points excluded from modelling.

b: Modelling of the same data as above using MODEL 2. Pattern of residuals and $\Sigma(Res^2)$ shows that MODEL 2 did not accurately describe the initial response. Exercise started at time 0. Plateau = 14.2 $l.min^{-1}$, t_D = 21.2 sec, τ = 38.3 sec, S/S = 40.1 $l.min^{-1}$, $\Sigma(Res^2)$ = 319. * denotes data points excluded from modelling.

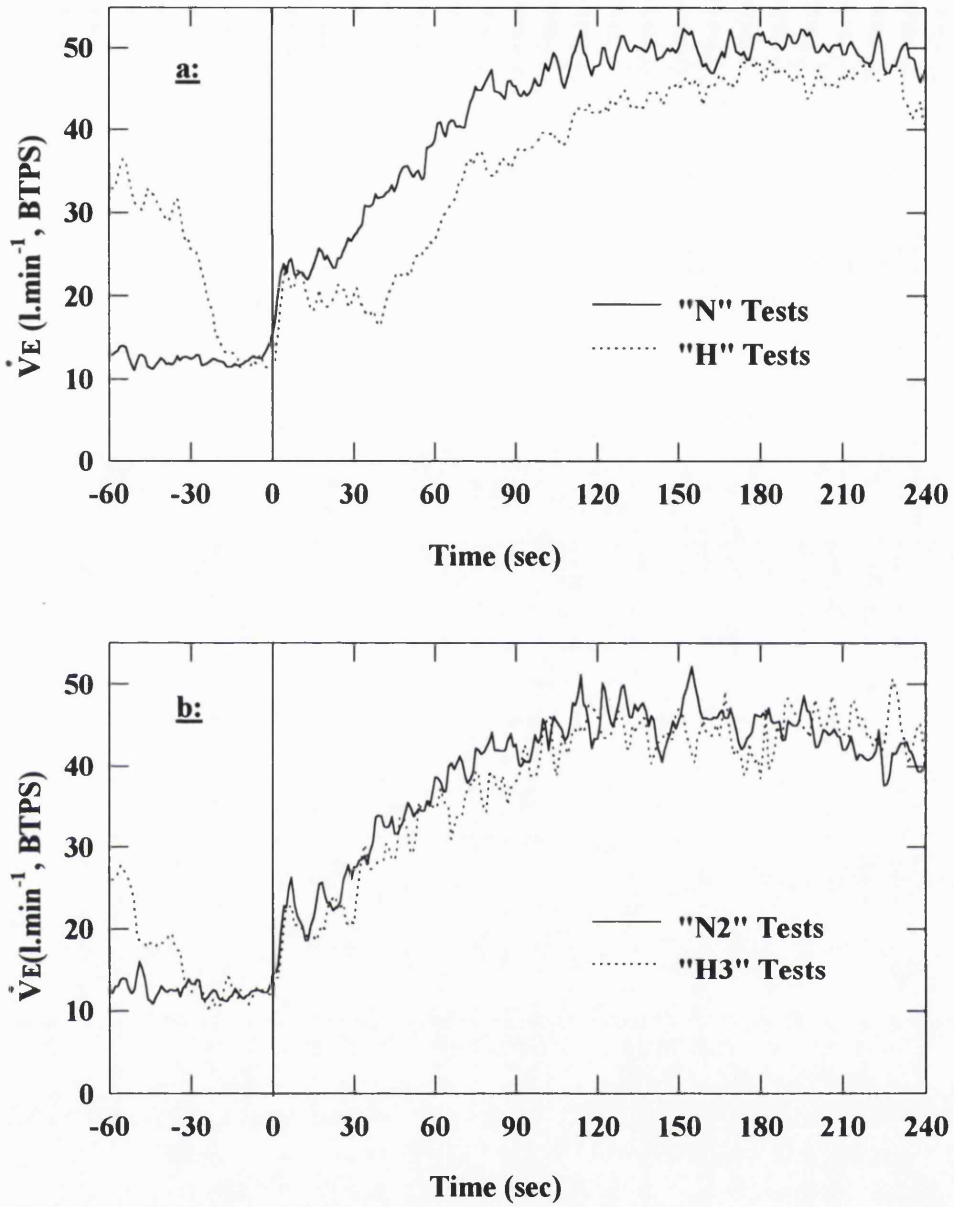


Figure 5.12a: Mean changes in $\dot{V}_E$ in response to exercise in tests "N" and "H". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

b: Mean changes in $\dot{V}_E$ in response to exercise in tests "N2" and "H3". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

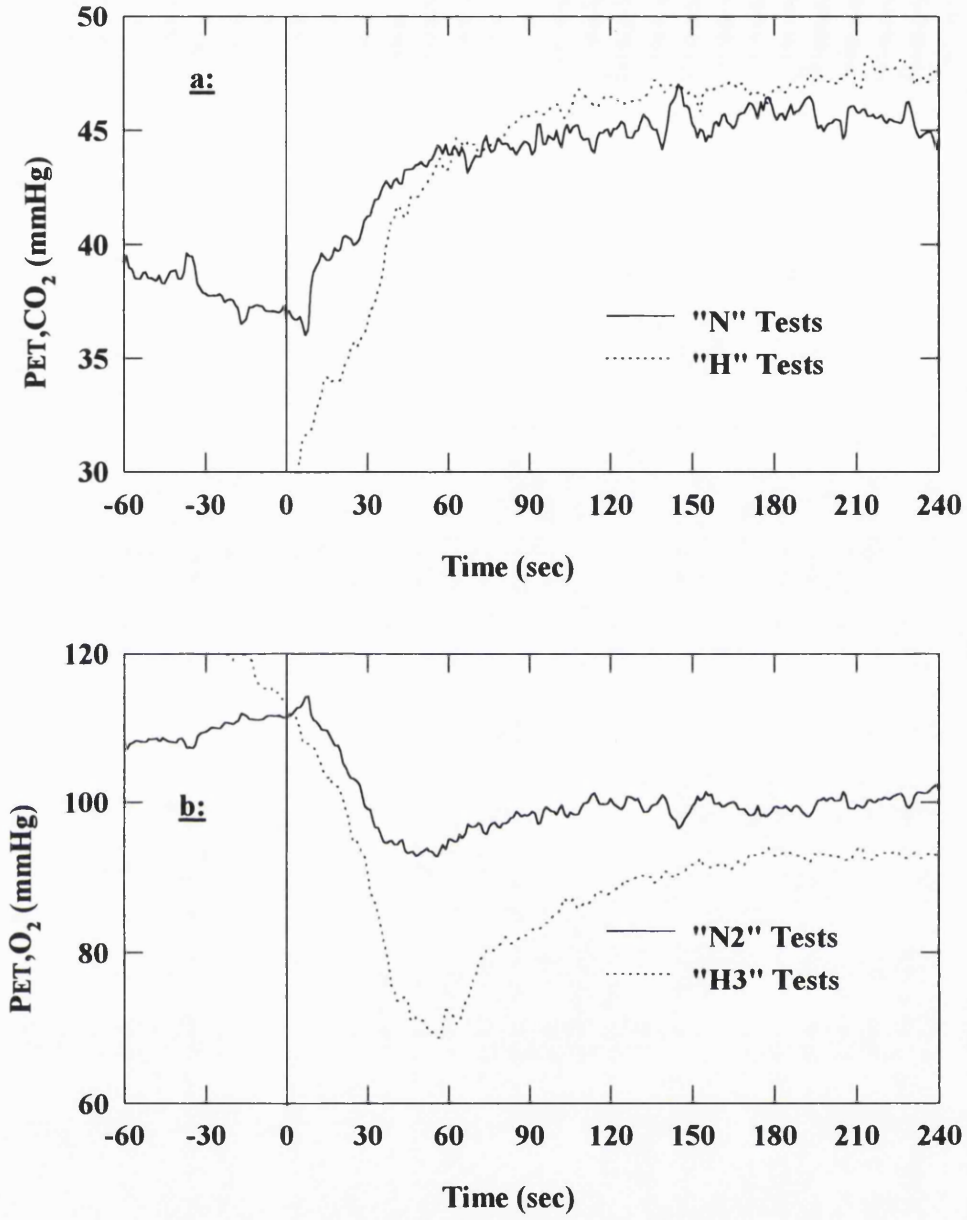


Figure 5.13a: Mean changes in P_{ET},CO_2 in response to exercise in tests "N" and "H". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

b: Mean changes in P_{ET},O_2 in response to exercise in tests "N" and "H". Data are interpolated at 1 sec intervals for 1 min prior to and 3 min following the onset of exercise. Time 0 represents the start of exercise.

The changes in P_{ET,CO_2} and P_{ET,O_2} seen during the immediate increase in $\dot{V}_E$ in the "N" tests were variable among the subjects tested. As a group, however, P_{ET,CO_2} and P_{ET,O_2} remained close to normal resting levels (See *Figs. 5.13a & b*). P_{ET,CO_2} then rose and P_{ET,O_2} fell during the subsequent plateau phase. In the "H" tests, P_{ET,CO_2} and P_{ET,O_2} continued to recover from the effects of the prior hyperventilation throughout both these phases (See *Figs. 5.13a & b*).

Later Responses to Exercise: The later, more gradual increases in $\dot{V}_{O_2}$, $\dot{V}_{O_2}$ and $\dot{V}_E$ were well described as a monoexponential increase to the steady-state incorporating a delay between the onset of exercise and the onset of the response.

The onset of this increase in $\dot{V}_{O_2}$ in the "N" tests coincided well with the onset of a fall in RER and P_{ET,O_2} and an increase in O_2 Pulse (See *Fig. 5.14*). In the "H" tests the increase in $\dot{V}_{O_2}$ also compared well with the increase in O_2 Pulse (See *Fig. 5.15*). The recovery from the hypocapnia meant that RER and P_{ET,O_2} were falling during the initial responses to exercise, rather than being (relatively) stable. In these tests, however, an increase in the slope of the fall of both variables could clearly be seen.

These findings are consistent with the definition of the onset of the later (Phase 2) response as the arrival at the lung of blood with altered gas tensions (Whipp & Ward, 1982; Whipp et al., 1982).

The durations of the early (Phase 1) response, the time constants of the later (Phase 2) response and steady-state (Phase 3) values for $\dot{V}_{O_2}$ were not affected by either the act of hyperventilation ("N2" vs. "H3" = *N.S.* See *Table 5.7*) or by the depletion of CO_2 stores consequent to prior hyperventilation ("N" vs. "H" = *N.S.* See *Table 5.6*).

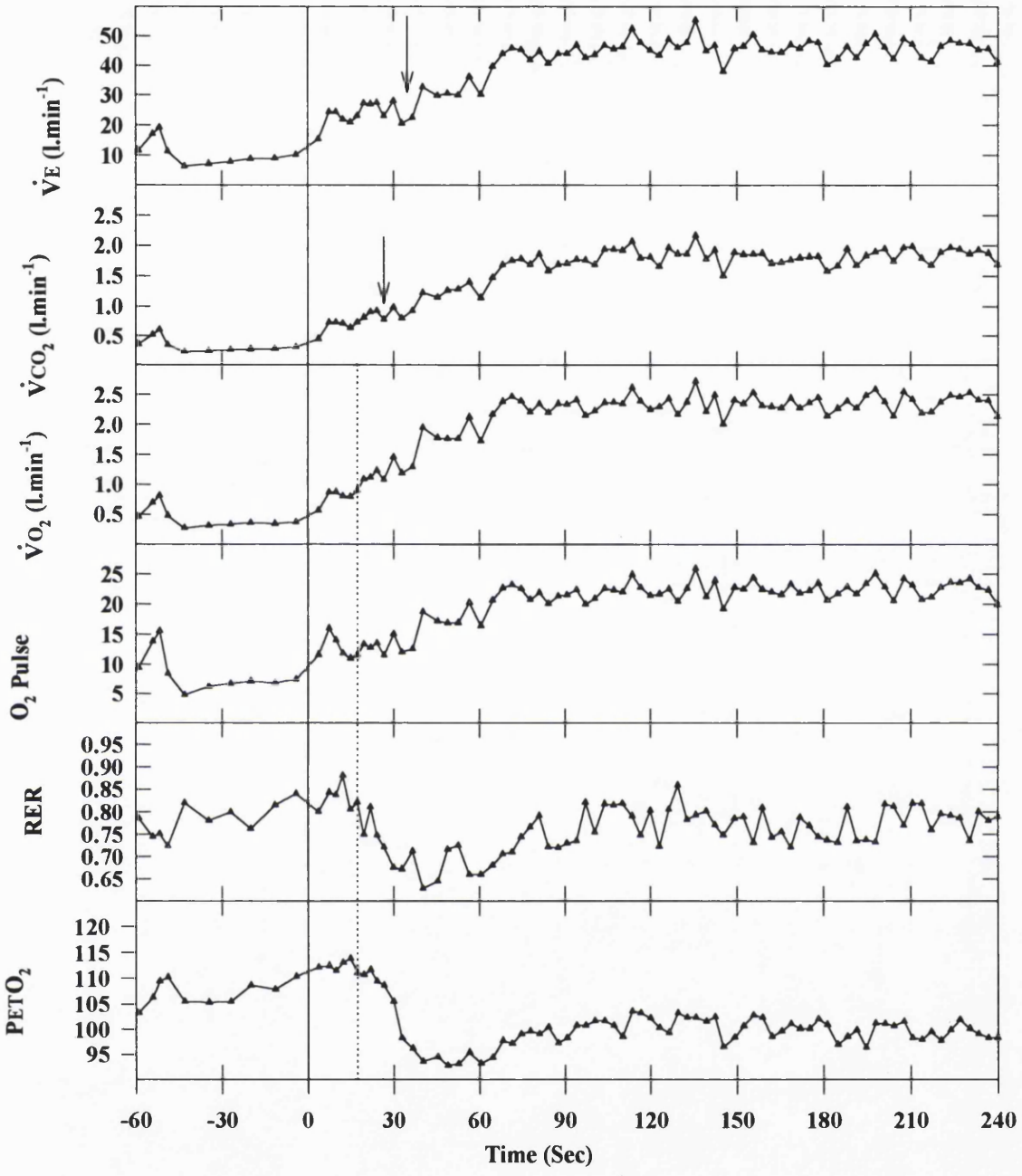


Figure 5.14: Breath-by-breath changes in $\dot{V}E$, $\dot{V}co_2$, $\dot{V}o_2$, O_2Pulse, PET,O_2 and RER from 1 min prior to until 3 min following the onset of exercise in test "N2" performed by subject M. The onset of the Phase 2 response can clearly be seen (marked by dotted line), while the onset of the later response to exercise for $\dot{V}E$ and $\dot{V}co_2$ occurs later (marked by arrows).

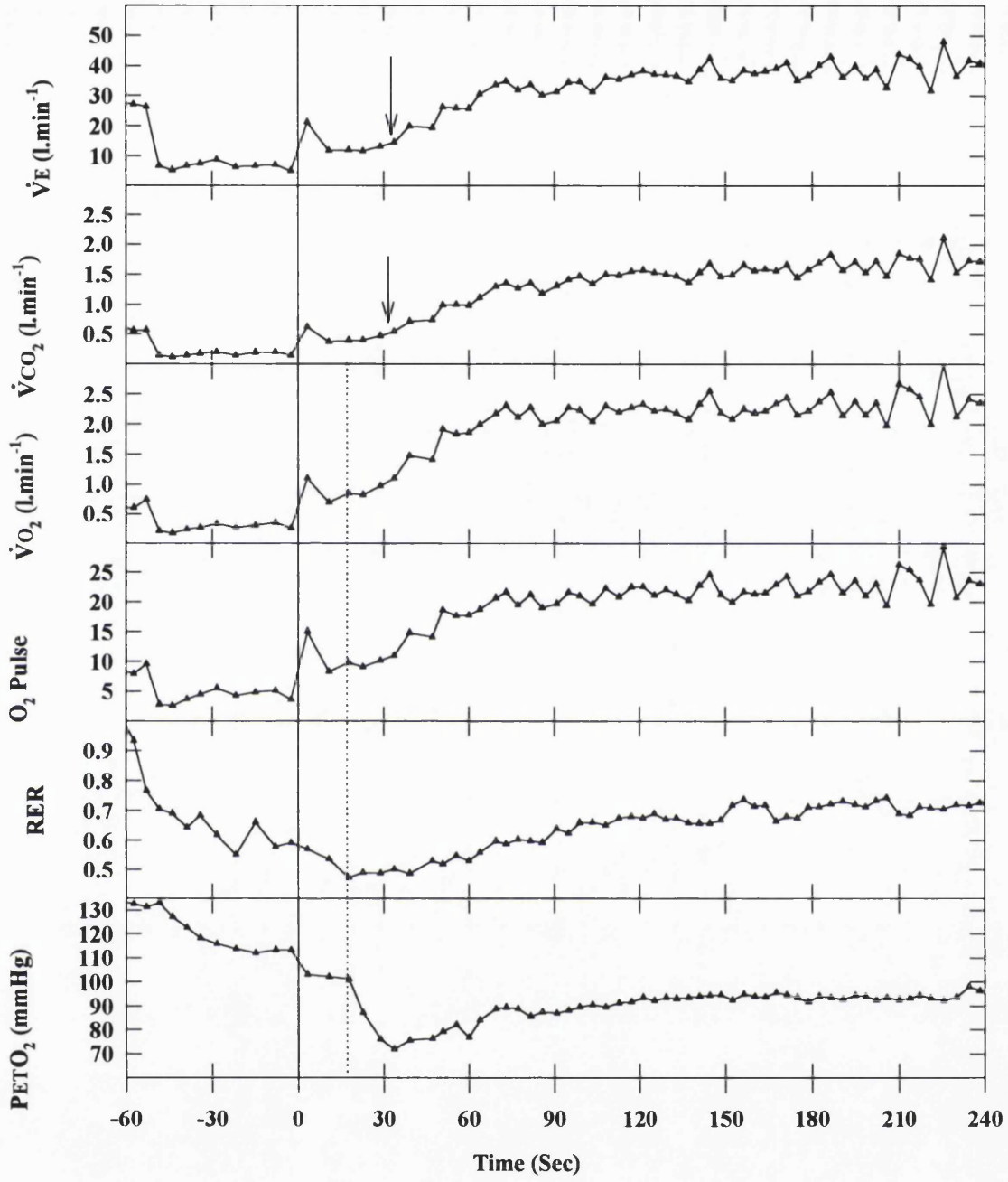


Figure 5.15: Breath-by-breath changes in $\dot{V}E$, $\dot{V}co_2$, $\dot{V}o_2$, O_2Pulse, PET,O_2 and RER from 1 min prior to until 3 min following the onset of exercise in test "H2" performed by subject M. The onset of the Phase 2 response can clearly be seen (marked by dotted line), while the onset of the later response to exercise for $\dot{V}E$ and $\dot{V}co_2$ occurs later (marked by arrows).

The delay in onset of the later response for $\dot{V}co_2$ was not affected by the act of hyperventilation ("N2" vs. "H3" = *N.S.* See *Table 5.7*). It was, however, significantly greater than the delay in the onset of the Phase 2 response as defined by O_2-related variables for all protocols. This disparity was greater in the "H" tests, reflecting the diversion of metabolic CO_2 from excretion in the lungs to replenishment of the CO_2 stores previously depleted by hyperventilation (See *Table 5.6*). The time constants were similar for all protocols and were longer than those for $\dot{V}o_2$. Steady-state values were also unaffected by events prior to the onset of exercise (See *Tables 5.6 and 5.7*).

The delay in onset of the later response for $\dot{V}E$ shows a similar pattern to that described above for $\dot{V}co_2$, i.e. it is unaffected by the act of hyperventilation, but the onset of the response was delayed by prior hypocapnic hyperventilation (See *Tables 5.6 and 5.7*). The onset of this later increase in $\dot{V}E$ was associated with P_{ET},CO_2 attaining a threshold value. The time constants and steady-state responses are again similar for all protocols (See *Tables 5.6 and 5.7*).

As mentioned earlier, fC increased rapidly from the start of exercise. Where applicable, the response was modelled as a monoexponential increase to the steady-state. The time constant of this response was similar for all protocols (See *Table 5.8*).

RER and P_{ET},O_2 fell during this phase as a result of dissociation between changes in $\dot{V}o_2$ and $\dot{V}co_2$ and $\dot{V}E$ respectively before partially recovering. The minimum values for RER and P_{ET},O_2 were significantly smaller in the "H" tests than in the "N" tests (Min P_{ET},O_2 = 88 ± 3 mmHg in "N" tests, 60 ± 4 mmHg in "H" tests; $p<0.05$. Min RER = 0.65 ± 0.06 in "N" tests, 0.47 ± 0.01 in "H" tests; $p<0.05$). The greater depth of the nadir in P_{ET},O_2 and RER seen in the "H" tests is simply a manifestation of the metabolic hyperbola. The steady-state values of P_{ET},O_2 and RER were similar in both the "N" and the "H" tests (See *Table 5.10*).

	N	H
VT	2.38 ± 0.21	2.33 ± 0.25
*f*BR	24.5 ±2.8	23.7 ± 3.5
P_{ET,CO_2}	47.6 ± 1.3	45.2 ± 1.2
P_{ET,O_2}	98.4 ± 3.7	99.1 ± 2.0
RER	0.88 ± 0.06	0.86 ± 0.04

Table 5.10: Mean (± S.E) steady-state values of VT, *f*BR, P_{ET,O_2}, P_{ET,CO_2} and RER in the "N" and "H" tests (n = 13). For explanation of symbols and units, see text.

There was no significant difference between the steady-state values of VT, *f*BR and P_{ET,CO_2} in the "N" and "H" tests (See *Table 5.10*), providing further evidence that the steady-state had been reached in both tests and changes in body CO_2 stores as a result of the onset of exercise were complete.

DISCUSSION

SINGLE REPETITIONS vs. MULTIPLE REPETITIONS:

In this study, each test was performed only once by each subject to obviate the possibility of a "learning effect" on the initial ventilatory response to exercise and to avoid the increased incidence of apnoeas following voluntary hyperventilation which have been reported to occur with increased repetitions (Bainton & Mitchell, 1966). Although repetitive transitions have been shown to reduce the inherent noise in the respiratory and pulmonary gas exchange signals (Lamarra et al., 1987), they would have reduced the naivety of the response that I was interested in. The pattern of ventilatory response seen at the onset of exercise was consistent amongst the individuals tested. This provides confidence in the data that might otherwise be questionable with single partitions and so few breaths at the onset of exercise.

MODEL DESIGN:

In deference to the detrimental effect of single tests per subject on the effective noise variance, the design of MODEL 3 was parsimonious and limited to a simple statement that "The initial increase in $\dot{V}E$ seen in response to the onset of a bout of moderate intensity exercise is greater that the subsequent plateau". The exact nature of the transition from the initial rise to the subsequent plateau was not addressed.

EFFECT OF HYPERVENTILATION ON CO_2 STORES:

Hypocapnic hyperventilation prior to exercise resulted in a depletion of body CO_2 stores. This was manifested as a fall in $PaCO_2$. The reasoning behind setting a lower limit of 20 mmHg for P_{ET},CO_2 during the hyperventilation period is discussed in Chapter 3.

It is well documented that rates of change in tissue CO_2 consequent to a change in $\dot{V}E$ are not uniform (Farhi & Rahn, 1960; Vance & Fowler, 1960; Sullivan et al., 1966; Cherniack et al., 1966, 1970; Irving et al., 1983). The major rate limiting factor would appear to be tissue perfusion (Farhi & Rahn, 1960; Vance & Fowler, 1960). Farhi and Rahn (1960) proposed a multi-compartment model to describe changes in CO_2 stores following changes in $\dot{V}E$ or rebreathing. Each compartment consisted of a discrete organ, the rate of change in compartment CO_2 stores being limited by tissue perfusion.

This model has since been adapted by Irving et al. (1983) from $H^{13}CO_3^-$ exchange studies to a 3-compartment model consisting of a central pool in communication with 2 peripheral pools of differing exchange kinetics (fast and slow). The central pool was attributed to blood, the fast peripheral pool to metabolically active, well perfused tissue (liver, intestine, heart and brain) and the slow peripheral pool to skeletal muscle and skin. The rate constants, pool sizes and half times for the 3 compartments reported by Irving et al. (1983) suggest that 2½ to 3 min hyperventilation would have a negligible effect on the size of the slow peripheral compartment, the majority of the excess CO_2 excreted originating in the central and fast peripheral pools.

This view is supported by the work of Fowle and Campbell (1964). They reported that the rate of rise of PCO_2 was constant at 6.0 mmHg/min between 40 sec and 3 min of rebreathing from a small bag. The linearity of this response suggests that there is no change in the CO_2 storage capacity during this time. The volume of tissue in which the retained CO_2 is distributed was calculated (from the storage capacity and the CO_2 dissociation curves of body fluids) to be approximately 10 l. This, they proposed, consisted of blood and fluid in tissue which had a high blood flow (brain, lungs, heart, kidney and liver).

EXERCISE DURATION:

In this study, exercise was performed for 4 min. This was adequate for the ventilatory and pulmonary gas exchange responses to exercise to reach steady-state (98% of a monoexponential response is acheived in 4 x τ) in both the "N" and the "H" tests: mean t_D + (4 x mean τ) = 229.3 sec. The kinetics of the ventilatory and pulmonary gas exchange responses seen in these subjects were faster than those reported in the literature for sedentary subjects (Whipp et al., 1982; Pearce & Milhorn, 1977). This agrees with the findings of Hagberg et al. (1980), that training results in faster responses to a transition from rest to exercise.

RESPONSES TO EXERCISE:

$\dot{V}o_2$ & f_C: The profile of the initial increase in $\dot{V}o_2$ was similar to those reported by Whipp et al. (1982), Wasserman & Whipp, (1983) and Ward et al. (1983) for their Phase 1 responses. The duration of the Phase 1 response fell at the lower end of the range described in the literature (15 to 30 sec: Whipp et al., 1982; Asmussen & Nielsen, 1948; Linnarsson, 1974; Bennett et al., 1981; Fujihara et al., 1973b; Whipp, 1983; Wasserman et al., 1986). This time is attributed to the circulatory transit time for blood with changed gas tensions to travel from the exercising muscle to the lungs.

In the majority of the subjects tested in this study, the increase in f_C clearly consisted of an initial, transient increase rapidly superseded by a further increase to steady-state. The profile of these changes in f_C are not compatible with the abrupt increase in conjunction with the onset of exercise described by Whipp et al. (1982), Pearce and Milhorn (1977) and Cummin et al. (1986b). The results of Loeppky et al. (1981), Linnarsson (1974) and Morikawa et al. (1989) are closer to those reported here, with a slower increase in heart rate following the start of exercise. Loeppky et al. (1981) reported that the increase in f_C was preceded by an increase in which they attributed to the mobilization of previously pooled blood from the viscera and large veins. This would explain the transient increase in stroke volume reported in the results of

Cummin et al. (1986b). It also allows some scope for an explanation of the difference between our results and those of Whipp et al. (1982).

It is well known that, when body weight is accounted for, athletes have a larger blood volume than non-athletes (Åstrand & Rodahl, 1986). This, in conjunction with a relatively larger left ventricular volume, will allow for a greater proportion of the initial increase in $\dot{Q}$ to be stroke volume (SV)-mediated, thus reducing the need for f_C to increase following the start of exercise.

The volume of pooled blood is finite and when it is exhausted the associated reduction in venous filling pressure must result in a fall in SV. If $\dot{Q}$ is to be maintained, f_C must increase until venous return to the heart increases again. This scenario may explain the peak in heart rate seen in some subjects, but it is not possible to justify such a statement as more than conjecture based on the results described here. It does, however, appear that the profile of the initial changes in f_C seen on the transition from rest to exercise differ between highly trained and sedentary individuals.

The magnitude and duration of the initial increases in $\dot{V}O_2$ were similar in all protocols. As the initial changes in $\dot{V}O_2$ in response to the onset of exercise are mediated by changes in $\dot{Q}_P$, these results show that initial changes in $\dot{Q}_P$ were similar in all protocols, despite pre-exercise f_C being higher when exercise was preceded by hyperventilation.

These results differ from those reported by Ward et al. (1983). They reported the initial increase in $\dot{V}O_2$ to be attenuated if exercise was preceded by hypocapnic hyperventilation (they do not report any values for eucapnic hyperventilation). They also report the duration of the initial response to be increased. These results imply that in their study, O_2 stores were elevated well above normal levels at the onset of exercise. This would reduce the impact of changes in $\dot{Q}_P$ on $\dot{V}O_2$ and also delay the start of the fall in venous P_{O_2} at the lung. This would be compatible with the longer period of hyperventilation and the shorter delay between the end of hyperventilation and the onset of exercise used in the protocol of Ward et al. (1983).

The results of modelling the changes in f_C seen in response to exercise yielded similar time constants and delays in both the "N" and "H" tests. This would suggest that the higher pre-exercise values of f_C seen in the "H" tests was not associated with an increase in Q and did not affect the circulatory responses to exercise.

The later rise in $\dot{V}o_2$ was well modelled by a monoexponential curve. The kinetics of the rise in $\dot{V}o_2$ seen during this phase are governed by the combined effect of changes in PO_2 at the lung and the continuing rise in $\dot{Q}_P$. The time constants arising from the modelling of the data were similar for all protocols. This supports the results from the changes in f_C, that the circulatory response to exercise was unaffected by prior hyperventilation.

$\dot{V}co_2$ and $\dot{V}_E$: In both tests, $\dot{V}co_2$ increased abruptly to a plateau in conjunction with the onset of exercise. The magnitude of the increase was reduced following hypocapnic hyperventilation ("H" tests). These results agree with those of Whipp et al. (1982) and Ward et al. (1983).

The reduction in the magnitude of the initial response to exercise is a manifestation of the depletion of the central CO_2 compartment (Irving et al., 1983) by the prior hyperventilation. This is consistent with the cardiodynamic nature of the Phase 1 responses (Whipp & Ward, 1982; Whipp et al., 1982).

In both protocols, the initial ventilatory responses to exercise were biphasic in nature, consisting of an abrupt, transient increase followed by a fall to a plateau. The response to the onset of exercise seen in the "N" tests could be mistaken for a single increase to a plateau due to the similarity of the magnitude of the 2 responses, but the fall in the plateau value consequent to the depletion of the CO_2 stores in the "H" tests highlighted the biphasic nature of the response. This profile of response is different from the profile traditionally described in the literature: an abrupt increase to a plateau (Dejours, 1963, Dejours, 1967; Whipp, 1981, 1983; Whipp et al., 1982; Wasserman et al., 1986; Whipp & Ward, 1982, 1991; Ward et al., 1983; Linnarsson, 1974; Pearce & Milhorn, 1977).

Dejours (1963) described the early response to exercise as an abrupt increase in $\dot{V}E$ to a plateau. This he attributed to the sudden appearance of a neurogenic drive to breathe, originating in the exercising muscles or the higher regions of the CNS. This stimulus was present throughout exercise, and its sudden removal was responsible for the abrupt decrease in VE associated with the cessation of exercise.

Whipp & Ward (1982) also described the initial ventilatory response to exercise as an abrupt increase to a plateau, but proposed that this increase was mediated by in increased CO_2 flux to the lung consequent to an abrupt increase in $\dot{Q}_P$.

An investigation into the validity of the traditional profile of the initial ventilatory response to exercise does not yield convincing results. In their 1982 paper, Whipp et al. present both the results from one test (*their fig.1*) and the pooled results from eight tests (*their fig.2*), both of which show an abrupt increase in $\dot{V}E$ in conjunction with the transition from rest to 100 W exercise, then a fall in $\dot{V}E$ before the onset of the Phase 2 response. In an earlier paper by the same group (Wasserman et al., 1975), only one out of five normal subjects represented in their figure has an initial response which agrees with the accepted view (*their fig.2*).

They are not alone in reporting a constant, square-wave Phase 1 response in a paper which also includes figures which patently do not support this view: D'Angelo and Torelli (1971), using multiple short bouts of exercise without full recovery between them, took the average level of $\dot{V}E$ during each exercise bout to represent the initial ventilatory response, despite there being dramatic changes in the breath-by breath values during the bout (*their fig.1*). Favier et al. (1983b) only present group data for the initial ventilatory response to exercise in chronically tracheotomized dogs, but these data definitely suggest that the initial ventilatory response is biphasic, consisting of an initial rise followed by a decrease to a plateau (*their fig.1*).

Pearce and Milhorn (1977) present data from three subjects tested over five days. One of the subjects consistently shows an initial overshoot in $\dot{V}E$ consequent to the start of exercise followed by a fall to a lower level, as seen in our results (*their fig.5*). The

results of the other two subjects vary between an abrupt increase to a plateau and a more blunted rise in $\dot{V}E$; more similar to the standard textbook description of the Phase 1 response.

Jensen et al. (1971, 1972b) mention in their discussion what they term "an initial mal-adjustment, a ventilatory overshoot on the start of work" seen in some of their results, while Krogh and Lindhard (1913) and Cummin et al. (1986b) state quite clearly that the initial ventilatory response to exercise tends to be biphasic in form; an initial rise followed by a fall. It has been considerably harder to find accurate reports in the literature which support the current view of the early ventilatory response to exercise than it has to find instances which refute it (Linnarsson, 1974; Asmussen, 1973; Asmussen & Nielsen, 1948).

Some authors have reported results consistent with those obtained in this study. Recently Cerretelli et al. (1994), using a similar protocol have reported results which agree with those described above; a biphasic early ventilatory response to exercise, highlighted by prior hyperventilation. Gardner & McConnell (1986) reported an abrupt increase in $\dot{V}E$ in conjunction with the start of exercise following hypocapnic hyperventilation. LeFrançois & Dejours (1964) reported that the initial increase in $\dot{V}E$ in response to the onset of exercise was unaffected by hypercapnia or hypocapnia, in spite of differences in the resting levels of ventilation. They also reported the initial response to last for only the first 1 or 2 breaths of exercise (shorter than in the model used here). The abrupt increase in $\dot{V}E$ seen in conjunction with the onset of exercise in these studies has been cited as evidence of neurogenic control of $\dot{V}E$ at this stage of exercise hyperpnoea.

Other authors have reported that the entire early ventilatory response to exercise was reduced by prior hypocapnic hyperventilation (Ward et al., 1983; Asmussen, 1973; Krogh & Lindhard, 1913), resulting in an entirely different profile to the early ventilatory response to exercise. These data would support the cardiodynamic theory of the control of exercise hyperpnoea.

It should be noted that the difference between the 2 patterns of response seen following prior hyperventilation lies only in the first 3 or so breaths of exercise. All available data agree that the subsequent plateau phase is reduced if CO_2 stores are depleted at exercise onset. These results are compatible with the theory of Whipp & Ward (1982), that $\dot{V}E$ during this phase is a function of CO_2 flux to the lung.

Ceretelli et al. (1994) suggested that the plateau phase of the early ventilatory response to exercise was under cardiodynamic control, as proposed by Whipp & Ward (1982) and Ward et al. (1983). This explanation seems quite satisfactory to me. They also proposed that the initial ventilatory response was a result of increased discharge of group III afferent fibres from the exercising muscles (Mitchell et al., 1977; Mitchell, 1990), the logic being that the profile of the change in $\dot{V}E$ mirrored the group III afferent fibre output.

I have 2 concerns with this theory. Firstly, Cerretelli et al. (1994) make no mention of the number of repetitions made by each subject. Counting the number of data points shown in their figures, it would appear that they also used single transitions. To re-open an earlier debate, the use of single transitions does limit the precision of the results obtained from analysis of the initial ventilatory responses to exercise. This is a result of the small number of breaths making up the response. For this reason, I have only commented on the relative size of the 2 responses and not ventured into discussing the profile of the responses. Cerretelli et al. (1994) certainly raise an interesting point, but I feel multiple repetitions would be needed to support such a theory (as group III afferent discharge is not known to change with increasing repetitions, there is no dogmatic reason for not performing multiple repetitions).

Secondly, Cerretelli et al. (1994) provide a credible explanation for their results, but do not attempt to explain the differences in the immediate ventilatory response to exercise which have been reported in the literature. I feel a more unifying approach is needed.
To this end, it is necessary to turn to the theory of Zuntz & Geppert (1886); that the initial ventilatory response to exercise is a result of an "Exercise reflex", i.e. an habituated response to the knowledge that exercise was starting, rather than an

intrinsic response to a change in some physiological variable. This would satisfactorily explain why the ventilatory response to exercise was unaffected by changes in the underlying level of ventilation (Lefrançois & Dejours, 1964; Gardner & McConnell, 1986). It would also explain the results of Krogh & Lindhard (1913) that if a subject is told the workload at which they are to exercise, the initial ventilatory response seen is applicable to that exercise load even if the subject were to perform unloaded pedalling.

There are a number of possible reasons why an abrupt increase in $\dot{V}E$ in conjunction with the onset of exercise was not reported by some authors. Krogh & Lindhard (1913) report the initial ventilatory response to exercise as considerably diminished following 1 min hyperventilation. They also reported incidences of prolonged apnoeas following hyperventilation. This is an unusual phenomenon in normal awake man (Meah & Gardner, 1994; Corfield et al., 1995).

Asmussen (1973) also reported a reduction in the initial ventilatory response to exercise following 3 min hyperventilation. He reported P_{ET},CO_2 to have fallen to 8-12 mmHg following the hyperventilation, considerably lower than was achieved in this study. Such a low level of $PaCO_2$ may have had significant effects on peripheral axonal excitability (Macefield & Burke, 1991) and the excitability of respiratory neurones (Folgering & Durlinger, 1983). Exercise was also started during an apnoea, something that was strenuously avoided in this study for reasons discussed in Chapter 4. Comparisons between their results and those reported here should therefore be made with caution.

Ward et al. (1983) also reported that the magnitude of the initial response was severely attenuated following hypocapnic hyperventilation. It is harder to account for the differences between the results of Ward et al. (1983) and those reported here.

The duration of the hyperventilation period used by Ward et al. (1983) was considerably longer (9 min in Ward et al., 1983) than was used in this study (2 to 3 min). While this will affect the slow peripheral compartment of the CO_2 stores, the level of depletion of the central CO_2 stores should be similar for both studies (P_{ET},CO_2

is similar at exercise onset). It is difficult to envisage how changing the slow peripheral CO_2 store may directly affect the immediate ventilatory response to exercise.

It was possible that a prolonged reduction in CNS CO_2 stores would result in the development of CNS dysfunction consequent to arterial vasoconstriction, decreased cerebral blood flow and a developing brain hypoxia. This scenario was unlikely to occur with the hyperventilation protocol used in this study and is addressed in the following Chapter. It is, however, possible that the prolonged period of hyperventilation used by Ward et al. (1983) allowed such a scenario to take place.

Their data present some circumstantial evidence for a more profound inhibition of respiratory drive than was achieved in this study: although the post-hyperventilation period lasted for only 15-20 sec, they report $\dot{V}E$ as falling abruptly to uncharacteristically low levels. The results reported in this Chapter and Chapter 4 show that by the end of the (longer) post-hyperventilation period, $\dot{V}E$ had only fallen to normal resting levels. Ward et al. (1983) qualify their results by stating that there was no evidence of post-hyperventilation apnoea in any of their subjects. Meah & Gardner (1994) and Corfield et al. (1995) have reported that when apnoeas occur, it is usually at approximately 60 sec after the cessation of hyperventilation. It would have been interesting to see whether apnoeas or periodic breathing occurred in any of the subjects if the post-hyperventilation period had been longer. It should be noted that the hyperventilation period used by Lefrançois & Dejours (1964) was similar to that used by Ward et al. (1983).

Another difference between the protocol used in this study and that of Ward et al. (1983) was the level of fitness of the subjects. My subjects were all above average fitness and the majority of them were competitive oarsmen. Athletes are purported to have a larger initial ventilatory response to exercise than normal subjects. Pearce & Milhorn (1977), Krogh & Lindhard (1913) and Asmussen (1973) report that the magnitude of the initial ventilatory response to exercise is workload-dependent (although this is not a universal finding Whipp, 1987; Jensen, 1972a). Using athletes allowed the workload to be high without encroaching on the subjects' ventilatory

anaerobic threshold. A high workload would therefore be of positive benefit in this study.

The performance of regular, high-intensity exercise by the competitive athletes studied here was likely to enhance any conditioned response to the onset of exercise. Conversely, the lack of reinforcement associated with not performing regular exercise may allow such a conditioned response to be weak or absent. This may explain the different response reported by Ward et al. (1983). This does not, however, explain the similarity between our data and that reported by Cerretelli et al. (1994) for untrained (and older) subjects, or the similarity between our results and those of Lefrançois & Dejours (1968), following a similar period of hyperventilation to that used by Ward et al. (1983).

It has been suggested that the immediate increase in $\dot{V}E$ seen in these subjects was due to a startle response to the command to start exercising, rather than a response to the exercise *per se*. This is an attractive theory and could account for the absence of an abrupt ventilatory response to exercise following hyperventilation reported by some authors (Ward et al., 1983; Asmussen, 1973; Krogh & Lindhard, 1913).
I consider this explanation unlikely on 2 accounts. Firstly, the commands were given in an audible, well modulated voice to avoid the possibility of inducing a startle response. Secondly, Jensen et al. (1971) reported the mode of command to have no effect on the initial ventilatory response to exercise.

The ideal proof would be to compare the changes in $\dot{V}E$ and fC seen in response to the start of exercise with known profiles of changes resulting from a startle response.

The onset of the later rise in both $\dot{V}E$ and $\dot{V}co_2$ was delayed in both "N" and "H" tests when compared to that reported for $\dot{V}o_2$. Whereas the delay for $\dot{V}o_2$ was unaffected by prior hyperventilation, the delay in onset of the later response for $\dot{V}co_2$ and $\dot{V}E$ was longer in the "H" tests than in the "N" tests. The time constants for $\dot{V}E$ were similar in the "N" and "H" tests, as were those for $\dot{V}co_2$.

One effect of this divergence of $\dot{V}E$ and $\dot{V}o_2$ was a transient fall in PET,O_2. The greater depth of this transient fall seen in the "H" tests was simply a manifestation of the metabolic hyperbola. Young & Woolcock (1978) reported a transient fall in PET,O_2 during the on-transient of exercise hyperpnoea to values of 65 ± 3.4 Torr. This is much more severe than the fall seen in the"N" tests (85 ± 6 mmHg See *Figs. 5.4*, *5.5* and *5.13b*). This is attributed in part to the different modes of exercise used (this study used cycle ergometry while Young & Woolcock (1978) used stair climbing; a form of exercise which, from personal experience, often induces breatholding or resipratory-locomotor coupling) and in part to the fact that training speeds up the kinetics of the later increase in $\dot{V}E$ (Hagberg et al., 1980). This will reduce the O_2 deficit occurring at this time.

Assuming that the respiratory quotient does not change appreciably during the non steady-state responses to exercise, the increase in metabolic CO_2 production will follow a similar time course as the increase in $\dot{V}o_2$ measured at the mouth. It is generally accepted that the disparity in the kinetics of $\dot{V}o_2$ and $\dot{V}co_2$ during the later response to exercise represents an increase in muscle CO_2 stores.

Given the time course of the increase in CO_2 stores on exercise, it must take place in the central and fast peripheral CO_2 compartments. Studies into $H^{13}CO_3^-$ kinetics have demonstrated that the central CO_2 compartment approximately doubles on transition from rest to exercise (Barstow et al., 1990). This has been attributed to the movement of exercising muscle from the slow peripheral compartment at rest to the central compartment during exercise (Barstow et al., 1992).

$PaCO_2$ is reported to remain constant on transition from rest to exercise in man (Pearce & Milhorn, 1977; Jensen et al., 1972b; Wasserman & Whipp, 1983; Linnarsson, 1974; Whipp et al., 1982), although this is not a universal finding (Dempsey et al., 1984b). The increased CO_2 content of the central stores must therefore occur in the venous blood or in the muscles. Given the values for tissue CO_2 storage capacity of 0.57 to 1.8 ml/mmHg/Kg (Fowle & Campbell, 1964; Hughson & Inman, 1985; Jones & Jurowski, 1979; Yano, 1986; Clode et al., 1967), an increase in

CO_2 stores which did not include muscle would result in unphysiologically large values for Pco_2 (Barstow et al., 1992).

The results obtained in this study support this view. Hyperventilation of the depth and duration used in this study would not be expected to significantly affect muscle CO_2 stores (Farhi & Rahn, 1960; Irving et al., 1983; Barstow et al., 1990; Barstow et al., 1994). At the onset of exercise, therefore, the central and fast peripheral CO_2 compartments were depleted, but the slow peripheral CO_2 compartment (containing resting skeletal muscle) was at normal resting levels. The time constants for the later rise in $\dot{V}co_2$ in response to exercise were unaffected by the prior hyperventilation.

Ward et al. (1983) used a longer period of hyperventilation than that used in this study. This would be expected to result in some depletion of muscle CO_2 stores. They reported the half-time of the total dynamic response for $\dot{V}co_2$ to be lengthened following hyperventilation. This could not be explained simply in terms of the increased duration of the initial component of the response. The depletion of muscle CO_2 stores would increase the muscle CO_2 storage capacity on exercise, resulting in a greater proportion of metabolic CO_2 production being diverted to increasing muscle CO_2 stores than would occur in exercise performed under normal conditions. This would reduce the amount of CO_2 excreted at the lung, i.e. the kinetics of the later rise in $\dot{V}co_2$ would be slowed.

An explanation of the disparity of the delay in onset of the later rise in $\dot{V}co_2$ and $\dot{V}o_2$ in both tests is more complicated and relies more on the principles of mass flow than on changes in CO_2 stores. The evidence from sinusoidal workload forcings would suggest that under normal conditions changes in $\dot{V}co_2$ slightly precede and drive changes in $\dot{V}E$ during this phase of the on-transient. On the other hand, Casaburi et al. (1979) reported that the kinetics of the later increase in $\dot{V}co_2$ were heavily affected by changes in the kinetics of $\dot{V}E$. Weissman et al. (1982) also published results showing that if $\dot{V}E$ is maintained at resting levels during the onset of exercise, $\dot{V}o_2$ increased in conjunction with the start of exercise, while $\dot{V}co_2$ did not. In both papers, the disparity

between changes in $\dot{V}o_2$ and $\dot{V}co_2$ (or $\dot{V}E$) were associated with changes in $PaCO_2$ or $PACO_2$.

In the tests performed in this study, the delay in onset of the later increase in $\dot{V}co_2$ was similar to the delay in onset of the later increase in $\dot{V}E$. It is proposed that during the period between the onset of the later response for $\dot{V}o_2$ and the onset of the later response for $\dot{V}co_2$ (and $\dot{V}E$), the lack of an increase in $\dot{V}E$ ablated any possible rise in $\dot{V}co_2$, rather than $\dot{V}E$ responding to changes in $\dot{V}co_2$. Under such circumstances the dissociation between CO_2 flux to the lung and $\dot{V}co_2$ must result in an increase in $PaCO_2$. It is not possible to comment on whether or not $PaCO_2$ really did change during this period as PET,CO_2, rather than $PaCO_2$, was measured in these tests. The changes in Q_P occurring at this time increase the slope of the alveolar phase of the expired Pco_2 profile. This inevitably means that PET,CO_2 will rise if $PaCO_2$ is unchanged.

However, steady-state $PaCO_2$ (predicted from PET,CO_2 using the formula of Jones at al. (1979)) was higher during exercise than at rest in both "N" and "H" tests for the majority of the subjects tested. This increase must have occurred during the non steady-state responses to the onset of exercise. Furthermore, the time between the onset of the later response for $\dot{V}o_2$ and the onset of the later response for $\dot{V}co_2$ was greater in the "H" tests, when the difference between arterial CO_2 stores prior to the onset of exercise and during the exercise steady-state was increased.

A mechanism is needed to account for the disparity between the onset of the later responses for $\dot{V}E$ and $\dot{V}co_2$ and the onset of the later responses for $\dot{V}o_2$. Several lines of evidence implicate the carotid chemoreceptors in the control of the time course of the later increase in $\dot{V}E$: Wasserman et al. (1975) reported the kinetics of the later ventilatory response to exercise to be slowed in humans who had undergone bilateral carotid body resection. Griffiths et al. (1986), Asmussen (1974), Cunningham et al. (1968) and Casaburi et al. (1978a) all reported the kinetics of the later increases in $\dot{V}E$ and $\dot{V}co_2$ to be slower than normal in hyperoxic conditions and faster than normal in hypoxic conditions. The time constant for $\dot{V}o_2$ was not affected. Cunningham et al.

(1968) also reported the initial ventilatory response to exercise to be prolonged under hyperoxic conditions.

One explanation for this disparity between the onset of the later responses for $\dot{V}O_2$ and $\dot{V}CO_2$ would be that the carotid chemoreceptor threshold increased on exercise in these subjects. The length of time between the onset of the later response for $\dot{V}O_2$ and the onset of the later response for $\dot{V}CO_2$ would be a function of the change in carotid chemoreceptor threshold and pre-exercise $PaCO_2$. However, it is hard to reconcile such a scenario with the results of Duffin & McAvoy (1988) who reported the carotid chemoreceptor threshold did not increase with exercise in sedentary man and Wiell et al. (1972) who reported carotid chemoreceptor sensitivity increased on exercise.

It is also possible that the depression in $\dot{V}E$ necessary to allow such a rise in $PaCO_2$ is a manifestation of a change in phase relationship between the respiratory cycle and oscillations in $PaCO_2$. The influence of $PaCO_2$ oscillations over exercise hyperpnoea have not been extensively studied in man, but Ward et al. (1977) reported a 17% change in $\dot{V}E$ with changes in the phase relationship in hypoxic man, while Cross et al. (1979) reported a 30% change in TE with changing phase relationship in dogs. Cross et al. (1979) also reported the effect of changes in the phase relationship to override changes in mean $PaCO_2$. Cross et al. (1982b) reported that the change in phase relationship seen with electrically-induced exercise in anaesthetized dogs was small and in the wrong direction to account for the changes in $\dot{V}I$ observed (i.e. an <u>increase</u> in $\dot{V}I$). The change in the phase relationship between arterial Pco_2 oscillations and the respiratory cycle would therefore be in the right direction to inhibit $\dot{V}E$ during the later response to exercise. This potential control mechanism needs further study in man.

The carotid chemoreceptors are also sensitive to changes in arterial plasma potassium concentration ($[K^+]_a$: Jarisch et al., 1952; Linton & Band, 1985; Burger et al., 1986; Band & Linton, 1986; Band & Linton, 1987; Burger et al., 1988; Band & Linton, 1988; Nye et al., 1994). $[K^+]_a$ has been shown to rise on transition from rest to exercise in man (Kilburn, 1966; Linton et al., 1984; Struthers et al., 1988; Medbø & Sejersted, 1990), the rise being in proportion to the rise in $\dot{V}E$ (Paterson et al., 1990; Newstead et

al., 1990; Yoshida et al., 1990; Busse et al., 1991) and the profile and timecourse of the rise being similar to that seen for $\dot{V}E$ during the later ventilatory response to exercise (Band et al., 1982; Conway et al., 1988; Paterson et al., 1989; Newstead et al., 1990). In addition, changes in $[K^+]_a$ of the size seen on transition from rest to exercise have been shown to result in an increase in $\dot{V}E$ (Linton & Band, 1985; Band et al., 1985; Sneyd et al., 1988). $[K^+]_a$ has been proposed as a possible mediator of exercise hyperpnoea (Band & Linton, 1986; Burger et al., 1988; Newstead et al., 1990).

Muir et al. (1990) have demonstrated that $[K^+]_a$ is affected by hypocapnic hyperventilation in the anaesthetized dog. To our knowledge this study has not been repeated in humans, although Kilburn (1965) reported $[K^+]_a$ to rise with acute respiratory acidosis. In addition the effect of hypocapnia on the rise in $[K^+]_a$ with exercise has not been studied. It is therefore possible that the changes in the kinetics of the later response for $\dot{V}E$ seen with prior hyperventilation are due to changes in the kinetics of the rise in $[K^+]_a$ and not changes in body CO_2 stores. The study of the effect of hyperventilation on both $\dot{V}E$ and $[K^+]_{aa}$ would be crucial to the opposing theories that CO_2 and $[K^+]_a$ are the prime mediators of the hyperpnoea of moderate-intensity exercise.

Although important, the carotid chemoreceptors are not the sole mediators of the later ventilatory response to exercise in man. Griffiths et al. (1986) reported the time constants of the ventilatory response to exercise in man to be slower when breathing pure O_2 compared to 30 % O_2, despite there being no discernible chemosensitivity at 30 % O_2. Whipp (1994) reported a slowing of the Phase 2 ventilatory kinetics when breathing an hyperoxic gas in subjects who had had their carotid bodies surgically denervated. The (as yet) undiscovered control mechanism responsible for these phenomena may also be responsible for the CO_2 retention on exercise observed in some of the subjects tested in this study.

A possible role for the higher centres of the CNS in this phenomenon cannot be ruled out either. Recently it has been suggested that the limbic system may influence $\dot{V}E$

(Heywood et al., 1994), while Corfield et al. (1995) have reported a change in limbic system activation on inhalation of CO_2. It is possible that CO_2 retention on exercise is a manifestation of a more relaxed emotional state of the subject.

VT & *f*BR: The pattern by which the increase in $\dot{V}E$ was achieved in the tests was highly variable between subjects, making comparisons between the "N" and "H" tests difficult. In general, however, the initial increase in $\dot{V}E$ seen in the "N" tests was largely due to an increase in both *f*BR and VT.

Beaver & Wasserman (1970) reported that the increase in $\dot{V}E$ seen on starting exercise was more normally mediated by increases in *f*BR than VT, although there was little consistency between subjects. Petersen (1987) also reported similar results.

The change in the way the initial increase in $\dot{V}E$ at the start of exercise was achieved is difficult to explain. As stated earlier, both VT and *f*BR were highly variable prior to the start of exercise in most subjects. In addition, mean *f*BR at the end of the post-hyperventilation period was still elevated above normal resting levels. It could be that the increase in *f*BR seen prior to the start of exercise precluded a further increase once exercise had begun. As a result, the influence of *f*BR over the initial increase in $\dot{V}E$ seen in the "H" test was reduced in some of those subjects for whom the initial increase in $\dot{V}E$ in the "N" test was due to an increase in both *f*BR and VT. This would therefore result in a rise in VT being responsible for most of the initial increase in $\dot{V}E$ seen in the "H" tests. It should also be noted that there is considerable debate in the literature as to how VT and *f*BR change following the start of exercise.

CONCLUSIONS:

The results reported in this Chapter bring into question the validity of the current models for the initial increase in $\dot{V}E$ seen in conjunction with the start of exercise. Firstly, there is little evidence to suggest that the profile of this increase is an abrupt increase to a plateau. Rather, it would appear that initial changes in $\dot{V}E$ in response to the onset of exercise are biphasic: $\dot{V}E$ increasing abruptly in conjunction with the onset of exercise, but then falling to a plateau level. This biphasic response may appear to be a plateau in cases where the magnitude of the 2 responses are similar.

The results obtained here would suggest that the immediate response, lasting for 3 or so breaths only, is neurogenic in origin while the plateau response is dependent on CO_2 flow to the lung (Whipp & Ward, 1982; Whipp et al., 1982).

It is hard to envisage an intrinsic neurogenic mechanism which could explain the immediate ventilatory response to the onset of exercise, or the lack of it previously reported in some studies. Perhaps a better explanation would be that of Zuntz & Geppert (1886): They attributed the initial increase in $\dot{V}E$ to an "Exercise reflex." It would be logical for such a reflex to be well developed in the highly trained athletes used as subjects in this study.

The kinetics of the later increases in $\dot{V}o_2$, $\dot{V}co_2$ and $\dot{V}E$ are consistent with the theory that the slower rise in $\dot{V}co_2$ compared to $\dot{V}o_2$ is due to an increase in muscle CO_2 stores, while the increased delay in onset of the later response for $\dot{V}co_2$ is due to an increase in arterial CO_2 stores. The delay in onset of the later increase in $\dot{V}E$ and $\dot{V}co_2$ when compared to $\dot{V}o_2$ cannot as yet be satisfactorily explained.

Prior hyperventilation has no long-term effect on the cardiorespiratory responses to exercise.

CHAPTER 6

THE EFFECT OF HYPERVENTILATION ON POSTURAL SWAY

INTRODUCTION:

Ward et al. (1983) reported that following hypocapnic hyperventilation the Phase 1 ventilatory response to exercise is severely attenuated and the Phase 2 response was both delayed in onset and an increase in $\tau(\dot{V}E)$. The results reported in Chapter 5, however, show that the initial increase in $\dot{V}E$ consequent to the start of exercise is unaffected by prior hypocapnic hyperventilation but $\dot{V}E$ is depressed following this period until the onset of the (delayed) Phase 2 response. This difference was attributed to differences in the protocols used, including the duration of the hyperventilation period; this was considerably longer in the study of Ward et al. (1983).

One possible explanation for this difference in results raised in that Chapter is that the longer period of hyperventilation used by Ward et al. (1983) may allow the development of physiological responses secondary to the reduced Pa,CO_2, in particular a reduction in central nervous drive manifested as a reduction in the ventilatory response to exercise. This may occur by the following mechanism: Firstly, arterial hypocapnia causes a generalised arterial vasoconstriction and consequently a reduction in, among other things, cerebral arterial bloodflow. There is some circumstantial evidence for this: Ramsay et al., 1993 reported a change in both regional and global brain bloodflow following hypocapnic hyperventilation. There are limits to how well these data may be extrapolated to describe changes which may be occurring in either the subjects used in Chapter 5 or those of Ward et al. (1983): In the study of Ramsay et al. (1993) the resting subjects were supine, whereas the subjects who were exercising were upright.

This reduction in bloodflow will inevitably reduce O_2 flux to the brain; the profile of the O_2 dissociation curve for haemoglobin means that the increase in Pa,O_2 associated with the act of hyperventilation will not significantly increase the O_2 carrying capacity of arterial blood. Furthermore, the left-shift of the O_2 dissociation curve associated with a fall in Pco_2 will reduce the ability of the cerebral tissue to extract O_2 from the blood. This reduction in O_2-supply may result in the development of a global hypoxia, which in turn may have a

detrimental effect on CNS function. As this includes the generation of the respiratory drive, it is entirely possible that following hypocapnic hyperventilation, the ventilatory response to a particular stimulus (in this case, exercise) may be attenuated. CNS depressants, for example tranquillisers and opiates, are known to cause respiratory depression. Maloney & Tatum (1930) also reported that the acute ventilatory response to sciatic nerve stimulation is reduced by morphine.

Having suggested that CNS depression may be the cause of the difference between my results and those of Ward et al. (1983), it is important to ensure that the degree and duration of hyperventilation used in this thesis did not cause a significant reduction in CNS drive. This raises the question of what is the best measure to take. As has already been mentioned, there is a change in brain bloodflow following hypocapnic hyperventilation (Ramsay et al., 1993). One problem with measuring bloodflow is that it is not a direct measure of CNS drive. A fall in bloodflow may be an indicator of a developing tissue hypoxia, but the level of hypoxia will depend on the disparity between O_2 supply and demand and the length of time over which it occurs. Furthermore, the sensitivity of the tissue to different levels of hypoxia needs to be addressed if an accurate assessment of the effect of a fall in brain bloodflow on CNS drive (and in particular, CNS tone in the respiratory centres) is to be made.

An investigation of this magnitude is obviously beyond the scope of this Chapter, therefore an alternative means of investigation must be sought. To help in this, it is beneficial to return to the hypothesis under investigation: "Does hypocapnic hyperventilation of the degree and duration reported in the previous Chapter result in CNS dysfunction?" In particular, could it be responsible for the fall in $\dot{V}E$ subsequent to the initial increase seen following the start of exercise? This is a functional question, rather than one based on measurable changes in physiological parameters. One approach would therefore be to see if hypocapnic hyperventilation causes a change in another cerebral function.

This was the approach which was taken and the function chosen for investigation was postural sway. Balance is a complex function involving the accurate integration of sensory information from vestibular, visual and proprioceptive inputs to generate the muscular forces necessary to counteract precisely any destabilising influences on the body (Bloedel & Courville, 1981). Similar to the neuroanatomy of breathing, the control of postural sway relies heavily on the structures of the brainstem while incorporating inputs from the higher centres of the brain.

Central nervous depressants known to induce a fall in resting $\dot{V}E$ have also been reported to increase postural sway. Woolacott (1983) reported a 42% to 49% increase in the latency for lateral sway adjustments following administration of sufficient alcohol to raise blood alcohol concentration to 0.1%, while Mills (1994c) reported that ingestion of alcohol equivalent to 2 double measures of vodka caused a "substantial" increase in sway. Battacharya et al. (1987) was able to detect subtle changes in postural sway in women with blood alcohol levels as low as 0.015%. Jansen et al. (1985) reported that oral administration of Diazepam (0.2 mg/Kg) produced a 37 % increase in sway, while Patat & Foulhoux (1985) report a "significant" increase in postural sway following ingestion of 2 mg Lorazepam. Postural control mechanisms have also been shown to be very sensitive to mild hypoxia (Fraser et al., 1987; Holness et al., 1982). Postural sway is relatively easy to measure with a minimum amount of discomfort to the patient. This makes it ideal for use in this experiment.

PURPOSE OF THE EXPERIMENT:

The purpose of this experiment was to determine whether hypocapnic hyperventilation of the severity and duration described in Chapter 5 could generate evidence of cerebral dysfunction as judged by postural sway either during or after the hyperventilation period.

Preliminary findings of this experiment have already been published (Howell, Butt & Cross, 1994a)

METHODOLOGY:

SUBJECTS:

Eleven subjects were tested, eight were female. Their anthropometric data are presented in *Table 6.1.* None of the subjects smoked and all had fasted for one hour prior to the experiment. None of the subjects participated regularly in any competitive sport. The use of untrained female subjects is a weakness of the protocol. It may be that highly trained athletes would have reacted differently, had they been tested. Unfortunately, the availability of the equipment precluded the testing of any athletes at a later date. This matter is discussed in more depth in the results section.

SUBJECT	AGE	HEIGHT	WEIGHT
101	23	1.79	75.5
102	19	1.77	72.5
103	20	1.9	77
104	19	1.61	55.5
105	20	1.56	66
106	21	1.63	50
107	19	1.6	72
108	20	1.63	60.5
109	20	1.73	63.5
110	20	1.61	66.5
111	21	1.52	57.5

Table 6.1: Anthropometric data for the subjects. Subjects 101 to 103 are male, subjects 104 to 111 are female.

PROTOCOLS:

Each subject was asked to perform two tests separated by approximately 20 min rest. Throughout both tests the subject stood on a Mills-McIntyre postural swaymeter with their eyes open, their hands by their sides and their feet shoulder width apart.

The protocols for the two tests were similar: Both tests started with the subject standing quietly for 3 min. Postural sway was measured at 1, 2 and 3 min of this period. This was followed by a period of hyperventilation of 2 to 3 min duration. The increase in $\dot{V}E$ was achieved by a 2 to 3-fold increase in VT while fBR was maintained at close to normal resting levels. Postural sway was measured at 2 and 3 min of the hyperventilation period. The two tests differed in the hyperventilation period: In the "+CO_2" test sufficient CO_2 was added to the inspirate to maintain P_{ET},CO_2 close to normal resting values, while in the "-CO_2" test hyperventilation resulted in a fall in P_{ET},CO_2 to between 20 and 25 mmHg. At the end of the hyperventilation period subjects were asked to breathe normally for a further 4 min. Postural sway was measured 1, 2 and 3 min following the end of the hyperventilation period. Subjects were not aware of when postural sway was being measured. The order of the two tests was randomised between subjects.

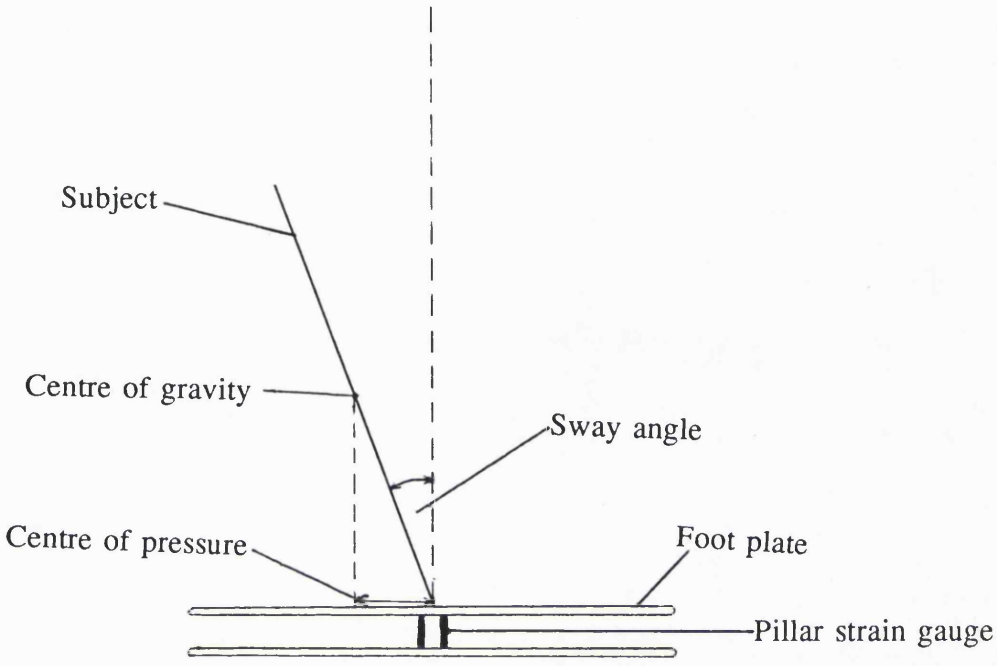
APPARATUS:

Cardiorespiratory variables were simultaneously recorded on magnetic tape and analysed using data acquisition program "EXTEST 2" as described in Chapter 2 and Appendix A.

Postural sway was measured using a Mills-McIntyre postural swaymeter. This consists of two aluminium plates separated by a 50 mm high four-sided aluminium column. This column has 4 semiconductor strain gauges mounted on it, connected as pairs on opposing faces of the pillar. Each pair forms half a Wheatstone bridge. As the subject moves their centre of gravity, the aluminium column distorts, changing the resistance of the

semiconductors. A constant current flows through each pair of semiconductors and therefore the output voltage will vary according to the torque applied to the central column. The changes in the output voltages are monitored by a computer program which then estimates the angular deviation of the subject's centre of gravity from its normal resting position, taking into account the subject's height and weight (see *Fig.6.1*). Data are collected over a 30 sec period, saved to disc and an on-line plot of the subject's sway path generated (see *Fig. 6.2*). From this the subject's mean angular sway can be calculated. The Mills-McIntyre Postural Swaymeter has been validated for use in humans (Mills, 1994a), with a 4 % coefficient of variation for sway measured in a group of subjects on two separate occasions. For a more thorough discussion of this piece of apparatus please refer to Mills et al. (1994a, b, c).

Throughout the tests the subjects had their eyes open. It is well recognised that postural sway increases if the eyes are closed (Mills, 1994c) and this would have increased the sensitivity of the test to any changes in CNS function. The subjects were not asked to keep their eyes closed for two reasons: Firstly, they needed to be able to see the oscilloscope during the hyperventilation period. Performing the rest of the test with eyes open would not only have excluded the possibility of direct comparisons between postural sway during hyperventilation and during the other stages, but also would have introduced changes in state for the subject (eyes open and eyes closed) which may have directly affected both the subjects' ventilation and postural sway. Secondly, a common sensation during hyperventilation is vertigo and disorientation. As was reported in Chapter 2, these sensations are occasionally associated with an increase in anxiety. It would be reasonable to assume that, if the subject's eyes were closed, these sensations would be magnified, leading to a more widespread incidence of anxiety, accompanied by chronic hyperventilation. This would inevitably weaken the results obtained from these subjects.



Angle of lean = Arc sin (Distance / (0.5 * stature))

Figure 6.1: Schematic diagram showing the calculation of the position of a subject's centre of pressure on the Postural Swaymeter. Equations are used to estimate sway angle.

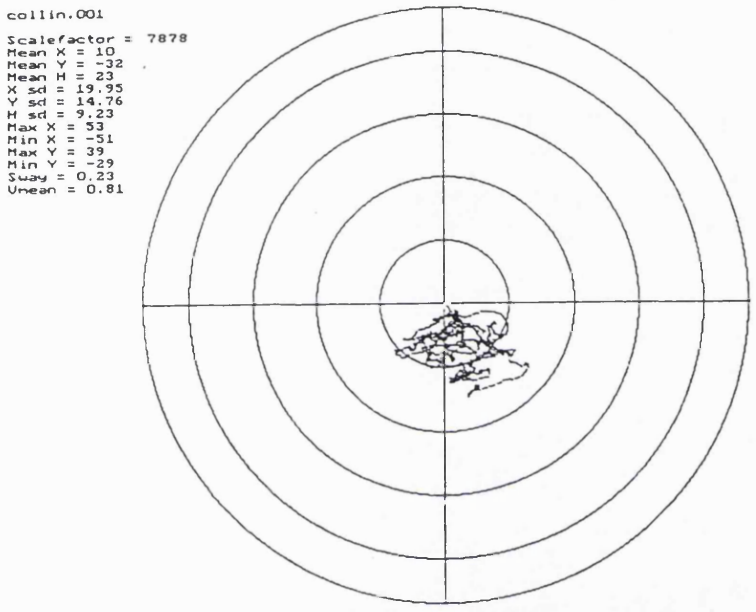


Figure 6.2: Typical example of sway path generated over 30 sec of data acquisition by the Postural Swaymeter and the results of its analysis. "Mean X" and "Mean Y" are mean lateral and sagittal sway respectively (mm), "Mean H" is mean sway (mm) and "X sd", "Y sd" and "H sd" are their standard deviations respectively. "Max x" and "Min X are the maximum and minimum values of lateral sway (mm) and "Max y" and "Min y" are the maximum and minimum values of sagittal sway (mm). "Sway" is the meaan sway (^{0}) and "Vmean" is the mean centre of pressure path. "Sway" is the parameter studied in this Chapter.

STATISTICAL ANALYSIS:

Mean values of $\dot{V}E$, VT, fBR, PET,CO_2, PET,O_2, $\dot{V}o_2$, $\dot{V}co_2$, RER and f_C. were calculated for each 30 sec period of postural sway measurement for each subject. These values were then used for the calculation of the population means and standard errors. Comparisons between the "$+CO_2$" and "$-CO_2$" tests was performed using non-paired t-tests assuming equal variance. Comparisons of values for 1, 2, and 3 min of rest were performed using single factor ANOVA.

The time-course of the changes in $\dot{V}E$ following the end of the hyperventilation period was modelled as a single order decay as used and described in Chapter 4 (p 145) and Appendix D (MODEL 1). The best fit function through the experimental data was determined using the least squares method and was calculated using the "Solver" function in Microsoft EXCEL 4.0.

RESULTS:

Of the eleven subjects tested, two were excluded from the analysis. One continued to hyperventilate after the end of the hyperventilation period (Subject 109) while the other had a marked increase in postural sway during the ("+CO_2") test (Subject 102). When questioned about his sensations at the end of the test he reported feeling increasingly uncomfortable throughout the test and being aware of shifting his weight from side to side.

RESTING VALUES:

With the exceptions mentioned above, $\dot{V}E$, f_{BR}, VT, P_{ET,CO_2}, P_{ET,O_2}, $\dot{V}o_2$, $\dot{V}co_2$, f_C and mean Sway Angle did not change significantly during the rest period. Equally, there was no significant difference between resting levels recorded at the start of the two tests. These are presented in *Table 6.2*.

	+CO_2	-CO_2
$\dot{V}E$	9.64 ± 1.02	9.22 ± 1.03
VT	0.79 ± 0.11	0.74 ± 0.12
f_{BR}	13.0 ± 1.4	13.1 ± 1.0
f_C	86 ± 4	86 ± 3
P_{ET,CO_2}	37 ± 1	37 ± 1
P_{ET,O_2}	105 ± 3	104 ± 3
SWAY	0.335 ± 0.084	0.268 ± 0.051

Table 6.2: Resting data for both tests. Values are mean ± S.E., n = 9.

HYPERVENTILATION:

$\dot{V}E$ increased during the hyperventilation period by a similar amount in both tests (see *Table 6.3*). This was achieved by an increase in VT and a slight (but significant) increase in f_{BR} over resting values.

	$+CO_2$	$-CO_2$
$\dot{V}E$	24.85 ± 3.1	24.37 ±2.94
VT	1.80 ± 0.31	1.86 ± 0.33
f_{BR}	14.8 ± 1.4	14.5 ± 1.1
f_C	89 ± 3*	105 ± 3
P_{ET},CO_2	36 ± 1*	23 ± 2
P_{ET},O_2	117 ± 1	117 ± 2
SWAY	0.446 ± 0.113	0.406 ± 0.081

Table 6.3: Hyperventilation data for both tests. Values are mean ± S.E. n = 9. * denotes a significant ($p<0.05$) difference between "$+CO_2$" and "$-CO_2$" tests.

P_{ET},CO_2 fell in the "$-CO_2$" test, to 23 ± 2 mmHg by the end of the hyperventilation period. In the "$+CO_2$" test, however, P_{ET},CO_2 was well maintained at close to normal resting levels. P_{ET},O_2 increased as a consequence of the hyperventilation in both tests. This probably was of little physiological consequence, given the already high level of saturation of haemoglobin seen at normal values.

f_C increased significantly over resting levels to 93 ± 3 bpm in the "$+CO_2$" test and 105 ± 3 bpm in the "$-CO_2$" test. The heart rates seen in the two hyperventilation periods differ significantly ($p<0.05$) from each other.

Postural sway increased, but not significantly, in both tests. This increase was attributable to one subject whose sway increased during hyperventilation in both tests, and one subject who presented with an abnormally high value for one of the collection periods in the "$-CO_2$" test (presumably due to her shifting her weight during the analysis period). There was no significant difference between postural sway in the "$+CO_2$" and "$-CO_2$" tests, despite

five of the subjects reporting sensations of dizziness and paraesthesia during and following hypocapnic hyperventilation. None of the subjects reported any such sensations during or after eucapnic hyperventilation.

POST-HYPERVENTILATION:

Mean interpolated responses to the end of hyperventilation in the "+CO_2" and "-CO_2" tests are presented in *Fig. 6.3.*

"+CO_2" Tests: In 4 subjects $\dot{V}E$ fell abruptly following the end of the hyperventilation period, returning to normal resting values within two breaths (See *Fig. 6.4*) . Modelling of the change in $\dot{V}E$ following the end of hyperventilation using MODEL 1 (See Methods section, Chapter 4 (p 145) and Appendix D) yielded a value for τ of less than 2 sec. In the remaining two subjects, $\dot{V}E$ fell more gradually. Modelling the change in $\dot{V}E$ using MODEL 1 in these 2 subjects yielded values for τ of 5.6 and 7.9 sec (Group mean (± S.E.) = 2.93 ± 1.27 sec).

	+CO_2		
	1 MIN	2 MIN	3 MIN
$\dot{V}E$	9.92 ± .85	10.21 ± 1.35	9.27 ± 1.04
VT	0.75 ± 0.12	0.73 ± 0.08	0.76 ± 0.16
f_{BR}	14.5 ± 1.4*	14.2 ± 1.2	13.8 ± 1.7
f_C	88 ± 4	87 ± 4	89 ± 4
P_{ET,CO_2}	36 ± 1	35 ± 1	36 ± 1
P_{ET,O_2}	117 ± 1*	112 ± 2*	106 ± 2
SWAY	0.343 ± 0.146	0.343 ± 0.122	0.406 ± 0.110

Table 6.4: Responses to eucapnic hyperventilation. Data are mean ± S.E. over the 30 sec periods of postural sway measurement. n = 9. * denotes statistically significant ($p<0.05$) difference between pre- and post-hyperventilation: values.

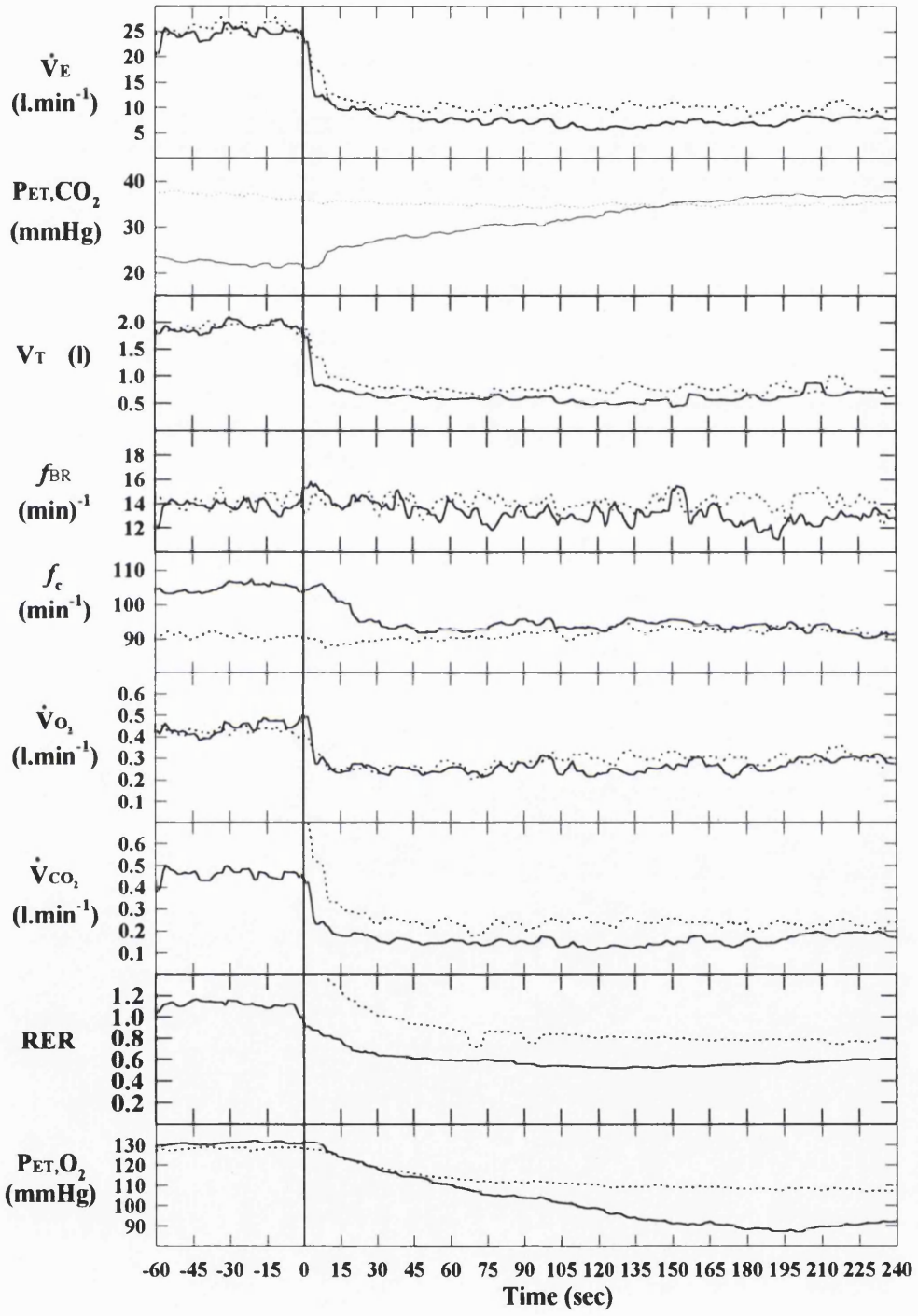


Figure 6.3: Mean changes in $\dot{V}E$, P_{ET,CO_2}, VT, f_{BR}, f_C, $\dot{V}o_2$, $\dot{V}co_2$, RER and P_{ET,O_2} for 1 min prior to and 4 min following the end of hyperventilation in the "+CO_2" (dotted lines) and "-CO_2" (solid lines) tests. Individual subjects' breath-by-breath data were interpolated over 1 sec intervals, time aligned and averaged. n = 9. Time 0 represents the end of hyperventilation.

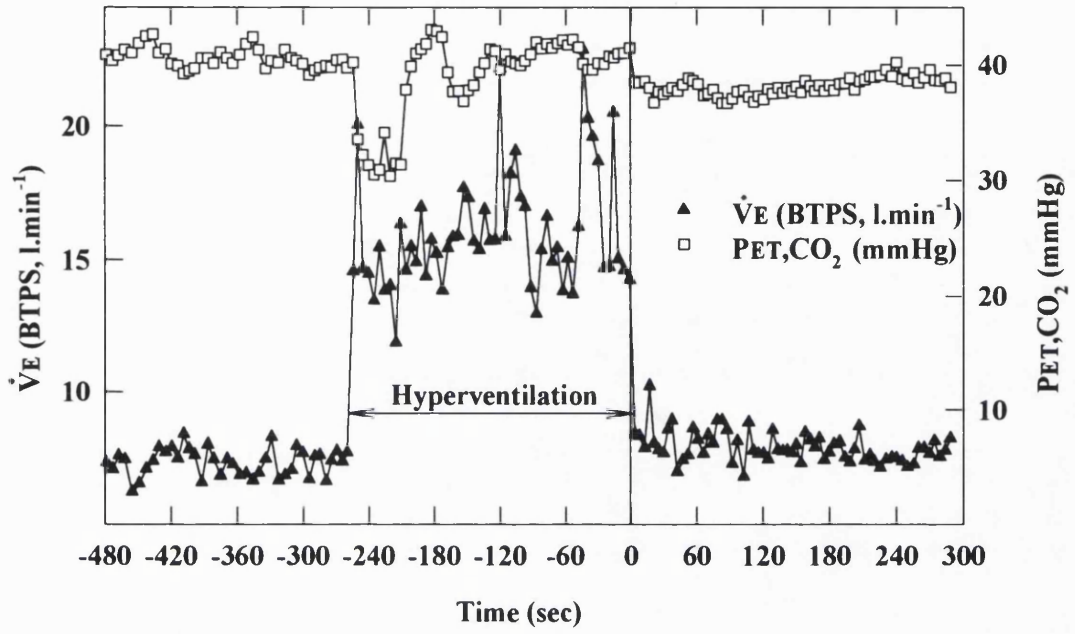


Figure 6.4: Breath-by-breath changes in $\dot{V}E$ and P_{ET,CO_2} during the "+CO_2" test performed by subject 104. Note the abrupt fall in $\dot{V}E$ on cessation of volitional hyperventilation. Time 0 represents the end of hyperventilation.

VE was not significantly different from pre-hyperventilation values 1, 2 or 3 min following the end of the hyperventilation period (see *Table 6.4*). *f*BR was slightly higher 1 min following the end of hyperventilation. This was almost certainly associated with the slight rise in *f*BR seen during hyperventilation. *f*BR had returned to normal (pre-hyperventilation) levels by the second and third minutes following hyperventilation. VT did not differ significantly from pre-hyperventilation values at 1, 2 or 3 min post-hyperventilation. Postural sway showed no perturbations following volitional eucapnic hyperventilation.

"-CO_2" Tests: The ventilatory consequences of hypocapnic hyperventilation were more variable than those of eucapnic hyperventilation described above. The most common pattern of change seen was an abrupt fall in $\dot{V}E$ over one or two breaths to a value close to normal resting levels, followed by a more gradual decline, reaching a nadir between one and three minutes after the end of the hyperventilation period (See *Figs. 6.3 & 6.5*). Modelling the change in $\dot{V}E$ following the end of hyperventilation using MODEL 1 (See Methods

section, Chapter 4 (p145) and Appendix D) yielded a mean (± S.E.) value for τ of 7.85 ± 2.71 sec. τ for 3 subjects was below 2 sec.

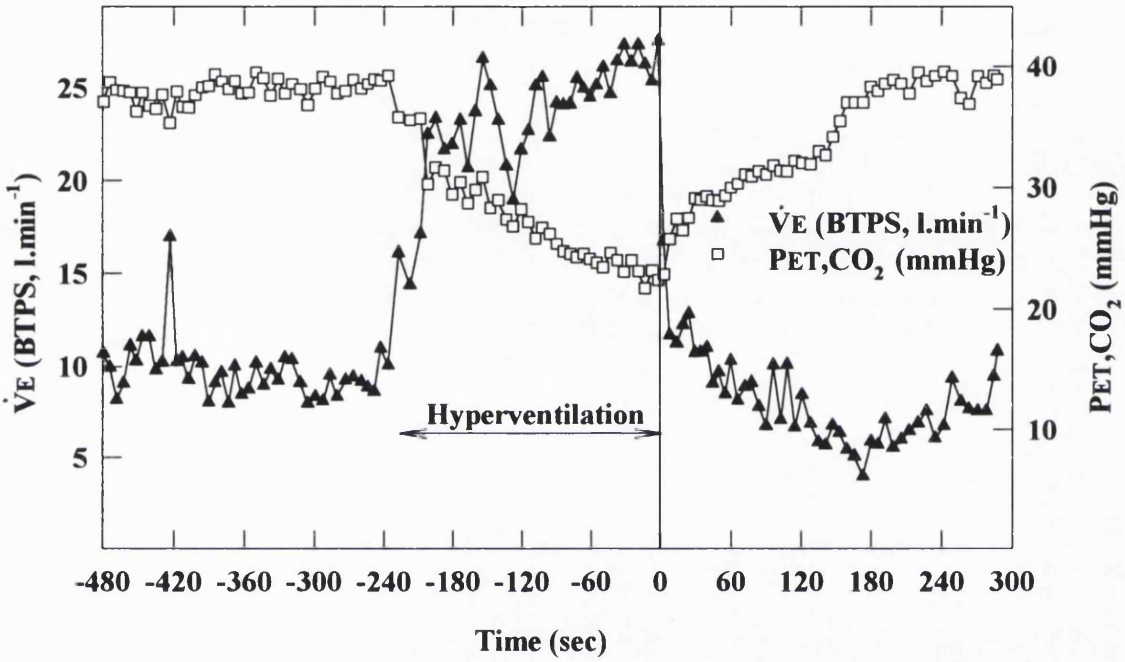


Figure 6.5: Breath-by-breath changes in $\dot{V}E$ and P_{ET,CO_2} during the "+CO_2" test performed by subject 104. Note the more gradual decline in $\dot{V}E$ on cessation of volitional hyperventilation. Time 0 represents the end of hyperventilation.

	-CO_2		
	1 MIN	2 MIN	3 MIN
$\dot{V}E$	8.43 ± .81	6.68 ± .78*#	7.62 ± 1.0
V_T	0.66 ± 0.6	0.6 ± 0.11*	0.76 ± 0.2
f_{BR}	14.7 ± 1.1*	14.2 ± 1.4	13.1 ± 1.7
f_C	92 ± 4*#	91 ± 5	89 ± 4
P_{ET,CO_2}	28 ± 1*#	31 ± .4*#	36 ± 1
P_{ET,O_2}	117 ± 2*	106 ± 2	95 ± 6*
SWAY	0.403 ± 0.135	0.397 ± 0.15	0.366 ± 0.121

Table 6.5: Responses to hypocapnic hyperventilation. Data are mean ± S.E. (n = 9) over the 30 sec periods of postural sway measurement. * signifies a significant ($p<0.05$) difference between pre and post hyperventilation values, # signifies a significant ($p<0.05$) difference between "+CO_2" and "-CO_2" values.

The result of these different responses to the hypocapnic hyperventilation was that as a group $\dot{V}E$ fell to around normal resting levels by one min post-hyperventilation, fell further by two min post-hyperventilation and had started to recover by three min post-hyperventilation (see *Table 6.5*). This fall was mostly due to changes in VT. fBR fell gradually to normal levels following hyperventilation, mirroring the changes seen in the "$+CO_2$" tests.

The fall in $\dot{V}E$ allowed P_{ET},CO_2 to rise, reaching normal values by 3 min post-hyperventilation (see *Table 6.5*). The relative hypoventilation consequent to the arterial hypocapnia also resulted in P_{ET},O_2 falling below normal resting values at 3 min post-hyperventilation.

f_C fell following the end of hyperventilation, but was still significantly higher than both normal resting values and "$+CO_2$" values at 1 min post-hyperventilation. By the second minute, however, it had returned to normal values and remained there for the rest of the test.

When questioned after the "$-CO_2$" test, all except one of the subjects tested reported feeling dizzy, woozy and numbness in the arms and chest. In contrast, only one of the subjects reported any abnormal sensations following the "$+CO_2$" test.

As can be seen in *Tables 6.4* and *6.5*, hypocapnia of the level seen in these tests does not result in a significant increase in postural sway, neither does the slight fall in P_{ET},O_2, despite the findings of Holness et al. (1982) concerning the detrimental effects of hypoxia on postural sway. Assuming that postural sway is a reliable indicator of cerebral dysfunction, it would therefore appear that hypocapnic hyperventilation of this severity and duration does not result in a significant level of cerebral dysfunction.

DISCUSSION:

POSTURAL SWAY AT REST:

The values for postural sway measured during the rest period at the start of each test were similar to the normal ranges quoted by Mills (1994c) for sway during quiet standing with eyes open: 0.25 ± 0.05° (mean ± S.E.) in a group of 9 healthy young males and 0.31 ± 0.05° for nine healthy young females. Both age and sex have been shown to affect postural sway; sway being greater in females than in males and in the elderly compared to young adults. All the subjects used in this study are of similar age and as the results for each subject are compared with themselves, it was not necessary to separate the subjects according to sex.

EFFICACY OF HYPERVENTILATION:

The protocol by which the necessary increase in $\dot{V}E$ was achieved in this study was similar to that used in the studies described in Chapters 4 and 5. The increase in fBR seen in these tests was not a desired outcome but was small and of a similar size in both tests. Although statistically significant, it was unlikely to exert an undue influence over the outcome of the test, or seriously compromise the extrapolation of the results from this study to those reported in Chapters 4 and 5.

The duration of the hyperventilation period was 235 ± 7 sec in the "+CO_2" tests and 237 ± 8 sec in the "-CO_2" tests. The effect of the duration of hyperventilation on the depletion of body CO_2 stores has been discussed previously in Chapters 4 and 5. The severity and duration of hyperventilation in these tests was similar to that used in the studies described in Chapters 4 and 5 and would therefore have a similar effect on body CO_2 stores as did the hyperventilation periods in the studies described in those 2 Chapters.

Mean postural sway increased during hyperventilation, but this was due to the influence of outlying results, as demonstrated by the lack of statistical significance for this difference. This would suggest that the perturbations of the thorax and abdomen associated with the act of hyperventilation do not affect a subject's postural sway (with the possible exception of the one subject mentioned above). These data do not agree with those of Hunter & Kearney (1981), who reported that a major portion of sway resulted from respiratory related-movements and that sway increased linearly with increases in respiratory activity. Nashner & McCollum (1985), however, hypothesised that the control of postural sway was essentially an open-loop control process, relying on a limited repertoire of distinct movement strategies for the correction of postural disturbances. The act of breathing is fundamental to life, therefore it would stand to reason that there exists in every repertoire a strategy designed to compensate for respiratory movements. It would be interesting to determine whether the accurate compensation for respiratory movements relies on a central irradiation from the respiratory pattern generators on a peripheral input from stretch receptors in either the lungs or the chest wall.

The differing effects of hyperventilation with and without added CO_2 on f_C do not agree with the results reported in Chapters 3 and 5. There is no obvious explanation for this difference. It may be that it is associated with changes in blood pressure which are more apparent when the subject is standing as opposed to sitting on a cycle ergometer. It is also possible that these data highlight a difference between the highly trained male athletes tested in Chapter 5 and the untrained male and female subjects used in this experiment.

POST-HYPERVENTILATION:

"+CO_2": The profile of the change in VE following the cessation of hyperventilation seen in this study differs somewhat from that reported in Chapter 4. The fall in $\dot{V}E$ seen in this study was much more abrupt than that reported in Chapter 4. This is highlighted by the smaller value for τ recorded in this study compared to that reported in Chapter 4. This

pattern of response to hyperventilation mediated by an increase in VT with little increase in *f*BR is similar to that reported by Folgering & Durlinger (1983), also for sedentary subjects. As expected, mean postural sway was not significantly different from normal resting levels following hyperventilation with added CO_2.

"-CO_2": The profile of the change in $\dot{V}E$ following the cessation of hyperventilation in the "-CO_2" protocol was similar to that described above in the "+CO_2" protocol, i.e. similar to that described by Folgering & Durlinger (1983). There are some differences; particularly the incidence of subjects whose ventilation falls abruptly to a basal level following cessation of hyperventilation (i.e. those for whom $\tau < 2$ sec) was less in the "-CO_2" protocol than in the "+CO_2" protocol.

Folgering & Durlinger (1983) reported τ of afterdischarge to decrease when hyperventilation was associated with a fall in $PaCO_2$, whereas the results obtained here would suggest that the opposite is the case. The results reported in Chapter 4 for the ventilatory response to hyperventilation in highly trained are equivocal concerning the possibility that arterial hypocapnia increases, rather than decreases, τ for afterdischarge. τ for afterdischarge was similar following hyperventilation with and without added CO_2, but the results of 2 subjects were not included in the analysis for Protocol A due to chronic hyperventilation following the cessation of hypocapnic volitional hyperventilation. These subjects had a ventilatory response to the cessation of eucapnic volitional hyperventilation (Protocol B) which was similar to that seen in the remainder of the subject group.

The ventilatory responses to the cessation of eucapnic and hypocapnic hyperventilation reported in this Chapter differ from those reported in Chapter 4. The timecourse of the decline in $\dot{V}E$ following the cessation of hyperventilation reported in Chapter 4 was longer than that reported in this Chapter. It is possible that this is a result of the different positions in which the hyperventilation was performed: Hyperventilation was performed in Protocol "A" (Chapter 4) with subjects seated on the bicycle while in this study the subjects were standing. This is unlikely, as the subjects of Folgering & Durlinger (1983), whose

ventilatory response to the cessation of volitional hyperventilation was similar to that seen in this study, were seated and sedentary.

An alternative hypothesis would be that the difference in the ventilatory response to the cessation of volitional hyperventilation reported in this Chapter and Chapter 4 is a reflection of the difference in fitness between the 2 subject populations. This is a fascinating possibility, as it implies that the act of training may have modified the neural pathways in the brainstem which are responsible for the phenomenon of afterdischarge (Eldridge, 1973). However, there is no evidence to suggest that the physiological origins of afterdischarge following voluntary hyperventilation are the same as following active hyperventilation elicited by calf squeezing in anaesthetised cats (Eldridge, 1973), by a square-wave hypoxic stimulus in awake goats (Engwall et al., 1991, 1994) or in asleep (Gleeson & Sweer, 1993) or awake humans (Gleeson & Sweer, 1993; Georopoulos et al., 1009). This observation needs further investigation.

$\dot{V}E$ gradually rose to normal resting levels by 3 min post-hyperventilation, demonstrating that for this subject group, 3 min was sufficient time for recovery from the effects of the hyperventilation.

P_{ET,CO_2} increased following the cessation of hyperventilation, reflecting the repletion of body CO_2 stores. P_{ET,CO_2} had returned to normal resting levels by 3 min post-hyperventilation. This supports the statement of the previous paragraph, that recovery from the effects of the hyperventilation was complete by the end of the test. The only physiological variable which had not returned to normal resting levels by 3 min post-hyperventilation P_{ET,O_2}, which had fallen to slightly below normal resting levels. Although the difference between normal resting P_{ET,O_2} and P_{ET,O_2} 3 min post-hyperventilation was statistically significant, the shape of the O_2 dissociation curve for haemoglobin makes it debatable as to whether this fall was of physiological significance.

The difference between the changes in f_C in response to hypocapnic and eucapnic hyperventilation were also present during the recovery from the hyperventilation in the 2 protocols. This difference was not seen in the highly trained subject group tested in Chapter 4.

It could be that the greater rise in f_C seen in the "-CO_2" tests was due to some apprehension on the part of the subjects arising from the (presumably) unusual sensations associated with hypocapnic hyperventilation. As PET,CO_2 rose and the sensations faded, so the subjects may have relaxed again, allowing their heart rate to return to normal levels.

Cummin et al. (1986) reported an increase in heart rate with hyperventilation achieved by an increase in VT. This is certainly seen in the results of Chapter 4 and 5, but in these results f_C rose substantially only in the "-CO_2" tests and not in the "+CO_2" tests. It would appear that the disparity lies with the "+CO_2" results, rather than those of the "-CO_2" tests. As mentioned above, there is no obvious explanation for this difference. Mills (1946) reported differences in the mechanical effects of diaphragmatic and thoracic hyperventilation on the cardiovascular system, but did not report any heart rate data.

It could be that differences in how the increase in VT was achieved may explain the differences in the f_C seen during and after the hyperventilation periods. This is, however unlikely: The similarity of the hyperventilation periods would suggest that they were achieved in a similar manner; the subjects were only advised to hyperventilate by increasing their VT, not how this should be done. It would be logical to assume that they achieved the increase in VT in an similar manner in both tests. Mills (1946) also used a much more extreme protocol of hyperventilation (or "Forced breathing", as he called it) than that used here. The variations in the mechanical effects of breathing he reported may not necessarily occur here. It seems that it is impossible to offer a coherent explanation for these results at this time.

Postural sway was not significantly different from normal resting levels following the cessation of volitional hypocapnic hyperventilation. There is therefore no evidence to support the theory that 4 min hyperventilation results in any CNS dysfunction, either during the hyperventilation or afterwards, when $\dot{V}E$ was low and CO_2 stores were replenishing.

CONCLUSIONS:

With the exception of one subject, the act of hyperventilation did not result in any perturbation of postural sway. In none of the subjects did hypocapnic hyperventilation adversely affect postural sway when compared to eucapnic hyperventilation. This was despite a marked difference in the incidence of sensations associated with hypocapnia (dizziness, numbness, feeling detached) reported in the two tests.

Following hyperventilation, $\dot{V}E$ fell rapidly in most tests to normal values in the "$+CO_2$" tests, but below normal levels in the "$-CO_2$" tests. These results agree with those reported in Chapter 4 for competitive oarsmen. This relative hypoventilation seen in the "$-CO_2$" tests allowed P_{ET},CO_2 to return to normal resting levels, but caused a transient fall in P_{ET},O_2. This was not associated with any change in postural sway either.

It would therefore appear that the hyperventilation protocol used in Chapter 5 is not associated with any significant reduction in CNS function. Therefore the effect of hypocapnic hyperventilation on the ventilatory response to exercise reported in the preceding Chapter is a direct result of the hypocapnia and not a result dependent on a developing cerebral dysfunction.

CHAPTER 7

THE EFFECT OF PRIOR HYPOCAPNIC HYPERVENTILATION ON THE VENTILATORY RESPONSE TO AN INCREASE IN WORKLOAD

INTRODUCTION:

The profile of the initial cardiorespiratory and pulmonary gas exchange responses to a step transition from rest to moderate intensity exercise is traditionally described as an abrupt increase to a plateau (Whipp & Ward, 1982; Whipp et al., 1982). The magnitude of the response for $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ are roughly in proportion (Whipp & Ward, 1982; Whipp et al., 1982), resulting in little change in RER, P_{ET},CO_2 or P_{ET},O_2. The credibility of this view of the initial responses to the onset of exercise has been discussed thoroughly in Chapter 5. The magnitude of the initial responses to exercise would also appear to be unaffected by the intensity of the exercise (Dejours, 1972; Jensen, 1972), although this is not a universal finding (Krogh & Lindhard, 1913; Linnarson, 1974).

The profile of the initial cardiorespiratory and pulmonary gas exchange responses to a step change from mild to moderate intensity exercise, on the other hand, is much smaller than that seen for the transition from rest to exercise, if present at all (Whipp et al., 1982; Linnarson, 1974; Miyamoto & Niizeki, 1992; Fijuhara et al., 1973a). The onset also has a slower time course (See *Fig. 7.1* and Whipp et al., 1982), being adequately described by a monoexponential function with negligible delay and τ of around 5 sec (Fujihara et al., 1973; Miyamoto & Niizeki, 1992; Bakker et al., 1981; Bennett et al., 1981).

This profile of response is not a universal finding, however: Beaver & Wasserman (1968) have reported an abrupt increase in $\dot{V}E$ coincident with an abrupt increase in workload against a background of light exercise.

It is possible that an increase in workload is associated with an abrupt increase in output from those pathways responsible for the initial ventilatory response to the onset of exercise, but the higher background level of ventilation suppresses its expression. Lowering ventilation prior to increasing the workload may therefore allow the

expression of such a previously occult phenomenon. As described in Chapter 4, one consequence of depleting body CO_2 stores by hyperventilation during exercise is an attenuation of the ventilatory response to exercise. Furthermore, the results from Chapter 5 suggest that, if the hypocapnia is sufficiently deep, the onset of the later ventilatory response will be delayed. This delay in onset of the later response to exercise will highlight whether such an increase is transient in nature.

PURPOSE OF THE EXPERIMENT:

The purpose of this experiment was to determine whether, having reduced $\dot{V}E$ during mild exercise by prior hypocapnic hyperventilation, an abrupt increase in $\dot{V}E$ could be seen in the first 3 breaths following an abrupt increase in workload.

Preliminary findings of this study have already been published (Howell & Cross, 1994a, 1995a)

METHODS:

SUBJECTS:

Twelve subjects performed the tests outlined below in the "Protocol" section. The anthropomorphic data for these subjects are presented in *Table 7.1.*

SUBJECTS	AGE	HEIGHT	WEIGHT	SPORT
C	23	1.9	75	ROWER
J	20	1.72	78	ROWER
K	20	1.77	77	ROWER
M	18	1.83	71	ROWER
P	23	1.85	88	ROWER
Q	18	1.89	85	ROWER
R	20	1.90	76	ROWER
S	22	1.68	76	ROWER
T	26	1.84	82.5	ROWER
U	25	1.80	77	CYCLIST
W	23	1.92	76.5	RUNNER
4	28	1.72	68	ROWER

Table 7.1: Anthropometric data on subjects who performed this experiment.

APPARATUS:

The apparatus used was the same as that described in Chapter 4, using the data acquisition and analysis program "EXTEST 2". Due to a technical fault, P_{ET},CO_2 and P_{ET},O_2 values were not obtained for the tests performed on five of the subjects.

PROTOCOLS:

Each subject performed two tests, outlined below. The tests were performed on the same day separated by a rest period of 20 to 30 min. Subjects were asked to refrain from eating and from drinking any beverage containing caffeine for 1 hour before the test. None of the subjects smoked. The order of the tests was randomised.

Test "NORM": The subjects sat quietly on the cycle ergometer for 4 min to obtain resting values. At the end of this period the command "Start pedalling now" was given, whereupon the subjects started to pedal at 75 rpm. Workload was 50 W. 4 min after the start of exercise the command "Workload going up now" was given and the workload was increased to 150 W for 4 min. At the end of this stage the command "Stop pedalling now" was given, denoting the end of the exercise stage of the test. Subjects then rested for approx. 2 min before the test was terminated.

Test "HYPER": Subjects started the test with 4 min rest. This was followed by exercise at 50 W, 75 rpm as described above. After 4 min, while continuing to exercise at 50 W, subjects were asked to breathe as deeply as they could without changing their respiratory rate. The oscilloscope method of monitoring the level of hyperventilation used in Chapter 4 was not used in this study as the level of ventilation required was unattainable simply by an increase in V_T; f_{BR} had to be increased as well. The instruction given, accompanied by verbal encouragement was the most efficacious method of achieving a sufficiently high level of ventilation. Subjects were also warned if their pedal frequency varied excessively from 75 rpm. The hyperventilation was maintained for 4 min or until P_{ET},CO_2 fell to 25 mmHg or below for more than five breaths. Once one of these end-points had been reached subjects were asked to "Breathe normally". Some 15 to 30 sec after the end of the hyperventilation stage the command "Workload going up now" was given and the workload was increased to 150 W for 4 min. At the end of this stage, subjects were asked to "Stop pedalling

now", marking the end of the exercise stage of the test. Again, subjects' recovery was monitored for 2 min post-exercise before the test was terminated.

In the tests performed by subject W the duration of the 50 W stages in both protocols was only 3 min.

DATA ANALYSIS:

Resting values: Mean resting values for $\dot{V}E$, VT, fBR, $\dot{V}o_2$, $\dot{V}co_2$, RER, P_{ET,CO_2}, P_{ET,O_2} and fC for each test were taken as the mean value for 1 min prior to the start of exercise. The group resting responses for the "NORM" and "HYPER" tests were then compared using Student's paired *t*-tests.

Initial responses to the onset of 50 W exercise: The initial response to the onset of exercise for $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ was taken as the maximum response seen over the first 3 breaths of exercise. This is consistent with MODEL 3, described in Chapter 5 and Appendix F. Attempts to model the ventilatory any pulmonary gas exchange responses to the transition from rest to 50 W were unsuccessful. This will be discussed more fully in the relevant sections of the Results and Discussion sections.

The initial responses to the onset of 50 W exercise for fBR and VT were taken as the values for the same breath as for $\dot{V}E$. The initial response to the onset of 50 W exercise for P_{ET,CO_2}, P_{ET,O_2} and RER was taken as the mean response over the first 3 breaths of 50 W exercise.

Steady-state responses to 50 W exercise: The steady-state values of $\dot{V}E$, VT, fBR, $\dot{V}o_2$, $\dot{V}co_2$, RER, P_{ET,CO_2}, P_{ET,O_2} and fC for each test were taken as the mean value for the last 30 sec of this stage. The values obtained for the two protocols were then compared using Student's paired *t*-tests.

Hyperventilation: Values of $\dot{V}E$, VT, fBR, $\dot{V}O_2$, $\dot{V}CO_2$, RER, P_{ET,CO_2}, P_{ET,O_2} and fC for the hyperventilation period were taken as the mean of the last 5 breaths of the hyperventilation period. These results were compared with the normal steady-state responses to 50 W exercise to determine the effects of the hyperventilation.

Post-Hyperventilation: The mean values of $\dot{V}E$, VT, fBR, $\dot{V}O_2$, $\dot{V}CO_2$, RER, P_{ET,CO_2}, P_{ET,O_2} and fC for the 3 breaths prior to the increase in workload were taken to represent the extent of recovery from the hyperventilation before the increase in workload.

Responses to 150 W exercise: The changes in $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$ and fC in response to a sudden increase in workload have previously been described in the literature (Casaburi et al., 1989a; Fujihara et al., 1973a,b). These authors report the profile of the response to be well characterised by two exponential components of the form:

$$Y_{(t)} = \left[A_1 * e^{-[(t-t_{D1})/\tau_1]}\right] + \left[A_2 * e^{-[(t-t_{D2})/\tau_2]}\right]$$

where Y(t) is the increase in the variable at time t, A_1 and A_2 are the increases in the variable Y associated with the initial and steady-state responses respectively, t is the time in seconds, t_{D1} and t_{D2} are the delays for the initial and later responses respectively and τ_1 and τ_2 are the time constants of the initial and later responses respectively. This model is called MODEL 4 (see *Fig. 7.1* and Appendix G). This model was used to describe the profile of the response to the abrupt change in workload from 50 W to 150 W for $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$.

The best fits of this model (defined as resulting in the lowest value for the sum of the squares of the residuals, ($\Sigma(Res^2)$) to each subjects' data for the "NORM" and "HYPER" tests were determined using the SOLVER function of EXCEL 4.0. The results of the modelling of the ventilatory and pulmonary gas exchange responses to the abrupt transition from 50 W to 150 W exercise were evaluated and the responses

seen in the "NORM" and "HYPER" tests compared.

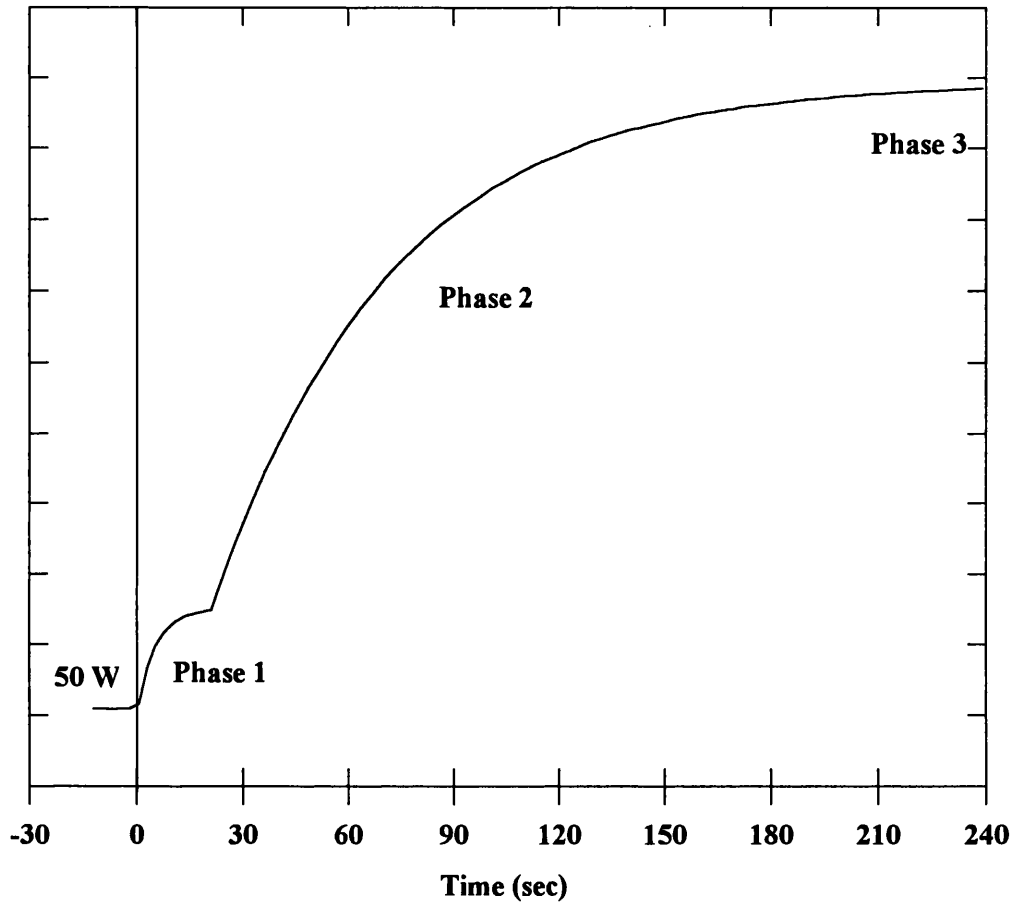


Figure 7.1: Profile of MODEL 4. τ_1 = 5 sec, t_{D1} = 0.4 sec, τ_2 = 50 sec, t_{D2} = 21 sec. Time 0 represents the increase in workload. Model is applicable to f_C, $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$.

The model described as MODEL 3 in Chapter 5 (See *Fig. 5.2*) and Appendix F was also used to describe the responses to the increase in workload. The rationale behind this decision is given in the relevant sections below. The best fit of this model to the experimental data was determined in exactly the same way as described above for MODEL 4. MODEL 3 defines the initial response as the maximum value for the first 3

breaths and the subsequent plateau as the mean response from the fourth breath to the onset of the later response. The later response is described as a monoexponential rise to the steady-state.

MODEL 3 was considered to provide a better fit to the experimental data than MODEL 4 if:

(i) $\Sigma(Res^2)$ for MODEL 3 was lower than for MODEL 4.

(ii) τ_1 obtained for MODEL 4 was less than 1 sec.

(iii) The initial response obtained using MODEL 3 was greater than the subsequent plateau.

The change in f_C in response to the abrupt increase in workload from 50 W to 150 W was modelled using a monoexponential curve of the form:

$$f_{c_{(t)}} = 50W + \left[(150W - 50W) * e^{-\left(t - t_D\right)/\tau} \right]$$

Where $f_C(t)$ is the value of f_C at time t, 50W and 150W are the steady-state values of f_C at 50W and 150W exercise and t_D and τ are respectively the delay and time constant for the response. This is the model used in Chapter 5.

The initial changes in f_{BR} and V_T were taken as the values of the breath with the maximum value for $\dot{V}_E$ in the first 3 breaths of 150 W exercise. The initial changes in P_{ET,CO_2}, P_{ET,O_2} and RER were taken as the mean values over the first 3 breaths of 150 W exercise.

Steady-state responses to 150 W exercise: The steady-state responses of $\dot{V}_E$, V_T, f_{BR}, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, RER, P_{ET,CO_2}, P_{ET,O_2} and f_C to 150 W exercise in each test were taken as the mean value for the last 30 sec of the stage.

RESULTS:

The breath-by-breath data for the "NORM" and "HYPER" tests performed by subject "P" are presented in *Fig. 7.2* and *7.3* respectively. Unfortunately values of P_{E,O_2} and P_{E,CO_2} were lost for part of hyperventilation due to temporary disconnection of the analyser probes from the mixing box.

RESTING VALUES:

There were no significant differences between the resting values of f_C, $\dot{V}_E$ (BTPS), $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, V_T, f_{BR}, P_{ET,CO_2} and P_{ET,O_2} in the "NORM" and "HYPER" tests (See *Table 7.2*). The results of subject J were discarded as his resting $\dot{V}_E$ was higher than that seen during 50 W. In addition, his P_{ET,CO_2} only fell to 37 mmHg at the end of hyperventilation in the "HYPER" test.

	NORM	HYPER
f_C	71 ± 3	73 ± 4
$\dot{V}_E$	12.1 ± 0.9	12.7 ± 1.1
f_{BR}	13.0 ± 1.2	13.1 ± 1.2
V_T	1.01 ± 0.09	1.09 ± 0.18
P_{ET,CO_2}	37 ± 2	36 ± 2
P_{ET,O_2}	107 ± 6	108 ± 3
$\dot{V}_{O_2}$	0.42 ± 0.02	0.45 ± 0.02
$\dot{V}_{CO_2}$	0.35 ± 0.03	0.37 ± 0.03
RER	0.78 ± 0.02	0.74 ± 0.03

Table 7.2: Mean (± SE) resting data for the "NORM" and "HYPER" tests. n = 7. There were no significant difference between the values obtained for the two protocols. For explanation of symbols see text.

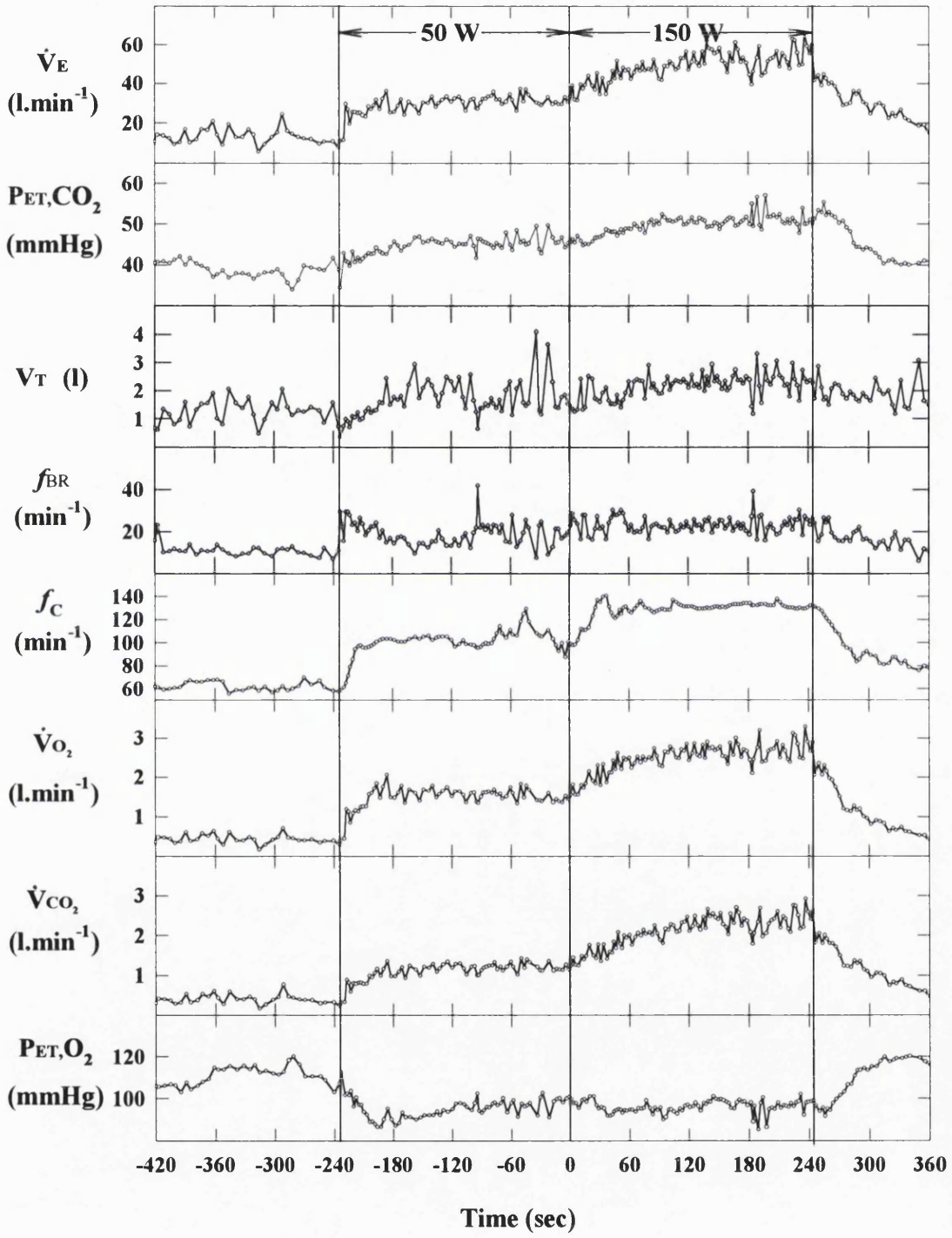


Figure 7.2: Breath-by-breath values of $\dot{V}E$, PET,CO_2, VT, fBR, f_C, $\dot{V}o_2$, $\dot{V}co_2$ and PET,O_2 throughout test "NORM" performed by subject P. Time 0 represents the increase in workload, other lines represent the start and finish of exercise respectively.

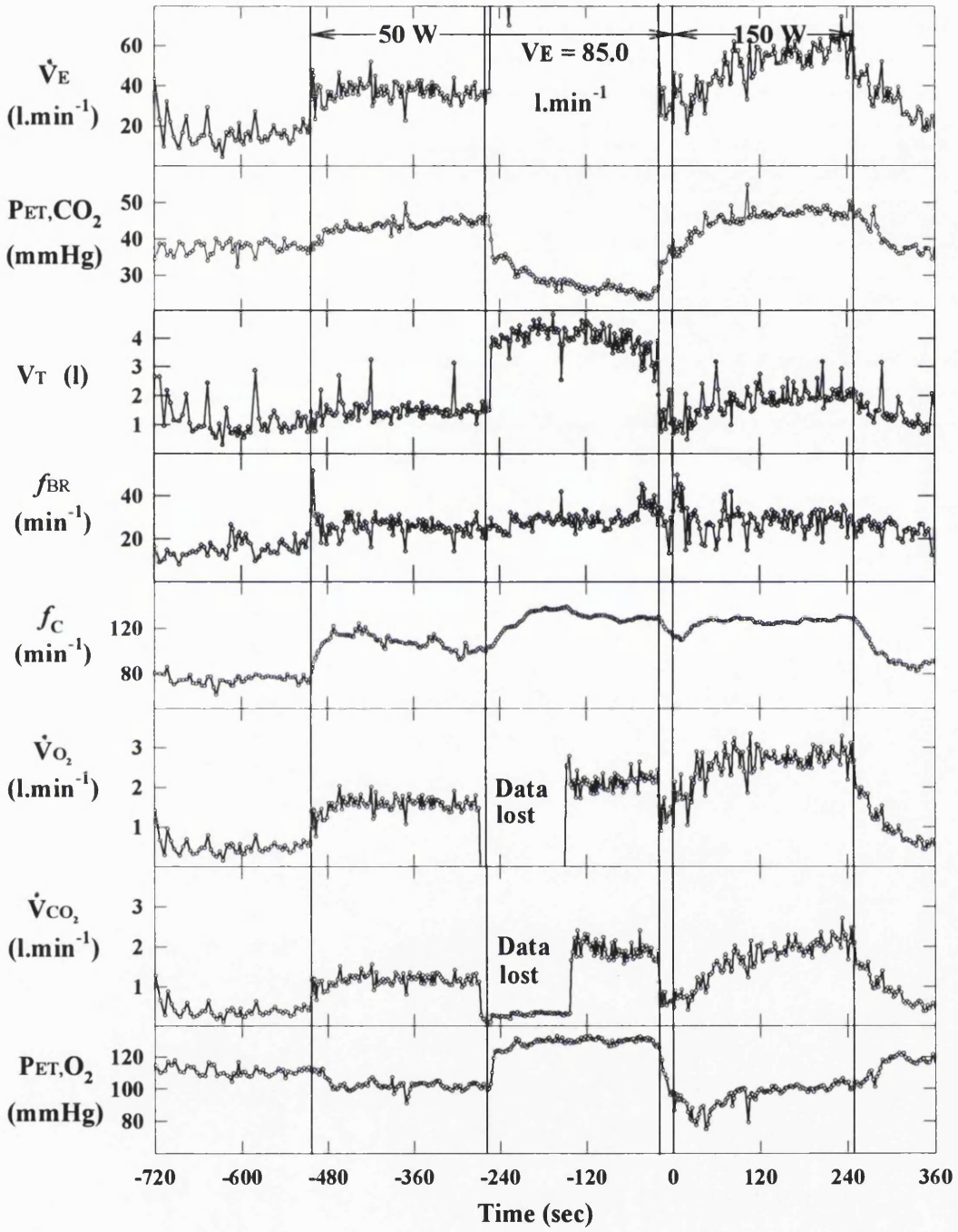


Figure 7.3: Breath-by-breath values of $\dot{V}_E$, P_{ET,CO_2}, V_T, f_{BR}, f_C, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and P_{ET,O_2} throughout test "HYPER" performed by subject P. Time 0 represents the increase in workload, other lines represent the beginning of exercise, the start and finish of hyperventilation and the end of exercise respectively.

INITIAL RESPONSES TO 50 W EXERCISE:

The initial ventilatory and pulmonary gas exchange responses to the onset of 50 W exercise were similar in the two tests (See *Table 7.3*, *Figs. 7.2, 7.3* and *7.4*) Attempts were made to model the ventilatory and pulmonary gas exchange responses to 50 W exercise using MODEL 3 and MODEL 2 respectively. These were not successful as the magnitude of the initial responses to the onset of exercise were of a similar magnitude to the steady-state response.

The individual results were interpolated over 1 sec intervals and time-averaged, so allowing greater definition of the underlying responses (See *Fig. 7.4*).

There was no evidence of an abrupt increase in f_C in either the individual results for each subject or the interpolated data for each protocol. A notch in an otherwise smooth monoexponential increase in f_C was seen in 2/6 subjects in the "NORM" tests and in 3/6 subjects in the "HYPER" tests (See *Fig. 7.2*, but not *Figs. 7.3* or *7.4*). The value of f_C at the notch was taken to be the magnitude of the initial response to the onset of exercise.

It was apparent from the individual data and the interpolated data that the onset of 50 W exercise was associated with abrupt increases in $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ in both the "NORM" and "HYPER" tests. This increase was transient for $\dot{V}E$ in the majority of the tests, falling to a plateau (See *Figs. 7.3* and *7.4* but not *7.2*). On the other hand, there was no evidence of a transient initial response for $\dot{V}O_2$ in either test (See *Figs. 7.2, 7.3* and *7.5*). The profile of the initial response for $\dot{V}CO_2$ was intermediate, falling between that of $\dot{V}E$ and $\dot{V}O_2$ (See *Fig. 7.4*).

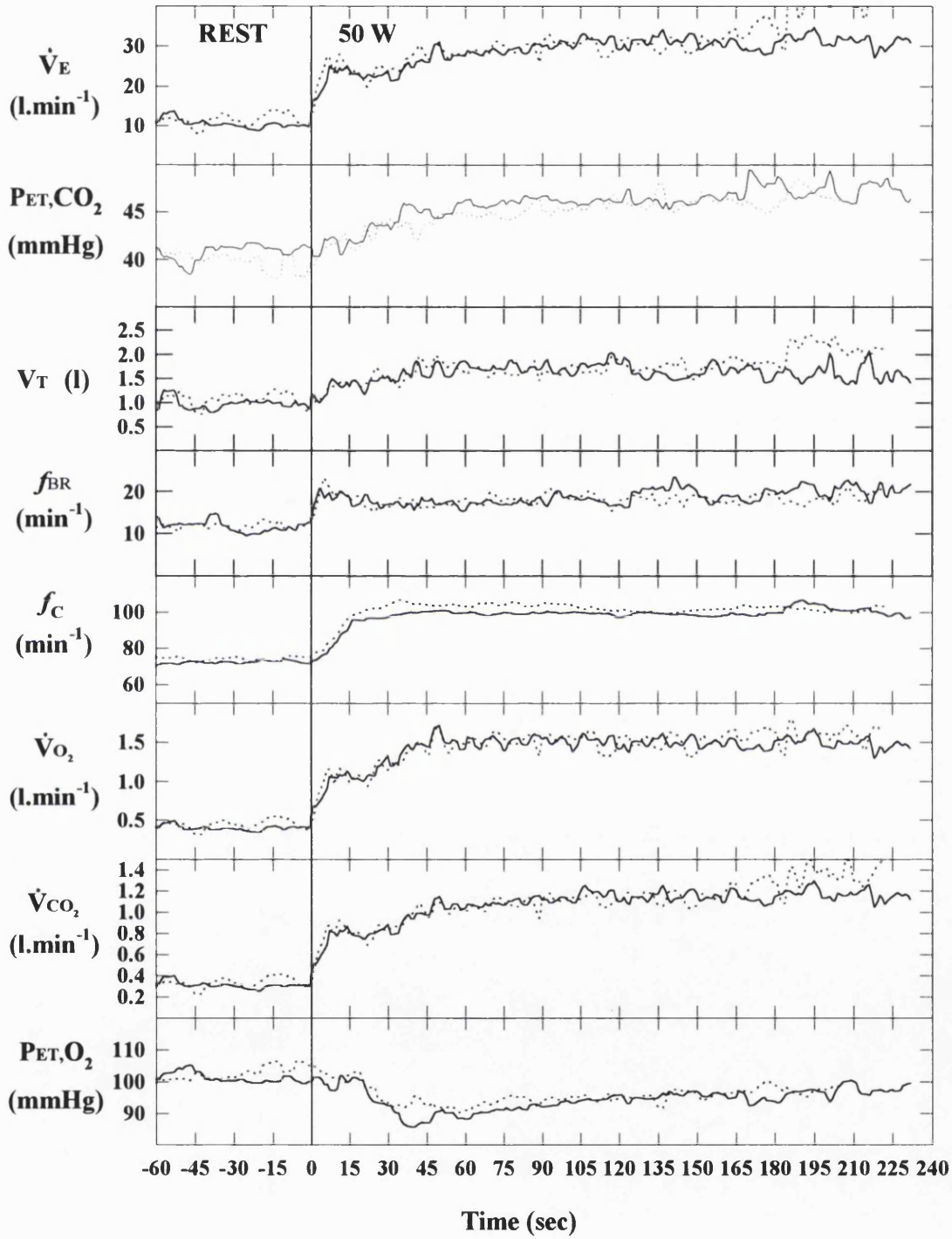


Figure 7.4: Sample mean values of $\dot{V}E$, PET,CO_2, VT, fBR, f_C, $\dot{V}o_2$, $\dot{V}co_2$ and PET,O_2 for 1 min prior to and approx. 4 min following the onset of 50 W exercise in the "NORM" (Solid lines) and "HYPER" (Dotted lines) tests. Individual subject data were interpolated over 1 sec intervals time aligned and averaged to produce a mean response. Time 0 represents the start of exercise; n = 5 for PET,CO_2 and PET,O_2, n = 6 for f_C, n = 7 for remainder.

	NORM	HYPER
f_C	106 ± 6*	111 ± 1
$\dot{V}_E$	28.33 ± 1.73*	32.19 ± 3.11*
f_{BR}	19.79 ± 2.31*	21.26 ± 2.22*
V_T	1.55 ± 1.24*	1.48 ± 0.17
P_{ET,CO_2}	38.8 ± 1.9	37.5 ± 2.9
P_{ET,O_2}	107.4 ± 5.5	100.1 ± 4.5
$\dot{V}_{O_2}$	1.21 ± 0.07*	1.34 ± 0.06*
$\dot{V}_{CO_2}$	0.94 ± 0.07*	0.98 ± 0.06*
RER	0.78 ± 0.01	0.76 ± 0.02

Table 7.3: Initial responses to the onset of 50 W exercise. n = 7. There were no significant difference between the values obtained for the two protocols. * denotes values are significantly ($p < 0.05$) different from resting values. For explanation of symbols see text.

Interpolated values of P_{ET,CO_2}, $P_{ET,O}$ and RER did not change from resting levels appreciably in either test, demonstrating that the transient nature of the initial rise in $\dot{V}_E$ did not involve hyperventilation (See *Table 7.3* and *Fig. 7.4*).

The pattern of changes in V_T and f_{BR} responsible for the initial increase in $\dot{V}_E$ varied between subjects and between tests. In the "NORM" tests, 2/7 subjects increased f_{BR} only, 2/7 increased V_T only and 3/7 increased both f_{BR} and V_T. In the "HYPER" tests, 2/7 subjects increased f_{BR} only, 1/7 subjects increased V_T only and 4/7 subjects increased both f_{BR} and V_T. The mean increase in f_{BR} was 172 ± 20 % in the "NORM" tests and 183 ± 28 % in the "HYPER" tests ("NORM" vs. "HYPER"; *NS*), while the mean increase in V_T was 160 ± 23 % in the "NORM" tests and 156 ± 25 % in the "HYPER" tests ("NORM" vs. "HYPER"; *NS*).

It was not possible to state categorically that the steady-state had been reached by the end of the 50 W exercise stage, due to the inability to effectively model the cardiorespiratory and pulmonary gas exchange responses to 50 W exercise. The interpolated data would suggest, however, that the steady-state was reached by 60 sec

of exercise for $\dot{V}O_2$, 120 sec of exercise for $\dot{V}CO_2$ and 120 sec of exercise for $\dot{V}E$ in the "NORM" tests. In the "HYPER" tests, it would appear that the steady-state was reached by 60 sec of exercise for $\dot{V}O_2$, 90 sec of exercise for $\dot{V}CO_2$ and 90 sec of exercise for VE (See *Fig. 7.4*).

Steady-state values for $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, RER, fC, fBR, VT, P_{ET,CO_2} and P_{ET,O_2} were similar in the "NORM" and "HYPER" tests (See *Table 7.4*, *Figs. 7.2, 7.3* and *7.4*).

	NORM	HYPER
fC	96 ± 3	98 ± 4
$\dot{V}E$	31.7 ± 0.9	31.4 ± 1.5
fBR	21.4 ± 1.6	19.7 ± 1.7
VT	1.56 ± 0.08	1.67 ± 0.11
P_{ET,CO_2}	43 ± 2	41 ± 2
P_{ET,O_2}	103 ± 5	96 ± 4
$\dot{V}O_2$	1.44 ± 0.04	1.36 ± 0.11
$\dot{V}CO_2$	1.17 ± 0.03	1.11 ± 0.09
RER	0.79 ± 0.02	0.78 ± 0.03
$fPED$	72.8 ± 1.1	72.9 ± 1.3

Table 7.4: Mean (± S.E.) steady-state responses to 50 W exercise in both tests. n = 7. There were no significant difference between the values obtained for the two protocols. For explanation of symbols see text.

HYPERVENTILATION:

The hyperventilation period lasted for 189 ± 21 sec (Mean ± S.E.). During the hyperventilation period, $\dot{V}E$ was increased by a factor of 3.0 ± 0.2 over the normal ventilatory response to 50 W exercise (See *Table 7.5*). This was achieved by increasing VT by a factor of 2.5 ± 0.2 and an increase in fBR by a factor of 1.6 ± 0.1.

By the end of the hyperventilation period, P_{ET,CO_2} had fallen to below 25 mmHg in 7 of the 12 subjects and was below 30 mmHg for all but 2 subjects (See *Table 7.5*). These 2 (subjects C and S) were therefore excluded from the analysis. Pa,CO_2 may

well be lower than this, due to the increase in the slope of the plateau phase of the P_{E,CO_2} profile. The formula of Jones et al. (1979) has not been validated under such conditions, therefore no attempt has been made to estimate Pa,CO_2 at this time.

	HYPER
f_C	120 ± 5*
$\dot{V}_E$	97.0 ± 6.7*
f_{BR}	24.9 ± 2.9*
V_T	4.15 ± 0.30*
P_{ET,CO_2}	25 ± 2*
P_{ET,O_2}	126 ± 6*
$\dot{V}_{O_2}$	2.43 ± 0.17*
$\dot{V}_{CO_2}$	2.27 ± 0.11*
RER	0.93 ± 0.07*
f_{PED}	80.8 ± 3.6*

Table 7.5: Pooled values for hyperventilation stage. * denotes hyperventilation values are significantly ($p < 0.05$) different from steady-state 50 W values. Values represent means ± S.E., n = 7. See text for explanation of symbols.

As discussed in Chapter 4, the increase in $\dot{V}_E$ necessary to reduce P_{ET,CO_2} to this level is associated with significant increases in f_{PED}, f_C, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and P_{ET,O_2}. The results obtained here are consistent with those described in that Chapter (See *Tables 7.5* and *4.3*).

POST-HYPERVENTILATION:

The duration of the post-hyperventilation period prior to the increase in workload was 22.0 ± 1.9 sec (mean ± S.E.) This is within the ideal period for increasing workload identified in Chapter 4.

Subject 4 continued to hyperventilate following the end of the hyperventilation period.

This was similar to his responses described in Chapter 4, therefore his data were not included in the analysis. Data from subject R were rejected for similar reasons.

	POST-HYPER
f_C	113 ± 4*
$\dot{V}_E$	23.1 ± 4.3
f_{BR}	18.6 ± 1.48
V_T	1.35 ± 0.29
P_{ET,CO_2}	33 ± 3*
P_{ET,O_2}	100 ± 5
$\dot{V}_{O_2}$	1.20 ± 0.16
$\dot{V}_{CO_2}$	0.71 ± 0.15*
RER	0.63 ± 0.07
f_{PED}	73.3 ± 1.9

Table 7.6: Responses following hyperventilation just prior to the increase in workload. Values are means ± S.E. (n = 7), * denotes a significant ($p < 0.05$) difference between steady-state 50 W and post-hyperventilation values. See text for explanation of symbols.

In the remaining 7 subjects, $\dot{V}_E$ had fallen to close to normal 50 W levels (See *Table 7.6*) just prior to the increase in workload. $\dot{V}_{CO_2}$ and P_{ET,CO_2} were significantly below the steady-state 50 W values (See *Table 7.6*), although P_{ET,CO_2} had risen significantly from hyperventilation levels (See *Figs. 7.3* and *7.5*).

$\dot{V}_{O_2}$ and P_{ET,O_2} were not significantly different from steady-state 50 W values (See *Table 7.6*), although P_{ET,O_2} was falling rapidly following hyperventilation (See *Figs. 7.3* and *7.5*).

f_C was still significantly raised above normal 50 W levels (See *Table 7.6*, *Figs. 7.3* and *7.5*), but as mentioned in Chapter 4, this was unavoidable if the ideal conditions of normal V_E and low P_{ET,CO_2} were to be achieved.

THE EARLY RESPONSE TO A STEP-INCREASE IN WORKLOAD:

Individual data for $\dot{V}E$, $\dot{V}o_2$, $\dot{V}co_2$, RER, fC, fBR, VT, PET,CO_2 and PET,O_2 were interpolated over 1 sec intervals, time aligned and averaged. The resultant mean responses are presented in *Fig. 7.5*.

$\dot{V}o_2$, $\dot{V}co_2$ and $\dot{V}E$: The respiratory and pulmonary gas exchange responses to the abrupt transition from 50 W to 150 W exercise were initially modelled using MODEL 4. It was not possible to model the Vco_2 data for the "NORM" test performed by subject W or the Vo_2 data for the "HYPER" test performed by subject W due to loss of some data during the tests. This model provided a reasonable fit to the changes in Vo_2 and Vco_2 seen in all of the "NORM" tests and to the changes in VE seen in 4 of the subjects (See *Fig. 7.6*). 3 subjects showed evidence of an abrupt increase in VE in conjunction with the increase in workload (See *Fig. 7.7*).

The mean (± S.E) values for τ_1, t_{D1} and the proportion of the total response attributable to the initial increase (A_1/A_2) obtained using MODEL 4 are presented in *Table 7.7*. The time constants for the initial response to the increase in workload (τ_1) were less than 1 sec for 4/7 of the $\dot{V}o_2$ responses, 2/7 of the $\dot{V}co_2$ responses and 4/6 of the $\dot{V}E$ responses.

The ventilatory and pulmonary gas exchange responses to the abrupt transition from 50 W to 150 W exercise in the "HYPER" tests were also modelled using MODEL 4, the results of which are presented in *Table 7.8*. A satisfactory fit to the ventilatory and pulmonary gas exchange responses to the increase in workload seen in subject Q could not be achieved using MODEL 4. In addition, τ_1 was less than 1.0 sec for 2/5 of the $\dot{V}o_2$ responses, 3/6 of the $\dot{V}co_2$ responses and 4/6 of the $\dot{V}E$ responses.

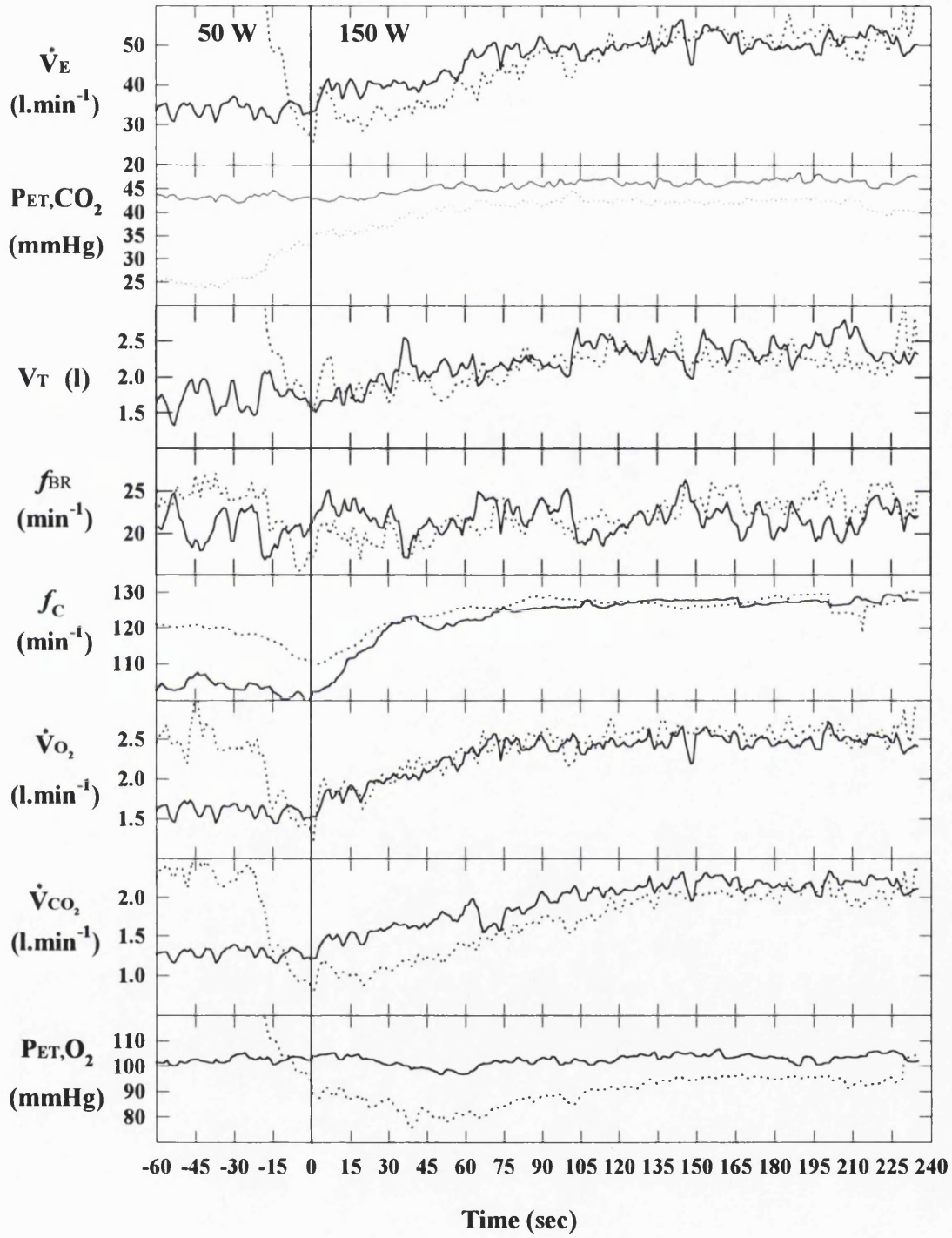


Figure 7.5: Sample mean values of $\dot{V}E$, P_{ET,CO_2}, V_T, f_{BR}, f_C, $\dot{V}o_2$, $\dot{V}co_2$ and P_{ET,O_2} for 1 min prior to and approx. 4 min following the transition from 50 W to 150 W exercise in the "NORM" (Solid lines) and "HYPER" (Dotted lines) tests. Individual subject data were interpolated over 1 sec intervals time aligned and averaged to produce a mean response. Time 0 represents the onset of 150 W exercise; n = 4 for f_C, n = 5 for P_{ET,CO_2} and P_{ET,O_2}. n = 7 for remainder.

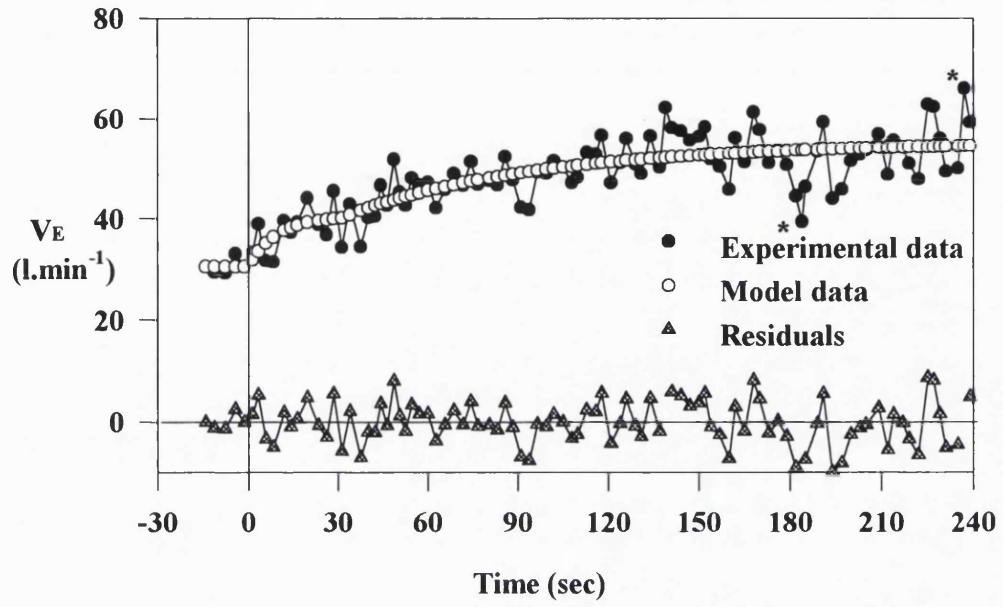


Figure 7.6: Example of modelling of the ventilatory response to the abrupt increase in workload in test "NORM." Test was performed by subject P. Data were breath-by-breath, model used was MODEL 4. Pattern of residuals reveals that the model accurately described the experimental data. τ_1 = 9.3 sec, t_{D1} = 0.0 sec, τ_2 = 67.2 sec, t_{D2} = 31.2 sec, $\Sigma(Res^2)$ = 1679. * denotes breath excluded from modelling.

	τ_1	t_{D1}	A_1/A_2 (%)	$\Sigma(Res^2)$
$\dot{V}O_2$	3.98 ± 1.89	0.05 ± 0.04	33.7 ± 5.0	2.49 ± 0.31
$\dot{V}CO_2$	5.06 ± 1.79	0.06 ± 0.04	27.6 ± 4.0	2.35 ± 0.26
$\dot{V}E$	4.41 ± 1.87	0.50 ± 0.16	32.5 ± 4.0	1864 ± 578

Table 7.7: Time constant (τ_1), delays (t_{D1}) and relative amplitudes (A_1/A_2) for the initial ventilatory and pulmonary gas exchange responses to an increase in workload in test "NORM", and the sum of the squares of the residuals for all subjects (n = 7).

The ventilatory and pulmonary gas exchange responses to the abrupt transition from 50 W to 150 W seen in both the "NORM" and the "HYPER" tests were then modelled using MODEL 3, the results of which are presented in *Tables 7.9* and *7.10*. $\Sigma(Res^2)$ was significantly lower ($p < 0.05$) for MODEL 3 than for MODEL 4 for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$. Furthermore, the initial response (See Methods section for definition) was greater the subsequent plateau (See Methods section for definition) in the "NORM"

tests in 7/7 subjects for $\dot{V}O_2$, 6/7 subjects for $\dot{V}CO_2$ and 7/7 subjects for $\dot{V}E$. In the "HYPER" tests, the initial response was greater than the subsequent plateau in 5/6 subjects for $\dot{V}O_2$, 6/7 subjects for $\dot{V}CO_2$ and 6/7 subjects for $\dot{V}E$ (See *Fig.7.8* for an example).

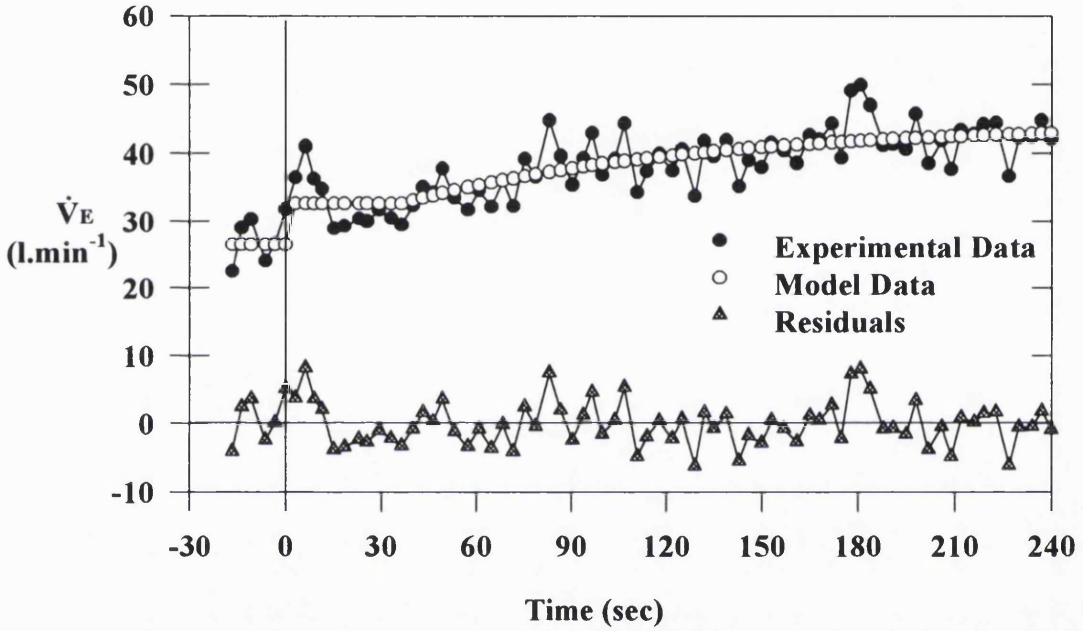


Figure 7.7: Another example of modelling the ventilatory response to an abrupt increase in workload from 50 W to 150 W. Test was test "NORM" performed by subject K, model was MODEL 4. Time 0 represents the change in workload. Pattern of residuals clearly demonstrate that MODEL 4 did not accurately represent the profile of the initial ventilatory response. $\tau_1 = 0.1$ sec, $t_{D1} = 0.6$ sec, $\tau_2 = 90.1$ sec, $t_{D2} = 36.5$ sec, $\Sigma(Res^2) = 753$.

	τ_1	t_{D1}	A_1/A_2 (%)	$\Sigma(Res^2)$
$\dot{V}O_2$	2.07 ± 0.86	0.05 ± 0.01	53.3 ± 6.0	4.07 ± 1.4
$\dot{V}CO_2$	2.82 ± 1.52	0.06 ± 0.01	25.7 ± 6.0	2.16 ± 0.41
$\dot{V}E$	1.58 ± 1.07	0.45 ± 0.24	4.7 ± 30.0	2735 ± 836

Table 7.8: Time constant (τ_1), delays (t_{D1}) and relative amplitudes for the initial ventilatory and pulmonary gas exchange responses to an increase in workload in test "HYPER", and the sum of the squares of the residuals for all subjects (For n, see text).

These results demonstrate the abrupt nature of the initial increases in $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$. The magnitude of the initial increases in $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ were not affected by prior hyperventilation (See Tables *7.9, 7.10, Figs. 7.2, 7.3* and *7.5*), but the magnitude of the subsequent plateau was reduced following hyperventilation for $\dot{V}CO_2$ and $\dot{V}E$ (See Tables *7.9, 7.10, Figs. 7.2, 7.3* and *7.5*). The magnitude of the subsequent plateau for $\dot{V}O_2$ was not affected by prior hyperventilation (See Tables *7.9, 7.10, Figs. 7.2, 7.3* and *7.5*).

	Initial Response	Plateau	$\Sigma(Res^2)$
$\dot{V}O_2$	1.96 ± 0.12*	1.69 ± 0.06	2.32 ± 0.3
$\dot{V}CO_2$	1.57 ± 0.07*	1.39 ± 0.05#	2.33 ± 0.31
$\dot{V}E$	42.85 ± 2.2*	36.81 ± 1.51#	1720 ± 558

Table 7.9: Mean (± S.E.) results of modelling the initial ventilatory and pulmonary gas exchange responses to the increase in workload in the "NORM" tests and the sum of the squares of the residuals. n = 7 for $\dot{V}O_2$ and $\dot{V}E$, n = 6 for $\dot{V}CO_2$. * denoted initial response significantly ($p < 0.05$) different from subsequent plateau; # denotes values are significantly ($p < 0.05$) different from "HYPER" test.

	Initial Response	Plateau	$\Sigma(Res^2)$
$\dot{V}O_2$	2.20 ± 0.12	1.88 ± 0.16	3.47 ± 0.66
$\dot{V}CO_2$	1.30 ± 0.16*	1.0 ± 0.1	2.14 ± 0.35
$\dot{V}E$	43.2 ± 4.97*	29.57 ± 2.29	2487 ± 852

Table 7.10: Mean (± S.E.) results of modelling the initial ventilatory and pulmonary gas exchange responses to the increase in workload in the "HYPER" tests and the sum of the squares of the residuals. n = 7 for $\dot{V}CO_2$ and $\dot{V}E$, n = 6 for $\dot{V}O_2$. * denotes initial response significantly ($p < 0.05$) different from subsequent plateau.

fC: Meaningful analysis of the changes in fC in response to the increase in workload was not possible in 3 subjects: the ECG of one subject was excessively affected by movement artefact in both tests, while the difference between fC at the start and end of the 150 W stage in the "HYPER" test was too small in the other two subjects. There was no evidence of an initial response to exercise in any of the tests (See *Figs. 7.2* and *7.3*).

$P_{ET}CO_2$, $P_{ET}O_2$ and RER: In the "NORM" tests, there was no appreciable change in $P_{ET}CO_2$, $P_{ET}O_2$ or RER over the first 15 sec of 150 W exercise (See *Table 7.11*), demonstrating that the abrupt increase in VE was in proportion with pulmonary gas exchange demands. In the "HYPER" tests, $P_{ET}O_2$ and RER fell rapidly and $P_{ET}CO_2$ rose rapidly following the abrupt transition from 50 W to 150 W exercise (See *Table 7.11*). This was an extension of the trends seen just prior to the change in workload (See *Fig. 7.5*).

As a result of the pattern of response to the abrupt transition from 50 W to 150 W exercise seen in $P_{ET}CO_2$, $P_{ET}O_2$ and RER in the "HYPER" test (See *Fig. 7.6*), it was impossible to determine the onset of the Phase 2 response according to the criteria used in Chapter 5.

	NORM	HYPER
VT	1.84 ± 0.18	2.2 ± 0.49
*f*BR	25.04 ± 1.46	22.42 ± 3.68
$P_{ET}O_2$	104.8 ± 5.6*	88.9 ± 6.2
$P_{ET}CO_2$	42.6 ± 2.4*	35.8 ± 3.1
RER	0.83 ± 0.03*	0.57 ± 0.06

Table 7.11: Initial responses to an abrupt transition from 50 W to 150 W workload in the "NORM" and "HYPER" tests. See text for explanation of symbols and n. * denotes significant ($p < 0.05$) difference between "NORM" and "HYPER" tests.

VT and *f*BR: The changes in VT and *f*BR on increasing the workload are variable between subjects, some electing to achieve the necessary changes in VE by altering VT, others by changes in *f*BR, or a mixture of both. Between test protocols, there was a tendency for the initial ventilatory response to the abrupt transition from 50 W to 150 W to be achieved by an abrupt, transient increase in *f*BR with little change in VT in the "NORM" tests (See *Table 7.11*). In the "HYPER" tests, the abrupt transition from 50 W to 150 W exercise was associated with an abrupt, transient increase in both *f*BR and VT.

LATER RESPONSES TO A STEP-INCREASE IN WORKLOAD:

$\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$: The time constants and delays which describe the later ventilatory and pulmonary gas exchange responses to the abrupt transition from 50 W to 150 W exercise are presented in *Table 7.12*. Surprisingly, there was no significant difference between the time constants or the delays in the "NORM" and "HYPER" tests for $\dot{V}O_2$, $\dot{V}CO_2$ or $\dot{V}E$. There was, however, marked variability between values for t_{D2} and τ_2 both between subjects and between protocols for all 3 variables. The profiles of the interpolated data for both tests would suggest that despite the lack of significance, the time course of the rises in $\dot{V}E$ and $\dot{V}CO_2$ were quicker in the "NORM" tests than in the "HYPER" test (See *Fig. 7.5*), while the time course of the rise in $\dot{V}O_2$ was similar in both tests.

		NORM	HYPER
$\dot{V}O_2$	t_{D2}	18.71 ± 2.89	20.7 ± 0.81
	τ_2	36.45 ± 3.72	26.95 ± 4.88
$\dot{V}CO_2$	t_D	36.45 ± 4.8	31.06 ± 6.39
	τ_2	41.52 ± 3.63	52.06 ± 6.82
$\dot{V}E$	t_{D2}	30.62 ± 5.42	35.7 ± 6.97
	τ_2	43.64 ± 8.19	53.29 ± 6.8

Table 7.12: Mean (± S.E.) time constants and delays in onset of the later responses to the abrupt increase in workload from 50 W to 150 W for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$. See text for n and symbols.

fC: The kinetics of the heart rate response to the abrupt transition from 50 W to 150 W were similar in the "NORM" and "HYPER" tests (See *Table 7.13*).

	t_D	τ
NORM	5.5 ± 2.7	28.1 ± 5.5
HYPER	3.8 ± 3.9	28.8 ± 11.4

Table 7.13: Mean (± S.E.) time constants(t_D) and delays (τ) in onset of the later responses to the abrupt increase in workload from 50 W to 150 W for *fC*. See text for n and symbols.

QUASI STEADY-STATE RESPONSES TO 150 W EXERCISE:

The time to steady-state can be taken to be $(4 \times \tau_2) + t_{D2}$. These times were calculated and are presented in *Table 7.14*. 7/7 subjects had reached their steady-state response for $\dot{V}O_2$ in the "NORM" tests and 5/6 subjects had reached their steady-state for $\dot{V}O_2$ in the "HYPER" tests. These ratios fell to 3/7 in the "NORM" tests and 2/7 in the "HYPER" tests for $\dot{V}E$ and 4/6 in the "NORM" tests and 0/7 in the "HYPER" tests for $\dot{V}CO_2$. The steady-state response for *fC* was reached in all the tests in which analysis was possible.

	NORM	HYPER
$\dot{V}E$	211.0 ± 30.0	248.9 ± 29.8
$\dot{V}O_2$	164.5 ± 13.8	128.5 ± 21.7
$\dot{V}CO_2$	196.7 ± 11.6	239.312.2

Table 7.14: Mean (± S.E.) times to attain the steady-state response to 150 W exercise for $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ in the "NORM" and "HYPER" tests. See text for n and explanation of symbols. * denotes significant ($p < 0.05$) difference between "NORM" and "HYPER" test results.

As a result, the mean responses over the last 30 sec of exercise are to be referred to as the quasi steady-state responses to 150 W exercise. These data are presented in *Table 7.15*.

These data demonstrate that the mean values of $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ were close the their steady state values in the "NORM" and "HYPER" tests, but replenishment of the CO_2 stores was not complete as P_{ET,CO_2} and RER were both significantly lower in the "HYPER" tests than in the "NORM" tests.

	NORM	HYPER
f_C	130 ± 3	131 ± 4
$\dot{V}E$	53.49 ± 2.43	53.59 ± 4.03
f_{BR}	22.74 ± 1.05	24.27 ± 1.76
VT	2.40 ± 0.06	2.26 ± 0.12
P_{ET,CO_2}	46.4 ± 2.4	42.4 ± 2.8*
P_{ET,O_2}	103.7 ± 4.7	96.1 ± 4.4
$\dot{V}O_2$	2.53 ± 0.08	2.60 ± 0.12
$\dot{V}CO_2$	2.24 ± 0.08	2.10 ± 0.14
RER	0.89 ± 0.02	0.80 ± 0.02*
f_{PED}	73.9 ± 1.1	73.1 ± 1.4

Table 7.15: Mean quasi steady-state responses to 150 W exercise in the "NORM" and "HYPER" tests. For n and explanation of symbols see text. * denotes significant ($p < 0.05$) difference between "NORM" and "HYPER" values.

DISCUSSION:

SINGLE REPETITIONS VS. MULTIPLE REPETITIONS:

The arguments for and against multiple repetitions per subject of each workload transition were discussed in Chapter 5. A stronger case could be made for the performance of multiple repetitions in these experiments on the grounds that the magnitude of the initial ventilatory and pulmonary gas exchange responses are much smaller than those reported in Chapter 5. Given the results of Lamarra (1987), that the effective noise variance for $\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ is independent of workload, the greater signal to noise ratio will mean that the accuracy of the modelling described in this Chapter will be compromised to some extent.

MODEL CHOICE:

The 2 models chosen to describe the profile of the ventilatory and pulmonary gas exchange responses to the abrupt increase in workload were MODEL 3 and MODEL 4.

MODEL 4 was designed to describe the traditional profile of the ventilatory and pulmonary gas exchange responses to an abrupt increase in workload. It consisted of an initial response described by a monoexponential increase to a plateau with negligible time delay and a time constant of around 5 sec. This was followed some 15 to 30 sec later by a second increase, also described by a monoexponential rise, to the steady-state.

MODEL 3 was also used to describe the ventilatory and pulmonary gas exchange responses to the increase in workload. Similar to its use in Chapter 5, MODEL 3 was

parsimonious in its design. Its description of the initial profiles of the ventilatory and pulmonary gas exchange responses to the increase in workload was limited to: (i) the increases in ventilatory and pulmonary gas exchange variables in conjunction with the changes in workload were abrupt and (ii) The initial, abrupt increase in the ventilatory and pulmonary gas exchange variables was transient in nature, falling to a plateau before the onset of the later response.

This is similar to the use of the model in Chapter 5. MODEL 3 does not attempt to describe the profile of the transition from the initial, abrupt increase in the ventilatory and pulmonary gas exchange responses to the subsequent plateau.

MODEL 2 was not used to describe the ventilatory response to the abrupt increase in workload on the grounds of the results reported in Chapter 5. MODEL 2 was also not considered to be the model of choice for the pulmonary gas exchange responses to the abrupt increase in workload primarily because the profiles of the initial responses were obviously transient in the majority of tests. This profile is best described by MODEL 3. The implications and possible causes of this transient increase in ventilatory and pulmonary gas exchange variables will be discussed later.

CHOICE OF WORKLOADS:

To perform this study, 2 workloads were required, one of low intensity and one of moderate intensity. 50 W was chosen over either 25 W or unloaded pedalling on the grounds of feedback from the subjects who performed the study reported in Chapter 3. They stated that 25 W exercise was uncomfortable, commenting that "Their legs flapped around" or that "There was nothing to push against". Similar comments were elicited by 50 W exercise at 90 rpm. As such, there was obviously a level of discomfort associated with these low levels of exercise in this particular subject group. It was therefore seemed sensible to use 50 W as the low-intensity workload for this study.

The results obtained in the study reported in Chapter 3 also intimated that for this group of subjects, 200 W exercise was close to their ventilatory anaerobic thresholds. To avoid any risk of exceeding the ventilatory anaerobic threshold in these tests, 150W was used as the upper workload. This was also the same workload as was used in Chapter 5.

50 W EXERCISE:

Initial responses: The profile of the on-transient for the ventilatory response to the abrupt transition from rest to 50 W exercise followed a similar pattern to that reported in Chapter 3 for the transition from rest to 50 W exercise and in Chapter 5 for the transition from rest to 150 W exercise.

It was not possible to apply MODEL 4 to the individual ventilatory responses to 50 W exercise due to the similarity between the initial and steady-state responses, but the transient nature of the initial responses was clearly visible when the individual data were interpolated over 1 sec intervals and time-averaged for the subject group (See *Fig. 7.6*).

The profile of the pulmonary gas exchange responses to the abrupt transition from rest to 50 W exercise differed from that described in Chapter 3 (There was no breath-by-breath pulmonary gas exchange data available for the study reported in Chapter 3). The profile of the initial pulmonary gas exchange response to the onset of 150 W exercise reported in Chapter 5 was an abrupt increase to a plateau. This was consistent with the profile reported by Whipp et al., (1982). It was not possible to apply either MODEL 3 or MODEL 4 to the pulmonary gas exchange responses to the onset of 50 W exercise for the same reason as for $\dot{V}E$, but the transient nature of the initial increases in $\dot{V}o_2$ and $\dot{V}co_2$ in response to the onset of exercise was clearly apparent in

the group mean interpolated data for both the "NORM" and "HYPER" tests (*Fig. 7.4*).

There are 3 possible mechanisms which may account for the transient nature of the initial pulmonary gas exchange responses to the onset of 50 W exercise.

Firstly, it is possible that the initial peak in $\dot{V}O_2$ and $\dot{V}O_2$ may be an artefact associated with the monitoring of pulmonary gas exchange responses at the mouth The breath-by-breath measurement of pulmonary gas exchange variables by the exercise testing program predicts $\dot{V}I$ from $\dot{V}E$ using a N_2 correction factor. The accuracy of these calculations can be affected by changes in functional residual capacity (FRC: Wessel et al., 1979). FRC has been shown to be lower during light and moderate exercise than at rest (Ward et al., 1979; Babb & Rodarte, 1991; Lind & Hesser, 1984; Lind, 1984; Linnarsson, 1974), While Ward et al. (1979) have reported FRC to fall (By up to 0.8 l in their subjects) over the first 10 sec of 100 W exercise. It should be stressed that values of $\dot{V}O_2$ and $\dot{V}CO_2$ measured at the mouth are not affected by the absolute value of FRC *per se*, but rather by the rate of change in FRC.

A rapid fall in FRC in conjunction with the onset of exercise in these tests would result in an overestimation of $\dot{V}CO_2$ and an underestimation of $\dot{V}O_2$ measured at the mouth. The increase in VT seen in conjunction with the onset of exercise would suggest there is some credence to this theory, in that a reduction in FRC without a concomitant increase in VT would be unlikely. Linnarsson (1974) reported the initial ventilatory response to the onset of exercise to be mediated entirely by in increase in VT, itself due to a fall in FRC. In these results, however, the increase in VT represented only a portion of the initial increase in $\dot{V}E$ in response to exercise.

Secondly, the initial phase of pulmonary gas exchange responses to the transition from rest to exercise has been termed the cardiodynamic phase (Whipp & Ward, 1982; Whipp et al., 1982). During this phase of the response, it is assumed that the gas

tensions of blood entering the pulmonary capillaries remain constant and the abrupt increases in $\dot{V}o_2$ and $\dot{V}co_2$ associated with the onset of exercise are entirely mediated by an increase in $\dot{Q}_P$.

The change in $\dot{Q}$ associated with the onset of exercise has been measured (Cummin et al., 1986b; Loeppky et al., 1981; Toska & Eriksen, 1994). All report the initial increase in $\dot{Q}$ seen in response to the onset of low-intensity exercise to be transient in nature. Loeppky et al. (1981) and Cummin et al. (1986b) attribute this to the mobilisation of blood pooled in the muscles and central venous system. According to the theory of Whipp & Ward (1982), an abrupt, transient increase in $\dot{Q}_P$ during the initial, cardiodynamic phase of the pulmonary gas exchange responses to exercise would result in an abrupt, transient increase in $\dot{V}o_2$ and $\dot{V}co_2$.

Thirdly, the assumption of Whipp and Ward (1982), that gas tensions of blood entering the pulmonary circulation remains constant during the initial, cardiodynamic phase of the pulmonary gas exchange responses to the transition from rest to exercise has been challenged. Casaburi et al. (1989b) have measured changes in So_2 and Pco_2 in the pulmonary artery during the transition from rest to moderate intensity exercise. They reported So_2 to fall and Pco_2 to rise in the pulmonary artery after the onset of exercise with no discernible delay. They attributed this phenomenon to the ejection of pooled blood which is more hypoxic and hypercapnic from the viscera into the systemic circulation in conjunction with the onset of exercise. Such a change in blood gas tensions, if transient, would manifest itself as a transient rise in $\dot{V}o_2$ and $\dot{V}co_2$ at the onset of exercise.

Of these 3 possible mechanisms, it is unlikely that the transient nature of the initial pulmonary gas exchange responses to the onset of 50 W exercise was a result of either an abrupt fall in FRC or a transient change in gas tensions of blood entering the pulmonary circulation.

Ward et al. (1979) state that a rapid fall in FRC would have the effect of overestimating $\dot{V}co_2$ and underestimating $\dot{V}o_2$ at the mouth. As such, only the initial response to exercise for $\dot{V}co_2$ would demonstrate a transient overshoot. Indeed on this basis, a rapid fall in FRC would result in a transient undershoot in the initial response to exercise for $\dot{V}o_2$. In the results presented in this Chapter, the profile of the initial changes in both $\dot{V}o_2$ and $\dot{V}co_2$ is an abrupt, transient increase, falling to a plateau.

Casaburi et al. (1989b) state that although So_2 fell and Pco_2 rose in conjunction with the onset of exercise, these changes were to a plateau, sustained until the onset of a further change in pulmonary artery blood gas composition occurred some 15 to 20 sec after the onset of exercise (Presumably due to the arrival of blood from the exercising muscles).

The mechanism most likely to be responsible for the transient nature of the initial pulmonary gas exchange responses to the abrupt transition from rest to 50 W exercise is therefore a transient increase in $\dot{Q}_P$. The changes in $\dot{Q}_P$ seen on transition from rest to exercise also provide a possible explanation of the different profiles of the initial pulmonary gas exchange responses to the onset of 50 W exercise and the onset of 150 W exercise (See Chapter 5). Cummin et al. (1986b) reported $\dot{Q}_P$ to increase abruptly in conjunction with the onset of exercise performed at 0 W, 50 W, 100 W and 150 W. This abrupt increase was transient in nature during exercise performed at 0 W and 50 W, but was sustained during exercise performed at 100 W and 150 W until a further rise occurred at 15 to 20 sec of exercise.

Steady-state responses: All subjects had reached the steady-state by the end of the 50 W exercise stage in both the "NORM" and "HYPER" tests. This finding supports the results of Chapter 5 and Hagberg et al. (1980) that training speeds up the kinetics of the later cardiorespiratory and pulmonary gas exchange responses to exercise. The attainment of the steady-state means that the changes in $\dot{V}E$ and $\dot{V}co_2$ seen in response to the abrupt increase in workload in the "NORM" tests were not subject to

interference from continuing changes in body CO_2 stores resulting from the performance of 50 W exercise. The same is true of interpretation of the effects of hyperventilation on body CO_2 stores in the "HYPER" tests.

HYPERVENTILATION:

The efficacy of hyperventilation: The purpose of the hyperventilation period was to deplete body CO_2 stores. P_{ET,CO_2} was used as a measure of the extent to which CO_2 stores had been depleted. The hyperventilation protocol was not performed as well in this study as it was in the study described in Chapter 5. Of the 12 subjects who performed this study, 2 subjects were unable to achieve a level of $\dot{V}_E$ sufficient to lower P_{ET,CO_2} below 30 mmHg while only 3 subjects were able to lower their P_{ET,CO_2} to between 20 and 25 mmHg. The level of ventilation needed during the hyperventilation period could not be achieved by an increase in V_T alone: All subjects had to increase their f_{BR} above steady-state 50 W levels during the hyperventilation period. All subjects found difficult to achieve the target level of ventilation and needed constant encouragement during the hyperventilation period. This was unexpected as the level of ventilation was almost certainly well below their $\dot{V}_E$ at maximum exercise. It would appear that the appropriateness of the exercise hyperpnoea is strongly controlled in these subjects.

Effects of hyperventilation on *fc* and pulmonary gas exchange: The start of hyperventilation was associated with abrupt increases in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. These increases were transient, $\dot{V}_{O_2}$ falling more rapidly than $\dot{V}_{CO_2}$. The transient increase in $\dot{V}_{O_2}$ could have been a result of a reduction in FRC consequent to the increase in V_T (Wessel et al., 1979: Ward et al., 1979) or a transient increase in $\dot{Q}_P$ An increase in $\dot{Q}_P$ could occur as a result of an increase in venous return consequent to the greater changes in thoracic and abdominal pressures resulting from the increase in $\dot{V}_E$.

After the transient increase in $\dot{V}o_2$ at the start of hyperventilation, $\dot{V}o_2$ fell to a steady-state. Steady-state $\dot{V}o_2$ was significantly greater than the steady-state $\dot{V}o_2$ for 50 W exercise alone (by approximately 1 $l.min^{-1}$). This value is similar to that reported in Chapter 4 for the same hyperventilation protocol. The cause of the increase in steady-state $\dot{V}o_2$ was the increased work of breathing. This has already been discussed in Chapter 4.

The fall in $\dot{V}co_2$ following its initial increase at the start of hyperventilation was slower than for $\dot{V}o_2$. This reflects the influence of body CO_2 stores on the kinetics of $\dot{V}co_2$ measured at the mouth and is consistent with the results reported in Chapter 4.

RER increased initially at the start of hyperventilation, but by the end of the hyperventilation period had returned to close to normal 50 W exercise levels. This is similar to the results reported in Chapter 4 and demonstrates that changes in the body CO_2 stores were nearly complete.

fc rose to a new steady-state during the hyperventilation period. This is a result of the increased metabolic rate associated with the increased work of breathing and possibly may also be due the heamodynamic changes associated with the increased pumping action on the veins of the respiratory cycle. The increase in *fc* seen in this study was similar to that reported in Chapter 4.

The effect of hyperventilation on body CO_2 stores: The effects of hyperventilation on body CO_2 stores differs significantly depending on whether hyperventilation is performed at rest (i.e. Chapters 4 and 5) or during exercise (i.e. Chapter 4 and this Chapter). The effects of hyperventilation during exercise on body CO_2 stores have been discussed and contrasted with the effects of hyperventilation at rest on body CO_2 stores in Chapter 4.

To summarise, body CO_2 stores may be separated into 3 major compartments: a central compartment, a fast peripheral compartment and a slow peripheral compartment (Irving et al., 1983). At rest, the physiological correlates of the central, fast peripheral and slow peripheral compartments are thought to be CO_2 stored in the blood and lungs, CO_2 stored in tissues metabolically active at rest, e.g. The heart, lungs, liver and intestine and CO_2 stored in tissues which are not metabolically active at rest, e.g. skeletal muscle and bone respectively (Irving et al., 1983; Hughson & Inman, 1985; Barstow et al., 1990, 1992).

Exercise is associated with a number of changes to body CO_2 stores: The quantity of CO_2 stored in the central compartment increases significantly (Hughson & Inman, 1985; Barstow et al., 1990; Barstow et al., 1992). Some increase in the quantity of CO_2 stored in the central compartment would be expected as a result of the increase in mixed venous Pco_2 on exercise. This mechanism cannot account for the entire increase in the quantity of CO_2 stored in the central compartment (Barstow et al., 1992). The most likely cause of the increase in the quantity of CO_2 stored in the central compartment on exercise is an increase in the CO_2 storage capacity of the central compartment, attributed to the movement of exercising muscle from the slow peripheral compartment to the central compartment (Barstow et al., 1992).

The effect on body CO_2 stores of hyperventilation during exercise will therefore differ from the effect on body CO_2 stores of hyperventilation at rest, as described in Chapters 4 and 5. Hyperventilation of the severity and duration performed in this study would be associated with a depletion of the central and fast peripheral CO_2 stores. Approximately 3 min of hyperventilation would have little effect on muscle CO_2 stores if performed at rest (See Chapters 4 and 5). The movement of muscle CO_2 stores from the slow peripheral compartment to the central compartment on exercise, however, means that the hyperventilation performed in this study would result in a depletion of muscle CO_2 stores.

INITIAL RESPONSES TO 150W EXERCISE:

In both the "NORM" and "HYPER" tests, $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ increased abruptly consequent to the transition from 50 W to 150 W exercise. These abrupt responses were transient in nature for $\dot{V}E$ and $\dot{V}co_2$. The results were equivocal on this matter for $\dot{V}o_2$.

Beaver & Wasserman (1968) reported an abrupt increase in $\dot{V}E$ consequent to an abrupt increase in workload in some subjects. Linnarsson (1974), Whipp et al. (1982), Fujihara et al., (1973a), Miyamoto & Niizeki (1992) and Pearce & Milhorn (1977) all report the rapid component of the ventilatory response to an abrupt increase in workload to be small and slowed in onset.

The values for τ_1 found here were similar to those reported by Fujihara et al. (1973a: 8 sec) and Miyamoto & Niizeki (1992: 4.7 sec) for step increases in workload, Bakker et al. (1980: 4.6 sec) for sinusoidal workload forcings and Bennett et al. (1981: 7.4 sec) for impulse forcings. However, modelling using MODEL 4 yielded a value for τ_1 of less than 1 sec (i.e. a total response time of less than 4 sec) in a high proportion of both the "NORM" and "HYPER" tests. In addition, the proportion of the total response attributable to the initial response (A_1/A_2: see *Table 7.7*) was much greater in this study than the 10% to 20 % reported in the literature (Fujihara et al.1973b; Bennett et al., 1981; Casaburi et al., 1977; Whipp et al., 1982). This would suggest that the monoexponential model of the early ventilatory responses to an abrupt increase in workload (As used in MODEL 4) does not adequately describe the response seen in these tests. As such, the profiles of the initial ventilatory and pulmonary gas exchange responses to the increase in workload recorded in this study were therefore not compatible with the profiles reported in the literature (with the exception of the results of Beaver & Wasserman, 1968).

Whipp et al. (1982), Miyamoto & Niizeki (1992) and Pearce & Milhorn (1977) also report the rapid component of the ventilatory response to an abrupt increase in workload to be in proportion with the rapid component of the pulmonary gas exchange responses. In the "NORM" tests, the early ventilatory and pulmonary gas exchange responses to the abrupt increase in workload are in proportion: RER, P_{ET,CO_2} and P_{ET,O_2} do not change appreciably during this phase. Given the cardiodynamic nature of this phase of the pulmonary gas exchange responses to the abrupt increase in workload, these data would suggest that in this study $\dot{Q}_P$ increased abruptly consequent to the abrupt increase in workload, while the changes in $\dot{Q}_P$ seen in the studies reported in the literature are likely to be small and gradual in onset.

The changes in f_C consequent to the abrupt increase in workload were very similar in profile to those described in Chapter 5 in response to an abrupt transition from rest to exercise. This is not in agreement with the results of Whipp et al. (1982), but is compatible with the results of Broman & Weigertz(1971) and Fujihara et al. (1973). The results reported by Miyamoto & Niizeki (1992) are similar to those reported here, but the results of their modelling would suggest that an initial response for f_C was more common in their results than was seen in this study.

The profiles of the early cardiorespiratory and pulmonary gas exchange responses to the abrupt increase in workload seen in the "HYPER" tests were similar to those seen in the "NORM" test. Proportionality of the ventilatory and pulmonary gas exchange responses during this phase was never an issue in these tests: metabolically produced CO_2 was diverted from excretion at the lung to replenish body CO_2 stores. As a result, RER and P_{ET,O_2} fell and P_{ET,CO_2} rose during this phase. While the initial $\dot{V}co_2$ response to the abrupt increase in workload was markedly (but not significantly[1]) lower in the "HYPER" tests than in the "NORM" tests, the initial ventilatory response

[1]The initial $\dot{V}co_2$ response to the abrupt increase in workload was smaller in the "HYPER" tests than in the "NORM" tests for all except 1 subject. This resulted in there being no significant difference between the initial increase in $\dot{V}co_2$ consequent to the increase in workload between the "NORM" and "HYPER" tests.

to the abrupt increase in workload was similar for the 2 protocols. This would suggest that CO_2 flow to the lung is not the prime controller of $\dot{V}E$ at this stage.

The subsequent plateau responses for both $\dot{V}E$ and $\dot{V}co_2$ were lower in the "HYPER" tests than in the "NORM" tests. This would suggest that CO_2 flow to the lung did exert some influence over $\dot{V}E$ during this stage.

This pattern of response is similar to that described for the early responses to the transition from rest to exercise with and without prior hyperventilation in Chapter 5. As such, it does not support the theory of cardiodynamic hyperpnoea proposed by Whipp & Ward (1982) or the theory of neurohumoral control proposed by Dejours (1963). Rather, it falls some way between them: These results suggest that the first 3 breaths or so following an abrupt increase in workload are under neural control, but the remainder of the early response is under the influence of CO_2 flow to the lung or $PaCO_2$ (It is not possible from these results to distinguish between the 2).

The early $\dot{V}o_2$ responses to the abrupt increase in workload were similar in both the "NORM" and "HYPER" tests. This demonstrates that the subjects had recovered from the effects of the hyperventilation on body O_2 stores and metabolic rate. It also demonstrates that the changes in Q_P which can be inferred from changes in $\dot{V}o_2$ were also not affected by the prior hyperventilation in the "HYPER" test. Similarly, the initial f_C response to the abrupt increase in workload (Where present) was unaffected by the prior hyperventilation.

LATER RESPONSES TO 150 W EXERCISE:

The marked variability in the kinetics of the later responses for $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ to 150 W exercise resulted in there being no significant difference between τ or t_D in the "NORM" and "HYPER" tests. The similarity between τ_2 and t_{D2} for $\dot{V}E$ and $\dot{V}co_2$ in

both protocols is in agreement with the results obtained from other square-wave (Whipp et al., 1982; Miyamoto & Niizeki, 1992; Pearce & Milhorn, 1977; Casaburi et al., 1989; Wasserman & Whipp, 1983; Linnarsson, 1974), impulse (Bakker et al., 1980), ramp (Miyamoto & Niizeki, 1992) and sinusoidal workload forcings (Casaburi et al., 1977; 1978).

There was a trend for τ_2 to be greater for $\dot{V}E$ and $\dot{V}co_2$ in the "HYPER" tests than in the "NORM" tests. This is in contrast with the effect of prior hyperventilation on the later responses to the transition from rest to exercise reported in Chapter 5 (Hyperventilation prior to the onset of exercise prolonged the delay in onset of the later responses for $\dot{V}E$ and $\dot{V}o_2$ but did not affect the kinetics of the responses).

This difference reflects the differing effects of hyperventilation at rest and during exercise on the body's CO_2 stores. Hyperventilation of the duration used in this study and the study described in Chapter 5 would result in a depletion of the central and fast compartments of the CO_2 stores at rest. However, the onset of exercise is associated with the movement of muscle CO_2 stores from the slow compartment to the central compartment (Barstow et al., 1990, 1992), resulting in an increase in the CO_2 storage capacity of the central compartment (Barstow et al., 1990, 1992, Hughson & Inman, 1985). This effect is not workload dependent (Barstow et al., 1992; Hughson & Inman, 1985). Lowering P_{ET},CO_2 to around 25 mmHg during exercise will result in a greater depletion of body CO_2 content than at rest. As a result, a greater quantity of metabolically produced CO_2 will need to be diverted from excretion at the mouth before body CO_2 stores are returned to their normal exercise levels. This would result in a slowing of $\dot{V}co_2$ kinetics at the mouth, with a concomitant effect on $\dot{V}E$.

τ for $\dot{V}o_2$ tended to be smaller in the "HYPER" tests than in the "NORM" tests. This was a reflection of the marked reduction in O_2 stores following the hyperventilation period. There were no significant differences between the values of τ or t_D for the later f_C responses to 150 W exercise in the "NORM" and "HYPER" tests.

QUASI STEADY-STATE RESPONSES:

The steady-state responses were not reached in these tests. However, based on the results obtained in this study and the study described in Chapter 5, there is no reason to believe hyperventilation would exert any long-lasting effect on the cardiorespiratory and pulmonary gas exchange responses to exercise.

CONCLUSIONS:

The results from the "NORM" tests demonstrate that for the subjects and protocol used in this experiment, the initial cardiorespiratory and pulmonary gas exchange responses to an abrupt increase in workload are abrupt in onset. This is in contrast to the majority of the findings reported in the literature and will be further investigated in the next Chapter. $\dot{V}o_2$ and $\dot{V}co_2$ increased in proportion with $\dot{V}E$.

Following hypocapnic hyperventilation, the initial ventilatory response to an increase in workload is characterised by an abrupt but transient increase in $\dot{V}E$ which then falls to a plateau before the onset of the later response.

The initial response to the abrupt increase in workload for $\dot{V}E$ is unaffected by the depletion of CO_2 stores in the "HYPER" tests, despite the initial response for $\dot{V}co_2$ being significantly lower than that seen in the "NORM" tests, highlighting its neurogenic origin. The subsequent plateau for $\dot{V}E$ is, however, reduced in magnitude in the "HYPER" tests.

CHAPTER 8:

THE EFFECT OF VERBAL COMMAND ON THE EARLY VENTILATORY RESPONSE TO AN INCREASE IN EXERCISE INTENSITY.

INTRODUCTION

The ventilatory response to a step increase in workload, as described in the preceding Chapter, differs significantly from that described by Whipp et al. (1982) and Broman & Weigertz (1971). The ventilatory response to both sinusoidal (Casaburi et al., 1977) and ramp (Niizeki et al., 1992) workload forcings support the findings of Whipp et al. (1982), i.e. the immediate ventilatory response to an increase in workload is smoother in onset and severely attenuated in size.

Certainly, the magnitude of the initial increase in $\dot{V}E$ reported in the previous Chapter was smaller than that seen on transition from rest to exercise in the same subjects (Chapter 5), but it was considerably larger than that described in the literature. In addition, the profile of the response was different to that described in the literature: the results of the "NORM" test showed it to be an immediate response, occurring in conjunction with the increase in workload, while prior hypocapnic hyperventilation ("HYPER" test) unmasked its transient nature. The task of this Chapter is to try and reconcile the ventilatory response to an abrupt increase in workload reported in the previous Chapter with that reported in the literature.

To do this it is necessary to review the differences in experimental protocol between Whipp's study and ours. One of the most obvious (and intentional) differences between the two tests was the subject group: our subjects were at least fit and most were highly trained rowers, whereas the subjects used by Whipp et al. (1982) were sedentary. As already stated, the decision to use highly trained athletes to form the bulk of our subject population was a deliberate one, based on the fact that highly trained athletes are reported to have a larger initial ventilatory response to the onset of exercise than sedentary individuals (Krogh & Lindhard, 1913).

It is possible their level of fitness also allows a modification of the work-to-work ventilatory response. This, however, would appear unlikely within the confines of a control mechanism responding to either neural irradiation from the motor cortex or an increased output from peripheral nerves. The interpretation of the results obtained from sinusoidal (Casaburi et al., 1977; 1978), step (Whipp et al., 1982; Wasserman & Whipp, 1983; Pearce & Milhorn, 1977; Casaburi et al., 1989), ramp (Miyamoto & Niizeki, 1992; Fujihara et al., 1973a,b) and impulse (Bakker et al., 1980) forcings would suggest these pathways are largely saturated once exercise has started, thereby explaining the grossly reduced size of the initial, neurogenic response to an increase in work rate reported in their data. This view is supported by the work of D'Angelo and Torelli (1971).

It could be argued that the subjects' high levels of fitness allowed a reduced stimulation of the neurogenic pathways, either central or peripheral, at low workloads thereby allowing the generation of a larger neurogenic ventilatory response to an increase in exercise intensity. If this were the case, the initial ventilatory response to the onset of mild exercise should be smaller than that recorded in normal, sedentary individuals, whereas the opposite is true (Krogh & Lindhard, 1913). Furthermore, in the experiments described in the previous Chapter, the initial workload was 50 W; greater than that used by Whipp et al. (1982) who imposed their higher workload against a background of unloaded pedalling. Again, the lower initial workload used by Whipp et al., (1982) should reduce the activity of the neural pathways, allowing the initial ventilatory response to be more apparent in their results than against the background of 50 W exercise used here.

The subjects studied here were also younger than those studied by Whipp et al. (1982). Although Babcock et al. (1994) has reported a slowing of the phase 2 ventilatory kinetics with age, there are no reports in the literature of the effect of age on the initial ventilatory response to either the onset of exercise or an abrupt increase in workload and it is difficult to envisage a way in which age could influence it.

There are also various methodological differences between the two investigations, for example the higher initial workload in our study. 50 W was used simply because it was the lowest workload that the subjects found comfortable to exercise at: both unloaded pedalling and 25 W were tried, but were deemed as being uncomfortable (a common complaint was the feeling that the legs were "just flapping about"). Chronic hyperventilation during an exercise test can be induced in the subject by apprehension, a failure to relax, or by physical discomfort, such as an uncomfortable seat or excessive heat, or, perhaps, by exercising at too low a workload. Such an occurrence would in these investigations necessitate the abortion of the test; obviously not a good outcome.

A second difference between the two methodologies is that Whipp et al. (1982) imposed their increase in workload without any warning, whereas we gave a verbal command in conjunction with the increase in exercise intensity. It is important to note that the commands were given in a well modulated voice to avoid both a hyperventilatory "startle" response which can occur if the command is too loud, and a hypoventilatory response resulting from the command being too quiet.

The giving of a verbal command in conjunction with the increase in exercise intensity is of fundamental importance to the validity of these results. The experimental protocol described in Chapter 7 was designed to mirror the protocol used in Chapter 5 with the exception of the background state from which the exercise was increased; i.e. in Chapter 5, 150 W exercise was imposed against a background of rest while in Chapter 7, 150 W exercise was imposed against a background of mild exercise. As it is impossible to achieve the transition from rest to volitional exercise without giving some command to the subject (in this case, the command was verbal), we were constrained to using a verbal command to signal the transition from mild to moderate exercise.

The difference between our results and those of Whipp et al. (1982) may be due to an abrupt increase in $\dot{V}E$ consequent to the verbal signal, rather than the increase in exercise intensity *per se*. Such a conditioned response would logically be of benefit for the

competing athlete: it is well known that the different time constants for Vo_2 and VE during the Phase 2 response allows the development of a transient hypoxaemia (Young & Woolcock, 1978; Whipp & Ward, 1980; this can be seen in my results as well). At moderate levels of exercise, this does not impinge on the limits of the respiratory system and is easily corrected.

At maximal exercise in highly trained athletes, however, this may not be the case. Exercise induced arterial hypoxaemia is recognised as occurring in a significant proportion of highly trained athletes (Dempsey et al., 1984a), and under such severe limitations, a further decrease in arterial O_2 saturation may be incompatible with continuing to exercise at such a high level, forcing the subjects to either stop or greatly reduce the intensity at which they are exercising. Such a scenario would be compatible with the hypothesis of Ferretti that during hypoxia the drop in $\dot{V}o_{2,max}$ is tightly linked to the intrinsic properties of the O_2 dissociation curve (Ferretti, 1990; Thomet et al., 1994). It would be of positive benefit to an athlete, therefore to increase $\dot{V}E$ in anticipation of the incipient chemical drive to minimise the hypoxaemia. Furthermore, it is difficult to envisage a real-life situation in which an already exercising individual was not aware of a forthcoming increase in exercise intensity.

PURPOSE OF THE EXPERIMENT:

An abrupt increase in $\dot{V}E$ coincident with the increase in workload was reported in the preceding Chapter. This experiment was designed to determine whether the abrupt increase in $\dot{V}E$ is a result of associative conditioning (Pavlovian reflex) to the expectation of an increase in exercise intensity, or an intrinsic response to the increased workload per se.

Preliminary findings of this study have already been published in abstract form (Howell & Cross, 1994c,e)

METHODOLOGY:

SUBJECTS:

Five subjects performed the tests described below. Two were college level competitive rowers, one was a club fell runner, one taught circuit training and one cycled regularly. Their anthropometric data are presented in *Table 8.1*. The tests were performed over two days, separated by between two and five days. On each day two tests were performed, separated by 20 min. The order of the tests was not totally random, the "SHAM" test always preceding the "HYPER" test. Test order was randomised as far as possible, given this limitation.

SUBJECT	AGE	HEIGHT	WEIGHT	SPORT
D	29	1.76	66	FELL RUNNER
E	25	1.74	76	CIRCUIT TRAINER
H	21	1.85	77.5	ROWER
T	27	1.84	82.5	ROWER
U	25	1.80	77	CYCLIST
3	25	2.02	95	ROWER

Table 8.1: Anthropometric data for the subjects used in this experiment.

APPARATUS:

All tests were performed using the apparatus described in Chapter 2. Data acquisition programs EXTEST 2 and EXTEST 3 were used in this study. These programs are described in Appendix A.

PROTOCOLS:

Tests "NORM" and "HYPER": These are as described in the preceding Chapter.

Tests "SHAM" and "SURPRISE": Prior to the start of the "SHAM" test, subjects were told that the protocol for the test would involve an increase in workload soon after the end of the hyperventilation period (i.e. the same as the "HYPER" protocol which they had yet to perform). Before the "SURPRISE" test they were told the test would involve hyperventilation during exercise, but no increase in workload (i.e. identical to test "C" in Chapter 4). Neither of these commands were true, but were specifically designed to mislead the subject.

Both tests started with 3 min rest followed by 3 min of normal 50 W exercise at a pedal frequency of 75 rpm. Subjects were then asked to hyperventilate by increasing their V_T as much as possible without increasing either f_{BR} or f_{PED} more than necessary. This was maintained for 4 min or until P_{ET,CO_2} fell to below 25 mmHg for more than five consecutive breaths, which ever occurred sooner. At this point subjects were asked to breathe normally.

Some 15 to 30 sec after the end of hyperventilation subjects were told "Workload going up .... now" in the "SHAM" test. In fact, workload was reduced by 2 W (the reduction was partly so subjects could detect some kind of change in workload at that point and partly to ensure that the experimenter went through the same motions as in the "HYPER" protocol) and remained at that level for 4 min.

Conversely, 15 to 30 sec after the end of hyperventilation the workload was abruptly increased to 150 W without any kind of warning to the subjects in the "SURPRISE" test. Again this level of exercise was maintained for 4 min. The last stage of exercise was followed by a short rest period before the test was concluded.

DATA ANALYSIS:

Resting Values: Mean resting values of $\dot{V}E$, VT, fBR, $\dot{V}O_2$, $\dot{V}CO_2$, RER, $P_{ET}CO_2$, $P_{ET}O_2$ and fC for each test were taken as the mean value for 1 min prior to the start of exercise. Abnormal breaths, e.g. sighs or coughing, were excluded from the analysis.

Steady-state responses to 50 W exercise: The steady-state values of $\dot{V}E$, VT, fBR, $\dot{V}O_2$, $\dot{V}CO_2$, RER, $P_{ET}CO_2$, $P_{ET}O_2$ and fC for each test were taken as the mean value for the last 30 sec of this stage.

Hyperventilation: Mean values of $\dot{V}E$, VT, fBR, $\dot{V}O_2$, $\dot{V}CO_2$, RER, $P_{ET}CO_2$, $P_{ET}O_2$ and fC for the hyperventilation period were taken as the mean of the last five breaths of the hyperventilation period.

Post-hyperventilation: The mean values of $\dot{V}E$, VT, fBR, $\dot{V}O_2$, $\dot{V}CO_2$, RER $P_{ET}CO_2$, $P_{ET}O_2$ and fC for the three breaths prior to the change in exercise intensity were taken to represent the extent of recovery from the hyperventilation just prior to the change in workload.

Modelling: Changes in $\dot{V}E$, $\dot{V}O_2$ and $\dot{V}CO_2$ in response to the increase in workload (Tests "N," "HYPER" and "SURPRISE") were characterised using MODEL 3, as described in Chapters 5 and 7 and in Appendix G. The best-fit function to each subjects' experimental data was determined using the least squares method. For the "SHAM" test, the initial ventilatory response to the change in workload was taken as the maximum value of the first three breaths, similar to the definition of the initial, abrupt increase used by MODEL 3.

Changes in fC in response to the increase in workload (Tests "NORM", "HYPER" and "SURPRISE") were characterised using MODEL 5, as described in Chapters 5 and 7. The best-fit function was determined using the least squares method.

Quasi steady-state values: The quasi steady-state ventilatory responses for $\dot{V}_E$, V_T, f_{BR}, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, P_{ET,CO_2}, P_{ET,O_2} and f_C to the change in workload was taken as the mean value for the last 30 sec of exercise.

Comparisons between the different tests were performed using a single factor NOVA with post-hoc analysis using a Student's paired *t*-test where significance was indicated.

RESULTS:

The breath-by-breath data for the "NORM", "HYPER", "SHAM" and "SURPRISE" tests performed by subject T are presented in *Figs. 8.1* to *8.4*.

REST AND 50 W EXERCISE:

Subjects responses at rest and to 50 W exercise followed a similar pattern to that described in the previous Chapter (see *Tables 8.2* and *8.3*).

	NORM	HYPER	SURPRISE	SHAM
f_C	71.0 ± 7.4	67.3 ± 3.1	69.9 ± 5.8	65.0 ± 4.0
$\dot{V}_E$	12.4 ± 1.3	11.6 ± 0.4	11.4 ± 1.0	11.9 ± 1.2
f_{BR}	14.5 ± 2.5	12.9 ± 2.4	12.2 ± 1.5	13.4 ± 1.2
V_T	1.11 ± 0.22	1.19 ± 0.21	1.11 ± 0.14	0.94 ± 0.08
P_{ET,CO_2}	39.3 ± 1.0	39.3 ± 0.9	40.7 ± 0.8	39.8 ± 0.9
P_{ET,O_2}	103.7 ± 4.1	102.8 ± 3.2	105.5 ± 2.2	100.7 ± 3.1
$\dot{V}_{O_2}$	0.43 ± 0.03	0.4 ± 0.05	0.4 ± 0.02	0.43 ± 0.02
$\dot{V}_{CO_2}$	0.35 ± 0.04	0.32 ± 0.02	0.35 ± 0.04	0.32 ± 0.03
RER	0.81 ± 0.06	0.82 ± 0.07	0.87 ± 0.06	0.74 ± 0.04

Table 8.2: Mean (± SE) resting results for the four protocols. Values are similar (*N.S.*) for all protocols, n = 6.

	NORM	HYPER	SURPRISE	SHAM
f_C	94.4 ± 8.2	91.7 ± 4.3	96.4 ± 7.5	91.0 ± 3.5
$\dot{V}_E$	31.1 ± 3.5	28.9 ± 2.4	33.4 ± 3.4	30.8 ± 2.1
f_{BR}	19.5 ± 2.5	18.4 ± 1.9	21.9 ± 2.2	20.7 ± 1.4
V_T	1.77 ± 0.19	1.72 ± 0.11	1.71 ± 0.21	1.56 ± 01
P_{ET,CO_2}	46.2 ± 0.8	45.2 ± 1.3	45.5 ± 1.2	44.6 ± 1.3
P_{ET,O_2}	97.1 ± 2.8	97.0 ± 2.0	100.7 ± 1.6	96.9 ± 1.8
$\dot{V}_{O_2}$	1.41 ± 0.11	1.31 ± 0.06	1.42 ± 0.1	1.40 ± 0.07
$\dot{V}_{CO_2}$	1.16 ± 0.13	1.09 ± 0.09	1.21 ± 0.2	1.08 ± 0.09
RER	0.82 ± 0.04	0.83 ± 0.06	0.84 ± 0.06	0.75 ± 0.02

Table 8.3: Mean (± SE) steady-state responses to 50 W exercise in all protocols. Values were similar (*N.S.*) for all protocols, n = 6.

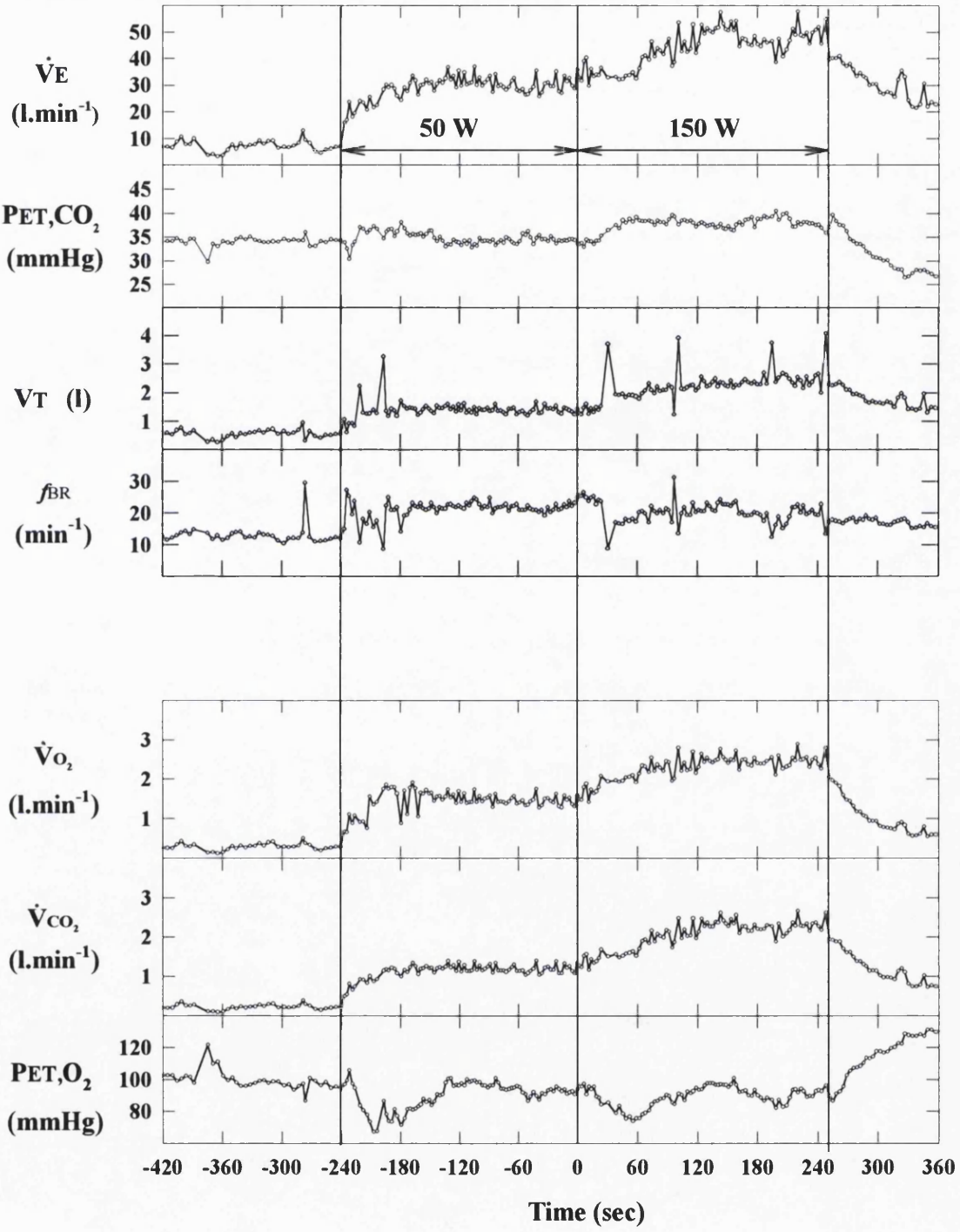


Figure 8.1: Breath-by-breath values of $\dot{V}_E$, P_{ET,CO_2}, V_T, f_{BR}, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and P_{ET,O_2} throughout test "NORM" performed by subject T. Time 0 represents the increase in workload, other lines represent the start and the end of exercise respectively. f_C data was not available for this test due to excessive noise in the signal.

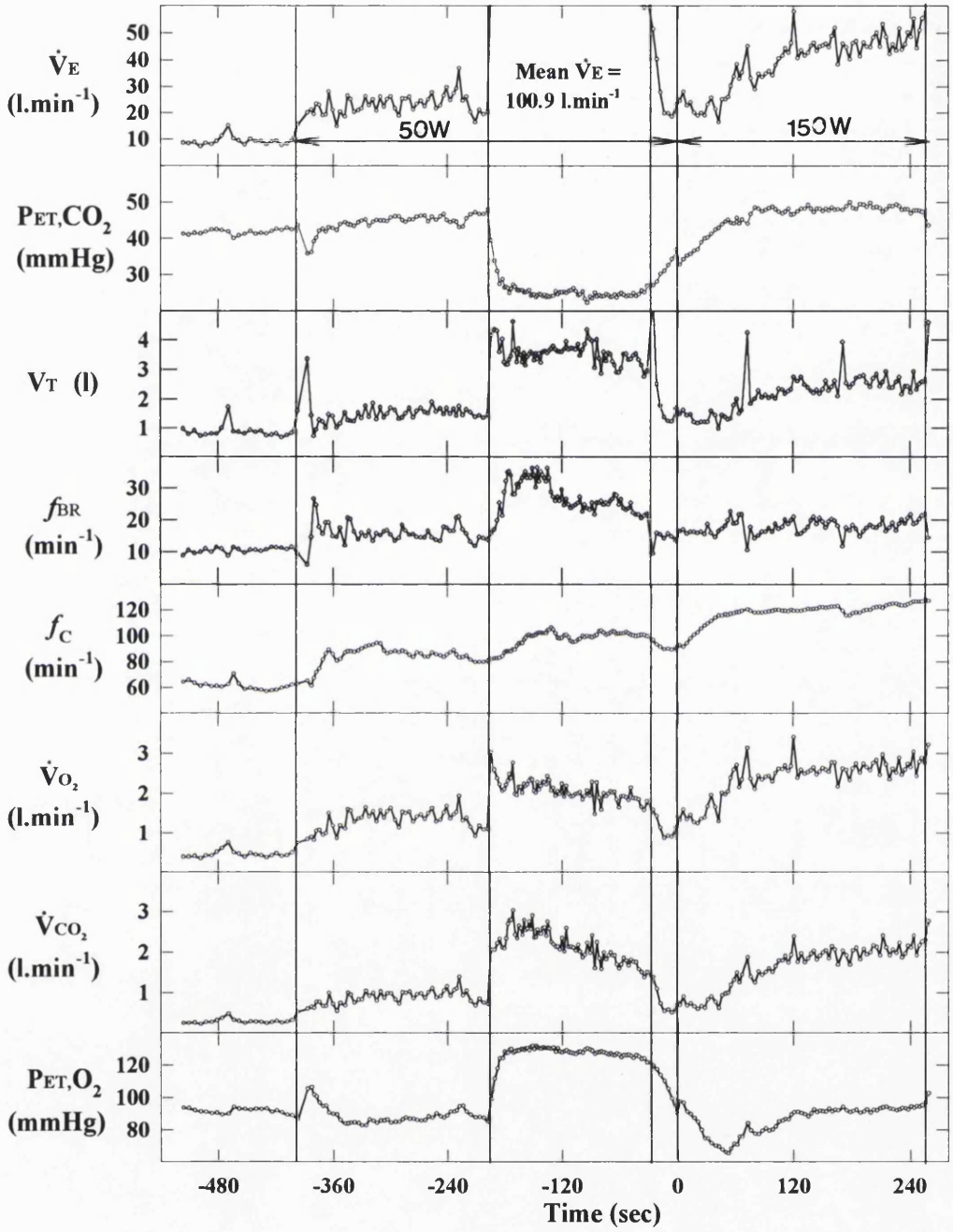


Figure 8.2: Breath-by-breath values of $\dot{V}E$, P_{ET,CO_2}, V_T, f_{BR}, f_C, $\dot{V}O_2$, $\dot{V}CO_2$ and P_{ET,O_2} throughout test "HYPER" performed by subject T. Time 0 represents the increase in workload, other lines represent the start of exercise, the start and end of hyperventilation and the end of exercise respectively. Mean VE during hyperventilation was 100.9 $l.min^{-1}$.

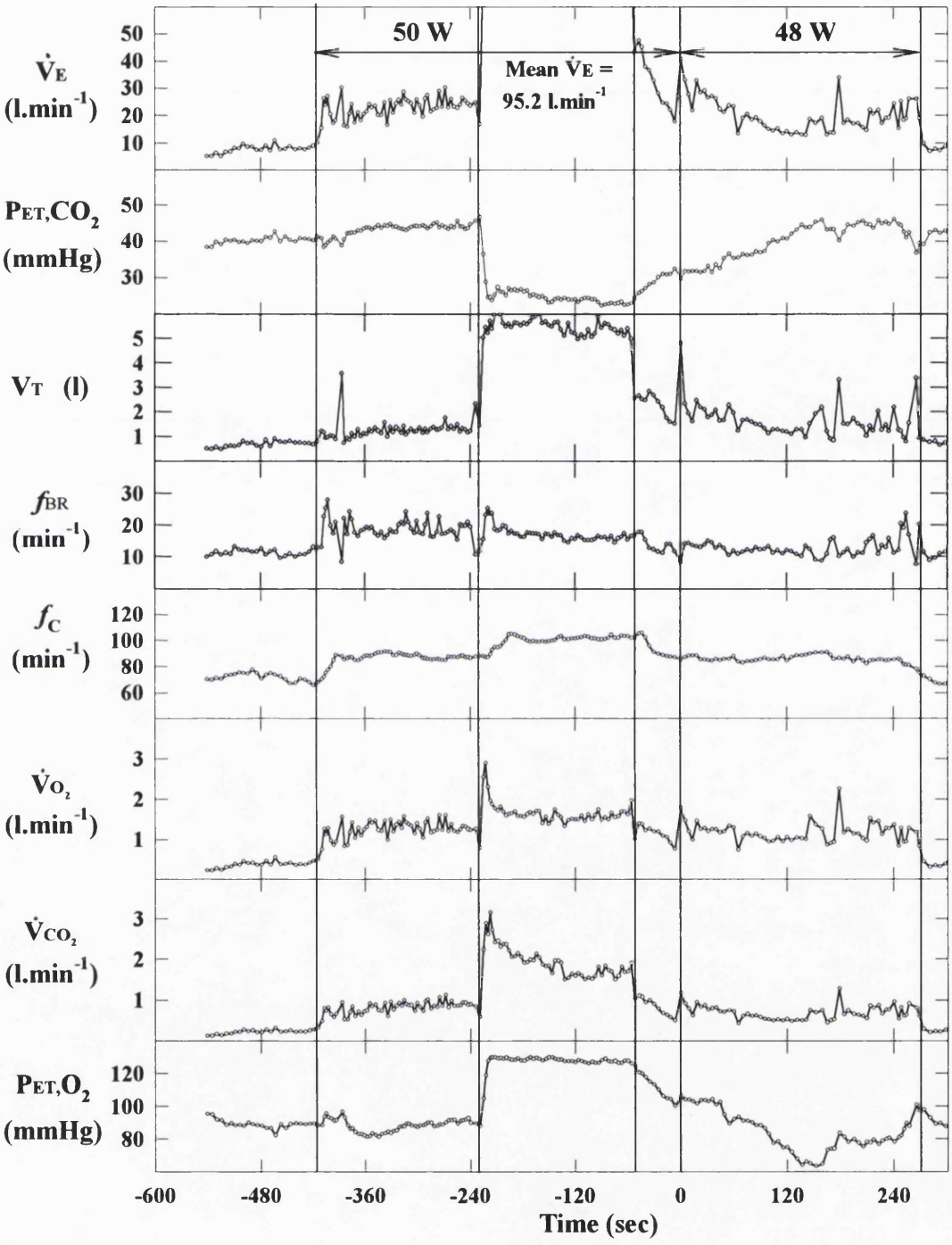


Figure 8.3: Breath-by-breath values of $\dot{V}E$, PET,CO_2, VT, fBR, f_C., $\dot{V}o_2$, $\dot{V}co_2$ and PET,O_2 throughout test "SHAM" performed by subject T. Time 0 represents the fall in workload, other lines represent the start of exercise, the start and end of hyperventilation and the end of exercise respectively. Mean VE during hyperventilation was 95.2 l.min^{-1}.

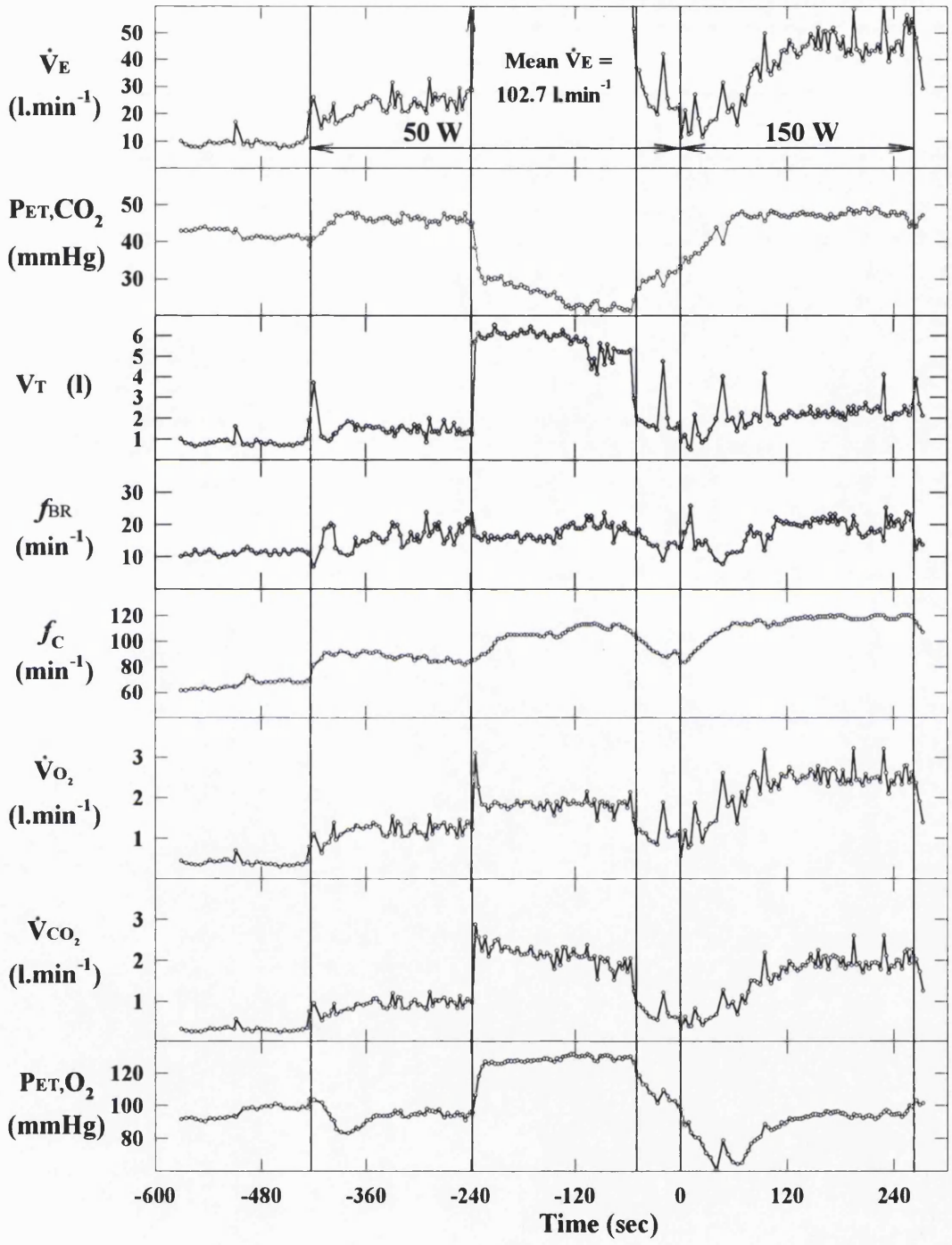


Figure 8.4: Breath-by-breath values of $\dot{V}E$, PET,CO_2, VT, fBR, f_C, $\dot{V}o_2$, $\dot{V}co_2$ and PET,O_2 throughout test "SURPRISE" performed by subject T. Time 0 represents the increase in workload, other lines represent the start of exercise, the start and end of hyperventilation and the end of exercise respectively. Mean VE during hyperventilation was 102.7 l.min^{-1}.

HYPERVENTILATION:

Similar to the results described in Chapter 5, $\dot{V}E$ increased during the hyperventilation phase to approx. 100 $l.min^{-1}$, in all four tests (see *Table 8.4*). This increase was due mostly to an increase in VT, but *f*BR also increased slightly (see *Table 8.4* and *Figs. 8.2* to *8.4*). There was no significant difference between the values of VT and *f*BR during hyperventilation in the "HYPER", "SURPRISE" and "SHAM" tests. P_{ET,CO_2} fell to around 25 mmHg by the end of hyperventilation in all tests and *f*C increased to 115-120 beats per min. Again, these values are similar to those reported in Chapters 4 and 7.

	HYPER	SURPRISE	SHAM
*f*C	106.6 ± 3.7	116.1 ± 11.2	107.9 ± 7.7
$\dot{V}E$	92.8 ± 6.6	109.1 ± 10.9	103.6 ± 11.7
*f*BR	23.1 ± 0.9	24.6 ± 2.1	22.8 ± 2.38
VT	4.23 ± 0.44	4.74 ± 0.35	4.74 ± 0.4
P_{ET,CO_2}	24.5 ± 0.78	25.0 ± 2.1	24.9 ± 1.5
P_{ET,O_2}	128.5 ± 1.6	129.8 ± 1.1	126.5 ± 2.18
$\dot{V}o_2$	1.73 ± 0.08	2.10 ± 0.22	2.05 ± 0.18
$\dot{V}co_2$	2.04 ± 0.14	2.37 ± 0.28	1.98 ± 0.11
RER	1.15 ± 0.1	1.14 ± 0.08	0.98 ± 0.04

Table 8.4: Mean (± SE) values at the end of hyperventilation. Values are similar (*N.S.*) for all protocols, n = 6.

POST-HYPERVENTILATION:

In all tests, $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ fell rapidly following the end of hyperventilation (See *Table 8.5*). The fall in $\dot{V}E$ was achieved by both VT and *f*BR decreasing. *f*C also fell, but consistent with the results reported in Chapter 5, not as fast as $\dot{V}E$. The mean duration of the post-hyperventilation phase was similar for the three protocols; around 25 sec. P_{ET,CO_2} rose and P_{ET,O_2} fell during this time, but neither had returned to normal values by the end of this stage.

	HYPER	SURPRISE	SHAM
f_C	99.7 ± 3.7	106.8 ± 10.8	98.7 ± 6.2
$\dot{V}_E$	21.9 ± 5.5	26.7 ± 4.0	21.6 ± 1.3
f_{BR}	19.1 ± 2.3	19.7 ± 3.7	17.4 ± 0.14
V_T	1.22 ± 0.19	1.5 ± 0.1	1.41 ± 0.14
P_{ET,CO_2}	34.5 ± 0.6	36.8 ± 2.3	35.0 ± 1.7
P_{ET,O_2}	102.3 ± 2.9	99.2 ± 4.9	98.1 ± 4.1
$\dot{V}_{O_2}$	1.0 ± 0.17	1.29 ± 0.21	0.94 ± 0.04
$\dot{V}_{CO_2}$	0.61 ± 0.15	0.74 ± 0.13	0.55 ± 0.01
RER	0.66 ± 0.05	0.57 ± 0.02	0.58 ± 0.03

Table 8.5: Mean (± SE) responses just prior to the change in workload. Values are similar (*N.S.*) for all protocols, n = 6.

INITIAL RESPONSES TO THE CHANGE IN WORKLOAD:

$\dot{V}_E$: $\dot{V}_E$ increased abruptly to similar levels in tests "NORM," "HYPER," and "SHAM", (Initial, abrupt increase: "NORM" vs. "HYPER" vs. "SHAM": *N.S.*) despite the workload decreasing in the "SHAM" test (see *Table 8.6* and *Fig. 8.5*). This increase was, however, transient. $\dot{V}_E$ fell in all three tests, to a plateau in the "NORM" and "HYPER" tests. The fall was greater following hyperventilation ("NORM" vs. "HYPER": $p < 0.05$; see *Table 8.6* and *Fig 8.5*).

	NORM	HYPER	SURPRISE	SHAM
Initial increase	43.7 ± 2.7	36.4 ± 3.7	28.9 ± 4.5*	36.1 ± 3.9
Subsequent Plateau	36.7 ± 2.6*	24.0 ± 3.9	24.5 ± 4.2	

Table 8.6: Early changes in $\dot{V}_E$ in response to an abrupt increase ("NORM", "HYPER" and "SURPRISE" tests) or decrease ("SHAM" tests) in workload (See Methods section for details). Shading denotes no results. * denotes values are significantly ($p < 0.05$) different from "HYPER" test. n = 6.

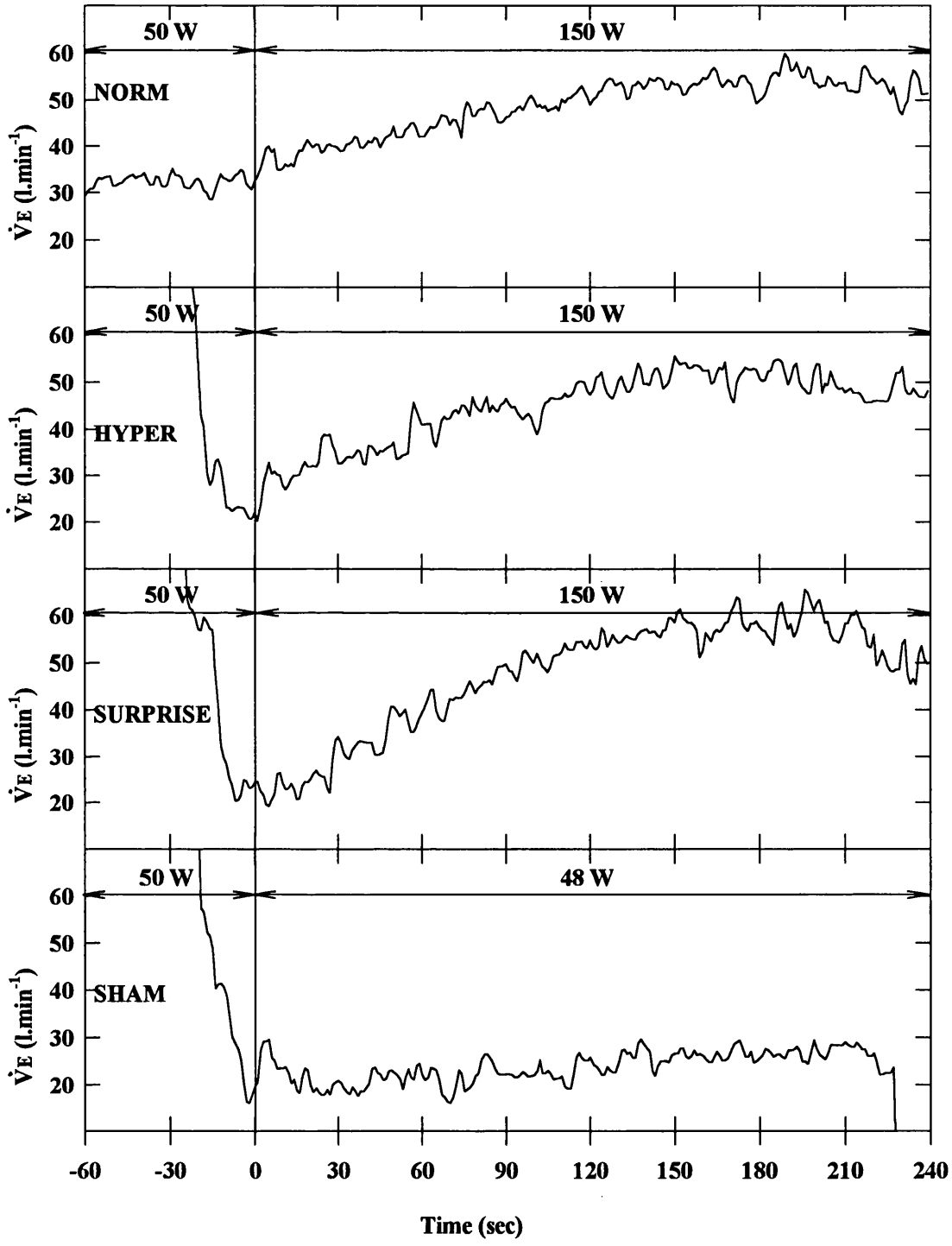


Figure 8.5: Mean changes in $\dot{V}E$ for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

The increase in workload in the "SURPRISE" test was associated with an increase $\dot{V}E$ (post-"HYPER" vs. initial response; $p < 0.05$, see *Tables 8.5* and *8.6*), but it was significantly smaller than that seen in the "NORM", "HYPER" or "SHAM" tests (See *Table 8.6*).

$\dot{V}o_2$ and $\dot{V}co_2$: Both $\dot{V}o_2$ and $\dot{V}co_2$ increased abruptly in conjunction with the change in workload in tests "NORM", "HYPER" and "SHAM" to similar levels (see *Table 8.7* and *Figs. 8.6 & 8.7)*, similar to the changes seen in $\dot{V}E$. $\dot{V}o_2$ and $\dot{V}co_2$ did not increase significantly on increasing workload in the "SURPRISE" test (See *Table 8.7* and *Figs. 8.6 & 8.7*).

		NORM	HYPER	SURPRISE	SHAM
$\dot{V}o_2$	Initial response	2.05 ± 0.11	1.7 ± 0.07	1.67 ± 0.31	1.86 ± 0.36
	Plateau	1.87 ± 0.1*	0.74 ± 0.28	1.55 ± 0.27	
$\dot{V}co_2$	Initial response	1.68 ± 0.08*	1.18 ± 0.13	0.84 ± 0.19*	0.96 ± 0.11
	Plateau	1.59 ± 0.1*	0.62 ± 0.11	0.77 ± 0.2	

Table 8.7: Early changes in $\dot{V}o_2$ and $\dot{V}co_2$ in response to an abrupt increase ("NORM", "HYPER" and "SURPRISE" tests) or decrease ("SHAM" tests) in workload (See Methods section for details). Shading denotes no results. * denotes values are significantly ($p < 0.05$) different from "HYPER" test. n = 6.

RER, P_{ET,CO_2} & P_{ET,O_2}:

At the time when the workload was changed in tests "HYPER", "SHAM" and "SURPRISE", RER and P_{ET,O_2} were still falling and P_{ET,CO_2} rising following hyperventilation. This process continued following the change in workload in all 3 protocols (See *Figs. 8.2* to *8.4*, *Figs 8.8* to *8.10* and *Tables 8.5* and *8.8*). RER, P_{ET,O_2} and P_{ET,CO_2} did not change appreciably from 50 W values over the first 3 breaths of 150 W exercise in test "NORM" (See *Tables 8.3* and *8.8*). There was no evidence to suggest the abrupt increase in $\dot{V}E$ seen in conjunction with the abrupt change in workload in the "NORM", "HYPER" and "SHAM" tests was associated with hyperventilation.

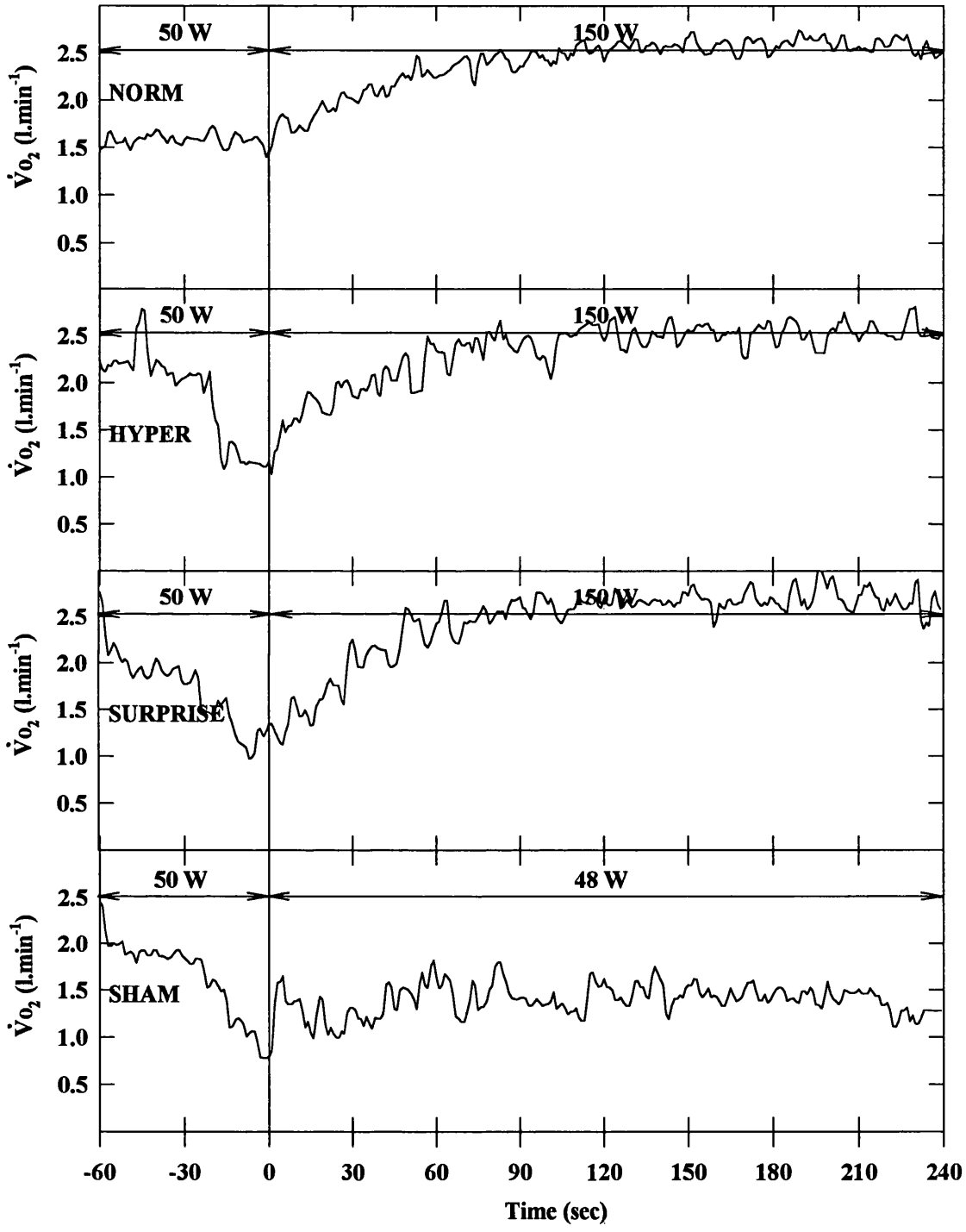


Figure 8.6: Mean changes in $\dot{V}o_2$ for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

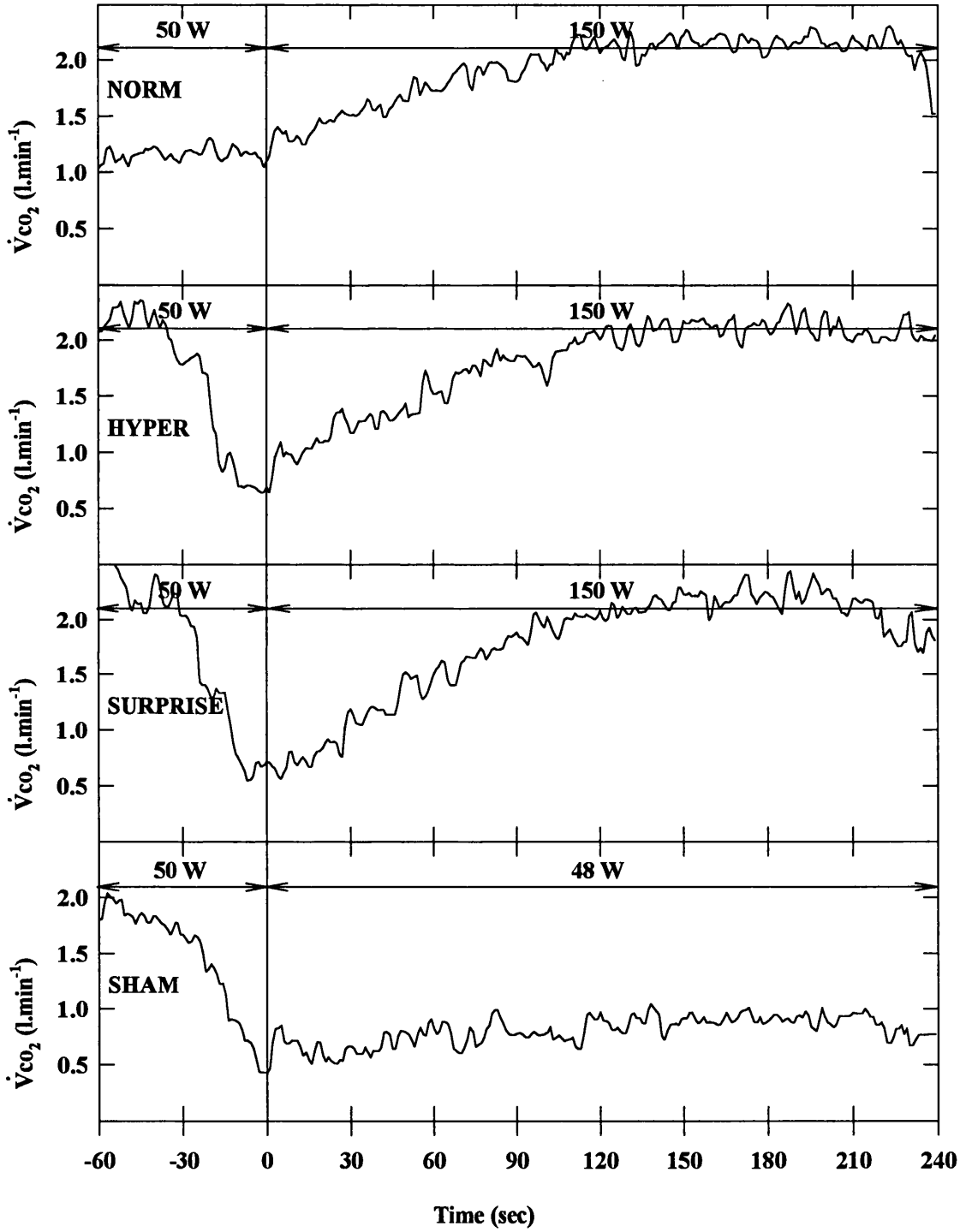


Figure 8.7: Mean changes in $\dot{V}co_2$ for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

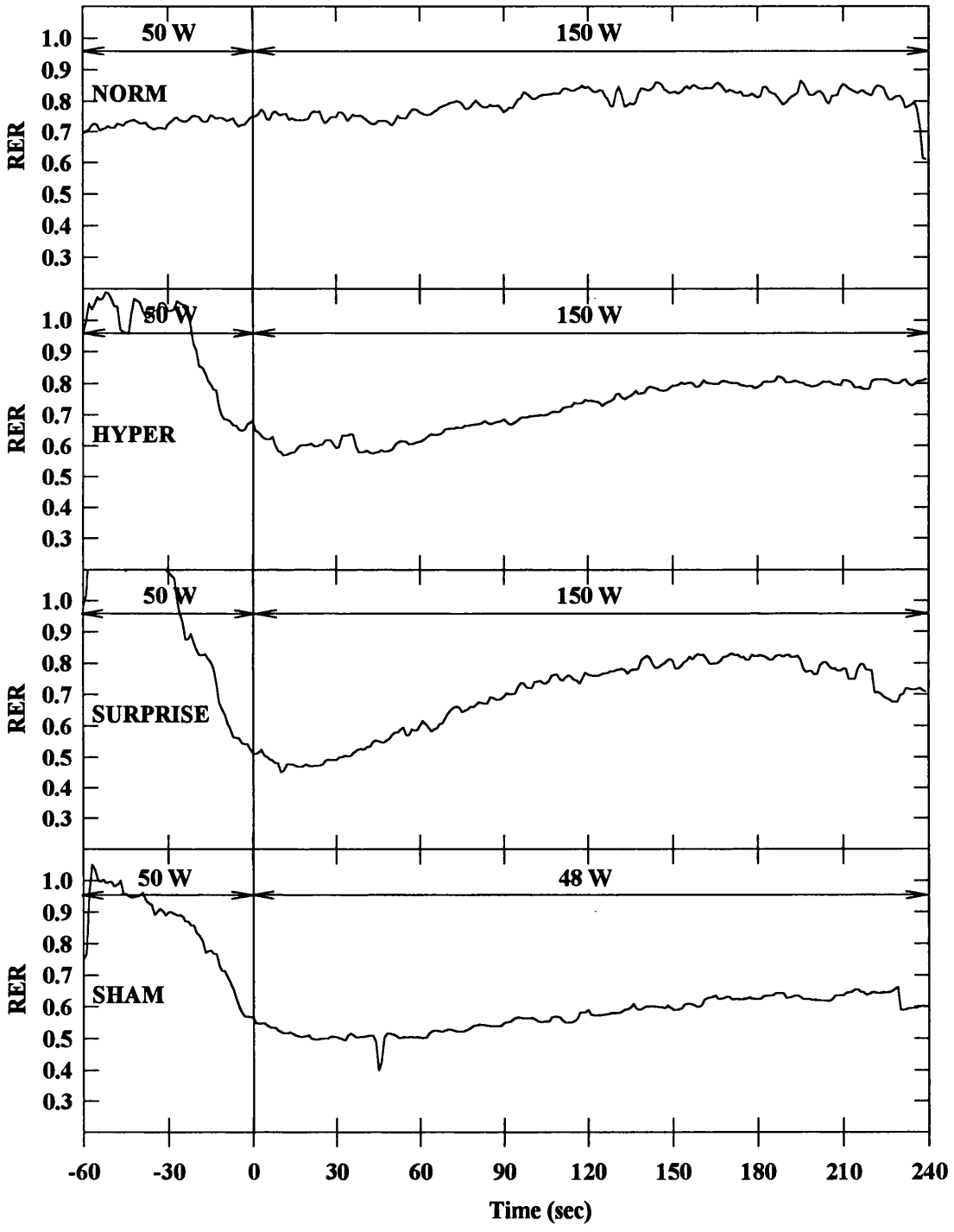


Figure 8.8: Mean changes in RER for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

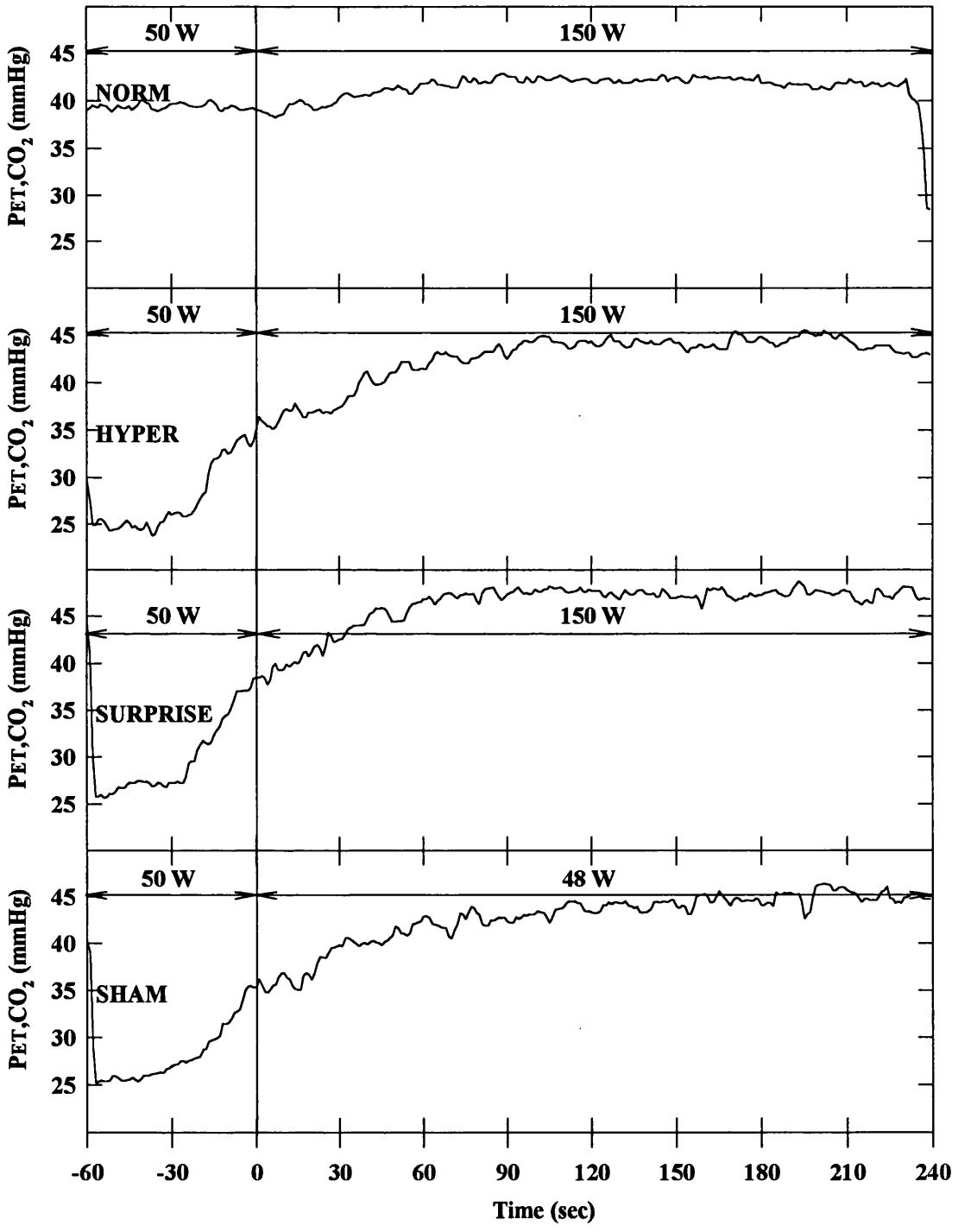


Figure 8.9: Mean changes in P_{ET,CO_2} for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

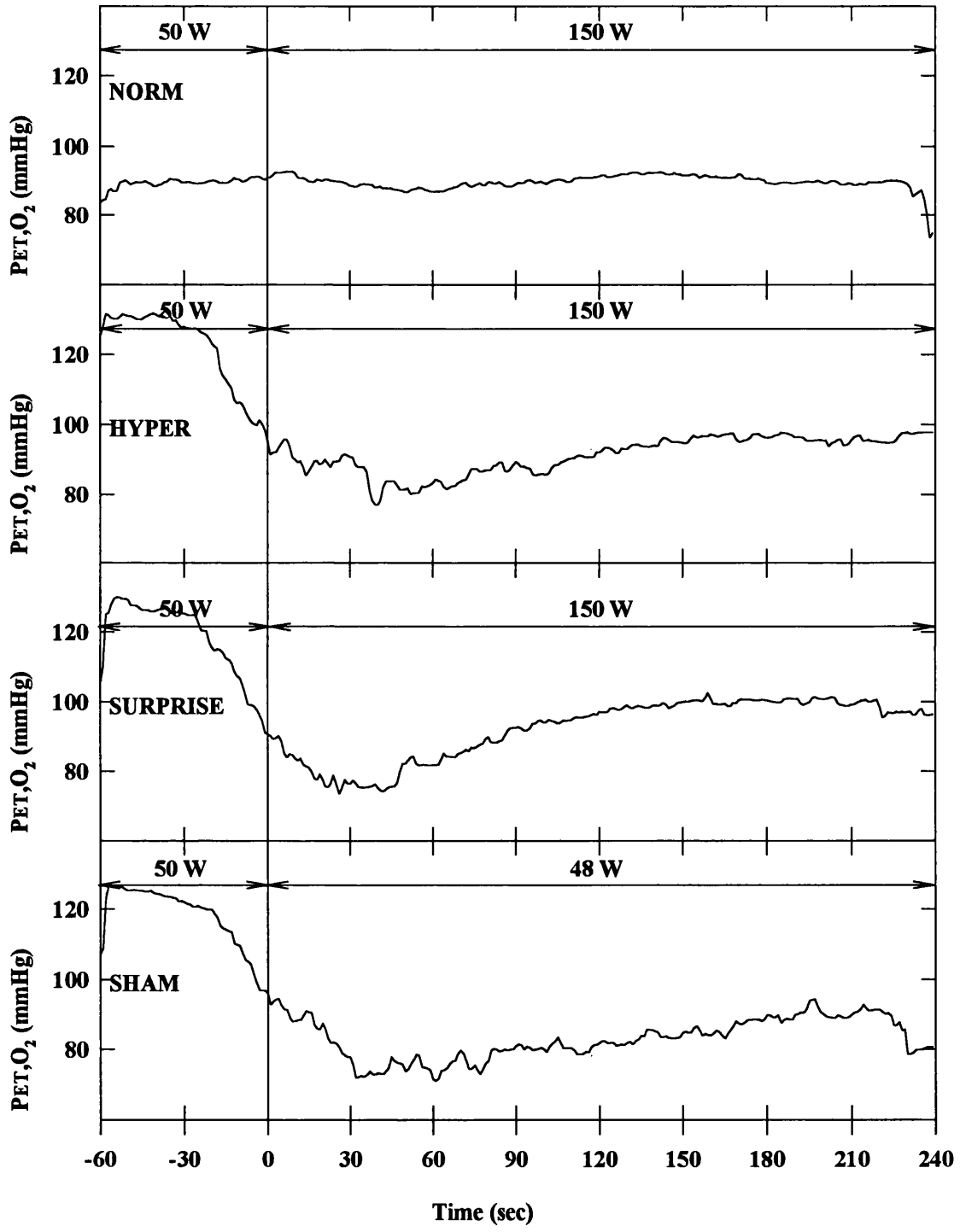


Figure 8.10: Mean changes in P_{ET,O_2} for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

	NORM	HYPER	SURPRISE	SHAM
RER	0.84 ± 0.03	0.58 ± 0.04	0.49 ± 0.03*	0.52 ± 0.05*
P_{ET,O_2}	101.3 ± 1.7	92.6 ± 5.6*	87.4 ± 3.9*	86.9 ± 5.7
P_{ET,CO_2}	46.2 ± 0.7	36.8 ± 0.8	38.6 ± 2.1*	36.8 ± 1.6

Table 8.8: Mean (± SE) values of RER, P_{ET,O_2} and P_{ET,CO_2} recorded over the first 3 breaths following the change in workload. * denotes values significantly ($p < 0.05$) different from post-"HYPER" values. N.B. Where significance was detected, the change was always indicative of hypoventilation and not hyperventilation. n = 6.

HEART RATE:

As has been mentioned before, f_C was still elevated above normal 50 W levels when exercise is increased in the "HYPER" and "SURPRISE" tests. This, in combination with the small change in heart rate associated with the 100 W increase in workload in subjects as fit as these, made meaningful modelling of the heart rate response to the increase in workload impossible in nearly all the tests. There was no evidence from the interpolated data of an abrupt change in f_C in conjunction with the change in workload (See *Fig 8.11*).

V_T and f_{BR}: As mentioned in the previous Chapter, the high state of flux associated with the rapid changes in V_E made it difficult to discern distinct changes in V_T and f_{BR} occurring in conjunction with the change in workload. No consistent pattern of response to the change in workload could be seen for any of the protocols.

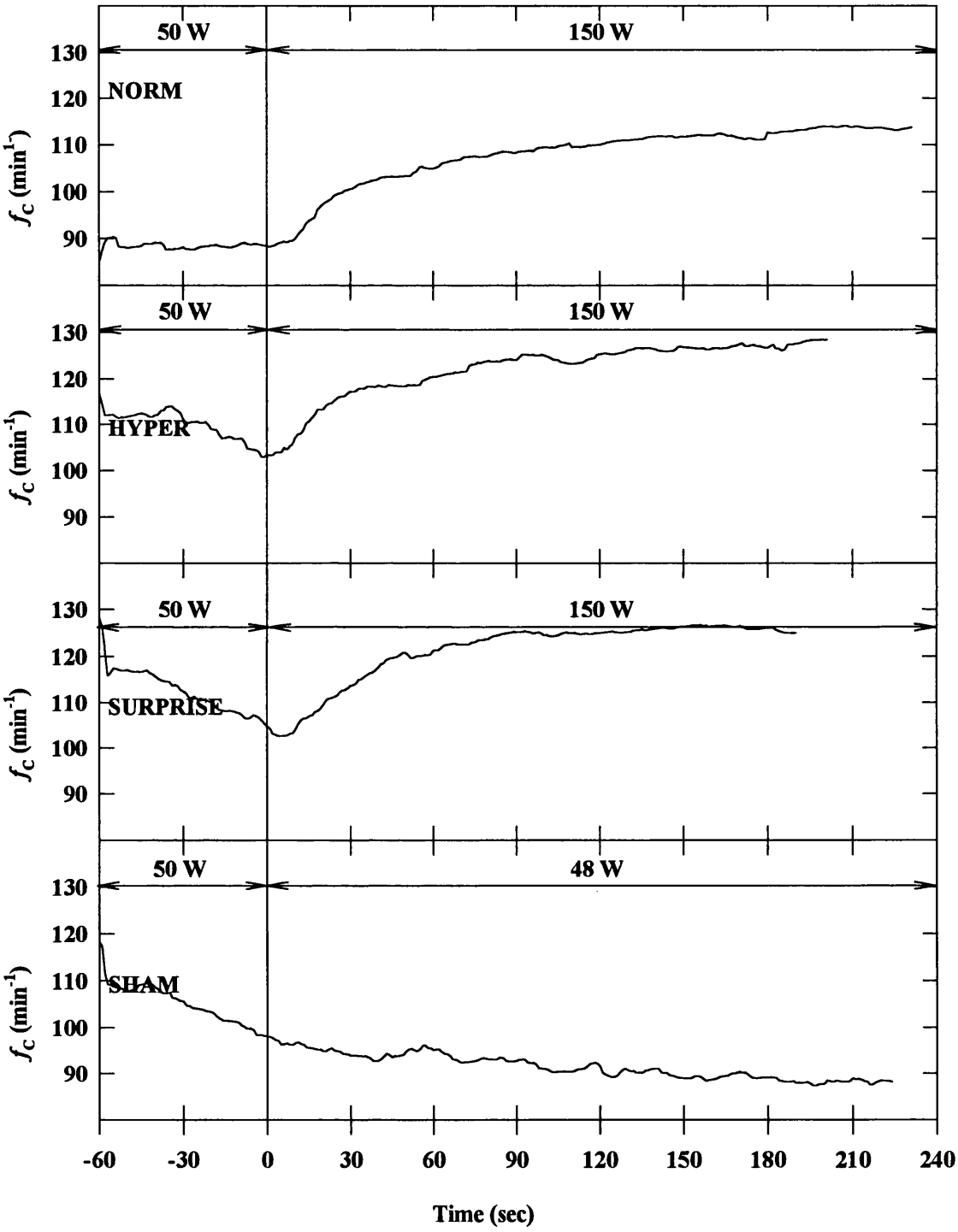


Figure 8.11: Mean changes in f_C for 1 min prior to and 4 min following the change in workload in the "NORM", "HYPER", "SHAM" and "SURPRISE" tests. Individual subject data were interpolated over 1 sec intervals, time aligned and averaged to produce a mean response. Time zero represents the change in workload. n = 6

LATER RESPONSES TO THE CHANGE IN WORKLOAD

$\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$: The time constants and delays which describe the later responses to the increase in workload (There are no results for the "SHAM" tests in this section) are presented in *Tables 8.9.*

		NORM	HYPER	SURPRISE
$\dot{V}_E$	τ	57.0 ± 7.1	51.1 ± 5.1	50.2 ± 6.8
	t_D	27.4 ± 6.1	21.2 ± 4.8	33.0 ± 8.0
$\dot{V}_{O_2}$	τ	36.0 ± 7.5	22.9 ± 2.6	26.3 ± 3.3
	t_D	25.6 ± 7.6	16.2 ± 5.7	20.7 ± 2.7
$\dot{V}_{CO_2}$	τ	51.7 ± 9.4	47.0 ± 2.0	52.4 ± 5.7
	t_D	21.9 ± 4.2	18.7 ± 6.4	21.8 ± 3.7

Table 8.9: Mean (± SE) values of τ and t_D which describe the later rises in $\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in response to the increase in workload in the "NORM", "HYPER" and "SURPRISE" tests. Values for each variable were similar in all 3 tests. n = 6.

QUASI STEADY-STATE RESPONSES:

The quasi steady-state responses to 150 W exercise in the "NORM", "HYPER" and "SURPRISE" tests and to 48 W in the "SHAM" tests are presented in *Table 8.10.*

	NORM	HYPER	SURPRISE	SHAM
fC	127.8 ± 8.0	126.0 ± 5.2	125.7 ± 9.6	88.4 ± 5.5
$\dot{V}_E$	58.6 ±3.7	57.2 ± 3.9	59.9 ± 6.2	27.3 ± 2.9
fBR	23.3 ± 2.0	24.0 ± 1.94	24.5 ± 2.3	20.4 ± 2.8
V_T	2.73 ± 0.27	2.53 ± 0.16	2.73 ± 0.35	1.5 ± 0.14
P_{ET,CO_2}	48.9 ± 0.8	46.7 ± 1.1	46.5 ± 0.8	44.9 ± 0.9
P_{ET,O_2}	102.2 ± 2.1	99.9 ± 2.0	101.6 ± 2.4	90.5 ± 2.8
$\dot{V}_{O_2}$	2.57 ± 0.11	2.67 ± 0.14	2.69 ± 0.13	1.48 ± 0.12
$\dot{V}_{CO_2}$	2.48 ± 0.17	2.31 ± 0.16	2.2 ± 0.24	0.92 ± 0.07
RER	0.97 ± 0.05	0.87 ± 0.03	0.81 ± 0.06	0.63 ± 0.04

Table 8.10: Mean (± SE) quasi steady-state responses following the change in workload in all 4 tests. Workload was 150 W for tests "NORM", "HYPER" and "SURPRISE". Workload was 48 W for test "SHAM". n = 8.

DISCUSSION

PROTOCOLS:

The protocols performed in this study were broadly in line with those presented elsewhere in this thesis. The "NORM" and "HYPER" tests were identical to those performed in Chapter 7. The "SURPRISE" test differed from the "HYPER" test only in that no command was given in conjunction with the increase in workload. In the "SHAM" test the workload was reduced slightly in conjunction with a verbal command identical to that given in the "NORM" and "HYPER" tests ("Workload going up . . . now"). The change in workload was necessary to ensure the experimenter performed the same movements in the "SHAM" test as in the "HYPER" test, thereby eliminating any visual clues as to the difference between the 2 protocols.

The change in workload was performed within the timeframe defined in Chapter 2, allowing the change in workload to occur at a time following the end of hyperventilation when $\dot{V}E$ and P_{ET,CO_2} were both below normal 50 W levels. This was comparable to the duration of the POST-HYPER period described in Chapter 7.

The duration of the second exercise stage was 4 min. As discussed in Chapter 7, this was insufficient to allow attainment of a true steady-state response. For this reason, the mean response over the last 30 sec was described as the "Quasi steady-state response".

The possibility of performing the "SHAM" and "SURPRISE" tests without hyperventilation was considered. It was rejected on the grounds that the combined effects of the onset of the later response and noise in the underlying signal would make it difficult to detect the initial ventilatory and pulmonary gas exchange responses to the change in workload. Given the purpose of the "SHAM" and "SURPRISE" protocols; to determine the effects of lying to the subject with regard to the impending workload; the performance

of multiple tests by each subject and subsequent time-averaging of the results to reduce the effective noise variance was not considered to be valid in this case.

Mathematical modelling of the ventilatory responses to the change in workload in this study and that described in Chapter 7 has demonstrated that the onset of the later response was not affected by prior hyperventilation and that the initial response was clearly visible in the "NORM" test.

INITIAL RESPONSES THE CHANGE IN WORKLOAD:

In the "NORM", "HYPER" and "SHAM" tests an abrupt increase in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ was seen in conjunction with the change in workload. This was despite the fact that the workload actually fell in the "SHAM" test. Conversely, there was no abrupt increase in $\dot{V}E$, $\dot{V}o_2$ or $\dot{V}co_2$ in conjunction with the 100 W increase in workload in the "SURPRISE" test, when no vocal command was given in conjunction with the increase in workload. The initial, abrupt increase in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ was transient in the "HYPER" and "SHAM" tests.

The results of the "NORM" and "HYPER" tests reported in this Chapter are similar to those reported in Chapter 7. This further supports the validity of the results and conclusions discussed in Chapter 7.

The results in this Chapter highlight the importance of perception on the early ventilatory and pulmonary gas exchange responses to an increase in exercise: If the subject expected the workload to increase, $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ increased abruptly in synchrony with the expected increase in workload. Equally, if an unexpected increase in workload occurred, an abrupt increase in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ was not seen. It therefore seems valid to conclude that the initial, abrupt increases in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ were dependent on the subject's perceived change of state, rather than the underlying change in workload *per se*.

It should be noted that the abrupt increase in $\dot{V}E$ seen in the "NORM", "HYPER" and "SHAM" tests was not associated with any signs of hyperventilation, i.e. a fall in P_{ET,CO_2} and an increase in both P_{ET,O_2} and RER. Quite the contrary, when significant changes in P_{ET,CO_2}, P_{ET,O_2} and RER did occur over the first 3 breaths of the new workload, they were indicative of hypoventilation.

These results explain the differences between the results reported in Chapter 5 and those in the literature: As mentioned earlier, previous studies into the ventilatory and pulmonary gas exchange responses to an increase in workload against a background of light exercise have reported a blunted, small initial response (Whipp et al., 1982; Broman & Weigertz, 1972). Such a response would be comparable to the initial response to the increase in workload seen in the "SURPRISE" test.

These results also raise doubts concerning the validity of comparing the ventilatory response to the onset of exercise from a background of rest (where it is impossible to start exercise without the subject being aware of a change in state) and an increase in workload from a background of light exercise without a warning (where the subject is unaware of the impending change in state). The justification of this protocol for a work to work transition has always been a desire to avoid any anticipatory response (Beaver & Wasserman, 1968, 1970; Broman & Weigertz, 1972), despite the fact that just such an anticipatory response is an integral part of any transition from rest to work.

When the commands are standardised, the initial ventilatory and pulmonary gas exchange responses to an increase in workload with and without prior hypocapnic hyperventilation from a background of rest (reported in Chapter 5) and from a background of light exercise (reported in Chapter 7) are similar in profile. This would suggest that there is some similarity between the control mechanisms involved. When the results of the "SHAM" and "SURPRISE" tests are also considered, these results would suggest that a significant portion of the initial, abrupt increase in $\dot{V}E$, $\dot{V}o_2$ and $\dot{V}co_2$ seen on transition from rest to

work is mediated by the perception of the increase in workload, rather than the increase in workload *per se*.

There is some support for this contention: Krogh and Lindhard (1913) have reported that if the subject believed the workload would be heavy but was in fact light, the initial ventilatory response to the start of exercise would be excessively large for the true workload, i.e. the subject's initial ventilatory response was similar to that seen on starting exercise at a high workload. Furthermore, the initial ventilatory response to electrically stimulated exercise is reported to be smaller than that seen for volitional exercise of the same intensity (Adams et al., 1987b).

These results therefore provide a possible explanation for the different profiles of the initial ventilatory and pulmonary gas exchange responses reported in the literature for transitions from rest to work and from one level of work to another.

CONCLUSIONS:

It is apparent from these results that the abrupt increase in $\dot{V}E$ seen in conjunction with the increase in workload in the previous Chapter is due to the expectation of an increase in workload rather than the increase *per se*.

These results highlight the effect of forewarning on a subject's ventilatory and pulmonary gas exchange responses to an increase in workload. As a result of this, the validity of comparing the initial ventilatory response to an increase in workload against a background of rest (where forewarning is unavoidable) and a background of light exercise when no warning is given must be questioned.

CHAPTER 9:

VENTILATORY RESPONSES TO EXERCISE IN ROWERS:

Normal patterns of ventilation, both at rest and during moderate intensity exercise have been discussed previously in this thesis, as have the proposed control mechanisms. This Chapter deals specifically with some abnormal trends seen on a consistent basis among the subjects used in this project, specifically subjects' patterns of breathing both at rest and during 150 W exercise and the difference between P_{ET,CO_2} at rest and during 150 W exercise. These observations are anecdotal and do not form part of the main argument of this thesis, but are sufficiently unusual to warrant comment. Little attempt has been made to determine the underlying causes of these responses.

Thirty one subjects have been tested during this project, 26 of whom have performed exercise at 150 W in at least one of the studies described in the preceding Chapters. Their steady-state values of f_C, $\dot{V}_E$, V_T, f_{BR}, T_I, T_{TOT}, P_{ET,CO_2} and P_{ET,O_2} both at rest and during 150 W exercise are presented in *Tables 9.1* and *9.2* respectively. Nineteen of these subjects were competitive oarsmen, the remainder are from a number of exercise disciplines.

Resting values were taken as the mean response over the last 30 sec of the initial rest period for the test in question. Steady-state responses to 150 W exercise were taken as the mean value over the last 30 sec of that exercise stage.

Data were not obtained from any tests which involved hyperventilation and data from the 70 rpm tests were used for the two subjects (A and B) who were subjects in Chapter 3 only. Some subjects have been tested for more than one study, in which case data were obtained from, in order of decreasing priority, the "N1" test in Chapter 5, the "NORM" test in Chapters 7 or 8 or the "70 RPM" test in Chapter 3.

SUBJECT	SPORT	f_C.	$\dot{V}E$	VT	f_{BR}	P_{ET,CO_2}	P_{ET,O_2}
A	ROW	89	16.5	1.74	9.8		
B	ROW	64	11.3	1.37	8.25		
C	ROW	89	7.7	0.72	10.7	44	90
D	FELL RUN	69	10.8	0.68	16.2	42	100
E	CIRCUITS	54	10.2	0.9	11.9	37	
F	SQUASH	53	12.2	0.95	13.1	42	104
G	ROW	68	12.2	0.58	21.1	37	104
I	HOCKEY	75	13.0	0.79	16.8	44	98
J	ROW	70	12.6	1.03	12.2	39	111
K	ROW	66	11.9	1.03	11.5	41	
M	ROW	46	7.7	1.34	6.9	41	104
N	ROW	62	16.8	1.15	17.4	31	119
O	ROW	67	12.7	0.81	18.9	38	105
P	ROW	62	11.7	1.13	12	38	112
Q	ROW	89	10.4	0.86	12.5	36	106
R	ROW	67	14.3	0.75	19.4		
S	ROW	70	15.9	1.01	16.2		
T	ROW	64	7.47	0.8	8.98	42	86
U	CYCLIST	71	11.4	0.62	19.8	39	99
V	ROW	71	15.6	0.95	17.4	38	
W	RUN	75	10.1	1.01	9.1	38	103
X	ROW	68	13.1	0.89	17.7	38	108
3	ROW	59	11.1	2.0	6.67	35	111
4	ROW	54	10.0	0.75	13.5	45	82
5	ROW	53	11.1	1.46	7.7	46	100
6	ROW	60	8.0	1.03	9.4	47	91

Table 9.1: Mean resting values for all subjects who performed 150 W exercise. Shading denotes results unavailable

SUBJECT	f_C	$\dot{V}E$	VT	fBR	P_{ET,CO_2}	P_{ET,O_2}	Pa,CO_2
A	127	47.3	2.02	24.2			
B	110	55.7	2.09	27.0			
C	146	55	2.90	19.4	52	99	47
D	123	66.2	1.93	34.5	45	108	42
E	100	46.5	1.57	31.1	42		40
F	128	50.4	2.68	18.8	54	100	48
G	118	49.3	1.98	23.3	45	102	41
I	136	60.1	2.08	28.5	50	99	46
J	127	41.5	2.33	17.9	55	91	50
K	123	47.7	2.99	16.0	51		45
M	105	45.3	2.93	18.6	46	99	41
N	103	45.4	2.62	19.8	42	99	38
O	110	43.8	2.22	23.5	43	98	40
P	130	56.2	2.31	24.7	51	98	46
Q	132	51.6	2.25	23.7	46	98	42
R	116	56.4	1.70	33.8			
S	134	65.4	2.86	22.9			
T	125	51.7	2.31	22.4	49	97	45
U	134	67.3	2.13	31.9	46	111	43
V	129	74.0	2.93	24.8	43		37
W	139	59.7	2.71	22.2	47	99	42
X	111	50.1	1.57	37.2	43	105	41
3	115	51.3	3.46	17.9	48	100	42
4	107	52.1	2.89	18.0	50	97	44
5	102	53.9	3.2	17.0	53	96	47
6	144	36.6	3.58	12.3	58	90	50

Table 9.2: Subjects' individual quasi steady-state values at 150 W exercise. Shading denotes results unavailable

PATTERN OF BREATHING:

A histogram (*Fig. 9.1*) shows the distribution of the subjects' resting fBR. As can be seen, a number of the subjects (36 %) have a resting fBR below 10 min^{-1}. This must be viewed as an unusual response: the textbook value for a normal resting fBR is 14 min^{-1}. Shea et al. (1987), studying a larger group of subjects, reported a wide range of resting values for fBR,

but with a range from 10 min^{-1} to 21 min^{-1}. They also reported mean resting $\dot{V}E$ to be 6.4 $l.min^{-1}$ in their male subjects, a lower value than reported here (11.8 $l.min^{-1}$). This difference may be explained in part by the different methods used to measure respiratory variables: Shea et al. (1987) used impedance plethysmography, while I used a mouthpiece and valvebox (see Chapter 2 for discussion). It would seem reasonable to expect a higher level of ventilation to be associated with an increase in f_{BR}, rather than a decrease, as seen in these subjects.

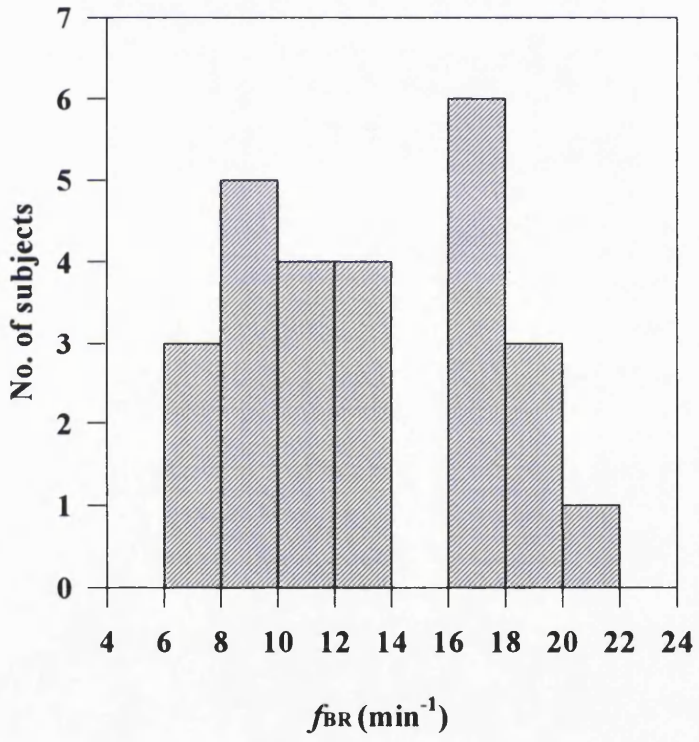


Figure 9.1: Distribution of mean resting f_{BR} for subjects tested in this project. Note high proportion of subjects with resting f_{BR} below 10 min^{-1}.

The majority (75 %) of the subjects with low resting values of f_{BR} were oarsmen (59 % of all subjects were oarsmen). This low f_{BR} was significantly correlated with an increase in V_T ($p < 0.05$), T_I and T_{TOT} (see *Figs. 9.2* and *9.3*), but was not associated with changes in V_T/T_I or T_I/T_{TOT} (See *Figs. 9.4* and *9.5*).

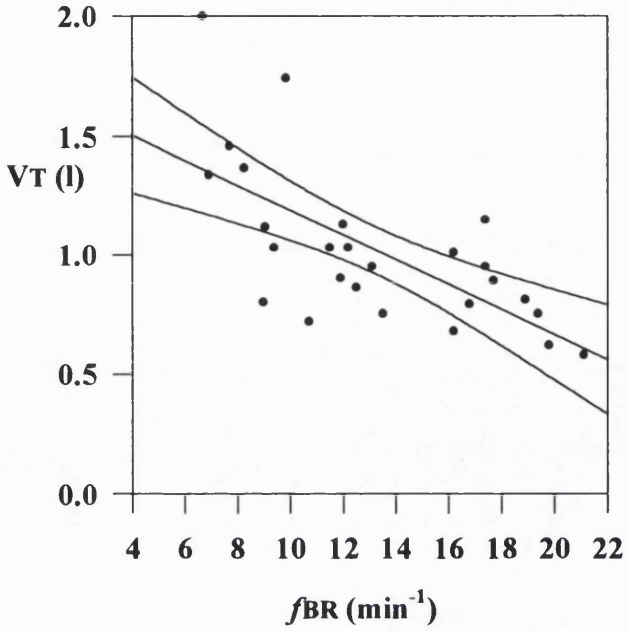


Figure 9.2: Relationship between resting f_{BR} and VT for all subjects tested in the project. Regression line (± 95 % confidence interval) is shown.

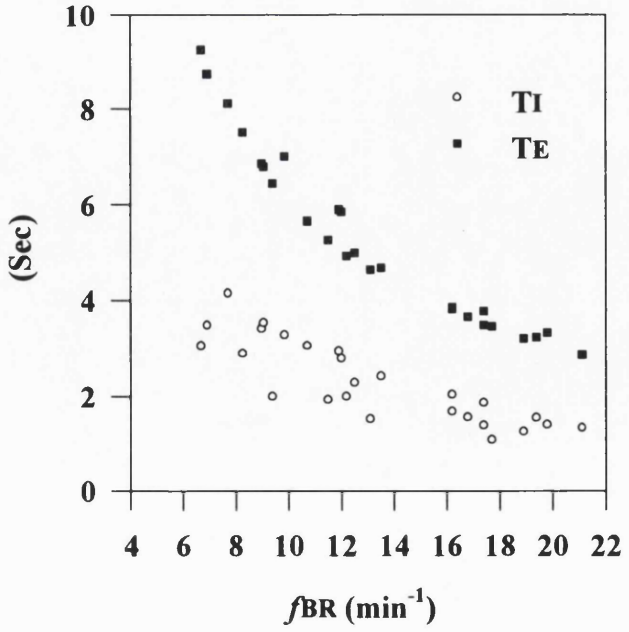


Figure 9.3: Relationship between resting f_{BR} and TI (○) and TE (■) for all subjects tested in the project.

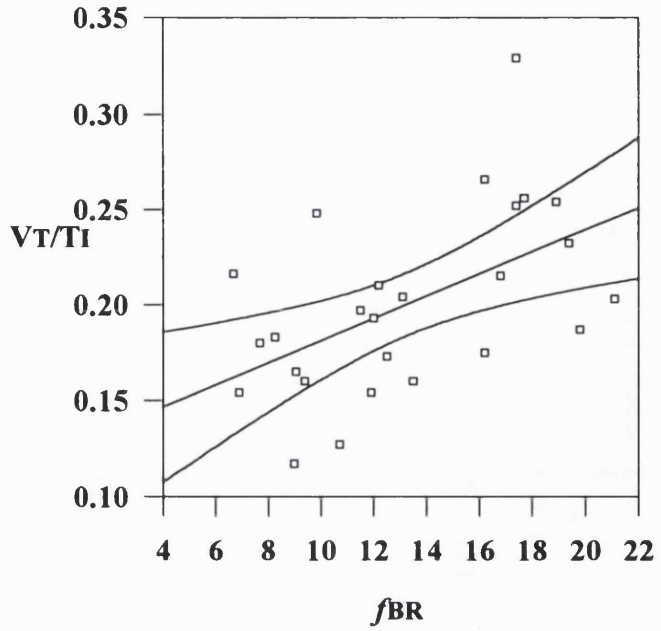


Figure 9.4: Relationship between mean inspiratory flow and *f*BR at rest for all subjects tested in this project. Regression line (± 95 % confidence interval) is shown.

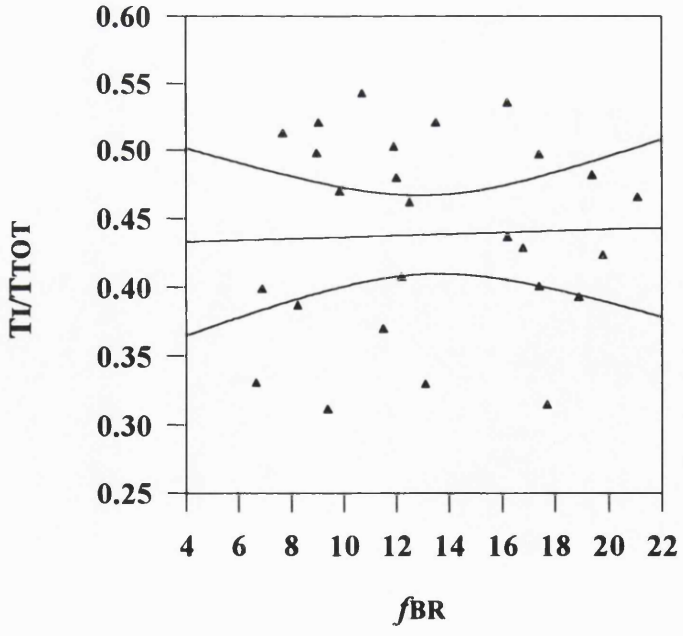


Figure 9.5: Relationship between resting *f*BR and TI/TTOT for all subjects tested in this project. Regression line (± 95 % confidence interval) is shown.

There is a significant correlation between f_{BR} at rest and f_{BR} during 150 W exercise, i.e. those with low f_{BR} at rest also have a low f_{BR} during exercise (see *Fig. 9.6*). It does not appear to be related to fitness (estimated in this case by heart rate response to 150 W), height or weight.

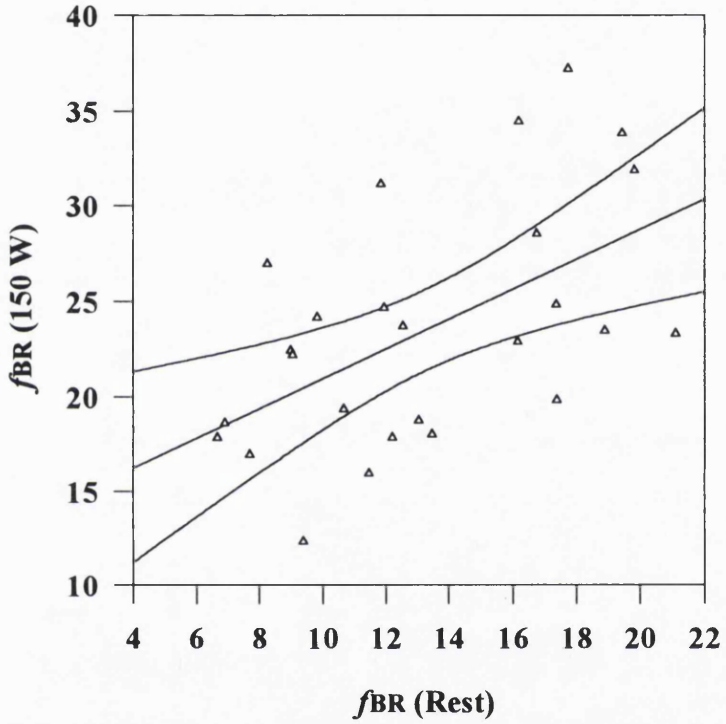


Figure 9.6: Relationship between mean f_{BR} at rest and during steady-state exercise at 150 W for all subjects tested in this project. Regression line (± 95 % confidence interval) is shown.

It is possible that the abnormal pattern of breathing described here is the result of a strategy adopted by the athletes to improve their rowing performance. Mahler et al. (1991a,b) have reported a high incidence of respiratory-locomotor coupling amongst oarswomen and have provided evidence that this is not an innate, but rather a learned response to the mode of exercise. Although this may result in an improvement in the overall efficiency of the subject's rowing stroke, it also limits the range over which f_{BR} can change to integers of the rowing stroke.

The majority of training and racing occurs at stroke rates of between thirty and forty. It is therefore apparent that the majority of the ventilatory response to rowing exercise will be achieved by changes in VT, with *f*BR being held at a relatively low level (Steinacker & Whipp, 1994). This would be a similar response to that seen here for cycle ergometry among competitive oarsmen. It should also be noted that any change from a 1:1 ratio for respiratory-locomotor coupling would be associated with a much higher rate of breathing. This may be the explanation of the high values for *f*BR seen in those rowers who do not maintain their *f*BR at a lower level.

HYPERCAPNIA DURING EXERCISE:

It has long been accepted that Pa,CO_2 is controlled at or near to its resting level during constant, moderate intensity exercise in humans. It is also recognised that although P_{ET},CO_2 may be a good predictor of Pa,CO_2 at rest, the increase in slope of the alveolar phase of P_E,CO_2 means that P_{ET},CO_2 is greater than Pa,CO_2 during exercise. It is, however, possible to estimate Pa,CO_2 from P_{ET},CO_2 using the formula first devised by Jones et al. (1979):

$$Pa,CO_2 = 5.5 + 0.9.P_{ET},CO_2 - 0.0021.V_T,$$

where VT was measured in ml. They reported Pa,CO_2 values predicted from P_{ET},CO_2 to have a 95 % confidence limit of ± 2 mmHg.

This formula was applied to the individuals' quasi steady-state responses to 150 W cycle ergometry to predict Pa,CO_2 and the results are presented in *Table 9.1.* It is clear from these results that Pa,CO_2 during exercise, predicted from P_{ET},CO_2 using the above formula is more than 2 mmHg higher than resting values for a sizeable (68 %) proportion of the subjects tested (75 % of oarsmen tested became hypercapnic on exercise). Again, these results must be considered unusual compared to those reported in the literature for normal

untrained subjects, although Dempsey et al. (1984b) reported that while the mean change in Pa,CO_2 on transition from rest to exercise may be small, there is a remarkable level of inter-individual variation. They reported mild exercise was associated with an increase in Pa,CO_2 of between 1.5 and 2.3 mmHg in most subjects. Furthermore, their *Fig. 2A* would suggest that cycle ergometry is associated with a greater increase in Pa,CO_2 than treadmill running.

The mode of exercise may therefore be responsible for some of this response. Equally, the high levels of fitness seen in these subjects may result in 150 W, a workload associated with severe exercise in many normal individuals, being quite light for these subjects. In support of this are the comments of the subjects: following the 90 rpm tests described in Chapter 3 all subjects complained that they felt out of control when exercising at 50 W due to a lack of any resistance in the pedal. 100 and 150 W were considered the most comfortable workloads at which to exercise. Unfortunately there is no correlation between steady-state heart rate at 150 W (used as a predictor of subject fitness) and the extent of CO_2 retention.

The difference in Pa,CO_2 seen at rest and during 150 W exercise is also unrelated to exercise $\dot{V}E$, f_BR, VT, VT/TI (*Figs. 9.7a* to *d*) or carotid body function (Howell & Cross, 1994d; see Appendix H).

To conclude, unusual patterns of ventilation and ventilatory responses to exercise have been seen in a high proportion of the subjects tested (particularly the oarsmen). These can be characterised as a slow, deep breathing pattern both at rest and during exercise and a tendency during exercise to allow Pa, CO_2 (as predicted from P_{ET},CO_2 by the formula of Jones et al., 1979) to rise by over 2 mmHg when compared to resting values. These two phenomena are not related. No explanation is proposed to account for these results.

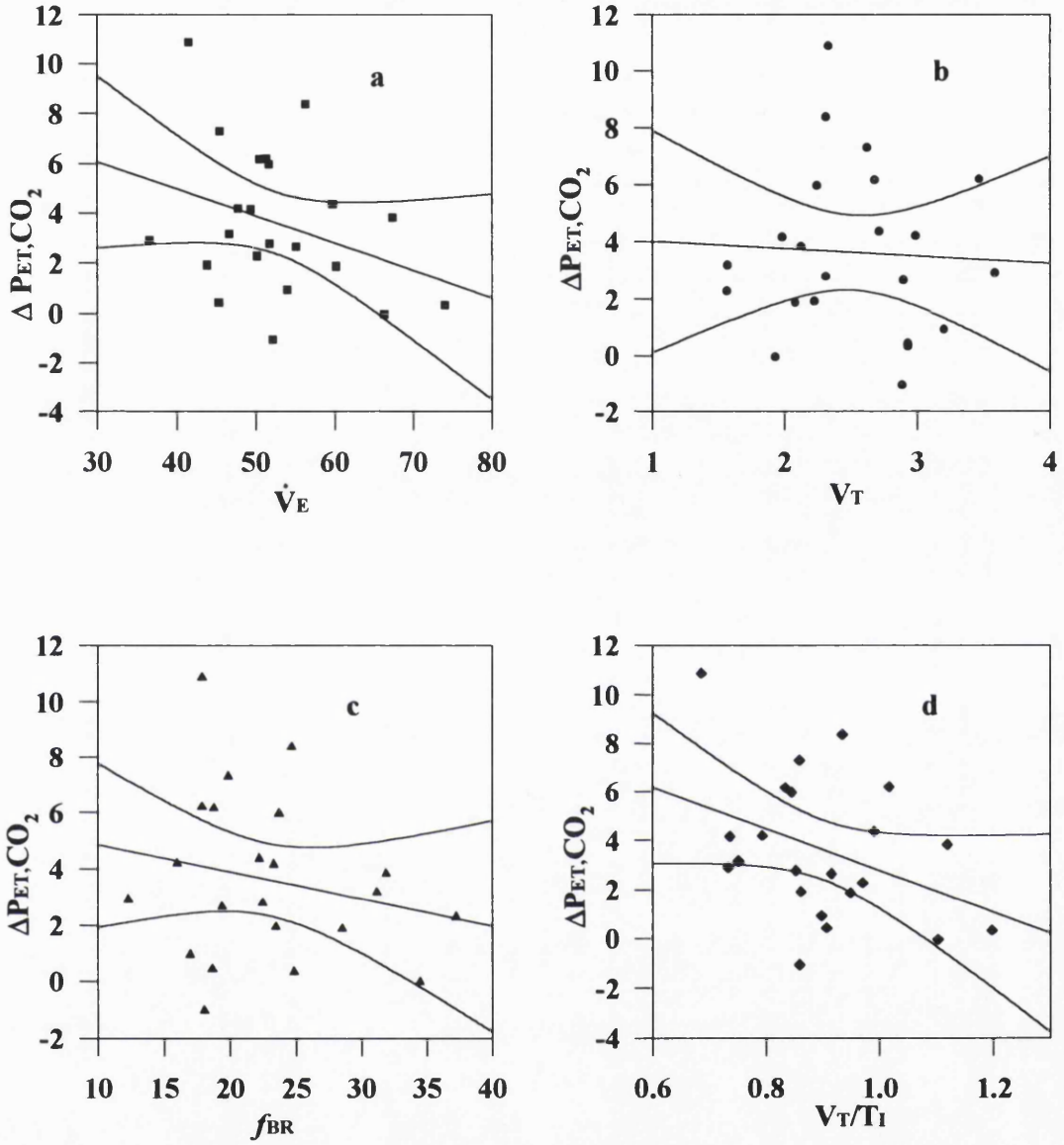


Figure 9.7: Relationships between the extent of CO_2 retention on 150 W exercise and ***a:*** steady-state $\dot{V}E$ at 150 W, ***b:*** steady-state VT at 150 W, ***c:*** steady-state fBR at 150 W and ***d:*** VT/TI at 150 W. Regression lines (± 95 % confidence intervals) are shown.

CHAPTER 10: CODA

CONCLUSIONS AND IMPLICATIONS FOR FURTHER RESEARCH.

The major results of this thesis can be summarised thus:

(i) If a preparatory warning is given, $\dot{V}E$ almost always increases abruptly in conjunction with the increase in workload, regardless of whether the increase is imposed from a background of rest or mild exercise.

(ii) This initial increase in $\dot{V}E$ is associated with the expectation of the increase in workload, rather than the increase in workload *per se*.

(iii) The initial, abrupt increase in $\dot{V}E$ is transient in nature, lasting for only two to three breaths. As a result the initial ventilatory response should be separated into (at least) two sections: the initial, abrupt increase (the first three breaths of the new workload) and the subsequent plateau (from the fourth breath to the onset of the later, more gradual rise). The transient nature of this initial response can be highlighted by reducing body CO_2 stores prior to the increase in workload.

(iv) Lowering body CO_2 stores prior to the increase in workload delays the onset of the later response for $\dot{V}E$ and $\dot{V}co_2$ if the step-change in workload was performed against a background of rest, but not if the step-change in workload was performed against a background of unloaded pedalling the time constants of the later responses were unaffected. These differences reflect the effect of exercise on the relative sizes of the body's CO_2 storage compartments. The changes seen in the later response for $\dot{V}E$ closely match those seen for $\dot{V}co_2$.

(v) There was some circumstantial evidence to suggest that the subsequent plateau response for $\dot{V}E$ was dependant on arterial Pco_2: its magnitude was reduced if the increase in workload was preceded by hypocapnic hyperventilation.

These results have some serious implications for the interpretation of the ventilatory response to moderate intensity exercise:

These results bring into question the validity of comparing the early ventilatory response to an increase in workload from a background of rest, where some form of preparatory warning to initiate the exercise cannot be avoided, and from a background of mild exercise if a preparatory warning is not given. In the former case the start of exercise heralds a distinct change in state for the subject, while in the latter case the subject might not immediately be aware that the workload has changed.

Without a preparatory warning, the most rapid response achievable will still be reactive in nature, as opposed to the proactive response seen if the subject is told exactly when the change in workload will occur (thereby highlighting the impending change in state to the subject). The ventilatory response to a workload imposed against a background of rest is inherently proactive in nature, while the ventilatory response to a transition from mild to moderate intensity exercise in the absence of any warning is inevitably reactive in nature.

The results reported in Chapter 5 bring into question the genesis and control of the early ventilatory response seen on transition from rest to exercise, particularly whether it can be explained simply in terms of an intrinsic response to a neurogenic stimulus. The early response seen here was biphasic in nature: an abrupt increase in $\dot{V}E$ which then declined somewhat before the onset of the later response. Current theory would predict that the neurogenic stimulus for the early response was present at a constant level throughout exercise with the humorally mediated response combined with it. It is difficult to see how this view can be reconciled with the results of the "N" tests in Chapter 5. The reduced subsequent plateau response seen in the "H" tests in Chapter 5 only serves to accentuate these differences.

The results from Chapter 7 would suggest that the abrupt increase in $\dot{V}E$ seen on transition from mild to moderate exercise was not due to intrinsic control mechanisms, but was the

result of a conditioned reflex stimulated by the perceived increase in workload. This would suggest that exercise hyperpnoea was, to some extent, under suprapontine control.

CO_2 has been proposed as the major controller of later and steady-state ventilatory responses to moderate intensity exercise. These results not only support this view, but also extend the sphere of influence of CO_2 to include the subsequent plateau response. It could be argued that, if the initial "reflex" response seen at the start of exercise were to be abolished, the sphere of influence of CO_2 could be extended further to include the entire ventilatory response to moderate intensity exercise.

The results reported in this thesis also suggest possible avenues for further research. Perhaps most importantly, the experiments need to be repeated in normal sedentary individuals to ensure that the changes in $\dot{V}E$ seen in conjunction with the start of exercise and the increase in workload are not specific to highly trained athletes. Furthermore, to my knowledge the experiments of Krogh & Lindhard (1913) investigating the magnitude of the early ventilatory response to exercise if the workload differs from what the subject has been led to expect have not been repeated. This situation needs to be redressed.

The results from Chapter 5 tantalise with the suggestion that the subsequent plateau response may be responsive to changes in Pa,CO_2. A more controlled pattern of hyperventilation needs to be carried out, using different levels of hyperventilation to vary the size of the subsequent fall in Pa,CO_2, to determine whether there is a relationship between Pa,CO_2 and the magnitude of the subsequent plateau response. The "bleep box" developed by Rafferty & Gardner (1994) may be the ideal method of controlling both f_{BR} and V_T during hyperventilation.

CO_2 is not the only proposed humorally mediated controller of exercise hyperpnoea: there is evidence to suggest that potassium has a role to play (Paterson et al., 1990; Newstead et al., 1990; Yoshida et al., 1990; Busse et al., 1991; Linton et al., 1984). It is therefore important to determine whether prior hypocapnic hyperventilation changes the time course

of the rise in arterial potassium on starting exercise. A pilot study for this experiment has already been done using arterialised venous blood samples taken from the antecubital vein. This will also allow the measurement of arterial Pco_2 in the subjects, giving an opportunity to discover if some subjects really do allow Pa,CO_2 to rise on exercise.

CO_2 retention on exercise is still not a widely recognised phenomenon, yet it has been seen in 75 % of oarsmen tested in this project. Just what the difference is between these subjects and those who do not retain CO_2 on exercise is has not yet been determined. A small study has been performed, preliminary results of which have been published (Howell, Allford & Cross, 1994d; See Appendix I). From these results it is possible to rule out a functional insufficiency of the carotid bodies as the cause of CO_2 retention on exercise.

Besides CO_2 retention on exercise, a high proportion of the rowers tested also presented with an unusually low resting fBR. The patterns of breathing seen in other groups of athletes needs to be investigated to whether rowers are unique in this response.

The experimental protocol used in Chapter 6 was highly specific in its design. A more general study into the effects of different levels and durations hyperventilation on postural sway is needed. The use of the "bleep box" developed by Rafferty & Gardner (1994) would allow a more precise control of the level of hyperventilation than the oscilloscope used in Chapter 6. It would also allow the studies to be performed with the subject's' eyes closed. This is known to increase postural sway (Mills, 1994), thereby making the test more sensitive.

Finally, the results of this study have a real life application for oarsmen and other athletes. It is apparent from these results that hyperventilation prior to a race is not a good idea: any depression of ventilation in the initial portion of a race will inevitably result in an increase in the O_2 debt. This may have undesired consequences in the final stages of the race, perhaps even at the cost of winning. This is not usually a desired outcome.

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APPENDIX A:

EXERCISE TESTING PROGRAMS EXPLAINED

Data acquisition and storage is a fundamental part of experimental technique. The decision to reject chart recorder paper and breath-by-breath measurements of analyser outputs from it as the method of data acquisition and storage was taken early on in the project. To this end, a computer program was written (in Microsoft Quickbasic) which would provide on-line analysis of the results and also store the data to disc for later study. These data were backed up by the storage on magnetic tape of the original analogue signals. During the course of the project the computer program underwent three major mutations, called (from earliest to latest respectively) "EXTEST 1", "EXTEST 2" and "EXTEST 3". These were run on an IBM P-c incorporating an analogue to digital converter (Amplicon P-c 26a).

Each program can be separated into three major areas: subject (and test) details, calibration of program inputs (i.e. analyser voltage output) and on-line analysis. Entering the subject and test details was very similar for all three versions of the program (see Appendix B for the wording used in "EXTEST 3"; subroutines TODAY and SUBJECT) The principle of calibration, two-point calibration curves for all analysers except the pneumotachograph(s) which used four-point calibration (see chapter 2), was the same in all versions of the program, simply updated to account for new pieces of equipment (the Airspec 2,600 mass spectrometer in "EXTEST 2" and the second pneumotachograph in "EXTEST 3").

The major differences between the three programs lay in the on-line analysis sections. To start with the crudest version, "EXTEST 1", only one pneumotachograph was available at that time, monitoring expiratory flow ($\dot{V}_E$). As such, the start of expiration was defined as the time when $\dot{V}_E > 0$ and the start of inspiration was defined as the time when $\dot{V}_E$ returned to 0 (or 2040, the A-D equivalent of 0 V), allowing the calculation of T_I, T_{TOT} and f_{BR}. The start of a breath was defined as the start of expiration, as this was the more easily determined endpoint. V_T was calculated by integrating $\dot{V}_E$, a method common to all versions of the program.

For reasons now unclear to me the calculation of $\dot{V}o_2$ and $\dot{V}co_2$ was performed approximately every twenty sec from mean values of $\dot{V}E$ (STPD), PE,O_2 and PE,CO_2

(measured at the end of each breath) during that period. This obviously reduces the sensitivity of the measurements when compared to breath-by-breath data. Furthermore, there was no correction for the 10.5 l volume lag between the measurement of $\dot{V}_E$ and the measurement of $P\bar{E},O_2$ and $P\bar{E},CO_2$. This invalidated all values except for those taken during steady-state, when values of $P\bar{E},O_2$ and $P\bar{E},CO_2$ and $\dot{V}E$ were by definition relatively constant.

"EXTEST 2" was associated with two major changes: firstly, the volume lag mentioned above was taken into account and $\dot{V}o_2$ and $\dot{V}co_2$ were expressed on a breath-by-breath basis, and secondly the Airspec 2,600 mass spectrometer became available, allowing the monitoring of $P\bar{E},O_2$ and $P\bar{E},CO_2$. From these, PET,O_2 and PET,CO_2 were calculated as the minimum and maximum values during the following inspiration respectively to account for the time lag of the analyser.

Both of these changes were achieved by essentially the same method: respiratory data from each breath were saved as a unit (called an array) in a temporary memory eighty arrays long. Each array was identified by a number corresponding to its position in the temporary memory. At the end of each inspiration the values of PET,O_2 and PET,CO_2 were added to the array of the preceding breath.

To account for the 10.5 l volume lag a variable was added for each breath-BIGVOL. BIGVOL was the total expired volume for the test and was updated at the end of each expiration. If BIGVOL for the earliest breath in the temporary memory was more than 10.5 l smaller than the current value, $P\bar{E},O_2$ and $P\bar{E},CO_2$ were measured, added to the array and the array transferred to the permanent file. When the temporary file was filled it started to save data at the beginning again, so creating a rolling memory system. This uses less RAM memory than would a continually expanding temporary file.

"EXTEST 3" incorporated a second pneumotachograph and Fleisch head for the monitoring of inspiratory flow ($\dot{V}_I$). This gave much clearer definition of the start of inspiration ($\dot{V}_I > 0$), allowing the start of a breath to be defined as the start of inspiration.

This program is featured in all the Appendices unless otherwise stated. It is validated in Appendix B and listed in Appendix C.

Calculation of $\dot{V}o_2$ and $\dot{V}co_2$: Algorithms.

$\dot{V}E$ (STPD), $\dot{V}o_2$ (STPD) and $\dot{V}co_2$ (STPD) were calculated by the exercise testing programs from direct measurements of $\dot{V}E$ (ATPS), $F\bar{E},O_2$ and $F\bar{E},CO_2$. $\dot{V}E$ (ATPS) was monitored by the expiratory pneumotachograph, $F\bar{E},O_2$ and $F\bar{E},CO_2$ were monitored directly from expired gases which had passed through a mixing chamber using the Medishield MS2 and Beckman LB-2 gas analysers respectively. This method differs from that of Beaver et al. (1973, 1981), who calculated $P\bar{E},O_2$ and $P\bar{E},CO_2$ by the integration of tidal changes in Po_2 and Pco_2.

$\dot{V}E$ (STPD):

$\dot{V}E$ was calculated on a breath-by-breath basis by the integration of $\dot{V}_E$:

$$\dot{V}E = [\int_{t1}^{t2} \dot{V}_E dt] \, x \, fBR \qquad (1)$$

$\dot{V}E$ (ATPS) then had to be converted to $\dot{V}E$ (STPD):

$$\dot{V}E\,(STPD) = \dot{V}E(ATPS)\, x \, \frac{B.P.-S.V.P.}{760} \, X \, \frac{273}{273+T} \qquad (2)$$

$\dot{V}o_2$:

In principle, the calculation of $\dot{V}o_2$ is very simple. It is the amount of O_2 absorbed from the inspired air, i.e.:

$$\dot{V}o_2 = (\dot{V}I \times FI,O_2) - (\dot{V}E \times FE,O_2) \quad (3)$$

In reality, the calculation of $\dot{V}I$ from the available information complicates the equation somewhat. Calculation of $\dot{V}I$ is possible as a result of Boyle's law and the law of conservation of mass: When corrected to STPD and assuming no change in FRC, the mean volume of N_2 inspired must equal the mean volume of N_2 expired (included with N_2 are a number of trace inert gases, notably Argon):

$$\dot{V}I,N_2 = \dot{V}E,N_2 \quad (4)$$

The volume of N_2 in each inspiration (or expiration) can be calculated easily:

$$\dot{V}E,N_2 = \int_{t1}^{t2} \dot{V}E \times (1-(FE,O_2 + FE,CO_2))dt \quad (5)$$

$\dot{V}I$ can therefore be calculated from $\dot{V}E$:

$$\dot{V}I = \dot{V}E \times \frac{FE,N_2}{FI,N_2} \quad (6)$$

Substituting into equation 3,

$$\dot{V}o_2 = \left(\left[\dot{V}E \times \frac{FE,N_2}{FI,N_2}\right] \times FI,O_2\right) - \left(\dot{V}E \times FE,O_2\right) \qquad (7)$$

Equation 7 can be rewritten as:

$$\dot{V}o_2 = \dot{V}E\left[\left(\frac{FE,N_2}{FI,N_2} \times FI,O_2\right) - FE,O_2\right] \qquad (8)$$

Substituting equation 5 into equation 8:

$$\dot{V}o_2(STPD) = \dot{V}E(STPD)\left[\left(FI,O_2 \times \frac{1-(FE,O_2+FE,CO_2)}{1-(FI,O_2+FI,CO_2)}\right) - FE,O_2\right] \qquad (9)$$

This is the equation used in the exercise testing programs.

$\dot{V}co_2$:

As FI,CO_2 is very nearly zero, the equation for the calculation of $\dot{V}co_2$ can be simplified somewhat:

$$\dot{V}co_2\,(STPD) = \dot{V}E(STPD) \times FE,CO_2 \qquad (10)$$

In the calculation of both $\dot{V}o_2$ and $\dot{V}co_2$ certain assumptions have been made:

When expired air leaves the mouth, it is at 37° C and saturated with water vapour. Upon leaving the mouth it will cool, so becoming more dense (according to Boyle's law) and losing water vapour (according to Charles's law). This will occur in the space between the mouthpiece and the Fleisch head. Thus the volume of expired air measured by the Fleisch head is smaller than that expired. Beaver et al. (1973) reported this volume to be small enough to be neglected and I have followed their example.

No allowance has been made for the added dead space of the mouthpiece and valvebox. The above formulae also do not take into account the effects of changes in FRC on measurement of $\dot{V}o_2$ and $\dot{V}co_2$ at the mouth. Wessel et al., (1979) reported a greater dispersion of data around the set point if $\dot{V}o_2$ and $\dot{V}co_2$ were measured at the mouth compared to the alveoli. Beaver et al. (1981) also reported a reduction in the signal to noise ratio when gas exchange variables measured at the mouth were corrected for changes in lung gas stores.

APPENDIX B:

VALIDATION OF EXTEST 3

INTRODUCTION:

It is important to determine whether the values generated by the data acquisition programs are a true representation of the changes in the physiological variables occurring at that time.

Accurate detection of $\mathbf{P_{ET,CO_2}}$ and $\mathbf{P_{ET,O_2}}$ is dependant on the use of a fast response analyser with a linear response over the physiological range. This is achieved by the use of a mass spectrometer. The only remaining problem then is to ensure that each end-tidal value is attached to its correct breath. This will depend on the mass spectrometer sample transit time: Due to the fast response characteristics of the Airspec 2 600, this is adequately achieved (for normal humans, at least) by taking P_{ET,CO_2} for a breath as the maximum P_{CO_2} recorded during the expiration and the subsequent inspiration (to account for the 0.3 time delay between changes in gas tensions at the mouth and changes in voltage output from the mass spectrometer). P_{ET,O_2} is the lowest P_{O_2} during that time.

$\mathbf{P_{E,O_2}}$ and $\mathbf{P_{E,CO_2}}$ can be accurately determined using rapid response gas analysers with a linear output over the physiological range. This is adequately achieved by the Medishield MS-2 and the Beckman LB-2 respectively. Care must be taken to ensure that the values for $\dot{V}_E$ and P_{E,O_2} and P_{E,CO_2} correspond to the same portion of gas. There is a volume lag of 10.5 l between the measuring of $\dot{V}_E$ (at the mouth) and the measuring of P_{E,O_2} and P_{E,CO_2} (at the end of the mixing box). This is corrected for by the exercise testing program.

In EXTEST 3 the incorporation of a second Fleisch head and pneumotachograph allowed the monitoring of changes in inspiratory and expiratory flow. From these data, it is possible to identify the start of a breath (taken as the start of inspiration, i.e. $\dot{V}_I > 0$, see *Fig. B.1*). **T_{TOT}** can therefore be calculated as the time to the start of the next inspiration. **f_{BR}** is calculated as $60/T_{TOT}$. **T_I** is taken as starting when $\dot{V}_I < 0$ and ending when $\dot{V}_E > 0$), allowing the calculation of **T_I/T_{TOT}**. **V_T** is calculated by integrating $\dot{V}_E$, the resulting volume then being corrected to **BTPS** (for expression of V_T and $\dot{V}_E$) and **STPD** for calculation of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$). **$\dot{V}_E$** can then be calculated as $f_{BR} * V_T$.

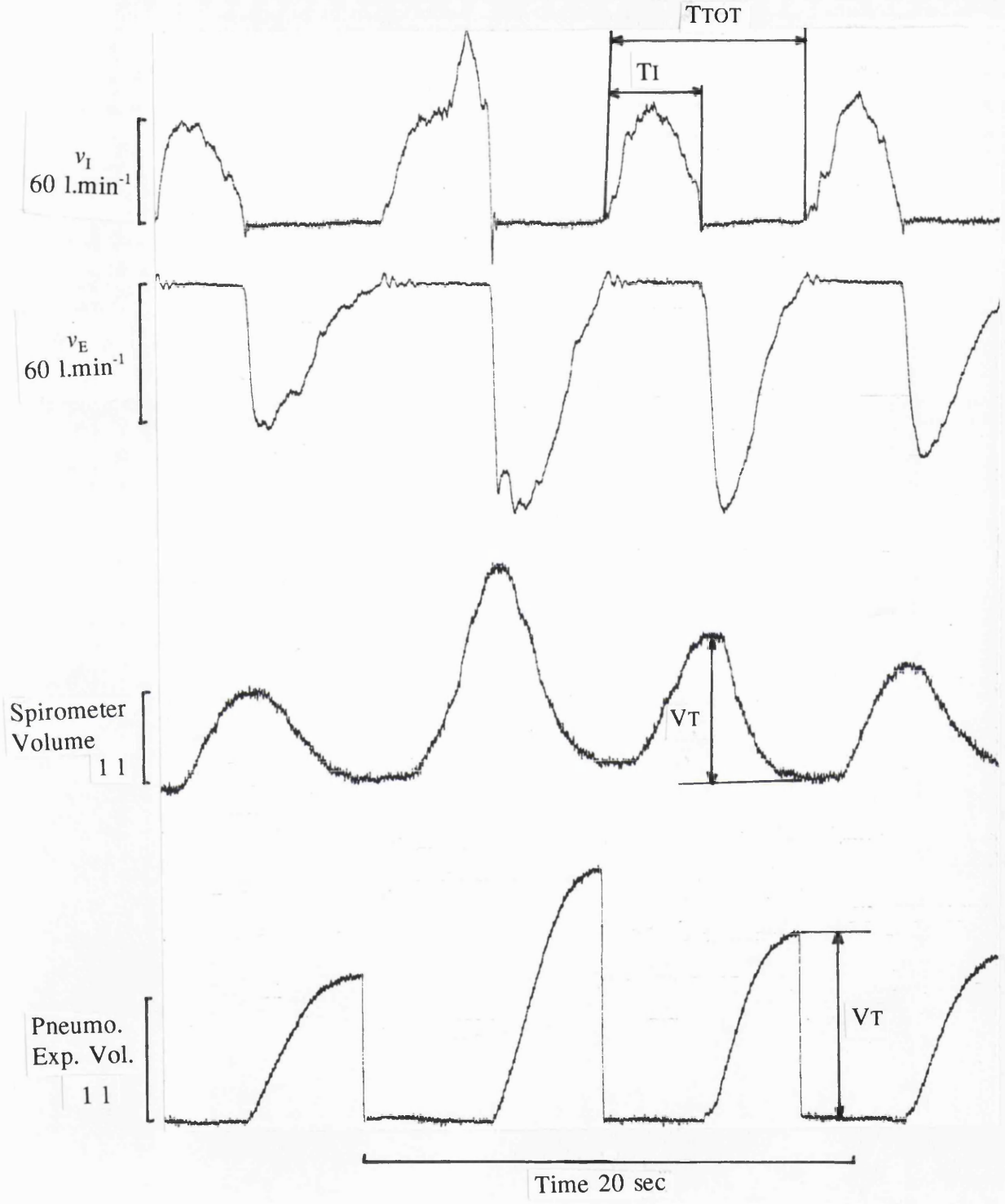


Figure B.1: Trace of recordings of v_I, v_E, expiratory volume (from pneumotachograph) and spirometer volume over a series of breaths. VT, TI and TTOT are all marked on the trace.

Appendix B

The accuracy of the respiratory results generated by the computer program will depend (assuming accurate calibration) on the accurate determination of the end-points for each breath and a sufficiently fast analysis rate to allow accurate integration of expiratory flow. The analysis frequency of the program was set at 20 Hz. The best method of checking the accuracy of the results generated by the program was, however, to compare its values to those measured by spirometry, i.e. in a real physiological situation. This has been done and the methodology and results are outlined below. These results have been published in abstract form (Howell & Cross, 1995b).

VALIDATION OF VENTILATORY VARIABLES:

The exercise testing program was calibrated in the usual manner. The subject breathed through a Hans Rudolph 2 700 series mouthpiece while wearing a noseclip. Inspiratory and expiratory flows and volumes were monitored by two Fleisch heads (No. 4) connected to two Gould pneumotachographs. These were then connected by way of elephant tubing to a spirometer (Harvard student model 9 l) which incorporated an analogue voltage output. The analogue outputs from all the apparatus were connected to a Racal DS-7 magnetic tape recorder, with the flow outputs connected in parallel to an IBM-Pc loaded with the data acquisition program EXTEST 3. The subject was asked to breathe normally for one minute and then to vary his pattern of breathing as he wished.

Once the sensation of dyspnoea associated with breathing from a confined volume of air became uncomfortable, the subject came off the mouthpiece and a calibrated gas syringe (Hans Rudolph No. 5530, 3 l) was inserted into the mouthpiece. A series of "breaths" of known volumes from the syringe were then passed through the system for calibration of the spirometer. The speed at which the syringe plunger was depressed was varied to simulate day-to-day variation and to determine what effect this had on the readings from the program and the volume outputs from the pneumotachographs.

DATA ANALYSIS:

Breath-by-breath values of V_T, T_I and T_{TOT} were measured from a chart recording of the taped data from both the spirometer and pneumotachographs. Using the spirometer data for V_T and the pneumotachograph data for T_I and T_{TOT} as the independent variable, regression analysis was used to compare these data with the corresponding values generated by the exercise testing program. Regression analysis was performed to determine the correlation line of best fit for the data. The line of best fit was, with the exception of the calibration curves, constrained such that the line passed through the origin.

RESULTS:

VT: Calibration of equipment. As described in Appendices A and C, the exercise testing program works by integrating the expiratory flow to calculate expiratory VT. Expiratory flow is calibrated at four flows. These are approximately 300 $l.min^{-1}$, 120 $l.min^{-1}$, 60 $l.min^{-1}$ and 20 $l.min^{-1}$. These values are used to generate two calibration curves; an unfortunate necessity due to the flow: voltage characteristics of the apparatus (see *Fig 2.1*).

The spirometer was calibrated by passing a number of "breaths" of varying flow-rates from a calibrated syringe (Hans Rudolph) through the system. The volume of the breaths varied between 0.5 l and 3 l in 0.5 l increments. The line of best fit through the data was determined by linear regression (See *Fig. B.2*) and used to convert the chart recorder deflection (mm) to volume (l) for the subject-generated breaths.

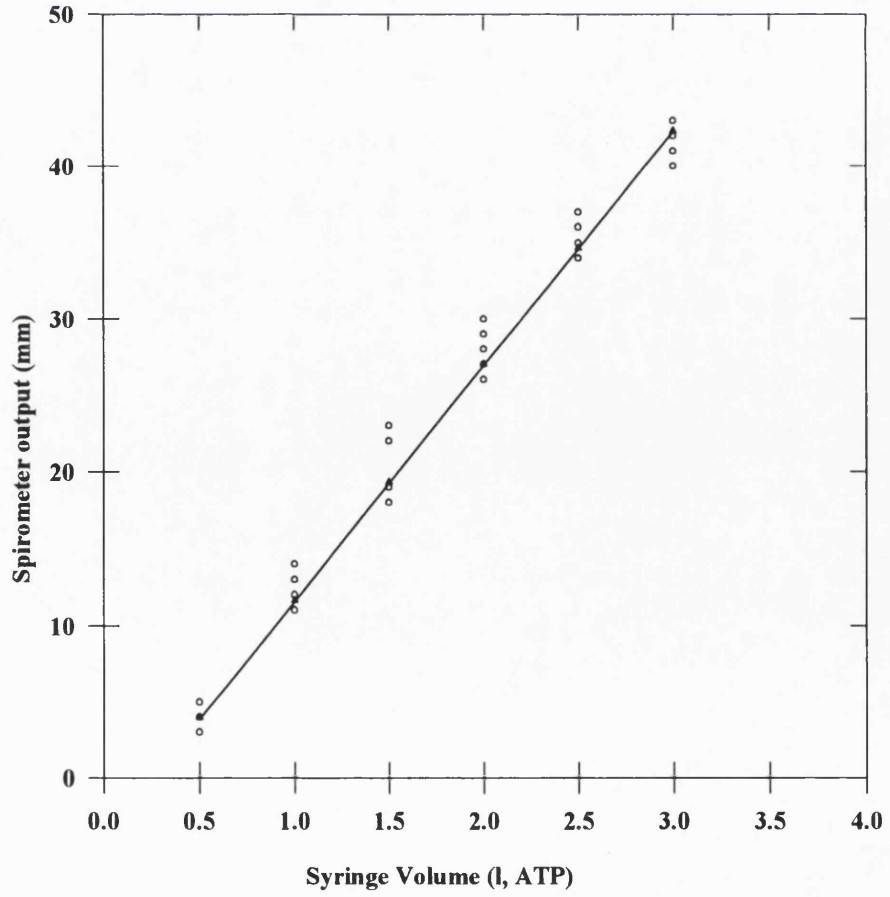


Figure B.2: Calibration line for spirometer output. R = 0.996, see text for equation.

The formula for the line was:

$$\text{Spirometer output (mm)} = 15.3 * (V_T, \text{ATP}) - 3.7$$

with an R-value of 0.996.

Initially, the pneumotachograph volume output was calibrated using the integral of the known flows used to calibrate the computer program. The four flows, however, produced a wide range of calibration values. Furthermore, tidal volumes calculated using the mean of these values were not comparable with the volumes measured using the program or the spirometer. As an alternative, a line of best fit was calculated for the data obtained from the syringe generated "breaths" in a similar manner as described above for the spirometer (See *Fig. B.3*).

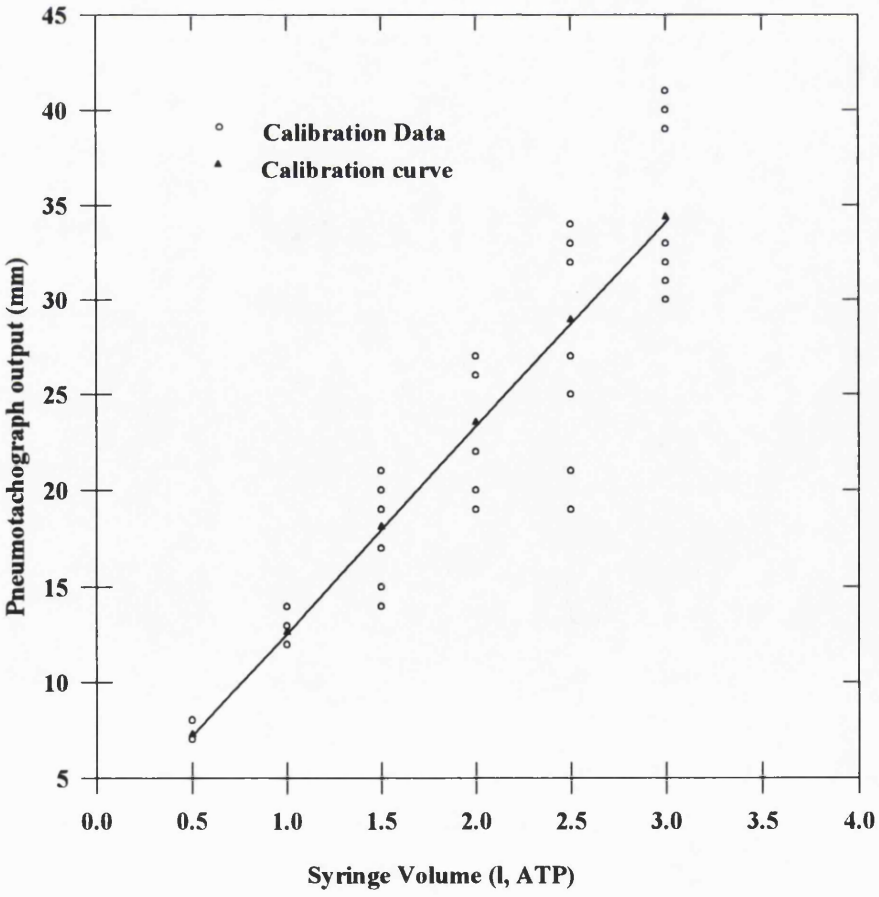


Figure B.3: Calibration line for pneumotachograph. R = 0.940, see text for equation.

The formula for the calibration curve, as determined by regression analysis was:

$$\text{Pneumotachograph output (mm)} = 10.8 * (V_T, ATP) + 1.83$$

The R-value was 0.940.

Correlation between the three methods of measurement: The spirometer is a direct measure of volume and therefore was used as the independent variable for the correlation and regression calculations. Thirty five breaths were taken by the subject and ten "breaths" (five at a low flow, five at a high flow) were performed at each calibration volume.

Breath-by-breath values for tidal volumes generated by the subject, as measured by the spirometer, were compared to the values given by the program. Regression analysis produced the formula:

$$V_{T,\,Program} = 0.99 * V_{T,\,Spirometer,}$$

with a 95 % confidence interval of 0.98 to 1.0 and an R-value of 0.995 (See *Fig.B.4*). There is little point in saying more than this is a very strong validation of the program's accuracy. It is certainly a smaller error than that resulting from the compression and distension of the elephant tubing resulting from the movement of the subject while exercising.

For the syringe-generated "breaths", regression generated the formula:

$$V_{T,Program} = 0.99 * V_{T,Spirometer,}$$

with a 95%confidence interval of 0.98 to 1.0 and an R-value of 0.996 (see *Fig. B.5*). Again, an extremely high level of accuracy.

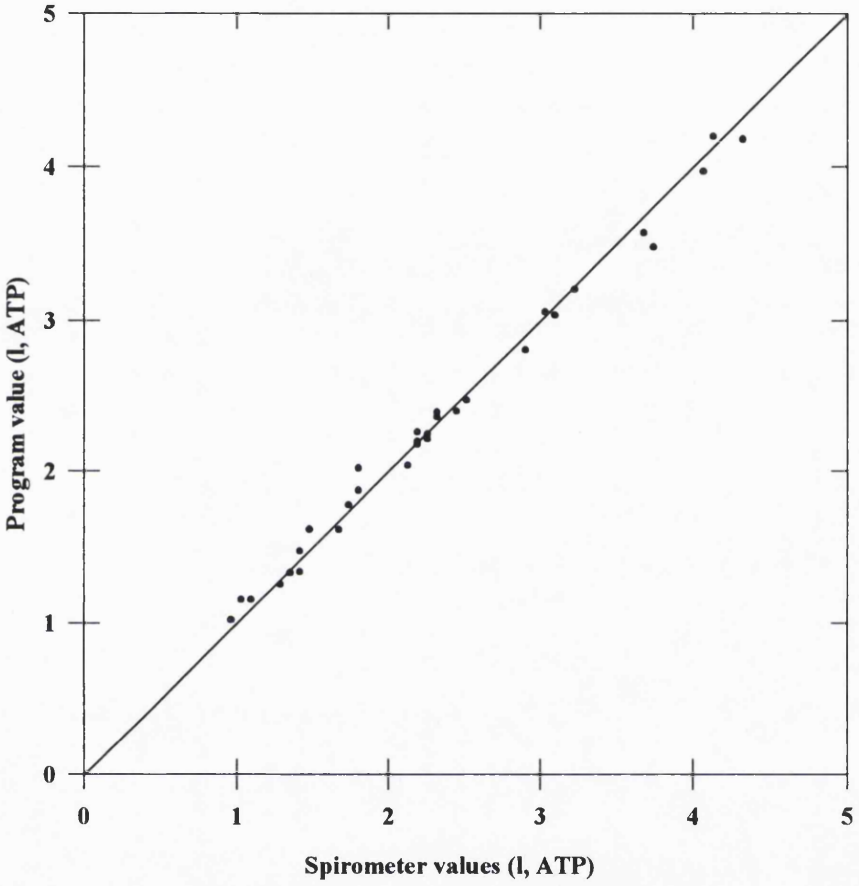


Figure B.4: Correlation between values for VT measured by the program and the spirometer. R = 0.995. Breaths were generated by a subject. Line of unity is shown.

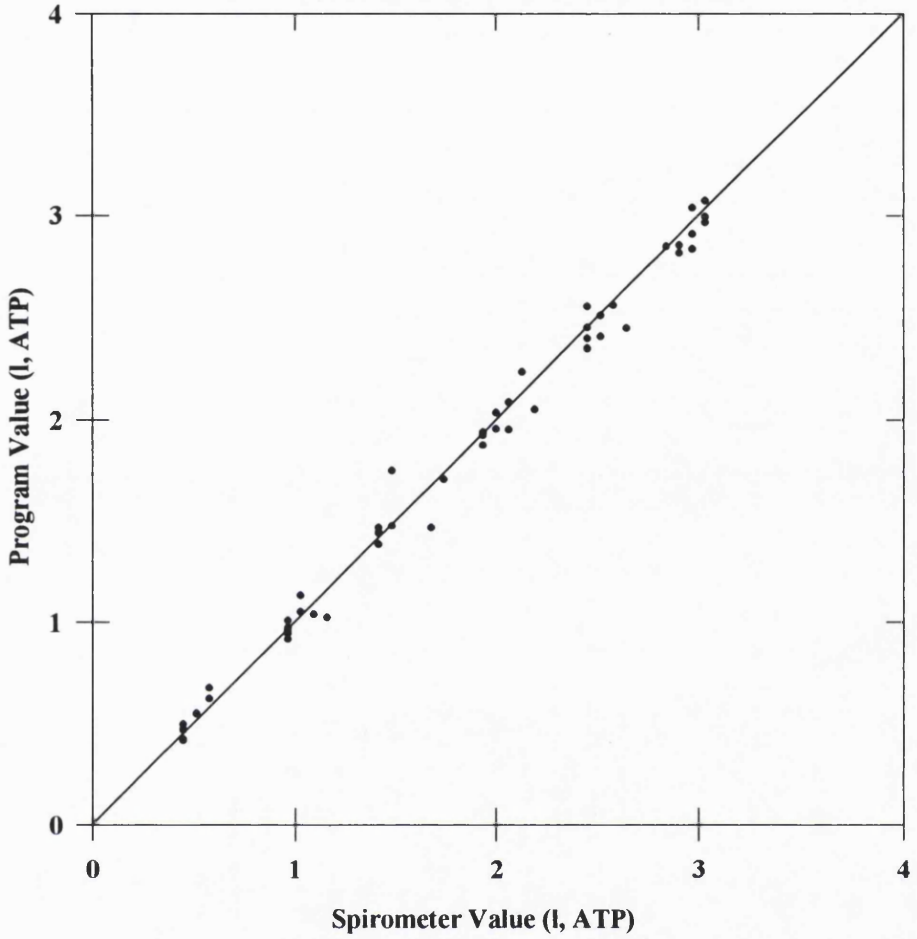


Figure B.5: Comparison of VT values from spirometer and program. R = 0.996. "Breaths" were generated by calibrated syringe. Line of unity is shown.

The pneumotachograph output for VT was also compared to the spirometer (see *Fig. B.6*); regression producing the formula:

$$V_{T,Pneumotachograph} = 1.13 * V_{T,Spirometer}.$$

The R-value of 0.970 is comparable to that obtained for the program, but the gradient of the line shows that it overestimated the tidal volume by 10% to 16 % (95 % confidence intervals). Given the high correlation, this would suggest a problem with calibration rather than with the equipment *per se*, which is consistent with the comments above. Despite this, it is still sufficiently accurate for research uses.

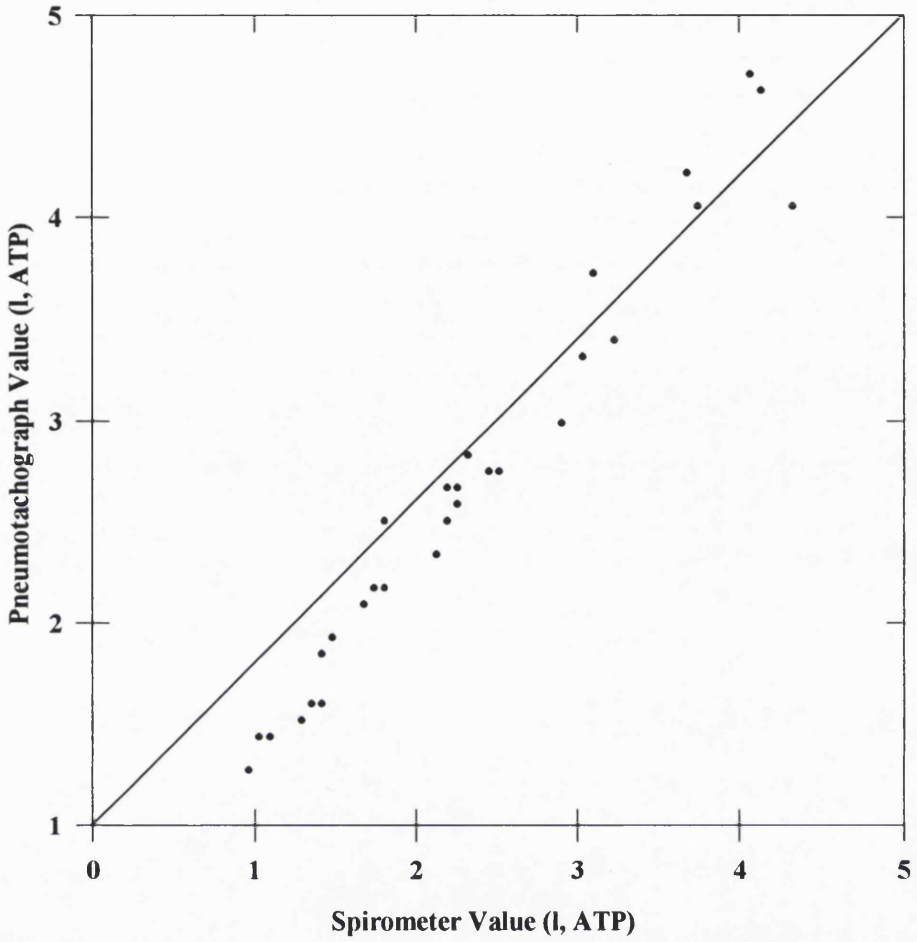


Figure B.6: Comparison of VT values generated by spirometer and pneumotachograph. R = 0.970. Breaths were generated by a subject. Line of unity is shown.

To conclude, the results generated by the program are certainly valid in terms of accuracy. It is well known that the pressure: flow characteristics of the Fleisch head vary with gas concentration. These results demonstrate that the difference between room air and expired gas does not adversely affect the accuracy of the exercise testing program.

TI and TTOT: TI and TTOT were measured from the chart recorder trace as shown in *Fig. B.1* and compared to the values measured by the program (see *Fig. B.7*). Regression analysis yielded a conversion factor of 0.953 (95 % confidence intervals = 0.935 to 0.971) with an R-value of 0.99 for TI and similarly a conversion factor of 0.999 (95 % confidence interval =

0.993 to 1.004) for TTOT with an R-value of 0.999. Again, these results speak for themselves and preclude any criticism of the accuracy of the results calculated by the program.

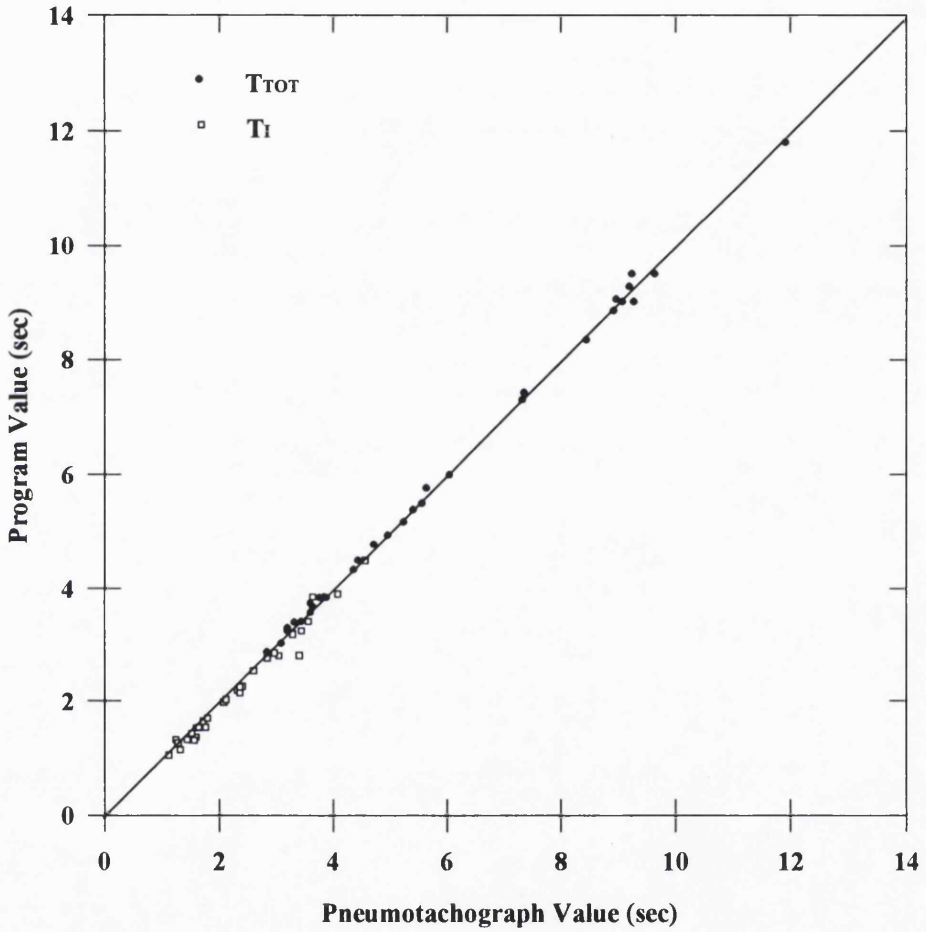


Figure B.7: Comparison of values for TI and TTOT from the pneumotachograph and program. R = 0.99 for TI and 0.999 for TTOT. Breaths were generated by a subject. Line of unity is shown.

CONCLUSION:

The data resulting from on-line analysis of the relevant physiological variables by the custom-written programs used in this PhD. are entirely accurate .

APPENDIX C:

LISTING OF "EXTEST 3"

```
'CURRENT TEST PROG, updated 20 jan '94
DECLARE SUB FLOWCAL2 ()
DECLARE SUB CHECK ()
DECLARE SUB INSPRESS ()
DECLARE SUB BIKEF ()
DECLARE SUB WORK ()
DECLARE SUB EXPPRESS ()
DECLARE SUB FINISH ()
DECLARE SUB PRESSURECAL ()
DECLARE SUB MAX ()
DECLARE SUB ADCONV ()
DECLARE SUB GAS ()
DECLARE SUB CALCS ()
DECLARE SUB FLOW1 ()
DECLARE SUB extest ()
DECLARE SUB TIME ()
DECLARE SUB AIRCHECK ()
DECLARE SUB FLOWCAL ()
DECLARE SUB gascal ()
DECLARE SUB today ()
DECLARE SUB flowmetcal ()
DECLARE SUB subject ()

TYPE TODATA                    Data about day of test
DD AS INTEGER                  Date
MM AS INTEGER                  Ditto
YY AS INTEGER                  Ditto
TIME AS SINGLE                 Time of test
TEMP AS INTEGER                Ambient temperature
BP AS INTEGER                  Ambient barometric pressure
END TYPE

TYPE SUBDATA                   Data about subject
SURN AS STRING * 10            Surname
CHRIS AS STRING * 10           Christian name
DA AS INTEGER                  Date of birth
MO AS INTEGER                  Ditto
YE AS INTEGER                  Ditto
HEI AS SINGLE                  Height
WEI AS SINGLE                  Weight
END TYPE
```

```
TYPE TESTDATA                    Information about test type
MODE AS STRING * 15
PEDAL AS STRING * 4
protocol AS STRING * 30
features AS STRING * 70
END TYPE

TYPE PHASE                       This is the data saved every breath
TIME1 AS SINGLE                      Time at the beginning of breath
BIGVOL AS SINGLE                     Cumulative volume throughout test
PEDALF AS SINGLE                     fPED
INPULSE AS INTEGER                   Pulse at end of inspiration
EXPULSE AS INTEGER                   Pulse at end of expiration
BPTS AS SINGLE                       E (BTPS)
VT AS SINGLE                         VT (BTPS)
VIN AS SINGLE                        Inspiratory tidal volume (STPD)
TTOT AS SINGLE                       Time taken for this breath
TI AS SINGLE                         Inspiratory time
PETCO2 AS SINGLE                     PET,CO2
PETO2 AS SINGLE                      PET,O2
peO2 AS SINGLE                       PE,O2
peCO2 AS SINGLE                      PE,CO2
END TYPE

TYPE conv                        Calibration data for pulse and pedal frequency
mpulse AS SINGLE
INTPULSE AS SINGLE
mrpm AS SINGLE
intrpm AS SINGLE
END TYPE

TYPE ASD                         Measurement of PO2 and PCO2 before and after
                                 testing
peO2 AS SINGLE
peCO2 AS SINGLE
PETO2 AS SINGLE
PETCO2 AS SINGLE
END TYPE

                                                 Defining variables
DIM SHARED ASD AS ASD
DIM SHARED TODATA AS TODATA
DIM SHARED SUBDATA AS SUBDATA
DIM SHARED PHASE(85) AS PHASE    Temporary memory capable of
                                 containing 85 breaths
DIM SHARED bbybdata AS PHASE
```

```
DIM SHARED TESTDATA AS TESTDATA
DIM SHARED conv AS conv
DIM SHARED FILENAME AS STRING * 8                    Filename for test
DIM SHARED TFLOW AS SINGLE, PFLOW AS SINGLE, T4 AS SINGLE, dflow
AS SINGLE  DIM SHARED ENDINSP  AS SINGLE, ENDEXP AS SINGLE
DIM SHARED VO2 AS SINGLE, vCO2 AS SINGLE
DIM SHARED VOLUME AS SINGLE, ATP AS SINGLE, STPD AS SINGLE,
CUVOL  AS LONG, VINAS SINGLE, BIGVOL AS SINGLE
DIM SHARED PO2 AS SINGLE, PCO2 AS SINGLE, PETCCO2 AS SINGLE,
petoo2 AS SINGLE
DIM SHARED conco2 AS SINGLE, concco2 AS SINGLE, conccco2 AS SINGLE,
concoo2 AS SINGLE
DIM SHARED AIRO2 AS SINGLE, AIRCO2 AS SINGLE, AIRCCO2 AS SINGLE,
AIROO2 AS SINGLE
DIM SHARED MO2 AS SINGLE, MOO2 AS SINGLE, MCO2 AS SINGLE,
MCCO2 AS SINGLE, INTO2
AS SINGLE, INTOO2 AS SINGLE, INTCO2 AS SINGLE, INTCCO2 AS SINGLE
DIM SHARED Zflow AS INTEGER, NOTH AS INTEGER, ING AS INTEGER,
CROSSFLOW AS INTEGER, CROSSFLOW2 AS INTEGER
DIM SHARED MFLOW1 AS SINGLE, INTFLOW1 AS SINGLE, MFLOW2 AS
SINGLE, INTFLOW2 AS SINGLE, MFLOW3 AS SINGLE, INTFLOW3 AS
SINGLE, MFLOW4 AS SINGLE, INTFLOW4 AS SINGLE
DIM SHARED LAG AS SINGLE
DIM SHARED mpulse AS SINGLE, INTPULSE AS SINGLE, mrpm AS SINGLE,
intrpm AS SINGLE
DIM SHARED CHAN AS INTEGER, FLOW AS INTEGER, A AS INTEGER, B
AS INTEGER, PRESS AS INTEGER, PULSE AS INTEGER, RPM AS INTEGER,
ETCO2 AS INTEGER, ETO2 AS INTEGER
DIM SHARED PETCO2 AS SINGLE
DIM SHARED WTIME AS SINGLE
DIM SHARED t0 AS SINGLE, T1 AS SINGLE, gr AS INTEGER
DIM SHARED CPRESS AS LONG, Q AS INTEGER
DIM SHARED SPEED1 AS SINGLE, SPEED2 AS SINGLE, AVGFLOW1 AS
SINGLE, AVGFLOW2 AS SINGLE
DIM SHARED CFLOW  AS SINGLE, P AS INTEGER
DIM SHARED d AS INTEGER, L AS INTEGER, W AS INTEGER, E AS
INTEGER, COUNT AS INTEGER, M AS INTEGER, N AS INTEGER, Y AS
INTEGER
BA% = &H700                  Setting up base address of PC-26-a Analogue to
OUT BA% + 3, &H92            Digital interface board
CLS                          Clear screen
```

```
TESTDAT:                          Asks for information about test design
INPUT "What is the exercise mode for this test"; TESTDATA.MODE
IF TESTDATA.MODE = "CYCLE ERGOMETER" THEN
INPUT "What is the desired pedal frequency"; TESTDATA.PEDAL
END IF
INPUT "Describe the test protocol:"; TESTDATA.protocol
INPUT "Are there any interesting features to this test"; TESTDATA.features
MENU:
CLS
PRINT "EXERCISE TESTING PROGRAM MAIN MENU."       Self-explanatory
PRINT : PRINT : PRINT "SELECT YOUR CHOICE FROM THE MENU:"
PRINT :  PRINT : PRINT "1:      Enter today's barometric conditions."
PRINT "2:      Enter subject's personal data."
PRINT "3:      Calibrate Oxygen and Carbon dioxide sensors."
PRINT "4:      Calibrate gas flowmeter."
REM PRINT "5:      Calibrate the pressure transducer."          Line not in use
PRINT "6:      Perform the exercise test."
PRINT "7:      Quit."
DO
INPUT i
LOOP UNTIL (i >= 1) AND (i <= 7) Choose which option is required from above
                                 menu.
SELECT CASE i
CASE 1                  Words following 'CALL' command refer to subprograms.
CALL today                       Listed below in alphabetical order
GOTO MENU
CASE 2
CALL subject
GOTO MENU
CASE 3
CALL GAS
PRINT "GAS METER CALIBRATION IS NOW COMPLETE. DO YOU WISH TO
REPEAT IT? Y/N"
DO                          Asks you if you want to repeat calibration of Airspec
ans4$ = UCASE$(INKEY$)  2 600, Medishield MS-2 and Beckman LB-2
LOOP UNTIL ans4$ = "Y" OR ans4$ = "N"
IF ans4$ = "Y" THEN CALL GAS
GOTO MENU
CASE 4
CALL flowmetcal
GOTO MENU
CASE 5
GOTO MENU
CASE 6
CALL extest
```

```
GOTO MENU
CASE 7
CLS
END SELECT
END


SUB ADCONV                          THIS SUBPROGRAM CONTROLS
THE
OUT &H702, 2                        ANALOGUE TO DIGITAL
INTERFACE.
OUT &H702, CHAN * &H10 + 2          Controls output of data to computor base
OUT &H702, CHAN * &H10 + 3          address
OUT &H702, CHAN * &H10 + 2
chval1 = (INP(&H701) AND &HF) * 256
chval2 = INP(&H700)                 Determines channel number to be read
CHVAL = chval1 + chval2
SELECT CASE CHAN                    Channel information:
CASE 1
FLOW = CHVAL                        VE
CASE 2
A = CHVAL                           PE,O2
CASE 3
B = CHVAL                           PE,CO2
CASE 4
GASP = CHVAL                        VI
CASE 5
PULSE = CHVAL                       fC
CASE 6
RPM = CHVAL                         fPED
CASE 7
ETCO2 = CHVAL                       PE,CO2
CASE 8
ETO2 = CHVAL                        PE,O2
CASE ELSE
END SELECT
END SUB
```

SUB CALCS ***THIS IS A SUBPROGRAM OF 'CHECK.'***

It calculates Vo_2, Vco_2 and RER for breath 10.5l prior to current breath.

```
VO2 = STPD * ((((conco2 / 100) * (1 - ((bbybdata.peO2 / 100) + (bbybdata.peCO2 /
100)))) / (1 -((conco2 / 100) + (concco2 / 100)))) - (bbybdata.peO2 / 100))
vCO2 = (STPD * (bbybdata.peCO2 / 100)):
RER = vCO2 / VO2
LAG = PHASE(N - 1).TIME1 - bbybdata.TIME1    Calculates time lag between
PRINT TAB(57);                               current breath and breath 10.5 l ago.
 PRINT USING "###"; LAG; : PRINT TAB(62);
PRINT USING "##.##"; VO2; : PRINT TAB(68);        Prints out values for Vo2,
PRINT USING "##.##"; vCO2; : PRINT TAB(74);            Vco2 and RER
PRINT USING "#.##"; RER;
END SUB
```

SUB CHECK ***THIS IS A SUBPROGRAM IN 'EXTEST.'***

```
IF BIGVOL > PHASE(M).BIGVOL + 10.5 THEN  Determines whether 10.5 L have
FOR CHAN = 2 TO 3 been expired since a particular breath, recorded as an array.
CALL ADCONV      Reads respective channels and calculates % PEO2 and %
PECO2.
NEXT CHAN
PHASE(M).peO2 = (MO2 * A) + INTO2
PHASE(M).peCO2 = (MCO2 * B) + INTCO2
bbybdata = PHASE(M)
PUT #2, , bbybdata   Saves all data corresponding to this breath stored in the array.
CALL CALCS                          Calls up subprogram "CALCS"
M = M + 1
IF M = 81 THEN       Moves on to the next breath in a rolling temporary memory

M = 1                capable of holding up to 80 arrays (i.e. breaths) at a time.
END IF
END IF
END SUB
```

This subprogram is crucial to the accurate calculation of Vo_2, Vco_2 and RER. The problem arises because the mixing box and the elephant tubing linking it to the mouthpiece has a deadspace of 10.5 l. In other words, air expired at the mouthpiece AND DETECTED IMMEDIATELY BY THE PNEUMOTACHOGRAPH does not reach the probes of the gas analysers responsible for the measurement of PE,O_2 and PE,CO_2 until a further 10.5 l of air have been expired. To account for this lag between the measurement of expiratory flow and PE,O_2 and PE,CO_2 (remember, this is a VOLUME LAG, NOT A CONSTANT TIME LAG), each breath is placed in an array (labelled PHASE) until 10.5 l of air have been expired, whereupon it is matched up with its respective PE,O_2 and PE,CO_2 measurements, renamed as BBYBDATA, and saved in a file. It is important to remember that the last breath saved at the end of a test was taken 10.5 l before the last breath shown on the computor screen. The

TIME LAG between these two breaths appears in the column labelled 'LAG'. It is sound policy to ask subjects to take five deep breaths at the end of each test to flush the system through and ensure that all the breaths taken during the test are saved!

```
SUB extest          THIS IS THE MAIN EXERCISE TESTING SUBPROGRAM
DIM TA  AS SINGLE
INPUT "What is the filename for this test"; FILENAME$
OPEN "ECGRPM.CAL" FOR RANDOM AS #3 LEN = LEN(conv)        Opens file
GET #3, , conv                containing calibration values for Heart Rate and fPED.
CLOSE #3
OPEN FILENAME$ + ".NO1" FOR BINARY AS #1
PUT #1, , TESTDATA                Opens one of the two files in which data is saved
SEEK #1, 150                      and saves some data.
PUT #1, , TODATA
SEEK #1, 200
PUT #1, , SUBDATA
OPEN FILENAME$ + ".NO2" FOR RANDOM AS #2 LEN = LEN(bbybdata)
Y = 0: FOR Y = 1 TO 3                                     Opens other data file.
TA = TIMER          Takes three measurements of room air pO2 and pCO2 prior
DO                                to starting the test,.....
LOOP UNTIL TIMER - TA > 3
FOR CHAN = 2 TO 3
CALL ADCONV
NEXT CHAN
FOR CHAN = 7 TO 8
CALL ADCONV
NEXT CHAN
ASD.peO2 = (MO2 * A) + INTO2    ...converts them to % values according to
ASD.peCO2 = (MCO2 * B) + INTCO2       calibration performed in subprogram,
ASD.PETCO2 = (MCCO2 * ETCO2) + INTCCO2          'GASCAL.....'
ASD.PETO2 = (MOO2 * ETO2) + INTOO2
SEEK #1, 330 + (Y * 16)      ...and saves them in one of the data acquisition files.
PUT #1, , ASD
NEXT Y
CLS
PRINT " TO START THE EXERCISE TEST, PRESS 'G'."
PRINT "": PRINT "TO STOP THE EXERCISE TEST, PRESS 'Q'.";
DO
J$ = UCASE$(INKEY$)
LOOP UNTIL J$ = "G"                    Starts the exercise test
CLS
WIDTH 80
PRINT "'W' CHANGE WORKLOAD; 'M' MAX. WORK; 'Q' STOP"
```

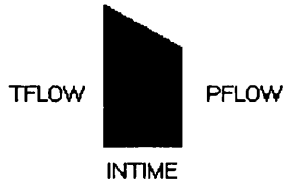
```
PRINT "TIME"; TAB(13); "RPM"; TAB(18); "VE"; TAB(23); "FREQ."; TAB(32);
"Vt"; TAB(39); "PetCO2";
TAB(57); "LAG"; TAB(62); "VO2"; TAB(68); "VCO2"; TAB(74); "RER"
LOCATE 3, 1
PRINT STRING$(80, "-")    Prints header on screen and separates it from the rest of
VIEW PRINT 4 TO 25                                    the screen.
START:                                    Start of the test proper.
BIGVOL = 0: N = 1: M = 1  Reset counters and set exercise test clock to zero.
t0 = TIMER          Ensures that first breath monitored starts with an inspiration.
DO          This stops program crashing because some important value is zero.
CHAN = 4
CALL ADCONV
LOOP UNTIL GASP <= (Zflow - 20)Detects whether subject is inspiring or expiring
GOTO INSP                                 If inspiring, goes to INSP
EXPIRE:                                Expiration phase of breath.
T4 = TIMER                Used in subprogram FLOW1 and below.
ENDINSP = TIMER           Takes time at beginning of expiration.
DO
MAAX$ = UCASE$(INKEY$)More detail in the specific subprograms listed, but
CALL FLOW1                basically expiratory flow is integrated to give volume.
CALL CHECK                      This process is repeated to the end of expiration.
IF MAAX$ = "W" THEN             Time marker, eg for beginning of exercise.
CALL WORK
END IF
DO
LOOP UNTIL TIMER > T4
LOOP UNTIL GASP <= (Zflow - 20)       Detects the beginning of inspiration.
FOR CHAN = 5 TO 6
CALL ADCONV               Measures pulse and pedal cadence, converts them into
NEXT CHAN          correct values and places them in the array for this breath.
PHASE(N).EXPULSE = (PULSE * conv.mpulse) + conv.INTPULSE
PHASE(N).PEDALF = (RPM * conv.mrpm) + conv.intrpm
PHASE(N).TTOT = TIMER - ENDEXP    Calculated time for this breath
(beginning of  inspiration to beginning of inspiration) and places it in the array for
this breath.
ENDEXP = TIMER                    Takes time at the beginning of inspiration.
PHASE(N).BIGVOL = BIGVOL          Records cumulative volume at end of breath in
                                                array for use in subprogram CHECK.
ATP = (VOLUME / PHASE(N).TTOT) * 60 Calculates VE (ATP) for current breath.
VOLUME = 0
PHASE(N).BPTS = ATP * (310 / (273 + TODATA.TEMP)) * (TODATA.BP /
(TODATA.BP - 47))
PHASE(N).VT = (PHASE(N).BPTS * PHASE(N).TTOT) / 60    Calculates VE
(STPD & BTPS) and Tidal volume for current breath and places it in relevant array.
phase(n).STPD = ATP * (273 / (273 + TODATA.TEMP)) * (TODATA.BP / 760)
```

```
FH = (60 / PHASE(N).TTOT) Calculates frequency of breathing for current breath.
INSP:                                   Start of measurement in inspiration.
                                        THIS IS THE START OF THE NEXT BREATH.
                                        N.B.This breath is not yet the current array.
DO
MAAX$ = UCASE$(INKEY$)
CALL INSPRESS   Integrates inspiratory flow to give inspiratory tidal volume.
Also continues to calculate PET,CO2 and PET,O2. thereby overcoming the time lag on
the analyser.
IF MAAX$ = "W" THEN
CALL WORK               Time marker as described in 'EXPIRE.'
END IF
LOOP UNTIL FLOW > (Zflow + 23) OR MAAX$ = "Q"
MI = INT(PHASE(N).TIME1 / 60): SE = PHASE(N).TIME1 - (MI * 60)
Calculates time at beginning of previous breath (i.e. breath in current array) in min
and sec.
PRINT TAB(1); : PRINT MI; ":";                  Prints this time.
PRINT USING "##.#"; SE; : PRINT TAB(11);
PRINT USING "###.#"; PHASE(N).PEDALF; : PRINT TAB(18); Prints fPED
PRINT USING "###.##"; PHASE(N).BPTS; :  PRINT TAB(25);  Prints VE (BTPS).
PRINT USING "##.#"; FH; : PRINT TAB(34);                Prints fBR
PRINT USING "#.##"; PHASE(N).VT; : PRINT TAB(41);       Prints VT
PRINT USING "##.##"; PHASE(N).PETCO2;                   Prints PET,CO2
N = N + 1Moves onto next array in rolling temporary memory capable of holding
IF N = 81 THEN      up to 80 arrays at one time. This is where the arrays looked at
N = 1                   in subprogram CHECK come from.
END IF                  N.B. CURRENT BREATH = CURRENT ARRAY
PHASE(N).VIN = VOLUME * (310 / (273 + TODATA.TEMP)) * (TODATA.BP
/(TODATA.BP - 47))
VOLUME = 0 Calculates inspiratory tidal volume (BTPS), inspiratory time and time
PHASE(N).TI = TIMER - ENDEXP   at start of breath, and places it in the current
array.
PHASE(N).TIME1 = TIMER - (PHASE(N).TTOT + t0)
IF MAAX$ = "W" THEN                     Time marker as described in 'EXPIRE.'
CALL WORK
ELSEIF MAAX$ = "Q" THEN     Press key 'Q' to end the test. There is also a cop-
PRINT "ARE YOU SURE?"  out clause which allows a return to the exercise test in
DO                          program in case 'Q' has been pressed by mistake.
ANS30$ = UCASE$(INKEY$)
LOOP UNTIL ANS30$ = "Y" OR ANS30$ = "N"
IF ANS30$ = "Y" THEN
GOTO DED
END IF
END IF
CHAN = 5Measures pulse, converts it to correct value and places it in current array.
```

```
CALL ADCONV
PHASE(N).INPULSE = (PULSE * conv.mpulse) + conv.INTPULSE
PHASE(N).PETCO2 = 0: PHASE(N).PETO2 = 200.8 Resets end-tidal O2 and CO2.
GOTO EXPIRE                                          values
DED:                        This only occurs at the end of the exercise test.
VIEW PRINT 1 TO 25          Returns screen to normal format.
CLS
CLOSE #2                              Closes data acquisition file.
BIGVOL = 0                  Resets cumulative volume and all arrays in the
FOR N = 1 TO 81                       temporary memory to zero
PHASE(N).TIME1 = 0: PHASE(N).BIGVOL = 0
NEXT N
FOR M = 1 TO 81
PHASE(M).BIGVOL = 0: PHASE(M).TIME1 = 0
NEXT M
FOR Y = 4 TO 6      Takes three measurements of room air pO2 and pCO2 prior to
TA = TIMER          starting the test as at the beginning of the exercise test and
DO                                    saves them in data acquisition file.
LOOP UNTIL TIMER - TA > 3                This gives a measure of any baseline
FOR CHAN = 2 TO 3                     drift on the gas analysers
CALL ADCONV
NEXT CHAN
FOR CHAN = 7 TO 8
CALL ADCONV
NEXT CHAN
ASD.peO2 = (MO2 * A) + INTO2
ASD.peCO2 = (MCO2 * B) + INTCO2
ASD.PETCO2 = (MCCO2 * ETCO2) + INTCCO2
ASD.PETO2 = (MOO2 * ETO2) + INTOO2
SEEK #1, 330 + (Y * 16)
PUT #1, , ASD
NEXT Y
W = 0                                 Resets counter for time marker WTIME.
CLOSE #1                                 Closes the two data acquisition files.
CLOSE #2
END SUB
```

```
SUB FLOW1                          THIS IS A SUBPROGRAM IN 'EXTEST.'
DIM INTIME AS SINGLE
PFLOW = TFLOW                      Part of the integration procedure (see below).
INTIME = (TIMER - T4)              Time between two measurements of flow used
                                   in the integration procedure.
T4 = TIMER                             Reset integration time clock to zero.
CHAN = 1                               Measure VE.
CALL ADCONV
FOR CHAN = 7 TO 8                      Measure PE,CO2 and PE,O2
CALL ADCONV
NEXT CHAN
CHAN = 4                   Check VI (for detection of beginning of inspiration).
CALL ADCONV
IF FLOW < CROSSFLOW THEN
Calculation of vE from raw data values.
TFLOW = (FLOW * MFLOW2) + INTFLOW2
ELSE
TFLOW = (FLOW * MFLOW1) + INTFLOW1

END IF
INTEG = ((PFLOW + TFLOW) / 2) * INTIME
VOLUME = VOLUME + INTEG            Integration calculations.
BIGVOL = BIGVOL + INTEG
PETCO2 = ((((ETCO2 * MCCO2) + INTCCO2) / 100) * (TODATA.BP - 47))
IF PETCO2 > PHASE(N).PETCO2 THEN
PHASE(N).PETCO2 = PETCO2
END IF      Shaded area represents integration of flow, i.e. volume.
PETO2 = ((((ETO2 * MOO2) + INTOO2) / 100) * (TODATA.BP - 47))
IF PETO2 < PHASE(N).PETO2 THEN
PHASE(N).PETO2 = PETO2             Calculation of end-tidal O2 and CO2.
END IF
END SUB
```




```
SUB FLOWCAL                        THIS IS A SUBPROGRAM OF 'FLOWMETCAL.'
DO
CHAN = 1                           Measures VE 100 times and summates values.
CALL ADCONV
CFLOW = CFLOW + FLOW
P = P + 1
LOOP UNTIL P = 100
END SUB
```

```
SUB FLOWCAL2          THIS IS A SUBPROGRAM OF 'FLOWMETCAL.'
DO
CHAN = 4                          Measures V̇ 100 times and summates values.
CALL ADCONV
CFLOW = CFLOW + FLOW
P = P + 1
LOOP UNTIL P = 100
END SUB


SUB flowmetcal
THIS IS THE MAIN FLOWMETER CALIBRATION SUBPROGRAM
PRINT "STAGE 4: CALIBRATION OF FLOW METER."
PRINT "": PRINT "": PRINT "":                    Prints instructions on screen.
PRINT "THIS INVOLVES CALIBRATING THE PNEUMOTACHOGRAPH AT
FOUR FLOWS."
PRINT : PRINT "THE VALUES OF WHICH MUST BE CLOSE TO THOSE
REQUESTED BY THE
PROGRAM."
TRUEVAL1:
PRINT "SWITCH ON CALIBRATION PUMP, SET FLOW TO APPROX. 300
L/MIN,"
PRINT "AND ENTER CALIBRATION FLOW-RATE."
INPUT SPEED1
IF SPEED1 < 280 OR SPEED1 > 320 THEN      Sets up calibration at approx.
PRINT "SET FLOW CLOSER TO 300 L/MIN."     300 l/min.
GOTO TRUEVAL1
END IF
SPEED1 = SPEED1 / 60                      Converts it to l/sec.
PRINT "Is this value correct?"
DO
ANS20$ = UCASE$(INKEY$)
LOOP UNTIL ANS20$ = "Y" OR ANS20$ = "N"   Cop-out clause allowing a
IF ANS20$ = "N" THEN GOTO TRUEVAL1        change in calibration flow rate.
PRINT "": PRINT "Press key 'G' to start calibration"
DO
go$ = UCASE$(INKEY$)
LOOP UNTIL go$ = "G"
PRINT "CALIBRATING"
CALL FLOWCAL
AVGFLOW1 = CFLOW / 100    Produces average of 100 readings of expiratory flow.
CFLOW = 0: P = 0                  Resets sum of flows and counter to zero
PRINT : PRINT : PRINT "PUT INSPIRATORY FLEISCH HEAD ON THE
ROTAMETER, CHECK THAT FLOW IS"; TRUEVAL1; "l/min AND PRESS 'G'."
```

```
CALL FLOWCAL2
AVGFLOW5 = CFLOW / 100  Produces average of 100 readings of inspiratory flow.
CFLOW = 0: P = 0                Resets sum of flows and counter to zero.
TRUEVAL2:
PRINT "": INPUT "CHANGE FLOW TO APPROX. 120 L/MIN AND ENTER NEW
FLOW."; SPEED2
IF SPEED2 < 100 OR SPEED2 > 140 THEN
PRINT "SET FLOW CLOSER TO 120 L/MIN"
GOTO TRUEVAL2
END IF          Prints instructions on screen for calibrating at approx 120 l/min.
SPEED2 = SPEED2 / 60  Converts value to l/sec, allows cop-out for new flow rate.
PRINT "Is this value correct?"
DO
ANS21$ = UCASE$(INKEY$)
LOOP UNTIL ANS21$ = "Y" OR ANS21$ = "N"
IF ANS21$ = "N" THEN GOTO TRUEVAL2
PRINT "": PRINT " Press key 'G' to start calibration:"
DO
G$ = UCASE$(INKEY$)
LOOP UNTIL G$ = "G"
PRINT "MEASURING . ."
CALL FLOWCAL                    Calculates average reading of expiratory flow
AVGFLOW2 = CFLOW / 100                  and resets values.
CFLOW = 0: P = 0
PRINT : PRINT : PRINT "PUT INSPIRATORY FLEISCH HEAD ON THE
ROTAMETER, CHECK THAT
FLOW IS"; TRUEVAL1; "l/min AND PRESS 'G'."
CALL FLOWCAL2                   Calculates average reading of inspiratory flow
AVGFLOW6 = CFLOW / 100                  and resets values.
CFLOW = 0: P = 0
TRUEVAL3:
PRINT : PRINT "CHANGE TO SMALL ROTAMETER, SET FLOW TO APPROX.
60 L/MIN"
PRINT " AND ENTER FLOW."
INPUT SPEED3
IF SPEED3 < 50 OR SPEED3 > 70 THEN
PRINT "SET FLOW CLOSER TO 60 L/MIN."
GOTO TRUEVAL3
END IF
SPEED3 = SPEED3 / 60            The same as above, only the required flow
PRINT "Is this value correct?"          is approx 60 l/min.
DO
ANS21$ = UCASE$(INKEY$)
LOOP UNTIL ANS21$ = "Y" OR ANS21$ = "N"
IF ANS21$ = "N" THEN GOTO TRUEVAL3
```

```
PRINT "": PRINT " Press key 'G' to start calibration:"
DO
G$ = UCASE$(INKEY$)
LOOP UNTIL G$ = "G"
PRINT "MEASURING . ."
CALL FLOWCAL                    Calculates average reading of expiratory flow.
AVGFLOW3 = CFLOW / 100
CFLOW = 0: P = 0
PRINT : PRINT : PRINT "PUT INSPIRATORY FLEISCH HEAD ON THE
ROTAMETER, CHECK THAT
FLOW IS"; TRUEVAL1; "l/min AND PRESS 'G'."
CALL FLOWCAL2                   Calculates average reading of inspiratory flow.
AVGFLOW7 = CFLOW / 100
CFLOW = 0: P = 0
TRUEVAL4:
PRINT "": INPUT "CHANGE FLOW TO APPROX. 20 L/MIN AND ENTER NEW
FLOW."; SPEED4
IF SPEED4 < 10 OR SPEED4 > 30 THEN
PRINT "SET FLOW CLOSER TO 20 L/MIN"
GOTO TRUEVAL4
END IF
SPEED4 = SPEED4 / 60            Last calibration flow: aprox 20 l/min.
PRINT "Is this value correct?"
DO
ANS21$ = UCASE$(INKEY$)
LOOP UNTIL ANS21$ = "Y" OR ANS21$ = "N"
IF ANS21$ = "N" THEN GOTO TRUEVAL4
PRINT "": PRINT " Press key 'G' to start calibration:"
DO
G$ = UCASE$(INKEY$)
LOOP UNTIL G$ = "G"
PRINT "MEASURING . ."
CALL FLOWCAL            Produces average of 100 readings of expiratory flow
AVGFLOW4 = CFLOW / 100  and resets sum of readings and counter.
CFLOW = 0: P = 0
PRINT : PRINT : PRINT "PUT INSPIRATORY FLEISCH HEAD ON THE
ROTAMETER, CHECK THAT FLOW IS"; TRUEVAL1; "l/min AND PRESS 'G'."
CALL FLOWCAL2           Produces average of 100 readings of expiratory flow
AVGFLOW8 = CFLOW / 100  and resets sum of readings and counter.
CFLOW = 0: P = 0
```

Calibration curve for each Fleisch head/Pneumotachograph assembly consists of two staight lines:

```
MFLOW1 = (SPEED1 - SPEED2) / (AVGFLOW1 - AVGFLOW2)
```

```
                                                    Slope of expiratory line 1.
INTFLOW1 = SPEED1 - (MFLOW1 * AVGFLOW1)
                                                    y-intercept of expiratory line 1.
MFLOW2 = (SPEED3 - SPEED4) / (AVGFLOW3 - AVGFLOW4)
                                                    Slope of expiratory line 2.
INTFLOW2 = SPEED3 - (MFLOW2 * AVGFLOW3)
                                                    y-intercept of expiratory line 2.
CROSSFLOW1 = (INTFLOW1 - INTFLOW2) / (MFLOW2 - MFLOW1)
                                                    Point at which lines cross.
MFLOW3 = (SPEED1 - SPEED2) / (AVGFLOW5 - AVGFLOW6)
                                                    Slope of inspiratory line 1.
INTFLOW3 = SPEED1 - (MFLOW3 * AVGFLOW5)
                                                    y-intercept of inspiratory line 1.
MFLOW4 = (SPEED3 - SPEED4) / (AVGFLOW7 - AVGFLOW8)
                                                    Slope of inspiratory line 2.
INTFLOW4 = SPEED3 - (MFLOW4 * AVGFLOW7)
                                                    y-intercept of inspiratory line 2.
CROSSFLOW2 = (INTFLOW3 - INTFLOW4) / (MFLOW3 - MFLOW4)
                                                    Point at which lines meet.
ZFLOW1:
PRINT "TO MEASURE ZERO FLOW, TURN OFF TAPS ON FRONT OF
PNEUMOTACHS AND
PRESS 'G'"
DO
GO2$ = UCASE$(INKEY$)  Set flow to zero on both pneumotachographs.....
LOOP UNTIL GO2$ = "G"
CALL FLOWCAL
NOTH = CFLOW / 100  .measure and calculate average reading for zero expiratory
                                    flow.
CFLOW = 0: P = 0
CALL FLOWCAL2
ING = CFLOW / 100                   ...repeat for inspiratory zero flow.....
CFLOW = 0: P = 0
Zflow = (NOTH + ING) / 2            ...calculate average value.....
PRINT "ZFLOW ="; Zflow              ...print it.
RIEN = (Zflow * MFLOW2) + INTFLOW2  Print value for flow calculated from
PRINT "EXPRIATORY ZERO FLOW ="; RIEN   zero reading on expiratory side
RIEN = (Zflow * MFLOW4) + INTFLOW4  Repeat process on inspiratory side.
PRINT "INSPIRATORY ZERO FLOW ="; RIEN  Both values must be < 0.03 l/sec.
CHECKFLOW1:
PRINT "": PRINT "Calibration complete. To check calibration, change flow and press
'G'."
DO
go$ = UCASE$(INKEY$)    Set rotameter to a particular value and check accuracy
LOOP UNTIL go$ = "G"            of calibration:
```

```
PRINT "": PRINT "MEASURING . . ."
CALL FLOWCAL
dflow = CFLOW / 100                          Take measurements.....
CFLOW = 0: P = 0
IF dflow < CROSSFLOW THEN      ...decide which calibration formula to use.....
CHECKFLOW = (dflow * MFLOW2) + INTFLOW2
ELSE
CHECKFLOW = (dflow * MFLOW1) + INTFLOW1      ...and calibrate flow.
END IF
PRINT "": PRINT "Flow = ";                   Print flow
PRINT USING "###.##"; CHECKFLOW;
PRINT "L/min.  A:D VALUE ="; dflow                  Print average measured
value.
PRINT "": PRINT "": PRINT ""
PRINT "CALIBRATION IS NOW COMPLETE. DO YOU WISH TO REPEAT IT?"
PRINT "'N' = NO, 'Y' = YES,'R' = REPEAT FLOWCHECK"
DO
REPEAT$ = UCASE$(INKEY$)
LOOP UNTIL REPEAT$ = "Y" OR REPEAT$ = "N" OR REPEAT$ = "R"
IF REPEAT$ = "Y" THEN
GOTO TRUEVAL1                Cop-out clause to allow recalibration of flow, or
END IF                                checking of more than one testflow.
IF REPEAT$ = "R" THEN
GOTO CHECKFLOW1
END IF
END SUB
```

SUB GAS
MAIN SUBPROGRAM FOR THE CALIBRATION OF THE GAS ANALYSERS

```
DIM HICALO2 AS SINGLE, LOCALO2 AS SINGLE, HICALCO2 AS SINGLE,
LOCALCO2 AS SINGLE,
HICALCCO2 AS SINGLE, LOCALCCO2 AS SINGLE, LOCALOO2 AS SINGLE,
HICALOO2 AS SINGLE
DIM HIO2 AS SINGLE, LO2 AS SINGLE, HICO2 AS SINGLE, LOCO2 AS
SINGLE
CLS
PRINT "STAGE 3: CALIBRATION OF GAS METERS"
PRINT "": PRINT ""
PRINT "": PRINT "SWITCH ON LOW CALIBRATION GAS, ENSURE GAS LINE
IS CONNECTED TO
ALL THE ANLYSERS AND PRESS KEY 'L'."
DO
```

```
go$ = UCASE$(INKEY$)     Instructions: set up equipment so all analysers are
LOOP UNTIL go$ = "L"                    reading test gas 1.
T = TIMER
CLS
PRINT "EQUILIBRATING WITH LOW GAS": PRINT ""
VALUES2:
INPUT ; "Oxygen concentration of low gas is ", LO2
PRINT " %": PRINT ""                    Input correct O2 and CO2 precentages.
INPUT ; "CO2 concentration of low gas is ", LOCO2
PRINT " %": PRINT ""
PRINT "Are these values correct?"
DO
ans5$ = UCASE$(INKEY$)          Cop-out clause to change values entered above.
LOOP UNTIL ans5$ = "Y" OR ans5$ = "N"
IF ans5$ = "N" THEN GOTO VALUES2
PRINT "Completing equilibration." Allow 20 sec for analysers to respond completely.
DO
LOOP UNTIL TIMER - T > 20
reading2:
CALL gascal
LOCALO2 = PO2 / 100: LOCALCO2 = PCO2 / 100: LOCALCCO2 = PETCCO2 /
100
LOCALOO2 = petoo2 / 100  Calculate average readings for O2 and CO2 from all
PO2 = 0: PCO2 = 0: PETCCO2 = 0: petoo2 = 0 four outputs.Reset sums of readings
CLS                                     and print average readings.
PRINT "co2"; LOCALCO2, "O2"; LOCALO2, "PETCO2"; LOCALCCO2, "PETO2";
LOCALOO2
PRINT "LOW GAS CALIBRATION IS NOW COMPLETE. DO YOU WISH TO
REPEAT IT? (Y/N)"
DO
ans3$ = UCASE$(INKEY$)          Ask whether or not to repeat readings.
LOOP UNTIL ans3$ = "N" OR ans3$ = "Y"
IF ans3$ = "Y" THEN GOTO reading2
PRINT "SWITCH ON THE HIGH CALIBRATION GAS, AND THEN PRESS KEY
'H'"
DO
go$ = UCASE$(INKEY$)            Change calibration gas to one with different
LOOP UNTIL go$ = "H"            concentrations of O2 and CO2.
T = TIMER
CLS
PRINT "EQUILIBRATING WITH HIGH GAS"
PRINT ""
VALUES1:
INPUT ; "Oxygen concentration of gas is ", HIO2  Set new calibration concentrations.
PRINT " %": PRINT
```

```
INPUT ; "CO2 concentration of gas is ", HICO2
PRINT " %": PRINT
PRINT "Are these values correct?"                    Cop-out clause in case values
DO                                                   are incorrectly entered.
ans4$ = UCASE$(INKEY$)
LOOP UNTIL ans4$ = "N" OR ans4$ = "Y"
IF ans4$ = "N" THEN GOTO VALUES1
PRINT "Completing gas equilibration"
DO                                                   Allow analysers to fully respond.
LOOP UNTIL TIMER - T >20
READING1:
CALL gascal                  Calculate average readings for gas from each analyser.
HICALO2 = PO2 / 100: HICALCO2 = PCO2 / 100
HICALCCO2 = PETCCO2 / 100: HICALOO2 = petoo2 / 100
PO2 = 0: PCO2 = 0: PETCCO2 = 0: petoo2 = 0       Reset sums of readings to zero.
CLS                                              Print average readings.
PRINT "CO2"; HICALCO2, "O2"; HICALO2, "PETCO2"; HICALCCO2, "PETO2";
HICALOO2
PRINT "HIGH CALIBRATION IS NOW COMPLETE. DO YOU WISH TO
REPEAT IT? (Y/N)"
DO
ans2$ = UCASE$(INKEY$)                   Allow readings to be repeated.
LOOP UNTIL ans2$ = "Y" OR ans2$ = "N"
IF ans2$ = "Y" THEN
GOTO READING1
END IF
PRINT "": PRINT "TURN OFF HIGH GAS. CALCULATING GAS CALIBRATION
EQUATIONS"
MO2 = (HIO2 - LO2) / (HICALO2 - LOCALO2)    Callibration slope and intercept
INTO2 = HIO2 - (MO2 * HICALO2)              for MedishieldMS2 (PE,O2).
MCO2 = (HICO2 - LOCO2) / (HICALCO2 - LOCALCO2) Callibration slope and
INTCO2 = HICO2 - (MCO2 * HICALCO2) intercept for Beckman LB-2 (PE,CO2).
MCCO2 = (HICO2 - LOCO2) / (HICALCCO2 - LOCALCCO2) Callibration slope
INTCCO2 = HICO2 - (MCCO2 * HICALCCO2) and intercept for airspec 2 600
                                                 (PET,CO2).
MOO2 = (HIO2 - LO2) / (HICALOO2 - LOCALOO2)  Callibration slope and
INTOO2 = HIO2 - (MOO2 * HICALOO2)  intercept for Airspec 2 600 (PET,O2).
PRINT "": PRINT "To check the calibration, check the inspired gas composition."
PRINT ""
PRINT "EXPOSE GAS METERS TO ROOM AIR." Expose gas analysers
T = TIMER                                        to room air
PRINT
PRINT "EQUILIBRATING WITH ROOM AIR."  allow analysers to fully respond
DO
LOOP UNTIL TIMER - T > 20
```

AIRCHECK:
CALL **gascal** *and take average readings to measure pO_2 and pCO_2 in room air.*
AIRO2 = PO2 / 100: AIRCO2 = PCO2 / 100: AIRCCO2 = PETCCO2 / 100:
AIROO2 = petoo2 / 100
PO2 = 0: PCO2 = 0: PETCCO2 = 0: petoo2 = 0
PRINT "O2"; AIRO2, AIROO2, "CO2"; AIRCO2, AIRCCO2
conco2 = (MO2 * AIRO2) + INTO2: concco2 = (MCO2 * AIRCO2) + INTCO2
conccco2 = (MCCO2 * AIRCCO2) + INTCCO2: concoo2 = (MOO2 * AIROO2) + INTOO2
PRINT "The inspired Oxygen concentration ";
PRINT USING "##.###"; conco2; *Print values and average measurements.*
PRINT "": PRINT "The inspired carbon dioxide concentration is ";
PRINT USING "#.####"; concco2;
PRINT "The end-tidal inspired oxygen concentration is ";
PRINT USING "##.##"; concoo2;
PRINT "The end-tidal CO2 concentration is ";
PRINT USING "#.####"; conccco2;
PRINT "": PRINT "": PRINT ""
PRINT "REPEAT CHECK?" *Ask if to repeat check on room air.*
DO
ANS12$ = UCASE$(INKEY$)
LOOP UNTIL ANS12$ = "Y" OR ANS12$ = "N"
IF ANS12$ = "Y" THEN
GOTO **AIRCHECK**
END IF
DEDD:
END SUB

SUB gascal ***PART OF SUBPROGRAM 'GAS.'***
PRINT "PERFORMING GAS ANALYSIS. "
DO
t10 = TIMER
FOR CHAN = 2 TO 3 *Read PE,O_2 and PE,CO_2*
CALL **ADCONV**
NEXT CHAN
FOR CHAN = 7 TO 8 *Read PE,CO_2 and PE,O_2*
CALL **ADCONV**
NEXT CHAN
O = O + 1
PO2 = PO2 + A *Summate each of above readings*
PCO2 = PCO2 + B
PETCCO2 = PETCCO2 + ETCO2
petoo2 = petoo2 + ETO2
DO

```
LOOP UNTIL TIMER - t10 > .2  Allow a gap of approx. 0.2 sec between readings.
LOOP UNTIL O = 100                    Sum is of 100 readings.
END SUB
```

SUB INSPRESS *SUBPROGRAM OF 'EXTEST.'*

```
DIM INTIME AS SINGLE
PFLOW = TFLOW                 Part of the flow integration process.
INTIME = (TIMER - T4)         Time between two flow measurements.
T4 = TIMER                    Reset time at start of integration period.
CHAN = 1                      measure expiratory flow.
CALL ADCONV
FOR CHAN = 7 TO 8             Measure PET,CO2 and PET,O2 .
CALL ADCONV
NEXT CHAN
CHAN = 4                      Measure inspiratory flow.
CALL ADCONV
IF GASP > CROSSFLOW2 THEN     Decide which calibration line to use.....
TFLOW = (FLOW * MFLOW4) + INTFLOW4
ELSE
TFLOW = (FLOW * MFLOW3) + INTFLOW3          ...and calculate value.
END IF
INTEG = ((PFLOW + TFLOW) / 2) * INTIME      Integrate flow to give volume.
VOLUME = VOLUME + INTEG
PETCO2 = (((ETCO2 * MCCO2) + INTCCO2) / 100) * (TODATA.BP - 47)
IF PETCO2 > PHASE(N).PETCO2 THEN  Calculate PET,CO2 and determine
PHASE(N).PETCO2 = PETCO2          whether it is greater than previous value in
END IF                        array. if it is, replace previous value with new one.
PETO2 = (((ETO2 * MOO2) + INTOO2) / 100) * (TODATA.BP - 47)
IF PETO2 < PHASE(N).PETO2 THEN    Calculate PET,CO2 and determine
PHASE(N).PETO2 = PETO2            whether it is smaller than previous value
 END IF                       in array. If it is, replace previous value with new one.
END SUB
```

SUB subject

THIS IS THE MAIN SUBPROGRAM FOR INPUTTING SUBJECT'S DATA

subjecta:

```
CLS
PRINT "": PRINT "": PRINT " STAGE 2: SUBJECT'S DETAILS."
PRINT "": INPUT ; " Enter subject's surname"; SUBDATA.SURN Input surname.
PRINT "": INPUT ; "Enter subject's first names"; SUBDATA.CHRIS Input christian
                                                              name.
PRINT : PRINT : INPUT ; "Enter subject's date of birth:", SUBDATA.DA  Input
INPUT INPUT ;"/", SUBDATA.MO: "/", SUBDATA.YE                 date of birth.
```

```
age% = TODATA.YY - SUBDATA.YE                          Calculate age.
IF SUBDATA.MO < TODATA.MM THEN
PRINT SUBDATA.CHRIS; SUBDATA.SURN; "is"; age%; "years old."   Print age.
ELSE
PRINT SUBDATA.CHRIS; " "; SUBDATA.SURN; "is"; (age% - 1); "years old."
END IF
PRINT "": PRINT "": INPUT ; "Enter subject's height (m):"; SUBDATA.HEI Input
                                                                    height.
PRINT "": PRINT "": INPUT ; "Enter subject's weight (Kg):"; SUBDATA.WEI
                                                                    Input weight
REM PRINT "": PRINT "": INPUT ; "Enter subject's % body fat:"; SUBDATA.FAT
                                                                    Line unused.
PRINT "": PRINT "": PRINT "Are these values correct ?"  Cop-out clause allowing
DO                                                      correction of any mistakes.
ANS$ = UCASE$(INKEY$)
LOOP UNTIL ANS$ = "Y" OR ANS$ = "N"
IF ANS$ = "N" THEN
GOTO subjecta
END IF
CLS
END SUB     This data is collated in the form of an array which is stored in
            'EXTEST.'
```

SUB today

THIS IS THE MAIN SUBPROGRAM FOR INPUTTING DATA ABOUT THE TEST DAY

```
today:
1 PRINT "STAGE 1: TODAY'S CONDITIONS"
PRINT : PRINT
INPUT ; "Enter today's date ", TODATA.DD: INPUT ; "\", TODATA.MM: INPUT ;
"\", TODATA.YY                                          Input date.
PRINT ""
INPUT ; "Enter the time ", TODATA.TIME                  Input time of test.
PRINT ""
INPUT ; "Enter the barometric pressure ", TODATA.BP     Input barometric.
PRINT " mmHg"                                           pressure
REM PRINT ""
INPUT ; "Enter the saturated vapour pressure ", SVP: PRINT " cm.H2O" Input
PRINT ""                                        saturated water vapour pressure
INPUT ; "Enter the temperature ", TODATA.TEMP           Input air temperature.
PRINT " oC"
PRINT ""
```

```
PRINT "ARE THESE VALUES CORRECT? (Y/N)"      Cop-out clause to allow
DO                                           correction of any mistakes.
ANS1$ = UCASE$(INKEY$)
LOOP UNTIL ANS1$ = "Y" OR ANS1$ = "N"
IF ANS1$ = "N" THEN
GOTO today
END IF
CLS
END SUB This data is collated in the form of an array which is stored in 'EXTEST.'
```

SUB WORK

THIS IS THE TIME MARKER SUBPROGRAM CALLED IN 'EXTEST.'

```
WTIME = TIMER - t0                    Calculates time since beginning of test.
PRINT "Workload changed at ";
MINS = INT(WTIME / 60)                Calculates time in min and sec.....
secs = ((WTIME / 60) - MINS) * 60
PRINT USING "##"; MINS;                    ...and prints it.
PRINT ":";
PRINT USING "##.##"; secs
SEEK #1, 274 + (W * 4)                Stores time in data collection file
PUT #1, , WTIME
W = W + 1
END SUB
```

APPENDIX D:

MODEL 1 EXPLAINED

The model described in this Appendix is MODEL 1. It has been used to describe the ventilatory and pulmonary gas exchange responses to a cessation of hyperventilation (as reported in Chapter 4).

In this model, the profile of the decline in ventilation and pulmonary gas exchange parameters is described as a monoexponential fall to a baseline (See *Figure D.1*). The best fit function was derived using the "Solver" function in Microsoft EXCEL using the least squares method. The Solver function will repeat a series of calculations, each time adjusting one or more specified constants until the best fit function is achieved.

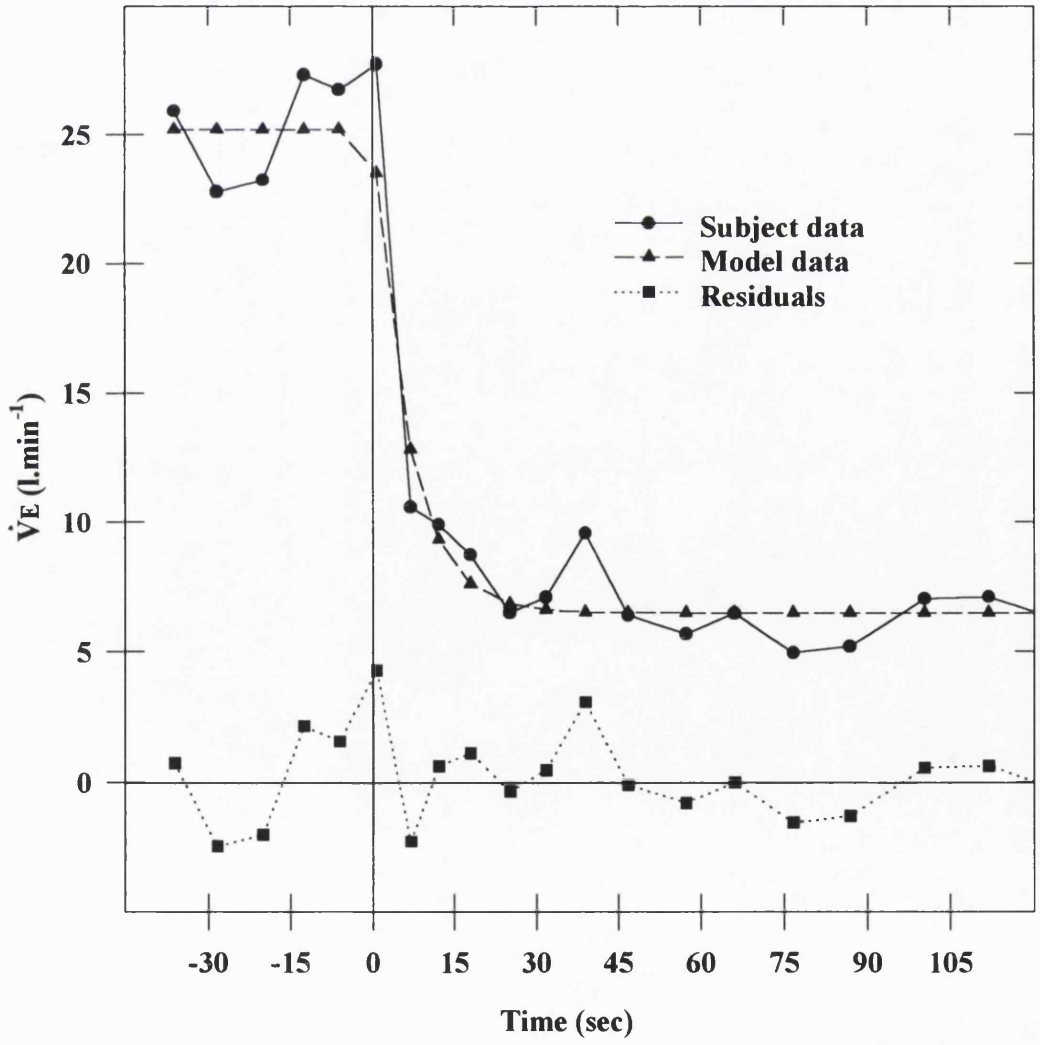


Figure D.1: Graph showing the complete model, model residuals and the data from which the model was derived. Time 0 denotes the end of hyperventilation

	A	B	C	D	E
1		HYPER	25.57623		
2		Recovery	6.471987		
3		Tau	6.359449		
4		Sum(Res^2)	20.90717		
5					
6	Time	Subject Data	Model	Residuals	res ^2
7	-36.07	25.947	25.20998	0.737	0.5432
8	-28.33	22.766	25.20998	-2.444	5.9745
9	-20.03	23.223	25.20998	-1.987	3.9484
10	-12.51	27.353	25.20998	2.1427	4.5912
11	-6.078	26.762	25.20998	1.5516	2.4074
12	0.7305	27.778	((hyper-recovery)*EXP(-time/tau))+recovery	subject data-model	Residuals^2
13	6.9922	10.583	12.83443	-2.252	5.0702
14	12.152	9.9063	9.298392	0.608	0.3696
15	17.981	8.711	7.602354	1.1086	1.229
16	25.172	6.4975	6.836833	-0.339	0.1152
17	31.762	7.0733	6.601432	0.4718	0.2226
18	39.012	9.562	6.513384	3.0486	9.2942
19	46.762	6.3875	6.484225	-0.097	0.0093
20	57.359	5.6863	6.474299	-0.788	0.6209
21	66.203	6.465	6.472562	-0.008	6E-05
22	76.641	4.943	6.472098	-1.529	2.3382
23	86.91	5.1922	6.472009	-1.28	1.6378
24	100.31	7.0201	6.471989	0.5481	0.3005
25	111.95	7.0878	6.471987	0.6158	0.3792
26	121.51	6.3993	6.471987	-0.073	0.0053

Table D.1: Spreadsheet used in MODEL 1.

APPENDIX E:

MODEL 2 EXPLAINED

Appendix E

The model described in this Appendix is MODEL 2. This model is used to describe the ventilatory and pulmonary gas exchange responses to an abrupt increase in workload, from a background of in Chapter 5. The profile of the model is an abrupt increase to a plateau coincident with time 0, superseded some time later by a monoexponential increase to the steady-state (See *Fig. E.1*). The magnitude of the plateau response is taken as the mean of the data included in that time domain.

The only constraints imposed on the model are:

(i) The final outcome yields the lowest possible value for the sum of the squares of the residuals ($\Sigma(Res^2)$).

(ii) The value of the plateau must be less than the value of the steady-state response.

(iii) The time constant (τ) must be greater than 10 sec.

The delay in onset of the later rise is taken as the time of interception between the monoexponential curve and the plateau (See *Fig. E.1*).

Determination of the line(s) of best fit was performed using the "Solver" function in Microsoft EXCEL. The spreadsheet is shown below (See *Fig. E.2*)

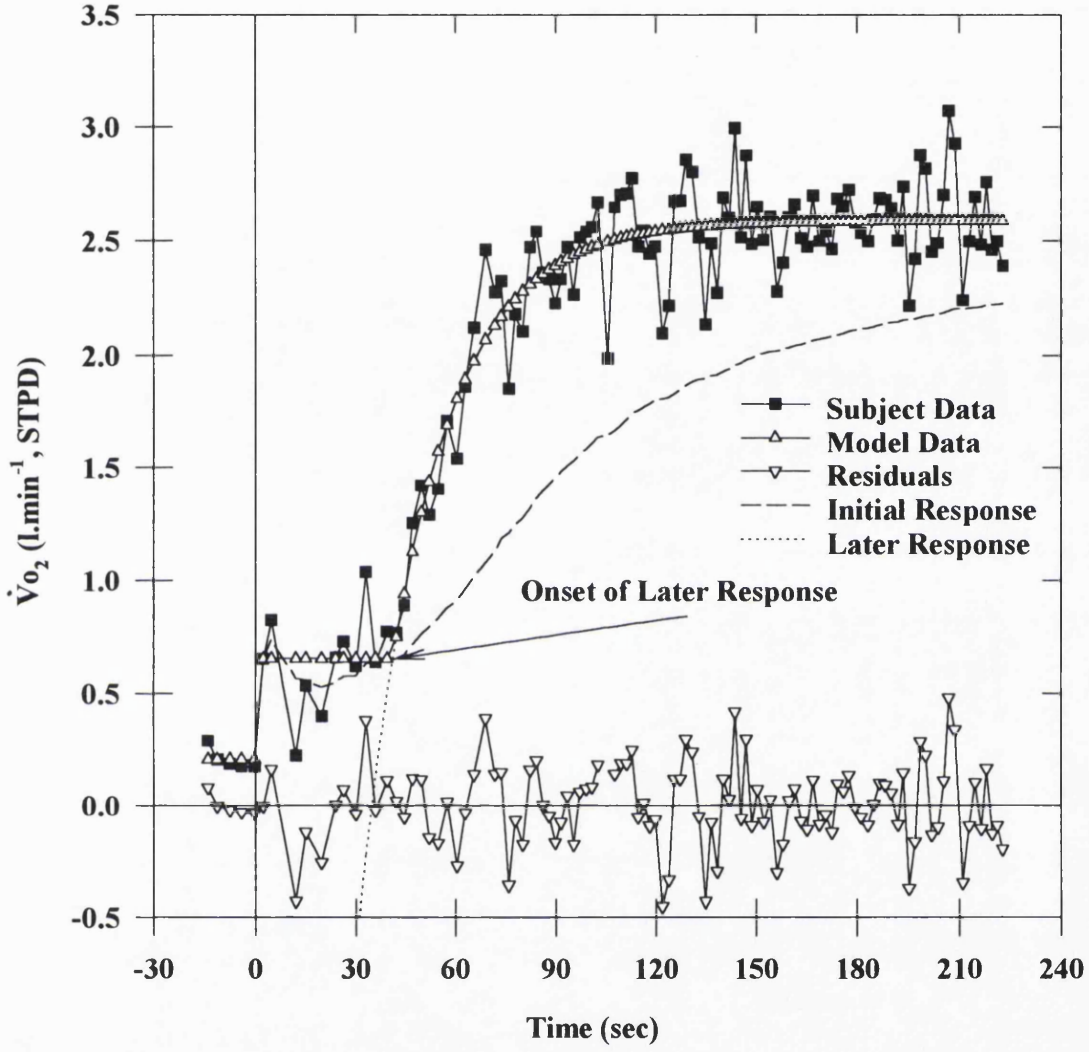


Figure E.1:Graph showing the complete model, model residuals and the data from which the model was derived. The onset of the later response is marked. Exercise began at time 0.

	A	B	C	D	E	F	G	H
1	Pre-Ex.	0.20939	REST	0.3939222	sum(RES^2)	3.918728431		
2	Initial Response	0.673132	Steady-state	2.5893765				
3			Delay	38.251553				
4			Tau	21.350748				
5								
6	Time	Subject Data	Model Data	Model Resid.	RES^2	Initial Response	Later Response	Mean Data
7	-14.008	0.292223	0.209389674	0.0828331	0.006861	0.209389674		
8	-11.27	0.208698	0.209389674	-0.000691	4.78E-07	0.209389674	D$1+((D$2-D$1)*(1-(EXP(-(A24-D$3)/D$4))))	
9	-7.5898	0.189491	0.209389674	-0.019899	0.000396	0.209389674	Rest+((S/S-Rest)*(1-(EXP(-(time-delay)/time const.))))	
10	-4.1289	0.179086	0.209389674	-0.030304	0.000918	0.209389674	-13.3908547	
11	-0.2305	0.177451	0.209389674	-0.031939	0.00102	0.209389674	-10.723929	
12	2.3008	0.653548	IF(H12>G12,F13,H12)	B12-C12	D12^2	IF(H12>G12,F13,H12)	-9.23550654	AVERAGE(B$12:B12)
13	4.7227	0.823329	0.673132493	0.1501965	0.022559	0.673132493	-7.9674433	0.73844
14	12.082	0.226753	0.673132493	-0.446379	0.199254	0.673132493	-4.8895275	0.56788
15	14.9922	0.535003	0.673132493	-0.13813	0.01908	0.673132493	-3.93654322	0.55966
16	19.8203	0.399304	0.673132493	-0.273828	0.074982	0.673132493	-2.61577757	0.52759
17	24.0508	0.659976	0.673132493	-0.013157	0.000173	0.673132493	-1.68016463	0.54965
18	26.3594	0.729912	0.673132493	0.05678	0.003224	0.673132493	-1.24259337	0.5754
19	29.9805	0.618127	0.673132493	-0.055006	0.003026	0.673132493	-0.64481308	0.58074
20	33	1.037628	0.673132493	0.3644959	0.132857	0.673132493	-0.21829295	0.63151
21	35.8594	0.634923	0.673132493	-0.03821	0.00146	0.673132493	0.13363265	0.63185
22	39.2695	0.772904	0.673132493	0.0997714	0.009954	0.673132493	0.49613954	0.64467
23	42.0117	0.769146	0.748437313	0.0207086	0.000429	0.673132493	0.74843731	Average $\dot{V}o2$ at onset of Phase 2
24	44.3711	0.890169	0.941035708	-0.050867	0.002587	0.673132493	0.94103571	0.67313
25	46.9492	1.253916	1.128525223	0.1253905	0.015723	0.714617012	1.12852522	0.71462
26	49.6523	1.421194	1.302246585	0.118947	0.014148	0.761722121	1.30224658	0.76172

27	52.0117	1.291876	1.436905653	-0.14503	0.021034	0.794856714	1.43690565	0.79486
28	54.6992	1.404378	1.57321287	-0.168835	0.028505	0.830710887	1.57321287	0.83071
29	57.3906	1.711121	1.693562149	0.0175585	0.000308	0.879622539	1.69356215	0.87962
30	60.4102	1.540168	1.81170446	-0.271536	0.073732	0.914388109	1.81170446	0.91439
31	62.8789	1.864216	1.896619722	-0.032404	0.00105	0.961879497	1.89661972	0.96188
32	65.5195	2.12106	1.977211532	0.1438483	0.020692	1.017078563	1.97721153	1.01708
33	68.9805	2.460401	2.068819312	0.3915814	0.153336	1.082684114	2.06881931	1.08268
34	71.7305	2.276731	2.131729271	0.1450018	0.021026	1.134599198	2.13172927	1.1346
35	73.5898	2.324098	2.169896837	0.1542008	0.023778	1.184161633	2.16989684	1.18416
36	75.8516	1.855381	2.212061777	-0.356681	0.127221	1.211010414	2.21206178	1.21101
37	77.8203	2.179859	2.245297216	-0.065438	0.004282	1.248273829	2.24529722	1.24827

Table E.1: Table of the spreadsheet used by MODEL 2 for the determination of the best fit function to (in this case) the changes in $\dot{V}o_2$ on transition from rest to exercise. The formulae used to generate the data in each column are shown near the top of the table.

APPENDIX F:

MODEL 3 EXPLAINED

Appendix F

The model described in this Appendix is MODEL 3. It has been used to describe the ventilatory and pulmonary gas exchange responses to an abrupt increase in work rate, either from a background of rest (as reported in Chapter 5), or from a background of mild exercise (as reported in Chapters 7 and 8). It evolved from MODEL 2, described in Appendix E.

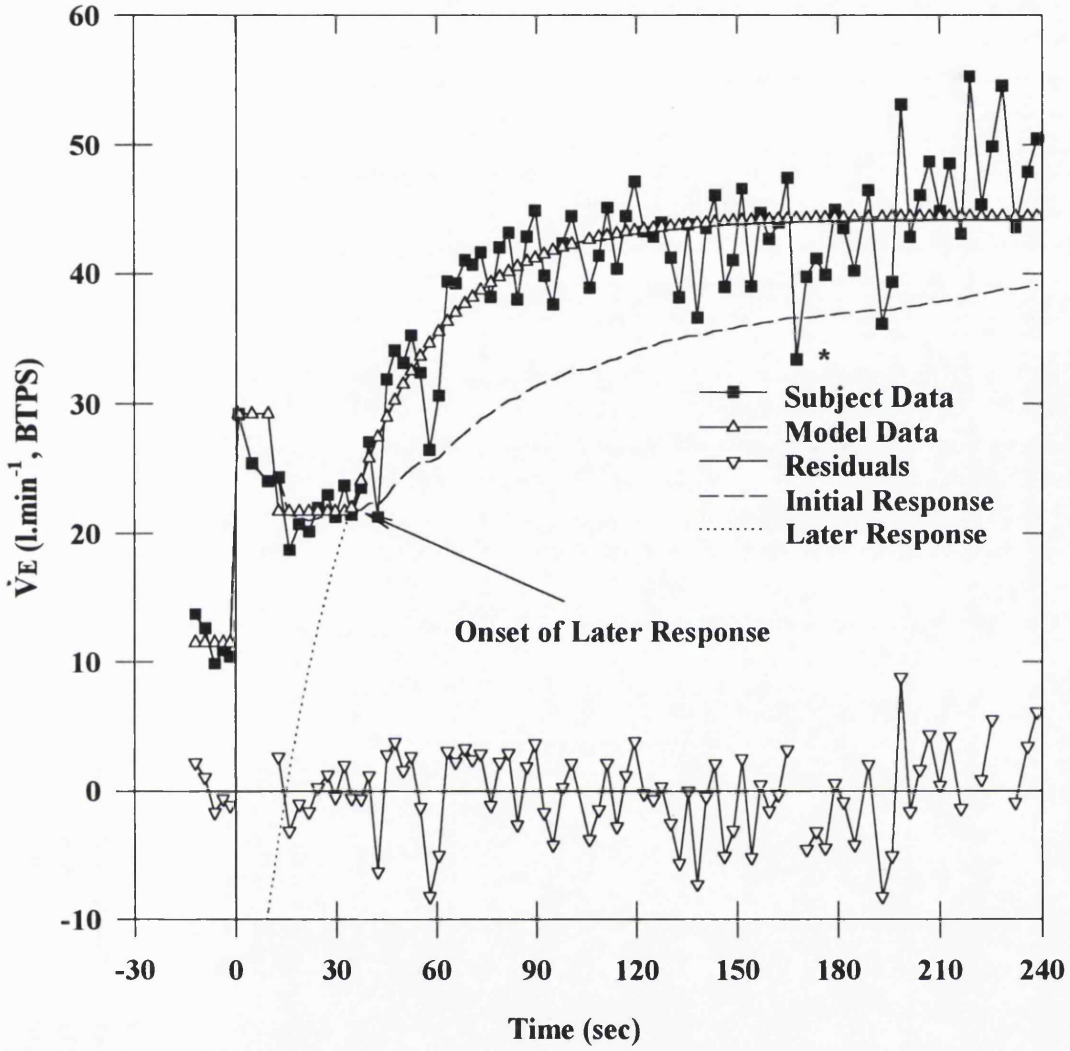
In this model, the plateau phase is taken as the mean of the data in that time domain between the fourth breath after time 0 and the onset of the later monoexponential rise to the steady-state. The first 3 breaths were considered to represent a separate response (the initial, abrupt increase) to that described by the plateau. The magnitude of the initial, abrupt increase was taken as the maximum response recorded in the first 3 breaths.

The constraints imposed on this model were the same as listed in Appendix E for MODEL 2, as was the definition of the delay in onset of the later response.

This model was deemed to have adequately described the profile of the experimental data if the initial response exceeded the 95% confidence interval for the plateau response. This was calculated as:

$$\text{Plateau Response} + (1.655 \times \text{S.D. of residuals})$$

1.655 was used as opposed to 1.96 as the 95% confidence interval was 1-tailed.



Appendix F.1: Graph showing the complete model, model residuals and the data from which the model was derived. The onset of the later response is marked. Exercise began at time 0. * denotes breath excluded from modelling process.

	A	B	C	D	E	F	G	H
1	Pre-ex.	C7	REST	13.776	sum(Res^2)	1210.675		
2	Initial Response	C12	S/S	44.433	model	21.733		
3	Plateau	C15	Delay	25.492	Later Response: Onset	34.022		
4			Time Const.	28.388				
5								
6	abs. time	val.	Model Data	Residuals	Residuals ^2	Initial Responses	Later Response	baseline
7	-12.141	13.7	11.501	2.199	4.835	11.501		
8	-9.281	12.591	11.501	1.09	1.187	11.501	D$1+((D$2-D$1)*(1-(EXP(-(A8-D$3)/D$4))))	
9	-6.371	9.861	11.501	-1.641	2.692	11.501	rest+((S/S-rest)*(1-(EXP(-(time-delay)/const))))	
10	-3.898	10.931	11.501	-.57	.325	11.501	-41.893	
11	-1.762	10.424	11.501	-1.077	1.161	11.501	-35.634	
12	.769	29.26	MAX(B12:B14)			MAX(B12:B14)	-28.804	
13	4.828	25.468	29.26			29.26	-19.048	
14	9.609	24.103	29.26			29.26	-9.208	
15	12.691	24.386	IF(F15>G15,F15,G15)	B15-C15	D15^2	IF(H15>G15,F16,G15)	-3.69	AVERAGE(B$15:B15)
16	15.93	18.703	21.733	-3.03	9.181	21.733	1.498	21.54461
17	18.898	20.75	21.733	-.983	.966	21.733	5.761	21.27982
18	21.809	20.168	21.733	-1.565	2.45	21.733	9.529	21.0018
19	24.441	22.035	21.733	.302	.091	21.733	12.621	21.20835
20	27.301	23.039	21.733	1.306	1.707	21.733	15.669	21.51351
21	29.66	21.269	21.733	-.464	.215	21.733	17.963	21.47862
22	32.352	23.761	21.733	2.028	4.115	21.733	20.357	21.76397
23	34.379	21.485	22.016	-.532	.283	21.733	22.016	21.73295
24	37.238	23.573	24.164	-.591	.349	Onset of later response	24.164	21.91696
25	39.711	27.105	25.855	1.25	1.562	22.389	25.855	22.38857
26	42.352	21.305	27.505	-6.2	38.438	22.298	27.505	22.29829
27	45.039	31.907	29.034	2.873	8.253	23.037	29.034	23.03741
28	47.512	34.122	30.318	3.804	14.468	23.829	30.318	23.82917

Table F.1: Spreadsheet used by MODEL 3 to determine the best fit function to the experimental data. Note differences in modelling at exercise onset compared with MODEL 2 (*Table E.1*).

APPENDIX G:

MODEL 4 EXPLAINED

Appendix G

The model described in this Appendix is MODEL 4. It has been used to describe the ventilatory and pulmonary gas exchange responses to an abrupt increase in work rate from a background of mild exercise (as reported in Chapters 7 and 8). It describes the traditional response reported in the literature (Whipp et al., 1982; Linnarson, 1974; Miyamoto & Niizeki, 1992; Fujihara et al., 1973a. See *Fig. G.1*).

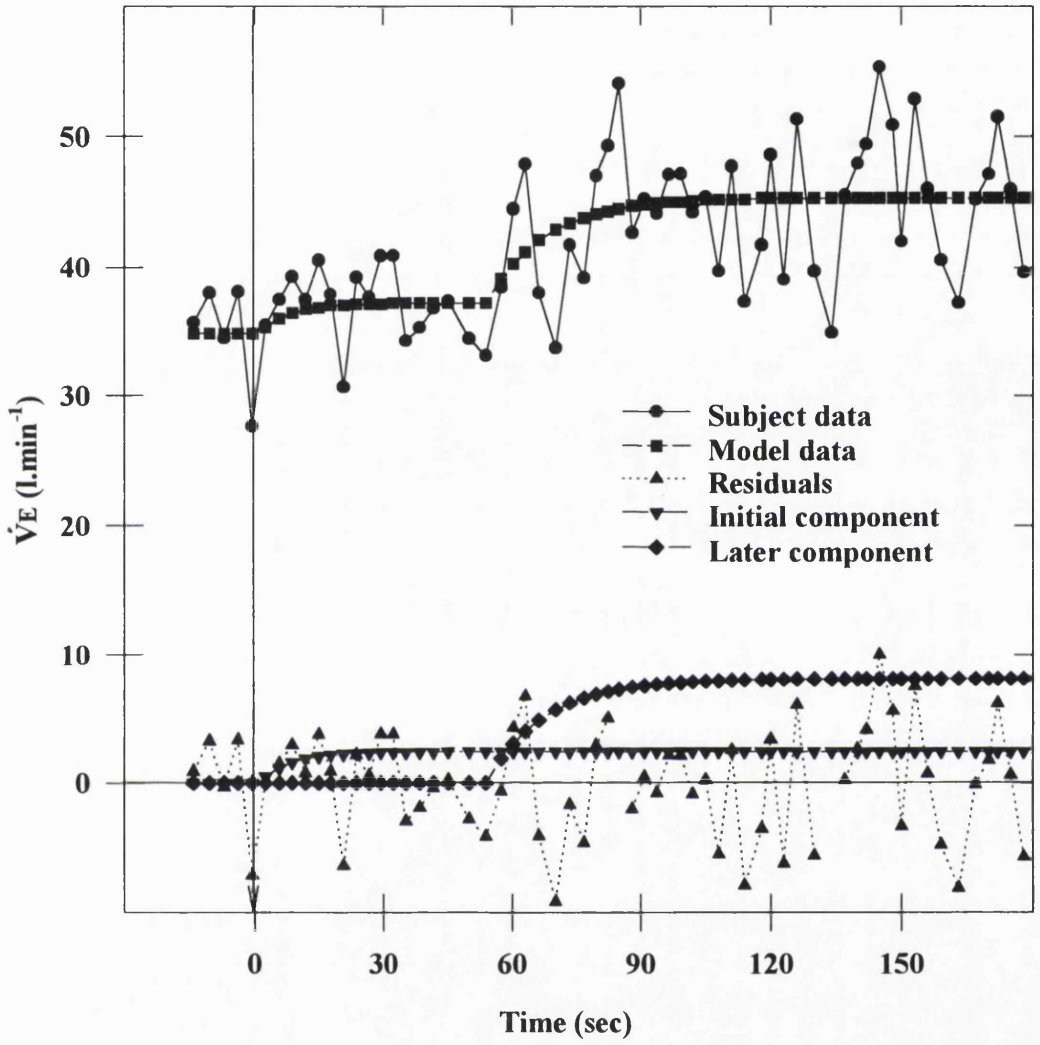
The "Solver" function in Microsoft Excel was again used to determine the best fit function to each subject's breath-by-breath data using the least squares method.

In this model, the early ventilatory and pulmonary gas exchange responses to an abrupt increase in work rate are described by a monoexponential rise of small amplitude. This is superseded by the later response of greater amplitude, again described by a monoexponential rise, to the steady-state.

The constraints imposed on this model were:

The time constant of the initial rise must be between 0 and 10 sec.

The time constant for the later response must be greater than 10 sec.



Appendix G.1: Graph showing the complete model, model residuals and the data from which the model was derived. In this model, the response prior to the increase in work rate, the initial component and the later component of the response to the increase in work rate were summed to produce the total response at any time. Exercise began at time 0.

	A	B	C	D	E	F	G
1	pre	34.8	50 w s/s	31.706	$\Sigma(res^2)$	133.076	
2	ph.1 peak	37.2	ph.2 peak	45.346			
3	ph.1 delay	0.947	ph.2 delay	53.859			
4	ph.1 time const.	7.3	ph.2 time const.	13.768			
5							
6							
7							
8							
9	time	val.	model	model res.	model res^2	Initial response	phase 2
10	-14.1	35.69	34.8	0.892	0.7957	0	0
11	-10.4	38.03	34.8	3.2342	10.46	0	0
12	-6.99	34.48	34.8	-0.315	0.0993	0	0
13	-3.81	38.13	34.8	3.3277	11.074	0	0
14	-0.51	27.66	34.8	-7.139	50.963	0	0
15	2.56	35.45	F15+G15+B1	B15-C15	(D15^2)	(B$2-B$1)*(1-(EXP(-(A15-B$3)/B$4)))	0
16	5.75	37.46	36	1.5027	2.2581	1.15648	0
17	8.77	39.3	36.4	2.9221	8.5386	1.57741	0
18	11.9	37.46	36.7	0.7931	0.629	1.86384	0
19	14.9	40.56	36.8	3.715	13.801	2.0427	0
20	17.7	37.88	37	0.9208	0.8478	2.15795	0
21	20.7	30.68	37	-6.363	40.483	2.23965	0
22	23.6	39.25	37.1	2.1643	4.684	2.29208	0
23	26.6	37.69	37.1	0.564	0.3181	2.32728	0
24	29.4	40.91	37.1	3.7628	14.159	2.35057	0
25	32.3	40.94	37.2	3.7717	14.226	2.36653	0
26	35.3	34.26	37.2	-2.919	8.5214	2.37758	0
27	38.5	35.28	37.2	-1.908	3.6418	2.3851	0

28	41.7	36.79	37.2	-0.394	0.1555	2.39007	0
29	45.1	37.39	37.2	0.1995	0.0398	2.39349	0
30	50	34.43	37.2	-2.767	7.6547	2.39625	0
31	53.9	33.1	37.2	-4.092	16.747	2.39743	0
32	57.5	38.48	39.1	-0.601	0.3614	2.3981	(D$2-(F32+B$1))*(1-(EXP(-(A32-D$3)/D$4)))
33	60.3	44.5	40.3	4.2399	17.977	2.39843	3.06
34	63.1	47.93	41.2	6.7393	45.418	2.39866	4
35	66.3	38.01	42.1	-4.038	16.307	2.39883	4.85
36	70.2	33.69	42.9	-9.169	84.071	2.39895	5.66
37	73.5	41.75	43.4	-1.644	2.7029	2.39902	6.2
38	76.8	39.19	43.8	-4.614	21.293	2.39906	6.61
39	79.7	47.01	44.1	2.9132	8.4868	2.39909	6.9
40	82.4	49.32	44.3	5.0027	25.027	2.3991	7.12
41	84.9	54.11	44.5		0	2.39911	7.3
42	88	42.67	44.7	-1.991	3.966	2.39912	7.46
43	90.8	45.24	44.8	0.4494	0.202	2.39913	7.59
44	93.7	44.14	44.9	-0.755	0.5708	2.39913	7.7

Table G.1: Part of the spreadsheet used by MODEL 4 to determine the best fit function to the experimental data.