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Ventilatory Response To Carbon Dioxide Stimuli In Aged Humans

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VENTILATORY RESPONSE TO CARBON DIOXIDE STIMULI IN AGED HUMANS

by

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ABSTRACT

This thesis examined age-related changes in the ventilatory response to exercise and in the ventilatory response to inhaled carbon dioxide (CO_2) at rest. Specifically, the purposes were to: 1) examine the ventilatory response to CO_2 production ($\dot{V}CO_2$) during graded exercise below the ventilation threshold ($T_{\dot{V}E}$) in men and women aged 55 to 86 yrs, 2) determine the ventilatory response to CO_2 at rest and evaluate the CO_2 sensitivity of the central and peripheral chemoreceptors in young (YS, n=7, 28.3 yrs) and old (OS, n=11, 76.1 yrs) humans, and 4) determine the temporal parameters of the ventilatory response to CO_2 in young (YS, n=4, 27.0 yrs) and old (OS, n=5, 74.2 yrs) men.

The first study showed a significant positive relationship between the ventilatory response to $\dot{V}CO_2$, referred to as $\Delta\dot{V}_E/\Delta\dot{V}CO_2$, and advancing age, increasing by 0.29/yr for men and by 0.20/yr for women. At a common metabolic demand ($\dot{V}CO_2 = 1.0\ \ell \cdot min^{-1}$), $\dot{V}_E$ was 14% higher in men aged 80-86 yrs compared to men aged 55-64 yrs while for women, there were no differences between age groupings. The men aged 75 to 86 yrs appear to have reached the appropriate exercise $\dot{V}_E$ primarily by an increase in breathing frequency (f_b) with a levelling off of V_T. The increased ventilatory response to $\dot{V}CO_2$ with advancing age may be related to an age-dependent increase in dead-space ventilation ($\dot{V}_D$) and to a greater non-uniformity of ventilation-perfusion ratio.

In the second study, the ventilatory responses to CO_2 (eucapnia and hypercapnia) were determined in hyperoxia and hypoxia and, for each subject, the ventilatory responses were fitted to the Lloyd equation, $\dot{V}_E = S(P_{ET}CO_2 - B)$ for the determination

of the CO_2 sensitivity (S). In hypercapnia, hypoxic $\dot{V}_E$ was 24% lower in OS (39.9 $\pm$ 2.7 (SE), $\ell \cdot min^{-1}$) compared to YS (52.2 $\pm$ 3.2) while there were no age differences in hyperoxic $\dot{V}_E$. In hypoxia, S was significantly lower in OS (3.25 $\pm$ 0.38 $\ell \cdot min^{-1} \cdot Torr^{-1}$) compared to YS (4.76 $\pm$ 0.37) and appeared to have resulted from a lower peripheral chemoreflex CO_2 sensitivity (OS, 0.86 $\pm$ 0.21 $\ell \cdot min^{-1} \cdot Torr^{-1}$; YS, 2.16 $\pm$ 0.43).

Finally, the third study determined the ventilatory response to CO_2 in euoxia, hyperoxia, and mild hypoxia. A double component exponential model was used to estimate the central and peripheral chemoreflex gains (g_c,g_p), time constants of the responses (τ_c,τ_p), and time delays (T_c,T_p). YS and OS showed similar characteristics for T_c, T_p, τ_c, and τ_p. In hypoxia, g_c and g_p were significantly smaller for OS (g_c, OS=1.27 $\pm$ 0.10 $\ell \cdot min^{-1} \cdot Torr^{-1}$ and YS=2.07 $\pm$ 0.23, p=0.0104; g_p, OS=0.91 $\pm$ 0.08 and YS=1.28 $\pm$ 0.14, p=0.0481). This study demonstrated that the ventilatory responses to CO_2 in euoxia and hyperoxia are similar for young and older men while in hypoxia, the response in older men is characterized by lower gains for the central and peripheral chemoreflex loops.

These studies have determined the ventilatory response to $\dot{V}CO_2$ during exercise and the ventilatory response to inhaled CO_2 at rest and suggest possible age-related alterations in the mechanisms that control these responses in the elderly.

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Finally, doctoral studies have provided me with an education which may perhaps best be summarized by the words of a well-known poet, Robert Frost: "Two roads diverged in a wood, and I, I took the one less traveled by, and that has made all the difference".

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

Ageing is associated with a decline in many physiological functions including a gradual decline in function of the human respiratory system (Levitzky, 1984). Interpretation of the alterations in the respiratory system associated with ageing is often made difficult however because a number of exogenous and deleterious factors such as exposure to pollutants, pulmonary infections, smoking, and differences in lifestyle may also bring alterations to the respiratory system (Levitzky, 1983; Vollmer et al., 1988) which are difficult to separate from those related strictly to the ageing process itself. To this end, Rowe and Kahn (1987) have termed "usual ageing" to define the combined changes due to ageing and other extrinsic factors, and "successful ageing" to define age-related changes unaffected by extrinsic factors and representing an ideal and elite population, free of overt diseases. Thus, in defining control populations to study age-related changes in function it is important to exclude subjects with symptoms of disease and to separate those who have aged "usually" from those who have aged "successfully" (Calne et al., 1991).

Furthermore, research of the age-related changes in the respiratory control system are often complicated by factors such as subject selection and study design. Subjects who volunteer for most studies do not represent the "usual" ageing population because subjects with symptoms of cardiovascular and respiratory diseases have been screened out (Fowler et al., 1987; Knudson et al., 1983) and therefore generalizing results from

these studies to the "usual" or normal population can only be done with reduced confidence. As well, because of practical implications, most information regarding respiratory control in aged humans has come from cross-sectional studies rather than from longitudinal studies. Such cross-sectional study designs however can overestimate normal declines in function of the respiratory control system with advancing age (Fowler et al., 1987; Knudson et al., 1983).

1.1 Thesis Outline

This thesis examines age-related changes in the control of breathing including the ventilatory response to exercise and the ventilatory response to inhaled carbon dioxide (CO_2). Chapter One serves as a general introduction and reviews (1) the historical developments in the study of the ventilatory response to inhaled CO_2, (2) the techniques used to examine the ventilatory response to CO_2, (3) the central and peripheral chemoreceptors, (4) the age-related changes in the human respiratory system, (5) the age-related changes in the ventilatory response to CO_2 production during exercise, and (6) the age-related changes in the ventilatory response to inhaled CO_2 at rest. Chapters Two, Three, and Four are each organized as research studies and include a brief Introduction, Methods, Results and Discussion. References have been grouped at the end of the thesis, and attempts have been made to limit explanation of methods common to more than one study.

In the first study (Chapter Two), the ventilatory response to CO_2 production ($\dot{V}CO_2$) during graded exercise will be examined in 128 men and 96 women aged 55 to

86 years. The relationship between ventilation ($\dot{V}_E$) and $\dot{V}CO_2$ will be examined for graded exercise below the ventilation threshold ($T_{\dot{V}E}$). Physiological mechanisms underlying the age-related differences in the ventilatory response to CO_2 during exercise will be discussed.

In Chapter Three, the ventilatory response to inhaled CO_2 at rest will be examined in hypoxia and in hyperoxia in groups of young and older humans in their eighth and ninth decades of life. This study will enable the determination of the CO_2 sensitivity of the central and peripheral chemoreflexes in healthy aged humans. No study has yet to examine the peripheral chemoreflex CO_2 sensitivity in aged humans.

In Chapter Four, the temporal parameters of the ventilatory response to CO_2 will be determined in groups of young and older humans. A double component exponential model will be used to estimate the temporal parameters in terms of central and peripheral chemoreflex gains (G_c,G_p), time constants of the response (τ_c,τ_p), and time delays (T_c,T_p).

A general conclusion in Chapter Five will summarize the findings from the three studies and discuss implications for future research.

1.2 Historical Perspective: Ventilatory Response to CO_2 at Rest

The realization that chemical stimuli could act on the respiratory system was known over one hundred years ago. In 1868, Pflüger used dogs to study the ventilatory responses to either nitrogen (N_2) or a mixture of CO_2 and oxygen (O_2). His results showed that both perturbations stimulated ventilation and he concluded that it was mainly O_2 that regulated respiration. A few years later Mieschер-Rüsch (1885), as cited in

Cunningham et al. (1986), observed that the addition of moderately high concentrations of CO_2 to inspired air had a greater effect on breathing in humans and showed that CO_2 was a more important humoral stimulus than O_2 in regulating respiration. In 1877, Walter demonstrated that the administration of intravenous injections of an acid solution caused hyperventilation and H^+ was a third chemical that acted as a stimulant to the respiratory system.

In 1905, Haldane and Priestley re-tested Miescher-Rüsch's hypothesis that CO_2 in the blood passing through the respiratory centre regulated respiration. Recognizing that under normal conditions the ventilation of the lungs would also be regulated to keep the CO_2 pressure (P_{CO2}) constant in alveolar air, they directed their research focus to that relationship. By varying the percentages of CO_2 in the inspired air of two subjects in a closed box, they demonstrated that the respiratory system was "extraordinarily" sensitive to changes in alveolar P_{CO2} (P_ACO_2). Thus Haldane and Priestley were the first to quantify the effect of CO_2 on $\dot{V}_E$ by showing that the regulation of the rate of alveolar ventilation ($\dot{V}_A$) depended strongly on the P_{CO2} in the respiratory centre.

The effect of ventilation on P_{CO2} is known as the metabolic hyperbola (Cunningham, 1974). For gas exchange in the alveoli the equation takes the form:

$$P_ACO_2 - P_ICO_2 = \dot{V}CO_2/\dot{V}_A$$

where P_ACO_2 is the alveolar partial pressure, P_ICO_2 is the inspiratory CO_2 partial pressure and is negligible unless CO_2 is inhaled, $\dot{V}CO_2$ is the rate of CO_2 output, and $\dot{V}_A$ is alveolar ventilation. At any constant $\dot{V}CO_2$, $\dot{V}_A$ and P_ACO_2 are inversely related and the relationship represents the effects that $\dot{V}_A$ has on the stimuli (P_{CO2}-H^+, P_{O2}) forming

the feedback loop.

The relationship between $\dot{V}_E$ and P_ACO_2 is known as the respiratory controller relationship (Cunningham et al., 1986) and has been used by many to describe the respiratory control system. Some of the early work in this area was done by Gray (1950) who advanced a multiple factor theory which stated that the effects of H^+, CO_2, and O_2 on respiration were independent from one another, that the effects summed algebraically to produce the whole ventilation, and that when the value of a stimulus fell below its resting value it became inhibitory and showed no threshold value.

Research studies by Neilsen and Smith (1952) and by the group in Oxford (Cormack et al., 1957; Cunningham et al., 1957; Lloyd et al., 1958) showed that in humans the effects of CO_2 and O_2 were more than additive (i.e. multiplicative interaction) and that the slope of the CO_2 response line of the P_ACO_2 - $\dot{V}_A$ relationship exhibited characteristics of a threshold value near eucapnia. Neilsen and Smith (1952) determined the steady-state pulmonary ventilation and P_ACO_2 in humans breathing a number of different gases with different values of P_{CO2} at constant levels of inspired O_2 pressure (P_{O2}). They reported that the relationship between $\dot{V}_E$ and P_ACO_2, for a given level of alveolar P_{O2} (P_AO_2), was linear over the eucapnic and hypercapnic ranges of P_ACO_2 and that the threshold value for CO_2 was about the same in euoxia or in different levels of hypoxia.

Lloyd and co-workers (1958) also used steady-state techniques to measure $\dot{V}_E$ and alveolar gas pressures in humans breathing various gas mixtures. They confirmed and extended the findings of Neilsen and Smith (1952). As well, they reported a mathematical

expression describing the linear relationship between $\dot{V}_E$ and P_ACO_2 at a constant P_{O2}. This expression is of the form:

$$\dot{V}_E = S(P_ACO_2 - B)$$

where $\dot{V}_E$ is minute ventilation, S the slope of the CO_2 response, P_ACO_2 the alveolar P_{CO2}, and B the CO_2 threshold. Lloyd and co-workers demonstrated that decreasing P_AO_2 had a highly reproducible and large effect of increasing the slope of the relationship with only minor effects on B, the intercepts of the lines extending to the P_{CO2} axis. Studies by Dejours (1962) have since shown that increasing P_AO_2 above euoxia (above 200 Torr) had the effect of reducing S, mainly due to the elimination of the hypoxic drive to breathe. Over the range of eucapnia to 15-20 Torr higher (moderate hypercapnia), the $\dot{V}_E$-P_ACO_2 relation has been shown to be effectively linear and steep, whereas at P_ACO_2 levels that exceed the physiological range, $\dot{V}_E$ reaches a plateau and eventually leads to narcosis (Cunningham et al., 1986).

More recently, many studies have attempted to determine the exact nature of the interaction between the drives mediated by CO_2 and O_2, initially demonstrated by Nielsen and Smith (1952) and by the research group at Oxford (Cormack et al., 1957; Cunningham et al., 1957; Lloyd et al., 1958). Since many studies have demonstrated that the ventilatory response resulting from an increase in the level of inhaled CO_2 arises from both the peripheral and central chemoreceptors, it has been suggested that the interaction arises from the peripheral chemoreceptors (Bellville et al., 1979; Berkenbosch et al., 1979; Bernards et al., 1966; Bouverot et al., 1963; Clement et al., 1992; Cunningham et al., 1965; DeGoede et al., 1985; Heymans et al., 1930; Hornbein and Roos, 1963;

Hornbein et al., 1961; Joels and Neil, 1961; Lahiri and DeLaney, 1975; Leitner et al., 1965; Miller et al., 1974; Neil and Joels, 1963; Swanson and Bellville, 1975; Van Beek et al., 1983; Ward and Bellville, 1983).

The early studies by Heymans and co-workers (1930) showed that arterial hypercapnia could stimulate the peripheral chemoreceptors and it has since been established that arterial P_{CO2} (P_aCO_2) stimulates the peripheral chemoreceptors mainly by its effect on arterial pH (Hornbein and Roos, 1963).

Experiments using animal models have examined whole carotid body afferent nerve responses (Hornbein et al., 1961) or single nerve fibre responses (Lahiri and Delaney, 1975; Neil and Joels, 1963) and have found evidence that a multiplicative interaction between hypoxic and hypercapnic drives occurred at the peripheral chemoreceptor rather than within the central respiratory controller. Lahiri and DeLaney (1975) showed that single chemoreceptor afferent fibres responded to changes in arterial P_{O2} (P_aO_2) and P_aCO_2 and that the two stimuli showed multiplicative interaction. They concluded that the sensory receptor at the carotid chemoreceptors may be activated through a single mechanism by the two stimuli (Lahiri and DeLaney, 1975).

Bouverot et al. (1963) used the latencies of the ventilatory responses to demonstrate the presence of a CO_2 peripheral chemoreflex drive in dogs. They noted that the administration of two tidal volumes of 7% CO_2 in awake dogs resulted in a sudden increase in $\dot{V}_E$ after a lag of approximately 5 seconds. When the same technique was applied in dogs deprived of their carotid bodies, they found that the ventilatory response to CO_2 was less and lagged by more than 15 seconds. They attributed this slower

response to a direct action of hypercapnic blood on the central chemoreceptors. They believed however, that the brisk ventilatory response to transient CO_2 breathing in normal dogs was mediated by the peripheral chemoreceptors because it was higher and more rapid when the dogs were made hypoxic but absent when these dogs were made hyperoxic. In the latter instance, the initial response to CO_2 was more like that of a dog whose chemoreceptors had been denervated.

Electrophysiological studies in cats have provided further evidence for the existence of a peripheral chemoreceptor mediated CO_2 drive. Leitner et al. (1965) observed in anaesthetized cats that the increase in $\dot{V}_E$ following the inhalation of CO_2 was paralleled by an increase in the discharge in the afferent fibres of the carotid chemoreceptors. These findings showed that chemoreceptor sensitivity to CO_2 was present in normal conditions and decreased with an increase in P_aO_2 (Hornbein et al., 1961; Joels and Neil, 1961). Thus, these studies have provided some evidence of a positive interaction at the level of the peripheral chemoreceptors between the O_2 and CO_2 ventilatory drives in dog and cats.

More recently, artificial brain perfusion techniques have been used in anaesthetized cats in order to physically separate the central and peripheral drives thereby providing them with separate perfusions and independent levels of P_aCO_2 and P_aO_2 (Berkenbosch et al., 1979; DeGoede et al., 1985; Van Beek et al., 1983). Results from these studies in anaesthetized cats have provided strong evidence of an independent and additive interaction between peripheral and central chemoreceptors and of a multiplicative hypoxic-hypercapnic interaction occurring within the peripheral chemoreceptors.

Evidence of a full central interaction with no peripheral interaction has been reported however, and that evidence is found mainly in studies by Kao and co-workers (Kao, 1963; Kao and Mei, 1978) who used artificial perfusion techniques in anaesthetized dogs. By isolating and perfusing the carotid chemoreceptors of the experimental dog with blood from a donor dog, they separated the perfusions of the central and peripheral chemoreceptors. They found no difference in the slope of the $\dot{V}_E$-P_ACO_2 response line in low and high P_aO_2 at the peripheral chemoreceptors but found an increase in the slope of the $\dot{V}_E$-P_ACO_2 response line in low P_aO_2 at the central chemoreceptors. Thus, the results from Kao et al. (1963 & 1978) support a central interaction of drives with no peripheral interaction.

In humans, because research is usually noninvasive, it has been more difficult to identify the exact nature and location of interaction between the drives. Dejours (1962) developed the technique of administering several breaths of CO_2 to CO_2-free inspired air to elicit transient respiratory response due to peripheral chemoreceptor stimulation. Results of his and other studies of on- and off- transient responses to CO_2 have shown alterations in $\dot{V}_E$ seemingly of peripheral chemoreceptor timing in euoxia and in hypoxia (not in hyperoxia) which suggested a peripheral multiplicative interaction (Bernards et al., 1966; Cunningham et al., 1965; Miller et al., 1974). Miller et al. (1974) examined the effect of withdrawing CO_2 for a couple of breaths in hyperoxic hypercapnia and in hypoxic hypercapnia. The short-latency fall in ventilation was only observed in hypoxic hypercapnia and this finding was attributed to reduced peripheral chemoreceptor activity. Their results suggested an interaction at the peripheral chemoreceptors.

The presence of an interaction at the peripheral or central control of ventilation has been proposed. Many studies in animals (Berkenbosch et al., 1979; Bouverot et al., 1963; DeGoede et al., 1985; Heymans et al., 1930; Hornbein and Roos, 1963; Hornbein et al., 1961; Joels and Neil, 1961; Lahiri and DeLaney, 1975; Leitner et al., 1965; Neil and Joels, 1963; Van Beek et al., 1983) and in humans (Bellville et al., 1979; Bernards et al., 1966; Clement et al., 1992; Cunningham et al., 1965; Miller et al., 1974; Swanson and Bellville, 1975; Ward and Bellville, 1983) have inferred that an interaction between hypoxic and hypercapnic stimuli occurs within the peripheral chemoreceptors rather than between the peripheral and central chemoreceptor neural impulses within the central controller, although the absence of central interaction has not been firmly established. Cunningham et al. (1986) have proposed a model consisting of three components to help establish the site of the occurrence of the multiplicative interaction between CO_2 and hypoxia. The three components of the model consist of the drives from the CO_2-H^+ stimulus complex, acting on the peripheral chemoreceptors, the drive from hypoxia also acting on the peripheral chemoreceptors, and the drive from CO_2-H^+, acting on the central chemoreceptors. The application of their model to the ventilatory responses of studies using steady-state techniques (Miller et al., 1974) supports the presence of peripheral multiplicative interaction.

More recently, studies have used dynamic forcing techniques to manipulate the inspired gas (Gelfand and Lambertsen, 1973) or the alveolar gas (Bellville et al., 1979; Dahan et al., 1990; Gardner, 1980; Gelfand and Lambertsen, 1973; Robbins, 1988; Swanson and Bellville, 1974; Swanson and Bellville, 1975) to study the characteristics

of the peripheral and central components of the response to CO_2 in order to determine the level of interaction between the peripheral and central chemoreceptors in humans.

Gelfand and Lambertsen (1973) were the first to use breath-by-breath measurements in order to attempt to separate and quantify the dynamic characteristics of central and peripheral components of respiratory control in humans. They administered step increases of 6 and 7.5% CO_2 against a background of euoxia or hyperoxia and characterized their dynamic responses in terms of a rapid component, attributed to the peripheral chemoreceptors, and two slower central components, attributed to two distinct central chemosensitive areas. During hyperoxia the peripheral component vanished but the central component remained at a decreased level. Their findings of a decrease in the central components in hyperoxia suggest that there is some central interaction between the drives.

Swanson and Bellville (1974) administered alveolar sine waves in end-tidal P_{CO2} ($P_{ET}CO_2$) in backgrounds of euoxia and hypoxia using a dynamic end-tidal forcing technique and found that the CO_2 response slope, defined by the magnitude of the sinusoidal ventilation response divided by the magnitude of the end-tidal CO_2 sinusoidal stimulus, decreased as frequencies were increased and the euoxic to hypoxic increase in gain was greater at the higher frequencies. Their results provided evidence of a peripheral CO_2-O_2 interaction, presumably at the carotid body.

Bellville et al. (1979) used the dynamic end-tidal forcing technique to administer step increases in $P_{ET}CO_2$ in backgrounds of euoxia and hypoxia in groups of normal humans and in four who had undergone carotid body resection. The ventilatory response

was studied by fitting a two compartment model that included peripheral and central components. Hypoxia increased the speed and magnitude of the response in the normal group while the responses in hypoxia were less and slower in the resected group. Furthermore, the magnitude of the central component was slightly higher in hypoxia in the normal group while it was much less in the resected group. They concluded that although their results on the normal group were consistent with a peripheral interaction, the results on the carotid body resected group suggested that the peripheral chemoreceptors might influence the functioning of the central control mechanisms (Bellville et al., 1979) and therefore may be indicative of an interaction between the central and peripheral chemoreceptors, at least in the carotid body resected group.

Ward and Bellville (1983) administered step increases in $P_{ET}CO_2$ using the dynamic end tidal forcing technique in humans under control conditions and in conditions when low-doses of dopamine were infused. Low doses of infused dopamine do not cross the blood-brain barrier and the primary site of action is assumed to be on the D_2 receptors in the carotid bodies where dopamine has been found to inhibit the hypercapnic and hypoxic responses (Sampson and Virduk, 1977; Ward and Bellville, 1982). Ward and Bellville (1983) found that the gain of the central chemoreflex loop was unchanged when the peripheral chemoreflex loop was decreased by dopamine and they suggested that there was no interaction between the peripheral and central chemoreflex loops. Ward and Bellville (1983) attributed the different findings from Bellville et al. (1979) in carotid body resected subjects to either central effects of the long-term denervation, the disease process itself, or to the denervation of the efferent and afferent fibres of the carotid

bodies.

Robbins (1988) used step changes in $P_{ET}CO_2$, and the different speeds of the central and peripheral chemoreceptors to temporally separate their chemical stimulation in humans. He used the end-tidal forcing technique to generate a period of time when the central chemoreceptors were exposed to hypercapnia while the peripheral chemoreceptors were exposed to eucapnia. Hypoxic sensitivity was measured against this background and when both the central and peripheral environments were eucapnic. In two out of three subjects the ventilatory response to hypoxia was increased when central P_{CO2} was high (i.e. hypercapnia), and therefore results tended to support the interaction theory between the central and peripheral chemoreceptors. There is also evidence for a degree of inter-individual variability in this function.

Dahan et al. (1990) also used the dynamic end-tidal forcing technique to administer step increases in $P_{ET}CO_2$ in backgrounds of euoxia, hyperoxia, and mild hypoxia in normal humans. The ventilatory responses were studied by fitting a two compartment model similar to the one used by Bellville et al. (1979) but with modifications to the model that enabled them to account for the noise and the drift in ventilation over time. The magnitude of the central component was unchanged in hypoxia but decreased in hyperoxia. Since Dahan et al. (1990) could not find any evidence of interaction between the peripheral and central chemoreflexes the lower central CO_2 sensitivity in hyperoxia was attributed to a central O_2-CO_2 interaction.

More recently, Clement et al. (1992) assessed the status of interaction between the central and peripheral chemoreflexes in seven young healthy men. In their study, the

ventilatory sensitivity to hypoxia was assessed at the same arterial pH in conditions when the central chemoreceptor activity was high (during CO_2 inhalation) and low (during exercise-induced acute metabolic acidosis). The ventilatory sensitivity to hypoxia at matched arterial pH values was found to be independent of central chemoreceptor activity and Clement et al. (1992) concluded that there was no interaction between peripheral and central chemoreflexes.

Thus, although the dynamic forcing techniques in humans support the presence of peripheral multiplicative interaction (Bellville et al., 1979; Clement et al., 1992; Swanson and Bellville, 1974; Ward and Bellville, 1983), there is also some evidence to indicate that a central interaction between the drives may exist (Robbins, 1988; Dahan et al., 1990). The reason why some experimental protocols demonstrate different degrees of interaction between the drives remains unclear.

Other techniques have also been used to measure the CO_2 thresholds and CO_2 sensitivities of the peripheral and central chemoreceptors. Although early attempts to measure the peripheral chemoreceptor threshold to CO_2 in humans at rest, using steady state techniques (Nielsen and Smith, 1952), were hindered by instabilities in ventilation, Duffin and McAvoy (1988) have recently been able to determine the parameters of the peripheral and central chemoreceptors. They used an adaptation of the Read rebreathing technique (1967) modified for use with mild hypoxia and prior hyperventilation or hyperoxia and prior hyperventilation to separate the peripheral and central CO_2 thresholds, respectively. Results from this work in humans at rest suggested no interaction between the peripheral and central chemoreceptors (McAvoy, 1993).

1.3 Techniques used to Examine the Ventilatory Response to CO_2

1.3.1 Steady-State Technique

The CO_2 response obtained by the steady state technique, described ventilatory responses to P_ACO_2 ($P_{ET}CO_2$) of subjects breathing a number of gas mixtures. These mixtures contained different concentrations of CO_2 presented for a few minutes at a time (Lloyd et al., 1958; Nielsen and Smith, 1952). In the past, use of this technique has been time consuming and sometimes unpleasant for the subjects. Considerable care had to be taken in determining the stimulus in these experiments as the P_aCO_2 depended not only on the concentration of CO_2 in the inspired gas, but also on the ventilatory response itself; with an increase in P_ICO_2, $\dot{V}_E$ increased and the P_aCO_2 decreased. In 1963, Fenn and Craig improved the steady state technique by administering pure CO_2 at different flow rates instead of the traditional method of administrating a fixed inspired CO_2. They found no difference in the resting CO_2 responses whether CO_2 was administered at a constant concentration or at a constant flow. The advantage of Fenn and Craig's technique was that the CO_2 loads no longer depended on $\dot{V}_E$, and normal feedback characteristics were obtained and steady state could be reached more quickly. Furthermore, small CO_2 loads could now be delivered with precision. Recently, Jacobi, Saunders and co-workers (1987a) have used the Fenn-Craig technique of constant inflow to study the characteristics of the CO_2 sensitivity in the physiological range of P_ACO_2 (35-45 Torr) and around the eucapnic control point at rest and during exercise (Jacobi et al., 1987a).

1.3.2 Rebreathing Technique

The principle of rebreathing is that subjects breathe in and out of a bag or spirometer, so that the P_{CO2} in the bag rises secondary to the subject's own CO_2 production. In early rebreathing techniques (Eckenoff et al., 1956), the volume of the rebreathing bag was quite large and the initial gas mixture did not contain CO_2. The CO_2 exchange occurring from the blood in the pulmonary capillaries to the alveolar gas (and rebreathing bag) created a number of problems such as a varying relationship between arterial P_{CO2} and the central chemoreceptors and a closed loop where the arterial and brain tissue P_{CO2} depended on the ventilatory response. The basis for rebreathing techniques for the determination of mixed venous P_{CO2} was established by having the subjects rebreathe from a smaller bag containing CO_2 and O_2. This enabled a quick P_{CO2} equilibrium to be developed between mixed venous blood, arterial blood, gas in the lung, and gas in the rebreathing bag (Collier, 1956; Campbell and Howell, 1962). In 1964, Fowle and Campbell demonstrated that the rebreathing technique could provide a CO_2 stimulus that was independent of the ventilatory response while in 1967 Read developed a rebreathing technique which used a small bag and an initial CO_2 close to that of mixed venous blood, thus opening the control loop between P_{CO2} and $\dot{V}_E$ (Read, 1967). In contrast to earlier methods, the Read rebreathing technique enabled the determination of the ventilatory response to CO_2 in a manner that was quick and efficient.

1.3.3 Dynamic End-Tidal Forcing Technique

Although steady-state and rebreathing techniques have traditionally given

information about linearity and overall gain of the $\dot{V}_E$-P_ACO_2 response over the eucapnic and hypercapnic ranges, they do not allow the determination of the time course of the response. Dynamic forcing techniques were developed which enable the determination of the time-courses of the ventilatory response to CO_2. Swanson and Bellville (1974; 1975) developed this technique in humans by using feedback control of inspired gas tensions to produce perturbations in the $P_{ET}CO_2$ and $P_{ET}O_2$. A second order model was developed (Swanson and Bellville, 1974 & 1975; Bellville et al., 1979) which estimated gains, time delays, and time constants for the fast and slow components of the ventilatory response to CO_2 which were attributed to the peripheral and central chemoreceptors respectively. The two compartment model initially proposed by Swanson and co-workers (Swanson and Bellville, 1974 & 1975; Bellville et al., 1979) was recently modified by Dahan et al. (1990) to include parameters which enable the modelling of the noise process and the drift in $\dot{V}_E$ over time resulting from CO_2 inhalation. DeGoede and co-workers (1985) provided important evidence that the fast and slow components of the two compartment model could in fact be attributed to the peripheral and central chemoreceptors. DeGoede's group used cats to compare the dynamic forcing technique with an artificial brain perfusion technique which separately perfused the central and peripheral chemoreceptors therefore isolating the dynamic responses of the chemoreceptors. DeGoede et al. (1985) found good correspondence between the dynamic forcing and artificial brain perfusion techniques in terms of gains, time constants, and time delays. This gave important support to the overall validity of the non-invasive dynamic forcing technique used in humans (Bellville et al., 1979; Dahan et al., 1990;

Swanson and Bellville, 1974 & 1975).

1.4 The Chemoreceptors

The human respiratory system regulates the levels of CO_2 and O_2 in the arterial blood by acting as a negative feedback loop (Cunningham et al., 1986). If CO_2 in the blood rises or the O_2 falls, the chemoreceptors sense these changes and afferent nerve impulses are sent to the respiratory centre located near the medulla in the central nervous system where the pattern of breathing is determined and where the activity of the motor nerves supplying the respiratory muscles is increased so that CO_2 is blown off or O_2 intake is increased.

Chemoreceptors are defined as receptors for which the adequate stimulus is a physiological chemical factor (Dawes and Comroe, 1954). The reflex arc of the respiratory chemoreflex which produces a change in ventilation is formed by (1) the chemoreceptors, (2) the afferent fibres to the respiratory centres, (3) the motor pathway to the thorax-lung apparatus, (4) and the information fed up to the respiratory centres from the chemoreceptors (Dejours, 1962).

Chemoreceptors are classified as peripheral and central. The peripheral chemoreceptors, located in the carotid bodies at the bifurcation of the carotid arteries, sense changes in concentrations of arterial blood CO_2 and O_2. Heymans and co-workers (1930) were the first to demonstrate that chemoreceptors were located in the aortic and sino-carotid areas and that the increase in pulmonary ventilation that occurred in hypoxia was due mainly to the reflexes from these chemoreceptors. The carotid bodies have a

high blood flow and a small vascular volume which promotes a rapid sensing of the chemical properties of arterial blood (Fidone et al., 1991).

The central chemoreceptors are located at the base of the brain and they sense the cerebral environment. They are believed to be on the brain side of the blood brain barrier. Evidence has shown that cells in the medulla are responsive to increases in CO_2 and are located in the ventrolateral portion within a millimetre of the surface (Millhorn and Eldridge, 1986) and it is these ventral cells that are the central chemoreceptors (Loeschcke, 1982; Mitchell and Loeschcke, 1963). The central chemoreceptors are separated from blood by the blood-brain barrier and respond to a change in $[H^+]$ determined by the ratio of $[CO_2]$ to bicarbonate ion concentration ($[HCO_3^-]$) beyond the blood-brain barrier. While CO_2 diffuses readily between the brain and blood, most ions, including H^+ and HCO_3^-, do not. Changes in blood and therefore alveolar CO_2 are thought to be detected as changes in brain $[H^+]$ (Cunningham, 1974; Loeschcke, 1982). The central chemoreceptors seem to be insensitive to decreases in P_{O2} and respond slower to changes in arterial pH compared to that of the peripheral chemoreceptors. It is believed that the changes in brain pH trigger a series of steps involving neurotransmitters which in turn generate action potentials. The neurotransmitters which are thought to exert excitatory effects on respiration include glutamate, tachykinins, and serotonin (Cherniack, 1991) although Dev and Loeschcke (1979) have recently proposed that H^+ can also alter respiratory discharge by inhibiting the metabolism of acetylcholine in the synapse.

1.5 The Age-Related Changes in the Human Respiratory System

The respiratory system undergoes a number of structural and functional changes throughout life. In normal healthy men and women, growth and development of the respiratory system is complete by the third decade (Polgar and Weng, 1979). Studies have shown that indices of pulmonary function reach a peak in the third decade and then progressively decline until the age of 60 to 70 years after which the rate of decline in most parameters of function seem accelerated (Knudson et al., 1983; Schoenberg et al., 1978). Recent studies indicate that prolonged endurance training may diminish the rate of decline in pulmonary function and volumes associated with ageing although the effects of training on pulmonary functions and lung volumes do not seem as great as those in other physiological systems (Hagberg et al., 1988).

The main changes that take place in lung function with ageing include a decrease in elastic recoil of the lung (Frank et al., 1957; Islam, 1980; Knudson et al., 1977; Turner et al., 1968), a stiffening of the chest wall (Wahba, 1983), a decrease in intervertebral spaces (Edge et al., 1964), and a loss of respiratory muscle strength (Black and Hyatt, 1969). The mechanical alterations in the respiratory system, as a result of ageing, therefore lead to alterations in lung volumes and flow rates compared to the age-predicted values at age 30 years (Fowler et al., 1987; Johnson et al., 1991a & 1991b; Knudson et al., 1983). These changes occur after the third decade and include declines in vital capacity (22-41 $ml \cdot yr^{-1}$), forced expiratory volume in 1 s (FEV_1) (21-51 $ml \cdot ^{-1}$), and in the ratio of FEV_1 to forced vital capacity (FVC) (FEV_1/FVC) (Ferris et al., 1965). Results from longitudinal studies however suggest significantly lower rates

of decline for those parameters (Knudson et al., 1983; Vollmer et al., 1988). Other alterations associated with ageing include declines in maximal expiratory flow rates as well as increases in functional residual capacity (FRC), residual volume (RV), and closing capacity (CC) while total lung capacity (TLC), normalized for height, remains unchanged (Wahba, 1983).

The loss of elastic recoil of the lungs with ageing has been demonstrated by a shift in the static pressure-volume relationship. In old age, the shape of the curve is not significantly altered but rather is shifted to the left (Frank et al., 1957; Wahba, 1983) so that at a given percentage of total lung capacity the recoil pressure is less with ageing. The compliance of the chest wall is decreased at any lung volume, contributing to a higher recoil pressure. This has been attributed to calcification of the costal cartilages (Mittman et al., 1965). The loss of elastic recoil has also been shown to be responsible for early closure of airways that depend on lung recoil for their external support and this leads to an increase in the closing volume or capacity with advancing age from approximately 30% of TLC at age 20 to 55% of TLC at age 70 years (Anthonisen et al., 1970; Leblanc et al., 1970). As well, closing volume (CV) may exceed FRC in elderly people (Leblanc et al., 1970) and this may lead to poorly ventilated or unventilated alveoli (Holland et al., 1968; Wahba, 1983) and may contribute to the decrease in P_aO_2 sometimes observed with ageing.

Results from studies examining age-related changes in the respiratory muscles of animals and humans suggest that the changes due to ageing appear to be insignificant. In rats, evidence suggests that there are no age-related alterations in the diaphragm

muscle as reflected by muscle fibre size or distribution and capillary density (Gosselin et al., 1988) or myosin heavy chain and light chains and diaphragmatic neuromuscular coupling (Smith, 1982; Smith and Rosenheimer, 1984).

In humans, results from studies examining the effects of lung volume and flow rate on pressure generation by the inspiratory muscles show little or no differences between young and older humans. This observation also suggests limited changes in the strength of the respiratory muscles with ageing in humans (Johnson et al., 1991b).

The efficiency of alveolar gas exchange has also been shown to decrease progressively with advancing age and may be related to a loss of elastic recoil (Anthonisen et al, 1970; Holland et al., 1968; Turner et al., 1968), a decreased alveolar surface area of the lung from about 75 m^2 at age 20 years to about 60 m^2 at age 70 years (Thurlbeck, 1967), decreases in pulmonary circulation (Emirgil et al., 1967), and to small increases in dead space ventilation (Brischetto et al., 1984; Fowler, 1950; Raine and Bishop, 1963; Rubin et al., 1982; Tenney and Miller, 1956). Small increases in dead space ventilation have been attributed to increases in anatomical and physiological dead space (Raine and Bishop, 1963; Tenney and Miller, 1956).

More comprehensive reviews of the changes that occur in the respiratory system with advancing age can be found in recent published reports (Johnson and Dempsey, 1991; Knudson, 1983; Levitzky, 1984; Wahba, 1983).

1.6 The Age-Related Changes in the Ventilatory Response to Exercise

During exercise, ventilation and gas exchange in the lungs are increased to

transfer O_2 to the arterial blood for utilization by the working muscles as well as to enable the clearance of CO_2 produced as a result of increased metabolism therefore maintaining normal acid-base status.

The increase in ventilation that occurs at the onset of dynamic exercise was first documented by Krogh and Lindhard (1913). Since then, advances into the control of ventilation at the onset of exercise have been made by many including Dejours (1964), Linnarsson (1974), and Whipp and co-workers (Whipp and Mahler, 1980; Whipp and Ward, 1991). For light to moderately intense exercise, the ventilatory response is believed to consist of three phases. Phase 1 includes a fast response at the onset . lowed by a plateau. A slower increase in ventilation follows (phase 2) which is characterized by a monoexponential increase over the next few minutes, leading to a steady state ventilatory response (phase 3) (Whipp and Ward, 1991).

The rapid change in ventilation during phase 1 is considered by some to be neurogenic, originating in the exercising limbs (Dejours, 1964; Kao, 1963), the cerebral cortex (Krogh and Lindhard, 1913), or from pathways that involve the hypothalamic motor area (Eldridge et al., 1985; Eldrige and Waldrop, 1991) although the similarities of the ventilatory and cardiovascular responses in phase 1 have led others to hypothesize that the increase in ventilation is directly linked to the cardiovascular system and has been referred to as cardiodynamic hyperpnoea (Wasserman et al., 1974; Wasserman et al., 1986).

The slower ventilatory response of phase 2 is thought to originate from a humoral mechanism although neurogenic mechanisms have also been proposed (Eldridge et al.,

1985). Evidence for a humoral control linked to CO_2 flow to the lungs is based on the observations that phase 2 begins with a time delay consistent with the exercising muscle-to-lung transit delay and is associated with a transient decrease in the respiratory exchange ratio resulting from an increased muscle tissue storage of metabolic CO_2 (Whipp and Ward, 1991). Furthermore, results from constant-load (Wasserman and Whipp, 1983), sinusoidal (Casaburi et al., 1977; Cunningham et al., 1993), and impulse forcing of work rate (Lamarra et al., 1989) have all shown that there is a close relationship between $\dot{V}_E$ and the rate of CO_2 exchange at the lung, with the time constant for the ventilatory response being slightly longer than for $\dot{V}CO_2$ by approximately 10%. The close relationship between $\dot{V}_E$ and $\dot{V}CO_2$ has provided evidence that the carotid bodies play an important role during phase 2. Studies on humans have shown that when the peripheral chemosensitivity is increased during exercise by introducing hypoxia (Griffiths et al., 1986) or metabolic acidosis (Oren et al., 1982), the time course of the ventilatory response is faster. Conversely, studies imposing a reduction on peripheral chemosensitivity by hyperoxia (Griffiths et al., 1986), metabolic alkalosis (Oren et al., 1982), and in subjects who had their carotid bodies resected (Wasserman et al., 1975) have found a slowing of the time course of the ventilatory response.

The steady state ventilatory response of phase 3 during light to moderate exercise is thought to arise from a combination of the mechanisms operating in phase 1 and phase 2 including humorally mediated mechanisms linked to CO_2 flow to the lungs. To date, suggested humorally mediated mechanisms include mixed venous chemoreception and CO_2 flux through the lungs which was originally proposed by Yamamoto (1960) as the

oscillating P_{CO2} theory. It has been suggested that the oscillating patterns of pulmonary venous P_{CO2} and H^+ during expiration and inspiration stimulate ventilation through their action on the peripheral chemoreceptors (Yamamoto, 1960).

Recent research studies on cats have shown that increased arterial potassium concentration stimulates $\dot{V}_E$ through action on the carotid bodies (Band et al., 1985; Burger et al., 1988) and this may provide evidence for another humorally-mediated mechanism accounting for a part of the exercise hyperpnoea during phases 2 and 3.

This dissertation will examine the ventilatory response to light and moderately intense exercise in aged humans (Chapter Two), and therefore, the mechanisms controlling ventilation in heavy exercise are not discussed. Rather, details on the major theories and hypotheses that have been developed regarding the control mechanisms of high intensity exercise, as well as a more comprehensive review on the control of exercise hyperpnoea during light and moderately intense exercise, can be found in a recent review by Wasserman et al. (1986).

Many studies have shown an increase in the ventilatory response to exercise in the elderly when compared to younger subjects. Some have related the observed increases in ventilatory rates to oxygen consumption ($\dot{V}_E/\dot{V}O_2$) (Benestad, 1965; Durnin and Mikulicic, 1965; Norris et al., 1955) while others have reported their findings of an increased ventilatory rate in terms of the ventilatory equivalent for $\dot{V}CO_2$ (i.e. $\dot{V}_E/\dot{V}CO_2$) (Johnson et al., 1991a; Patrick et al., 1983; Yerg II et al., 1985). Since $\dot{V}_E$ is coupled to CO_2 flow in the lung (Whipp and Pardy, 1986) and because the ventilatory equivalent decreases from rest to moderately intense exercise (Hesser et al., 1977), $\dot{V}_E/\dot{V}CO_2$ does

not represent the precise response of $\dot{V}_E$ to increasing $\dot{V}CO_2$ (Davis et al., 1980). Rather, the slope of the relationship between $\dot{V}_E$ and $\dot{V}CO_2$, referred to as $\Delta\dot{V}_E/\Delta\dot{V}CO_2$, has been shown to accurately describe the characteristics of ventilatory control during exercise (Davis et al., 1980). Thus, although it is generally agreed that the ventilatory response to exercise increases with advancing age, little is known regarding the mechanisms linking $\dot{V}_E$ to the metabolic demand in aged humans. The few studies that have examined $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ in the elderly have reported a significantly steeper gradient compared to younger groups (Brischetto et al., 1984; McConnell and Davies, 1992).

Brischetto et al. (1984) examined the ventilatory response to exercise in a group of 10 elderly men (aged 65-72 years) and reported that $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was 17% higher than that of younger subjects. $\dot{V}_E$ was also compared at a given work rate (50 watts) on the cycle ergometer and similarly, was found to be higher (26%) in the old group with no differences in the $\dot{V}CO_2$ between the groups at this intensity of exercise. Since the increased $\dot{V}_E$ was not related to arterial desaturation or to an increase in anaerobic metabolism, it was suggested that the increased $\dot{V}_E$ served to compensate for increased inefficiency of gas exchange attributed to an increase in the physiological dead space (Brischetto et al., 1984; Harris and Thompson, 1958), thereby resulting in a normal $\dot{V}_A$ and P_aO_2 at the higher ventilatory responses. An increase in physiological dead space in older humans has been confirmed by others (Johnson et al., 1989) who have taken direct measures of P_aO_2 in older subjects and found the physiological dead space (i.e. V_D/V_T) was 30% higher than that of younger subjects. Furthermore it has been shown that older subjects who have expiratory flow limitations during heavy exercise commonly adopt an

inefficient tachypneic breathing pattern during exercise, possibly resulting in an increase of up to 25% in $\dot{V}_E$ to achieve the same $\dot{V}_A$ at maximal exercise (Johnson et al., 1991a).

The central command theory of exercise has been shown to be related to cardiovascular and respiratory responses to exercise (Eldridge et al., 1985) and may also explain some of the ageing differences that have been previously reported. Most studies have compared the ventilatory response to exercise in young and older humans at specific absolute steady state work rates. Since maximal aerobic power ($\dot{V}O_2max$) decreases with advancing age, it is clear that at any specific absolute work rate the elderly are exercising at a greater percentage of their maximum capacities. Asmussen et al. (1965), using partial curarization to reduce the strength of the exercising muscles, showed that $\dot{V}_E$ was increased over the control level although work load, $\dot{V}O_2$, and P_aO_2 remained constant. Thus, in older humans an increase in central command signals may be activated and possibly are necessary in order to maintain a certain level of performance in light of the decrease in maximal capacities.

To date, studies examining the ventilatory response to $\dot{V}CO_2$ have restricted their work to smaller samples of relatively young elderly subjects (60-72 yrs), most of them men, and very little is known regarding the ventilatory response to exercise in men and women over the age of 75 years. The study described in Chapter Two will examine the ventilatory response to light and moderate intensity graded exercise in a large sample of men and women aged 55 to 86 years.

1.7 Age-Related Changes in the Ventilatory Response to Inhaled CO_2

The effects of changing P_ACO_2 on $\dot{V}_A$, is known as the $\dot{V}_A$-P_ACO_2 controller relation (Cunningham et al., 1986); an increased inspired CO_2 results in steep and linear increases in $\dot{V}_A$ in the eucapnic-hypercapnic range, and shallow and linear increases in the hypocapnic range. In constant hypoxia, the relation is steeper in the upper range of P_ACO_2 and elevated in the lower range (Lloyd et al., 1958; Neilsen and Smith, 1952) as illustrated in Figure 1. Studies examining the effects of ageing on the ventilatory response to CO_2 have used the slope of the $\dot{V}_A$-P_ACO_2 relationship as an index of CO_2 sensitivity for comparison with younger humans.

To date, the results of the studies examining the effects of ageing on the ventilatory response to inhaled CO_2 are perplexing. While some studies report that ageing is associated with declines of 30-50% in the ventilatory response to CO_2 (Altose et al., 1977; Brischetto et al., 1984; Kronenberg and Drage, 1973; Peterson et al., 1981), others have found little or no difference (Hirshman et al., 1975; Kawakami et al., 1981; Patrick and Howard, 1972; Rubin et al., 1982). One study used a steady-state technique which maintained end-tidal P_{O2} ($P_{ET}O_2$) at 95 mm Hg (Kawakami et al., 1981) while all other studies have used rebreathing techniques similar to that described by Read (1967) to examine the CO_2 response. The rebreathing technique assesses CO_2 sensitivity in hyperoxia and therefore is effectively a measurement of the CO_2 sensitivity of the central chemoreceptors as the peripheral chemoreceptors are reported to be silenced by hyperoxia (Dejours, 1962).

Since the ventilatory response to CO_2 represents the overall response of the

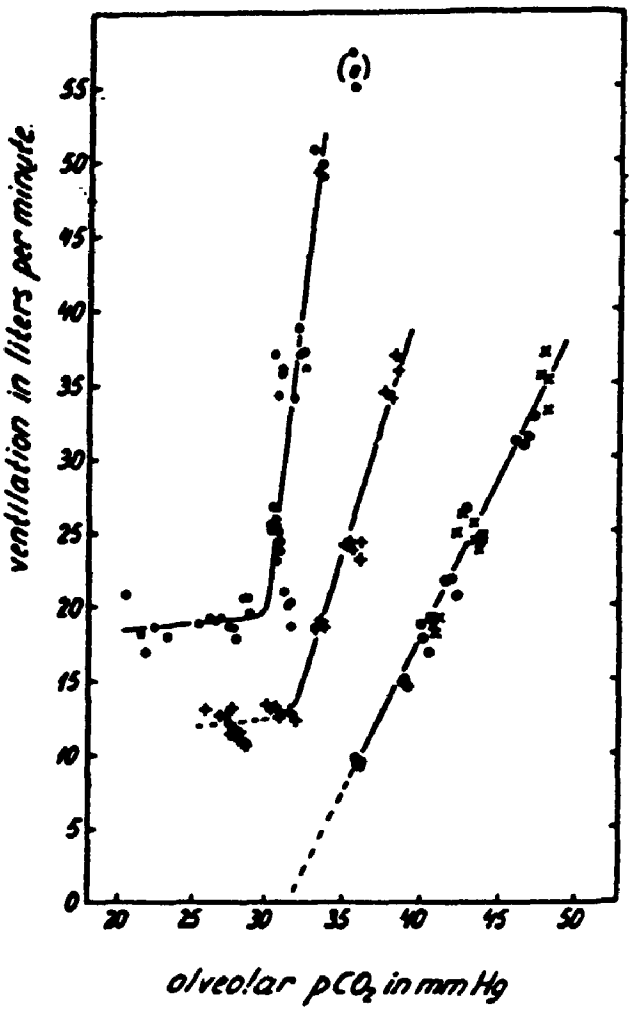


Figure 1. Relationship between ventilation and alveolar P_{CO2} at four constant levels of alveolar P_{O2} (●, 36.9; +, 47.2; ○, 110.3; X, 168.7 mm Hg). The figure illustrates the linearity of the ventilatory response to CO_2 in eucapnia and hypercapnia. The effect of hypoxia is predominantly on the slopes of the lines and only marginally on their intercepts on the P_{CO2} axis (Reproduced, with permission, from Acta Physiologica Scandinavica, Neilsen and Smith, vol. 24:293-313, 1952).

respiratory system, age-related differences could be due to a number of factors including chemoreceptor function, central neural processing, strength of the respiratory muscles, or to mechanical properties of the respiratory system (Peterson et al., 1981). Studies reporting an age-related decline in the ventilatory response to CO_2 have often inferred a decline in chemoreceptor function with advancing age although other factors unrelated to chemoreceptor function may not always have been excluded.

Kronenberg and Drage (1973) reported a 41% decrease in the hypercapnic ventilatory drive in elderly men (aged 64-73) compared to young controls (mean age 26 years). It was suggested that the decrease in the ventilatory response to CO_2 resulted from an attenuation of the peripheral chemoreceptor contribution to hypercapnic drive or in the integrating pathways for the peripheral chemoreceptor impulses within the central nervous system. The suggestion by Kronenberg and Drage (1973) was based on the assumptions that the peripheral chemoreceptors account for about half of the hypercapnic drive in man (Dejours, 1962), and that in their subjects, hypoxic drive had been reduced in a similar amount to hypercapnic drive and this was similar to findings of studies on high altitude natives (Lefrancois et al., 1972; Sorensen and Cruz, 1969). In another study, Altose et al. (1977) reported a 33% decrease in the ventilatory response to CO_2 in men aged 63 years. They, as well, attributed their findings to an age-related attenuation of chemoreceptor function.

Peterson et al. (1981) recognized that mechanical properties of the respiratory system such as the stiffening of the chest wall with advancing age (Mittman et al., 1965) could be responsible for the diminished ventilatory drive to hypercapnia. They studied

the ventilatory responses and the mouth occlusion pressure responses to CO_2 in aged humans to determine if the decreases in the responses were related to changes in mechanical properties of the lungs or to changes in the neuromuscular output to the respiratory muscles. Peterson and co-workers (1981) showed that ventilatory responses to CO_2 of the elderly men (aged 65-80 years) were 47% lower compared to younger men and the lower responses were paralleled by decreases of 49% in the mouth occlusion pressure (P_{100}) response slopes to hypercapnia. Peterson et al. (1981) suggested that these changes were not due to differences in respiratory timing (T_I/T_T) or to changes in chest wall compliance which are reflected as a change in the proportion of $\dot{V}_E$ supplied by the rib cage which was determined by the analysis of compartmental ventilation by magnetometery (Peterson et al., 1981). Thus the age related changes in the ventilatory responses to CO_2 reported by Peterson's group were not accounted for by changes in lung mechanics or weakness of the respiratory muscle but rather were attributed to alterations in central processing or in chemoreceptor function (Peterson et al., 1981).

Brischetto et al. (1984) reported a 33% decrease in the ventilatory response to hypercapnia in elderly men (aged 65-72 years) compared to young men (aged 27 years). The decline in the ventilatory response to CO_2 was attributed to an altered central mechanism based on the observation from Peterson et al. (1981) that changes in lung mechanics and respiratory muscle strength in healthy untrained elderly people were not large enough to explain the reductions in the hypoxic and hypercapnic ventilatory responses.

Other studies have failed to demonstrate age-related differences in the ventilatory

response to CO_2. Hirshman et al. (1975) examined the ventilatory response to CO_2 in 40 males and 4 females aged 21 to 51 years and found no effect of age in the age-range studied suggesting that age may only play an important role in chemoreceptor function in much older humans.

Patrick and Howard (1972) found that the slope of the response line relating $\dot{V}_E$ to P_ACO_2 was not significantly decreased in older men (mean age 44 years) but the slope of the line relating $\dot{V}_E$ to tidal volume (V_T) during hyperoxic rebreathing was inversely related to age, showing that the older men in their study tended to achieve a given $\dot{V}_E$ by an altered breathing pattern which combined a lower breathing frequency (f_b) and a larger V_T. Rubin et al. (1982) also observed changes in the respiratory cycle in the elderly which were characterized by lower inspiratory flow rates (V_T/T_I) and a longer proportion of time spent in inspiration (T_I/T_{Tot}), possibly representing an effort to improve gas exchange or reduce the energy cost of breathing (Turner et al., 1968).

Ahmed et al. (1991) compared the ventilatory responses from the subjects in their study to those in the study by Kronenberg and Drage (1973) and noted that the age differences reported by Kronenberg and Drage may be more a result of the inclusion of young atypical subjects rather than a true decline with advancing age. Rubin et al. (1982) reported no significant difference in the ventilatory response to CO_2 in a group of elderly men and women aged 66 years; their results remained unchanged when normalized for lung size (slope of response/VC). When they compared their results to those from others (Altose et al., 1977; Kronenberg et al., 1973; Patrick and Howard, 1972) they found that the results from the younger groups were more variable than those of the older

groups and often appeared to determine whether the differences between the elderly and the young groups were statistically significant. When they averaged the results from those four studies, the elderly had a significantly lower response than the younger controls (Rubin et al., 1982).

To date, no study has assessed CO_2 sensitivity in the elderly in terms of both the central and peripheral chemoreceptors. The study described in Chapter Three will examine the ventilatory response to CO_2 in hyperoxia and in hypoxia in young and older aged humans. The inherent assumption in this study is that the ventilatory responses to CO_2 measured in hyperoxia reflect the CO_2 sensitivity of the central chemoreflex loop while the ventilatory responses to CO_2 measured in hypoxia reflect the total CO_2 sensitivity of the respiratory control system (central and peripheral chemoreflex components). The CO_2 sensitivity of the peripheral chemoreflex loop will therefore be calculated as the difference between the CO_2 sensitivity in hypoxia and the CO_2 sensitivity in hyperoxia. A similar protocol was used previously to examine the central and peripheral CO_2 sensitivity in young humans (Bascom et al., 1990).

If the central chemoreflex CO_2 sensitivity is lower in the older group, one would expect to find a lower slope of the $\dot{V}_E$-P_ACO_2 response line in hyperoxia ($S_{HYPEROXIA}$, Figure 2) compared to the response slope of young humans. Alternately, a decrease in total CO_2 sensitivity should be reflected by a decrease in the slope of the $\dot{V}_E$-P_ACO_2 response line in hypoxia ($S_{HYPOXIA}$, Figure 2). A difference between the slopes of the $\dot{V}_E$-P_ACO_2 response lines in hypoxia and hyperoxia should reflect a decrease in the peripheral CO_2 sensitivity in the elderly.

To date, no information is presently available regarding the temporal parameters of the peripheral and central chemoreceptors in older humans. Furthermore, the quantitative contribution of the central and peripheral chemoreceptors to ventilation in older humans remains unknown. Thus, to further examine the peripheral and central chemoreceptor function in older humans, the study described in Chapter Four will determine the temporal parameters of the ventilatory response to CO_2 in euoxia, hyperoxia, and in hypoxia. A two component exponential model will be used to estimate the gains, time delays, and time constants for the fast and slow components, attributed to the peripheral and central chemoreceptors respectively (see Figure 3). Any differences in chemoreceptor function between the young and the older groups should therefore be reflected in the temporal parameters of the chemoreceptors. Thus, the ventilatory response to CO_2 in young and aged humans will be compared in terms of the above temporal parameters.

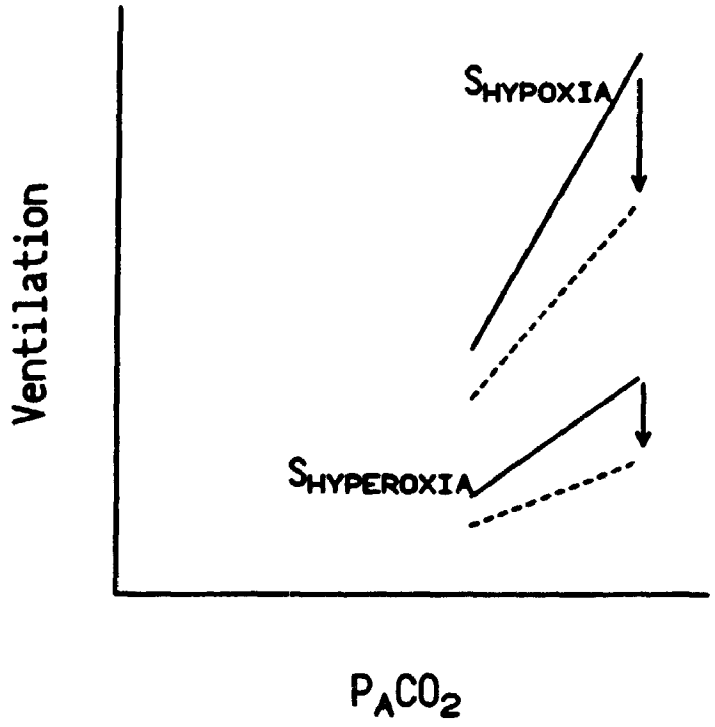


Figure 2. Determination of central and peripheral CO_2 sensitivity. If central chemoreflex CO_2 sensitivity is lower in the elderly, the slope of the $\dot{V}_E$-P_ACO_2 response line in hyperoxia ($S_{HYPEROXIA}$) will be lower than that found in young humans. An age-related decrease in total CO_2 sensitivity will be reflected by a reduced slope of the $\dot{V}_E$-P_ACO_2 response line in hypoxia ($S_{HYPOXIA}$). As a result, a difference between the slopes of the $\dot{V}_E$-P_ACO_2 response lines in hypoxia and hyperoxia will reflect an age-related difference in the peripheral CO_2 sensitivity.

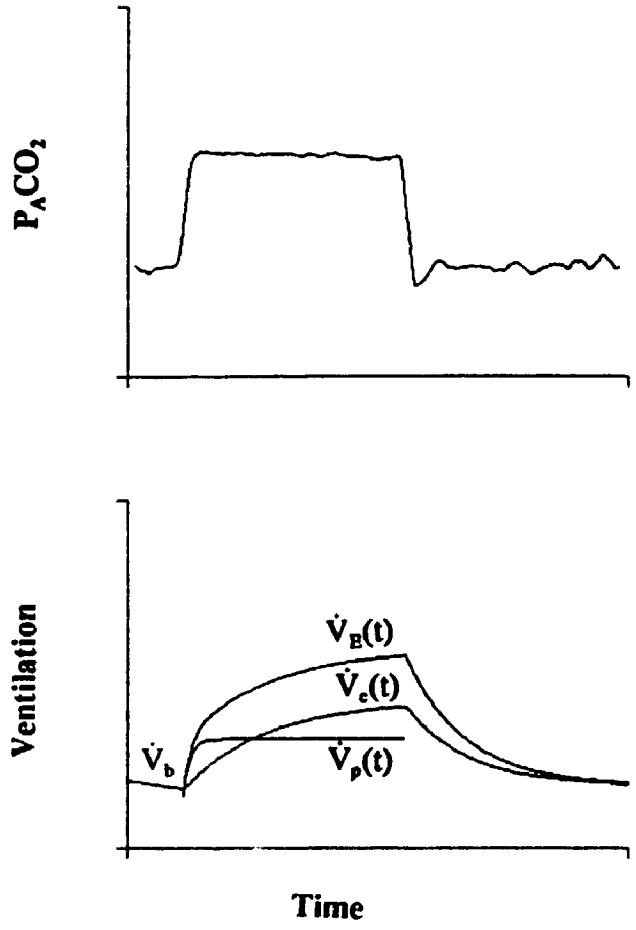


Figure 3. Determination of the temporal parameters of the ventilatory response to CO_2. The ventilatory response to a step increase in P_ACO_2 ($P_{ET}CO_2$) can be analyzed in terms of a two-component model which would describe the temporal parameters of the central and peripheral chemoreflex components. The model is of the form: $\dot{V}_E(t) = \dot{V}_b + \dot{V}_c(t) + \dot{V}_p(t)$, where the baseline ventilation is $\dot{V}_b$ and $\dot{V}_E(t)$ is the time-dependent variation in $\dot{V}_E$. $\dot{V}_c(t)$ and $\dot{V}_p(t)$ represent the outputs of the central and peripheral chemoreflex components which are described in terms of gains, time constants of the responses, and time delays. Differences in chemoreceptor function in the elderly should therefore be reflected in the temporal parameters of the chemoreceptors.

CHAPTER 2

VENTILATORY RESPONSE TO EXERCISE IN MEN AND WOMEN AGED 55 TO 86 YEARS

2.1 Abstract

This study examined the relationship between minute ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}CO_2$) during exercise in men (n=128) and women (n=96), aged 55 to 86 yrs. The means for the slopes of $\dot{V}_E$-$\dot{V}CO_2$ ($\Delta\dot{V}_E/\Delta\dot{V}CO_2$), examined for graded exercise below the ventilation threshold ($T_{\dot{V}E}$), increased significantly for men, from 25.0 ± 0.7 (SEM) at mean age 58 (55-59) yrs to 32.2 ± 1.8 at mean age 83 (80-86) yrs ($p<0.0001$) but did not change for women, from 22.3 ± 0.9 at mean age 58 (56-59) yrs to 24.2 ± 2.4 at mean age 79 (75-85) yrs ($p=0.0812$). A correlation which was significantly greater than zero was found between $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ and age. The increase in $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was 0.29/yr for men ($r=0.47$, $p<0.001$) and 0.20/yr for women ($r=0.28$, $p=0.0051$). In both cases the explained variance was small (men = 22%; women = 8%). $\dot{V}_E$, tidal volume (V_T), and breathing frequency (f_b) were examined at $\dot{V}CO_2$ = 1.0 $\ell \cdot min^{-1}$; the highest intensity that most older men and women could exercise without exceeding $T_{\dot{V}E}$. $\dot{V}_E$ was significantly higher by 14% in men aged 80-86 (38.2 ± 1.4 $\ell \cdot min^{-1}$) compared to men aged 55-59 years (33.5 ± 0.8) while there were no differences in $\dot{V}_E$ across ages for the women. For both men and women, there were no significant differences across ages in V_T although there was a trend for an increase in f_b with advancing age in men (20.1±1.1 to 24.2±1.2 for men aged 55-59 and 80-86 years respectively). Thus in men

and women aged 55 to 86 years, the slope of $\dot{V}_E/\dot{V}CO_2$ during submaximal exercise was significantly correlated to age; the ventilatory response to metabolic demand was highest in men aged 80 to 86 years.

2.2 Introduction

Ageing has been shown to affect many physiological systems including the control of the respiratory system at rest and during exercise (Levitzky, 1984). The ventilatory response to exercise, as demonstrated by the absolute change in $\dot{V}_E$ per change in $\dot{V}CO_2$ (Johnson and Dempsey, 1991; Patrick et al., 1983; Yerg II et al., 1985) or by the slope of the $\dot{V}_E$-$\dot{V}CO_2$ relationship (Brischetto et al., 1984; McConnell and Davies, 1992), has been shown to be 11-19% higher in older men in their seventh and eight decades compared to that of younger men. Findings of McConnell and Davies (1992) suggested a critical $\dot{V}CO_2$ (0.75 $l \cdot min^{-1}$) above which the $\dot{V}_E$-$\dot{V}CO_2$ relationship in the elderly was higher, but below which the $\dot{V}_E$-$\dot{V}CO_2$ was actually lower than the young group. In their study the highest intensity at which the elderly could work without exceeding the $T_{\dot{V}E}$ was at a $\dot{V}CO_2$ equal to 0.90 $l \cdot min^{-1}$. Thus in this aerobic working range, the elderly subjects showed ventilatory responses that were similar to those of young counterparts.

The higher $\dot{V}_E$-$\dot{V}CO_2$ found with advancing age has been associated with a small but significant age-dependent rise in dead space ventilation giving older subjects a $\dot{V}_A$-$\dot{V}CO_2$ and P_aCO_2 very similar to younger subjects at any given $\dot{V}CO_2$ (Johnson and Dempsey, 1991). Low end-tidal CO_2 ($P_{ET}CO_2$) values observed in elderly men at rest and during exercise (Overend et al., 1992) are in contrast however, to the measurements

of normal P_aCO_2 values reported by Johnson and Dempsey (1991) and this would suggest an age-related increased end-tidal to arterial CO_2 gradient ($P_{ET-a}CO_2$).

This study examined $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ during graded exercise below the $T_{\dot{V}E}$ in a sample of non-institutionalized men (n=128) and women (n=96), aged 55 to 86 yrs. The inclusion of a large number of men and women covering a wide age range enabled the investigation of any critical age or ages at which increases in $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ might occur. Furthermore, this is the first study to report results on $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ during exercise in men and women in the ninth decade.

2.3 Methods

Subjects. The sampling frame for this study, provided by the municipal assessment list, was comprised of non-institutionalized men and women, aged 55 to 86 years, in the city of London (population 280,000) in the province of Ontario. The study design has been described in detail by Koval et al. (1992). In brief, a stratified sample was drawn, with the strata defined by 5-year age groups. The goal was to obtain 35 subjects in each of the 6 strata. Randomly selected subjects were contacted by letter and up to 6 follow-up telephone calls, following which, if contact had not been made, potential subjects were classified as non-responders. Those selected, who were resident in chronic care facilities or non-ambulant, were excluded.

The study requirements were fully explained (in written and verbal forms; Appendix II) to all participants and each signed an informed consent approved by the University's Review Committee for Research Involving Human Subjects (Appendix II).

Testing. Subjects were requested not to eat or drink coffee within two hours prior to their scheduled testing session in the laboratory. The protocol required subjects to visit the laboratory for a comprehensive fitness assessment lasting 2-3 hours. Each participant was given a medical examination including a medical history and 12-lead electrocardiogram (ECG). Lung function tests were also completed. Subjects were required to perform a treadmill (ramp) test to determine $\dot{V}O_2max$ and $T_{\dot{V}E}$. Health assessment questionnaires were also completed. The focus of this chapter is the respiratory data.

Calibration and equipment. During all treadmill and spirometry tests, inspired and expired ventilation flow rates were measured using a bi-directional turbine (Alpha Technologies, VMM 110) calibrated daily with a syringe of known volume (3.01 l). Inspired and expired gases were sampled continuously (1 $ml \cdot sec^{-1}$) at the mouth and analyzed by a mass spectrometer (Perkin-Elmer MGA-1100) calibrated daily with precision-analyzed gas mixtures. Analog signals were sampled and digitized every 10 milliseconds by a microcomputer. Data were stored on the hard disc system for later analysis. Changes in gas concentration signals were aligned with the inspired and expired volumes by measuring the time delays for a bolus of gas passing the turbine to a resulting change in gas concentration. Breath-by-breath determination of $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$, RER, $P_{ET}O_2$ and $P_{ET}CO_2$, $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ was performed using the algorithms of Beaver et al. (1981). Heart rate (HR) was monitored continuously via ECG electrodes by means of a modified V-5 configuration.

Pulmonary function tests. Lung function tests were performed using a bi-

directional turbine (Alpha Technologies, VMM 110) interfaced with a computerised data collection system which has been validated for spirometry against a 9-litre water-seal Stead-Wells spirometer. FVC and FEV_1 were measured. The manoeuvres have been described in detail in a previous report (Smith et al., 1992a). FEV_1 and FVC were reported as a percent of predicted from age and height, calculated from the equations of Knudson et al. (1983) for nonsmoking Caucasian men and women.

Maximal treadmill "ramp" test. The protocol was initiated with a two minute warm-up at a walking velocity of 1.07 $m \cdot s^{-1}$ and zero percent grade. The velocity, or grade, or combination of velocity and grade, were then increased in specific small increments to elicit a ramp-like test. The protocols were designed to elicit oxygen demand increases of 1-3 $ml \cdot kg^{-1} \cdot min^{-1}$ and the protocol for each subject was selected to result in a test of 8-12 minutes. Subjects were verbally encouraged throughout the test. At the end of the test, the subjects were required to walk on the treadmill for another two minutes at zero percent grade and at 1.07 $m \cdot s^{-1}$ to properly cool-down. The highest $\dot{V}O_2$ during the ramp test was examined, using a computer routine, to determine the occurrence of a plateau in $\dot{V}O_2$ ($\dot{V}O_2max$) despite a continuing increase in work rate (Govindasamy et al., 1992). The use of an exercise test, in which the work rate continuously increases as a ramp function (Whipp et al., 1981) and in which the rate of increase in the work rate is designed to elicit a short test, allows the subjects to achieve a plateau in $\dot{V}O_2$ before encountering exercise limiting muscle fatigue (Buchfuhrer et al., 1983).

Criteria for stopping the tests. The criteria for stopping the exercise tests were

those recommended by the American College of Sports Medicine, (1991); namely undue fatigue, symptom limitations including angina, and ECG abnormalities.

Determination of ventilation threshold ($T_{\dot{V}E}$). The $\dot{V}O_2$ at $T_{\dot{V}E}$ was determined according to the criteria of a systematic increase in the ventilatory equivalent of $\dot{V}O_2$ ($\dot{V}_E/\dot{V}O_2$) and $P_{ET}O_2$ with no concomitant rise in the $\dot{V}_E/\dot{V}CO_2$ ratio or decrease in $P_{ET}CO_2$, identifying the period of isocapnic buffering (Davis et al., 1979). Two independent investigators determined the $T_{\dot{V}E}$.

Determination of the slopes for $\dot{V}_E$-$\dot{V}CO_2$. $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was examined for exercise below $T_{\dot{V}E}$ by using a computer routine. Briefly, for all tests, a linear regression was fitted for the segment starting at the breath corresponding to the onset of workload (A) and finishing at the breath corresponding to 15 s prior to $T_{\dot{V}E}$ (t_2). For each segment, linear regressions were fitted, starting at A + n breaths (n at start = 0; interval = 1 breath; minimum allowable segment length $\geq$ 20 breaths) and finishing at t_2. Thus, the segment with the regression having the least mean square error was selected as the slope for $\dot{V}_E$-$\dot{V}CO_2$ and started at t_1 and finished at t_2.

Data analysis. Cohort and age-group strata analyses were performed by one-way analysis of variance and when indicated, Newman-Keul post-hoc analysis was applied. The means for f_b, V_T, $P_{ET}CO_2$, and RER were calculated as 15 s means, reported at $\dot{V}CO_2 = 1.0\ \ell \cdot min^{-1}$ as well as for the first 15 s (t_1) and the last 15 s (t_2) of the $\dot{V}_E$-$\dot{V}CO_2$ slope segment. The level of significance was $p < 0.05$.

2.4 Results

Subjects. The descriptive data of the subjects including age, height, and weight are listed in Table 1. There were no significant differences across age groups for height and weight. Men. A total of 209 men aged 55 to 86 years participated in the study; 23 (11.0%) did not complete the treadmill test due to medical problems at rest (including neuromuscular or cardiovascular problems (n=11)), medical problems during the warm-up (n=7), poor performance tests on the treadmill (n=3), and equipment failure (n=2). Of the remaining 186 men who did complete a successful treadmill ramp test, $T_{\dot{V}E}$ could not be determined in 45 subjects (24.2%). Of the remaining 141 men, $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ could not be determined in 13 (9.2%) subjects. Thus, the final sample comprised 128 men (61.2%) for analysis of slopes for $\dot{V}_E/\dot{V}CO_2$ across ages.

Women. A total of 232 women aged 55 to 85 years participated in the study; 37 (16.0%) did not complete the treadmill test due to medical problems at rest (including neuromuscular or cardiovascular problems (n=10)), medical problems during the warm-up (n=6), poor performance tests on the treadmill (n=18), and equipment failure (n=3). Of the remaining 195 women who completed a treadmill ramp test, $T_{\dot{V}E}$ could not be determined in 75 subjects (38.5%). Of the remaining 120 participants, $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ could not be determined in 24 (20.0%) subjects. Thus, the final sample comprised 96 women (41.4%) for analysis of slopes for $\dot{V}_E$-$\dot{V}CO_2$ across ages.

For both men and women, the loss of data for $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ (i.e. 24 women and 13 men) was due to unacceptable values for the slope of $\dot{V}_E$-$\dot{V}CO_2$ in concert with the known increase in metabolic rate for these power outputs. This was a result mainly of

Table 1. Descriptive variables for men (n=128) and women (n=96) aged 55 to 86 years.

	Age groups (years)					
	55-59	60-64	65-69	70-74	75-79	80-86
Men	(n=28)	(n=29)	(n=23)	(n=18)	(n=15)	(n=15)
					75-85	
Women	(n=18)	(n=21)	(n=26)	(n=17)	(n=14)*	
Age (years)						
M	58.1	62.1	67.4	72.8	76.9	82.8
	(0.2)	(0.3)	(0.3)	(0.3)	(0.4)	(0.4)
W	57.7	63.0	67.4	72.4	78.8	
	(0.3)	(0.3)	(0.3)	(0.3)	(0.7)	
Height (cm)						
M	172.9	174.1	172.4	172.3	170.6	172.2
	(1.1)	(1.3)	(1.1)	(1.2)	(1.4)	(2.0)
W	157.6	160.2	160.1	157.8	155.3	
	(1.5)	(1.3)	(1.0)	(1.1)	(1.8)	
Weight (kg)						
M	81.2	81.9	79.0	81.5	72.8	73.8
	(1.2)	(2.2)	(3.1)	(1.8)	(1.7)	(2.4)
W	64.9	67.4	64.4	60.9	62.3	
	(2.1)	(2.5)	(1.6)	(1.6)	(3.1)	

Values are means ± (SEM)

* age group includes three women aged 80-85 yrs

tests with high noise to signal ratios in the breath-by-breath data. This complication is often unavoidable when people undertake an exercise test for the first time.

Pulmonary function tests. The results for lung function are reported for a smaller number of men (104/128; 81%) and women (83/96; 86%) than are reported elsewhere in the study. This is a result of technical difficulties that were encountered for a number of lung function tests. Those individuals remained in the study because examination of their data revealed normal ventilation and gas exchange.

There were no significant differences across age groupings in men for FEV_1 and FVC reported as a percent of predicted for height and age, although FEV_1 for women aged 75-85 yrs was significantly higher than all other women's age groups (Table 2). In all groups, FEV_1 and FVC were within the clinically accepted "normal ranges" of predicted values (Table 2). For men, the mean FEV_1 at mean ages 73 (70-74), 77 (75-79), and 83 (80-86) yrs was significantly lower from the value at age 58 (55-59) yrs (Table 2). From age 58 to 83 yrs, FEV_1 decreased by 25% at a rate 24.5 $ml \cdot yr^{-1}$. Similarly, compared to the 55-59 yr group FVC was lower in the 75-79 and 80-86 yr groups. From age 58 to 83 yrs, FVC decreased by 23% at a rate 27.7 $ml \cdot yr^{-1}$. For the women, the means for FEV_1 and FVC at mean age 79 (75-85) yrs were not significantly lower (3.9% and 4.9% respectively), from the values at mean age 58 (56-59) yrs (Table 2).

A previous report from this laboratory (Smith et al., 1992a) described the smoking status for this cohort and therefore has not been reported here. Briefly for men, lifelong nonsmokers accounted for 19.8% of the group, ex-smokers 62.1%, and smokers

Table 2. Pulmonary function tests for men (n=114) and women (n=87) aged 55 to 86 years.

	Age groups (years)					
	55-59	60-64	65-69	70-74	75-79	80-86
Men	(n=18)	(n=25)	(n=20)	(n=15)	(n=14)	(n=12)
					75-85	
Women	(n=15)	(n=19)	(n=23)	(n=15)	(n=11)*	
FEV_1 (litres, BTPS)						
M	3.03	2.94	2.66	2.63†	2.33†	2.27†
	(0.12)	(0.11)	(0.13)	(0.14)	(0.10)	(0.14)
W	2.04	2.05	2.01	1.84	1.96	
	(0.12)	(0.10)	(0.08)	(0.07)	(0.10)	
FVC (litres, BTPS)						
M	3.73	3.62	3.31	3.31	3.05†	2.87†
	(0.15)	(0.13)	(0.14)	(0.18)	(0.47)	(0.18)
F	2.44	2.43	2.44	2.22	2.32	
	(0.10)	(0.11)	(0.11)	(0.07)	(0.12)	
FEV_1/FVC (%)						
M	81.5	82.2	80.3	80.3	77.3	79.3
	(1.4)	(1.8)	(1.7)	(2.6)	(3.2)	(1.3)
W	82.9	84.2	83.4	82.9	85.0	
	(2.1)	(2.5)	(1.9)	(2.1)	(2.0)	
FEV_1 (% predicted)‡						
M	91.9	90.8	88.3	93.1	92.3	92.1
	(3.1)	(3.3)	(3.3)	(4.2)	(5.4)	(6.4)
W	88.3	90.2	91.9	90.6	107.2 §	
	(4.8)	(4.5)	(3.4)	(3.1)	(5.0)	
FVC (% predicted) ‡						
M	91.3	95.0	87.5	92.0	94.2	89.7
	(2.8)	(5.8)	(2.6)	(3.9)	(4.8)	(6.3)
F	86.5	85.5	87.8	85.3	97.5	
	(3.7)	(3.2)	(3.4)	(2.3)	(5.6)	

Values are means ± (SEM)

* Age group includes one woman aged 80-85 yrs

† significantly different from 55-59 and 60-64 yr groups

‡ calculated from equations based on age and height (Knudson et al., 1983)

§ significantly different from 55-59, 60-64, 65-69, and 70-74 yr groups

19.1%. The ex-smokers had stopped smoking a mean of 20.4 yrs previously. For women, lifelong nonsmokers accounted for 62.3% of the group, ex-smokers 25.9%, and smokers 11.8%. The ex-smokers had stopped smoking a mean of 17.8 yrs previously. In that report (Smith et al., 1992), although the overall decline in FEV_1 was higher in men than women, rates of decline by smoking status did not reach statistical significance.

Responses to graded exercise. For the men, $\dot{V}O_2max$ decreased significantly by 36% from 2.13 $\ell \cdot min^{-1}$ at age 55-59 yrs to 1.36 $\ell \cdot min^{-1}$ at 80-86 yrs while for the women, $\dot{V}O_2max$ decreased significantly by 31% from 1.46 $\ell \cdot min^{-1}$ at age 56-59 yrs to 1.01 $\ell \cdot min^{-1}$ at 75-85 yrs. Similar age-related decreases were found for $\dot{V}CO_2max$ and $\dot{V}_Emax$ (Table 3). For the men, the treadmill ramp-like protocols elicited oxygen demand increases of 2.93 to 1.73 $ml \cdot kg^{-1} \cdot min^{-1}$ each minute, from ages 55-59 to ages 80-86 years respectively. For the women, the protocols elicited oxygen demand increases of 2.28 to 1.46 $ml \cdot kg^{-1} \cdot min^{-1}$ each minute from ages 56-59 to ages 75-85 years respectively. The maximal exercise $\dot{V}_E/\dot{V}CO_2$ was not different across ages for men or women (Table 3).

Ventilatory responses to CO_2 production. For the men, the slope of $\dot{V}_E/\dot{V}CO_2$ increased significantly by 28.8% from 25.0 $\pm$ 0.7 at age 58 (55-59) yrs to 32.2 $\pm$ 1.8 at age 83 (80-86) yrs (Table 4). $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was correlated with age, increasing at a rate of 1.23% per year ($r = 0.47$; $p < 0.0001$; $\dot{V}_E/\dot{V}CO_2 = 0.29(age) + 7.69$) (Figure 4, Top Panel). When $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was extrapolated to a $\dot{V}CO_2$ of zero, there were no significant differences in the $\dot{V}_E$-intercepts (Table 4). $\dot{V}CO_2$ at t_1 was not different across age groups but $\dot{V}CO_2$ at t_2 was 24.9% lower in men aged 80-86 yrs compared to that in

Table 3. Results for respiratory variables at maximal exercise during the treadmill ramp test for men (n=128) and women (n=96) aged 55 to 86 years

	Age groups (years)					
	55-59	60-64	65-69	70-74	75-79	80-86
Men	(n=28)	(n=29)	(n=23)	(n=18)	(n=15)	(n=15)
					75-85	
Women	(n=18)	(n=21)	(n=26)	(n=17)	(n=14) •	
$\dot{V}_E$ ($\ell \cdot min^{-1}$)						
M	80.4	67.5 †	72.1	64.3 †	55.1 †	50.2 ‡
	(3.7)	(3.8)	(5.4)	(3.9)	(3.6)	(1.8)
F	50.3	42.6	44.5	43.2	38.5 †	
	(2.8)	(2.8)	(1.8)	(2.3)	(2.6)	
$\dot{V}CO_2$ ($\ell \cdot min^{-1}$)						
M	2.28	2.15	2.01	1.81 ‖	1.58 ‡	1.37 ¶
	(0.10)	(0.10)	(0.12)	(0.12)	(0.10)	(0.06)
F	1.54	1.29 †	1.32 †	1.27 †	1.08 †	
	(0.09)	(0.07)	(0.04)	(0.06)	(0.07)	
$\dot{V}_E/\dot{V}CO_2$						
M	36.2	32.1	35.7	36.0	34.9	36.9
	(1.9)	(1.2)	(1.4)	(1.4)	(1.3)	(1.1)
F	33.1	32.9	33.9	34.3	35.9	
	(1.1)	(0.9)	(0.9)	(1.4)	(1.3)	

Values are means ± SEM

• Age group includes three women aged 80-85 yrs

† significantly different from 55-59 yr group

‡ significantly different from 55-59, 60-64, and 65-69 yr groups

‖ significantly different from 55-59 and 60-64 yr groups

¶ significantly different from 55-59, 60-64, 65-69, and 70-74 yr groups

Table 4. Relationship of $\dot{V}_E$ to $\dot{V}CO_2$ from t_1 to ventilation threshold (t_2).

	Age groups (years)					
	55-59	60-64	65-69	70-74	75-79	80-86
Men	(n=28)	(n=29)	(n=23)	(n=18)	(n=15)	(n=15)
					75-85	
W^1	(n=18)	(n=21)	(n=26)	(n=17)	(n=14)*	
W^2	(n=14)	(n=16)	(n=18)	(n=14)	(n=6)	
Slope $\dot{V}_E/\dot{V}CO_2$						
M	25.0	25.5	26.4	28.2	28.4	32.2 †
	(0.7)	(0.7)	(0.8)	(1.3)	(1.1)	(1.8)
W^1	22.3	21.4	24.0	25.9	24.8	
	(0.9)	(1.2)	(1.0)	(1.4)	(1.1)	
W^2	22.4	20.9	24.2	25.5	25.4	
	(1.0)	(0.9)	(1.3)	(1.3)	(2.1)	
Intercept						
M	9.7	7.1	7.8	6.4	4.6	5.4
	(1.2)	(0.8)	(1.0)	(1.6)	(1.5)	(1.8)
W^1	8.5	10.3	7.5	6.3	7.7	
	(1.4)	(1.2)	(0.8)	(1.2)	(0.9)	
W^2	9.2	11.3	7.5	6.8	6.7	
	(1.7)	(1.3)	(1.0)	(1.3)	(1.6)	

Values are means ± (SEM)

* Age group includes three women aged 80-85 yrs

W^1 data for 96 women including 28 who did not reach $\dot{V}CO_2 = 1.0\ \ell \cdot min^{-1}$ at $T_{\dot{V}E}$.

W^2 data for 68 women who reached $\dot{V}CO_2$ equal or greater to $1.0\ \ell \cdot min^{-1}$ at $T_{\dot{V}E}$.

† significantly different from all other age groups

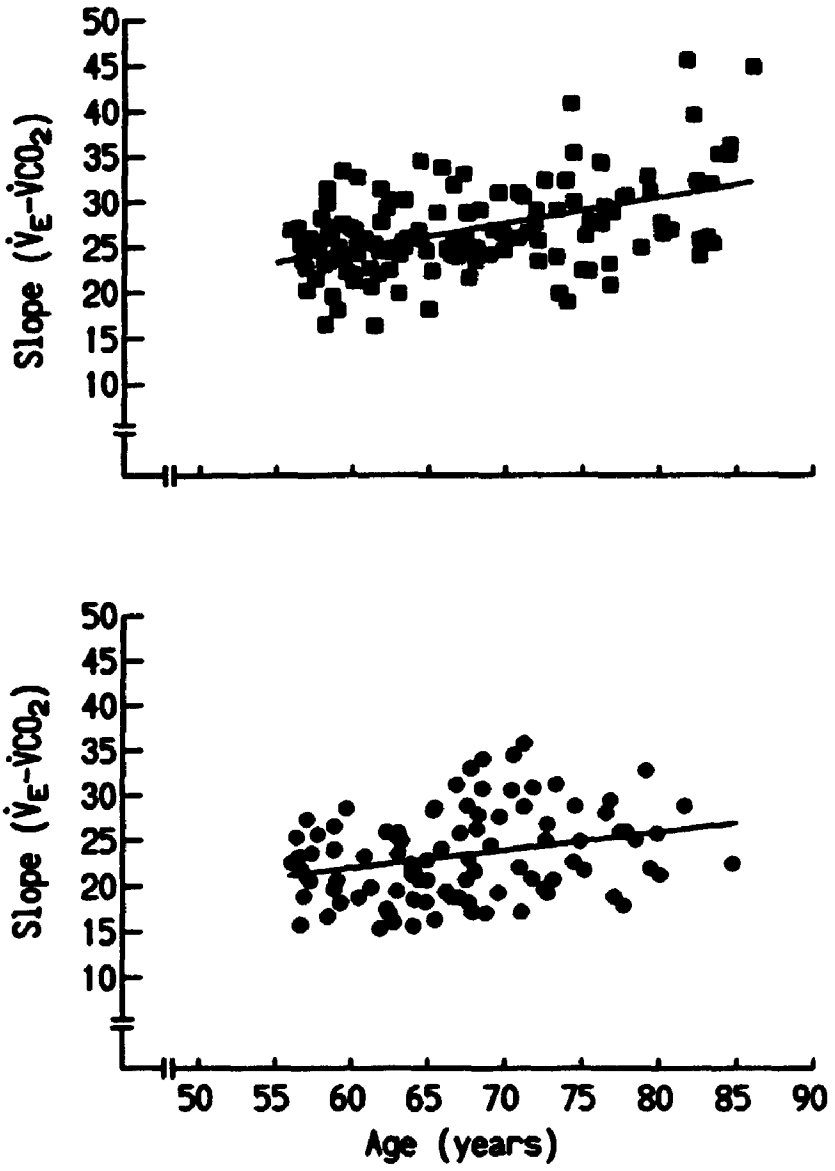


Figure 4. Relationship between the slope of $\dot{V}_E$-$\dot{V}CO_2$ and advancing age. Top panel shows men (■) aged 55-86 yrs (n=128); the slope of $\dot{V}_E$-$\dot{V}CO_2$ was highly correlated to age increasing at a rate of 1.23% per year ($r = 0.47$; $p < 0.0001$; $\Delta\dot{V}_E/\Delta\dot{V}CO_2 = 0.29(age) + 7.69$). Bottom panel shows women (●) aged 56-85 yrs (n=96); the slope of $\dot{V}_E$-$\dot{V}CO_2$ was also correlated to age increasing at a lower rate of 0.93% per year ($r = 0.28$; $p = 0.0051$; $\Delta\dot{V}_E/\Delta\dot{V}CO_2 = 0.20(age) + 10.08$).

men aged 55-59 yrs (Figure 5). There were no differences in f_b or V_T at t_1 or at t_2 between age groups (Figure 5). There were no differences in RER at t_1 or at t_2 across the age groups. Although t_2 was below $T_{\dot{V}E}$ for all, $\dot{V}CO_2$ at t_2 corresponded to 80% of $\dot{V}CO_2$max for men aged 55-59 yrs while $\dot{V}CO_2$ at t_2 corresponded to 92% of $\dot{V}CO_2$max for men aged 80-86 yrs. $\dot{V}CO_2$=1.0 $\ell \cdot min^{-1}$ corresponded to 44% of $\dot{V}CO_2$max for men aged 55-59 yrs while $\dot{V}CO_2$=1.0 $\ell \cdot min^{-1}$ corresponded to 73% of $\dot{V}CO_2$max for men aged 80-86 yrs. At a $\dot{V}CO_2$ of 1.0 $\ell \cdot min^{-1}$, $\dot{V}_E$ was 14% higher in men aged 80-86 yrs compared to men aged 55-64 yrs. The higher $\dot{V}_E$ in the older men was associated with similar V_T although there was a trend for f_b to increase with advancing age (Table 5).

For women, no significant differences were found in $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ between the six age groups (22.3 $\pm$ 0.9 at age 58 (56-59) yrs to 24.8 $\pm$ 1.1 at age 79 (75-85) yrs (Table 4)). The slope of $\dot{V}_E/\dot{V}CO_2$ was, however, correlated with age, increasing at a rate of 0.93% per year ($r = 0.28$; $p=0.0051$; $\dot{V}_E/\dot{V}CO_2 = 0.20(age) + 10.08$) (Figure 4, Lower Panel). When $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was extrapolated to a $\dot{V}CO_2$ of zero, there were no signi...ant differences in the $\dot{V}_E$-intercepts (Table 4). $\dot{V}CO_2$ at t_1 and at t_2 were not significantly different across age groups although the $\dot{V}CO_2$ at t_2 was 35% lower at age 79 yrs (1.20 $\ell \cdot min^{-1}$ at age 58 to 1.04 $\ell \cdot min^{-1}$ at age 79 yrs) (Figure 6).

There were no differences in f_b and V_T at t_1 or at t_2 between age groups (Figure 6). No significant differences were found in RER either at t_1 or at t_2 across age groups. Similar to the results for men, $\dot{V}CO_2$ at t_2 corresponded to 80% of $\dot{V}CO_2$max for women aged 56-59 yrs while $\dot{V}CO_2$ at t_2 corresponded to 89% of $\dot{V}CO_2$max for women aged 75-85 yrs. $\dot{V}CO_2$=1.0 $\ell \cdot min^{-1}$ corresponded to 65% of $\dot{V}CO_2$max for women aged 55-59

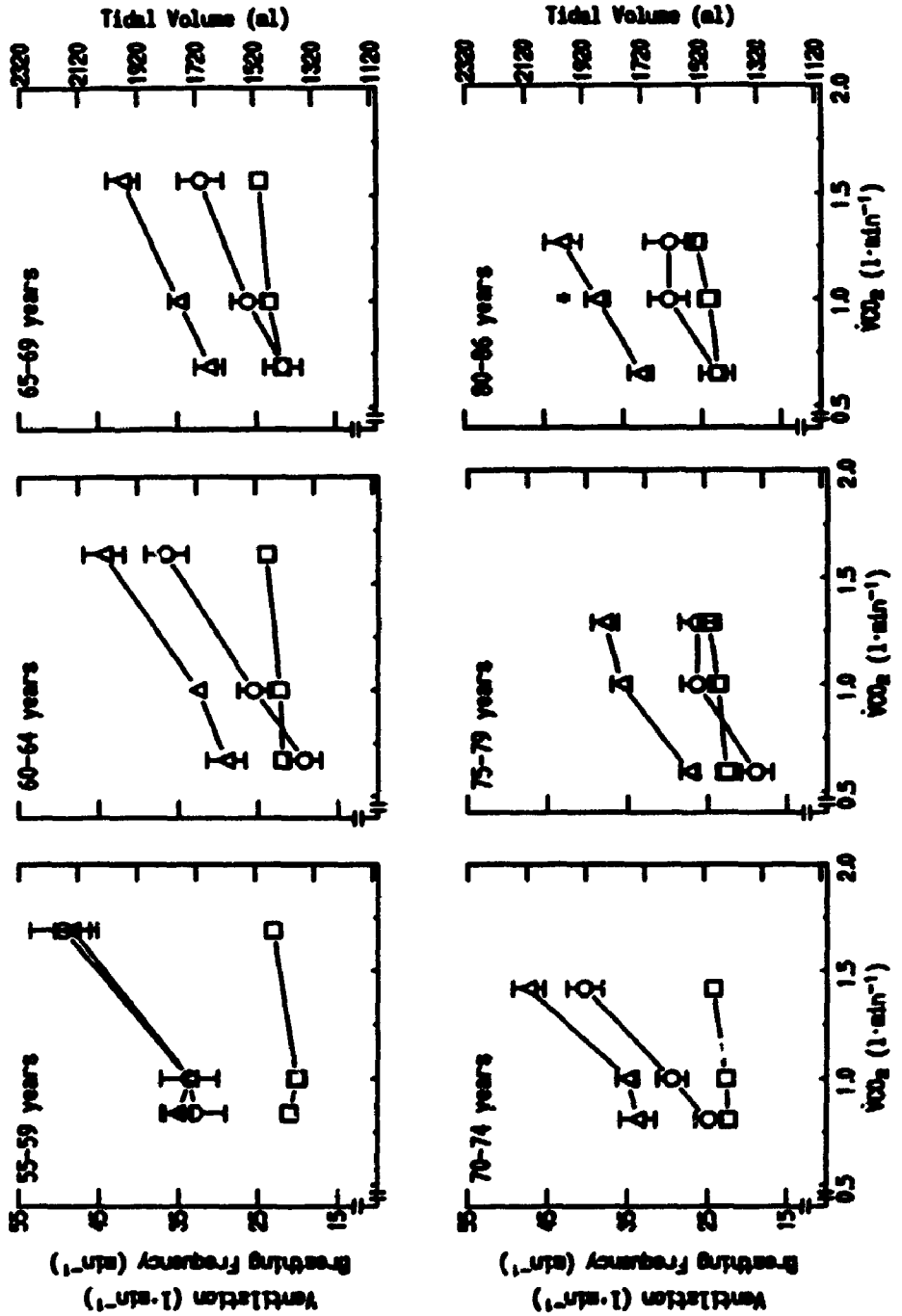


Figure 5. Relationship between $\dot{V}_E$ (▵, ℓ·min^{-1}), f_b (□, min^{-1}), $\dot{V}_T$ (○, ml) and $\dot{V}CO_2$ (ℓ·min^{-1}) at t_1, $\dot{V}CO_2$ at 1.0 ℓ·min^{-1}, and $\dot{V}CO_2$ at t_2. Panels show means for men aged 55-59 (n=28), 60-64 (n=29), 65-69 (n=23), 70-74 (n=18), 75-79 (n=15), and 80-86 (n=15) years. (Values are means ± (SEM); * $\dot{V}_E$ at $\dot{V}CO_2$ = 1.0 ℓ·min^{-1} for men aged 80-86 yrs is significantly different from $\dot{V}_E$ at $\dot{V}CO_2$=1.0 ℓ·min^{-1} for men aged 55-59 and 60-64 yrs).

Table 5. Values for $\dot{V}_E$, f_b, and V_T at a $\dot{V}CO_2$ of 1.0 $\ell \cdot min^{-1}$ for men and women aged 55 to 86 years.

	Age groups (years)					
	55-59	60-64	65-69	70-74	75-79	80-86
Men	(n=28)	(n=29)	(n=23)	(n=18)	(n=15)	(n=15)
					75-85	
W²	(n=14)	(n=16)	(n=18)	(n=14)	(n=6)*	
$\dot{V}_E$ ($\ell \cdot min^{-1}$) ‡						
M	33.5	32.5	34.9	35.0	35.8	38.2 †
	(0.8)	(0.9)	(1.1)	(1.3)	(1.2)	(1.4)
W²	31.0	34.3	32.2	33.8	34.3	
	(1.5)	(1.8)	(1.0)	(1.4)	(1.2)	
f_b (breaths $\cdot min^{-1}$) ‡						
M	20.1	22.3	23.5	22.6	23.7	24.2
	(1.1)	(0.7)	(1.0)	(0.7)	(1.1)	(1.2)
W²	26.2	27.4	24.7	26.0	28.5	
	(1.7)	(1.7)	(1.4)	(1.1)	(2.1)	
V_T (mls) ‡						
M	1740.0	1522.9	1538.9	1625.8	1541.6	1622.1
	(96.2)	(52.2)	(55.4)	(50.1)	(55.0)	(66.0)
W²	1234.0	1314.4	1363.7	1334.7	1232.4	
	(70.7)	(79.6)	(68.2)	(59.0)	(76.6)	
V_T/FVC						
M	0.47	0.41	0.49	0.52 **	0.52 **	0.58 **
	(0.03)	(0.02)	(0.02)	(0.02)	(0.03)	(0.05)
W²	0.51	0.56	0.57	0.62	0.53	
	(0.03)	(0.05)	(0.04)	(0.02)	(0.04)	

Values are means ± (SEM)

* Age group includes one woman aged 80-85 yrs

W² data for 68 women who reached $\dot{V}CO_2$ equal or greater to 1.0 $\ell \cdot min^{-1}$ at $T_{\dot{V}E}$.

† significantly different from 55-59 and 60-64 yr groups

‡ values are 15 s means at $\dot{V}CO_2$=1.0 $\ell \cdot min^{-1}$

** significantly different from 60-64 yr group

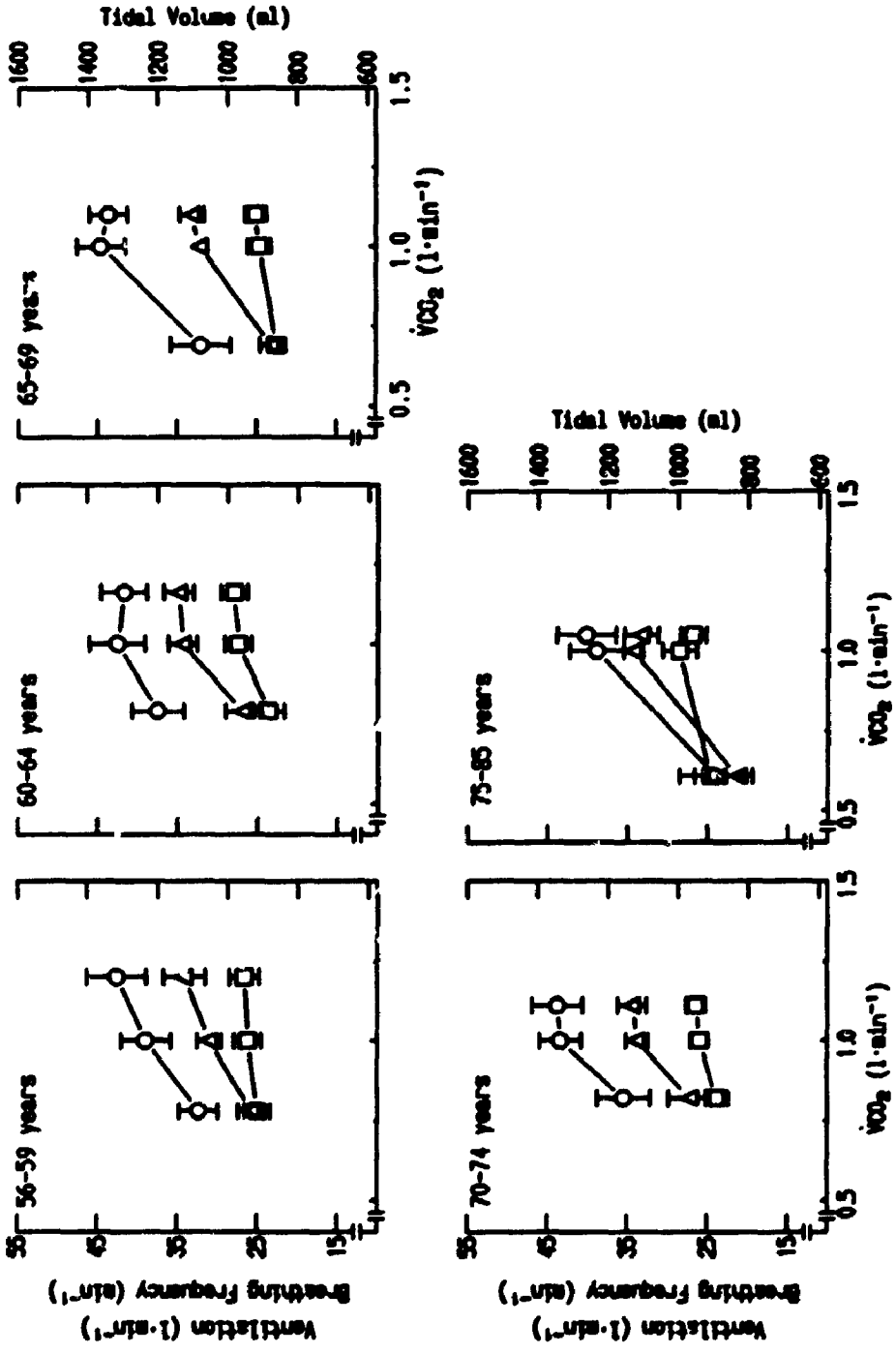


Figure 6. Relationship between $\dot{V}_E$ (▲, $\ell \cdot min^{-1}$), f_b (□, min^{-1}), $\dot{V}_T$ (○, ml) and $\dot{V}CO_2$ ($\ell \cdot min^{-1}$) at t_1, $\dot{V}CO_2$ at 1.0 $\ell \cdot min^{-1}$, and $\dot{V}CO_2$ at t_2. Panels shows means for women aged 56-59 (n=14), 60-64 (=16), 65-69 (=18), 70-74 (=14), and 75-85 (=6) years. (Values are means ± 1 SEM)

yrs while $\dot{V}CO_2 = 1.0\ \ell \cdot min^{-1}$ corresponded to 93% of $\dot{V}CO_2max$ for women aged 75-85 yrs. At a $\dot{V}CO_2$ of $1.0\ \ell \cdot min^{-1}$, there were no differences in $\dot{V}_E$, V_T, and f_b across ages (Table 5).

End-tidal PCO_2 during graded exercise. When comparisons were made within each age group for men and women, there were no significant differences between $P_{ET}CO_2$ at t_1 and $P_{ET}CO_2$ at t_2. Thus in all age groups, $P_{ET}CO_2$ did not show a decline over the exercise range studied but rather the exercise $P_{ET}CO_2$ remained essentially isocapnic.

When comparing $P_{ET}CO_2$ either at t_1 or at t_2 in men, the mean $P_{ET}CO_2$ for the 80-86 yrs group was significantly lower compared with the means for the 55-59 and 60-64 yr groups at t_1 and the means of the younger three age groups at t_2 (Figure 7, Top Panel). For the women's groups, there were no significant differences in $P_{ET}CO_2$ at t_1 although at t_2 $P_{ET}CO_2$ for the 56-59 yr group was significantly higher than all other age groups (Figure 7, Lower Panel).

2.5 Discussion

This study demonstrated that the ventilatory response to CO_2 production during exercise increased with advancing age in a sample of 128 men and 96 women aged 56-85 years. The slope of $\dot{V}_E$-$\dot{V}CO_2$ was significantly correlated to age for both men and women. A significantly larger increase in the slope of $\dot{V}_E$-$\dot{V}CO_2$ during graded exercise below the $T_{\dot{V}E}$ was reported for men in the ninth decade of life. This same group had an increased ventilatory response at $\dot{V}CO_2 = 1.0\ \ell \cdot min^{-1}$ compared to men aged 55-59 and 60-64 years (Figure 5, Table 5).

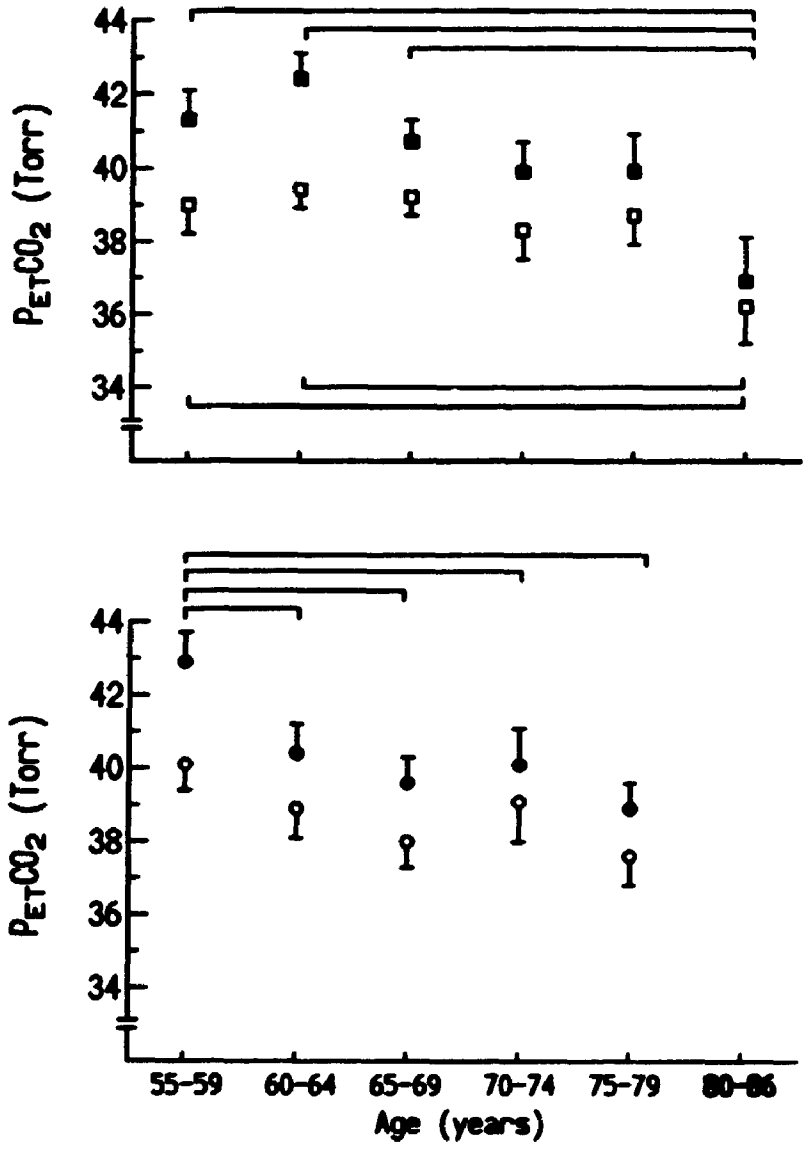


Figure 7. Top Panel: Exercise $P_{ET}CO_2$ (Torr) at t_1 (□) and t_2 (■) in men aged 55-86 years (n=128). Bottom panel: Exercise $P_{ET}CO_2$ at t_1 (○) and t_2 (●) in women aged 56-85 years (n=96). (Values are means ± 1 SEM; lines connect significantly different values at $p < 0.05$).

This study represents an attempt to determine the ventilatory response to exercise ($\Delta\dot{V}_E/\Delta\dot{V}CO_2$) in a large random sample of 441 men and women aged 55 to 86 years. This is the first paper to report such data for men and women in the ninth decade. Unfortunately, many of the subjects were not able to complete the exercise test due to health reasons (60, 14%) including cardiovascular, respiratory, or neuromuscular problems. The data from many other subjects had to be excluded (157, 36%) due to several complications during the exercise tests including medical problems and poor exercise performance. In most cases, these complications made it impossible to identify $T_{\dot{V}E}$ and thus, to determine $\Delta\dot{V}_E/\Delta\dot{V}CO_2$. As such, the study may be criticized on the basis that a bias was introduced toward the fitter and healthier elderly. Although the criticism is somewhat valid, the required ability of older men and women to perform successful exercise testing is such that the bias remains an inherent limitation to this type of study.

The increase in $\dot{V}_E$ from light to moderate work below the $T_{\dot{V}E}$ was linked to the increase in work rate (i.e. $\dot{V}CO_2$) and represented a normal hyperpnea of exercise and did not appear to be a function of the stimulus from metabolic acidosis. Although we did not measure the blood lactate directly, it is unlikely that the increase in $\dot{V}_E$ during exercise was a result of an increase in lactic acid production, since the exercise range studied in all participants was terminated 15s prior to, and below, each individual's measured $T_{\dot{V}E}$. Paired t-tests of the slopes of $\dot{V}_E$-$\dot{V}CO_2$ at t_1 (the lowest work rate) and at t_2 (the highest work rate) yielded no significant differences in any of the age groups, suggesting that there was a tight and linear coupling between $\dot{V}_E$ and $\dot{V}CO_2$ throughout

the entire exercise range studied. The linear relationship between $\dot{V}_E$ and $\dot{V}CO_2$ has been demonstrated previously and continues until the onset of metabolic acidosis at which point an additional compensatory ventilation increment is induced (Wasserman et al., 1973).

The slopes of the regression lines for the relationship of $\dot{V}_E$-$\dot{V}CO_2$ with advancing age were examined for men and women, and for both groups the slopes were significantly different from zero. It is unlikely that the higher $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ in the older men and women was the result of anaerobic glycolysis because the RER was low at the start of the test (0.84 ± 0.02 and 0.80 ± 0.03 for men and women respectively) and did not increase significantly to the value measured just below $T_{\dot{V}E}$ (0.91 ± 0.03 and 0.88 ± 0.02 for men and women respectively).

Although $P_{ET}CO_2$ was lower in men aged 80-86 yrs and women aged 75-85 years, $P_{ET}CO_2$ did not fall during the range of exercise studied. Presumably, $P_{ET}CO_2$ remained at its control value through work rates up to the anaerobic threshold, indicating that exercise remained isocapnic (Davis et al., 1980). Therefore, even if the increased $\dot{V}_E$ during exercise in the oldest groups of men and women was due to inefficiencies of gas exchange, the ventilatory response achieved was sufficient to maintain normal end-tidal values for CO_2.

The increased ventilatory response to CO_2 production in men aged 80-86 yrs may have served to compensate for an increase in dead-space ventilation (Brischetto et al., 1984; Rubin et al., 1982) and greater non-uniformity of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) relative to the young (i.e. higher physiological dead space) (Wagner et al., 1974). In

light of the alterations in dead-space ventilation and in the ventilation perfusion relationship that may occur with advancing age, arterial P_{CO2} homeostasis and $\dot{V}_A$-$\dot{V}CO_2$ would appear to be similar in the elderly and younger subjects at any given $\dot{V}CO_2$.

The increased ventilatory response at $\dot{V}CO_2$=1.0 $\ell \cdot min^{-1}$ for the men aged 80-86 yrs was achieved with a similar absolute V_T as the younger men, but, relative to FVC, V_T represented 58% of FVC compared to 47% of FVC for men aged 55-59 yrs (Table 5). There was a trend for a higher (20%) breathing frequency in men aged 80-86 yrs compared to men aged 55-59 yrs. Johnson and co-workers (1991b) previously reported data for older fit and younger adults and found a tendency to increase $\dot{V}_E$ primarily through increases in V_T during lighter exercise loads, with a levelling off of V_T at 58% of vital capacity. After that point, primarily a frequency of breathing response to exercise was noted (DeVries and Adams, 1972; Johnson et al., 1991b). Thus, the oldest men in this study appear to have reached the appropriate exercise $\dot{V}_E$ primarily due to an increase in f_b. At this time, V_T had levelled off at an age-related functional limit (58% of FVC) thus minimizing any further increase in V_T.

For a given $\dot{V}_E$, the oxygen cost of breathing is higher in older subjects (Johnson et al., 1991b) and appears to increase dramatically as mechanical limits for flow and pressure development are approached (Collett and Engel, 1986). The higher oxygen cost of breathing significantly increases the need for blood flow to the respiratory muscles and this possibly compromises blood flow to the working muscles (Johnson et al., 1991b).

In this study, age alone explains only a very small percentage of the change in $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ in men (22%) and in women (8%). The unexplained variance may be due

to many other factors (i.e. neural, mechanical, or humoral stimuli) which were not measured in the present investigation. These factors are known to be stimuli for exercise ventilation (Eldridge and Waldrop, 1991). Furthermore, although $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was examined below $T_{\dot{V}E}$, $\dot{V}CO_2$ of 1.0 $\ell \cdot min^{-1}$ and $\dot{V}CO_2$ at $T_{\dot{V}E}$ represented greater percentages of $\dot{V}CO_2max$ for the oldest men. Thus, other factors such as an increase in central neurogenic drive (Asmussen et al., 1965), or increases in exercise related catecholamines (Galbo, 1986) and arterial potassium levels (Paterson et al., 1990) may be related to the increased ventilatory response to exercise in the very old men aged 80-86 yrs.

The results in this study of isocapnic ventilation in older men and women are in agreement with those of previous reports (Brischetto et al., 1984; Johnson et al., 1991a). Brischetto and co-workers measured serial changes in P_aCO_2 during steady-state exercise in two elderly men (age=70 years) with very high ventilatory responses to exercise and showed that exercise remained isocapnic. Johnson's group (1991a) took direct measures of P_aCO_2 in a sample of eighteen very fit elderly men who performed incremental exercise. From their measures of P_aCO_2, V_D/V_T was calculated to be 30% higher during heavy exercise in the older men compared to that of younger controls.

The low $P_{ET}CO_2$ values in the elderly observed in this study and that by Overend et al. (1992) at rest and during exercise suggest a progressive age-related increase in the P_{ET}-$_aCO_2$ gradient with advancing age. The direct measurements of P_aCO_2 from Johnson et al. (1991a) would indicate that P_aCO_2 is independent of the ageing process at rest and during exercise. Greater nonuniformity of ventilation-perfusion ratios has been reported

previously in aged humans relative to young at rest and during exercise (Wagner et al., 1974) and ventilation-perfusion inequality has also been shown to increase with exercise in some persons (Schaffartzik et al., 1992). Although no study is known in which $P_{ET}CO_2$ and P_aCO_2 have been determined in the same elderly subjects at rest or during exercise, such a comparison has been made with younger subjects (Robbins et al., 1990). Results demonstrated a reasonable degree of association between the Jones corrected $P_{ET}CO_2$ and measured P_aCO_2 (Robbins et al., 1990). With ageing however, an increase in ventilation-perfusion inequalities (Johnson and Dempsey, 1991; Wagner et al., 1974) invalidates the use of the Jones equation (Jones et al., 1966 & 1980). No age specific equation is presently available.

This study examined the slope of the $\dot{V}_E$-$\dot{V}CO_2$ relationship between the onset of workload and the $T_{\dot{V}E}$ during graded exercise. We found that the $\dot{V}CO_2$ at t_2, the work rate just below $T_{\dot{V}E}$, decreased by 27% from age 55 to 86 yrs in men and by 13% from age 56 to 85 yrs in women. McConnell and Davies (1992) reported that a $\dot{V}CO_2$ of 0.9 $\ell \cdot min^{-1}$ was the higher limit of work possible before men aged 71 years exceeded the $T_{\dot{V}E}$. Although in that study exercise was performed on a cycle ergometer, results from this study for exercise performed on the treadmill are not dissimilar showing the higher limit for $\dot{V}CO_2$ before $T_{\dot{V}E}$ to be 1.14 $\ell \cdot min^{-1}$ for men aged 80-86 years and 1.04 $\ell \cdot min^{-1}$ for women aged 75-85 years. Unlike the results of McConnell and Davies (1992) of a crossing of the $\dot{V}_E$-$\dot{V}CO_2$ relationship for young and elderly at a $\dot{V}CO_2 = 0.75\ \ell \cdot min^{-1}$, below which the ventilatory response of the elderly was similar to, or less than that of young subjects, this study did not find such a crossing. In this study, for light through

moderate exercise, the very old men aged 80-86 yrs had a higher ventilatory response to CO_2 production, demonstrated by a higher slope for the $\dot{V}_E$-$\dot{V}CO_2$ relationship as well as by the higher $\dot{V}_E$ at $\dot{V}CO_2$=1.0 $\ell \cdot min^{-1}$.

CHAPTER 3

VENTILATORY SENSITIVITY TO CO_2 IN HYPEROXIA AND HYPOXIA IN YOUNG AND OLDER HUMANS

3.1 Abstract

Findings from studies on the effects of ageing on the human respiratory controller are equivocal. This study assessed the ventilatory response to CO_2 in hyperoxia and in hypoxia in groups of younger (YS) and older (OS) humans. Two protocols were used. In the first, $P_{ET}CO_2$ was clamped at 1-2 Torr above rest (eucapnia), and in the second, $P_{ET}CO_2$ was clamped at 7-8 Torr above resting $P_{ET}CO_2$ (moderate hypercapnia). $P_{ET}O_2$ was clamped at 100 Torr throughout except for 2-two minute periods at 500 and 50 Torr. The ventilatory responses for each subject at each P_{O2} were fitted to the linear equation, $\dot{V}_E = S(P_{ET}CO_2 - B)$, where $\dot{V}_E$ is minute ventilation, S is the response curve slope, $P_{ET}CO_2$ is end-tidal P_{CO2} (Torr), and B is the response curve threshold (Torr). In eucapnia, there were no differences in hypoxic and hyperoxic $\dot{V}_E$ between YS and OS. In hypercapnia, hypoxic $\dot{V}_E$ was 24% lower in OS (39.93 ± 2.71(SE), $\ell \cdot min^{-1}$) compared to YS (52.16 ± 3.17). In hypoxia S was significantly lower in OS (3.25 ± 0.38 $\ell \cdot min^{-1} \cdot Torr^{-1}$) compared to YS ($4.76 \pm 0.37$). In older humans, $\dot{V}_E$ was lower in hypoxia during moderate hypercapnia, and this may have resulted, at least in part, from a decrease in peripheral chemoreflex CO_2 sensitivity.

3.2 Introduction

The ageing process affects many physiological systems including the respiratory control system (Levitzky, 1984). Some studies have reported that it is associated with large declines in the ventilatory responses to hypercapnia and hypoxia (Altose et al., 1977; Brischetto et al., 1984; Kronenberg and Drage, 1973; Peterson et al., 1981) whereas other investigations have reported little or no effects on the ventilatory responses to hypercapnia (Kamakami et al., 1981; Rubin et al., 1982) or to acute isocapnic hypoxia (Ahmed et al., 1991; Smith et al., 1992b). To date, no study has examined the effects of ageing on the ventilatory responses to CO_2 in terms of both the central and peripheral chemoreflex sensitivities to CO_2. Earlier studies which have examined the ventilatory responses to hypercapnia in aged humans have used hyperoxic ($P_AO_2 \simeq 200$ Torr) rebreathing techniques, assessing the ventilatory response which is largely mediated by the central chemoreceptors since arterial chemoreceptor activity is suppressed during hyperoxia (Cunningham et al., 1986; Read, 1967).

Thus, the purposes of this study were to examine the ventilatory response to CO_2 and to determine the $P_{ET}CO_2$-$\dot{V}_E$ response curve slopes, in hypoxia and in hyperoxia, in groups of healthy old and young humans. This study has been reported in abstract form (Cunningham et al., 1992).

3.3 Methods

Subjects. The subjects were separated into two age groups, one young (age =28.3 $\pm$ 2.7 yrs (S.E.)) and one old (age=76.1 $\pm$ 1.2). All subjects were males

except for one female in each of the YS and OS groups. The elderly subjects were volunteers some of who participated in regular physical activity; the younger subjects were students or research assistants. All subjects were non-smokers. The study requirements were fully explained (in written and verbal forms) to all participants, with each subject giving informed consent prior to participating in the study (Appendix III). The research was approved by the University's Ethics Committee on Human Research.

Testing. Subjects were requested not to eat or drink caffeine-containing beverages within four hours prior to scheduled testing sessions in the laboratory. Subjects reported to the laboratory, at the same time of day, on four occasions, each session lasting 1-3 hours. On the first session each participant was given a medical examination including a medical history, a 12-lead electrocardiogram (ECG), blood pressure measurement, anthropometric measurements (including height, weight, and five skinfolds thicknesses), pulmonary function tests, and a treadmill test to determine maximal oxygen uptake ($\dot{V}O_2max$). At this point, individuals with a history of, and those showing overt symptoms of cardiorespiratory disease, were excluded from the study. On the second visit, subjects were acquainted with the breathing apparatus. During a thirty minute test, subjects sat quietly and breathed combinations of hypoxic or hypercapnic gas mixtures, administered in a step-wise fashion; the 12 lead ECG and blood pressure measurements were taken during each of the different steps. On each of the third and fourth visits, two tests were performed. These tests served to establish the CO_2 sensitivities in euoxia, hyperoxia, and hypoxia and each lasting 35-45 minutes.

Calibration and equipment for exercise testing and spirometry. During all

treadmill and spirometry tests, inspired and expired ventilation flow rates were measured using a low resistance bi- directional turbine (Alpha Technologies, VMM 110) calibrated daily with a syringe of known volume (3.01 l). Inspired and expired gases were sampled continuously (20 ml·sec^{-1}) at the mouth and analyzed by a mass spectrometer (AIRSPEC MGA2000) calibrated daily with precision-analyzed gas mixtures. Analog signals were sampled and digitized every 20 milliseconds by computer. Data were stored on the hard disc system for later analysis. Gas concentration signals were aligned with the inspired and expired volumes after correcting for the time delay appropriate for the instrument. Breath-by-breath determination of $\dot{V}_E$, O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), respiratory exchange ratio (RER), end-tidal O_2 and CO_2 partial pressures ($P_{ET}O_2$ and $P_{ET}CO_2$), $\dot{V}_E/\dot{V}O_2$, and $\dot{V}_E/\dot{V}CO_2$ was performed using the algorithms of Beaver et al. (6). The data for alveolar $\dot{V}O_2$ were filtered to remove breaths deviating by more than 20% from a five breath moving average. Heart rate (HR) was monitored continuously via ECG electrodes by means of a modified V-5 configuration.

Pulmonary function tests. The computerised data collection system had been validated for spirometry against a 9-l waterseal Stead-Wells spirometer (unpublished work from our laboratory). Forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), peak expiratory flow rate (PEFR), maximal voluntary ventilation (MVV; measured over 10 s and extrapolated to 60 s), and maximal expiratory flow rate at 50% of vital capacity ($\dot{V}max_{50}$) were measured. Following explanations, FEV_1 maneuvers were performed from total lung capacity in a good sitting position with the subject wearing a nose-clip. The FEV_1 was repeated until satisfactory results were recorded. The FEV_1 was

reported corrected to BTPS and taken from the best curve. Tests with poor starts were back-extrapolated by computer according to the American Thoracic Society recommendations (1987) and rejected if the extrapolated volume exceeded 5% of the FVC or 100 ml, whichever was greater.

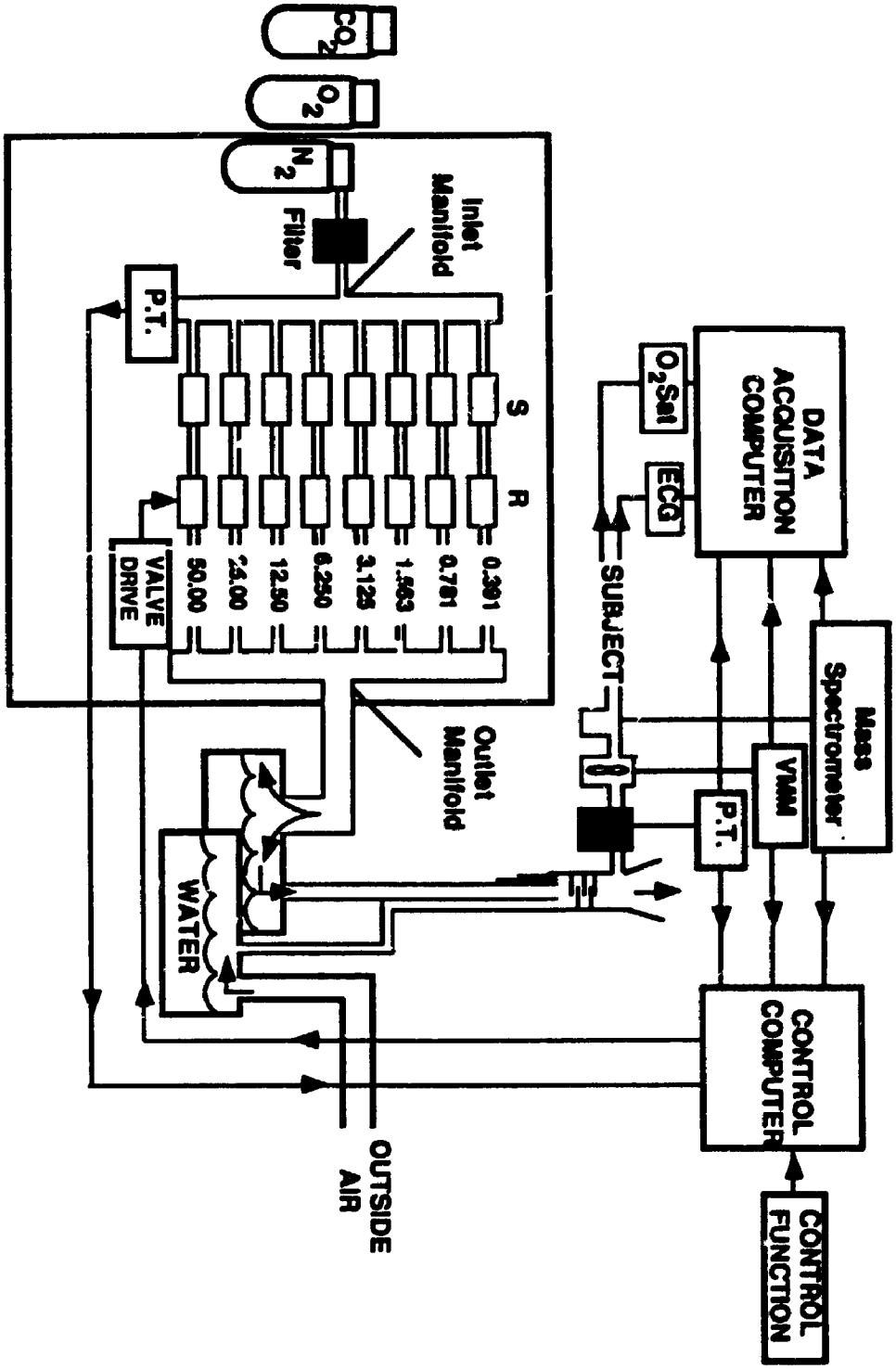
Maximal treadmill "ramp" test. A maximal effort treadmill test was performed by the subjects and served two purposes. First, as part of the screening process, it served to exclude from the study any volunteer showing clinical symptoms of cardiorespiratory disease including angina and ECG abnormalities. Second, it served to establish the high level of aerobic fitness of the subjects which may be important for the development of any age-associated changes in respiratory control. The protocol was initiated with a two minute warm-up at a walking velocity of 1.07 $m \cdot s^{-1}$ and zero percent grade. The velocity, or grade, or combination of velocity and grade, were then increased in specific small increments to elicit a ramp-like increase in O_2 demand of between 1 and 4 $ml \cdot kg^{-1} \cdot min^{-1}$ each minute and the protocol for each subject was selected to result in a test of 8-12 minutes. Subjects were verbally encouraged throughout the test. At the end of the test, the subjects were required to walk on the treadmill for at least two minutes at zero percent grade and at 1.07 $m \cdot s^{-1}$ to warm-down properly. The highest $\dot{V}O_2$ during the ramp test was examined to determine the occurrence of a plateau in $\dot{V}O_2$ ($\dot{V}O_2max$) despite a continuing increase in work rate. Data of $\dot{V}O_2$ versus time were averaged over 15 s periods. A plateau at maximum power output was achieved when the highest $\dot{V}O_2$ differed from the prior $\dot{V}O_2$ by only 50% or less of the $\dot{V}O_2$-time (work rate) slope. This slope was found during the submaximal exercise period.

Criteria for stopping the treadmill tests. The criteria for stopping the exercise tests were those recommended by the American College of Sports Medicine (1991); namely undue fatigue, and symptom limitations including angina, and ECG abnormalities.

Apparatus and technique for dynamic-end-tidal forcings at rest. Accurate control of the end-tidal gases was achieved using a computer-controlled fast gas mixing system similar to that previously described in more detail by Howson et al. (1987) and Robbins et al. (1982) and presented schematically in Figure 8. Subjects sat quietly in a chair and breathed through a mouthpiece with the nose occluded. Respiratory volumes were measured with a turbine and volume transducer (SensorMedics VMM-2A). Respiratory flows and timing information were obtained using a pneumotachograph (Hans Rudolph, Inc. Model 3800) and differential pressure transducer (Validyne MP45-871). Gas was sampled at the mouth at a rate of 20 $ml \cdot min^{-1}$ and analyzed by mass spectrometer (Airspec MGA2000) for fractional concentrations of O_2, CO_2, and N_2. Two microcomputers were used. One functioned as a data acquisition computer (DAC) and the other functioned as a control computer (CC). The DAC collected the experimental variables every 20 msec (i.e. data collected from the mass spectrometer, turbine expiratory and inspiratory channels, pneumotachograph, electrocardiogram, and ear oximeter) and stored for later analysis.

At the start of the each experiment, subjects breathed humidified air for ten minutes; the first five minutes served as an habituation period to the mouthpiece while the last five minutes served as the start of the collection period. The subject's resting

Figure 8. Schematic representation of the computer-controlled fast gas mixing system used to administer dynamic end-tidal forcing functions. Subjects sat in a chair and breathed through a mouthpiece with the nose occluded. Respiratory volumes were measured with a turbine and volume transducer (VMM). Respiratory flows and timing were obtained using a pneumotachograph and differential pressure transducer (P.T.; shown immediately below VMM). Gas was sampled at the mouth and analyzed by mass spectrometer for fractional concentrations of O_2, CO_2, and N_2. Two microcomputers were used; one functioned as a data acquisition computer (DAC) and the other functioned as a control computer (CC). The DAC collected data from the mass spectrometer, VMM, P.T., electrocardiogram (ECG), ear oximeter (O_2Sat), and stored them for later analysis. At the start of the each experiment, subjects breathed humidified air from outside. The subject's eucapnic $P_{ET}CO_2$ was clamped at 1 Torr above the resting $P_{ET}CO_2$. At the start of the actual experiment, the CC found the end of first expiration (sensed by the P.T.). The CC compared the measured end-tidal tensions with the target end-tidal tensions (entered as a control function into the CC before the experiment according to the protocol). The variables used for feedback control were $P_{ET}CO_2$ and $P_{ET}O_2$. The inspired PCO_2 and PO_2 required (predicted inspired likely to achieve the desired end-tidal pressures was set before the start of the experiment) were converted by an algorithm into appropriate values for flows of CO_2, O_2, and N_2, provided by the opening and closing several solenoid valves (S). The sensing process for $P_{ET}CO_2$ and $P_{ET}O_2$ was repeated at the end of each breath and the CC adjusted the gas mixture to force the end-tidal PO_2 and PCO_2 towards the desired values. Thus, the control of the new inspiratory mixture delivered was on the next breath.

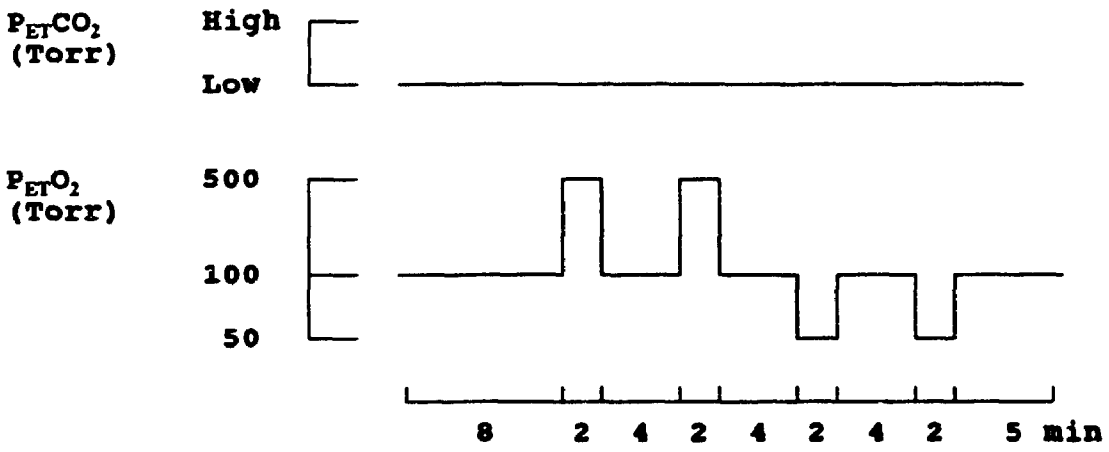

CO_2
O_2
N_2
Filter
Inlet Manifold
P.T.
S
R
0.391
0.781
1.563
3.125
6.250
12.50
25.00
50.00
VALVE DRIVE
Outlet Manifold
WATER
OUTSIDE AIR
O_2Sol
ECG
DATA ACQUISITION COMPUTER
SUBJECT
P.T.
VMM
Mass Spectrometer
CONTROL COMPUTER
CONTROL FUNCTION

$P_{ET}CO_2$ was determined as the mean of the last ten $P_{ET}CO_2$ values of the five minute collection period and the eucapnic $P_{ET}CO_2$ was clamped at 1 Torr above the resting $P_{ET}CO_2$. At the start of the actual experiment, the end of the first expiration was determined as sensed by the pneumotachograph signal for flow and timing. The measured end-tidal tensions were compared with the target end-tidal tensions (entered into the CC before the experiment according to the protocol). The variables used for feedback control were $P_{ET}CO_2$ and $P_{ET}O_2$. The inspired PCO_2 and PO_2 required (predicted inspired likely to achieve the desired end-tidal pressures was set before the start of the experiment) were converted by an algorithm into appropriate values for flows of CO_2, O_2, and N_2. The sensing process for $P_{ET}CO_2$ and $P_{ET}O_2$ was repeated at the end of each breath by the CC and the gas mixture was automatically adjusted to force the end-tidal PO_2 and PCO_2 towards the desired values. Thus, the control of the new inspiratory mixture delivered was on the next breath. This experimental design is noted for the constancy of the desired end-tidal forcings in the face of a constantly changing ventilation as well as the squareness of the alveolar steps (Swanson and Bellville, 1975).

Determination of CO_2 sensitivities. CO_2 sensitivity was determined at two levels of $P_{ET}O_2$ (hypoxia=50 Torr; hyperoxia=500 Torr) in backgrounds of eucapnia and hypercapnia (figure 9). In both protocols, $P_{ET}O_2$ was held at 100 Torr throughout except for 2-two minute periods at 500 Torr and 2-two minute periods at 50 Torr. Four minutes separated each of the $P_{ET}O_2$ steps from one another. The acute ventilatory response to each of the hyperoxic and hypoxic exposures was obtained by taking the mean of the last 30s of the two minutes exposure, while the ventilatory responses in euoxia, were taken

EXPERIMENTAL PROTOCOL

PROTOCOL I



PROTOCOL II

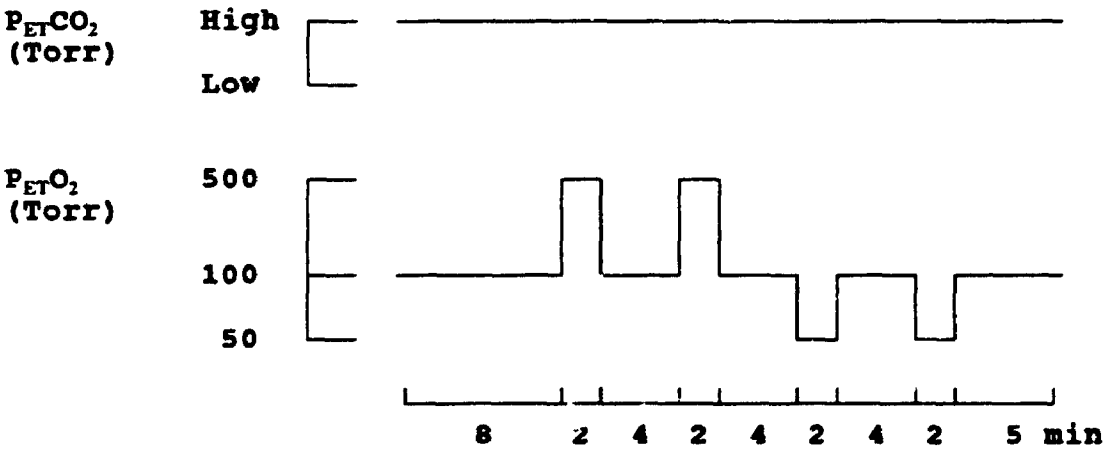


Figure 9. Experimental protocols describing the time related changes in gas forcing functions. Two protocols were employed. In both protocols I and II $P_{ET}O_2$ was held at 100 Torr throughout except for 2-two minute periods at 500 Torr and 2-two minute periods at 50 Torr. Protocol I: $P_{ET}CO_2$ held near eucapnia (1-2 Torr above resting $P_{ET}CO_2$). Protocol II: $P_{ET}CO_2$ held 7-8 Torr above resting $P_{ET}CO_2$. The ventilatory responses to hyperoxia and hypoxia were obtained by taking the mean of the last 30s of the two minute exposures while the baseline ventilation in euoxia was taken as the mean of the last 30s before the first hyperoxic exposure.

as the mean of the last 30s before the first hyperoxic step. The CO_2 sensitivities in high, normal, and low oxygen were obtained by fitting the data to the Lloyd and Cunningham equation (1958), $\dot{V}_E = S(P_{ET}CO_2 - B)$, for the calculation of the response curve threshold (B) and the slope of the response (S, CO_2 sensitivity parameter). The slopes of the lines in hyperoxia were taken as a measure of the central chemoreflex CO_2 sensitivity (g_c) while the slopes of the lines in hypoxia were taken as a measure of the central and peripheral chemoreflex CO_2 sensitivities ($g_c + g_p$). The peripheral chemoreflex CO_2 sensitivity (g_p) was calculated as the difference between the slopes of the $\dot{V}_E$-$P_{ET}CO_2$ response lines in hypoxia and hyperoxia. A similar protocol was used previously to examine the central and peripheral chemoreflex CO_2 sensitivities in young humans (Bascom et al., 1990).

Data analysis. Group analyses were performed using one-way analysis of variance and when indicated Student Newman-Keul post-hoc analysis was applied. Within-group comparisons were made using Student Paired T-tests. The level of significance was $p < 0.05$.

3.4 Results

Subjects. A total of 7 young and 16 old subjects agreed to participate in the study. After initial medical examination, 5 older subjects were excluded due to a history of cardiovascular disease. Thus, the number of subjects was 7 young and 11 old. The physical characteristics of the subjects are listed in Table 6.

Pulmonary function tests. Results of the pulmonary function tests are shown in

Table 6. Subject characteristics, maximal exercise performance, and pulmonary function

Variables	YOUNG (n=7)	OLD (n=11)
Height (cm)	177.9 ± 2.2	175.0 ± 2.0
Mass (kg)	78.5 ± 3.3	74.2 ± 4.2
FEV_1, (ℓ)	4.50 ± 0 31	2.90 ± 0.14 *
FEV_1, (% pred) †	100.1 ± 3.1	100.8 ± 3.7
FVC, (ℓ)	5.80 ± 0.26	4.14 ± 0.15 *
FVC, (% pred) †	108.1 ± 2.5	113.2 ± 4.2
FEV_1/FVC (%)	77.3 ± 2.7	70.8 ± 2.4
$\dot{V}max_{50}$,($\ell \cdot sec^{-1}$)	5.41 ± 0.65	2.89 ± 0.31 *
$\dot{V}max_{50}$,(% pred) †	92.7 ± 9.46	80.6 ± 9.3
PEFR ($\ell \cdot sec^{-1}$)	9.34 ± 0.74	7.86 ± 0.57
MVV ($\ell \cdot min^{-1}$)	188.0 ± 15.9	114.8 ± 7.9 *
$\dot{V}O_2max$,($\ell \cdot min^{-1}$)	3.77 ± 0.33	1.92 ± 0.20 *
$\dot{V}O_2max$,($ml \cdot kg^{-1} \cdot min^{-1}$)	48.8 ± 3.2	26.6 ± 2.4 *
$\dot{V}O_2max$,(% pred) ‡	117.7 ± 9.2	146.4 ± 12.6 *
$\dot{V}_Emax$, ($\ell \cdot min^{-1}$)	151.8 ± 10.1	76.5 ± 7.7 *
$\dot{V}_Emax$/MVV (%)	82.2 ± 4.1	67.6 ± 6.3
$\dot{V}CO_2max$ ($\ell \cdot min^{-1}$)	4.64 ± 0.46	2.24 ± 0.27 *
HRmax,(beats·min^{-1})	189.7 ± 6.4	147.7 ± 3.6 *

Values are means ± SEM

* significantly different from young group at $p < 0.05$

Abbreviations: $\dot{V}max_{50}$=maximal flow after exhaling 50% of FVC; PEFR=peak expiratory flow rate; MVV = maximal voluntary ventilation.

† Normal predicted values for FVC and FEV_1 are based on age and height (Knudson et al., 1983)

‡ Normal predicted values for $\dot{V}O_2max$ (based on age and weight) (Jones, 1988)

Table 6. All measures were within 10% of the normal age-predicted values from the data of Knudson et al. (1983) from nonsmoking Caucasian men and women, and demonstrated little or no differences between the young and older groups.

Responses to graded exercise. As shown in Table 6, YS had a mean $\dot{V}O_2max$ that was 118 percent of predicted while OS had a mean $\dot{V}O_2max$ of 148% of the age-predicted maximum of 18.0 $ml \cdot kg^{-1} \cdot min^{-1}$ (Jones, 1988).

Eucapnic $\dot{V}_E$ responses in euoxia, hyperoxia, and hypoxia. In eucapnia, there were no differences between groups for $\dot{V}_E$ in euoxia, hypoxia, and hyperoxia (Table 7). Both groups showed significant within-group increases for $\dot{V}_E$ in hypoxia compared to euoxia with $\dot{V}_E$ in hypoxia being 94.1% (YS) and 70.3% (OS) higher than that in euoxia (Table 7). The increases in $\dot{V}_E$ were due to significant increases in both breathing frequency and tidal volume, with significant increases in V_T/T_I (inspiratory flow). Both groups reached the same levels of arterial O_2 saturation (%) in hypoxia (Table 7). The HR response in hypoxia was significantly greater for YS, increasing by 10 $beats \cdot min^{-1}$, while the HR response for OS increased by 6 $beats \cdot min^{-1}$ (Table 7).

For YS, $\dot{V}_E$ in hyperoxia was 9% higher than $\dot{V}_E$ in euoxia. No differences were found between $\dot{V}_E$ in hyperoxia and euoxia for OS. Both groups reached the same levels of arterial O_2 saturation (%) during the hyperoxic challenges. There was a 4% decrease in HR for YS in response to hyperoxia. No differences were found in the HR responses for OS.

Hypercapnic $\dot{V}_E$ responses in euoxia, hyperoxia, and hypoxia. There were no significant group differences in the $\dot{V}_E$ responses to hyperoxia. In euoxia, $\dot{V}_E$ was 14%

Table 7. Ventilatory responses in euoxia, hypoxia, and hyperoxia in a background of eucapnia ($P_{ET}CO_2$ = 1-2 Torr above resting).

Variables	Group	euoxia	hyperoxia	hypoxia
$\dot{V}_E$ ($\ell \cdot min^{-1}$)				
	YS	9.89 ± 0.41	10.82 ± 0.45 *	19.20 ± 1.93*
	OS	11.32 ± 0.54	11.67 ± 0.43	19.28 ± 0.56*
f_b (breaths·min^{-1})				
	YS	14.55 ± 0.72	14.41 ± 0.59	16.28 ± 0.76*
	OS	16.86 ± 0.77	16.68 ± 0.75 †	18.21 ± 0.77*
V_T (ml)				
	YS	645 ± 41	709 ± 31	1078 ± 101 *
	OS	668 ± 31	670 ± 41	990 ± 47 *
T_I (s)				
	YS	1.48 ± 0.07	1.62 ± 0.09	1.51 ± 0.10
	OS	1.72 ± 0.23	1.72 ± 0.19	1.46 ± 0.07
V_T/T_I (ml·s^{-1})				
	YS	436 ± 20	449 ± 24	726 ± 73 *
	OS	419 ± 25	413 ± 19	684 ± 20 *
T_I/T_T	YS	0.37 ± 0.01	0.39 ± 0.01	0.42 ± 0.01 *
	OS	0.44 ± 0.02 †	0.44 ± 0.01 †	0.44 ± 0.01
O_2 Sat (%)				
	YS	96.8 ± 0.3	99.2 ± 0.2 *	86.2 ± 0.6 *
	OS	96.5 ± 0.3	99.2 ± 0.2 *	86.3 ± 0.5 *
HR (beats·min^{-1})				
	YS	63.0 ± 5.2	60.4 ± 5.2 *	73.2 ± 4.8 *
	OS	63.3 ± 2.3	62.0 ± 2.7	69.2 ± 2.2 *

Values are means ± SEM
Each interval is the average of breath-by-breath data over 30 s; (YS, n=7),(OS, n=11)
V_T/T_I, mean inspiratory flow (ml·s^{-1}); T_I/T_T, inspiratory fraction of breath time
* significantly different from within group euoxic eucapnic condition at $p < 0.05$
† significantly different from young group at $p < 0.05$

lower for OS compared to YS (Table 8). In hypoxia, $\dot{V}_E$ was 24% lower for OS compared to YS, and this was due mainly to lower tidal volumes (16%) with no difference in breathing frequency (Table 8). In hypoxia, mean inspiratory airflow (V_T/T_I) was 22% lower for OS and there were no differences in inspiratory time (T_I) or the inspiratory fraction of breath time (T_I/T_T). Both groups achieved similar levels of arterial O_2 saturation (%) in hypoxia and in hyperoxia, and there were no group differences in the HR responses to hypoxia or hyperoxia (Table 8).

CO_2 sensitivity (S) and CO_2 Threshold (B). The individual $\dot{V}_E$-$P_{ET}CO_2$ response curves ($\ell \cdot min^{-1} \cdot Torr^{-1}$) are presented in Figure 10. There were no group differences in the hyperoxic CO_2 sensitivity (S) (Table 9). For OS compared to YS however, CO_2 sensitivity was lower by 22% in euoxia and by 32% in hypoxia (Table 9). For YS, S in hypoxia was significantly higher than that found in euoxia (39%) or hyperoxia (45%). For OS, there were no differences for S in euoxia, hypoxia, and hyperoxia (Table 9).

The central and peripheral chemoreflex CO_2 sensitivities were calculated from the CO_2 sensitivities in hyperoxia and in hypoxia (Table 9). There were no group differences in the gain of the central chemoreflex CO_2 sensitivity (g_c, measured CO_2 sensitivity in hyperoxia). The measured CO_2 sensitivity in hypoxia (sum of the gains of the central (g_c) and peripheral (g_p) chemoreflexes) was 32% lower in OS. This was due mainly to a 64% decrease in the gain of the peripheral chemoreflex, calculated as the difference between the slopes in hyperoxia and hypoxia (Table 9).

For OS, the CO_2 threshold (B) was 20% lower in euoxia, 22% lower in hypoxia, and 16% lower in hyperoxia compared to YS (Table 9). For both groups, there were

Table 8. Ventilatory responses in euoxia, hypoxia, and hyperoxia in a background of hypercapnia ($P_{ET}CO_2$ = 7-8 torr above resting).

Variables	Group	euoxia	hyperoxia	hypoxia
$\dot{V}_E$ ($\ell \cdot min^{-1}$)				
	YS	28.06 ± 1.14 *	26.37 ± 2.24 *	52.16 ± 3.17*
	OS	24.18 ± 1.16 * †	24.59 ± 1.28 *	39.93 ± 2.71*†
f_b (breaths·min^{-1})				
	YS	15.37 ± 2.72	18.43 ± 0.92 *	20.26 ± 1.25*
	OS	18.79 ± 0.71 *	18.97 ± 0.63 *	21.12 ± 1.05*
V_T (ml)				
	YS	1451 ± 66 *	1320 ± 64 *	2170 ± 113*
	OS	1264 ± 83 *	1236 ± 72 *	1830 ± 80 *†
T_I (s)				
	YS	1.45 ± 0.06	1.40 ± 0.06	1.27 ± 0.05 *
	OS	1.48 ± 0.07	1.45 ± 0.06	1.40 ± 0.08
V_T/T_I ($ml \cdot s^{-1}$)				
	YS	1002 ± 38 *	955 ± 74 *	1734 ± 116 *
	OS	861 ± 50 *	858 ± 45 *	1347 ± 90 *†
T_I/T_T	YS	0.44 ± 0.01 *	0.43 ± 0.01 *	0.46 ± 0.01 *
	OS	0.44 ± 0.01	0.45 ± 0.01	0.46 ± 0.01
O_2 Sat (%)				
	YS	96.7 ± 0.2	98.7 ± 0.4 *	85.6 ± 0.7 *
	OS	96.7 ± 0.2	99.0 ± 0.2 *	86.8 ± 0.5 *
HR (beats·min^{-1})				
	YS	65.3 ± 4.8	61.5 ± 4.9	75.3 ± 5.4 *
	OS	60.1 ± 2.7	59.5 ± 2.9	70.4 ± 3.6 *

Values are means ± SEM
Each interval is the average of breath-by-breath data over 30 s; (YS, n=7),(OS, n=11)
V_T/T_I, mean inspiratory flow ($ml \cdot s^{-1}$); T_I/T_T, inspiratory fraction of breath time
* significantly different from within group euoxic eucapnic condition at $p < 0.05$
† significantly different from young group at $p < 0.05$

Figure 10. Individual $P_{ET}CO_2$-$\dot{V}_E$ response curves obtained in euoxia (■——■), hypoxia (●----●), and hyperoxia (▲·····▲) in young (Top seven frames, prefix "Y-" prior to each subject's ID number) and old (Bottom eleven frames, prefix "O-" prior to each subject's ID number) humans. Each point represents $\dot{V}_E$ when $P_{ET}CO_2$ was elevated 1-2 Torr or 7-8 Torr above resting control levels for $P_{ET}CO_2$.

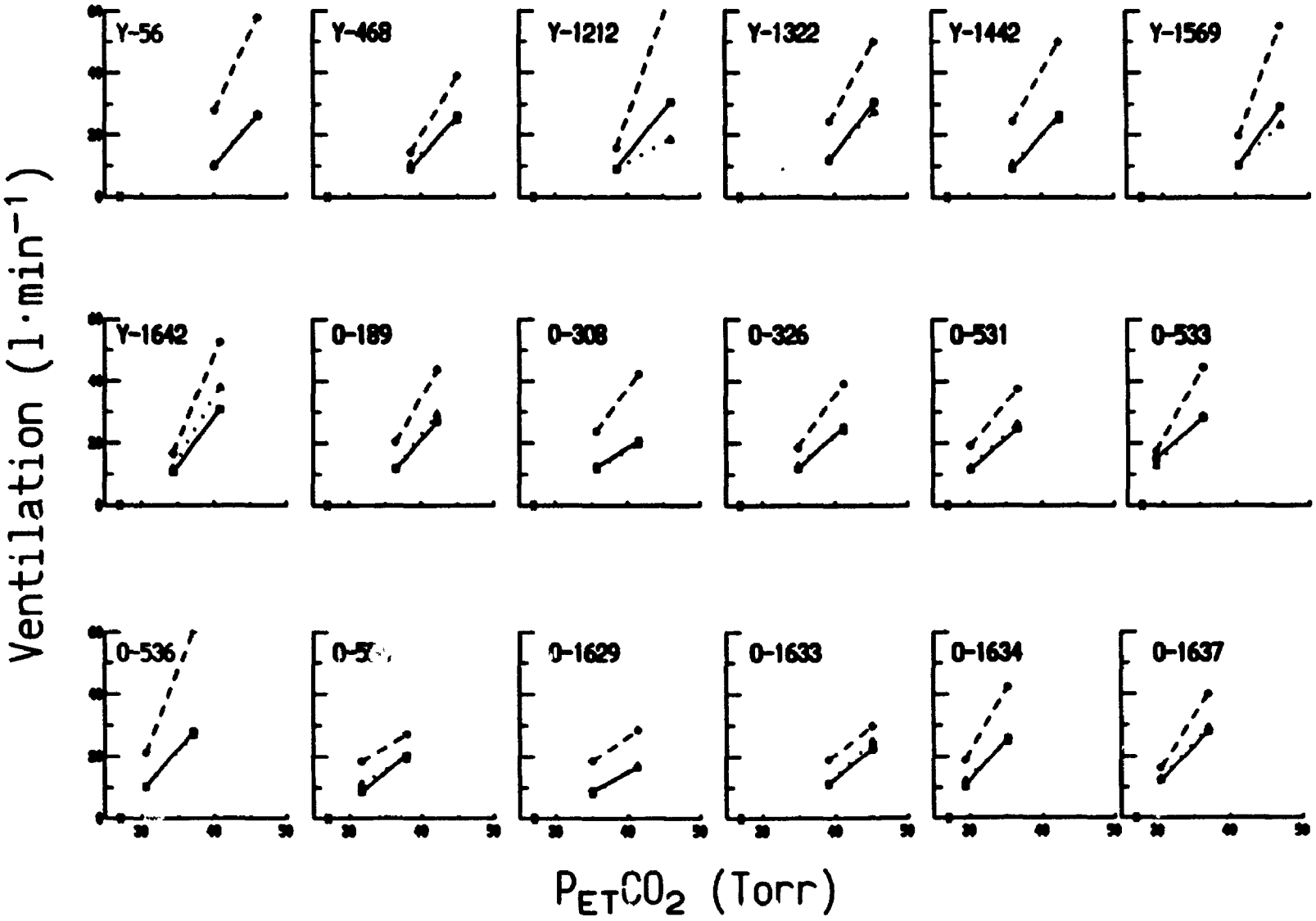

Y-56
Y-468
Y-1212
Y-1322
Y-1442
Y-1569
Y-1642
0-189
0-308
0-326
0-531
0-533
0-536
0-1629
0-1633
0-1634
0-1637
Ventilation (l·min⁻¹)
PETCO2 (Torr)

Table 9. Measured CO_2 sensitivities in hyperoxia ($P_{ET}O_2$ = 500 Torr), hypoxia ($P_{ET}O_2$ = 50 Torr), and euoxia ($P_{ET}O_2$ = 100 Torr), the calculated peripheral CO_2 sensitivity in hypoxia. Carbon dioxide threshold (B) in hyperoxia, hypoxia, and euoxia are also included.

Subject number	Measured CO_2 sensitivity in hyperoxia (gc) ($l \cdot min^{-1} \cdot Torr^{-1}$)	Measured CO_2 sensitivity in hypoxia (gc + gp) ($l \cdot min^{-1} \cdot Torr^{-1}$)	Calculated peripheral CO_2 sensitivity in hypoxia (gp) ($l \cdot min^{-1} \cdot Torr^{-1}$)	Measured CO_2 sensitivity in euoxia ($l \cdot min^{-1} \cdot Torr^{-1}$)	B in hyperoxia (Torr)	B in hypoxia (Torr)	B in euoxia (Torr)
YOUNG (n=7)							
0056	2.74	4.32	1.59	2.54	36.0	33.1	36.3
0468	1.91	3.45	1.54	2.41	32.0	34.3	34.8
1212	2.12	5.93	3.81	2.56	38.4	35.7	35.6
1322	2.45	3.70	1.25	2.93	34.0	31.6	35.0
1442	2.55	4.81	2.26	2.98	32.6	32.6	33.6
1569	2.16	5.79	3.63	2.99	35.2	36.2	36.2
1642	4.32	5.34	1.02	3.91	31.6	31.1	32.6
OLD (n=11)							
0189	2.93	3.65	0.72	2.78	32.1	30.6	32.4
0308	1.84	3.01	1.17	1.56	30.8	27.4	28.1
0326	1.71	3.42	1.71	2.16	27.6	29.4	29.4
0531	2.33	2.73	0.40	2.07	25.6	23.2	24.6
0533	3.19	4.31	1.12	2.07	26.6	25.4	21.8
0536	4.04	5.84	1.80	3.35	30.7	26.8	28.5
0554	1.18	1.51	0.33	2.15	21.7	19.9	28.9
1629	1.34	1.51	0.17	1.14	30.9	22.1	27.2
1633	2.03	2.34	0.31	1.83	35.7	30.7	30.8
1634	3.19	3.62	0.43	2.88	28.0	23.8	26.1
1637	2.51	3.75	1.24	2.75	25.4	26.8	26.7
Means YS	2.61 ± 0.31	4.76 ± 0.37	2.16 ± 0.43	2.90 ± 0.19	34.2 ± 1.0	33.5 ± 0.7	34.9 ± 0.5
OS	2.39 ± 0.25	3.25 ± 0.38*	0.86 ± 0.21*	2.25 ± 0.19†	28.7 ± 1.2†	26.0 ± 1.1†	27.9 ± 1.0†
Bascom (1990)	2.52 ± 0.49	4.37 ± 1.15	1.85 ± 0.71				
Y ‡	2.58 ± 0.25	4.62 ± 0.45	2.05 ± 1.19				

Values are means ± SEM

Y‡ Mean of 11 subjects including 7 from the present study and 4 from that of Bascom et al. (1990)

* significantly different from YS and Y‡ at $p < 0.05$

† significantly different from YS at $p < 0.05$

no intra-group differences in the CO_2 thresholds between euoxic, hypoxic, and hyperoxic conditions. Thus the level of $P_{ET}O_2$ did not have any effect on the CO_2 threshold.

3.5 Discussion

Findings from studies of the effects of ageing on the respiratory control system are equivocal. Although some studies have reported a blunting of the hypoxic and hypercapnic drives with advancing age (Altose et al., 1977; Brischetto et al., 1984; Kronenberg and Drage, 1973; Peterson et al., 1981) others have found little or no differences (Ahmed et al., 1991; Kawakami et al., 1981; Patrick and Howard, 1972; Rubin et al., 1982; Smith et al., 1992b). In the present study there were no age-related differences in the ventilatory response to CO_2 measured in hyperoxia, but there were significant differences in the ventilatory response to CO_2 measured in euoxia and hypoxia. Information regarding the possible mechanisms contributing to the lower ventilatory response to CO_2 in hypoxia in aged humans is provided.

This study differs in several important ways from previous studies investigating the ventilatory response to CO_2 in the elderly. Previous studies have used the rebreathing technique introduced by Read (1967), which assesses CO_2 sensitivity in a range of P_{CO2} 10-30 mm Hg above the physiological range and giving consistently higher estimates of CO_2 sensitivity than those of steady-state responses which give a reliable estimate of CO_2 sensitivity in the physiological range (Jacobi et al., 1987b). As well, the rebreathing technique maintains P_AO_2 at approximately 200 Torr, representing a measurement of central CO_2 sensitivity. Although there is general agreement that during

hyperoxia the peripheral chemoreceptors are silent (Cunningham et al., 1986; Dejours, 1962), recent evidence suggests a possible peripheral chemoreflex component in hyperoxia for certain individuals (Dahan et al., 1990), and therefore in this study $P_{ET}O_2$ was clamped at 500 Torr to attenuate the peripheral chemoreflex during the measurement of central CO_2 sensitivity.

This study used the non-invasive technique of dynamic end-tidal forcings (DEF) and the feedback method introduced by Swanson and Bellville (1975) and later modified by Robbins et al. (1982) to produce perturbations in $P_{ET}CO_2$ and $P_{ET}O_2$ to stimulate the respiratory control system. The DEF technique produces specific patterns in $P_{ET}O_2$ and $P_{ET}CO_2$ independent of the $\dot{V}_E$ response to mixed venous blood composition thus opening the feedback loop from $\dot{V}_E$ to $P_{ET}CO_2$ and $P_{ET}O_2$ (Swanson and Bellville, 1975). This technique has been used by Bascom et al. (1990) in young humans to examine the CO_2 sensitivity in hyperoxia and hypoxia but the present study is the first to use the DEF technique to examine the ventilatory response to CO_2 in hyperoxia and hypoxia in aged humans.

Step increases in $P_{ET}CO_2$, limited to 7-8 Torr above resting $P_{ET}CO_2$, were administered for two reasons. First, this level of inhaled CO_2 minimizes the possibility of a drift in $\dot{V}_E$ towards the end of the 30 minute protocol which has been reported in previous studies examining prolonged steady-state hypercapnia at rest with relatively high levels of hypercapnia of greater than 8-10 Torr above resting $P_{ET}CO_2$ (Easton and Anthonisen, 1988; Reynolds et al., 1972). Secondly, 7-8 Torr above resting $P_{ET}CO_2$ avoids imposing a ventilation greater than 50 $\ell \cdot min^{-1}$ at rest, which is frequently

associated with discomfort that can influence the ventilatory responses (Berkenbosch et al., 1989), and could approach possible mechanical limitations such as expiratory flow limitations that have been reported when older humans are subjected to ventilatory rates approaching those required at the level of $\dot{V}O_2max$ (Johnson et al., 1991b).

Previous studies have shown that in humans, the hypocapnic region, commonly called the dogleg, is unaffected by changes in $P_{ET}CO_2$ (Cunningham et al., 1986). Thus, this study was careful to avoid the dogleg region and examined the ventilatory response to CO_2 in eucapnia and hypercapnia only. In this $P_{ET}CO_2$ range, the use of only two points for the calculation of the $P_{ET}CO_2$-$\dot{V}_E$ response curve slope has been accepted in humans (Cunningham et al., 1961) and in anesthetized dogs (Lee and Milhorn, 1975).

It was the purpose of this study to measure the hypoxic CO_2 sensitivity before the onset of hypoxic ventilatory depression. The hypoxic challenges, with a background of a constant eucapnia or hypercapnia, were limited therefore to only two minutes. Several studies, using forcing techniques similar to the one used in this study, have provided evidence which suggests that the acute ventilatory response to hypoxia occurs within the first two minutes of this challenge (Bascom et al., 1990; Bascom et al., 1992; Khamnei and Robbins, 1990; Smith et al., 1992b). Thus, although the peak ventilatory response to hypoxia may be individually different, recent findings from several studies suggest that two minutes is most appropriate to reach peak ventilatory responses in hypoxia.

Results for the CO_2 sensitivity measured in hyperoxia and in hypoxia are presented in Table 9 (group means) and in Figure 10 (individual responses). No age-related differences were found in the measurement of the central chemoreflex CO_2

sensitivity, measured in hyperoxia (representing $S_{HYPEROXIA}$ from Figure 2, page 35), in contrast to the findings of previous studies (Altose et al., 1977; Brischetto et al., 1984; Kronenberg and Drage, 1973; Peterson et al., 1981). Although it has been suggested that statistically significant differences between young and old groups are often determined by atypical results reported for young groups (Ahmed et al., 1991; Rubin et al., 1982), the results for CO_2 sensitivity in hyperoxia for our young group are well within the range of normal, and similar to other studies reporting values for young adults (Bascom et al., 1990; Irsigler, 1976; Reynolds et al., 1972). Thus, it is quite unlikely that our lack of age-related differences were due to abnormally high or atypical CO_2 sensitivity measurements. In fact, for each young subject, CO_2 sensitivity in hyperoxia was classified as an "intermediate response" based on a three point scale including low, intermediate, and high ranges of the responses observed in the normal population (Irsigler, 1976).

Peripheral chemoreflex CO_2 sensitivity, calculated as the difference between the CO_2 sensitivity in hyperoxia and hypoxia (difference between $S_{HYPEROXIA}$ and $S_{HYPOXIA}$ from Figure 2, page 35), was 64% lower for the old group. While no other data is available for comparison of the peripheral chemoreflex CO_2 sensitivity in older humans, it is important to highlight that results from this study for the young group are not atypical but rather very similar to those previously reported by Bascom and co-workers for four young adults using a similar technique (Bascom et al., 1990). Their CO_2 sensitivity results have been included in Table 9 for comparison; analysis of variance revealed no differences between their young group and ours. When the present study's

results for the central and peripheral chemoreflex CO_2 sensitivity in young (n=7) were combined with those (n=4) from the study of Bascom et al. (1990) for a total of 11 (Y ‡, Table 9), the same differences between young and older humans were found as those reported when comparing only the young and old subjects from this study.

In this study, peripheral chemoreflex CO_2 sensitivity was calculated from the difference between the hypoxic and hyperoxic $P_{ET}CO_2$-$\dot{V}_E$ response curve slopes. The peripheral chemoreflex CO_2 sensitivity calculated in this manner may have included a central effect. Hypoxia and hypercapnia both act to substantially increase cerebral blood flow (Cohen et al., 1967; Kety and Schmidt, 1948) and may lead to differences between the local P_{CO2} of the central chemoreceptors and that of the arterial blood. To date, however, the importance of this difference in P_{CO2} to depress ventilation remains unclear. Van Beek et al. (1984) have suggested that, in the anaesthetized cat, the ventilatory depression during brain stem hypoxaemia may be due to a decrease in brain tissue CO_2 tension associated with the hypoxaemic increase in cerebral blood flow while Neubauer et al. (1985), using anesthetized peripherally chemodenervated cats, showed that mild hypoxia was associated with ventral medullary alkalosis and modest respiratory depression. Khamnei and Robbins (1990) however, have presented a model which provides evidence to suggest that in humans, the depression of ventilation by hypoxia may involve an alteration of peripheral chemoreflex sensitivity.

In light of the finding of an apparent decrease in peripheral chemoreflex CO_2 sensitivity with advancing age, it is important to examine other factors that could contribute to the lower ventilatory response to hypoxic hypercapnia. It is known that

several alterations in lung mechanics occur with advancing age. These include a loss in elastic recoil of the lungs, a decrease in lung compliance, early airway closure, an increase in residual volume, and a decrease in vital capacity and maximal expiratory airflow rates (Johnson et al., 1991b; Levitzky, 1984; Peterson et al., 1981). Previous studies have demonstrated however, that changes in lung mechanics or respiratory muscle strength in the elderly are not large enough to explain the observed reductions in the ventilatory responses to chemical perturbations similar to those imposed in this study (Peterson et al., 1981; Rubin et al., 1982).

Wahba (1983) proposed a physiological model for the control of breathing in which the relationship $\dot{V}_E = V_T/T_I \cdot T_I/T_T \cdot 60$ is used to separate the ventilatory response into a "drive" and "timing" component, respectively. This study and others (Peterson et al., 1981; Rubin et al., 1982) have failed to demonstrate any changes in the control of respiratory timing (T_I/T_T) in the elderly in response to chemical stimuli. Rather, the lower ventilatory response to hypoxic hypercapnia was a result of a significantly lower drive (V_T/T_I). Although the lower drive could be related to changes in the mechanical properties of the respiratory system, analysis of compartmental ventilation by magnetometry has demonstrated that the proportion of ventilation supplied by the rib cage compartment does not change with age (Peterson et al., 1981). A diminished neural output drive to the respiratory muscles, demonstrated by decreases in occlusion pressure responses which are unaffected by the compliance of the respiratory system (Peterson et al., 1981; Rubin et al., 1982; Wahba, 1986), seems more likely responsible for the differences in the ventilatory response to CO_2 with advancing age. Finding from this

study of a loss in peripheral chemoreflex CO_2 sensitivity with advancing age would in fact result in a diminished neural output drive.

Hypoxic hypercapnia was the highest ventilatory drive that was imposed on our subjects and the older group responded with ventilatory rates that corresponded to 52% of maximal exercise ventilation and to 35% of maximal voluntary ventilation. Since in this study the only age-related difference in ventilatory rates was found at the highest ventilatory drive, it would appear that the loss of chemoreceptor function in older humans may be dependent on the overall magnitude of the stimulus rather than the type of stimulus. This observation is supported by the work of Lahiri and DeLaney (1975) suggesting multiplicative interaction between hypoxia and hypercapnia at the carotid chemoreceptors; they provided evidence in cats showing that individual nerve fibres from the carotid chemoreceptors respond to both hypoxia and hypercapnia and that the sensory receptors in the carotid bodies may be activated through a mechanism common to both stimuli.

It is unlikely that any age-related differences in the ventilatory responses to hypoxic hypercapnia are related to the central or peripheral effects of hypoxia. Findings of previous studies in humans and in animals show that the effects of hypoxia do not interfere with the hypercapnic ventilatory responses (Georgopoulos et al., 1990; Van Beek et al., 1984). Van Beek and co-workers (1984) demonstrated in anesthesied cats, using the technique of separate perfusion of brain stem and carotid bodies, that although hypoxia depressed ventilation, it does so without affecting the central and peripheral sensitivities to CO_2. Georgopoulos et al. (1990) demonstrated in humans that 25

minutes of sustained moderate hypoxia did not effect the ventilatory responses to CO_2. In humans, sustained hypoxia most-likely involves some modulation of the peripheral chemoreflex sensitivity (Khamnei and Robbins, 1990). Differential effects of hypoxia on peripheral hypoxic and peripheral hypercapnic sensitivities also imply a peripheral chemoreceptor origin for the effects of sustained hypoxia (Bascom et al., 1990). Although some of the above studies are complicated by anesthesia and species differences, the results do support the argument that the functional capability of brain stem neurons is not impaired by moderate hypoxia.

This study cannot rule out the effects of age on the cerebral vascular response to hypoxia and hypercapnia in explaining our findings. Although this study did not measure cerebral blood flow responses, evidence has been reported which suggests possible age-associated alterations in the cerebral blood flow at rest. Kety (1956) examined the effects of age on cerebral blood flow at rest, using the nitrous oxide technique, and reported a gradual and continuous decline of 28% in cerebral blood flow from approximately 58 $ml \cdot 100g^{-1} \cdot min^{-1}$ at age 25 yrs to 42 $ml \cdot 100g^{-1} \cdot min^{-1}$ at age 95 yrs. Thus, the possibility exists that age may influence the cerebral vascular response to hypoxia and hypercapnia.

In summary, the human ventilatory response to chemical stimuli represents the overall response of the respiratory system and the output is dependent on both chemoreceptor function and mechanical properties of the respiratory system. In this study, a lower ventilatory response to hypoxic hypercapnia has been reported for older humans and appears to be a result, at least in part, of a loss in peripheral chemoreflex CO_2 sensitivity.

CHAPTER 4

THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN YOUNG AND OLDER HUMANS

4.1 Abstract

The purpose of this study was to examine the ventilatory response to CO_2 in young (YS; n=4) and older (OS; n=5) men. Square-wave steps of $P_{ET}CO_2$ were administered in euoxia ($P_{ET}O_2$=100 Torr), hyperoxia ($P_{ET}O_2$=500 Torr), and mild hypoxia ($P_{ET}O_2$=60 Torr). The ventilatory responses for each individual were ensemble-averaged and fitted to a two component exponential model which divided the ventilatory responses into a fast and a slow component, attributed to the peripheral and central chemoreflex loops respectively. The peripheral and central chemoreflex loops were described by a gain (g_p, g_c), time constant of the response (τ_p, τ_c), and a time delay (T_p, T_c). The young and older men showed similar characteristics for T_p and T_c, with T_p being 3 to 5 seconds shorter than T_c. No group differences were found in τ_p and τ_c. In hypoxia, the ventilatory responses of the old group were characterized by a significantly smaller g_c (OS, 1.27 ± 0.10 (SE) $\ell \cdot min^{-1} \cdot Torr^{-1}$; YS, 2.07 ± 0.23; p=0.0104), and a smaller g_p (OS, 0.91 ± 0.08; YS, 1.28 ± 0.14; p=0.0481). In hypoxia, τ_c was significantly shortened in YS but not in OS. Thus, this study demonstrated that in older men, the ventilatory responses to CO_2 in euoxia and hyperoxia are similar to younger men while in hypoxia, the ventilatory response is characterized by smaller gain terms and a longer response time.

4.2 Introduction

The ageing process is associated with declines in function of many physiological systems including the respiratory control system (Levitzky, 1984). Some studies have reported that ageing is associated with large declines in the ventilatory responses to hyperoxic hypercapnia or to eucapnic hypoxia (Altose et al. 1977; Brischetto et al. 1984; Kronenberg and Drage 1973; Peterson et al. 1981) but other investigators have reported little or no age-related changes in the ventilatory responses to hyperoxic hypercapnia (Kawakami et al. 1981; Rubin et al. 1982) or to acute isocapnic hypoxia (Ahmed et al., 1991; Smith et al., 1992b). Since the control of ventilation in humans depends largely on the chemical signals that stimulate the peripheral and central chemoreceptors, studies which have reported declines in the ventilatory responses to hypercapnia or to hypoxia in older humans have often inferred a decline in peripheral and central chemoreceptor function.

To date however, studies examining the age-related changes in the ventilatory response to hypercapnia have used either steady state (Kawakami et al., 1981) or rebreathing techniques in hyperoxic conditions (Altose et al., 1977; Brischetto et al., 1984; Hirshman et al., 1975; Kronengerg and Drage, 1973; Patrick and Howard, 1972; Peterson et al., 1981; Rubin et al., 1982), when the peripheral component of the CO_2 response is quite small (Dahan et al., 1990) or attenuated (Cunningham et al., 1986; Dejours, 1962). Thus, no information is presently available regarding peripheral chemoreflex CO_2 sensitivity in older humans. Furthermore, the temporal parameters of the peripheral and central chemoreceptors as well as the quantitative contribution of the

chemoreceptors to ventilation in older humans remain unknown.

A non-invasive dynamic end-tidal CO_2 forcing (DEF) technique, developed by Swanson and Bellville (1975) and later modified by Robbins et al. (1982), forces the alveolar P_{CO2} ($P_{ET}CO_2$) to follow specific time-related patterns against a constant $P_{ET}O_2$ and enables the determination of the temporal characteristics of the peripheral and central chemoreflex loops including the response gains, time constants, and transport delays. This study used the DEF technique to examine the dynamics of the respiratory control system in healthy older humans based on the same assumption as in young humans, that end-tidal changes in CO_2 and O_2 will be reflected by changes in arterial blood CO_2 and O_2 (Swanson and Bellville, 1975). A two component exponential model was utilized which incorporates fast and slow gains, transport delays, and time constants to examine the ventilatory response to CO_2. Previous studies have used similar DEF techniques in young humans and have incorporated two compartment models, including fast and slow components, to examine the ventilatory response to CO_2 (Bellville et al., 1979; Dahan et al., 1990; Swanson & Bellville, 1974 & 1975). Validation of the DEF technique comes from a study which compared the ventilatory response to CO_2 using the technique of DEF to that obtained using a technique of artificial brain stem perfusion (ABP) in anesthesized cats, and showed good agreement between the two techniques (DeGoede et al., 1985). Furthermore, the direct comparison of the DEF and ABP techniques showed that the slow ventilatory response to changes in end-tidal CO_2 can be equated with the central chemoreflex loop and the faster ventilatory response to the peripheral chemoreflex loop (DeGoede et al., 1985).

Thus the purpose of this study was to examine the ventilatory response to CO_2 in euoxia, hypoxia, and hyperoxia, at rest, in groups of young and older men. This is the first study to provide an estimation of the temporal parameters of the peripheral and central chemoreceptors in older humans.

4.3 METHODS

Subjects. Young (YS) and older (OS) men volunteered for this study. The older men were in their eighth decade of life and were physically active in a fitness club or had volunteered for previous studies; the younger subjects, in their third decade, were students or research assistants. The study requirements were fully explained (in written and verbal forms) to all participants, with each subject giving informed consent (Appendix III) prior to participating in the study. The research was approved by the University's Ethics Committee on Human Research.

Testing. Subjects were requested not to eat or drink caffeine-containing beverages within four hours prior to their scheduled testing sessions in the laboratory. Subjects reported to the laboratory, at the same time of day on nine occasions, each lasting 2-3 hours. On the first session each participant was given a medical examination which included a medical history, 12-lead electrocardiogram (ECG), blood pressure, height, weight, five skinfolds thicknesses, pulmonary function, and a treadmill test to determine maximal oxygen uptake ($\dot{V}O_2max$). None of the participants had a history of cardiovascular or respiratory diseases. On the second visit, subjects were acquainted with the breathing apparatus. During a thirty minute test, subjects sat quietly and breathed

combinations of hypoxic and hypercapnic gas mixtures, administered in a step-wise fashion; a 12 lead ECG and blood pressure measurements were taken during each of the different steps. The data from these tests were not used in the determination of the temporal parameters of the ventilatory responses to CO_2. On each of the other seven visits, two or three tests were performed, each lasting 30-45 minutes. These tests served to establish the ventilatory response to CO_2 in euoxia, hyperoxia, and hypoxia.

Calibration and equipment for exercise testing and spirometry. Calibration procedures and equipment requirements were as described in Chapter Three (pp. 65).

Pulmonary function tests. The procedures and measurements used to assess lung function were as described in Chapter Three (pp. 66).

Maximal treadmill "ramp" test. The procedures for carrying out the maximal effort treadmill test and subsequent determination of $\dot{V}O_2max$ were as described in Chapter Three (pp. 67).

Apparatus and technique for dynamic-end-tidal forcings at rest. The technique used for accurate control of the end-tidal gases was as described in Chapter Three (pp. 68).

Determination of the ventilatory responses to CO_2. Steps in $P_{ET}CO_2$ with constant $P_{ET}O_2$ were performed in euoxia (Protocol I; $P_{ET}O_2$ = 100 Torr), hyperoxia (Protocol II; $P_{ET}O_2$ = 500 Torr), and mild hypoxia (Protocol III; $P_{ET}O_2$ = 60 Torr), see Figure 11. For each protocol, six repetitions were obtained. For protocols I and II, three repetitions were obtained during each session while for protocol III only two repetitions were obtained during each session to allow for complete recovery of hypoxic ventilatory

EXPERIMENTAL PROTOCOL

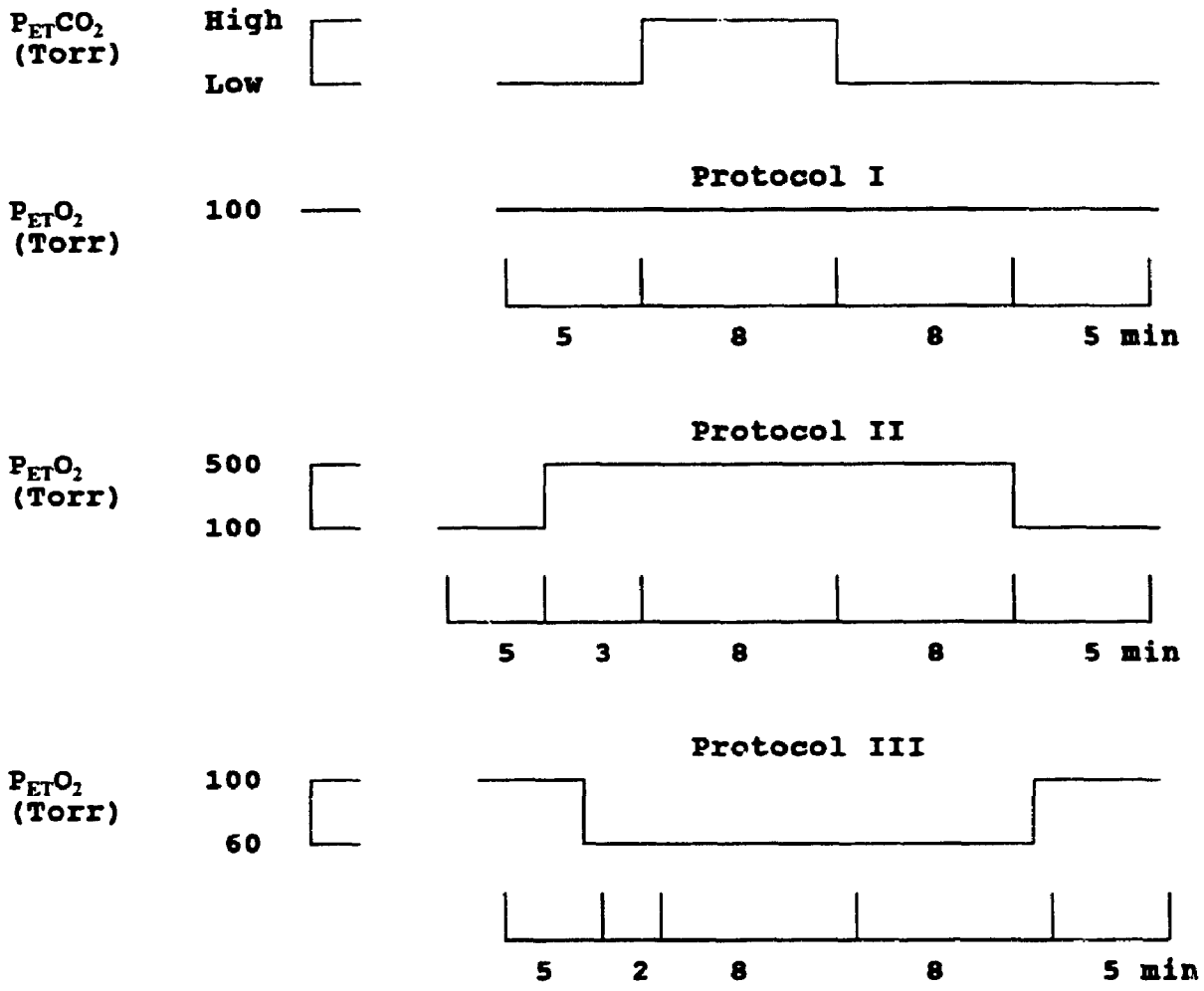


Figure 11. Experimental protocols describing the time related changes in gas forcing functions. Steps in $P_{ET}CO_2$ with constant $P_{ET}O_2$ were performed in euoxia (Protocol I; $P_{ET}O_2$ = 100 Torr), hyperoxia (Protocol II; $P_{ET}O_2$ = 500 Torr), and mild hypoxia (Protocol III; $P_{ET}O_2$ = 60 Torr). $P_{ET}CO_2$ was held near eucapnia (1-2 Torr above resting $P_{ET}CO_2$) for several minutes before the $P_{ET}CO_2$ was elevated in one step within one or two breaths to 7-8 Torr above resting $P_{ET}CO_2$ and maintained constant for 8 minutes and then returned in one step to the eucapnic value for a further 8 minutes. In protocol II, $P_{ET}O_2$ was elevated 3 minutes prior to the step increase in $P_{ET}CO_2$; in protocol III, $P_{ET}O_2$ was lowered 2 minutes prior to the step increase in $P_{ET}CO_2$.

depression that may have arisen from the previous hypoxic exposure (Easton et al., 1988). For each session, the assigned protocol was randomly selected.

After arrival at the laboratory, the subjects rested for 20-30 minutes before the experiments. Each experiment started with an accommodation period for the mouthpiece lasting 10-15 minutes after which the $P_{ET}CO_2$ was elevated slightly (1-2 Torr) above resting $P_{ET}CO_2$ and maintained at that level for five minutes. The $P_{ET}CO_2$ was then elevated in one step within one or two breaths to 7-8 Torr above resting $P_{ET}CO_2$ and maintained constant for eight minutes and then returned in one step to the original value and maintained constant for a further eight minutes. The $P_{ET}O_2$ was held constant at the euoxic, hyperoxic, or hypoxic value throughout. During protocols I and II, the subjects rested for 20-30 minutes between the repetitions while in Protocol III subjects rested for 60 minutes between each repetition. The technique of dynamic end-tidal forcings has been described in detail by Swanson & Bellville (1975) and Robbins et al. (1982).

Data analysis. For each individual, the breath-by-breath data for $\dot{V}_E$, $P_{ET}CO_2$, and $P_{ET}O_2$ from each test were interpolated over one second intervals and all tests for a given protocol were ensemble-averaged to increase the signal to noise ratio. The analyses of the ventilatory responses were performed utilizing a two-component exponential model which describes the temporal parameters of the central and peripheral chemoreflex loops:

$$\dot{V}_E(t) = \dot{V}_b + \dot{V}_c(t) + \dot{V}_p(t) + \text{Drift}(t)$$

where,

$$\dot{V}_c(t) = G_c \cdot (1 - e^{-(t-Tc)/\tau c})$$

and,

$$\dot{V}_p(t) = G_p \cdot (1 - e^{-(t-Tp)/\tau p})$$

The baseline ventilation is $\dot{V}_b$ and $\dot{V}_E(t)$ is the time-dependent variation in $\dot{V}_E$. $\dot{V}_c(t)$ and $\dot{V}_p(t)$ are the outputs of the central and peripheral chemoreflex loops. The parameters G_c, τ_c, and T_c are the gain ($\ell \cdot min^{-1}$), time constant of the response (s), and time delay (s) of the central chemoreflex loop, respectively, while the parameters G_p, τ_p, and T_p are the gain ($\ell \cdot min^{-1}$), time constant of the response (s), and time delay (s) of the peripheral chemoreflex loop, respectively. The apnoeic threshold B was calculated as the extrapolated $P_{ET}CO_2$ of the steady-state $\dot{V}_E$-$P_{ET}CO_2$ response curve at zero $\dot{V}_E$ by fitting the data to the Lloyd equation (Lloyd et al., 1958). Central CO_2 sensitivity (g_c) was calculated as $G_c/\Delta P_{ET}CO_2$ (difference between the steady-state hypercapnic and eucapnic $P_{ET}CO_2$) and peripheral CO_2 sensitivity (g_p) was calculated as $G_p/\Delta P_{ET}CO_2$. A drift term [Drift(t)] was also included in the model. Thus, the total ventilatory response is made up of the sum of the contributions of the central and peripheral chemoreflex loops and the drift term.

To obtain optimal parameter estimation, a computerized optimization routine was applied. All combinations between 1 and 25 s, with increments of 0.1 s and with the constraint $T_c \geq T_p$ were used. If the residual sum of squares was minimal, with T_c equal to 25 s, the range of possible time delays was extended until a minimum in the residual sum of squares was found. The minimum time delays were chosen to be 1 s and τ_p was constrained to be at least 0.3 s based on previous studies (Bellville et al., 1979; Dahan et al., 1990).

The ventilatory responses to the step decreases in $P_{ET}CO_2$ were fitted separately, using a decaying exponential function which allowed for the determination of the central

time constant for the off response (τ_{off}).

Group analyses were performed using one-way analysis of variance and when indicated Student Newman-Keul post-hoc analysis was applied. Within-group comparisons were made using Student Paired T-tests. Between-group analyses were also performed using the Mann-Whitney *U* test, a nonparametric test for independent samples used to evaluate populations that are not normally distributed (Witte, 1989). Mean data for the respiratory variables ($\dot{V}_E$, $\ell \cdot min^{-1}$, $P_{ET}CO_2$ and $P_{ET}O_2$, Torr; V_T, ℓ; and f_b, breaths$\cdot$min^{-1}), arterial oxygen saturation (%), and heart rate (beats$\cdot$min^{-1}) were calculated for the last 30 s before the step increase in $P_{ET}CO_2$ (baseline), the last 30 s before the step decrease in $P_{ET}CO_2$ (peak), and between 7.5 and 8.0 minutes after the step decrease in $P_{ET}CO_2$ (recovery). The probability level denoting statistical significance was $p \leq 0.05$.

4.4 RESULTS

Subjects. Four young (YS) and five old (OS) subjects participated in the study. All subjects were non-smokers and free of overt symptoms of cardiovascular and cardiorespiratory diseases. The physical characteristics of the subjects are listed in Table 10.

Pulmonary function tests. Results of the pulmonary function tests are shown in Table 10 and were at or above the normal age-predicted values, and demonstrated little or no differences as a percent of predicted between the young and older groups. The results for the older men showed typical age-related declines in FEV_1 and FVC. Maximal Voluntary Ventilation (MVV) averaged 64% of the value reached by YS.

Table 10. Physical characteristics of subjects

Variables	YOUNG (n=4)	OLD (n=5)
Age (yrs)	27.0 ± 2.2	74.2 ± 1.1 *
Height (cm)	177.3 ± 2.4	178.4 ± 2.2
Mass (kg)	82.0 ± 2.8	82.0 ± 4.7
BMI ($kg \cdot m^2$)	26.1 ± 0.8	25.8 ± 2.1
BSA (m^2)	3.15 ± 0.08	3.19 ± 0.08
FEV_1, (ℓ)	4.56 ± 0.31	2.92 ± 0.17 *
FEV_1, (% pred) +	101.4 ± 2.7	91.7 ± 4.5
FVC, (ℓ)	5.79 ± 0.33	4.17 ± 0.21 *
FVC, (% pred) +	107.6 ± 1.6	103.1 ± 4.1
FEV_1/FVC (%)	78.7 ± 1.2	71.6 ± 3.3
$\dot{V}max_{50}$,($\ell \cdot sec^{-1}$)	6.01 ± 0.24	3.45 ± 0.50 *
$\dot{V}max_{50}$,(% pred) +	103.1 ± 4.2	87.1 ± 12.0
PEFR ($\ell \cdot sec^{-1}$)	605.4 ± 56.9	498.3 ± 43.5
MVV ($\ell \cdot min^{-1}$)	194.0 ± 17.7	124.1 ± 12.4 *
$\dot{V}O_2max$,($\ell \cdot min^{-1}$)	4.40 ± 0.25	2.40 ± 0.21 *
$\dot{V}O_2max$,($ml \cdot kg^{-1} \cdot min^{-1}$)	52.2 ± 3.5	30.5 ± 3.9 *
$\dot{V}O_2max$,(% pred) ++	113.6 ± 8.9	161.2 ± 19.1 *
$\dot{V}_Emax$, ($\ell \cdot min^{-1}$)	164.1 ± 14.5	93.5 ± 9.8 *
$\dot{V}_Emax$/MVV (%)	84.7 ± 2.0	77.7 ± 9.6
$\dot{V}CO_2max$ ($\ell \cdot min^{-1}$)	5.41 ± 0.44	2.90 ± 0.69 *
RERmax	1.23 ± 0.04	1.20 ± 0.05
HRmax,(beats $\cdot min^{-1}$)	196.0 ± 9.1	153.6 ± 3.8 *
HRmax,(% pred) ++	102.2 ± 5.7	105.6 ± 3.0

Values are means ± SEM

* significantly different from young group at $p < 0.05$

Definition of abbreviations: $\dot{V}max_{50}$ = maximal flow after exhalation of 50% of FVC; MVV = maximal voluntary ventilation.

\+ Normal predicted values for FVC and FEV_1 are based on age and height (from Knudson et al. 1983)

++ Normal predicted values for $\dot{V}O_2max$ (based on age and weight) and for HRmax from Jones (1988)

Responses to graded exercise. As shown in Table 10, OS had a mean $\dot{V}O_2max$ of 161% of the age-predicted maximum for normal older people (Jones, 1988). OS reached $\dot{V}O_2max$ at a slightly higher heart rate than aged-predicted maximum. YS had a $\dot{V}O_2max$ that was not significantly different from age-predicted maximum with a $\dot{V}O_2max$ of 113.6% of predicted (Jones, 1988). The ratio of ventilation at maximal exercise($\dot{V}_Emax$) to MVV (i.e. $\dot{V}_Emax/MVV$) was similar for both groups (YS=84.7; OS=77.7).

$\dot{V}_E$ responses to hypercapnia. Typical end-tidal PCO_2 steps and corresponding ventilatory responses with model fits in euoxia, hypoxia, and hyperoxia are shown for a young subject (ID# 1643; Figure 12) and for an older subject (ID# 308; Figure 13). The remainder of the individual model estimated parameters are listed in Appendices IV-VI while the individual ventilatory responses, model fits, and residuals are shown in Appendix VII. In Figures 12 and 13, minor imperfections in the $P_{ET}CO_2$ clamps can be noted at the on- and off- steps of $P_{ET}CO_2$. For all protocols, after a period of steady state ventilation the $P_{ET}CO_2$ was increased by 7-8 Torr above resting $P_{ET}CO_2$ by elevating the inspired CO_2 concentrations. After 8 min of hypercapnia the $P_{ET}CO_2$ was returned to the starting level. During the experiments the inspired O_2 was regulated to maintain a constant $P_{ET}O_2$ despite the changes in $\dot{V}_E$. The mean ventilatory responses (means $\pm$ SEM) in euoxia, hypoxia, and hyperoxia are shown for young and older groups in Figure 14. For each group, the mean ventilatory responses were interpolated over 15s intervals and represent an ensemble-average of the mean ventilatory responses of each subject, whose mean response is an ensemble-average of 6 repetitions.

Figure 12. Ventilatory responses in euoxia ($P_{ET}O_2$=100 Torr), hypoxia ($P_{ET}O_2$=60 Torr), and hyperoxia ($P_{ET}O_2$=500 Torr) and model fits for young subject (ID 1643=33 yrs). The top panels show the $P_{ET}CO_2$ stimulus. The bottom panels show the ventilatory response. The curves through the data are the model fits, $\dot{V}_E(t)$; it is the sum of the slow, $\dot{V}_c(t)$, and the fast, $\dot{V}_p(t)$, components, and a drift term. The estimated parameter values are: *Euoxia*; B 33.6 Torr, G_c 2.27 $\ell \cdot min^{-1} \cdot Torr^{-1}$, G_p 1.25 $\ell \cdot min^{-1} \cdot Torr^{-1}$, τ_c 182.7s, τ_p 14.5 s, T_c 1.9 s, T_p 1.7 s, Drift 5.0 $ml \cdot min^{-2}$, and sum of squares 207.1. *Hypoxia*; B 32.1 Torr, G_c 2.48 $\ell \cdot min^{-1} \cdot Torr^{-1}$, G_p 1.42 $\ell \cdot min^{-1} \cdot Torr^{-1}$, τ_c 52.6 s, τ_p 9.4 s, T_c 1.7 s, T_p 1.6 s, Drift 9.0 $ml \cdot min^{-2}$, and sum of squares 321.1. *Hyperoxia*; B 31.2 Torr, G_c 2.16 $\ell \cdot min^{-1} \cdot Torr^{-1}$, G_p 0.34 $\ell \cdot min^{-1} \cdot Torr^{-1}$, τ_c 129.3 s, τ_p 46.3 s, T_c 7.5 s, T_p 1.1 s, Drift 9.0 $ml \cdot min^{-2}$, and sum of squares 423.8.

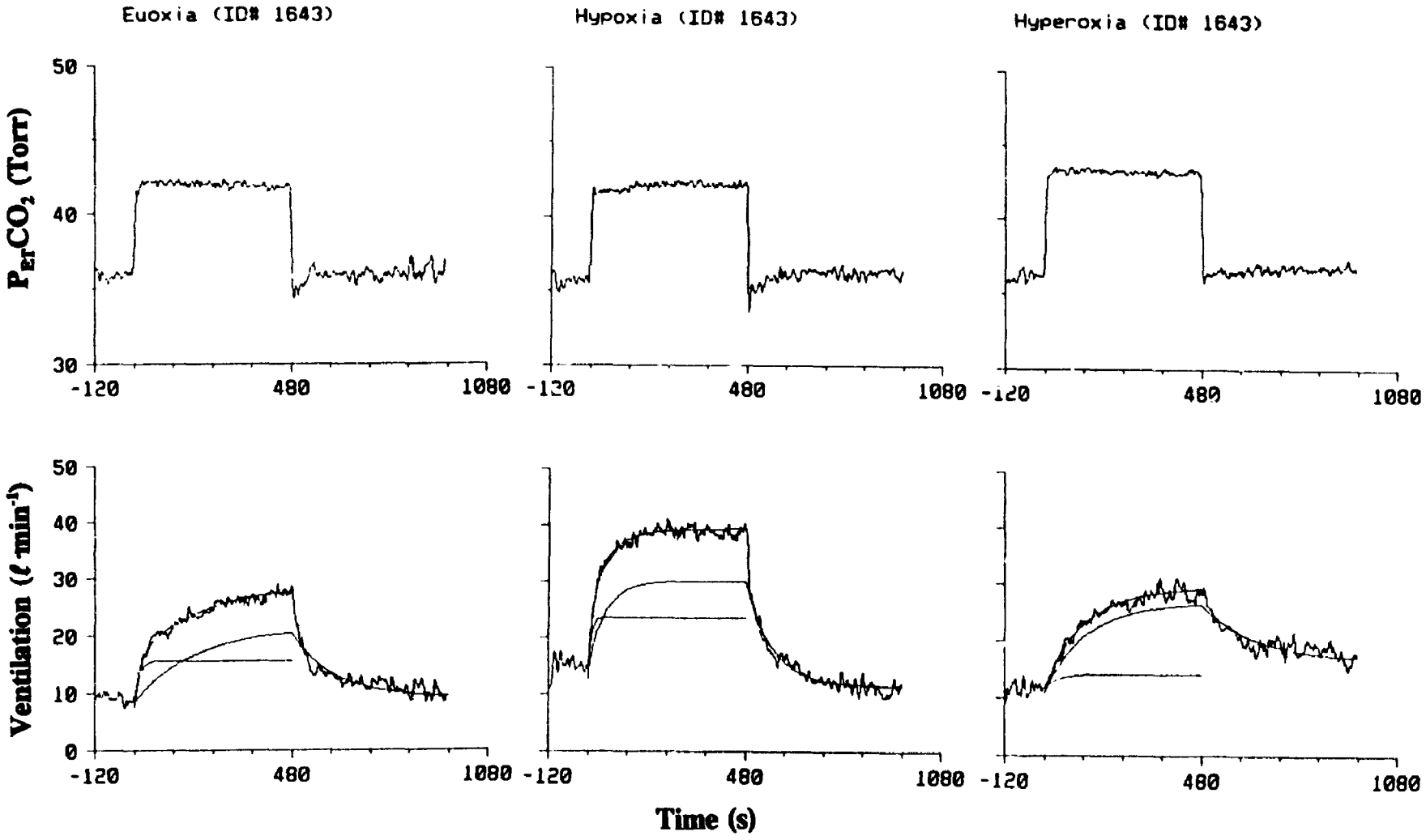

Euoxia (ID# 1643)
Hypoxia (ID# 1643)
Hyperoxia (ID# 1643)
$P_{ET}CO_2$ (Torr)
50
40
30
-120
480
1080
Ventilation ($\ell \cdot min^{-1}$)
50
40
30
20
10
0
Time (s)

Figure 13. Ventilatory responses in euoxia ($P_{ET}O_2$=100 Torr), hypoxia ($P_{ET}O_2$=60 Torr), and hyperoxia ($P_{ET}O_2$=500 Torr) and model fits for old subject (ID 308=77 yrs). The top panels show the $P_{ET}CO_2$ stimulus. The bottom panels show the ventilatory response. The curves through the data are the model fits, $\dot{V}_E(t)$; it is the sum of the slow, $\dot{V}_c(t)$, and the fast, $\dot{V}_p(t)$, components, and a drift term. The estimated parameter values are: *Euoxia*; B 30.2 Torr, G_c 1.21 $\ell \cdot min^{-1} \cdot Torr^{-1}$, G_p 0.74 $\ell \cdot min^{-1} \cdot Torr^{-1}$, τ_c 150.4s, τ_p 9.5 s, T_c 2.1 s, T_p 1.9 s, Drift 3.0 $ml \cdot min^{-2}$, and sum of squares 171.0. *Hypoxia*; B 28.9 Torr, G_c 1.14 $\ell \cdot min^{-1} \cdot Torr^{-1}$, G_p 0.93 $\ell \cdot min^{-1} \cdot Torr^{-1}$, τ_c 134.2 s, τ_p 9.4 s, T_c 3.3 s, T_p 3.3 s, Drift 4.0 $ml \cdot min^{-2}$, and sum of squares 264.8. *Hyperoxia*; B 27.2 Torr, G_c 1.06 $\ell \cdot min^{-1} \cdot Torr^{-1}$, G_p 0.33 $\ell \cdot min^{-1} \cdot Torr^{-1}$, τ_c 178.0 s, τ_p 15.6 s, T_c 10.4 s, T_p 9.6 s, Drift 7.0 $ml \cdot min^{-2}$, and sum of squares 148.4.

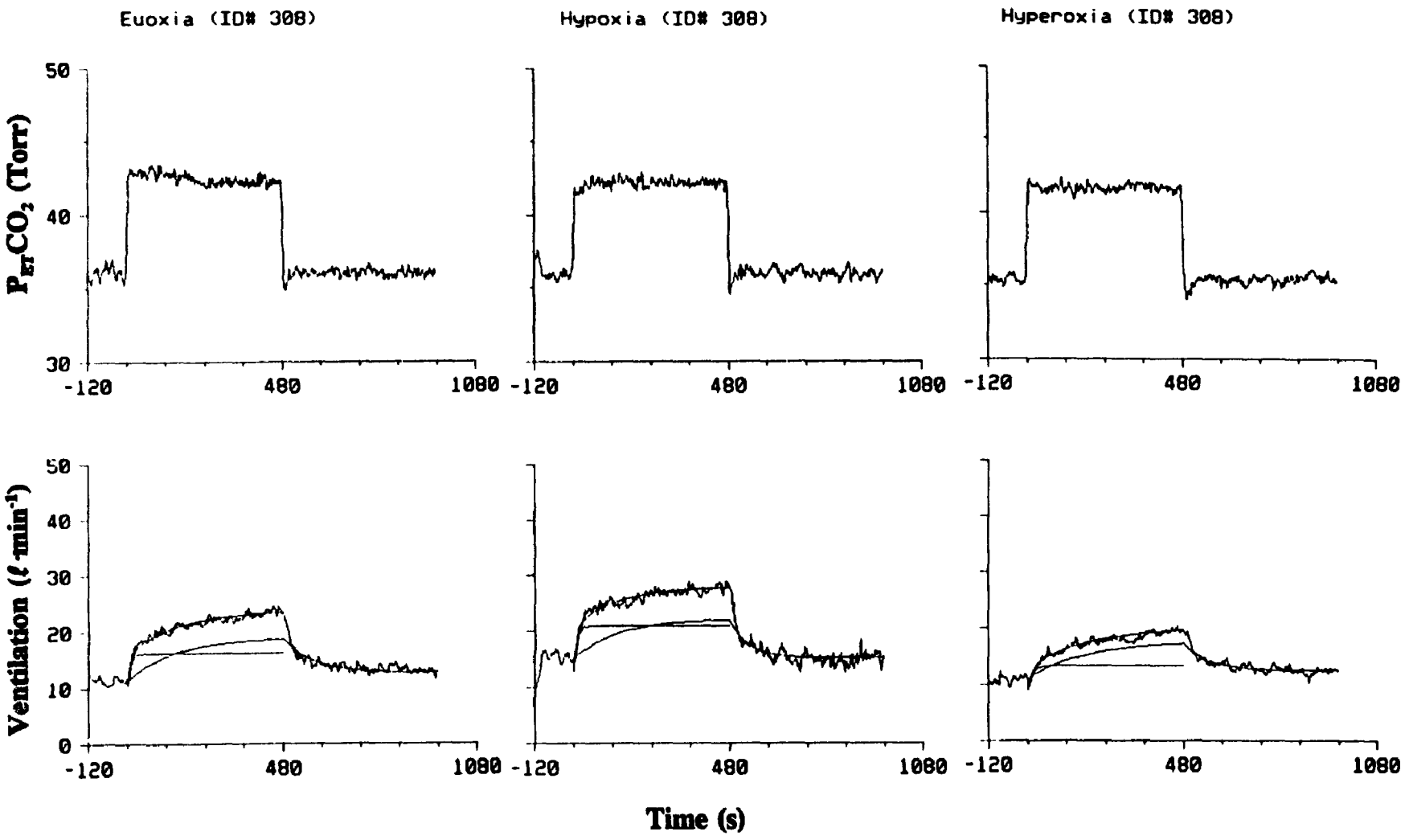
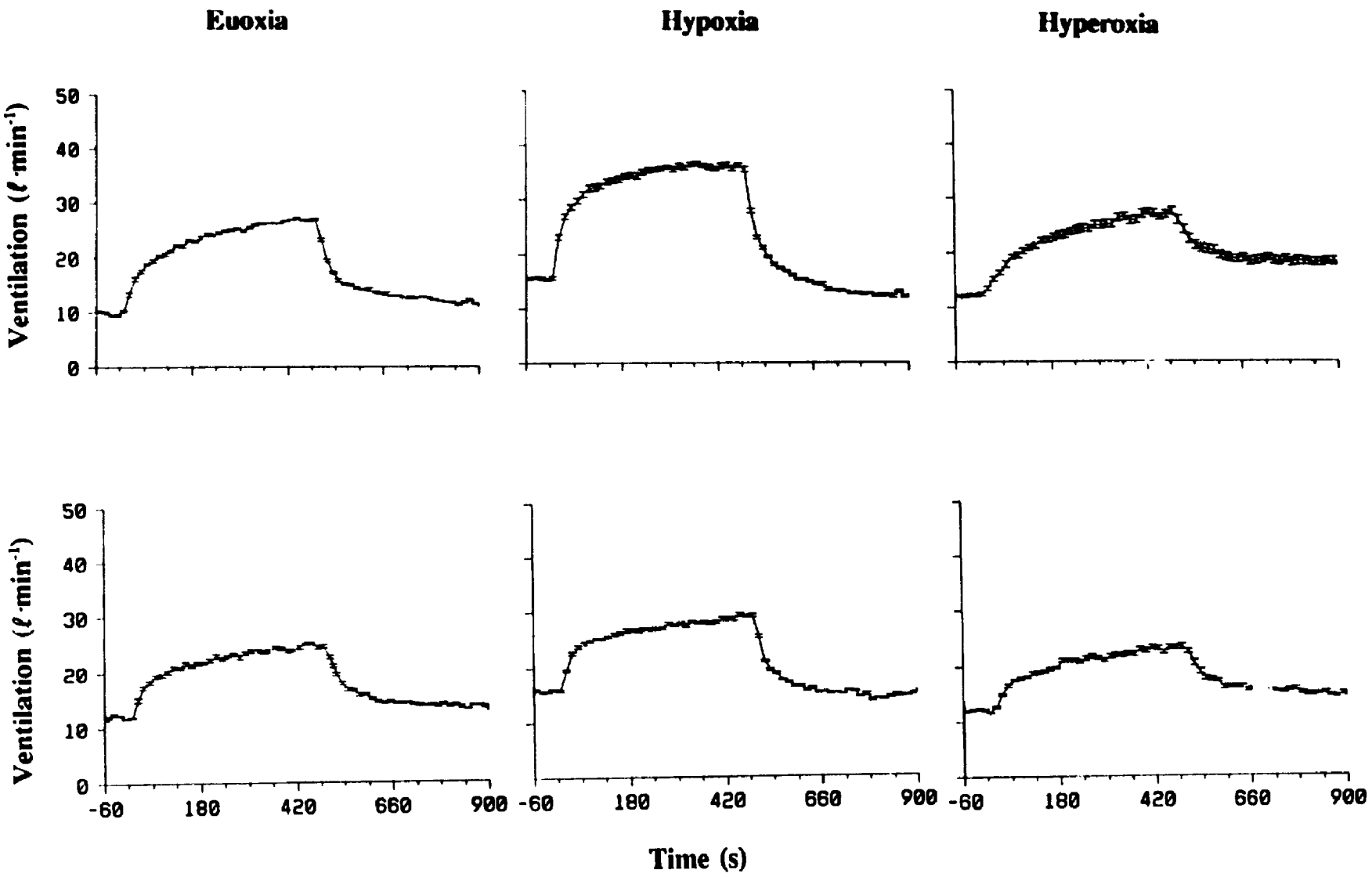

Euoxia (ID# 308)
Hypoxia (ID# 308)
Hyperoxia (ID# 308)
$P_{ET}CO_2$ (Torr)
50
40
30
-120
480
1080
Ventilation ($\ell \cdot min^{-1}$)
50
40
30
20
10
0
Time (s)

Figure 14. Ventilatory responses (mean ± SEM) in euoxia ($P_{ET}O_2$=100 Torr), hypoxia ($P_{ET}O_2$=60 Torr), and hyperoxia ($P_{ET}O_2$=500 Torr) for young (Top panels) and old (Bottom Panels) groups. For each group, the mean ventilatory responses were interpolated over 15s intervals and represent an ensemble-average of the mean ventilatory responses of 4 (YS) and 5 (OS) subjects. Each subject's mean response was an ensemble-average of 6 repetitions.


Euoxia
Hypoxia
Hyperoxia
Ventilation (ℓ·min⁻¹)
50
40
30
20
10
0
-60
180
420
660
900
Time (s)

Euoxia. There were no group differences in τ_c, τ_p, T_c, and T_p. g_p was 21% (NS) lower in OS while g_c was significantly lower by 28% (Table 11). The ratio of g_p to the total CO_2 response was 0.33 and 0.35 for YS and OS respectively. For both age groups, the ventilatory response characteristics in euoxia showed a rapid response (τ_p) followed by a slower response (τ_c). The CO_2 threshold (B) was 19% lower in OS compared to YS. There was no difference in the amplitude of the $P_{ET}CO_2$ step (OS, eucapnia 34.6 ± 1.7 Torr, hypercapnia 40.5 ± 1.7; YS, 39.3 ± 1.1, 45.4 ± 1.2).

Hypoxia. Young group. The magnitude and speed of the ventilatory on-response were increased when compared to the euoxic response. g_p increased by 21% (NS) compared to g_p estimated in euoxia. This resulted in a significant increase in the ratio of the peripheral to total CO_2 sensitivity of 0.38 in hypoxia from 0.33 in euoxia (Table 11). There were no significant differences in g_c, T_p, T_c between the on-steps in hypoxia and euoxia. In hypoxia, τ_c was significantly shorter by 36% compared to the euoxic value (hypoxia, 119.7 ± 40.0s; euoxia, 187.9 ± 25.5). The CO_2 threshold B was 5% lower than in euoxia. The ventilatory response characteristics showed a rapid response (τ_p) followed by a slower response (τ_c) (Table 11).

Old group. The magnitude of the ventilatory on-response was increased compared to euoxia but the speed of the response remained unchanged. The ventilatory response characteristics, however, also indicated a rapid response (τ_p) followed by a slower response (τ_c) (Table 11). Unlike the results found for YS in hypoxia, τ_c was similar to that for euoxia (euoxia, 160.3 s; hypoxia, 174.5 s). In hypoxia, τ_c was 46% (NS) longer for OS compared to YS (OS, 174.5 ± 57.5 s; YS, 119.7 ± 40.0). The gains in hypoxia

Table 11. Values for the estimated temporal parameters of the ventilatory response to CO_2 in euoxia, mild hypoxia, and hyperoxia (B, the CO_2 threshold in Torr; g_c and g_p, the central and peripheral gain terms in $\ell \cdot min^{-1} \cdot Torr^{-1}$; τ_c and τ_{off}, the central time constants of the 'on' and 'off' response in s; τ_p, the peripheral time constant in s; T_c and T_p, the time delays of the central and peripheral chemoreflex loops in s; D, drift term in $ml \cdot min^{-2}$).

	B	g_c	g_p	$g_p/(g_p+g_c)$	τ_c	τ_{off}	τ_p	T_c	T_p	D
Euoxia										
Young	36.0	2.09	1.01	0.33	187.9	116.9	15.2	6.3	2.4	8.0
	(0.9)	(0.14)	(0.08)	(0.02)	(25.5)	(14.4)	(4.7)	(2.6)	(1.1)	(1.0)
Old	29.1*	1.51*	0.80	0.35	160.3	103.2	15.1	6.3	3.8	7.0
	(1.7)	(0.13)	(0.07)	(0.02)	(16.0)	(16.7)	(4.3)	(2.3)	(1.1)	(1.0)
p value	.0137	.0202	.0957	.4552	.3711	.5671	.9917	.9944	.4257	.5383
Mild Hypoxia										
Young	34.3†	2.07	1.28	0.38†	119.7†	102.1	10.3	6.3	2.8	8.0
	(1.2)	(0.23)	(0.14)	(0.01)	(48.0)	(16.8)	(1.5)	(2.7)	(0.8)	(1.0)
Old	27.3*	1.27*	0.91	0.42†	174.5	82.3	11.9	7.9	3.2	6.0
	(1.9)	(0.10)	(0.08)	(0.02)	(57.5)	(19.0)	(0.9)	(2.4)	(1.1)	(1.0)
p value	.0203	.0104	.0481*	.1910	.5036	.4713	.3763	.6722	.7464	.4247
Hyperoxia										
Young	33.4†	2.04	0.42†	0.17†	208.5	121.8	29.7	9.4	6.3	7.0
	(1.0)	(0.13)	(0.06)	(0.02)	(26.7)	(24.1)	(8.3)	(2.5)	(3.1)	(1.0)
Old	28.3*	1.59	0.39†	0.20†	171.1	140.7	19.8	9.4	6.1	6.0
	(1.8)	(0.17)	(0.09)	(0.04)	(40.4)	(41.5)	(3.1)	(1.8)	(1.1)	(2.0)
p value	.0537	.0834	.8053	.6170	.4907	.7240	.2620	.9946	.9542	.5337

Values are means ± (SEM); * significantly different from young at $p \leq 0.05$; † significantly different from euoxia at $p \leq 0.05$

were similar to those estimated from the euoxic on-steps. The ratio of the peripheral to total CO_2 sensitivity increased significantly by 20% to 0.42 in hypoxia from 0.35 in euoxia. Compared to YS, g_c was significantly lower by 39% while g_p was also lower by 29%. T_p and T_c were similar to the euoxic values. The CO_2 threshold (B) for OS was significantly lower by 20% compared to YS. In OS, there were no differences in B between euoxic and hypoxic conditions. There was no difference in the amplitude of the $P_{ET}CO_2$ step (OS, eucapnia 34.8 ± 1.7 Torr, hypercapnia 41.1 ± 1.8; YS, 39.5 ± 1.2, 46.0 ± 1.4).

Hyperoxia. Young group. The ratio of g_p to the total CO_2 sensitivity averaged 0.17 and this was significantly lower by 52% from the ratio in euoxia. The CO_2 threshold B significantly decreased by 7% in hyperoxia. Compared to values in euoxia, there was no change in g_c but g_p decreased significantly by 58% in hyperoxia (Table 11). There were no differences in τ_p and τ_c between hyperoxia and euoxia. The peripheral and central time delays were slightly longer than in euoxia but the differences were not significant.

Old group. The ratio of g_p to the total CO_2 sensitivity averaged 0.20 and this was significantly lower by 53% from its ratio in euoxia. The CO_2 threshold B was unchanged from euoxia. There was no change in g_c while g_p decreased significantly by 51% in hyperoxia (Table 11). There was no difference in τ_p and τ_c between hyperoxia and euoxia. The peripheral and central time delays were slightly longer than in euoxia but the differences were not significant. Compared to YS the CO_2 threshold B for OS was significantly lower by 15% (Table 11). There was no difference in the amplitude of the

$P_{ET}CO_2$ step (OS, eucapnia 34.9 ± 1.6 Torr; hypercapnia 41.3 ± 1.7; YS, 38.9 ± 0.9, 45.5 ± 0.8).

The sum of squares of the residuals (Appendices IV-VI) and the residuals (Appendix VII) for the individual model fits are included to indicate the goodness of fit of the model to the data in euoxia, hypoxia, and hyperoxia.

Group analyses performed by using either a one-way analysis of variance or by using the Mann-Whitney nonparametric test for independent samples showed the same significant differences between the young and the old groups.

4.5 DISCUSSION

This study examined the ventilatory response to inhaled CO_2, at rest, in groups of young and older men. The ventilatory responses to step increases in alveolar P_{CO2} ($P_{ET}CO_2$) in backgrounds of euoxia, mild hypoxia, and hyperoxia were fitted to a two component exponential model which included gain terms, time constants of the responses, and time delays. The fast and slow components of the ventilatory responses were attributed to the peripheral and central chemoreflex loops respectively.

The young and old men in this study showed similar characteristics for the peripheral and central time delays and for the peripheral and central time constants. The central gain in euoxia and hypoxia as well as the peripheral gain in hypoxia were significantly smaller in the old group. Thus, the findings from this study suggest significant age-related differences in the gains of the chemoreflex loops and provide information regarding possible mechanisms responsible for these differences.

The peripheral and central time delays reported in this study for YS and OS are similar to those reported by others (Bellville et al., 1979; Dahan et al., 1990). The peripheral time delays were 3 to 5 seconds shorter than the central time delays and most likely reflect the differences between the peripheral and central lung-chemoreceptor transit times (Dahan et al., 1990). It is of interest to note that the peripheral time delay and time constant reported for YS, in response to the step increase in $P_{ET}CO_2$ in hypoxia, were similar to those of Paterson et al. (in press), who administered a step decrease in $P_{ET}O_2$ (from 73 to 48 Torr) in hypercapnia and estimated the parameters from a first order model.

The magnitude of the step increase in $P_{ET}CO_2$ was chosen to be 7-8 Torr above resting $P_{ET}CO_2$ values for several reasons which are described in detail in chapter three (pp. 83). Briefly, this level was chosen to minimize the drift in $\dot{V}_E$ often found with higher levels of hypercapnia (Easton and Anthonisen, 1988; Reynolds et al., 1972), to avoid imposing high ventilation levels at rest which are frequently associated with discomfort (Berkenbosch et al., 1989), and to avoid imposing levels of ventilation that could have resulted in expiratory flow limitations in the older men (Johnson et al., 1991b). Furthermore, additional efforts were taken to minimize other possible cortical influences on breathing. This was achieved by familiarizing the subjects with the breathing apparatus before the start of the experiments, and by encouraging them to read and listen to non-rhythmical music during the actual experiments.

The ageing process is associated with a number of structural and functional alterations to the respiratory system, any of which may influence the factors within the

chemoreflex loops that contribute to the determination of the temporal parameters of the chemoreceptors. These factors have been highlighted previously by others (Swanson and Bellville, 1975; Ward and Bellville, 1983) and include (1) delivery of inspired gas to the alveoli, (2) alveolar-capillary gas exchange of CO_2, (3) circulation time from the pulmonary gas exchange area to the peripheral and central chemoreceptors, (4) response kinetics of the peripheral and central chemoreceptors, (5) relative contribution of the peripheral and central chemoreceptors to overall ventilatory drive, (6) central processing, (7) neural pathways involved in respiratory control, and (8) lung and chest wall dynamics. Furthermore, additional factors that play a role in determining the CO_2 exchange in the area of the central chemoreceptors include local brain tissue blood flow, local brain tissue volume, and local brain tissue CO_2 exchange with cerebral spinal fluid (Swanson and Bellville, 1975).

The elderly subjects in this study were very healthy and in fine physical condition. They had excellent lung function and pulmonary gas exchange as indicated by results for FEV_1, FVC, MVV, $\dot{V}max_{50}$, and PEFR. Furthermore, they were very fit ($\dot{V}O_2max$ = 161 percent of predicted) and were free of any overt symptoms of cardiovascular and respiratory diseases. Although we did not measure other indices of gas exchange that have been shown to decline with advancing age such as diffusion capacity of carbon monoxide in the lung (Horvath and Borgia, 1984; Thurlebeck, 1967), our results show minimal declines in lung function and $\dot{V}O_2max$ and suggest that other usual age-related decreases in lung function may have also been minimal. Furthermore, although age-related declines in FEV_1, FVC, and MVV were observed, this did not appear to

influence the results of the ventilatory responses to hypercapnia because the ratio of the peak $\dot{V}_E$ elicited by the hypercapnic steps to MVV were low in both groups (OS, 0.24; YS, 0.18).

Previous studies examining age-related changes in lung mechanics and respiratory muscle strength have demonstrated that it does not appear that age-related changes in mechanics and strength are large enough to explain reductions in the ventilatory responses to chemical perturbations similar to those imposed in this study (Peterson et al., 1981; Rubin et al., 1982). Peterson et al. (1981) recognized that the diminished ventilatory drive to hypercapnia in aged humans could be associated with the age-related alterations in the mechanical properties of the respiratory system such as a stiffening of the chest wall (Mittman et al., 1965) or the loss of elastic recoil of the lungs (Frank et al., 1957; Islam, 1980; Turner et al., 1968). Thus, they studied the ventilatory responses and the mouth occlusion pressure responses to CO_2 in aged men (65-80 years) to determine if the decreases in the responses were related to changes in mechanical properties of the lungs or to changes in the neuromuscular output to the respiratory muscles. Results showed parallel decreases in the ventilatory responses to CO_2 (47%) and in the mouth occlusion pressure (P_{100}) response slopes (49%) to hypercapnia in the elderly compared to young controls. Furthermore, no differences were found in respiratory timing (T_I/T_T) or changes in chest wall compliance, reflected as a change in the proportion of $\dot{V}_E$ supplied by the rib cage which was determined by the analysis of compartmental ventilation by magnetometery (Peterson et al., 1981). The age related changes in the ventilatory responses to CO_2 reported by Peterson's group (1981) were

not accounted for exclusively by changes in lung mechanics or weakness of the respiratory muscles but rather were attributed to an alteration in central processing or in chemoreceptor function (Peterson et al., 1981).

Thus, in this sample of very healthy and fit older men, it is unlikely that age-related alterations in pulmonary gas exchange or in lung mechanics accounted for much of the age-related differences in the temporal parameters of the central and peripheral chemoreceptors that are reported. If they did, one would expect to find a significant increase in the circulation time from the pulmonary gas exchange area to the peripheral and central chemoreceptors as reflected by a longer T_c and T_p; this was not the case in the present study.

The study in the previous chapter reported an age-related decrease in g_p but not in g_c. Those findings do not necessarily conflict with the results of this study but rather may be a function of the different analyses that were performed in both studies. To confirm that the results from both studies were in agreement with each other, the analyses used in the previous chapter to determine central and peripheral CO_2 sensitivities were performed on the results from this study and striking similarities were found. The previous study showed no age-related differences in g_c, as assessed by the ventilatory response to CO_2 in hyperoxia, but did show a 32% decrease in the total gain in hypoxia which was due to a 64% decrease in g_p, calculated as the difference between the gain in hypoxia and the gain in hyperoxia. The same analyses performed on this study showed no differences in g_c but did show a 29% decrease in the total gain in hypoxia which was attributed to a 74% decrease in g_p.

In light of the findings by previous investigators of a peripheral component contributing to the ventilatory response to CO_2 in hyperoxia (Berger et al., 1973; Dahan et al., 1990; Gelfand and Lambertsen, 1973; Olievier et al., 1989), it is possible that the analyses used in the previous chapter may have underestimated g_p in hyperoxia. To confirm the presence or absence of a fast peripheral ventilatory component in hyperoxia, the hyperoxic ventilatory responses to CO_2 from the present study were fitted to a one component exponential model which resulted in a value for the total gain (equivalent to the sum of g_c and g_p). For both the young and the older groups however, the summed square difference between the model response and the experimental data for the two component exponential model were significantly lower than for the monoexponential model, as determined by an F-test (Motulsky and Ransnas, 1987). For this reason, the two component exponential model was accepted as the best representation of the ventilatory response in hyperoxia. Thus, it appears that the results from this study support the presence of a fast component in hyperoxia albeit much less than that in euoxia, decreasing by 56% and 51% for YS and OS respectively. The ratio of the CO_2 sensitivity of the fast component to the total CO_2 sensitivity in hyperoxia averaged 0.18 and 0.20 for YS and OS respectively and these are similar to the results from Dahan et al. (1990) who reported ratios of 0.12 and 0.24 in two different groups.

The presence of two components in hyperoxia has been reported previously in cats (Olievier et al., 1989), dogs (Berger et al., 1973), and humans (Dahan et al., 1990; Gelfand and Lambertsen, 1973). Although some studies have attributed both components to the central chemoreceptors (Berger et al., 1973; Gelfand and Lambertsen, 1973),

results from studies using cats provide evidence that the two-component model in hyperoxia correctly estimates the central and peripheral chemoreflex loops (Berkenbosch et al., 1989; DeGoede et al., 1985; Olievier et al., 1989; Van Beek et al., 1983). Berkenbosch et al. (1989) used the artificial brain perfusion technique in cats to administer step increases in CO_2 of the blood perfusing the brain stem and found evidence of only one central component contributing to the ventilatory response while others (DeGoede et al., 1985; Olievier et al., 1989; Van Beek et al., 1983) have also used the ABP technique in cats and found evidence of one peripheral component during hyperoxia.

In the past, the longer latency times in hyperoxia, defined as the period between the step in $P_{ET}CO_2$ and the first significant change in ventilation (Miller et al., 1974; Ward & Bellville, 1983), were interpreted as evidence that the peripheral chemoreceptors did not contribute to ventilation in hyperoxia. Recently however, Dahan et al. (1990) questioned the validity of the technique of latency time determination as a means of determining the contribution of the peripheral component in hyperoxia. They determined the latency of the ventilatory responses in hyperoxia and compared them to the results from the data that they fitted to a two compartment model. Because of low signal to noise ratios in the baseline ventilation, it was not possible to determine the contribution of the peripheral component to ventilation in hyperoxia by using the technique of latency time determination.

Previous studies in young humans have used two compartment models to describe the fast and slow components of the ventilatory response to step increases in $P_{ET}CO_2$,

attributed to the temporal parameters of the peripheral and central chemoreflex loops respectively (Bellville et al., 1979; Dahan et al., 1990; Swanson and Bellville, 1975). This technique of forcing the system and the analysis utilizes differences in the speed of the responses and transport delay times to separate the ventilatory components and is attractive for studies with humans because it is a noninvasive method that allows the determination of the temporal parameters of the chemoreceptors. This technique was recently validated in an invasive study with cats. This was performed to determine if the fast component was exclusively of peripheral and the slow component exclusively of central origins (DeGoede et al., 1985). These investigators compared results of the ventilatory response to step increases in $P_{ET}CO_2$ (using the DEF technique) with results of the ventilatory response using a technique of artificial brain stem perfusion (ABP). The ABP technique perfused the central chemoreceptors artificially while the peripheral chemoreceptors were perfused with blood from the systemic circulation and therefore central and peripheral blood P_{CO2} and P_{O2} were controlled independently. Results showed good agreement between both techniques, implying that in the DEF experiments the slow ventilatory response can be attributed to the central chemoreflex loop and the faster ventilatory response to the peripheral chemoreflex loop (DeGoede et al., 1985).

The major difference between the empirical model used in this study and the empirical models used in previous studies lies in the handling of the input function ($P_{ET}CO_2$). This study assumed a perfect step in the input function (i.e. $P_{ET}CO_2$) and therefore did not account for minor deviations that might have occurred in the $P_{ET}CO_2$ input when modelling the ventilatory responses. Previous studies have used empirical

two-compartment models that related the actual input ($P_{ET}CO_2$) to the output ($\dot{V}_E$) to account for slight deviations in the actual $P_{ET}CO_2$ steps from the ideal step functions (Bellville et al., 1979; Dahan et al., 1990; Ward and Bellville, 1983; Swanson and Bellville, 1975). In light of this difference, the data in this study for young and older men were well fitted to a two component exponential model. This is demonstrated by the small residual sum of squares iterated by our fitting routines (Appendices IV-VI). Furthermore, the residuals did not appear to systematically deviate from zero and it seems reasonable that the residuals represent only experimental error (Motulsky and Ransnas, 1987).

Findings from previous studies regarding the symmetry of the on- and off- central time constants are equivocal. Some studies have shown that the time constant of the central component of the on-step is faster than the time constant of the off-step (Bellville et al., 1979) while others have reported faster off- transients (Ward and Bellville, 1983) or similar transients between the on- and off- responses (Dahan et al., 1990; Gardner, 1980). The faster on- response has been attributed to an increase in cerebral blood flow with hypercapnia (Bellville et al., 1979). The existence of a central after-discharge, mediated by brainstem neurons which maintain an increased but slowly decaying respiratory activity after the removal of the stimulus, has been proposed by some (Eldridge and Gill-Kumar, 1980; Millhorn et al., 1980) to account for the slow off-response. In this study, there was a large variability in the on- and off- responses for different subjects but this was not unlike results published by others (Dahan et al., 1990; Ward and Bellville, 1983). The central time constants for the on-responses were at times

faster, similar, or slower than the central time constants for the off-responses. Direct comparisons with other studies is made difficult however, because these have fitted the on- and off- responses simultaneously (Bellville et al., 1979; Dahan et al., 1990) whereas this study fitted the on- and off- responses in two separate steps. Thus, the variability reported in this study may be a function of the different modelling procedures.

For both age groups, the time constants for the peripheral chemoreceptors in euoxia and hyperoxia were unchanged. These results are similar to those of previous studies (Dahan et al., 1990; Millhorn and Reynolds, 1976; Bellville et al., 1979). The central and peripheral time constants in hypoxia were not significantly different between groups, but in YS, the central time constant in hypoxia was significantly shorter than in euoxia. Similar decreases in the time constants have been reported by others (Bellville et al., 1979) and may be related to an increased cerebral perfusion in hypoxia (Bellville et al., 1979; Kety and Schmidt, 1948). The central time constant in hypoxia for OS was not shortened from that in euoxia and this age-related difference may be related to factors that play a role in determining CO_2 exchange in the area of the central chemoreceptors such as local brain tissue blood flow, local brain tissue volume, and local brain tissue CO_2 exchange with cerebral spinal fluid (Swanson and Bellville, 1975). Alterations in cerebral blood flow with advancing age have previously been noted (Kety, 1956).

In euoxia, the contributions of the peripheral chemoreceptor gains were 33 and 35% for YS and OS respectively and this is similar to those reported by previous investigators (Bellville et al., 1979; Dahan et al., 1990; Lugliani et al., 1971; Swanson and Bellville, 1975; Ward and Bellville, 1983). In hypoxia, both groups showed a non-

significant increase in the peripheral chemoreceptor gain. An increase in g_p in hypoxia has been interpreted as evidence of a positive and multiplicative interaction at the peripheral chemoreceptors in humans (Bellville et al., 1979; Cunningham et al., 1986; Miller et al., 1974; Swanson and Bellville, 1974; Ward and Bellville, 1983) and in animals (Lahiri and DeLaney, 1975). Although there were some small individual differences for g_c in hypoxia, no significant within-group differences were found in g_c between euoxia and hypoxia.

For the young group, the similarities between the central chemoreceptor gains in euoxia and hypoxia suggest that the mild hypoxia imposed on the subjects did not cause central ventilatory depression. This finding is consistent with findings from previous studies examining the ventilatory response to CO_2 in hypoxia (Bascom et al., 1990; Bellville et al., 1979; Berkenbosch et al., 1992; Dahan et al., 1990; Lahiri, 1976; Severinghaus, 1972). The behaviour of the central chemoreceptor gain in hypoxia for the older group however, makes the interpretation more difficult. Although not significant, the mean central gain in hypoxia was 16% lower than in euoxia. This resulted from a decrease in the central gain for three subjects, an increase in one subject, and no difference in the other subject. These findings suggest that there may have been some effect of central hypoxic depression in the old group.

Previous studies in young humans (Bascom et al., 1990; Berkenbosch et al., 1992; Dahan and Ward, 1989; Easton et al., 1986; Georgopoulos et al., 1989; Georgopoulos et al., 1990) and in animals (Melton et al., 1988; Van Beek et al., 1984) have shown that although prolonged hypoxia causes hypoxic depression of ventilation,

the temporal parameters of the ventilatory response to CO_2 remain unaffected. In this study, there was evidence of hypoxic depression of $\dot{V}_E$ in the young group as recovery $\dot{V}_E$ (12.0 $\pm$ 0.5 $\ell \cdot min^{-1}$) was significantly lower than baseline $\dot{V}_E$ (15.4 $\pm$ 0.9). Georgopoulos and co-workers (1990) examined the ventilatory response to CO_2 in humans before and after 25 minutes of eucapnic hypoxia. They found that sustained hypoxia did not effect the ventilatory response to CO_2 but that it selectively depressed hypoxic sensitivity. Berkenbosch et al. (1992) also examined the euoxic ventilatory response to CO_2 before and after 25 minutes of hypoxia. They found that the ventilatory CO_2 sensitivities of the peripheral and central chemoreflex loops after hypoxia were unchanged from their prehypoxic values. Their results, similar to those of Dahan and Ward (1989), indicated that there was no long lasting depressant effect of hypoxia on the peripheral and central ventilatory CO_2 sensitivities. Furthermore, Van Beek et al. (1984) demonstrated in cats, using the ABP technique to separately perfuse the brain stem and the carotid bodies, that although hypoxia depressed ventilation by a central action, it did not affect the central and peripheral sensitivities to CO_2. In another study, Melton et al. (1988) used chemodenervated cats and depressed the phrenic nerve activity by inducing brain hypoxia with CO inhalation. They observed that although there was hypoxic depression, the ability of the phrenic nerve to respond to CO_2 was not limited. The most direct evidence that hypoxic depression does not affect the early ventilatory response to CO_2 comes from the study by Bascom et al. (1990) who administered one minute pulses of hypercapnia at selective periods during the development of hypoxic ventilatory depression and found no differences in hypercapnic sensitivity until 17 minutes into

hypoxia. In the present study, the on- step in $P_{ET}CO_2$ was completed after 10 minutes of hypoxia while the off- step was completed after 18 minutes of hypoxia. Thus, it is unlikely that our results were affected by the hypoxic period.

In contrast to the $\dot{V}_E$ response of the young group in hypoxia, there was less evidence of hypoxic depression of $\dot{V}_E$ in the old group as recovery $\dot{V}_E$ (14.9 $\pm$ 0.6 $\ell \cdot min^{-1}$) was similar to baseline $\dot{V}_E$ (15.8 $\pm$ 0.7). Ahmed et al. (1991) have previously noted a tendency for the ventilatory decline in sustained hypoxia to be less in the elderly (n=14, mean age 62 years), but because of the great deal of overlap in the data, it was concluded that there was no age difference in the ventilatory decline due to hypoxia.

A close look at the recovery ventilatory responses in this study indicates that 8 minutes may not have been long enough to allow a full recovery from step increases in $P_{ET}CO_2$ of the magnitude of 7-8 Torr above resting values. In euoxia, after 8 minutes of recovery, $\dot{V}_E$ was still significantly higher than baseline $\dot{V}_E$ for both groups while recovery $\dot{V}_E$ was higher for OS compared to YS. Previous studies have proposed that an increase in $\dot{V}_E$ after step increases in CO_2 may be due to slow changes in brain tissue or cerebrospinal fluid pH or to a continued neural afterdischarge (Eldridge and Waldrop, 1991; Eldridge and Gill-Kumar, 1980; Millhorn et al., 1980). Neural afterdischarge can last as long as 30 minutes after the removal of the stimulus and is apparently related to the properties of the synapses of firing neurons of the respiratory control system and their own increased activity (Eldridge and Waldrop, 1991).

In hyperoxia, the higher $\dot{V}_E$ after 8 minutes of recovery compared to baseline values was apparent in both age groups, and was higher in YS compared to OS. The

higher recovery $\dot{V}_E$ may be related to a slow excitatory effect of hyperoxia on ventilation (Easton et al., 1988). The decreased CO_2 threshold for the young group in hyperoxia may be related to an increased cerebrovascular resistance and a subsequent decrease in cerebral blood flow as well as to a reduction of the Haldane effect (Dautrebande and Haldane, 1921; Kety & Schmidt, 1948).

In this study, resting values for $P_{ET}CO_2$ tended to be lower in the older men and this may represent a lower set-point in aged humans although the reason for this remains unclear. While some studies have reported similar tendencies in older humans for $P_{ET}CO_2$ (Kawakami et al., 1981; Overend et al., 1992), P_aCO_2 (Brischetto et al., 1984) and for mixed-expired CO_2 (Brischetto et al., 1984), others have reported similar values for P_aCO_2 in young and aged men (Johnson and Dempsey, 1991). There is little longitudinal data available that examines the constancy of P_aCO_2 over time but it is worth noting that even in the early part of this century individual differences were reported in the stability of P_ACO_2 over the years. P_ACO_2 values for C.G. Douglas were 37-38 Torr in 1905-1908 as well as in 1949 whereas J.B.S. Haldane's P_ACO_2 showed more change, from 39 Torr at 11 years of age to 35 Torr more than two decades later (Cunningham et al., 1986).

In summary, this study examined the temporal parameters of the central and peripheral chemoreflex loops in young and older men. Similar characteristics were reported for the peripheral and central time delays and the peripheral and central time constants in euoxia and hyperoxia. In euoxia, the central gain was significantly smaller while in hypoxia, both the central and peripheral gains were smaller in the older men.

CHAPTER 5

GENERAL SUMMARY AND IMPLICATIONS

5.1 General

The purpose of the first study was to accurately describe the characteristics of ventilatory control during graded exercise below the $T_{\dot{V}E}$ in a sample of non-institutionalized men and women aged 55 to 86 years. The slope of the $\dot{V}_E$-$\dot{V}CO_2$ relationship ($\Delta\dot{V}_E/\Delta\dot{V}CO_2$), examined across five year age groups, increased significantly by 29% for men between the ages of 58 to 83 years but did not change for women aged 57 to 82 years. The individual data however, showed a significant positive relationship between $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ and advancing age, increasing at a rate of 0.29/yr for men and at a rate of 0.20/yr for women. The increase in $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ may be related to an age-dependent increase in dead space ventilation or to a greater non-uniformity of ventilation-perfusion, giving older subjects a $\dot{V}_A$-$\dot{V}CO_2$ and P_aCO_2 similar to younger subjects at any given metabolic demand (Johnson and Dempsey, 1991).

At a $\dot{V}CO_2$ of 1.0 $\ell \cdot min^{-1}$, the highest intensity that most older men and women could exercise without exceeding $T_{\dot{V}E}$, $\dot{V}_E$ was significantly higher (14%) in men aged 80-86 years compared to men aged 55-64 years. There were no differences in $\dot{V}_E$ across ages for the women. At a $\dot{V}CO_2$ of 1.0 $\ell \cdot min^{-1}$, for both men and women, there were no significant differences across ages in V_T although for men, there was a trend for an increase in f_b with advancing age. The very old in this study reached the appropriate exercise $\dot{V}_E$ primarily by an increase in f_b as V_T appeared to have levelled-off at an age-

related limit, thus minimizing further increases in V_T. In this study, although the ventilatory response to exercise was higher in the older age-group, it was sufficient to maintain normal end-tidal values for CO_2 and did not appear to be a function of a stimulus from metabolic acidosis. The inclusion of a large number of men and women covering a wide age range enabled us to investigate the concept of a critical age at which greater increases in $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ might occur. In the men, it appears that the ventilatory response to exercise was well suited to metabolic demand until at least 80 years of age, at which point there was a marked increase in $\dot{V}_E$ for a given $\dot{V}CO_2$. For the women, the ventilatory response to exercise seemed appropriate across all ages studied. This is the first study to report results for $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ during exercise in men and women in their ninth decade of life.

The purpose of the second study was to assess the ventilatory response to CO_2 in hyperoxia and in hypoxia in groups of young and older humans. This is the first study to examine the age-related changes in the ventilatory response to CO_2 in hypoxia and in hyperoxia and to describe the responses in terms of both the central and peripheral chemoreflex sensitivities to CO_2. The ventilatory responses, for each subject at each P_{O2}, were fitted to the Lloyd equation, $\dot{V}_E=S(P_{ET}CO_2 - B)$, for the determination of the response curve slope (S, CO_2 sensitivity). In eucapnia, there were no differences in hypoxic and hyperoxic $\dot{V}_E$ between the age groups. In hypercapnia, although there was no difference in hyperoxic $\dot{V}_E$, hypoxic $\dot{V}_E$ was significantly lower (24%) in the older compared to the young group. Furthermore, in hypoxia, S was significantly lower by

32% in the older compared to the young group. The results for peripheral CO_2 sensitivity, calculated as the difference between the CO_2 sensitivity in hyperoxia and hypoxia, was 64% lower for the older group.

The elderly subjects who participated in this study were fit and healthy and it appears unlikely that age-related alterations in lung mechanics or respiratory muscle strength accounted for the observed reductions in the ventilatory responses to the CO_2 perturbations imposed. This study and others (Peterson et al., 1981; Rubin et al., 1982) have failed to demonstrate any changes in the control of respiratory timing in the elderly in response to CO_2. Furthermore, the highest drive imposed upon the older subjects was light to moderate, corresponding to approximately 52% of maximal exercise ventilation and to 35% of MVV. Rather, the findings from this study for the old group suggest that the lower ventilatory responses to hypoxic hypercapnia may have resulted, at least in part, from a decrease in peripheral chemoreflex CO_2 sensitivity.

The third study examined the hypercapnic ventilatory response in backgrounds of euoxia, hyperoxia, and mild hypoxia in groups of young and older men. The ventilatory responses to the step increases in $P_{ET}CO_2$ were achieved by using a dynamic end-tidal forcing system and were analyzed by fitting a double exponential model, which separated the ventilatory responses into slow and fast components, attributed to the central and peripheral chemoreflex loops respectively. The young and older men showed similar characteristics for the peripheral and central time delays and in the peripheral and central time constants. In hypoxia, the ventilatory responses of the old group were

characterized by a significantly smaller central gain (39% lower) and a smaller peripheral gain (29% lower).

The second study reported age-related differences mainly in g_p while the third study reported age-related differences in both g_c and g_p. It may be that the analyses used in the second study have underestimated the contribution of g_p in hyperoxia since the modelling used in Chapter Four found a small contribution of g_p in hyperoxia, similar to that reported previously by others (Dahan et al., 1990).

It cannot be firmly established that the age-related differences in the temporal parameters of the chemoreflexes reported in the third study are not associated to alterations in central processing, neural pathways involved in respiratory control, local brain tissue blood flow, local brain tissue volume, and local brain tissue CO_2 exchange with cerebral spinal fluid. It is suggested however that age-related alterations in pulmonary gas exchange or in lung mechanics may not have accounted for much of the differences reported as one would expect to find significantly longer time delays for the peripheral and central chemoreceptors but this was not the case in this study.

Thus, this study demonstrated that in older men, the ventilatory responses to CO_2 in euoxia and hyperoxia were similar to those of young men while in hypoxia, the ventilatory responses were characterized by lower central and peripheral chemoreflex sensitivities to CO_2.

Within the limitations of the studies in this thesis, the results suggest that there may be alterations in the mechanisms controlling the ventilatory response to CO_2 and the ventilatory response to inhaled CO_2 in aged humans.

5.2 Recommendations for Future Study

1. Determination of direct measurements of P_aCO_2 in healthy elderly subjects in order to develop a standard prediction equation for P_aCO_2, calculated from an empirical relationship involving $P_{ET}CO_2$ and V_T, for use in healthy elderly populations. This would also evaluate the suggestion that there may be age-related alterations in the P_aCO_2 set-point and in physiological dead space (i.e. V_D/V_T).

2. Determination the cerebral blood flow responses to alterations in blood gas tensions in the elderly. This would be achieved by combining the technique of Doppler pulsed ultrasound, to measure intracerebral blood flow velocities, with the technique of dynamic end-tidal forcing, to study the dynamic responses of cerebral blood flow to step changes in the alveolar ($P_{ET}CO_2$) gas partial pressures. This study would indicate if the age-related alterations in the temporal parameters of the central chemoreceptors are due to alterations in intracerebral blood flow.

3. Validation of the model used in Chapter Four by comparing the temporal parameters estimated from the double component exponential model to those estimated by the double component model used by others (Bellville et al., 1979; Dahan et al., 1990). The model in Chapter Four assumed a perfect step in the input function whereas the models used by others (Bellville et al., 1979; Dahan et al., 1990) were fitted to the actual input function.

APPENDICES

APPENDIX I

GLOSSARY OF VARIABLES AND UNITS

PARTIAL PRESSURES

Partial Pressure	the pressure required to support a column of mercury 1.0 mm high, expressed in mm Hg or in Torr (1 Torr = 1 mm Hg at O°C)
Euoxia	A normal amount of oxygen in the air, blood, or tissues
Hypercapnia	A greater than normal arterial carbon dioxide tension
Hypoxia	A lower than normal partial pressure of oxygen or arterial saturation, or both
Hyperoxia	A greater than normal amount of oxygen in the air, blood, or tissues
P_{CO2}	partial pressure of carbon dioxide (Torr)
P_{O2}	partial pressure of oxygen (Torr)
P_aCO_2	arterial partial pressure of carbon dioxide (Torr)
P_ACO_2	alveolar partial pressure of carbon dioxide (Torr)
P_aO_2	arterial partial pressure of oxygen (Torr)
P_AO_2	alveolar partial pressure of oxygen (Torr)
$P_{ET}CO_2$	end-tidal partial pressure of carbon dioxide (Torr)
$P_{ET}O_2$	end-tidal partial pressure of oxygen (Torr)

LUNG VOLUMES AND CAPACITIES

FVC	Forced Vital Capacity (litres, BTPS)
FEV_1	Forced Expired Volume in 1 second (litres, BTPS)
FRC	Functional Residual Capacity
MVV	Maximal Voluntary Ventilation ($\ell \cdot min^{-1}$)

RV	Residual Volume
TLC	Total Lung Capacity

RESPIRATORY VARIABLES

O_2	Oxygen
CO_2	Carbon Dioxide
f_b	breathing frequency (breaths·min^{-1})
N_2	Nitrogen
RER	respiratory exchange ratio (carbon dioxide production/ oxygen consumption)
T_E	duration of expiration (s)
T_I	duration of inspiration (s)
T_I/T_{Tot}	T_I/total cycle duration ($T_I + T_E$)
$T_{\dot{V}E}$	ventilation threshold
$\dot{V}_A$	alveolar ventilation (ℓ·min^{-1})
$\dot{V}CO_2$	carbon dioxide production (ℓ·min^{-1})
V_D	Dead space or physiologic dead space (ml)
$\dot{V}_D$	Dead space ventilation (ℓ·min^{-1})
V_D/V_T	Ratio of dead space to tidal volume
$\dot{V}_E$	expired ventilation (ℓ·min^{-1})
$\dot{V}_E/\dot{V}CO_2$	ventilatory quotient for carbon dioxide
$\Delta\dot{V}_E/\Delta\dot{V}CO_2$	slope of relationship between $\dot{V}_E$ and $\dot{V}CO_2$
$\dot{V}_E/\dot{V}O_2$	ventilatory quotient for oxygen
$\dot{V}O_2$	oxygen consumption (ℓ·min^{-1})

$\dot{V}O_2max$	maximal oxygen consumption ($\ell \cdot min^{-1}$)
V_T	tidal volume (ml)
V_T/T_I	inspiratory flow rate ($ml \cdot s^{-1}$)

TEMPORAL PARAMETERS, CONTROL OF BREATHING, AND MODELLING

CO_2 sensitivity (S)	Slope of the response line describing a change in ventilation resulting from a change in alveolar or end-tidal partial pressure of CO_2 ($\ell \cdot min^{-1} \cdot Torr^{-1}$)
Exponential function	a function of type e^{At}, where e is the base of the natural logarithm and A is the characteristic time constant of the particular growth or decay process.
τ_c	time constant, central chemoreflex loop (s)
τ_p	time constant, peripheral chemoreflex loop (s)
G_c	gain, central chemoreflex loop ($\ell \cdot min^{-1} \cdot Torr^{-1}$)
G_p	gain, peripheral chemoreflex loop ($\ell \cdot min^{-1} \cdot Torr^{-1}$)
T_c	time delay, central chemoreflex loop (s)
T_p	time delay, peripheral chemoreflex loop (s)

STATISTICAL NOTATIONS

SD	standard deviation
SEM	standard error of the mean
n	number of obervations
r	correlation coefficient
p	probability
$p \leq 0.05$	denoting probability of significant difference
Residuals	the distance from a data point to a regression line. The residuals represent the unexplained variation after fitting the model.

APPENDIX II

LETTER OF INFORMATION AND CONSENT FORM

FOR STUDY DESCRIBED IN CHAPTER 1

Dear

The University of Western Ontario is undertaking a research project to determine the effectiveness of a simple safe walking test as a measure of physical fitness in older adults. We hope that this study will enable doctors to use this simple walking test to determine physical fitness instead of more expensive and cumbersome methods.

You have been randomly selected from the people in the city of London and your participation in this study would greatly contribute to our future health care. You will receive $30.00, when you come to the University, to cover any incidental costs.

Our project coordinator, Mrs. Nancy Ecclestone, will contact you by telephone to explain your involvement.

You would have a unique opportunity to visit our facilities at the Research Centre for Activity and Aging and see the type of work that we have done for the past ten years.

If you would like to contact us before Mrs. Ecclestone calls you, our telephone number is 679-2111, Ext 8362.

Yours Sincerely,

Peter Rechnitzer, MD.

THE UNIVERSITY OF WESTERN ONTARIO
Research Centre for Activity and Aging
Room 118B, Thames Hall
London, Canada
N6A 3K7

Dear

May 3, 1988

This letter is to confirm our telephone conversation regarding your participation in the walking study with which we hope to show a relationship between a self-selected walking speed and physical fitness.

It will involve approximately 3 hours of your time. You will be given a medical examination which will include a history and a clinical examination, simple measurements of height, weight, flexibility, muscle strength, skinfold thickness as well as an electrocardiogram both at rest and during the exercise stress test. The benefit to you will be a medical assessment of your cardiovascular health.

You will be asked to walk 80 metres at 4 speeds that you select yourself (slow, normal, fast, as fast as possible).

The exercise stress test will be on a motorized treadmill during which the collection of respired gas will be made using a mouthpiece and a noseclip. You will be asked to fill out a questionnaire and you may refuse to answer any questions.

When you arrive at the University you will receive $30.00 for expenses incurred.
The following information confirms the appointment set up during our telephone conversation.

TIME: 8:00 to 11:30 A.M. DATE: Monday, May 9, 1988
LOCATION: ROOM 28, THAMES HALL, University of Western Ontario
PARKING: LOT NEAR ALUMNI HALL ($4.00 deposit, $.50/hr)
or THAMES HALL ($6.00 deposit, $.75/hr)
DRESS: Shorts or slacks, soft-soled shoes, and T-shirt(change facilities are available)
DIET RESTRICTIONS:
1. Please eat only a light meal before you come.
2. Avoid coffee, tea, alcohol and smoking in the 2 hours prior to your appointment.

MEDICATIONS: Please bring prescriptions or bottles with labels with you.
All information obtained will be regarded as confidential.

I am looking forward to meeting you and thank you for your consent to participate in this important study.
Sincerely,
Coordinator 679 - 2111 Ext 8362

CENTRE FOR ACTIVITY & AGING
THE UNIVERSITY OF WESTERN ONTARIO

INFORMED CONSENT

I agree to participate in a study that will compare a self- selected walking pace with an exercise stress test on a treadmill.

I agree to a preliminary medical examination that will include a detailed history and a clinical examination, simple measurements of height, weight, flexibility, muscle strength, skinfold thickness as well as an electrocardiogram both at rest and during the exercise stress test.

I understand that I will be asked to complete a questionnaire.

The self-selected walking test is a simple test which measures the speed of walking 80 metres at each of four speeds that I decide as being (1) slow, (2) normal, (3) fast, and (4) as fast as possible. The exercise stress test will be a standard treadmill test during which the collection of respired gas during exercise (using a mouthpiece and a nose clip) will be made. I understand that I might feel tired or weak while walking on the treadmill and that this type of activity may actually cause chest pain. This test will be closely monitored by a physician and I can ask to stop it at any time.

The time involved for these tests and measurements will be approximately 3 hours.

I have read and understand the letter of confirmation and explanation of this project and know that I am not obliged to participate. I also understand that I may withdraw from the study at any time. Complete confidentiality will be maintained.

DATE:_____

SIGNED:_____

APPENDIX III

LETTER OF INFORMATION AND CONSENT FORM

FOR STUDIES DESCRIBED IN CHAPTERS 2 AND 3

THE CONTROL OF BREATHING IN THE OLDER PERSON

Dear.....

During the course of life the body undergoes many changes and adaptations. We believe the responses of an older person to breathing a low oxygen (50-70% normal), high oxygen, and slightly altered carbon dioxide concentrations are substantially different from a young adult, in both degree and duration, but may be modifiable by exercise training.

We wish to conduct a series of experiments using computer controlled equipment which will alter the concentrations of oxygen and carbon dioxide you breathe. The effects of the changes in the gas you breathe will be monitored by instruments and observation, and adjustments made to avoid untoward symptoms and to produce the effects under study.

The breathing studies will involve sitting in a chair, or doing light exercise, breathing from a mouthpiece while wearing a nose clip, an oxygen sensor on the ear, and ECG leads. Each visit to the laboratory will last 2 - 2.5 hours and involve a pair of related experiments with a break in between. It is anticipated this would involve approximately 7 visits to the laboratory.

During the series of experiments blood tests may be requested (2-3 teaspoons) to measure your haemoglobin concentration and to study further the response to low and high oxygen tension. This would not be a regular event.

During these experiments you may feel your breathing change, which is to be expected in what we are studying, but it is extremely unlikely you will experience any faintness. The blood tests may cause some temporary bruising, but precautions will be taken to avoid serious bruising, discomfort and infection. You may indicate you wish to stop an experiment at any time and an experiment will be stopped if untoward signs are observed.

Part of the research programme will be to assess the effect of exercise training on the control of breathing. If you are participating in this arm of the programme, a carefully

controlled maximal exercise test will be carried out on entry (breathing air) and later to assess improvements in fitness with exercise training. On completion, the control of breathing will be re-studied.

The exercise programme would be conducted at the Thompson Arena with the Retirement Research Associations under the guidance of exercise leaders and progress will be monitored by the researchers. Training sessions would be held three mornings weekly and involve 10 minutes of warm-up exercises, 40 minutes of aerobic training, such as walking or jogging according to ability, and ends with a further 10 minutes of cool-down and flexibility exercises. The intensity of training would be aimed at 70% of your capability, sufficient to improve fitness without causing distress.

Because caffeine can affect the breathing, it is important you do not consume any tea, coffee, colas, or any preparation which contain it for four hours prior to attending the laboratory. For similar reasons, smoking and eating should be avoided for four hours prior to attending the laboratory.

You are free to withdraw from any or all of the experiments at any time. Your records will be remain confidential and securely stored, listed by reference number rather than name, and on completion of all study the computer and written record will be destroyed.

Further information regarding the study may be obtained from
Dr.D.A.Cunningham (661-1605), Dr. W.D.F. Smith (661-1611),
Dr.D.H.Paterson (661-1606), or Marc Poulin (661-1614).

CONSENT FORM

THE CONTROL OF BREATHING IN THE OLDER PERSON

I have read the letter of explanation.

I agree to participate in a study designed to examine the control of breathing in the older person.

I understand I am free to withdraw at any time from the study and that complete confidentiality of my records will be maintained. Further information regarding the study may be obtained from Marc Poulin (661-1614), Dr. D.A. Cunningham (661-1605), Dr.D.H.Paterson (661-1606).

Name: _____

Signed: _____

Date: _____

APPENDIX IV

VALUES FOR THE ESTIMATED TEMPORAL PARAMETERS FOR INDIVIDUAL SUBJECTS IN EUOXIA

Values for the estimated parameters in euoxia (ID, subject ID number; B, the CO_2 threshold in Torr; g_c and g_p, the central and peripheral gain terms in $\ell \cdot min^{-1} \cdot Torr^{-1}$; τ_c and τ_{off}, the central time constants of the 'on' and 'off' response in s; τ_p, the peripheral time constant in s; T_c and T_p, the time delays of the central and peripheral chemoreflex loops in s; D, drift term in $ml \cdot min^{-2}$; SS, sum of squares of the residuals).

ID	B	g_c	g_p	$g_p/(g_p+g_c)$	τ_c	τ_{off}	τ_p	T_c	T_p	D	SS
Young											
468	37.0	1.89	0.96	0.34	202.1	147.3	20.5	11.2	5.7	9.0	202.3
1442	35.9	1.81	0.97	0.35	121.9	112.9	2.2	1.8	1.0	9.0	208.7
1569	37.5	2.39	0.87	0.27	244.7	79.1	23.6	10.6	1.1	8.0	267.8
1643	33.6	2.27	1.25	0.36	182.7	128.3	14.5	1.9	1.7	5.0	207.1
Old											
189	32.8	1.78	0.75	0.30	196.3	45.2	13.9	14.5	2.3	8.0	399.9
308	30.2	1.21	0.74	0.38	150.4	93.3	9.5	2.1	1.9	3.0	171.0
326	32.3	1.61	0.76	0.32	183.0	111.6	31.9	7.5	7.1	6.0	197.9
531	23.6	1.18	0.66	0.36	167.7	145.1	12.2	5.7	5.7	9.0	504.3
533	26.8	1.75	1.09	0.38	104.3	120.9	8.3	1.8	1.8	8.0	333.0

APPENDIX V

VALUES FOR THE ESTIMATED TEMPORAL PARAMETERS FOR INDIVIDUAL SUBJECTS IN HYPOXIA

Values for the estimated parameters in hypoxia (ID, subject ID number; B, the CO_2 threshold in Torr; g_c and g_p, the central and peripheral gain terms in $\ell \cdot min^{-1} \cdot Torr^{-1}$; τ_c and τ_{off}, the central time constants of the 'on' and 'off' response in s; τ_p, the peripheral time constant in s; T_c and T_p, the time delays of the central and peripheral chemoreflex loops in s; D, drift term in $ml \cdot min^{-2}$; SS, sum of squares of the residuals).

	ID	B	g_c	g_p	$g_p/(g_p+g_c)$	τ_c	τ_{off}	τ_p	T_c	T_p	D	SS
Young												
	468	35.0	1.69	1.17	0.41	139.6	97.6	12.5	6.3	4.5	6.0	323.8
	1442	32.9	1.66	0.93	0.36	39.5	150.7	6.4	3.2	1.3	9.0	501.5
	1569	37.3	2.46	1.59	0.39	247.2	77.7	13.0	14.0	4.0	6.0	359.6
	1643	32.1	2.48	1.42	0.36	52.6	82.5	9.4	1.7	1.6	9.0	321.1
Old												
	189	32.9	1.47	1.12	0.43	157.2	37.1	13.2	13.3	2.2	8.0	790.3
	308	28.9	1.14	0.93	0.45	134.2	56.9	9.4	3.3	3.3	4.0	264.8
	326	28.5	0.97	0.68	0.41	67.1	118.9	14.3	6.5	6.2	9.0	322.0
	531	22.8	1.51	0.78	0.34	396.7	135.3	11.2	13.8	1.8	5.0	517.7
	533	23.4	1.27	1.03	0.45	117.5	63.1	11.3	2.7	2.6	6.0	276.9

APPENDIX VI

VALUES FOR THE ESTIMATED TEMPORAL PARAMETERS FOR INDIVIDUAL SUBJECTS IN HYPEROXIA

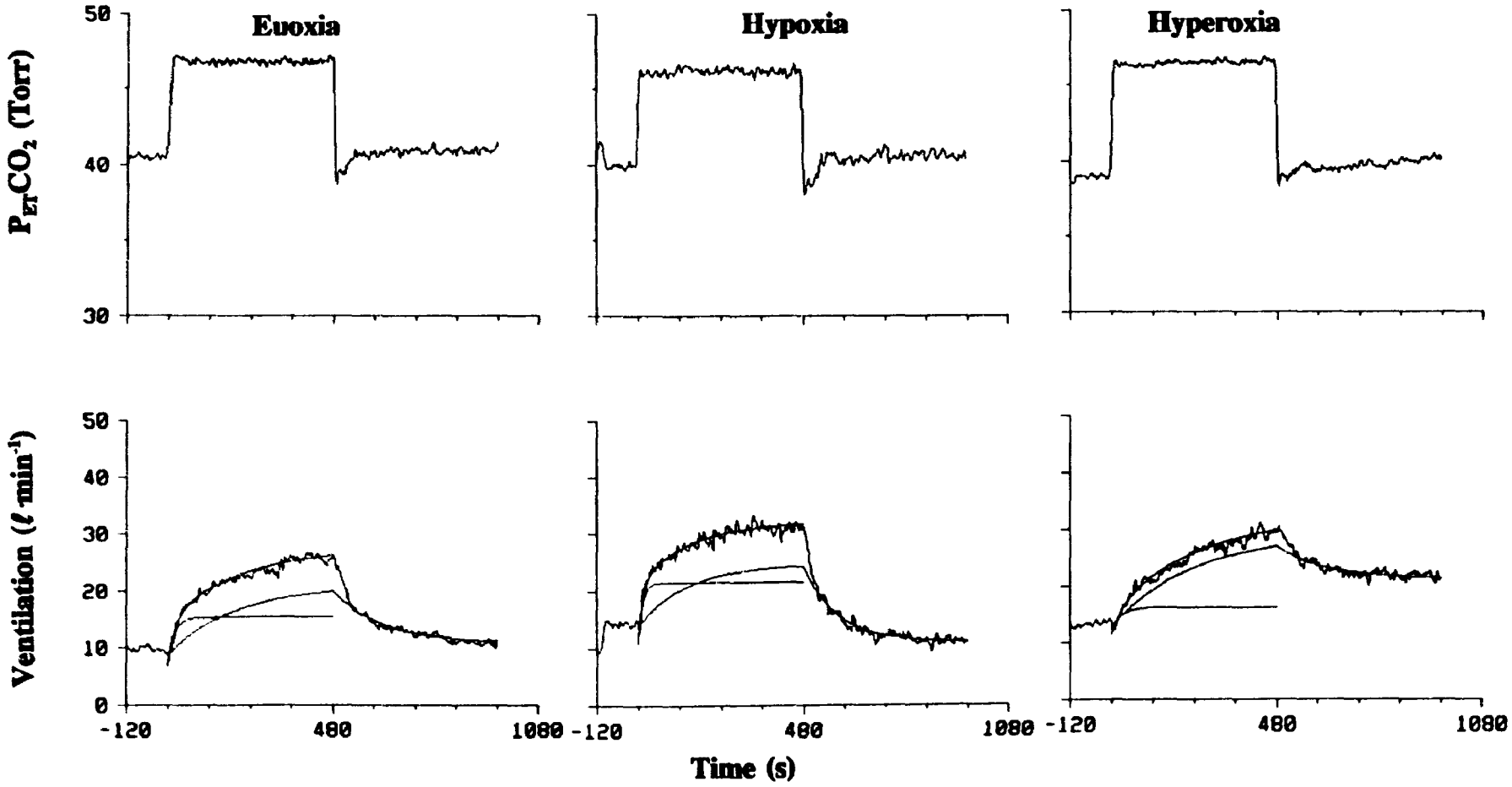
Values of the estimated parameters in hyperoxia (ID, subject ID number; B, the CO_2 threshold in Torr; g_c and g_p, the central and peripheral gain terms in $\ell \cdot min^{-1} \cdot Torr^{-1}$; τ_c and τ_{off}, the central time constants of the 'on' and 'off' response in s; τ_p, the peripheral time constant in s; T_c and T_p, the time delays of the central and peripheral chemoreflex loops in s; D, drift term in $ml \cdot min^{-2}$; SS, sum of squares of the residuals).

	ID	B	g_c	g_p	$g_p/(g_p+g_c)$	τ_c	τ_{off}	τ_p	T_c	T_p	D	SS
Young												
	468	32.7	2.12	0.33	0.13	239.2	143.9	30.3	15.0	13.3	10.0	297.9
	1442	33.9	2.21	0.58	0.21	224.2	132.0	7.0	3.5	1.1	4.0	182.2
	1569	36.0	1.66	0.44	0.21	241.3	51.6	35.3	11.4	9.9	6.0	237.8
	1643	31.2	2.16	0.34	0.14	129.3	159.6	46.3	7.5	1.1	9.0	423.8
Old												
	189	33.7	1.85	0.61	0.25	145.9	145.6	18.5	11.4	3.8	8.0	503.9
	308	27.2	1.06	0.33	0.24	178.0	77.4	15.6	10.4	9.6	7.0	148.4
	326	31.1	2.03	0.48	0.19	322.9	299.9	28.2	14.0	12.5	2.0	298.4
	531	23.9	1.61	0.10	0.06	104.2	93.9	25.5	7.3	1.0	4.0	342.3
	533	25.8	1.41	0.45	0.24	104.3	86.9	11.3	3.7	3.6	9.0	306.8

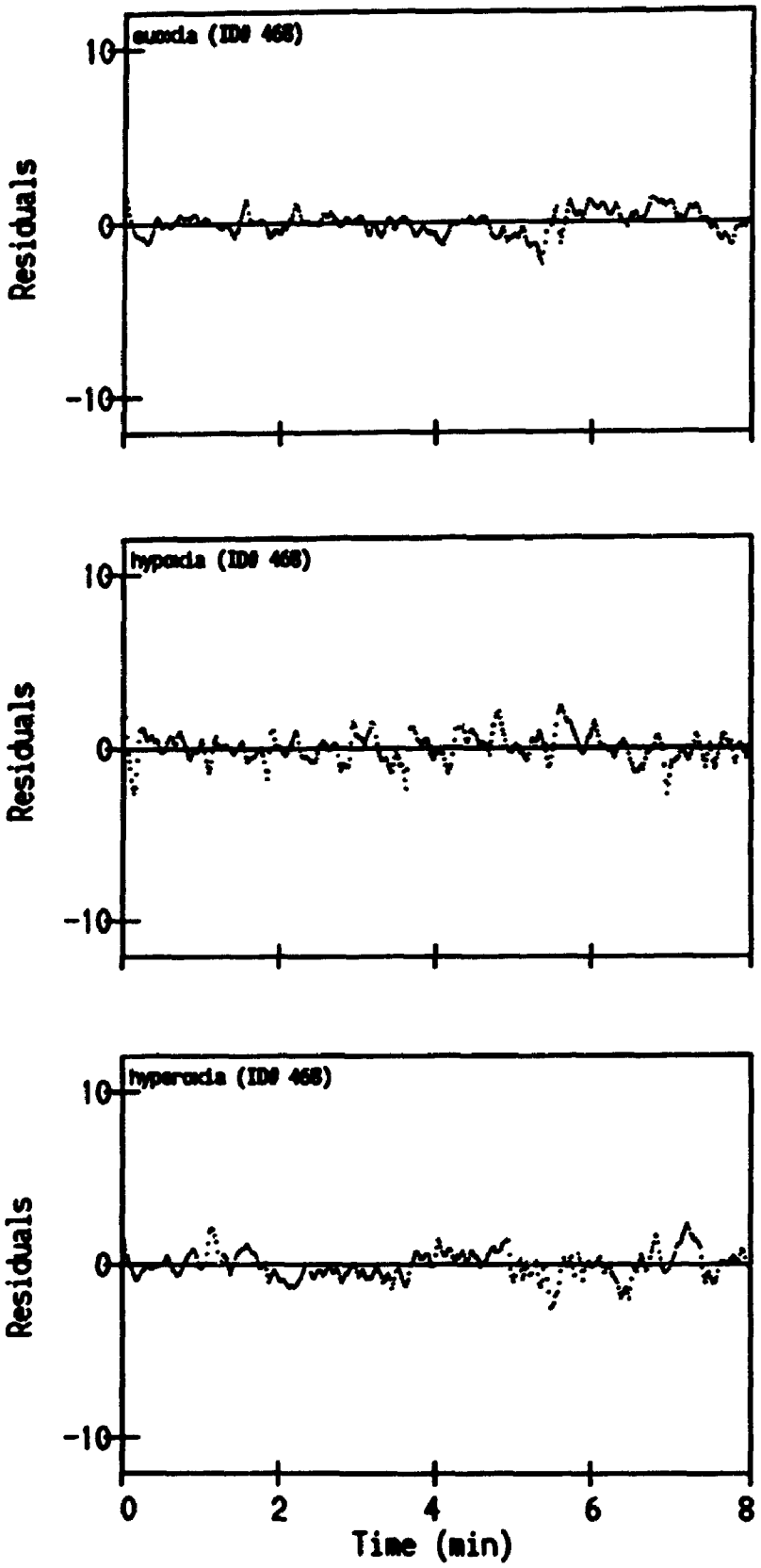
APPENDIX VII

VENTILATORY RESPONSES, MODEL FITS, AND RESIDUALS FOR INDIVIDUAL SUBJECTS

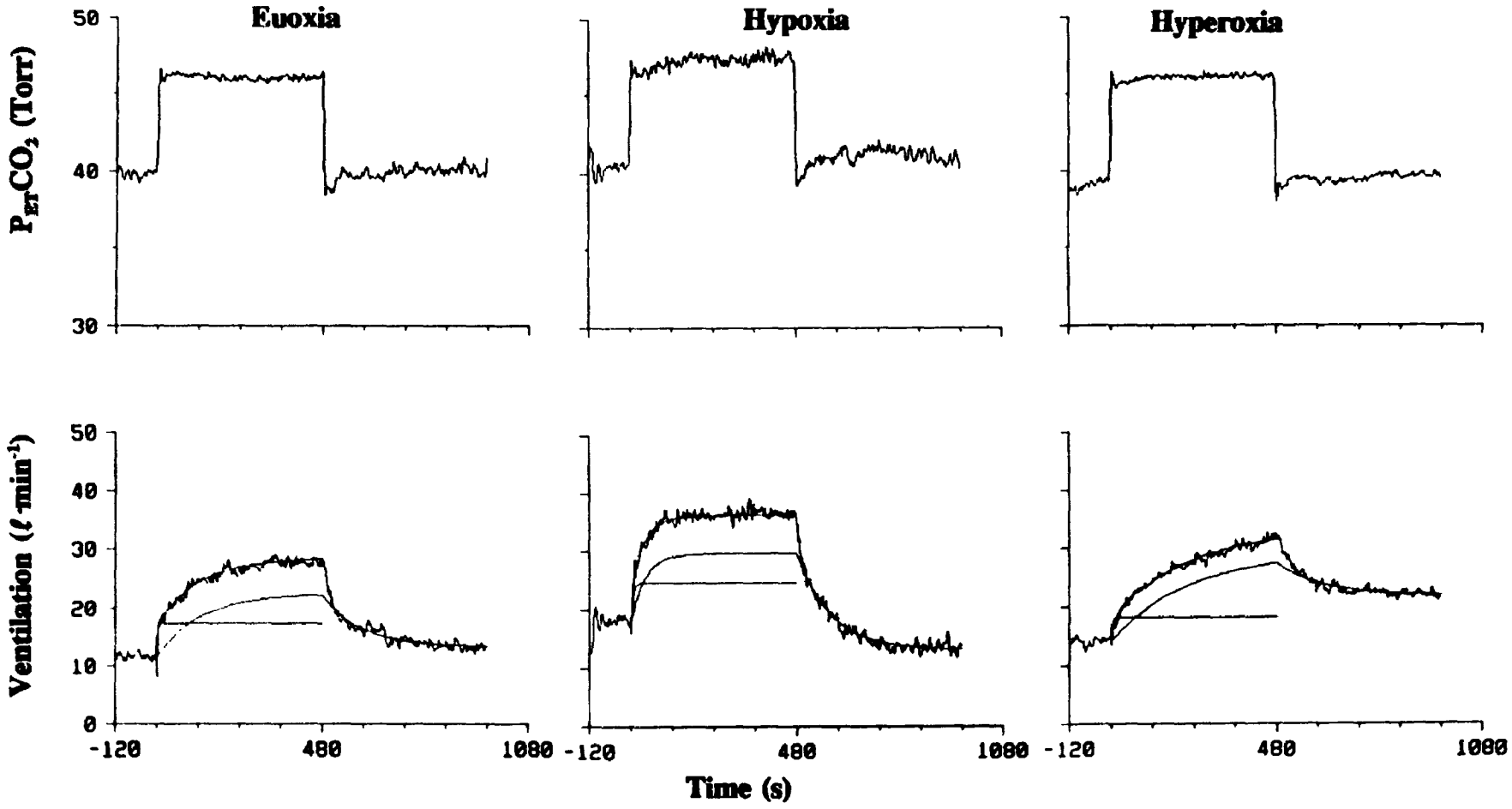
VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 468

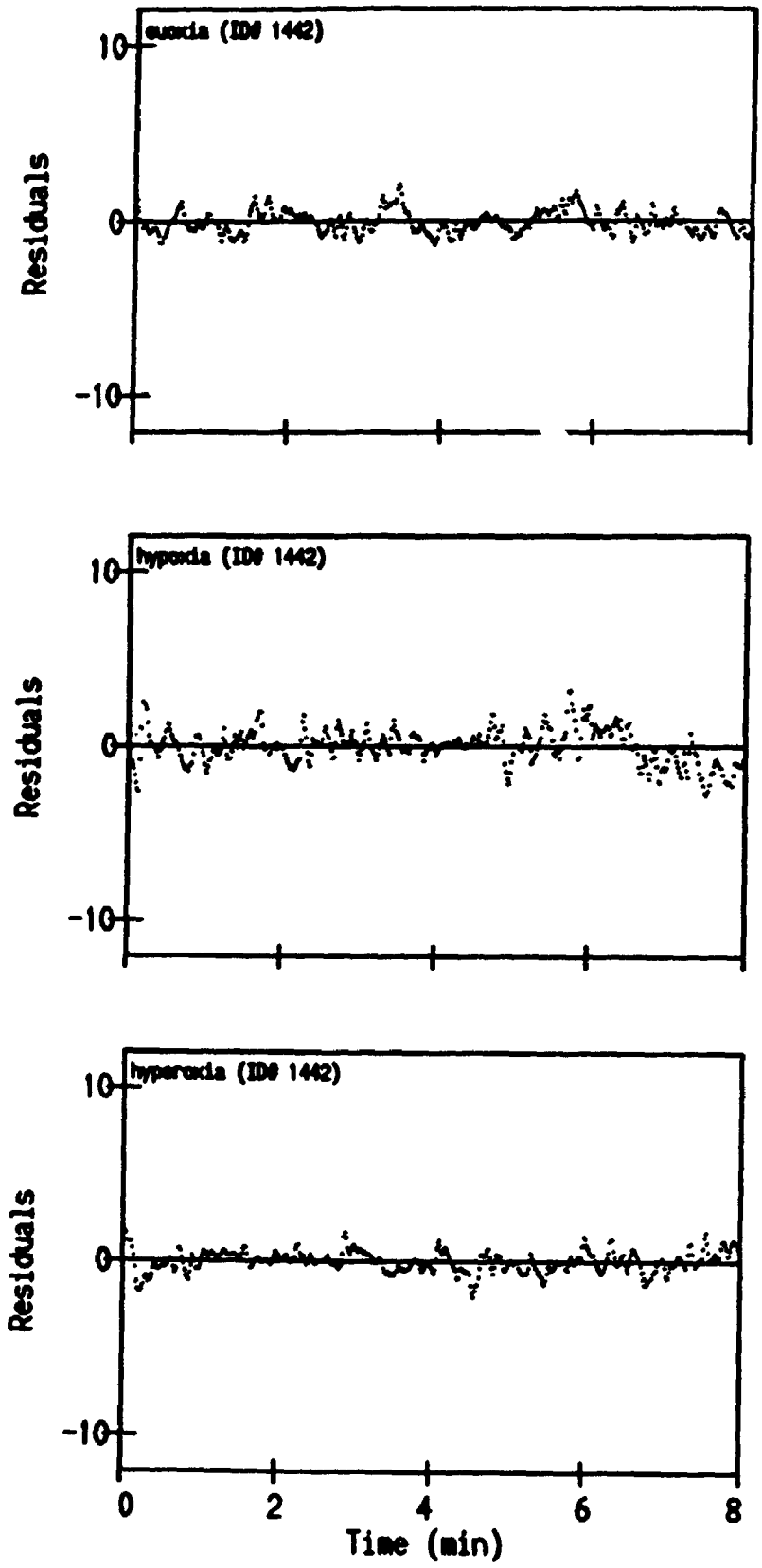


RESIDUALS FOR MODEL FITS (SUBJECT ID 468)

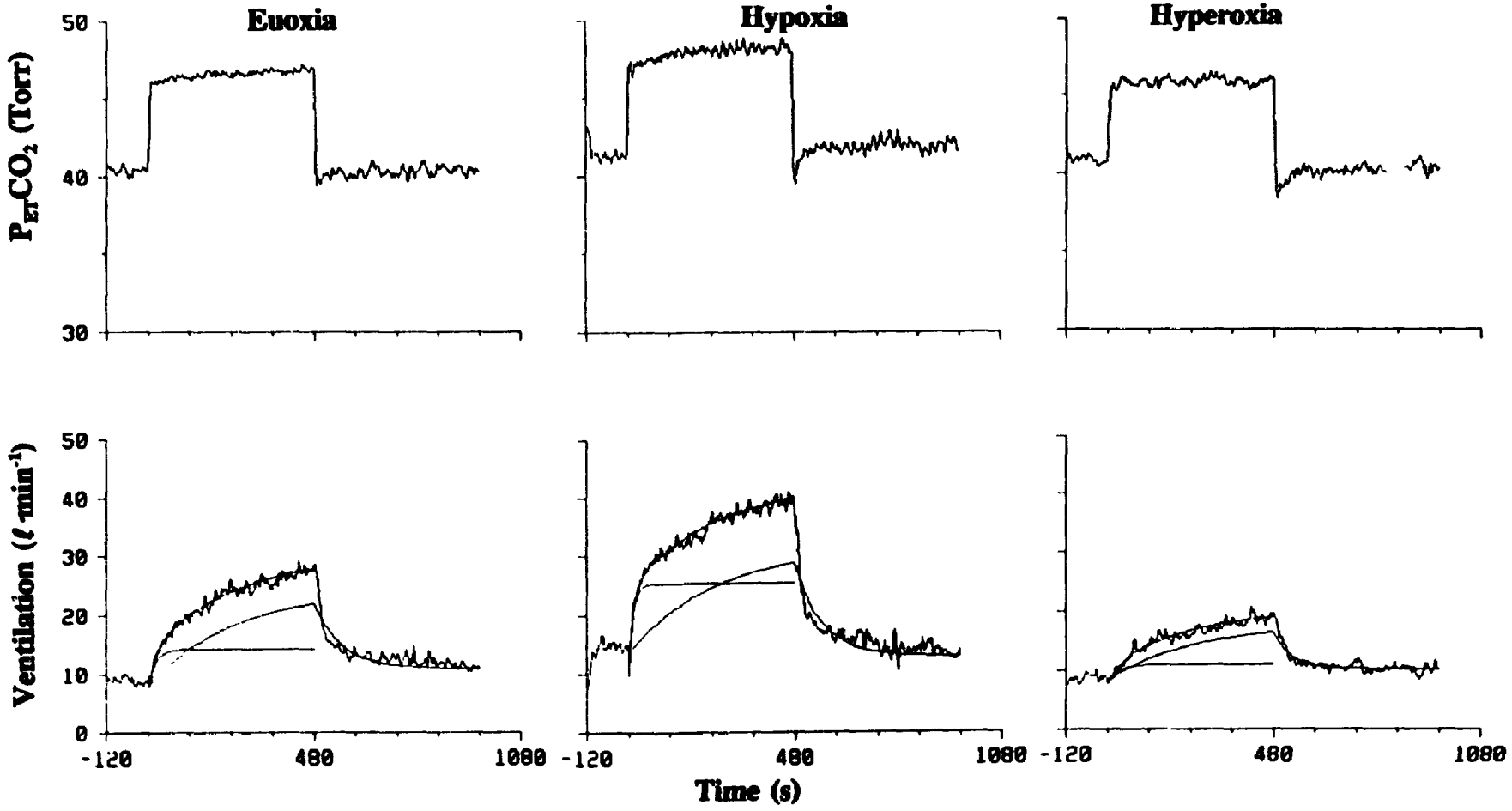


VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 1442

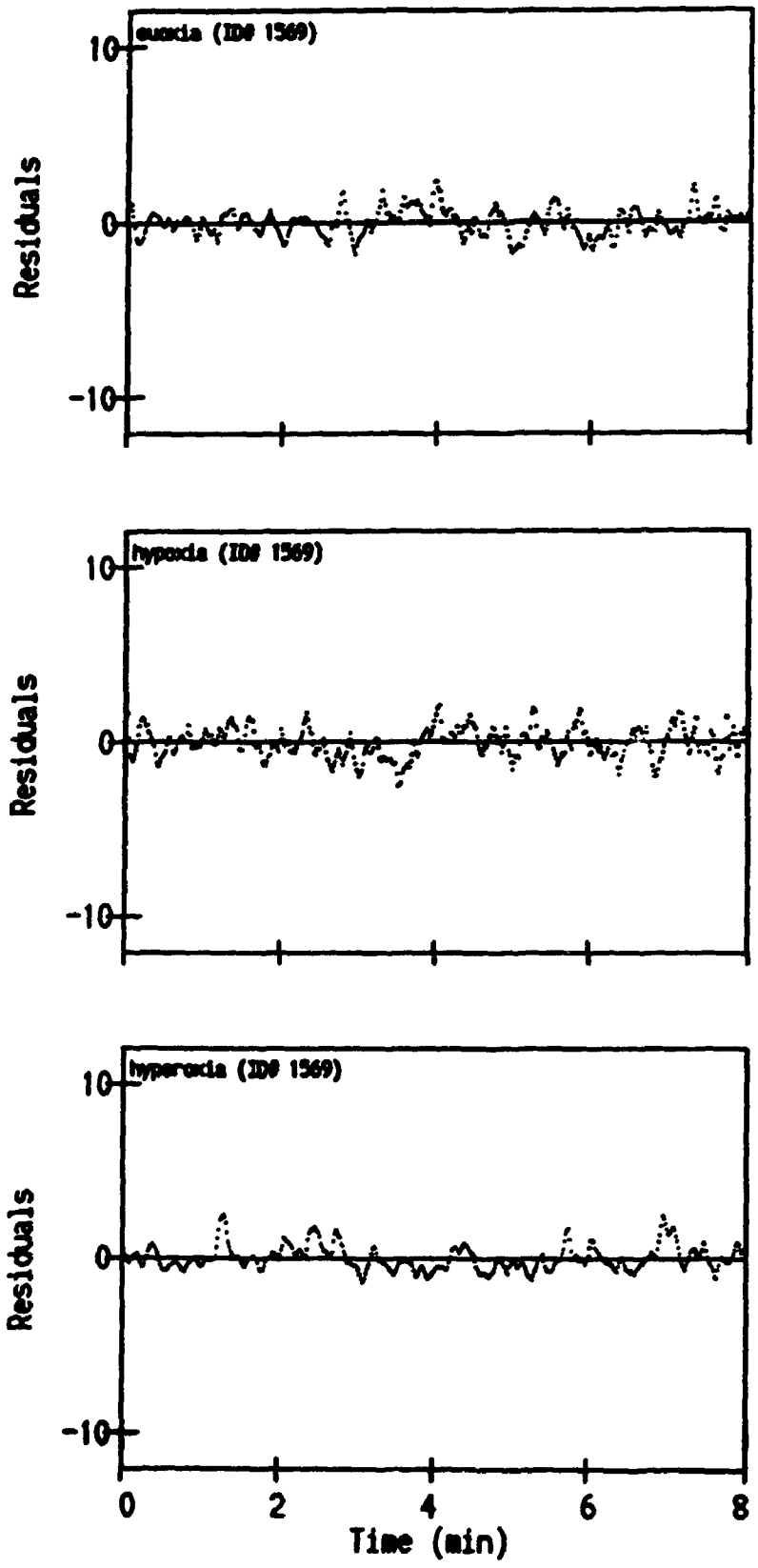



eunoia (ID# 1442)
hypoxia (ID# 1442)
hyperoxia (ID# 1442)
Residuals
10
0
-10
0
2
4
6
8
Time (min)

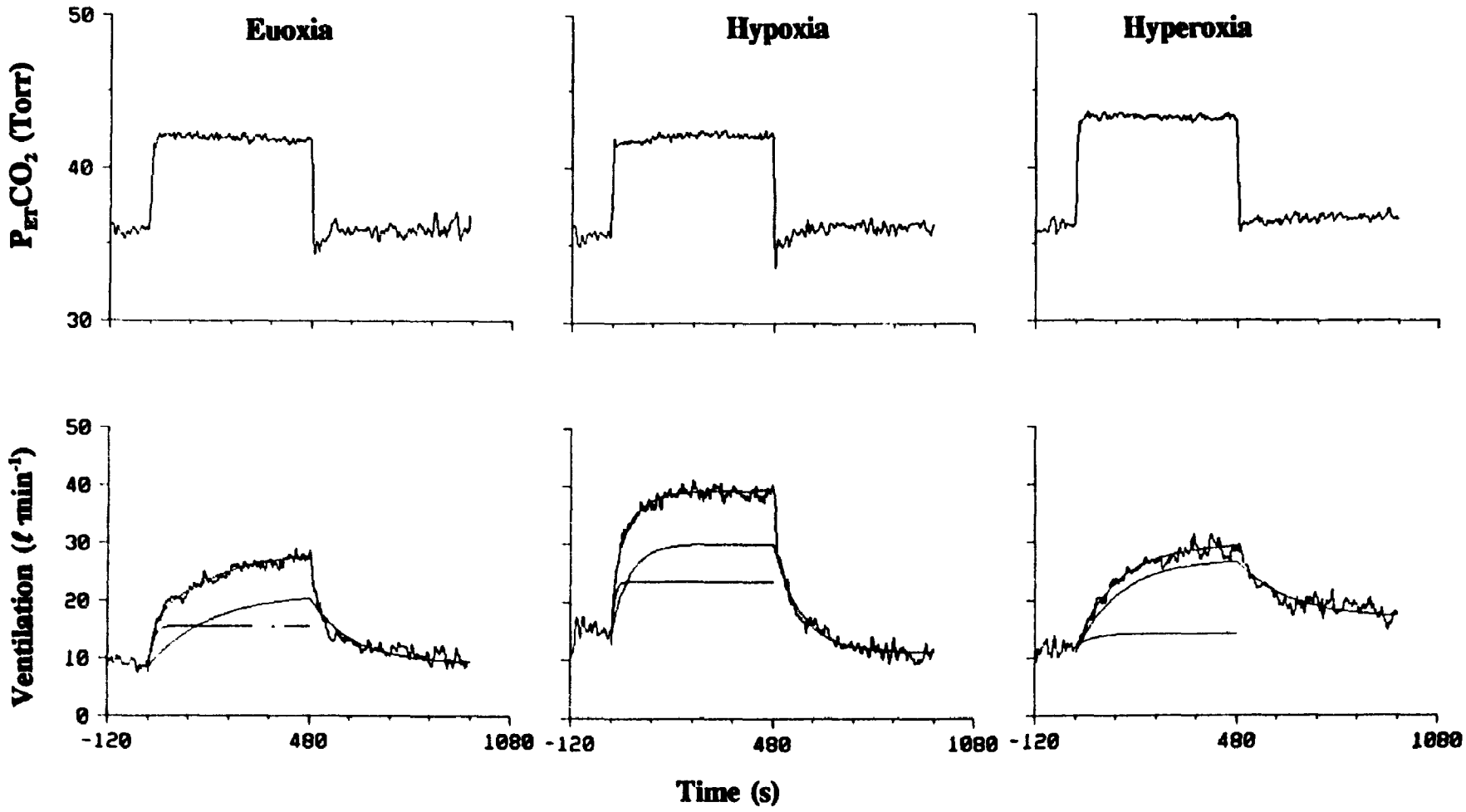
VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 1569



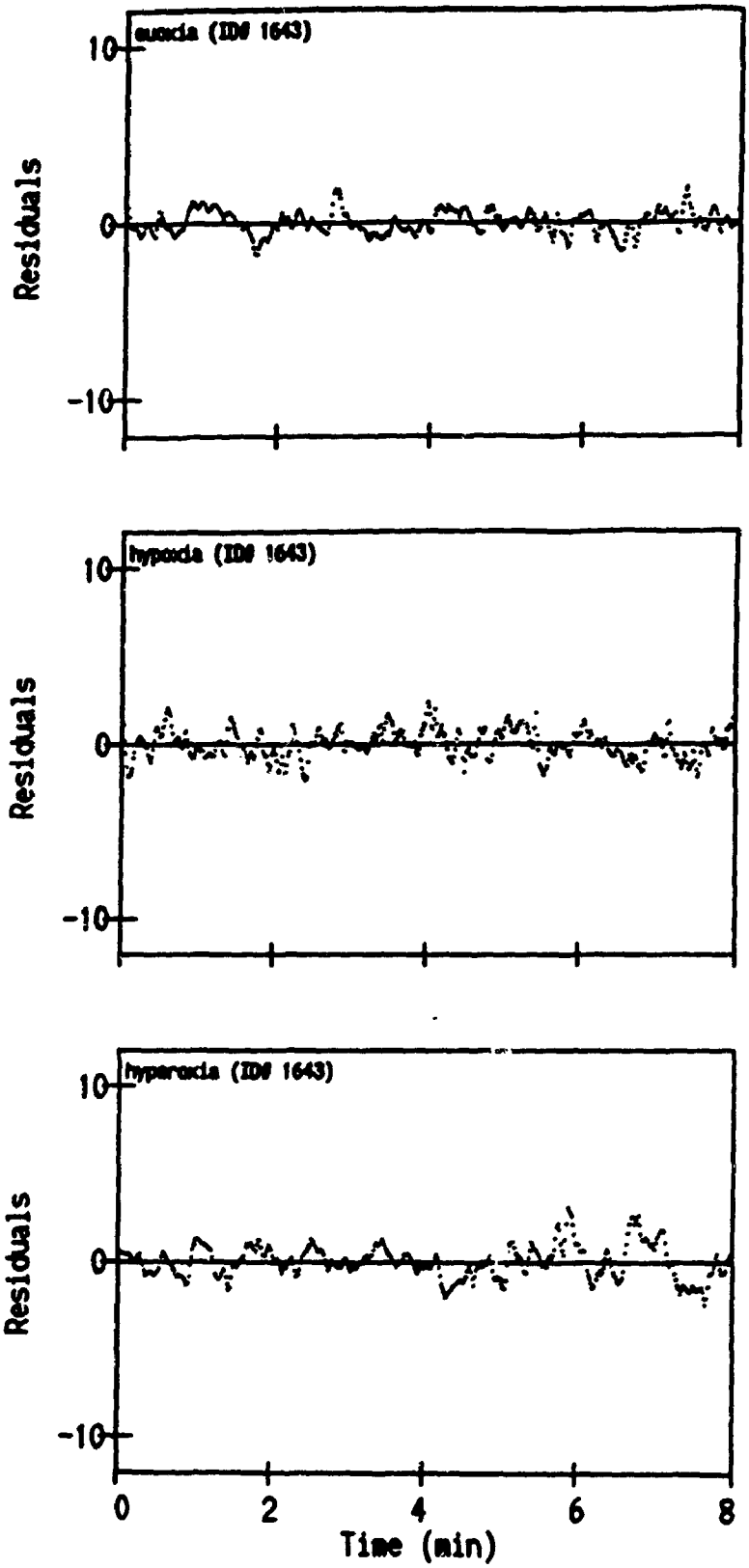
RESIDUALS FOR MODEL FITS (SUBJECT ID 1569)



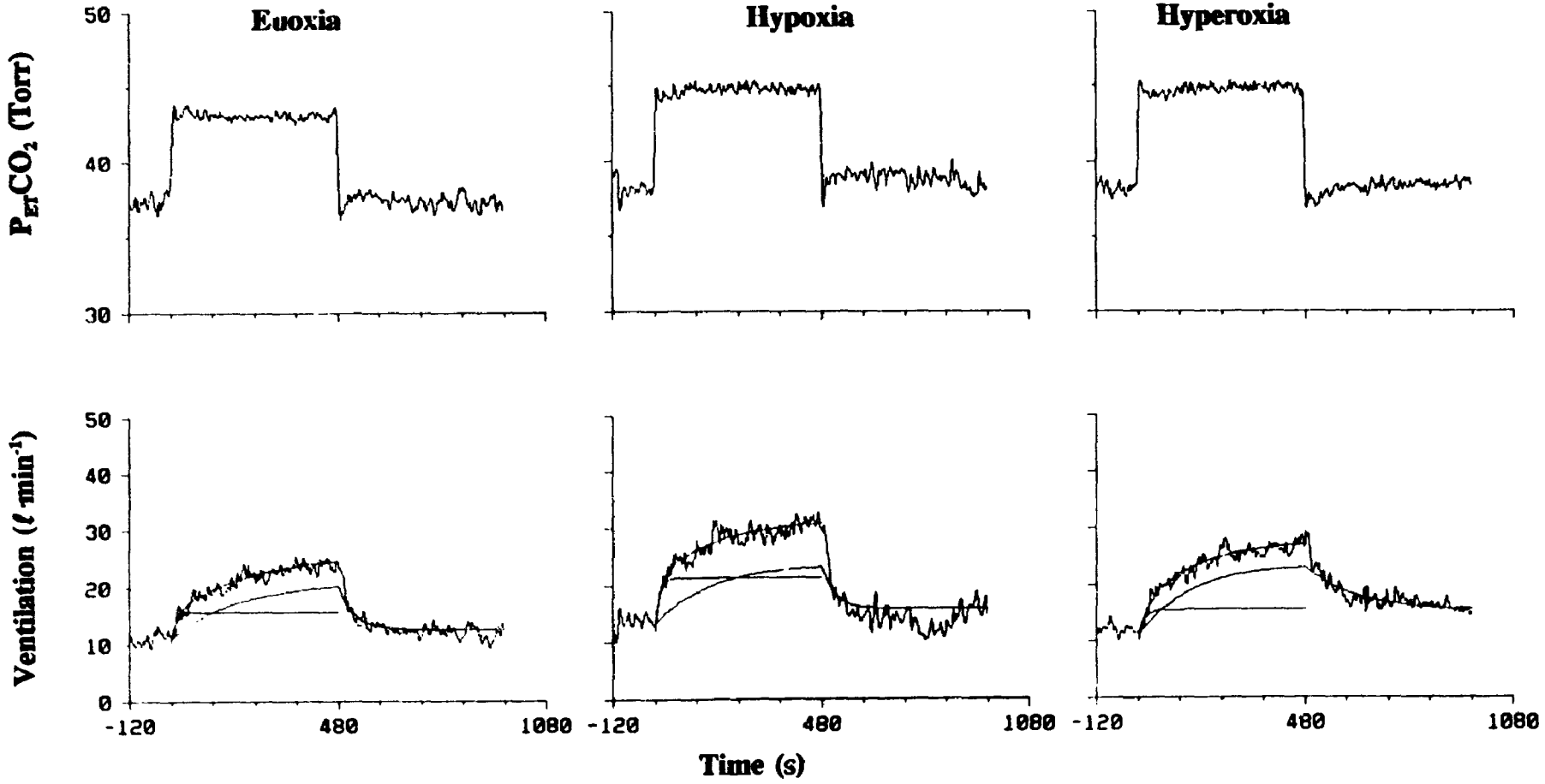
VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 1643

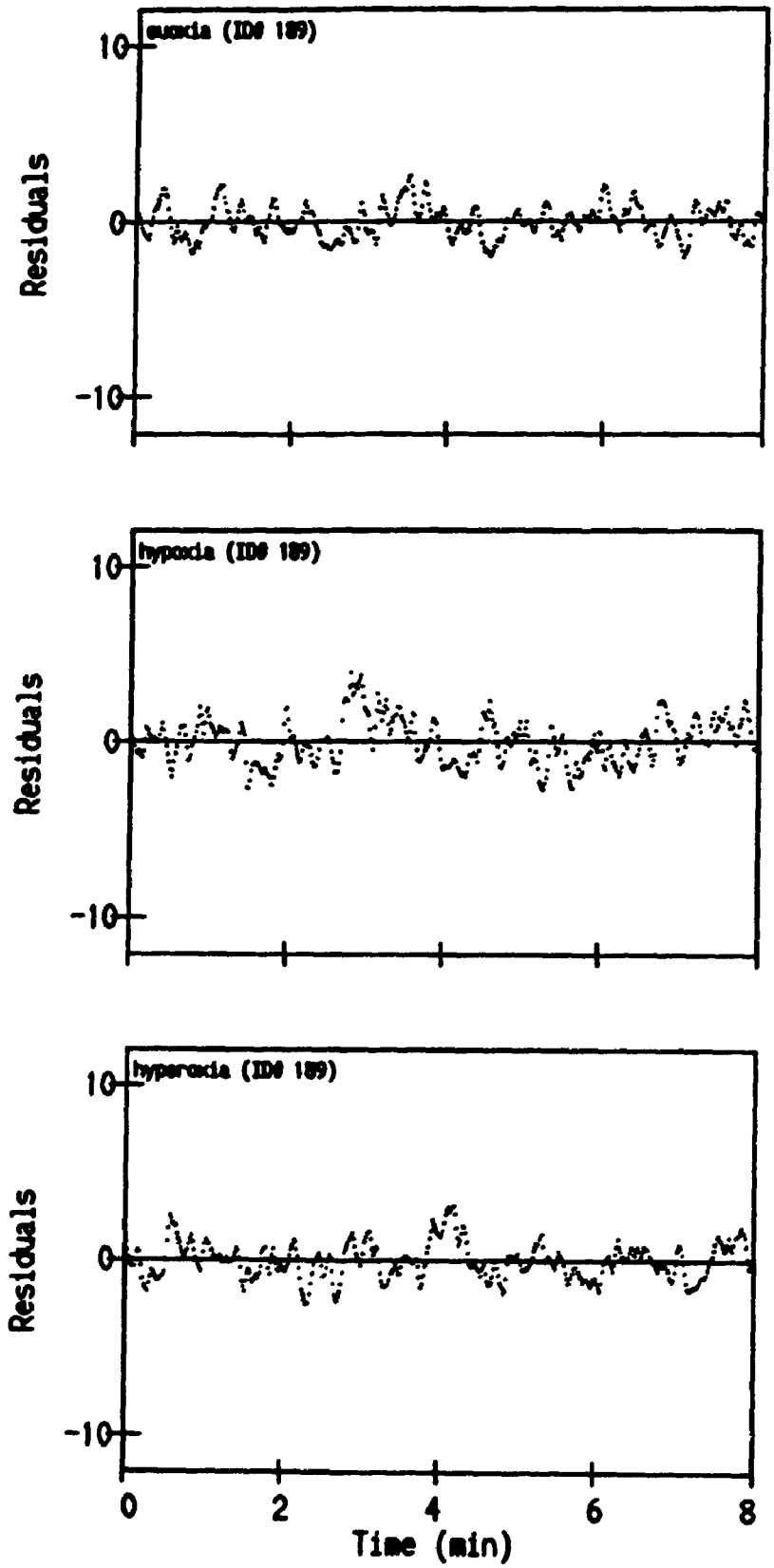


RESIDUALS FOR MODEL FITS (SUBJECT ID 1643)

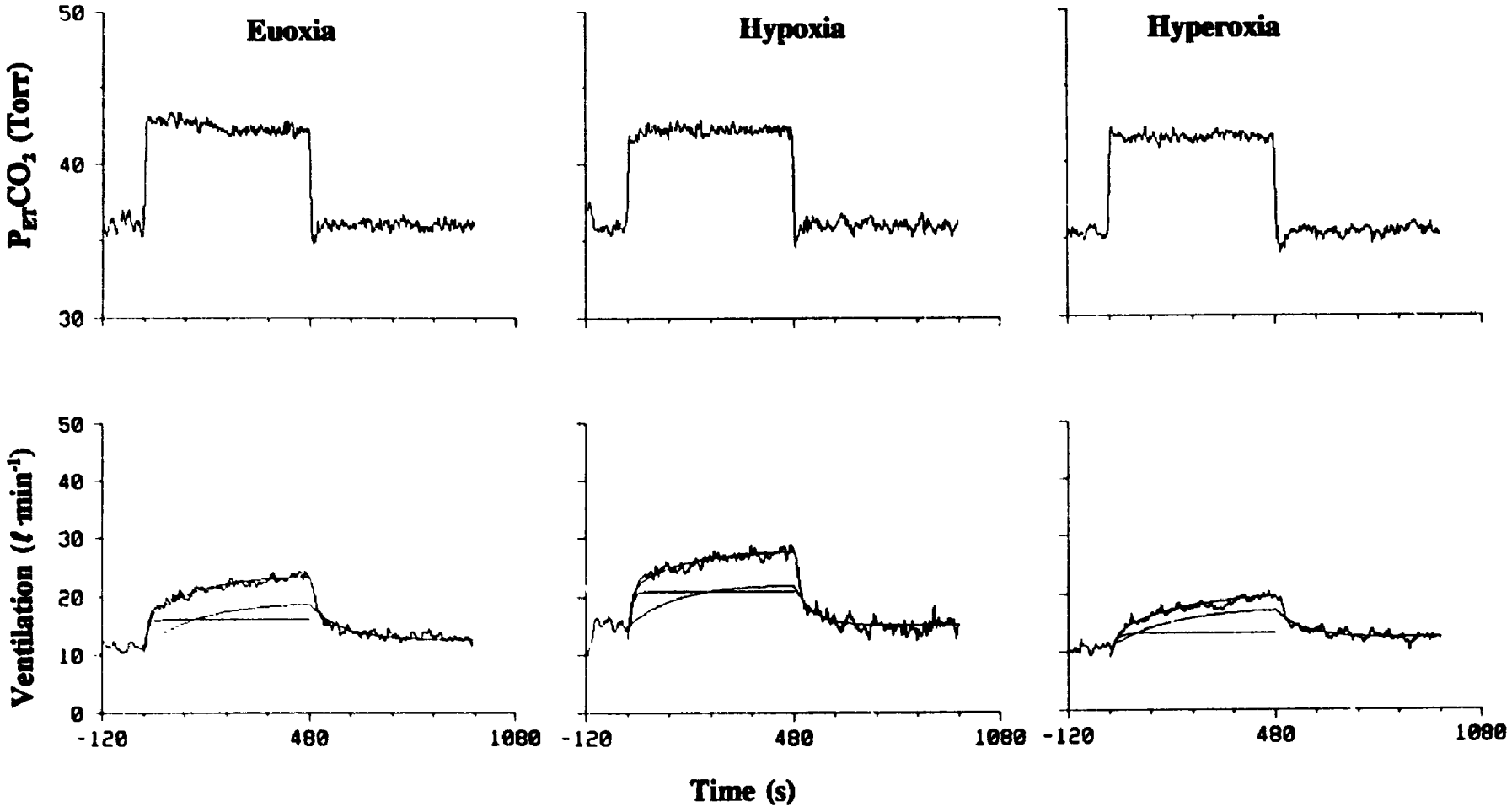


VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 189

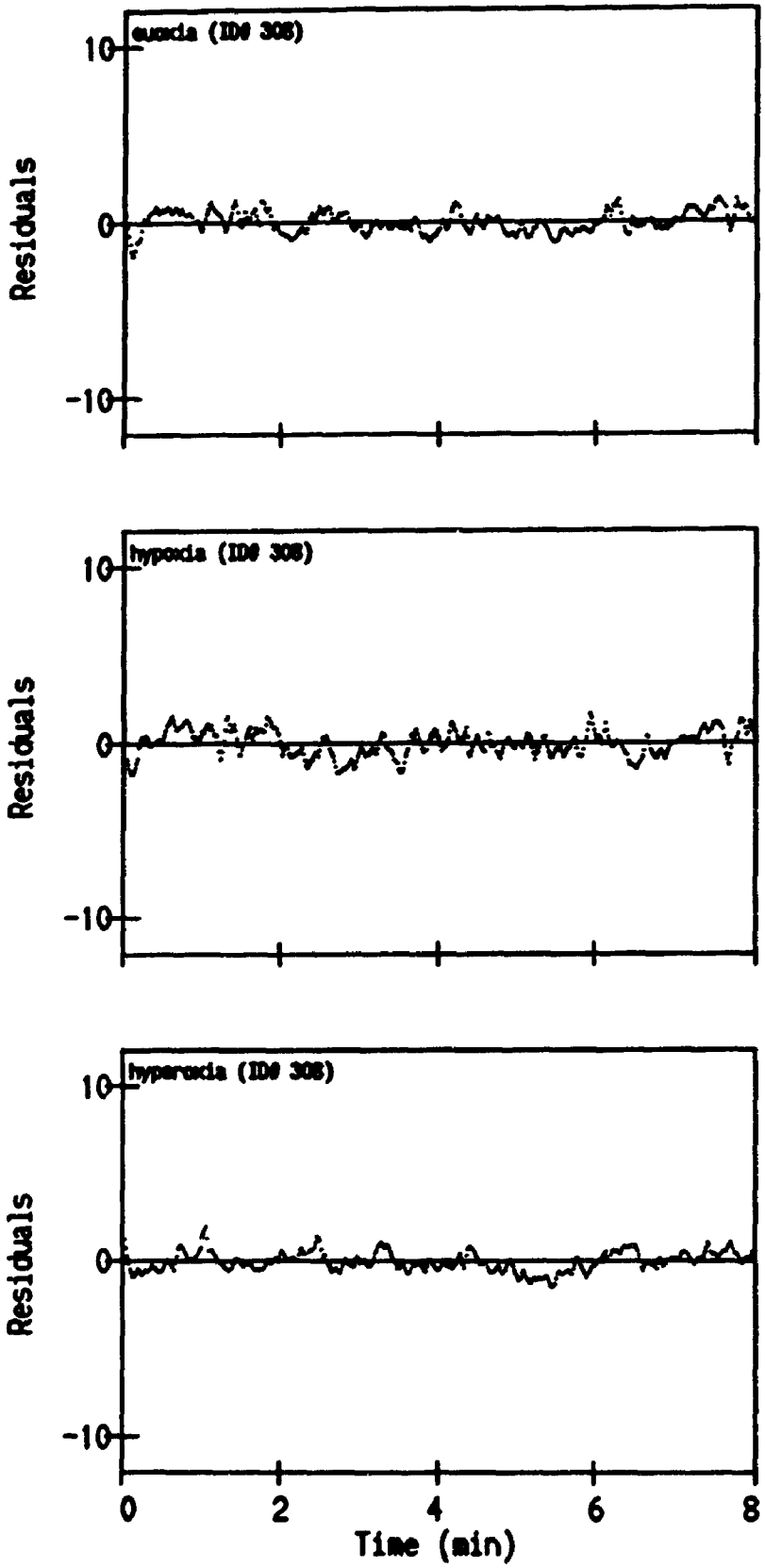



eucapnia (ID# 189)
hypocapnia (ID# 189)
hypercapnia (ID# 189)
Residuals
10
0
-10
0
2
4
6
8
Time (min)

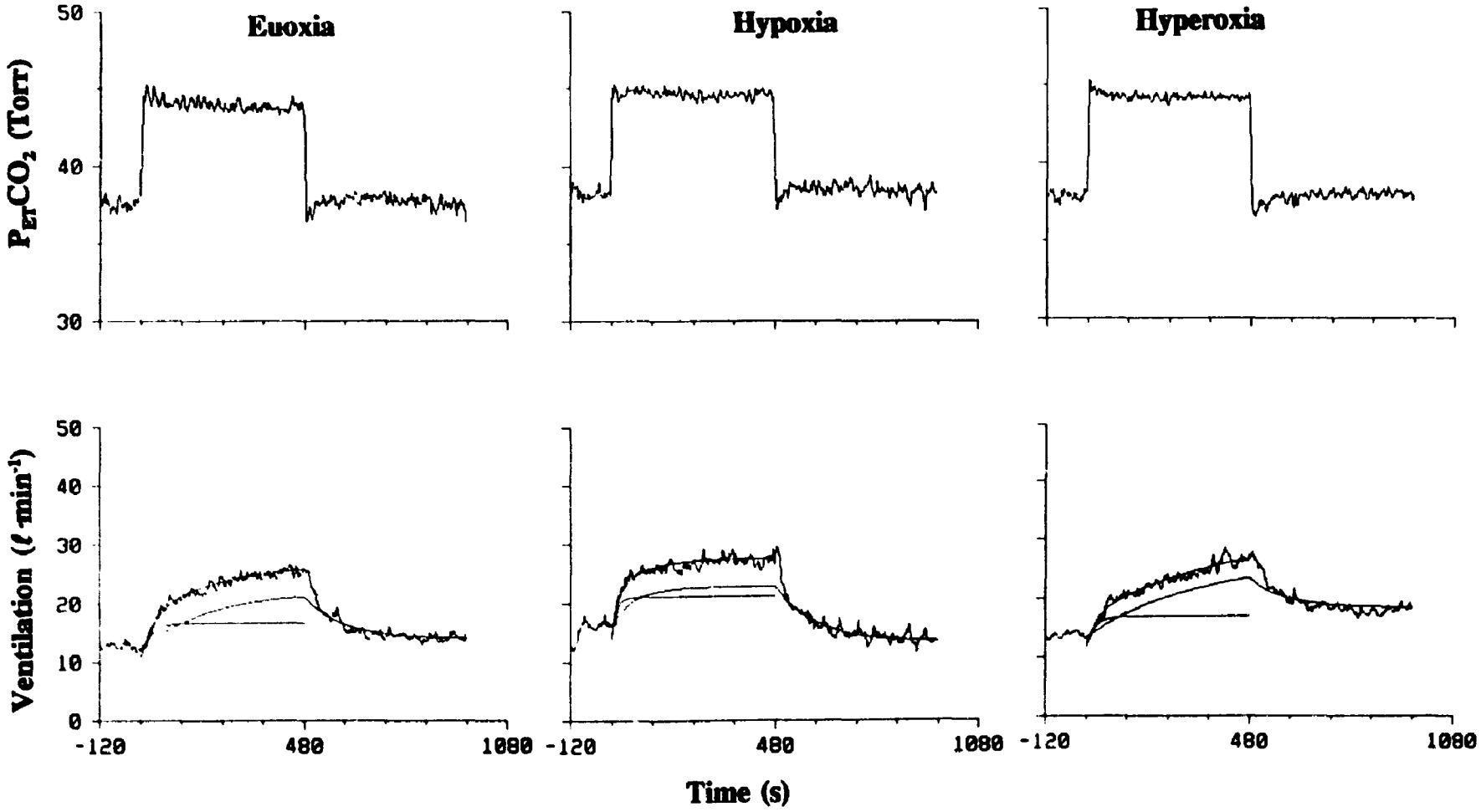
VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 308



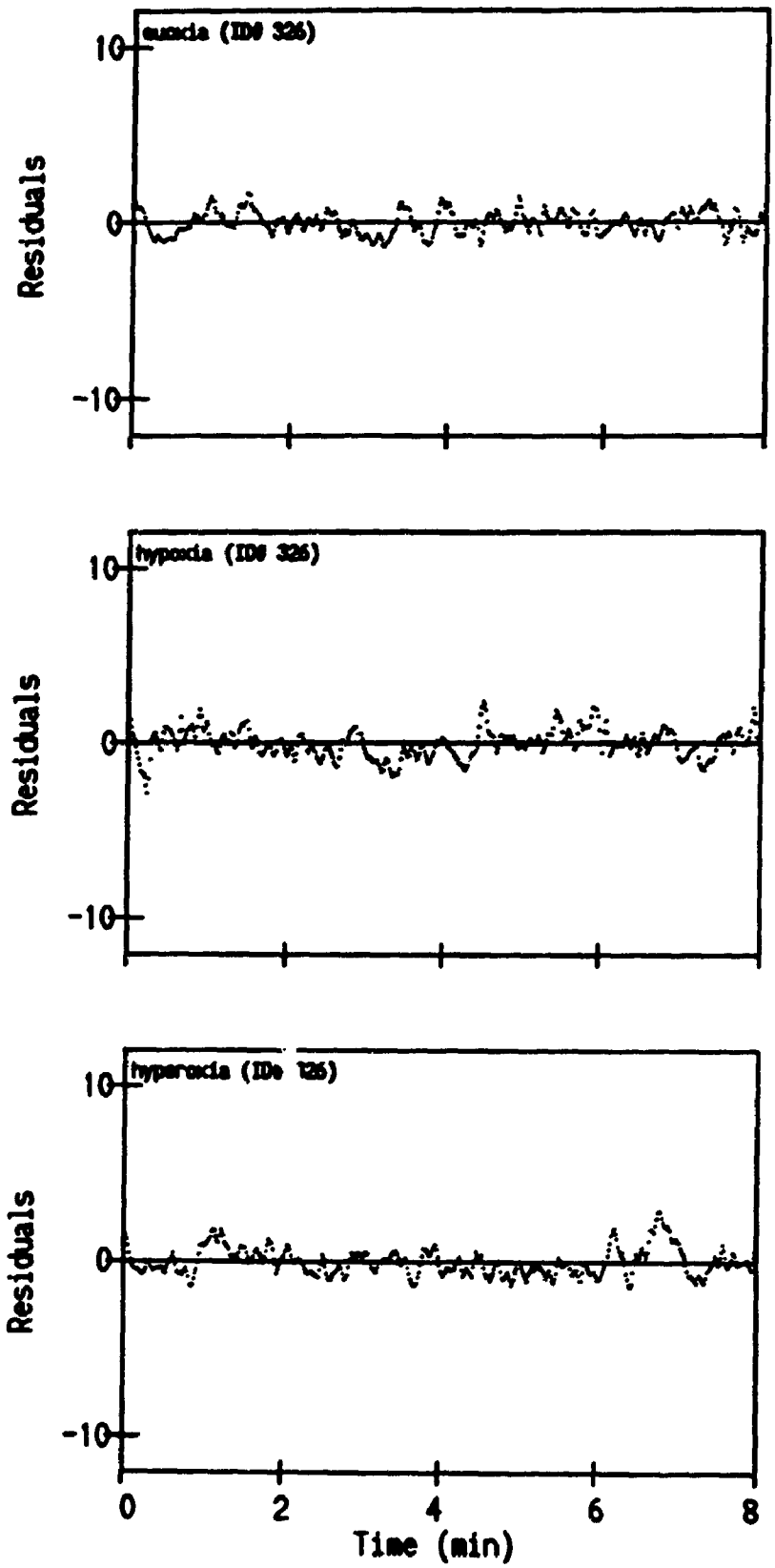
RESIDUALS FOR MODEL FITS (SUBJECT ID 308)



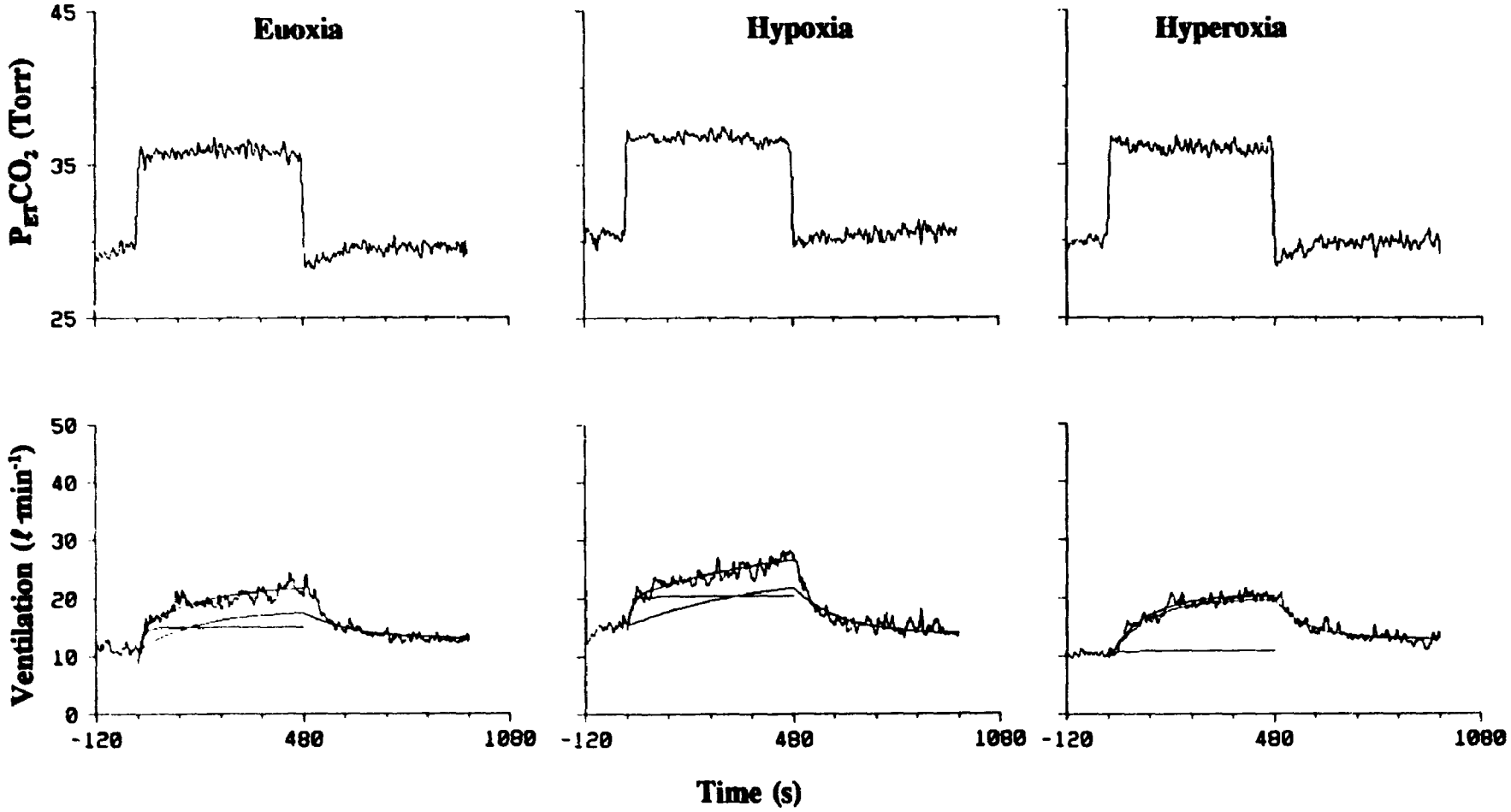
VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 326



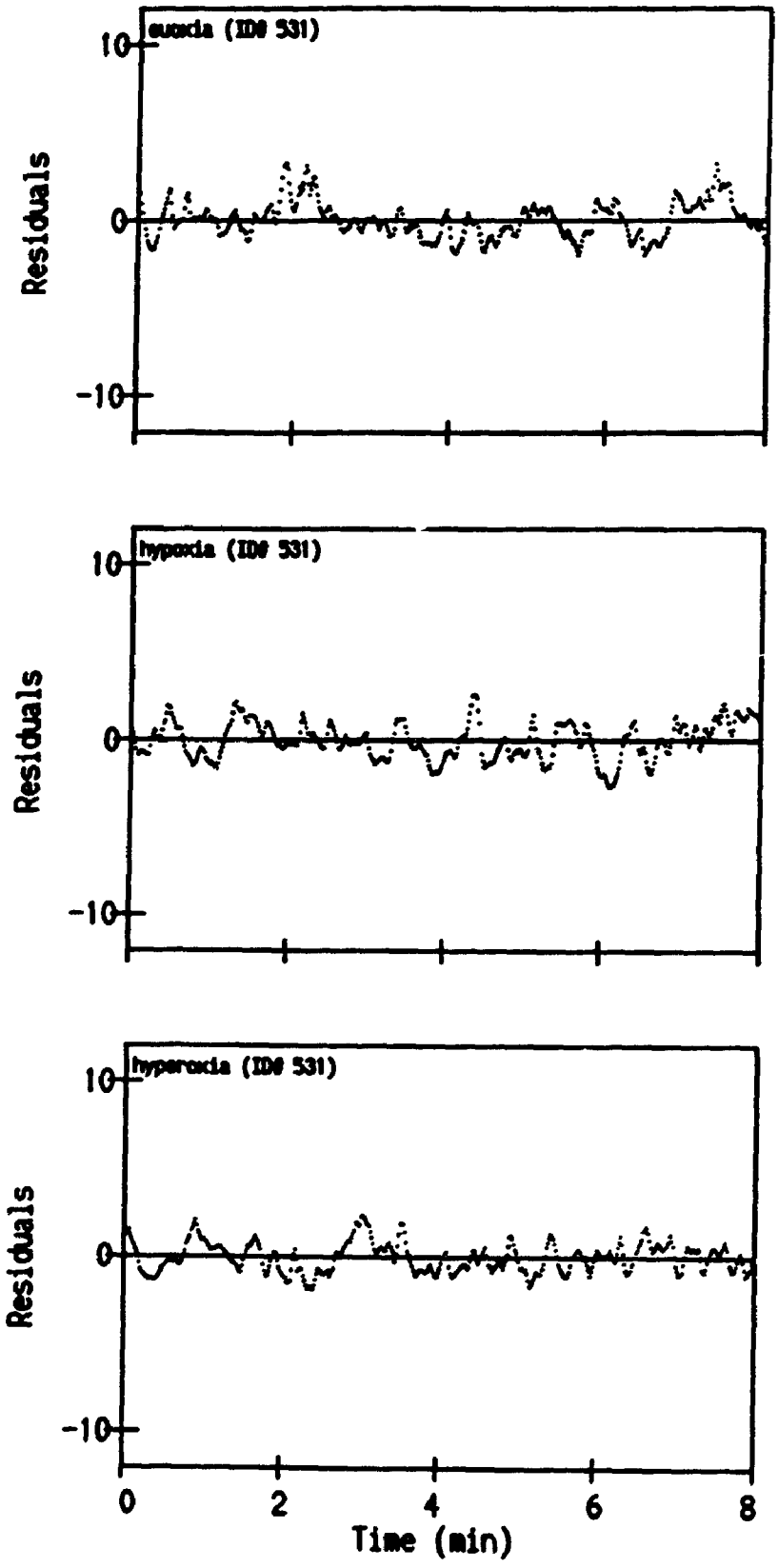
RESIDUALS FOR MODEL FITS (SUBJECT ID 326)



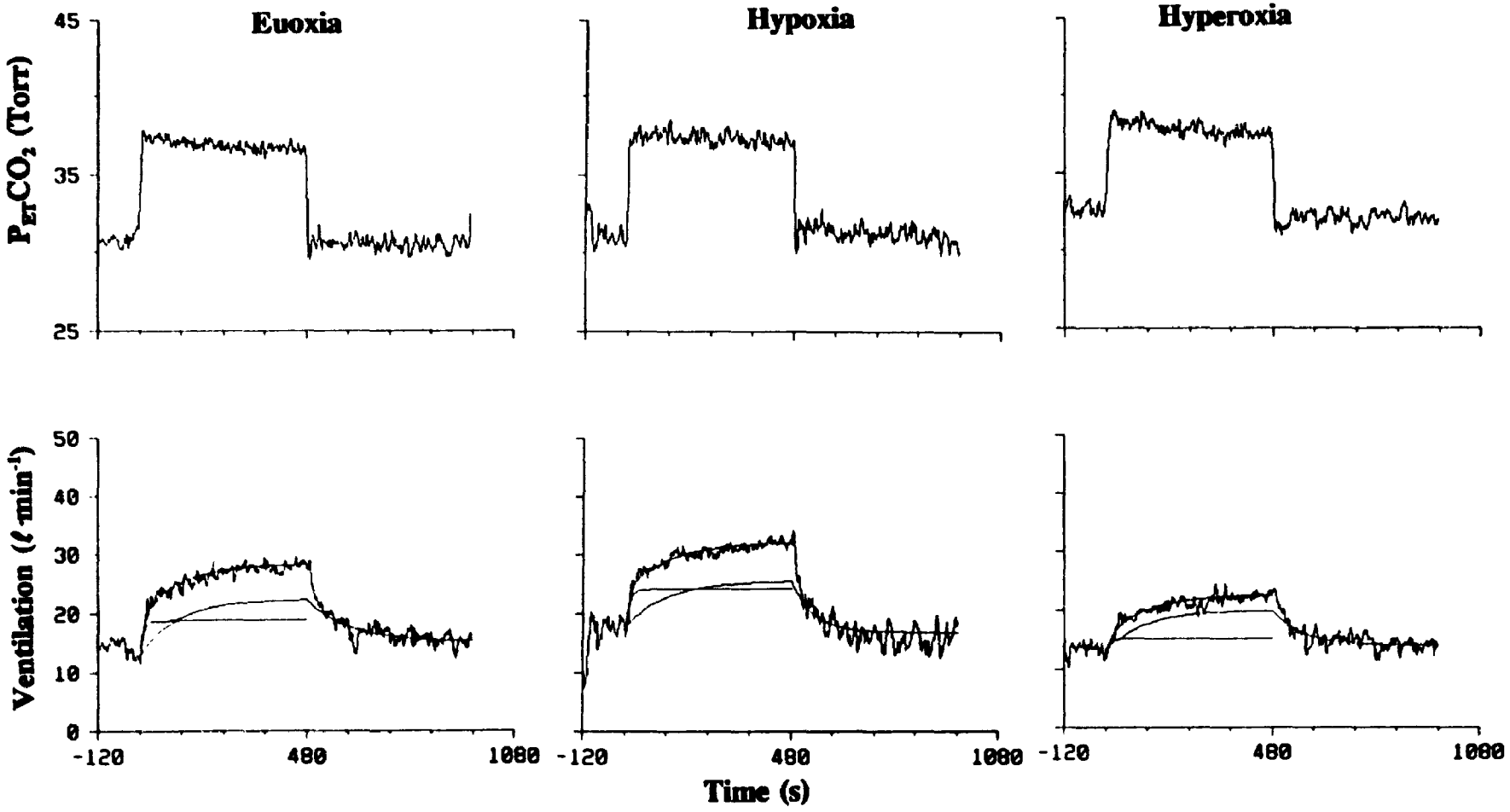
VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 531

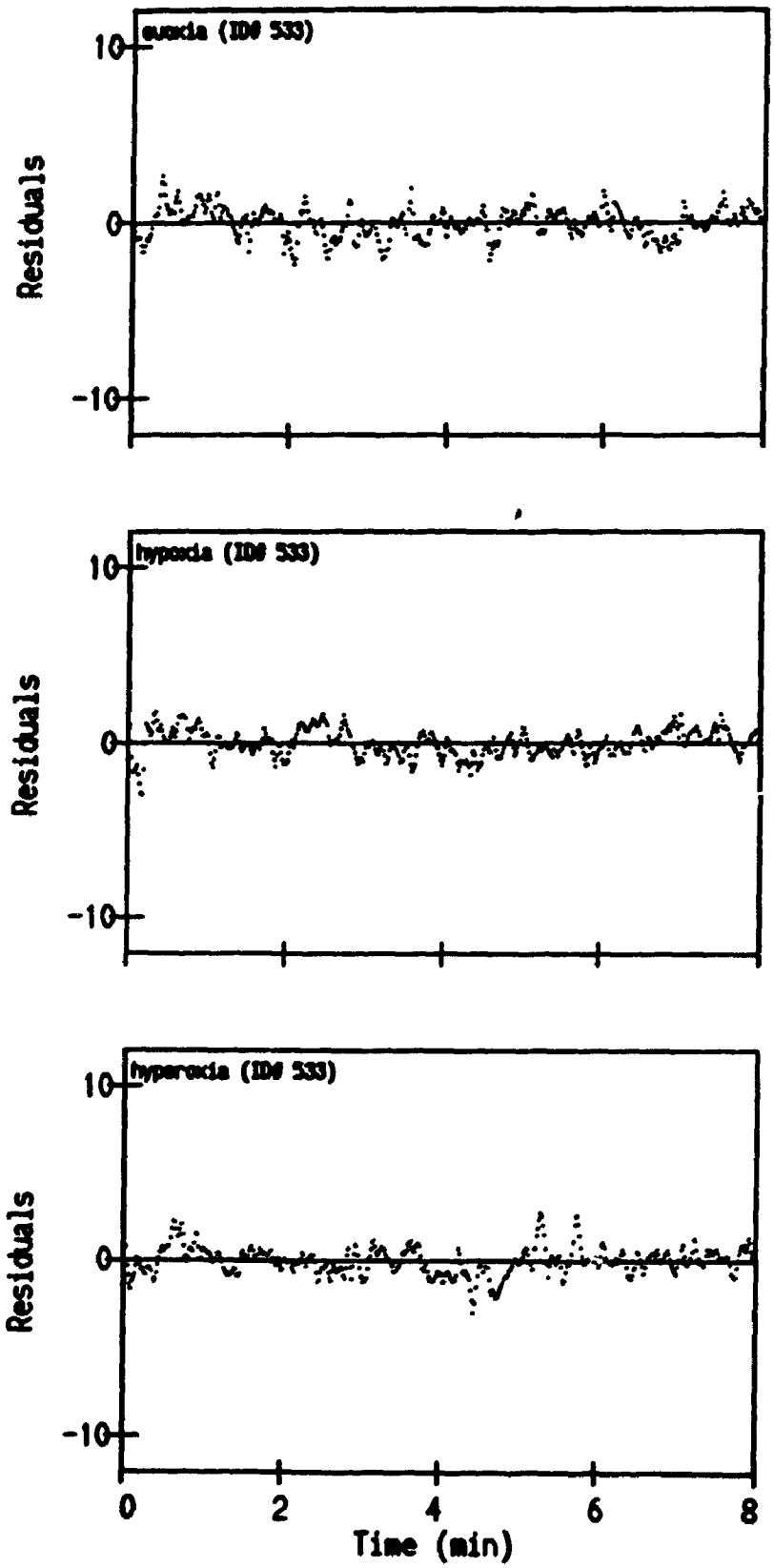


RESIDUALS FOR MODEL FITS (SUBJECT ID 531)



VENTILATORY RESPONSES AND MODEL FITS FOR SUBJECT ID 533




eunoia (ID# 533)
hypoxia (ID# 533)
hyperoxia (ID# 533)
Residuals
10
0
-10
0
2
4
6
8
Time (min)

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