Measurement of Hypoxic Ventilatory Drive at Rest and During Exercise in Normal Man

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CONTENTS

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I, Susan Caroline De Cort, declare that the research within, and the composition of this thesis are my own work.

ABSTRACT

Methods of assessing the carotid chemoreceptor mediated hypoxic ventilatory drive were compared in normal conscious humans.

The conventional progressive isocapnic method, which may underestimate the ventilatory response due to central hypoxic depression of ventilation was compared with transient hypoxia and three minute step-changes in inspired O_2. Measurements were made during moderate steady-state exercise, to potentiate hypoxic ventilatory drive thus maximising the signal-to-noise ratio of the response; this was particularly important during transient hypoxia.

The ventilatory response to step-change hypoxia (expressed as the slope of the $\dot{V}_E inst/S_a O_2$ relationship during hypoxia) was significantly greater than that to transient hypoxia for the whole group, although in two of the subjects it was very much smaller. The response to progressive isocapnic hypoxia was not significantly different from that to step-change or transient hypoxia. Fourier deconvolution of the $\dot{V}_E inst/S_a O_2$ relationship for transient and step-change hypoxia resulted in amplitude/frequency plots which were different for the two stimuli. This implies that the ventilatory response to hypoxia depends upon the time course as well as the magnitude of the hypoxia.

Measurement of ventilatory responses to repeated hypoxic stimuli and to step-change hypoxia of ten minutes duration showed that the differences in responses were not due to potentiation caused by prior exposure to hypoxia, or to central hypoxic depression of ventilation. Furthermore, the brief hypocapnia which occurred following transient hypoxia did not limit the ventilatory response, since responses to isocapnic transient hypoxia and transient hypoxia during which $P_{ET}CO_2$ was allowed to fall were not significantly different.

There was no difference in carotid chemoreceptor responses to transient and step-change hypoxia in anaesthetised cats, which suggests that the differences observed in humans may be a result of differences in brainstem modulation of the chemoreceptor input.

Studies of the effect of exercise, physical fitness and training showed that the extent to which exercise potentiates the ventilatory response to step-change hypoxia varies inversely with physical fitness. Physical training may decrease hypoxic ventilatory drive.

In conclusion, both transient and step-change hypoxic stimuli are required to assess the carotid chemoreceptor mediated hypoxic ventilatory drive. The differences in ventilatory response to these two types of hypoxic stimulus are likely to be a result of variable brainstem modulation of the carotid chemoreceptor response to hypoxia. Some of the individual variation in the normal population for hypoxic ventilatory drive measured during exercise is due to the individual level of physical fitness.

The overall purpose of this project was to develop a suitable method of assessing whether or not there exists, in the normal population, a group of individuals who have an unusually low carotid chemoreceptor mediated hypoxic ventilatory drive. This characteristic may play a role in athleticism, in altitude sickness and in the development of "blue bloater" symptoms in chronic obstructive airways disease.

CHAPTER 1 : INTRODUCTION

Chemical control of respiration by O_2, CO_2 and pH aims to maintain arterial blood gas tensions to cope with changing demands, for example the increase in metabolic requirements during exercise, or the decrease in inspired PO_2, at high altitude. The increase in ventilation which occurs in response to a fall in P_aO_2 (the hypoxic ventilatory drive) is mediated by chemosensory tissue in the peripheral chemoreceptors (carotid and aortic bodies). The increase in ventilation which occurs in response to an increase in P_aCO_2 (or a decrease in arterial pH) is mediated both by the peripheral chemoreceptors and by central receptors situated on the ventral medullary surface.

At sea level, where the ambient PO_2 is 20kPa and in individuals with normal lung function P_aO_2 is approximately 14.7kPa, hypoxic ventilatory drive does not play an important role in the control of breathing (Weil et al 1970), however it becomes important if P_IO_2 falls, for example at high altitude, or if P_aO_2 falls due to ventilation/perfusion mismatching in lung disease. Hypoxic and hypercapnic ventilatory drives vary between healthy individuals, and the intensity of these drives may determine the ability of an individual to acclimatise to high altitude (King and Robinson 1972), and may also be important in the pathogenesis of chronic obstructive lung disease. Dornhorst (1955) divided sufferers of this disease into two groups; the "blue bloaters" who have low P_aO_2, CO_2 retention, pulmonary hypertension and right heart failure, and "pink puffers" who have relatively well preserved P_aO_2 and P_aCO_2. The two groups have the same pathology and the same degree of airflow obstruction. Flenley et al (1970) suggested that patients with the "blue and bloated" syndrome had low hypoxic ventilatory drives, and if this was a premorbid characteristic, then detection of the low hypoxic ventilatory drive at an early stage of the disease may aid in the clinical management. The frequent observation that athletes have lower hypoxic ventilatory drives than non-athletes (Byrne-Quinn et al 1971, Leitch et al 1975, Scoggin et al 1978) suggests that hypoxic ventilatory drive may play some part in determining athletic performance, although this may only be true of endurance athletes. Low hypoxic ventilatory drive is known to be at least partly inherited (Hudgel et al 1974, Leitch et al 1975, Moore et al 1976, Scoggin et al 1978, Kawakami et al 1982), so it might be possible to

predict the potential of an athlete in the early stages of his career by measuring his hypoxic ventilatory drive

Development of an accurate method of measuring the peripheral chemoreceptor mediated hypoxic ventilatory drive in conscious man is therefore potentially useful to both scientists and clinicians for quantifying the pathophysiological mechanisms involved in the regulation of respiration by hypoxia.

I Sensitivity to Hypoxia

Paul Bert first demonstrated in 1878 that the reduced partial pressure of oxygen (Pa_{O_2}) was responsible for the increase in ventilation observed in human subjects at high altitude rather than the reduction in atmospheric pressure. In man, the most important receptors involved in this ventilatory response are the carotid chemoreceptors, located in the common carotid artery at the bifurcation into internal and external carotid arteries. The sensitivity of the carotid chemoreceptors to P_aO_2 and P_aCO_2 and to pH (independently of CO_2) was shown by Heymans and colleagues (Heymans and Bouckaert 1930, Heymans et al 1930, Heymans and Neil 1958). Both the aortic chemoreceptors, located in the ascending aorta, and the "miniglomera" located in the carotid arteries may be important in the mediation of the ventilatory response to hypoxia in animals (Comroe 1939, Matsuura 1973). These receptors, however, do not appear to contribute much to hypoxic ventilatory drive in man, as removal or denervation (surgical or chemical) of the carotid bodies abolished the the ventilatory response to both steady-state hypoxia (Guz et al 1966, Holton and Wood 1965, Wade et al 1970, Lugliani et al 1971, Wasserman et al 1975) and to transient changes in inspired O_2 (Wasserman 1976, Wasserman and Whipp 1976, Whipp and Davies 1979, Whipp and Wasserman 1980). In the presence of hypercapnia, however, the aortic bodies may play some part in mediation of hypoxia-induced hyperpnea (Swanson et al 1978, Honda et al 1979).

i) The Carotid Chemoreceptors

The first anatomical description of the carotid bodies was by Winslow (1732), but it was not until nearly two centuries later that DeCastro (1928) related the anatomical structure to function and suggested that they might act as sensors for blood-borne substances. Each carotid body is very small (approximate volume one cubic

millimetre) and has a complex structure consisting of glomus cells (type I cells), which are in close contact with capillaries and surrounded by the processes of sustentacular cells (type II cells). Each receives an extensive blood flow of about two litres per minute per 100 grammes of tissue (Daly et al 1954) via the glomic artery, which can be controlled independently of the systemic blood flow by a sphincter of smooth muscle in the glomic artery. Thus a wide variation in systemic arterial blood pressure does not affect chemoreceptor function until the closing pressure of the arteries (about 60mmHg) is approached (Purves 1970). The local blood flow to the glomus cells can also be controlled by precapillary sphincters. In vitro studies have shown that carotid chemoreceptor activity is affected by blood flow (Eyzaguirre and Zapata 1968), and "autoregulation" of the carotid body blood flow is important to maintain chemoreceptor function in adverse conditions.

The carotid body has both an afferent and an efferent nerve supply, the afferent pathway being mainly via fibres in the ganglioglomerular nerve which synapse with the glomus cells (DeCastro 1928, Hess and Zapata 1972, McDonald and Mitchell 1975). Additional innervation to the glomus cells may be provided by ganglion cells within the carotid body, preganglionic sympathetic fibres, (McDonald and Mitchell 1975), postganglionic sympathetic fibres (Verna 1981) or projections from the nucleus ambiguus and retrofacial nucleus (Hess and Cassady 1983). The efferent nerve supply consists of pre- and postganglionic sympathetic fibres (O'Regan 1977, 1981), with the postganglionic fibres mostly in the ganglioglomerular nerve (Eyzaguirre and Uchizono 1961) and vagal parasympathetic fibres (Neil and O'Regan 1971, Sampson 1972, O'Regan 1975, Willshaw 1975). As the afferent synapses on the glomus cells and the sympathetic nerve endings are in very close proximity (Verna 1981) it is possible that either glomus cell catecholamines are inactivated by uptake of catecholamines by the sympathetic nerve cells, or that the activity of the sympathetic efferents modifies that of the glomus cells as a result of the release of chemical products

The exact role of the glomus and sustentacular cells and the efferent and afferent nerve endings in chemoreception has still not been determined. As there are sensory synapses within the carotid body, this suggests that the ganglioglomerular afferent fibres themselves are not the chenmoreceptive elements, rather that this function is fulfilled by

either the glomus or the sustentacular cells. Studies in which the carotid body has been reinnervated following carotid nerve destruction suggest that the glomus cells play an important role in chemoreception (review : Eyzaguirre and Zapata 1984), although the mechanisms involved have not been clearly established. As glomus cells are known to contain dopamine, it is possible that dopamine release changes the sensory properties of the afferent fibres (Eyzaguirre et al 1983). The role of the efferent nerve supply is also very uncertain. Histological studies in animals have demonstrated the existence of sympathetic postganglionic (Verna 1979) and preganglionic (McDonald and Mitchell 1975, Kondo 1976) nerve endings close to the glomus cells, and it has been suggested that the glomus cells act as mediators of efferent inhibition of chemosensory output (Mitchell and McDonald 1975, McDonald and Mitchell 1975).

The effects of autonomic nerve stimulation on chemosensory output are very varied (O'Regan 1981) and evidence for the involvement of catecholamines in both inhibition (Sampson 1971, 1972, 1975, Mitchell and McDonald 1975, Willshaw 1975, Sampson et al 1976) and excitation (Neil and Joels 1963, Lee et al 1964) of chemosensory activity has been reported.

ii) The Hypoxic Stimulus

There is a linear relationship between arterial oxygen saturation (S_aO_2) and ventilation (Edelman et al 1973) and also between S_aO_2 and carotid chemoreceptor activity (Von Euler et al 1939). Comroe et al (1938), however, showed that when the carotid body of the dog was perfused with blood equilibrated with carbon monoxide (i.e. blood with a high level of carboxyhaemaglobin, (P_aO_2) and low S_aO_2), there was no increase in ventilation, which suggests that the chemoreceptors were sensitive to PO_2 rather than S_aO_2. This was confirmed in man by Chiodi et al (1941) and Assmusson and Chiodi (1941). Other studies have also demonstrated the lack of ventilatory and chemoreceptor response to a decrease in S_aO_2 caused by anaemia, carboxyhaemaglobinaemia and methaemaglobinaemia, without a change in P_aO_2 (Duke et al 1952, Hornbein 1968, Bartlett and Tenney 1970, Hatcher et al 1978, Fitzgerald and Traystman 1980, Lahiri et al 1981). Hebbel et al (1977) also found that subjects with haemaglobin with a high affinity for oxygen had an unusually high hypoxic ventilatory drive when ventilation was compared to S_aO_2, whereas their hypoxic ventilatory drive fell within the normal

range when ventilation was compared to P_aO_2, suggesting that it was P_aO_2 that was the stimulus to ventilation. The linearity of the relationship between ventilation or carotid chemoreceptor activity and S_aO_2 is a result of the sigmoid shape of the O_2 dissociation curve - the curve relating ventilation or carotid chemoreceptor activity and P_aO_2 is an hyperbola.

II Central Pathways

Although the exact pathways and synaptic connections linking the input from the carotid chemoreceptors to central neural structures are not yet known, there is evidence that input from the carotid chemoreceptors converges on the ventral medullary surface area (intermediate areas), which may be a site for integration of this input, before travelling to the central respiratory control system. See (1976) recorded evoked potentials (from the carotid sinus nerve) just below the intermediate areas in the dog, and Schlaefke et al (1979) found that although a respiratory response to hypoxia still existed following ablation of the intermediate areas, it was attenuated. Millhorn et al (1982) showed that the respiratory response (recorded as phrenic nerve activity) to carotid sinus nerve stimulation was reduced by cooling, and that this effect was increased as the level of cooling became more severe. Neuroanatomical studies have shown that carotid sinus nerve afferents project to the nucleus tractus solitarius (Berger 1979, Panneton and Loewy 1980), which is near the dorsal surface of the medulla, and is likely to be the first synapse of the carotid chemoreceptor afferents.

From the ventrolateral medulla, the input originating from the carotid chemoreceptors is relayed to the central respiratory controller. This consists of a voluntary component, governed by the cortex and an automatic component located in the brainstem, consisting of three separate "centres" and having inherent rhythmicity (review : Berger 1977), which is modified by chemoreceptor input.

III The Effector System

Output from the respiratory control areas in the medulla oblongata reaches the effector muscles (the intercostal muscles and diaphragm) via the phrenic, intercostal and abdominal nerves and determines the rate and depth of breathing.

The ventilatory response to hypoxia is likely to be in part determined by the ability of the effector system to respond. In healthy subjects, the vital capacity might be a limiting factor to an increase in ventilation - for example during heavy exercise when ventilation is already increased to a level close to the maximum, inhalation of a hypoxic gas mixture would not produce a very large change in ventilation. In patients, weakness of the respiratory muscles or lack of elasticity of the lungs might limit the ventilatory response to hypoxia, as might airways obstruction. Diseases affecting neural transmission (e.g. demyelinating disease) or generation of contraction within muscles (e.g. myasthenia gravis) will limit the ventilatory response to hypoxia. The ability to increase ventilation in response to hypoxic stimuli is also reduced in the presence of airflow obstruction (as in chronic obstructive airways disease or asthma) or restrictive defects of the lungs such as fibrosis or of the chest wall, such as hyphosis.

IV Measurement of the Chemoreceptor Response to Hypoxia

Three approaches can be used to assess the carotid chemoreceptor response to an hypoxic stimulus:

1) electrical recording of the chemoreceptor afferent activity in the carotid nerve. Although providing direct assessment of carotid chemoreceptor activity, such measurements obviously cannot be made in conscious healthy human subjects. Furthermore, the carotid chemoreceptor discharge may be affected by both the anaesthetics (Biscoe and Millar 1968, Edwards et al 1980), and the trauma caused by surgical procedures used in animal studies. These are some of the problems which must be taken into account when comparing measurements of carotid chemoreceptor activity in anaesthetised or decerebrate animals with ventilatory measurements in conscious humans

2) measurement of the changes in ventilation following inhalation of hypoxic gas mixtures. Although avoiding the problems involved in direct recordings from the carotid sinus nerve, changes in ventilation will be affected by neural integration of the chemoreceptor afferent activity within the brainstem and the mechanics of the lungs and chest wall as well as the chemoreceptor response to hypoxia. The three basic methods of measuring the ventilatory response to hypoxia are steady-state (either inhalation of an hypoxic gas mixture until steady-state

ventilation has been reached, or comparison of slopes of V_E/P_aCO_2 response lines during steady-state hypoxia for different percentages of inhaled CO_2), progressive isocapnic (a gradual reduction in the percentage of inhaled O_2, while isocapnia is maintained) and transient (inhalation of several breaths of an hypoxic gas mixture). Different methods of measuring the ventilatory response to hypoxia are compared in chapter two.

3) measurement of the occlusion pressure as an indexof the respiratory centre output. This technique involves the measurement of pressure generated by the inspiratory muscles against an obstructed airway 100msec after the onset of inspiration from residual capacity ($P_{0.1}$, Whitelaw et al 1975). This measurement is independent of pulmonary and chest wall mechanics, and avoids factors affecting respiratory pattern , in particular the vagal volume related reflex, as it measures the rate of rise of inspiratory activity, and not the peak activity. This method has the disadvantage that in some subjects an occlusion time of only 170msec may influence the pattern of breathing Also, it is usually only measured every 3-5 breaths and is therefore not suitable for studying transients, as every breath would need to be recorded.

VI Variability of Hypoxic Ventilatory Drive

Hypoxic ventilatory drive varies widely both in humans (Dripps and Comroe 1947, Leitch 1976, Hirshman et al 1975, Sahn et al 1977) and in cats (Vizek et al 1987a). This variability may occur as a result of inherent differences in the responses of the carotid chemoreceptors (Vizek et al 1987a) and central control and integration mechanisms between individuals (i.e. true variability), or it may be caused by other factors affecting either the carotid body chemoreceptor response to hypoxia or the translation of the carotid chemoreceptor response into ventilatory terms. Studies of hypoxic ventilatory drive in twins (Collins et al 1978, Leitch et al 1975) and sons of patients with chronic obstructive pulmonary disease (Kawakami et al 1982) suggests that part of the variability in hypoxic ventilatory drive between individuals is due to inherited characteristics. Variability may also be caused by factors affecting either the carotid chemoreceptor response to hypoxia,

such as interaction of hypoxia with hypercapnia or pH at the chemoreceptors, or central processing of the carotid chemoreceptor input.

1 Factors Affecting the Carotid Chemoreceptor Response to Hypoxia

i) The Autonomic Nervous System

Stimulation of sympathetic nerves in the cat was found to have no effect on the carotid chemoreceptor activity of approximately half the cats studied by O'Regan (1981). In the remaining preparations, however, it caused not only two different types of excitatory effects (i.e. with different latencies and half-times), but also an inhibitory effect in a small proportion of the animals. Excitatory effects of sympathetic nerve stimulation on chemosensory activity have also been observed by others in cats (Floyd and Neil 1952, Biscoe and Purves 1967). Evidence of inhibitory effects has also been demonstrated by Neil and O'Regan (1969, 1971a), Majcherczyck et al (1974) and Hatcher et al (1978). The role of the autonomic nervous system in the modification of chemoreceptor response to hypoxia is uncertain. During normoxia in anaesthetised cats, cutting the sympathetic and parasympathetic nerve supply to the carotid bodies did not result in any change in chemosensory discharge (Floyd and Neil 1952, Neil and O'Regan 1971a, Carmody and Scott 1974, Majcherczyck et al 1974), although the sympathetic nerve supply is thought to exert a stabilising effect upon carotid chemoreceptor discharge (Biscoe and Purves 1967,). During hypoxia, Carmody and Scott (1974) reported that the increase in ventilation was less well maintained after elimination of the sympathetic nerve supply to the carotid body, which suggests that the sympathetic nerves may modulate chemosensory activity during hypoxia. Floyd and Neil (1952) found in the cat that ganglioglomerular nerve efferent activity increased during hypoxia. Biscoe and Purves (1967), however, found even marked changes in P_aO_2 maintained for up to 30 seconds did not result in changes in the activity of efferent fibres in the ganglioglomerular nerve, although this may have been due to the shorter duration of hypoxia used by Floyd and Neil (1952). Parasympathetic efferent activity, however, may exhibit a more marked effect upon chemosensory discharge during hypoxia. In anaesthetised cats, Neil and O'Regan (1969, 1971a) and Sampson and Biscoe (1970) showed that parasympathetic fibres exert a depressant effect on the carotid

chemoreceptor response to hypoxia, and this effect has also been observed during chronic hypoxia (Smatresk et al 1981).

Because autonomic efferent fibres do appear to be active during hypoxia, other factors thought to affect autonomic nerve activity, for example exercise (Hornbein and Roos 1962, Biscoe and Purves 1967) or alkalinity of the cerebrospinal fluid (Trzebski 1976) could influence the carotid chemoreceptor response to hypoxia if it was measured either during exercise or alkalosis.

ii Circulating Catecholamines

The catecholamines contained in the carotid body are considered to be putative neurotransmitters (review : Alfes et al 1977), although this is highly debated. The glomus cells of the carotid body are known to contain dopamine, and the intracellular dopamine level has been shown to increase during chronic hypoxia in rabbits and rats. Dopamine can have both excitatory and inhibitor effects on the carotid chemoreceptors. The action of catecholamines on chemosensory activity appears to depend upon the catecholamine concentration. Bisgard et al (1979) reported that large doses of dopamine caused an excitatory effect upon carotid chemoreceptor activity, whereas smaller doses or slow infusion resulted in chemosensory inhibition. In low doses, dopamine acts as a β_1 agonist, whereas in high doses it has both direct and indirect stimulatory effects at α receptors (Goodman and Gilman 1975). Inhibition of the spontaneous discharge of the carotid chemoreceptors by intra-carotid injection of adrenaline, noradrenaline and dopamine has been demonstrated by Sampson (1971), whereas in the studies of Neil and Joels (1963), Lee et al (1964) and O'Regan (1981) injection of adrenaline and noradrenaline are associated with an increase in carotid chemoreceptor activity. Circumstances which initiate the "fight or flight" reflex are known to cause a release of catecholamines from the adrenal glands into the bloodstream, for example cold, apprehension and exercise. Any of these which occur during the measurement of hypoxic ventilatory drive could therefore affect this measurement. Cunningham et al (1963) have also observed that noradrenaline increases ventilatory sensitivity to hypoxia independently of the increase in metabolic rate caused by this hormone.

iii) Interaction of Hypoxia With Hypercapnia

Interaction of hypoxia and hypercapnia, resulting in an increase in ventilation greater than that caused by either stimulus alone was first observed in human subjects by Nielson and Smith (1952) and has since been confirmed in many other studies (review:Lloyd and Cunningham 1963). Stimulus interaction (i.e. interaction of hypoxia with hypercapnia) at the level of carotid chemoreceptors has been demonstrated in both single fibre and whole nerve preparations in animals (Eyzaguirre and Lewin 1961, Hornbein 1968, Fitzgerald and Parks 1971, Lahiri and Delaney 1975). There is also evidence for peripheral/central interaction of stimuli. An area exists within the ventro-lateral medulla, originally thought only to be sensitive to pH (Mitchell et al, 1963, Loeschcke 1982) has recently been shown to cause changes in ventilation in response to pH and CO_2 independently of one-another (Teppema et al 1983, Shams et al 1984, Eldridge et al 1985). Multiplicative interaction of the chemoreceptor input and the medullary response to CO_2 and pH has been shown both in animals and in man (Lee et al 1975, Adams et al 1978, Kao and Mei 1978) , although some authors argue that the interaction of CO_2 and O_2 in humans can be entirely accounted for by the carotid chemoreceptors (Cunningham 1974, Whipp et al 1976).

Because of this interaction of O_2 and CO_2 either at peripheral or central locations, it is important to maintain isocapnia at the normoxic level when measuring hypoxic ventilatory drive, as hyper- or hypocapnia would result in falsely high or low measurements of hypoxic drive respectively.

2 Factors Affecting Central Control of Ventilation

i) Central Hypoxic Depression of Ventilation

Although there is evidence for central chemosensitivity to CO_2 (see above), there is no evidence for central stimulation of ventilation by hypoxia. Moyer and Beecher (1942) found an increase in ventilation during hypoxia after carotid denervation in lightly anaesthetised dogs, but this may have been aortic chemoreceptor stimulation, as these receptors may play a role in the mediation of the ventilatory response to hypoxia in animals (Comroe et al 1939). It has been suggested that rather than an having an excitatory effect on ventilation, hypoxia may act centrally to depress ventilation, thus decreasing the overall

ventilatory response to hypoxia (Holton and Wood 1965, Weiskopf and Gabel 1975). This is probably an indirect effect, due to increased cerebral blood flow during hypoxia causing central hypocapnia (Weiskopf and Gabel 1975). An alternative explanation is that rather than a depressant effect as such it may be a result of the biphasic response to hypoxia, known to exist in newborn infants (Crosse and Oppe 1952, Rigatto et al 1972), and thought to be a centrally mediated effect, possibly a result of increased alkalinity (Vizek et al 1987a). This characteristic is retained by some subjects into adult life (Easton et al 1986). If some subjects exhibit this "central hypoxic depression" to a greater extent than others, as suggested by Edelman et al (1970) and Shaw et al (1982) then this could affect the variability of hypoxic ventilatory drive. This is discussed in detail in chapter four of this thesis.

ii) Input from Muscle Afferents

The potentiation of the ventilatory response to hypoxia by muscular exercise is well documented in man (Cunningham et al 1968, Bhattacharyya et al 1970, Weil et al 1972, Martin et al 1978). As passive exercise (i.e. no change in oxygen consumption) was found to increase carotid chemoreceptor and sympathetic efferent activity in cats during normoxia (Biscoe and Purves 1967)it was suggested that this potentiation effect may occur at the carotid chemoreceptors as a result of discharge of muscle afferents causing activation of sympathetic efferent fibres. Davies and Lahiri (1973), however, found no modification of the carotid chemoreceptor response to hypoxia by electrically induced or passive exercise in anaesthetised cats, although they did observe potentiation of the ventilatory response to hypoxia by exercise. They concluded, therefore, that the interaction of exercise and hypoxia occurs at a central location.

The degree of potentiation of hypoxic ventilatory drive depends upon the level VO_2 reached during exercise (Weil et al 1972, Martin et al 1978), this could greatly contribute to intersubject variability of hypoxic ventilatory drive if it is measured during exercise , as standardisation of exercise levels is a complex problem. Studies investigating the effects of exercise level upon hypoxic ventilatory drive are described in chapter seven.

iii) Hypothalamic Influences

Hypoxic ventilatory drive is known to be increased by increased body temperature (Natalino et al 1977), so this is another factor which must be taken into account when assessing the variability of hypoxic ventilatory drive. Although the carotid chemoreceptors themselves have been shown to have a small reaction to changes in temperature (McQueen and Eyzaguirre 1974) in the cat, afferent fibres project from the carotid chemoreceptors to the hypothalamus (Yamashita 1977, Calaresu and Ciriello 1980), which is the temperature regulating centre of the body. Interaction between chemosensory afferent input and temperature regulation may therefore occur within the hypothalamus.

The hypothalamus may also modify the hypoxic ventilatory drive depending on the state of wakefulness of the subject. As the reticular activating system within the hypothalamus determines the state of wakefulness, and the carotid chemoreceptors have projections to the hypothalamus, hypothalamic influences may cause the fall in hypoxic ventilatory drive during sleep stage 4 (Gothe et al 1982, Douglas et al 1982, Berthon-Jones et al 1982, Hedemark and Kronenberg 1982)

iii) Cortical Influences

Personality is known to affect hypercapnic ventilatory drive (Saunders et al 1972), more extrovert people having higher hypercapnic ventilatory drives. The effect of personality or mood upon hypoxic ventilatory drive, however, has not been studied. Factors such as fatigue, which may affect mood, or anxiety concerning the experiments could affect hypoxic ventilatory drive. Awareness of events during studies in which the ventilatory response to adrenaline was investigated has been shown to significantly affect the ventilatory responses (Lloyd and Cunningham 1958).

3 Other Factors Affecting Hypoxic Ventilatory Drive

Apart from the effects on hypoxic ventilatory drive of the increase in neural output of muscle afferents and in circulating catecholamines, exercise also increases metabolic rate. Increased metabolic rate by mechanisms other than exercise, such as hyperthyroidism, are known to be accompanied by an increase in hypoxic ventilatory drive (Doekel et al 1976, Zwillich et al 1977), and there is evidence

of a correlation between resting metabolic rate and hypoxic ventilatory drive, at least in men (White et al 1983). The mechanisms for this are unknown.

Correlations between hypoxic ventilatory drive and body height, weight and surface area have also been observed (Hirshman et al 1975). These correlations are likely to be a consequence of the relationship between hypoxic ventilatory drive and metabolic rate.

Hypoxic ventilatory drive is attenuated by increasing age (Kronenberg and Drage 1973, Peterson et al 1981), and although the mechanisms of this effect are not known, it appears to be a result of changed central neural output to the lungs rather than of changed lung mechanics in the elderly (Peterson et al 1981).

Acclimatisation to high altitude causes an initial increase in hypoxic ventilatory drive, followed by a decrease proportional to the duration of stay at high altitude (Forster et al 1971, Weil et al 1971). Lifelong residents at high altitude, however, have a diminished hypoxic ventilatory drive (Milledge and Lahiri 1967, Lahiri et al 1970, 1972) which is retained even after many years subsequent residence at sea level (Sorensen and Severinghaus 1968).

The aims of this study were therefore :

1) to determine the optimal method and conditions for measuring the peripheral chemoreceptor mediated hypoxic ventilatory drive in normal conscious man.

2) to investigate the effect of duration and repetition of the hypoxic stimulus on hypoxic ventilatory drive,

3) to investigate the effect of physical fitness and exercise level on hypoxic ventilatory drive.

CHAPTER 2 : METHODS AND EQUIPMENT USED TO MEASURE HYPOXIC VENTILATORY DRIVE IN NORMAL MAN

The experimental methods and equipment used to measure hypoxic ventilatory drive in all the studies involving human subjects are described below. Variations specific to each study are described in the appropriate chapters, along with experimental protocols and statistical methods.

I Subjects and General Methods

The subjects were either healthy volunteers drawn from laboratory staff or army recruits. They had no history of respiratory or cardiovascular disease, and were taking no medication at the time of the study.

The aims and nature of the studies were explained in detail to all the subjects. Ethical permission had been given for all studies by the Ethics of Medical Research Sub-Committee of the Lothian Health Board.

Age, height, weight and smoking history were recorded for each subject. FEV_1, FVC, lung volumes by helium dilution, single breath carbon monoxide diffusing capacity, and airways resistance by body plethysmography were also measured. The methodology used complied with the Report of Snowbird Workshop on Standardisation of Spirometry (1977). Predicted values for women were from Hall et al (1979) for lung volumes and TCO from Billiet et al (1963). For men the predicted values for lung volumes were from Crapo et al (1981, [illegible]) and TCO from Cotes (1965). Results are tabulated in appendices II and III.

Measurements were made with the subject either at rest seated in a comfortable armchair, or during exercise on a treadmill. The subjects breathed through a respiratory valve using a mouthpiece and noseclip. Respiratory variables were measured breath-by-breath and mixed expired gas was analysed over two-minute periods to calculate gas exchange. Details of these procedures are described below.

III Equipment

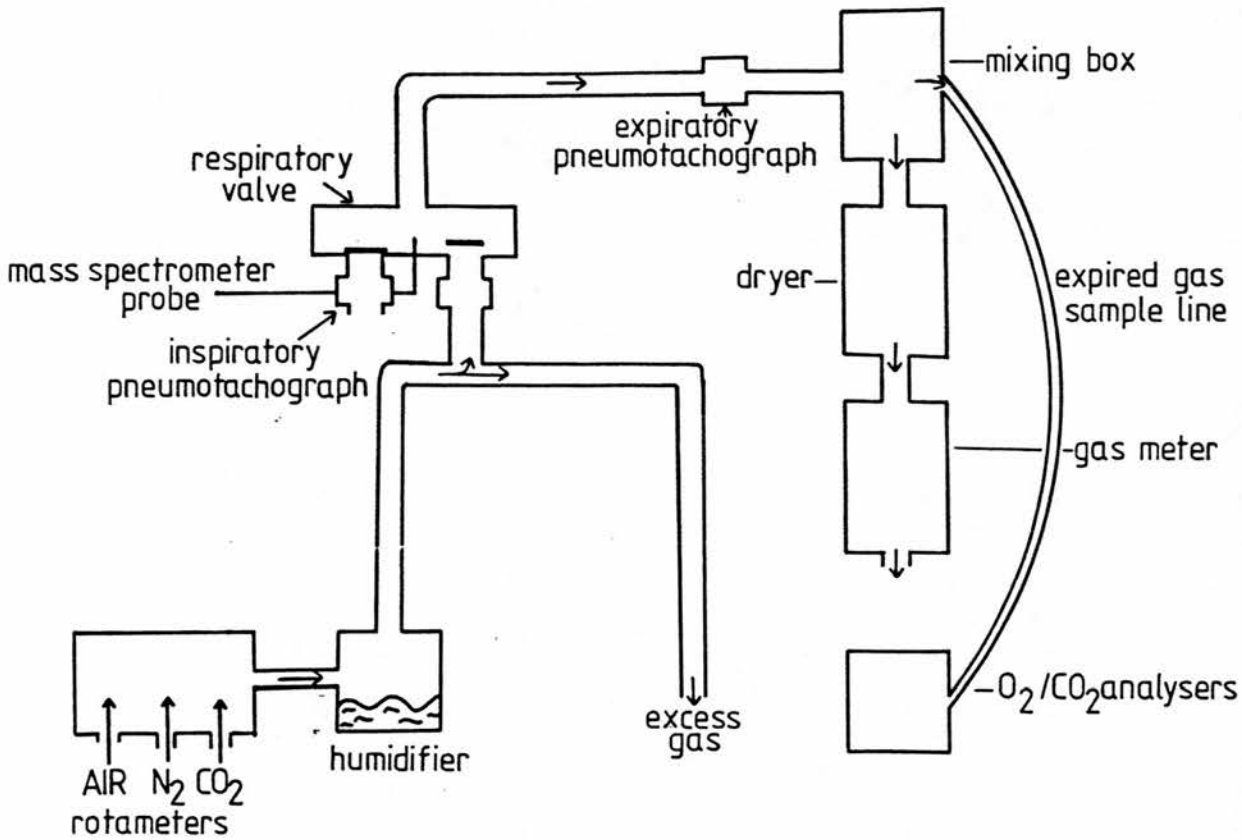
i) Breathing Circuits

Figures 2.1 and 2.2 show the circuits used for step-change, progressive and transient hypoxia used in chapters three and four. Modifications used in chapters six to eight are described below.

In chapters three and four a low resistance (range 0-4.8 cmH_2O over a flow range 0-110 $lmin^{-1}$, fig 2.3) custom-made valve with a dead space of 90ml was used. The valve had two inlet ports, either of which could be selected by use of a mechanically operated remote control switch, out of sight of the subject. Mouth pressure was measured via a port between the inspiratory and expiratory flaps of the valve, and a mass spectrometer probe was positioned close to the mouth for continuous inspired and expired gas analysis. In chapters six to eight where a choice of more than two inspiratory ports was required, a five-way valve (Hans-Rudolph 2440 series, five-way Gatlin shape valve) with a dead space of 95ml was connected to one inspiratory port of the original valve (fig 2.4). The Hans-Rudolph valve had a similar pressure-flow relationship to the custom-made valve (fig 2.3). Each port was closed by a pneumatically operated silicone rubber balloon. The balloons could be inflated and deflated very rapidly by means of a remote controller (Hans-Rudolph series 2430). Use of either the custom-made valve alone or in combination with the five-way valve allowed very abrupt changes in inspired gas. Addition of the five-way valve to the circuit did not change the mouth pressure over a range of flow of 0-110 $lmin^{-1}$ (fig. 2.5) i.e. inspiratory resistance was not changed.

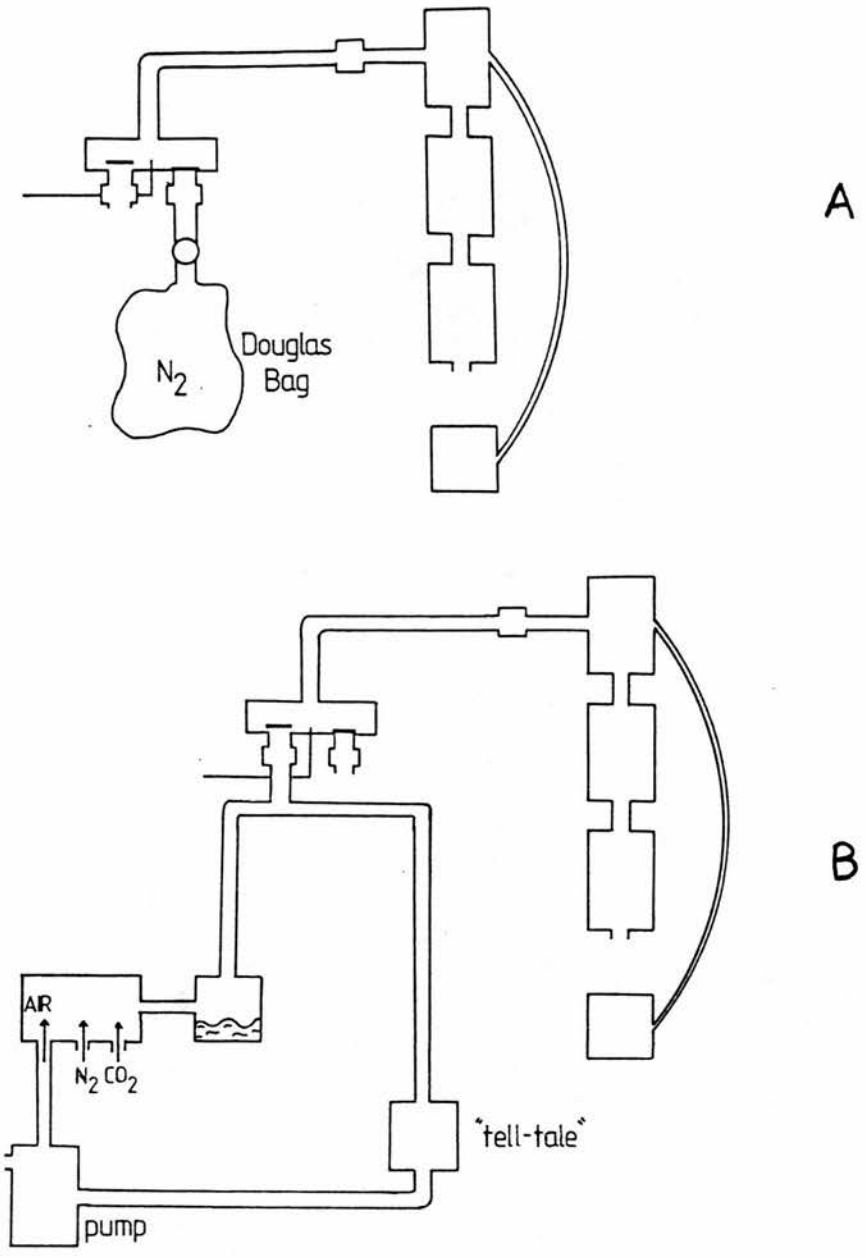
Gas mixtures of varying O_2 and CO_2 concentrations were made from room air, 100% N_2 and 100% CO_2 supplied from cylinders of primary gases. For studies requiring a continuous supply of low inspired O_2 (progressive isocapnic and a step-change in inspired O_2), the mixtures were made up using a system of rotameters (Rotameter Manufacturing Co. Ltd.) connected to a 10.5 litre mixing box. Room air was supplied by a pump through a 0-200 l min^{-1} rotameter, 100% N_2 through a 0-50l min^{-1} rotameter, and 100% CO_2 through a 0-10 l min^{-1} rotameter either to the mixing box (chapters 3 and 4) or directly to the inspiratory line close to the mouth (chapters 6-8) The output from the rotameters passed through a T-piece connected to one inspiratory port of the respiratory valves (figs 2.1 and

fig 2.1 : Breathing Circuit For a Step-Change in Inspired Gas



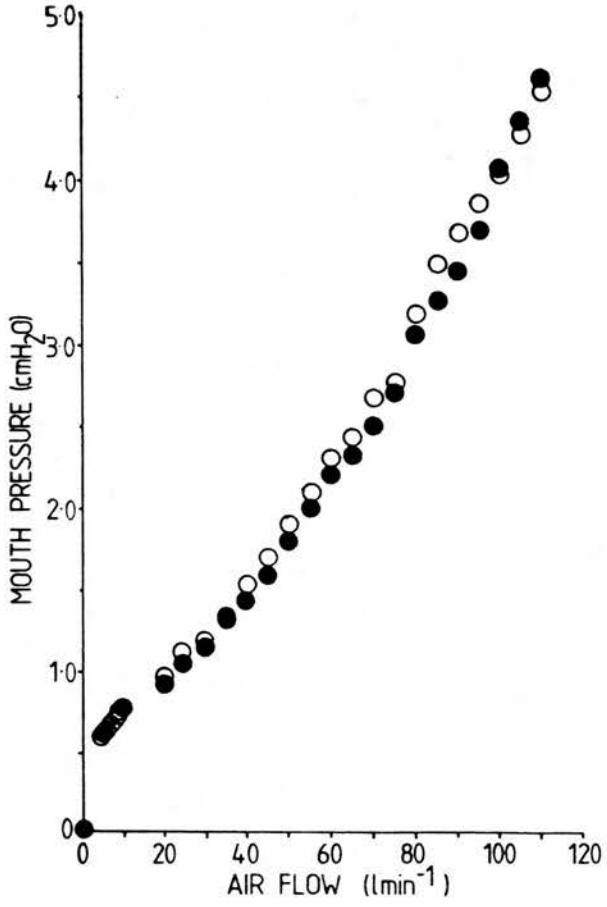
The circuit used for a step-change in inspired gas is shown as used in chapters 3 and 4. In chapters 6-8, the humidifier was not included, a five-way breathing valve was attached to the left-hand inlet port of the custom-made valve, through which all gas mixtures were supplied, and CO_2 was supplied via the inspired line close to the mouth.

fig. 2.2 : Breathing Circuits for Transient and Progressive Isocapnic Hypoxia.



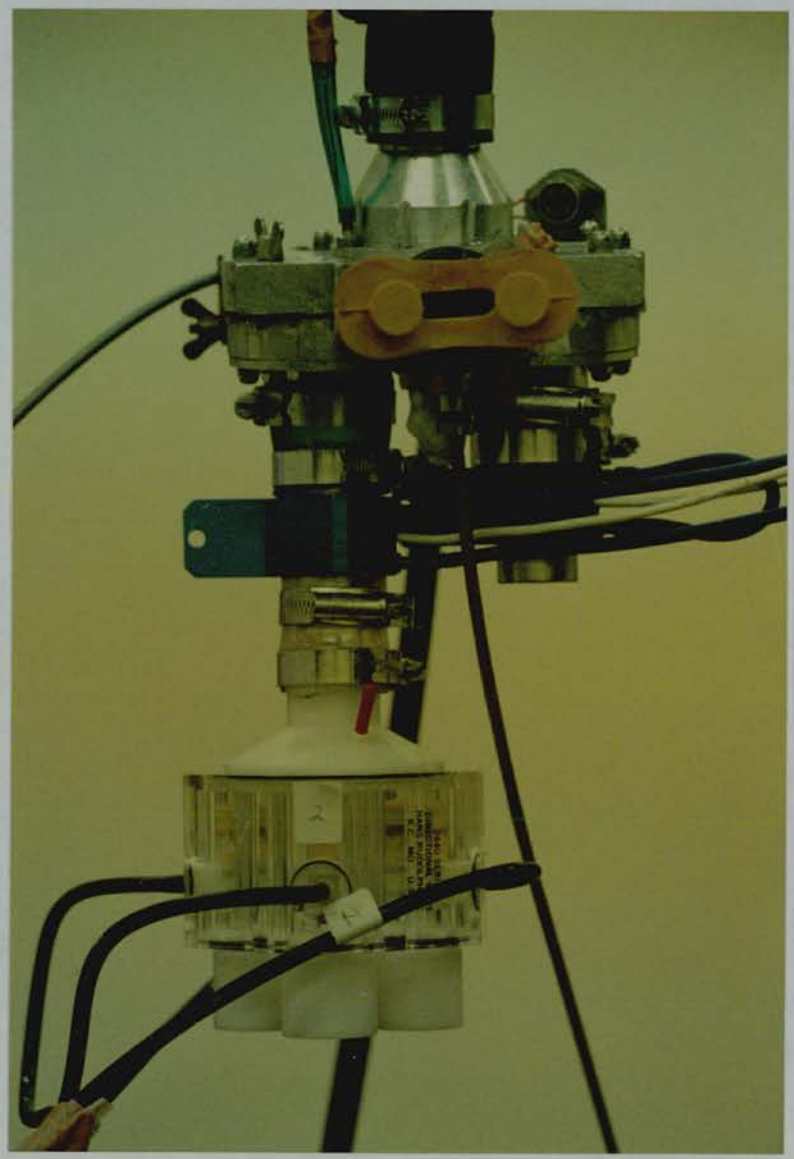
Modifications of the breathing circuit for transient (A) and progressive (B) isocapnic hypoxia are shown as used in chapters 3 and 4 (see text for details). In chapters 6-8, the five-way Hans Rudolph valve was attached to the left-hand inlet port of the custom made valve, and CO_2 was supplied via the inspired line close to the mouth.

fig 2.3 : Pressure-Flow Relationships for The Custom-Made and Five-Way Respiratory Valves.



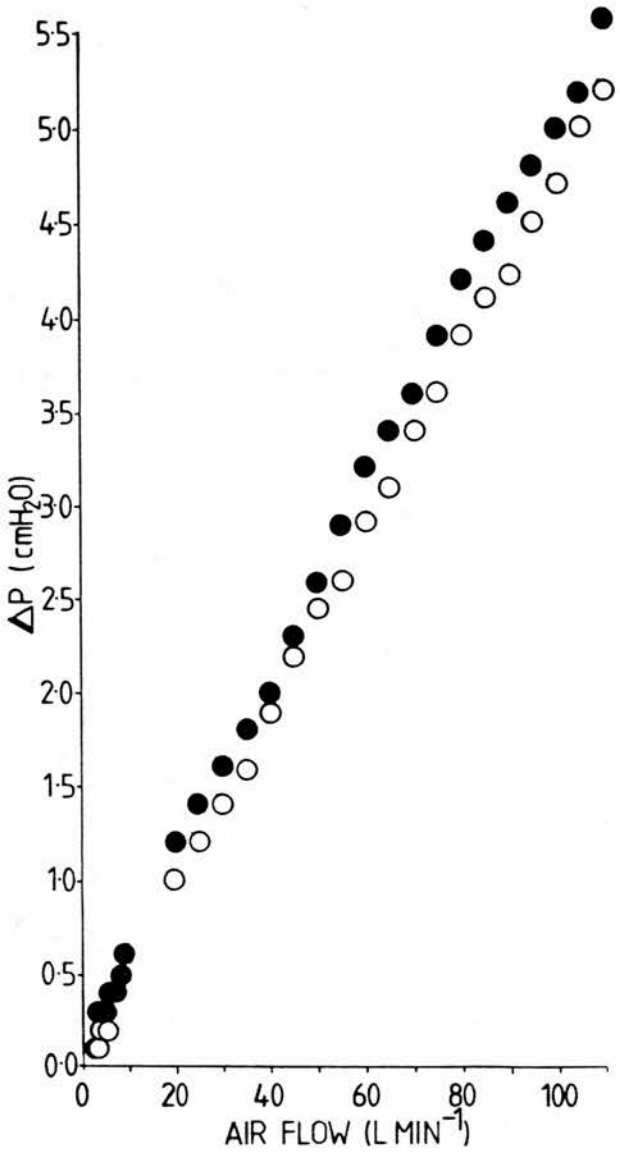
Pressure-flow relationships were determined by passing known constant flows of room air at 20°C (supplied from the rotameters) through the valves and measuring the pressure difference between the inlet and outlet ports using a Furness Controls FCO/4 Micromanometer.

fig 2.4 : Respiratory Valves



In chapters 6-8, a five-way Hans-Rudolph valve was attached to the left hand inlet port of the custom-made respiratory valve, through which all inspired gases were supplied.

fig 2.5 : Pressure-Flow Relationships of The Respiratory Valves Alone and In Combination.



Pressure-flow relationships were measured by passing constant flows of room air (20 C) through the custom-made valve alone, and then in combination with the five-way valve, and measuring the pressure difference across the valves using a Furness Controls FCO/4 Micromanometer. Open circles represent data for the custom-made valve with the inspiratory pneumotachograph, closed circles for both valves plus the pneumotachograph.

2.2). Gas mixtures were from the rotameters were supplied at a total flow rate of 100l min^{-1}. Excess gas was either withdrawn from the downstream end of the T-piece using a pressure compensating circuit (fig 2.2) using a "tell-tale" to indicate the pressure within the circuit and a variable pump with which the airflow and therefore the pressure could be adjusted (during progressive isocapnic hypoxia only), or passed along a 2 metre tube of 5 cm diameter (fig 2.1, step-changes in inspired gas only). This ensured that the gas supply from the rotameters exceeded respiratory requirements, that room air was not entrained into the respiratory mixture, and that positive pressure was not applied to the inspiratory side of the respiratory valve. In chapters 3 and 4, the hypoxic gas supplied during progressive isocapnic and step-changes in inspired PO_2 was warmed and humidified. This was discontinued in later studies (chapters 6-8) to exclude the possibility that subjects were able to distinguish between humidified and non-humidified gases.

To provide transient hypoxic stimuli, 100% N_2 was supplied from a Douglas bag connected to one port of the respiratory valve (fig 2.2). A second valve, operated mechanically by foot a pedal, was positioned between the Douglas bag and the respiratory valve. Simultaneous operation of both the foot pedal and the remote control switch of the respiratory valve was required before the subject could inhale from the Douglas bag, to prevent accidental inhalation of 100% N_2.

Expired gas passed from the respiratory valve along a straight metal tube via a pneumotachograph (Fleisch no.2) to a 3.2 litre mixing chamber. It was then dried by cooling, and continued to a dry gas meter (Parkinson-Cowan CD4). Mixed expired gas was sampled from the mixing chamber at 500ml min^{-1} and analysed for O_2 (Sybron-Taylor Servomex Oxygen Analyser 570A) and CO_2 (Gould-Godart Capnograph Mk III) concentrations as required for calculation of steady-state gas exchange.

ii Recording Devices

The gas composition was sampled continuously seven centimetres from the mouth by the heated probe of a mass spectrometer (VG-Medical Spectralab M) with a sampling rate of 20-25mlmin^{-1} and a typical transit time of 100-200ms. The 10-90% response time was 60ms (calculated as a mean of ten measurements of the response to abrupt changes from air to gas mixtures containing 8% CO_2 and 5% O_2). Before each study, the mass

spectrometer was calibrated for N_2, CO_2, O_2 and Argon with six gases of known composition. The mixtures used were 100% N_2, air (from a cylinder) and four O_2/CO_2 mixtures (O_2 range 5-21%, CO_2 2-8%).The O_2/CO_2 mixtures used were obtained from the British Oxygen Corporation with certificates of analysis, analysed to a tolerance within the range $\pm$ 2.5% of the analysed value. The commercial software operating the mass spectrometer calculated the average difference between the measured and expected concentrations for each gas. The calibration was accepted if the average error was less than 1% Analysis of room air immediately after calibration and after three hours (the duration of the longest study) showed that the calibration was stable over this period (table 2.1)

Expiratory gas flow was recorded using an heated pneumotachograph (Fleisch no. 2), the differential pressure across which was measured using a Furness Controls Ltd FCO/4 micromanometer. The pressure/flow relationship of the pneumotachograph is shown in fig 2.6).

Mouth pressure was recorded using a micromanometer (Furness Controls FCO/4) from a port positioned between the inspiratory and expiratory flaps of the custom-made respiratory valve.

Ear oxygen saturation was recorded throughout all studies using a Hewlett-Packard 47201A ear oximeter with fibreoptic earprobe. The oximeter was used in the mode with a delay time of 0.34 seconds and a time constant of 1.61 seconds (Douglas et al 1979).

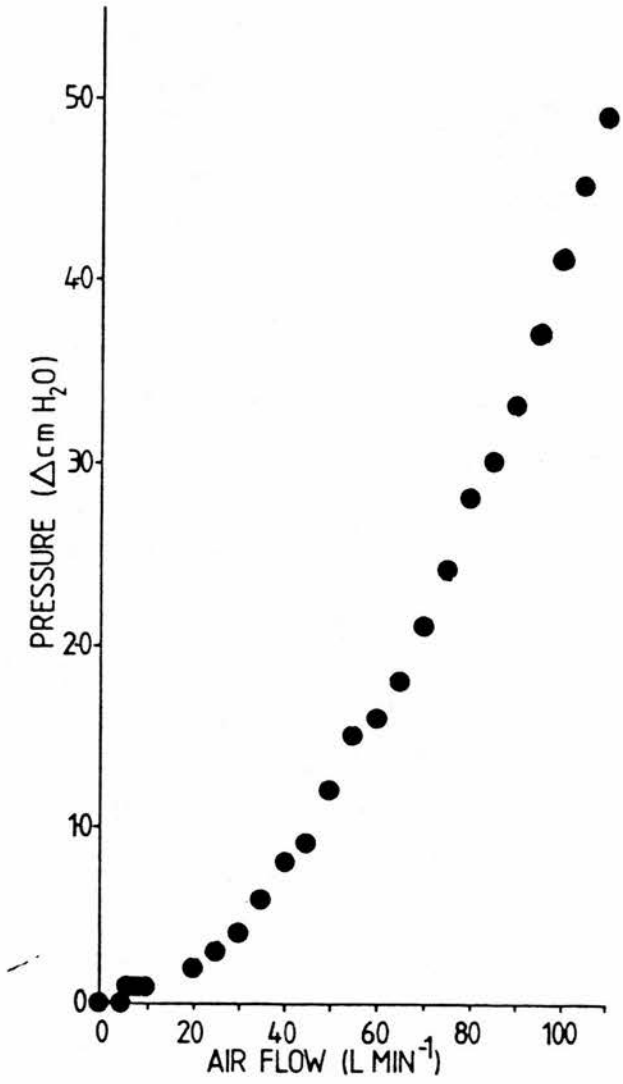
The electrocardiogram (ECG) and heart rate (measured from the r-r interval) were also recorded throughout all studies. (Hewlett-Packard 78351A Electrocardiogram monitor).

iii) On-Line Data Aquisition

Analogue signals from the recording devices were sampled every 16.67 milliseconds by a PDP 11/73 computer (Digital Equipment Corporation) using custom written programs.

The beginning and end of the respiratory phase of each breath was identified by the computer using the mouth pressure signal. High frequency noise generated by movement was reduced in the mouth pressure signal by adding a resistance (a needle, the diameter of which wasempirically chosen) in the sampling line. The beginning of inspiration was determined as the time at which the mouth pressure fell below

fig 2.6 : Pressure Flow Relationship of Expiratory Pneumotachograph.



The pressure/flow relationship was calculated by passing known constant flows of room air (supplied from the rotameters) through the pneumotachograph and measuring the differential pressure using a Furness Controls FCO/4 micromanometer.

table 2.1 : Stability of the Mass Spectrometer

GAS	concentration (time 0 min) (%)	concentration (time 180 min) (%)
N_2	78.03	78.00
O_2	20.99	21.03
Argon	0.93	0.93
CO_2	0.04	0.04

Composition of room air measured by the mass spectrometer directly after calibration (time 0 min) and again after three hours (time 180 min)

a negative threshold (empirically determined), and the beginning of expiration as the time at which mouth pressure rose above a positive threshold equal in size to the negative threshold. The inspiratory and expiratory times (T_I and T_E) were derived for each breath. Breathing frequency (f_R) was then calculated as $60/(T_I+T_E)$.

The output of the expiratory pneumotachograph was integrated to give expired volume. This volume was corrected using a calibration factor derived every 10litres from the output of the dry gas meter. The flow integrator was reset every breath (using the mouth pressure signal as a marker), thus giving a breath-by-breath measurement of tidal volume.This was then used together with breathing frequency to calculate instantaneous minute ventilation (breathing frequency x tidal volume).

The analogue signal from the mass spectrometer was calibrated for O_2, CO_2, N_2 and Argon onto the computer for each study day, using five gas mixtures (100% N_2, air from a cylinder and three O_2/CO_2 gas mixtures O_2 range 5 20%, CO_2 range 2-8%). Each was sampled by the mass spectrometer, and the least-squares linear regression relationship was calculated between the analogue signal and the expected gas concentration. The residual root sum squared for O_2, CO_2 and N_2, the largest individual variation in O_2, CO_2 and N_2 and the cylinder in which it occurred, the delay time of the mass spectrometer probe and the measured composition of room air were displayed on the computer screen. The calibration was only accepted if the delay time was less than 800ms and the largest individual variation was less than 0.25% for O_2, CO_2 and N_2. The delay time was used to offset all other variables to synchronise the measurements.

The composition of the inspired gas was calculated as an average over 150 milliseconds, 750 milliseconds after the onset of inspiration (so that dead space gas was not analysed). End-tidal PCO_2 ($P_{ET}CO_2$) was determined as the maximal value during the expiration, with end-tidal PO_2 recorded simultaneously.

The ear oximeter analogue output signal was also calibrated onto the computer by using the electrical signals for 0 and 100% saturation, and assuming linearity of the relationship between the ear oxygen saturation and the analogue signal between these two extremes. Ear oxygen saturation was recorded as a mean over each breath .

Mean heart rate of the previous eight breaths was also recorded breath-by-breath at the end-tidal point (i.e. simultaneously with end-tidal PCO_2)

Data was archived onto floppy discs for subsequent off-line analysis.

iv) Analogue and Digital Displays

The computer screen displayed digital values for inspired and end-tidal $\%O_2$ and $\%CO_2$, tidal volume, minute ventilation, breathing frequency, S_aO_2, heart rate and breath number, which was updated every five breaths. In addition, end-tidal PCO_2 was displayed on another screen.

An oscilloscope (Lan Electronics Ltd.) gave a continuous analogue display of PCO_2, tidal volume, expiratory gas flow and mouth pressure. The same information was displayed on a four channel time-based recorder (Watenabe Linear Corder mark VII) throughout the study.

Ear oxygen saturation, heart rate (in digital form) and ECG were also displayed continuously throughout all studies by their respective recording devices.

II Procedures

i) Step-Change Hypoxia

The inspired gas was changed without the subjects knowledge during expiration to an hypoxic gas mixture. (12% O_2 at rest, 15% O_2 during exercise) for three minutes which caused a fall in S_aO_2 to approximately 90%. The inspired gas was then returned to room air, again during expiration. The subjects than breathed room air for five minutes. The three minute hypoxic stimulus was then repeated using a lower concentration of O_2 (10% O_2 at rest, 12% O_2 during exercise) causing a fall in S_aO_2 to approximately 80%. Isocapnia was maintained by addition of 100% CO_2 to the inspired gas such that $P_{ET}CO_2$ was kept constant during the onset and duration of the hypoxic stimulus. No attempt was made, however, to maintain isocapnia during the recovery after returning the inspired gas to room air.

ii) Progressive Hypoxia

A modified method of Weil et al (1970) was used. The inspired O_2 concentration was reduced progressivley in 1% steps over 7-10 minutes to

reduce S_aO_2 overall to approximately 80%. The subjects then breathed room air for five minutes and the progressive hypoxic stimulus was repeated. Isocapnia was maintained during hypoxia by addition of 100% CO_2 to the inspired gas so that $P_{ET}CO_2$ was kept constant.

iii) Transient Hypoxia

The inspired gas was changed from room air to 100% N_2 during an expiration without the subjects knowledge. The subjects then took between two and four breaths of 100% N_2 so as to cause S_aO_2 to fall to approximately 80%. The inspired gas was then changed back to room air, again during an expiration. These transient hypoxic stimuli were repeated six to eight times, each stimulus separated by at least 60 breaths of room air.

IV Off-Line Data Analysis

i) Gas Exchange Variables

The volume of expired gas was recorded over a period of two minutes, using the digital output of the dry gas meter. Over the same two-minute period, the percentage of O_2 in the mixed expired gas was recorded as an average of three measurements taken at time 45, 75, and 105 seconds after the start of the mixed expired gas collection. The percentage of CO_2 in the mixed expired gas, recorded as millimetres deflection of the chart paper of the CO_2 analyser, was read off the calibration curve constructed that day for the analyser. Oxygen consumption, carbon dioxide elimination, minute ventilation and respiratory quotient were then calculated off-line (Cotes 1965). Minute ventilation was expressed as $lmin^{-1}$ BTPS and $\dot{V}O_2$ and $\dot{V}CO_2$ as $lmin^{-1}$ STPD. The resilts are given as the mean of all values obtained during each period of steady-state exercise or rest.

ii) Analysis of Data Recorded Breath-by-Breath.

Data was analysed off-line using custom-written programs with a PDP 11/73 computer.

Elimination of Spurious Breaths

Breaths during which the subject swallowed, sighed or coughed produced spurious values for inspiratory and expiratory timing, and thus unusually large or small values for $\dot{V}_E$inst. Breaths were therefore

eliminated from analysis using a custom-written computer program, if they did not conform to the following criteria:

1) 2kPa < $P_{ET}CO_2$ < 10kPa

2) $P_{ET}O_2$ >2kPa

3) V_T > 0.15L

4) T_E > 300ms

5) T_I > 500ms

Not all spurious breaths could be identified, however, by this method, especially those associated with swallowing. During swallowing, mouth pressure and expiratory flow were simultaneously zero (fig 2.8). The analogue trace of these variables was therefore used to identify swallowing and exclude the breath before and after a swallow.

Calculation of Hypoxic Ventilatory Drive

Hypoxic ventilatory drive was expressed as the slope of the linear regression relationship between $\dot{V}_E$inst and S_aO_2.

For the ventilatory response to step-change and progressive isocapnic hypoxia, data for ten breaths before the onset of hypoxia, and all the breaths during the hypoxic period were included in the calculation. Data from repeated step-change stimuli were pooled, as was data from repeated progressive hypoxic stimuli.

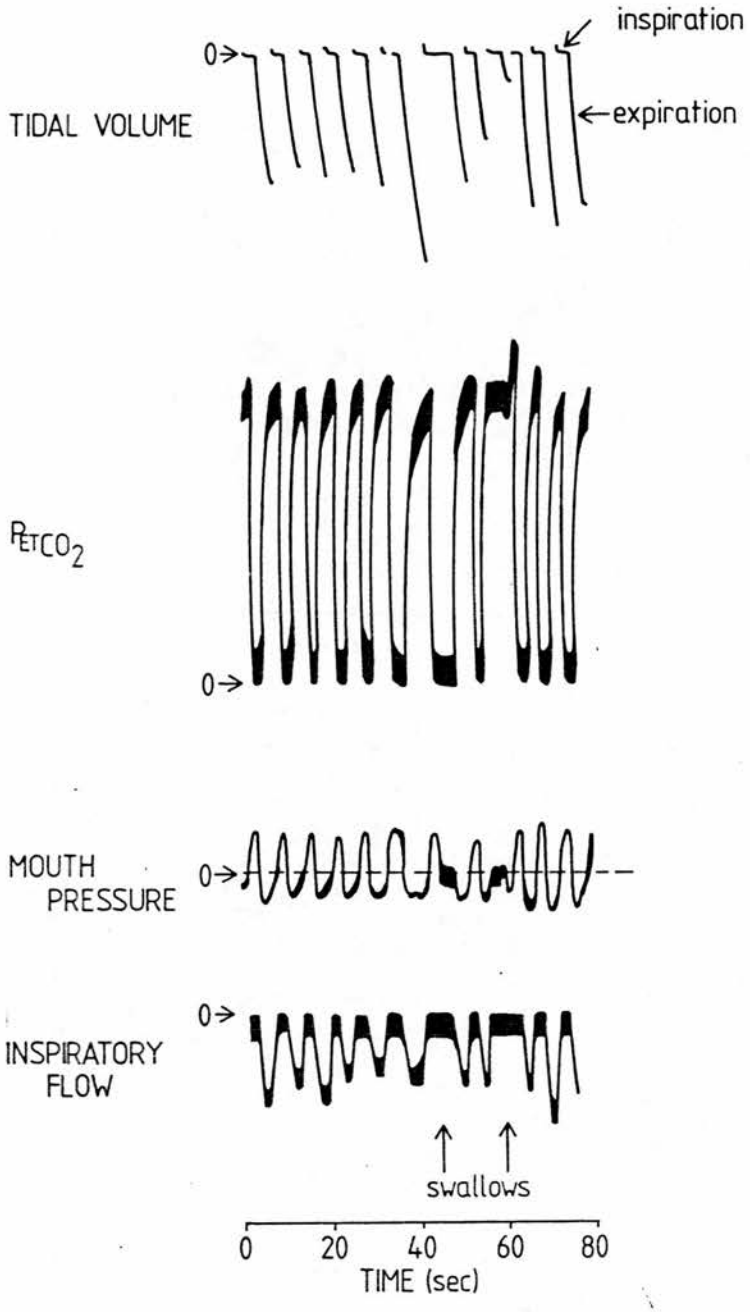
For transient hypoxia, data from the breath before the onset of hypoxia and the breaths up to and including the breath with the lowest S_aO_2 (i.e the "on-phase" of the ventilatory response) were included in the calculation. Data from repeated transient hypoxic stimuli were also pooled, but three criteria had to be met in order for data to be included in the calculation of hypoxic ventilatory drive:

1) there were no spurious breaths for ten breaths before or eight breaths after the onset of hypoxia,

2) S_aO_2 fell to at least 90%,

3) the lowest S_aO_2 reached during hypoxia for all the data from pooled tests was within 10%.

fig 2.7 : Identification of Swallows



Analogue trace showing tidal volume, $P_{ET}CO_2$, mouth pressure and expiratory flow. Mouth pressure and expiratory flow are simultaneously zero during a swallow.

To take into account physiological and instrumentation lag, an iterative procedure was used to calculate the best relationship between $V_E$inst and S_aO_2 during the response to transient hypoxia, using the equation:

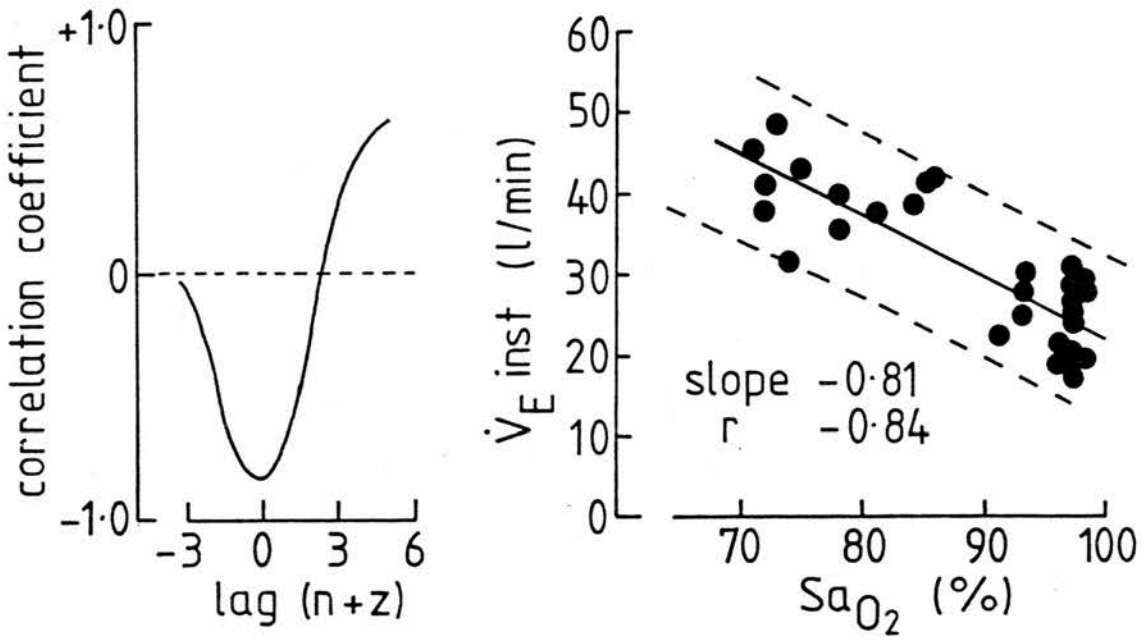
$$\dot{V}_E\text{inst (breath n+z)} = a+b\ (\ S_aO_2\ ,\ \text{breath n})$$

where z was allowed to vary from -5 to +5. Correlation coefficients (r) of these relationships were calculated and the slope of the $V_E$inst/ S_aO_2 relationship at the most significant negative correlation was used to express hypoxic ventilatory drive (fig. 2.8).

Calculation of Baseline $P_{ET}CO_2$and $P_{ET}CO_2$ during Hypoxia

Baseline $P_{ET}CO_2$ was calculated for step-change and transient hypoxia as the mean of 20 breaths before the onset of hypoxia. For progressive isocapnic hypoxia, data was only collected from 10-15 breaths before the onset of hypoxia, so the baseline $P_{ET}CO_2$was calculated as a mean of ten breaths before each hypoxic episode. End-tidal $P_{ET}CO_2$ during hypoxia was calculated as a mean of that for all the breaths included in the calculation of hypoxic ventilatory drive.

fig 2.8 : Calculation of Hypoxic Ventilatory Drive



The relationship between $\dot{V}_E$inst and S_aO_2 at lags (z) ranging from -3 to +5. The slope with the highest negative correlation (greatest r) was used to express hypoxic ventilatory drive.

CHAPTER 3 : A COMPARISON OF THREE METHODS OF MEASUREMENT OF HYPOXIC VENTILATORY DRIVE

I INTRODUCTION

The techniques used to measure hypoxic ventilatory drive can be divided into three basic groups:

i) steady-state hypoxia, in which the ventilation is measured only after the subject has been hypoxic for long enough for his ventilation to become stable,

ii) progressive hypoxia, in which the ventilation is measured continuously as the oxygen content of the inspired gas is gradually reduced. This includes rebreathing techniques, in which the inspired P_{O_2} is gradually reduced by rebreathing the expired gas,

iii) transient techniques, which involve measurement of either the increase in ventilation following several breaths of an hypoxic gas mixture or the decrease in ventilation following several breaths of an hyperoxic gas mixture against a background of hypoxia.

Each of the techniques has both practical and physiological advantages and limitations.

i) Steady-State Hypoxia

The basis of the steady-state method originated in the work of Nielson and Smith (1951). They measured the ventilatory response to inspired hypercapnic gas mixtures during several degrees of steady-state hypoxia (i.e. after at least ten minutes of breathing the hypoxic gas mixture) in man. Ventilation increased linearly with increasing P_aCO_2 and the slope of this linear relationship was increased by hypoxia. They suggested that the slopes of the $\dot{V}_E/P_ACO_2$ lines could be compared at two different levels of hypoxia to give an index of hypoxic sensitivity. they therefore divided the $\dot{V}_E/P_ACO_2$ slopes obtained at P_AO_2 values of 40 and 150mmHg to calculate the index S40/S150. This concept was also used by Flenley and Millar (1967), who compared the slopes of the CO_2 response lines at P_aO_2s of 70 and 120 mmHg to give the index S70/S120. A similar experimental method with a different method of analysis was used by Lloyd et al (1958), using several different levels of P_AO_2.

They expressed the linear part of the V/P_ACO_2 relationship by the equation

$$\dot{V} = S(P_aCO_2 - B)$$

where S is the slope of the V/P_ACO_2 line and B its intercept on the x-axis. They observed that although the intercept, B, did not change with changing P_AO_2, the slope, S, did, the lower P_AO_2, the greater the slope. They used the equation

$$S = D\{1 + \frac{A}{P_AO_2 - C}\}$$

to describe the relationship between S and P_AO_2, where D is the slope of the $\dot{V}/P_ACO_2$ line at infinite P_AO_2, A is the shape of the hyperbola and C is the P_AO_2 at which $\dot{V}$ tends to infinity. A can be regarded as a measure of hypoxic ventilatory drive.

Severinghaus et al (1966) used a similar experimental technique, but analysed the results in a different way. They constructed two CO_2 response lines, one at a steady-state P_aO_2 of 200mmHg and one at 40mmHg. They then defined their measure of hypoxic ventilatory drive, $\dot{V}40$, as the increase in ventilation resulting from a decrease in P_aO_2 from 200 mmHg (26.7kPa) to 40 mmHg (5.3kPa) at a standardised "normal" P_aCO_2. The "normal" P_aCO_2, derived for each subject, is the P_aCO_2 at which the hyperoxic response line intersects with a ventilation of 4litres/min, which is defined as normal resting ventilation.

A specific disadvantage of the $\dot{V}40$ technique is that a P_aO_2 of 40mmHg falls on the steep part of the $\dot{V}/P_AO_2$ response curve, thus very small changes in PO_2 result in very large changes in ventilation. A slight inaccuracy in technique could therefore cause large variations in results, making this test of hypoxic ventilatory drive difficult to carry out.

There are several disadvantages of steady-state techniques in general. Subjects with a high hypoxic ventilatory drive find it difficult and uncomfortable to maintain the ventilation at a steady-state level due to multiplicative interaction of hypoxia and hypercapnia as ventilatory stimuli (Nielson and Smith 1951) thus limiting the data points at the more hypoxic end of the hyperbola. This method is also very time-consuming, as at each level of steady-state P_AO_2,

ventilation must be measured at several levels of steady-state P_ACO_2, which could take several hours to complete. Analysis of the data is also difficult. As such a small number of data points are obtained, one inaccurate measurement could have a significant effect upon the final calculated hypoxic ventilatory drive. Expression of the data in the form of an hyperbolic relationship between ventilation and P_AO_2 can also has limitations, as the shape parameter, A, of the hyperbola is very sensitive to changes in C, the P_AO_2 at which ventilation tends to infinity. Lloyd et al (1958) set C at a constant value of 32 in all their calculations, however C has been found to vary considerably (mean $\pm$ SD 32.2$\pm$7.6) by Cunningham et al (1964). Furthermore, Slutsky et al (1979) found that values of C between 8 and 35 could increase the correlation coefficient of the hyperbolic relationship between ventilation and P_AO_2. A single value for C of 32 is not applicable to all subjects. A further disadvantage is that hyperbolae are not necessarily the same shape for identical values of A. The single parameter A is therefore insufficient to express hypoxic ventilatory drive accurately, and the other parameters in the equation must be determined. Finally, steady-state hypoxia may underestimate the hypoxic ventilatory drive due to central hypoxic depression of ventilation, which may occur within five minutes of the onset of hypoxia (Weil and Zwillich 1970, Lahiri 1974, Kagowa et al 1982, Easton et al 1986).

ii) Progressive Isocapnic Hypoxia

Progressive isocapnic hypoxia was first introduced by Weil et al (1970). Their method involved the gradual reduction of $P_{ET}O_2$ from 120mmHg (16kPa) to approximately 40mmHg (5.3kPa) by adding N_2 to the inspired gas over 15-20 minutes. Carbon dioxide was added to the inspired gas as ventilation increased, to keep $P_{ET}CO_2$ constant. The use of this non steady-state method was justified because the rate of ventilatory response to a change in inspired O_2 was fast enough (18-23 sec) to keep up with the rate of reduction in $P_{ET}O_2$. This method allows construction of a continuous curve relating V_E and P_AO_2. The shape of the curve could be described by the equation

$$\dot{V}_E = \dot{V}_E^{\circ} + A/(P_AO_2 - 32)$$

where A is the shape parameter of the curve and $\dot{V}_E^{\circ}$ is the asymptote for ventilation at infinite P_AO_2. The constant 32 is the P_AO_2 at which the

V_E/P_AO_2 slope tends to infinity, as used by Cunningham et al (1958) in studies of the ventilatory response to steady-state hypoxia.

Other workers have used the progressive method in various forms. Kronenberg et al (1972) used a method in which P_AO_2 was reduced from 120 to 40 mmHg (16-5.3kPa) in 3-4 minutes, which has the advantage of being shorter and therefore less stressful for the subjects than the original method of Weil et al (1970). The results were analysed by relating the log of incremental ventilation to P_AO_2, which resulted in a straight line plot. A constant, k, used as an index of hypoxic ventilatory drive, was defined as the exponential slope constant required to increase ventilation by e (2.718), which was used as an index of hypoxic ventilatory drive. Because P_aO_2 was determined by blood sampling every 10mmHg (1.3kPa) reduction in P_AO_2, this method has the disadvantage of having very few data points. Similar methods were used by Sahn et al (1977), who reduced $P_{ET}O_2$ from 155 to 40mmHg (20.7-5.3kPa) in 7 minutes, and Shaw et al (1982) who reduced S_aO_2 from 100 to 78% in 5-7 minutes. Instead of taking arterial blood samples, ventilation was related to P_AO_2 and to S_aO_2 in the respective studies.

Rebuck and Campbell (1974) developed a simple rebreathing method based on that of Read (1967) in which the subjects rebreathed from a six litre bag containing 7% CO_2 and 24% O_2, causing a very rapid fall in $P_{ET}O_2$ from 140-160mmHg to 30-40mmHg (18.7-21.3 to 4-5.3kPa) within four minutes. Ear oxygen saturation was measured continuously throughout the procedure. Unlike Read (1967), who allowed $P_{ET}CO_2$ to rise, Rebuck and Campbell (1974) maintained isocapnia throughout. $P_{ET}CO_2$ was held constant at "mixed venous" level, which was determined from the $P_{ET}O_2$ plateau obtained within 15-20 seconds of the start of rebreathing. The advantages to this method are its simplicity, its non-invasive nature, and the fact that many data points are collected over a short period of time. Analysis of the data was very simple, with hypoxic ventilatory drive expressed as the slope of the linear regression relationship between minute ventilation and S_aO_2. Use of ear oximetry, however has disadvantages. Firstly, at the time when this work was done, the available ear oximeters were very unstable and thus unreliable (Saunders et al 1976). Secondly, there is a short delay between changes in P_aO_2 and the response of the ear oximeter, which could affect the results. Furthermore, S_aO_2 is not the true stimulus to the chemoreceptors (Chiodi

et al 1941, Duke et al 1952, Hornbein 1968, Bartlett and Tenney 1979, Hebbel et al 1977, Hatcher et al 1978, Fitzgerald and Traystman 1980, Lahiri et al 1981)

This method of measurement of hypoxic ventilatory drive also has the disadvantage that the ventilatory response to even periods of progressive isocapnic hypoxia as short as three to four minutes may be affected by central hypoxic depression of ventilation, a problem which is discussed in detail in chapter 4.

iii) Transient Hypoxia

Central hypoxic depression of ventilation is avoided by using transient hypoxic stimuli lasting only a few breaths. The brief duration of such stimuli only involves the carotid chemoreceptors in mediating the ventilatory response, as central hypoxic depression of ventilation develops gradually over a longer time course (Lahiri 1974, Lee and Millhorn 1975). The transient method evolved as a "single-breath test", in which the subject inhaled one breath of an hypoxic or hyperoxic gas mixture (Dejours 1957, Girard et al 1959, Hornbein et al 1961, Dejours 1960). To produce an adequate change in P_aO_2 at rest, the subject is required to take a vital capacity breath of the test gas mixture (Kronenberg et al 1972, Gabel et al 1973). This has two disadvantages, firstly, the breathing pattern is disturbed by this procedure and secondly, the subject is aware of inhaling the test gas mixture, and may consciously or subconsciously change his breathing pattern. As the ventilatory response to such a brief stimulus only lasts a few breaths, these factors could alter the measured ventilatory response to hypoxia considerably. This technique was later modified by giving subjects several breaths of the test gas mixture without the knowledge of the subject. Stockley (1977) gave subjects 20 seconds of 100% inspired O_2 (against a background of air), but this method has the disadvantage that the change in ventilation is very small, and may be difficult to quantify due to the normal breath to breath variation in ventilation at rest. Lahiri and Edelman (1969) in a study of high altitude natives, overcame these problems by changing the inspired gas from air to 100% O_2 for 3-5 breaths without the subjects knowledge. Flenley et al (1973) used a similar approach giving two or three tidal breaths of 100% at rest and during exercise to measure hypoxic ventilatory drive in mine rescue workers. In both these studies, only the change in ventilation was

measured, and the magnitude of the change in P_aO_2 was not taken into account in assessing the hypoxic ventilatory drive. Since the effect of inhalation of a few breaths of O_2 or N_2 on the chemoreceptors is likely to vary widely between individuals, depending upon factors such as tidal volume, FRC and cardiac output, quantification of the stimulus is necessary. Edelman et al (1973) used ear oxygen saturation recorded with an ear oximeter as a measure of the hypoxic stimulus. They recorded S_aO_2 and breath-by-breath $\dot{V}_E$ during 15-20 transient stimuli in each subject, consisting of varying numbers of breaths of 100% N_2, causing S_aO_2 to fall to levels ranging from 62-99%. They calculated the peak $\dot{V}_E$ as the mean of the two breaths with the greatest $\dot{V}_E$ following each hypoxic stimulus, and hypoxic ventilatory drive was expressed as the slope of the linear regression relationship between V_E and S_aO_2. Use of S_aO_2 rather than P_aO_2 in the expression of the results attracts the same criticism as in the progressive hypoxia methods, i.e., the slow response of ear oximeters available in the 1970's and their instability makes them unreliable, particularly during such brief hypoxic stimuli. This criticism is not as significant , however in a similar method used by Shaw et al (1982), who used the Hewlett-Packard 47201A Ear Oximeter, which has a very rapid response time (Douglas et al 1979).

Improvements to this method were made by Flenley et al (1979). Subjects were given five tidal breaths of 30% O_2 six times, against a background of 14% inhaled O_2 during moderate treadmill exercise. Ventilation and $P_{ET}O_2$ were recorded breath-by-breath and the results pooled. Hypoxic ventilatory drive was expressed as the slope of the $\dot{V}_E$/ $P_{ET}O_2$ relationship for the pooled data, which instead of just the peak response, included all breaths during both the the initial decrease inventilation transient relief of hypoxia and the return to the hypoxic level. This was done using an iterative process, which removes the subjectivity of peak-picking and also includes more data points. This method has the advantage of being shorter than that of Edelman et al (1973), and is a convenient test. It may, however, be criticised in that $P_{ET}O_2$ is used in the analysis of the results, which may not equal P_aO_2, which is the actual stimulus to the carotid chemoreceptors. PO_2 is known to change during exercise, (Whipp and Wasserman 1969), with an increase in the arterial-alveolar PO_2 difference, which means that the relationship between ventilation and $P_{ET}O_2$ also changes. The method of analysis

described by Flenley et al (1979) was subsequently modified by the same group (Gould et al 1984), who demonstrated that as the relationship between $P_{ET}O_2$ and $\dot{V}_E$ is not the same during the increase in ventilation following inhalation of 2-3 breaths of N_2, and the return to normoxia, thus analysis using all these data points gives different results to using only the points during the initial increase in ventilation.

iv) Comparison of the Three Methods of Measuring Hypoxic Ventilatory Drive

Comparisons of the three methods of measuring hypoxic ventilatory drive have been made by several investigators. Kronenberg et al (1972) compared the results of the steady-state method (using the $\dot{V}_{40}$ index described by Severinghaus in 1966), the progressive isocapnic method (reducing P_aO_2 over 3-4 minutes from 120 to 40mmHg) and the transient method (single vital capacity breath test) in nine normal young men at rest. Although their method of analysis of the results of each of the tests did not permit quantitative comparisons, there was a significant correlation between the results to the steady-state and the progressive methods. There was also a significant correlation between ventilatory responses to steady-state and single breath tests, but no correlation between the responses to progressive and single breath tests.

Edelman et al (1973) compared ventilatory responses to transient and steady-state hypoxia in normal subjects at rest. The response to steady-state hypoxia was expressed as the ratio of the slopes of $\dot{V}_E/P_ECO_2$ lines under euoxic conditions, and that to transient hypoxia as the ratio of iso-saturation $\dot{V}_E/P_ACO_2$ lines constructed from the data from transient tests using various mixtures of O_2 and CO_2 thus quantitative comparison of the data was possible. There was a correlation between responses to transient and steady-state hypoxia, but the response to transient hypoxia was on average 18% greater than that to steady-state hypoxia.

Progressive isocapnic (reduction in S_aO_2 to approximately 78% over five to seven minutes) and transient (two to seven breaths of 100% N_2) hypoxic stimuli were compared by Shaw et al (1982) at rest. The ventilatory responses to the two tests correlated significantly , but the response to transient hypoxia was lower than that to progressive hypoxia in all but one of the subjects studied. In most cases, both transient and

progressive methods identified subjects with an unusually low hypoxic ventilatory drive.

Warren et al (1984) compared the ventilatory responses to progressive isocapnic and steady-state (ratio of slopes of iso-oxic $V_E CO_2$ lines) hypoxia at rest and to transient hypoxia (three to four breaths of 100% N_2) during exercise in normal subjects. Although ranking of the responses to transient and progressive hypoxia was not consistent for all subjects, a significant correlation between the results of the two methods was found. Steady-state hypoxic ventilatory responses were found not to correlate with those measured by other methods. Quantitative comparison of the results could not be made because the ventilatory responses to steady-state and progressive hypoxia were made at rest, whereas that to transient hypoxia was made during exercise.

Thus, although several groups have shown correlation between steady-state or progressive and transient methods of measuring hypoxic ventilatory drive, some have shown that the ventilatory response to transient hypoxia is smaller than that to other types of stimulus. Furthermore, Airlie et al (1988) have found that although the chemoreceptor stimulant drug Almitrine potentiated hypoxic ventilatory drive measured by progressive isocapnic hypoxia, it did not consistently affect the ventilatory response to transient hypoxia. The lower response to transient hypoxia may be due to the time course of the ventilatory response to hypoxia (Reynolds and Milhorn 1973)

The aims of this study are therefore, to make a quantitative comparison of all three methods of measuring hypoxic ventilatory drive during exercise, and to develop a test of hypoxic ventilatory drive which avoids central hypoxic depression of ventilation yet allows adequate time for full development of the ventilatory response.

II METHODS

Hypoxic ventilatory drive was measured using step-change, progressive isocapnic and transient hypoxia during moderate treadmill exercise. The subjects were each studied at the same time on two separate days. For women the two days were either consecutive or on the same day of the menstrual cycle in two consecutive months. The two parts of the study were carried out in random order.

i) Subjects

The subjects were ten healthy fasting volunteers drawn from laboratory staff, four female and six male (Index II : subject numbers 1-10). Age, height, weight, lung volumes, TCO and airways resistance are tabulated in index II.

ii) Equipment and Methods

The methods and equipment are described in detail in chapter two. The subject walked on a level treadmill (the speed required to raise $\dot{V}O_2$ approximately $1.0 l min^{-1}$ was predetermined for each subject, and used on both study days) breathing air through a respiratory valve (metal valve only) until steady-state gas exchange had been reached. Two-minute collections of expired gas were made between minutes seven and nine, and nine and eleven after the start of exercise, and used to calculate gas exchange variables. Steady-state gas exchange was judged to have been reached if the two measurements of $\dot{V}O_2$ were within 100ml, if not, then further collections of expired gas were made until two consecutive measurements of $\dot{V}O_2$ within 100 ml were obtained. Further measurements of $\dot{V}O_2$ were made after the first three transient stimuli and again at the end of each set of transient, step-change and hypoxic stimuli. The following methods were then used to measure hypoxic ventilatory drive during steady-state exercise :

Day A : Transient hypoxia (six repeated stimuli)

Progressive isocapnic hypoxia (measurements made in duplicate, separated by five minutes breathing room air)

Day B : Transient hypoxia (six repeated stimuli)

Step-change hypoxia (four alternating periods of 15 and 12% inspired O_2, each lasting three minutes and separated by five minutes breathing room air, with isocapnia maintained throughout hypoxia).

Between each set of measurements (i.e. between measurement of hypoxic ventilatory drive by transient and progressive isocapnic hypoxia, and between measurement by transient and step-change hypoxia) the subject rested for at least ten minutes, or until he was prepared to continue the study.

iii) Analysis of Results and Statistics

Hypoxic ventilatory drive expressed as the negative slope of the $\dot{V}_E inst/S_aO_2$ curve was calculated as described in chapter two. The mean $P_{ET}CO_2$ before and during hypoxia was also calculated as described in chapter two.

Half-Time of the Ventilatory Response to Step-Change Hypoxia

Mean values of $\dot{V}_E inst$ were calculated for baseline (twenty breaths before hypoxia) and for the maximal response to 12% inhaled O_2 (the last ten breaths during hypoxia of both periods of inhalation of 12% O_2). The time taken for $\dot{V}_E inst$ to reach 50% of the maximal response (the half-time, $t_{1/2}$) was then calculated from the onset of inspiration of the first breath of 12% O_2 to the end of expiration of the breath before $\dot{V}_E inst$ rose above 50% of the maximal response.

Duration of the Transient Hypoxic Stimulus

The duration of each transient hypoxic stimulus was calculated as the time from the onset of of inspiration of the first breath of 100% N_2 to the end of expiration of the last breath of 100% N_2. The mean duration was calculated for those transient hypoxic stimuli used in the estimation of hypoxic ventilatory drive on each occasion in an individual.

Deconvolution

Using custom-written computer programs, a "filter function" (i.e. the Fourier Transform of the convolution function) was derived for each subject for transient and step-change (from air to 12% O_2) hypoxia. The convolution function is the function with which the input (S_aO_2) signal must be convolved to produce the output ($\dot{V}_E inst$) signal. The "filter function" describes how every frequency in the input waveform is affected by the filter (i.e. the carotid chemoreceptor response to a

change in S_aO_2, brainstem modification and central nervous system processing of the carotid chemoreceptor input), thus amplitude/frequency plots for step-change and transient hypoxia are obtained for each subject. This procedure was not applied to the response to progressive hypoxia, as not enough different frequencies occur to make an amplitude/frequency plot meaningful.

Statistics

Friedmans Analysis of Variance was used to compare gas exchange variables ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$) for each section of the study (for step-change hypoxia, progressive hypoxia and transient hypoxia on both days) and baseline $P_{ET}CO_2$, $P_{ET}CO_2$ during hypoxia and the lowest S_aO_2 reached during hypoxia were compared by the same method. Hypoxic ventilatory drive measured by the three methods were compared by Wilcoxons test for signed ranks, using the Bonferoni correction for multiple comparisons. The ventilatory responses to step-change hypoxia with and without the humidifier in the circuit were also compared by Wilcoxons test for signed ranks.

III RESULTS

1 Baseline Ventilation and Gas Exchange

Gas exchange variables during steady-state exercise for each method of measurement of hypoxic ventilatory drive are shown in table 3.1. There were no significant differences in $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ on each occasion.

The mean baseline $P_{ET}CO_2$ was similar for each set of measurements of hypoxic ventilatory drive. The range of standard deviation about the mean value when breathing room air was 0.08-0.22kPa (table 3.2).

2 The Ventilatory Response to Hypoxia

i) Step-Change Hypoxia

A step-change in F_IO_2 from room air to 15% or 12% O_2 reduced S_aO_2 to approximately 90% and 80% respectively and caused an increase in $\dot{V}_E$inst (fig 3.1.), which was maintained throughout the duration of the hypoxic stimulus.

Hypoxic ventilatory drive expressed as the slope of the least squares linear regression relationship between $\dot{V}_E$inst and S_aO_2 for the pooled data showed varied widely from $-0.44 l min^{-1}\%^{-1}$ to $-9.78 l min^{-1}\%^{-1}$ (table 3.3). There was no significant difference between hypoxic ventilatory drive measured with the humidifier in the breathing circuit and without the humidifier for eight subjects (table 3.4). One subject, however, (subject 6) did show a marked reduction in hypoxic ventilatory drive when the humidifier was omitted from the circuit. This subject also happened to be the one with the greatest hypoxic ventilatory drive.

$P_{ET}CO_2$ was maintained within 0.12-0.19kPa of the mean (table 3,5) which was a similar degree of variability as during normoxia (table 3.2).

ii) Progressive Isocapnic Hypoxia

The gradual reduction in S_aO_2 which was a result of progressive replacement of inspired air with 100% N_2 was accompanied by a gradual increase in $V_E$inst, which continued throughout hypoxia (fig. 3.2).Hypoxic ventilatory drive ranged from -0.49 to $-4.46\ l min^{-1}\%^{-1}$ (table 3.3).

The standard deviation about the mean $P_{ET}CO_2$ varied from 0.09 to 0.22kPa (table 3.5) during hypoxia, as compared to 0.09 to 0.18kPa during

table 3.1 : Gas Exchange Variables During Steady-State Exercise

Day A

	Transient			Progressive		
Subject	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$
		(l min^{-1})			(l min^{-1})	
1	0.93	0.78	22.08	0.88	0.78	22.22
2	1.00	0.79	28.03	0.95	0.82	25.94
3	1.05	0.93	24.15	1.18	0.98	25.94
4	0.99	0.84	18.59	1.18	0.98	25.28
5	0.98	0.80	21.27	1.01	0.80	22.59
6	0.98	0.90	27.24	1.00	0.87	26.40
7	1.06	1.02	30.15	1.03	0.98	29.68
8	0.90	0.77	19.72	0.92	0.76	21.04
9	0.94	0.87	23.61	0.97	0.81	22.88
10	0.76	0.69	21.80	0.72	0.67	21.03

Day B

	Transient			Step-Change		
1	0.98	0.84	22.92	0.93	0.80	23.12
2	0.90	0.84	26.80	0.93	0.88	27.09
3	1.04	0.84	22.51	1.14	0.97	25.19
4	1.01	0.84	19.43	0.99	0.83	19.24
5	0.95	0.80	22.24	0.95	0.78	22.56
6	1.04	0.90	27.86	1.07	0.92	28.07
7	0.96	0.94	29.53	0.99	1.01	28.42
8	0.89	0.78	20.56	0.96	0.83	22.00
9	0.93	0.84	24.02	0.95	0.81	21.56
10	0.79	0.69	20.61	0.78	0.66	21.06

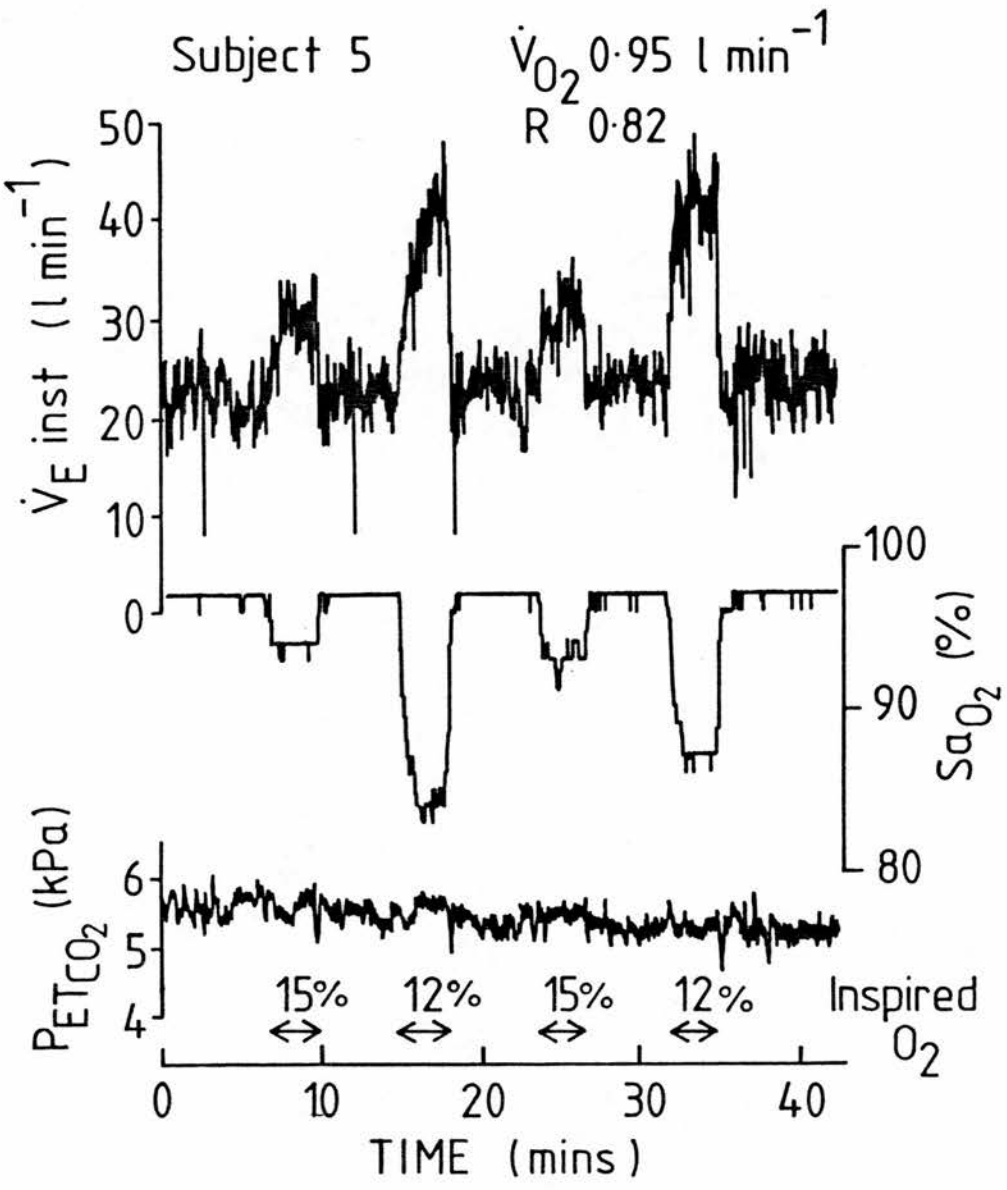
$\dot{V}_E$, expressed as l min^{-1} BTPS, $\dot{V}O_2$ and $\dot{V}CO_2$ expressed as l min^{-1} STPD

table 3.2 : Baseline $P_{ET}CO_2$

	Day A		Day B	
	Transient	Progressive	Transient	Step-Change
Subject	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)
1	5.68±0.11	5.67±0.13	5.93±0.13	5.88±0.15
2	4.73±0.10	4.98±0.13	5.03±0.09	5.01±0.12
3	5.84±0.18	5.76±0.12	5.84±0.17	5.61±0.15
4	6.18±0.18	5.90±0.17	6.19±0.16	5.95±0.19
5	5.68±0.21	5.51±0.18	5.49±0.16	5.44±0.22
6	5.24±0.10	5.18±0.14	5.16±0.08	5.09±0.13
7	5.60±0.13	5.53±0.14	5.46±0.17	5.69±0.17
8	5.39±0.17	5.33±0.13	5.66±0.18	5.35±0.22
9	5.57±0.08	5.54±0.14	5.62±0.15	5.60±0.13
10	5.08±0.08	5.00±0.09	5.12±0.11	4.99±0.08

Baseline $P_{ET}CO_2$ calculated as the mean±SD of ten breaths before each transient hypoxic stimulus,ten breaths before each progressive hypoxic stimulus or twenty breaths before each step-change hypoxic stimulus

Fig 3.1 : Ventilatory Response to Step-Change Hypoxia



Ventilatory response to step-change hypoxia in a normal subject (subject 5). Step-changes in inspired O_2 from room air to 15 or 12% caused falls in S_aO_2 (middle trace) and increases in $\dot{V}_E$inst (upper trace). The $P_{ET}CO_2$ was maintained constant except at the end of each hypoxic period.

table 3.3 : Hypoxic Ventilatory Drive During Transient, Progressive and Step-change Hypoxia.

	Day A		Day B	
	$\dot{V}_E inst/S_aO_2$ ($l\ min^{-1}\ \%^{-1}$)		$\dot{V}_E inst/S_aO_2$ ($l\ min^{-1}\ \%^{-1}$)	
Subject	Transient	Progressive	Transient	Step-Change
1	-1.13	-1.33	-1.40	-1.71
2	-0.75	-1.53	-0.40	-1.05
3	-0.38	-2.34	-0.47	-3.26
4	-0.48	-0.62	-0.22	-0.80
5	-0.45	-1.11	-0.72	-1.53
6	-4.62	-4.46	-5.27	-9.78
7	-1.59	-1.17	-1.03	-0.70
8	-0.50	-0.80	-0.43	-0.96
9	-1.18	-0.49	-0.91	-0.44
10	-0.94	-1.65	-0.78	-1.70

Hypoxic ventilatory drive expressed as the negative $\dot{V}_E inst/S_aO_2$ slope for pooled data for transient (day A and day B) progressive (day A) and step-change (day B) hypoxia. $\dot{V}_E inst/S_aO_2$ was significantly greater ($p<0.01$) on day B between transient and step-change hypoxia.

table 3.4 : Hypoxic Ventilatory Drive Measured During Step-Change Hypoxia With and Without the Humidifier in the Breathing Circuit.

	With Humidifier	Without Humidifier
Subject	$\dot{V}_E inst/S_aO_2$ (l min^{-1} $\%^{-1}$)	$\dot{V}_E inst/S_aO_2$ (l min^{-1} $\%^{-1}$)
1	-1.71	-1.09
2	-1.05	-0.99
3	-3.26	-
4	-0.80	-0.90
5	-1.53	-1.20
6	-9.78	-4.21
7	-0.70	-0.87
8	-0.96	-
9	-0.44	-0.56
10	-1.70	-1.53

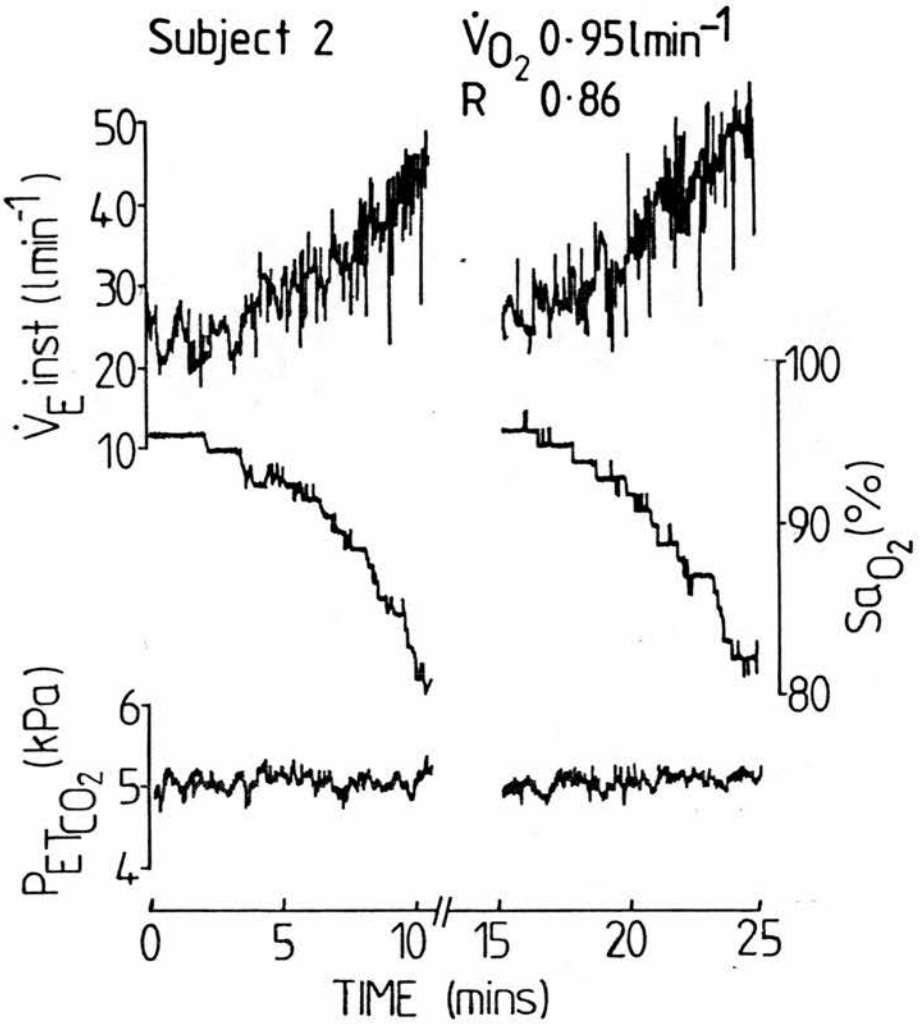
hypoxic ventilatory drive measured by step-change hypoxia (data from this chapter) with the humidifier included in the breathing circuit, and from chapter four (pooled data from four periods of step-change hypoxia from room air to 12% inspired O_2) without the humidifier included in the circuit.

table 3.5 : $P_{ET}CO_2$ During Hypoxia

	Day A		Day B	
	Transient	Progressive	Transient	Step-Change
Subject	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)
1	5.26±0.37	5.67±0.15	5.61±0.39	5.82±0.16
2	4.55±0.22	5.02±0.11	4.87±0.22	4.94±0.14
3	5.62±0.27	5.61±0.14	5.26±0.28	5.68±0.14
4	6.07±0.27	5.85±0.15	6.06±0.27	5.46±0.19
5	5.27±0.26	5.44±0.22	5.51±0.16	5.46±0.19
6	4.77±0.53	5.14±0.16	4.60±0.53	5.08±0.12
7	5.49±0.20	5.42±0.12	5.31±0.34	5.54±0.14
8	5.26±0.25	5.30±0.16	5.51±0.24	5.38±0.19
9	5.34±0.29	5.54±0.15	5.41±0.23	5.53±0.18
10	4.92±0.23	5.08±0.09	4.82±0.24	5.00±0.12

$P_{ET}CO_2$ expressed as the mean±SD for all the breaths used in the calculation of hypoxic ventilatory drive for pooled data.

Fig 3.2 : Ventilatory Response to Progressive Isocapnic Hypoxia



Duplicate measurements of hypoxic ventilatory drive in a normal subject (subject 2) using progressive isocapnic hypoxia, with the two measurements separated by five minutes breathing room air. Reduction of P_IO_2 over each ten-minute period was accompanied by a progressive fall in S_aO_2 (middle trace) and a gradual rise in $\dot{V}_E$inst (upper trace). $P_{ET}CO_2$ was maintained constant throughout.

the normoxic baseline measurement (table 3.2).

iii) Transient Hypoxia

Inhalation of two to four breaths of 100% N_2 was followed by a sudden fall in S_aO_2 and a rapid transient increase in $\dot{V}_E$inst (fig. 3.3).

The range of hypoxic ventilatory drive expressed as the $\dot{V}_E$inst/S_aO_2 slope was -0.38 to -4.62 $lmin^{-1}\%^{-1}$ ((table 3.3) on day A (the same day as progressive isocapnic hypoxia) and -0.22 to -5.27 on day B (the same day as step-change hypoxia). The measurements of hypoxic ventilatory drive made on day A and day B were not significantly different.

Mean baseline $P_{ET}CO_2$ varied between individuals (table 3.2) with a range of standard deviation about the mean from 0.08 to 0.21kPa. There was no significant difference between the baseline $P_{ET}CO_2$ for transient hypoxia and that for progressive and step-change hypoxia. As no attempt was made to maintain isocapnia during the ventilatory response to transient hypoxia, a brief fall in $P_{ET}CO_2$ occurred following hypoxia (fig. 3.3, lower trace), The difference between the mean baseline $P_{ET}CO_2$ and the mean $P_{ET}CO_2$ during hypoxia ranged from -0.11 to -0.47kPa on day A and +0.02 to -0.56kPa on day B (table 3.6).

iv) Comparison of Ventilatory Responses to Different Hypoxic Stimuli.

Ranking of the ventilatory responses to the three types of hypoxic stimulus was inconsistent, the only subjects in whom any consistency was observed were subject 6, who had the highest hypoxic drive in the group, measured by all three methods, and subject 8, who had a consistently low hypoxic drive (although not the lowest), and who ranked third or fourth lowest for all three methods (table 3.7). The lowest hypoxic ventilatory drive measured by both step-change and progressive isocapnic hypoxia was shown by subject 9, who had the 7th and 8th highest responses to transient hypoxia on days A and B respectively. Subject 3, who had the 2nd greatest response to both step-change and progressive hypoxia, had the fourth smallest and the smallest responses to transient hypoxia on days A and B respectively.

Hypoxic ventilatory drive measured by step-change hypoxia was greater than that measured by transient hypoxia in eight out of the ten subjects, a difference which achieved significance for the whole group of subjects ($p<0.04$) In two subjects (subjects 7 and 9), however, the ventilatory response to transient hypoxia was greater than that to step-change hypoxia. Although seven of the ten subjects had a greater

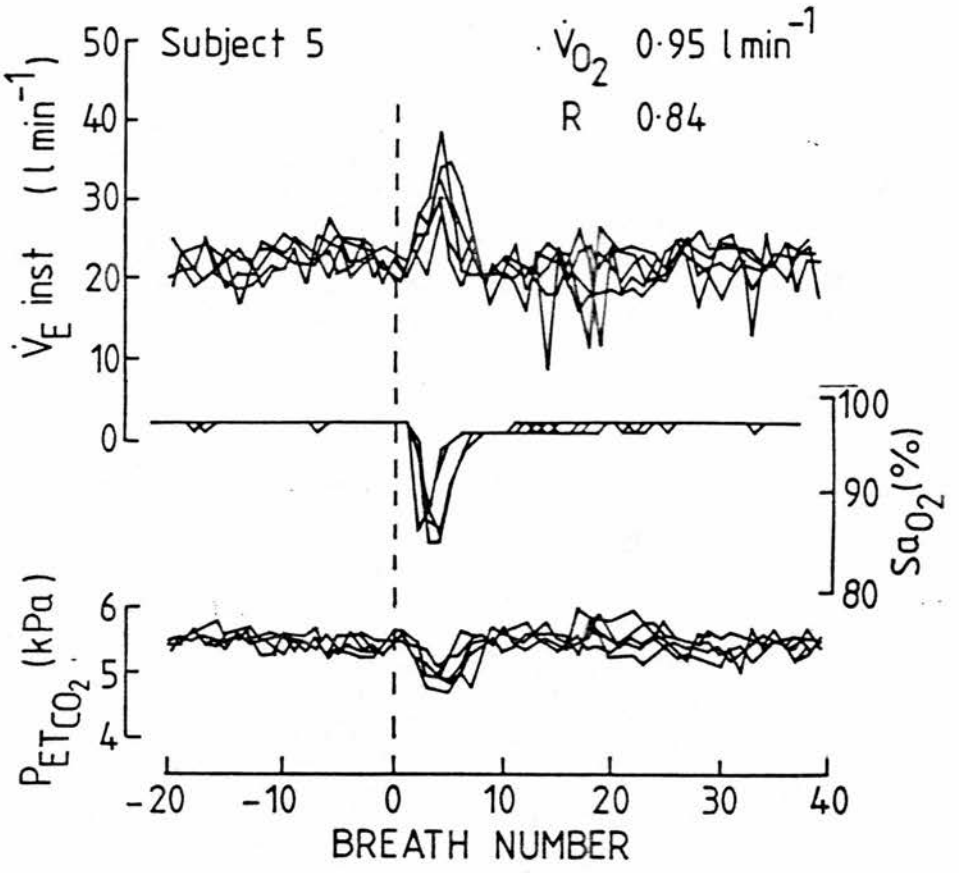
ventilatory response to progressive hypoxia than to transient hypoxia, this was not significant for the whole group of subjects, nor was there any significant difference between responses to progressive and step-change hypoxia.

End-tidal $P_{ET}CO_2$ during hypoxia was not significantly different for each set of measurements of hypoxic ventilatory drive, (table 3.4) nor was the lowest S_aO_2 reached during hypoxia (table 3.8).

The rate of fall of S_aO_2 following transient hypoxia was faster than that following step-change hypoxia (fig 3.3). The half-time of the ventilatory response to a step-change from room air to 12% inspired O_2 varied from 18 to 68 seconds (mean 33.8seconds). The duration of the transient stimulus varied from 8.0 to 14.5 seconds (mean 9.7 seconds) i.e approximately one third of the half-time of the ventilatory response to inhalation of 12% O_2. (table 3.9,)

The amplitude/frequency plots of the "filter function" for both transient and step-change hypoxia are compared in fig 3.5. In subjects 3,4,6,8,9 and 10, these plots were qualitatively different, whereas in the remaining subjects they were similar.

Fig 3.3 : Ventilatory Response to Transient Hypoxia



Ventilatory response to three breaths of 100% N_2 in a normal subject (subject 5), measured six times at intervals of 60 breaths. Data from only four episodes of hypoxia are included in analysis in this case, as these fulfilled the criteria described in chapter 2. Transient hypoxia was followed by a rapid decrease in S_aO_2 (middle trace) and increase in $\dot{V}_E$inst (upper trace). $P_{ET}CO_2$ fell briefly during the ventilatory response to hypoxia (lower trace).

table 3.6 : Differences Between Mean Baseline $P_{ET}CO_2$ and $P_{ET}CO_2$ During Transient Hypoxia

	Day A	Day B
Subject	$P_{ET}CO_2$ Difference (kPa)	$P_{ET}CO_2$ Difference (kPa)
1	-0.42	-0.32
2	-0.17	-0.16
3	-0.22	-0.58
4	-0.11	-0.13
5	-0.41	+0.02
6	-0.47	-0.56
7	-0.11	-0.15
8	-0.13	-0.15
9	-0.23	-0.21
10	-0.16	-0.30

negative differences represent a fall in $P_{ET}CO_2$ from the baseline measurement. In one subject, (subject 5) there was a small increase in $P_{ET}CO_2$ during hypoxia on day B, however this fell within the standard deviation in $P_{ET}CO_2$ during normoxia, and was therefore a result of the normal variation, made obvious by the fact that this subject had a low ventilatory response to transient hypoxia, thus there was very little tendency for $P_{ET}CO_2$ to fall as a result of an increase in ventilation.

Table 3.7 : Ranking of Hypoxic Ventilatory Drive Measurements

	Day A		Day B	
	Transient	Progressive	Transient	Step-Change
Subject	Rank	Rank	Rank	Rank
1	4	3	2	1
2	3	1	4	2
3	4	2	3	1
4	3	2	4	1
5	4	2	3	1
6	3	4	2	1
7	1	2	3	4
8	3	2	4	1
9	1	4	2	3
10	3	2	4	1

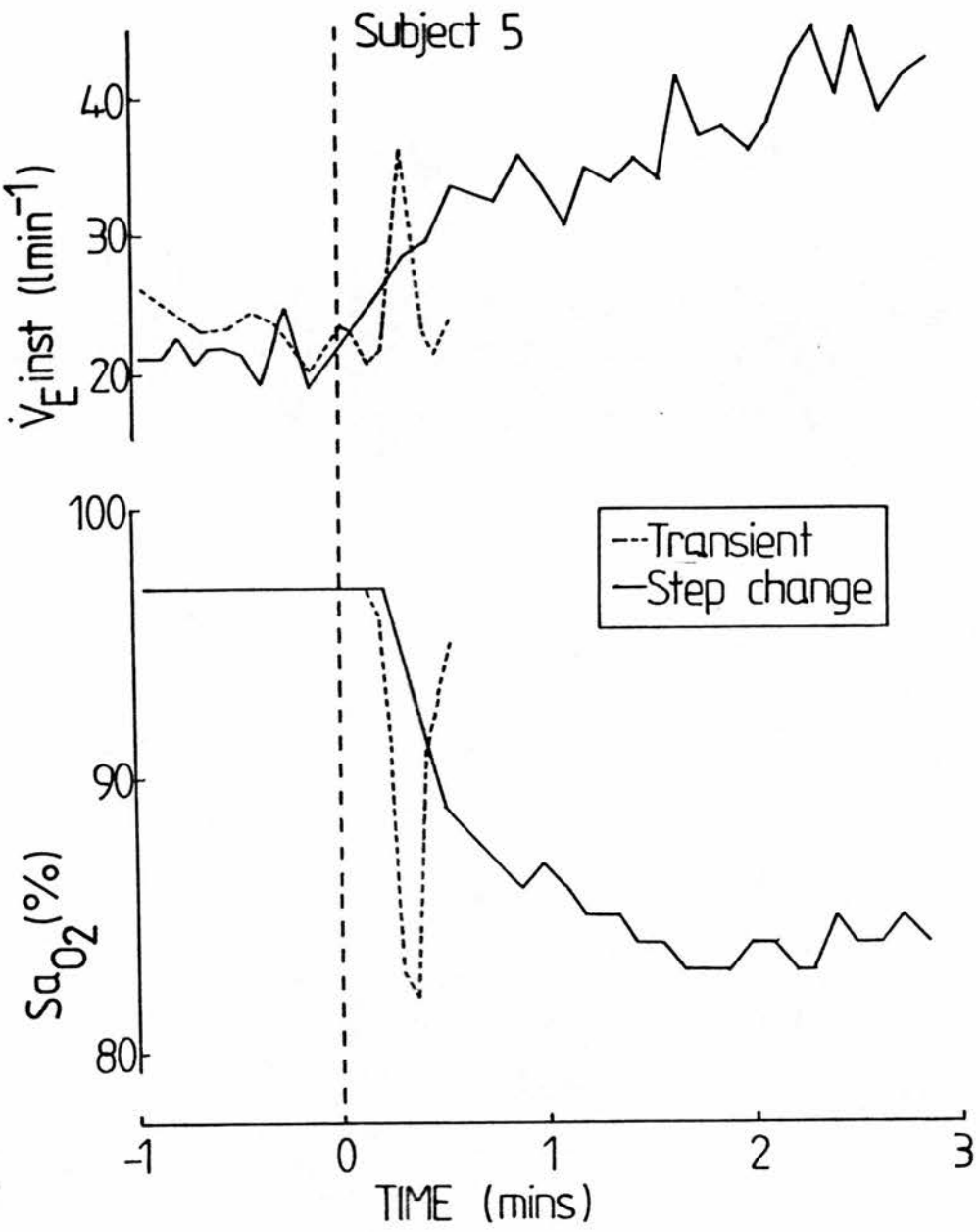
Ranking of the ventilatory responses to transient, progressive and step-change hypoxia measured by the negative slope of the $V_E inst/S_a O_2$ relationship. The most negative measurements have the lowest ranks.very marked. Two subjects (subjects 7 and 9), however, showed a greater response to transient hypoxia than to step-change hypoxia.

table 3.8 : The Lowest S_aO_2 Reached During Hypoxia

	Day A		Day B	
	Transient	Progressive	Transient	Step-Change
Subject	S_aO_2 (%)	S_aO_2 (%)	S_aO_2 (%)	S_aO_2 (%)
1	81	79	83	75
2	84	81	82	84
3	80	85	76	86
4	87	79	78	78
5	85	81	85	85
6	86	89	85	89
7	87	82	83	82
8	87	82	83	81
9	82	81	87	79
10	84	77	82	83

Mean lowest S_aO_2 reached for pooled data from transient hypoxia (day A and B) progressive isocapnic hypoxia (duplicate measurements) and step-change hypoxia (from air to 12% O_2).

fig 3.4 : S_aO_2 During Transient and Step-Change Hypoxia



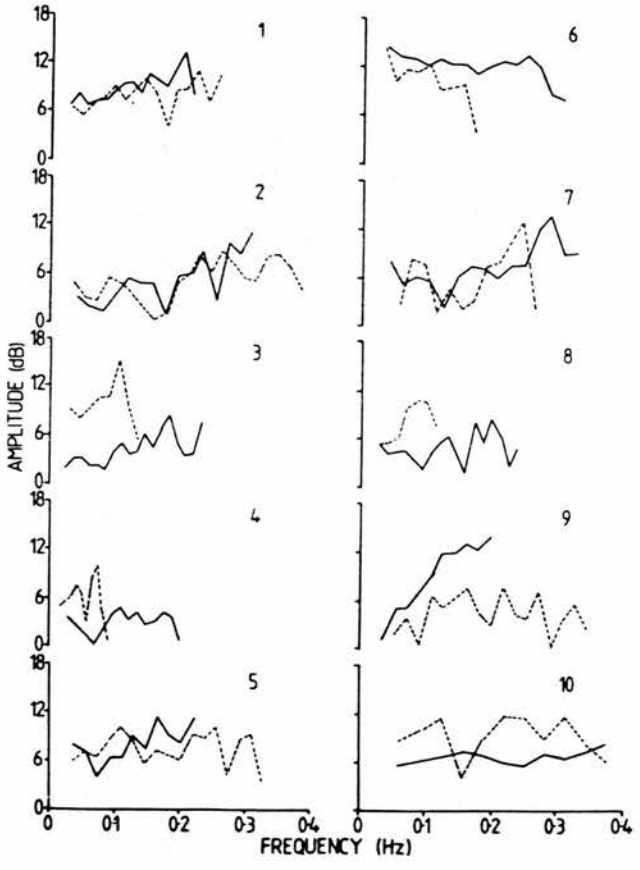
The rate of change of S_aO_2 is faster following inhalation of three breaths of N_2 than after a step-change in F_IO_2 from room air to 12% O_2 (lower trace). The ventilatory response to transient hypoxia is also faster than that to step-change hypoxia

table 3.3 : Half-Time of the Ventilatory Response to Step-Change Hypoxia and Duration of the Transient Hypoxic Stimulus.

Subject	Step-Change $t_{1/2}$ (sec)	Transient Duration (sec)
1	18.0	10.5
2	23.0	8.0
3	37.5	13.0
4	44.0	12.0
5	30.5	9.0
7	19.5	9.5
8	36.5	9.0
9	68.0	11.0
10	27.0	14.5

The half-time ($t_{1/2}$) of the ventilatory response to a step-change in inspired gas from room air to 12% O_2 was approximately one-third of the duration of the duration of the transient stimulus. Data was not obtained from subject six, as the ventilatory response to step-change hypoxia did not reach a plateau, which is necessary for calculation of $t_{1/2}$.

fig 3.5 : Amplitude/Frequency Plots For Transient and Step-Change Hypoxia



The amplitude frequency plots derived from the Fourier transform of the convolution functions for the ventilatory responses to transient and step-change hypoxia (12% O_2) were quantitatively different in six of the ten subjects. Solid lines show the transient-derived function, broken lines show the step-change derived function.

IV DISCUSSION

Hypoxic ventilatory drive measured using step-change hypoxia was significantly greater than that measured using transient hypoxia for the whole group of subjects, despite the fact that S_aO_2 fell to the same level during both procedures. In two of the subjects, however, the ventilatory response to transient hypoxia was greater than that to step-change hypoxia. Ventilation and gas exchange measurements during steady-state exercise were similar for both transient and step-change hypoxia.

The range of hypoxic ventilatory drive measured using transient hypoxia agrees with that previously obtained during exercise at a $\dot{V}O_2$ of approximately 1.0 $lmin^{-1}$ in normal subjects by Airlie et al (1988). The results obtained using progressive isocapnic hypoxia cannot be compared quantitatively with those of other authors who have only made measurements at rest (Edelman et al 1972, Rebuck and Campbell 1974, Hirshman et al 1975, Sahn et al 1977,Shaw et al 1982, Airlie et al 1988), whereas these results are obtained during exercise, which increases hypoxic ventilatory drive (Weil et al 1970, Martin et al 1978). Step-change hypoxia has not previously been used to measure hypoxic ventilatory drive, so again, comparison with the results of other authors is not possible.

There are two possibilities which could account for the observed differences between ventilatory responses to the three types of hypoxic stimulus; firstly, carotid chemoreceptor mediated hypoxic ventilatory drive is overestimated by using step-change hypoxia, and to some extent by progressive isocapnic hypoxia, secondly it is underestimated by transient hypoxia,

Warming and humidification of the inspired gas when measuring the response to step-change and progressive isocapnic hypoxia may have contributed to the greater response in the majority of subjects. Some subjects claimed to have been aware of a change in temperature of the inspired gas on changing to the hypoxic gas mixture, which may have incrased their ventilatory responses. Comparison of ventilatory responses to step-change hypoxia with and without the humidifier included in the apparatus in seven subjects (table 3.4) showed that this was unlikely to significantly affect the results in the majority of subjects. One subject (subject six) did show a large decrease in hypoxic ventilatory drive when the humidifier was omitted, but since the difference between results

obtained for step change hypoxia with and without the humidifier was similar to the difference between those for progressive isocapnic and step-change hypoxia both with the humidifier, the effect may have reflected wide day-to day variability in hypoxic ventilatory drive in this subject.

The development of hypocapnia following transient hypoxia may have contributed to the lower hypoxic ventilatory drive measured by this method, as the carotid chemoreceptors respond very rapidly to changes in PCO_2 (Lahiri et al 1980). Shaw et al (1982) also found a smaller ventilatory response to transient than to progressive isocapnic hypoxia at rest in all but one subject. They suggested that this could be a result of hypocapnia developing during the increase in ventilation following transient hypoxia, as hypocapnia is known to limit the ventilatory response to hypoxia (Reynolds and Milhorn, 1973). In the study by Shaw et al, the transient stimulus consisted of between two and seven breaths of 100% N_2. Assuming a respiratory rate of ten breaths per minute at rest, the duration of the hypoxia stimulus could have ranged from 12 to 42 seconds, and the hypocapnia resulting from the rise in ventilation may have been considerable and prolonged. In contrast, the present study was carried out during exercise, and both the rate and depth of breathing would be greater than at rest, thus the number of breaths of N_2 required to achieve a satisfactory fall in S_aO_2 and the duration of the hypoxic stimulus would have been smaller than in the study of Shaw et al (1982). Nevertheless, in the present study a fall in $P_{ET}CO_2$ was still observed during the ventilatory response to transient hypoxia (fig 3.3).

The extent of the limitation of the ventilatory response to hypoxia by the fall in $P_{ET}CO_2$ would depend upon both the magnitude of the fall in $P_{ET}CO_2$ and the sensitivity of the carotid chemoreceptors to changes in $P_{ET}CO_2$. The site of interaction of hypoxia and hypocapnia is most likely to be the peripheral chemoreceptors rather than the medullary chemoreceptors, as the carotid chemoreceptors respond rapidly to changes in $P_{ET}CO_2$ (Lahiri et al 1980) particularly during hypoxia (Miller et al 1974, Drysdale et al 1981). The ventilatory response to CO_2 was not measured in the present study, but a positive correlation has been shown between hypoxic and hypercapnic ventilatory drives (Rebuck et al 1973). Individuals with a high hypoxic ventilatory drive may therefore have greater sensitivity to changes in $P_{ET}CO_2$, thus the ventilatory response to hypoxia would be limited to a greater extent in these

subjects than in subjects with a low hypoxic ventilatory drive, by hypocapnia. Such an interaction would account for the results in subject three, who had a high hypoxic ventilatory drive measured using progressive and step-change hypoxia, and had the lowest hypoxic ventilatory drive measured by transient hypoxia on one day and the fourth lowest on the other day. Subject six, however, had the greatest hypoxic ventilatory drive measured by all three methods, although the ventilatory response to transient hypoxia was smaller than that to step-change hypoxia, it was very similar to that to progressive isocapnic hypoxia. Furthermore two subjects had a greater response to transient than to step-change and progressive isocapnic hypoxia, despite the hypocapnia. Thus although hypocapnia may have contributed to the lower ventilatory responses to transient hypoxia, it does not fully explain the observed differences in ventilatory responses to the three types of hypoxic stimulus in all subjects.

The method of analysis of the response to transient hypoxia may contribute to the errors in the estimated hypoxic ventilatory drive. The wide variation in normoxic ventilation (Tobin et al 1988) gives a low signal-to noise ratio for the brief ventilatory response to transient hypoxia. Accurate quantification of the response therefore poses problems especially in individuals with a low hypoxia ventilatory drive.The method of analysis used in this study, in which the best statistical relationship between $V_E$inst and S_aO_2 was calculated using an iterative process both avoids the subjectivity of selecting the peak response, and includes more data points than in the methods of Edelman et al (1973) and Shaw et al (1982), thus improving the power of analysis. Pooling the data further improves the measurement. The number of data points included in the analysis of the ventilatory response to transient hypoxia, however, was still small compared to step-change and progressive isocapnic hypoxia. Seven or eight breaths were included for each transient hypoxic test, and since the minimum number of stimuli which were pooled for analysis was four, the total number of breaths included could be as low as 28. Despite the potentiation of the ventilatory response to transient hypoxia during exercise (Weil et al 1972, Martin et al 1978) there was still a low signal to noise ratio in some subjects, which could significantly affect the assessment of the ventilatory response to transient hypoxia, especially when such a small number of breaths are included in the analysis. This is unlikely, however, to be the full explanation, since the ventilatory response to

transient hypoxia was reproducible day to day, and one would expect overestimation of the ventilatory response to occur as frequently as underestimation.

A further problem, which could affect the analysis of the data particularly at low respiratory rates, is that S_aO_2 was measured as the mean during each breath. The true minimum S_aO_2 during transient hypoxia may therefore not be recorded, thus affecting the $\dot{V}_E inst/S_aO_2$ relationship. This effect is likely to have been small, however, as all the measurements were made during exercise when the respiratory rate is greater than at rest. Furthermore, this would have resulted in overestimation of hypoxic ventilatory drive, as the fall in S_aO_2 would be underestimated due to averaging over a whole breath.

Periods of hypoxia longer than just a few breaths may activate a "central gain system", resulting in facilitation of the ventilatory response to step-change hypoxia. This could either occur within the brainstem, modifying the carotid chemoreceptor input without affecting the carotid bodies themselves, or it could be a positive feedback system to the carotid bodies, possibly via the sympathetic nervous system. This hypothesis is supported by the observation that sympathetic efferents in the ganglioglomerular nerve are active during hypoxia in cats (Floyd and Neil 1952), and that sympathetic nerves can have an excitatory action on chemosensory output (O' Regan 1981). This "central gain system" could thus cause facilitation of the ventilatory response to step-change and progressive isocapnic hypoxia without being activated during transient hypoxia.

Some investigators have found that prior exposure to step-change hypoxia potentiates the ventilatory response to progressive hypoxia (Davidson and Cameron 1985). An increase in the ventilatory response to progressive isocapnic hypoxia when the ventilatory response was measured repeatedly was observed by Jennett and Walker (1983) but not by Davidson and Cameron (1985) or Sahn et al (1977). If potentiation of hypoxic ventilatory drive occurred during repeated episodes of step-change or progressive isocapnic hypoxia, pooling of results of such tests would cause overestimation of the hypoxic ventilatory drive, and could account for the differences in ventilatory responses to step-change or progressive isocapnic compared transient hypoxia seen in the majority of subjects in the present study. There did not appear to be an increase in the ventilatory response to step-change hypoxia as a result of

repeated stimuli in this study (for example, fig 3.1), although this was difficult to assess as the two levels of hypoxia were studies alternately.

The short duration of the transient hypoxic stimulus may be responsible for underestimation of hypoxic ventilatory drive using this method. The half-time for the steady-state response to rapid onset hypoxia (9% inspired PO_2) is on average 78 seconds (Reynolds and Milhorn 1973). In this study, the duration of the transient hypoxic stimulus was on average 9.7 seconds (table 3.6), thus the transient stimulus was withdrawn well before the time required to reach the maximal response and might therefore be attenuated. This may contribute to the relatively small ventilatory response to transient hypoxia compared to step-change hypoxia, but is not the entire explanation for the differences in response to the different hypoxic stimuli, since in subjects seven and nine, the ventilatory response to transient hypoxia was greater than that to step-change hypoxia.

Other authors have also noted a minority of subjects who have a higher ventilatory response to transient hypoxia than to progressive hypoxia (Shaw et al 1982, Kronenberg et al 1972) and steady-state hypoxia (Kronenberg et al 1972). The low ventilatory response to longer periods of hypoxia in these subjects and in subjects seven and nine of the present study may be due to variability in the extent of central hypoxic depression of ventilation (Holton and Wood 1965, Lahiri 1974, Lee and Millhorn 1975, . Weiskopf and Gabel 1975) or in the timing of a biphasic (i.e. an initial increase in ventilation followed by a decrease) response to hypoxia. The mechanism responsible for the biphasic response to hypoxia is not known, but proposed mechansms include central hypocapnia and central release of adenosine (Easton et al 1986). Weil and Zwillich (1970) noted that the initial rise in ventilation during hypoxia lasted only five to ten minutes, and Kagowa et al (1972) found that V_I increased during the first five minutes of hypoxia, and than decreased thereafter. Kronenberg et al (1972) suggested that hypoxic ventilatory depression occurred in some of their subjects within three to four minutes. Easton et al (1986) have demonstrated a biphasic response to hypoxia in which ventilation increases to a plateau at around five minutes after the onset of hypoxia, and then decreases to a new plateau level after approximately 15 minutes. As in all physiological systems, there is likely to be some individual variation in the timing of the onset of hypoxic ventilatory depression, the degree of hypoxia required to

initiate it and the extent to which ventilation is affected. The smaller ventilatory responses to progressive isocapnic and step-change hypoxia than to transient hypoxia in two subjects might therefore be explained by differences in the sensitivity and time course of either the central depression or the biphasic mechanisms although an initial increase in ventilation followed by a decrease as hypoxia continued was not observed in any of the subjects.

A problem with comparison of ventilatory responses to transient and step-change hypoxia is that the different rates of desaturation at the onset of hypoxia are not taken into account by expression of hypoxic ventilatory drive as the linear $\dot{V}_E inst/S_aO_2$ relationship, thus it is assumed that the stimulus/ response relationship is linear under all conditions. The filter functions derived by deconvolution for transient and step-change hypoxia were different. This suggests that in fact the stimulus/response relationship is not linear under all conditions, therefore use of $\dot{V}_E inst/S_aO_2$ does not adequately describe the response. The ventilatory response to transient hypoxia may not, therefore, accurately reflect carotid chemoreceptor mediated hypoxic ventilatory drive.

Different ventilatory responses were obtained to transient and to step-change hypoxia. The results of deconvolution analysis suggest that the ventilatory response may depend upon the rate of onset of hypoxiaemia. The response to transient hypoxia, however, may heve been affected by hypocapnia, and that to step-chnge hypoxia by either potentiation or depression of the response due to the more prolonged hypoxia.These factors are considered in the following chapter.

CHAPTER 4 : THE EFFECT OF REPEATING OR PROLONGING THE HYPOXIC STIMULUS ON THE MEASURED HYPOXIC VENTILATORY DRIVE.

I INTRODUCTION

Use of the conventional steady-state or progressive isocapnic methods may underestimate the hypoxic ventilatory drive due to central hypoxic depression of ventilation caused by the relatively prolonged hypoxia. The step-change hypoxic stimulus (abrupt change of inspired gas from room air to 15 or 12% O_2) aimed to avoid central depression of ventilation by limiting the duration of hypoxia to three minutes, whilst allowing sufficient time for the ventilatory response to develop maximally. Repeated exposure to hypoxia, however, (as with duplicate measurements of the ventilatory response to progressive isocapnic hypoxia or repeated step-change hypoxia) may potentiate the ventilatory response to hypoxia. Such depression or potentiation would influence the intensity of the hypoxic ventilatory drive, causing underestimation or overestimation respectively

The conditions under which potentiation of hypoxic ventilatory drive occurs are not clear, and the degree and/or duration of hypoxia causing it may be critical. It is therefore important to investigate the possibility that potentiation of hypoxic ventilatory drive could occur under the conditions specifically used in the present project.

i) Potentiation of the Ventilatory Response to Hypoxia

Acclimatisation to high altitude involves an initial increase in chemosensitivity to hypoxia within 48 hours (Vizek et al 1987b). Resting ventilation is increased (Rahn and Otis 1949, Severinghaus et al 1963, Dempsey et al 1972, , Huang et al 1984), and the ventilatory responses to CO_2/H+, exercise and hypoxia are enhanced (Severinghaus 1963, Klausen et al 1970, Forster et al 1971, Forster et al 1974, Dempsey et al 1972, Cruz et al 1980, Huang et al 1984, Vizek et al 1987b), an effect which persists after return to normoxia at sea level (Rahn and Otis 1949, Forster et al 1971, Klausen et al 1970).

Even periods of hypoxia lasting only a few minutes may cause potentiation of hypoxic ventilatory drive. Anderton et al (1964) measured the ventilatory response to steady-state hypoxia twice, separated by an

interval of 20 minutes breathing room air in normal subjects. The ventilatory response to steady-state hypoxia was greater during the second measurement when P_ACO_2 was 1-2mmHg (0.1-0.3kPa) above the air breathing level and this potentiation was even more pronounced when the hypoxia was combined with a P_ACO_2 of 6-8mmHg (0.8-1.1kPa) above that of the normal air breathing level. Jennett and Walker (1983) also reported that the ventilatory response to a second period of hypoxia was greater than the first, provided that PCO_2 was kept at the normoxic level or above, and that the enhancement of the ventilatory response to hypoxia increased as PCO_2 was raised. No information was given regarding the degree or duration of hypoxia in this study. They also found that, unlike the acclimatisation process, neither resting ventilation nor the ventilatory response to steady-state exercise were potentiated 20 minutes after5 minute periods of breathing 9% O_2 in N_2, 9% O_2 and 5%CO_2 in N_2 or 5% CO_2 in N_2, although the increase in ventilation at the start of exercise was more rapid 20 minutes after breathing the hypoxic and hypercapnic gas mixture.

The ventilatory response to progressive isocapnic hypoxia (a reduction in $P_{ET}O_2$ from 155mmHg (20.6kPa) to 40mmHg (5.3kPa) over seven minutes) was not enhanced when measured at 30 minute intervals over a two hour period (Sahn et al 1977). Davidson and Cameron (1985) also found that progressive isocapnic hypoxia (reducing S_aO_2 to 70% over 7-9 minutes) did not cause a greater ventilatory response to a similar period of progressive isocapnic hypoxia administered 20 minutes later, whereas a priming dose of 7-8% inspired O_2 lasting five minutes did potentiate the response to progressive isocapnic hypoxia given 20 minutes later.

Both carotid chemoreceptor input and central mechanisms appear to be necessary for the potentiation of the ventilatory response to repeated hypoxic stimuli. Millhorn et al (1980) suggested that the long-lasting increase in baseline phrenic nerve discharge following repeated periods of electrical stimulation of the carotid sinus nerve was a result of activation of a ponto-medullary mechanism by carotid chemoreceptor input, the effect of which was to increase ventilation. Their studies, in anaesthetised cats, ruled out the possibility of the actual locus of the potentiation being the carotid chemoreceptors, since it was initiated by controlled stimulation of the carotid sinus nerve. As Millhorn et al (1980) also reported that the potentiation effect was not abolished by

decerebration or section of the spinal cord between C_7 and T_1, then spinal reflexes and higher centres are not the locus for potentiation of the ventilatory response to hypoxia. Millhorn et al (1979) suggested that a long-acting central neurotransmitter such as serotonin may be involved.

ii) Hypoxic Depression of Ventilation.

Some authors have suggested that the ventilatory responses to progressive isocapnic and steady-state hypoxic stimuli are reduced by central hypoxic depression of ventilation occurring during periods of hypoxia lasting longer than only a few breaths, thus resulting in smaller ventilatory responses than to transient hypoxia of similar severity (Kronenberg et al 1972, Weil and Zwillich 1976, Shaw et al 1982). Furthermore, a biphasic response to hypoxia (an initial increase in ventilation followed by a decrease) exists in newborn or preterm infants (Crosse et al 1951, Crosse and Oppe 1952, Sankaran et al 1979), and this characteristic may be retained in some individuals into adulthood (Easton et al 1986). Early evidence for central hypoxic depression of ventilation was provided by the studies of Dumke et al (1941), Watt et al (1943) and Astrom (1942) who observed a decrease in ventilation during hypoxia in carotid denervated anaesthetised dogs, and it has since been observed in many studies in both animals and man.

Like potentiation, the existence and the extent of hypoxic ventilatory depression may depend upon thresholds for the duration and the degree of hypoxia. The threshold level of hypoxia at which ventilatory depression occurs has not been clearly established, and differences in the reported levels may be a result of the duration of hypoxia, or may be due to species differences. Lahiri (1974) reported a P_aO_2 threshold for central depression of ventilation in anaesthetised and carotid denervated cats of about 130mmHg (17.3 kPa). This threshold, which was determined by measuring ventilation at several levels of steady-state hypoxia, was not altered by hypercapnia, although the magnitude of the ventilatory depression rose with increasing PCO_2. A slightly different approach was used by Morrill et al (1975) to determine the threshold for ventilatory depression in anaesthetised dogs. The dogs initially breathed 23-30% O_2 in N_2, and N_2 was then added progressively to the inspired gas mixture over six to nine minutes. Isocapnia was maintained throughout. In carotid denervated dogs, ventilation increased gradually

until $P_{I}O_2$ reached the threshold level (mean±SD 21.8±0.8mmHg or 2.9±0.1kPa), when it began to decrease. The threshold was only slightly lower in dogs which had intact carotid sinus nerves (18.6+0.6mmHg or 2.5±0.1kPa), and was found not to be affected by anaesthesia, hypo- or hypercapnia. Lee and Millhorn (1975) reported a higher threshold for P_aO_2 (around 40-45mmHg or 5.7-6.0 kPa), in anaesthetised dogs, which was derived from studies in which the dogs breathed several levels of P_IO_2 each for six minutes while the carotid bodies were separately perfused with different levels of P_aO_2. Van Beek et al (1984) found that the decrease in ventilation observed in anaesthetised cats with artificially perfused brainstem was most pronounced below a central P_aO_2 of 100mmHg (13.3kPa), although there was a continuous decrease in ventilation as central P_aO_2 was reduced progressively under isocapnic conditions from hyperoxaemia to hypoxaemia. In human subjects, the P_aO_2 threshold for hypoxic depression of ventilation has not been determined. Holton and Wood (1965) observed a decrease in ventilation during inhalation of 10% O_2 within four minutes of onset of hypoxia in two subjects after bilateral carotid body resection. In these studies, the subjects were fully conscious, thus the possibility that anaesthesia could cause central hypoxic depression was eliminated. The subjects both had a normal ventilatory response to ten percent inhaled O_2 prior to surgery. Lugliani et al (1971), however, found no depression of ventilation in seven carotid body resected subjects when they inhaled 12% O_2 for 6 minutes during exercise. Honda et al (1979) observed depression of ventilation during progressive isocapnic and steady- state hypoxia in two subjects who had bilateral carotid body resection approximately 25 years previously, but in nine further subjects who had undergone the same surgical procedure, there was evidence of regeneration of peripheral chemoresponsiveness. This could explain why the subjects of Lugliani et al (1971), who were studied between two weeks and eight years after surgery did not exhibit any central hypoxic depression, but those of Holton and Wood (1965) who were all studied two weeks after carotid body resection both did.

Guz et al (1966) chemically denervated the carotid bodies in one subject using lignocaine to block glossopharyngeal nerve activity and atropine to block vagus nerve activity. Prior to nerve blocking, there was an increase in ventilation during inhalation of eight percent oxygen, which was abolished after nerve block. They concluded that the nerve

block was not complete and there remained some carotid chemoreceptor activity which masked central hypoxic depression of ventilation. As only a minority of subjects, however, demonstrate central hypoxic ventilatory depression (Edelman et al 1970, Kronenberg et al 1972, Weil and Zwillich 1976, Shaw et al 1982), the subject studied by Guz et al (1966) may not have had very pronounced central hypoxic depression.

Weiskopf and Gabel (1975) reduced P_AO_2 gradually from 120 to 40mmHg (16.0-5.3kPa) in normal human subjects under isocapnic conditions over a period of five minutes, and then reversed the process. A plot of P_AO_2 against ventilation, showed an hysteresis in the recovery phase. They found that for the same level of P_AO_2, minute ventilation was higher during the development of hypoxia than during the return to normoxia. Thus hypoxic ventilatory depression was taking place at a P_aO_2 greater than or equal to 40mmHg (5.3kPa). Kagawa et al (1982) found that normal subjects with carotid bodies intact demonstrated hypoxic ventilatory depression while breathing an hypoxic gas mixture which gave a $P_{ET}O_2$ of approximately 45mmHg (6.0kPa), and the normal adult subjects studied by Huang et al (1984) showed hypoxic ventilatory depression during isocapnic and poikilocapnic hypoxia at S_aO_2 of around 82%. Easton et al (1986) showed hypoxic ventilatory depression in normal subjects while breathing an hypoxic gas mixture containing eight to ten percent O_2, resulting in S_aO_2 of about 80%, and Nishimura et al (1987) demonstrated that hypoxic ventilatory depression occurs at a $P_{ET}O_2$ of 40-50mmHg (5.3-6.6kPa) in normal subjects. None of these studies actually determined a P_aO_2 threshold below which central depression of ventilation occurred.

Hypoxic depression of ventilation is dependent upon the duration as well as the degree of hypoxia. Lahiri et al (1974) showed that in anaesthetised chemodenervated cats hypoxic ventilatory depression was a gradual process which first became evident after two to three minutes. In the studies of Huang et al (1984) hypoxic ventilatory depression occurred within five to ten minutes of the onset of hypoxia in human subjects, and similar times were observed in 1982 by Kagowa et al (a decrease in ventilation within five minutes) in humans and in 1987 by Vizek et al (within ten minutes) in awake and anaesthetised cats. Nishimura et al (1987) carried out a study in which progressive isocapnic hypoxia was induced over five minutes, and then the P_aO_2 was maintained

at around 47mmHg. Four out of eight subjects showed a decrease in ventilation five minutes after the onset of sustained hypoxia..

Although most previous studies suggest that depression occurs after 5-10 minutes exposure to hypoxia (Kagowa et al 1982, Huang et al 1984, Nishimura et al 1987, Vizek et al 1987), short durations have been reported in cats (Lahiri et al 1974). hypoxic ventilatory depression may therefore occur during the step-change or progressive hypoxic stimuli used in the present project. The threshold for the degree of hypoxia required to initiate hypoxic depression in humans has not been precisely defined, the degree of hypoxia used in the present project may be low enough to cause hypoxic depression provided the period of hypoxia is long enough. Although the hypoxic ventilatory drive measured using progressive and step-change hypoxia is greater than that measured using transient hypoxia in the majority of the subjects in chapter two of this thesis, two of these subjects did show a very low ventilatory response to step-change hypoxia compared to that to transient hypoxia, and this may be a result of inter-subject variability in the extent of central hypoxic depression of ventilation, these two subjects being more sensitive to it than the others.

Hypoxic depression of ventilation could occur either at the carotid chemoreceptors or in the central nervous system. Since a further increase in P_IO_2 imposed during ventilatory depression following an initial decrease in P_IO_2 causes an increase in ventilation in neonatal lambs, Bureau et al (1984) suggested that hypoxic depression of ventilation was a result of accommodation of the carotid chemoreceptor discharge during prolonged periods of hypoxia. Other evidence, however, does not support this hypothesis. Morrill et al (1975) showed that the P_AO_2 threshold below which ventilatory depression occurs in anaesthetised dogs was only slightly higher in carotid denervated dogs than in dogs with the carotid sinus nerves intact, and Lahiri (1974) reported that hypoxic ventilatory depression still occurred during continuous stimulation of the carotid sinus nerve in anaesthetised cats. Vizek et al (1987a) found in both anaesthetised and awake cats that ventilation and phrenic nerve activity decreased in response to isocapnic hypoxia after an initial rise, but carotid sinus nerve activity remained constant.

Evidence for central mediation of hypoxic ventilatory depression comes from work by Lee and Milhorn (1975), who perfused the carotid

bodies of anaesthetised dogs by a technique of cross-perfusion with blood of a donor dog. When the carotid bodies were perfused with normoxic or hyperoxic blood, systemic hypoxia (and therefore central hypoxia) resulted in ventilatory depression, the magnitude of which was dependent upon the degree of hypoxia. Tenney and Ou (1977) demonstrated the existence of a cortical inhibitory influence on ventilation during hypoxia indirectly, by showing that removal of the cortex resulted in an increase in ventilation in anaesthetised cats. It is also known that electrical stimulation of certain areas of the cortex results in inhibition of ventilation (Bailey and Sweet 1940).

Mechanisms to account for central hypoxic depression of ventilation include the proposition that a decrease in brain metabolism may be responsible (Cherniack et al 1971). No decrease in energy production of the cerebrum was found by Cohen et al (1967), however, so this hypothesis appears unlikely. Release of central neurotransmitters during hypoxia such as adenosine (Winn et al 1981) or glutamate-γ-aminobutyric acid (Chiang et al 1984, Hoop et al 1984) or endorphins (Grunstein et al 1981) may also inhibit ventilation and thus be responsible for hypoxic ventilatory depression. Naloxone, which reverses the ventilatory depression caused by endogenous opioides (i.e. endorphins) does not affect hypoxia induced ventilatory depression however, (Kagowa et al 1982).

Thee aims of the present study are therefore to investigate the possibility that the ventilatory response to hypoxia may be potentiated by repetition of hypoxic stimuli, and to establish whether prolonged hypoxic stimuli, such as step-change and progressive isocapnic hypoxia as used in this project, are likely to be affected by central hypoxic depression of ventilation.

II METHODS

i) Subjects

Eleven subjects (7 male, 4 female ; Appendix II : numbers 1-10, 12) recruited from laboratory staff were studied. Details of age, height, weight, lung volumes, TCO and airways resistance are given in appendix II. The ventilatory response to repeated three-minute step-change hypoxic stimuli was measured during steady-state exercise in 9 of the 11, subjects (appendix II, numbers 1,2,4,5,6,7,9,10,12) and to prolonged step-change hypoxia lasting ten minutes in 7 of the 11 subjects (appendix II, numbers 1,2,5,6,9,10,12). The ventilatory response to duplicate episodes of progressive isocapnic hypoxia and repeated transient hypoxic stimuli were studied in 10 of the 11 subjects (appendix II, numbers 1-10).

ii) Methods and Equipment

The breathing circuits used were as described in chapter 2 for step-change, transient and progressive isocapnic hypoxia. (figs 2.1 and 2.2). For repeated and prolonged step-change hypoxia, the humidifier was excluded from the circuit. Only the 3-way custom-made respiratory valve was used.

Measurements of the ventilatory responses to repeated step-change hypoxia, prolonged step-change hypoxia, duplicate episodes of progressive isocapnic hypoxia and repeated transient hypoxia were made on four separate days. The ventilatory response to repeated step-change hypoxia was measured on one day, the response to prolonged hypoxia on another day, and the data for progressive isocapnic (one day) and transient hypoxia (two days) was taken from chapter three. In each case, the subject walked on a level treadmill ($\dot{V}O_2$ approximately $1.0 l min^{-1}$) breathing room air until steady-state gas exchange was reached. This was assessed by analysis of two-minute collections of mixed expired gas made between 7 and 9, and 9 and 11 minutes after the start of exercise. Steady-state gas exchange was considered to have been reached if the calculated $\dot{V}O_2$ for these two measurements was within 100ml. If not, further gas exchange measurements were made. Ventilatory responses to hypoxia were then measured, and another collection of mixed expired gas was made (five minutes after the last episode of step-change or progressive isocapnic hypoxia, two minutes after the last transient

stimulus) before the subject stopped exercising. The following procedures were used to measure the ventilatory response to hypoxia during steady-state exercise:

Repeated Step-Change Hypoxia

The inspired gas was changed during expiration from room air to 12% O_2 or 15% O_2 (subject 6 only) for three minutes, after which the inspired gas was returned to room air, again during expiration. The three minute step-change hypoxic stimuli were given four times with the subject breathing room air for at least five minutes between each and also five minutes after the last hypoxic period. Isocapnia was maintained throughout. The ventilatory response was expressed as the negative slope of the $\dot{V}_E inst/S_aO_2$ relationship for each hypoxic episode. Mean baseline $\dot{V}_E inst$ was calculated using 20 breaths before each hypoxic episode and 20 breaths taken five minutes after the last hypoxic episode. Mean baseline $P_{ET}CO_2$ during hypoxia was calculated separately for each hypoxic episode, using all the breaths used to calculate hypoxic ventilatory drive.

Prolonged Step-Change Hypoxia

The inspired gas was changed during expiration from room air to 12% O_2 or 15% O_2 (subject 6 only) for ten minutes, and then returned to room air, again during expiration. Isocapnia was maintained throughout. Minute ventilation was calculated as a mean over the minute before the onset of hypoxia, each minute during hypoxia and each of three minutes after the return to normoxia.

Repeated Progressive Isocapnic Hypoxia

The arterial oxygen saturation was reduced over 7-10 minutes to approximately 80% by adding N_2 to the inspired air. The subject then breathed room air for at least five minutes, and the procedure was then repeated. Isocapnia was maintained throughout. Hypoxic ventilatory drive was expressed as theslope of the $\dot{V}_E inst/S_aO_2$ relationship for each episode of hypoxia. Mean baseline $P_{ET}CO_2$ was calculated using ten breaths before each episode of hypoxia, and $P_{ET}CO_2$ during hypoxia was calculated as mean of all the breaths used to calculate the $\dot{V}_E inst/S_aO_2$ slope.

Repeated Transient Hypoxia.

The inspired gas was changed from room air to 100% N_2 during expiration for 2-4 breaths so as to reduce S_aO_2 to approximately 80%, and then back to room air again during expiration. This was repeated 6 to 8 times at intervals of 60 breaths, on two days, one of which was the same day as the measurement of the ventilatory response to progressive isocapnic hypoxia (see chapter 3 for details). Hypoxic ventilatory drive was expressed as the relationship between $\dot{V}_E$inst and S_aO_2 with the best correlation (largest negative correlation coefficient) using an iterative procedure described in chapter 2, for each transient hypoxic stimulus.

iii) Statistics

Mean $\dot{V}_E$inst immediately before and during each of the three minutes recovery from prolonged step-change hypoxia was compared using Friedmans Analysis of Variance with Scheffés test of significance.

Wilcoxons Test for Signed Ranks was used to compare other variables. The coefficient of variation for each subject was calculated for measurements of the ventilatory response to repeated episodes of transient and step-change hypoxia.

III RESULTS

i) Repeated Step-Change Hypoxia

Gas exchange variables and minute ventilation are shown in table 4.1 as averages of all measurements made during steady-state exercise.

There was no obvious trend in either direction for successive measurements of baseline $\dot{V}_E$inst (table 4.2, fig 4.1), and there was no significant difference between the first and final measurements. In subject 12, in whom $\dot{V}_E$inst was not measurable after the final period of hypoxia because he was coughing, the value for $\dot{V}_E$inst after the third hypoxic period was used in the statistical comparison instead.

Each hypoxic step-change in inspired gas was followed by an increase in $\dot{V}_E$inst, which was maintained throughout the three minutes of hypoxia (fig 4.2). Values for the negative slope of the $\dot{V}_E$inst/S_aO_2 relationship for each hypoxic period are given in table 4.3. There was no consistent trend in the ventilatory response to the repeated step-change hypoxic stimuli (fig 4.2), and there was no significant difference between the first and last measurement of $\dot{V}_E$inst/S_aO_2 (table 4.3). The coefficient of variation ranged from 3.6 to 37.1%. In subject 12, it was not possible to calculate the $\dot{V}_E$inst/S_aO_2 relationship during the final period of hypoxia, since he was coughing, so the third measurement of the $\dot{V}_E$inst/S_aO_2 slope was used in the statistical analysis in place of the fourth.

Mean $P_{ET}CO_2$ during hypoxia was not significantly different for the first and last measurements of hypoxic ventilatory drive (table 4.4).

ii) Prolonged Step-Change Hypoxia

Gas exchange variables and ventilation expressed as averages of all measurements made during steady-state exercise, for the subjects taking part in this section of the study are shown in table 4.5

Ventilation increased following a step-change in inspired gas from room air to either 15% O_2 (subject six only) or 12% O_2, and was maintained throughout the duration of hypoxia (fig 4.3) in four of the seven subjects (table 4.6). Subjects 2, 5 and 12, however, showed an

table 4.1 : Gas Exchange and Ventilation During Steady-State Exercise For Subjects Given Repeated Step-Change Hypoxia.

Subject	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}CO_2$
	($l min^{-1}$)	($l min^{-1}$)	($l min^{-1}$)
1	21.66	0.88	0.84
2	26.07	0.94	0.84
4	19.42	0.99	0.92
5	21.28	0.84	0.71
6	24.22	0.96	0.85
7	28.75	1.09	0.91
9	21.29	0.88	0.73
10	19.32	0.79	0.62
12	25.61	0.95	0.82

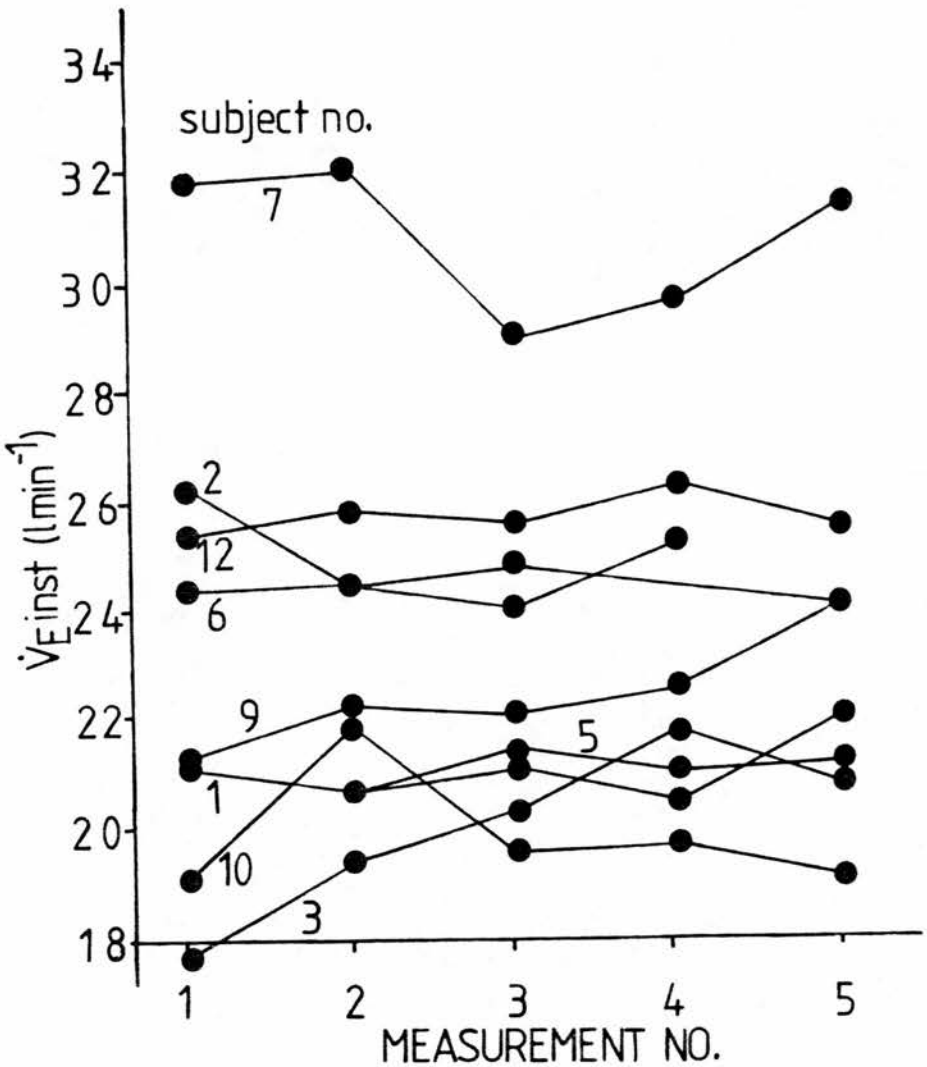
Measurements are expressed as a mean of two values taken during steady-state exercise before hypoxia and one taken five minutes after the last episode of hypoxia. $\dot{V}_E$ is in l min^{-1} BTPS, $\dot{V}O_2$ and $\dot{V}CO_2$ in l min^{-1} STPD

table 4.2 : Mean Baseline $\dot{V}_E$inst Before and After Repeated Step-Change Hypoxia.

	$\dot{V}_E$inst Measurement Number				
	1	2	3	4	5
	($l min^{-1}$)	($l min^{-1}$)	($l min^{-1}$)	($l min^{-1}$)	($l min^{-1}$)
Subject					
1	21.11	20.69	21.13	20.56	22.09
2	25.38	25.81	25.55	26.36	25.52
3	17.68	19.40	20.33	21.72	20.71
5	21.28	20.71	21.43	21.01	21.19
6	24.43	24.46	24.81	22.48	24.04
7	31.90	32.14	29.10	29.75	31.52
9	21.22	22.23	22.13	22.54	24.09
10	19.12	21.93	19.62	19.69	19.00
12	26.28	24.47	24.08	25.33	-

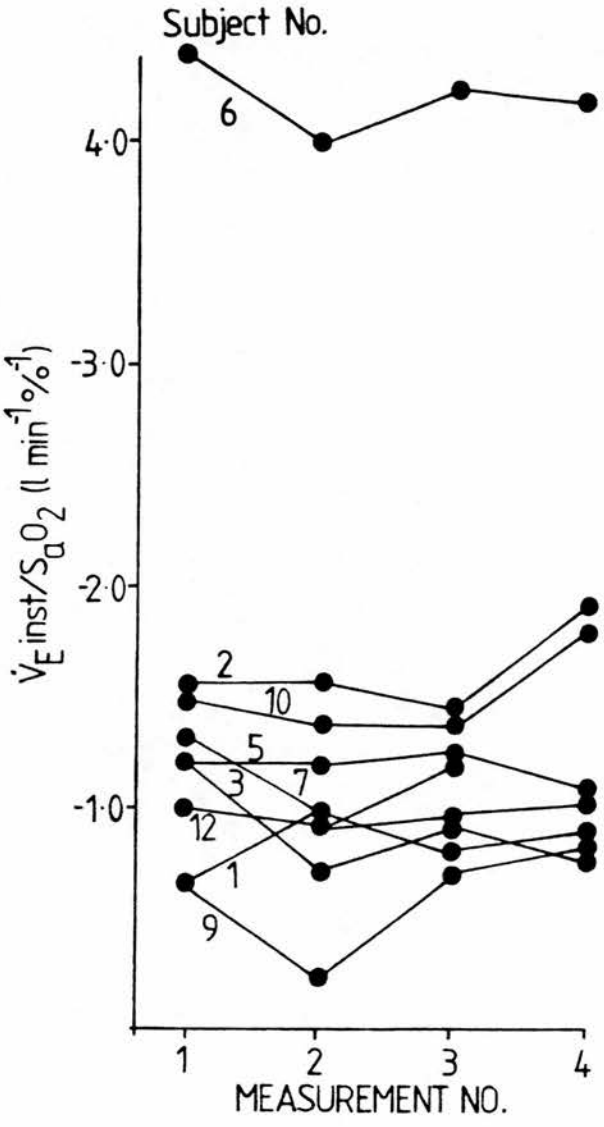
Mean $\dot{V}_E$inst 20 breaths before each and five minutes after the last hypoxic episode. Measurements are numbered from 1 (before the first hypoxic episode) to 5 (five minutes after the last hypoxic episode). Data was not obtained for subject 12, since he was coughing at this time.

fig 4.1 : Baseline $\dot{V}_E$inst Before Each and Five Minutes After the Last Episode of Step-Change Hypoxia



Data are means of twenty breaths before the onset of hypoxia and five minutes after the last hypoxic episode. There was no significant difference between the first and last measurement of baseline $\dot{V}_E$inst.

fig 4.2 : Ventilatory Response to Repeated Step-Change Hypoxia



S_aO_2, $\dot{V}_E$inst and $P_{ET}CO_2$ during repeated episodes of 12% inhaled O_2 in a normal subject (subject 5). There was no significant difference between the first and last ventilatory response to step-change hypoxia for the whole group.

table 4.3 : $\dot{V}_E inst/S_aO_2$ Slope During Repeated Step-Change Hypoxia

	$\dot{V}_E inst/S_aO_2$ Measurement Number				
	1	2	3	4	C.V.
	($l min^{-1} \%^{-1}$)	($l min^{-1} \%^{-1}$)	($l min^{-1} \%^{-1}$)	($l min^{-1} \%^{-1}$)	(%)
Subject					
1	-1.32	-0.97	-1.19	-	12.5
2	-1.00	-0.88	-0.99	-1.02	5.6
4	-1.23	-0.73	-0.91	-0.79	21.1
5	-1.20	-1.20	-1.25	-1.09	4.9
6	-4.39	-4.02	-4.24	-4.39	3.6
7	-0.67	-0.94	-0.80	-0.90	12.6
9	-0.65	-0.23	-0.71	-0.82	37.1
10	-1.51	-1.38	-1.39	-1.80	11.2
12	-1.56	-1.57	-1.46	-1.90	10.2

Hypoxic ventilatory drive expressed as the negative $\dot{V}_E inst/S_aO_2$ slope during repeated episodes of step-change hypoxia. No data ws obtained for the fourth episode of hypoxia for subject 1, since he was coughing. The column labelled C.V. shows the coefficient of variation.

table 4.4 : $P_{ET}CO_2$ During Repeated Step-Change Hypoxia.

	Mean $P_{ET}CO_2$ Measurement Number			
	1	2	3	4
	(kPa)	(kPa)	(kPa)	(kPa)
Subject				
1	5.80	5.68	5.87	-
2	5.34	5.30	5.29	5.32
4	6.28	6.20	5.58	5.98
5	5.43	5.72	5.58	5.32
6	5.48	5.41	5.34	5.37
7	5.51	5.67	5.44	5.59
9	5.20	5.40	5.46	5.42
10	5.49	5.40	5.46	5.42
12	5.13	5.37	5.13	5.10

Data are means for all breaths involved in calculation of the ventilatory response to hypoxia. No data was obtained for subject number 1 during the last period of hypoxia, as he was coughing.

table 4.5 : Gas Exchange Variables and Ventilation During Steady-State Exercise For Subjects Given Prolonged Step-Change Hypoxia

Subject	$\dot{V}_E$ ($l min^{-1}$)	$\dot{V}O_2$ ($l min^{-1}$)	$\dot{V}CO_2$ ($l min^{-1}$)
1	21.40	0.84	0.75
2	26.13	0.99	0.90
5	21.11	0.87	0.74
6	24.10	0.96	0.83
9	20.87	0.89	0.71
10	20.50	0.83	0.65
12	25.04	0.91	0.89

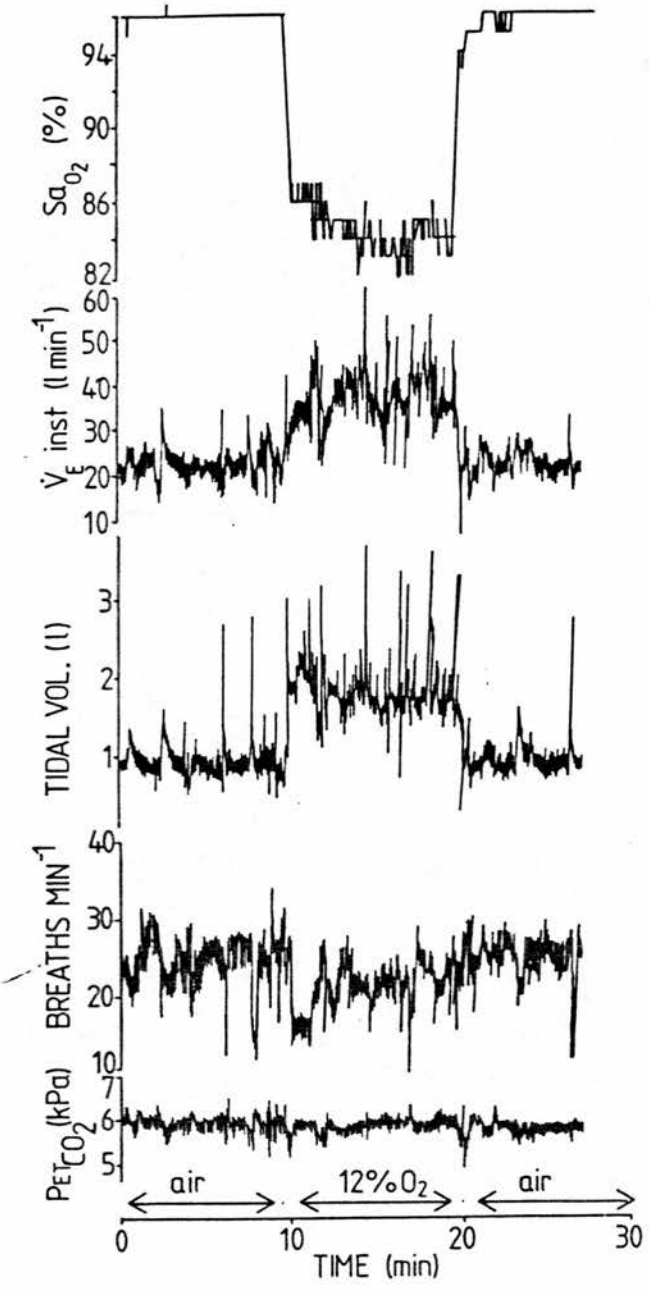
Data are means of two measurements taken before and one taken after hypoxia. $\dot{V}_E$ is in $l\ min^{-1}$ BTPS and $\dot{V}O_2$ and $\dot{V}CO_2$ are in $l\ min^{-1}$ STPD

table 4.6 : Minute Ventilation Before, During and After Prolonged Step-CHange Hypoxia.

	Subject						
	1	2	5	6	9	10	12
Time (min)	Minute Ventilation (l min^{-1})						
Baseline	22.9	25.5	20.1	22.9	22.4	20.1	25.6
hypoxia							
0-1	28.9	33.4	27.5	31.9	25.1	30.5	32.3
1-2	36.8	41.4	35.7	38.0	32.0	37.2	37.6
2-3	34.9	43.3	39.8	38.8	35.0	38.2	38.4
3-4	38.9	45.1	39.9	37.0	35.9	38.0	37.7
4-5	39.4	45.4	39.5	37.1	37.0	37.8	37.7
5-6	36.3	45.3	41.2	38.7	37.2	38.4	38.3
6-7	36.4	45.8	40.5	37.1	36.9	37.8	36.9
7-8	38.6	44.6	37.9	39.9	36.0	37.3	36.4
8-9	36.7	43.5	36.5	40.1	37.1	38.0	36.4
9-10	38.8	42.9	34.0	38.8	38.1	37.1	36.2
recovery							
10-11	23.2	28.7	21.5	26.9	23.5	23.9	29.0
11-12	23.3	26.1	20.1	24.5	21.8	20.1	23.2
12-13	22.1	26.9	21.0	23.8	20.0	20.5	23.3

Data are averages over each minute starting one minute before hypoxia (baseline), each minute during hypoxia, and three minutes after hypoxia (recovery).

fig 4.3 : Absence of Depression of Ventilation During Prolonged Step-Change Hypoxia.



S_aO_2, $\dot{V}_E$inst, V_T, breathing frequency and $P_{ET}CO_2$ during ten minutes of 12% inhaled O_2 in a normal subject (subject 10). This subject did not exhibit depression of ventilation during hypoxia.

decrease in $\dot{V}_E$inst following a peak after the fifth, sixth and sixth minutes of hypoxia respectively, and this was accompanied by a fall in S_aO_2 (fig 4.4). The difference between the peak mean $\dot{V}_E$inst and that in the final minute of hypoxia was 2.9lmin^{-1} for subject 2, 7.2lmin^{-1} for subject 5 and 2.1lmin^{-1} for subject 12. The decrease in $V_E$inst was a result of decreases in both V_t and breathing frequency.

There was no significant difference between mean baseline $V_E$inst and the mean $V_E$inst in any of the three minutes following the return to normoxia.

End-tidal P_{ETCO_2} did not fall during hypoxia (fig 4.3 and 4.4)

iii) Repeated Progressive Isocapnic Hypoxia

Gas exchange variables and ventilation measured during steady-state exercise for subjects taking part in this section of the study are shown in table 3.1.

There was no significant difference between baseline minute ventilation measured before the first episode of hypoxia and that measured five minutes after the second episode of hypoxia (table 4.7)

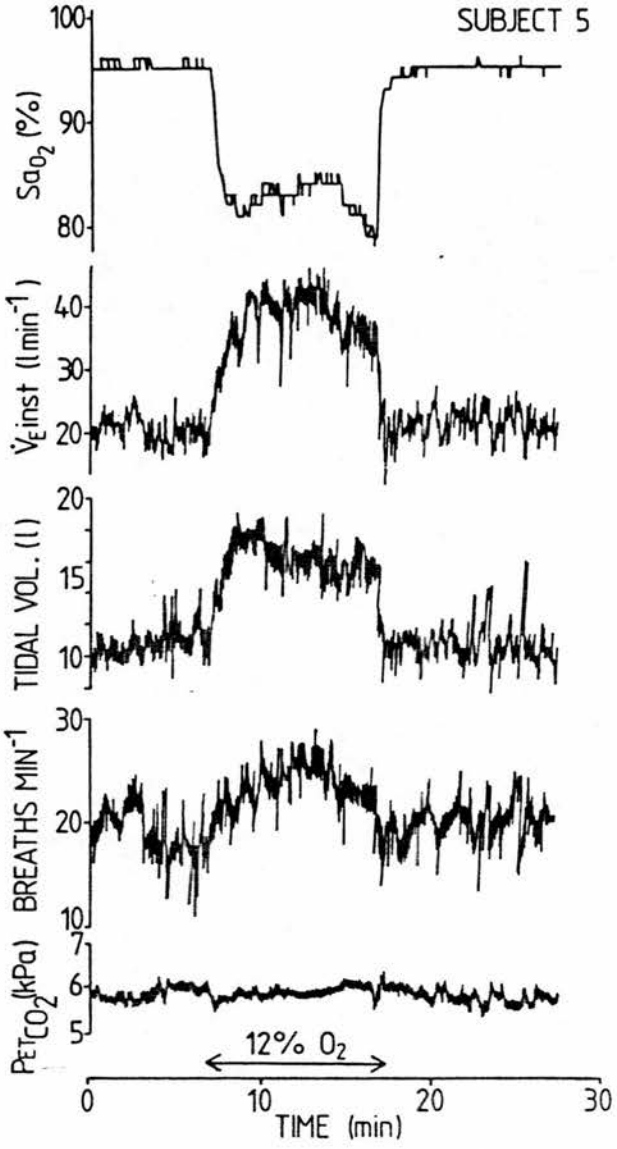
In 8 of the 10 subjects, the ventilatory response (expressed as the slope of the $\dot{V}_E$inst/S_aO_2 relationship) was higher during the second episode of progressive isocapnic hypoxia. (table 4.8), although this difference did not achieve statistical significance. Mean end-tidal PCO_2 (table 4.8) was not significantly different during the first and second episodes of progressive isocapnic hypoxia.

iv) Repeated Transient Hypoxia

Gas exchange variables and minute ventilation during steady-state exercise (mean of all measurements taken during steady-state exercise) for subjects taking part in this section of the study are shown in table 3.1. (previous chapter).

In three out of ten subjects (subjects one, six and ten) there was an upward trend in successive ventilatory responses to transient hypoxia on one of the days on which it was measured (fig 4.5). In none of these three subjects did this occur on both days. In four subjects (subjects

fig 4.4 : Depression of Ventilation During Prolonged Step-Change Hypoxia



S_aO_2, $\dot{V}_E$inst, V_T, breathing frequency and $P_{ET}CO_2$ during inhalation of 12% O_2 for ten minutes in a normal subject (subject 5). Depression of ventilation occurred after the 6th minute of hypoxia, accompanied by a fall in S_aO_2. $P_{ET}CO_2$ was maintained throughout.

table 4.7 : Ventilation Before and After Two Episodes of Progressive Isocapnic Hypoxia

	$\dot{V}_E$ inst Measurement Number	
	1	2
Subject	($l min^{-1}$)	($l min^{-1}$)
1	21.34	23.09
2	24.17	27.39
3	24.84	24.99
4	18.29	18.28
5	21.08	23.53
6	27.92	25.40
7	30.47	28.89
8	19.74	22.33
9	23.17	22.59
10	21.03	20.99

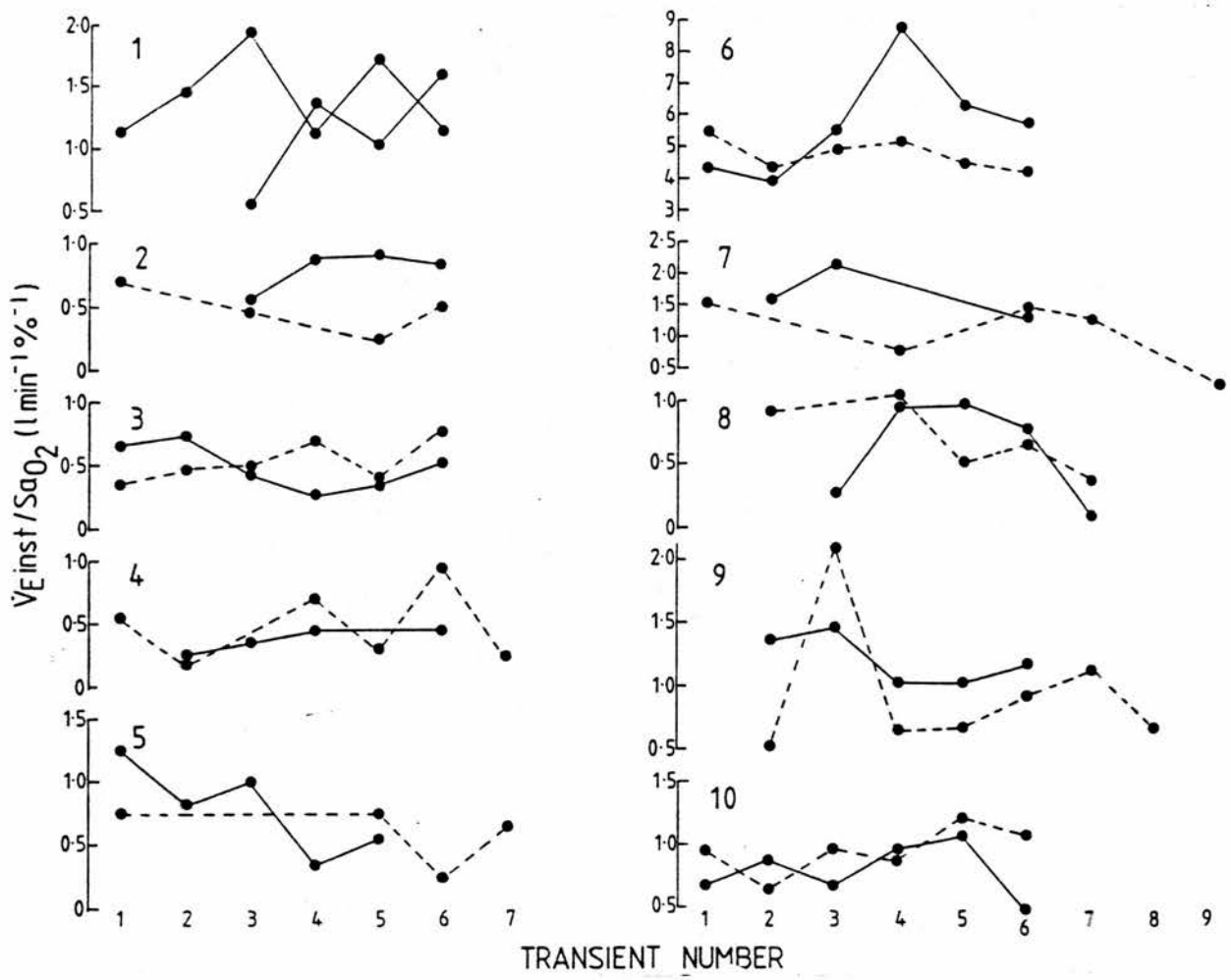
Measurement number 1 is the mean ventilation calculated from two two-minute collections of mixed expired gas made during steady-state exercise before hypoxia, number two is from a single two-minute collection of expired gas made five minutes after the final measurement of the ventilatory response to hypoxia.

table 4.8 : Hypoxic Ventilatory Drive and $P_{ET}CO_2$ During Hypoxia for Repeated Progressive Isocapnic Hypoxia.

	1		2	
	$\dot{V}_E$inst/S_aO_2 ($l min^{-1}\%^{-1}$)	$P_{ET}CO_2$ (kPa)	$\dot{V}_E$inst/S_aO_2 ($l min^{-1}\%^{-1}$)	$P_{ET}CO_2$ (kPa)
Subject				
1	-1.17	5.70	-1.61	5.64
2	-1.39	5.05	-1.59	4.99
3	-2.46	5.62	-3.37	5.58
4	-0.49	5.92	-0.75	5.80
5	-1.45	5.64	-1.11	5.27
6	-4.21	5.20	-5.20	5.09
7	-0.76	5.44	-1.67	5.43
8	-0.74	5.29	-0.85	5.30
9	-0.53	5.55	-0.46	5.46
10	-1.57	5.16	-1.91	5.04

Hypoxic ventilatory drive was expressed as the slope of the $\dot{V}_E$inst relationship during duplicate episodes of progressive isocapnic hypoxia, and $P_{ET}CO_2$ as a mean of all the breaths included the calculation of hypoxic ventilatory drive.

fig 4.5 : Hypoxic Ventilatory Drive During Repeated Transient Hypoxic Stimuli



Hypoxic ventilatory drive expressed as the slope of the $\dot{V}_E inst / Sa O_2$ relationship during repeated episodes of transient hypoxia. Where data points are missing, the stimuli did not fulfil the criteria described in chapter 2, i.e., all transient stimuli for an individual being within an $S_a O_2$ of 10% and all falling below 90%.

two,five, eight and nine) there was a slight downward trend in successive measurements of hypoxic ventilatory drive, but again this was not repeated on both days on which hypoxic ventilatory drive was measured. The fall in S_aO_2 which followed inhalation of 2-4 breaths of 100% N_2 was within 10% for an individual for each set of measurements on each da. The coefficient of variation ranged from 10.4 to 58.7% (table 4.9).

table 4.9 : Coefficient of Variation For Ventilatory Responses to Repeated Transient Hypoxia.

	Day A	Day B
Subject	C.V. (%)	C.V. (%)
1	34.0	18.0
2	39.7	35.6
3	32.0	29.3
4	58.7	24.0
5	39.3	32.2
6	27.3	10.4
7	21.9	40.9
8	53.9	29.8
9	53.8	13.1
10	24.1	18.3

Coefficient of variation (C.V.) for each subject on the two days on which the ventilatory responses to repeated episodes of transient hypoxia were measured.

V DISCUSSION

i) Potentiation of Hypoxic Ventilatory Drive

The ventilatory responses to step-change (lasting 3 minutes) and transient (lasting only 2-4 breaths) hypoxia were reproducible when repeated several times, the coefficient of variation ranging from 3.6 to 37.1 % and 10.4 to 58.7% for step-change and transient hypoxic stimuli respectively. This range is comparable with the results of Sahn et al (1977), who found that the coefficient of variation for the ventilatory response to progressive isocapnic hypoxia measured every 30 minutes over a period of two hours in normal subjects ranged from 7.3 to 63.8%. In this study the second of two measurements of progressive isocapnic hypoxia (lasting 7-10 minutes) was greater than the first in eight out of ten subjects, although this difference was not significant for the group. Baseline (normoxic) $\dot{V}_E$inst was not increased following repeated episodes of either step-change or progressive isocapnic hypoxia.

The effect of a three minute period of step-change hypoxia on subsequent ventilatory responses to hypoxia has not previously been investigated. Steady-state hypoxia, however, (Anderton et al 1964), five minutes of 9% O_2 (Jennett and Walker 1985) and five minutes of 7-8% O_2 (Davidson and Cameron 1985) have all been shown to potentiate subsequent ventilatory responses to hypoxia, provided that $P_{ET}CO_2$ was kept at or above the air-breathing level. Potentiation may thus depend upon thresholds for either duration or degree of hypoxia, or both, which were exceeded in previous studies but not in this study. Since the lowest S_aO_2 reached during step-change, progressive isocapnic and transient hypoxia were similar, it is unlikely that a threshold for the degree of hypoxia was the only important factor for activating the potentiation mechanism, as potentiation would then have occurred following all three types of stimulus. The observation that ventilatory response to progressive hypoxia lasting 7-10 minutes, however, <u>is</u> potentiated in the majority of subjects, but responses to hypoxic stimuli of similar severity but shorter total duration were <u>not</u>, suggests that the total duration of hypoxia is important in initiating potentiation.

Potentiation of the ventilatory response to progressive isocapnic hypoxia has not been found by other workers. Neither Sahn et al (1977) nor Davidson and Cameron (1985) found that progressive isocapnic hypoxia

lasting seven and ten minutes respectively when measured at rest, potentiated the subsequent ventilatory responses to hypoxia, despite the fact that the degree of hypoxia was greater than that in the present study. Davidson and Cameron (1985) suggested that the absence of potentiation was because a low level of S_aO_2 was only reached briefly at the end of the period of progressive isocapnic hypoxia. This implies that there exists a threshold for P_aO_2 (or S_aO_2) which was not crossed until relatively late in the progressive hypoxic procedure, i.e. not until less than five minutes from the end of the study (since they found that five minutes of seven to eight percent P_IO_2 did potentiate subsequent ventilatory responses to hypoxia). A difference between the methods used by Sahn et al (1977) and Davidson and Cameron (1985) and those of the present study is the time elapsing between measurements of the ventilatory response to hypoxia. In the present study, the subjects breathed air for only five minutes between measurements, whereas in previous studies the time between measurements was approximately 20 minutes. It is therefore possible that the potentiation mechanism adapts within twenty minutes of removal of the hypoxic stimulus, thus accounting for the potentiation of the hypoxic response when measurements are repeated within 5 minutes as in this study, but not after 20 minutes as in the studies of Sahn et al (1977) and Davidson and Cameron (1985). The results of this and other studies therefore suggest that the duration and severity of hypoxia together with the time between hypoxic exposures are linked in a complex way to generate potentiation. Thus, in this study, when S_aO_2 was maintained for three minutes at 80% as in the step-change method, the ventilatory response to a similar step-change imposed five minutes later was not potentiated, whereas more severe hypoxia (F_IO_2 of 0.07-0.08) maintained for five minutes potentiated the response 20 minutes later (Davidson and Cameron 1985). With gradual onset hypoxia, where the same overall severity of hypoxia may be achieved ultimately as in the step-change and progressive isocapnic methods used in this study, but where only a short period of time is spent at this level of hypoxia, potentiation only occurs for a short period (i.e. for five minutes as in this study) but not for periods lasting 20 minutes (Sahn et al 1977, Davidson and Cameron 1985)

Arterial PCO_2 may be important in initiating potentiation of the ventilatory response to hypoxia, since several authors have reported that

it only occurs at normoxic PCO_2 or during hypercapnia, and that increased P_ICO_2 or P_ACO_2 increase the degree of potentiation (Anderton et al 1964, Jennett and Walker 1983). Hypoxia has also been found to potentiate subsequently measured ventilatory responses to CO_2 (Anderton et al 1964, Davidson and Cameron 1982, 1983, 1985). The potentiation of ventilation might therefore be due to increased chemosensitivity to CO_2 i.e. at the same level of P_ACO_2 there is a greater drive to breathing. If there was increased chemosensitivity to CO_2, however, baseline (normoxic) ventilation would also be increased, an effect which was not seen in the present study nor in those of other authors (Jennett and Walker 1983, Davidson and Cameron 1985). Furthermore, both the baseline $P_{ET}CO_2$ and $P_{ET}CO_2$ during hypoxia were similar in individuals for step-change hypoxia, the response to which was not potentiated, and progressive isocapnic hypoxia, which was potentiated in some subjects, so $P_{ET}CO_2$ is not likely to play an important role in this study.

The results of the present study are consistent with the hypothesis that there exists a ventilatory potentiation mechanism, the operation of which depends upon the duration, the degree of hypoxia and the time between hypoxic episodes.

ii) Hypoxic Depression of Ventilation.

Ventilation was depressed during ten minutes of hypoxia in only three of the seven subjects studied. This is consistent with some previous studies in which only a minority of healthy normal subjects with intact carotid bodies have shown a very low response to steady-state or progressive isocapnic hypoxia (Edelman et al 1970, Kronenberg et al 1972, Weil and Zwillich 1976, Shaw et al 1982). It does not, however agree with data from studies by Kagowa et al (1982), Huang et al (1984) and Easton et al (1986) in which all the subjects studied demonstrated hypoxic ventilatory depression. Whether or not depression of ventilation occurs may depend upon the duration of hypoxia.In humans, ventilatory depression has been observed within five to ten minutes during hypoxia at rest (Kagowa et al 1982, Huang et al 1984, Nishimura et al 1987), although two of the eight subjects studied by Nishimura et al (1987) still continued to increase their ventilation even after 15 minutes of hypoxia, which suggests that the time course of the

ventilatory depression is variable within individuals. The variability may be due to differences in the relative contribution of opposing mechanisms tending to increase and depress ventilation during hypoxia. Since the carotid chemoreceptor response to hypoxia (P_aO_2 approximately 40mmHg) was constant for 1 hour after the onset of hypoxia in anaesthetised goats (Nielsen et al 1988), it does not seem likely that accommodation of the carotid chemoreceptor response to hypoxia occurs during prolonged hypoxia. The occurrence of depression of ventilation might therefore be dependent upon the ability of the mechanism responsible to overcome the carotid chemoreceptor drive to ventilation. Subjects with a high peripherally mediated hypoxic ventilatory drive would be less likely to show hypoxic ventilatory depression. This idea is supported by the fact that the subjects who developed depression of ventilation most rapidly in the studies of Nishimura et al (1987) had the lowest ventilatory response to progressive isocapnic hypoxia. In this study, however, this was not the case, the three subjects who showed depression of ventilation (numbers 2,5, and 12) having the sixth, fourth and second highest out of nine ventilatory responses to step-change hypoxia respectively. Subjects 2 and 5 also had ventilatory responses to progressive isocapnic hypoxia ranked fifth and fourth out of ten respectively.

The degree of hypoxia may also be important in determining whether or not hypoxic ventilatory depression occurs. In the studies of Huang et al (1984), Easton et al (1986), however, the fall in S_aO_2 was approximately the same as in the present study and in the investigation of Nishimura et al (1987) i.e. to about 80%, so this is not likely to explain why depression of ventilation was observed in all the subjects in their studies but not in the this investigation.

One mechanism proposed to explain the occupance of hypoxic depression is that cerebral hypocapnia develops during hypoxia. It is known that during hypoxia, cerebral blood flow increases (McDowall et al 1966, Cohen et al 1967) resulting in a decrease in central P_aCO_2, thus decreasing the activity of the medullary chemoreceptors and therefore ventilation. Weiskopf and Gabel (1975) suggested on the basis of calculations using the data of McDowall et al (1966) and Cohen et al (1967) that central P_aCO_2 could fall sufficiently during progressive isocapnic hypoxia (a reduction in P_aO_2 from 120 to 40mmHg (16 to 5.3

kPa) in five minutes) and a subsequent reversal of the process (i.e. within ten minutes) to account for the observed depression of ventilation, although the carotid chemoreceptor P_aCO_2 had been maintained constant throughout the procedures, as in the present study. Although significant central hypocapnia was observed during progressive hypoxia in human subjects by Nishimura et al (1987), there was no significant correlation between the ventilatory response to progressive isocapnic hypoxia and the magnitude of the fall in brain tissue PCO_2. There was a correlation between the ventilatory response to withdrawal of hypoxia and that to progressive isocapnic hypoxia suggesting that the major influence on intersubject variability of the ventilatory response to hypoxia was determined by variation in the carotid chemoreceptor response rather than the magnitude of the central hypocapnia (Nishimura et al 1987). Furthermore, an increase in P_aCO_2 was found to increase the magnitude of hypoxic depression of ventilation (Lahiri 1974), whereas the opposite would be expected if decreased brain P_aCO_2 was responsible for this effect. Variation in the degree of cerebral hypocapnia is therefore unlikely to explain why three of the nine subjects in this study developed depression of ventilation.

One difference between the present study and those previously done is that while in this investigation all measurements were made during exercise, those of some other authors, who found that all their subjects showed hypoxic ventilatory depression, were done at rest. Exercise is known to potentiate the hypoxic ventilatory drive (Weil et al 1972, Martin et al 1978). Interaction of the carotid chemoreceptor response to hypoxia and afferent input from the exercising muscles is thought to be at some central location rather than at the carotid chemoreceptors (Davies and Lahiri 1973), and may override hypoxic depression of ventilation in some subjects. Although variability of both the degree of potentiation of hypoxic ventilatory drive during exercise and the extent of central hypoxic depression of ventilation between individuals could explain why not all the subjects in this study showed hypoxic depression of ventilation, it does not explain why only a minority of the subjects demonstrated this characteristic in the studies of Edelman et al (1970), Kronenberg et al (1972), Weil and Zwillich (1976) and Shaw et al (1982), since these investigations were carried out at rest.

The ventilatory responses to repeated step-change and transient hypoxia were reproducible, and there was no evidence of potentiation with repeated hypoxic stimuli. In some individuals, however, the second of two measurements of the ventilatory response to progressive isocapnic hypoxia was potentiated. Some individuals show depression of the ventilatory response to step-change hypoxia within seven minutes, which is less than the duration of the progressive hypoxic stimulus. The ventilatory response to progressive isocapnic hypoxia may therefore be affected by other factors than carotid chemoreceptor discharge, and may not give an adequate measurement of the carotid chemoreceptor mediated hypoxic ventilatory drive. The difference in ventilatory responses to transient and step-change hypoxia seen in chapter 3 cannot be explained by potentiation of the ventilatory response to step-change hypoxia. To find out whether the greater ventilatory response to step-change hypoxia is due to differences in the chemoreceptor response to step-change and transient hypoxia because of the differences in rate of onset and duration of the two hypoxic stimuli, direct recording of carotid chemoreceptor activity is required. This is investigated in the next chapter.

CHAPTER 5 : CAROTID CHEMORECEPTOR RESPONSES TO HYPOXIA AND ALMITRINE IN ANAESTHETISED AND PARALYSED CATS.

I INTRODUCTION

In the study in human subjects described earlier (chapter 3), the ventilatory response to transient hypoxia was generally smaller than that to step-change hypoxia, although in two subjects the converse was found. Furthermore, Airlie et al (1988) were unable to demonstrate a consistent potentiation of the ventilatory response to transient hypoxia by Almitrine, which is thought to act specifically on the peripheral chemoreceptors (Laubie and Diot 1972, Laubie and Schmitt 1980, Bisgard 1980). These results suggest that the ventilatory response to transient hypoxia does not reflect chemoreceptor activity as previously suggested (Girard et al 1959, Leitch 1976), but may depend on the rate of onset or duration of the hypoxic stimulus, or both.

i) Carotid Chemoreceptor Responses to Hypoxia.

Heymans and colleagues first showed that the carotid and aortic chemoreceptors were involved in the ventilatory response to hypoxia in the 1930s (Heymans et al 1930, Heymans and Bouckaert 1930, review Heymans and Neil 1958), in anaesthetised dogs. The carotid chemoreceptor response to hypoxia has since been investigated extensively using several different techniques. Early demonstrations of hypoxic sensitivity of arterial chemoreceptors in animals used either cold block or section of the chemoreceptor afferent nerves, which abolished the previously observed increase in ventilation associated with hypoxia (Gesell et al 1940, Watt et al 1943). In later studies in conciuos human subjects who had undergone carotid body resection or denervation for clinical purposes, the ventilatory response to hypoxia was abolished or ventilatory depression occurred during hypoxia (Holton and Wood 1965, Wade et al 1970, Lugliani et al 1971, Wasserman 1975, Honda et al 1979), suggesting that in humans the carotid chemoreceptors play a major role in the control of breathing during hypoxia while the aortic chemoreceptors, which do contribute to the ventilatory response to hypoxia in animals (Comroe 1939) are unimportant in humans.

Carotid chemoreceptor activity was recorded directly by Von Euler et al (1939) and Astrand (1954), who demonstrated that carotid

chemoreceptor discharge increased in response to hypoxia. Von Euler et al (1939) also found that there is a linear relationship between carotid chemoreceptor discharge and S_aO_2 in anaesthetised cats. Later studies investigated this response in more detail. Hornbein et al (1961) studied the relationship between carotid chemoreceptor discharge and P_aO_2 in anaesthetised and paralysed cats. The chemoreceptor output was measured in the whole carotid sinus nerve (after baroreceptor fibres had been removed) during different steady-state levels of P_aO_2, which was varied by changing P_IO_2. Both P_aCO_2 and pH, which affect carotid chemoreceptor discharge (Heymans et al 1930, Bartels and Witzleb 1956, Grey 1968, Joels and Neil 1960, Biscoe et al 1970), were kept constant throughout the recordings, and the sympathetic nerve supply to the carotid body was left intact. Hornbein et al (1961) found that the relationship between P_aO_2 and carotid chemoreceptor discharge was hyperbolic. A similar hyperbolic relationship was found between the percentage of inhaled O_2 and chemoreceptor discharge by Eyzaguirre and Lewin (1961).

Hypoxia and hypercapnia are known to interact multiplicatively at the carotid chemoreceptors, the combination of the two stimuli resulting in a greater increase in carotid chemoreceptor discharge than would be expected from the sum of the increases in response to each of the stimuli alone. The hyperbolic relationships between P_aO_2 and carotid chemoreceptor discharge and P_IO_2 and carotid chemoreceptor discharge were found to be shifted to the right, in addition to the increase in baseline discharge, when hypercapnia and hypoxia were imposed simultaneously (Hornbein et al 1961, Eyzaguirre and Lewin 1961). Eyzaguirre and Lewin (1961) also demonstrated that single chemoreceptor fibres responded to both hypoxia and hypercapnia. Interaction of hypoxia and hypercapnia at the carotid chemoreceptors has also been observed in many other studies (Nielsen and Smith 1951, Lloyd et al 1958, Fitzgerald and Parks 1971, Lahiri and Delaney 1975).

The carotid chemoreceptor response to hypoxia in anaesthetised cats is very rapid. Black et al (1971) found that perfusing the carotid body with blood tonometered with 5-14% O_2 produced the maximum carotid chemoreceptor response within 1-5 seconds. Eyzaguirre and Lewin (1961) found that during *in vitro* perfusion of cat carotid bodies, a sudden reduction in PO_2 caused an overshoot in carotid chemoreceptor discharge

followed by the return to a lower constant level of discharge. In contrast, Hornbein et al (1961) did not observe any overshoot in chemoreceptor activity at the onset of hypoxia in anaesthetised cats, and suggested that this was because the rate of change of P_aO_2 produced by changing the inspired gas compared to changing the composition of the carotid body perfusate was not rapid enough. A decrease in the PO_2 in the blood perfusing the carotid body produces a near square-wave hypoxic stimulus, with a very rapid onset, whereas changing the inspired gas as will not produce a sudden change in P_aO_2 at the carotid bodies due to mixing in the lungs and the lung-to-carotid transit time. Black et al (1971) only occasionally observed adaptation of the carotid chemoreceptors to a very rapid change in inspired O_2 in anaesthetised cats, and this effect was not very pronounced. De Goede et al (1983) demonstrated ventilatory adaptation to isocapnic step-changes in $P_{ET}O_2$ in anaesthetised cats, but this was abolished by hyperoxic perfusion of the brainstem during systemic hypoxia, which suggests that it was due to brainstem modification of the carotid chemoreceptor response to hypoxia, rather than adaptation of the carotid chemoreceptors themselves.

The relationships between intensity of hypoxia and carotid chemoreceptor discharge and ventilation, and the time courses of carotid chemoreceptor and ventilatory responses have thus been investigated during steady-state hypoxia. The carotid chemoreceptor response to transient hypoxia, however, has not previously been compared to the carotid chemoreceptor response to steady-state hypoxia.

ii) Carotid Chemoreceptor Responses to Almitrine

The effects of Almitrine upon ventilation and carotid chemoreceptor activity were first demonstrated by Laubie and Diot in 1972. In anaesthetised and unanaesthetised dogs, intravenous or oral Almitrine was followed by an increase in V_E and respiratory frequency, which was maintained for more than one hour. This was accompanied by a decrease in P_aCO_2, although $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were unchanged. Laubie and Diot found that local injection of Almitrine into the carotid artery was followed by a large and rapid increase in ventilation, which suggested that this was a likely site of action for Almitrine. The effect of Almitrine upon carotid chemoreceptor activity is now well documented. Laubie and Schmitt (1980) reported that the dose-dependant increase in ventilation following Almitrine injection was abolished after section of

the carotid sinus and vagus nerves in anaesthetised dogs. They also found that the directly recorded carotid sinus nerve discharge increased after Almitrine. Other workers have also demonstrated an increase in discharge of single or few-fibre preparations of the carotid sinus nerve afferents in anaesthetised dogs (Bisgard 1980) and anaesthetised, paralysed rabbits (Roumy and Leitner 1981) after Almitrine. Gautier and Bonara (1982) and Dhillon and Barer(1982) both demonstrated that Almitrine caused an increase in ventilation which was abolished after carotid denervation and vagus nerve section in conscious cats and anaesthetised rats respectively. Further evidence that Almitrine acts at the carotid chemoreceptors rather than centrally is that ventilation did not increase in response to Almitrine in dogs with both vagi and carotid sinus nerves cut, and that intracisternal or intervertebral injection of Almitrine had no effect on ventilation (Laubie and Diot 1972). Laubie and Schmitt (1980) found that the chemostimulant effect of Almitrine was dependent upon P_aO_2, the higher P_aO_2, the smaller the increase in V_E, suggesting that Almitrine may act at the same site as hypoxic stimuli. This idea was supported by Bisgard (1980), who found that in anaesthetised dogs, although the magnitude of responses of single carotid chemoreceptor fibres to intracarotid Almitrine injections varied widely between individual animals, qualitative responses were generally the same in all cases, i.e. peak chemoreceptor discharge following Almitrine injection was inversely related to P_aO_2, and the peak response was reached more quickly during hypoxia.

Bisgard (1980) found that Almitrine produced a greater than additive effect on carotid chemoreceptor activity as P_aO_2 was reduced, which suggests that there is interaction between Almitrine and hypoxia, resulting in increased sensitivity of the carotid chemoreceptors to hypoxia after Almitrine. Enhancement of the ventilatory response to hypoxia, and to some extent, hypercapnia, has also been seen in human subjects (Connaughton et al 1984, Stradling et al 1982, Stanley et al 1983). Airlie et al (1988) agreed with other authors in that the ventilatory response to progressive isocapnic hypoxia was increased after Almitrine ingestion, however the effect of Almitrine upon the ventilatory response to during transient hypoxia was very variable. Because evidence from other studies indicates that Almitrine acts specifically at the carotid chemoreceptors (Laubie and Diot 1972, Laubie

and Schmitt 1980, Bisgard 1980), Airlie et al (1988) suggested that the ventilatory response to transient hypoxia does not reflect carotid chemoreceptor activity.

Direct recordings of carotid body chemoreceptor discharge were therefore made in anaesthetised and paralysed cats

i) to determine whether chemoreceptor discharge differs in response to transient and step-change hypoxia for a given fall in arterial oxygen saturation,

ii) to investigate the effect of Almitrine on the carotid chemoreceptor responses to step-change and transient hypoxia.

II METHODS

Electrical activity was recorded from 2-3 active fibres of a cut carotid sinus nerve in eight healthy female cats (Appendix I, weight range 2.4 3.5kg) which were anaesthetised, paralysed and artificially ventilated. Carotid chemoreceptor responses to transient and step-change hypoxia were recorded, with isocapnia maintained by adding CO_2 to the inspired gas as necessary. The hypoxic stimuli were then repeated within one hour of injection of the peripheral chemoreceptor stimulant drug Almitrine. Arterial oxygen saturation was calculated from femoral arterial P_{O_2}. At the end of each study, an asphyxia test was carried out by stopping the respiratory pump for 90 seconds in order to measure the maximum possible chemoreceptor discharge. Data was recorded on magnetic tape, with one channel used to record speech so that events such as changes in inspired gas and arterial blood sampling could be marked accurately.

1) SURGICAL PROCEDURES

The animals were anaesthetised with Sodium Pentobarbitone (May and Baker, 42mgKg^{-1} i.p. initially, then supplemented as necessary i.v. approximately every 1½-2 hours throughout the study). Both femoral arteries were cannulated, one for withdrawal of blood samples, the other for monitoring of systemic arterial blood pressure. A femoral vein was cannulated for injection of drugs i.v., and a lingual artery for intracarotid (i.c.) injection of drugs. The animals were paralysed with Gallamine Triethiodide (May and Baker, 3mgKg^{-1} i.v., supplemented as necessary). A tracheostomy was performed for the purposes of mechanical ventilation. The sinus nerve on the same side as the lingual cannula was sectioned, and few-fibre filaments teased out for recording of carotid chemoreceptor activity. Exposed tissues were covered with warm mineral oil at 37 C. The ganglioglomerular (sympathetic) and contralateral sinus nerves were left intact.

2) EXPERIMENTAL PROCEDURES

i) Ventilation and Hypoxic Gas Mixtures

The cats were ventilated with room air (Scientific Research Instruments ventilation pump) at a frequency and tidal volume which maintained P_aCO_2 and P_aO_2 at the same level as before paralysis (determined by taking an arterial blood gas measurement before

paralysis). Tidal volume was approximately 50-60ml and frequency about 20 breaths per minute. Two ventilation pumps operating in phase at the same volume and frequency were used. The first pump, supplying room air, was attached close to the trachea, (dead space 1.6ml). The second pump was primed with the required hypoxic gas mixture. Very rapid changes in inspired gas mixture were achieved by changing between the two pumps.

Nitrogen was supplied directly from a cylinder to the ventilation pump, and CO_2 was also added to the inspired gas close to the trachea directly from a cylinder. Other gas mixtures were made using combinations of air, N_2 and O_2, measured using rotameters (capacity 5lmin^{-1}) and mixed in a distensible anaesthetic bag used as a reservoir before entering the ventilation pump.

ii) Physiological Recordings

Carotid Chemoreceptor Activity

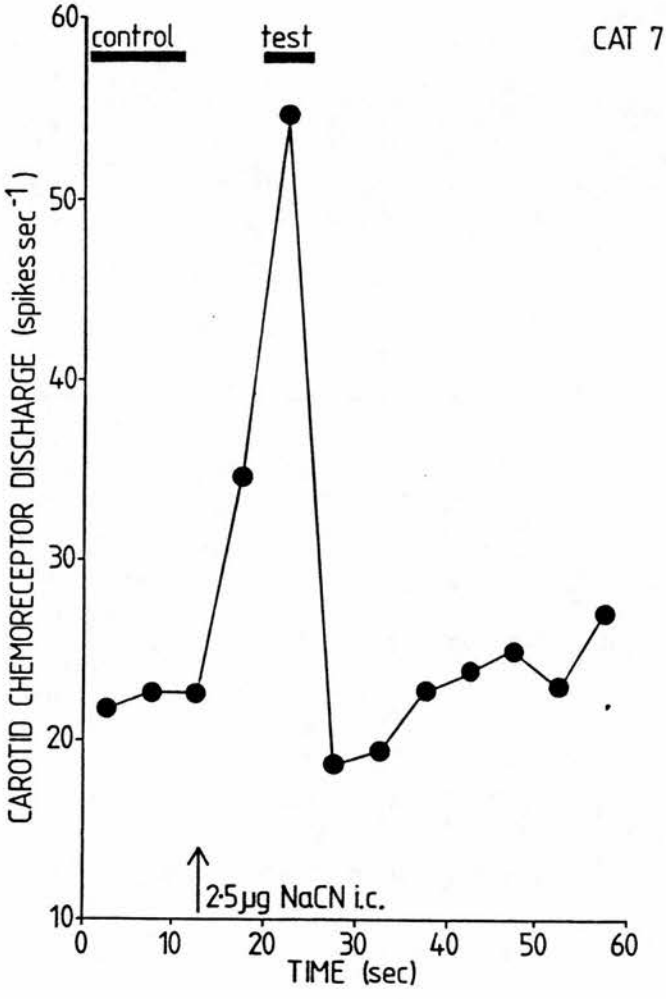
Electrical activity, recorded from the carotid sinus nerve using bipolar platinum-iridium electrodes, was filtered to reduce high frequency interference and amplified (Neurolog, Digitimer). The signal was displayed on an oscilloscope (Tektronix 5103N) for quality control and on one channel of a chart recorder (Lectromed), and recorded onto magnetic tape using a four-channel recorder (Tandberg Instrumentation Series 115, frequency response d.c. to 1250 Hz) for later analysis.

Chemoreceptor units were identified by their random discharge (Eyzaguirre and Lewin 1961), their response to hypoxia and their brisk response to NaCN or KCN (Sigma, 0.25-0.50 units i.c., fig. 5.1). Single units were identified by the constant shape and amplitude of their action potentials. Injections of KCN or NaCN were given at intervals throughout the studies to check that the carotid vasculature was not blocked.

Arterial Blood Gases and Calculation of S_aO_2

Blood samples (0.3ml) withdrawn from the femoral artery were analysed using either a Radiometer Acid-Base Laboratory ABL2 analyser (calibrated every ten samples with two test solutions, pH7.38, PCO_2 40mmHg (5.5kPa) and pH6.84, PCO_2 80mmHg, or 10.6 kPa,) or a radiometer BMS3 Mk 2 analyser (calibrated several times daily with two

fig 5.1 : Carotid Chemoreceptor Response to Sodium Cyanide



2.5µg NaCN (dissolved in modified Locke solution) was injected into the lingual artery and washed in with 0.5ml warmed modified Locke solution, as described in the text. Data are means over 5 seconds. Solid bars indicate the timing of collection of data for analysis.

buffer solutions pH 7.38 and 6.84 and two gas mixtures 10%CO_2, 40%O_2, 50%N_2 and 5%CO_2, 95%N_2). Arterial oxygen saturation was calculated from P_aO_2 using an oxygen dissociation curve constructed from the data of Bartels and Harms (1958) for cats, and corrected for pH using their derived Bohr correction factor.

End-Tidal CO_2

End-tidal PCO_2 was monitored throughout using an infra-red CO_2 analyser (Med 1A, Grubb-Parsons) and displayed on one channel of the chart recorder. The chart recording was used to monitor $P_{ET}CO_2$ so that CO_2 from a cylinder could be added to the inspired gas mixture via a needle in the inspired line close to the trachea as necessary during hypoxia to keep $P_{ET}CO_2$ constant.

Arterial Blood Pressure

Systemic arterial blood pressure was monitored throughout the studies using a pressure transducer (Bell and Howell 4-442), which was calibrated and recorded onto the magnetic tape and the chart recorder.

iii) Almitrine

Almitrine Bismesylate (Vectarion Servier lot #3K9101, 0.1-0.5mgKg^{-1}) dissolved in malic acid (1-1.5ml) was injected i.v. over 2-3 seconds and washed in with 0.5ml warm (37°C) modified Locke solution (equilibrated with 95% air, 5% CO_2). Neither malic acid nor modified Locke solution had any effect upon carotid chemoreceptor activity (figs 5.4 and 5.3). Femoral arterial blood samples (2.5ml) taken for Almitrine assay were mixed with 100 units of heparin, the samples spun at 10,000G for 90 seconds and the plasma removed and frozen at -20° C. The samples were assayed for Almitrine by Servier Laboratories using gas-liquid chromatography.

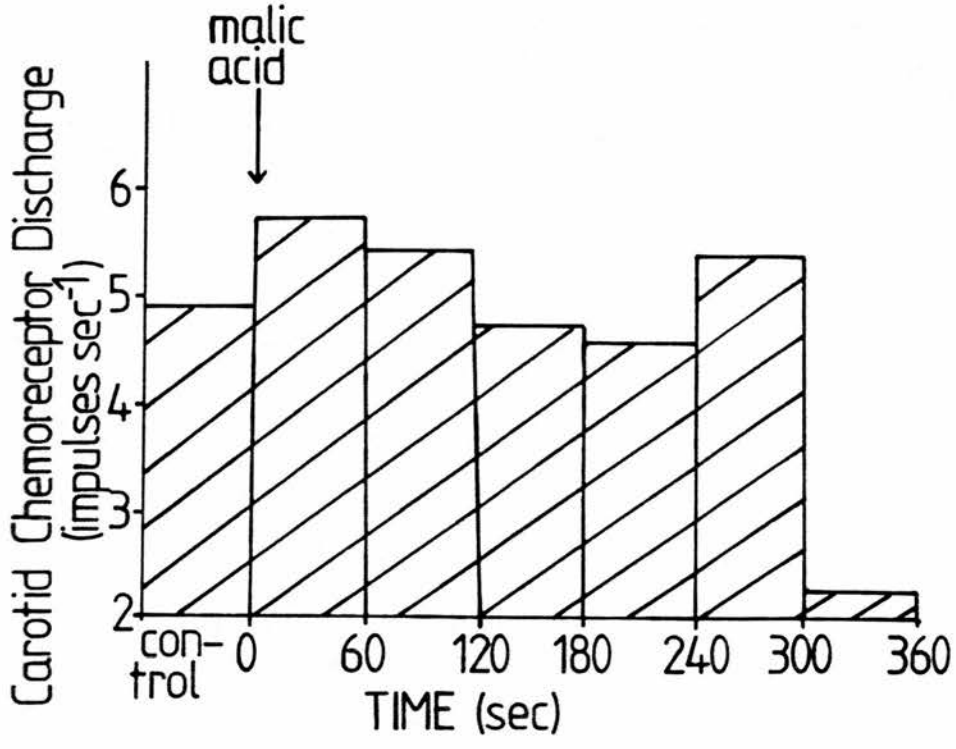
3) PROTOCOL

The carotid chemoreceptor responses to hypoxia and Almitrine were measured in five cats (nos. 4-8), and in the remainder the carotid chemoreceptor response to Almitrine only was measured.

Carotid Chemoreceptor Responses to Hypoxia

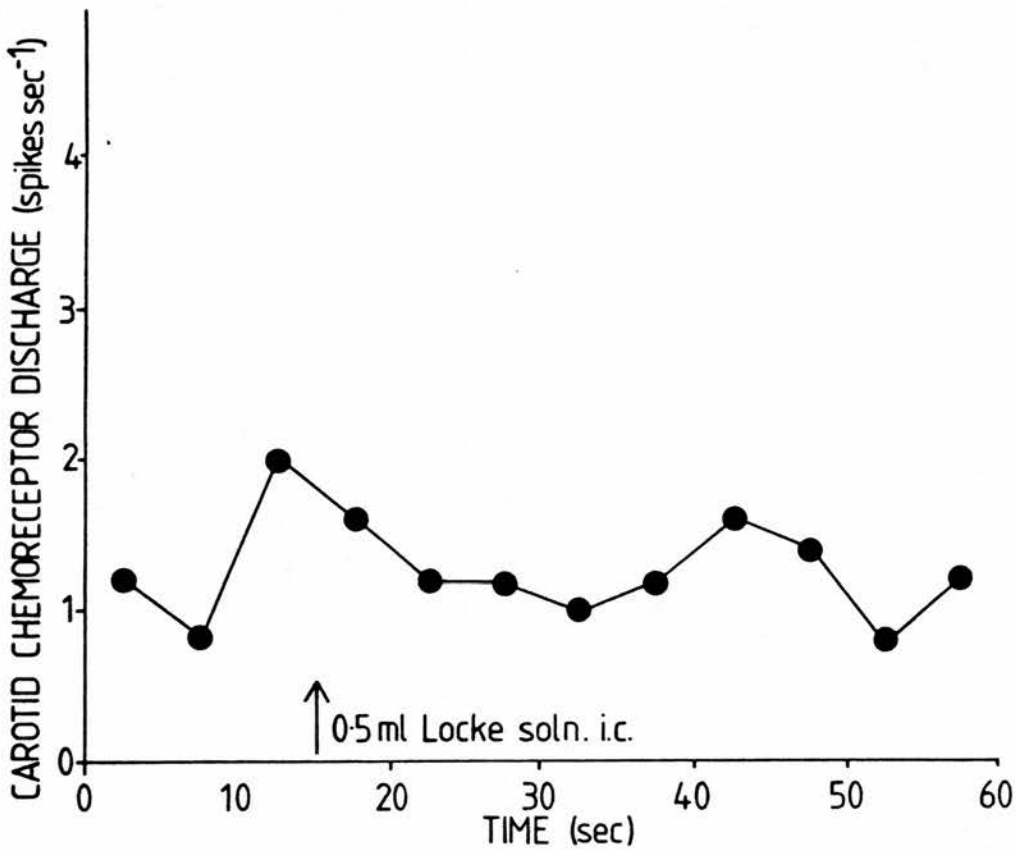
The carotid chemoreceptor response to three-minute step-changes in inspired gas from room air to both approximately 18% O_2 and 14%O_2

fig 5.2 : Carotid Chemoreceptor Discharge Following Injection of Malic Acid



1-1.5ml 0.6% w/v malic acid as was injected into the lingual artery (time 0), and the carotid chemoreceptor discharge plotted as means over each successive minute following injection. Data is from D.S. McQueen, personal communication.

fig 5.3 : Carotid Chemoreceptor Discharge Following Injection of Modified Locke Solution



0.5ml Locke solution at 37°C equilibrated with 95% air, 5% O_2 was injected into the lingual artery and the carotid chemoreceptor activity recorded for the following 45 seconds. Solid circles represent means over five seconds in one cat (number 5)

was measured, the two periods of hypoxia separated by five minutes ventilation with room air. Arterial blood samples were taken for blood gas analysis before, 30 and 165 seconds after the onset of hypoxia. The response to transient hypoxia (two breaths of 100%N_2) was measured six times, separated by two minutes ventilation with room air. Arterial blood samples were taken before and ten seconds after the onset of transient hypoxia (empirically chosen to coincide with the maximum carotid chemoreceptor discharge after transient hypoxia). The two types of hypoxic stimulus were given in random order, and the responses were studied before, and between ten and 60 minutes after injection of Almitrine.

In one cat (no. 4) nine different hypoxic gas mixtures were given, each hypoxic episode lasting three minutes and separated by five minutes ventilation with room air. The hypoxic mixtures caused falls in S_aO_2 ranging from 35 to 97%. Arterial blood samples were taken 165 seconds after the onset of hypoxia in each case.

Carotid Chemoreceptor Responses to Almitrine

Carotid chemoreceptor activity was recorded over 1 minute periods before and 5, 15, 30, and 60 minutes after Almitrine injection, and expressed as a mean for each recording. The carotid chemoreceptor response to Almitrine was calculated both as a percentage of the maximum response (measured by recording the carotid chemoreceptor response to anoxia), and as a percentage of the pre-Almitrine basline value. Femoral arterial blood samples were taken at corresponding times for Almitrine assay.

4) DATA ANALYSIS

The magnetic tape was replayed and the output from the channel in which electrical discharge from the carotid chemoreceptors was recorded was displayed on an oscilloscope (Tektronix 5103N). This signal was filtered to eliminate high frequency interference not already removed during the recording procedure, then passed through a voltage discriminator (WP Instruments), the window of which was adjusted to include only the discharge from 2-3 active chemoreceptor units. Analysis was only performed if these units remained active throughout the study. The signal was amplified and the impulses counted (Neurolog, Digitimer) and relayed to a microcomputer

(Commodore series 3032) where the impulses were averaged into 0.01 second bins for off-line analysis. If there was no obvious increase in carotid chemoreceptor discharge after hypoxia, the data was discarded, as this could indicate that the carotid vasculature was blocked (this possibility was tested by injection of NaCN or KCN, as already described).

Systemic arterial blood pressure was measured from the magnetic tape recording concomittantly with measurements of carotid chemoreceptor discharge.

Baseline Measurements

Baseline arterial blood gas measurements were expressed as means of all those taken throughout the study before Almitrine injection and all those taken after injection.

Step-Change Hypoxia

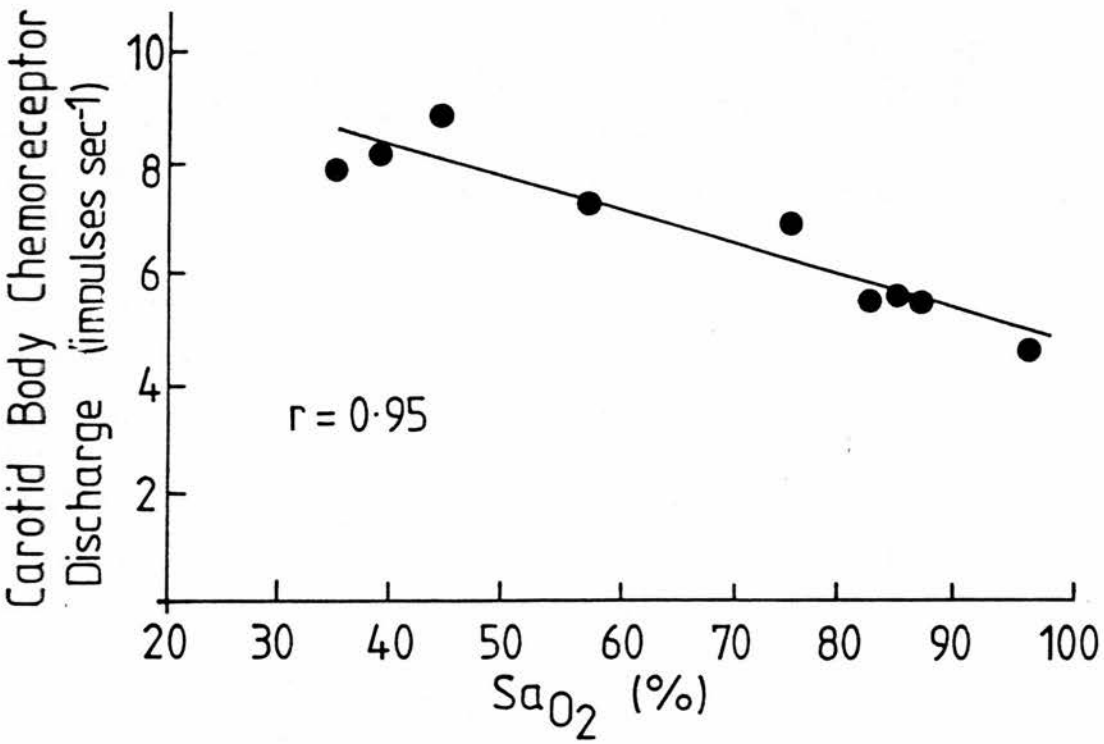
Mean carotid chemoreceptor discharge was calculated as over five seconds at times coinciding with femoral arterial blood samples before and 165 seconds after the onset of hypoxia.

In cat number 8, the carotid chemoreceptor discharge was plotted against S_aO_2 for each of the nine gas mixtures (fig 5.4). Calculation of the least squares regression relationship gave a correlation coefficient of 0.95, confirming the finding of Von Euler et al (1939) that carotid chemoreceptor discharge and S_aO_2 are linearly related. The carotid chemoreceptor response to step-change hypoxia was therefore expressed as the slope of least squares regression line relating carotid chemoreceptor discharge to S_aO_2 calculated from the mean of the two normoxic control measurements the measurements taken at 165 second after the onset of the two periods hypoxia.

Transient Hypoxia

Responses were only included in the analysis for those transient stimuli which caused a fall in S_aO_2 within a 10% range. The reproducibility of the response was assessed by comparing the slope of the chemoreceptor discharge/S_aO_2 relationship calculated from the normoxic control and hypoxic value, for each episode of transient hypoxia both before and after Almitrine. The mean S_aO_2 and carotid chemoreceptor discharge were also calculated for the pooled responses

fig 5.4 : Relationship Between Carotid Chemoreceptor Discharge and Arterial Oxygen Saturation



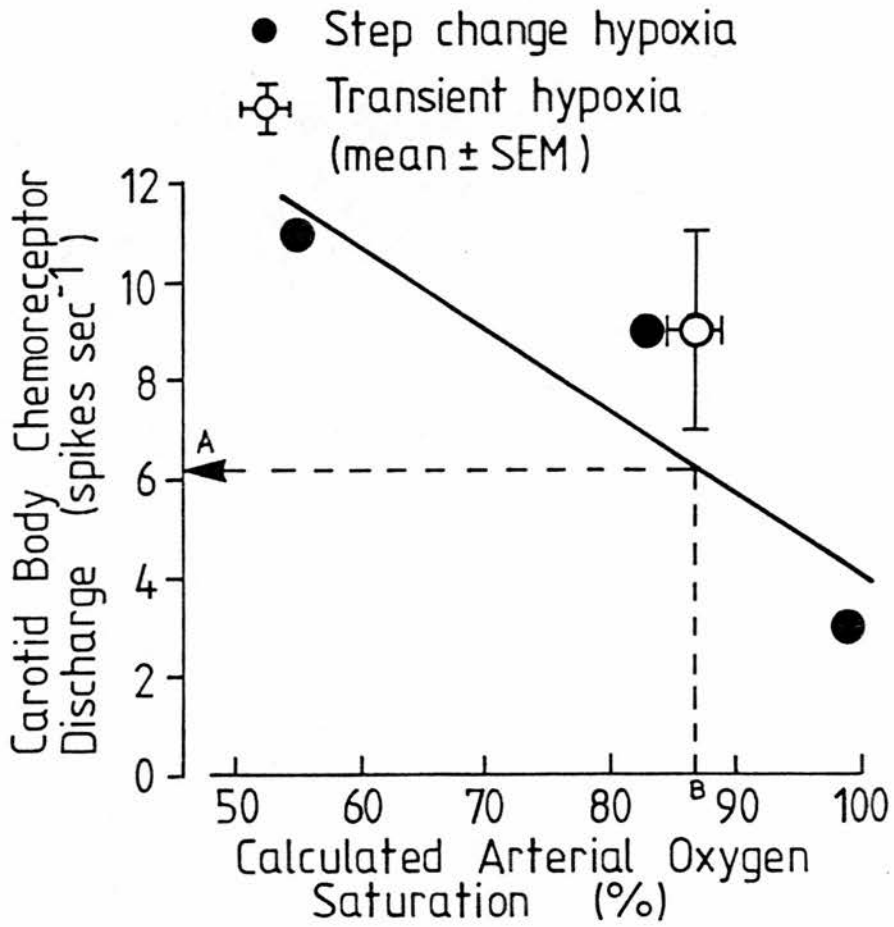
The linear regression relationship between carotid chemoreceptor activity and S_aO_2 during 9 different levels of inspired O_2. Data are means over five seconds, taken 165-170 seconds after the onset of each period of hypoxia.

to transient hypoxia for measurements made before and after Almitrine. The carotid chemoreceptor discharge which would have been expected in response to step-change hypoxia at the mean S_aO_2 produced by transient hypoxia ws then calculated from the linear regression line relating chemoreceptor discharge and S_aO_2 in response to step-change hypoxia (fig 5.5).

Statistical Methods

Carotid chemoreceptor activity before and at 5,15,30,and 60 minutes after Almitrine injection were compared by Friedmans Analysis of Variance, with Scheffés test of significance. All other comparisons were made using Wilcoxons Test for Signed Ranks.

fig 5.5 : Comparison of Carotid Chemoreceptor Responses to Transient and Step-Change Hypoxia



A schematic diagram to illustrate the method of comparison of carotid chemoreceptor responses to transient and step-change hypoxia. The carotid chemoroceptor response to step-change hypoxia (A) is calculated at the mean S_aO_2 for repeated transient hypoxic stimuli (B). The open circle represents the mean±SD for pooled episodes of transient hypoxia, the closed circles represent data for step-change hypoxia (see text for details), and the straight line represents the least squares regression relationship between S_aO_2 and carotid chemoreceptor discharge during step-change hypoxia.

III RESULTS

Carotid Chemoreceptor Responses to Hypoxia

Step-Change Hypoxia

A change in inspired gas from room air to an hypoxic gas mixture was followed by a gradual increase in carotid chemoreceptor discharge, which could still be elicited after Almitrine injection (fig 5.6). No overshoot in carotid chemoreceptor activity was observed in any of the cats at the onset of hypoxia. In the four cats in which measurements were made, the carotid chemoreceptor discharge did not increase to above 50% of the anoxic maximum during step-change hypoxia either before or after Almitrine (table 5.1) There was no significant difference between the slopes of the carotid chemoreceptor discharge/S_aO_2 relationships before and after Almitrine (table 5.2). values for P_aCO_2 during normoxia and hypoxia both before and after Almitrine are given in table 5.3. There was no significant difference between P_aCO_2 during hypoxia before and after Almitrine.

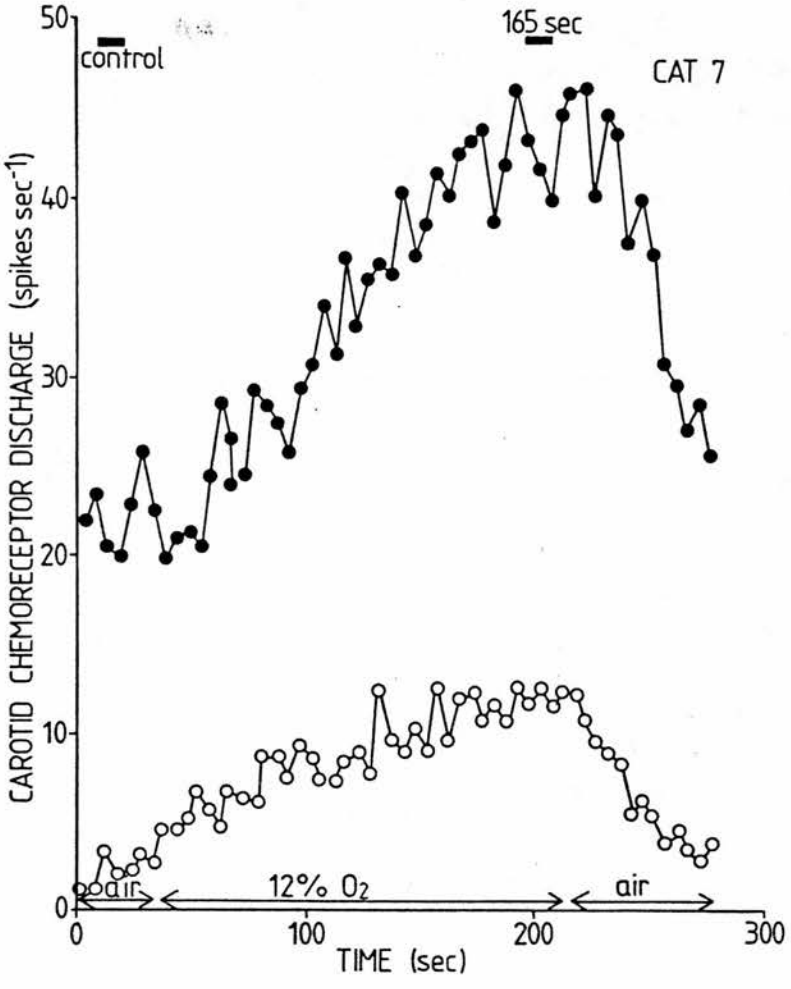
Transient Hypoxia

Inhalation of two breaths of 100% N_2 was followed by a rapid transient increase in carotid chemoreceptor discharge (fig 5.7). The rate of onset of hypoxia was greater than that of step-change hypoxia (fig 5.8). There was no consistent trend either before or after Almitrine in the slope of the carotid chemoreceptor discharge/S_aO_2 relationship in response to transient hypoxia, thus repetition of transient hypoxic stimuli up to 6 times did not therefore appear to cause either potentiation or depression of the response (fig 5.9a and b). P_aCO_2 was not significantly different during transient hypoxia from the baseline measurement (table 5.4), either before or after Almitrine.

Comparison of Responses to Step-Change and Transient Hypoxia

When the mean carotid chemoreceptor discharge obtained from the pooled data from all the episodes of transient hypoxia (before or after Almitrine) was compared with the carotid chemoreceptor discharge during step-change hypoxia at the same S_aO_2 (fig 5.10, table 5.5), four out of five cats showed a slightly greater response to transient hypoxia than to step change hypoxia. After Almitrine injection, the variability of the

fig 5.6 : Carotid Chemoreceptor Response to Step-Change Hypoxia Before and After Almitrine



Carotid chemoreceptor discharge increased during ventilation with 14% O_2 both before (open circles) and after (closed circles) injection of 0.5mg kg^{-1} Almitrine. Data is plotted as five-second averages.

table 5.1 : Carotid Chemoreceptor Discharge During Step-Change Hypoxia Before and After Almitrine

		Carotid Chemoreceptor Discharge			
		Before Almitrine		After Almitrine	
Cat No.	Max. Spikes sec^{-1}	Spikes sec^{-1}	% Max.	Spikes sec^{-1}	% Max.
4	20.2	9.0	44.5	18.5	91.5
				(0.5mgKg^{-1})	
				6.7	33.2
				(0.1mgKg^{-1})	
5	-	3.9	-	9.6	-
6	68.2	6.0	8.8	5.9	8.6
7	103.2	10.4	10.1	44.7	43.3
8	18.8	4.3	22.8	8.8	46.8

Carotid Chemoreceptor Discharge 165 Sec After the Onset of Step-Change Hypoxia (FIO_2 approximately 0.14) expressed as absolute spikes sec^{-1} and as a percentage of the maximum carotid chemoreceptor discharge during asphyxia. In cat 4, measurements were made following both injection of 0.5 and 0.1 $mgkg^{-1}$ Almitrine.

table 5.2 : Slope of the Carotid Chemoreceptor/S_aO_2 Relationship During Step Change Hypoxia Before and After Almitrine

	Carotid Chemoreceptor Discharge/S_aO_2 (impulses sec^{-1} $\%^{-1}$)	
Cat No.	Before Almitrine	After Almitrine
4	-0.11	-0.12
5	0.08	-0.06
6	-0.06	-0.09
7	-0.17	-0.45
8	-0.06	-0.06

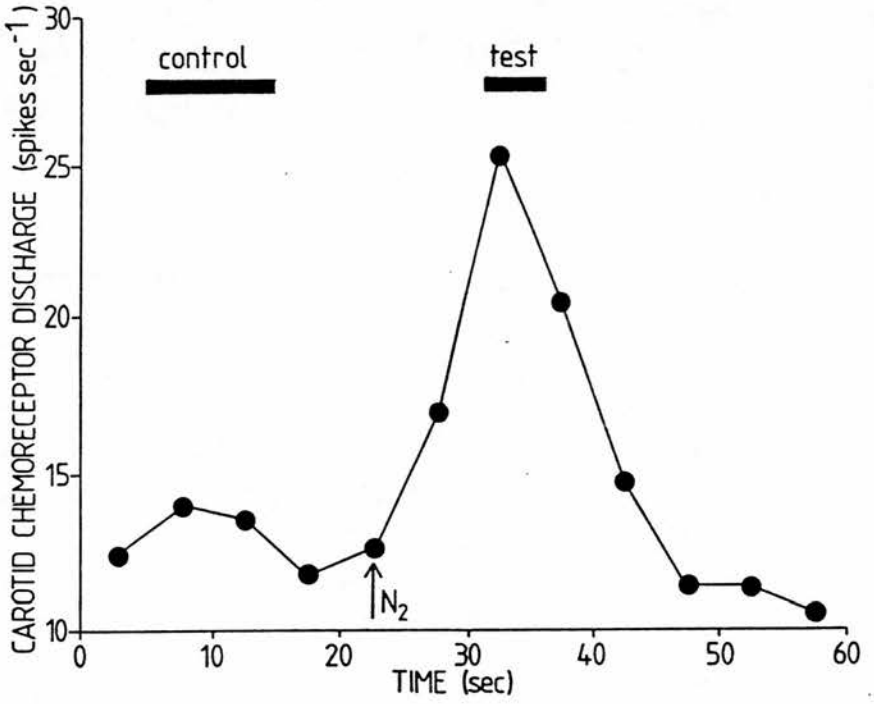
Slope of the linear regression relationship between carotid chemoreceptor discharge and S_aO_2 calculated from values taken during normoxia and 105 second after the onset of hypoxia (14 and 18% inspired O_2)

table 5.3 : P_aCO_2 Before and During Step-Change Hypoxia

	Before Almitrine				After Almitrine			
	$PaCO_2$ (kPa)				P_aCO_2 (kPa)			
Cat No.	Air	18% O_2	Air	14% O_2	Air	18% O_2	Air	14% O_2
4	5.2	3.9	5.2	4.9	4.4	3.9	4.4	4.8
5	3.6	3.7	3.7	2.9	3.2	2.8	3.5	3.9
6	6.1	3.9	4.0	4.0	4.1	3.9	4.1	4.5
7	4.8	3.9	3.9	3.9	5.1	5.3	4.9	4.8
8	4.6	3.9	4.6	4.6	5.2	5.1	4.6	5.8

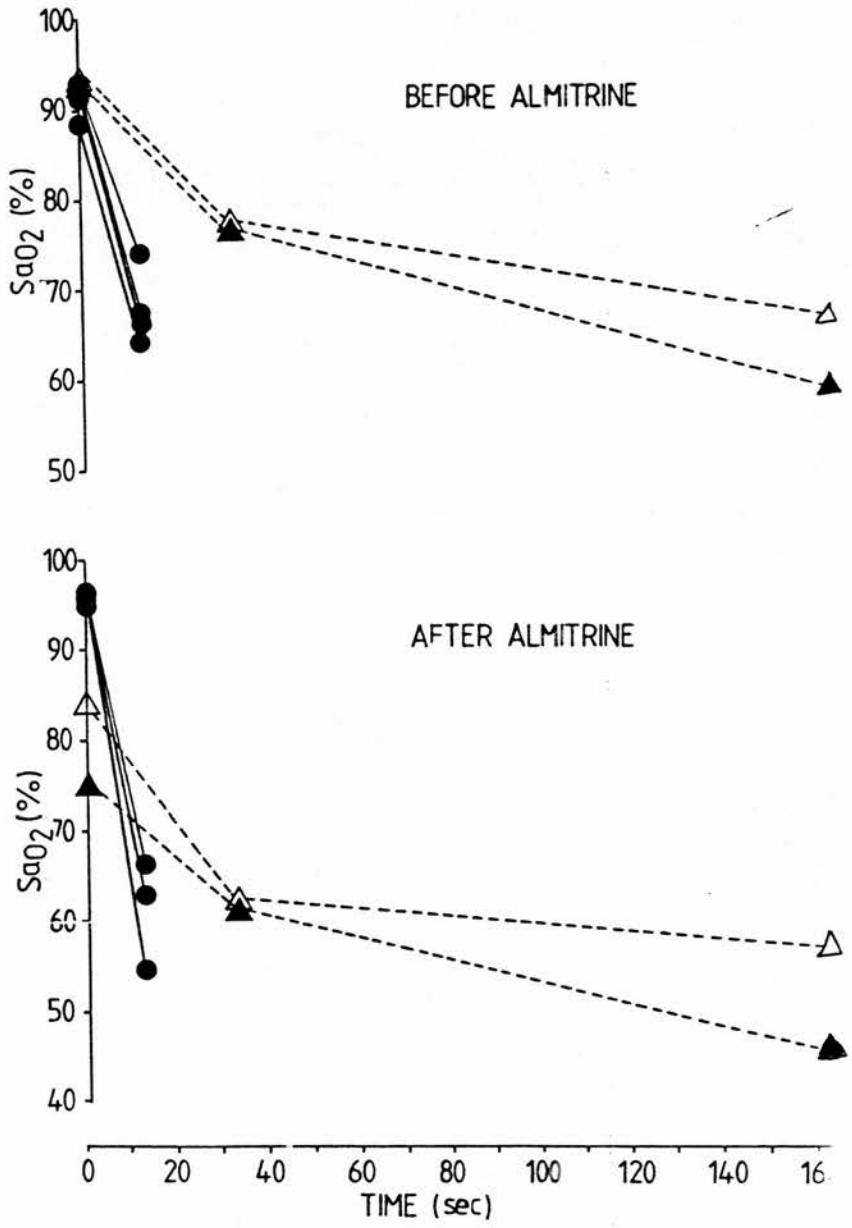
Femoral arterial PCO_2 before and 165 seconds after the onset of step-change hypoxia (a change in inspired gas from room air to 18 and 14% O_2).

fig 5.7 : Carotid Chemoreceptor Response to Transient Hypoxia



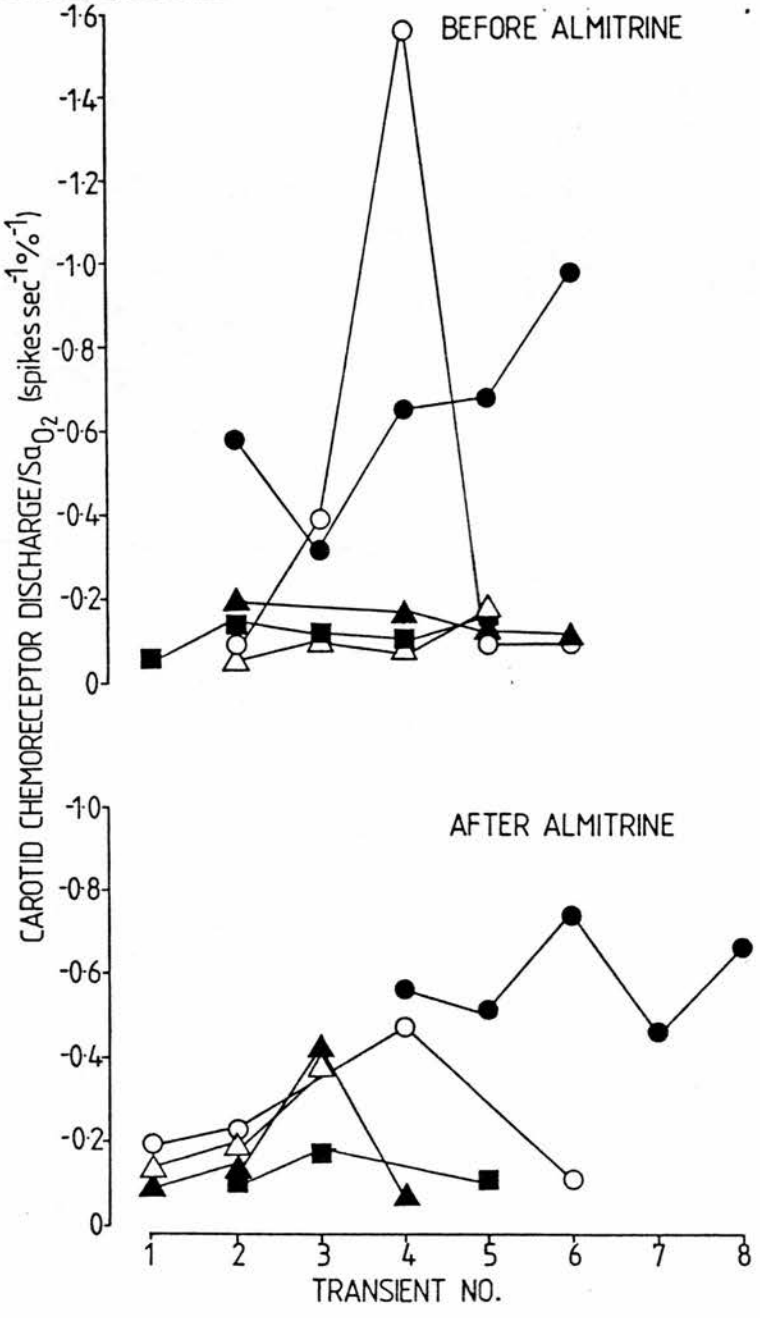
Following inhalation of two breaths of 100% N_2, there was a rapid transient increase in carotid chemoreceptor discharge. Values are plotted as five-second means, and solid bars indicate the timing of femoral arterial blood sampling. A similar pattern of response was seen both before and after Almitrine ; this measurement was taken in cat number 7 after injection of 0.5mg kg^{-1} Almitrine

fig 5.8 : S_aO_2 During Transient and Step-Change Hypoxia



Time course of the fall in S_aO_2 during transient (●) hypoxia and a step-change from inspired air to 14% (▲) and 18% (△) O_2. The rate of onset of hypoxia was greater for transient than for step-change hypoxia both before (upper panel) and after (lower panel) injection of 0.5mg kg^{-1} Almitrine.

fig 5.9 : Carotid Chemoreceptor Discharge/ S_aO_2 During Transient Hypoxia Before and After Almitrine



Carotid chemoreceptor discharge/S_aO_2 calculated for successive transient hypoxic stimuli before (A) and after (A) Almitrine. Values for cats 4 (△), 5 (▲), 6 (○), 7 (●) and 8 (■) are plotted. Some values were not plotted since the measurements were invalid either due to electrical interference or blockage of the carotid vasculature.

table 5.4 : P_aCO_2 During Normoxia and Transient Hypoxia Before and After Almitrine.

	Before Almitrine		After Almitrine	
	P_aCO_2 (kPa)		P_aCO_2 (kPa)	
Cat No.	normoxia	hypoxia	normoxia	hypoxia
4	4.9	4.8	4.4	4.5
5	4.0	3.7	4.1	4.2
6	4.0	4.1	4.1	4.2
7	4.5	4.5	5.4	5.3
8	5.1	4.9	4.9	4.9

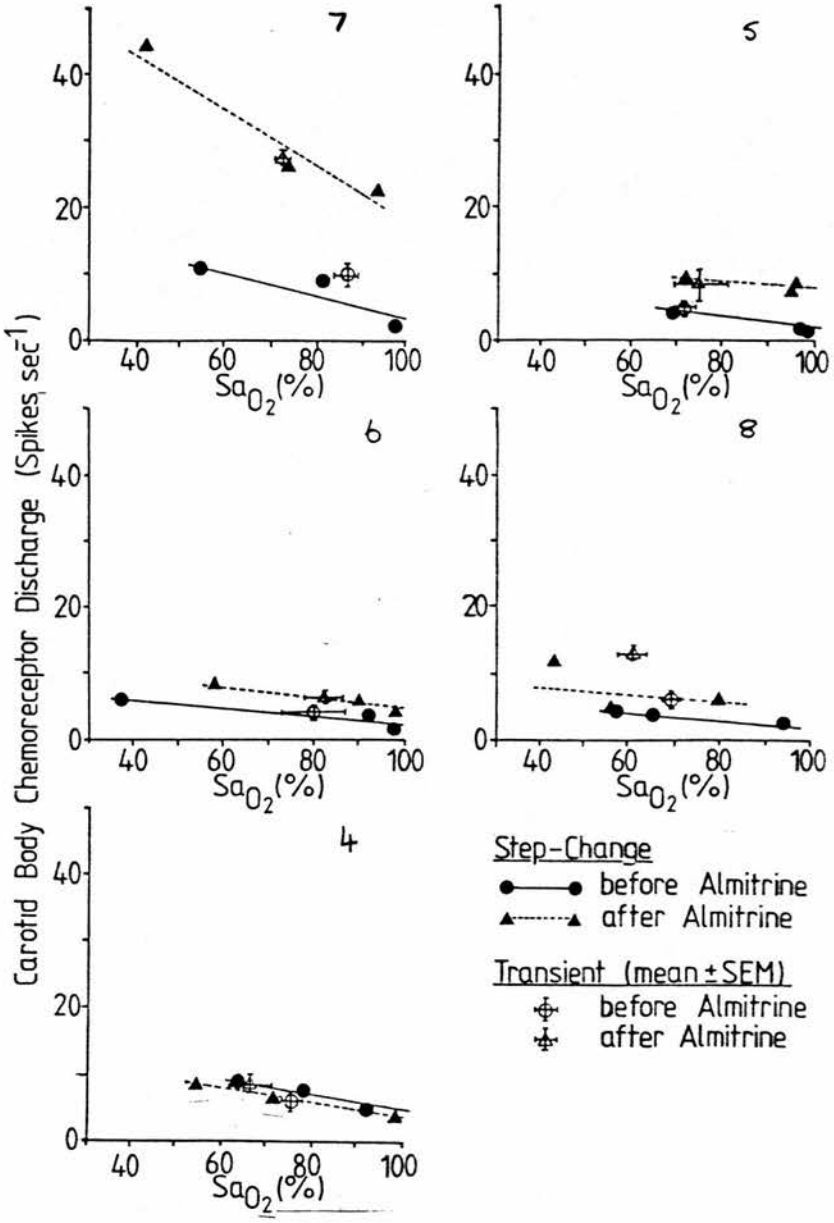
Values are means for pooled episodes of transient hypoxia, and pooled baseline measurements (taken before each period of hypoxia)

table 5.5 : Comparison of Carotid Chemoreceptor Responses to Transient and Step-Change Hypoxia

	Before Almitrine		After Almitrine	
	Transient	Step-Change	Transient	Step-Change
Cat No	(impulsessec^{-1})	(impulsessec^{-1})	(impulsessec^{-1})	(impulsessec^{-1})
4	6.2±1.1	7.9	8.8±0.8	8.3
5	4.8±0.6	3.6	8.4±2.4	9.4
6	4.2±0.5	3.6	6.2±0.8	5.7
7	9.7±1.6	5.8	27.2±1.1	30.2
8	6.1±0.4	3.5	12.7±0.3	6.6

Carotid chemoreceptor discharge during transient hypoxia (mean±SD for pooled data) and that at the same S_aO_2 during step-change hypoxia.

fig 5.10 : Comparison of Carotid Chemoreceptor Responses to Step-Change and Transient Hypoxia



Least squares regression lines for step-change hypoxia before (closed circles, solid lines) and after (triangles, broken lines) Almitrine and mean±SD of carotid chemoreceptor responses to transient hypoxia (open circles, before Almitrine, open triangles, after Almitrine). Cats 5-8 had an injection of 0.5mg kg^{-1} Almitrine, cat 4 received 0.1 mg kg^{-1} Almitrine

table 5.5 : Comparison of Carotid Chemoreceptor Responses to Transient and Step-Change Hypoxia

	Before Almitrine		After Almitrine	
	Transient	Step-Change	Transient	Step-Change
Cat No	(impulses sec^{-1})	(impulses sec^{-1})	(impulses sec^{-1})	(impulses sec^{-1})
4	6.2±1.1	7.9	8.8±0.8	8.3
5	4.8±0.6	3.6	8.4±2.4	9.4
6	4.2±0.5	3.6	6.2±0.8	5.7
7	9.7±1.6	5.8	27.2±1.1	30.2
8	6.1±0.4	3.5	12.7±0.3	6.6

Carotid chemoreceptor discharge during transient hypoxia (mean±SD for pooled data) and that at the same S_aO_2 during step-change hypoxia.

carotid chemoreceptor response to hypoxia between cats was much greater (table 5.5). One cat (no.8) had a response to transient hypoxia which was almost double that to step-change hypoxia, and of the others, two showed a slightly smaller response to transient hypoxia and two slightly bigger. Overall, the carotid chemoreceptor response to transient and step-change hypoxia were not significantly different.

ii) Effects Of Almitrine Injection

Baseline P_aO_2 was significantly lower ($p<0.05$) after Almitrine for the group of five cats in which the carotid chemoreceptor response to hypoxia was measured (table 5.6). Arterial PCO_2, however, was unchanged following Almitrine injection.

Injection of $0.5mgkg^{-1}$ Almitrine was followed by an increase in plasma Almitrine level (fig 5.11, upper panel, values obtained in 5 cats), carotid chemoreceptor activity (fig 5.11, middle panel, 7 cats) and systemic arterial blood pressure (fig 5.11, lower panel, 4 cats). The highest recorded plasma Almitrine level occurred five minutes after injection in all five cats Plasma Almitrine level decreased rapidly between the measurements taken after five minutes and 30 minutes, and then more slowly thereafter. By 90 minutes after injection, Almitrine was still present in the plasma in the two cats in which measurements were obtained.

The carotid chemoreceptor response to $0.5mgkg^{-1}$ Almitrine varied between animals. In cat 4, $0.5mg\ kg^{-1}$ caused an increase in carotid chemoreceptor activity of more than 50% of the maximum anoxic value. Chemoreceptor activity was therefore allowed to return to baseline before a dose of $0.1mg\ kg^{-1}$ Almitrine was given, following which the responses to hypoxia were measured. To avoid the possibility of prolonged anaesthesia causing tachyphylaxis of the chemoreceptor response to hypoxia, carotid chemoreceptor responses to Almitrine were not measured, and blood samples were not taken for Almitrine assay in this experiment, in order to limit the duration of the study.

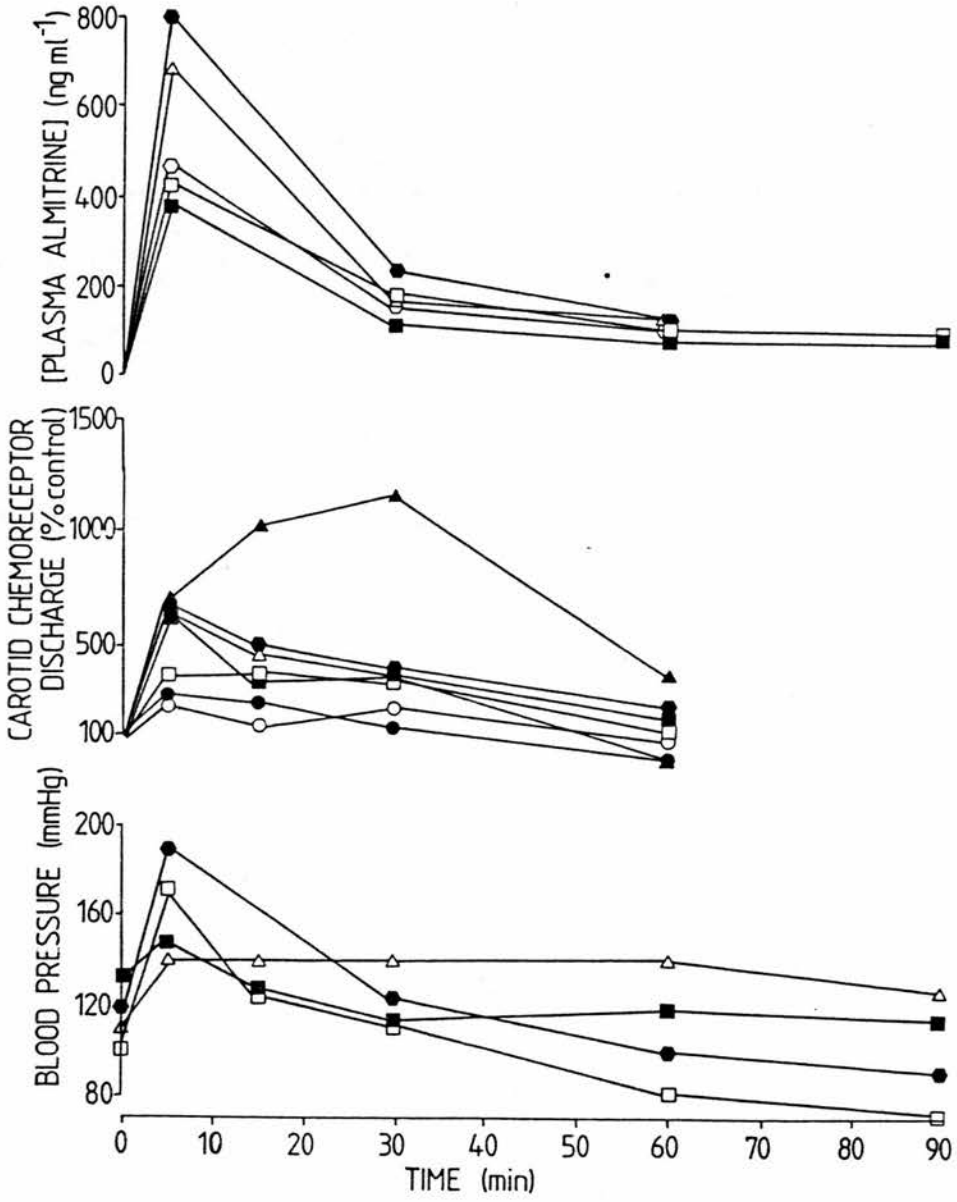
The highest level of carotid chemoreceptor discharge was recorded five minutes after Almitrine injection in six out of seven cats. In the remaining cat (no. 3) carotid chemoreceptor discharge continued to increase until 30 minutes after injection (fig 5.12, middle panel), although it had decreased by 60 minutes after injection. For all 7 cats,

table 5.6 : Mean P_aO_2 and P_aCO_2 Before and After Injection of Almitrine

	Before Almitrine		After Almitrine	
	P_aO_2 (kPa)	P_aCO_2 (kPa)	P_aO_2 (kPa)	P_aCO_2 (kPa)
Cat No.				
4	10.1	4.9	9.8	4.5
5	15.8	3.8	9.9	3.7
6	17.3	4.0	14.6	4.1
7	15.3	4.6	10.0	5.3
8	10.0	4.9	8.8	4.9

Data are means of all baseline measurements made throughout the studies.

fig 5.11 : Plasma Almitrine Level, Carotid Chemoreceptor Activity and Systemic Arterial Blood Pressure After Injection of 0.5mg kg $^{-1}$ Almitrine

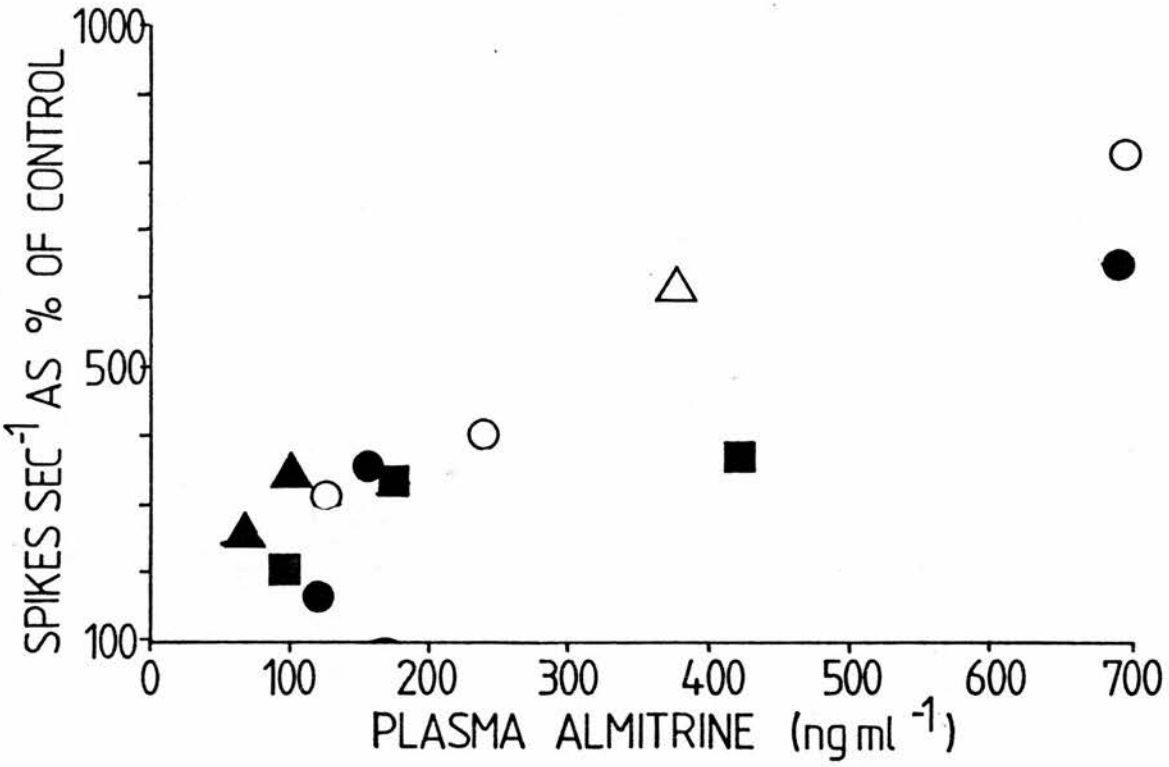


Values for cat number 4 are excluded from this figure, since they were only obtained after injection of 0.1mg kg^{-1} Almitrine. Plasma Almitrine levels were obtained for 5 cats (upper panel) carotid chemoreceptor discharge, expressed as a percentage of the baseline (pre-Almitrine) discharge is plotted as a mean over a period of 1 minute 5, 15, 30 and 60 minutes after injection in 7 cats (middle panel) and femoral arterial blood pressure was measured 5, 15, 30, 60 and 90 minutes after injection in 4 cats.

the mean increase above the pre-Almitrine normoxic baseline measurement was 505+78% five minutes after injection.The increase in carotid chemoreceptor activity was statistically significant at both five ($p<0.01$) and 15 minutes ($p<0.05$) after injection. When the data obtained from cat no. 3 was excluded from the analysis, carotid chemoreceptor activity was only significantly different from the pre-Almitrine level ($p<0.01$) five minutes after injection. Carotid chemoreceptor activity remained elevated for up to an hour after injection, the mean$\pm$SD being 136$\pm$46% of the pre-Almitrine level at 60 minutes after injection. The carotid chemoreceptor discharge expressed as a percentage of the pre-Almitrine baseline level increased with increasing plasma Almitrine level (fig 5.12).

Systemic arterial blood pressure measurements were obtained in cats 5-8 (although systemic arterial blood pressure was monitored throughout the other studies, it was not recorded onto the magnetic tape). There was an increase in blood pressure within five minutes of Almitrine injection from a mean of 115mmHg to 162mmHg, however this was not maintained and by 30 minutes after injection it had fallen to a mean value of 122mmHg.

fig 5.12 : Relationship Between Carotid Chemoreceptor Discharge and Plasma Almitrine Level



For four cats, numbers 5 (▲), 6 (○), 7 (●) and 8 (■) measurements of carotid chemoreceptor activity (mean for one minute) and plasma Almitrine level were plotted for between 5 and 60 minutes after Almitrine injection.

IV DISCUSSION

The carotid chemoreceptor responses to step-change and transient hypoxia were similar, both before and after Almitrine. Although Almitrine increased baseline carotid chemoreceptor discharge proportionally to the plasma Almitrine level, there was no difference between the slope of the carotid chemoreceptor discharge/S_aO_2 relationship for step-change hypoxia either before or after Almitrine injection. Arterial PO_2 during normoxia was significantly reduced after Almitrine, but P_aCO_2 was unchanged.

The observation that the carotid chemoreceptor responses to transient and step change hypoxia for a given fall in S_aO_2 were not significantly different suggests that the differences in the ventilatory response to these two types of stimulus seen in normal subjects (chapter 3) are not generated at the level of the carotid chemoreceptors. The long-lasting increase in carotid chemoreceptor discharge followed by a slow decay is in accordance with observations of other authors in animals (Laubie and Diot 1972, Bisgard 1980, Laubie and Schmitt 1980, Roumy and Leitner 1981, Dhillon and Barer 1982, Gautier and Bonara 1982, O'Regan et al 1983), but the carotid chemoreceptor response to hypoxia was not found to be enhanced by Almitrine in the present study, as it was by Bisgard et al (1980). Almitrine did not increase the slope of the carotid chemoreceptor discharge/S_aO_2 relationship in this study, whereas in humans an increase in the $\dot{V}_E/S_aO_2$ response to progressive isocapnic hypoxia has been reported after Almitrine (Connaughton et al 1982, Stradling et al 1982, Stanley et al 1983). These results again suggest that factors other than carotid chemoreceptor discharge determine the ventilatory response to hypoxia in humans.

Possible explanations for the differences between the observations in human subjects and in the present study in cats include methodological differences between the cat and human studies, technical and analytical difficulties associated with the studies in cats, or a species difference in the carotid chemoreceptor response to hypoxia. Also, other physiological mechanisms such as central processing of the carotid chemoreceptor input may account for the differences in the ventilatory and carotid chemoreceptor responses to the two stimuli.

Use of animal preparations allow direct recording of carotid chemoreceptor discharge in response to hypoxic stimuli. Differences in techniques between studies must be considered, however, when comparing the results with ventilatory responses to hypoxia obtained in human subjects. Firstly, measurements of the carotid chemoreceptor response to hypoxia were only obtained in five cats in this study, which may have resulted in a type 2 statistical error. In addition, continuous measurement of S_aO_2 was not possible as in the human studies, so S_aO_2 had to be derived from arterial blood gas samples which limited the number of data points for each cat. Thus the carotid chemoreceptor response to step-change hypoxia was expressed as the slope of a linear regression relationship calculated from only three points. Obviously if even only a very slight error was made in obtaining one of these data points, this could change the slope of the line.

A major difference between cat and human studies is that the cats were anaesthetised and the humans were fully conscious. Although anaesthesia may affect the ventilatory response to hypoxia (Moyer and Beecher 1942), anaesthetics act centrally rather than at the carotid chemoreceptors, and are not therefore likely to affect the carotid chemoreceptor response to hypoxia recorded in cats. The human subjects, however, were fully conscious and cerebral effects may have influenced their ventilatory responses to hypoxia. Awareness of the proceedings may significantly influence the results (Cunningham et al 1963) Although the inspired gas mixtures were changed without the subjects knowledge, some individuals, particularly those with a brisk hypoxic ventilatory drive, noticed the increase in ventilation which followed a change to an hypoxic gas mixture. Although the transient hypoxic stimulus is so short that it would be over before the subject was aware of any change, this is not true of the step-change hypoxic stimulus. The ventilatory response to transient hypoxia may thus be affected by awareness of events to a lesser extent than that to step-change hypoxia, which could account for the differences in ventilatory responses in human subjects. Personality has been shown to affect hypercapnic ventilatory drive by Saunders et al 1972; it could also affect hypoxic ventilatory drive in human subjects.

Another difference between the studies done in this chapter and those involving human subjects in chapter three is that the cats were

artificially ventilated and the human subjects were not. During the ventilatory response to transient hypoxia in human subjects, the increase in ventilation resulted in a small transient decrease in $P_{ET}CO_2$. This brief hypocapnia may have limited the carotid chemoreceptor and therefore the ventilatory response to transient hypoxia (Reynolds and Milhorn 1973) resulting in a smaller ventilatory response to transient than to step-change hypoxia. This fall in $P_{ET}CO_2$ following transient hypoxia did not occur in the cats, however, as there was no increase in ventilation and this may account for the similarity of the carotid chemoreceptor response to transient and step-change hypoxic stimuli.

Although the ventilatory response to hypoxia in cats is similar to that in humans i.e. hypoxia causes an increase in ventilation, there may be species differences in the carotid chemoreceptor response to hypoxia between cats and humans, which could account for the observed differences in ventilatory and carotid chemoreceptor responses. As it is not possible to record carotid chemoreceptor activity directly in humans, comparison of ventilatory and carotid chemoreceptor responses to hypoxia requires the assumptionthat the time courses of the carotid chemoreceptor responses to hypoxia are the same.

Although differences in methodology may contribute to the observed differences in carotid chemoreceptor response in cats and the ventilatory response in humans to transient and step-change hypoxic stimuli, these are unlikely to be the entire explanation. Physiological mechanisms may be involved. The overshoot in carotid chemoreceptor activity during the onset of hypoxia, followed by a fall to a steady-state level, as seen by Eyzaguirre and Lewin (1961) may result in an overestimation of the transient hypoxic response as it is measured during the rise in ventilation, whereas calculation of the $\dot{V}_E inst/S_aO_2$ during step-change hypoxia includes a majority of values obtained during the lower, steady-state phase. In this study, however,there was no overshoot in carotid chemoreceptor response during the onset of hypoxia. The higher ventilatory response to transient than to step-change hypoxia seen in two of the subjects in chapter three is therefore unlikely to be due to an initially high carotid chemoreceptor response to hypoxia.

The differences between ventilatory responses to transient and step-change hypoxia may be a result of integration of chemoreceptor afferent activity within the brainstem. This may be dependent upon

the rate of onset or the duration of the stimulus, or factors such as exercise, temperature or cerebral effects which although they may not influence carotid chemoreceptor discharge itself, may also be involved in determining how the carotid chemoreceptor input is processed. Although the sympathetic nervous system may be activated by hypoxia (Biscoe and Purves 1967, Carmody and Scott 1974), and sympathetic nerve activity is known to increase carotid chemoreceptor activity in cats (Floyd and Neil 1952, Biscoe and Purves 1967, O'Regan 1981), the sympathetic nervous system is unlikely to be the reason for the difference between carotid chemoreceptor and ventilatory responses to hypoxia in cats and humans, since the sympathetic nerves were intact in both cases.

The human studies were done during exercise, but the cat studies were not. Activity of muscle afferents is known to influence ventilation (Senepati 1966, Eldridge 1974, Eldridge and Gill-Kumar 1980), resulting in an increase with increasing exercise level (Cunningham et al 1968, Bhattacharyya et al 1970, Weil et al 1972, Martin et al 1978). Exercise may also potentiate the ventilatory response to hypoxia (Weil et al 1972, Martin et al 1978). Although Biscoe and Purves (1967) suggested that the muscle afferents act directly upon the carotid chemoreceptor complex, resulting in an increase in carotid chemoreceptor discharge, Davies and Lahiri (1973) found that neither passive nor electrically induced exercise caused an increase in carotid chemoreceptor activity during normoxia or hypoxia, despite increases in ventilation. This suggests that any interaction between exercise and hypoxia as ventilatory stimulants is at a more central location. Thus, the actual carotid chemoreceptor response in humans to transient and step-change hypoxia may have been the same (as seen in the cat experiments) but the muscle afferent activity resulting from the exercise may have led to modification of the ventilatory response in humans.

The dose of Almitrine used may be important in determining whether or not the baseline carotid chemoreceptor discharge and the carotid chemoreceptor response to hypoxia are enhanced. Increases in carotid chemoreceptor discharge have been observed following doses of Almitrine varying from $0.2mgkg^{-1}$ to $3.0mgkg^{-1}$ i.v., $0.02mgkg^{-1}$ to $0.5mgkg^{-1}$ i.c. or $0.75mgkg^{-1}$ infusion in anaesthetised dogs (Bisgard 1980) cats (O'Regan et al 1983) and rabbits (Roumy and Leitner 1981) and increases in normoxic resting ventilation have been seen in dogs (Laubie and Diot

1972, Laubie and Schmitt 1980), cats (Gautier and Bonara 1982) and rats (Dhillon and Barer 1982) following doses of Almitrine of 0.2-3.5mgKg^{-1} i.v. or 5mgKg $^{-1}$ orally. In human subjects, however, similar doses of Almitrine (varying from 1.5mgkg^{-1} to 100mg orally or 0.25-1.0mgkg^{-1}Hour^{-1} infusion) did nor produce an increase in baseline ventilation (Guillerm and Radiszewski 1974, Powell et al 1981, Connaughton et al 1982, Stradling et al 1982, Stanley et al 1983, Airlie et al 1988). It seems unlikely that the differences between animal and human studies can be explained by differences in plasma Almitrine levels, since no increase in ventilation was observed at plasma Almitrine levels ranging from 260 to 488ngml^{-1} by Stradling et al (1982) nor at levels ranging from 50 to 514ngml^{-1} by Stanley et al (1983), whereas increases in carotid chemoreceptor discharge were observed at plasma Almitrine levels between 67 and 811ngml^{-1} in the present study. This also applies to the difference in findings in the present study concerning enhancement of the carotid chemoreceptor response to hypoxia by Almitrine. The doses of Almitrine used in the present study were similar or smaller than those used in the studies of Connaughton et al (1982), Stradling et al (1982), Stanley et al (1983) and Airlie et al (1988), all of whom observed an increase in the V_E/S_aO_2 relationship or an increase in the shape parameter A of the hyperbolic relationship between ventilation and P_aO_2. No increase in the slope of the carotid chemoreceptor discharge/S_aO_2 relationship was seen , however, in this study.

The dose of Almitrine was chosen to give only a moderate increase in carotid chemoreceptor activity, so any subsequent increase in the carotid chemoreceptor response to hypoxia did not approach the maximum , and therefore result in underestimation of the carotid chemoreceptor response to hypoxia. In four of the cats (numbers 4,6,7,8) the carotid chemoreceptor discharge measured 165 seconds after the onset of hypoxia (approximately 14% P_IO_2) was less than 50% of the maximum discharge as measured by asphyxia (table 5.1). The other cat (no. 5) died before an asphyxia test could be performed. Keeping the carotid chemoreceptor discharge below 50% of the maximum was intended to minimise the effects of approaching the maximum on the response to hypoxia. It is therefore unlikely that the failure to demonstrate an increase in the slope of the

carotid chemoreceptor discharge/S_aO_2 relationship was due to chemoreceptor discharge reaching the maximal level.

The results of the present study do not agree with those of Bisgard et al (1980) in that in their studies in anaesthetised dogs, they did observe an enhancement of the carotid chemoreceptor response to hypoxia after Almitrine. One difference between their studies and the present study is that in the present study the sympathetic nerves were left intact whereas in Bisgard et als studies they were cut. This may suggest some role for the sympathetic nervous system, possibly as an inhibitory rather than an excitatory influence on carotid chemoreceptor activity during hypoxia after Almitrine (McQueen et al 1987, personal communication) This is not, however, consistent with the observations in human subjects, in which ventilation increased while the sympathetic supply to the carotid body was intact.

The observation that the carotid chemoreceptor response to hypoxia is not enhanced by Almitrine, although the ventilatory response is, suggests that the enhancement may occur at a higher locus than the carotid chemoreceptors. Alternatively, it may suggest that the increase in slope of the $\dot{V}_E$ inst S_aO_2 relationship occurs because the normoxic ventilation in normal subjects is not increased after Almitrine, i.e. during normoxia, the carotid chemoreceptor input is suppressed by the brainstem, but during hypoxia it is not. Thus in addition to the increased baseline carotid chemoreceptor discharge after Almitrine, there is removal of this suppression during hypoxia, so the total increase in ventilation during hypoxia after Almitrine is proportionally greater than the increase in directly recorded carotid chemoreceptor discharge, which is not itself suppressed during normoxia.

The increase in systemic arterial blood pressure following Almitrine injection, which has also been observed by Laubie and Diot (1972) in dogs, and by O'Regan et al (1983) in cats may have influenced measurements of carotid chemoreceptor activity. Carotid chemoreceptor discharge is known to decrease with increasing blood pressure over the range 60-160mmHg in cats (Biscoe et al 1970), and the systemic blood pressure did vary within this range during the period over which carotid chemoreceptor responses to hypoxia were measured. The possible influence of changes in systemic arterial blood pressure on carotid chemoreceptor discharge was minimised, however, firstly by making measurements between

10 and 60 minutes after injection of Almitrine, thus avoiding the initial large increase in blood pressure recorded five minutes after injection of Almitrine (fig. 5.12), and secondly by measuring the carotid chemoreceptor responses to transient and step-change hypoxia in random order, so that one or other responses was not always measured when the blood pressure was highest.

The fall in P_aO_2 following Almitrine seen in this study has previously been reported in anaesthetised cats and dogs (Barer et al 1983). In hypoxaemic patients, P_aO_2 increases after Almitrine due to increased ventilation, however no effect of Almitrine on normoxic P_aO_2 in normal subjects has been reported. Almitrine is known to cause vasoconstriction in the lungs, which leads to ventilation-perfusion mismatching (Barer et al 1983). The absence of an increase in ventilation in the artificially ventilated closed chest cats used in this study might cause an fall in P_aO_2 after Almitrine.

This study shows that there is no difference between the carotid chemoreceptor responses to transient and step-change hypoxia in cats. As ventilation was not measured in the cats, it is not possible to say whether the ventilatory responses to the two types of hypoxic stimulus would have been different, as in human subjects, or whether the differences in ventilatory responses are a result of variable brainstem processing of the carotid chemoreceptor input. There were two differences between the cat and human experiments which might account for the greater ventilatory response to step-change than to transient hypoxia seen in humans. Firstly, transient hypocapnia occurred in the human subjects as a result of the increase in ventilation following transient hypoxia, which did not occur in the cats, as they were artificially ventilated. This hypocapnia may have limited the carotid chemoreceptor and thus the ventilatory response to transient hypoxia in human subjects. Secondly, the ventilatory responses to hypoxia in humans were measured during exercise, which may account for the differences in ventilatory responses. These possibilities are considered in the following chapters.

CHAPTER 6 : IS THE VENTILATORY RESPONSE TO TRANSIENT HYPOXIA LIMITED BY THE RESULTANT HYPOCAPNIA?

I INTRODUCTION

The ventilatory response to transient hypoxia was smaller than that to step-change hypoxia in the majority of subjects, despite similar falls in S_aO_2 (chapter three). The difference between these ventilatory responses could not be explained by potentiation of the response to step-change hypoxia due to repeated hypoxic stimuli (chapter four). In addition, there was no difference between carotid chemoreceptor responses to transient and step-change hypoxia in anaesthetised and paralysed cats (chapter five), which suggests that the differences in ventilatory response may result from modification of the carotid chemoreceptor input at a higher location. Before this conclusion can be reached, however, the possibility must be eliminated that the response to transient hypoxia in the normal subjects was not being limited by the hypocapnia resulting from the rise in ventilation. Such hypocapnia did not occur following transient hypoxia in the cats, as they were mechanically ventilated throughout at a constant rate and tidal volume.

There is evidence for both central (Leusen 1954, Loeschke 1979, Loeschke et al 1958) and peripheral (Torrance 1968, Biscoe 1971, Biscoe et al 1970, Lahiri and Delaney 1975 and 1976) sensitivity to CO_2, a rise in P_aCO_2 resulting in an increase in ventilation mediated by either or both of the central and peripheral chemoreceptors. A decrease in P_aCO_2 from a hypercapnic level causes a fall in ventilation (Gardner 1980). A fall in $P_{ET}CO_2$ below the normal air-breathing-level might therefore also be expected to cause a decrease in ventilation, thus limiting the ventilatory response to transient hypoxia as suggested by Leitch (1976). Since the hyperventilation following transient hypoxia during exercise is brief (lasting only 6-8 breaths), and causes only a small decrease in P_aCO_2 then the ventilatory response to hypocapnia would need to be fast and sensitive to small changes. Furthermore, a decrease in ventilation would only occur for a fall in P_aCO_2 from above the ventilatory threshold for P_aCO_2. Although the central chemoreceptor response to changes in P_aCO_2 is the chief stimulus to ventilation during steady-state changes, with the carotid chemoreceptor response providing only a small stimulus both in humans and animals (Mitchell 1965, Pappenheimer 1967, Whipp and Wasserman 1980), the central response is a

result of changes in cerebro-spinal fluid composition, and is therefore slower than the carotid chemoreceptor response. Any effect of P_aCO_2 upon the ventilatory response to transient hypoxia is not, therefore, likely to involve the central chemoreceptors. Aortic chemoreceptors are much less sensitive to changes in P_aCO_2 than are carotid chemoreceptors (Paintal and Riley 1966), thus ventilatory responses to transient changes in P_aCO_2 are probably almost exclusively mediated by the carotid chemoreceptors.

Samaan and Stella in 1935 showed that in anaesthetised cats during normoxia, the P_aCO_2 threshold of the carotid chemoreceptors was around 32-35mmHg (4.3-4.7kPa). If this threshold applies equally to humans, then the chemoreceptors will be actively responding to CO_2 at normal gas tensions (around 40mmHg or 5.3kPa). Nielson and Smith (1951) reported a P_aCO_2 threshold of 31.5mmHg (4.2kPa) in human subjects, which suggests that the carotid chemoreceptors are indeed active at normal P_aCO_2 levels. Thus reduction in P_aCO_2 below that in normocapnia would reduce carotid chemoreceptor activity and therefore ventilation. Samaan and Stella (1935) also noted that the carotid chemoreceptor response to changes in P_aCO_2 was very rapid, although they did not give any quantitative information on this subject. Black et al (1971) reported a time of 1-3 seconds for completion of the response of single- or few-fibre preparations of cat carotid sinus nerve to a sudden increase in PCO_2 of the blood perfusing the carotid body, and an almost equally rapid reduction in carotid sinus nerve activity upon withdrawal of the hypercapnic stimulus. They also noted a brief undershoot in carotid chemoreceptor activity before the return to a new steady level of activity, upon sudden withdrawal of hypercapnia, which, if it occurred when P_aCO_2 was reduced from normocapnia to hypocapnia, would make the resultant fall in ventilation larger. Ponte and Purves (1974) recorded a carotid chemoreceptor response time of 1.2-2.2 seconds to hypercapnia induced by a sudden change in PCO_2 in the blood perfusing the carotid body of anaesthetised cats. A latency of 3.9 seconds for the carotid chemoreceptor response to an increase in $P_{ET}CO_2$ in cats was reported by Lahiri et al (1980). The carotid chemoreceptor response to changes in P_aCO_2 therefore appears to be, in animals at least, very rapid. Black et al (1971), Ponte and Purves (1974) and Lahiri et al (1980) all reported that the carotid chemoreceptor response to hypoxia was slower than that

to hypercapnia (although they did not quote the response time to hypoxia).

Ventilatory responses to changes in P_aCO_2 also appear to very rapid Bouverot et al (1965) demonstrated a latency of 10-15 seconds for the ventilatory response to inhalation of one or two breaths of 7% CO_2 in air in dogs, and Dutton et al (1967) reported a latency of five seconds for the ventilatory response to an step increase in PCO_2 in blood perfusing the carotid bodies, also in dogs. They also noted that the ventilatory response to a return to normocapnia was not complete within 15 seconds, but they did not report the latency of this response. Reynolds et al (1972) found in human subjects that the half-time for return to air-breathing after inhalation of 3-7% CO_2) ranged from 12 to 43 seconds.which agrees with the timing of the responses measured by Dutton et al (1967), however the on-transient half-time for the ventilatory response to inhalation of 3-7% CO_2 was found to be much longer by Reynolds et al (1972), ranging from 64-135 seconds. The ventilatory response to a change in F_ICO_2 (Reynolds et al 1972) will obviously be slower than that to a change in PCO_2 of carotid chemoreceptor perfusate (Dutton et al 1967) due to the lung-carotid circulation time, but this still does not account for the difference between these results and those found by Bouverot et al (1965) who measured the ventilatory response to changes in inhaled PCO_2. This may have been because Bouverot et al (1965) were measuring the half-time of the ventilatory response to a transient CO_2 stimulus, lasting only one or two breaths, whereas Reynolds et al (1972) were measuring the response to a steady-state stimulus. Where the ventilatory response to a transient stimulus would be mediated entirely by the carotid chemoreceptors, the ventilatory response to a steady-state stimulus would also involve the central chemoreceptors and would therefore have a much longer half-time.

The level of P_aO_2 is important in determining the latency of the ventilatory response to changes id P_aCO_2. Lambertson et al (1965) found that the response to a sudden withdrawal of a hypercapnic stimulus in man, in normoxia, had three components with different latencies, (4 , 16 , and 160sec), and time constants of 6, 12 and 128 sec respectively. the fastest latency was not present when the study was repeated on a background of hyperoxia. They suggested that this may indicate the involvement of three separate receptor

systems, the fastest reacting of which is inactivated by hyperoxia. These three latencies are consistent with those of the carotid chemoreceptors (which respond to a fall in $P_{ET}CO_2$ from 48 to 24mmHg or 6.4-3.2kPa within five seconds ; Lahiri et al 1980), the aortic chemoreceptors (which have a latency of approximately 25 seconds longer than that of the carotid chemoreceptors to the same fall in $P_{ET}CO_2$; Lahiri et al 1980) and the central chemoreceptors (which respond very slowly to changes in P_ACO_2 with a time constant of about 60 seconds ; Gelfand and Lambertson 1973, Berger et al 1973).

The importance of P_aO_2 in the short latency response to changes in P_aCO_2 has also been demonstrated in man by Lefrancois et al (1972), who showed that the response to transient hypercapnia was faster in hypoxia than in normoxia. Miller et al (1974) showed that a decrease in P_ICO_2 from 40 to 0mmHg (5.3 to 0 kPa) in man resulted in a fall in ventilation within about 13 seconds (the fifth breath after withdrawal of the hypercapnic stimulus) in hyperoxia, whereas the latency of the response was reduced to around seven seconds (within three breaths of withdrawal of the hypercapnic stimulus) during hypoxia. This is in agreement with Drysdale et al (1981), who demonstrated that removal of a hypercapnic stimulus in hypoxia in man had a ventilatory response with a latency of 4.8-10.2 seconds (within one to three breaths of removal of the hypercapnic stimulus).

The ventilatory response to a reduction in P_aCO_2 may therefore be fast enough to inhibit the ventilatory response to transient hypoxia. The response is likely to be mediated by the carotid chemoreceptors, and is dependent upon P_aO_2, being abolished by hyperoxia and occurring more rapidly during hypoxia. There also exists a slower component of the ventilatory response to changes in P_aCO_2, which is likely to involve the central chemoreceptors, and is too slow to affect the ventilatory response to transient hypoxia.

The aim of the present study is therefore to investigate whether the small brief fall in $P_{ET}CO_2$ occurring during the ventilatory response to transient hypoxia limits the ventilatory response and could therefore account for the smaller ventilatory response to transient hypoxia as compared to that to step-change hypoxia, observed in chapter three.

II METHODS

1) Subjects

Ten normal subjects (Appendix II : numbers 1,2,3,6,9-13,17) recruited from laboratory staff were studied. Details of age, height, weight, lung volumes, TCO and airways resistance are documented in Appendix II.

2) Equipment and Methods

Measurements were made using the equipment described in chapter two (fig 2.2) for transient hypoxia, using the 5-way Hans-Rudolph valve (fig 2.4) A Douglas bag filled with 100% N_2 was connected to one inspiratory port of the Hans Rudolph valve, while air was supplied from the rotameter trolley to another of the inspiratory ports. A line from the CO_2 rotameter was positioned in the inspiratory line very close to the air inlet to the Hans-Rudolph valve for addition of CO_2 to the inspired air.

The subjects walked on a level treadmill breathing room air through the respiratory valve. During minutes seven to nine and nine to eleven after the start of exercise, expired gas collections were made and gas exchange variables calculated. If measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ were not within 100ml (the criteria used to assess steady-state gas exchange), further collections of mixed expired gas were made until steady-state gas exchange was reached. Measurements of hypoxic ventilatory drive were made only when steady-state exercise ($\dot{V}O_2$ of approximately $1.0 l min^{-1}$) had been attained. Two minutes after the final measurement of hypoxic ventilatory drive, a further collection of mixed expired gas was made, and gas exchange variables were expressed as the mean of all measurements made during steady-state exercise.

The inspired gas was changed abruptly during expiration from room air to 100% N_2 for two to four breaths, to reduce S_aO_2 to approximately 80%. The inspired gas was then returned to room air, again during expiration. This procedure was repeated 12 times at intervals of at least 60 breaths. During 6 transient hypoxic episodes chosen at random, CO_2 was added to the inspired gas to maintain $P_{ET}CO_2$ constant (isocapnic transient hypoxia). In the remaining 6, CO_2 was not added and $P_{ET}CO_2$ allowed to fall (non-isocapnic transient hypoxia).

Data was collected on-line and archived onto floppy discs for analysis, the methods of which are described in detail in chapter two. Data was pooled in two groups for isocapnic hypoxia and non-isocapnic hypoxia. Hypoxic ventilatory drive was expressed as the slope of the $\dot{V}_E$inst S_aO_2 relationship for each set of pooled data. Baseline $P_{ET}CO_2$ was calculated as a mean of ten breaths before the onset of hypoxia for both sets of pooled data (i.e. a mean of a total of 60 breaths). For both sets of pooled data, the $P_{ET}CO_2$ during hypoxia was calculated as a) the mean value for <u>all</u> breaths used in the analysis of the hypoxic response and b) the mean of the <u>lowest</u> $P_{ET}CO_2$ recorded during each hypoxic episode. The fall in $P_{ET}CO_2$ was then expressed as a) the difference between the mean baseline $P_{ET}CO_2$ and the mean $P_{ET}CO_2$ during the ventilatory response to hypoxia, and b) the difference between the mean baseline $P_{ET}CO_2$ and the mean lowest $P_{ET}CO_2$ reached during the ventilatory response. To compare the level of hypoxia during during isocapnic and non-isocapnic hypoxia, the mean lowest recorded S_aO_2 was calculated for the two sets of pooled data. The mean time from the onset of hypoxia to the breath with the maximal $\dot{V}_E$inst was calculated for both isocapnic and non-isocapnic hypoxia. The mean time to the lowest recorded $P_{ET}CO_2$ was also calculated for non isocapnic hypoxia only.

Day-to-Day Variability of the Ventilatory Response to Transient Hypoxia

To assess variability of the ventilatory response to transient hypoxia, additional measurements of the response to isocapnic hypoxia were made in five subjects (numbers 1,2,3,6, and 10) on a different day, and of the response to non-isocapnic hypoxia in six subjects (numbers 1,2,3,6,9 and 10) on two separate days (data from chapter 3). The measurements were not made at the same time of day.

3) <u>Statistics</u>

Friedmans Analysis of Variance with Scheffés correction factor was used to compare $P_{ET}CO_2$ during each successive breath after the onset of hypoxia for pooled data for both isocapnic and non-isocapnic hypoxia. All other comparisons were made using Wilcoxons Test for Signed Ranks, with Bonferoni's correction where appropriate.

III RESULTS

Gas exchange variables and ventilation during steady-state exercise are shown in table 6.1.

i) Ventilatory Response to Hypoxia.

Following two to four breaths of N_2 there was a fall in S_aO_2 (fig. 6.1, upper panel), and an increase in $\dot{V}_E$inst (fig. 6.1, middle panel). The falls in S_aO_2 were similar during both isocapnic and non-isocapnic transient hypoxia (table 6.2).The highest $\dot{V}_E$inst reached during the ventilatory response to non-isocapnic hypoxia and to isocapnic hypoxia occurred 15.3+3.7 and 15.9±4.3seconds (mean±SD) respectively after the onset of hypoxia (table 6.3). There was no significant difference between these times. The slope of the $\dot{V}_E$inst/S_aO_2 relationship measured in response to isocapnic transient hypoxia was greater than that to non-isocapnic transient hypoxia in six out of ten subjects and smaller in the remaining four (fig. 6.2, table 6.4). There was no significant difference, however, for the whole group.

The difference between measurements of hypoxic ventilatory drive during non-isocapnic and isocapnic hypoxia made on the same day for individual subjects ranged from 0.09 to 0.671 min^{-1} $\%^{-1}$. Table 6.5 summarises the measurements of hypoxic ventilatory drive during isocapnic and non-isocapnic transient hypoxia made on different days. The greatest difference in $\dot{V}_E$inst/S_aO_2 slope during non-isocapnic transient hypoxia on the three separate days within individuals ranged from 0.03 to 0.981 min^{-1} $\%^{-1}$, and for isocapnic transient hypoxia on two separate days the range of differences was 0.04 to 0.63 l min^{-1} $\%^{-1}$. The difference in $\dot{V}_E$inst slopes measured during isocapnic and non-isocapnic hypoxia on the same day within individuals is thus similar to the day-to-day variability of the $\dot{V}_E$inst/S_aO_2 slope within individuals.

ii) End-Tidal PCO_2 During the Ventilatory Response to Hypoxia

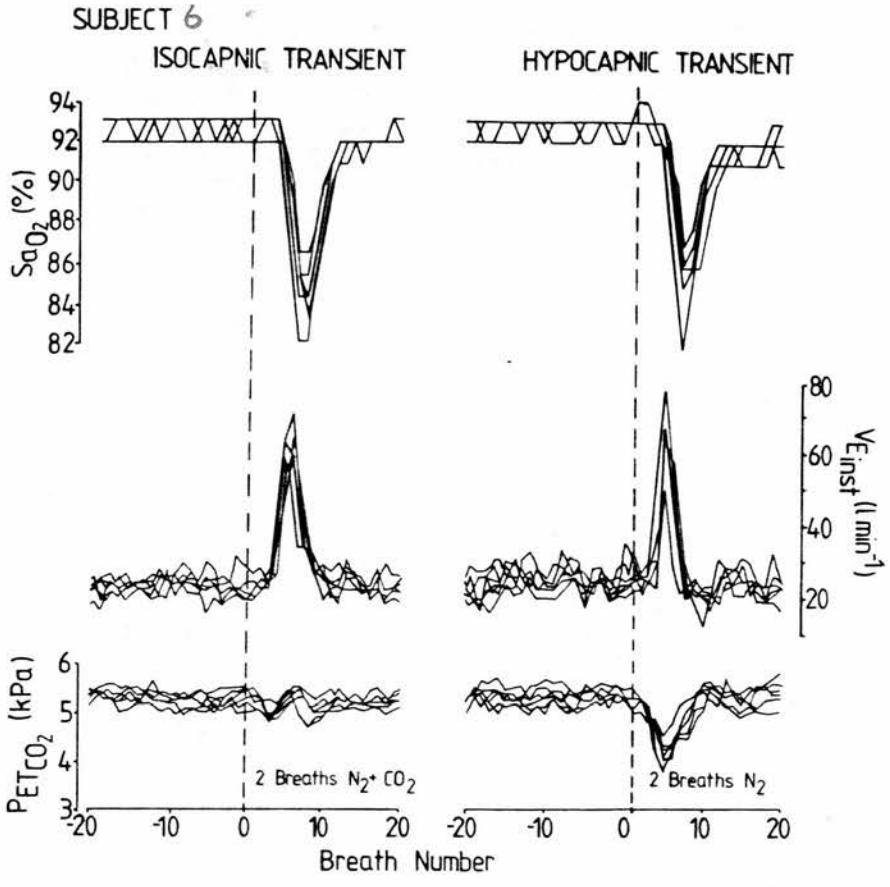
During the ventilatory response to transient hypoxia there was a fall in $P_{ET}CO_2$ (fig 6.1, lower panel). Comparison of the changes in $P_{ET}CO_2$ during hypoxia, when expressed as the mean of all the breaths used in the analysis of the ventilatory response to hypoxia (calculation of the $\dot{V}_E$inst/S_aO_2 slope) showed that during non-isocapnic hypoxia, there was a significant difference between the baseline $P_{ET}CO_2$ and the

table 6.1 : Gas Exchange Variables During Steady-State Exercise.

Subject	$\dot{V}O_2$ ($l min^{-1}$)	$\dot{V}CO_2$ ($l min^{-1}$)	$\dot{V}_E$ ($l min^{-1}$)
1	1.02	0.85	23.07
2	0.87	0.79	24.55
3	0.84	0.82	21.62
6	0.92	0.87	25.50
9	0.98	0.85	23.72
10	0.59	0.49	15.67
11	0.96	0.78	23.50
12	1.04	0.83	24.91
14	0.93	0.90	23.42
17	0.83	0.74	21.78

Ventilation and gas exchange variables expressed as a means of all measurements taken during steady-state exercise.

fig 6.1 : S_aO_2, $\dot{V}_E$inst and $P_{ET}CO_2$ Following Non-Isocapnic and Isocapnic Transient Hypoxia.



Superimposed traces for several episodes of non-isocapnic and isocapnic transient hypoxia in a normal subject (subject number 6). Following both non-isocapnic and isocapnic transient hypoxia, there was a fall in S_aO_2 and an increase in $\dot{V}_E$inst. During the ventilatory response to non-isocapnic hypoxia, there was a fall in $P_{ET}CO_2$ (lower trace, right hand side).

table 6.2 : Lowest Recorded S_aO_2 During Non-Isocapnic and Isocapnic Transient Hypoxia.

Subject	Non-Isocapnic Hypoxia S_aO_2 (%)	Isocapnic Hypoxia S_aO_2 (%)
1	87±2	87±2
2	86±3	85±3
3	87±1	89±1
6	82±2	85±1
9	82±2	82±3
10	77±3	81±3
11	72±3	75±3
12	83±2	83±2
13	89±1	88±1
17	80±4	86±1

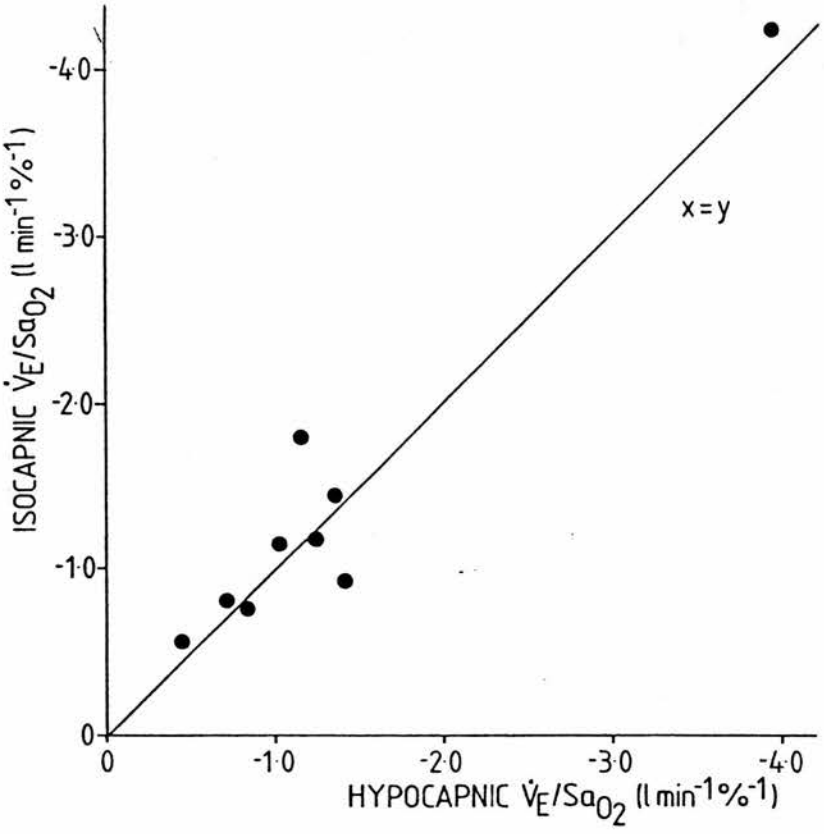
Values are given the mean±SD of the lowest recorded S_aO_2 for pooled episodes of both non-isocapnic and isocapnic transient hypoxia for each subject.

table 6.3 : Time Course of the Ventilatory and $P_{ET}CO_2$ changes Following Transient Hypoxia

	Non Isocapnic Hypoxia		Isocapnic Hypoxia
Subject	Lowest $P_{ET}CO_2$	Peak $\dot{V}_E$inst	Peak $\dot{V}_E$inst
	time (sec)	time (sec)	time (sec)
1	14.21	15.64	13.93
2	10.14	13.75	16.62
3	19.97	18.31	20.25
6	10.86	10.31	10.82
9	16.65	15.44	14.48
10	15.93	15.50	18.55
11	22.06	20.06	13.57
12	18.34	18.00	20.25
13	13.95	15.18	15.87
17	12.02	11.36	13.80

Mean values (± SD) are given for each subject for the time to reach peak $V_E$inst and lowest $P_{ET}CO_2$ following the onset of non-isocapnic hypoxia, and for the time to reach peak $\dot{V}_E$inst following the onset of isocapnic hypoxia.

fig 6.2 : Comparison of Hypoxic Ventilatory Drive During Isocapnic and Non-Isocapnic Transient Hypoxia.



Plot of hypoxic ventilatory drive (expressed as the slope of the $\dot{V}_E$inst/S_aO_2 relationship) measured during isocapnic (y-axis) and non-isocapnic (x-axis) transient hypoxia. Each point represents the results of pooled data in an individual subject. The line is the line of identity

table 6.4 : Hypoxic Ventilatory Drive During Non-Isocapnic and Isocapnic Transient Hypoxia.

	Non-Isocapnic Hypoxia	Isocapnic Hypoxia
Subject	$\dot{V}_E inst/S_aO_2$ ($l min^{-1}\%^{-1}$)	$\dot{V}_E inst/S_aO_2$ ($l min^{-1}\%^{-1}$)
1	-1.15	-1.82
2	-0.72	-0.81
3	-1.36	-1.46
6	-3.96	-4.19
9	-1.41	-0.92
10	-0.81	-0.94
11	-1.26	-1.19
12	-1.15	-1.03
13	-0.58	-0.46
17	-0.85	-0.78

Mean values for the slope of the $\dot{V}_E inst/S_aO_2$ relationship for the pooled responses to non-isocapnic and isocapnic transient hypoxia in each subject.

table 6.5 : Day-to-Day Variability of the Hypoxic Ventilatory Drive Measured by Transient Hypoxia

	Non-Isocapnic Hypoxia $\dot{V}_E$inst/S_aO_2 ($lmin^{-1}\%^{-1}$)			Isocapnic Hypoxia $\dot{V}_E$inst/S_aO_2 ($lmin^{-1}\%^{-1}$)	
Subject	A	B	C	A	D
1	-1.15	-1.17	-1.71	-1.82	-1.93
2	0.72	0.85	0.40	0.81	-0.85
3	-1.36	-0.38	-0.47	-1.46	-0.83
6	-3.96	-4.62	-5.27	-4.19	-4.29
9	-1.41	-1.18	-0.99	-	-
10	-0.81	-1.65	-0.78	-0.94	-0.70

Values are for pooled episodes of transient hypoxia. The two columns marked 'A' contain measurements during non-isocapnic and isocapnic hypoxia made on the same day, columns B and C contain measurements of the $\dot{V}_E$inst/S_aO_2 slope made during non-isocapnic hypoxia on two days in chapter 3 and column D contains additional measurements of the $\dot{V}_E$inst/S_aO_2 slope during isocapnic transient hypoxia made on a separate day.

$P_{ET}CO_2$ during hypoxia ($p<0.01$). There was no significant difference, however, between the baseline $P_{ET}CO_2$ and the mean $P_{ET}CO_2$ during the ventilatory response to isocapnic transient hypoxia (table 6.6).

The difference between the mean baseline $P_{I,}CO_2$ and the mean lowest recorded $P_{ET}CO_2$ during the ventilatory response to transient hypoxia for pooled data (table 6.7) ranged from 0.34 to 1.17kPa during non-isocapnic hypoxia, and 0.15 to 0.63kPa during isocapnic transient hypoxia. The lowest $P_{ET}CO_2$ reached following non-isocapnic transient hypoxia occurred 15.4±4.2seconds (mean±SD) after the onset of hypoxia (table 6.3), coinciding with the highest $\dot{V}_E$inst reached. End-tidal PCO_2 was significantly lower in the 5th, 6th and 7th breaths after the onset of non-isocapnic hypoxia than that of the breath immediately preceding hypoxia ($p<0.05$). Although there was a small drop in $P_{ET}CO_2$ during the ventilatory response to isocapnic transient hypoxia, this did not reach significance.

iii) The Relationship Between Hypoxic Ventilatory Drive and The Fall in $P_{ET}CO_2$.

There was no correlation between the differences in the $\dot{V}_E$inst/S_aO_2 slopes following isocapnic and non-isocapnic hypoxia, and the fall in $P_{ET}CO_2$ when $P_{ET}CO_2$ was expressed as either the mean of all the breaths used for calculation of the $\dot{V}_E$inst/S_aO_2 slope (fig 6.4) or as a mean of the lowest recorded $P_{ET}CO_2$ (fig 6.3). The absolute $\dot{V}_E$inst/S_aO_2 slope during isocapnic transient hypoxia did not correlate either with $P_{ET}CO_2$ expressed as a mean of all breaths used in calculation of the $\dot{V}_E$inst slope (fig 6.5), or as a mean of the lowest recorded $P_{ET}CO_2$ (fig 6.6)

table 6.6 : Baseline $P_{ET}CO_2$ and $P_{ET}CO_2$ During Hypoxia For Non-Isocapnic and Isocapnic Hypoxia.

	Non-Isocapnic Hypoxia		Isocapnic Hypoxia	
	baseline $P_{ET}CO_2$	hypoxic $P_{ET}CO_2$	baseline $P_{ET}CO_2$	hypoxic $P_{ET}CO_2$
Subject	(kPa)	(kPa)	(kPa)	(kPa)
1	6.10±0.05	5.80±0.07	6.08±0.08	5.96±0.05
2	5.41±0.11	5.25±0.06	5.37±0.08	5.36±0.08
3	5.71±0.12	5.67±0.14	5.71±0.13	5.71±0.09
6	5.33±0.12	4.76±0.15	5.32±0.14	5.22±0.22
9	5.40±0.05	5.16±0.05	5.37±0.05	5.32±0.03
10	5.51±0.03	5.22±0.08	5.40±0.03	5.28±0.11
11	5.42±0.14	5.37±0.11	5.42±0.15	5.37±0.09
12	5.32±0.05	5.16±0.05	5.35±0.03	5.18±0.03
13	6.03±0.09	5.93±0.06	6.08±0.05	6.09±0.05
17	5.14±0.13	5.11±0.05	5.14±0.12	5.14±0.05

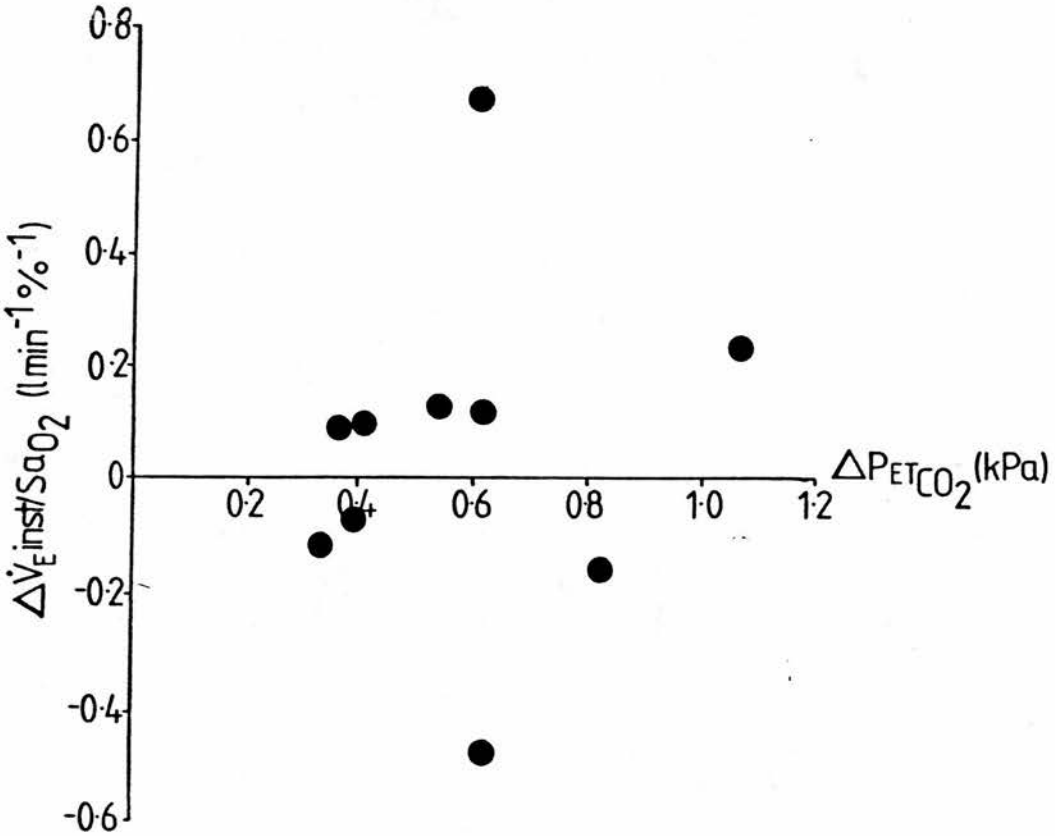
Mean baseline $P_{ET}CO_2$ was calculated from ten breaths before each episode of transient hypoxia for pooled data, and $P_{ET}CO_2$ during hypoxia was calculated as a mean of all breaths used in the analysis of the ventilatory response to transient hypoxia, again for pooled data.

table 6.7 : Difference Between Baseline $P_{ET}CO_2$ and Lowest $P_{ET}CO_2$ During Hypoxia

Subject	Non-Isocapnic Hypoxia $P_{ET}CO_2$ (kPa)	Isocapnic Hypoxia $P_{ET}CO_2$ (kPa)
1	0.61	0.30
2	0.37	0.15
3	0.41	0.18
6	1.17	0.33
9	0.61	0.29
10	0.35	0.29
11	0.82	0.63
12	0.62	0.37
13	0.34	0.18
17	0.40	0.21

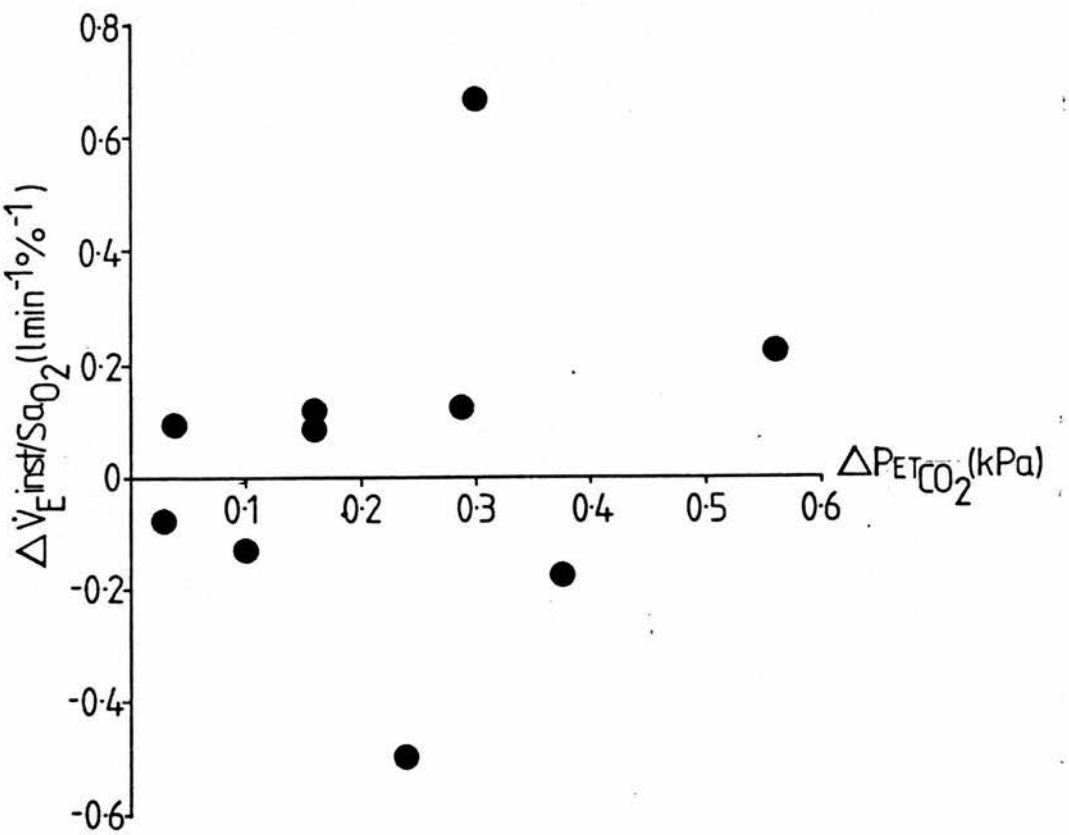
The difference between the mean baseline $P_{ET}CO_2$ and the mean lowest $P_{ET}CO_2$ recorded during hypoxia for the pooled responses to non-isocapnic and isocapnic transient hypoxia.

fig 6.3 : Relationship Between The Difference in $V_E inst/S_aO_2$ Slopes During Isocapnic and Non-Isocapnic Transient Hypoxia, and the Greatest Fall in $P_{ET}CO_2$ During Non Isocapnic Transient Hypoxia.



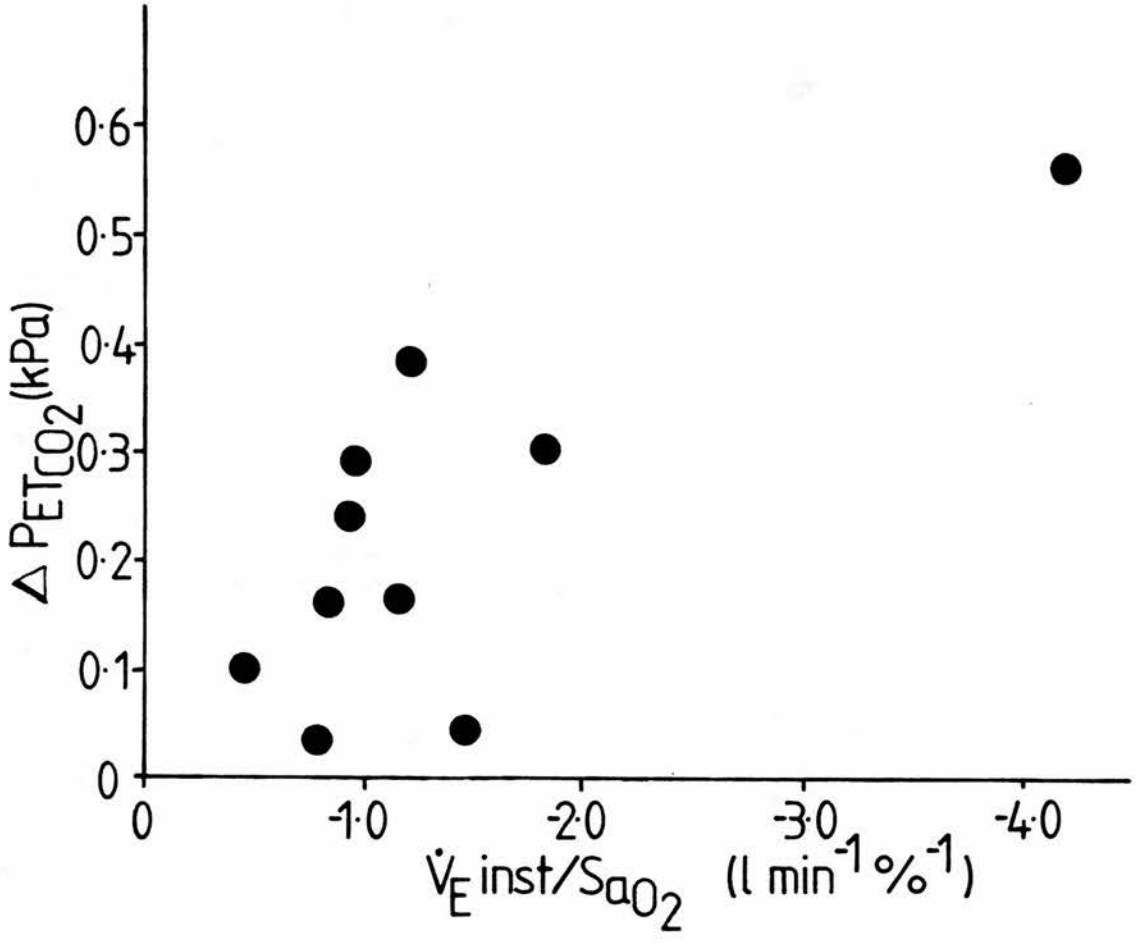
The difference in $\dot{V}_E/S_aO_2$ slopes during isocapnic and non-isocapnic transient hypoxia plotted against the fall in $P_{ET}CO_2$ during non-isocapnic hypoxia expressed as the mean lowest recorded value.

fig 6.4 : Relationship Between the Difference in $\dot{V}_E inst/S_aO_2$ Slopes During Isocapnic and Non-Isocapnic Transient Hypoxia, and the Mean Fall in $P_{ET}CO_2$ During Non-Isocapnic Transient Hypoxia.



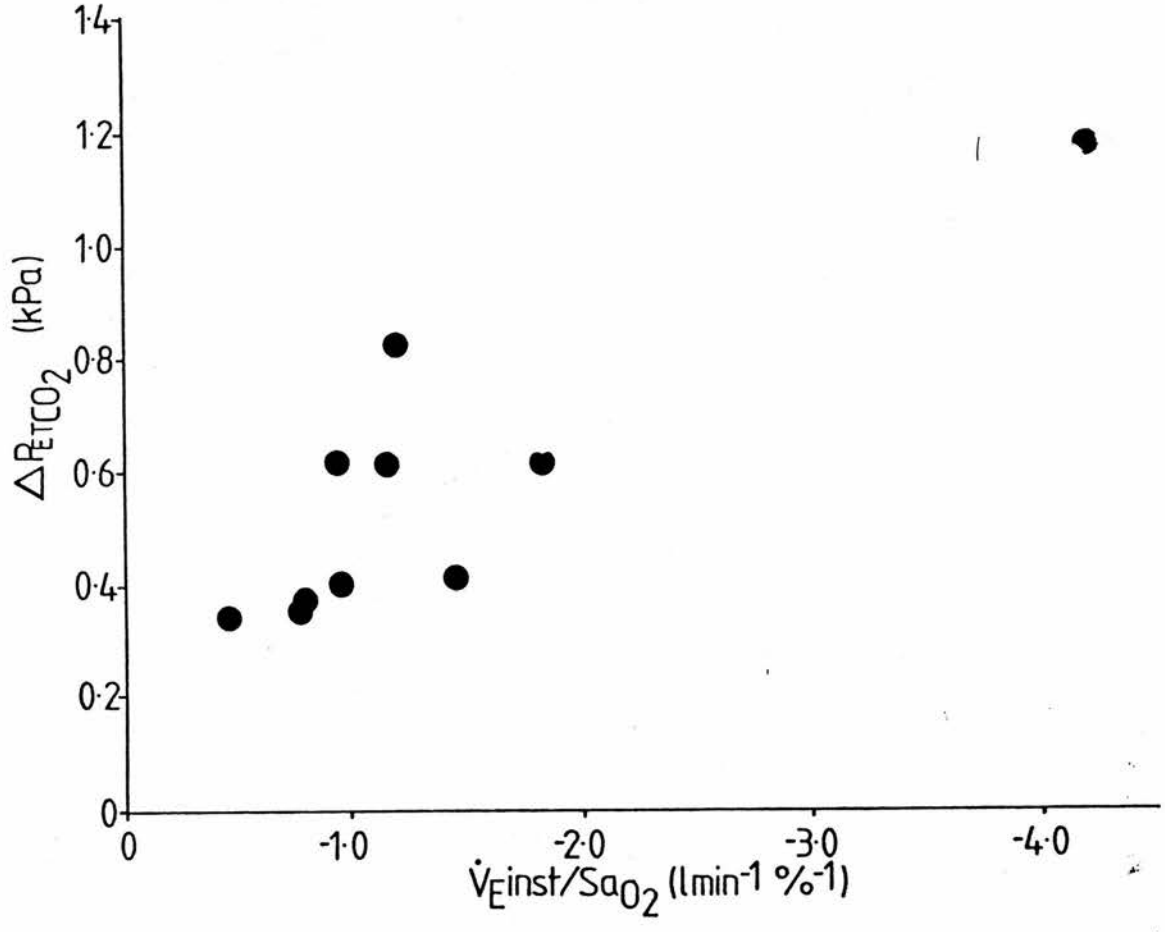
The difference between the $\dot{V}_E inst/S_aO_2$ slopes during isocapnic and non-isocapnic transient hypoxia plotted against the fall in $P_{ET}CO_2$ during non-isocapnic transient hypoxia, expressed as the mean $P_{ET}CO_2$ for all the breaths used in the calculation of the $\dot{V}_E inst/^{S_aO_2}$ slope.

fig 6.6 : Relationship Between The Mean Fall in $P_{ET}CO_2$ During Non-Isocapnic Transient Hypoxia and The $\dot{V}_E inst/S_aO_2$ Slope During Isocapnic Transient Hypoxia



The fall in $P_{ET}CO_2$ (expressed as the mean baseline $P_{ET}CO_2$ minus the mean $P_{ET}CO_2$ for all the breaths used to calculate the $\dot{V}_E inst/S_aO_2$ slope) during non-isocapnic hypoxia plotted against the $\dot{V}_E inst/S_aO_2$ slope during isocapnic hypoxia.

fig 6.6 : Relationship Between the Greatest Fall in $P_{ET}CO_2$ During Non-Isocapnic Hypoxia and the $\dot{V}_E inst/S_aO_2$ Slope During Isocapnic Transient Hypoxia



The greatest fall in $P_{ET}CO_2$ (expressed as the difference between the mean $P_{ET}CO_2$ during the breath immediately preceding the onset of hypoxia for pooled data minus the mean lowest recorded $P_{ET}CO_2$) during non-isocapnic transient hypoxia plotted against the $\dot{V}_E inst/S_aO_2$ slope during isocapnic transient hypoxia

IV DISCUSSION

Following transient hypoxia during which no attempt was made to maintain $P_{ET}CO_2$ (non-isocapnic transient hypoxia) a significant fall in $P_{ET}CO_2$ occurred. During those episodes of transient hypoxia in which CO_2 was added to the inspired gas, a small decrease in $P_{ET}CO_2$ did develop, but this was not statistically significant. There was no significant difference between the hypoxic ventilatory drive expressed as the $\dot{V}_E inst/S_aO_2$ slope during hypoxia during non-isocapnic and isocapnic transient hypoxia for the whole group of subjects studied.

These results agree with those of Calverley et al (1982) who also measured ventilatory responses to non-isocapnic and isocapnic transient hypoxia during exercise, in four male subjects. They found that addition of $P_{ET}CO_2$ as a stimulus variable to the regression equation relating $\dot{V}_E inst$ and $P_{ET}O_2$, which they used to express hypoxic ventilatory drive, did not improve the residual variance in $\dot{V}_E inst$. They therefore concluded that the fall in $P_{ET}CO_2$ which occurred during the ventilatory response to hypoxia did not affect this response, despite the fact that all four subjects were shown to have a hypercapnic ventilatory drive. Furthermore, the observation in this study that the time to reach peak $V_E inst$ was similar in response to isocapnic and non-isocapnic hypoxia is compatible with the findings of Reynolds and Milhorn (1973), who found that although the steady-state ventilatory response to step-change hypoxia was reduced when hypocapnia was allowed to develop, the initial rate of rise of ventilation was not affected by the already developing hypocapnia.

The effect of the hypocapnia on the ventilatory response to transient hypoxia will be determined by three factors, the sensitivity of the carotid chemoreceptors to CO_2, the $P_{ET}CO_2$ threshold of the carotid chemoreceptors and the relationship between $P_{ET}CO_2$ and the actual stimulus, P_aCO_2.

Only small changes in PCO_2 are needed to change the ventilatory response to hypoxia. The sensitivity of the carotid chemoreceptors to changes in P_aCO_2 has been shown to be greatest around the control (normoxic) level during exercise (Cummin et al 1986), an observation which is important in the context of this study, as any changes in $P_{ET}CO_2$ which occur are around the control point. Metias et al (1981)

showed that in normal subjects, alternate breath oscillation in $P_{ET}CO_2$ between normocapnic values and 1.1kPa above caused an increase in ventilation, which suggests that the carotid chemoreceptors are very sensitive, at least to rapid increases in $P_{ET}CO_2$. Grindlay Moore et al found that the ventilatory response to progressive hypoxia was reduced when falls of between 0.2 and 1.7kPa in $PACO_2$ were allowed to occur, and Reynolds and Milhorn (1973) found that the steady-state ventilatory responses to 7,8, and 9% O_2 were reduced if P_ACO_2 was allowed to fall. After ten minutes of hypoxia, P_ACO_2 had fallen by 0.85, 1.1 and 1.5 kPa respectively, however closer inspection of the data revealed that the ventilatory response to steady-state hypoxia was reduced by even smaller falls in P_ACO_2. The plateau level of ventilation was reached within 4-5 minutes after the onset of hypoxia, and was clearly lower when hypocapnia was allowed to develop, although by this time the P_ACO_2 had fallen by only approximately 0.6kPa. Thus falls in $PACO_2$ as low as 0.2kPa have been shown to reduce the ventilatory responses to progressive or steady-state hypoxia. The falls in $P_{ET}CO_2$ during non-isocapnic transient hypoxia in this study, which ranged from 0.3 to 1.2kPa for the lowest recorded $P_{ET}CO_2$ would therefore be expected to affect the ventilatory response. Although the fall in $P_{ET}CO_2$ which occurred during the ventilatory response to non isocapnic transient hypoxia was great enough to affect ventilation, there was no correlation between the difference between the $\dot{V}_E inst/S_aO_2$ slopes during non-isocapnic and isocapnic hypoxia, and the fall in $P_{ET}CO_2$, expressed either as a mean for all breaths during hypoxia or as the mean lowest $P_{ET}CO_2$. This agrees with the findings of Reynolds and Milhorn (1973) and Grindlay Moore et al (1981). Of the five subjects who showed a fall in $P_{ET}CO_2$ of 0.6kPa or more (greatest recorded fall), two actually showed a decrease in the ventilatory response to transient hypoxia when isocapnia was maintained, rather than an increase. This suggests that although the fall in $P_{ET}CO_2$ which occurred during the ventilatory response to transient hypoxia probably was large enough to affect ventilation, other factors affected the ventilatory response. As suggested by Grindlay Moore et al (1981), the reduction in ventilatory response to hypoxia which occurs when hypocapnia is allowed to develop may depend upon the hypercapnic ventilatory drive of the individual rather than the absolute fall in P_ACO_2, which could account for this lack of correlation. As the

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on the ventilatory response to transient hypoxia, since some breaths during which hypocapnia does not occur are included in the calculations. The observation that hypocapnia does not affect the measured ventilatory response to transient hypoxia is, however, compatible with the findings of Reynolds and Milhorn (1973), who found that the initial rate of rise of of the ventilatory response to hypoxia was not affected by the developing hypocapnia. The fall in P_ACO_2 only became important during the steady-state, which suggests that the on-phase of the ventilatory response to hypoxia (which is used in this study to calculate the V_Einst/S_aO_2 slope during transient hypoxia) is unaffected by hypocapnia.

Of the five subjects who showed a fall in $P_{ET}CO_2$ of 0.6kPa or more (greatest recorded fall), two actually showed a decrease in the ventilatory response to transient hypoxia when isocapnia was maintained, rather than an increase. This suggests that although the fall in $P_{ET}CO_2$ which occurred during the ventilatory response to transient hypoxia probably was large enough to affect ventilation, other factors affected the ventilatory response.

One problem with the technique used to maintain isocapnia in this study is that it is difficult to assess isocapnia from $P_{ET}CO_2$. The P_ACO_2 fluctuates throughout the breathing cycle, with the highest level being at the end of expiration as a result of continuous delivery of CO_2 into a decreasing lung volume (DuBois et al 1951). During exercise, this fluctuation results in a positive $P_{ET}CO_2-P_aCO_2$ difference, due to the increased delivery of CO_2 to the lungs (Galdston and Wollack 1947, Jones et al 1966, Wasserman et al 1967, Jones et al 1979). Use of $P_{ET}CO_2$ as an estimation of P_aCO_2 during exercise would therefore result in overestimation. As all measurements of the ventilatory response to hypoxia in this study are made during steady-state exercise, the baseline error in estimation of P_aCO_2 is constant. During hypoxia, the increase in breathing frequency would tend to decrease $P_{ET}CO_2$ in relation to P_aCO_2, and the increase in tidal volume would tend to increase $P_{ET}CO_2$ relative to P_aCO_2 (Jones et al 1979). The effect upon true isocapnia would depend upon the relative contributions of the increase in tidal volume and respiratory frequency to the increase in ventilation during hypoxia, and this may affect the ventilatory responses to hypoxia, as an increase in $P_{ET}CO_2$ relative to P_aCO_2 would result in underestimation of the amount of CO_2 added to the inspired gas, thus

resulting in hypocapnia, and vice versa. This requires further investigation Although in some subjects, the $\dot{V}_E inst/S_aO_2$ slope during isocapnic hypoxia was greater than that during non-isocapnic hypoxia, the difference between the two measurements was not as great as the difference between the ventilatory responses to transient and step-change hypoxia in chapter 3 (for example, in chapter 3, the difference between $\dot{V}_E inst/S_aO_2$ during step-change and transient hypoxia for subject 3 was 2.791 min $^{-1}$ %$^{-1}$ whereas the difference between $\dot{V}_E inst/S_aO_2$ during isocapnic and non isocapnic transient hypoxia in this chapter was 0.101 min^{-1} %$^{-1}$). Furthermore, the range of differences in $\dot{V}_E inst/S_aO_2$ slope between isocapnic and non isocapnic transient hypoxia fall within the day-to-day variability of the ventilatory response to non-isocapnic hypoxia.

Isocapnia may have slightly increased the ventilatory response to transient hypoxia in some subjects. This effect was small, however, and would not account for the difference between ventilatory responses to transient and step-change hypoxia in chapter 3.

CHAPTER 7 : THE EFFECT OF EXERCISE UPON HYPOXIC VENTILATORY DRIVE

I INTRODUCTION

Hypoxic ventilatory drive has long been known to increase during exercise. The first studies which suggested an increase in hypoxic chemosensitivity in human subjects were those of Briggs (1920), Hickham et al (1951), Assmusson and Neilson (1957) and Dejours (1964), all of whom found that the depression of ventilation which occurs upon inhalation of 100% O_2 was greater during exercise than at rest. This may, however, merely reflect the increase in ventilation due to exercise rather than any actual potentiation of the peripheral chemoreceptor-mediated hypoxic drive. Further evidence for an increase in hypoxic chemosensitivity during exercise comes from the studies of Hornbein and Roos (1962). They reported that while the threshold for the ventilatory response to hypoxia was below a P_AO_2 of 60mmHg (8kPa) at rest, during exercise, a reduction in P_AO_2 from 100mmHg (13.3kPa) to 94mmHg (12.5kPa) was sufficient to cause a significant increase in ventilation. No quantitative information concerning the relationship between exercise level and hypoxic ventilatory drive can be derived from their study however. Bhattacharyya et al (1970) found that the ventilatory response to hypoxia was augmented during mild bicycle exercise in normal male subjects, and Masson and Lahiri (1974) also reported that the increment in ventilation which occurred during hypoxia was greater during exercise than at rest in eight normal male subjects, and that the slope of the relationship between V_E and VO_2 was increased by hypoxia despite the development of hypocapnia and respiratory alkalosis. Again, only one level of exercise was used in each of these studies and they therefore do not show the effect on hypoxic ventilatory drive of increasing levels of exercise.

More sophisticated studies were carried out by Weil et al (1972), who investigated the effect of exercise upon hypoxic ventilatory drive measured using progressive isocapnic hypoxia in eight normal subjects at rest and at three levels of exercise (mean $\dot{V}O_2$ of 0.58, 0.78 and 1.02 l min^{-1}). They found that with increasing exercise level, there was an increase in the shape parameter **A** of the V_E/P_aO_2 curve. Similar results were obtained by Martin et al (1978) who also used progressive isocapnic hypoxia to measure hypoxic ventilatory drive at rest and during light (1/3 VO_2max) and heavy (2/3 VO_2max) exercise in 16 male

athletes. Neither Weil et al (1972) nor Martin et al (1978) commented directly upon the quantitative relationship between hypoxic ventilatory drive and VO_2. In a review of hypoxic and hypercapnic ventilatory drives during exercise, Flenley and Warren (1983) recalculated the hypoxic ventilatory drive measured by Weil et al (1972) as the negative slope of the linear V_E/S_aO_2 relationship and found that the hypoxic ventilatory drive increased with increasing exercise level in a curvilinear fashion. In a study of four male subjects, Flenley et al (1979) also showed that transient inhalation of 30% O_2 on a background of hypoxia (inspired O_2 of 14%) resulted in a greater reduction of ventilation at higher levels of exercise, and that the relationship between hypoxic ventilatory drive (expressed as the slope of the $\dot{V}_E/S_aO_2$ relationship during transient relief of hypoxia) was not linear, there being a greater rate of increase of hypoxic ventilatory drive between VO_2s of 1 and 2lmin^{-1} than between resting VO_2 and 1lmin^{-1}. Thus there does not seem to be a simple linear relationship between metabolic rate (expressed in terms of $\dot{V}O_2$) and the hypoxic ventilatory drive.

The mechanism responsible for the augmentation of the ventilatory response to hypoxia during exercise is not clear. There is evidence to suggest that in humans it is mediated by the carotid chemoreceptors, an idea first suggested by Assmusson and Neilson (1958). This is supported by the fact that the ventilatory response to transient hypoxia is increased by exercise (Leitch 1976), as is the ventilatory response to transient relief of hypoxia (Flenley et al 1979), both of which were considered to be measures of peripheral chemoreceptor activity. Lugliani et al (1971) found that the ventilatory response to hypoxia during exercise was abolished in carotid body resected subjects , although the ventilatory response to exercise itself was intact. Although Lugliani et al (1971) did not observe augmentation of the ventilatory response to hypoxia during exercise in subjects with carotid bodies intact, they concluded that the reason for this difference between their results and those of other authors, such as Weil et al (1972) was that other studies had been carried out during conditions of isocapnia or at high enough exercise levels to cause metabolic acidosis, whereas Lugliani et al (1971) had allowed P_aCO_2 to vary with increased ventilation. Their results suggest that the ventilatory response to hypoxia is mediated entirely by the carotid chemoreceptors.

Input from the carotid chemoreceptors is thus necessary in order to elicit any response to hypoxia although this does not necessarily mean that these receptors are the actual site at which potentiation of the hypoxic ventilatory drive occurs. Although the carotid chemoreceptors may initiate the immediate increase in ventilation at the onset of exercise, Lugliani et al (1971) found no difference between steady-state ventilation during exercise in the control subjects and the carotid body resected patients. Other factors such as central regulation, circulating chemical mediation or muscle efferent activity must contribute to the regulation of ventilation during exercise, and these may be responsible for the potentiation of hypoxic ventilatory drive.

Although Biscoe and Purves (1967) found that passive exercise caused a rapid increase in carotid chemoreceptor activity in normoxia in anaesthetised cats, Davies and Lahiri (1973) found that carotid chemoreceptor activity in conscious, anaesthetised or decerebrate cats was not increased by passive hindlimb movement, either during hypoxia or normoxia, despite the fact that ventilation was enhanced by passive hindlimb movement during hypoxia. They concluded that the interaction of exercise and hypoxia as ventilatory stimulants occurs at some central location rather than at the carotid chemoreceptors. Masson and Lahiri (1974) did not find an increase in carotid chemosensitivity to hypoxia or hypercapnia during exercise as assessed from the slopes of the V_E/P_aCO_2 relationships during normoxia and hypoxia, although ventilation was higher during hypoxia than normoxic exercise. This again implicates more central structures in the mediation of this effect. Although Weil et al (1972) found that the proportion of ventilation attributable to the hypoxic stimulus increased with increasing exercise level, this was not found either by Martin et al (1978) at exercise levels ranging to 2/3 VO_2max nor by Stockley (1977) at exercise levels ranging only to 0.64$lmin^{-1}$. Stockley (1977) concluded that since he was using a transient O_2 stimulus, which was considered to be a measure of peripheral chemosensitivity alone, reflex hypoxic ventilatory drive did not increase with exercise, although it did provide a stimulus proportional to the total increase in ventilation.

As mentioned above, several mechanisms have been suggested to explain the possible potentiation of the ventilatory response to hypoxia during exercise, some implicating the carotid chemoreceptors, others

suggesting that central structures may be responsible.One hypothesis, originally suggested by Yamamoto (1960) is that oscillations in P_aCO_2 or pH might be involved. The rate of change of pH/P_aCO_2 increases during exercise in conscious humans (Bond et al 1980) and in anaesthetised dogs (Cross et al 1982) as a result of the increase in cardiac output (Saunders 1980) and during hypoxic exercise this effect would be enhanced, as the cardiac output is even greater for the same VO_2 (Flenley et al 1979). Carotid chemosensitivity to CO_2 has been found to be increased during hypoxia (Fitzgerald and Parks 1971, Lahiri and Delaney 1975) and by some investigators during exercise (Weil et al 1972, Clark et al 1980, Hulsbosch et al 1981,), although others have found that there is no change in the V_E/P_aCO_2 slope during exercise (Assmusson and Neilson 1957, Duffin et al 1980) or even decreases (Miyamura et al 1976). Cummin et al (1986) suggested that although there is controversy over chemoresponsiveness to CO_2, this controversy is caused by alinearity of the ventilatory response when it is measured over the range required to construct a CO_2 response curve, whereas round the control point, chemoresponsiveness <u>is</u> increased during exercise. Their conclusions, however, are based on variations in P_aCO_2 of less than 0.3kPa (2mmHg), which is within the error of measurement (Flenley et al 1967). Masson and Lahiri (1974) and Bhattacharyya et al (1970) suggested that the carotid chemoreceptor P_aCO_2 threshold was reduced during hypoxic exercise. The combination of an increase in the rate of change of the oscillating P_aCO_2 or pH signal with either or both increased carotid sensitivity and decreased ventilatory threshold for P_aCO_2 during hypoxic exercise could result in an increase in the ventilatory response to hypoxia.

During exercise, there is an increase in the plasma levels of adrenaline and noradrenaline (Christensen et al 1979). Noradrenaline is known to potentiate the hypoxic ventilatory response at rest (Cunningham et al 1963). During hypoxic exercise, both ventilation and plasma noradrenaline level are higher than during normoxic exercise (Clancy et al 1975), which suggests that ventilation during hypoxic exercise may be influenced by noradrenaline. Further evidence for the involvement of noradrenaline in the ventilatory response to hypoxic exercise is that inhalation of 100% O_2 lowered both $\dot{V}_E/\dot{V}O_2$ and noradrenaline levels (Hesse et al 1981). As catecholamines exist within the glomus cells of

the carotid bodies (Alfes et al 1977) and are putative neurotransmitters, it is possible that noradrenaline particularly may be at least partly responsible for the potentiation of hypoxic ventilatory drive during exercise. It is also possible that this mechanism is due to an increase in intra-carotid catecholamine level as a result of sympathetic efferent activity, which could be initiated by central input from muscle afferents (Biscoe and Purves 1967), rather than a direct effect of circulating catecholamines on the carotid chemoreceptor activity,

An increase in muscle afferent activity, caused either by a local build-up of anaerobic metabolites in exercising and hypoxic muscle or an increase in muscle stretch receptor activity during exercise, may cause an increase in hypoxic sensitivity. Exercise is known to reduce PO_2 in blood leaving the exercising muscles (Donald et al 1957, Myhre et al 1971). Sergeant et al (1981) found that the increase in ventilation which accompanied leg exercise was maintained if the muscle circulation was occluded painlessly during and after exercise using cuffs around the thigh, which supports the hypothesis that increased muscle afferent activity as a result of a build-up of metabolites may be responsible for the potentiation of the ventilatory response to hypoxia during exercise, particularly since an increase in blood lactate level was observed following release of the cuffs. As carotid chemoreceptor activity was found not to increase during hypoxic exercise in anaesthetised cats (Davies and Lahiri 1973), it is likely that muscle afferents interact centrally rather than causing reflex alteration of peripheral chemosensitivity perhaps via sympathetic efferents.

The potentiation of hypoxic ventilatory drive during exercise is therefore likely to require both the carotid chemoreceptor response to hypoxia and modification of this response by central mechanisms. The mechanism of the potentiation probably involves a combination of factors, which may include input from muscle afferents and circulating catecholamines.

The ventilatory response to transient hypoxia (Leitch 1976) or transient hyperoxia (Flenley et al 1979) was measured during exercise for two reasons. Firstly, because tidal volume is greater during exercise, an adequate stimulus to the carotid chemoreceptors can be achieved within three breaths, without involving the conscious cooperation of the subject or disturbing the breathing pattern , as in

the studies of Kronenberg et al (1972) and Gabel et al (1973), in which the subjects were asked to take vital capacity breath of the test gas mixture. Other studies, in which the subject was not aware of the experimental procedures, used stimuli lasting up to ten breaths at rest (Shaw et al 1982) but this has the disadvantage of being too long to be considered a true transient stimulus, and the ventilatory response may therefore involve central as well as peripheral mechanisms. Secondly, because of the greater increase in ventilation during hypoxic exercise, the signal-to-noise ratio in response to a transient stimulus (i.e. the ratio of the ventilatory response to hypoxia and the baseline ventilation) is increased, making analysis of the results easier.

The exercise level was previously standardised at $1 l min^{-1}$ for all subjects, because the subjects studied using the technique of transient hypoxia during exercise were all male and fairly uniform in size (Leitch 1976, Flenley et al 1979). This level of $\dot{V}O_2$ was therefore achieved at comfortable walking pace, below the anaerobic threshold. In this project, however, subjects of different sex and widely varying in their degree of physical fitness and size were studied. For example, some of the women taking part in the studies were considerably smaller than the men, and were unable to reach a $\dot{V}O_2$ of $1.0 l min^{-1}$ at a comfortable walking pace. These subjects may have exceeded their anaerobic threshold at a $\dot{V}O_2$ of $1.0 l min^{-1}$, whereas taller subjects, who found this level of exercise relatively easy, would not.

When the data of Weil et al (1972) is plotted as the shape parameter A against VO_2 as a percentage of $\dot{V}O_2max$, there is a sudden large increase in A above a $\dot{V}O_2$ of around 33% of VO_2max which suggests that the physical fitness (measured by $\dot{V}O_2max$) of the subject must be taken into account. If the exercise $\dot{V}O_2$ is above this critical point when hypoxic ventilatory drive is measured, small changes in $\dot{V}O_2$ would cause large changes in hypoxic ventilatory drive, i.e. the degree of potentiation of hypoxic ventilatory drive would vary widely, thus comparison of hypoxic ventilatory drive measurements between subjects may not be appropriate at a standard VO_2.

The purpose of the present study is therefore to investigate a) whether the hypoxic ventilatory drive is related to the absolute level of VO_2 or the relative metabolic rate ($\dot{V}O_2$ as a proportion of the $\dot{V}O_2max$) and b) to determine whether a standard exercise level can be

used for all subjects regardless of size, physical fitness, age or other variables, to enable intersubject comparisons of hypoxic ventilatory drive to be measured during exercise.

II METHODS

The subjects were studied on two separate occasions. On one day, hypoxic ventilatory drive was measured using step-change hypoxia at rest and at three levels of exercise. One subject (number 11) was studied at four levels of exercise. On a second day, maximum oxygen consumption ($\dot{V}O_2max$) was measured. To minimise possible effects of physical training and (in females) hormonal influences on ventilatory control, the two study days were within one week except in two subjects. Subject 14 (female) had a one-month interval between study days, but was studied on the same day of her menstrual cycle on both occasions and did not change her exercise habits during this time. Subject 7 (male) had a five week interval between studies, but again did not change his exercise habits during this period.

1 Subjects

Subjects were nine healthy volunteers drawn from laboratory staff (appendix II ; subject numbers 1,6,7,9,10,11,14,15,16). None were taking any medication at the time of the study apart from subject 11, who suffered from mild hayfever, and was taking Terfenadine. Subjects 1, 11 and 16 were undergoing physical training at the time of the study. Lung volumes, TCO and airways resistance are documented in appendix II.

2 Equipment and Methods

i) Measurement of Maximum Oxygen Consumption

Maximal oxygen consumption was measured using a protocol similar to that used by Buchfuhrer et al (1983). The subject walked at a brisk pace (3.5-5mph) on a level treadmill breathing room air through a three-way Hans-Rudolph valve (dead space 100ml) held in place by a head support. After two minutes walking, the incline of the treadmill was increased by 1° every minute, until the subject could no longer continue. Throughout exercise, the expired gas passed from the respiratory valve to an MGC 2001 system (Medical Graphics Corporation) which recorded on-line breath-by-breath data for time, respiratory rate, $\dot{V}_E$, $P_{ET}CO_2$, $P_{ET}O_2$, $\dot{V}CO_2$, $\dot{V}O_2$ and RQ (calculated using commercial software from V_E and expired gas concentrations by the standard algorithms of Beaver et al 1973), and heart rate. The MGC 2001 system tended to overestimate VO_2

measurements by 6% over the range 0.18-1.711 min^{-1} (Hill et al 1988). The MGC 2001 system was calibrated each day. The expired gas volume (calculated by integration of the air flow across a pneumotachograph in the expiratory line) was calibrated using a three litre syringe at flows ranging from 0.2-6.0lsec^{-1}. A volume calibration was accepted if the difference between the calculated value and known syringe volume was less than 1%. The expired gas PCO_2 and PO_2, sampled via a probe positioned close to the mouth were measured by an infrared CO_2 analyser and a zirconium fuel cell O_2 analyser within the MGC 2001 system, which were calibrated every day with room air and a gas mixture containing 16% O_2 and 4% CO_2 (BOC, analysed by gas-liquid chromatography). The phase delay (i.e. the time between measurement of volume by the pneumotachograph and measurement of expired gas concentrations by the analysers due to the analyser delay time and the time taken for the expired gas sample to pass along the tubing to the analysers) was only considered acceptable if it was within 0.5 seconds, since any time longer than this could indicate blockage of the sample line or technical problems within the analysers.

ii) Measurement of Hypoxic Ventilatory Drive

Equipment used was as described for step-change hypoxia in chapter two (fig 2.1) using the five-way Hans-Rudolph valve. The levels of exercise at which hypoxic ventilatory drive was measured ranged between rest and the fastest speed at which each individual could comfortably walk for at least half an hour (the approximate time required to measure hypoxic ventilatory drive). Hypoxic ventilatory drive was always measured first at rest with the subject seated comfortable in an armchair, and then at the various exercise levels in random order. The subjects rested for 15 minutes between each level of exercise.

At rest and at each level of exercise the subjects initially breathed room air until steady state conditions were established (i.e. two consecutive measurements of VO_2 taken after seven minutes within 100ml). For the rest measurements, an abrupt onset, sustained fall in S_aO_2 to about 90% was produced by changing the inspired gas to 1% O_2 for two breaths followed by a change to 12% O_2 for three minutes. The subjects then breathed room air for five minutes after which an abrupt

onset, sustained fall in S_aO_2 to about 80% was produced by changing the inspired gas to 1% O_2 for two breaths followed by a change to 10% O_2 for three minutes. During exercise, similar falls in S_aO_2 were achieved by changing from room air to 1% O_2 for one breath followed by three minutes of 15% inspired O_2 for the first period of hypoxia, and by changing to 1% O_2 for two breaths followed by three minutes 12% O_2 for the second period of hypoxia. All changes in inspired gas were made during expiration.

3 Analysis and Statistics

Analysis

i) Maximum Oxygen Consumption

The software of the MGC 2001 system eliminated on-line, breaths which did not meet certain criteria ($0.2 < RQ < 2.0$, $\dot{V}O_2 > 0$ $lmin^{-1}$, $\dot{V}CO_2 > 0$ $lmin^{-1}$). Oxygen consumption for all remaining breaths was averaged over each 30 second period of exercise. The VO_2 was considered to reach a plateau if the last four consecutive 30-second averages were within 100ml. The $\dot{V}O_2max$ was calculated as the average $\dot{V}O_2$ in the last minute of exercise. As the maximum $\dot{V}O_2$ reached is equal to the VO_2max in normal subjects, even in those who do not reach a $\dot{V}O_2$ plateau (Wasserman et al 1987), $\dot{V}O_2max$ was calculated as the mean $\dot{V}O_2$ in the last minute of exercise in all subjects.

ii) Hypoxic Ventilatory Drive

The method of analysis is described in detail in chapter 2. Gas exchange and ventilation measurements are expressed as means of all measurements taken during steady-state exercise. The data from both episodes of hypoxia was pooled for calculation of hypoxic ventilatory drive, which was expressed as the negative $\dot{V}_E/S_aO_2$ slope at rest and each level of exercise.

The mean baseline $P_{ET}CO_2$ was calculated as the mean of 20 breaths before each episode of hypoxia, and that during hypoxia as the mean of all the breaths used in the analysis of the hypoxic ventilatory drive.

Statistics

Friedmans analysis of variance with Scheffés test of significance was used to compare baseline $P_{ET}CO_2$ at rest and at the different levels

of exercise, $P_{ET}CO_2$ during hypoxia at rest and each level of exercise, and hypoxic ventilatory drive at the various levels of VO_2.

Correlations between variables were calculated using least squares linear regression.

III RESULTS

1 Maximum Oxygen Consumption

The duration of the maximum exercise test ranged from eleven to twenty-one minutes, all subjects continuing until they were exhausted. In all subjects except numbers six and nine, $\dot{V}O_2$ reached a plateau towards the end of the exercise period i.e. the last four 30-second average $\dot{V}O_2$ measurements of the exercise period were within 100ml. VO_2max ranged from 2.00lmin^{-1} to 4.00lmin^{-1} (32.5-54.1mlmin^{-1}kg^{-1} table 7.1).

2 The Effect of Exercise

i) Baseline Measurements

Only one subject (number eleven) completed measurements at four levels of exercise. The results obtained at the highest level of exercise ($\dot{V}O_2$ 1.14lmin^{-1}) are given in tables 7.2-5 and figs 7.2-4 but are not used for comparisons between subjects.

In all the subjects, $\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$ increased with increasing exercise level (table 7.2). The mean±SD for resting $\dot{V}O_2$ was 0.17±0.05 l min^{-1}, (range 0.09 to 0.24lmin^{-1}, 4.2-8.55 of $\dot{V}O2max$). At the highest level, $\dot{V}O_2$ was between 0.9-1.1 lmin^{-1} in all 4 men but in only one woman. In the remaining 4 women, $\dot{V}O_2$ was between 0.7-0.8 l min^{-1} at the highest level of exercise. The mean values for VO_2 at the three levels of exercise were : level 1, 0.51±0.09l min^{-1},(range 0.40-0.67 l min^{-1} 14.8-22.6% $\dot{V}O_2max$), level 2, 0.67±0.10 l min^{-1} (range 0.53-0.87 l min^{-1}, 17.0-29.4% $\dot{V}O_2max$), level 3, 0.91±0.15 l min^{-1} (range 0.71-1.04 l min^{-1}, 23.0-36.5% of $\dot{V}O_2max$).

The respiratory quotient was less than 1.0 in all subjects at all exercise levels except subject 15, in whom it was slightly above 1.0 at the two highest exercise levels (1.02 and 1.03 at exercise levels 2 and 3 respectively).

Baseline $P_{ET}CO_2$ was not significantly different for rest and the three levels of exercise (table 7.3). Isocapnia was maintained throughout hypoxia (standard deviation ranging from 0.07 to 0.21kPa), and there were no significant differences between the mean $P_{ET}CO_2$ during hypoxia at rest and the three levels of exercise.

table 7.1 : Maximum Oxygen Consumption

Subject	$\dot{V}O_2$max ($l min^{-1}$)	($ml min^{-1} kg^{-1}$)
1	3.62	50.9
6	2.06	32.5
7	3.12	51.1
9	4.00	50.0
10	2.38	41.0
11	3.68	54.1
14	2.15	37.7
15	2.00	35.6
16	2.70	48.2

Oxygen consumption measured as a mean during the last minute of a maximal treadmill exercise test, and expressed as the absolute $\dot{V}O_2$ in $l min^{-1}$ and as $ml min^{-1}$ per kg body weight.

table 7.2 : Ventilation and Gas Exchange Variables At Rest and During Steady State Exercise

Subject	Exercise Level	$\dot{V}O_2$ ($l\,min^{-1}$)	$\dot{V}O_2$ (% of Max)	$\dot{V}CO_2$ ($l\,min^{-1}$)	$\dot{V}_E$ ($l\,min^{-1}$)	RQ
1	rest	0.17	5.2	0.17	6.96	0.90
	1	0.58	16.0	0.47	14.66	0.81
	2	0.81	22.4	0.70	21.17	0.86
	3	0.96	26.5	0.84	22.90	0.88
6	rest	0.20	6.8	0.18	7.22	0.89
	1	0.67	22.6	0.54	18.29	0.81
	2	0.87	29.4	0.73	23.05	0.84
	3	1.03	34.8	0.95	29.10	0.92
7	rest	0.17	5.4	0.13	6.22	0.79
	1	0.50	16.0	0.48	16.29	0.95
	2	0.58	18.5	0.53	16.32	0.92
	3	0.91	29.2	0.82	24.35	0.90
9	rest	0.20	5.0	0.19	6.40	0.89
	1	0.59	14.8	0.54	16.19	0.87
	2	0.68	17.0	0.78	18.65	0.91
	3	0.92	23.0	0.96	25.80	0.91
10	rest	0.15	6.3	0.12	4.89	0.80
11	rest	0.24	6.5	0.19	6.01	0.79
	1	0.55	14.9	0.52	15.28	0.95
	2	0.71	19.3	0.65	17.00	0.91
	3	1.04	28.3	0.90	24.53	0.79
	4	1.14	31.0	1.08	28.29	0.94
14	rest	0.09	4.2	0.09	3.74	0.97
	1	0.47	21.8	0.42	13.20	0.91
	2	0.53	24.7	0.46	14.38	0.88
	3	0.77	35.8	0.70	19.08	0.92
15	rest	0.17	8.5	0.14	6.23	0.86
	1	0.40	20.0	0.39	11.79	0.98
	2	0.58	29.0	0.59	16.98	1.02
	3	0.73	36.5	0.75	19.95	1.03
16	rest	0.18	6.6	0.16	5.10	0.79
	1	0.45	16.7	0.36	12.40	0.81

table 7.3 : Baseline $P_{ET}CO_2$ and $P_{ET}CO_2$ During Hypoxia

Subject	Exercise Level	Baseline $P_{ET}CO_2$ (kPa)	Hypoxic $P_{ET}CO_2$ (kPa)				
1	rest	5.46±0.15	5.37±0.12	11	rest	5.72±0.13	5.59±0.11
	1	5.58±0.13	5.51±0.10		1	5.60±0.13	5.63±0.13
	2	5.64±0.12	5.62±0.14		2	5.71±0.12	5.52±0.09
	3	5.75±0.15	5.75±0.14		3	5.64±0.17	5.60±0.15
6	rest	4.99±0.07	4.93±0.09		4	5.36±0.24	5.41±0.17
	1	5.01±0.12	5.07±0.15	14	rest	5.38±0.17	5.37±0.13
	2	5.09±0.11	5.10±0.13		1	5.33±0.18	5.29±0.13
	3	5.07±0.10	5.16±0.19		2	5.36±0.11	5.30±0.12
7	rest	6.11±0.11	6.03±0.13		3	5.63±0.14	5.56±0.18
	1	5.44±0.12	5.48±0.13	15	rest	5.18±0.21	5.22±0.17
	2	5.57±0.19	5.65±0.13		1	5.46±0.09	5.52±0.20
	3	5.49±0.12	5.52±0.15		2	5.43+0.16	5.40±0.09
9	rest	5.48±0.10	5.53±0.07		3	5.50±0.15	5.42±0.18
	1	5.43±0.28	5.49+0.17	16	rest	5.52±0.09	5.45±0.19
	2	5.60±0.19	5.64±0.15		1	5.45±0.15	5.39±0.19
	3	5.55±0.22	5.66±0.15		2	5.40±0.13	5.43±0.14
10	rest	5.31±0.13	5.32±0.11		3	5.59±0.13	5.54±0.21

ii) Hypoxic Ventilatory Drive

There was no significant difference between the lowest S_aO_2 reached during inhalation of 12% O_2 at each level of exercise and 10% O_2 at rest (table 7.4).

At rest, $\dot{V}_E inst/S_aO_2$ varied from +0.02 to 1.85 l min^{-1} $\%^{-1}$ (table 7.5). Resting $\dot{V}_E inst/S_aO_2$ did not correlate with either body surface area (fig 7.1, upper panel) or body weight (fig 7.1, lower panel), so hypoxic ventilatory drive was expressed as the absolute $\dot{V}_E inst/S_aO_2$ slope, rather than per m^2 body surface area or per kg body weight. At rest, $\dot{V}_E inst/S_aO_2$ did not correlate with either $\dot{V}O_2$ (fig 7.2, upper panel) or $\dot{V}O_2/\dot{V}O_2max$ (fig 7.2 lower panel)

In all nine subjects, the $\dot{V}_E inst/S_aO_2$ slope tended to increase with increasing $\dot{V}O_2$ (fig 7.3, table 7.5). For the whole group, the increase in slope was significant ($p<0.01$) at exercise levels 2 and 3 when compared to the $\dot{V}_E inst/S_aO_2$ slope at rest.

At a given exercise level, the values of $\dot{V}O_2$ varied between individuals (table 7.2). The $\dot{V}_E inst/S_aO_2$ relationship was therefore compared at a $\dot{V}O_2$ ranging from 0.70 to 0.92 l min^{-1} (exercise level 2 for subjects 1,6 and 11, exercise level 3 for subjects 7,9,10,14,15,and 16). There was a wide degree of variability in the extent of the potentiation of hypoxic ventilatory drive measured at an absolute $\dot{V}O_2$ of between 0.70 and 0.92 l min^{-1}, with the percentage increase from the rest value varying from 153 to 494%. The $\dot{V}_E inst/S_aO_2$ relationship measured in this range of $\dot{V}O_2$ did not correlate with absolute $\dot{V}O_2$, $\dot{V}O_2$ per kg body weight, $\dot{V}O_2/\dot{V}O_2max$ or resting $\dot{V}_E inst/S_aO_2$ slope. It did, however, correlate with $\dot{V}O_2max$ (fig 7.4). The degree of potentiation of hypoxic ventilatory drive at a $\dot{V}O_2$ of 0.70-0.92 l min^{-1} expressed as the $\dot{V}_E inst/S_aO_2$ slope was calculated as the difference in slopes measured at rest and exercise at this level of $\dot{V}O_2$ per l min^{-1} $\dot{V}O_2$ (i.e. the slope of the line joining the the values obtained at rest and during exercise in fig. 7.5). Potentiation of hypoxic ventilatory drive expressed in this manner tended to decrease with increasing $\dot{V}O_2max$ per kg body weight (fig 7:6), although this was only a weak correlation with $0.02>p>0.01$ and $r=-0.78$.

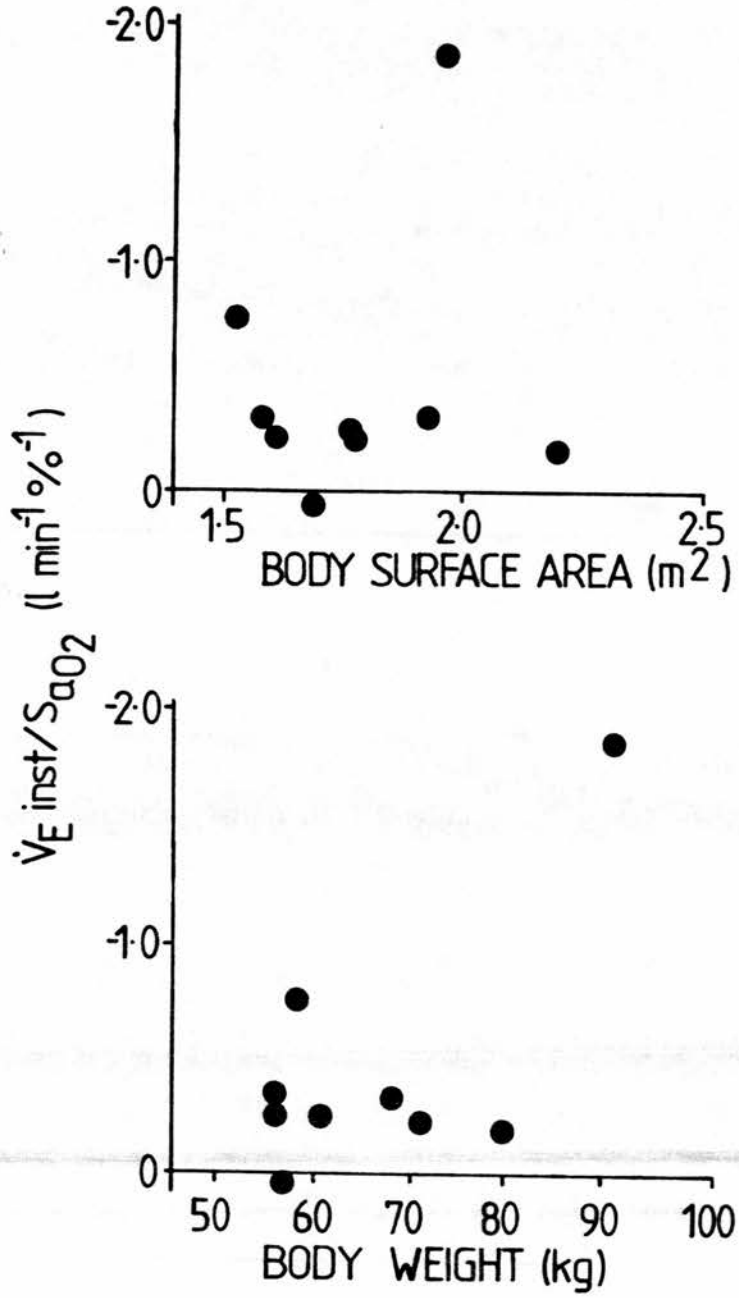
To determine whether the relative intensity of the hypoxic ventilatory drive between subjects was influenced by by increasing $\dot{V}O_2$,

table 7.4 : Lowest S_aO_2 During Hypoxia

	Exercise Level				
Subject	Rest	1	2	3	4
	S_aO_2 (%)	S_aO_2 (%)	S_aO_2 (%)	S_aO_2 (%)	S_aO_2 (%)
1	83	84	84	81	-
6	84	89	87	85	-
7	84	84	83	80	-
9	83	82	82	83	-
10	87	89	87	85	-
11	82	89	85	81	87
14	82	78	82	77	-
15	82	87	87	81	-
16	81	83	84	77	-

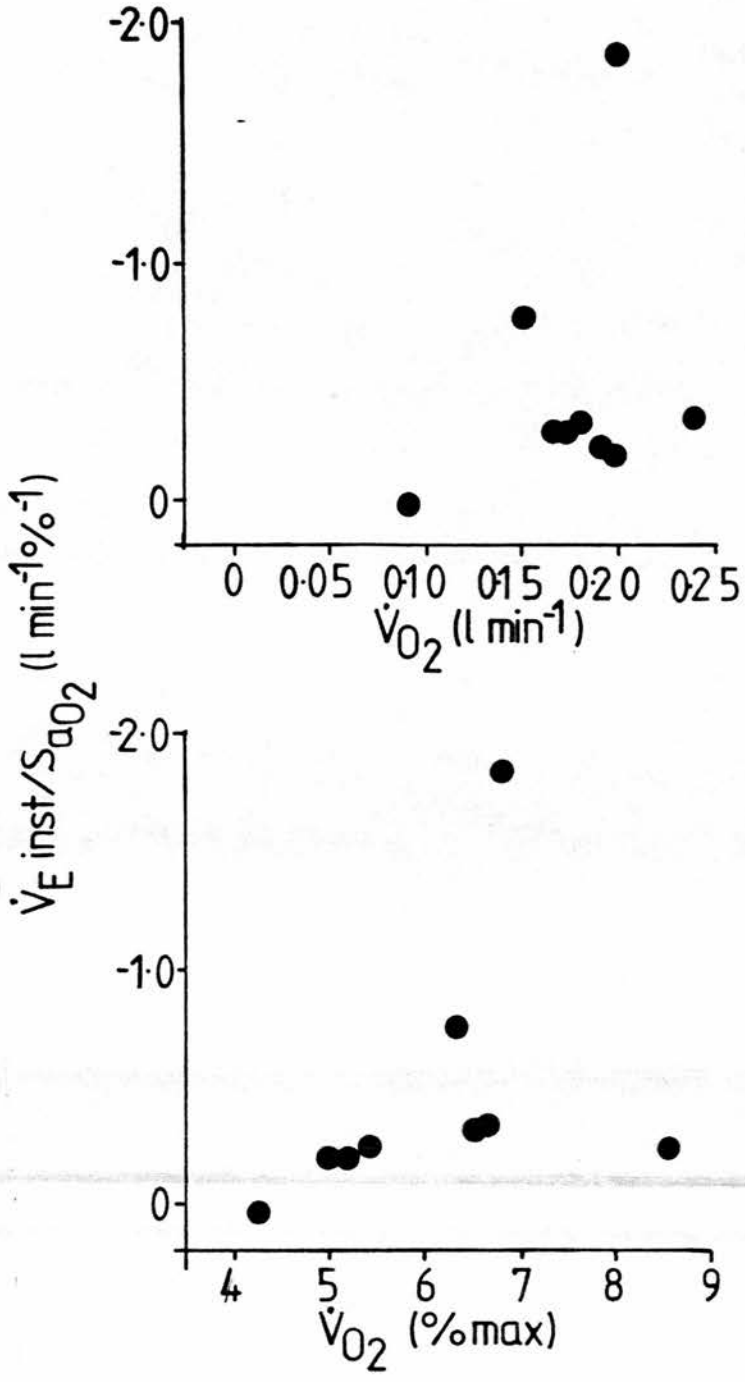
Lowest S_aO_2 reached during inhalation of 10% O_2 (at rest) or 12% O_2 (during exercise) for three minutes. Exercise levels are arranged in order of increasing $\dot{V}O_2$

fig 7.1 : Relationship Between $\dot{V}_E inst/S_aO_2$ at Rest and Body Surface Area and Body Weight



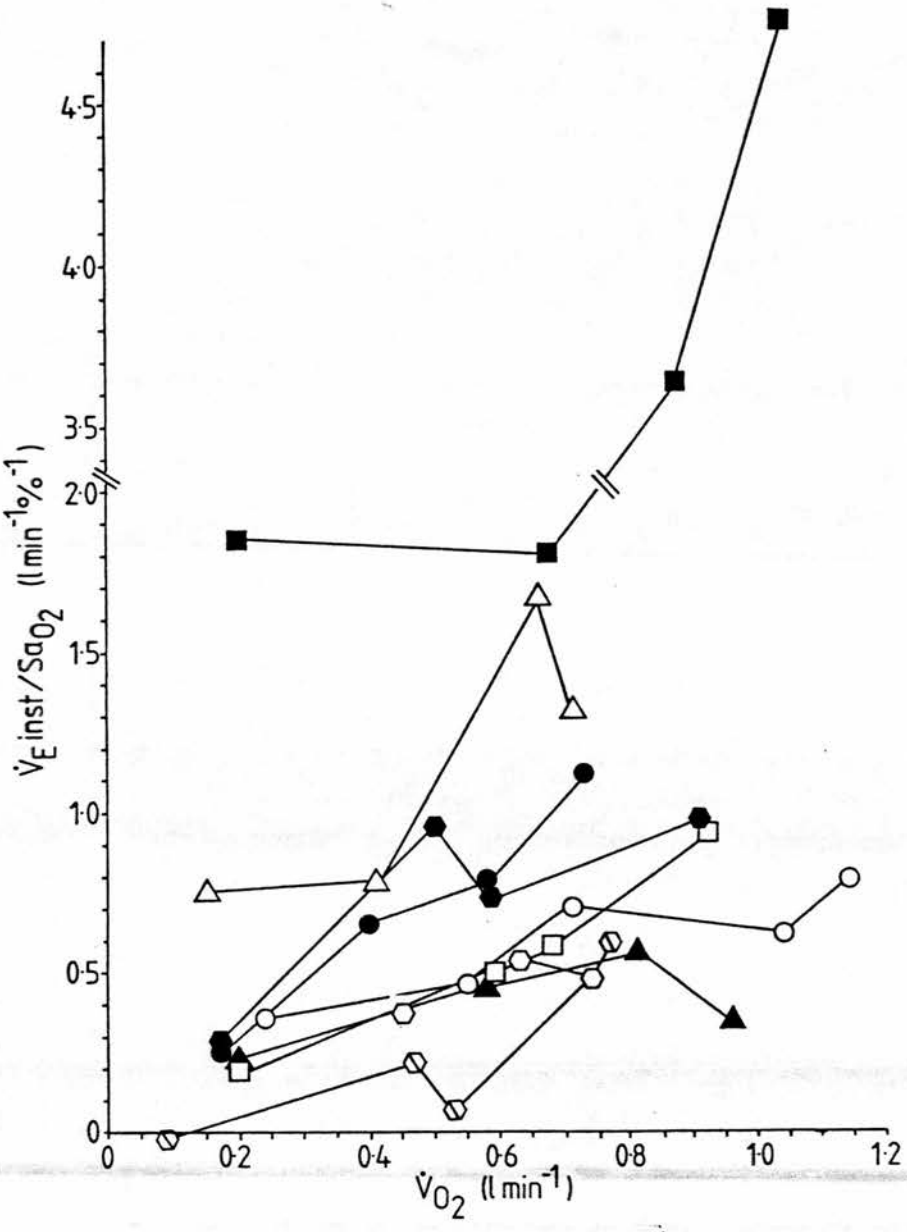
There was no correlation between the $\dot{V}_E inst$ slope at rest and either body surface area (upper panel) or body weight (lower panel)

fig 7.2 : Relationship Between $\dot{V}_E inst/S_aO_2$ Measured at Rest and Absolute $\dot{V}O_2$ and $\dot{V}O_2/\dot{V}O_2 max$.



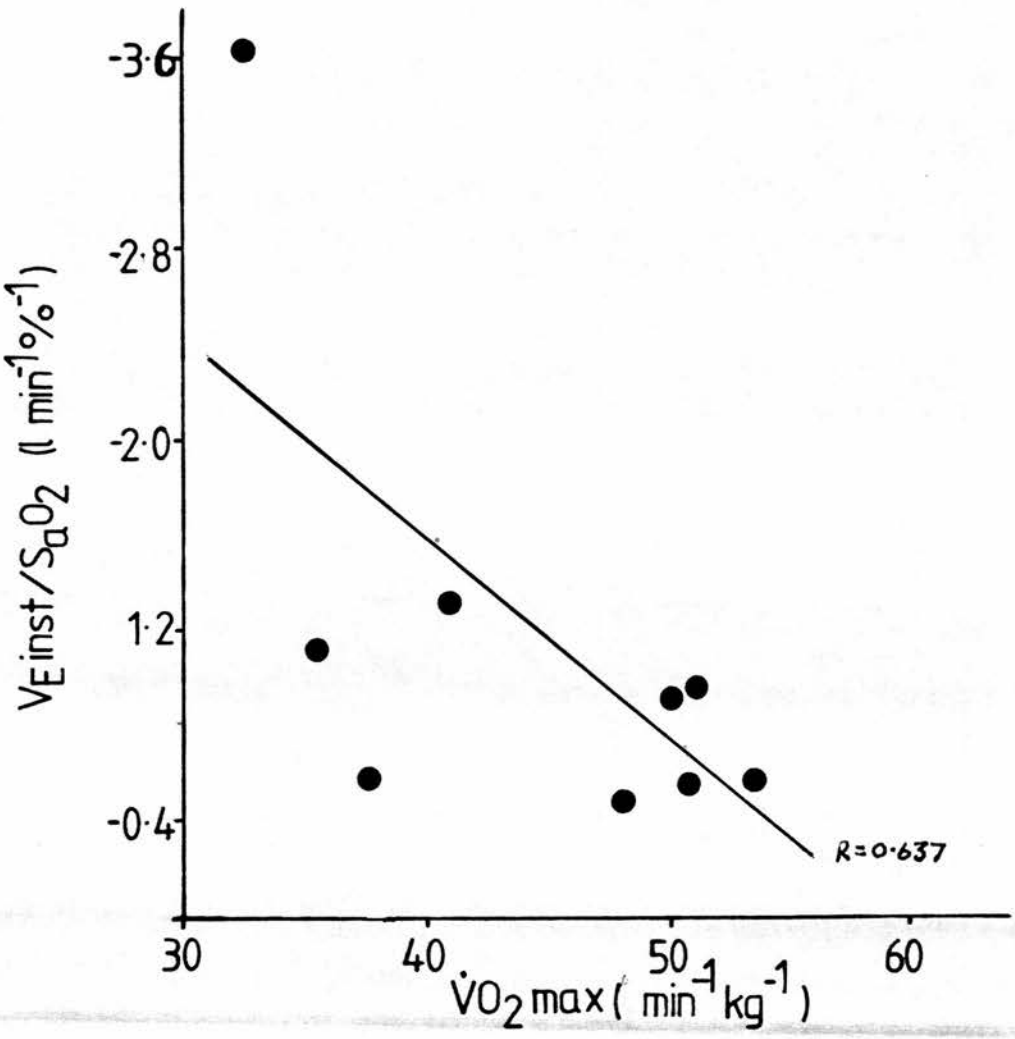
There was no correlation between the $\dot{V}_E inst/S_aO_2$ slope measured at rest and either absolute $\dot{V}O_2$ at rest (upper panel) or $\dot{V}O_2$ as a percentage of $\dot{V}O_2 max$ (lower panel)

fig 7.3 : $\dot{V}_E$inst/S_aO_2 at Different Exercise Levels



Hypoxic ventilatory drive expressed as the $\dot{V}_E$inst/S_aO_2 slope increased with increasing exercise level. Subjects are represented thus : subject number 1 (▲), 6 (■), 7 (⬟), 9 (□), 10 (△), 11 (○), 14 (◇), 15 (●), and 16 (⬡).

fig 7.4 : Relationship Between the $\dot{V}_E inst/S_aO_2$ Slope and $\dot{V}O_2 max$



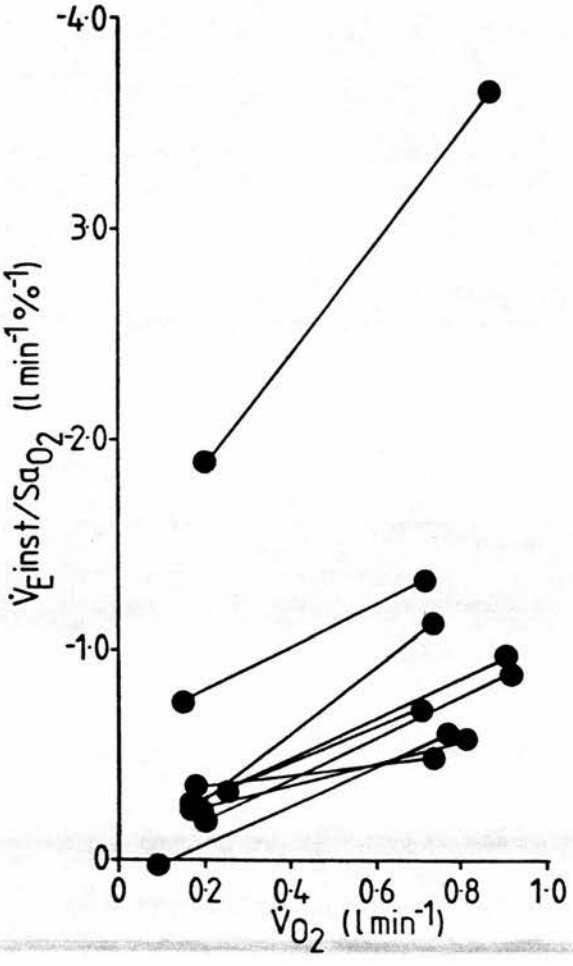
The $\dot{V}_E inst/S_aO_2$ slope measured during exercise at $\dot{V}O_2$ from 0.7 to 0.92 l min^{-1} is plotted against $\dot{V}O_2 max$

table 7.5 : $\dot{V}_E inst/S_aO_2$ Slopes at Rest and During Steady-State Exercise.

	$\dot{V}_E inst/S_aO_2$ ($l min^{-1} \%^{-1}$)				
	Rest	Level 1	Level 2	Level 3	Level 4
Subject					
1	0.23	-0.45	-0.56	-0.35	-
6	-1.85	-1.70	-3.63	-4.66	-
7	-0.26	-0.96	-0.73	-0.96	-
9	-0.19	-0.49	-0.57	-0.94	-
10	0.75	-0.77	-1.57	-1.32	-
11	-0.33	-0.46	-0.70	-0.62	-0.79
14	-0.02	-0.22	-0.06	-0.59	-
15	-0.25	-0.65	-0.79	-1.12	-
16	-0.32	-0.37	-0.53	-0.49	-

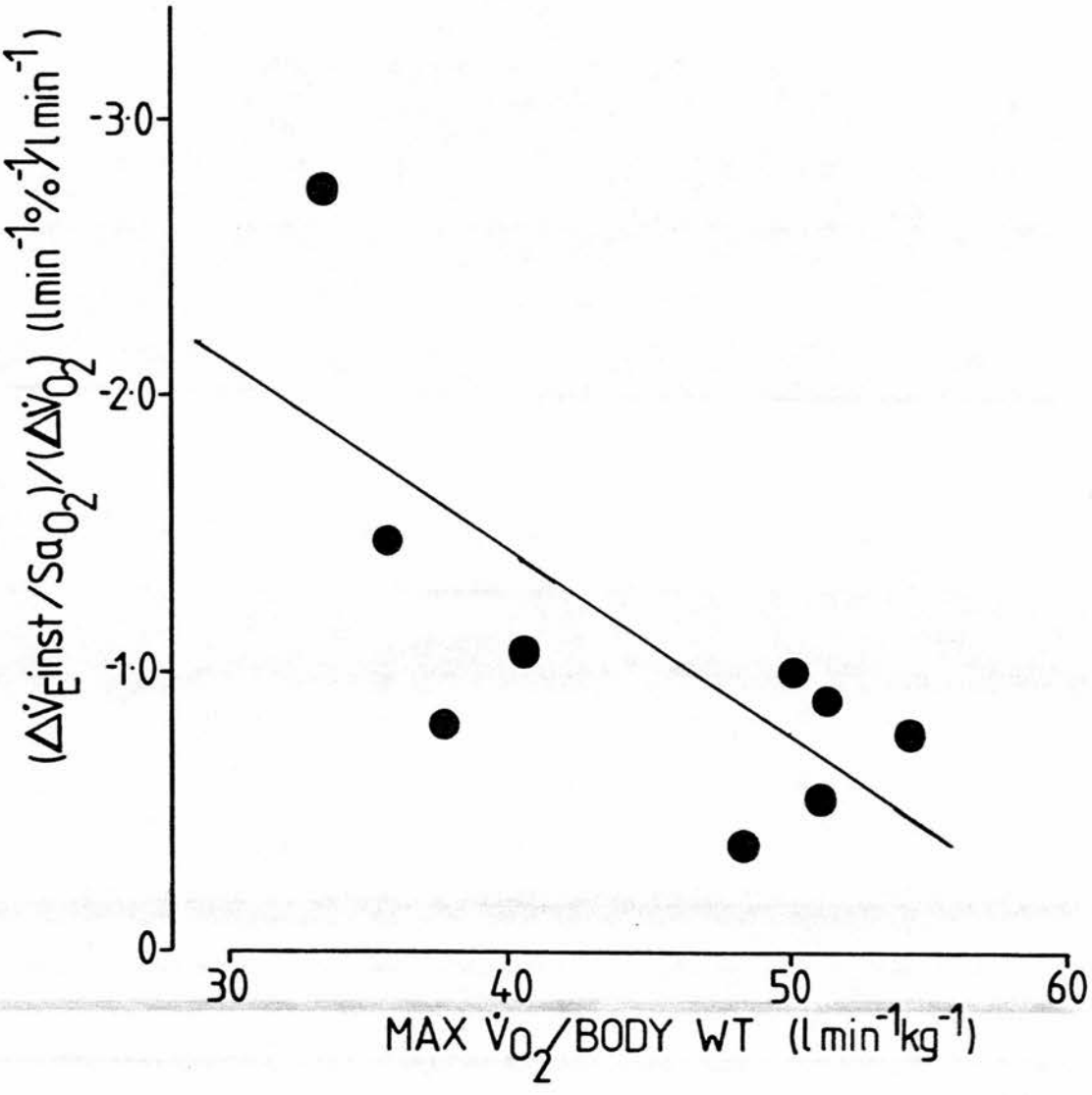
Hypoxic ventilatory drive expressed as the slope of the $\dot{V}_E inst/S_aO_2$ relationship at rest and at three levels of steady-state exercise, the exercise levels arranged in order of increasing $\dot{V}O_2$.

fig 7.5 : $\dot{V}_E$inst/S_aO_2 Slope at Rest and at $\dot{V}O_2$ 0.70-0.92



There was a wide variation in the increase in $\dot{V}_E$inst/S_aO_2 slope between rest and a $\dot{V}O_2$ of 0.70-0.92 l min^{-1}

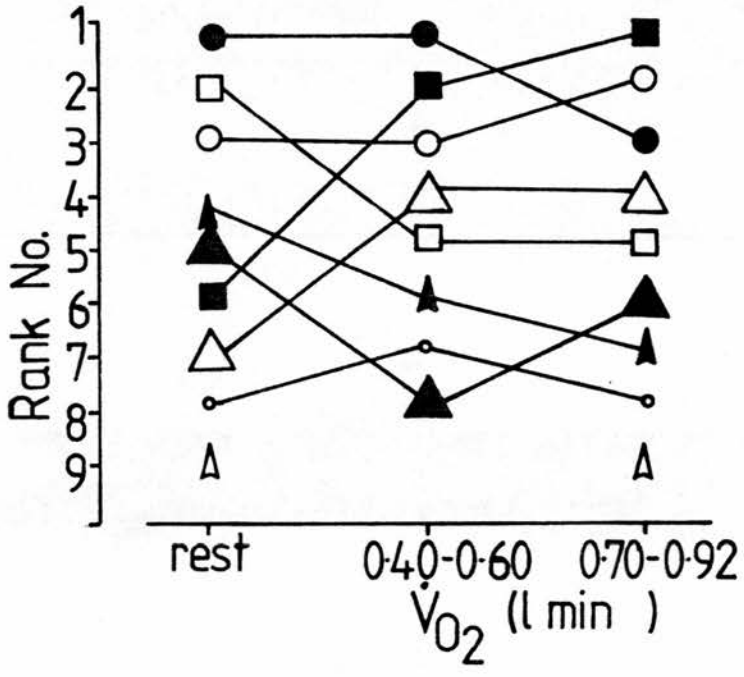
fig 7.6 : Relationship Between Potentiation of the $\dot{V}_E inst/S_aO_2$ Slope and $\dot{V}O_2 max/kg$



The change in $\dot{V}_E inst/S_aO_2$ slope per unit change in $\dot{V}O_2$ between rest and exercise ($\dot{V}O_2$ 0.70-0.92 l min^{-1}) plotted against $\dot{V}O_2 max/kg$ body weight. There is a weak correlation, with $0.02>p>0.01$ and $r=-0.78$

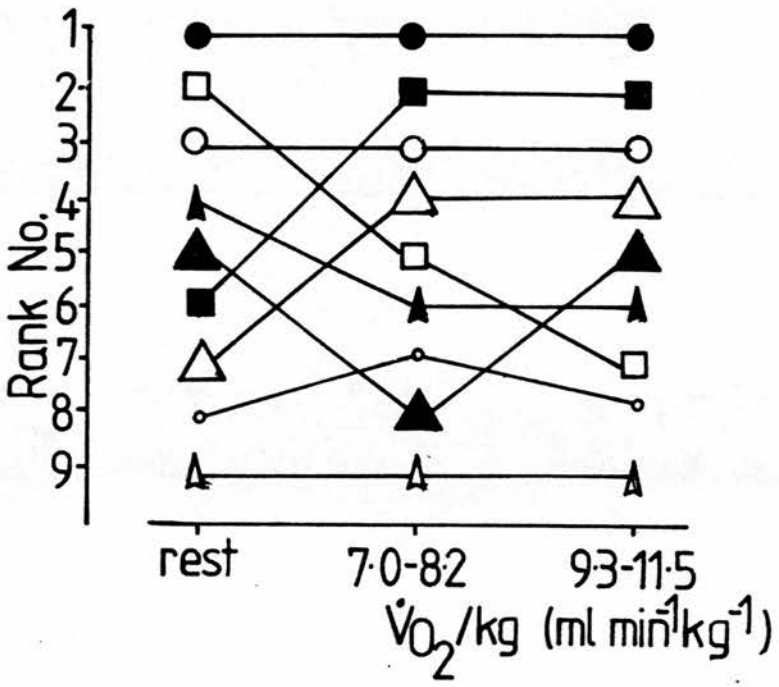
subjects were ranked in ascending order of intensity of hypoxic ventilatory drive. Because of the variation of absolute levels of $\dot{V}O_2$ at the 3 levels of exercise, the intensity of hypoxic ventilatory drive was compared at rest and two selected ranges of $\dot{V}O_2$ (0.4-0.6 l min^{-1} and 0.71-0.92l min^{-1}) and $\dot{V}O_2$/kg (7.0-8.2 and 9.3-11.5 ml min^{-1} kg^{-1}). Ranking of the $V_E inst/S_aO_2$ slope using the absolute level of $\dot{V}O_2$ resulted in some variability of ranking order in all subjects (fig. 7.7). Use of $\dot{V}O_2$/kg resulted in more consistent ranking orders, however, (fig 7.8), with 4 subjects (numbers 1,6, 10 and 14) showing little or no change in ranking order at the 3 levels of $\dot{V}O_2$. Other subjects varied in ranking order, however these subjects all tended to have similar hypoxic ventilatory drives (table 7.5)

fig 7.7 : Ranking of the $\dot{V}_E$inst/S_aO_2 Slope in Increasing Order Using Absolute $\dot{V}O_2$



When subjects are arranged into two groups according to absolute $\dot{V}O_2$ (rest and $\dot{V}O_2$ 0.4–0.6 and 0.70–0.93 l min^{-1}) there is variability in the ranking order of the intensity of hypoxic ventilatory drive.

fig 7.8 : Ranking of the $\dot{V}_E$inst/S_aO_2 Slope in Increasing Order Using $\dot{V}O_2$ per kg Body Weight



When subjects are grouped according to $\dot{V}O_2$/kg (rest and 7.0-8.2 and 9.3-11.5 ml min^{-1} kg^{-1}) there is much less variability in ranking order than when grouped according to absolute $\dot{V}O_2$

IV DISCUSSION

Hypoxic ventilatory drive, expressed as the negative slope of the $\dot{V}_E inst/S_aO_2$ curve, was greater during exercise than at rest, and rose with increasing exercise. The effect of exercise upon hypoxic ventilatory drive was variable between individuals. At the level of exercise at which hypoxic ventilatory drive is usually measured ($\dot{V}O_2$ approximately 0.70-0.92 l min^{-1}), the percentage increase in $\dot{V}_E inst/S_aO_2$ slope from the rest value varied from 153-494 %. At rest, there was no correlation between the $\dot{V}_E inst\ S_aO_2$ slope and body weight or surface area, absolute $\dot{V}O_2$ or $\dot{V}O_2$ as a percentage of $\dot{V}O_2max$, or $\dot{V}O_2max$/kg body weight. During exercise, ($\dot{V}O_2$ 0.70-0.92 l min^{-1}) there was no correlation between the $\dot{V}_E inst$ slope and absolute $\dot{V}O_2$, $\dot{V}O_2$ as a percentage of $\dot{V}O_2max$, $\dot{V}O_2$ per kg body weight or resting $\dot{V}_E inst/S_aO_2$ slope. The $\dot{V}_E inst/S_aO_2$ slope did show a weak negative correlation with $\dot{V}O_2max$ and $\dot{V}O_2max\ kg^{-1}$, however. There was also a negative correlation between the degree of potentiation of the hypoxic ventilatory drive expressed as the difference in $\dot{V}_E inst/S_aO_2$ slope between rest and exercise per 1 min^{-1} $\dot{V}O_2$ and $\dot{V}O_2max$/kg.

The increase in hypoxic ventilatory drive with exercise confirms the findings of many previous studies, the most recent being those of Weil et al (1972) and Martin et al (1978). At higher levels of $\dot{V}O_2$ there was a wider range of $\dot{V}_E inst/S_aO_2$ values than at rest (+0.02 to -1.85 l $min^{-1}\%^{-1}$ at rest and -0.49 to 3.63 l $min^{-1}\%^{-1}$ at $\dot{V}O_2$ range 0.70-0.92), which agrees with Weil et al (1972) who found a range (expressed as the shape parameter A) during exercise at a mean $\dot{V}O_2$ of 0.781 min^{-1} (similar to that used in these experiments) of 192.7-596.5 compared to a range of 68.7-184.7 at rest. Although there was a wider range of $\dot{V}_E inst/S_aO_2$ slopes at higher $\dot{V}O_2$ values, within the group of subjects, an individual tended to be ranked at the same level of intensity of hypoxic ventilatory drive. In particular, those at either end of the range were consistently highest or lowest, especially if $\dot{V}O_2$ was expressed per kg. Ranking was not always consistent, however, and there may be interaction with some other factor which varies between individuals.

The fact that there was no correlation between hypoxic ventilatory drive at rest and $\dot{V}O_2max$ agrees with the finding of Hirshman et al (1975), who also found no correlation in non-athletes at rest, but does not agree with the studies of Byrne-Quinn et al (1971) or Weiser et al

(1975) who both found a correlation at rest in a group consisting of both athletes and non-athletes. This discrepancy may be because Byrne-Quinn et al (1978) and Weiser et al (1975) combined the results of athletes and non-athletes for statistical analysis, which may be inappropriate, since in both these studies athletes were shown to have a lower hypoxic ventilatory drive than non athletes. Since it is not known whether the intensity of the hypoxic ventilatory drive in athletes is inherited or acquired as a result of training (see chapter 8), the two populations should probably be considered separately. Indeed, if the data for non-athletes only from the study of Byrne-Quinn et al (1978) is examined, there is in fact only a very poor degree of correlation between the resting hypoxic ventilatory drive and $\dot{V}O_2max$. The correlation of $\dot{V}O_2max$ with hypoxic ventilatory drive measured during exercise in this study has not previously been documented.

The $\dot{V}O_2max$ is considered to be a measure of fitness (Astrand and Rohdahl 1977). The negative correlation between $\dot{V}O_2max$ and the degree of increase in hypoxic ventilatory drive with exercise suggests that the level of fitness of an individual may partly determine the hypoxic ventilatory drive during exercise. Although not previously reported, the plot of the $\dot{V}_Einst/S_aO_2$ slope against $\dot{V}O_2$ (Flenley and Warren 1983) suggests that for similar increases in $\dot{V}O_2$, the increase in the negative $\dot{V}_Einst/S_aO_2$ slope was less for the athletes of Martin et al (1978) than for the non-athletes of Weil et al (1972).

There are several possible sources of error in this study, which could affect the results. Firstly, errors could be introduced in the measurement of $\dot{V}O_2max$ as a result of lack of motivation of the subjects could which could result in an underestimation of the $\dot{V}O_2max$. In the present study, all the subjects were recruited from laboratory staff and were highly motivated. Furthermore, the $\dot{V}O_2$ of only two subjects failed to reach a plateau (subject numbers 6 and 9). Subject 6 was the only obese subject studied, and reported that the exercise was limited by breathing rather than leg muscle fatigue. Subject 9 had a previous history of mild exercise induced asthma. However both were highly motivated andit was therefore concluded that the greatest $\dot{V}O_2$ measured was in fact their maximum effort. It was therefore unlikely that $\dot{V}O_2max$ was underestimated as a result of lack of motivation.

The duration of the hypoxic ventilatory drive study could also have affected the measurements, as the total time taken to measure hypoxic ventilatory drive at rest and three levels of exercise was at least two hours, possible resulting in fatigue. To minimise this problem, subjects were rested for at least fifteen minutes between each level of exercise, and the different workloads were given in random order to avoid fatigue affecting one workload more than another. Metabolic acidosis associated with sever exercise could also affect hypoxic ventilatory drive by acting at both the carotid chemoreceptors and the central chemoreceptors. As the VO_2 at the highest workload was less than 50% of VO_2max for all the subjects and the respiratory exchange ratio was less than 1.0 for all subjects except subject 15 (in whom it rose to 1.03 and 1,.04 at the two higher levels of exercise) it is unlikely anaerobic threshold was exceeded (Buchfuhrer et al 1983) during the steady-state exercise and therefore metabolic acidosis is not likely to have contributed to the variability of the hypoxic ventilatory drive.

The evidence in the present study suggests that physical fitness may partly determine the degree of potentiation of hypoxic ventilatory drive during exercise. Potentiation of the hypoxic ventilatory drive may be mediated by the carotid chemoreceptors. One possible mechanism is differences in the rate of change of the oscillating arterial PCO_2 or pH. Athletes are known to have a lower V_E and heart rate for a given VO_2 (Astrand and Rohdahl 1970), therefore the rate of increase of the oscillating P_aCO_2 or pH, during exercise (Band et al 1980, Cross et al 1982) may be less the fitter the individual, resulting in a smaller stimulus to ventilation via the carotid chemoreceptors and thus a smaller degree of potentiation of the hypoxic ventilatory drive. Alternatively, the level of circulating noradrenaline (a putative carotid body neurotransmitter which is known to potentiate hypoxic ventilatory drive ; Cunningham et al 1963) released during hypoxic exercise (Clancy et al 1975) may be higher in unfit subjects and therefore cause a greater carotid body mediated potentiation of the hypoxic ventilatory drive in the less fit. Lahiri et al (1975) however, showed that there was no increase in carotid body chemoreceptor discharge caused by exercise during hypoxia. Other sites of action must therefore be considered.

Another possibility is that the input from muscle afferents to central structures (Davies and Lahiri 1973) varies with physical fitness. There is evidence that a build up of metabolites such as potassium or lactate in exercising muscle causes an increase in ventilation during normoxic exercise probably as a result of muscle afferent activation (Tibes et al 1977, Sergeant et al 1981). If there was a smaller stimulus to ventilation from the muscle afferents in physically fitter individuals during exercise, this could result in a smaller degree of potentiation of the ventilatory response to hypoxia. Tibes et al (1977) found that during bicycle exercise, the increase in venous potassium concentration increased more in untrained than in trained individuals. As venous potassium concentration was also found to mirror the increase in ventilation both in athletes and non-athletes, it is possible that the difference in potassium levels in the two groups of subjects may be partly responsible for the lower ventilatory response to exercise (similar VO_2 in athletes and non-athletes) in the athletes. There may therefore be a smaller stimulus to ventilation from the muscle afferents in athletes than in non-athletes.

Finally, differences in cortical influence upon the control of ventilation may result in intersubject variability of the potentiation of hypoxic ventilatory drive during exercise. Evidence for an "effort-dependant" component to ventilation during exercise comes from the studies of Galbo et al (1987) who found that ventilation following partial curarisation was greater than before curarisation for the same VO_2 during handgrip exercise, and that the effort required to perform this exercise (assessed by Borg scale) at the same level of VO_2 was increased after partial curarisation. The cortically mediated "effort dependent" component to the increase in ventilation during exercise may be less in a physically fit than an unfit individual for a given level of VO_2, and this, coupled with a smaller carotid chemoreceptor mediated hypoxic ventilatory drive may result in a lower overall ventilatory response to hypoxia in fit subjects.

It is not possible to draw any conclusions about the mechanisms responsible for the variation in potentiation of hypoxic ventilatory drive with physical fitness from the present study, however, if the potentiation is mediated by central mechanisms, then this raises the

question of whether the negative $V_E inst/S_aO_2$ slope is a valid measure of the peripherally mediated hypoxic ventilatory drive during exercise.

The present study demonstrates that comparison of hypoxic ventilatory drive in different subjects at the same absolute $\dot{V}O_2$ (or the same $\dot{V}O_2$/kg body weight) during exercise, as has been previously done is a valid procedure for use in epidemiological studies, as subjects with high or low hypoxic ventilatory drives can be identified. Other factors such as fitness, possibly acting through mechanisms such as muscle afferents, circulating noradrenaline, or indirectly via an "effort dependent" effect may influence the ventilatory response to hypoxia during exercise. The absolute value of $\dot{V}_E inst/S_aO_2$ must therefore be treated with caution.

CHAPTER 8 : THE EFFECT OF PHYSICAL TRAINING ON HYPOXIC VENTILATORY DRIVE.

I INTRODUCTION

The idea that physical fitness might affect hypoxic ventilatory drive was first suggested by Briggs (1920), and later supported by Cotes and Meade (1959), who found that the depression of ventilation resulting from inhalation of 100% O_2 was smaller in physically conditioned subjects than in untrained individuals both at rest and during exercise. Further evidence was provided by Byrne Quinn et al (1971) who measured the ventilatory response to progressive isocapnic hypoxia at rest and to steady-state non isocapnic hypoxia during exercise in athletes and non-athletes. They found that the hypoxic ventilatory drive in athletes averaged 35% that of the non-athletes at rest, although there was no significant difference between hypoxic ventilatory responses during exercise. During exercise, however, the absolute level of ventilation in the non-athletes was greater than that in the athletes at the same $\dot{V}O_2$. The non athletes may therefore have developed a greater degree of hypocapnia during hypoxia on exercise then the athletes, which would cause more limitation of the ventilatory response to hypoxia (Reynolds and Milhorn 1973) and account for the failure to demonstrate a difference in hypoxic ventilatory drive between the two groups during exercise. This idea is supported by the fact that Byrne-Quinn et al (1971) also found that the ventilatory response to hypercapnia was smaller in athletes than in non-athletes, which would result in less O_2/CO_2 interaction at the carotid chemoreceptors and less limitation of the ventilatory response to hypoxia by hypocapnia in the athletes.

Scoggin et al (1978) also found that the ventilatory response to progressive isocapnic hypoxia in endurance athletes at rest was significantly smaller than that of non-athletes, and other authors have reported unusually low hypoxic ventilatory responses in physically fit individuals. Leitch et al (1975) showed that the ventilatory responses to transient hypoxia during exercise ($\dot{V}O_2$ 0.95lmin^{-1}) in identical twin athletes was unusually low compared to their previously defined normal range (Flenley et al 1973).

Not all authors agree, however, that athletes do have significantly lower ventilatory responses to hypoxia than non-athletes. Godfrey et

al (1971) found that the slightly smaller ventilatory response to progressive isocapnic hypoxia in athletes as compared to untrained athletes at rest was not significant, and this agrees with a more recent study by Mahler et al (1982), in which the ventilatory response to progressive isocapnia at rest in athletes was found to be smaller, but not significantly so, than in non-athletes.

The discrepancy between the findings in different studies may be due to the type of athlete studied, as there is may be a difference in the ventilatory responses of endurance (for example, marathon runners) and non-endurance (for example, sprinters) athletes. Rebuck and Read (1971) found that the ventilatory responses of endurance athletes to CO_2 were consistently lower than those of sprinters, and since hypoxic and hypercapnic ventilatory drives are known to show a positive correlation in both athletes and non-athletes (Byrne-Quinn et al 1971, Rebuck et al 1973), this may also mean that hypoxic ventilatory drive is lower in endurance athletes. Martin et al (1978) found that although the difference between the hypercapnic ventilatory responses of endurance and non-endurance athletes was not significant, endurance athletes did tend to have lower ventilatory responses to hypoxia than non-endurance athletes. If endurance athletes have low hypoxic ventilatory responses, but sprinters do not, comparison of sprinters and endurance athletes with untrained subjects would give different outcomes. Godfrey et al (1971) did not specify which events the athletes in their study took part in. Their failure to observe a significant difference between the hypoxic ventilatory responses of athletes and non-athletes might have been because they were studying sprint athletes. Scoggin et al (1978) found that long distance runners had lower hypoxic ventilatory drives than non-athletes. Byrne-Quinn et al (1971) also reported that athletes had lower ventilatory responses to hypoxia than non-athletes. Although the type of athlete was not specified, at least some of them were cross country skiers (i.e. endurance athletes). This hypothesis is not, however, supported by the studies of Mahler et al (1982) which showed no significant difference between hypoxic ventilatory responses in endurance athletes and non-athletes.

It has not been established whether the low hypoxic ventilatory responses observed in athletes is a result of physical training or is an inherited characteristic which predisposes individuals to become athletic.

The similarity of the ventilatory responses to hypoxia in the identical twin athletes studies by Leitch et al (1975) would suggest an inherited component to the low response to hypoxia. Scoggin et al (1978) found that the non athletic relatives of long-distance runners had similarly small responses to hypoxia to the runners, which again were significantly lower than those of non-related non-athletes. Further evidence for an inherited low hypoxic drive comes from studies of the families of patients with respiratory failure (Hudgel et al 1974, Moore et al 1976, Kawakami et al 1982, Fleetham et al 1984). There is very little documented evidence that physical training results in a reduction in hypoxic ventilatory drive. The only direct evidence is from the studies of Cotes and Meade (1959), who observed a diminution of the decrease in ventilation observed on switching the inspired gas from air to 100% O_2 during exercise, after physical training, which may indicate a decrease in the hypoxic ventilatory drive. Several authors (Byrne-Quinn et al 1971, Weiser et al 1975) have noted a negative correlation between resting hypoxic ventilatory drive and $\dot{V}O_2max$ in athletes and non-athletes, and this agrees with the findings in the previous chapter during exercise in laboratory staff. This was not seen, however, by Hirshman et al (1975). A correlation between hypoxic ventilatory drive and $\dot{V}O_2max$ might suggest that physically fitter individuals, with a higher $\dot{V}O_2max$ (Astrand and Rohdahl 1977), have a lower hypoxic ventilatory drive, and that training might therefore decrease hypoxic ventilatory drive. Alternatively, people with an inherited low hypoxic ventilatory drive may be predisposed to become athletes, and training merely increases $\dot{V}O_2max$ completely independently of the hypoxic ventilatory drive, rather than one being the cause of the other. Furthermore, it has been shown that $\dot{V}O_2max$ can only be increased by 10-20% by physical training (Astrand and Rohdahl 1977), so any effect of training on hypoxic ventilatory drive will be limited if it is related to changes in $\dot{V}O_2max$.

The mechanism of the low hypoxic ventilatory response in athletes (whether inherited or the result of training) is important when determining the normal range of hypoxic ventilatory drive in the general population and when considering the implications of a low drive in the pathogenesis of respiratory disease such as the "blue and bloated" form of chronic obstructive lung disease (Flenley et al 1970). If it is an

inherited characteristic, than variation in hypoxic ventilatory drive probably represents true variation in the carotid body mediated response, but if training has a significant effect on hypoxic ventilatory drive, a low drive could simply represent a very physically active individual. Also, day-to-day comparisons of hypoxic ventilatory drive would be affected in individuals whose level of physical fitness was not constant.

The aim of the present study is therefore to determine whether physical training has any significant effect upon hypoxic ventilatory drive in normal subjects.

II METHODS

Hypoxic ventilatory drive was measured using step-change hypoxia in new Army recruits, before, and after 12 and 18-20 weeks of the Army physical training course. In the first 12 weeks training involved 3-6 mile runs and marches, team sports such as football, rugby and basketball and upper body exercises. In the next 6-8 weeks the emphasis was on endurance training, with longer runs of 6-7 miles carrying full packs of approximately 40lb weight. Physical fitness was assessed on each occasion by measuring $\dot{V}O_2$max and oxygen pulse ($\dot{V}O_2$/HR) during steady-state exercise within two days of the hypoxic ventilatory drive measurement. Both hypoxic ventilatory drive and $\dot{V}O_2$max were measured at the same time of day for each individual. Resting ventilation and breath-holding time were also measured.

1 Subjects

Subjects were sixteen male Army recruits (Appendix III : subject numbers 18-33). All were healthy, had no history of respiratory or cardiovascular disease and were taking no medication at the time of the study Half of the subjects were smokers, half non-smokers, carboxyhaemaglobin measurements along with measurements of volumes, TCO and airways resistance before and after 12 and 18-20 weeks training are tabulated in Appendix III. The subjects were not fasting.

2Equipment and Methods

i) Measurement of Resting V_E, Gas Exchange and Breath-Holding Time

Breath-holding time was initially measured by asking the subject to hold his breath for as long as possible while timing himself with a stopwatch. Measurements were made on the same day, but always before the $\dot{V}O_2$max measurement.

For measurement of resting gas exchange variables, The subject sat in a comfortable armchair, breathing room air through the three-way Hans-Rudolph valve for ten minutes, while respiratory variables were recorded breath-by-breath using the MGC 2001 system, as described in chapter seven.

ii) Measurement of Maximum Oxygen Consumption.

Maximum oxygen consumption was measured as described in chapter seven, using the method suggested by Buchfuhrer et al (1983). The subject walked at a brisk pace (3.5-5mph) on a level treadmill breathing room air through a three-way Hans-Rudolph valve. After two minutes, the incline of the treadmill was raised by 1° every minute, until the subject was exhausted. Respiratory variables were recorded breath-by-breath using the MGC 2001 system as described in chapter seven. .

iii) Measurement of Hypoxic Ventilatory Drive and Oxygen Pulse

The experimental set-up was as described for step-change hypoxia in chapter two (fig.2.2) using the five-way Hans-Rudolph respiratory valve. The subject walked on a level treadmill breathing room air ($\dot{V}O_2$ approximately 1.0 $lmin^{-1}$).To measure gas exchange, two-minute collections of expired gas were made 7-9 and 9-11 minutes after the start of exercise, and further gas collections made if steady-state gas exchange had not been reached (i.e. two consecutive measurements of $\dot{V}O_2$ within 100ml). Hypoxic ventilatory drive was then measured during two step-changes in inspired gas, the first consisting of a step to 1% O_2 for one breath, immediately followed by three minutes of 15% inspired O_2, the second consisting of two breaths of 1% O_2 followed by three minutes of 12% O_2. The two periods of hypoxia were given five minutes apart and isocapnia was maintained throughout by adding CO_2 to the inspired gas to maintain $P_{ET}CO_2$ constant. Hypoxic ventilatory drive was measured at the same $\dot{V}O_2$/kg body weight on each of the three visits to the laboratory.

Oxygen pulse, which can be used as a measure of physical fitness (Wasserman et al 1987) was calculated as $\dot{V}O_2$ during steady-state exercise (calculated from analysis of mixed expired gas collections) divided by the mean heart rate during steady-state exercise (calculated as the mean of 20 breaths before each episode of hypoxia)

3 Analysis of Results and Statisics

i) Baseline Data

Ventilation, $\dot{V}O_2$/kg and $\dot{V}CO_2$/kg were calculated as means of all expired gas collections during steady-state exercise. Wilcoxons test for signed ranks with Bonferoni's correction was used to compare gas exchange data, body weight, FEV_1, VC, breath-holding time and baseline

(normoxic) $P_{ET}CO_2$ (calculated as a mean for 20 breaths before each episode of hypoxia) during steady-state exercise before and after 12 and 18-20 weeks training. The Mann-Whitney test was used to compare gas exchange measurements, FEV_1 and VC between smokers and non-smokers before training.

ii) Resting V_E and VO_2 and VO_2max

Details of elimination of spurious breaths from data collected using the MGC 2001 system are described in chapter seven. Resting V_E and VO_2 were calculated as a mean over the last two minutes of the rest period. To estimate $\dot{V}O_2max$, $\dot{V}O_2$ was averaged over each 30 seconds of the exercise test and $\dot{V}O_2max$ calculated as the mean $\dot{V}O_2$ over the last minute of exercise as described in chapter seven. As changes in body weight were possible, $\dot{V}O_2max$ was expressed per kg body weight.

The Mann-Whitney test was used to compare resting V_E and VO_2 and $\dot{V}O_2max$ for smokers and non-smokers before training, and Wilcoxons test for signed ranks with Bonferoni's correction was used to compare resting $\dot{V}_E$, and $\dot{V}O_2$ before and after 12 and 18-20 weeks training.Least squares regression analysis was used to calculate the correlation between resting VO_2 and VO_2max.

ii) Hypoxic Ventilatory Drive

The method of analysis of the ventilatory response to hypoxia is described in detail in chapter two. The data from both episodes of hypoxia was pooled, and the hypoxic ventilatory drive expressed as the negative slope of the $\dot{V}_E inst/S_aO_2$ relationship, which was compared before and after 12 and 18-20 weeks training using Wilcoxons test for signed ranks and Bonferoni's correction. Correlations between variables were calculated using least squares regression analysis.

III RESULTS

Although 16 volunteers attended the laboratory for the first set of measurements (before physical training), it was not possible to obtain measurements for all of them on all the three visits to the laboratory. The ventilatory response to hypoxia could not be analysed in one subject (number 20) on the first visit to the laboratory due to his irregular breathing pattern, and several of the subjects had the symptoms of upper respiratory tract infections at the time of the study. (Subjects were not studied within two weeks of any viral infection to comply with the safety recommendations of the Ethical Committee). In the 18-20 week training period several of the recruits left the Army and were no longer available for study, and in the final set of measurements a software fault in the MGC 2001 system meant that $\dot{V}O_2$max data was lost for two subjects. In consequence, full sets of data for all three visits to the laboratory were obtained on only three subjects, and for pre-training and after 18-20 weeks training in an additional two subjects.

i) Lung Function and Body Weight

Before training, there was no significant difference between FEV_1 or VC between smokers and non-smokers (Appendix III). There was no significant difference between FEV_1 or VC measured before and after 12 weeks (8 subjects) or before and after 18-20 weeks (7 subjects) training. Body weight did not change significantly after 12 weeks training (10 subjects), but after 18-20 weeks there was a significant reduction (7 subjects)

ii) Resting $\dot{V}O_2$ and $\dot{V}_E$ and Breath-Holding Time.

Resting $\dot{V}O_2$ ranged from 3.0 to 9.1 $mlmin^{-1}kg^{-1}$ before training, and there was no significant difference between smokers and non-smokers (table 8.1).There was no significant change in resting $\dot{V}O_2$ either after 12 or 18-20 weeks training. Resting $\dot{V}_E$ ranged from 7.27 to 17.51min^{-1} (table 8.1) before training, and again there was no significant difference between smokers and non-smokers, nor was there any significant change after 12 or 18-20 weeks training.

Total breath-holding time ranged from 22 to 91 seconds before training, and there was no difference between smokers and non-smokers

table 8.1 : Resting $\dot{V}O_2$ and $\dot{V}_E$ Before and After 12 and 18-20 Weeks Physical Training

Subject	Before Training		After 12 Weeks		After 18-20 Weeks	
	$\dot{V}O_2$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}_E$
	($ml\,min^{-1}\,kg^{-1}$)	($l\,min^{-1}$)	($ml\,min^{-1}\,kg^{-1}$)	($l\,min^{-1}$)	($ml\,min^{-1}\,kg^{-1}$)	($l\,min^{-1}$)
18	5.9	12.2	5.1	11.1	6.3	10.6
19	7.3	10.1	3.1	7.3	-	-
20	7.7	12.3	7.3	10.6	-	-
21	6.1	9.6	5.9	8.5	3.5	8.8
22	8.6	13.3	7.8	11.4	-	-
23	6.7	10.3	5.4	13.5	5.6	10.6
24	6.1	11.5	6.3	10.5	-	-
25	9.1	17.5	11.7	12.5	6.9	9.2
26	6.4	10.1	-	-	-	-
27	5.5	9.9	-	-	-	-
28	4.1	11.3	-	-	-	-
29	3.8	7.9	-	-	6.2	10.5
30	3.0	9.5	5.5	9.7	3.9	8.5
31	4.8	10.4	5.1	8.9	6.2	12.7
32	4.6	10.1	-	-	-	-
33	6.1	13.2	-	-	-	-

Oxygen consumption and ventilation averaged over the last two minutes of a ten-minute rest period.

(table 8.2). There was a significant increase after 12 weeks training in nine subjects ($P<0.02$). After 18-20 weeks training there was no significant difference between the measurements obtained before training in 6 subjects.

iii) Maximum Oxygen Consumption and Oxygen Pulse

The duration of the exercise period ranged from 8.5 to 24.5 minutes, with the mean±SD being 15.7±4.4 minutes. Maximum oxygen consumption expressed as VO_2max/kg body weight (table 8.3) ranged from 37.9 to 50.6 $mlmin^{-1}kg^{-1}$ before training, and there was no significant difference between smokers and non-smokers. After 12 weeks training, VO_2max was measured in five subjects (numbers 19,20,22,30 and 31 and ranged from 43.5 to 62.8 $mlmin^{-1}kg^{-1}$. Four of these five subjects showed an increase in $\dot{V}O_2$ max and one showed a decrease. After 18-20 weeks training, VO_2max was measured in subjects 21,23,29,30 and 31, and ranged from 46.6 to 68.1 ml min^{-1} kg^{-1}. Three showed an increase in $\dot{V}O_2max$ from the pre-training measurement, one stayed the same and one decreased slightly (fig 8.1). There was no correlation between resting $\dot{V}O_2$ and $\dot{V}O_2max$ (fig 8.2).

The oxygen pulse measured during steady-state exercise (VO_2 approximately $1.0lmin^{-1}$) ranged from 6.44 to 10.72 $mlmin^{-1}beat^{-1}$ before training (table 8.4) and there was no difference between smokers and non-smokers. After 12 weeks training the range was 5.16-11.06 $mlmin^{-1}beat^{-1}$, and there was no significant difference from the pre-training measurements (9 subjects). After 18-20 weeks, the range was 7.54-11.48$mlmin^{-1}beat^{-1}$ (seven subjects). There was still no significant change in oxygen pulse from the pre-training measurement for these seven subjects.

iv) Steady-State Exercise and Hypoxic Ventilatory Drive

There were no significant differences between $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ during steady-state exercise (table 8.5) for smokers and non-smokers before training, nor were there any significant differences before and after 12 weeks (9 subjects) or 18-20 weeks (7 subjects). Baseline (normoxic) $P_{ET}CO_2$ (table 8.6) was also similar before and after 12 weeks

table 8.2 : Breath-Holding Time Before and After 12 and 18-20 Weeks Physical Training

Subject	Before Training Time (sec)	After 12 Weeks Time (sec)	After 18-20 Weeks Time (sec)
18	22	91	30
19	66	93	-
20	56	87	-
21	91	110	-
22	51	67	81
23	80	68	63
24	35	92	-
25	35	108	-
26	31	-	-
27	43	-	-
28	29	-	-
29	37	-	67
30	61	-	67
31	67	74	74
32	86	-	-
33	35	-	-

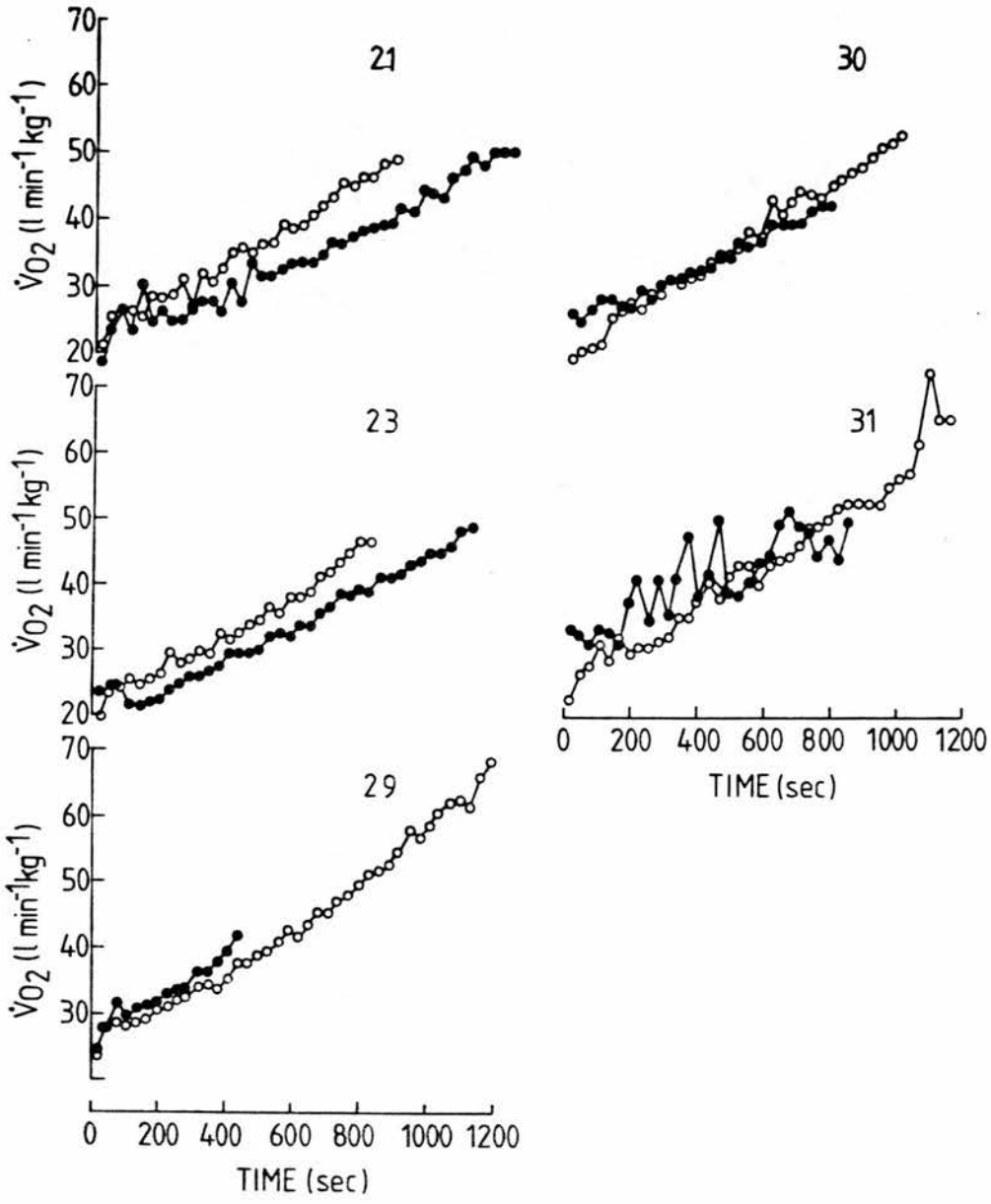
Maximum possible breath-holding time measured before any exercise studies took place.

table 8.3 : Maximum Oxygen Consumption Before and After 12 and 18-20 Weeks Physical Training

Subject	Before Training $\dot{V}O_2$max (mlmin^{-1}kg^{-1})	After 12 Weeks $\dot{V}O_2$max (mlmin^{-1}kg^{-1})	After 18-20 Weeks $\dot{V}O_2$max (mlmin^{-1}kg^{-1})
18	43.7	-	-
19	38.8	56.3	-
20	48.0	43.5	-
21	50.0	51.9	49.8
22	44.0	-	-
23	48.7	-	46.6
24	47.7	-	-
25	50.6	-	-
26	40.2	-	-
27	44.6	-	-
28	37.9	-	-
29	41.9	-	68.1
30	49.9	54.6	53.1
31	49.9	62.8	53.1
32	-	-	-
33	45.4	-	-

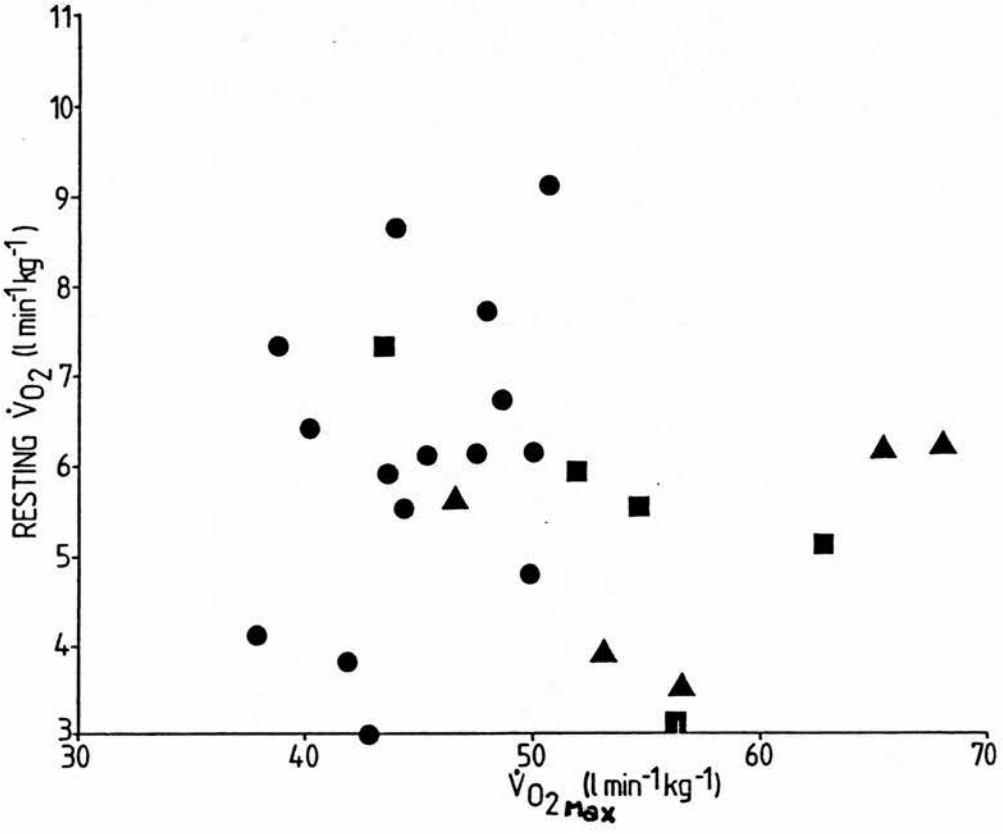
Maximum oxygen consumption averaged over the last minute of an incremental exercise test and expressed as mlmin^{-1}kg body weight^{-1}

fig 8.1 : Maximum Oxygen Consumption Before and After 18-20 Weeks Training



Oxygen consumption during a maximal exercise test for five subjects before and after 18-20 weeks training. Closed circles represent 30-second averages before training, open circles 30-second averages after training.

fig. 8.2 : Relationship Between Resting $\dot{V}O_2$ and $\dot{V}O_2$max



Data is for before training (●), after 12 weeks training (■) and after 18-20 weeks training (▲) There was no correlation between resting $\dot{V}O_2$ and $\dot{V}O_2$max.

table 8.4 : Oxygen Pulse Before and After 12 and 18-20 Weeks Physical Training

Subject	Before Training $\dot{V}O_2$/HR(mlmin^{-1}bt^{-1})	After 12 Weeks $\dot{V}O_2$/HR (mlmin^{-1}bt^{-1})	After 18-20 Weeks $\dot{V}O_2$/HR(mlmin^{-1}bt^{-1})
18	10.63	-	11.48
19	10.72	5.16	-
20	8.22	9.03	-
21	9.02	10.05	10.28
22	10.65	9.38	-
23	10.27	11.06	10.99
24	9.56	11.03	-
25	7.98	8.40	7.54
26	-	-	-
27	6.44	-	-
28	8.81	-	-
29	10.20	-	11.02
30	7.98	8.06	9.15
31	8.74	10.34	11.82
32	-	-	-
33	8.07	-	-

Oxygen pulse calculated as the mean $\dot{V}O_2$ during steady-state exercise ($\dot{V}O_2$ approximately 1.0lmin^{-1}) divided by the mean heart rate twenty breaths before each episode of hypoxia.

table 8.5 : Gas Exchange Variables During Steady-State Exercise Before and After Physical Training.

Subject	Before Training			After 12 Weeks			After 18-20 Weeks		
	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}_E$
	$(ml\,min^{-1}\,kg^{-1})$		$(l\,min^{-1})$	$(ml\,min^{-1}\,kg^{-1})$		$(l\,min^{-1})$	$(ml\,min^{-1}\,kg^{-1})$		$(l\,min^{-1})$
18	12.9	11.7	25.7	-	-	-	14.3	13.8	26.5
19	14.1	11.6	17.7	7.4	7.9	12.8	-	-	-
20	15.6	12.7	26.5	16.1	15.8	28.8	-	-	-
21	14.3	10.8	23.3	16.0	14.8	25.8	16.6	14.3	25.7
22	14.5	13.7	30.5	13.7	12.9	27.9	-	-	-
23	12.6	11.2	28.5	13.2	12.2	29.9	13.2	11.7	30.5
24	14.4	14.3	28.3	14.8	13.4	27.7	-	-	-
25	13.7	12.4	25.0	14.5	14.7	26.8	15.0	14.3	24.5
26	-	-	-	-	-	-	-	-	-
27	18.8	16.8	28.9	-	-	-	-	-	-
28	15.3	12.5	21.7	-	-	-	-	-	-
29	15.9	13.4	25.2	-	-	-	15.5	13.1	22.1
30	13.9	12.4	23.8	15.7	13.5	24.2	14.5	13.1	24.9
31	14.6	12.9	25.7	16.1	14.4	22.9	15.5	13.8	24.9
32	-	-	-	-	-	-	-	-	-
33	15.9	15.1	24.0	-	-	-	-	-	-

Gas exchange variables calculated as means during steady-state exercise and expressed as either ml $min^{-1}kg^{-1}$ ($\dot{V}O_2$ and $\dot{V}CO_2$) or l min^{-1} ($\dot{V}_E$)

training (8 subjects) and before and after 18-20 weeks training (table 8.6, 7 subjects

Before training there was no difference between hypoxic ventilatory drive expressed as the slope of the $\dot{V}_E inst/S_aO_2$ relationship for smokers and non-smokers (table 8.7) and the range was -0.23 to -2.44 l min^{-1} $\%^{-1}$ (13 subjects). After 12 weeks training, the range of values was -0.63 to 1.91 l min^{-1} $\%^{-1}$ (8 subjects ; 1 subject excluded from this range as no pre-training measurement had been made), with no consistent trend in the direction of change between individuals, and the differences were not significant. After 18-20 weeks training, the range of $\dot{V}_E inst/S_aO_2$ slope was -0.36 to -1.88 l $min^{-1}\%^{-1}$, and there was still no consistent trend in the direction of change. Data for the five subjects in whom hypoxic ventilatory drive was measured before and after 18-20 weeks training are shown in fig. 8.3.

There was no correlation between hypoxic ventilatory drive and either , $\dot{V}O_2max$ (fig 8.4) or oxygen pulse (fig 8.5), nor was there any correlation between the change in hypoxic ventilatory drive and the change in oxygen pulse (fig 8.6) expressed as the difference between the pre- and post-training values.

table 8.6 : End-Tidal PCO_2 During Hypoxia Before and After 12 and 18-20 Weeks Physical Training

	Before Training	After 12 Weeks	After 18-20 Weeks
Subject	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)	$P_{ET}CO_2$ (kPa)
18	-	-	5.38±0.15
19	6.54±0.30	6.32±0.16	-
20	5.51±0.18	5.61±0.14	-
21	5.79±0.14	6.16±0.17	6.45±0.27
22	5.60±0.11	5.52±0.12	-
23	5.33±0.11	5.06±0.14	5.46±0.14
24	5.62±0.10	5.76±0.15	-
25	5.18±0.10	5.44±0.19	5.34±0.12
26	-	-	-
27	5.31±0.12	-	-
28	6.13±0.15	-	-
29	5.79±0.17	-	5.45±0.13
30	5.06±0.14	5.48±0.12	5.27±0.13
31	5.76±0.15	6.14±0.12	5.86±0.13
32	-	-	-
33	5.90±0.10	-	-

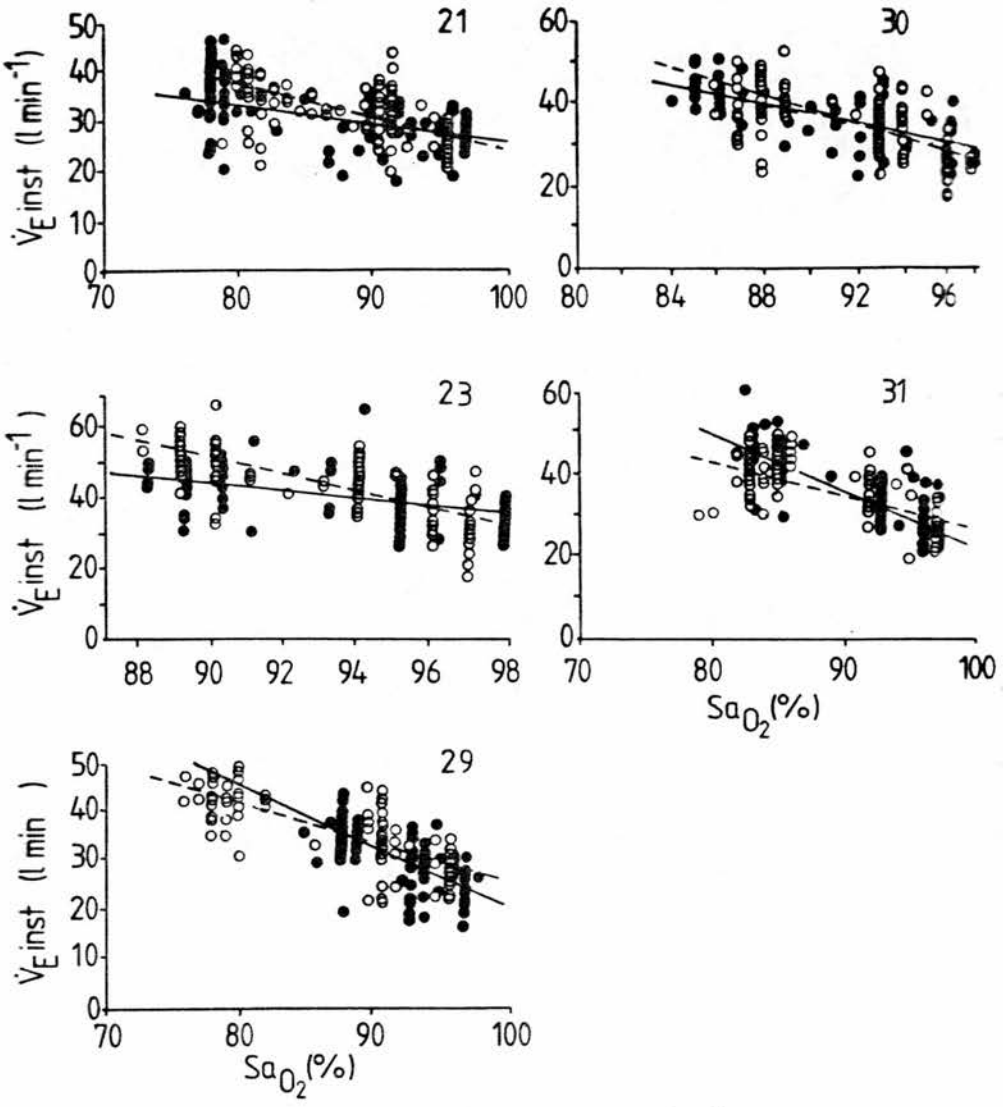
End-tidal PCO_2 during hypoxia expressed as the mean±SD for all the breaths used in the calculation of hypoxic ventilatory drive.

table 8.7 : Hypoxic Ventilatory Drive Before and After 12 and 18-20 Weeks Physical Training

Subject	Before Training $\dot{V}_E inst/S_aO_2$ ($l min^{-1}\%^{-1}$)	After 12 Weeks $\dot{V}_E inst/S_aO_2$ ($l min^{-1}\%^{-1}$)	After 18-20 Weeks $\dot{V}_E inst/S_aO_2$ ($l min^{-1}\%^{-1}$)
18	-1.87	-	-1.88
19	-	-0.39	-
20	-0.69	-0.69	-
21	-0.67	-0.63	-0.36
22	-1.30	-1.91	-
23	-2.44	-1.46	-1.09
24	-0.71	-0.66	-
25	-1.72	-0.91	-1.03
26	-	-	-
27	-1.31	-	-
28	-0.23	-	-
29	-0.79	-	-1.40
30	-1.34	-1.44	-1.21
31	-0.83	-1.01	-1.47
32	-	-	-
33	-0.58	-	-

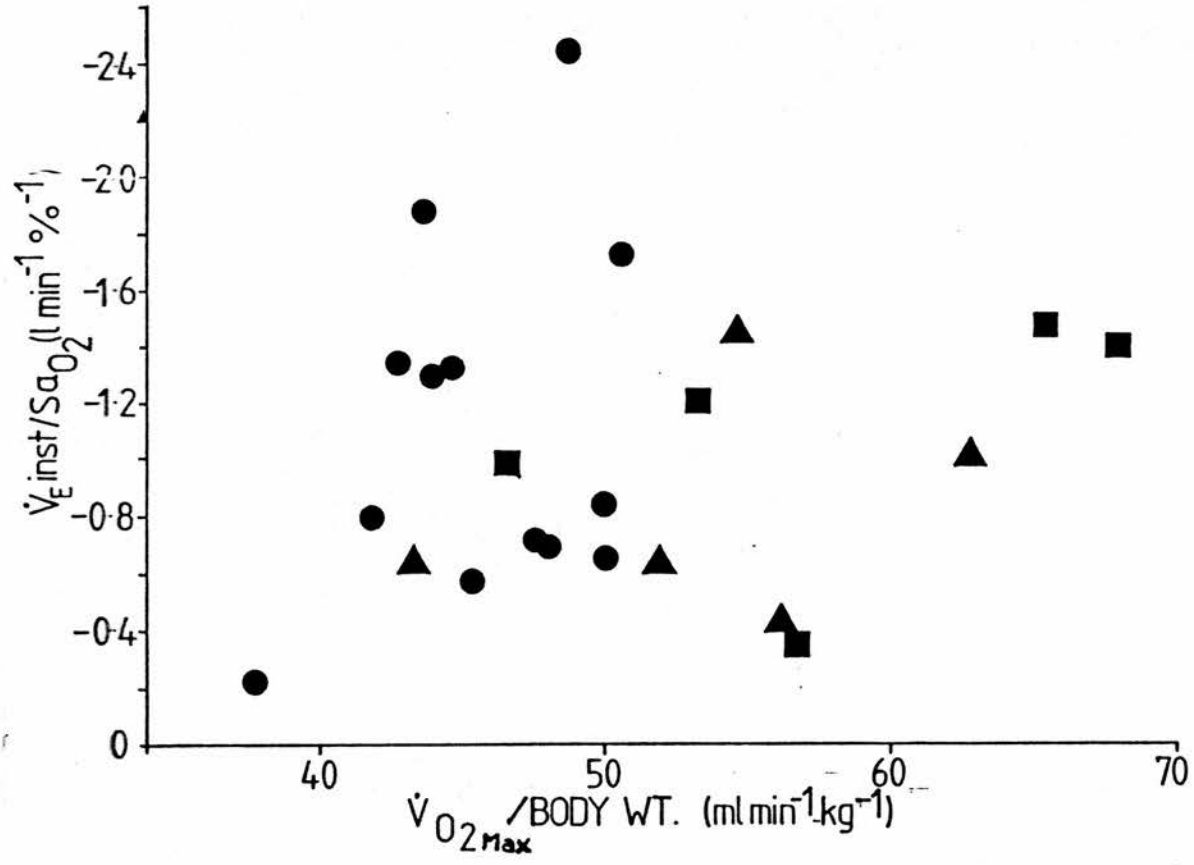
Hypoxic ventilatory drive calculate from pooled data from two episodes of hypoxia and expressed as the $\dot{V}E inst/S_aO_2$ slope.

fig 8.3 : Hypoxic Ventilatory Drive Before and After 18-20 Weeks Training



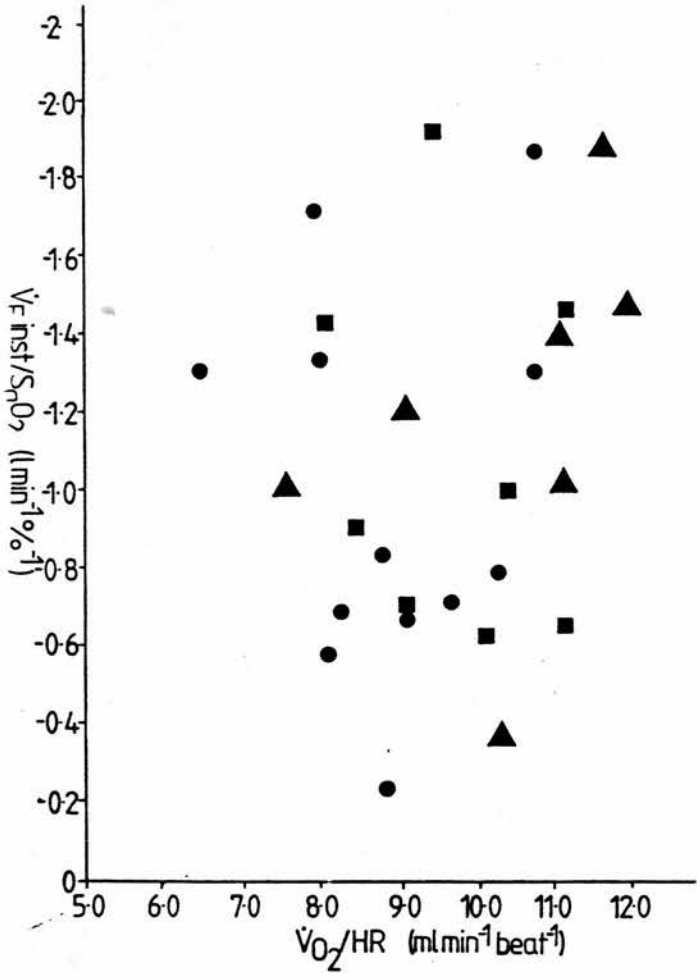
$\dot{V}_E$inst plotted against S_aO_2 during pooled episodes of hypoxia before (●) and after (○) 18-20 weeks training in the five subjects in whom VO_2max was measured on both occasions. Dashed lines represent the least squares regression relationship between $\dot{V}_E$inst and S_aO_2 before training, solid lines, after training.

fig 8.4 : Relationship Between Hypoxic Ventilatory Drive and Maximum Oxygen Consumption



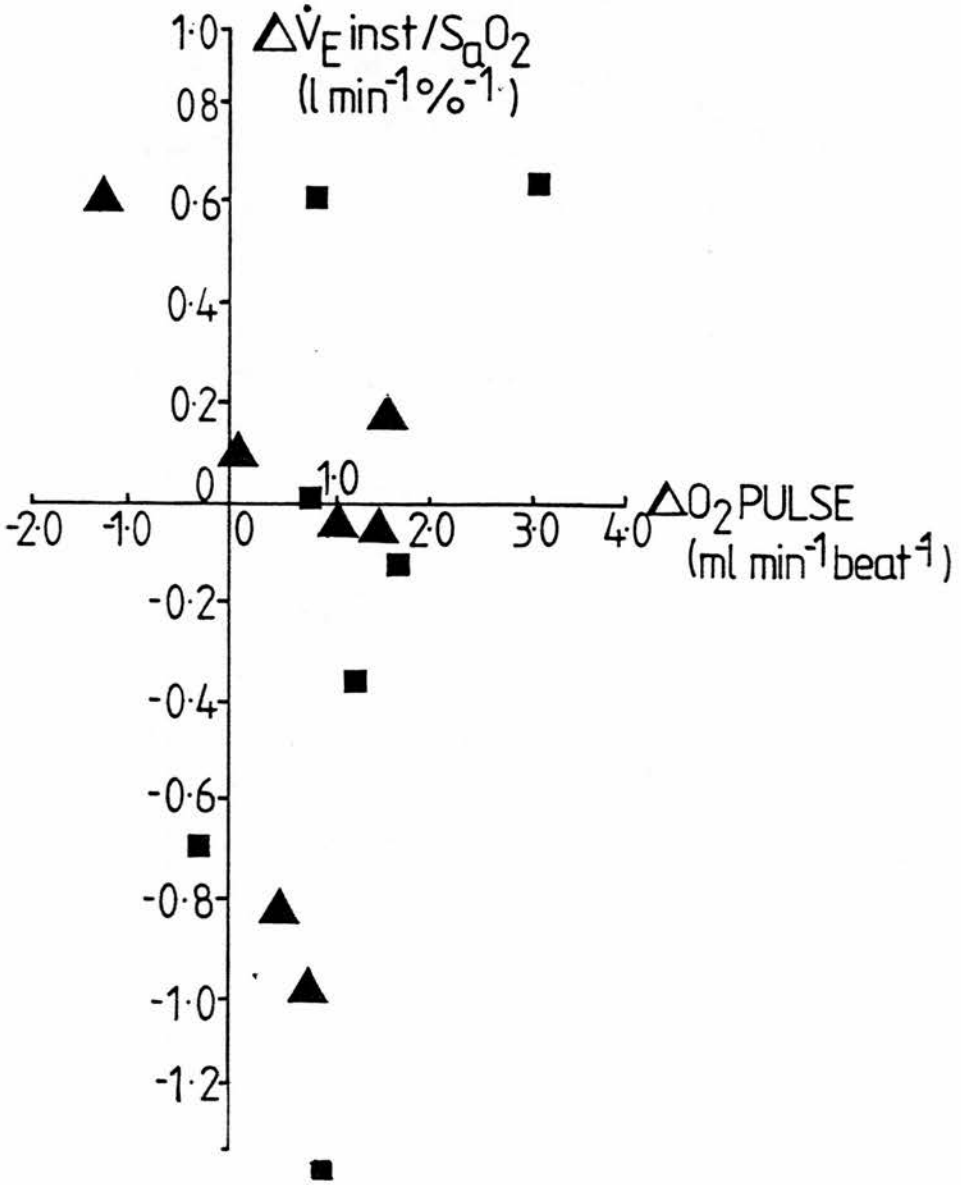
Hypoxic ventilatory drive (expressed as the $\dot{V}_E inst/S_aO_2$ slope) plotted against $VO_2 max$ kg^{-1} body weight before (●) and after 12 (▲) and 18-20 (■) weeks training.

fig 8.9 : Relationship Between Hypoxic Ventilatory Drive and Oxygen Pulse Before and After Training



Hypoxic ventilatory drive ($\dot{V}_E$inst/S_aO_2 slope) plotted against oxygen pulse (mean $\dot{V}O_2$ during steady-state exercise/mean heart rate for 20 breaths before each episode of hypoxia) before (●) and after 12 (■) and 18-20 (▲) weeks training.

fig 8.6 : Relationship Between The Change in O_2 Pulse and The Change in Hypoxic Ventilatory Drive After Training



Change in hypoxic ventilatory drive ($\dot{V}_E inst/S_aO_2$ slope), plotted against the change in O_2 pulse during steady-state exercise after 12 (▲) and 18-20 (■) weeks training. Values are calculated as the difference between the pre-and post-training measurements.

IV DISCUSSION

Physical training for 12 weeks did not increase physical fitness, as measured by VO_2max or by oxygen pulse during steady-state exercise (VO_2 approximately 1.0lmin^{-1}) to a significant extent, nor was there any consistent change in hypoxic ventilatory drive expressed as the negative slope of the $V_E$inst/S_aO_2 relationship during hypoxia. Hypoxic ventilatory drive did not correlate either with $\dot{V}O_2$max or oxygen pulse. After 12 weeks training, there was a significant increase in breath-holding time, but after 18-20 weeks this difference was not statistically significant. Resting ventilation and VO_2 remained unchanged from the pre-training control measurements, both after 12 and 18-20 weeks training. Resting VO_2 did not correlate with hypoxic ventilatory drive during steady-state exercise or VO_2max

There is no evidence in this data of a correlation between hypoxic ventilatory drive and any estimate of physical fitness (VO_2 or O_2 pulse). These results are contrary to those in the previous chapter and to the studies of Cotes and Meade (1959), who found that there was a smaller depression of ventialtion caused by inhalation of 100% O_2 following physical training. Cotes and Meade (1959) did not, however, state the duration or nature of the training programme, nor did they measure the physical fitness of the subjects.

There are several problems associated with the present study, which limit the conclusions which can be drawn from the results. Firstly, the number of subjects who were able to complete all the procedures was small due to factors such as availability of subjects, upper respiratory tract infections and equipment problems. Maximum oxygen consumption measurements were thus only obtained for five subjects after 12 weeks training, and for a different group of five subjects after 18-20 weeks training. Interpretation of the statistics is difficult due to the small numbers of of subjects studied, thus the results may be subject to a type II error.

Another problem is fatigue, anxiety and lack of motivation of the subjects. As young Army recruits, the subjects suffered from considerable lack of sleep, and most reported that they were suffering from fatigue. They fell asleep very easily during the measurement of resting ventilation and gas exchange and fatigue could also have affected the

measurement of the ventilatory response to hypoxia. Although the subjects appeared to have reached exhaustion during the measurement of $\dot{V}O_2$max, the majority did not reach a plateau of $\dot{V}O_2$ at the end of exercise (for example, fig 8.3), in contrast to the measurements in laboratory staff in the previous chapter, where the majority did reach a plateau of $\dot{V}O_2$. Despite the fact that competition between subjects was encouraged, this may indicate lack of motivation, resulting in underestimation of $\dot{V}O_2$max and account for the lack of increase in $\dot{V}O_2$max in some subjects even after 18-20 weeks training.

Anxiety could also affect measurements of resting $\dot{V}O_2$, $\dot{V}O_2$max and hypoxic ventilatory drive. For many of the subjects, this was the first time they had been away from home, and this major change in lifestyle could have made them anxious. They also may have been apprehensive about the experimental procedures, although few admitted to this. Another problem was that the Army schedules did not allow time for an acclimatisation run, to familiarise the recruits with the equipment, which was done in the laboratory staff. The fact that there was an increase in breath-holding time after 12 weeks training may indicate that the recruits were less anxious about the procedures on the second visit to the laboratory, although there was no change in resting ventilation, which would be expected to be high if the subjects were anxious. In one subject (number 25) resting ventilation was unusually high (17.5 l min^{-1}) on the first visit to the laboratory, and fell on subsequent occasions, which could have indicated anxiety on the first visit.

The type or the duration of the training program may not have been suitable to produce an adequate increase in physical fitness. Army recruits were chosen as subjects for this study because they were about to start a very strenuous and controlled training programme, designed to increase their physical fitness and endurance. Only one subject (subject 18) had previously taken part in any sort of physical training, and the recruits were therefore relatively physically unfit ($\dot{V}O_2$max range before training 37.9-50.6 ml min^{-1} kg^{-1}) thus the potential for an increase in $\dot{V}O_2$max and oxygen pulse (indices of physical fitness) was high. Despite this, not all the subjects showed an increase in $\dot{V}O_2$max even after 18-20 weeks training. This may have been due to lack of motivation or the fact that they had just returned from a night survival course and may have been particularly exhausted.

Another problem is that these subjects were not fasting, as were the laboratory staff in previous chapters, and this could have affected hypoxic ventilatory drive (Zwillich et al 1977). Measurements were made at the same time of day in individuals to minimise any possible effect this may have had.

Because of the problems associated with this study, any conclusions drawn from the results must be treated with caution. There was no change in hypoxic ventilatory drive expressed as the negative slope of the $V_E inst/S_a O_2$ relationship during exercise after training, nor was there any correlation between hypoxic ventilatory drive and oxygen pulse. This suggests that physical training does not affect hypoxic ventilatory drive, and that the low hypoxic ventilatory drive which is associated with athleticism is an inherited characteristic. Alternatively, it may be that the increase in physical fitness required to cause a decrease in hypoxic ventilatory drive is either greater than that which can be developed within 18-20 weeks training, or that long-term physical fitness is required before any change in hypoxic ventilatory drive is seen.

SUMMARY and CONCLUSIONS

Comparison of three different methods of measuring hypoxic ventilatory drive during moderate steady-state exercise in normal man showed that in the majority of subjects, hypoxic ventilatory drive (expressed as the slope of the $\dot{V}_E inst/S_{a}O_2$ relationship) was smaller as measured using transient hypoxia than when using progressive isocapnic or isocapnic step-change hypoxia, despite the fact that $S_{a}O_2$ was reduced to approximately 80% on each occasion. In two subjects, however, the ventilatory response to transient hypoxia was much greater than that to step-change and progressive isocapnic hypoxia. This raised the question of whether the ventilatory response to transient hypoxia accurately reflects the carotid chemoreceptor response as suggested by previous workers. On average, the half-time of the ventilatory response to a step-change in inspired gas from room air to 12% O_2 for three minutes was three times the duration of the transient hypoxic stimulus, which suggested that the brevity of the transient stimulus may limit the ventilatory response. This mechanism could not, however, fully account for the difference between the ventilatory response to transient and to step-change hypoxia, since in two subjects the ventilatory response to transient hypoxia was the greater. Transient hypoxia produced a faster rate of fall in $S_{a}O_2$ than step-change hypoxia. Fourier deconvolution of the ventilatory responses to transient and step-change hypoxia showed that the relationship between $V_E inst$ and $S_{a}O_2$ was not linear under all circumstances, and may depend upon the time course of the hypoxic stimulus. Thus, although the brevity of the transient stimulus may contribute to the limitation of the ventilatory response, it is not the full explanation for the difference in ventilatory responses to transient and step-change hypoxia.

As previous exposure to hypoxia may potentiate hypoxic ventilatory drive, and calculation of hypoxic ventilatory drive involved pooling of data from several repeated tests,the effect of repeated measurements of hypoxic ventilatory drive by step-change, progressive isocapnic and transient hypoxia was investigated. The ventilatory responses to repeated stimuli of all three types (transient, progressive and step-change) were reproducible, thus the larger ventilatory responses to step-change and progressive hypoxia was not a result of potentiation due to repeated measurements.

As there is evidence for central hypoxic depression of ventilation during prolonged periods of hypoxia, this was investigated as a possible explanation for the lower ventilatory responses to step-change and progressive isocapnic hypoxia than to transient hypoxia in two of the subjects. In only one subject was there any evidence of depression of ventilation during inhalation of 12% O_2, and this did not occur until the fifth minute of hypoxia. Furthermore, she was <u>not</u> one of the subjects who had a small ventilatory response to step-change hypoxia. It was therefore concluded that central depression of ventilation during hypoxia did not affect the ventilatory response to step-change hypoxia, however it is a potential problem when measuring the ventilatory response to progressive isocapnic hypoxia, which lasts up to ten minutes.

The differences in ventilatory responses to different types of hypoxic stimulus may originate at the carotid chemoreceptors, or could be a result of differences in processing of the carotid chemoreceptor input at a higher locus. Carotid chemoreceptor responses to transient and isocapnic step-change hypoxia were found to be similar in anaesthetised and paralysed cats. As there was no ventilatory response to hypoxia due to paralysis in the cats, however, the brief hypocapnia which develops during the ventilatory response to transient hypoxia in human subjects did not occur. To determine whether this hypocapnia limited the ventilatory response to transient hypoxia in human subjects, ventilatory responses to transient hypoxia were measured in which isocapnia was maintained. There was no difference between the ventilatory response to isocapnic and hypocapnic transient hypoxia. These observations suggest, together with the results of direct measurement of carotid chemoreceptor activity in cats, that the differences in ventilatory responses to the two stimuli in human subjects are more likely to be a result of central integration of the carotid chemoreceptor input than of differences in the actual carotid chemoreceptor responses to hypoxia.

Measurement of hypoxic ventilatory drive using transient hypoxia had previously been done during exercise, in order to produce an adequate stimulus with only 2-3 breaths of N_2 and to improve the signal-to-noise ratio of the response as a result of the exercise-induced potentiation of hypoxic ventilatory drive, however, intersubject comparison of ventilatory responses to hypoxia at a given level of $\dot{V}O_2$ of approximately 1.0 l min^{-1}

may be invalid, since this may represent a different relative level of exercise for individual subjects, depending upon factors such as physical fitness, sex and height and weight. The effects of increasing the level of exercise and of physical training on the hypoxic ventilatory drive was therefore studied using step-change hypoxia. The ventilatory response to this stimulus had been shown to be reproducible when repeated at five minute intervals, and was unaffected by either central depression of ventilation (as may occur with more prolonged hypoxia such as in the progressive isocapnic method), or the brevity of the stimulus (as may occur with transient hypoxia). In subjects drawn from laboratory staff, the degree of physical fitness as assessed by the $\dot{V}O_2$max/kg body weight was inversely related to the hypoxic ventilatory drive at a given moderate level of exercise ($\dot{V}O_2$ 0.7-0.9 l min^{-1}) and the degree of potentiation of the hypoxic ventilatory drive between rest and this level of exercise. Results on the direct effect of physical training on hypoxic ventilatory drive in Army recruits were inconclusive due to the small number studies as a result of technical problems and subject availability.

To conclude, measurement of hypoxic ventilatory drive in normal man is affected by the time course of the hypoxic stimulus, by exercise and possibly by physical fitness. Differences between subjects in central integration of the carotid chemoreceptor response to step-change and transient hypoxia result in different ventilatory responses to these stimuli. The ventilatory response to transient hypoxia may not therefore reflect the carotid chemorecepor mediated hypoxic ventilatory drive as previously suggested. In the majority of subjects, step-change hypoxia is likely to be the best method of estimating the carotid chemoreceptor mediated hypoxic ventilatory drive, as it is too short to be affected by central hypoxic depression, yet long enough to allow the ventilatory response to hypoxia to develop fully. In a minority of subjects, however, the ventilatory response to step-change hypoxia is smaller than that to transient hypoxia, and in such individuals, an additional measurement of the ventilatory response to transient hypoxia may be useful in determining the existance of a truly low hypoxic ventilatory drive. Exercise potentiates hypoxic ventilatory drive to an extent dependent upon physical fitness. Both physical fitness and body weight must be taken into account when interpreting absolute values of $V_E inst/S_a O_2$ as a measure of hypoxic ventilatory drive during exercise.

Several questions arise from this research, the answers to which may provide a fuller understanding of the control of breathing during hypoxia and exercise in normal man. Firstly, what is an abnormally low hypoxic ventilatory drive? Do individuals fall into two distinct groups with low and normal hypoxic ventilatory drives, or is there a continuous spectrum? Both these questions may be determined by measuring the hypoxic ventilatory drive in a much larger group of subjects than has previously been studied. It may be possible to derive "normal" ranges of hypoxic ventilatory drive measured by step-change hypoxia at a standardised exercise level for different groups of people (i.e. people of different sex, age, weight and physical fitness). This would also require a more extensive assessment of day-to-day reproducibility of the ventilatory response to step-change hypoxia than has been reported.

In chapter eight, insufficient evidence was obtained to answer the question of whether or not hypoxic ventilatory drive changes after physical training. This topic requires further investigation, using a larger number of subjects with a training program more suitable for this study. The training program would need to be more prolonged and very strictly enforced. Ideally, the training would fit into the normal life of the subjects, so that they would not suffer undue fatigue which might affect the measurement of hypoxic ventilatory drive.

Another question is, how important is a low hypoxic ventilatory drive in relation to athletic performance? This topic may be approached by artificially raising the hypoxic ventilatory drive in athletes in whom a low measurement has been obtained (perhaps using a drug such as Almitrine, although side effects such as raised pulmonary artery pressure must be taken into account)and comparing the athletic performance with the pre-drug assessment.

Two groups of people may exist who have a low hypoxic ventilatory drive: 1)athletes and 2)those who develop the "blue and bloated" form of chronic obstructive airways disease. The mechanisms responsible for the low hypoxic ventilatory drive in these two groups may be completely different, for example the athletes may have enhanced central hypoxic depression of ventilation, while the other group may have a diminished carotid chemoreceptor mediated hypoxic ventilatory drive rather than it being of central origin.

APPENDIX I : DETAILS OF CATS USED IN CHAPTER 5

Cat Number	Sex	Weight
1	F	2.5
2	F	3.2
3	F	3.3
4	F	3.0
5	F	3.4
6	F	2.4
7	F	2.8
8	F	3.5
9	F	3.0

APPENDIX II : SUBJECT DETAILS : Laboratory Staff

Subject number	Sex	Age (years)	Height (m)	Weight (kg)	FEV$_1$ (l)	FEV$_1$ (% pred.)	VC (l)	VC (% pred.)	FEV$_1$/VC (%)	FEV$_1$/VC (% pred.)	TLC (l)	TLC (% pred)	RV (l)	RV (% pred.)	RV/TLC (%)	FRC (l)	FRC (% pred)	ERV (l)	TLCO (mmol/kPa.min)	TLCO (% pred)	RAW	SGAW	GAW
1	M	30	1.72	78.6	3.69	90	4.69	96	79	94	6.82	109	2.01	102	24	2.10	69	0.55	11.25	90	0.20	5.00	1.42
2	F	23	1.73	66.3	4.01	108	4.61	105	86	105	6.33	112	1.53	104	24	2.27	73	1.02	9.38	93	0.21	4.76	1.40
3	M	36	1.82	74.0	5.00	115	5.88	104	89	109	7.50	106	1.75	97	24	4.07	115	2.32	11.12	99	-	-	-
4	M	32	1.71	67.5	3.61	88	4.73	96	76	92	6.59	105	1.55	102	24	2.10	69	0.55	11,25	90	-	-	-
5	F	30	1.68	66.7	3.07	91	3.73	92	84	105	5.25	98	1.27	84	24	3.23	109	1.96	10.72	106	-	-	-
6	F	37	1.64	92.4	3.08	106	3.70	100	83	106	5.37	101	1.33	79	25	2.14	97	0.92	9.85	104	0.16	6.25	1.75
7	M	32	1.76	64.0	3.86	89	4.20	81	81	111	7.16	106	3.20	195	42	4.60	138	1.40	9.04	82	0.09	11.63	2.11
8	M	27	1.70	70.6	4.20	89	5.30	98	80	102	6.35	95	1.11	74	17	3.30	67	1.07	9.10	103	-	-	-
9	M	29	1.84	74.5	3.83	81	5.42	93	79	96	7.91	105	1.95	110	25	4.07	110	2.70	12.39	84	0.10	10.00	2.15
10	F	23	1.54	61.5	2.61	84	3.02	79	86	105	3.84	77	0.68	62	18	1.42	56	0.74	8.00	89	0.20	5.00	2.24
11	M	24	1.88	73.0	4.32	86	5.76	94	75	91	7.87	102	1.89	111	24	3.85	99	1.96	13.00	105	0.33	3.03	1.07
12	M	36	1.78	68.0	4.26	99	5.38	102	79	96	7.90	114	2.53	140	32	4.65		2.12	11.69	105	-	-	-
13	M	22	1.78	64.0	3.71	80	4.85	87	87	94	6.17	90	1.32	90	21	3.37	102	2.05	11.49	80	-	-	-
14	F	25	1.76	57.0	3.59	100	4.21	92	86	106	5.39	86	1.18	69	21	2.89	71	1.71	8.24	81	0.16	6.25	1.69
15	F	28	1.67	56.0	3.23	98	3.69	90	87	109	4.73	83	1.18	73	25	2.89	83	1.71	7.20	76	0.17	5.88	1.54
16	F	25	1.61	56.0	3.16	105	3.98	105	79	97	5.51	111	1.36	94	25	2.56	92	1.20	1.50		0.26	3.85	1.49
17	F	31	1.64	59.0	3.10	97	3.90	95	80	105	5.40	91	1.50	76	27	3.30	67	1.07	9.10	103	0.25	4.00	1.81

APPENDIX III : SUBJECT DETAILS : Army Recruits

Before Training

Subject number	Age (years)	Height (m)	Weight (kg)	smoker?	Hb (%)	COHb (%)	FEV$_1$ (l)	FEV$_1$ (% pred)
18	18	1.79	75.9	N	16.6	0.3	3.61	91
19	21	1.84	67.0	N	15.7	1.0	3.34	68
20	18	1.78	68.5	Y	18.2	3.2	4.56	80
21	19	1.87	69.4	N	15.2	0.2	3.85	70
22	19	1.77	71.0	Y	14.5	2.6	3.50	71
23	18	1.78	79.2	Y	17.6	3.8	4.82	102
24	21	1.76	73.5	Y	14.6	3.1	4.90	90
25	18	1.74	60.5	N	16.6	0.1	3.88	84
26	19	1.63	55.0	Y	15.2	2.8	3.39	83
27	18	1.63	49.5	Y	14.3	1.5	4.00	97
28	22	1.82	67.8	Y	16.4	3.2	4.12	86
29	18	1.77	68.0	Y	15.9	1.2	5.45	68
30	18	1.78	66.5	N	17.2	0.0	3.60	71
31	23	1.70	72.8	N	14.6	0.9	4.52	100
32	18	1.72	63.4	N	18.0	0.1	3.86	87
33	18	1.75	62.1	N	17.1	0.1	4.56	98

Subject number	VC (l)	VC (% pred)	FEV$_1$/VC (%)	FEV$_1$/VC (% pred)	TLC (l)	TLC (% pred)	FRC (l)	FRC (% pred)	ERV (l)	TLCO (mmol/kPa.min)	TLCO (% pred)	RAW	SGAW	GAW
18	5.27	91	68	99	7.73	111	4.25	128	2.33	9.63	65	0.20	5.00	1.05
19	4.86	82	68	83	6.67	91	3.10	87	1.94	10.11	66	0.24	4.17	1.20
20	5.12	89	89	89	6.87	102	3.46	109	1.57	12.04	84	0.10	10.00	2.51
21	5.52	85	69	82	7.33	97	1.94	122	2.02	12.44	79	0.19	5.26	1.07
22	4.50	79	78	89	5.41	80	0.81	59	1.70	9.70	67	0.18	5.56	1.59
23	5.51	98	87	104	6.74	98	1.38	100	1.48	12.19	83	0.13	7.69	1.95
24	4.97	90	98	115	6.69	99	1.98	141	1.14	8.35	59	0.12	8.33	1.96
25	4.38	81	88	104	6.20	95	1.90	150	1.57	8.47	60	0.16	6.25	1.68
26	4.24	90	80	93	5.16	90	0.89	83	1.15	10.15	96	0.20	5.00	1.26
27	4.52	91	88	106	6.10	107	1.62	154	1.88	6.89	65	0.14	7.10	1.87
28	5.03	87	82	99	6.94	96	1.72	112	2.16	10.66	87	0.14	7.10	1.40
29	6.60	118	83	98	7.74	114	1.10	85	2.36	13.71	112	0.16	6.25	1.40
30	4.20	66	85	107	6.11	82	1.88	123	1.48	9.08	69	-	-	-
31	5.24	97	86	102	6.72	100	1.29	78	1.41	15.92	112	0.16	6.25	2.00
32	4.69	87	82	98	6.23	97	1.29	105	1.97	8.86	76	0.14	7.40	1.78
33	5.02	91	90	108	7.02	107	1.69	129	1.91	10.77	90	0.25	4.00	1.01

After 12 Weeks Training

Subject number	Weight (kg)	FEV$_1$ (l)	FEV$_1$ (% pred)	VC (l)	VC (% pred)	FEV$_1$/VC (%)	FEV$_1$/VC (% pred)	TLC (l)	TLC (% pred)	RV (l)	RV (%pred)	RV/TLC (%)	FRC (l)	FRC (% pred)	ERV (l)	TLCO (mmol/kPa.min)	TLCO (% pred)	RAW	SGAW	GAW
18	76	4.30	89	5.53	96	78	92	7.41	111	2.05	156	28	4.19	129	2.14	10.05	68	0.15	6.89	1.65
19	64.5	4.68	96	5.21	84	90	114	7.41	100	2.04	128	28	3.56	92	1.07	-	-	0.14	7.14	1.52
20	64.5	4.66	98	5.20	94	89	105	7.12	104	1.92	137	27	3.63	111	1.71	12.06	84	0.27	3.70	1.36
21	67	3.73	66	5.22	83	71	80	7.15	93	1.90	115	27	3.88	87	1.48	12.22	77	0.23	4.35	1.22
22	67	4.03	80	4.64	80	86	100	5.76	82	1.05	76	18	2.39	77	1.34	9.04	60	0.20	5.00	1.48
23	82	4.42	82	5.61	78	79	104	7.20	83	1.73	86	24	3.41	78	1.68	10.05	56	0.22	4.55	1.24
24	73.5	4.85	105	5.28	95	91	111	7.23	105	1.97	131	27	3.27	100	1.30	9.58	67	0.25	4.00	2.00
25	60	3.84	81	4.28	76	89	106	5.68	85	1.42	112	25	2.92	90	1.50	9.61	66	0.23	4.35	1.42
26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	58	5.25	130	6.28	143	83	97	9.19	165	2.71	238	30	5.08	192	2.37	13.30	106	-	5.68	1.19
30	61	3.84	81	4.40	74	87	104	5.71	73	1.36	74	24	3.74	83	2.38	9.18	71	-	10.00	1.90
31	68.9	4.88	110	5.67	102	86	100	7.13	98	1.33	73	19	3.24	80	1.91	12.97	107	-	7.14	1.87
32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

After 18-20 Weeks Training

Subject number	Weight (kg)	$FEV_{1.0}$ (l)	$FEV_{1.0}$ (% pred)	VC (l)	VC (% pred)	$FEV_{1.0}$/VC (%)	$FEV_{1.0}$/VC (% pred)	TLC (l)	TLC (% pred)	RV (l)	RV (% pred)	RV/TLC (%)	RV/TLC (% pred)	FRC (l)	FRC (% pred)	ERV (l)	TLCO (mmol/kPa.min)	TLCO (% pred)	RAW	SGAW	GAW
18	76.5	4.50	90	6.00	105	78	93	7.30	105	1.84	131	25	125	3.92	118	1.86	-	-	0.15	1.44	6.67
19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21	68.5	3.73	73	5.33	87	69	84	7.35	97	1.97	124	26	130	3.70	99	1.73	12.86	97	0.24	0.88	4.14
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23	78.5	4.90	102	5.73	104	85	85	-	-	-	-	-	-	-	-	-					
24	77	4.70	102	5.37	97	87	102	7.06	104	1.74	148	24	133	2.96	91	1.22	10.95	90	-	-	-
25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	58	5.25	130	6.28	143	83	92	9.19	148	2.71	238	30	157	5.08	192	2.37	12.50	106	0.17	1.19	5.88
30	61	3.89	81	4.40	74	89	105	5.69	73	1.34	74	24	130	3.72	83	2.38	13.00	71	0.10	1.90	10.00
31	69.5	5.67	102	4.88	110	86	87	7.07	98	1.27	73	18	97	3.18	80	1.91	12.79	107	0.14	1.87	7.14
32	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

notes: 1)all subjects were caucasian, with the exception of subject number 17, who was black.

BIBLIOGRAPHY

ADAMS, JM. ATTINGER, FM. ATTINGER, EO, Carotid chemoreceptor interaction for mild stimuli. Pflugers Arch Ges Physiol.374:39-45 (1978)

AIRLIE, M.A.A. FLENLEY, D.C. WARREN P.M. Effect of Almitrine on hypoxic ventilatory drive measured by transient and progressive isocapnic hypoxia in normal men ; in press. (1988)

ALFES, H. KINDLER, J. KNOCHE, H. MATTHIESSEN, D. MOLLMAN, H. PAGNICCO, R. The biogenic amines in the carotid body ; Prog. Histochem. Cytochem. 10:1-69 (1977)

ANDERTON, J.L. HARRIS, E.A. SLAWSON, K.B. The repeatability of ventilatory responses to excess of carbon dioxide and lack of oxygen ; Q.J. Exp. Physiol. 49:43-51 (1964)

ASSMUSSON, E. CHIODI, H. The effect of hypoxiaemia on ventilation and circulation in man ; Am. J. Physiol. 132:426-436 (1941)

ASSMUSSON, E. NIELSON, M. Ventilatory response to CO_2 during work at normal and at low oxygen tensions ; Acta Physiol. Scand. 39:27-35 (1957)

ASSMUSSON, E. NIELSON, M . Pulmonary ventilation and effect of oxygen breathing in heavy exercise ; Acta Physiol. Scand. 43:365-378 (1958)

ASTRAND, P.O. The respiratory activity in man exposed to prolonged hypoxia ; Acta Physiol. Scand. 30:343-368 (1954)

ASTRAND, P-O. ROHDAHL,K. Textbook of Work Physiology ; (2nd ed.) New York: McGraw (1977)

ASTROM, A. (1942)

BAILEY, P. SWEET, W.H. Effects on respiration, blood pressure and gastric motility of stimulation of orbital surface of frontal lobe ; J. Neurophysiol. 3:276-281 (1940)

BAND, D.M. WOLFF, C.B. WARD, J. COCHRANE, G.M. PRIOR, J. Respiratory oscillations in arterial carbon dioxide tension as a control signal in exercise ; Nature 283:84-85 (1980)

BARNARD, P. et al. Time-dependent effect of hypoxia on carotid body chemosensory function ; J. Appl. Physiol. 63:685-691 (1987)

BARER, G.R. BEE,D. WACH, R.A. GILL, G.W. DHILLON, D.P. SUGGETT, A.J. EVANS, T.W. Does Almitrine Bismesylate improve V/Q mismatching? An animal study; Eur. J. Resir. Dis. Suppl. 126(64):209-214 (1983)

BARTELS, H. WITZLEB, E. W. Der Einfluss des arteriellen CO_2-Druckes auf die chemoreceptorischen Aktionspotentiale im Carotisssinusnerven ;Pflügers Arch. ges Physiol. 262:466-472 (1956)

BARTLETT, D. Jr. TENNEY, S.M. Control of breathing in experimental anaemia: Resp Physiol 10:384-395 (1970)

BEAVER, W.L. WASSERMAN, K. WHIPP, B.J. On-line computer analysis and breath-by-breath graphical displays of exercise function tests ; J. Appl. Physiol. 34:128-132 (1973)

BERGER, A.J. KRASNEY, A.J. DUTTON, R.E. Respiratory recovery from CO_2 breathing in intact and chemodenervated awake dogs ; J. Appl. Physiol. 35:35-41 (1973)

BERGER, A.J. MITCHELL, R.A. SEVERINGHAUS, J.W. Medical Progress : Regulation of respiration ; N. Eng, J. Med. 297:92-97, 138-143, 194-201 (1977)

BERGER, A.J. Distribution of carotid sinus nerve afferents to solitry tract nuclei of the cat using transganglionic transport of horseradish peroxidase ; Neurosci. Lett. 14:153-158 (1979)

BERT, P. La pression barometrique. Paris. Masson. (1878)

BERTHON-JONES, M. SULLIVAN, C.E. Ventilatory and arousal responses to hypoxia in sleeping humans ; Am Rev Resp Dis 125:632-639 (1982)

BHATTACHARYYA, N.K. CUNNINGHAM, D.J.C GOODE, R.C. HOWSON, M.G. LLOYD,B.B. Hypoxia, ventilation, PCO_2 and exercise ; Resp. Physiol. 9:329-347 (1970)

BILLIET, L. BAISIER, W. NAIDTS, JP. Effect of size, sex and age upon the pulmonary diffusing capacity of the norml adult. J. Physiol. (Paris) 55:1-34 (1983)

BISCOE, T.J. Carotid body : structure and function ; Physiol Rev. 51:437-495 (1971)

BISCOE, T.J. MILLAR, R.H. Effect of inhalation anaesthetics on carotid body chemoreceptor activity ; Br. J. Anaesth. 40:2012 (1968)

BISCOE, TJ. PURVES, MJ. Factors affecting the carotid chemoreceptor and cervical sympathetic activity with special refernce to passive hindlimb movements ; J. Physiol. (Lond) 190:425-441 (1967)

BISCOE, TJ. PURVES, MJ. SAMPSON, SR. The frequency of nerve impulses in single carotid chemoreceptor afferent fibres recorded in vivo with intact circulation.J.Physiol. (Lond) 208:121-131 (1970)

BISGARD, G.E. The response of few-fibre carotid chemoreceptor preparations to Almitrine in the dog ; Can. J. Physiol. Pharmacol. 59:396-401 (1980)

BISGARD, G.E. MITCHELL, R.A. HERBERT, D.A. Effects of dopamine, norepinephrine and 5-hydroxytryptamine on the carotid body of the dog ; Resp Physiol. 37:61-80 (1979)

BLACK, AMS. McCLOSKEY, DI. TORRANCE, RW. The response of carotid body chemoreceptors to sudden changes of hypercapnic and hypoxic stimuli ;

Resp. Physiol. (1971) 13:36-49

DuBOIS, A.B. BRITT, A.G. FENN, W.O. Alveolar CO_2 during the respiratory cycle ; J. Appl. Physiol. 4:535-548 (1951)

BOUVEROT, P. FLANDROIS, R. PUCCINELLI, R. DEJOURS, P. Étude du rôle des chémorécepteurs artériels dans la regulation de la respiration pulmonaire chez le chein éveillé ; Arch. Int. Pharmacodyn. 157:253-271 (1965)

BRIGGS, H. Physical exertion Fitness and breathing ; J.Physiol. 54:292-318 (1920)

BUREAU, M.A. CÔTÉ, A. BLANCHARD, P.W. HOBBS, S. FOULON, P. DALLE, D. Exponential and Diphasic ventilatory response to hypoxia in concious lambs ; J. Appl. Physiol. (1986) 61(3):836-842

BUCHFUHRER, M.J. HANSEN, J.E. ROBINSON, T.E. SUE,D.Y. WASSERMAN, K. WHIPP, B.J. Optimising the exercise protocol for cardiopulmonary assessment ; J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 55:1558-1564 (1983)

BYRNE-QUINN, E. WEIL, J.V. SODAL, I.E. FILLEY, G.F. GROVER R.F. Ventilatory control in the athlete ; J. Appl. Physiol. (1971) 30(1):91-98

CALERESU, F.R. CIRIELLO, J. Projections to the hypothalamus from buffere nerves and nucleus tractus solitarius in the cat ; Am. J. Physiol. 239:R130-R136 (1980)

CALVERLEY, P.M.A. MIDDLETON,W. BRASH, H.M. WRAITH, P.K. FLENLEY, D.C. Do human artrial chemoreceptors respond to transient changes in CO_2 tension during exercise? Clin. Sci 56 : 36pP 1984

CARMODY, J.J. SCOTT, M.J. Respiratory and cardiovascular responses to prolonged stimulation of the carotid body chemoreceptors in the cat. J. Exp.Biol. Med. Sci. 52:271-283 (1974)

CHERNIACK, N.S. EDELMAN, N.H. LAHIRI, S. Hypoxia and hypercapnia as respiratory stimulants and depressants ; Resp. Physiol 11:113-126 (1971)

CHIANG, C.H. HOOP, B. SHIH, V.E. KAZEMI, H. Relationship between CNS amino acid neurotransmitters during hypoxiaemia and control of breathing ; AM. Rev. Respir. Dis. 129:A265 (1984)

CHIODI, H. DILL, D.B. CONSOLAZIO, F. HORRATH, S.M. Respiratory and circulatory responses to acute carbon monoxide poisoning. Am. J. Physiol. 134:684-693 (1941)

CHRISTENSEN, N.J. GALBO, H. HANSEN, J.F. HESSE, B. RICHTER, E.A. TRAP-JENSEN, J. Catecholamines and exercise ; Diabetes 28 (suppl 1):58-62

CLANCY, L.J. CRITCHLEY, J.A.J.H. LEITCH, A.G. KIRBY, B.J. UNGAR, A. FLENLEY, D.C. Arterial catecholamines in hypoxic exercise in man ; Clin. Sci. Mol. Med. 49:503-506 (1975)

CLARK,J.M. SINCLAIR, R.D. LENOX, J.B. Chemical and nonchemical components of ventilation during hypercapnic exercise in man ; J. Appl. Physiol. 48(6):1065-1076 (1980).

COHEN, P.J. ALEXANDER, J.S.C. SMITH, T.C. REIVICH, M. WOLLMAN, H. Effects of hypoxia and normocarbia on cerebral blood flow and metabolism in conscious man ; J. Appl. Physiol. 23:183-188 (1967)

COLLINS, DD. SCOGGIN, CH. ZWILLICH, CW. WEIL, JV. Hereditary aspects of decreased hypoxic response. J. Clin. Invest. (1978) 62:105-110

COMROE, J.H. Jr. The location and function of the chemoreceptors of the aorta ; Am. J. Physiol. 127:176-191 (1939)

COMROE, J.H. Jr. SCHMITT, C.F. The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog ; Am. J. Physiol. 121:75-97 (1938)

CONNAUGHTON, J. CALVERLEY, P.M.A. McNEE,W. CRITCHLEY,J.A.H.A. FLENLEY,D.C. The effects of Almitrine on the ventilatory response to hypoxia and hypercapnia in normal man ; Clin. Sci. 62:5p (1982)

COTES,J Lung Function (2nd Ed) (1965).

COTES, J.E. MEADE, F. Physical training in relation to the energy expenditure of walking and factors controlling respiration during exercise Ergonomics 1:195-206 (1959)

CRAPO, R.O. MORRIS, A.H. GARDNER,R.M. Reference spirometric values using techniques and equipment that meet ATS recommendations ; Am. Rev. Resp. Dis. 123:659-664 (1981)

CRAGG, P.A. DRYSDALE, D.B. Interaction of hypoxia and hypercapnia on ventilation, tidal volume and respiratory frequency in the anaesthetised rat ; J. Appl.Physiol. (1984) 57:263p

CROSS, B.A. DAVEY, A. GUZ, A. KATONA, P.G. MACCLEAN, M. MURPHY, K. SEMPLE,S.G.J. STIDWILL, R. The pH oscillations in arterial blood during exercise ; a potential signal for the ventilatory response in the dog ; J. Physiol. 329:57-73 (1982)

CROSS, K.S. OPPE, T.W. The effect of high and low concentrations of oxygen on the respiration of the premature infant ; J. Physiol. (Lond) 117:38-55 (1952)

CRUZ, J.C. REEVES, T.J. GROVER, R.F. MAHER, J.T. McCULLOUGH, R.E. CYMERMAN, A. DENNISTON, J.C. Ventilatory acclimatisation to high altitude is prevented by CO_2 rebreathing ; Respiration 39:121-30 (1980)

CUMMIN, A.R.C. ALISON, J. JACOBI, M.S. IYAWE, V.I. SAUNDERS, K.B. Ventilatory sensitivity to inhaled CO_2 around the control point during exercise ; Clin. Sci. 71:17-22 (1986)

CUNNINGHAM, D.J.C. HEY, E.N. PATRICK, J.M. LLOYD, B.B. The effect of noradrenaline infusion on the relation between pulmonary ventialtion and the alveolar PO_2 and PCO_2 in ma ; Ann. N.Y. Acad. Sci. 109:756-771 (1963)

CUNNINGHAM, DJC. PATRICK, JM. LLOYD, BB. The respiratory response of man to hypoxia, in Oxygen in the Animal Organism. Edited by F. Dickens and E. Neil. Elmsford NY. Pergamon Press. pp277-293. (1964)

CUNNINGHAM, DJC. Intergrative aspects of the regulation of breathing:A personal view. (1974) In MTP International Review of Science: ser. 1, Physiology; Vol. 2, Respiratory Physiology. Edited by AC. Guyton and JG. Widdicombe. Baltimore, University Park Press, pp.303-369.

CUNNINGHAM, D.J.C. SPURR, D. LLOYD, B.B. The drive to ventialtion from arterial chemoreceptors in hypoxic exercise ; in: Arterial Chemoreceptors ed. R.W. Torrance. Oxford. England. Blackwell Scientific Publications pp 301-321 (1968)

DALY, M. De B. LAMBERTSON, CJ. SCHWEITZER, A. Observations on the volume of blood flow and oxygen utilisation of the carotid body in the cat.J. Physiol. (Lond) ((1954)125:67-89

DAVIDSON, A.C. CAMERON, I.R. Potentiation of the ventilatory response to inhaled CO_2 following acute exposure to hypoxia ; Clin. Sci. 63:18 (1982)

DAVIDSON, A.C. CAMERON, I.R. The effect of acute hypoxia on subsequent cardiorespiratory responsiveness in normal man ; Bull. Eur. Physiopathol. Respir. 19:32-33p (1983)

DAVIDSON,A.C. CAMERON,I.R. Ventilatory control in normal man following five minutes exposure to hypoxia ; Resp. Physiol. (1985) 60:227-236

DAVIES, R.O. LAHIRI, S. Absence of carotid chemoreceptor response during hypoxic exercise in the cat ; Resp. Physiol. 18:92-100 (1973)

DeCASTRO, F. Sur le structure et l'innervation du sinus carotidien de l'homme et les mammifères:nouveaux faits sur l'innervation et la fonction du glomus caroticum. Trav.Lab. Rech. Biol. Univ. Madr. (1928) 25:330-380.

DEJOURS, P. Interèt méthodologique de l'étude d'un organisme vivant a la phase initiale de rupture d'un équilibre physiologique. Compte Rende. Acad. Sci. Paris (1957) 245:1946-1948

DEJOURS, P. The regulation of ventilation during muscular exercise in man; J. Physiol (Paris) 51:929-35 (1960)

DEJOURS, P. Chemoreflexes in breathing. Physiol. Rev. (1962) 42:335-358

DEMPSEY, J.A. FORSTER,H.V. BIRNBAUM, M.L. REDDAN, W.G. THODEN, J. GROVER, R.F. RANKIN, J. Control of exercise hyperpnea under varying durations of exposure to moderate hypoxia ; Resp. Physiol. 16:213-231 (1972)

DHILLON, D.P. BARER, G.R. Respiratory stimulation by Almitrine during acute or chronic hypoxia/hypercapnia in rats; Bull. Eur, Physiopath. Resp. 18:751-764 (1982)

DOEKEL, R.C. Jr. ZWILLICH, C.W. SCOGGIN, C.H. KRYGER, M. WEIL, J.V. Clinical semi-starvation : Depression of hypoxic ventilatory response ; N.Eng. J. Med. :358-361 (1976)

DONALD, K.W. WORMALD, P.N. TAYLOR, S.H. BISHOP, J.M. Changes in the oxygen content of femoral venous blood and leg blood flow during leg exercise in relation to cardiac output response ; Clin. Sci. 16:567-591 (1957)

DORNHURST, A.C. Respiratory insufficiency ; Lancet 1:1185-1187 (1955)

DOUGLAS, N.J. BRASH, H.M. WRAITH, P.K. CALVERLEY,P.M.A. LEGGETT, R.J.E. McELDERRY,L. FLENLEY, D.C. Accuracy, sensitivity to carboxyhaemaglobin and speed of response of the Hewlett-Packard 47201A ear oximeter ; Am. Rev. Res. Dis. 119:311-313 (1979)

DRIPPS, RD. AND COMROE, JH. Jr. The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. Am. J. Physiol. 149:277 (1947)

DRYSDALE, D.B. JENSEN, J.I. CUNNINGHAM, D.J.C. The short-latency response to sudden withdrawal of hypercapnia and hypoxia in man ; Q.J. Exp. Physiol. 66:203-210 (1981)

DUKE, H.N. GREEN, J.H. NEIL, E. Carotid chemoreceptor impulse activity during inhalation of carbon monoxide mixture ; J. Physiol. (Lond) 118: 520-527 (1952)

DUFFIN, J. BECHBACHE, R.R. GOODE, R.C. CHUNG, S.A. The ventilatory response to carbon dioxide in hyperoxic exercise ; Resp. Physiol 40:93-105 (1980)

DUMKE, P.R. SCHMIDT, C.F. CHIODI, H. Part played by carotid body reflexes in respiratory response of the dog to anoxemia with and without simultaneous hypercapnia ; Am. J. Physiol 133:1-20 (1941)

DUTTON, R.E. HODSON, W.A. DAVIES, D.G. CHERNIACK, V. Ventilatory adaptation to a step-change in PCO_2 at the carotid bodies ; J. Appl. Physiol. 23:195-202 (1967)

EASTON, P.A. SLYKERMAN, L.J. ANTHONISEN, N.R. Ventilatory response to sustained hypoxia in normal adults ; J.Appl. Physiol. 61(3):906-911 (1986)

EDELMAN, N.H. EPSTEIN, P.E. CHERNIACK N.S. et al Control of cerebral blood flow in the goat:role of the carotid rete ; Am. J. Physiol. 233:615-619 (1972)

EDELMAN, NH. EPSTEIN, PE. LAHIRI, S. CHERNIACK, NS. Ventilatory response to

transient hypoxia and hypercapnia in man ; Resp. Physiol. 17:303-314. (1973)

EDELMAN, N.H. LAHIRI, S. BRAUDO, L. CHERNIACK, N.S. FISHMAN, A.P. The blunted ventilatory response to hypoxia in cyanotic congenital heart disease ; N. Eng J. Med. 282:405-411 (1970)

EDWARDS, M.W.Jr. DAVIES, R.O. LAHIRI, S. Halothane depresses the response of carotid body chemoreceptors to hypoxia and hypercapnia in the cat ; Fed. Proc. 39:828 (1980)

ELDRIDGE, F.L. Central neural respiratory stimulatory effects of active respiration ; J. Appl. Physiol. 37:723-735 (1974)

ELDRIDGE, F.L. GILL-KUMAR, P. Central respiratory effects of CO_2 and carotid sinus nerve and muscle afferents ; J, Physiol. 300:75-87 (1980)

ELDRIDGE, F.L. KILEY, J.P. MILLHORN D.E. Respiratory responses to medullary hydrogen ion changes in cats : Different effects of respiratory and metabolic acidoses. ; J.Physiol. (Lond) 358:285-297 (1985)

EYZAGUIRRE, C. LEWIN, J. Chemoreceptor activity of the carotid body of the cat ; *J. Physiol. (Lond)* 159:222-237 (1961)

EYZAGUIRRE, C. MONTI-BLOCH, L. HAYASHIDA, Y. BARON, M. Biophysics of the carotid body chemoreceptor complex ; in: Physiology of the Peripheral Arterial Chemoreceptors, ed. H. Acker and R.G.O'Regan. New York. Elsevier. pp59-87 (1983)

EYZAGUIRRE, C. UCHIZONO, K. Observations on the fibre content of nerves reaching the carotid body of the cat ; J. Physiol. (Lond) 159:268-281 (1961)

EYZAGUIRRE, C. ZAPATA, P. Pharamcology of pH effects on carotid body chemoreceptors in vitro ; J. Physiol. (Lond) 195:557-588 (1968)

EYZAGUIRRE, C. ZAPATA,P. . Perspectives in carotid body research ; J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 57:931-957 (1984)

FITZGERALD,RS. PARKS, DC. Effect of hypoxia on carotid chemoreceptor response to carbon dioxide in cats ; Respir. Physiol. 12:218-229 (1971)

FITZGERALD, R.S. TRAYSTMAN, R.J. Peripheral chemoreceptors and the cerebral vascular response to hypoxiaemia ; Fed. Proc. 39:2674-2677 (1980)

FLEETHAM, J.A. ARNUP, M.E. ANTHONISEN, N.R. Familial aspects of ventilatory control in patients with chronic obstructive pulmonary disease ; Am. Rev. Respir Dis. 129:3-7 (1984)

FLENLEY, D.C. MILLAR, J.S. REES, H.A. Accuracy of oxygen and carbon dioxide electrodes ; Brit. Med. J. 2:349-352 (1967)

FLENLEY, D.C. BRASH, H. CLANCEY, L. COOKE, N.J. LEITCH, A.G. MIDDLETON, W. WRAITH, P.K. Ventilatory response to steady-state exercise in hypoxia in humans ; J. Appl. Physiol. 46(3):438-446 (1979)

FLENLEY, D.C. MILLAR, J.S. Ventilatory response to transient hypoxia and hypercapnia in man ; Resp. Physiol 17:302-314 (1967)

FLENLEY, DC. FRANKLIN, DH. MILLER, JS. The hypoxic drive to breathing in chronic bronchitis and emphysema ; Clin. Sci. 38:503-518 (1970)

FLENLEY, D.C. COOKE, N.J. KING, A.J. LEITCH,A.G. BRASH, H.M. The hypoxic drive to breathing in normal man and in hypoxic patients with chronic bronchitis and emphysema. (1973)

FLENLEY, D.C. WARREN, P.M. Ventilatory responses to O_2 and CO_2 during exercise ; Ann. Rev. Physiol. 45:415-26 (1983)

FLOYD, W.F. NEIL, E. The influence of the sympathetic innervation of the carotid bifurcation on chemoreceptor and baroreceptor activity in the cat ; Arch. Int. Pharmacodyn. 91:230-239 (1952)

FORSTER, H.V. DEMPSEY, J.A. VIDRUK, E. DO PIKO, G. Evidence of altered regulation of ventilation during exposure to hypoxia ; Resp. Physiol. 20:379-392 (1974)

FORSTER, H.V. DEMPSEY, J.A. BIRNBAUM, M.L. REDDAN, W.G. THODEN, J. GROVER, R.F. RANKIN, J. Effect of chronic exposure to hypoxia on ventilatory response to CO_2 and hypoxia ; J. Appl. Physiol. 31(4):586-592 (1971)

GABEL, R.A. KRONENBERG, R.S. SEVERINGHAUS, J.W. Vital capacity breaths of 5% or 15% CO_2 in N_2 of O_2 to test carotid chemosensitivity ; Resp.Physiol. 17:195-208 (1973)

GALBO, H. KJAER, M. SECHER, N.H. Cardiovascular, ventilatory and catecholamine responses to maximal dynamic exercise in partially curarised man ; J. Physiol. 389:557-568 (1987)

GALDSTON, M. WOLLACK A.C. Oxygen and carbon dioxide tension of alveolar air and arterial blood in healthy young adults at rest and after exercise; Am. J. Physiol. 151:276-281 (1947)

GARDNER, W.N. The pattern of breathing following step-changed of alveolar partial pressures of CO_2 and O_2 in man ; J. Physiol. 300:55-73 (1980)

GAUTIER, H. BONARA, M. Effects of hypoxia and respiratory stimulants in conscious intact and carotid denervated cats ; Bull. Eur. Physiopath Resp. 18:565-582 (1982)

GAUTIER, H. Pattern of breathing during hypoxia or hypercapnia in the awake or anaesthetised cat ; Resp. Physiol. 27:193-206 (1976)

GELFAND, R. LAMBERTSON, C.J. Dynamic respiratory response to abrupt change

of inspired CO_2 at normal and high PO_2 ; J. Appl. Physiol. 35:903-913 (1973)

GESELL, R. LAPIDES, J. LEVIN, M. The interaction of central and peripheral chemical control of breathing ; Am. J. Physiol. 130:155-170 (1940)

GIRARD, F. TEILLAC, A. LEFRANCOIS, R. LACAISSE, A. Étude du stimulus oxygène de la ventilation en hypoxie aiguë ; J. Physiol. (Paris) 51:469-470 (1959)

GODFREY, S. EDWARDS,R.H.T. COPLAND, G.M. GROSS, P.L. Chemosensitivity in normal subjects, athletes and patients with chrinic airways obstruction ; J. Appl. Physiol. 30(2):193-199 (1971)

DeGOEDE, J. VAN DER HOEVEN, N. BERKENBOSCH,A. OLIEVIER, C.N. VAN BEEK, J.H.G.M. Ventilatory responses to sudden isocapnic changes in end-tidal O_2 in cats ; in : Modelling and Control of Breathing ed. B.J. Whipp and D.M. Wilberg. Elsevier Science Publishing Co. Inc. (1983)

GOODMAN, N.W. Some observations on the homogeneity of the response of single chemoreceptor fibres ; Resp. Physiol. 20:271-281 (1974)

GOODMAN, L.S. GILMAN, A. ed. The Pharmacological Basis of Therapeutics 5th ed. New York McMillan (1975)

GOTHE, B. GOLDMAN, M.D. CHERNIACK, N.S. MANTEY. P. Effect of progressive hypoxia during sleep ; Am Rev Resp Dis 126:97-102 (1982)

GOULD,G.A. AIRLIE, M.A.A. BRASH, H.M. WRAITH, P.K. WARREN, P.M. FLENLEY,D.C. The on-phase of ventilatory response to transient hypoxia to assess carotid chemoreceptor mediated ventilatory drive during exercise. Clin Sci 68:62P (1984)

GRAY, B. Response of the perfused carotid body to changes in pH and PCO_2 ; Resp. Physiol. 4:229-245 (1968)

GRINDLAY-MOORE, L. HUANG, S.Y. McCULLOUGH R.E. SAMPSON, J.B. MAHER, J.T. WEIL, J.V. GROVER, R.F. ALEXANDER, J.K. REEVES J.K. Variable inhibition by falling CO_2 of hypoxic ventilatory response in humans ; J. Appl. Physiol. 56(1):207-210 (1984)

GRUNSTEIN, M.M. HAZINSKI, T.A. SCHLEUTER, M.A. Respiratory control during hypoxia in newborn rabbits :implied action of endorphins; J. Appl Physiol 51:122-30 (1981)

GUILLERM, R. RADZISZEWSKI, E. Effets ventilatiores chez l'homme sain un nouvel analeptique respiratiore le S2620 Bull Physiopath Resp. (Nancy) 10:775-91 (1974)

GUZ, A. NOBLE, M.L.M. WIDDICOMBE,J.G. TRENCHARD, D. MUSHIN, W.W. Peripheral chemoreceptor block in man ; Resp. Physiol. 1:38-40 (1966)

HALL, A.M. HAYWOOD, C. COTES, J.E. Lung Function in Healthy British Women ; Thorax 34:359-65 (1979)

HALDANE, JS. PRIESTLEY, JG. The regulation of the lung ventilation ; J. Physiol. (Lond) 32:225-266 (1905)

HATCHER, J.D. CHIU, L.K. JENNINGS, D.B. Anemia as a stimulus to aortic and carotid chemoreceptors in the cat ; J. Appl. Physiol. 44:696-702 (1978)

HEBBEL, R.P. KRONENBERG, R.S. EATON, J.W. Hypoxic ventilatory response in subjects with normal and high oxygen affinity haemaglobins ; J. Clin. Invest. 60:1211-15 (1977)

HESS, A. CASSADY, I. Efferent fibres from the brainstem neurones in the rat carotid sinus nerve ; Soc. Neurosci. Abst. 9:978 (1983)

HESS, A. ZAPATA, P. Innervation of the cat carotid body; normal and experimental studies ; Fed. Proc. 31:1365-1382 (1972)

HESSE, B. KANSTRUP, I.L. CHRISTENSEN, N.J. INGEMANN-HANSEN, T. HALKJAER-KRISTENSEN, J. PETERSEN F.B. Reduced norepinephrine response to dynamic exercise in human subjects during O_2 breathing ; J. Appl. Physiol. 51:176-78 (1981)

HEYMANS, C. BOUCKAERT, J.J. Sinus carotidienne et reflexes respiratoires ; Compte Rend Soc de Biol 103:498-500 (1930)

HEYMANS, C. BOUCKAERT, J.J. DAUTREBANDE, L. Sinus carotidien et réflexes respiratoires; sensibilité des sinus carotidiens aux substances chimiques. Action stimulante respiratoire réflexe du sulfure, de sodium du cyanure, de potassium, de la nicotine et de la lobeline ; Arch. Int. Pharmacodyn. Ther. 40:54-91 (1931)

HEYMANS, C. NEIL, E. Reflexogenic Areas of the Cardiovascular System ; London. Churchill. (1958)

HEDEMARK, L.L. KRONENBERG, R.S. Chemical regulation of Resiration ; Chest 82(4):488-494 (1982)

HICKHAM, J.B. PRYOR, W.W. PAGE, E.B. ATWELL, R.J. Respiratory regulation during exercise in unconditioned subjects ; J. Clin. Invest. 30:503-16 (1951)

HILL, J.E. MERCHANT, S. WARREN, P.M. FLENLEY, D.C Evaluation of the 2001 system for measuring breath-by breath ventilation and gas exchange ; Clin. Sci 74 (suppl 18):3P

HIRSHMAN, CA. MCCULLOUGH, RE. WEIL, JV. Normal values for hypoxic and hypercapnic ventilatory drives in man ; J. Appl. Physiol. 38:1095-1098 (1975)

HOLTON, P. WOOD, J.B. The effects of bilateral removal of the carotid bodies and denervation of the carotid sinuses in two human subjects ; J. Physiol. (Lond) 181:365-378 (1965)

HONDA, Y. WATENABE, S. HASHIGUME, I. SATOMURA. Y. HATA, N. SAKAKIBARA, Y. SEVERINGHAUS, J.W. Hypoxic chemosensitivity in asthmatic patients two decades after carotid body resection ; J. Appl. Physiol. 46:632-638 (1979)

HOOP, B. CHIANG, C.H. PAPPAGIANOPOULOS, P. SHIH, V.E. KAZEMI, H. CNS amino acid neurotransmitter metabolism during respiratory acidosis ; Am. Rev. Resp. Dis. 129:A264 (1984)

HORNBEIN, T.F. The relation between the stimulus **to chemoreceptors and their response ; in : Arterial Chemoreceptors. Ed, R.W. Torrance. Oxford, England. Blackwell Scientific Publications pp 65-78 (1968)**

HORNBEIN, T.F. ROOS, A. Effect of mild hypoxia on ventilation during exercise ; J. Appl. Physiol. 17:239-242 (1962)

HORNBEIN T.F. GRIFFO, Z.F. ROOS, A. Quantitation of chemoreceptor activity: interrelation of hypoxia and hypercapnia ; J.Neurophysiol. 24:561-568 (1961)

HUANG, S.Y. ALEXANDER, J.K. GROVER, R.F. MAHER, J,T, McCULLOUGH, R.G. MOORE, L.G. SAMPSON, J.B. WEIL,J.V. REEVES, J.T. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude ; J.Appl. Physiol. 56:602-606 (1984)

HUDGEL, D.W. WEIL, J.V. Asthma associated with with decreased hypoxic ventilatory drive. Ann INtern. Med. 80:622-625 (1974)

HULSBOSCH, M.A.M. BINKHORST, R.A. FOLGERING, H.T. Effects of positive and negative exercise on ventilatory CO_2 sensitivity ; Eur, J. Physiol. 47:73-81 (1981)

JENNETT,S. WALKER, G. Effect of brief hypoxia on subsequent ventilatory responses in healthy people ; J. Physiol. 350:38p (1984)

JENSEN, JI. VEJBY-CHRISTENSEN, H. PETERSEN, ES. Short latency ventilatory responses to sudden withdrawal of hypoxia at normal and raised body temperature in man ; Acta. Physiol. Scand. 102:257-264 (1978)

JOELS, N. NEIL, E. Chemoreceptor impulse activity evoked by perfusion of the glomus at various PCO_2 and pH values ; J. Physiol. (Lond) 154:7p (1960)

JONES, N.L McHARDY, G.J.R. NAIMARK, A. CAMPBELL, E.J.M. Physiological dead space and alveolar-arterial gas pressure differences during exercise ; Clin. Sci. 31:19-29 (1966)

JONES, N.L. ROBERTSON, D.G. KANE, J.W. Difference between end-tidal PCO_2 in exercise ; J. Appl. Physiol. 47(6):954-960 (1979)

KAWAKAMI, Y. IRIE, T. SHIDA, A. YOSHIKAWA, T. Familial factors affecting arterial blood gas values and respiratory chemosensitivity in chrinic

obstructive pulmonary disease ; Am. Rev. Resp. Dis. 125:420-425 (1982)

KAGAWA, S. STAFFORD, M.J. WAGGENER, T.B. SEVERINGHAUS,J.W. No effect of Naloxone on hypoxia-induced ventilatory depression in adults ; J. Appl. Physiol. 52:1030-1034 (1982)

KAO, F.F. MEI, S.S. The central multiplicative interaction of PO_2 and PCO_2 on ventilation ; in:The Regulation of Respiration during sleep and anaesthesia. Ed. R.S.Fitzgerald, J. Gautier and S. Lahiri. New York Plenum Press pp403-414 (1978)

KING, A.B. ROBINSON, S.M. Ventilation response to hypoxia and acute mountain sickness ; Aerosp. Med. 43:419-421 (1972)

KLAUSEN, K. DILL, D.B. HORVATH, S.M. Exercise at ambient and high oxygen pressure at high altitude and at sea level ; J. Appl. Physiol 29:456-463 (1970)

KONDO, H. Innervation of the carotid body of the adult rat ; Cell Tissue Res. 173:1-15 (1976)

KRONENBERG, R.S. DRAGE, C.W. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal man ; J. Clin. Invest 52:1812-1819 (1973)

KRONENBERG, R. HAMILTON, F.N. GABEL,R. HICKEY, R. READ, D.J.C. SEVERINGHAUS,J. Comparison of 3 methods for quantitating the respiratory response to hypoxia in man ; Resp. Physiol. 16:109-125 (1972)

LAHIRI, S. KAO, F.F. VELASQUEZ, T. et al Respiration of man during exercise at high altitude : highlander vs lowlander Resp. Physiol 8:351-75 (1970)

LAHIRI, S. MILLEDGE, J.S. SORENSEN, S.C. Ventilation in man during exercise at high altitude ; J. Appl .Physiol. 32:766-769 (1972)

LAHIRI,S. Depressant effect of acute and chronic hypoxia on ventilation ; in; Morphology and Mechanisms of Chemoreceptor ed. A.S. Paintal Nachvetan Press (P) Ltd. India. (1974)

LAHIRI, S. EDELMAN, N.H. Peripheral chemoreflexes in the regulation of breathing of high altitude natives ; Resp.Physiol. 6:375-385 (1969)

LAHIRI, S. DELANEY, RG. Stimulus interaction in responses of carotid body chemoreceptor single afferent fibers ; Respir. Physiol. 24:249-266 (1975)

LAHIRI, S. DELANEY, R.G. Relationship between carotid chemoreceptor activity and ventilation in the cat ; Resp. Physiol. 24:267-286 (1975a)

LAHIRI, S. GELFAND, R. Mechanisms of acute ventilatory responses ; in: Regulation of Breathing ed. T.F. Hornbein, part II pp 773-843 (1981)

LAHIRI, S. MOKASHI, A. MULLIGAN, E. NISHINO, T. Comparison of aortic and

carotid chemoreceptor responses to hypercapnia and hypoxia ; J. Appl. Physiol. 51:55-61 (1981)

LAHIRI, S. NISHINO, T. MULLIGAN, E. MOKASHI, A. Relative latency of responses of chemoreceptor afferents from aortic and carotid bodies ; J.Appl. Physiol. 48:362-369 (1980)

LAMBERTSON, C.J. GELFAND, R. KEMP. R.A. Dynamic response characteristics of several CO_2-reactive components of the respiratory control system. In : Cerebrospinal Fluid and the REgualtion of Ventilation ed. C. Mc Brooks, F.F. Kao, and B.B. Lloyd, Philadelphia. Davis pp 211-240 (1965)

LAUBIE, M. Respiratory neurones in the chemoreceptor pathway activated by Almitrine Bismesylate ; Eur. J. Respir. Dis. Suppl. 126:191-195 (1983)

LAUBIE, M. DIOT, F. A pharmacological study of the respiratory stimulant action of S2620. The role of the carotid and aortic chemoreceptors ; J. Pharmacol. (paris) 3:363-374 (1972)

LAUBIE, M. SCHMITT, H. Long-lasting hyperventilation induced by Almitrine: evidence for a specific effect on carotid and thoracic chemoreceptors ; Eur. J. Pharmacol. 61:125-136 (1980)

LEE, L-Y. MILHORN, H.T. Central ventilatory responses to O_2 and CO_2 at three levels of carotid chemoreceptor stimulation ; Resp. Physiol. 25:319-333 (1975)

LEFRANCIOS, R. GAUTIER, H. PASQUIS, P. CEVAER, A.M. HELLOT, M.F. LEROY, J. Chemoreflex ventilatory response to CO_2 in man at low and high altitudes ; Resp. Physiol. 14:296-306 (1972)

LEITCH, A.G. The hypoxic drive to breathing in normal man. Ph.D. Thesis University of Edinburgh (1976)

LEITCH, A.G. CLANCEY, L.J. COSTELLO, J.F. et al Intravenous infusion of Salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal man ; Br. Med, J. 1:365-7 (1976)

LEITCH, AG. CLANCY, L. FLENLEY, DC. Maximal oxygen uptake, lung volume and ventilatory response to carbon dioxide and hypoxia in a pair of identical twin athletes ; Clin. Sci. Mol. Med. 48:235-238. (1975)

LEITCH, A.G. CLANCY, L. FLENLEY, D.C. Measurement of the hypoxic drive to breathing at rest and on exercise using transient, progressive and steady-state hypoxic methods in normal subjects ; Clin. Sci. Mol. Med. 51:12p (1976)

LEUSEN, I.R. Chemosensitivity of the respiratory centre: influence of Co_2 in the cerebral ventricles on respiration ; Am. J. Physiol. 176:39-44 (1954)

LLOYD,B.B. JUKES, M.G.M. CUNNINGHAM,D.J.C. The relation between alveolar oxygen pressure and the respiratory response to CO_2 in man ; Q.J. Exp. Physiol. 43:214-221 (1958)

LOESCHCKE, H.H. Central chemosensitivity and the reaction theory ; J. Physicl. (Lond) 332:1-24 (1982)

LOESCHCKE, H.H. GERTZ, H.H. Einfluss des O_2-Druckes in der Einatmungsluftauf die Atemtätigkeit des Menschen, geprüft unter Konstanthaltung des alveolaren CO_2-Druckes ; Pflüg. Arch. Ges. Physiol. 267:460-477 (1958).

LOESCHCKE, H.H DELATTRE, J. SCHLAFKE, M.E. et al Effects on respiration and circulation of electrically stimulating the ventral surface of the medulla oblongata ; Resp. Physiol 10 :184-197 (1970)

LUGLIANI, R. WHIPP, BJ. SEARD, C. WASSERMAN, K. Effect of bilateral carotid resection on ventilatory control at rest and during exercise in man ; N. Eng. J. Med. 285:1105-1111 (1971)

MAHLER, D.A. MORITZ,E.D. LOKE, J. Ventilatory responses at rest and during exercise in marathon runners ; J. Appl. Physiol. 52:388-392 (1982)

MAJCHERCZYK, S. CHRUSCIELEWSKI, L. TRZEBSKI, A. Effect of stimulation of carotid body chemoreceptors upon ganglioglomerular nerve activity and on chemoreceptor discharges in contralateral sinus nerve ; Brain Res. 76:167-170 (1974)

MARTIN, B.J. WEIL,J.V. SPARKS, K.E. McCULLOUGH, R.E. GROVER. R.F. Exercise ventilation correlated positively with ventilatory chemoresponsiveness ; J. Appl. Physiol. 45: 557-564 (1978)

MASSON, R.G. LAHIRI, S. Chemical control of breathing during hypoxic exercise ; Resp. Physiol. 22:241-262 (1974)

MATSUURA,S. Chemoreceptor properties of glomus tissue found in the carotid region of the cat ; J. Physiol. (Lond) 235:57-63 (1973)

McDONALD, DM. AND MITCHELL, RA. The innervation of glomus cells, ganglion cells, and blood vessels in the rat carotid body: a quantitative ultrastructural analysis ; **J. Neurocytol. 4:117-230 (1975)**

McQUEEN, D.S. EYZAGUIRRE,C. Effects of temperature on carotid chemoreceptor and baroreceptor activity ; J. Neurophysiol. 37:1287-1296 (1974)

McDOWALL, D.G. Interrelationships between blood oxygen tension and cerebral blood flow in : Oxygen measurements in blood and tissues ed. J.P.Payne and D.W. Hill. London Churchill. pp 205-214 (1966)

METIAS, E.F. CUNNINGHAM, D.J.C. HOWSON, M.G. PETERSEN, E.S. WOLFF, C.B. Reflex

effects on human breathing of breath-by-breath changes of the time profile of alveolar PCO_2 during steady-state hypoxia ; Pflügers Arch. 389:243-250 (1981)

MILLEDGE, J.S. LAHIRI, S. respiratory control in lowlanders and Sherpa highlanders at altitude Resp. Physiol 2:310-22 (1967)

MILLER, J.P. CUNNINGHAM, D.J.C. LLOYD, B.B. YOUNG, J.M. The transient repiratory effects in man of sudden changes in alveolar CO_2 in hypoxia and in high oxygen ; Resp. Physiol. 20:17-31 (1974)

MILLER, M.J. TENNEY, S.M. Hypoxia-induced tachypnea in carotid-deafferented cats ; Resp. Physiol. 23:31-39 (1975)

MILLHORN, D.E. ELDRIDGE, F.L. WALDROP, T.G. Stimulation of respiration by a central endogenous serotonergic mechanism ; Physiologist 22:89 (1979)

MILLHORN, D.E. ELDRIDGE, F.L. WALDROP, T.G. Prolonged stimulation of respiration by a new central neural mechanism ; Resp. Physiol. 41:87-103 (1980)

MILLHORN, D.E. ELDRIDGE, F.L. WALDROP, T.G. Effects of medullary area $I_{(m)}$ cooling on the respiratory response to chemoreceptor inputs ; Resp. Physiol. 49:23-39 (1982).

MITCHELL, R.A. McDONALD, D.M. Adjustment of chemoreceptor sensitivity in the cat carotid body by reciprocal synapses. The Peripheral Arterial Chemoreceptors ed. M.J. Purves London, Cambridge University Press pp 269-282 (1975)

MITCHELL, R.A. LOESCHKE, H.H. MASSION, W,H, et al Respiratory responses mediated through superficial chemosensitive areas on the medulla ; J. Appl. Physiol. 18:523-533 (1963)

MOORE,L.G. ZWILLICH, C.W. BATTAGLIA,J.D. COTTON, E.K. WEIL,J.V. Respiratory failure assosciated with familial depression of ventilatory response to hypoxia and hypercapnia ; N. Eng. J. Med. 295: 861-865 (1976)

MORRILL, C.G. MEYER, J.R. WEIL, J.V. Hypoxic ventilatory depression in dogs; J. Appl. Physiol. 38:143-146 (1975)

MOUNTAIN, R. ZWILLICH, C.W. WEIL, J.V. Hypoventialtion in obstructive lung disease. The role of familial factors ; N. Eng. J. Med. 298:521-525 (1978)

MOYER, C.A. BEECHER, H.K. Effect of barbiturate anaesthesia (epival and pentothal sodium) upon integration of respiratory control mechanisms. Study directed towards improvement of methods for preclinical evaluation of anaesthetic agents J. Clin. Invest 21:429-455 (1942)

McQUEEN, D.S. A quantitative study of the effects of cholinergic drugs on carotid chemoreceptors in the cat ; J. Physiol. 273: 515-532 (1977)

MITCHELL, R.A. The regulation of respiration in metabolic acidosis and alkalosis. Cerebrospinal fluid and the aregulation of ventilation. ed. C. McBrooks, F.F. Kao, B.B. LLoyd, Oxford, Blackwell (1965)

MIYAMURA, M. YAMASHINA, T. HONDA, Y. Ventilatory responses to CO_2 rebreathing at rest and during exercise in untrained subjects and athletes ; Jpn. J. Physiol. 26:245-254 (1976)

MYHRE, K. ANDERSEN, K.L. Respiratory responses to static muscular work ; Resp. Physiol 12:77-89 (1971)

NATALINO, M.R. ZWILLICH,C.W. WEIL, J.V. Effects of hyperthermia on hypoxic ventilatory response in normal man ; J. Lab. Clin. Med. 80:564-572 (1977)

NEIL, E. AND JOELS, N. The carotid glomus sensory mechanism. The Regulation of Human Respiration. Edited by DJC Cunningham, BB Lloyd. Oxford, Blackwell, pp. 163-172. (1963)

NEIL, E. O'REGAN, R.G. Effects of sinus and aortic nerve efferents on arterial chemoreceptor function ; J. Physiol. (Lond) 200:69-71p (1969

NEIL, E. O'REGAN, R.G. Efferent and afferent impulse activity recorded from few-fibre preparations of otherwise intact sinus and aortic nerves; J. Physiol. (Lond) 215:33-47 (1971a)

NIELSEN, A.M. BISGARD, G.E. VIDRUK, E.H. Carotid chemoreceptor activity during acute and sustained hypoxia in goats ; J. Appl. Physiol. 65:1796-1802 (1988)

NIELSON , M. SMITH, H. Studies on the regulation of repiration in acute hypoxia ; Acta Physiol. Scand. 24:293-313 (1951)

NISHIMURA, M. SUZUKI,A. NISHIURA, Y. YAMAMOTO, H. MIYAMOTO, K. KISHI, F. KAWAKAMI, Y. Effect of brain blood flow in hypoxic ventilatory response in humans ; J.Appl. Physiol. 63:1100-1106 (1987)

O'REGAN, R.G. Control of carotid body chemoreceptors by autonomic nerves; Ir. J. Med. Sci. 146:199-205 (1977)

O'REGAN, R.G. Efferent control of chemoreceptors ; in : Morphology and Mechanisms of Chemoreceptors ed. A.S.Paintal Nachvetan Press (P) Ltd. India. (1976)

O'REGAN,R.G. Responses of carotid body chemosensory activity and blood flow to stimulation of sympathetic nerves in the cat ; J. Physiol (Lond) 315:81-98 (1981)

O'REGAN, R.G. MAJCHERCZYK, S. PRZYBYSZEWSKI, A. Effects of Almitrine Bismesylate on activities recorded from nerves supplying the carotid bifurcation in the cat ; Eur. J. Respir. Dis. Suppl.126 64:197-202 (1983)

PAINTAL, A.S. RILEY, R.L. Responses of aortic chemoreceptors ; J. Appl.

Physiol. 21:543-548 (1966)

PANNETON, W.M. LOEWY, A.D. Projections of the carotid sinus nerve to the nucleus of the solitary tract in the cat ; Brain Res. 191:239-244 (1980)

PAPPENHEIMER J.R. FENCL, V. HEISEY, S.R. et al Role of cerebral fluids in control of respiration as studied in unanaesthetised goats ; Am. J. Physiol. 208:436-450 (1963)

PETERSON, D.D. PACK, A.I. SILAGE, D.A. FISHMAN, A.P. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. Am. Rev. Resp. Dis. 124:387-391 (1981)

PONTE, J. PURVES, M.J The role of the carotid body chemoreceptors and carotid sinus baroreceptors in the control of cerebral blood vessels ; J. Physiol 237:315-40 (1974)

POWELL, E. FEINGOLD, A. GRASSINO, A. Effects of Almitrine on ventilation in normal human subjects ; Am. Rev. Resp. Dis. 123:206 (1981)

PURVES, M.J. The effect of hypoxia, hypercapnia, and hypotension upon carotid body blood flow and oxygen consumption in the cat ; J. Physiol. (Lond) 209:395-416 (1970)

RAHN, H. OTIS, A.B. Mans's respiratory response during and after acclimatisation to high altitude ; Am. J. Physiol. 157:445-462 (1969)

READ, D.J.C. A clinical method for assessing the ventilatory response to carbon dioxide ; Australas. Ann. Med 16:20-32 (1967)

REBUCK, A.S. CAMPBELL, E.J.M. A clinical method for assessing the ventilatory response to hypoxia ; Am. Rev. Resp. Dis. 109:345-350 (1974)

REBUCK, A.S. KANGALEE, M. PENGELLY, D. CAMPBELL,E.J.M. Correlation of ventilatory responses to hypoxia and hypercapnia ; J. Appl. Physiol. 35:173-177 (1973)

REYNOLDS, W.J. MILHORN, H.T.Jr. Transient ventilatory response to hypoxia with and without controlled alveolar PCO_2 ; J. Appl. Physiol. 35:187-196 (1973)

REYNOLDS, W.J. MILLHORN, H.T Jr HOLLOMAN G.H. Jr Transient ventilatory response to graded hypercapnia in man J. Apl. Physiol 33:47-54 (1972)

RIGATTO, H. BRADY, J.P. de la TORRE VERDUZCO, R. Chemoreceptor reflexes in preterm infants: I The effect of gestational and postnatal age on the ventilatory response to inhalation of 100% and 15% oxygen ; Pediatrics 55:604-613 (1975)

ROUMY, M. LEITNER, L.M. Stimulant effect of Almitrine (S2620) on the rabbit carotid chemoreceptor afferent activity ; Bull. Eur. Physiopath. Resp. 17:255-259 (1981)

SAMAAN, A. STELLA, G. The response of the chemical receptors of the carotid sinus to the tension of the CO_2 in the arterial blood in the cat; J. Physiol.85:309-319 (1935)

SAHN, S.A. ZWILLICH,C.W. DICK, N. McCULLOUGH, R.E. LAKSHMINARYAN, S. WEIL, J.V. Variability of ventilatory responses to hypoxia and hypercapnia ; J. Appl. Physiol. 43 : 1019-1025 (1977)

SAMPSON, S.R. Effects of mecamylamine on responses of carotid body chemoreceptors in vivo to phsiological and pharmacological stimuli ; J. Physiol. (Lond) 212:655-666 (1971)

SAMPSON, S.R. Mechanism of efferent inhibition of carotid body chemoreceptors in the cat ; Brain Res. 45:266-270 (1972)

SAMPSON, S.R. Pharmacology of feedback inhibition of carotid chemoreceptors in the cat ; in: The pePeripheral Arterial Chemoreceptors ed. M.J. Purves New York. Cambridge Uni. Press. pp207-217 (1975)

SAMPSON, S.R. BISCOE, T.J. Efferent control of the carotid body chemoreceptor ; Experientia 26:261-2 (1970)

SANKARAN, K. WIEBE, H. SESHIA, M.M.K. BOYCHUK, R.B. CATES, D. RIGATTO, H. Immediate and late ventilatory response to high and low O_2 in preterm infants and adult subjects ; Pediatr. Res. 13:875-878 (1979)

SAUNDERS, N.A. HEILPERN, S. REBUCK, A.S. Relation between personality and ventilatory response to carbon dioxide in normal subjects : A role in asthma? ; Brit. Med. J. 1:719-721 (1972)

SAUNDERS, N.A. LEEDER, S.R. REBUCK A.S. Ventilatory response to carbon dioxide in young athletes : a family study ; Am. Rev. Resp. Dis. 113:497-502 (1976)

SCHLAEFKE, M.E. SEE, W.R. HERKER_SEE, A. LOESCHCKE, H.H. Respiratory response to hypoxia and hypercapnia after elimination of centrral chemosensitivity ; Pflügers Arch. 381:241-248 (1979)

SEE, W.R. respiratory drive in Hyperthermia, interaction with central chemosensitivity In: Loeschcke h.h. ed. :Acid-Base Homeostasis of the Brain Extracellular Fluid and the Respiratory Control System p122-9 Stuttgart Thieme 1976**SENEPATI,J.M.** Effect of stimulation of muscle afferents on ventilation in dogs ; J. Appl. Physiol. 21:242-246 (1966)

SERGEANT, A.J. ROULEAU, M.Y. SUTTON, J.R. JONES, N.L. Ventilation in exercise studied with circulatory occlusion ; J. Appl. Physiol. 50:718-723 (1981)

SEVERINGHAUS, J.W. MITCHELL, R.A. RICHARDSON, B.W. Respiratory control at high altitude suggesting active transport regulation of CSF pH ; J. Appl. Physiol.18:1155-1166 (1963)

SEVERINGHAUS, J.W. BAINTON, C.R. CARCELEN, A. Respiratory insensitivity to hypoxia in chronically hypoxic man ; Resp. Physiol. 1:308-334 (1966)

SHAMS, H. Differential effects of CO_2 and H^+ as central stimuli of respiration in the cat ; J. Appl. Physiol. 58:357-364 (1984)

SHAW, R.A. SCHONFELD,S.A. WHITCOMB, M.E. Progressive and transient hypoxic ventilatory drive tests in normal subjects ; Am. Rev. Resp. Dis. 125:37-40 (1982)

SCOGGIN, CH. DOEKEL, RD. KRYGER, MH. ZWILLICH, CW. Familial aspects of decreased hypoxic drive in endurance athletes ; J. Appl. Physiol:Respirat. Environ. Exercise Physiol. 44:464-468 (1978)

SMATRESK. N. LAHIRI. S. POKORSKI, M. BERNARD, P. Physiologist 26:629 (1981) Augmented efferent inhibition of carotid body chemoreceptors in chronically hypoxic cat

REPORT OF THE SNOWBIRD WORKSHOP ON STANDARDISATION OF SPIROMETRY R.M. Gardner, Chairman ATS News 3 (no 3) (1977)

SORENSON, S.C. SEVERINGHAUS, J.W. Respiratory sensitivity to acute hypoxia in man born at sea level living at high altitude ; J. Appl. Physiol. 25:211-216 (1968)

STANLEY, N.N. GALLOWAY, J.M. GORDON, B. PAULY, N. Increased respiratory sensitivity induced by infusing Almitrine intravenously in healthy man ; Thorax 38:200-204 (1983)

STOCKLEY, R.A. The estimation of the resting reflex drive to respiration in normal man ; Resp. Physiol. 31: 217-230 (1977)

STRADLING, J.R. BARNES, P. PRIDE, N.B. The effects of Almitrine on the ventilatory response to hypoxia and hypercapnia in normal subjects ; Clin. Sci. 63:401-404 (1982)

SWANSON, G.D. WHIPP, B.J. KAUFMAN, R.D. AQLEH,K.A. WINTER, B. BELLVILLE, J.W. Effect of hypercapnia on hypoxic ventilatory drive in normal and carotid body-resected man ; J.Appl. Physiol. 45: 971-977 (1978)

TENNEY, S.M. OU, L.C. Ventilatory response of decorticate and decerebrate cats to hypoxia and CO_2 ; Resp. Physiol. 29:81-92 (1977)

TEPPEMA, L.J. BARTS, P.W.J.A. FOLGERING, H.T. EVERS, J.A.M. Effects of respiratory and (isocapnic) metabolic acid-base disturbances on medullary extracellular fluid pH and ventilation in cats ; Resp. Physiol. 53:379-395 (1983)

TIBES, U. HEMMER, B. BONING, D. Heart rate and ventilation in relation to venous [K^+], osmolality, pH PCO_2, PO_2 [orthophosphate], and [lactate] at transition from rest to exercise in athletes and non-athletes ; Eur. J. Appl. Physiol. 36:127-140 (1977)

TOBIN, M.J. MADOR, M.J. GUENTHER, S.M. LODATO, R.F. SACKNER, M.A. Variability

of respiratory drive and timing in healthy subjects J. Appl. Physiol 65:309-17 (1988)

TORRANCE, R.W. Prolegomena. In: Proceedings of Wates Foundation Symposium on Arterial Chemoreceptors ; Oxford : Alden and Mowbray pp1-40 (1968)

TRZEBSKI, A. MAJCHERCZYK, S. SZULCZYK, P. et al Direct nervous mechanisms as possible pathways if interaction of the central and peripheral chemosensitive areas. in :Loeschcke H.H. ed Acid Base Homeostasis of the brain extracellular fluid and the respiratory control system. Stuttgart Thieme (1976)

VAN BEEK, J.H. BERKENBOSCH, A. DE GOEDE, J. OLIEVIER, C.N. Effects of brainstem hypoxiaemia on the regulation of breathing Resp. Physiol. 57:171-88 (1984)

VERNA, A. Ultrastructural localisation of postganglionic sympathetic nerve endings in the rat carotid body ; in: Arterial Chemoreceptors. Proceedings of the Sixth International Meeting. ed. C. Belmonte, D. Acker, and S. Fidone. Leicester U.K. Leicester University Press p336-343 (1981)

VIZEK, M. PICKETT, C.K. WEIL, J.V. Biphasic ventilatory response of adult cats to sustained hypoxia has central origin ; J. Appl. Physiol. 63:1658-1664 (1987)

VIZEK, M. PICKETT, C.K. WEIL, J.V. Interindividual variation in hypoxic ventilatory response: potential role of the carotid body ; J. Appl. Physiol. 63:1884-1889 (1987a)

VIZEK, M. PICKETT, C.K. WEIL, J.V. Increased carotid body hypoxic sensitivity during acclimatisation to hypobaric hypoxia ; J.Appl.Physiol. 63:2403-2410 (1987b)

VON EULER, U.S. LILJESTRAND, G. ZOTTERMAN, Y. The excitation mechanism of the chemoreceptors of the carotid body ; Skand. Arch. Physiol. 83:132-152 (1939)

WADE, J.G LARSON, C.P. Jr. HICKEY, R.F. EHRENFELD, W.K. SEVERINGHAUS, J.W. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man : N. Eng. J. Med. 282:823-829 (1970)

WARREN , P.M. CALVERLEY, P.M.A. LEITCH, A.G. WRAITH,P.K. BRASH, H.M. FLENLEY,D.C. Comparison of three techniques for assessing hypoxic drive in normal subjects ; Clin Sci 64:42P (1983)

WASSERMAN, K. VAN KESSEL, A.L. BURTON, G.G. Interaction of physiological mechanisms during exercise. J.Appl.Physiol. 22:71-85 (1967)

WASSERMAN, K. WHIPP, B.J. KOYAL, S.N. CLEARY, M.G. Effect of carotid body resection on ventilatory and acid-base control during exercise ; J. Appl.

Physiol. 39:354-358 (1975)

WASSERMAN K. WHIPP, B.J. The carotid bodies and respiratory control in man; in: Morphology and Mechanisms of Chemoreceptors ed. A.S. Paintal Delhi, Vallabhbhai Patel Chest Inst. pp156-174 (1976)

WASSERMAN, K. HANSEN, J.E. SUE, D.Y. WHIPP, B.J. Princplles of exercise testing and interpretation. Febiger. Philadelphia (1987)

WATT, J.G. DUMKE, P.R. COMROE, J.H.Jr. Effects of inhalation of 100 per cent and 14 per cent oxygen upon respiration of unanaesthetised dogs before and after chemoreceptor denervation ; Am. J. Physiol. 138:610-617 (1943)

WEIL, J.V. BYRNE-QUINN, E. SODAL, I.E. FRIESEN, W.O. UNDERHILL, B. FILLEY, G.F. GROVER, R.F. Hypoxic ventilatory drive in normal man ; J. Clin. Invest. 49:1061 (1970)

WEIL, J.V. BYRNE-QUINN, E. SODAL, I.E. et al Aquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. J. Clin. Invest 50:186-95 (1971)

WEIL, J.V. BYRNE-QUINN, E. SODAL, I.E. KLEIN, J.S. McCULLOUGH, R.E. FILLEY, G.F. Augmentation of chemosensitivity during mild exercise in normal man; J.Appl. Physiol. 33:813-819 (1972)

WEIL, J.V. ZWILLICH, C.W. Assessment of ventilatory response to hypoxia ; Chest 70(suppl):124-128

WEISER, P.C. McCULLOUGH, R.E. GROVER R.F. Hypoxic ventilatory drive during exercise in athletes and non-athletes ; Med. Sci Sports 7:80 (1975)

WEISKOPF, R.B. GABEL, R.A. Depression of ventilation during hypoxia in man; J.Appl.Physiol. 39:911-915 (1975)

WEST, J.B Diffusing capacity of the lung for carbon monoxide at high altitude J. Appl. Physiol. 421:421 (1962)

WHIPP, B.J. DAVIES, J.A. Peripheral chemoreceptors and exercise hyperpnea ; Med. Sci. Sports 11:204-212 (1979)

WHIPP, B.J. DRYSDALE, D.B. CUNNINGHAM, D.J.C. PETERSEN E.S. The interaction of peripheral and intercranial respiratory drive in man studied by transients ; Bull. Eur. Physiopathol. Resp. 14:254-255p (1976)

WHIPP, B.J. WASSERMAN, K. Alveolar-arterial gas tension differences during graded exercise ; J. Appl. Physiol. 27:361-365 (1969)

WHIPP, B.J. WASSERMAN, K. Carotid bodies and ventilatory control dynamics in man ; Fed. Proc. 39:2668-2673 (1980)

WILLSHAW, P. Sinus nerve efferent fibres as alink between central and peripheral chemoreceptors ; in: The Peripheral Arterial Chemoreceptors ed. M.J. Purves Cambridge. Cambridge University Press. (1975)

WINN, H.R. RUBIO, R. BERNE, R.M. Brain adenosine concentration during hypoxia in rats Am J. Physiol. 241:h235-42 (1981)

WHITE,DP. DOUGLAS,NJ, PICKETT, CK. WEIL, JV. ZWILLICH, CW. Sexual influence on the control of breathing ; J. Appl. Physiol. 54:874-879 (1983)

WHITELAW, WA. DERENNE, J-P. MILIC-EMILI, J. Occlusion pressure as a measure of respiratory centre output in conscious man ; Respir. Physiol. 23:181-199 (1975)

WINSLOW, J.B. Exposition anatomique de la structure du corps humain ; Paris : Desprez and Desessartz p463 (Traite des Nerfs, Para 371-373 Amsterdam :Réimprimé aux depens de la Compagnie, 1732, vol 3 p222)

YAMASHITA, H. Effect of baro and chemoreceptor activation on supraoptic nuclei neurons in the hypothalamus ; Brain Res. 126:551-556 (1977)

YAMOMOTO, W.S. Mathematical anlysis of the time course of alveolar IO_2 J. Apll. Phsiol. 15:215-219 (1960)

ZWILLICH, CW, SAHN, SA. AND WEIL, JV. Effect of hypermetabolism on ventilation and chemosensitivity; J. Clin Invest. 60:900-906 (1977)

Ammendments to Bibliography

ASTROM, A.. On the action of combined carbon dioxide excess and oxygen deficiency in the regulation of breathing Acta Physiol Scand 27 (suppl98) 1-6

BARTEL, H. AND HARMS, H. Sauerstoffdissoziationskurven des Blutes von Saugetieren. Arch Ges PHysiol 268 334-365 (1959)

DEJOURS, P. Control of respiration in muscular exercise. in: Handbook of Physiology Section 3 Respiration Vol. 1 ed. WO Fenn and H Rahn. Washington DC American Physiological Society p631-648 (1964)

DOUGLAS, NJ. WHITE, DP. WEIL, JV. PICKETT, CK. MARTIN, RJ. HUDGEL, DW. ZWILLICH, CW. Hypoxic ventilatory response decreases during sleep in normal man.

LEE, KD. MAYOU, RA. AND TORRANCE, RW.The effect of blood pressure upon carotid chemoreceptor discharge to hypoxia, and the modificaton of this effect by the sympathetic adrenal system Q.J. Exp. Physiol. 49:171-83 (1964)

LLOYD, BB. AND CUNNINGHAM, DJC. A quantitative approach to the regulation of human respiration in:The regulation of Human Respiration ed. DJC Cunningham and BB Lloyd Oxford. Blackwell p331-349 (1963)

McQUEEN, DS AND EYZAGUIRRE, E. Effects of temperature on carotid chemoreceptor and baroreceptor activity. J. Neurophysiol. 37:1287-1296 (1974)

REBUCK, JS. AND READ, J. Patterns of ventilatory response to carbon dioxide during recovery from severa asthma Clin Sci 41:13-21 (1971)

SAMPSON, SR. AMINOFF, MJ, JAFFE, RA et al A Pharmacological analysis of neurally induced inhibition of carotid chemoreceptor activity in cats. J. pharmacol Exp. Ther. 197 (1):119-125 (1976)

SAUNDERS, KB Oscillations of arterial CO2 tension in a respiratory model: some implications for the control of breathing in exercise J Theor Biol 84:163-79 (1980)

SLUTSKY, SR. MAHUTTE, CK. REBUCK, RS. A critique of presently used hypoxic sensitivity parameters. Hypoxia Symposium. Arctic Institute of North America p894 (1979)

GLOSSARY

P_I	partial pressure of inspired gas (kPa or mmHg)
P_{ET}	partial pressure of end-tidal gas (kPa or mmHg)
P_A	partial pressure of alveolar gas (kPa or mmHg)
P_a	partial pressure of arterial gas (kPa or mmHg)
F_I	fractional concentration of inspired gas (%)
F_E	fractional concentration of expired gas (%)
$\dot{V}_E$	expired ventilation (l min^{-1})
$\dot{V}_E inst$	instantaneous expired minute ventilation (l min^{-1})
$\dot{V}_t$	tidal volume (l)
f	respiratory frequency (breaths min^{-1})
$\dot{V}O_2$	oxygen consumption (l min^{-1})
$\dot{V}CO_2$	carbon dioxide elimination (l min^{-1})
RQ	respiratory exchange ratio (VCO_2/VO_2)
$\dot{V}O_2 max$	maximum oxygen consumption (l min^{-1})
S_aO_2	arterial oxygen saturation (%)
FEV_1	forced expiratory volume in 1 second (l)
VC	vital capacity (l)
TLC	total lung capacity (l)
RV	residual volume (l)
FRC	fuctional residual capacity (l)
ERV	expiratory reserve volume (l)
TLCO	single-breath carbon monoxide diffusion factor (mmol/kPa.min)
RAW	airways resistance (kPa.sec)/l
GAW	airways conductance l $(kPa.sec)^{-1}$
SGAW	airways specific conductance $(kPa.sec)^{-1}$
BTPS	body temperature and pressure, saturated
STPD	standard temperature and pressure, dry