THE HYPOXIC DRIVE TO BREATHING

IN NORMAL MAN

by

ANDREW GORDON LEITCH

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ACKNOWLEDGEMENTS

NOTE OF PREVIOUS PUBLICATIONS

Some results of this study have been previously published as:-

1. The hypoxic drive to breathing during exercise in normal man and in hypoxic patients with chronic bronchitis and emphysema. (1973) Flenley, D.C., Cooke, N.J., King, A.J., Leitch, A.G. and Brash, H.M. Bulletin de Physiopathologie Respiratoire 9, 689-691.

2. The effect of bendrofluazide and frusemide on the ventilatory response to carbon dioxide and hypoxia in normal man. (1974) Leitch, A.G., Clancy, L.J. and Flenley, D.C. Clinical Science and Molecular Medicine 47, 377-385.

3. Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal man. (1976) Leitch, A.G., Clancy, L.J. and Flenley, D.C. British Medical Journal 1, 365-367.

4. Papers with similar titles and content have been read by A.G. Leitch to the Scottish Society for Experimental Medicine, the European Society for Clinical Investigation and the Medical Research Society.

ABSTRACT

The first part of the thesis examines the possibility that there may exist, in a normal population, individuals who have an absent or diminished hypoxic drive to breathing. The method used to assess hypoxic drive in a group of mine rescue workers measured their ventilatory response to transient hypoxia on exercise. The method proved reproducible and identified a wide range of hypoxic drive to breathing in the subjects, including two subjects with reproducibly low responses. The hypoxic drive measured by this method did not compare well with the hypoxic drive measured by conventional steady state CO_2 response studies at rest in a sub-group of the mine rescue workers.

The second part of the thesis therefore examines repeated measurements of the hypoxic drive to breathing, at rest and on exercise, using transient, progressive and steady state hypoxia methods in four normal subjects. Considerable variability in indices of hypoxic drive is found with all methods but, when mean values for each index are used, the ranking of the four subjects for hypoxic drive is, in general, consistent with all methods. One subject with a low ventilatory response to transient hypoxia on exercise was ranked higher with other methods of measuring hypoxic drive. On the basis of the findings in this subject, it is suggested that an individual's ventilatory response to transient hypoxia on exercise may be explained by considering the effect of exercise on his steady state ventilatory response to CO_2 in hypoxia and hyperoxia. Subjects with an apparently low ventilatory response to tran-

sient hypoxia on exercise may have a normal hypoxic drive when this is assessed by other methods. This would explain the discrepancy between ventilatory responses to transient and steady state hypoxia in the sub-group of mine rescue workers studied by both methods.

The last part of the thesis examines the effect of oral therapy with bendrofluazide or frusemide and intra-venous therapy with salbutamol on the normal steady state ventilatory response to CO_2 in hypoxia and hyperoxia. Frusemide produces a hypokalaemic metabolic alkalosis with a parallel shift to the right of the CO_2 response line which is related to the degree of alkalosis. The drug also causes a rise in resting end-tidal PCO_2. Bendrofluazide produces a hypokalaemic metabolic alkalosis with a signi-ficant decrease in the slope of the hyperoxic CO_2 response line and a significant increase in the intercept of the hypoxic CO_2 response line. The end-tidal PCO_2 after the drug is unchanged. Salbutamol infusion causes an increase in the slope of the CO_2 response line in hyperoxia and hy-poxia with no change in intercept. The drug also causes a hypokalaemia associated with rises in plasma glucose and serum insulin, suggesting a shift of potassium from the extracellular to the intracellular space. The clinical im-plications of these effects are discussed.

CHAPTER 1

I   CARBON DIOXIDE

   i)   Introduction

   The first experiments describing the effect of carbon
dioxide on ventilation were reported by Pfluger in 1868.
His false conclusion that CO_2 was a less effective ventila-
tory stimulant than O_2 lack was due to his use of 30% CO_2,
a very effective narcotic.   In 1885 Miescher-Rusch related
the exhaled CO_2 concentration to ventilation in man and
concluded that the resting human ventilation was primarily
regulated by carbon dioxide concentration.

   In 1905 Haldane and Priestley, using their alveolar
gas sampling method, showed that the alveolar PCO_2 remained
remarkably constant at 5.3 kPa, at Oxford, with a baro-
metric pressure of 100 kPa;   on the summit of Ben Nevis,
despite soaking with rain and a barometric pressure of
86 kPa;   at the bottom of the Dolcoath mine in Cornwall
with a barometric pressure of 111 kPa;   and, finally, in
the pressure chamber in the Brompton Hospital at a baro-
metric pressure of 168 kPa.   During these various conditions
the alveolar PO_2 varied from 8.3 to 60 kPa.   They also noted
in this paper that a rise in P_ACO_2 of 0.2% of an atmosphere
would double alveolar ventilation and in a later paper
(Campbell, Douglas, Haldane and Hobson, 1913), showed that
the ventilatory response to inspired carbon dioxide could
be studied quantitatively in man by an approximately steady
state technique, the rise in ventilation for a given rise
in P_ACO_2 being unaffected by added oxygen.

Schaefer (1958) has documented the enormous variability in ventilatory response to CO_2 in normal man. There is evidence in man that the ventilatory response to inhaled CO_2 is mediated centrally, provided that the peripheral chemoreceptors are 'chemically denervated' by raising arterial PO_2 to about 30 kPa (Lefrancois, Gautier, Pasquis, Cevaer, Hellot and Leroy, 1972). Three important techniques have been used to determine the hyperoxic ventilatory response to inhaled CO_2; the Oxford steady-state method (Lloyd, Jukes and Cunningham, 1958); the rebreathing CO_2 method (Read, 1967; Read and Leigh, 1967) and the progressive hypercapnia method of Weil and his colleagues (Weil, Byrne-Quinn, Sodal, Filley and Grover, 1971). A normal range for the ventilatory response to CO_2 in hyperoxia has been established with values for SCO_2 (the slope of the line relating ventilation to PCO_2 (see Fig. 1)) of 4.3 - 61.3 $l.min^{-1} kPa^{-1} PCO_2$ using the rebreathing method (Rebuck and Read, 1971; Hirshman, McCullough and Weil, 1975).

ii)   <u>Factors influencing the ventilatory response to CO_2</u>

Genetic factors appear to be important in determining the ventilatory response to CO_2 (Beral and Reid, 1971; Leitch, Clancy and Flenley, 1975; Leitch, 1976). Arkinstall, Nirmel, Klissouras and Milic-Emili (1974) were unable to show any differences in the variance for CO_2 responses between monozygous and dizygous twins. They attributed this to differences between twins in their tidal volume and frequency response to inhaled CO_2, the frequency response

$$S = \dot{V}E\,(PCO_2 - B)$$
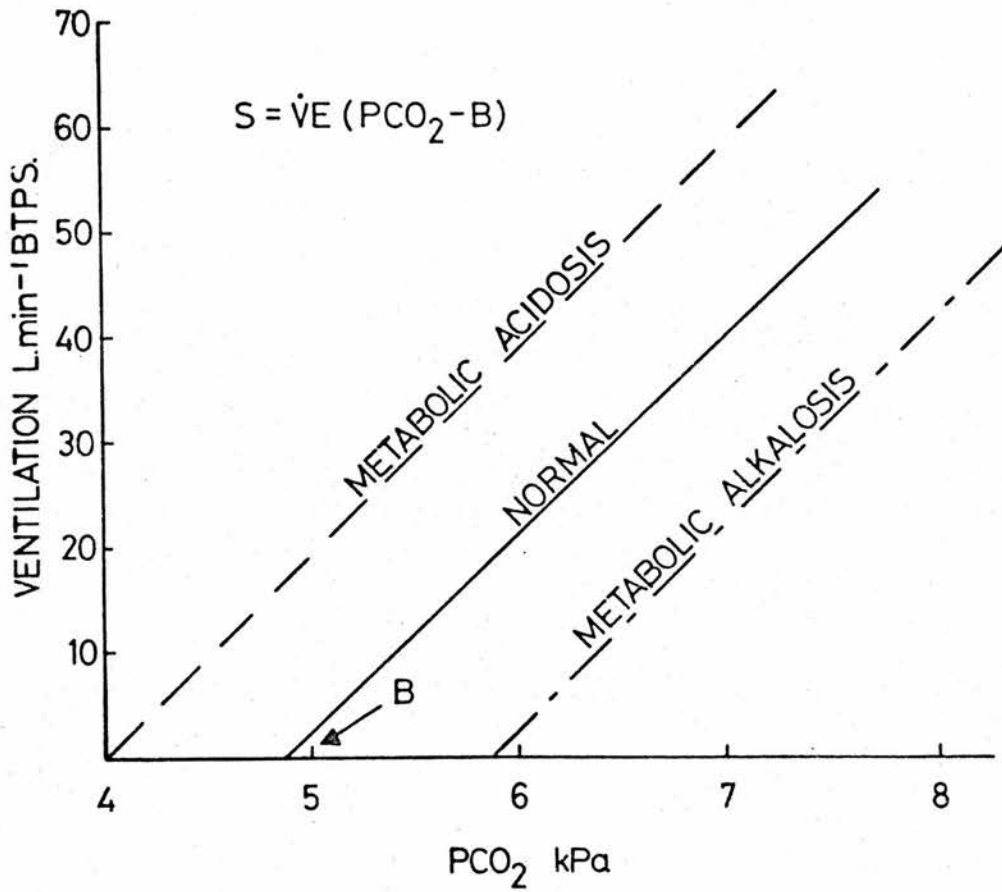
Figure 1

The ventilatory response to inhaled CO_2. The figure shows
the normal linear relationship between ventilation and
arterial or alveolar PCO_2. The line is defined by its
slope (S) and its intercept B. Also shown are the effects
of metabolic acidosis and alkalosis on the relationship;
a decrease and increase in B respectively with no change
in S. Hypoxia, on the other hand, increases S without
altering B.

being determined by personality factors whereas there is a strong genetic component to the tidal volume response. Saunders, Heilpern and Rebuck (1972) have shown a relation between extraversion score and CO_2 responsiveness in women which may have a similar basis.

Rebuck, Rigg, Kangalee and Campbell (1974) have shown that CO_2 responsiveness is directly related to vital capacity and that differences in the tidal volume response to CO_2 is the major factor relating to interindividual differences in ventilatory response to CO_2. In dogs, Cherniack, Stanley, Tuteur, Altose and Fishman (1975) have shown that a decrease in lung volume decreases, and an increase in lung volume increases the ventilatory response to CO_2. In man, Guz, Noble, Widdicombe, Trenchard and Mushin (1966) have shown, by bilateral block of the vagus and glossopharyngeal nerves, that the normal ventilatory response to CO_2 is dependent on the integrity of afferent information from the lungs.

Other factors known to diminish the ventilatory response to CO_2 are sleep (Bellville, Howland, Seed and Houde, 1959; Birchfield, Sieker and Heyman, 1958; Reed and Kellogg, 1958; Bulow, 1963) and mechanical loading (Eldridge and Davis, 1959; Clark and Cochrane, 1972). Induced metabolic acid-base changes produce changes in the intercept of the V/PCO_2 line on the PCO_2 axis (Fig. 1). Acidosis lowers the intercept and alkalosis increases it, neither condition producing a change in slope (Cunningham, Shaw, Lahiri and Lloyd, 1961; Goldring, Cannon, Heinemann and Fishman,

1968). These findings have recently been confirmed with the steady-state technique (Cameron, Davis, Linton and Poole-Wilson, 1972) but, surprisingly, with the rebreathing technique, acidosis and alkalosis had no effect on the intercept but increased and decreased the slope of the line respectively.

Recently, the ventilatory response to carbon dioxide has been shown to be positively correlated with the ventilatory response to hypoxia (Rebuck, Kangalee, Pengelly and Campbell, 1973; Hirshman, McCullough and Weil, 1975). Also, in a small group of subjects with a very extreme range of ventilatory response to exercise, Rebuck, Jones and Campbell (1973) have shown a positive correlation between the ventilatory responses to exercise and CO_2. In this respect, it is interesting to note that Byrne-Quinn, Weil, Sodal, Filley and Grover (1971) found a diminished ventilatory response to CO_2 in athletes, while Rebuck and Read (1971) have found the ventilatory response to CO_2 to be very high in sprint athletes and very low in endurance athletes.

iii) <u>Peripheral and central response to CO_2</u>

In normoxia, the ventilatory response to CO_2 has a peripheral as well as at least one central component (Gelfand and Lambertson, 1973). Denervation of the carotid bodies in man for the treatment of asthma (Nakayama, 1961) has been reported to cause no change (Holton and Wood, 1965) or a 30% decrease (Lugliani, Whipp, Seard and Wasserman, 1971) in the slope of the $\dot{V}/PCO_2$ line. Similar studies, in

patients submitted to carotid endarterectory for transient
ischaemic attacks, show a decrease in the slope of the
$\dot{V}/PCO_2$ line by 15% (Wade, Larson, Hickey, Ehrenfeld and
Severinghaus, 1970), a finding which is confirmed in un-
anaesthetised chemodenervated dogs (Mitchell, 1965). In
normal man oxygen breathing will also depress the venti-
latory response to CO_2 by about 15% (Lambertsen, Hall,
Wollman and Goodman, 1963; Cunningham, Patrick and Lloyd,
1964). Using transient hypercapnia in normal man,
Edelman, Epstein, Lahiri and Cherniack (1973) attribute
roughly one third of the ventilatory response to CO_2 to
the peripheral chemoreceptors.

In high altitude residents where the ventilatory
response to hypoxia is markedly reduced and, presumably,
carotid body function depressed, the ventilatory response
to CO_2 appears to be normal (Milledge and Lahiri, 1967;
Lahiri, Kao, Velasquez, Martinez and Pezzia, 1969), an
apparent decrease noted by Weil, Byrne-Quinn, Sodal,
Filley and Grover (1971) probably being related to the PO_2
at which they made their measurements. However, it may be
that loss of peripheral chemosensitivity to oxygen lack in
these subjects is not accompanied by a loss of sensitivity
to CO_2. From the evidence available from studies in nor-
mal man it would seem that as much as 15-30% of the venti-
latory response to CO_2 in euoxia is dependent on the peri-
pheral chemoreceptors. The remainder of the ventilatory
response in euoxia, and the entire response in hyperoxia,
is mediated by the central chemoreceptors.

II H$^+$ AND CENTRAL CHEMORECEPTORS

i) Early Observations

In 1877 Walter described the ventilatory stimulation
which resulted from the administration of large doses of
dilute hydrocholoric acid in the rabbit. In 1908 Lawrence
Henderson applied the Law of Mass Action to the dissociation
of carbonic acid in living tissues and described the re-
lationship between the carriage of carbon dioxide by, and
the acidity of, the blood. The logarithmic transposition
of his equation by Hasselbalch in 1916 gave the Henderson-
Hasselbalch equation which described the quantitative re-
lationship between acidity and PCO_2 in a fluid if the bi-
carbonate concentration, PCO_2 and dissociation constant for
CO_2 were known. In 1911 Hans Winterstein proposed that
the acidity of the blood was the principal determinant of
ventilation and the PCO_2 merely a reflection of the physico-
chemical consequences of the Henderson-Hasselbalch equation.

This theory was generally accepted but, in 1919, Haldane,
Kellas and Kennaway and, in 1920, Haggard and Henderson
pointed out that hypoxic hyperventilation was associated
with alkalosis, not acidosis, and could not therefore be
caused by increased acidity in the blood. Winterstein
modified his Reaction Theory in 1921 to cope with this ob-
jection and postulated that the acidity of the cells of
the respiratory centre, and not of the blood, was the de-
terminant of ventilation. Anaerobic metabolites in the
respiratory centre were the cause of hypoxic hyperventila-
tion. Gesell (1923, 1925) concurred with this view but,

lacking knowledge of the peripheral chemoreceptors, it is clear that "the peculiar effects of oxygen" were creating difficulties for the physiologists of the 'twenties. Gesell (1925) wrote "for various reasons this phase of the subject has proved to be exceedingly elusive. A review of the literature indicates uncertainty and vacillation". He could only suggest that anoxaemia acted by creating lactic or other acidosis in the centre itself.

ii) The localisation of the central chemoreceptors

Further developments on the effect of CO_2 and H^+ on the respiratory centres had to wait until the 1950's. In 1952 Astrom argued, on the basis of his observation that barbiturate anaesthesia abolished the ventilatory response to CO_2 in animals, at a time when the response to anoxia was well maintained, that a "chemocentre" must exist for CO_2, which normally transmitted its signals to the "respiratory reflex centre" and which was depressed by barbiturate anaesthesia. Leusen (1950, 1954a, 1954b) observed that perfusion of the cerebral ventricles of a dog with artificial CSF, containing increased CO_2 and H^+, stimulated ventilation, whereas solutions containing less CO_2 and H^+ depressed ventilation. The stimulating effect of CO_2 might be related to its ability to diffuse rapidly across cell membranes (Jacobs, 1920a, b). These findings were confirmed by Loeschke, Koepchen and Gertz (1958) who attributed more importance to H^+ concentration in the fluid than to CO_2, a controversy which has continued (Leusen, 1972; Loeschke, 1974). Most workers now agree that the effect of CO_2 is mediated by

changes in H^+ and Cunningham (1974) uses the term (CO_2, H^+) to denote this.

In 1963, Mitchell, Loeschke, Massion and Severinghaus localised an area of chemosensitivity on the ventrolateral surface of the medulla oblongata of dogs and cats (area M) and, in 1970, Schlafke, See and Loeschke described a further area (area L), caudal to area M, which also, when stimulated with H^+, caused an increase in ventilation. Cooling of an area (area S) between the two chemosensitive areas, after vagotomy and section of both sinus nerves, resulted in ventilatory arrest, suggesting that central chemosensitive activity is relayed through area S to the respiratory centre.

Recent reviews of the neurophysiology and anatomy of the "respiratory centre" (Cohen, 1970; Karczewski, 1974) emphasise how little is known about the central mechanism regulating ventilation. The chemosensitive cells have not been positively identified, nor have the postulated pathways to the "respiratory centre" been demonstrated. Recent work (Majcherzyk and Willshaw, 1973) has shown that peripheral chemoreceptor activity in the cat is inhibited when the ventral brain stem surface is perfused with alkaline fluid. If this is substantiated, the influence of the central chemoreceptors on the control of breathing may prove to be more complex than is currently believed.

iii) Central chemoreceptors and acid-base disturbances

Mitchell, Carman, Severinghaus, Richardson, Singer and
Shnider (1965) found CSF H^+ to be within the normal range
in chronic states of respiratory or metabolic acidosis or
alkalosis in man. Their findings led them to suggest the
existence of an active transport mechanism regulating CSF
H^+. More recent work in rats (Ponten and Siesjo, 1967)
goats (Fencl, Miller and Pappenheimer, 1966) and man (Fencl,
Vale and Broch, 1969) has shown that CSF H^+ follows arte-
rial H^+ in chronic acid-base disturbances, although the
change in CSF H^+ is only 1/10 of the change in arterial
H^+. Discussion on the existence of an active transport
regulation of CSF H^+ continues (Leusen, 1972; Siesjo, 1972)
but, at present, there is no definite evidence to support
the suggestion. Mitchell and Singer's (1965) belief that
ventilatory adjustment to chronic acid-base disturbances
is mediated by the peripheral chemoreceptors with subse-
quent active regulation of CSF H^+ is not sustained by the
work quoted above. Fencl, Miller and Pappenheimer (1966)
have shown that ventilation is a single function of CSF H^+
in unanaesthetised goats and have demonstrated the ex-
quisite sensitivity of the central chemoreceptors to small
changes in CSF H^+.

Earlier work (Lambertsen, Semple, Smyth and Gelfand,
1961) had shown that 45% of the ventilatory response to
PCO_2 could be removed by restoring arterial H^+ to normal,
the remaining 55% of the ventilatory response being attri-
buted to changes in CSF H^+. This observation is consistent

with the suggestion of Fencl et al (1969) that the chemo-
receptor cells are located three-quarters of the way along
a gradient from CSF to blood, and are influenced by the H^+
of cerebral interstitial fluid which, in turn, is dependent
on the H^+ of arterial blood and CSF.

Current concepts therefore suggest that the central
chemoreceptor is sensitive to cerebral interstitial fluid
H^+. It is largely responsible for the ventilatory response
to increases in arterial PCO_2 (mediated by increased inter-
stitial fluid PCO_2), and in H^+ (since CSF HCO_3- and hence
interstitial fluid HCO_3- follows arterial HCO_3-).

The importance of the central chemoreceptors to spon-
taneous respiration is seen in the anaesthetised or dece-
rebrate cat where spontaneous ventilation ceases if peri-
pheral chemoreceptors are denervated and area S is cooled
or ablated (Schlaefke, 1974; Kille, Folgering and Herker, 1972).

III OXYGEN DEFICIENCY

i) Introduction

The "dephlogisticated air" which Joseph Priestley col-
lected on 1st August 1774 was later shown by Lavoisier to
be consumed in human respiration, but its relevance to the
control of ventilation was not appreciated until the follow-
ing century. Bert (1878) demonstrated that the physiolo-
gical effects of high altitudes arose from the diminution
in the partial pressure of oxygen (PO_2) in the inspired
gas. From his experiments on cats, guinea pigs, sparrows
and himself, in a chamber at a simulated altitude of
28,000 feet, he concluded "oxygen tension is everything,

barometric pressure itself does nothing, or almost nothing".
Rosenthal (1862) considered that the oxygen content of the
blood controlled ventilation, but Hoppe-Seyler in 1879
showed that the arterial blood was almost fully saturated
with oxygen when breathing air, and also that changing from
oxygen to air in a spirometer scarcely altered ventilation.
Boycott and Haldane (1908) showed that the alveolar PCO_2
only began to fall as the inspired PO_2 fell below 15.5 kPa
where the alveolar PO_2 was about 8 kPa. They concluded that
"want of oxygen is at best a very feeble direct stimulus
to ventilation". With the demonstration that hypoxic hy-
perventilation produced a respiratory alkalosis (Haldane,
Kellas and Kennaway, 1919; Haggard and Henderson, 1920),
it became accepted, in terms of Winterstein's Reaction
Theory (1921), that hypoxia stimulated ventilation by an
action on the respiratory centre.

In 1927, Heymans and Heymans demonstrated that the
carotid and aortic region of the dog contained structures
sensitive, not only to changes in blood pressure but also
to O_2 lack and CO_2 excess in the blood. Further studies
(reviewed by Heymans and Neil, 1958) established that the
responsible chemoreceptor structures were the carotid and
aortic bodies. The anatomy of the carotid body had al-
ready been described in detail by de Castro (1926, 1928).

ii) The function of the carotid body

The sensitivity of the carotid body to oxygen lack
(von Euler, Liljestrand and Zotterman, 1939; Hornbein,
Griffo and Roos, 1961), CO_2 excess (von Euler et al, 1939;

Hornbein and Roos, 1963; Biscoe, Purves and Sampson, 1970; Lahiri and Delaney, 1975a) and H^+ (Joels and Neil, 1960; Hornbein and Roos, 1963; Biscoe et al, 1970; Lahiri and Delaney, 1975a) has since been established. The question posed by Winterstein's latest formulation of the Reaction Theory (1956) as to whether all of these stimuli finally act on the carotid body by altering H^+ at a receptor site has not been resolved. Discussion of possible activation mechanisms can be found in a recent symposium (Torrance, 1968) and reviews (Biscoe, 1971; Torrance, 1974). Other suggested mechanisms include an acid-receptor hypothesis, the receptor being free nerve endings sensitive to H^+ and lying in the space between Type I and Type II cells, the pH of the space being regulated by a PO_2 sensitive pump (Torrance, 1975). Lahiri and Delaney (1975a) have postulated the presence of a chromophobe group in the carotid body with the facility to reversibly bind with oxygen, the binding being influenced by CO_2 and H^+.

The physiological role of chemoreceptors led to an early dispute between Heymans and Comroe (Comroe and Schmidt, 1938; Schmidt and Comroe, 1940), the latter proposing that chemoreceptors played little active part in normal breathing, only being called into action or prominence by anaesthesia, decerebration, severe anoxia or hypercapnia. They showed that denervation of the carotid bodies had little effect on the breathing of lightly anaesthetised animals. Studies in man by Dejours (Dejours, Girard, Labrousse and

Raynaud, 1957; Dejours, Labrousse, Raynaud and Teillac,
1957; Dejours, Labrousse, Raynaud, Girard and Teillac,
1958; Dejours, 1962) and Hornbein (Hornbein, Roos and
Griffo, 1961; Hornbein and Roos, 1962), employing tran-
sient increases in inspired PO_2 have demonstrated that
the peripheral chemoreceptor accounts for 10-15% of resting
ventilation and 6-8% of exercise ventilation at sea level
and as much as 50% of the ventilatory drive after accli-
matisation to high altitude (Dejours, Girard, Labrousse
and Teillac, 1959). The threshold for chemoreceptor acti-
vity in man appears to be about 30 kPa. The parallelism
of the ventilatory response to inhaled O_2 and the chemo-
receptor response has been demonstrated in cats (Leitner,
Pages, Puccinelli and Dejours, 1965).

Less is known about the ventilatory response to hypo-
xia than the ventilatory response to CO_2 largely because
of the difficulties inherent in its measurement (see
later). The hypoxic drive is said to diminish with age
(Kronenberg and Drace, 1973); show a wide range of
values (Hirschman, McCullough and Weil, 1975); be unaf-
fected by added resistive loads (Rebuck and Juniper, 1975)
and be unchanged by acclimatisation to high altitude
(Michel and Milledge, 1963; Lefrancois, Gautier and
Pasquis, 1968; Lahiri, 1972).

iii) <u>Interaction between CO_2 and O_2</u>

Peripheral chemoreceptor block with local anaesthetic
(Guz, Noble, Widdicombe, Trenchard and Mushin, 1966), bi-
lateral carotid body resection (Holton and Wood, 1965;

Lugliani, Whipp, Seard and Wasserman, 1971) or bilateral
carotid endarterectomy (Wade, Larson, Hickey, Ehrenfeld
and Severinghaus, 1970) destroy the human ventilatory
response to hypoxia with some small diminution in the ven-
tilatory response to CO_2. When hypercapnia and hypoxia
are presented together to intact man the stimuli interact
in a multiplicative way in their effect on ventilation
(Neilsen and Smith, 1952; Cormack, Cunningham and Gee,
1957; Lloyd and Cunningham, 1963; Rebuck and Woodley,
1975). Torrance (1968), in his review of the neurophysio-
logy of the carotid body, cast doubt on whether the whole
of this multiplicative interaction could be accounted for
by CO_2/O_2 interaction at the carotid body of the degree
found in animal experiments. Subsequent comparisons
between ventilatory responses to transient and steady state
hypoxia and hypercapnia in man (Edelman, Epstein, Lahin
and Cherniack, 1973) suggested that, in man at least, most
of the interaction of CO_2 excess and O_2 deficit occurred
centrally.

Since Torrance's review the work of Fitzgerald and
Parks (1971) and Lahiri and Delaney (1975a) have demonstrated
unequivocal multiplicative interaction of these two stimuli
in single and multiple recordings from the carotid body.
Lahiri and Delaney (1975b) have taken the matter to its
logical conclusion by simultaneously studying the effects
of CO_2 excess and O_2 lack on ventilation and single fibre
discharge in anaesthetised cats. They conclude that multi-
plicative stimulus interaction does occur at the carotid

body and will contribute to the interaction seen in the ventilatory response. However, from their calculations, the ventilatory equivalent of the mean activity of carotid chemoreceptors alone was <u>not</u> enough to account for the ventilatory interaction of hypoxia and hypercapnia. It would seem therefore that the simple alternatives (central multiplication with peripheral addition and central addition with peripheral multiplication of CO_2 and O_2) proposed by Cunningham (1974) in his theoretical analysis of the interaction sites, are not acceptable, at least for the cat, and we are unlikely to discover whether they do apply in man.

iv) Oscillations in blood gas tension as ventilatory stimuli

The intermittent nature of lung ventilation causes swings in alveolar PO_2 and PCO_2, the amplitude and rate of change of which increases when the rate of CO_2 elimination is increased, as in exercise (Haldane and Priestley, 1905; Krogh and Lindhard, 1913; Dubois, Britt and Fenn, 1952). These swings went without comment until Yamamoto and Edwards (1960) increased the load of CO_2 carried in the venous blood of anaesthetised rats and observed that the animals' ventilation increased in proportion to the load, so that the extra CO_2 was excreted without change of mean arterial PCO_2. They suggested that changes in PCO_2 oscillations in arterial blood might be responsible for this effect. Although some doubt has been cast on these observations and their interpretation (Lamb, 1966; Lewis, 1975), they have

been enthusiastically pursued by workers in the field of the chemical control of breathing.

It is known that the oscillations in alveolar gas tensions are transmitted to arterial blood (Purves, 1966; Band, Cameron and Semple, 1969; Fitzgerald, Leitner and Liaubet, 1969) and carotid body afferents have been found which discharge with the periodicity of respiration (Biscoe and Purves, 1967; Gehrich and Moore, 1973; Goodman, Nail and Torrance, 1974). Dutton, Fitzgerald and Gross (1968) have shown that square wave forcing of CO_2 at 10/min at the carotid body produces a greater increase in ventilation than the same steady mean rise in PCO_2. These and other observations of the chemoreceptor response to sudden changes of PO_2 and PCO_2 (Black, McLoskey and Torrance, 1971) suggest that the oscillations in chemoreceptor activity reflect oscillations in arterial PCO_2.

A series of papers from Oxford have reported the respiratory effects of tube breathing and of altering the time patterns of alveolar CO_2 in man. Earlier work had shown that ventilation would follow alternate breaths of high and low CO_2 mixtures provided that hypoxia was present (thus implicating the carotid body) but there was no mean increase in ventilation with this procedure (Cunningham, Lyen, McPherson, Marsh and Pearson, 1973; Marsh, Lyen, McPherson, Pearson and Cunningham, 1973). However, if the time pattern of the alveolar CO_2 oscillations was altered by tube breathing or adjustment of the inspired gases (Goode, Brown, Howson and Cunningham, 1969; Cunningham,

1972; Cunningham, Howson and Pearson, 1973) then an increased drive to breathing could be detected. This finding fitted well with observations that the timing of a stimulus to the carotid body was important in determining its effect on ventilation (Band, Cameron and Semple, 1970; Black and Torrance, 1971).

The significance of all these observations remains to be determined. In the dog, oscillations may be important determinants of ventilatory responses (Dutton and Permutt, 1968). It is true, however, that oscillations (and their effects) are most prominent at low breathing rates (Band, Cameron and Semple, 1969). Sophisticated studies by Ponte and Purves (1974) in cats have demonstrated that at physiological breathing frequencies the phase lag and intensity of the chemoreceptor response to oscillations begins to fall off - a finding which the authors find difficult to reconcile with a prominent physiological role for the phenomenon.

The findings in man do not point to any definite physiological role, although Cunningham (1975) has produced a model, based on his own and others experimental results, emphasising the importance of the timing of chemoreceptor activity in relation to "the period of central respiratory excitation". Sharpening of grouping of chemoreceptor impulses into bursts by, for example, mild exercise, might enhance hypoxic sensitivity and explain the hyperpnoea of exercise or the hyperventilation of hypoxic exercise (see below). At the other extreme, derangement of such a

mechanism might explain the disordered control of ventilation seen in some situations in cardiorespiratory disease.

IV THE HYPERPNOEA OF MUSCULAR EXERCISE

i) Neurogenic vs. Chemical Control

In 1913, Krogh and Lindhard noted a sudden increase in ventilation at the initiation of exercise which "in many cases was proportional to the work load". They attributed this increase in ventilation to irradiation of motor impulses to the respiratory centre. Asmussen, Christensen and Nielsen (1943), using cuffing of exercising limbs, demonstrated that a nervous rather than a humoral effect was responsible for the increase in ventilation. In a companion paper (Asmussen, Nielsen and Wieth-Pederson, 1943) they showed that electrically induced exercise produced similar increases in ventilation to natural exercise and concluded that a reflex from the exercising limbs was more likely to be responsible than the cortical irradiation of Krogh and Lindhard. They attributed most of the ventilatory increase during light exercise to this reflex effect (Asmussen and Nielsen, 1947). Comroe (1944) supported this view as a result of his experiments on man and animals (Comroe and Schmidt, 1943) and dismissed any contribution from reflexes arising from chemical receptors in the limbs, lungs, great veins, atria and peripheral chemoreceptors.

Dejours, Mithoefer and Labrousse (1957) considered that the local chemical environment of the "proprioceptors" was an important determinant of the ventilatory response to

exercise but, in their experiments, as in subsequent experiments on the ventilatory response to static exercise (Wiley and Lind, 1971; Myrhe and Anderson, 1971), it is impossible to exclude a contribution from pain receptors. The elegant cross-circulation experiments of Kao (Kao, Michel, Mei and Li, 1963; Kao, Michel and Mei, 1964) further confirmed that the major contribution to the increase in ventilation in exercising, anaesthetised dogs was neural, not humoral.

The conventional view expressed by Dejours (1963, 1964) ascribes the rapid increase in ventilation which happens at the start of exercise, occurs within the first half breath (Jensen, Vejby-Christensen and Strange-Petersen, 1972), and is unrelated to the prevailing chemical background (Cunningham, Lloyd and Spurr, 1966), to a reflex originating in exercising limbs. The contribution of this reflex appears to persist throughout exercise and to make a larger contribution to total ventilation in unaccustomed exercise such as downhill walking rather than conventional walking (D'angelo and Torelli, 1971). Beaver and Wasserman (1968, 1970) do not necessarily find rapid transients at the start of exercise and feel that the differences in individual response indicate that the ventilatory response to the start of exercise is a conditioned reflex.

The receptors for this reflex have not been identified positively. Comroe and Schmidt considered that they lay around the articular capsule; evidence for (Flandrois, Lacour, Islas-Maroquin and Charlot, 1967; Kindermann and Pleschka, 1973) and against (McLoskey, Matthews and Mitchell,

1972) a contribution from muscle spindles has been pre-
sented and at least two groups of workers (Kalia, Senapati,
Panda and Panda, 1972; McLoskey and Mitchell, 1972) con-
sider that the reflex arises from group III myelinated or
unmyelinated fibres in the muscles.

In 1963 and 1967 Cunningham, reviewing the literature,
was able to state that the hyperpneoa of exercise could be
attributed to the sum of contributions from neurogenic
sources and from observed chemical changes particularly
in PCO_2 and H^+ reported by himself and others.

ii) The role of the peripheral chemoreceptor

It had long been known that addition of oxygentto
inspired air (Asmussen and Nielsen, 1947, 1958; Bannister
and Cunningham, 1954) reduced ventilation in light and
moderate to severe exercise, implying a role for the peri-
pheral chemoreceptors in this hyperpnoea. However, ex-
periments in patients with carotid body resection revealed
no differences between their ventilatory response to exer-
cise and those of controls, implying that the peripheral
chemoreceptor contribution in euoxia was small, if present
(Lugliani, Whipp, Seard and Wasserman, 1971). More recent
studies on similar patients have shown that carotid body
resection has no effect on the first breath of exercise
or on the steady-state ventilation although the rate of
rise of ventilation is diminished (Wasserman, Whipp, Koyal
and Cleary, 1975). This observation might suggest that
peripheral chemoreceptors are essential for a rapid adapta-
tion to exercise but that, in their absence, other mecha-

nisms, e.g. central chemoreceptors, are able to compensate. It also dismisses, as experiments in animals (Parida, Senapati and Kalia, 1969; Davies and Lahiri, 1973) and man (Eisele, Ritchie and Severinghaus, 1967) already have, the possibility that sympathetic activation of the chemoreceptor is important for the control of ventilation during exercise (Biscoe and Purves, 1967a and b).

The importance of the peripheral chemoreceptors for the increase in ventilation in hypoxic steady state exercise is also shown in Lugliani's study, although he did not observe the same potentiation of the effect of hypoxia on ventilation during exercise which has been observed by others (Asmussen and Nielsen, 1957; Cunningham, Spurr and Lloyd, 1968; Flenley, Cooke, King, Leitch and Brash, 1973; Masson and Lahiri, 1975). However, when the subject is euoxic the contribution of the peripheral chemoreceptor to ventilation during exercise constitutes the same or a smaller percentage of the total ventilation as at rest, although the absolute value will obviously increase with increasing levels of exercise (Masson and Lahiri, 1975; Dejours, 1962).

In hypoxic exercise, however, the effect of hypoxia on ventilation appeared to be greater during exercise than at rest (Masson and Lahiri, 1975), resulting in falls in PCO_2 and H^+. The same workers noted that the ventilatory effect of hypoxic exercise was increased if PCO_2 was maintained constant at resting levels and that addition of CO_2 to inspired gas during this stabilisation procedure

increased ventilation even if PCO_2 was below the resting threshold. They also showed that the effect of exercise on the ventilatory response to CO_2 in hypoxia and hyperoxia was to produce parallel shifts of the slopes of the response to the left with a reduction in the intercept, i.e. exercise did not increase hypoxic sensitivity, in keeping with the finding of Davies and Lahiri, in the hypoxic anaesthetised cat, that chemoreceptor activity is not increased in exercise.

Possible explanations of the increased ventilation in hypoxic exercise include;

a)   a major contribution from arterial PCO_2 oscillations (Cunningham, 1972, 1974) which requires proof.

b)   a contribution from the known effect of catecholamines on the ventilatory response to hypoxia (Cunningham, Hey and Lloyd, 1958; Cunningham, Hey, Patrick and Lloyd, 1963) which would be possible in man (Clancy, Critchley, Leitch, Kirby, Ungar and Flenley, 1975; Clancy, Critchley and Leitch, 1975) but would not explain the increased drive seen in the cat (Davies and Lahiri, 1973).

c)   the neurogenic component of the exercise stimulus to breathing may interact centrally with other afferent inputs from e.g. the peripheral and central chemoreceptors, hence the lowering of threshold of the ventilatory response to CO_2 in hypoxia and hyperoxia which most workers find.

It seems unlikely that the nature of the contributions of different components of the control system will be clear until the central interactions are open to study. It is probably true, as Guz (1975) says, that "It does not seem as though the question of the existence and meaning of the neurogenic component can be solved with present methods".

CHAPTER 2 BACKGROUND TO THE PRESENT STUDY

I   CONTROL OF VENTILATION IN CHRONIC RESPIRATORY FAILURE

   i) Diminished ventilatory response to CO_2 and O_2
       therapy

In 1920 Scott noted that "the ease and apparent comfort
with which emphyrematous patients inspire high percentages
of carbon dioxide for short periods is very striking". Nu-
merous studies since then have confirmed that the ventila-
tory response is markedly reduced in patients with chronic
airways obstruction and chronic respiratory failure (Donald
and Christie, 1949;   Tenney, 1954;   Alexander, West, Wood
and Richards, 1955;   Clark, 1968;   Godfrey, Edwards, Copland
and Gross, 1971). This diminished sensitivity to CO_2 can-
not be explained by the observed alterations in the buffer-
ing capacity of the blood (Flenley, Franklin and Miller,
1970) or the increased work of breathing (Flenley and
Miller, 1968) found in these patients and depression of the
sensitivity of the respiratory centre (presumably the cen-
tral chemoreceptors) to CO_2 has been suggested.

In patients with type II respiratory failure in which
hypoxaemia is combined with CO_2 retention (Campbell, 1965)
acute exacerbations of disease can lead to worsening of
the hypoxia and hypercapnia. The hazards of oxygen therapy
were first described in 1949 by Barach and Donald and sub-
sequently documented in greater detail (Comroe, Bainson
and Coates, 1950;   Westlake, Simpson and Kaye, 1955). In-
appropriately high inspired oxygen concentrations in these
patients will relieve their hypoxaemia but produce marked

elevation of arterial PCO_2, resulting in CO_2 narcosis and often death. The mechanism of this was believed to be related to inhibition of the hypoxic drive to breathing in these patients by the high arterial oxygen tensions obtained. Since such patients had a poor ventilatory response to CO_2, they were dependent on their hypoxic drive to continue ventilation. Treatment with controlled oxygen therapy (Hutchison, Flenley and Donald, 1964; Campbell, 1965), allowed restoration of PO_2 to levels at which tissue oxygenation was adequate, and which were not so high as to abolish the all-important hypoxic drive to breathing.

ii) Pink Puffers and Blue Bloaters

The disease spectrum of chronic bronchitis and emphysema has been divided, on the basis of pathological, clinical and physiological observations, into two extreme types (Robin and O'Neill, 1963; Burrows, Fletcher, Heard, Jones and Wootliff, 1966; Filley, Beckwith, Reeves and Mitchell, 1968; Schuren and Huttemann, 1973). Type A disease, in the 'pink and puffing' patient, consists of predominant emphysema with an increase in the total lung capacity (TLC), a decrease in transfer factor for carbon monoxide (TCO) and surprisingly normal arterial PO_2 and PCO_2. Type B disease, in the 'blue and bloated' patient, is characterised by predominant bronchitis, a reduction in TLC and a normal TCO combined with hypoxia and hypercapnia. These patients develop polycythaemia, pulmonary hypertension and right heart failure and the diminished ventilatory response to CO_2, which has been reported in chronic obstructive

airways disease, is most prominent in this group of patients where it appears to be related to the degree of CO_2 retention (Flenley, Franklin and Miller, 1970; Howell, 1973).

iii) <u>Hypoxic drive to breathing in chronic bronchitis</u>

Quantitation of the hypoxic drive to breathing in such patients has been hampered by the need for arterial blood gas sampling, and most workers have been satisfied by the observation that, if relief of hypoxaemia depresses ventilation in such patients, then an important hypoxic drive to breathing must exist. The definitive study of the hypoxic drive to breathing in such patients was reported by Flenley, Franklin and Miller in 1970. In this study, using the Oxford steady state method of assessing the hypoxic drive to breathing, these authors demonstrated absence of a hypoxic drive to breathing in two patients. These two patients had been known to be hypoxic, hypercapnic, polycythaemic and to have right heart failure for many years, i.e. they were 'blue bloaters'.

The absence of hypoxic drive in these two patients may simply have been a consequence of their disease. An alternative explanation is that these men had always lacked a hypoxic drive to breathing and that with the development of chronic bronchitis, they were therefore predisposed to the hypoxic complications of the disease, namely polycythaemia, pulmonary hypertension and right heart failure. Is it possible that a person's premorbid hypoxic drive to breathing could determine the clinical presentation and course of chronic bronchitis and emphysema in some patients?

II   EVIDENCE FOR ABSENT HYPOXIC DRIVE TO BREATHING IN MAN

In 1905 Haldane and Priestley described a subject who
"continued to breathe from a bag air with a gradually di-
minishing oxygen percentage until unconsciousness occurred.
No marked hyperpnoea or even discomfort was experienced at
any part of the experiment". Other isolated cases of ab-
sent ventilatory response to hypoxia have been recorded in
normal man (Brown, 1956) and an absent or markedly diminished
hypoxic drive to breathing has been recorded in two groups
of subjects, high altitude residents and patients with cyan-
toic congenital heart disease.

There is now an extensive literature on the diminished
hypoxic drive to breathing found in high altitude natives.
This diminished hypoxic drive is found in natives of the
Himalayas and Andes, both at rest (Milledge and Lahiri,
1967; Lahiri, Kao, Velasquez, Martinez and Pezzia, 1969;
Lefrancois, Gautier and Pasquis, 1968; Lefrancois, Gautier,
Pasquis, Cevaer, Hellot and Leroy, 1972; Severinghaus,
Bainton and Carcelen, 1966) and on exercise (Lahiri,
Milledge, Chattopadhyay, Bhattacharyya and Suiha, 1967;
Lahiri and Edelman, 1969; Lahiri, Kao, Velasquez, Martinez
and Pezzia, 1970; Lahiri, Milledge and Sorensen, 1972)
whether the method used involves transient or steady state
hypoxia. One study (Sorensen and Severinghaus, 1968a) has
confirmed the findings of others that the defect in hypoxic
drive persists when high altitude residents have lived at
sea level for many years, and suggests that birth at, and
exposure to, altitude for only 2-4 years is associated with

a diminished ventilatory response to hypoxia. In contrast,
when sea level man lives at high altitude for many years
(Sorensen and Severinghaus, 1968b), he retains a normal
hypoxic drive to breathing. Whether the change in hypoxic
drive is related to hypoxia at birth at these high altitudes
or has a genetic basis will only be resolved by studies of
the offspring of high altitude natives born at sea level.

Another group of workers have found a similar atte-
nuation of hypoxic drive to breathing in native residents
of Leadville, Colorado (3,100 m), but this group (Weil,
Byrne-Quinn, Sodal, Filley and Grover, 1971) also found
attenuation of the drive in non-native residents which was
proportional to the time of residence at high altitude.
In another study (Byrne-Quinn, Sodal and Weil, 1972) they
found that children born and resident in Leadville had simi-
lar hypoxic drives to those living in Denver (1,600 m) and
they were therefore forced to conclude that the altered
physiology must be a result of prolonged exposure to hypoxia.
The possibility of genetic differences between the North
American subjects and the Himalayan and Andean subjects may
explain the different findings. However, it may be that
hypoxic drive to breathing is lost by exposure to hypoxia
in the first four years of life.

The conclusions from studies of hypoxic drive in patients
with cyanotic congenital heart disease are also equivocal.
Sorensen and Severinghaus (1968c), using steady state methods,
studied 5 patients more than one year after correction of
Tetralogy of Fallot and found an absent hypoxic drive to

breathing in this group. Edelman, Lahiri, Brando, Cherniack and Fishman (1970) studied six patients with cyanotic congenital heart disease before operation using a transient hypoxic stimulus and confirmed these findings. However, the two patients in this group who were restudied after corrective surgery had normal hypoxic drives to breathing. The findings of the first group are consistent with the hypothesis that hypoxia from the stage of birth permanently depresses the hypoxic drive to breathing whereas the second study suggests that the depression is reversible. In view of the small numbers studied, a firm conclusion cannot be made from these results, but, taken with the evidence from the high altitude studies, it does raise the possibility that hypoxia at birth or following it may depress the hypoxic drive to breathing.

A recent study (Zwillich, Sutton, Pierson, Creagh and Weil, 1975) has demonstrated marked reduction of hypoxic ventilatory drive in patients with the obesity-alveolar hypoventilation syndrome and suggested that, in obesity, diminished hypoxic drive may contribute to the hypoxia and hypercapnia which is found in these patients. A further study of these patients has shown marked improvement of clinical state, blood gases and hypoxic drive to breathing after prolonged treatment with progesterone (Sutton, Zwillich, Creagh, Pearson and Weil, 1975) with relapse on withdrawal of therapy.

The evidence that people with absent or diminished hypoxic drive to breathing are found in special situations

such as cyanotic congenital heart disease, high altitude
and the obesity alveolar hypoventilation syndrome has sti-
mulated the present search for such individuals in a normal
population.

III THE PURPOSE OF THE PRESENT INVESTIGATION

1. The first part of the present investigation was stimu-
    lated by the finding of an absent hypoxic drive to
    breathing in 2 patients with chronic obstructive air-
    ways disease who had the more severe hypoxic manifes-
    tations of this disease.

2. Review of the literature confirms the findings of iso-
    lated cases of normal people who do not increase their
    ventilation in response to a hypoxic stimulus.

3. Absence of the hypoxic drive to breathing has also been
    recorded in high altitude natives and in patients with
    cyanotic congenital heart disease or the obesity alveo-
    lar hypoventilation syndrome. Review of the literature
    on these fields does not allow a firm conclusion on
    whether the absence of drive is congenital, or acquired
    as a result of lifelong hypoxia in such situations.

4. The hypothesis is therefore advanced that there may
    exist in the normal population a number of individuals
    who may lack a hypoxic drive to breathing. Should these
    then develop obstructive airways disease, they may be
    more predisposed to the complications of hypoxia, with
    the development of polycythaemia, pulmonary hypertension
    and right ventricular failure (as seen to be the case

in the obesity-alveolar hypoventilation syndrome).

5. The object of this investigation is to quantitate the
    hypoxic drive to breathing in a normal population with
    the object of detecting such individuals who may have
    a diminished or absent hypoxic drive to breathing.

CHAPTER 3   METHODS OF MEASURING THE HYPOXIC DRIVE TO BREATHING

I   STEADY STATE METHODS

A number of methods have been used to demonstrate and attempt to quantitate the hypoxic drive to breathing. The earliest used, based on the pioneer studies of Nielsen and Smith (1951), was the steady state method. With this method the ventilatory response to CO_2 is measured at different PO_2 levels after a steady state of ventilation has been achieved (Lloyd, Jukes and Cunningham, 1958). The ventilatory response to CO_2 is found to be linear at any PO_2 and, if the line is extrapolated to the PCO_2 axis (Fig. 1), defines an intercept or 'threshold' for PCO_2. The effect of hypoxia on this line is to increase the slope of the line without, in general, influencing the intercept. The relationship between ventilation and carbon dioxide can be expressed in the form $\dot{V} = S(PCO_2 - B)$, where S is the slope of the line and B the intercept on the CO_2 axis. The relationship between S and PO_2 can be described by a hyperbolic relationship where the expression $S = D\left(1 + \dfrac{A}{PaO_2 - C}\right)$ can be applied. Combination of the two equations gives one single equation representing the whole $\dot{V}$, PCO_2, PO_2 relationship at PCO_2s above the resting level by $\dot{V} = D(PCO_2 - B)\left(1 + \dfrac{A}{PO_2 - C}\right)$

The methods for determining the various parameters of these equations have been described (Lloyd and Cunningham, 1963) (Fig. 2), the parameter A, the shape parameter of the hyperbola, and C, the PO_2 at which S tends to become infinite,

The figure shows a curve with the equations:

$$S = D\left(1 + \frac{A}{PO_2 - C}\right)$$

$$S = \frac{\dot{V}E}{PCO_2 - B}$$

The y-axis is labelled SCO_2 L.min^{-1} kPa. and the x-axis is labelled PO_2 kPa.

The parameters C, D, A and AD are marked on the graph.
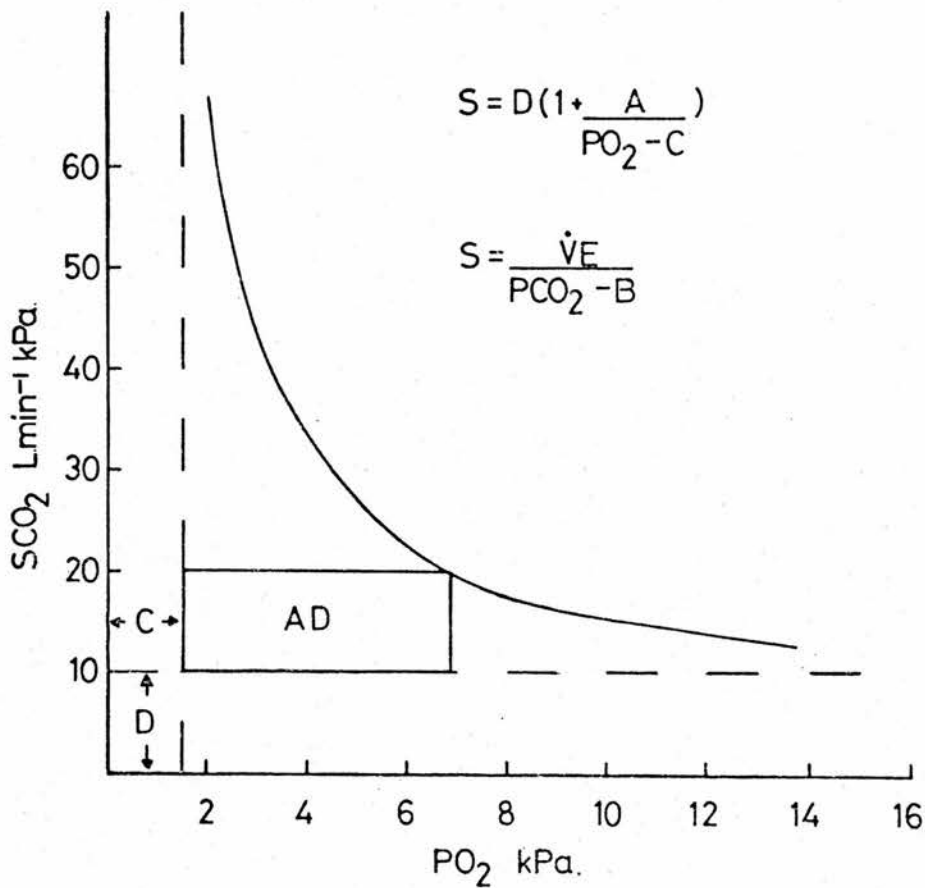
Figure 2

The parameters of the Cunningham equation (from Lloyd and Cunningham, 1963). The relationship between the slope (SCO_2) of the ventilatory response to CO_2 and the PO_2 at which that slope was measured. The slope (SCO_2) equals $\frac{V_E}{(PCO_2 - B)}$ (see Fig. 1).

D = the slope of the response at infinite PO_2.
C = the PO_2 at which ventilation tends towards infinity.
A = the shape parameter of the curve and is used as a measure of hypoxic drive.

being measures of hypoxic drive. Determination of these
parameters for any one subject is time consuming but the
method has been used, e.g., to determine the effect of nora-
drenaline on the hypoxic sensitivity parameter A (Cunningham,
Hey, Patrick and Lloyd, 1963). The method is time consuming
and other authors have applied the method in alternative
ways. Flenley, Franklin and Miller (1970) measured the
slope of the CO_2 response line at high and low PO_2 and used
the ratio of the slopes as a measure of hypoxic drive.
Kronenberg, Hamilton, Gabel, Hickey, Read and Severinghaus
(1972) defined the slopes of the CO_2 response in hyperoxia
and at a PAO_2 of 40 mmHg and used as their index of hypoxic
sensitivity the $\Delta \dot{V}40$, defined as the increase in ventilation
caused by lowering PO_2 to 40 mmHg at a CO_2 tension which
gives $\dot{V}E = 4\ell/min/m^2$ in hyperoxia. This method has been
used in the investigation of blunted hypoxic drive at high
altitude (Severinghaus et al, 1966; Sorensen and Severinghaus,
1968a and b) and in cyanotic congential heart disease
(Sorensen and Severinghaus, 1968c).

Apart from the time required to establish a suitable
steady=state for enough measurements, the steady-state method
is open to further criticism, if it is to be used to detect
absent drive, for there is now evidence that the effect of
hypoxia on ventilation may be the resultant of two opposing
forces: a peripheral chemoreceptor drive to ventilation
and a central nervous system depressant effect (Cherniack,
Edelman and Lahiri, 1973). A depressant effect of steady-
state hypoxia on ventilation in familial dysantonomia, where

circulatory reflexes are impaired, and cerebral blood flow
falls with the resulting hypotension, has been demonstrated
(Edelman, Cherniack, Lahiri, Richards and Fishman, 1970),
but these subjects did respond with ventilatory stimulation
to transient hypoxia, showing that an active peripheral
chemoreceptor reflex was being overcome by central depression.
The studies of Kronenberg, Hamilton, Gabel, Hickey, Read
and Severinghaus (1972) have also demonstrated the presence
of hypoxic depression of ventilation during the determina-
tion of steady-state CO_2 response lines in hypoxia.

II PROGRESSIVE ISOCAPNIC HYPOXIA

A recent development has been the introduction of me-
thods using progressive isocapnic hypoxia where PO_2 is
lowered progressively over 15 mins (Weil, Byrne-Quinn,
Sodal, Filley and Grover, 1970) or 4 mins (Kronenberg et
al, 1972), while the resultant hypocapnia is prevented by
the addition of PCO_2 to the inspired gas. With this method
the relationship between $\dot{V}_E$ and PO_2 can again be expressed
by an exponential equation of the form

$$\dot{V}_E = \dot{V}_O + \frac{A}{PAO_2 - 32}$$

where $\dot{V}_O$ is the ventilation at infinitely high PO_2, A is
the shape parameter of the curve and the constant 32 is the
average PO_2, obtained by extrapolation in 18 studies in 6
normal subjects, at which ventilation tends to infinity.

Objections to the use of this method are the need for
sophisticated computer facilities to allow control of PCO_2
and again the demonstration, in some subjects, of significant

hypoxic depression of ventilation (Kronenberg et al, 1972).

III TRANSIENT HYPOXIA

The use of transient methods with transient induction
of hypoxia by giving the subject several breaths of N_2, or
relief of hypoxia by giving several breaths of 100% O_2,
while the subject is breathing a hypoxic gas mixture, has
been pioneered by Dejours and his co-workers (Dejours,
Girard, Labrousse and Raynaud, 1957; Dejours, Labrousse,
Raynaud and Teillac, 1957; Dejours, Labrousse, Raynaud,
Girard and Teillac, 1958; Dejours, 1959, 1963, 1968).
Other workders have used single breaths of high concentra-
tions of CO_2 as a test of carotid chemosensitivity (Sorensen
and Cruz, 1964; Gabel, Kronenberg and Severinghaus, 1973)
but this is open to the objection that the subjects can
'taste' such concentrations of CO_2 (Cunningham, 1972), that
there may be CO_2 receptors in the airways (Rybak, 1974)
and that vital capacity manoeuvres imply cognition with
possible effects on the response. The absolute changes
measured during a transient stimulus can be increased by
giving it during exercise, just as exercise will potentiate
the increase in ventilation observed during steady-state
hypoxia (Flenley, Cooke, King, Leitch and Brash, 1973).
The advantage of the use of transients is that the changes
in ventilation observed simply reflect chemoreceptor ac-
tivity without the complication of CNS depression. The
disadvantage is that the change in ventilation produced by
carotid body stimulation produces secondary changes, parti-

TYPES OF TRANSIENTS
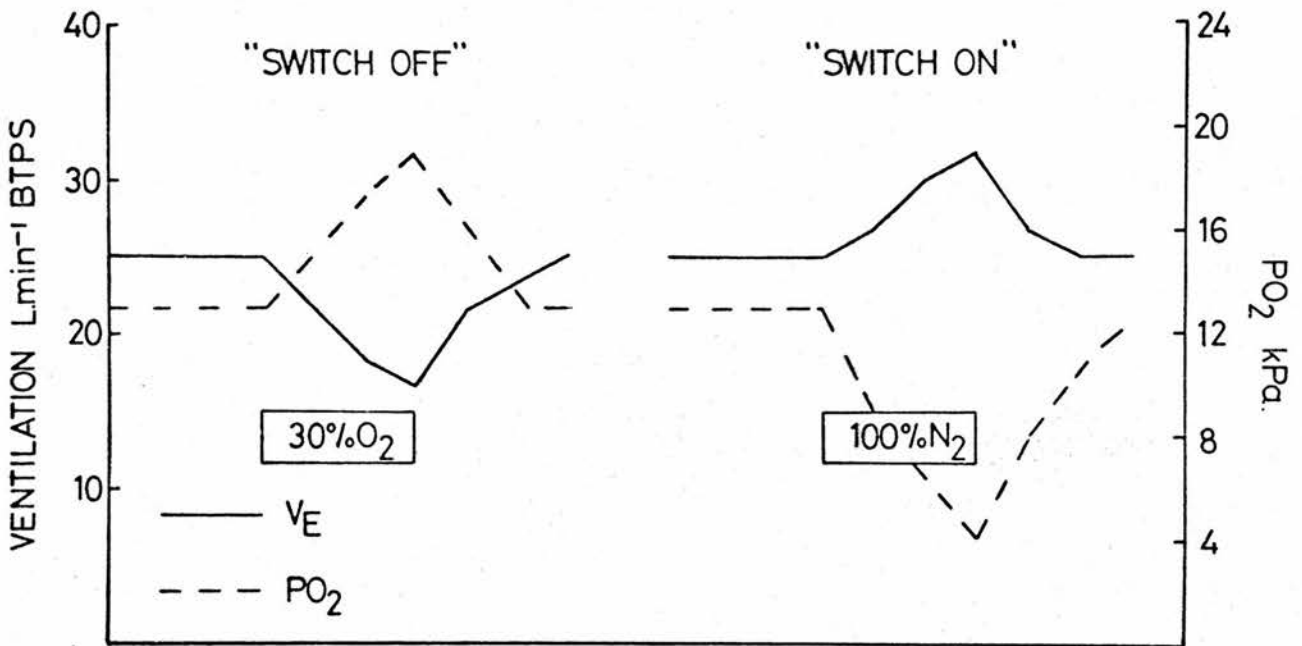
Figure 3

To show the effect of 3 breaths of 30% oxygen or 3 breaths of nitrogen on ventilation and PO_2 during mild exercise breathing air. With 30% oxygen there is a rise in PO_2 with "switching off" of the peripheral chemoreceptors and a resulting fall in ventilation; with nitrogen there is a fall in PO_2, with "switching on" of the peripheral chemoreceptors and a resultant increase in ventilation.

cularly in PCO_2, which act at the chemoreceptor, and later centrally, to modify the chemoreceptor response. Reynolds and Millhorn (1973) have shown that the transient ventilatory response to hypoxia follows the same course for the first minute after the hypoxic stimulus whether the $P_A CO_2$ is controlled or not and it may be that this test is more useful quantitatively than Dejours himself believes (Dejours, 1962). The use of the 'oxygen test' (Dejours, 1963) was considered for this study but discarded on the grounds of inconvenience in preparing and supplying large volumes of hypoxic gas mixtures and the difficulties caused by alterations in mass spectrometer sensitivity, when it was exposed, even for a short time, to high concentrations of O_2. Instead, the N_2 test was selected and mild steady state exercise was used to magnify the ventilatory changes observed. (Fig. 3)

The method selected, of giving breaths of N_2 to the subject while he breathes air, has been used before at rest (Lefrancois, Gautier, Pasquis, Cevaer, Hellot and Leroy, 1972) and on exercise (Lahiri and Edelman, 1969) to demonstrate that the decreased hypoxic drive of high altitude natives is due to lack of carotid body chemosensitivity, rather than to hypoxic depression of ventilation. It appears to be a sensitive and capable method of assessing the absence of a hypoxic drive to breathing although its value in quantitating a present hypoxic drive has yet to be determined.

SUMMARY

1. Review of presently available methods of assessing the
    hypoxic drive to breathing has shown that the steady-
    state and progressive hypoxia methods pose problems
    respectively of time consumption and the need for ex-
    tensive computer facilities. Both methods appear to
    pose the problem of hypoxic central depression of ven-
    tilation.

2. Transient hypoxia appears to be a sensitive index of
    the presence of a hypoxic drive to breathing mediated
    by the carotid bodies, although it may be less satis-
    factory for adequate absolute quantitation of the res-
    ponse because of the associated secondary changes.
    Exercise magnifies the absolute response to transient
    hypoxia and this method has been used successfully to
    demonstrate a poor peripheral chemoreflex drive to
    breathing in high altitude natives.

3. The use of transient hypoxia induced by inhalation of
    3 breaths of nitrogen during mild exercise has therefore
    been selected as the test of hypoxic drive to breathing
    for this study.

CHAPTER 4   HYPOXIC DRIVE TO BREATHING : METHODS

Studies were undertaken in the years 1971, 1972 and
1974. The results to be presented later are based on the
study of 43 subjects carried out in 1972. 26 of these
subjects were also studied in 1971 and 9 were restudied in
1974 when, in addition to the transient hypoxic drive to
breathing, the steady state ventilatory response to CO_2
and hypoxia was also measured.

Subjects and Procedure

The subjects were all mine rescue workers from the
mining districts around Edinburgh, who were attending a
Mine Rescue course in Edinburgh at the time. All were
familiar with the use of breathing apparatus and mouthpieces
and volunteered for the studies, after the nature and pur-
pose of the experiments had been explained to them.

On arrival at the Department of Medicine in the after-
noon, each subject had his height, weight, $FEV_{1.0}$, FVC and
lung volumes measured. The MRC Questionnaire on Respira-
tory Symptoms was administered and a routine examination
of the cardiovascular and respiratory systems was carried
out. A venous blood sample was withdrawn for haemoglobin
estimation and a 12-lead electrocardiograph (ECG) was taken.
All ECG's were normal and no abnormalities were detected
on examination.

The design of the transient hypoxic drive experiment
is shown in figure 4. After recording of gas and volume
calibrations on an analogue magnetic tape, the study began.
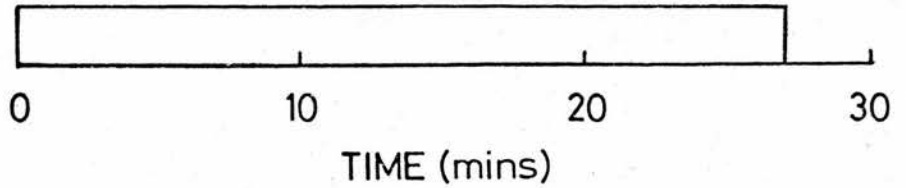
Figure 4

The design of the transient hypoxia studies in the miners. The vertical black bars in the inspired gas section indicate inspiration of three breaths of N_2. The hatched areas above indicate when $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were measured and when data ($P_{ET}O_2$, $P_{ET}CO_2$, V_T, f) were recorded respectively.

The subjects were studied in the treadmill room of the
Department of Medicine at least 2 hours after a meal.
They walked on a level treadmill at about 3 m.p.h. breath-
ing air through the breathing valve and its attached as-
sembly. Between the 7th and 9th minutes of exercise
mixed expired gas samples were collected and ventilation
was measured on the dry gas meter to allow calculation of
oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$) and
respiratory exchange ratio (R.Q.). At intervals of 2-3
minutes thereafter (see fig. 4) a tap was turned to allow
the inspiration of three tidal volumes of nitrogen with
return to air breathing afterwards. Two minutes after
the final three breaths of nitrogen, the $\dot{V}O_2$ and $\dot{V}CO_2$ were
again measured over a 2 minute period. Following this
measurement another tap was turned to allow the subject
to breathe a mixture of 14% O_2 in nitrogen for 6 minutes,
the ventilation again being measured in the last two
minutes of this period.

Data were collected on the tape recorder (see later)
before, during and after each transient inhalation of
nitrogen.

Methods

The general arrangement of apparatus for the experi-
ment is shown diagrammatically in figure 5.

Treadmill

From each subject's height and weight, a speed of
level walking was selected, using the nomogram of Workman
and Armstrong (1964), which was predicted to produce an
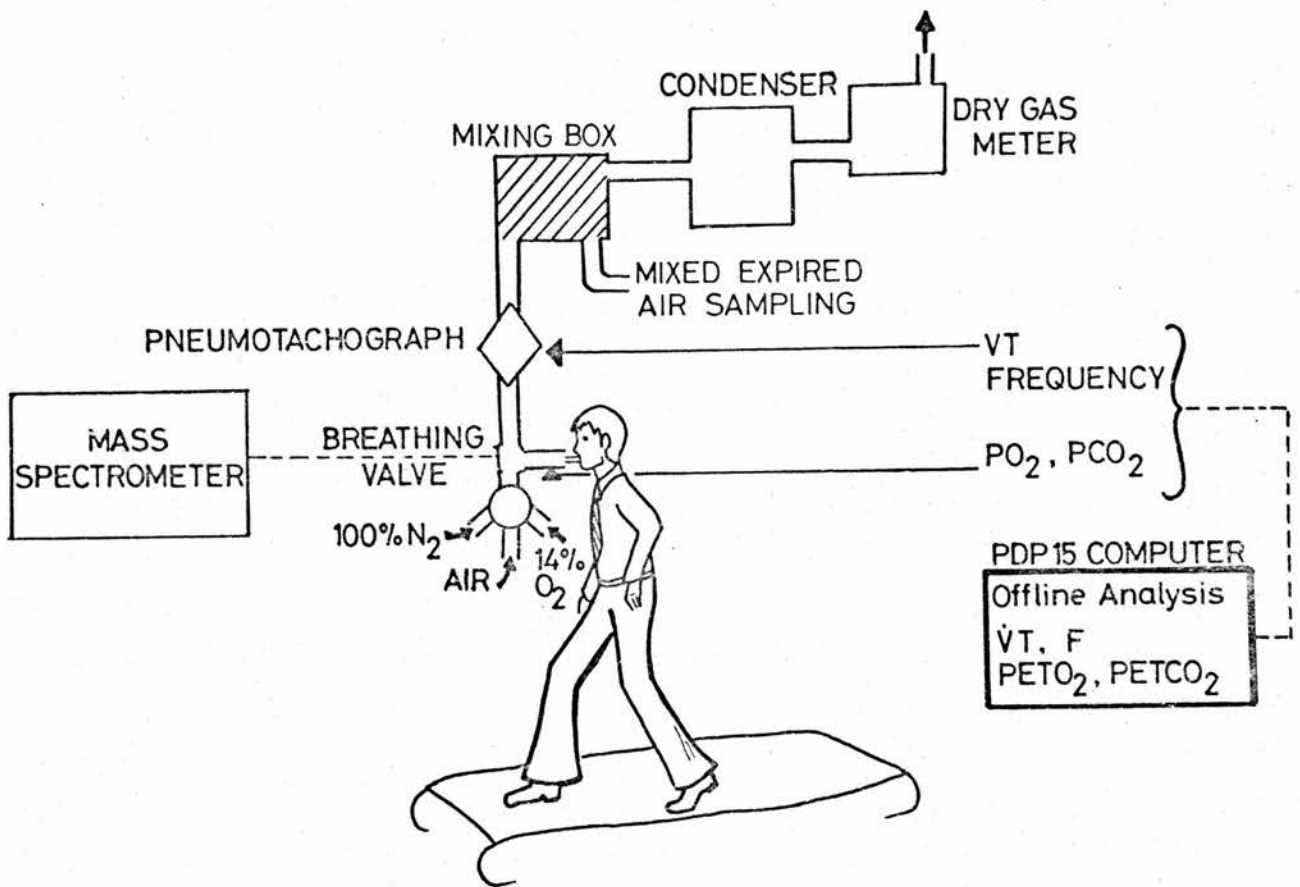
Figure 5

General arrangement of apparatus for studies of transient
hypoxic drive on exercise. The subject walks on a level
treadmill breathing through a valve to which air, N_2 or
14% O_2 can be supplied as inspired gas. The expired gas
passes through the valve, a pneumotachograph, a mixing
box and a condenser to a dry gas meter. A mass spectro-
meter probe continuously samples PO_2 and PCO_2 near the
lips. The off-line analysis of the data thus obtained is
discussed in the text.

oxygen consumption of 1000 ml.min^{-1}.

Breathing Valve

The subject breathed through an Otis-McKerrow breath-
ing valve which had been modified to allow insertion of
the mass spectrometer probe three centimetres from the
mouthpiece. In later experiments, the pressure near the
lips was also recorded from a similar site in the valve.
The expiratory pressure for the valve at different constant
flow rates is shown in figure 6 for the valve and tubing
alone and also when the valve was attached to the rest
of the breathing assembly. By a system of two taps at-
tached to the inspiratory side of the valve it was possible
to switch the inspired gas from air to either 100% N_2,
from a suspended Douglas bag, or to 14% O_2 in nitrogen,
which was stored in a 350 litre Collins spirometer. The
subjects were not blindfolded in 1971 and 1972 and it is
difficult to exclude the possibility that they may have
seen the turning of the tap. Every attempt was made to
disguise this, and the close correspondence between re-
sults obtained in 1971/72 and those in 1974, when the sub-
jects were blindfolded, supports the belief that conscious
effects on respiration were unimportant in determining the
responses observed (see Results).

Pneumotachograph and Integrator

The expired air from the respiratory valve passed
through a heated Fleisch No. 3 pneumotachograph. The dif-
ferential pressure across the pneumotachograph was recorded
by a Furness controls micromanometer (± 12,5 mm.Wg) and
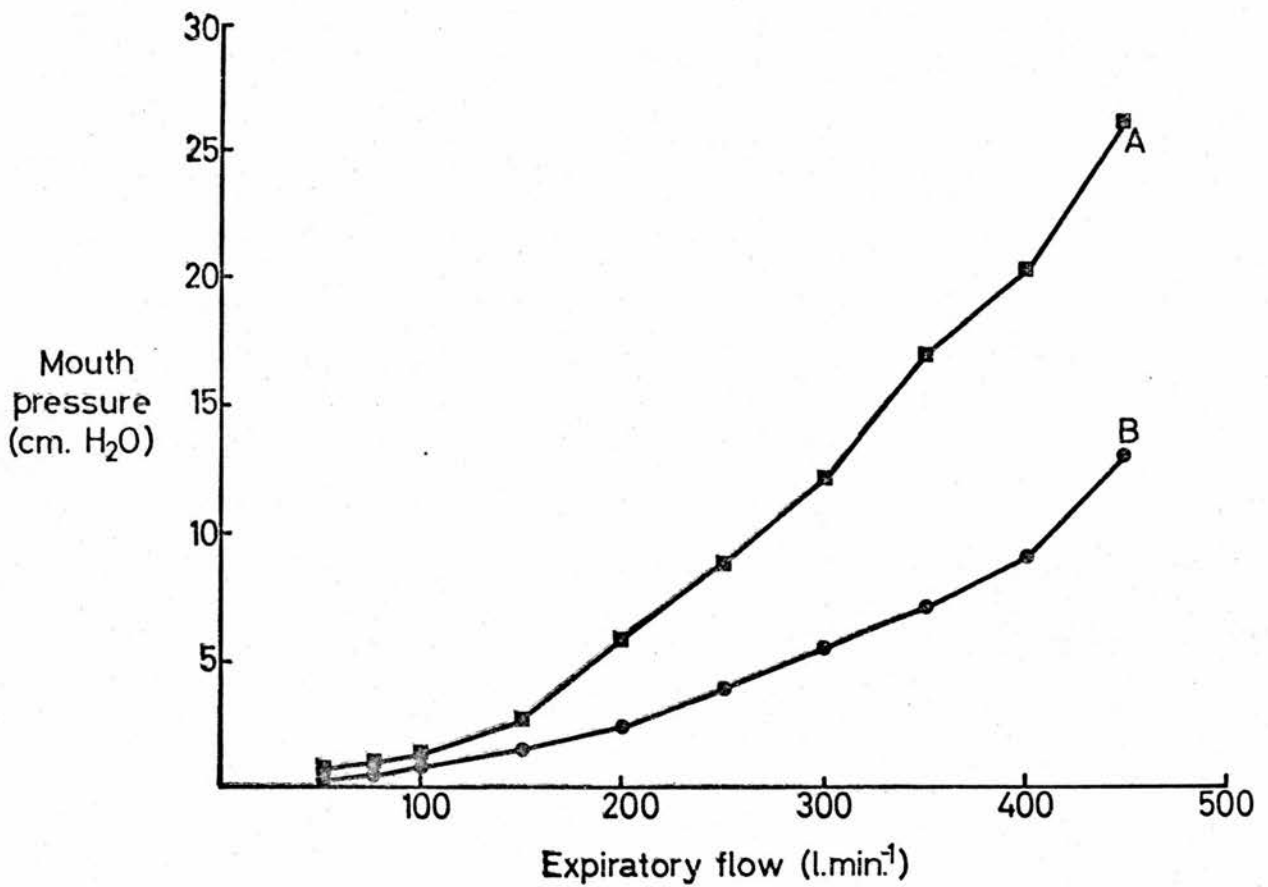
Figure 6

The expiratory pressure-flow characteristics of the Otis-McKerrow breathing valve at constant flow rates B, with valve only and A, with valve plus pneumotachograph, mixing-box, condenser and dry gas meter on the expiratory side of the valve.

flow was electronically integrated to provide tidal volume
for each breath. The integrator was automatically zeroed
during inspiration by venting both pressure lines to at-
mosphere, thus minimising integrator drift.

The relationship between a constant flow of humidified
air at $37^{O}C$ and the output of the pressure transducer is
shown in figure 7. This was linear. The relationship
between integrated transducer output and breathing fre-
quency for a constant tidal volume is shown in figure 8.
This relationship showed that frequency changes in the
physiological range did not affect measurement of volume
from the integrated output of the pneumotachograph. The
effect of different gas mixtures on the pressure trans-
ducer output is shown in figure 9. 30% O_2, air and 100%
N_2, humidified, and at $37^{O}C$, produced similar relationships
between pressure transducer output and flow. In contrast,
100% oxygen under the same conditions, produced a higher
transducer output for a given flow rate. On the basis of
these findings no oxygen mixtures of greater than 30%
were used in hyperoxic studies, thus avoiding the need for
a correction factor for volume.

In 1971 and 1972 the pneumotachograph was calibrated
by pumping air, using a 2 litre syringe, through the valve
and pneumotachograph 5 times before and after each study
on one subject. These volume calibration signals were re-
corded on the tape recorder with an identifying marker
trace. The mean value of the 10 calibrations was taken,
for analysis of the tape recorded data, to be 2 litres.
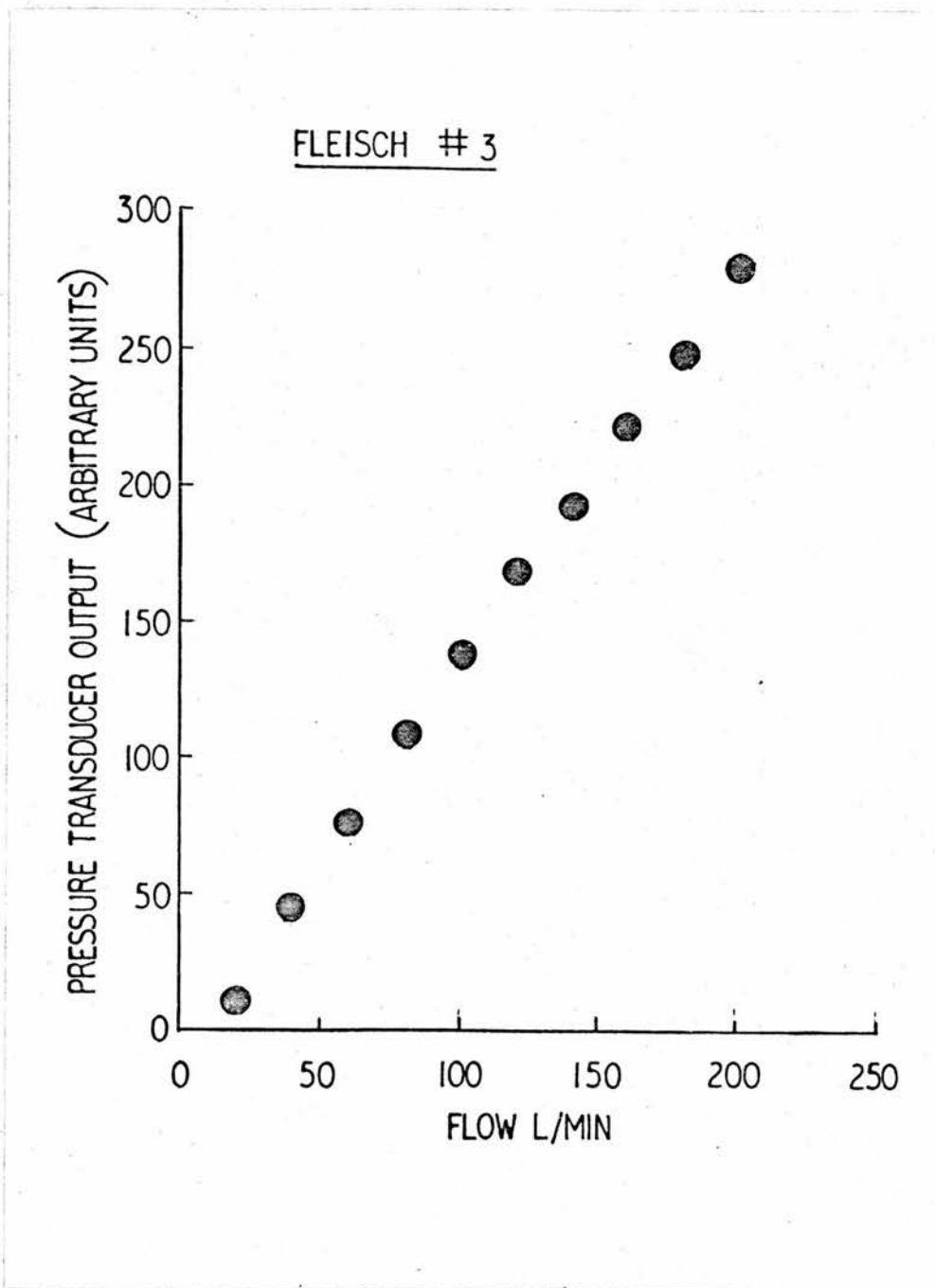
FLEISCH # 3

Figure 7

The relationship between pressure transducer output from
the Fleisch no. 3 pneumotachograph (arbitrary units) and
constant flow of humidified air at 37°C through the pneu-
motachograph (ℓ.min)
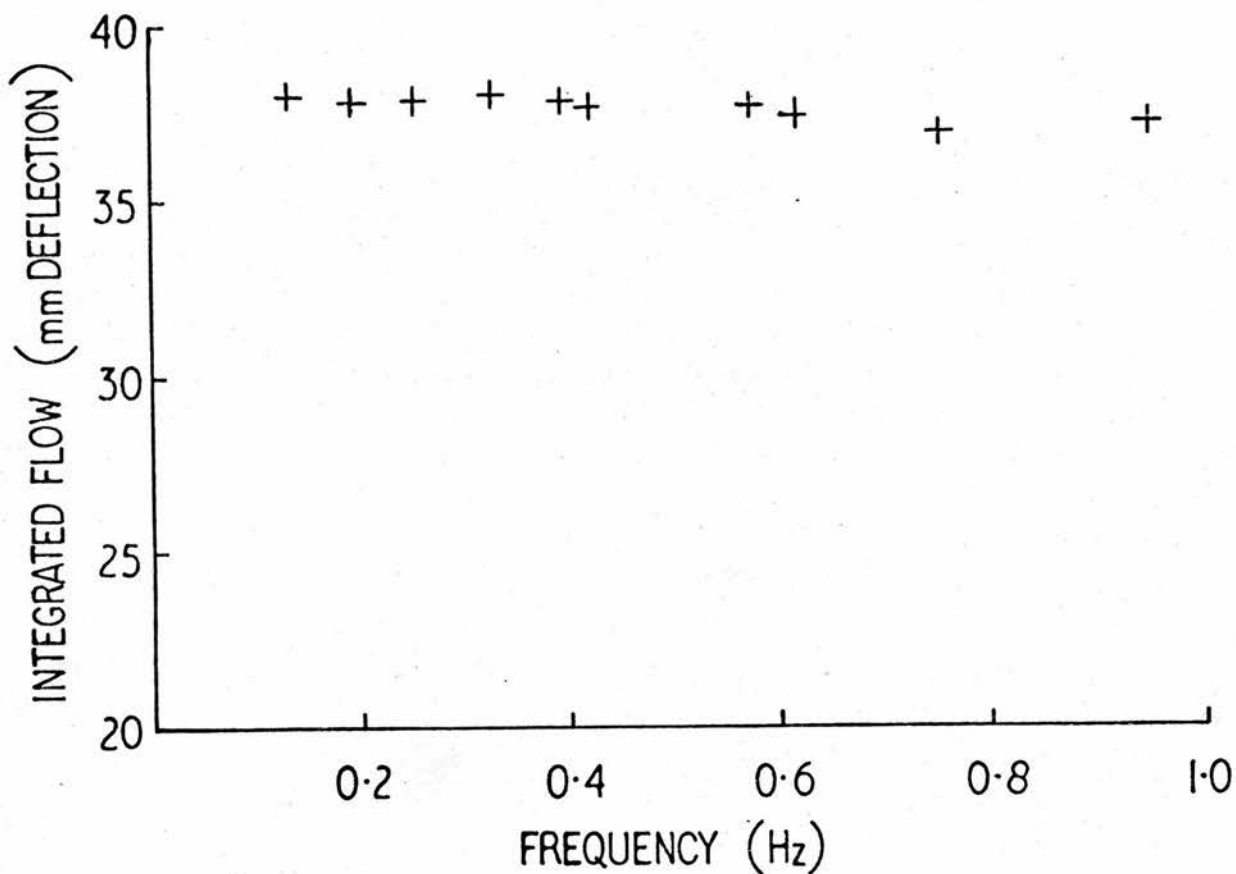
Figure 8

The relationship between frequency of breathing (H_2) at
constant tidal volume (300 ml) and integrated flow from
the Fleisch no. 3 pneumotachograph (mm deflection on
Mingograph recorder).
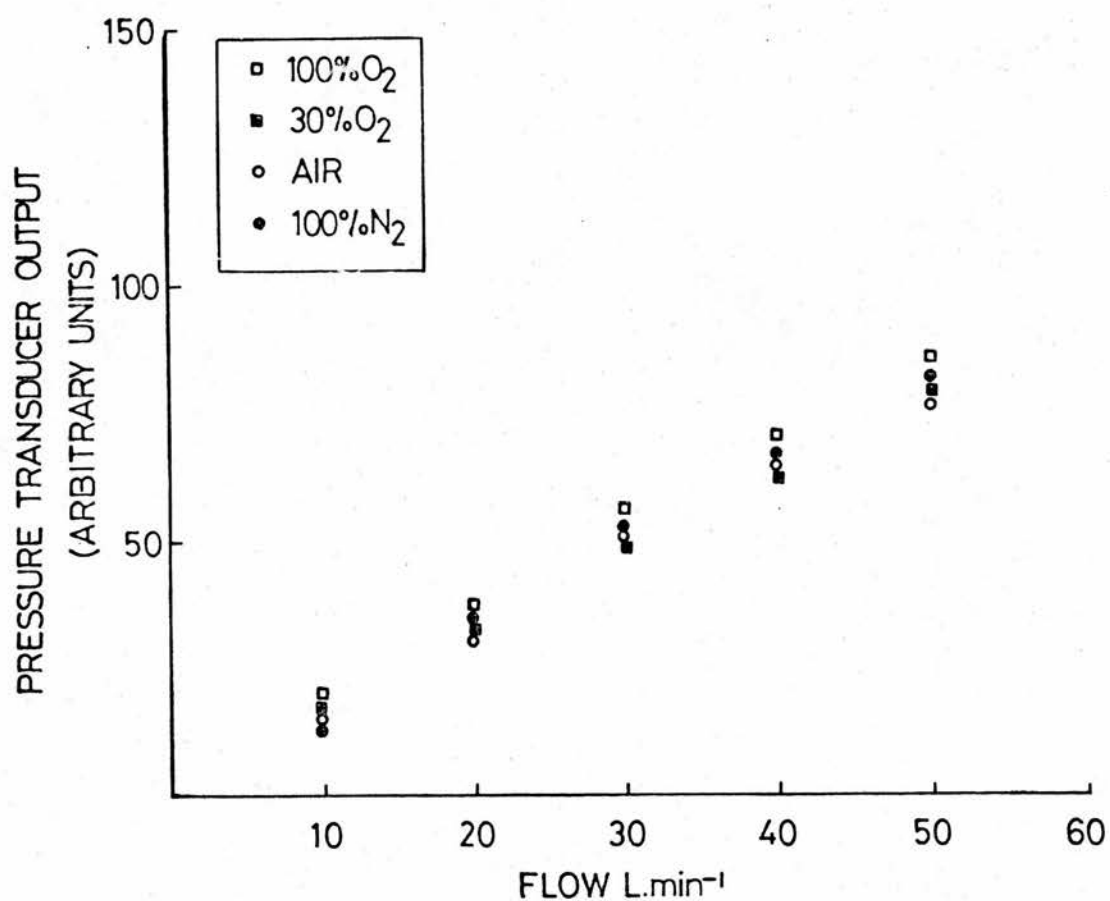
Figure 9

The relationship between pressure transducer output from
the Fleisch no. 3 pneumotachograph (arbitrary units) and
flow of different humidified gases at a temperature of
37ºC (ℓ.min^{-1}).

In 1974, with on-line computer facilities, a more accurate method of calibration was used. The pneumotachograph signal was integrated in the computer between successive rotations (10.6 litres) of the CD4 dry gas meter dial. From this comparison, together with the barometric pressure and the temperature of the gas in the dry gas meter, the calibration factor of the pneumotachograph to volume expressed as BTPS could be derived. The calibration factor used was not updated instantly. Instead, a weighted average of the last seven calibration factors was used. Hence the system is not calibrated until 63.6 litres of gas have passed through the system, taking about 6 minutes for studies at rest and 2-3 minutes for exercise studies at 3 m.p.h. breathing air. (Fig. 10)

Thereafter, the volume calibration factor remained steady, and any marked deviation from the mean level indicated a defect in the tidal volume recording system, e.g. failure of the heater on the pneumotachograph with resultant changes in sensitivity. Experiments in which this happened were discarded. An additional theoretical advantage of the updating system was that minor discrepancies in pneumotachograph recorded volume occurring throughout the experiment would be corrected in terms of the dry gas meter measured volume.

Mixed expired air sampling

Expired air passed from the pneumotachograph to a mixing box and mixed expired air was sampled from the outlet of this box, after flushing of the dead space, in two
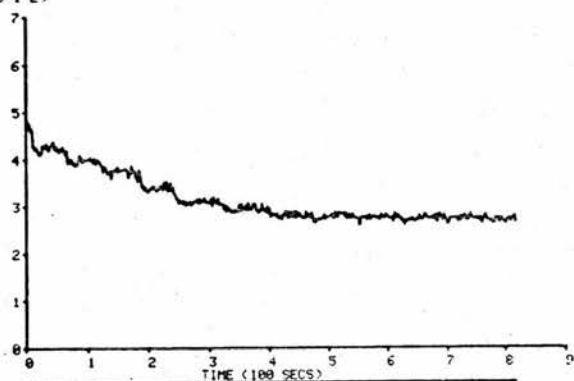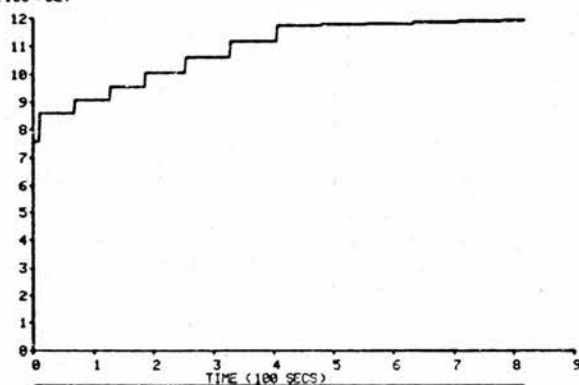
Figure 10

To show the operation of the on-line computer volume cali-
bration factor. An animal respirator "breathed" through
the breathing valve and assembly with a constant tidal
volume of 285 ml.min^{-1} at a rate of 27 breaths min^{-1}. The
graph on the left shows the computer measure of tidal volume
against time, the volume reaching a constant value after
400 secs. On the right, the graph shows the volume cali-
bration factor (see text) also plotted against time. This
factor also achieves constancy after 400 secs. As discussed
in the text, achievement of volume calibration factor stabi-
lity at the start of an experiment was essential to ensure
fidelity of tidal volume measurements by the computer.

50 ml syringes driven by a Harvard pump. This gas was ana-
lysed for oxygen concentration using the Servomex 101A
paramagnetic oxygen analyser (Ellis and Nunn, 1968) cali-
brated with air and 100% N_2. Carbon dioxide concentration
was measured using the Uras 111 infra-red carbon dioxide
analyser (Patrick, 1963) previously calibrated with gases
analysed on the Lloyd-Haldane apparatus.

Parkinson-Cowan CD4 Dry Gas Meter

From the mixing box expired air passed through a con-
denser to a Parkinson-Cowan CD4 dry gas meter. Figure 11
shows the calibration of the dry gas meter using a Tissot
spirometer, which had itself been calibrated by water dis-
placement. All volumes measured by the dry gas meter were
corrected using the correction factor of 1.06 derived from
the calibration data. The temperature of the gas leaving
the dry gas meter was measured by a thermistor thermometer.
The volume recorded by the dry gas meter was detected by
a photoelectric cell placed under the dial and converted
to a digital display for easy recording.

Varian M3 Mass Spectrometer

The Varian M3 Mass Spectrometer was used to continuously
measure oxygen and carbon dioxide tensions near the lips.
Samples were taken through a 2 metre heated probe which
was inserted into the breathing valve close to the mouth-
piece attachment. N_2 and Argon concentrations were also
measured. The mass spectrometer sampled 7.5 cc of gas per
minute with a delay of 700-800 msecs. The mass spectro-
meter proved extremely stable. In 1971 and 1972, the mass
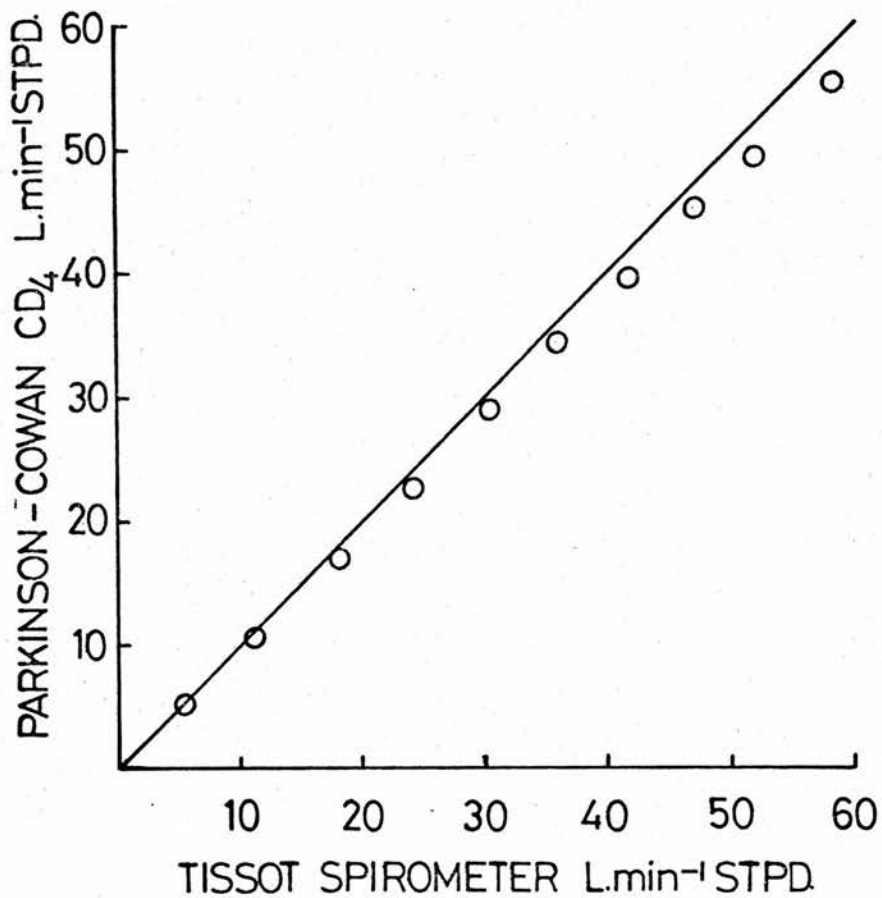
Figure 11

Calibration of the Parkinson-Cowan CD4 dry gas meter against a Tissot spirometer. All volumes in $\ell.min^{-1}$ STPD. The straight line is the line of identity. By comparison of the actual with the identical relationship the CD4 calibration factor of 1.06 was derived and used to correct all volumes measured on the CD4 dry gas meter.

spectrometer was calibrated with 100% N_2 and 3 or 4 CO_2/O_2 gas mixtures, previously analysed by the Lloyd-Haldane apparatus, at the start of each experimental day. These calibration signals were recorded on the tape recorder and were used for the entire afternoon (generally studies on 3 subjects).

In 1974, a trolley carrying 100% N_2 and 4 CO_2/O_2 mixtures, previously analysed by the Lloyd-Haldane apparatus, was used to calibrate the mass spectrometer. The Lloyd-Haldane analyses and barometric pressure were typed into the computer, the calibration gas mixtures then being sampled in turn by the mass spectrometer probe. A line of best fit, using least squares linear regression, was then derived by the computer, relating mass spectrometer output on each of its four gas channels (tuned to O_2, CO_2, N_2 and Ar) to the gas compositions derived from the Lloyd-Haldane analysis. The computer programme then produced a display, following calibration of:

1. The residual root sum squared of O_2, CO_2 and N_2 in %.

2. The largest individual deviation of O_2, CO_2 and N_2 in %, identifying the calibration gas concerned.

3. The probe delay time.

4. The dry gas composition of air based on the calibration gases.

An example of such a calibration procedure output is shown in text table 1.

TEXT TABLE 1

The computer display following gas calibration
(see text)

CO_2 Residual RSS Deviation of %   0.058
          Largest Individual Deviation of %   0.044   Tap 5

O_2 Residual RSS Deviation of %   0.162
          Largest Individual Deviation of %   0.114   Tap 2

N_2 Residual RSS Deviation of %   0.682
          Largest Individual Deviation of %   0.398   Tap 3

Delay 740 msec

Measured dry air composition:

CO_2 0.10%
O_2 21.16%
N_2 77.81%
Ar   0.93%

In computing gas composition thereafter, the programme first converted the four mass spectrometer outputs to percentage compositions and then adjusted these compositions by multiplying each by a common factor so as to make the sum equal 100%. In this way, the dry gas composition was obtained, corrected for any gain drift in the mass spectrometer common to all four channels as, for example, changes in sensitivity due to blocking of the input probe, or any change in the barometric pressure since calibration.

This calibration procedure proved useful in detecting 'rogue' calibration gases, for example, after a new calibration mixture had been prepared in a fresh cylinder, and served as a check on the accuracy of the Lloyd-Haldane analysis, assuming that the calibration was linear.

This calibration facility also allowed accurate assessment of the stability of the mass spectrometer with time. Text table 2 shows the results of O_2 and CO_2 estimations after initial calibration using 4 O_2/CO_2 mixtures and 100% nitrogen. The O_2 and CO_2 percentages are shown as measured by the mass spectrometer at time 0 mins and time 180 mins compared with the gas concentrations determined by Lloyd-Haldane analysis. The mass spectrometer percentage for O_2 and CO_2 at zero minutes agrees well with the Lloyd-Haldane measurements with the exception of the difference of 0.18% for oxygen in the second mixture (tap 2). After 3 hours the maximum changes in O_2 and CO_2 percentage recorded when the mass spectrometer is again exposed to the same calibration mixtures is 0.08% for CO_2 and 0.03% for

TEXT TABLE 2

Percentage O_2 and CO_2 in 100% N_2 and four CO_2/O_2 mixtures as analysed by the Lloyd Haldane apparatus and, following calibration of the mass spectrometer with these gases, at 0 and 180 minutes on the mass spectrometer (same calibration as Text Table 1)

		CO_2%				O_2%	
	Haldane	Mass Spec. 0 mins	Mass Spec. 180 mins	Haldane	Mass Spec. 0 mins	Mass Spec. 180 mins
Tap 1	0	-0.02	-0.03	0	0.02	0.05
2	2.05	2.03	2.01	7.27	7.09	7.09
3	8.25	8.27	8.19	20.92	20.96	20.99
4	4.45	4.43	4.39	19.16	19.17	19.17
5	7.37	7.35	7.28	14.87	14.89	14.91

O_2. The results shown in text table 2 refer to the same
calibration as text table 1 where tap 2 was identified as
having the largest individual deviation. In practice,
largest individual deviations of up to 0.25% were tolerated
in experiments in the current series.

In earlier studies using the mass spectrometer a rise
in measured PCO_2 was recorded transiently after the probe
has been exposed to 100% O_2. This was attributed by the
manufacturers to the production of CO_2 inside the mass
spectrometer by the oxidation of omnipresent carbides. It
was therefore important to assess the effect on PCO_2 of
exposing the probe to 100% N_2 and also to 30% O_2, repre-
senting the extremes of oxygen percentages used in the
present study. Figures 12 and 13 show the results of ex-
periments carried out using an animal respirator instead
of a subject to "breathe" a 5% CO_2 in air mixture through
the breathing assembly described above. The mass spectro-
meter probe continuously sampled O_2 and CO_2 concentrations
near the mouthpiece of the valve. Figure 12 shows the
effect of inhalation of 4, 3 and 7 breaths of 100% N_2 on
the measurement of the % CO_2 inspired. Within 4 breaths
of exposure to 100% N_2 the inspired CO_2 % has returned to
the control value. The depression of CO_2 by 0.2-0.3% for
4 breaths may be due to the effect of the nitrogen which
could therefore cause a minimal "artificial" hypocapnia
in the experimental studies. In contrast, in Figure 13,
the effect of switching from a mixture of 5% CO_2 in air
to a mixture of 4.8% CO_2 and 30% O_2 in nitrogen for 7

DK0:CAL02 .DAT   03-FEB-76
CAL PROCEDURE
CAL PROCEDURE
SECTION 1 BREATHS 1 TO 149

% CO2 INSP
(%)
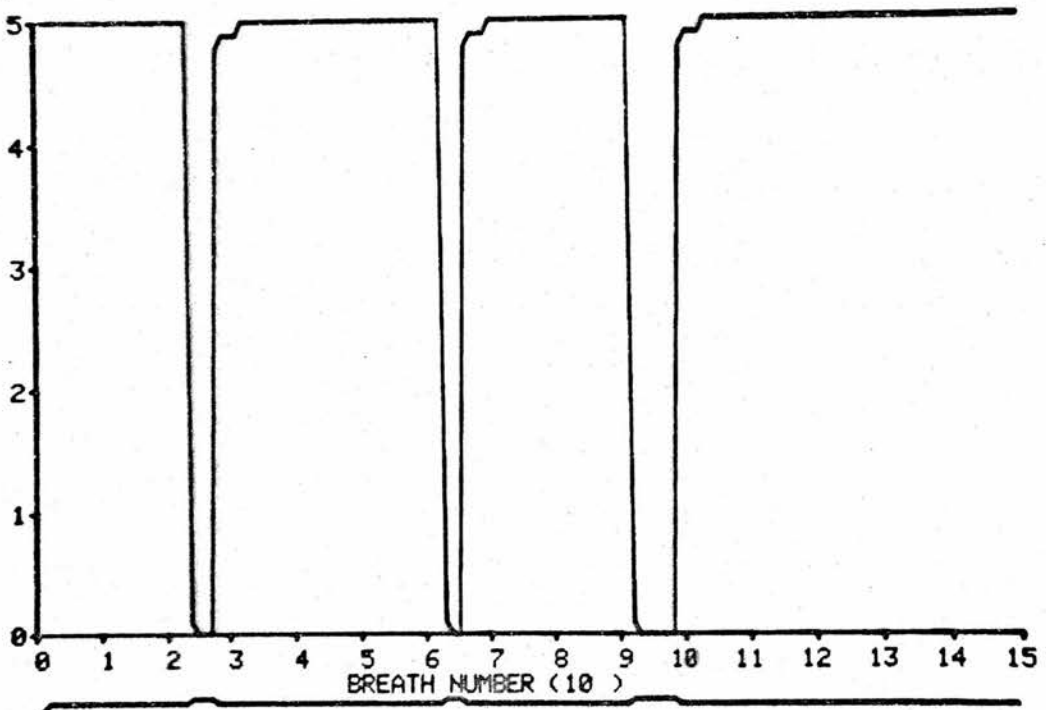
BREATH NUMBER (10)

Figure 12

The effect of a brief exposure to 100% N_2 on the mass spec-
trometer sensitivity to CO_2. The mass spectrometer is
sampling the percentage CO_2 inspired (5%) in air displayed
on the y axis, and breath number is displayed on the x axis. (x10)
At the points indicated by the upward deflections on the
marker trace, 4, 3 and 7 breaths of 100% nitrogen were in-
spired. See text for further explanation.

```
DK0:CAL03 .DAT    03-FEB-76
CAL PROCEDURE 02
AS ABOVE
SECTION  1 BREATHS  1 TO  155
% CO2 INSP
(%)
```
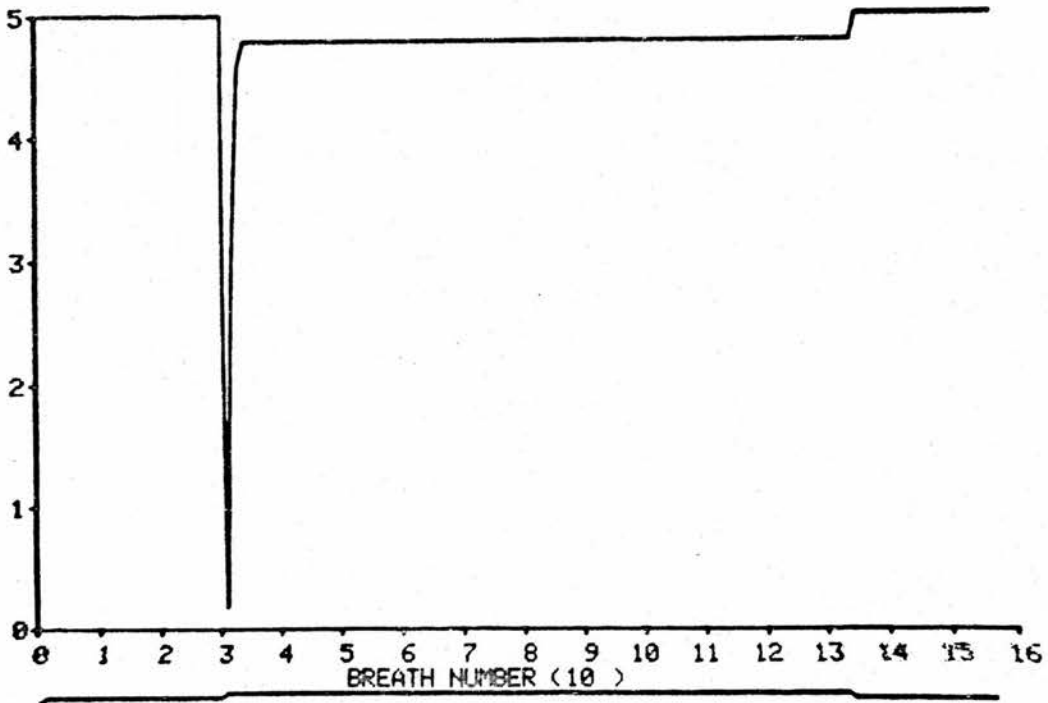
Figure 13

The effect of a 7 minute exposure to 30% O_2 in 4.8% CO_2 and N_2 on the mass spectrometer sensitivity to CO_2. The mass spectrometer is sampling the percentage CO_2 inspired (5%) in air displayed on the y axis, and breath number is displayed on the x axis. At breath number 30 the inspired gas is switched to 4.8% CO_2 in 30% O_2 and N_2 (the initial rapid downward deflection is due to CO_2 free gas in the dead space). At breath 133, the inspired gas is restored to 5% CO_2 in air. See text for further explanation.

minutes can be seen to be negligible with a rapid return
of inspired CO_2 percentage to normal when the inspired
gas is changed back to 5% CO_2 in air.

Data Processing

1971 and 1972

In 1971 and 1972, the analogue data (tidal volume
(VT), oxygen tension ($P_{ET}O_2$) and carbon dioxide tension
($P_{ET}CO_2$) were displayed during the experiment on a large
screen oscilloscope (Fig.14) and recorded as required on
a Bell and Howell VR 3360 FM tape recorder along with a
marker track which indicated the data being recorded. Gas
calibrations were performed at the start of an experimental
period using 100% N_2 and 4 CO_2/O_2 mixtures which had been
analysed on the Lloyd-Haldane apparatus. Volume calibra-
tions were performed at the beginning and end of each in-
dividual study using a 2 litre syringe as previously des-
cribed. For each subject the analogue data were recorded
on tape for the three episodes of transient hypoxia to
include 15 breaths preceding and 10 breaths following the
first breath of nitrogen. The tapes for the entire series
with the tape recorder and information on the barometric
pressure, relative humidity and gas calibrations for each
study were then transferred to the Edinburgh Regional Com-
puting Centre for off-line analysis on the PDP-15 computer.

For each study on one subject there were available 10
volume calibrations, 5 before and 5 after the experimental
data. Each volume calibration was digitised at 100/sec
and the highest value for each accepted. The mean of the
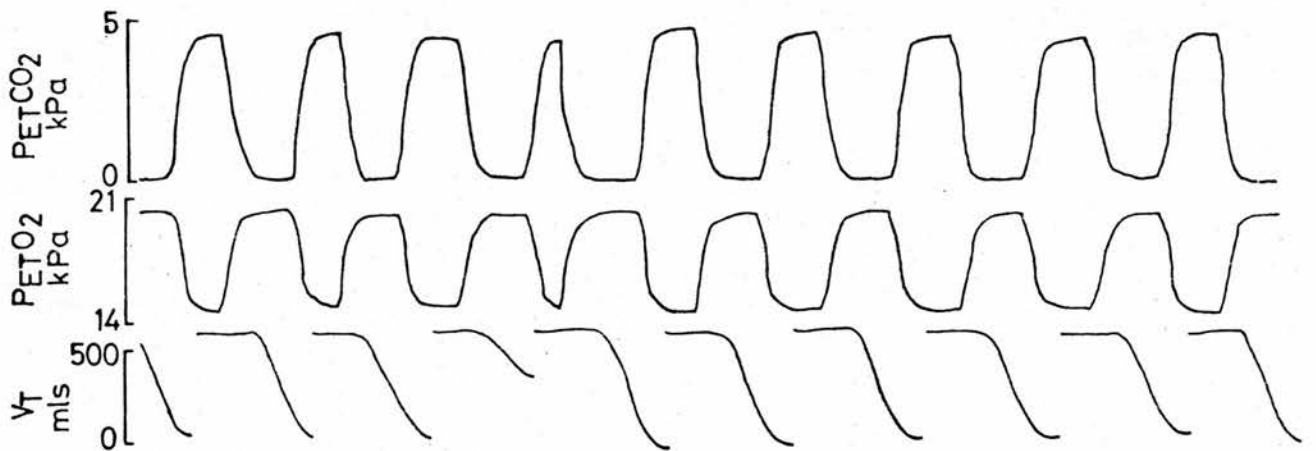
Figure 14

The analogue data of PO_2, PCO_2 and tidal volume from which
the analogue to digital conversion was made. The diagram
was traced by hand from a Mingograph paper reproduction for
the purpose of photography.

10 highest values was set to equal 2 litres and provided
the calibration for analysis of the intervening tidal
volumes. Each of these was digitised in the same way and
converted into volume units (ml) by reference to the cali-
bration. The computer also measured the interval between
end of expiration for a given breath (i.e. the time at
which tidal volume had returned to zero) and the end of
expiration of the following breath, so giving a value for
the duration of each breath. The computer than calculated
for each breath a value for instantaneous minute ventila-
tion ($\dot{V}_E$ inst) from the relationship

$$\dot{V}_E \text{ inst} = \dot{V}_T \times \frac{60}{\text{breath duration}}$$

The gas calibrations/readings were also digitised at
a rate of 100/sec. With the known value of barometric
pressure these dry gas calibrations could be converted
into partial pressures of oxygen and carbon dioxide. The
digital value for a given gas calibration was taken as the
mean of 100 consecutive readings at 100/sec. From the li-
near regression of partial pressure on digital value any
subsequent measured partial pressure could be interpreted.
The end-tidal values of PCO_2 were determined by digitising
the analogue signal for CO_2 at the lips measured by the
mass spectrometer, again at 100/sec. and, using a "moving
window" technique, with an aperture of 8 digits, identify-
ing the point at which PCO_2 fell consistently. The end-
tidal PCO_2 was then expressed as the average PCO_2 over 8
digitised values before PCO_2 fell at the start of inspi-
ration. The end-tidal PO_2 was measured over the same time

interval as the end-tidal PCO_2.

The computer then produced a print out identifying the subject and the date of the experiment, followed by breath by breath values for time (from start of the study), breath duration, tidal volume, $\dot{V}_E$ inst, $P_{ET}O_2$, $P_{ET}CO_2$ and a marker indicating when the tap had been turned to nitrogen. Subsequent analysis of the data was carried out by hand using conventional desk calculators.

1974

In 1974, the data were handled on line by the Department of Medicine PDP 11-40 computer, programmed by Dr. P.K. Wraith. Before an experiment, the Lloyd-Haldane analyses of the gas calibrations were entered via the visual display unit, along with the value for barometric pressure into the computer. The initial calibration relating dry gas meter volume to pneumotachograph volume was performed electronically by switching a predetermined voltage into the input of the flow measuring amplifier. The gas calibration mixtures were then presented to the mass spectrometer probe and the computer displayed the parameters of the linear regressions between the calibration analysis and the mass spectrometer readings, as shown in text table 1, with the value for probe delay and the composition of air, as measured by the mass spectrometer set on the gas calibration mixtures.

When the experiment began, the computer received as analogue signals, $P_{ET}O_2$, $P_{ET}CO_2$, $P_{ET}N_2$, $P_{ET}Ar$, gas flow dry gas meter volume and gas temperature and an inspira-

tory/expiratory signal from mouth pressure. The computer
integrated flow for each breath and the pneumotachograph
volume output was continuously updated, as discussed pre-
viously, in terms of dry gas meter volume throughout the
experiment. The programme produced an on-line digital
display of inspired O_2 and CO_2 percentage, end-tidal
PO_2 and PCO_2, tidal volume, frequency and volume and gas
calibration data. The data were stored on disc or dec-
tape and could be retrieved in the form of a digital print
out of the entire experiment, a statistical summary of
sections or as a graphic display on a visual display unit
which could be hardcopied on paper.

Data Analysis

For each subject data before, during and after three
separate switches to N_2 were available, each consisting
of about 20 control breaths followed by the three N_2
breaths and, on average, 7 post-switch breaths. Since
breath frequency for any one subject was similar for all
three switches, the data were analysed by superposition
of the data from the three switches (see Fig. 15). The
control value for ventilation was taken as the mean of the
60 control breaths from the three switches, with the signi-
ficance limits calculated as $\pm \frac{2SD}{\sqrt{3}}$ of this population.
The superposition method (Fig.15) allowed a smoothing out
of the natural breath by breath fluctuation in $\dot{V}_E$ inst.
The maximal ventilation following the nitrogen breaths
from the superposed data was expressed as a percentage of
the control mean to give a "mean highest breath value for
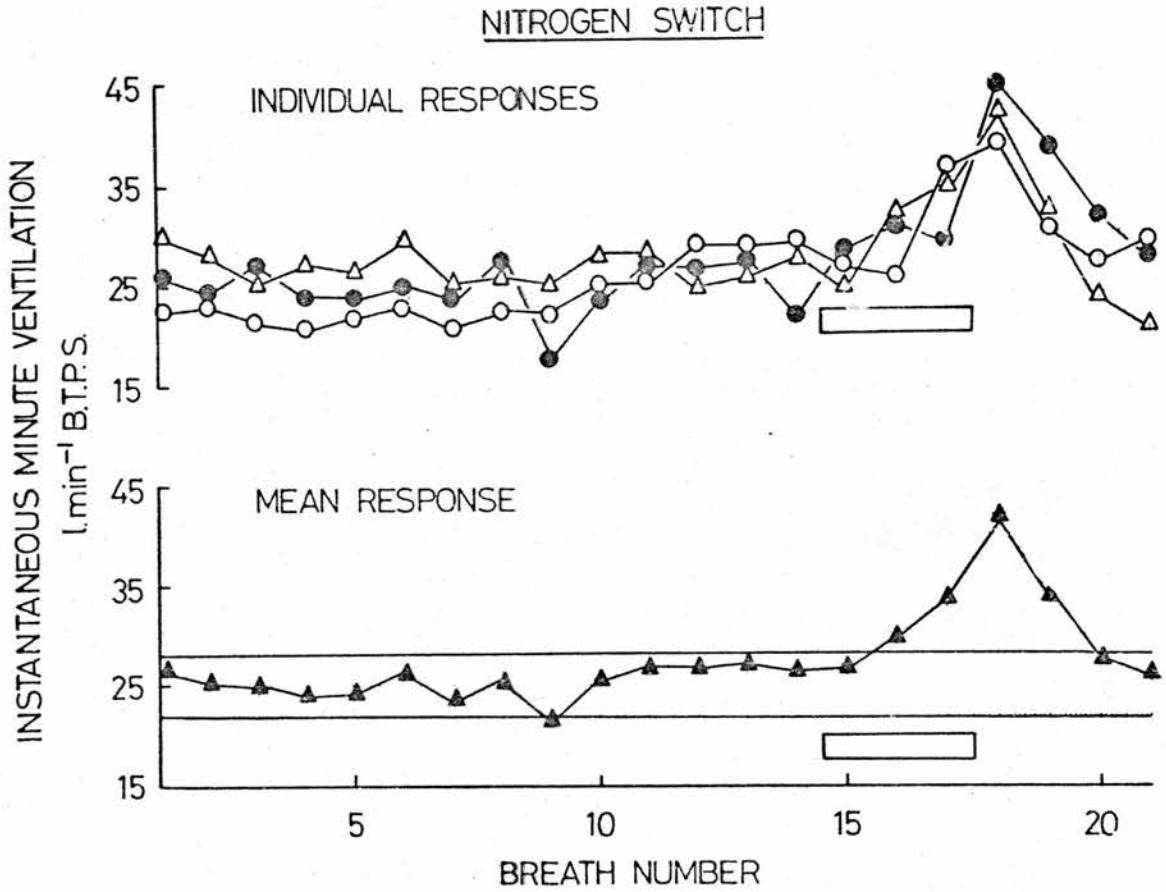
Figure 15

To illustrate the principle of "superposition". The graphs
show a plot of instantaneous minute ventilation for each
breath plotted against breath number. The top graph shows
breath by breath values for ventilation before, during (in-
dicated by the box) and after three breaths of nitrogen had
been substituted for air on three occasions in the same
subject. The lower graph is derived from the upper by
lining up the breath numbers on the first breath of nitro-
gen and taking the mean of the three superimposed breaths
which results. The parallel lines on the lower graph in-
dicate the 95% confidence limits of the control ventilation
derived as described in the text.

each subject.

Relationship between end-tidal PO_2 and PaO_2 during
inhalation of three breaths of N_2 on exercise

The normal relationship between alveolar and arterial
PO_2 will be disturbed by the inhalation of 3 breaths of
100% N_2 and one might predict reversal of the alveolar to
arterial oxygen tension gradient at some stage during this
procedure. The arterial and end-tidal PO_2 during such a
switch were therefore studied.

Arterial PO_2 was obtained by rapid sampling in 5
syringes linked by a tap system to an indwelling arterial
catheter in 3 subjects. The time of each arterial sample
was indicated by a signal marker on the output which, for
this experiment, was recorded on a Mingograph. This al-
lowed, when the delay time of the mass spectrometer probe
had been corrected, a temporal consideration of the end
tidal and arterial PO_2 during a switch. Arterial blood
PO_2 was measured by a Radiometer electrode calibrated by
tonometered blood.

The result of one such study is shown in Fig. 16
where the close correspondence between lowest end-tidal
and lowest arterial PO_2 is demonstrated. The results of
this and 4 other studies on 2 subjects are shown in Table
1. The lowest arterial PO_2 recorded was always within
2 kPa of the lowest end-tidal PO_2 with a tendency for
PaO_2 to be lower than $P_{ET}O_2$.

EFFECT OF 3 BREATHS N$_2$ ON ARTERIAL AND END-TIDAL PO$_2$
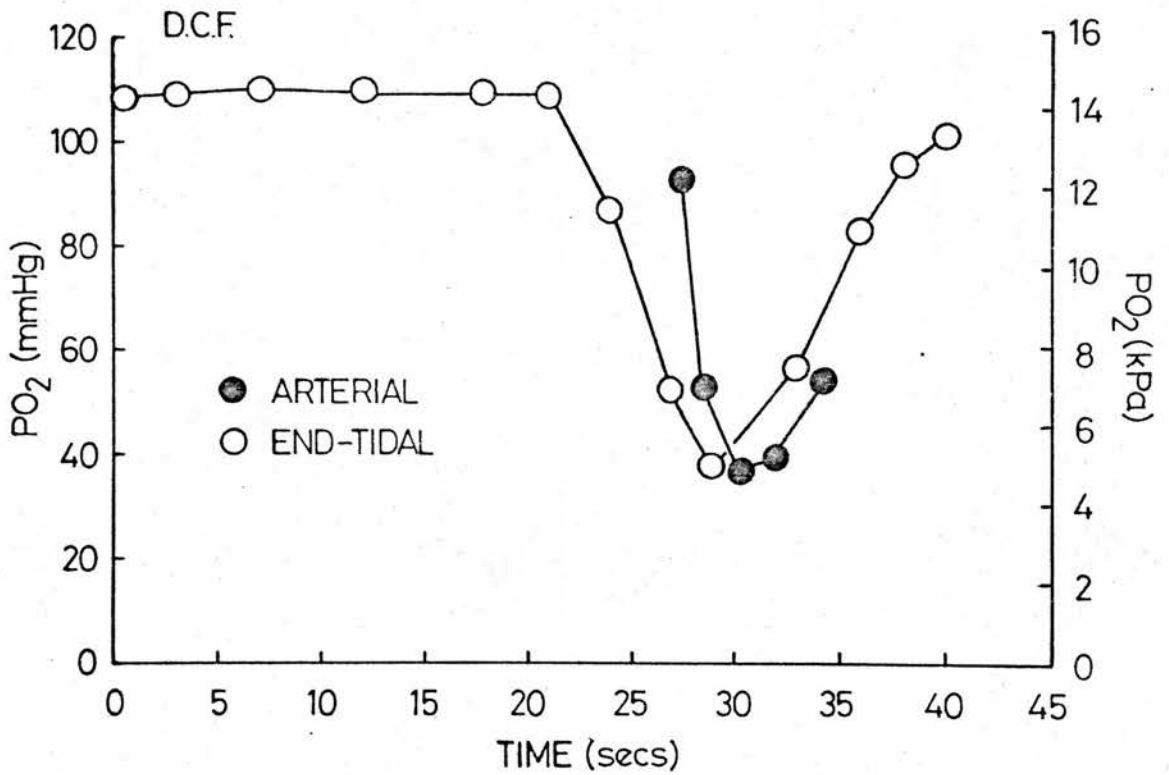
Figure 16

The effect of three breaths of 100% N$_2$ on the arterial
and end tidal PO$_2$ in one study in one subject using rapid
sampling of arterial blood.

Steady state ventilatory response to CO_2 and hypoxia

These studies were performed on 10 mine rescue workers in 1974 using the on-line computer facilities. The subjects sat in a comfortable chair listening to classical music through headphones, breathing through the assembly described above. Gases were supplied to the inspiratory side of the valve at a flow of 100 l/min from a rotameter which could supply any O_2, N_2 or CO_2 mixture required. The gases passed from the rotameter through a humidifier past the inspiratory inlet of the breathing valve, and then to a compliant reservoir in which the pressure was adjusted to fluctuate about atmospheric by applying variable suction with a vacuum cleaner.

The computer digital display allowed the operator to adjust the inspired gases to ensure $P_{ET}O_2$ values of 6.7 or 25 kPa and the ventilatory response to CO_2 was measured at these two $P_{ET}O_2$s. The order of inspired gases was air, 2% CO_2 at a $P_{ET}O_2$ of 25 kPa, 2% CO_2 at a $P_{ET}O_2$ of 6.7 kPa, 5% CO_2 at a $P_{ET}O_2$ of 25 kPa and 5% CO_2 at a $P_{ET}O_2$ of 6.7 kPa. The data were stored within the computer in the last three minutes of each ten minute period on a given gas mixture, provided that the operator was certain from the display and the minute by minute dry gas meter readings that ventilation and $P_{ET}CO_2$ were stable. If they were unstable, which happened rarely, the period on that particular inspired gas was prolonged until stability was achieved and data were only then stored in the computer.

The computer could produce a simple print-out of the breath by breath respiratory variables recorded but, in addition, it was programmed to produce a statistical summary of the data. This summary excluded breaths outside 3 standard deviations of the mean ventilation, a simple device which proved effective in rejecting artefactual breaths caused, for example, by swallowing. A visual graphic display was also prepared for each subject showing the CO_2 response lines ± 95% confidence limits at a $P_{ET}O_2$ of 6.7 and 25 kPa. This display could be copied and retained for use (Fig. 17). Each breath was accepted for inclusion in this graph if the $P_{ET}O_2$ lay within 20-30 kPa for the hyperoxic and 6.25-7.00 kPa for the hypoxic line. All breaths at a given inspired CO_2 were accepted if they were within ± 0,25 kPa of the mean $P_{ET}CO_2$.
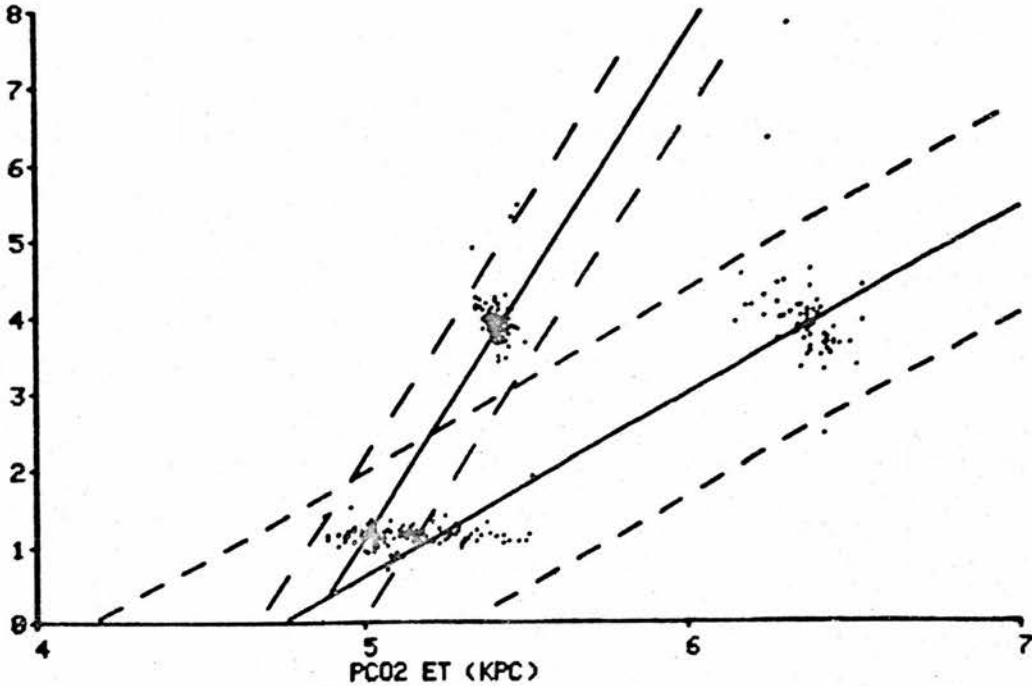
Figure 17

An example of the hard copy of a CO_2 response study re-
corded from the computer graph plotting assembly. Venti-
lation is displayed on the y and $P_{ET}CO_2$ on the x axis. Each
point represents a single breath and the lines indicate the
lines of best fit at $P_{ET}O_2$s of 6.7 and 25 kPa with their
95% confidence limits. The values for the slope (S) and
the intercept (B) of the hypoxic and hyperoxic line are
shown in the top right hand corner of the copy.

CHAPTER V - <u>HYPOXIC DRIVE TO BREATHING : RESULTS</u>

    i) <u>Subjects</u>

The height, weight, age, FEV, FEV/FVC ratio, Hb and smoking history of the subjects studied are shown in Table 2 and represented graphically in Fig. 18. Their age ranged from 20 to 44 years. None of the subjects w&Se anaemic and all, except one, had FEV/FVC ratios of greater than 65%. Twenty six of the 43 subjects were smokers.

    ii) <u>Exercise</u>

The basic data obtained in 1971 and 1972 ($\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, RQ, $\dot{V}E/\dot{V}O_2$ and $\dot{V}E_{14}/\dot{V}E_{21}$ are shown in Table 3.

The mean ventilation, measured by the dry gas meter, for the subjects studied in 1971 was 28.83 ± 5.33 (SD) $1.min^{-1}$ BTPS. The mean $\dot{V}O_2$ was 1216 ± 148 $ml.min^{-1}$ with a mean RQ of 0.84 ± 0.03. The ratio of ventilation to $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$) was 23.6 ± 3.0 $1.min^{-1}\ell^{-1}$. The ratio of ventilation measured in the last 2 minutes of the 6 minute period breathing 14% O_2 to the ventilation breathing air ($\dot{V}E_{14}/\dot{V}E_{21}$) was $109.6 \pm 8.4\%$ with a range of 97-125%.

In 1972 the mean ventilation was 29.25 ± 4.86 $1.min^{-1}$ BTPS. The mean $\dot{V}O_2$ was 1198 ± 158 $ml.min^{-1}$ with a mean RQ of 0.90 ± 0.04. The $\dot{V}E/\dot{V}O_2$ ratio was 24.4 ± 2.4 and the $\dot{V}E_{14}/\dot{V}E_{21}$ ratio was 112.3 ± 7.6 with a range of 93-128%.

Linear regression analysis of the data available for the subjects who were studied in both 1971 and 1972 showed a significant correlation for $\dot{V}E/\dot{V}O_2$ ($r = 0.83$, $n = 25$, $P<0.001$) between the two years but an insignificant corre-
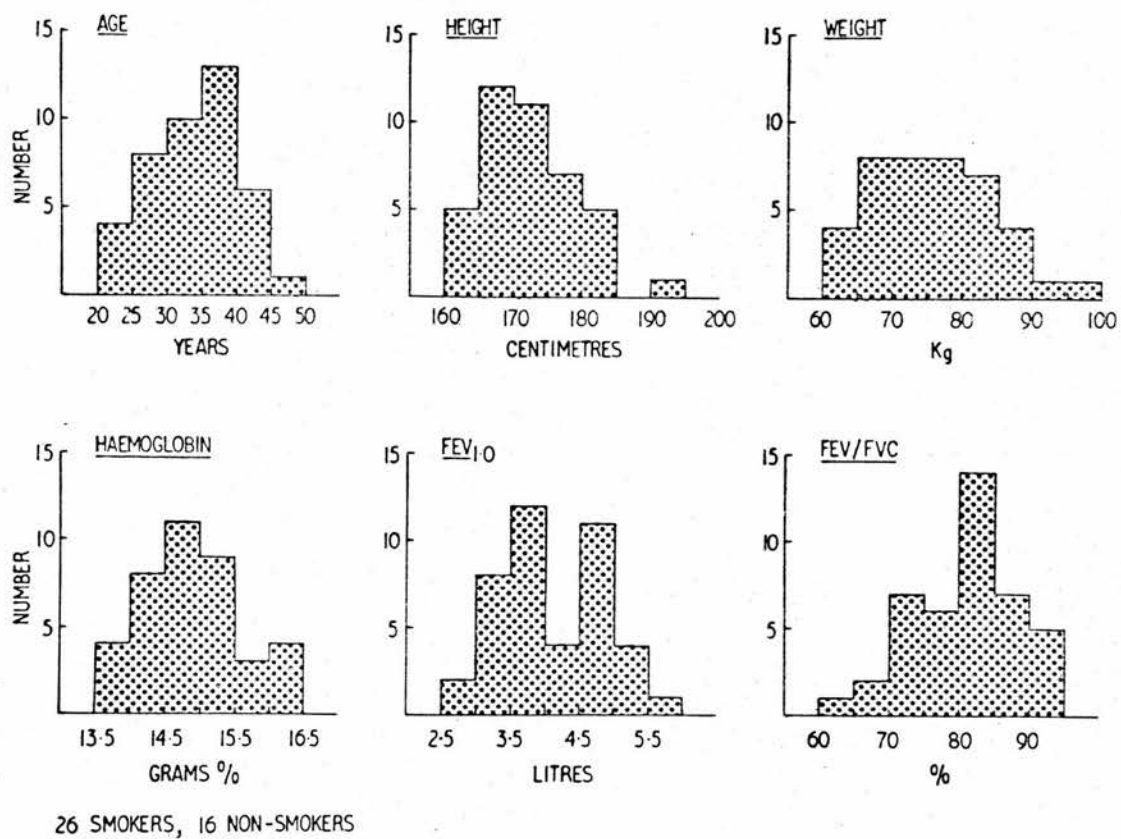
FIGURE 18   Histograms showing the age, height, weight, haemoglobin concentration, forced expiratory volume in one second and the forced expiratory volume - forced vital capacity ratio in the 42 miners of the study (subject 43 is not included in the histograms).

lation for $\dot{V}E_{14}/\dot{V}E_{21}$ ($r = 0.37$, $n = 26$, $P<0.1$). The $\dot{V}E/\dot{V}O_2$ ratio for each subject would thus appear to be highly reproducible from year to year whereas the $\dot{V}E_{14}/\dot{V}E_{21}$ ratio is not reproducible.

iii) The Control Period

The mean control ventilation, measured by pneumotachograph, tidal volume and frequency with 95% confidence limits, $P_{ET}O_2$ and $P_{ET}CO_2$ in 1971 and 1972 are shown in Table 4.

In 1971 the control tidal volume was 1542 ± 366 ml with a frequency of 19.4 ± 5.3 breaths min^{-1}. The mean $P_{ET}O_2$ and $P_{ET}CO_2$ for the control period were 13.42 ± 0.71 kPa and 5.56 ± 0.51 kPa respectively.

In 1972 the mean control tidal volume was 1385 ± 255 ml with a frequency of 19.3 ± 3.9. The mean control $P_{ET}O_2$ was 13.38 ± 0.8 kPa and the mean $P_{ET}CO_2$ was 6.03 ± 0.43 kPa.

Comparison of results in the subjects studied in 1971 and 1972 shows a high correlation for frequency of breathing ($r = 0.90$, $n = 26$, $P<0.001$). There was a significant correlation between 1971 and 1972 control values for $P_{ET}O_2$ ($r = 0.44$, $n = 26$, $P<0.05$) and PCO_2 ($r = 0.52$, $n = 26$, $P<0.01$). However, the difference in mean PCO_2 between 1971 and 1972 (Table 4) suggests that some methodological error is present and the results are therefore displayed graphically in Fig.19, where all the points lie to one side of the line of identity suggesting the possibility of a consistent error.
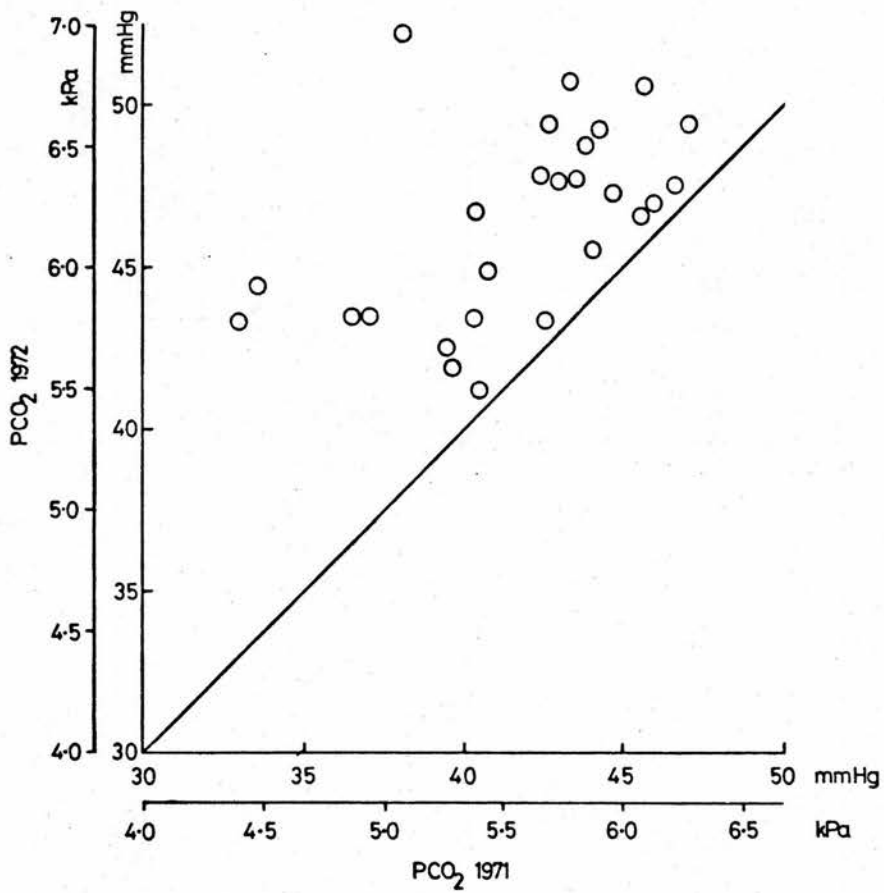
FIGURE 19   Control end tidal PCO_2 values on exercise for
subjects studied in 1971 and 1972. The straight
line is the line of identity.

It is unlikely that the difference observed was physiological since the level of exercise and the resistance of the breathing circuit were the same in both years. The possibility of a shift in the zero or gain of the mass spectrometer is excluded by the check of these variables carried out at the end of each day and also by the absence of similar differences in $P_{ET}O_2$. The possibility remains of a consistent error in the off line data analysis by the Regional Computing Centre for the 1972 PCO_2 data. It is not inconceivable that an error in the $P_{ET}CO_2$ zero was incorporated into the en bloc analysis of the 1972 data. The 1971 data produces values for $P_{ET}CO_2$ which are physiological and agree with values found in later studies of this and other kinds in 1974. It is important to stress that, because of this inconsistency, the PCO_2 data for 1972 has been excluded from further analysis. It is not relevant to the main theme of this thesis.

iv) <u>The Effect of Inhaling 3 Breaths of Nitrogen During Exercise</u>

<u>On PO_2</u> (Table 5)

The lowest PO_2 always occurred after the third breath of nitrogen and averaged, in 1971 4.21 ± 1.16 kPa and, in 1972, 3.71 ± 1.0 kPa. The lowest PO_2 in 1971 for each subject was highly correlated with the 1972 value (r = 0.50, n = 26, P<0.001).

Analysis of the 1972 data where FRC was measured shows that the lowest PO_2, as might be expected, correlated with the ratio, mean tidal volume of N_2 divided by FRC, and this

relationship is shown in Fig. 20.

On Ventilation

The ventilatory response to the hypoxic stimulus is expressed as the ratio of the highest $\overset{\bullet}{V}E$ inst occurring after the 3 breaths of nitrogen to the mean control ventilation. The mean highest breath value (mean HBV) (Table 5) is derived from superposition of three studies in each individual as described in methods (Fig. 15). In order to indicate the variation between single studies in each subject the highest breath values for each of the three studies on each individual in 1972 are shown in Fig. 21.

The range of mean HBV was 114-217% in 1972 and 100-204% in 1971. The reproducibility of the test is shown in Fig. 22 where the 1971 values are plotted against the 1972 values for the 26 subjects who were studied on both occasions. There is a highly significant relationship between these values ($r = 0.67$, $n = 26$, $P<0.001$) and, more importantly, the subjects with the two lowest values in 1971 also had the two lowest values in 1972. The histogram of mean HBV in 1972 for the 42 miners is shown in Fig. 23.

The first breath to achieve a significant increase in $\overset{\bullet}{V}E$ inst was on average 3.2 (1971) or 3.5 (1972) breaths after the first inspiration of nitrogen. The greater the ventilatory response the earlier the first breath to significance was likely to be (see Table 5). The position of the highest breath was on average at breath 4.0 in 1971 and 4.8 in 1972, the difference probably being related to the overall greater magnitude of ventilatory responses in
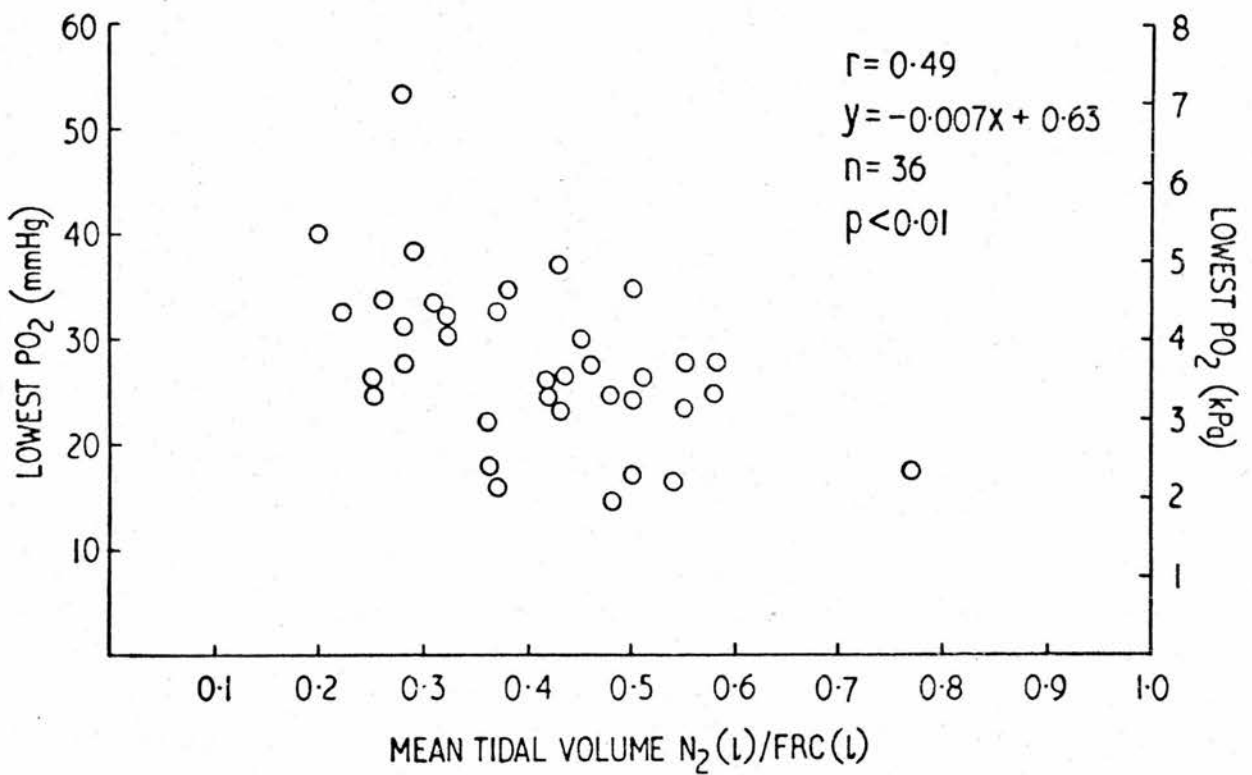
FIGURE 20   The relationship between the lowest $P_{ET}O_2$ obtained with three breaths of nitrogen on exercise and the ratio for each subject of the mean tidal volume of nitrogen inspired to his functional residual capacity in 1972. The linear regression equation, r and P values are shown. Measurement of functional residual capacity was done in only 36 subjects.
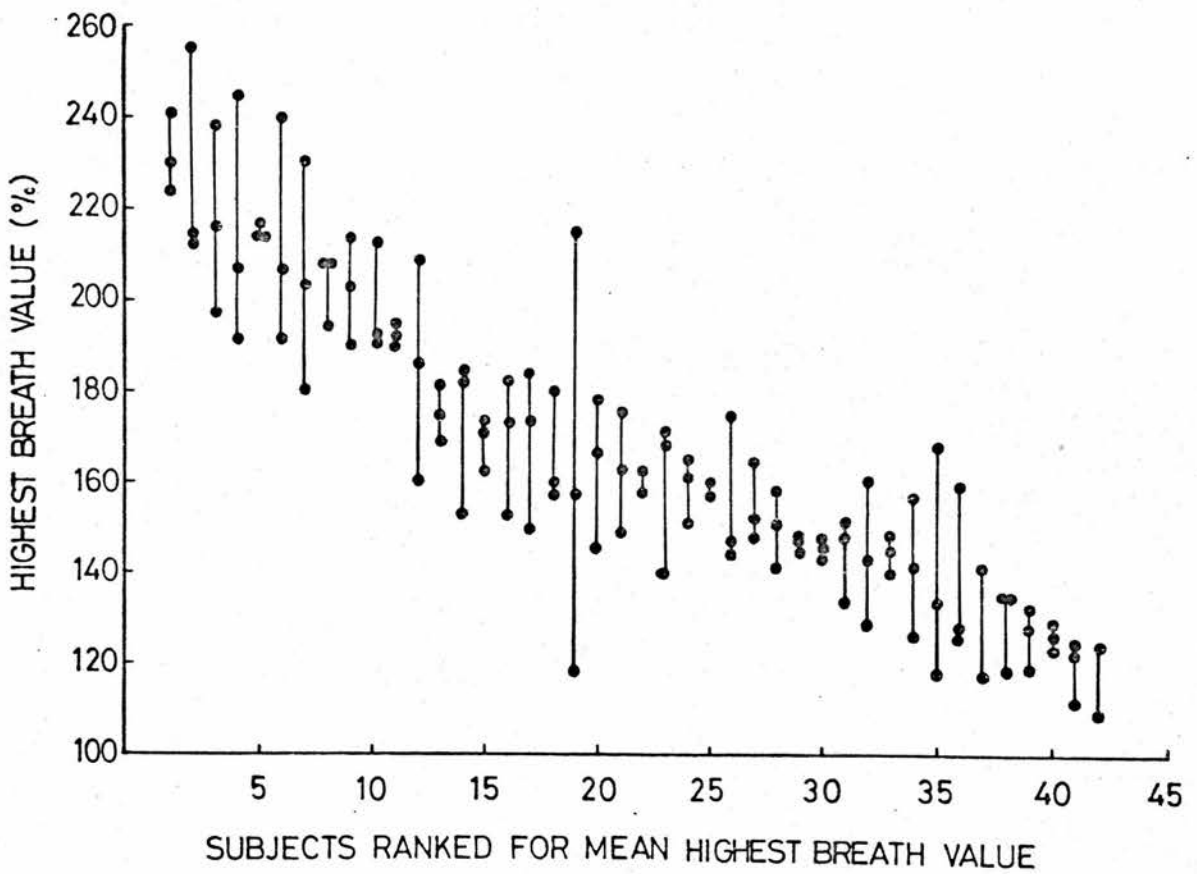
FIGURE 21   The individual highest breath values for each
subject studied in 1972 plotted against that
subject's ranking on the basis of his mean
highest breath value.
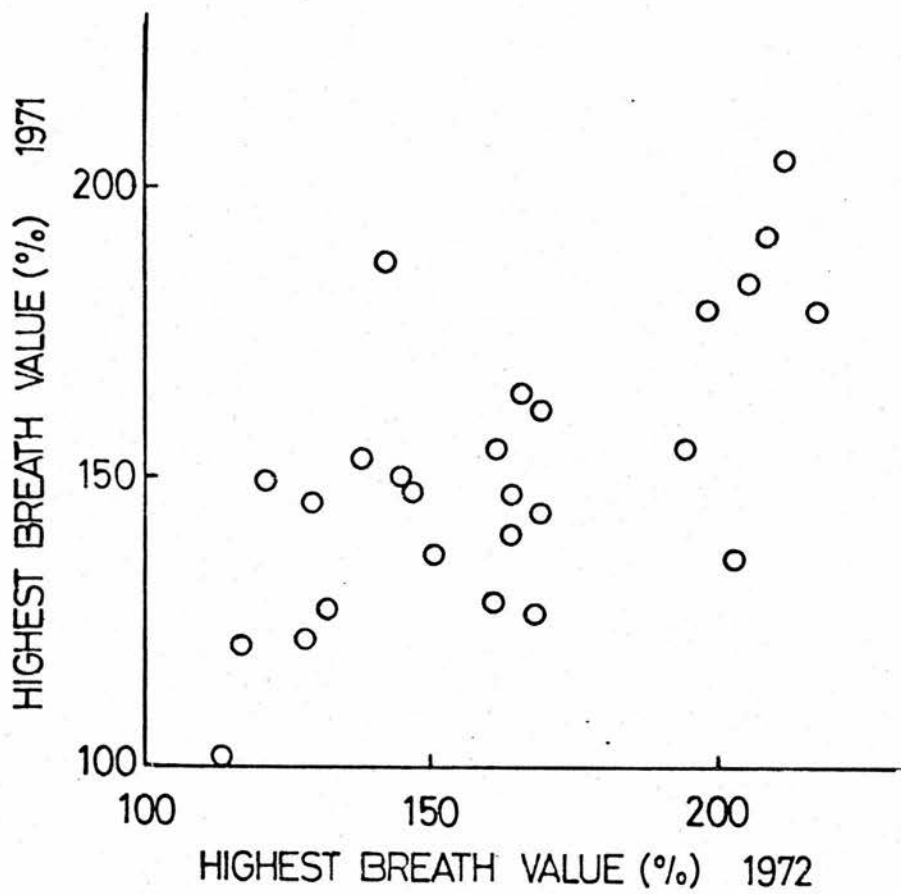
FIGURE 22   The mean highest breath value in 1971 plotted
             against the mean highest breath value in 1972
             in 26 subjects.   There was a significant rela-
             tionship between the values for the two years
             on linear regression (r = 0.67, n = 26, P<0.001)

MEAN HBV IN 42 MINERS
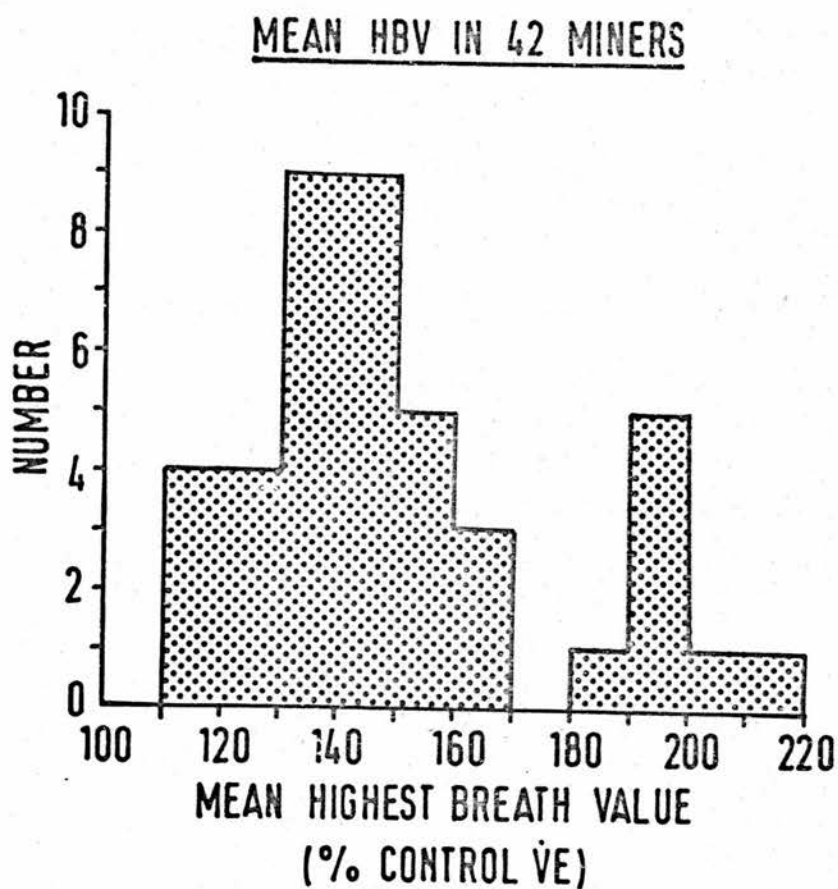
FIGURE 23 Histogram showing the mean highest breath values
in 1972 for the 42 miners who were studied.

1972.

In only one subject, subject 42, did the rise in ventilation fail to achieve significance in both studies in 1971 and 1972. Subject 18 had no significant rise in 1971 but this subject showed the greatest variation in control ventilation in that study with resultant stretching of the 95% confidence limits of the control ventilation. Subject 41 had consistently low values for HBV in 1971 and 1972 with a very late, but significant, rise in ventilation. Subject 43 did not achieve a significant rise in ventilation but the reasons for this are discussed below.

The major component of the increase in ventilation was that due to changes in tidal volume (Table 5). This increased following the N_2 stimulus on average to 162% in 1971 and 165% in 1972, whereas breathing frequency increased to a maximum on average for the groups of 125% in 1971 and 122% in 1972. Not surprisingly, the great majority of changes in tidal volume achieved 95% significance whereas fewer of the frequency changes did so (Table 5).

Examples of a high, middle and low ventilatory response are shown in Fig. 24 with the associated $P_{ET}O_2$ and $P_{ET}CO_2$ changes.

On PCO_2

The hyperventilation secondary to the transient hypoxia was associated with falls in PCO_2 to mean lowest values for the groups in 1971 of 4.81 ± 0.39 kPa and, in 1972, of 4.81 ± 0.51 kPa. The average position of the lowest PCO_2 was 3.8 ± 0.7 and 4.1 ± 0.8 breaths after the first breath

TYPICAL RESPONSES.
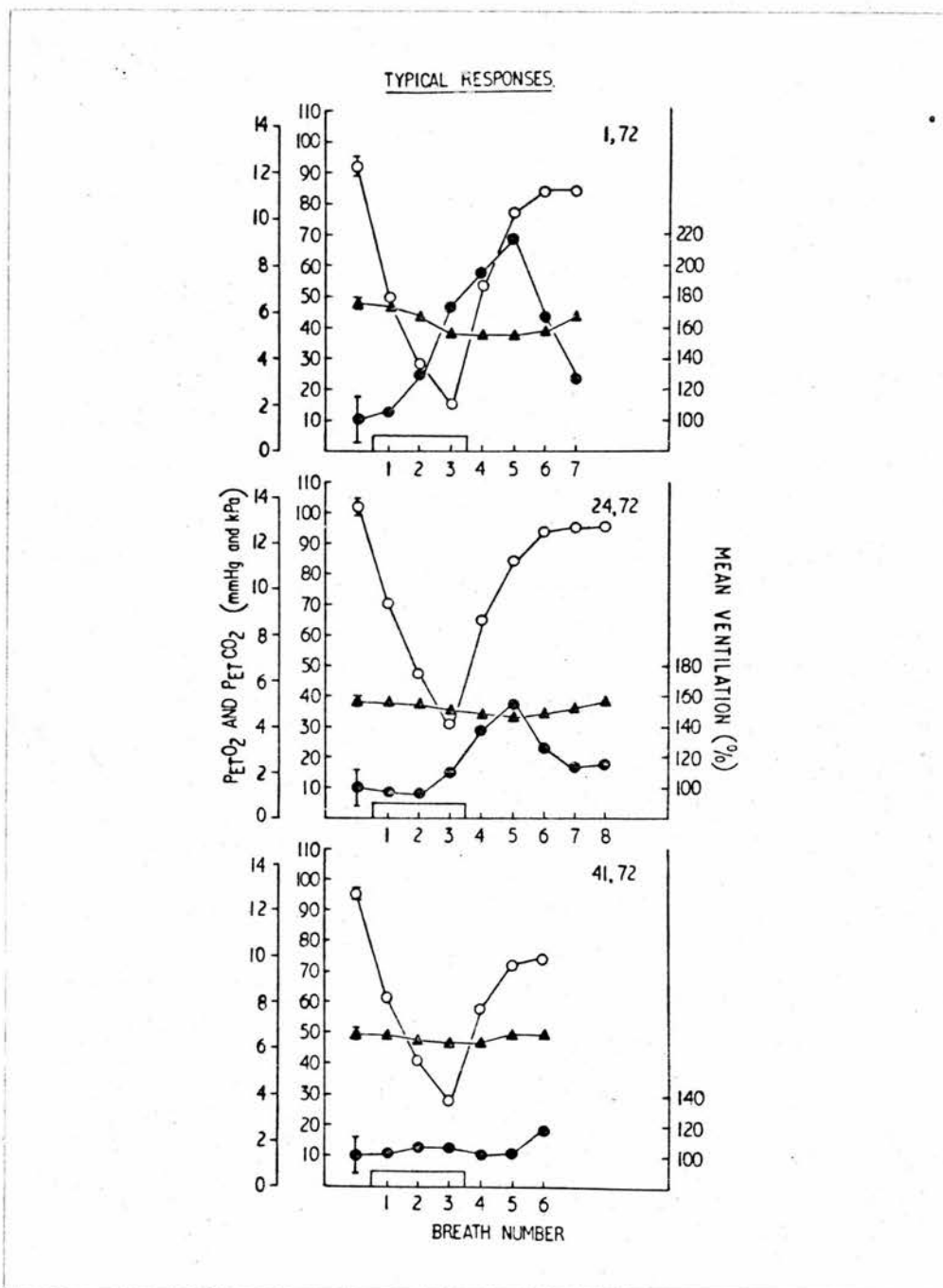
FIGURE 24   Examples of high, medium and low ventilatory
             responses to three breaths of nitrogen in sub-
             jects 1, 24 and 41 of the 1972 study. The minute
             ventilation for each breath (●————●) is the
             mean value from three studies. The end tidal
             PO_2 (O————O) and end tidal PCO_2 (▲————▲)
             for each breath are shown, derived in a similar
             way. The control values for ventilation, $P_{ET}O_2$
             and $P_{ET}CO_2$ are shown as the mean ± 95% confidence
             limits derived from 60 control breaths.

of nitrogen (Table 5).

v) Regression Analysis of the 1972 Data

Multiple regression analysis of the 1972 data using the Edinburgh Multi-Access System (EMAS) reveals that 25.3% of the variance in mean HBV can be explained on the basis of differences in $P_{ET}O_2$. Addition of other variables explains only a further 9% of the variance..

Variable	Degrees of freedom	% variance in mean HBV explained by regression
Lowest $P_{ET}O_2$	41	25.3
$\dot{V}O_2$	40	30.4
Control $P_{ET}O_2$	39	31.9
Control $P_{ET}CO_2$	38	32.1
Control $\dot{V}E$	37	34.0

I presume that the remaining variance (66%) results from differences in hypoxic drive.

Linear regression analysis showed a strongly negative correlation between lowest PO_2 and mean HBV ($r = -0.50$, $n = 42$, $P<0.001$). Linear regression analysis also revealed a weakly positive correlation between $\dot{V}E_{14}/\dot{V}E_{21}$ and mean HBV ($r = 0.38$, $n = 42$, $P<0.05$) and a weakly negative correlation between $\dot{V}E/\dot{V}O_2$ and HBV ($r = 0.30$, $n = 42$, $P<0.05$).

vi) Studies in 1974

Repeat studies with N_2 transients were carried out in 1974 in 6 subjects who had been studied both in 1971 and 1972 and in 3 subjects who had been studied only in 1972. They were selected largely on the basis of having had high

or low mean HBVs in the previous studies, the intention
being to repeat the transient hypoxia studies and also to
measure the steady state ventilatory response to inhaled
CO_2 at PO_2s of 6.7 and 25-30 kPa at rest. In addition,
in four subjects, 3 "dummy" switches were performed with
3 breaths of air to exclude subjective responses to the
turning of the taps.

N_2 transients

The control and experimental data are shown for the
1974 studies in Table 6. The $\dot{V}O_2$ was slightly lower in
all subjects than in previous studies with a mean value
of 1068 ± 76 (SD) ml.min^{-1}. The lowest $P_{ET}O_2$ achieved was
also slightly higher than in previous studies with a mean
value of 5.12 ± 1.2 kPa. Subjects 1 and 2, who had high
values for mean HBV in 1971 and 1972, had similarly high
values on this occasion (Table 7). Subject 43 hyperventi-
lated during the study as he had done in 1972 with high
$\dot{V}E/\dot{V}O_2$, low $P_{ET}CO_2$ and high $P_{ET}O_2$ values and, once again,
showed no significant ventilatory response to transient
hypoxia. All the other subjects showed significant rises
in ventilation although the responses in subjects 18 and
36 were less than on previous occasions, possibly also re-
lated to hyperventilation in these 2 subjects (Tables 6
and 7). Subject 41, who had previously shown minimal but
significant rises in 1971 and 1972, had a similar response
on this occasion. Subject 42, who had previously had no
significant rise in 1971 and 1972, achieved a mean HBV of
149% on this occasion (Tables 6 and 7).

The results of the four subjects who had three 'dummy' breaths of air as well as three breaths of N_2 on 3 occasions are shown in Fig. 25. There was no significant ventilatory response when air was substituted for nitrogen in these four subjects with widely differing responses.

The steady state ventilatory response to inhaled CO_2 at PO_2 6.7 and 25-30 kPa in the 9 subjects restudied in 1974

A typical CO_2 response plot is shown in Fig. 17. The control data breathing air for these studies are shown in Table 8. The tabulated values for hypoxic and hyperoxic slopes and intercepts of the CO_2 response line are shown in Table 9. The hypoxic drive as calculated from these graphs is presented in the same table with hypoxic drive expressed as i) the ratio of the hypoxic to the hyperoxic slopes; ii) as $\Delta V50$ where $\Delta V50$ is the change in ventilation when $P_{ET}O_2$ is lowered from 25-30 kPa to 6.7 kPa at the subject's control resting $P_{ET}CO_2$ in the same study. (Fig. 26)

It is clear from the control ventilation and end tidal PO_2 and PCO_2 in 3 of these studies in subjects 18, 36 and 43 that the subjects were hyperventilating before the studies began. It is not surprising therefore that they had low values for the intercept of the lines on the $P_{ET}CO_2$ axis. This hyperventilation, which was seen previously in subject 43 on exercise, is presumably cortically mediated and therefore renders the CO_2 response lines difficult to interpret. This added drive may have been constant throughout the study, in which case the ratio of the slopes of the lines is still meaningful. However, it is much more likely that
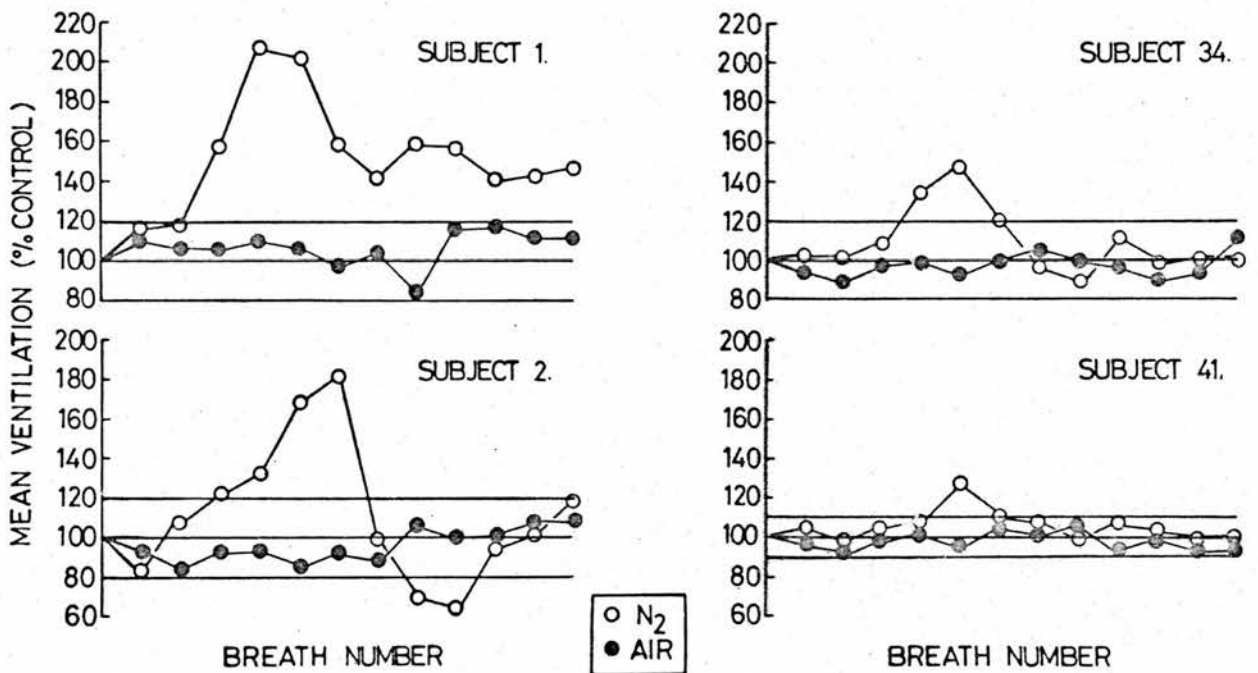
FIGURE 25 Studies in four subjects in 1974 showing the mean
ventilation for each breath derived from 3 studies
in which either three breaths of nitrogen (O———O)
or three breaths of air (●———●) were given on
exercise. The lines above and below the 100% line
represent the 95% confidence limits of the control
ventilation derived as described in the text.
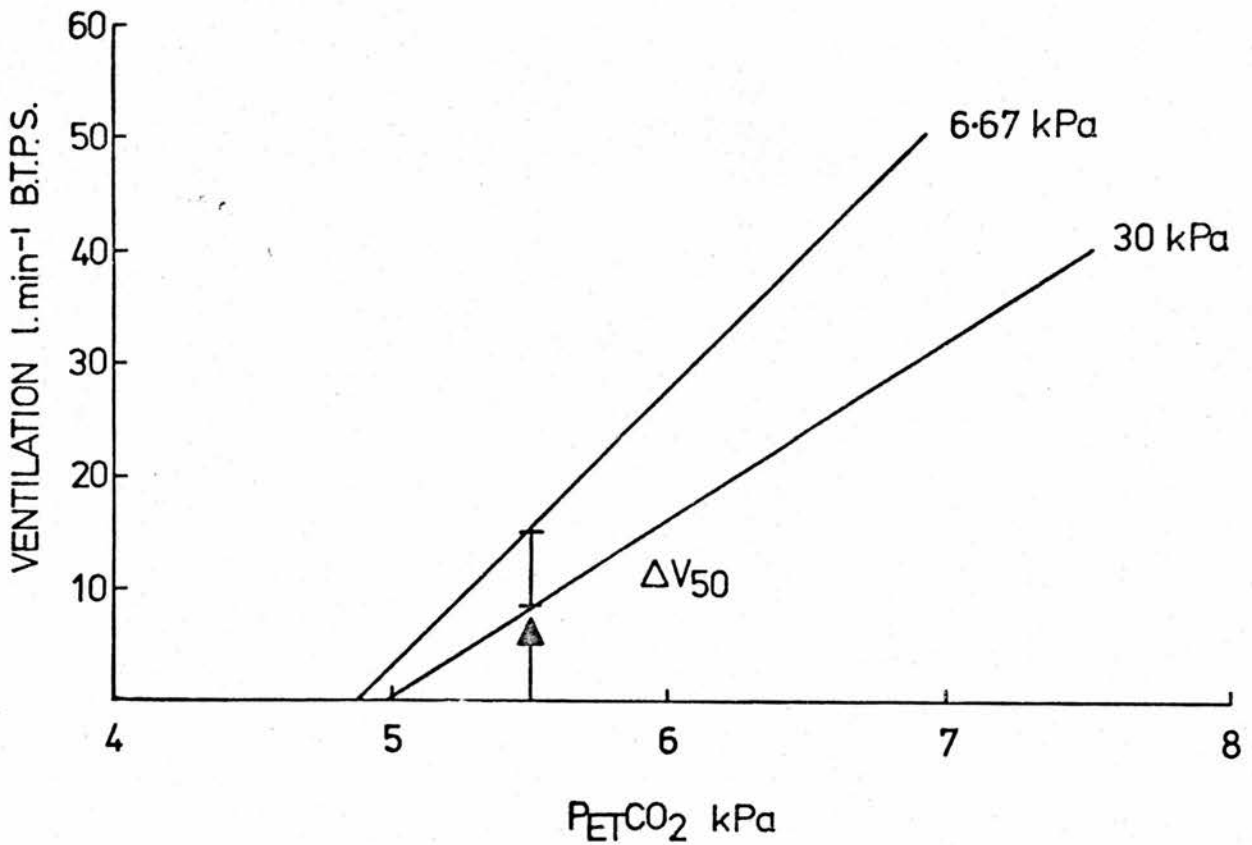
FIGURE 26   To show the derivation of $\Delta V50$ used in the present study. The graph shows the ventilatory response to CO_2 at $P_{ET}O_2$s of 6.7 kPa and 30 kPa. The arrow indicates the subjects mean $P_{ET}CO_2$ when breathing air. The $\Delta V50$ is the difference in minute ventilation between the hypoxic and hyperoxic lines at this $P_{ET}CO_2$.

the cortically mediated drive varied throughout the CO_2 response study and it would therefore be unwise to base any conclusions on these results alone.

The mean HBV values from the 1974 subjects is shown plotted against the ratio of the slopes in Fig. 27 and it is clear that there is no obvious relationship between these two variables in this small group. When mean HBV is plotted against $\Delta V50$, it is possible that a very loose linear relationship might exist but more points in the middle range would have to be established before the significance of this could be commented on (Fig. 28).

In view of the finding of hyperventilation in three of these subjects during the procedure, the possibility that hyperventilation alkalosis might have been responsible for the range of HBV established in 1971 and 1972 was re-examined. Only one subject, 43, persistently hyperventilated in 2 studies on exercise and he did indeed have a low ventilatory response to transient hypoxia on both occasions. However, there is no evidence of overventilation in any of the other subjects in either 1971 or 1972 ($\dot{V}E/\dot{V}O_2$ ratios, $P_{ET}CO_2$) and there is no significant association between mean HBV and $P_{ET}CO_2$ on either occasion.

The possibility is further examined in Fig. 29 where comparisons between HBV measured in 1971 and 1974 are compared with $P_{ET}CO_2$ in 1971 and 1974. In only one subject (18) can the differences in HBV be explained on the basis of differences in $P_{ET}CO_2$ and he was a subject who was
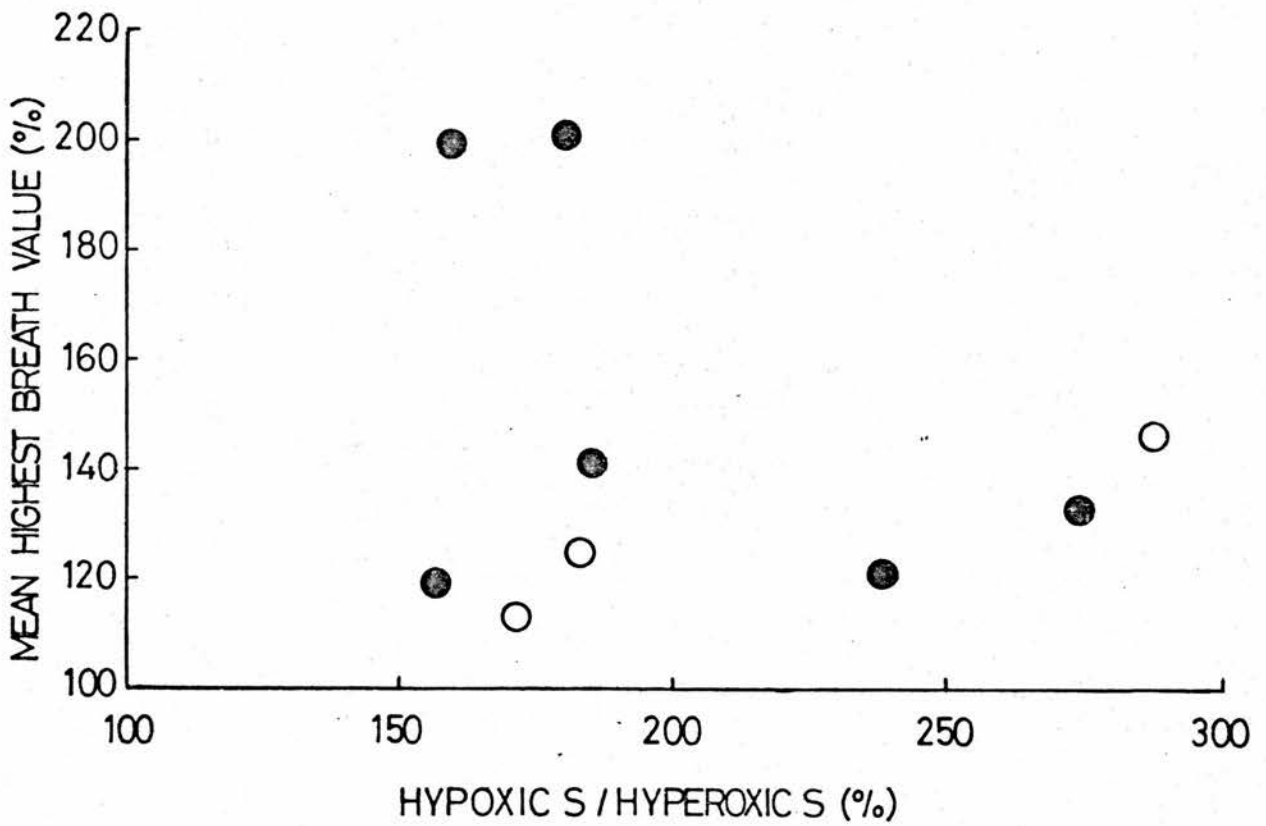
FIGURE 27   To show the relationship between mean highest
            breath value and the ratio of the hypoxic to the
            hyperoxic CO_2 response line slopes in the 9 sub-
            jects studied in 1974. The open circles repre-
            sent the subjects who were identified as hyper-
            ventilating (see text).
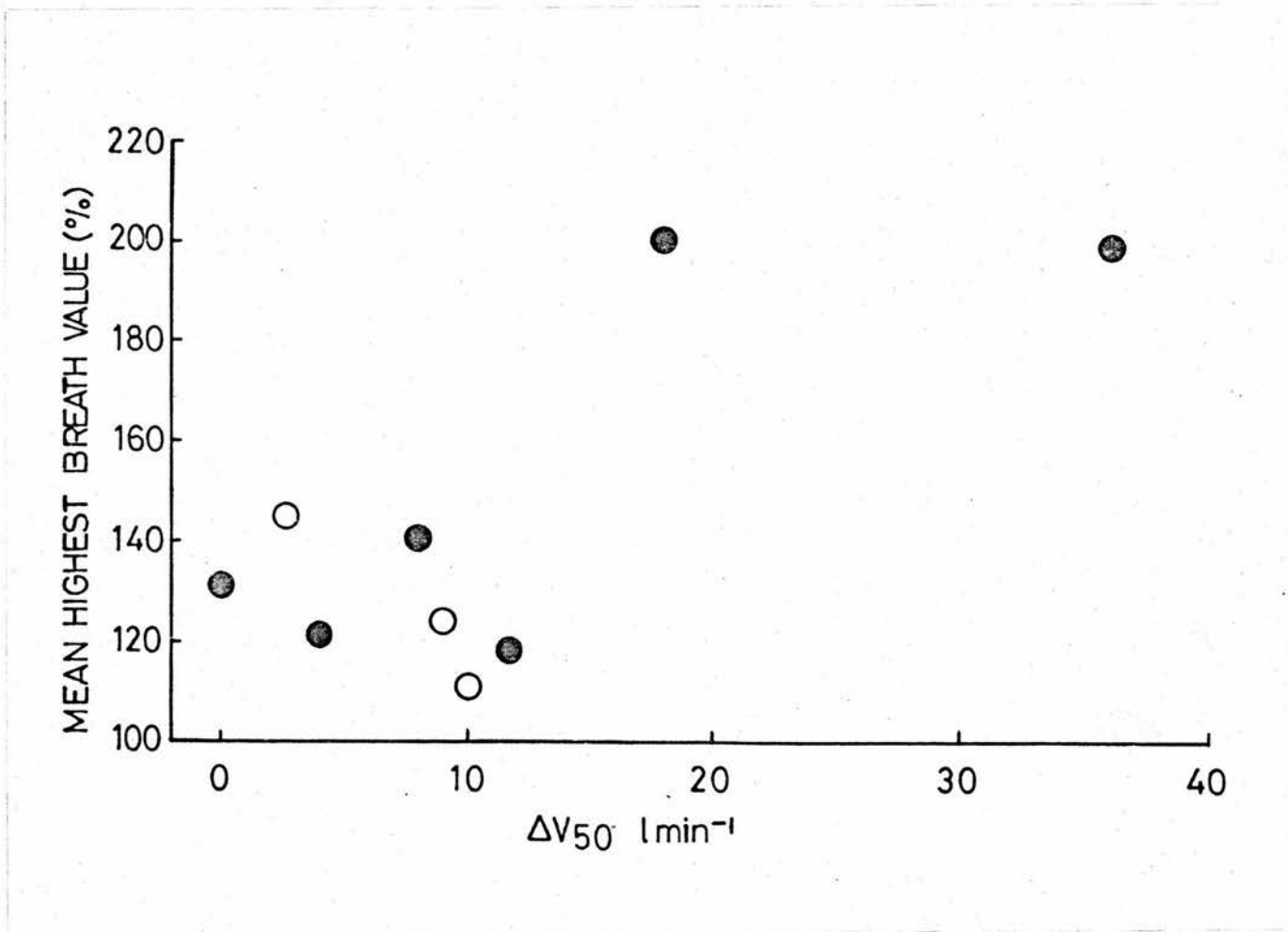
FIGURE 28   To show the relationship between the mean highest breath value and the $\Delta V50$ (ℓ.min^{-1}BTPS) in the 9 subjects studied in 1974. The open circles represent the subjects who were identified as hyperventilating (see text).
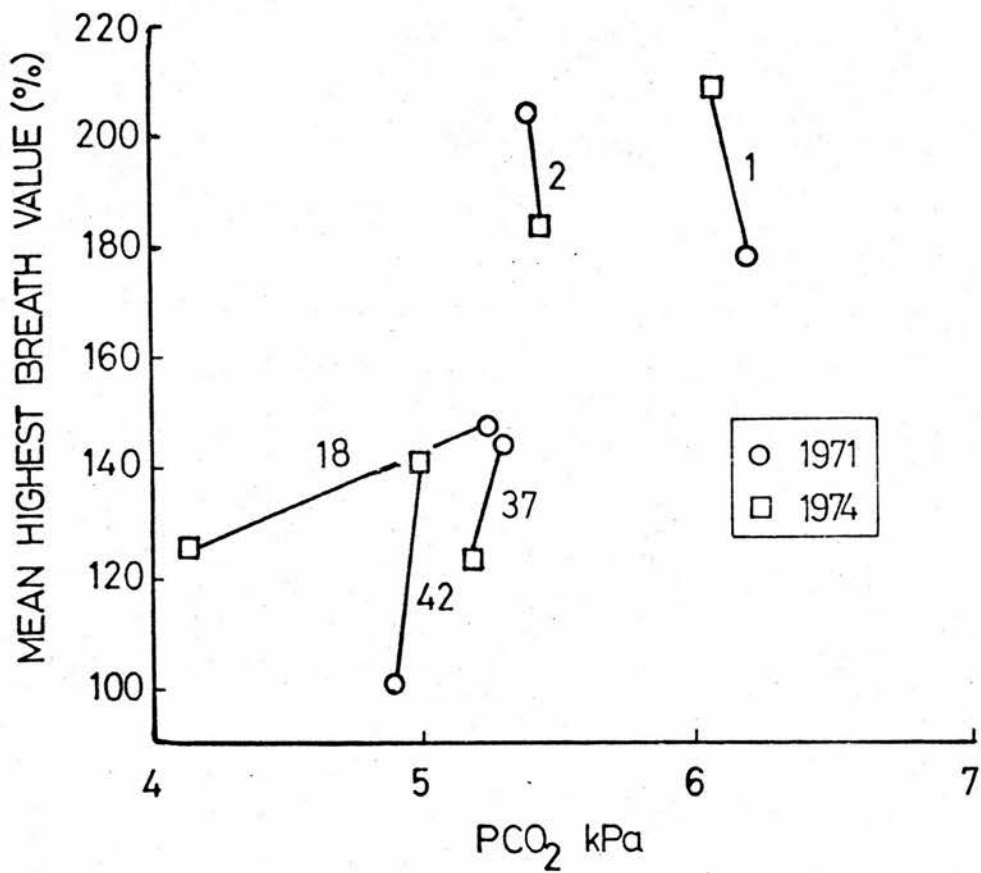
FIGURE 29   To show the mean highest breath value plotted
            against the control end tidal PCO_2 for 5 sub-
            jects studied in 1971 and 1974. The subjects
            are identified by their numbers. See text for
            explanation.

readily identified in 1974 as a hyperventilator. In view of the difficulties in interpreting $P_{ET}CO_2$ in 1972, no conclusions have been based on the PCO_2 data from that study.

It would seem that there is little or no relationship between the hypoxic drive when measured as the ventilatory response to transient hypoxia on exercise and the hypoxic drive when measured as the ventilatory response to steady state hypoxia during CO_2 inhalation at rest for those 9 subjects in whom this comparison has been made.

CHAPTER 6 <u>HYPOXIC DRIVE TO BREATHING : DISCUSSION</u>

The present study has demonstrated a wide range of ventilatory response to transient hypoxia during exercise, identifying one subject with a persistently low response on three occasions, and another who did not achieve a significant increase in ventilation when exposed to transient hypoxia on 2 out of 3 separate occasions on exercise.

Exercise of the type employed has proved to be a useful method for studying subjects unaccustomed to laboratory experimentation in whom the opportunities and time available for training in the laboratory are not available. Modest treadmill exercise at a speed of about 3 m.p.h. on the level was sufficient to distract all the subjects from the procedure being carried out and the values for $\dot{V}E/\dot{V}O_2$ and RQ obtained for the subjects indicate that a satisfactory exercise steady state was obtained. Only one subject hyperventilated in the study in 1972 and the later limited studies in 1974 indicate that, at least in the four subjects studied, the ventilatory responses obtained were found only when three breaths of nitrogen were given and were absent when air was substituted for nitrogen in the circuit. The ventilatory responses obtained bore no relation to the age, height, weight, TLC, FEV, FEV/FVC ratio, smoking history or Hb level of the men and were unrelated to the $\dot{V}O_2$ achieved on exercise.

The magnitude of the ventilatory response was shown to bear some relation to the $P_{ET}O_2$ achieved following the

3 breaths of nitrogen but this only explained one quarter
of the variance of the observations. The unexplained re-
mainder was presumably a reflection of the hypoxic drive
to breathing present in the subjects.

The timing of the ventilatory response, with the maxi-
mum instantaneous ventilation being achieved on average
1-2 breaths after the lowest end-tidal PO_2, is in keeping
with a reflex from the carotid body, the lung to carotid
body circulation time at this modest degree of exercise
being about 5-6 seconds. The quality of the response,
which was largely mediated by changes in tidal volume, is
in keeping with the finding of Pearson and Cunningham (1973)
that, following step changes in chemical drive, the imme-
diate ventilatory response is mediated almost entirely by
changes in VT and not frequency, this representing a de-
parture from the Hey relationship (Hey, Lloyd, Cunningham,
Jukes and Bolton, 1966).

The ventilatory response to transient hypoxia on
exercise is reproducible, as the comparison of the 1971
and 1972 results shows and, from the point of view of the
present study, importantly, the two lowest responders in
1971 were also the two lowest responders in 1972. Neither
of the low responders were hyperventilators and this is
important for it would appear that hyperventilation on
exercise, as was seen in subject 43, may result in appa-
rent absence of the hypoxic drive. This would be in keep-
ing with Masson and Lahiri's (1975) observations that pro-

nounced lowering of PCO_2 during hypoxic exercise can produce striking changes in minute ventilation probably because the effect of hypoxia on the carotid body is multiplied by CO_2 at normal PCO_2 levels (Lahiri and Delaney, 1975). It has been said (Dejours, 1962) that transients are an unsatisfactory way of quantitating the hypoxic drive, mainly because the changes secondary to hypoxic hyperventilation, like hypocapnia with its resultant effects on the carotid body (Delaney and Lahiri, 1975) and cerebral blood flow (Lassen, 1959) will interfere with the responses. Certainly, this may be true for subjects with a vigorous ventilatory response, in whom the hypocapnia at the height of the response is considerable, but this is less likely to influence the response in subjects with only small increases in ventilation, and therefore similarly small decreases in PCO_2. The primary aim of this study was not to "absolutely" quantify the hypoxic drive to breathing but to identify subjects with little or no hypoxic drive to breathing.

The study has succeeded in identifying one subject with a response which is persistently low but significant in its presence on three occasions. One other subject had no significant response on two occasions but, on the third occasion, the response was significant and moderate in quantity. This latter observation, coupled with the reproducibility data where marked differences are seen in individuals (although in the group the response is reproducible) suggests that there may be considerable day to

day or within day variation in the entity referred to as the "hypoxic drive to breathing". This is an area which has been poorly investigated but is well recognised in, and accounts for some of the difficulties of, estimating the steady state ventilatory response to CO_2 in hypoxia (Cunningham, 1974).

The studies of steady state ventilatory response to CO_2 in hypoxia and hyperoxia at rest in the subjects were performed, in both high and low responders to transient hypoxia on exercise, to determine if the exercise test had defined subjects with an absent hypoxic drive. Steady state CO_2 responses have been used successfully to demonstrate reduced hypoxic drive both in high altitude natives (Milledge and Lahiri, 1967; Lahiri, Kao, Velasquez, Martinez and Pezzia, 1969) and in patients with cyanotic congenital heart disease (Sorensen and Severinghaus, 1967), whereas transient hypoxia on exercise has only been used for this purpose in a few normal and high altitude subjects (Lahiri and Edelman, 1969).

The results of these CO_2 response studies were disappointing. Three of the nine subjects hyperventilated during the procedure (emphasising once again how exercise was useful in this respect), thus rendering interpretation of their CO_2 response curves of dubious value. However, even if these results are ignored, there appears to be no relation between the mean highest breath value and the ratio of the slope of the hypoxic to the hyperoxic CO_2

response line. The lack of correlation is exemplified by
the finding of the lowest slope ratio in subject 42 who
had the lowest mean HBV in 1971 and 1972 and an almost
identical slope ratio. in subject 2 who had the second
highest mean HBV response in 1972 (Text Table 4). Simi-
larly, a very high slope ratio was found in subject 41,
the one subject with a consistently low mean HBV in 1971,
1972 and 1974. The possibility that the differences might
be due not only to differences in slope but also in inter-
cept of the hypoxic and hyperoxic lines was examined by
comparison with the $\Delta V50$ (which is related to Sorensen
and Severinghaus' (1967) $\Delta V40$). When $\Delta V50$ is plotted
against mean HBV for this group of nine there is some sug-
gestion that there may be a linear relationship, but this
is largely because of the considerable differences in hy-
poxic and hyperoxic intercepts found in the two highest
HBV responders resulting in higher values for $\Delta V50$. Further
steady state CO_2 response studies would be needed to con-
firm that a real linear relationship exists between mean
HBV and $\Delta V50$ in this situation. However, this finding is
an indication that a ratio of slopes is _not_ necessarily
an accurate indication of hypoxic drive - differences in
intercepts of the hypoxic and hyperoxic lines can cause
large differences in ventilation at resting PCO_2 (which is
the level which concerns us in this study) between indi-
viduals who have the same slope ratio (see graphs of HBV
vs $\Delta V50$ and vs $\frac{S50}{S200}$.

Lahiri, Kao, Velasquez, Martinez and Pezzia (1969),
in high altitude natives, found a mean change in slope
of 6.75 $1.min^{-1}$ kPa^{-1} in 6 high altitude natives compared
with a change in slope of 12.0 $1.min^{-1}$ kPa^{-1} in normals
when slopes at 20 and 6.7 kPa were compared. When the
present 1974 results are viewed in this way (Text Table
3), 5 subjects tend towards the value established in the
high altitude natives; 4 of them had low drives on testing
with transients (subjects 34, 36, 42 and 43) and one (sub-
ject 1) had the highest drive on transient testing in
1972. Four subjects had normal or supranormal values for
ΔS; subjects 2 and 18 were known to have high and moderate
drives on transient testing; subject 41 was known to have
a persistently low drive on transient testing and subject
37, who had a supranormal ΔS, was at the lower end of the
transient responses. Comparison of the results in this
way does little further to explain the discrepancies be-
tween hypoxic drive as assessed by these transient and
steady state methods.

It is possible to compare the present data in terms
of slope ratios with the results of Sorensen and Severinghaus
on normal subjects, high altitude natives (1968a) and also
in patients with corrected Tetralogy of Fallot (1968b).
Their results are expressed as the ratio of slope at 5.3
kPa to slope at 33 kPa. Using my own data from detailed
steady state studies in 4 subjects (Chapters 7 and 8), I
have used the mean ratios of their slopes at 5.3 and 6.7

TEXT TABLE 3

To show the results of measurement of hypoxic drive
using the steady state ventilatory response to CO_2
at two different PO_2s.   The table shows the change
in slope recorded when the response is measured at a
PO_2 of 6.7 kPa in comparison with that recorded at a
PO_2 of 20 kPa.   The data for highlanders and low-
landers are taken from the work of Lahiri, Kao,
Velasquez, Martinez and Pezzia (1969).

	Change in slope PO_2 20 → 6.7 kPa ($\ell.min^{-1}\ kPa^{-1}\ PCO_2$)
6 highlanders (at altitude)	6.75 ± 4.5
2 lowlanders (at sea level)	12.0
Present Study. Subject 1	6.80
2	15.40
18	15.54
34	7.71
36	6.26
37	41.81
41	10.26
42	8.10
43	8.91

kPa to adjust the data of Sorensen and Severinghaus to a
ratio of the slope at 6.7 kPa to the hyperoxic slope.
The values of these corrected slopes are shown for normal
people, high altitude natives, natives with chronic moun-
tain sickness and patients with corrected Fallots Tetralogy
in Text Table 4. Two of the present subjects have slope
ratios of the same order as the mean slope for the high
altitude natives, but one (subject 2) is a vigorous and
one (subject 42) a weak responder to transient hypoxia on
exercise. Three others, subjects 18, 37 and 41 with mo-
derate, low and low responses to transient hypoxia on
exercise respectively, are unequivocally in the high nor-
mal range while the remainder, containing individuals with
high and low responses to transient hypoxia on exercise
occupy an intermediate position. None of the subjects in
this study reach the low values for slope ratio which are
found in patients with chronic mountain sickness and cor-
rected Tetralogy of Fallot.

The results of the present study raise one important
problem. There seems to be, in the subjects studied by
both methods, no consistent relationship between the venti-
latory response to transient hypoxia on exercise and the
ventilatory response to steady state hypoxia during CO_2
breathing at rest.

The lack of correlation may be related to the obvious
differences between the two tests. There is now a consi-
derable body of evidence to suggest that ventilation in

TEXT TABLE 4

To show values for the ratio of the ventilatory response to CO_2 (S) at 6.7 kPa over the response at 20 kPa for different groups of subjects studied by Sorensen and Severinghaus (1968) and the nine subjects of the present study.

	Mean ratio S6.7/S20
23 sea level natives	2.10
9 high altitude natives	1.60
9 chronic mountain sickness	1.10
5 Tetralogy of Fallot	0.90
Present Study. Subject 1	1.80
2	1.60
18	2.87
34	1.85
36	1.83
37	2.74
41	2.38
42	1.57
43	1.71

hypoxia is greater on exercise than at rest (Asmussen and Nielsen, 1957; Cunningham, Spurr and Lloyd, 1968; Masson and Lahiri, 1975) so it therefore seems unlikely that the inability to demonstrate hypoxic drive on exercise in two subjects who had an apparently considerable hypoxic drive at rest, is related only to differences in muscular activity. Another difference between the two studies is in the use of transient hypoxia in the one and steady state hypoxia in the other. Here the arguments would again run counter to the actual findings, for transient hypoxia produces greater ventilatory changes than equivalent steady state hypoxia (Dejours, 1962) and steady state hypoxia may depress ventilation (Kronenberg, Hamilton, Gabel, Hickey, Read and Severinghaus, 1969), further lowering the response.

It seems more likely that the differences result from the fact that, in the rest study, the ventilation in hypoxia was measured against a background of hypercapnia, whereas, in the exercise study, the subjects were, more or less, normocapnic.

It would appear that this study has identified subjects who have little or no ventilatory response to transient hypoxia in normocapnic exercise although all do have a hypoxic drive when this is measured by steady state methods in hypercapnia. Since the augmentation of ventilation by hypoxia during exercise appears to be due to some form of central interaction which is dependent on

the peripheral chemoreceptor afferent input (Masson and
Lahiri, 1975), it seems reasonable to suggest that the
subjects with a low mean HBV have little or no peripheral
chemoreceptor response to hypoxia in normocapnic exercise.
It is possible that this lack of response is related to
activity of inhibitory efferents to the carotid body
(Biscoe, 1971) but such an effect has never been demon-
strated in animal studies. Since the augmenting effect
of exercise on hypoxic ventilation is dependent on PCO_2
(Masson and Lahiri, 1975), it may be that these subjects
have higher thresholds for PCO_2 during exercise than nor-
mal man (although there is no evidence that they are any
different at rest). If this were so, in normocapnia,
there would be little PO_2/PCO_2 interaction at the carotid
body with resultant diminution in the effect of carotid
body activity on ventilation (Lahiri and Delaney, 1975).
In the hypercapnic steady state studies at rest however,
with the PCO_2 threshold exceeded, multiplicative inter-
action between PO_2 and PCO_2 with respect both to chemore-
ceptor activity and ventilation would occur.

It seems unlikely that changes in oscillation in ar-
terial PCO_2 (Cunningham, 1972) will play a major role in
determining the response to transient hypoxia, for they
would not be expected to change during the inhalation of
three breaths of nitrogen.

The remaining possibility, that in subjects with a
low mean HBV, the peripheral chemoreceptor is being stimu-

lated but that its input to the brain stem is, instead of being magnified by the altered central excitatory state induced by exercise (Masson and Lahiri, 1975), being ignored. This possibility has never been described in animal studies nor is our understanding of 'central interaction' as yet adequate enough to allow that it will soon be possible to refute the suggestion.

Whether subjects with a diminished hypoxic drive as assessed by transient hypoxia on exercise would be predisposed to the hypoxic complications of chronic bronchitis is unclear. The two chronic bronchitics with such hypoxic complications quite clearly had no hypoxic drive in steady state studies at rest whereas the subjects of the present study had.

In view of the poor correlation between hypoxic drive as assessed by steady state studies at rest and transients on exercise, it was decided to conduct further studies in detail in 4 subjects with repeated measurements of the hypoxic drive using transients, progressive and steady state hypoxia at rest and during exercise. These studies will allow the assessment of the variability of each measurement and also permit examination of the relationship, if any, between them with a view to clarifying the relevance of the findings which are discussed above.

SUMMARY

1. The use of transient hypoxia during exercise has de-
    tected a wide range of hypoxic drive to breathing in
    43 healthy mine resuce workers.

2. The reproducibility of the method has been established
    in repeat studies at yearly intervals in 26 of these
    miners although variation of the response appears to
    occur in some individuals.

3. Two subjects had little or no significant hypoxic
    drive to breathing on three separate occasions on
    which it was measured by the transient method. These
    subjects would therefore appear to fit into the cate-
    gory of normal men with diminished or absent hypoxic
    drive to breathing who may be predisposed to the hy-
    poxic complications of chronic bronchitis and emphy-
    sema should they develop the disease.

4. There was little or no relationship between the hy-
    poxic drive expressed as mean HBV and the hypoxic d
    drive demonstrated in steady state ventilatory res-
    ponse to CO_2 studies at two different PO_2s.

5. Because of the differences between the steady state
    and transient findings, further examination of the
    interaction between rest/exercise, transient/steady
    state and normocapnic/hypercapnic states is proposed
    in order to compare the different available methods
    of measuring hypoxic drive to breathing and establish
    their reproducibility.

CHAPTER 7   COMPARISON OF METHODS OF MEASURING
            THE HYPOXIC DRIVE TO BREATHING :
            METHODS AND RESULTS

I   METHODS

With the facility of on-line computation it was possible
to investigate the disparity between hypoxic drives assessed
by the 2 different methods as discussed in the last chapter.
The first method used involved transient hypoxia in normo-
capnic subjects during exercise; the second method involved
steady state hypoxia during CO_2 inhalation at rest. The
present study was concerned to assess the hypoxic drive
in normal subjects using transient hypoxia at rest and on
exercise, steady state hypoxia at rest and on exercise and
also one further technique, previously described by Weil,
Byrne- Quinn, Sodal, Filley and Grover, 1970, progressive
hypoxia at rest and on exercise. The ventilatory response
to exercise in normoxia and hypoxia was also determined for
each subject.

Subjects

The subjects were two male doctors aged 29 and 33, and
two male laboratory technicians aged 22 and 23. The heights,
weights, lung volumes determined by helium dilution and
transfer factor determined by the single breath method are
shown in Table 10. All were normal. Informed consent was
obtained, before the study started, to all the procedures but,
since subjects were always blindfolded and listening to
stereo music of their choice throughout the experimental
period, they were usually unaware of the nature of the ex-
periment being performed on any particular occasion.

Methods

The apparatus has been described in detail in Chapter 4. All of the present experiments were performed using the on-line computing facilities provided by the PDP 11-40 computer. Throughout the experiments a visual display unit displayed averaged values for inspired CO_2 and O_2 percentage, end-tidal PO_2 and PCO_2, tidal volume, frequency and instantaneous minute ventilation for every 10 breaths. An error monitor was also used in experiments where $P_{ET}O_2$ was being kept constant to display the $P_{ET}O_2$ of every breath and allow appropriate adjustments to inspired gases to be made on the basis of any persistent shift in $P_{ET}O_2$ which was detected.

Transient hypoxia

Each subject was studied at least 2 hours post prandially on 2 occasions each at rest and at a level of exercise on the treadmill calculated to give an oxygen consumption of about one litre per minute. In each rest study the subject was given transients of 1, 3, 5 or 7 breaths of 100% nitrogen in random order on three occasions with intervals of 5 (after 1 and 3 breaths) or 7 minutes (after 5 or 7 breaths) between each transient. The computer was switched on after 10 minutes rest during which $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were measured and remained on throughout the study, continuously recording for each breath the inspired O_2 and CO_2 percentage, $P_{ET}O_2$, $P_{ET}CO_2$, tidal volume, frequency and instantaneous minute ventilation.

The exercise studies followed a similar pattern. $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were measured between the 7th and 10th minutes of steady state exercise and thereafter 1, 2, 3 or 4 breaths of nitrogen were administered in random order each transient being repeated on three occasions. Intervals of 3 minutes (after 1 and 2 breaths of N_2) or 5 minutes (after 3 or 4 breaths of nitrogen) were left between transients. A continuous computer recording was also obtained.

Steady state ventilatory response to CO_2 in hypoxia and hyperoxia

The studies at rest were performed along similar lines to the previous studies on the miners. However, since the intention was to derive the respiratory parameters (Lloyd and Cunningham, 1963) from these studies, measurements were made not only at $P_{ET}O_2$s of 6.67 and 30 kPa but also at 5.33 and 9.33 kPa. The sequence of inspired gas mixtures was as follows: air, 2% CO_2 at $P_{ET}O_2$ 30 kPa, 2% CO_2 at 6.67 kPa, 5 or 6% CO_2 at 30 kPa, 5 or 6% CO_2 at 9.33 kPa $P_{ET}O_2$, 5 or 6% CO_2 at 6.67 kPa and 5% CO_2 at 5.33 kPa. An attempt was made to keep ventilation constant at the high CO_2 measurements which meant that small reductions in inspired CO_2 were required as the $P_{ET}O_2$ was reduced. The computer was switched on to record all variables between the 7th and 10th minutes on any one inspired gas mixture, provided ventilation and $P_{ET}O_2$ had been constant for the preceding 2 minutes. The computer produced a statistical summary of the data recorded for each section from which the CO_2 response lines could be drawn by hand. Alternatively,

the data could be produced in the same form as the miners'
CO_2 response data on the graph plotter with the CO_2 response
lines drawn for $P_{ET}O_2$s of 6.67 and 30 kPa. Each study was
repeated three times on different days on each subject.
The CO_2 response on exercise was measured at the same exer-
cise level as for the transient studies. Early studies
showed that attempts to define a hypoxic and hyperoxic CO_2
response line with several points on each line was too
exhausting during exercise if the steady state was rigidly
ensured. The subjects therefore had their hypoxic ($P_{ET}O_2$
6.67 kPa) and hyperoxic lines determined on 2 occasions on
separate days. The subject exercised breathing air and the
$\dot{V}O_2$, $\dot{V}CO_2$ and RQ were measured between 7 and 10 minutes.
Thereafter the $P_{ET}O_2$ was adjusted using rotameters to either
6.67 or about 30 kPa and a computer recording taken for 3
minutes when a steady state had been achieved. This was re-
peated on several other occasions with increasing concentra-
tions of CO_2 in the inspired gas. The steady state was de-
fined as above. The CO_2 response lines in hypoxia and hy-
peroxia were then drawn from the statistical summary of the
data and their slope and intercept determined by conventional
linear regression techniques.

Progressive hypoxia

The ventilatory response to progressive hypoxia as
described by Weil, Byrne-Quinn, Sodal, Filley and Grover,
1970, was determined at rest and on exercise of the same
degree as above. In the control period the usual measure-
ments of $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were carried out in the 7-10

minute period with the subject breathing air. The inspired
gas was supplied in the closed circuit previously described
at a flow rate of 100 $\ell.min^{-1}$. From the computer display
the mean $P_{ET}CO_2$ was determined in the control period. Follow-
ing measurement of $\dot{V}O_2$ breathing air, the inspired gas had
4 litres min^{-1} of N_2 added to it and 4 litres min^{-1} air
subtracted every minute, until the end-tidal PO_2 had fallen
to about 5.33 kPa (on the error monitor). CO_2 was added to
the inspired gas in $\frac{1}{2}$-1% amounts when the $P_{ET}CO_2$ fell per-
sistently below the control value so that, throughout the
study, $P_{ET}CO_2$ was maintained at the resting value. The study
was continuously recorded on the computer which was able to
display graphically the $\dot{V}E_{inst}/P_{ET}CO_2$ plot for each breath
in the study. Each subject had 3 progressive hypoxia studies
performed at rest and on exercise on separate days.

Data processing

Curves were fitted by the computer to the progressive
hypoxia $\dot{V}E_{inst}/P_{ET}O_2$ plot according to the equation

$$\dot{V}E = 1 + \frac{2}{P_{ET}O_2 - 3}$$

where parameter 1 = ventilation at infinite $P_{ET}O_2$, parameter
2 = the shape parameter of the curve and parameter 3 = the
$P_{ET}O_2$ at which ventilation tends towards infinity. Similarly,
by plotting $\dfrac{\dot{V}E}{P_{ET}CO_2 - B}$ against $P_{ET}O_2$, the parameters of the
Cunningham equation were determined, using the same programme
for curve fitting, to describe the steady state CO_2 response
relationships. Examples of curves determined in this way
for progressive hypoxia at rest and on exercise and for the

steady state CO_2 response are shown in Figs. 30-32.

The transient data were analysed in the way described for the miners' study, taking 30 control breaths before each transient, and expressing the response for each transient as the ratio of the highest $\dot{V}E_{inst}$ to the control ventilation. In addition, each group of 6 transients at rest and on exercise were superposed to give the average response curve with significance limits and the mean highest breath value determined from this curve.

Steady state ventilatory response to exercise in normoxia, hypoxia and isocapnic hypoxia

Using on-line computer facilities the $\dot{V}E_{inst}$, $P_{ET}O_2$ and $P_{ET}CO_2$, $\dot{V}O_2$ and $\dot{V}CO_2$ were determined in the steady-state at rest and on exercise for each of three states –

a) normoxia

b) hypoxia (end tidal PO_2 controlled at 6.67 kPa)

c) isocapnic hypoxia (end tidal PO_2 at 6.67 kPa; end tidal PCO_2 controlled at the level in the air study).

The level of exercise was identical to that in previous exercise studies in the same subjects. For both the rest and exercise studies, the following proforma was observed:

1) Air breathing for 10 minutes. $\dot{V}O_2$ and $\dot{V}CO_2$ measured between 7-10 minutes.

2) $P_{ET}O_2$ lowered to 6.7 kPa and $\dot{V}E_{inst}$, $P_{ET}CO_2$ and $P_{ET}O_2$ measured between 17-20 minutes and stored on computer.

3) Air substituted for hypoxic gas mixture. $\dot{V}E_{inst}$, $P_{ET}CO_2$ and $P_{ET}O_2$ measured between 27-30 minutes and stored on

DK PHO2.ASC   AGL   PROGRESSIVE HYPOXIA AT REST

VEINST
(10 L/MIN)

PO2ET(KPA)
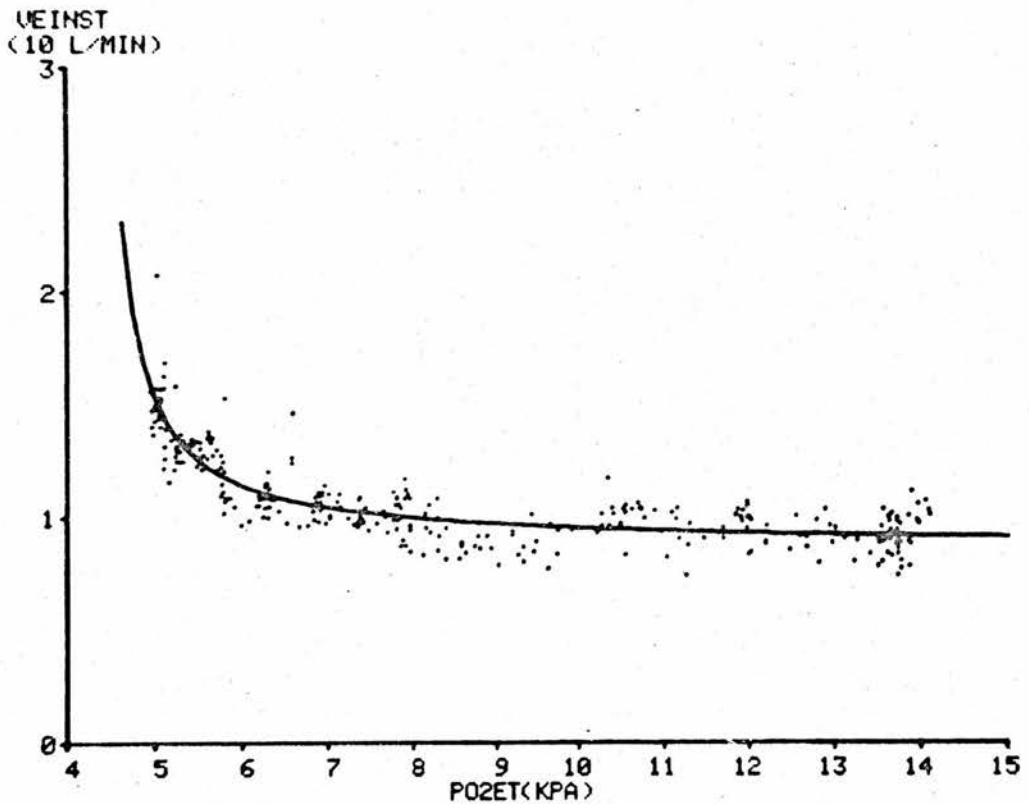
FIGURE 30   An example of an isocapnic progressive hypoxia
study at rest in subject II. The illustration
is a photograph of the hard copy of the computed
results displayed on a graph plotter. Each point
represents the instantaneous minute ventilation
and end-tidal PO_2 for a single breath. The curve
was fitted by the computer.

DK : PH29.ASC   LUKE PROGRESIVE HYPOXIA ON EXERCISE

VEINST (10 L/MIN)
PO2ET(KPA)
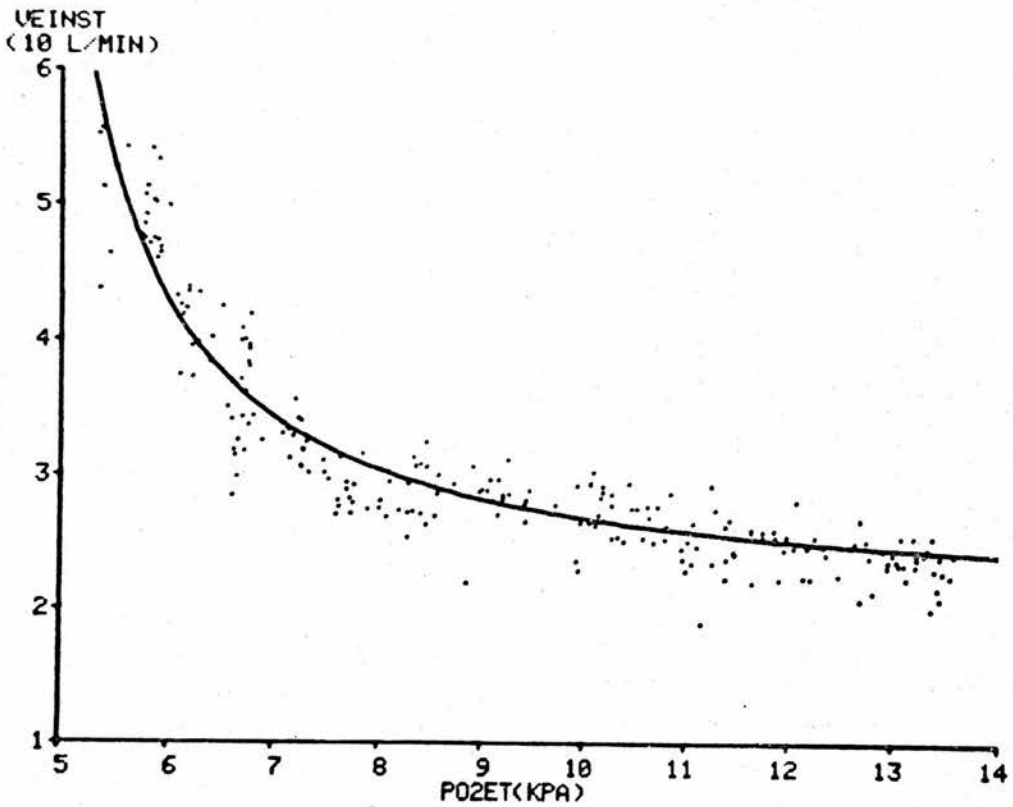
FIGURE 31   An example of an isocapnic progressive hypoxia
study on exercise in subject III. The illustra-
tion is a photograph of the hard copy of the com-
puted results displayed on a graph plotter. Each
point represents the instantaneous minute venti-
lation and end-tidal PO_2 for a single breath.
The curve was fitted by the computer.
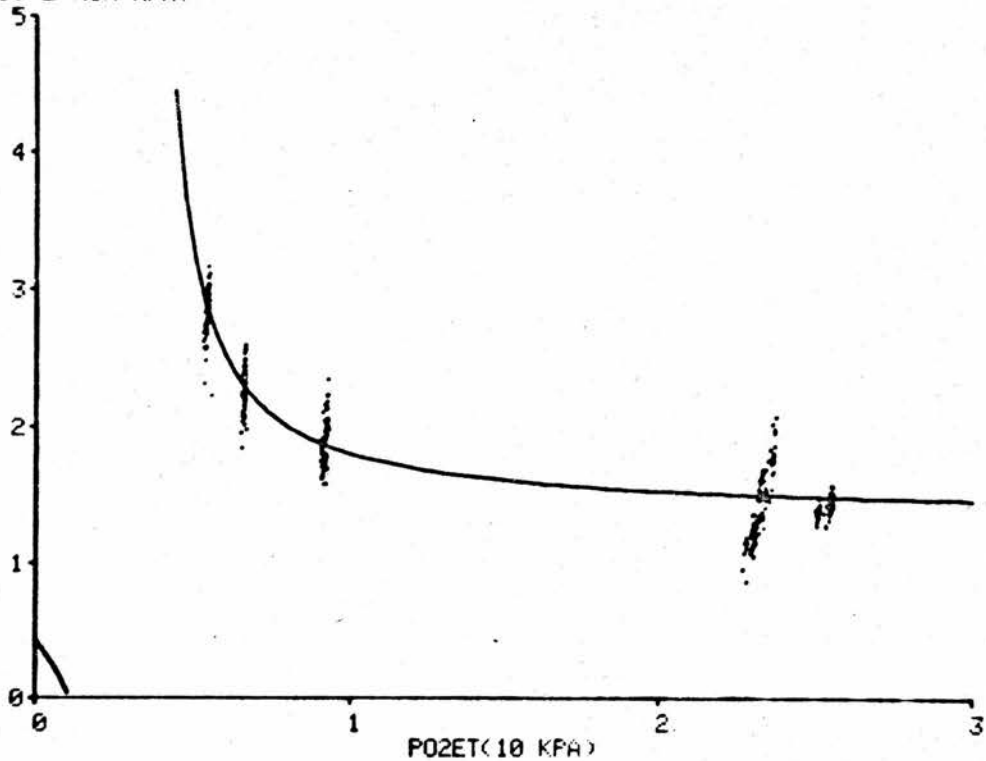
FIGURE 32   An example of the results of the steady state
ventilatory response to CO at rest in subject
I with a computer fitted curve. The slope of
the ventilatory response to CO_2 (SCO_2 or VE_{inst}/
PCO_2 - B) is plotted against the $P_{ET}O_2$ at which
that slope was measured. Each point represents
values for a single breath.

computer.

4) $P_{ET}O_2$ lowered to 6.7 kPa and $P_{ET}CO_2$ stabilised at the level obtaining in section 3). $\dot{V}E_{inst}$, $P_{ET}CO_2$ and $P_{ET}O_2$ measured between 37-40 minutes and stored on computer.

II   RESULTS

The results to be reported in this section are divided into three main sections, ventilatory responses to transient, progressive and steady state hypoxia, and each section in turn is concerned with the responses at rest and on exercise. A fourth section reports the results of the ventilatory responses to exercise.

1.   (a)   Transient hypoxia at rest : N_2 transients

Fig. 33 shows an example of the ventilatory response to 1, 3, 5 and 7 breaths of nitrogen at rest. This figure shows the response from 6 separate studies with each number of transients superposed, taking the first breath of N_2 as the index breath in the manner described in Chapter 4. Table 11 gives the metabolic data for each study in all four subjects, the $\dot{V}O_2$, $\dot{V}CO_2$ and RQ for each subject being acceptable. The control data for each subject (control ventilation ± SD, control $P_{ET}O_2$ ± SD, control $P_{ET}CO_2$ ± SD) are given in Tables 12-15 and were all within the normal range. Tables 12-15 also show the lowest $P_{ET}O_2$ obtained following the inhalation of N_2, the highest $\dot{V}E_{inst}$ in the 6 breaths following the lowest $P_{ET}O_2$ and the ratio of the highest $\dot{V}E_{inst}$ to control $\dot{V}E$ (the highest breath value) for each individual transient
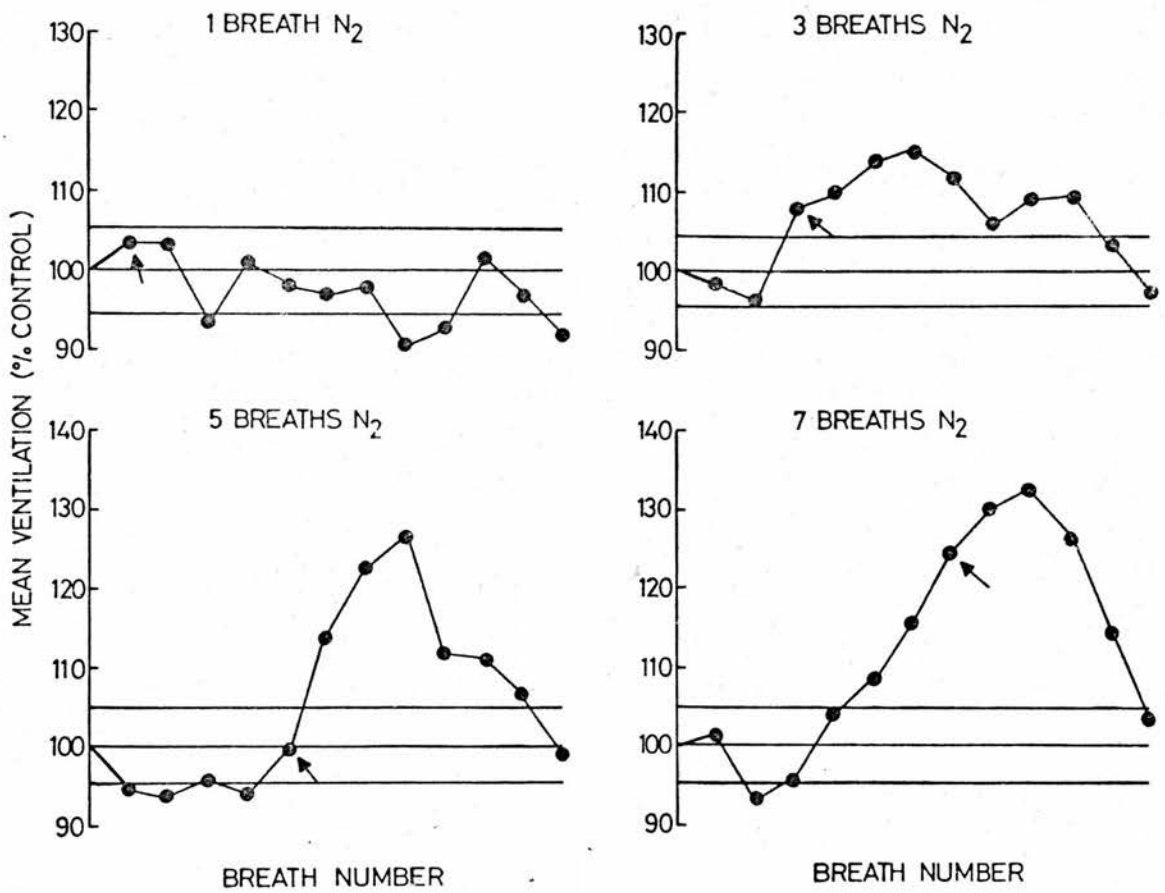
FIGURE 33   An example of the mean breath by breath venti-
latory response to 1, 3, 5 and 7 breaths of nitro-
gen in subject II.   The arrows indicate the final
breath of nitrogen.   The lines represent the 95%
confidence limits of the control ventilation (see
text).

study. Table 16 shows the mean highest breath values derived
from the superposed curves (e.g. Fig. 33) with details of
the highest breath position and of the first breath after
the switch to nitrogen to achieve significance at the 95%
level.

With one breath of nitrogen the mean lowest $P_{ET}O_2$
(tables 12-15) obtained ranged from 11.11 kPa in subject
I to 11.50 in subject II. None of the subjects had sig-
nificant ventilatory responses to this minimal stimulus.
With 3 breaths of nitrogen the mean lowest $P_{ET}O_2$ ranged
from 8.17 kPa in subject I to 8.84 kPa in subject III.
This degree of hypoxia resulted in significant stimulation
of ventilation in subjects II, III and IV with percentage
increases in ventilation ranging from 7-15% (Table 16),
the highest breath value occurring 3 breaths on average
after the lowest $P_{ET}O_2$. Five breaths of nitrogen caused a
fall to a mean lowest $P_{ET}O_2$ ranging from 5.81 kPa in sub-
ject I to 6.77 kPa in subject IV. A significant increase
in ventilation was seen in all 4 subjects, ranging from
13-27% and occurring on average 2 breaths after the lowest
$P_{ET}O_2$. Seven breaths of nitrogen further reduced the mean
lowest $P_{ET}O_2$, which ranged from 4.64 kPa in subject I to
4.97 kPa in subject 4 and the resulting significant increase
in ventilation ranged from 32-57%.

The individual ventilatory responses for each subject
are shown in Fig. 34, significant increases in HBV (i.e.
outside 2SD of control ventilation) being indicated by the
closed circles.
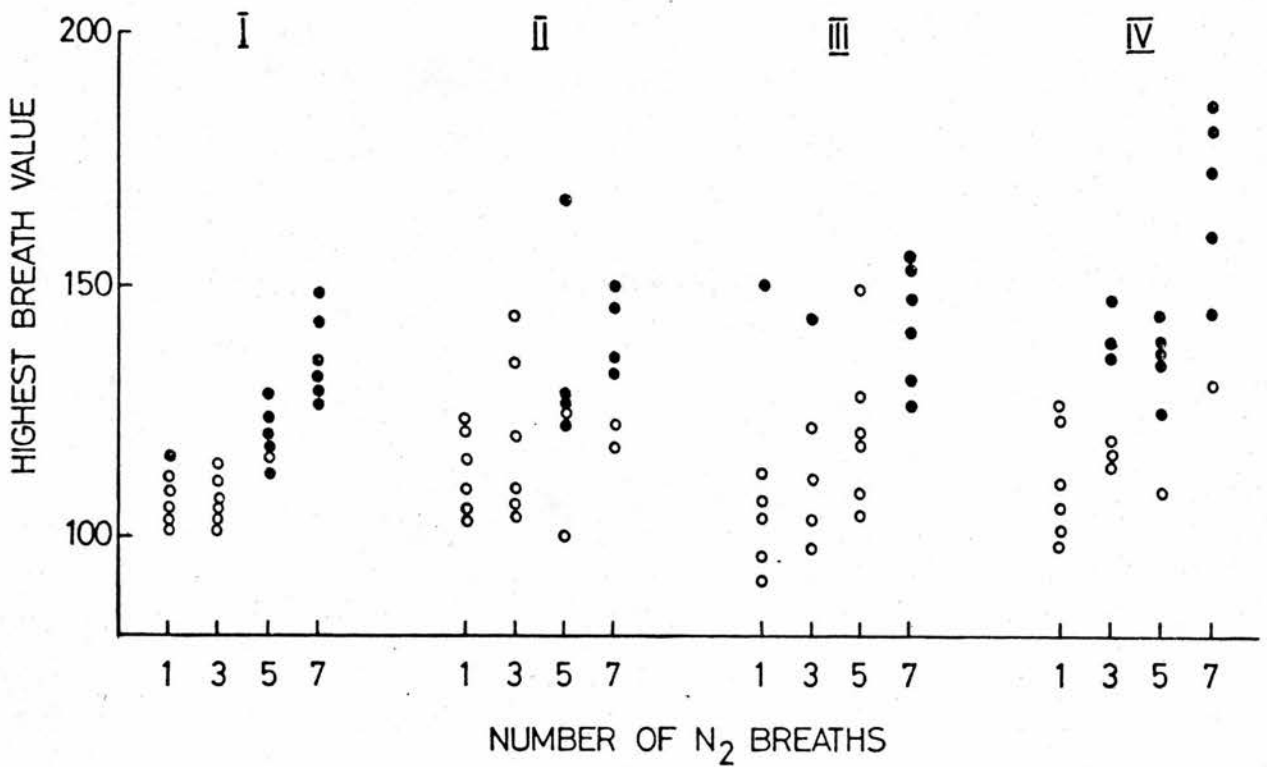
FIGURE 34   To show the individual highest breath values ob-
             tained in subjects I-IV with 1, 3, 5 and 7 breaths
             of nitrogen at rest. The closed circles indicate
             values which were outside the 95% confidence li-
             mits of the control ventilation (see text).

1.   (b)   <u>Transient hypoxia on exercise : N_2 transients</u>

An example of the ventilatory responses to 1, 2, 3 and 4 breaths of N_2 during steady state exercise in subject III is shown in Fig. 35, which represents the "smoothing out" of 6 separate studies for each stimulus level by superposition. The metabolic data are shown in Table 11, a mean $\dot{V}O_2$ on exercise of 986 ml.min^{-1} being obtained. The control data for each subject ($\dot{V}E$, $P_{ET}O_2$, $P_{ET}CO_2$) are shown in Tables 17-20. The control $P_{ET}CO_2$ was on average slightly higher on exercise, the mean $P_{ET}CO_2$ for all subjects being 5.22 kPa compared with a mean resting $P_{ET}CO_2$ of 5.09 kPa. The mean exercise ventilation ranged from 23.55 ℓ.min^{-1} for subject III to 30.25 ℓ.min^{-1} for subject IV, with $\dot{V}E/$ $\dot{V}O_2$ ratios ranging from 22.9 ℓ.min$^{-1}\ell^{-1}$ in subject III to 27.5 ℓ.min$^{-1}\ell^{-1}$ in subject I. Tables 17-20 also show the lowest $P_{ET}O_2$, the highest $\dot{V}E_{inst}$ and the highest breath values for each individual transient study. Table 16 shows the mean highest breath values derived from the superposed curves (e.g. Fig. 35) with details of the highest breath position and of the first breath after the switch to nitrogen to lie outwith the 95% confidence limits of the control $\dot{V}E_{inst}$ before the switch.

With one breath of N_2 the mean lowest $P_{ET}O_2$ ranged from 9.21 kPa in subject III to 10.29 kPa in subject II (Tables 17-20). Significant increases in $\dot{V}E_{inst}$ were seen only in subjects III and IV with mean highest breath values of 108 and 109% respectively (Table 16). 2 breaths of N_2
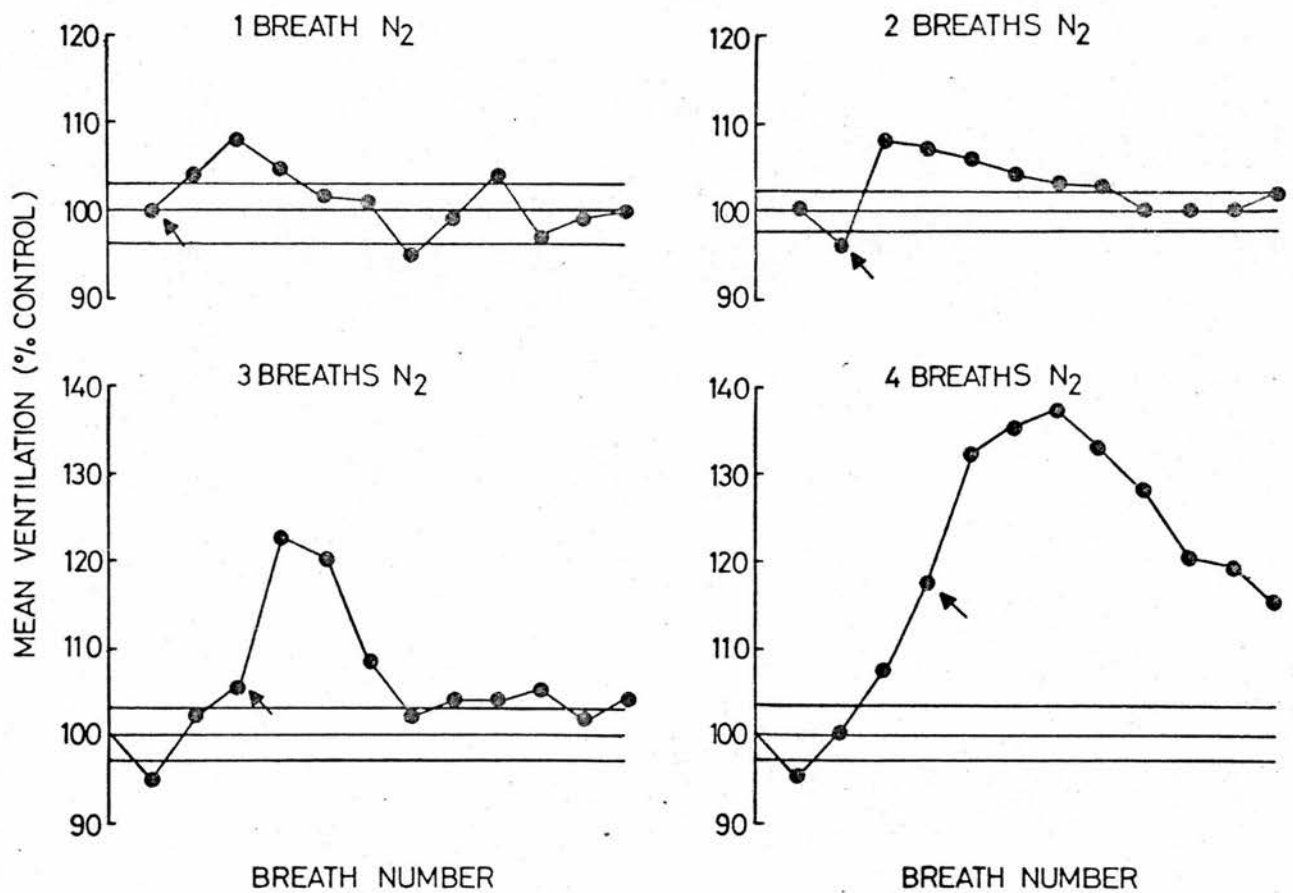
FIGURE 35   An example of the mean breath by breath ventila-
tory response to 1, 2, 3 and 4 breaths of nitrogen
on exercise in subject III. The arrows indicate
the final breath of nitrogen. The lines represent
the 95% confidence limits of the control ventila-
tion (see text).

caused a fall to a mean lowest $P_{ET}O_2$ ranging from 6.29 kPa
in subject III to 7.40 kPa in subject IV and significantly
increased mean highest breath values of 108-112% were seen
in all subjects except subject IV, the highest breath value
being observed on average 3 breaths after the lowest $P_{ET}O_2$.
Following three breaths of nitrogen the mean lowest $P_{ET}O_2$
ranged from 4.61 kPa in subject III to 5.72 kPa in subject
IV. Significant increases in ventilation were seen in all
subjects although that seen in subject IV lay on the 95%
confidence limits. The mean highest breath value ranged
from 109-122% and the position of the highest breath value
was on average 2 breaths after the lowest $P_{ET}O_2$. Four
breaths of N_2 caused falls to a mean lowest $P_{ET}O_2$ ranging
from 3.40 kPa in subject III to 4.16 kPa in subject IV.
All subjects had significant increases in ventilation, the
mean highest breath value ranging from 113-137% and occurring
on average 2 breaths after the lowest $P_{ET}O_2$.

The individual ventilatory responses for each subject
are shown in Fig. 36, significant increases in HBV (i.e.
outside 2SD of control ventilation) being indicated by the
closed circles. As in the rest studies, there is consi-
derable variation between individual measurements at one
stimulus level in one subject but, when the studies are com-
pared, the most striking feature is the marked response of
subject IV to transient hypoxia at rest whereas, on exercise,
there is little or no response until 4 breaths of N_2 have
been given (Fig. 40). He would certainly have qualified as
a low responder to 3 breaths of N_2 on exercise had he been
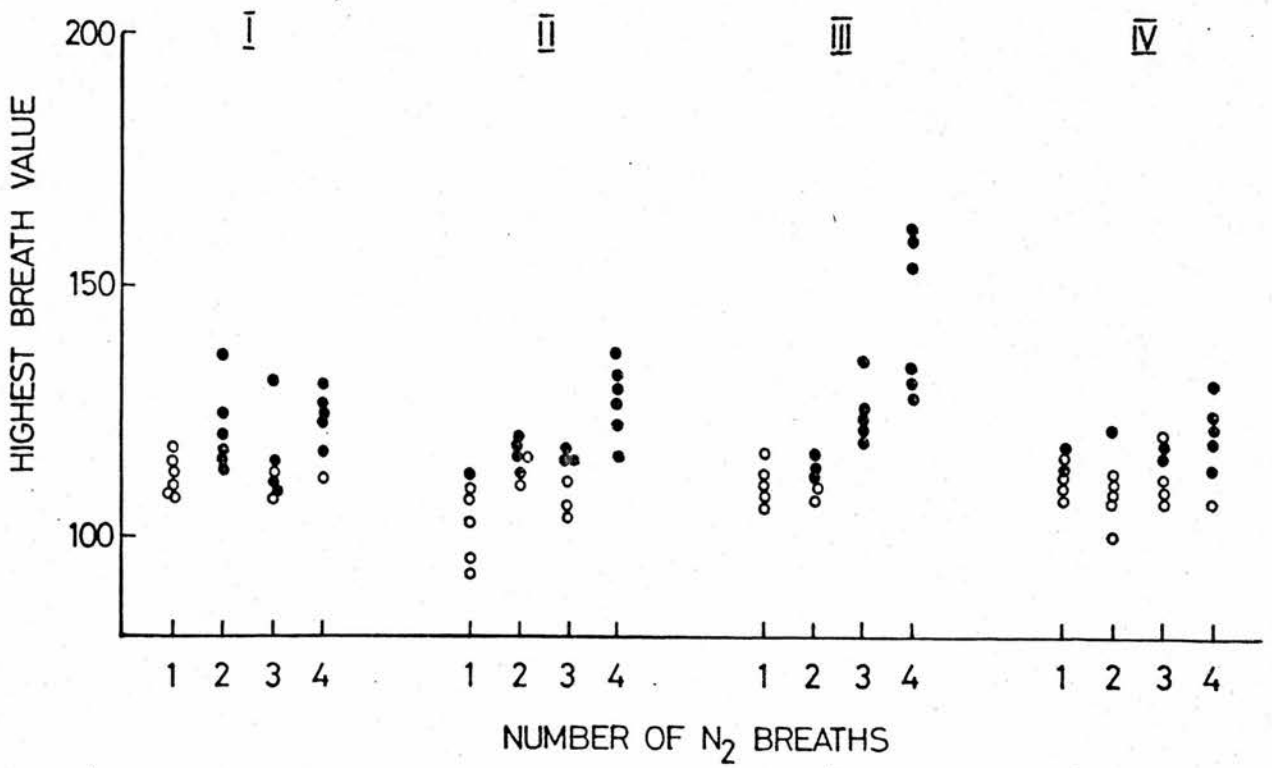
FIGURE 36   To show the individual highest breath values ob-
            tained in subjects I-IV with 1, 2, 3 and 4 breaths
            of nitrogen on exercise. The closed circles in-
            dicate values which were outside the 95% confi-
            dence limits of the control ventilation (see text).

included in the miners' study for, in him, all measurements of response to three breaths of N_2 give HBVs of less than 120%. When the six studies are superposed, the mean HBV for this subject with three breaths of N_2 is only 108% and barely reaches statistical significance. With 4 breaths of N_2 the mean HBV is still the lowest of the 4 subjects, reaching only 115%.

1. (c) <u>Comparison of ventilatory responses to transient hypoxia at rest and on exercise</u>

Figs. 37-40 show the equivalent of the $\dot{V}E/PO_2$ plots for all the transient hypoxia studies in subjects I-IV. The figures show the plot of the HBV for each transient study plotted against the lowest $P_{ET}O_2$ attained in that study. The significant responses are shown by closed circles and their significance determined by the fact that the HBV exceeded 2SD of the 30 control breaths. The most striking finding from these plots is that, for a given $P_{ET}O_2$, if only the significant responses are considered, the HBV is greater at rest than on exercise. That is, for a given $P_{ET}O_2$, the increase in ventilation observed after a given hypoxic stimulus is greater at rest than on exercise, when expressed as a percentage of the control ventilation. In subject IV particularly, who had a strikingly low and marginally significant response to 3 breaths of nitrogen on exercise, there appears to be a much more striking response to similar changes in $P_{ET}O_2$ when they are induced at rest.

Fig. 41 shows the transient data presented in a way which attempts to relate the ventilatory response to the de-

SUBJECT Ī

EXERCISE

REST

LOWEST $P_{ET}O_2$
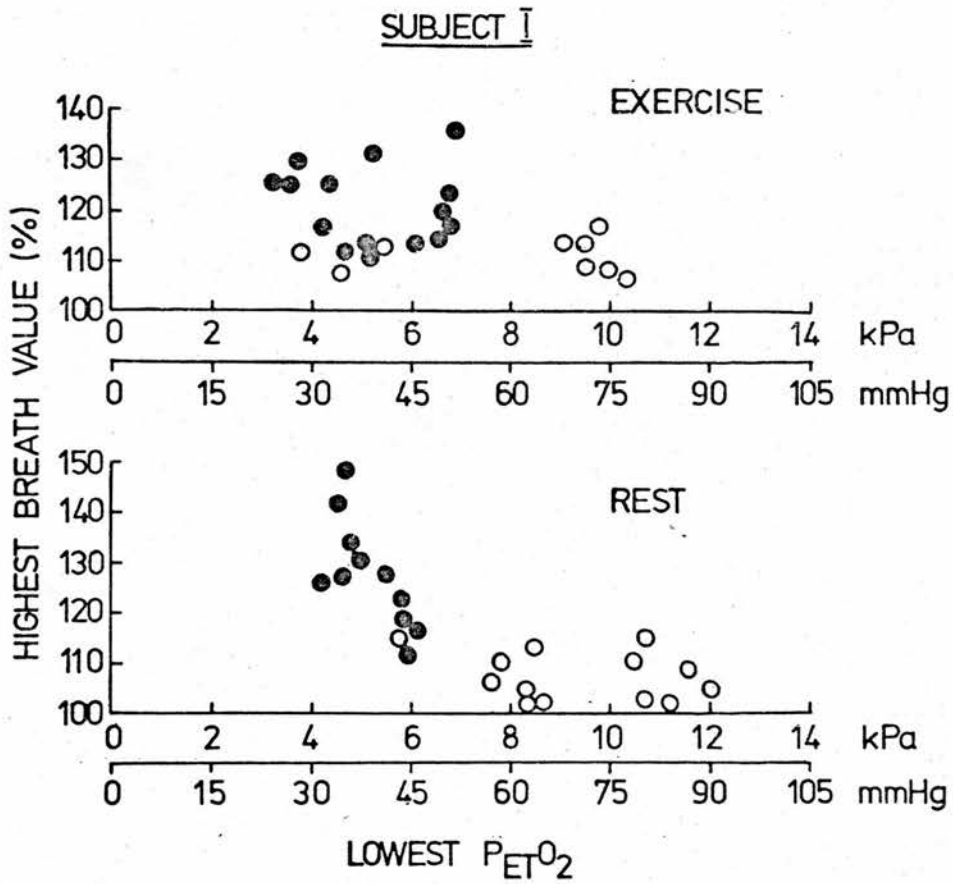
FIGURE 37   To show the individual highest breath values
from all the transient studies at rest and on
exercise in subject I plotted against the
lowest end tidal PO_2 preceding the response.
The closed circles represent values outside
the 95% confidence limits of the control ven-
tilation.

SUBJECT II

EXERCISE

REST

LOWEST $P_{ET}O_2$
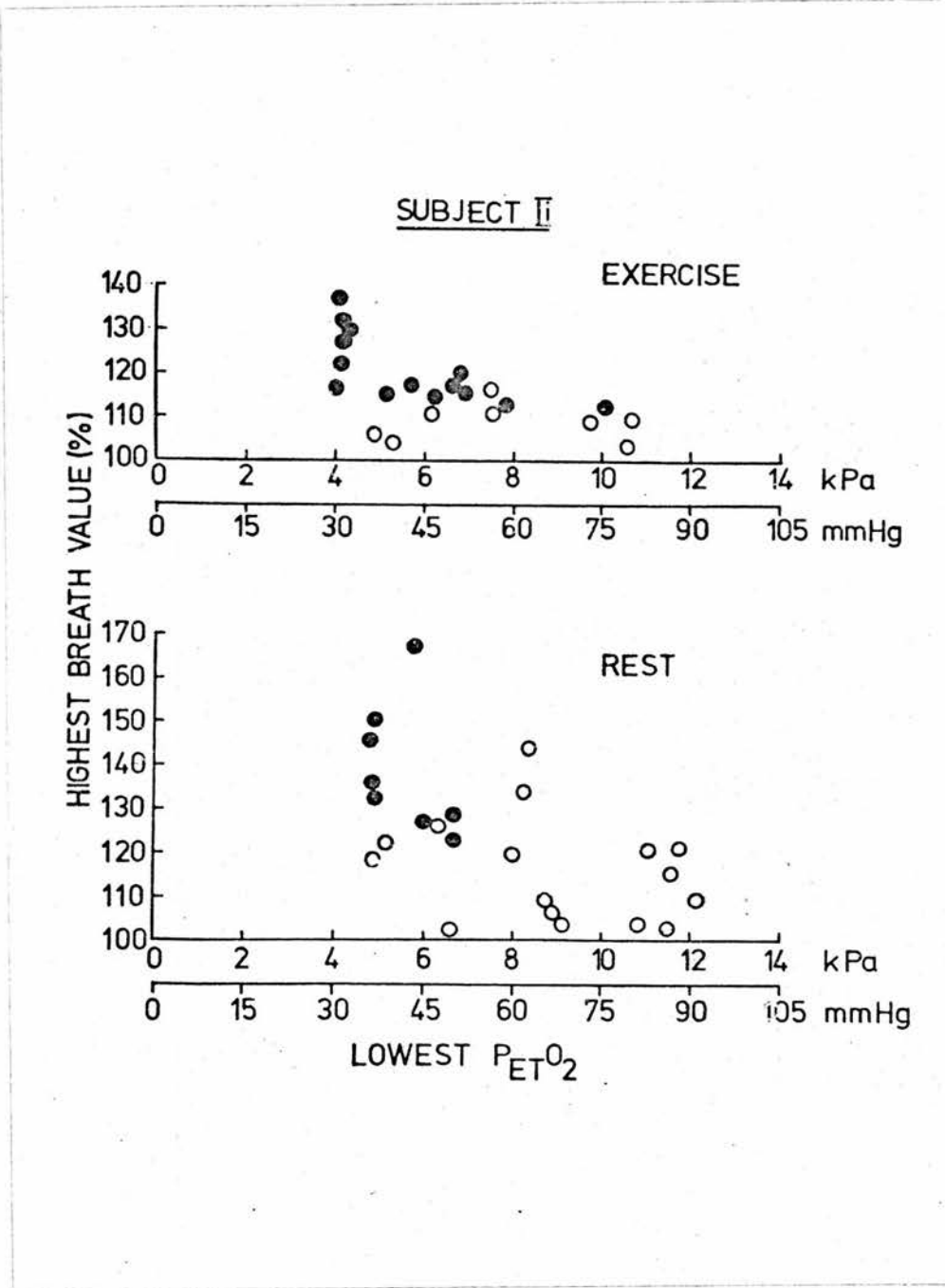
FIGURE 38   To show the individual highest breath values
             from all the transient studies at rest and
             on exercise in subject II plotted against the
             lowest end tidal PO_2 preceding the response.
             The closed circles represent values outside
             the 95% confidence limits of the control
             ventilation.
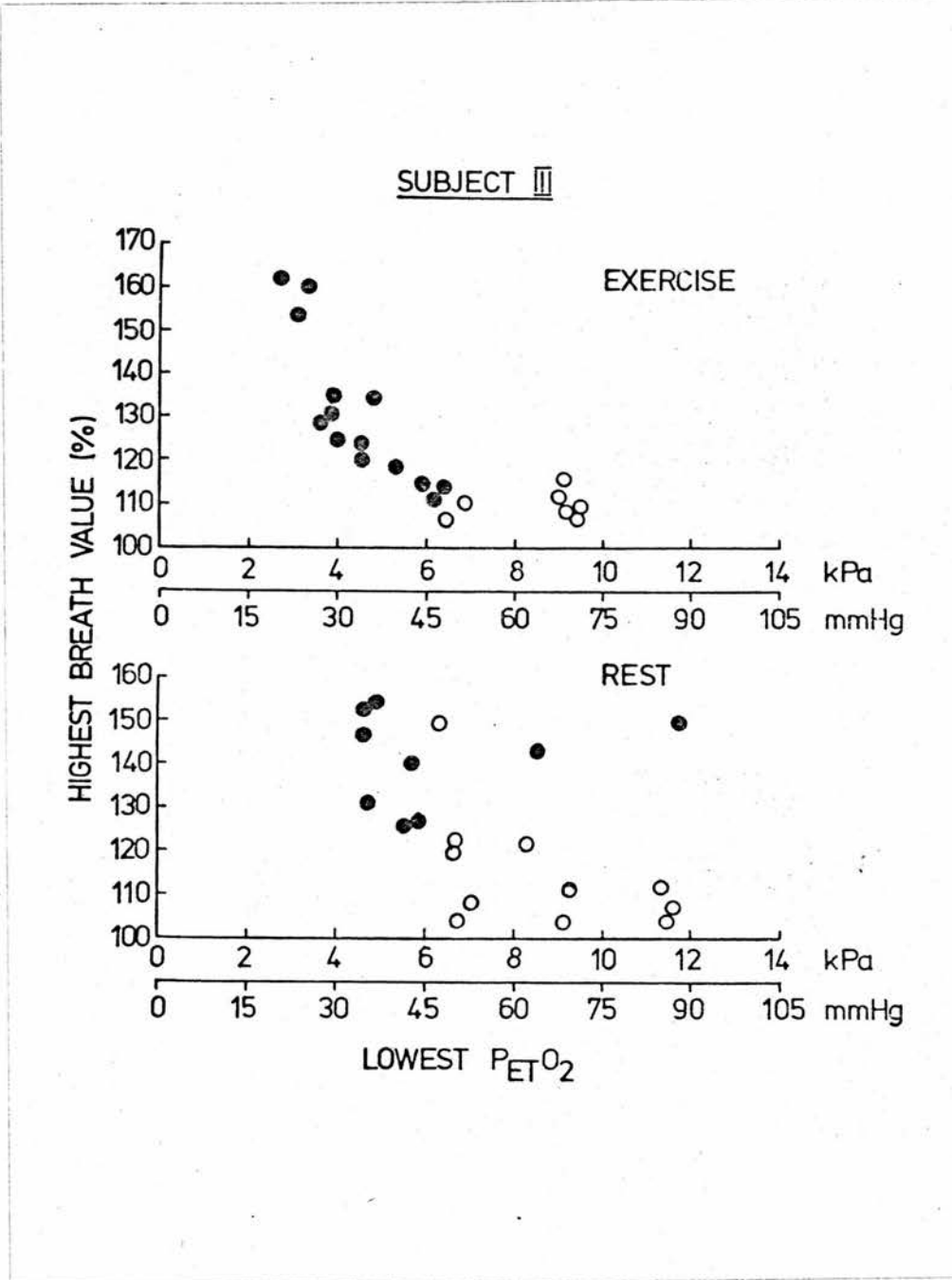
SUBJECT Ⅲ

FIGURE 39   To show the individual highest breath values
            from all the transient studies at rest and on
            exercise in subject III plotted against the
            lowest end tidal PO_2 preceding the response.
            The closed circles represent values outside
            the 95% confidence limits of the control ven-
            tilation.
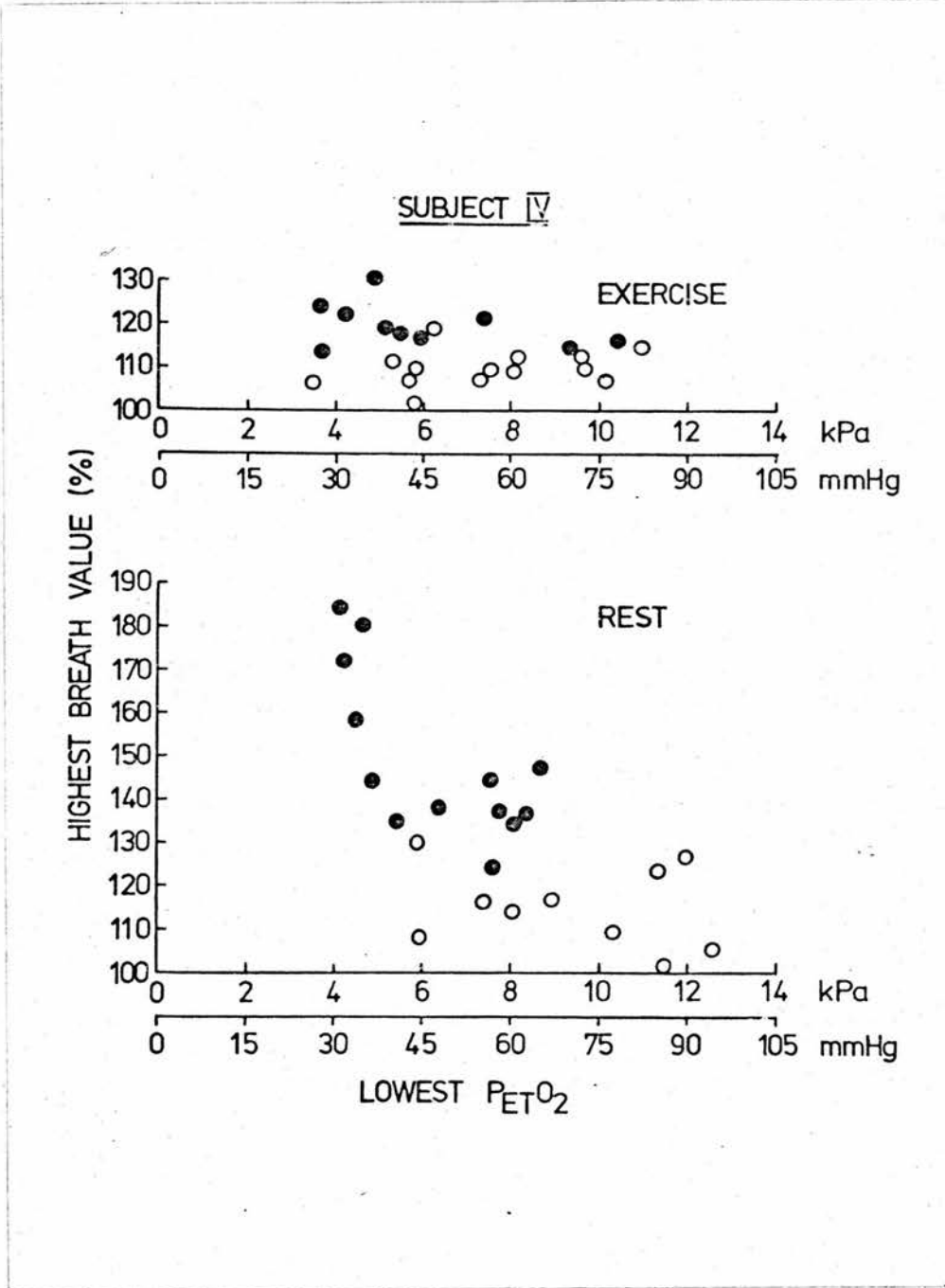
FIGURE 40   To show the individual highest breath values
            from all the transient studies at rest and on
            exercise in subject IV plotted against the
            lowest end tidal PO$_2$ preceding the response.
            The closed circles represent values outside
            the 95% confidence limits of the control ven-
            tilation.
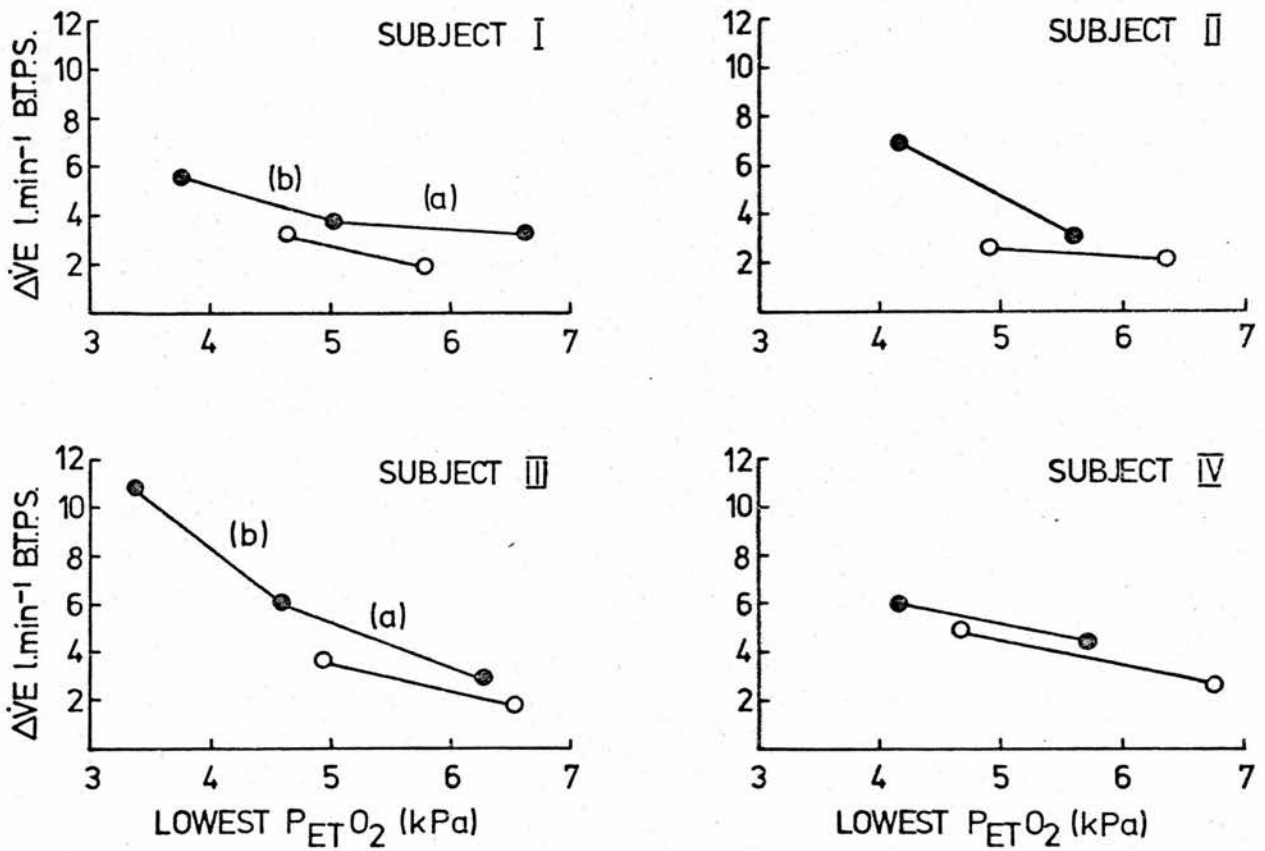
FIGURE 41   To show the mean transient $\dot{V}E/PO_2$ relationship
at rest (O————O) and on exercise (●————●)
at low PO_2s for subjects I-IV. Each point rep-
resents the mean lowest $P_{ET}O_2$ following a given
number of breaths of nitrogen and the mean
highest increase in ventilation from control
($\Delta\dot{V}E$) observed. In subjects I and III three
exercise points are shown. (see text)

gree of hypoxic stimulus for the studies at rest and on exer-
cise. In the Figure, the maximal change in $\dot{V}E_{inst}$ from
control observed after a given stimulus is plotted against
that stimulus (the lowest $P_{ET}O_2$). Each $\dot{V}E_{inst}/P_{ET}O_2$ point
is the mean of six observations, the open circles represent-
ing measurements made at rest and the closed circles measure-
ments made on exercise. The points selected are all below
a $P_{ET}O_2$ of 7 kPa and, although it is appreciated that the
$\dot{V}E/P_{ET}O_2$ plot is hyperbolic, in this region of low $P_{ET}O_2$,
where the curve is steepening and a small range of $P_{ET}O_2$ is
being considered, the slopes of the lines joining the points
do provide some indication of each subject's sensitivity to
transient hypoxia. The calculated slopes of the $\dot{V}E/P_{ET}O_2$
lines are given in Table 22. The values of these slopes
confirm the fact that, at rest, subject IV ranks high for
sensitivity to transient hypoxia whereas, on exercise, if
comparable $P_{ET}O_2$ ranges are considered, subject IV ranks
lowest for ventilatory response to transient hypoxia.

2. (a) Progressive hypoxia studies at rest

The results of the progressive hypoxia studies at rest
are shown in Table 23. Three studies were performed on
three subjects, but only 2 studies on subject III. The re-
sults show the values of parameters 1, 2 and 3 from the
equation $\dot{V}_E = 1 + \dfrac{2}{PO_2 - 3}$. Parameter 1 is the ventilation
at infinite $P_{ET}O_2$; parameter 2 is the shape parameter of
the hyperbola (the A of Weil et al, 1970), which represents
hypoxic sensitivity and parameter 3 is the $P_{ET}O_2$ at which

ventilation tends towards infinity. The values for para-
meter 1 were fairly constant for each individual as were the
values for parameter 3 (Table 23). Parameter 2, however,
was less reproducible. In subject I the mean value was
9.24 with a range of 9.15 - 9.36. However, the range of
values in the other three subjects was greater and, in sub-
ject II, the mean value was 4.15, with a range from 2.46 -
5.82. On the basis of the mean values for parameter 2, the
ranking of subjects in order of sensitivity to progressive
hypoxia at rest was III > I > II > IV, III and I being simi-
lar and having approximately twice as large a value for
parameter 2 as subjects II and IV.

The $P_{ET}CO_2$ at rest was maintained constant at resting
end tidal $P_{ET}CO_2$ levels during these studies and the values
for mean $P_{ET}CO_2$ ± SD are also given in Table 23. An example
of the breath by breath $P_{ET}CO_2$ during such a study in one
subject is shown in Fig. 42.

2.   (b) Progressive hypoxia studies on exercise

The $\dot{V}O_2$ achieved on exercise is shown in Table 24. The
same parameters as were derived for the rest studies have
been derived for the exercise studies and the results and
the mean $P_{ET}CO_2$ ± SD for each study are shown in Table 25.
Parameters 1 and 3 for each subject were less reproducible
than at rest, the range of parameter 1 being 19.75 - 20.79
in subject I and 8.29 - 21.96 in subject II, while parameter
3 varied from 4.38 - 4.83 in subject I and from 2.41 - 4.46
in subject 2.
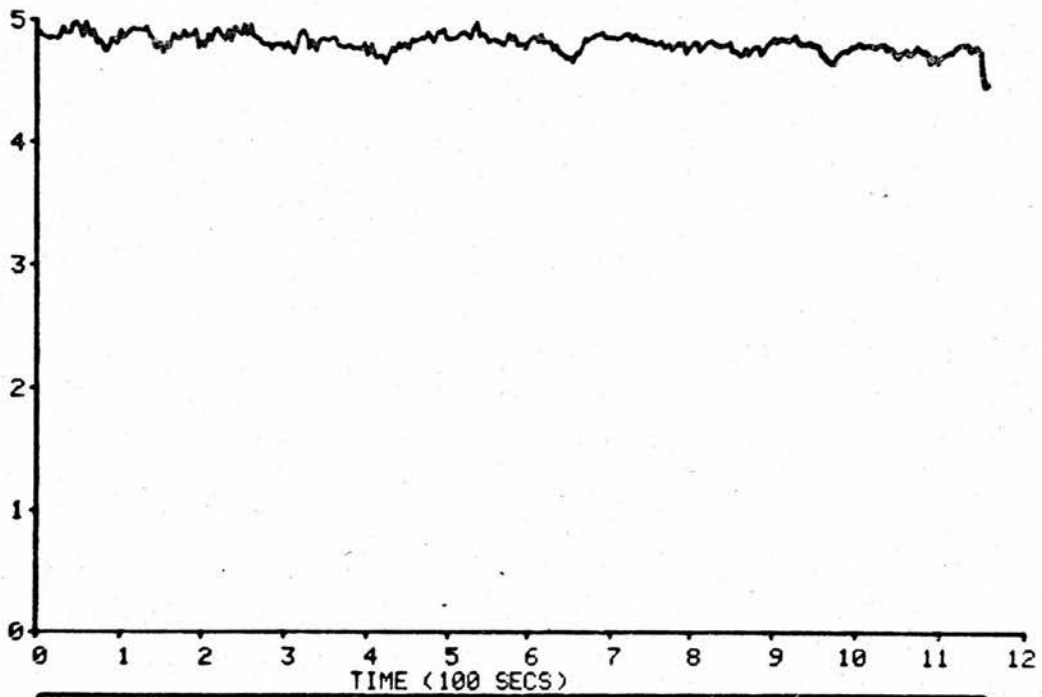
FIGURÉ 42   The end tidal PCO_2 for each breath plotted against time for an isocapnic progressive hypoxia study at rest in subject II (same study as Fig. 30).

Exercise produced an increase in parameter 2 for all subjects but, again, the ranges of the results in an individual subject varied, being 27.62 - 30.16 in subject II and as wide as 22.38 - 41.6 in subject IV. The mean $P_{ET}CO_2$ on exercise was higher in all subjects than the mean $P_{ET}CO_2$ in the rest study. The differences were less than 0.25 kPa in three subjects and, in the other, subject III, the exercise $P_{ET}CO_2$ was 0.47 kPa greater than the rest $P_{ET}CO_2$ (Tables 22 and 24).

An example of the $P_{ET}CO_2$ during a study is shown in Fig. 43. Ranking of subjects in order of mean response to progressive hypoxia on exercise is as follows: I > III > IV > II, I and III having almost identical values.

3. (a) <u>Steady state CO_2 response studies at rest</u>

Three studies were performed in each subject to define the slope of the ventilatory response to CO_2 at $P_{ET}CO_2$s of 25-30 kPa, 9.33 kPa, 6.67 kPa and 5.33 kPa. The $P_{ET}O_2$ at which the measurements were obtained, the slope of the ventilatory response to CO_2 at the given $P_{ET}O_2$ s (assuming a common BCO_2 equal to that determined for the hyperoxic line), the values for BCO_2 at high $P_{ET}O_2$ and at a $P_{ET}O_2$ of 6.67 kPa, and the ratios of the slopes of the various hypoxic lines to the hyperoxic slope are shown in Table 26.

The mean values for BCO_2 at $P_{ET}O_2$s of 25-30 kPa and 6.67 kPa did not differ by more than 0.30 kPa which was certainly within the differences in BCO_2 observed for the hyperoxic line alone observed in any one subject and, therefore, the use of a common B, namely that of the hyperoxic line for

DT1 PH29   DAT   05-SEP-75
LUKE
PROGRESIVE HYPOXIA ON EXERCISE

SECTION 1 BREATHS 1 TO 245
PCO2 ET
(KPC)

TIME (100 SECS)
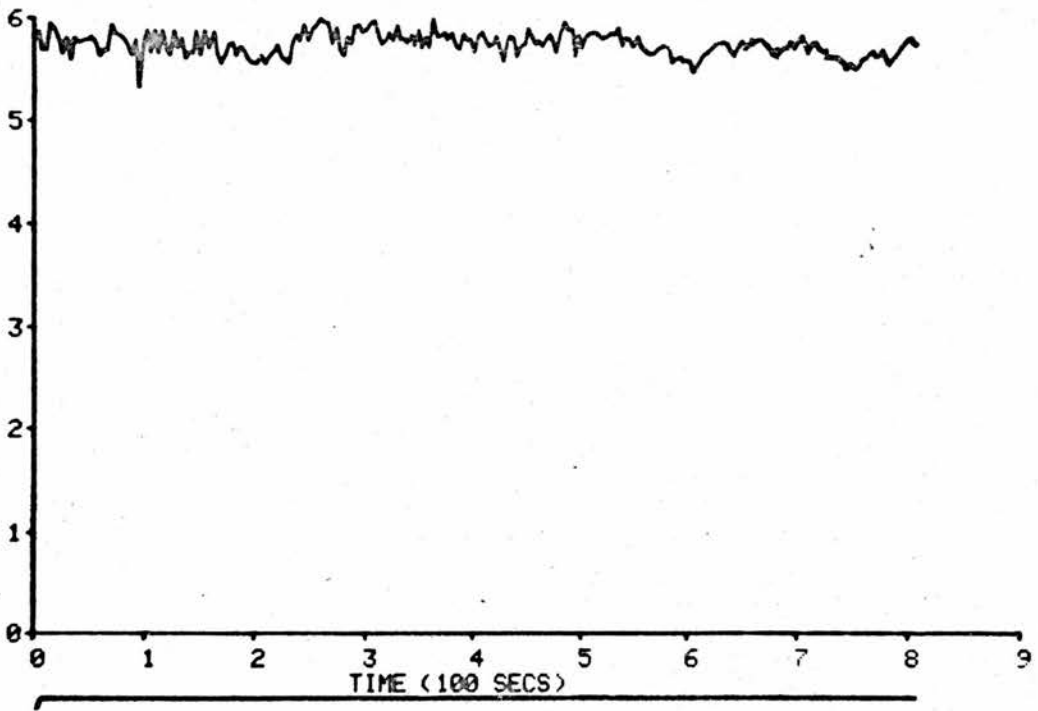
FIGURE 43   The end tidal PCO_2 for each breath plotted
against time for an isocapnic progressive
hypoxia study on exercise in subject III
(same study as Fig. 31).

determining the slopes of the hypoxic lines was felt to be permissible. The mean hyperoxic BCO_2 ranged from 4.38 to 5.02 kPa $P_{ET}CO_2$ in the four subjects.

The mean slope of the hyperoxic line ranged from 10.65 $\ell.min^{-1}kPa^{-1}$ in subject I to 20.52 $\ell.min^{-1}kPa$ in subject II. The hyperoxic slope was reproducible, the narrowest range of values observed being from 12.96 - 14.16 $\ell.min^{-1}kPa$ in subject I and the widest range being from 12.50 - 16.94 $\ell.min^{-1}kPa$ in subject III.

The hypoxic lines were much less reproducible even although the $P_{ET}O_2$ at which a given line was measured never varied by more than 0.4 kPa and was, in most cases, much less variable than this. Nor could the differences in slope at a given $P_{ET}O_2$ be related in any way to the minor differences between $P_{ET}O_2$s observed in different studies. The ranges obtained at a given $P_{ET}O_2$ in the same subject are shown in Table 26, with the mean values for each study quoted and the range expressed as a percentage of the mean.

The poor reproducibility of all but the hyperoxic line is evident from the results presented in Table 26. The percentage range to mean value for the three studies in each subject show that this percentage varies from 8.9 - 30.7% for the hyperoxic line, 18.7 - 42.4% for the line at $P_{ET}O_2$ of 9.33 kPa, 19.0 - 62.1% for the line measured at $P_{ET}O_2$ of 6.67 kPa and 19 - 53.9% for the line measured at a $P_{ET}O_2$ of 5.33 kPa.

The average increase in slope over the hyperoxic slope

for this group of four subjects was 38% at a $P_{ET}O_2$ of 9.33 kPa, 66% at a $P_{ET}O_2$ of 6.67 kPa and 101% at a $P_{ET}O_2$ of 5.33 kPa. If the ratio of mean slopes at the two lower $P_{ET}O_2$s are used as an index of hypoxic drive, the ranking at a $P_{ET}O_2$ of 6.67 kPa is III > II > I > IV and, at a $P_{ET}O_2$ of 5.33 kPa, III > IV > II > I.

The parameters of the equation

$$\dot{V} = D(P_{ET}CO_2 - B)(1 + \frac{A}{P_{ET}O_2 - C})$$

can be derived from the parameters established by the curve fitting programme when $\dot{V}E/P_{ET}CO_2 - B$ is plotted against $P_{ET}CO_2$. In the equation

$$\frac{\dot{V}E}{P_{ET}CO_2 - B} = \text{Parameter 1} + \frac{\text{Parameter 2}}{P_{ET}CO_2 - \text{Parameter 3}}$$

Parameter 1 is D, Parameter 2 is AD and Parameter 3 is C. BCO_2 is already known, i.e.

$$\frac{\dot{V}E}{P_{ET}CO_2 - B} = D + \frac{DA}{P_{ET}O_2 - C}$$

The values for Parameters 1, 2 and 3 and for Parameters A, B. C and D derived from all three studies in each of the four subjects are shown in Table 27. Again, as would be expected from the earlier analysis of slopes, considerable variation from study to study is observed within each subject. The values for D correspond closely, as would be expected, with each subject's hyperoxic slope. On the basis of the mean values for A, which is used as index of hypoxic drive, the ranking of the subjects for hypoxic drive measured

by this method is III > I > IV > II.

3.　(b)　<u>Steady state CO_2 response studies on exercise</u>

The steady state ventilatory response to CO_2 was measured four times in each subject, twice at a $P_{ET}O_2$ of 6.67 kPa and twice at a $P_{ET}O_2$ of 25-30 kPa.

<u>Hyperoxic Steady State CO_2 Response on Exercise</u>

The mean $\dot{V}O_2$ measured breathing air in these studies for the group of subjects was 1046 ml.min^{-1}, with a mean RQ of 0.82 (Table 28). The two $\dot{V}E/P_{ET}CO_2$ relationships for each subject in hyperoxic are shown in each subject in Figs. 44 and 45, where the mean hyperoxic CO_2 response line at rest is provided for comparison. It is obvious from the figures that the $\dot{V}E/P_{ET}CO_2$ relationship is linear in hyperoxic exercise. The slopes and intercepts of these lines derived by linear regression are detailed in Table 29. The slopes are similar to the slopes obtained at rest (a mean value of 15.68 compared with 14.75 ℓ.min^{-1}kPa^{-1} at rest) and the most striking effect of exercise, which is also clear in the figures, is to diminish the intercept B of the CO_2 response line so that, on exercise, the mean value for the group is 3.54 kPa $P_{ET}CO_2$ compared with a mean value for BCO_2 at rest of 4.62 kPa.

<u>Hypoxic Steady State CO_2 Response on Exercise</u>

In the hypoxic studies performed at a mean $P_{ET}O_2$ of 6.57 kPa, the mean $\dot{V}O_2$ breathing air was 991 ml.min^{-1} with a mean RQ of 0.83.

The two $\dot{V}E/P_{ET}CO_2$ relationships in hypoxia for the four
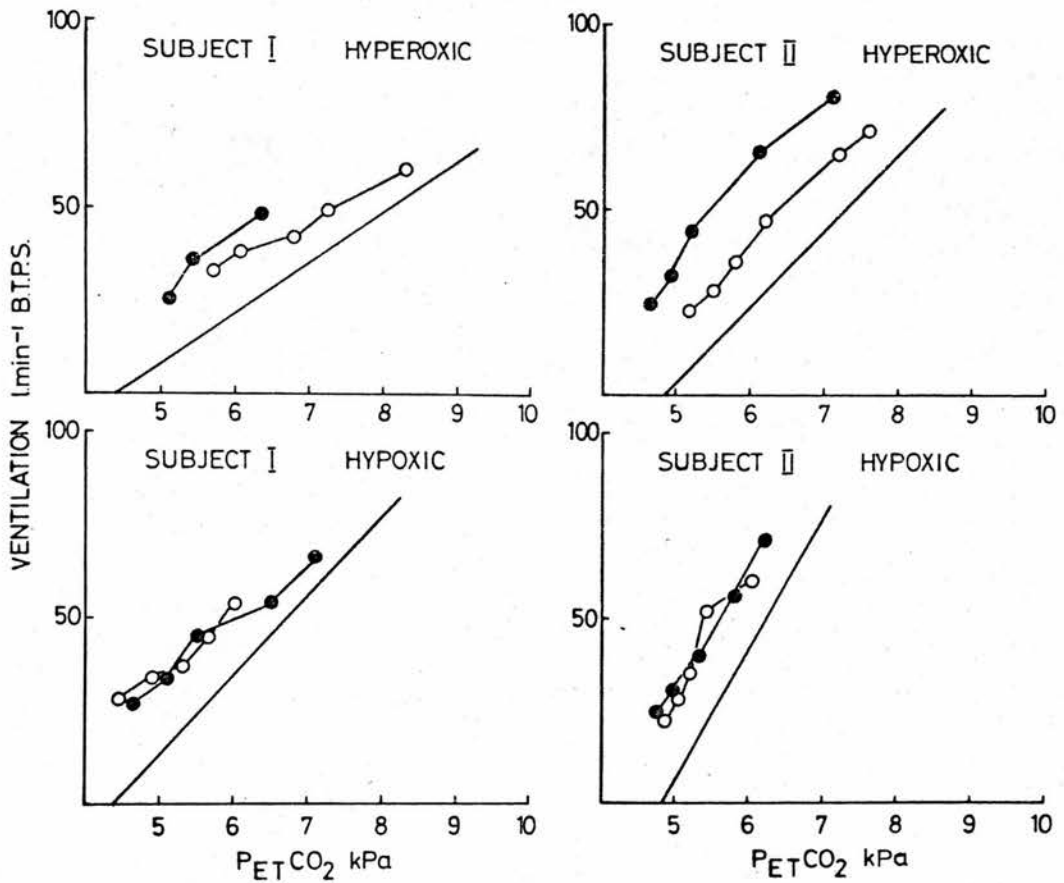
FIGURE 44   Duplicate studies of the ventilatory response
to CO_2 on exercise in hyperoxia and hypoxia
($P_{ET}O_2 \sim 6.67$ kPa) in subject I and II.   The
continuous lines represent the equivalent
ventilatory responses to CO_2 at rest in these
subjects.
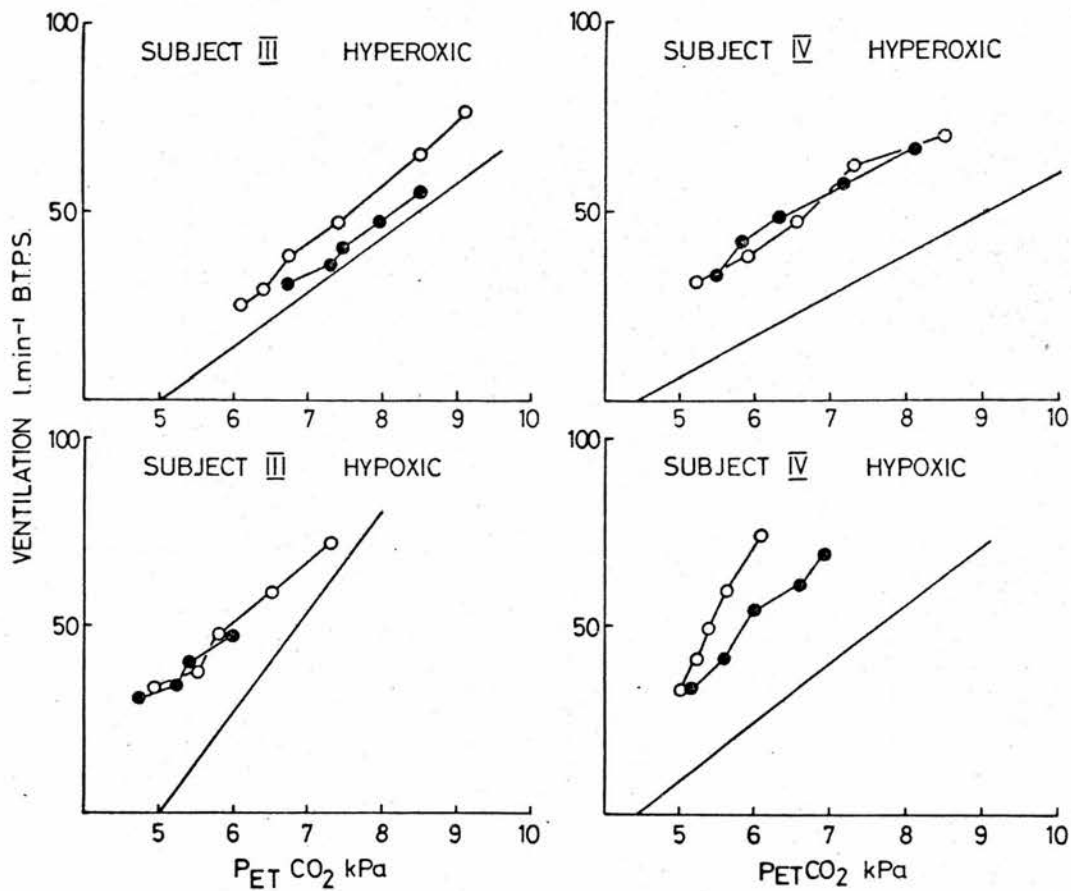
FIGURE 45   Duplicate studies of the ventilatory response
to exercise in hyperoxia and hypoxia ($P_{ET}O_2 \sim$
6.67 kPa) in subjects III and IV. The con-
tinuous lines represent the equivalent venti-
latory responses to CO_2 at rest in these
subjects.

subjects are shown in Figs. 44 and 45, where the CO_2 response line at the same $P_{ET}O_2$ at rest is drawn for comparison. The relationships were linear, as in hyperoxia, and reproducible except in subject IV where one line had, on linear regression, almsot twice the slope of the other (Table 29). The values for $P_{ET}O_2$, SCO_2 and BCO_2 for the other subjects are also shown in Table 29. The mean exercise slope in hypoxia on exercise was very slightly less than at rest (22.89 compared with 24.85$\ell.min^{-1}kPa^{-1}PCO_2$). As in hyperoxia, the main effect of exercise was to lower the intercept of the line on the $P_{ET}CO_2$ axis, the mean intercept for the group being 3.42 kPa compared with a mean value of 4.78 kPa at a $P_{ET}O_2$ of 6.67 kPa at rest.

Comparison of Hypoxic Drive at Rest and on Exercise between Subjects

The results for "hypoxic drive" as determined by these different methods have all been reported earlier in this chapter with the exception of the steady state exercise studies. Quantitation of hypoxic drive is difficult to compare in these exercise studies for those in hypoxia and hyperoxia were carried out on different days. The method least likely to give rise to error is to calculate, using the slope and intercept for each individual study, the ventilation at the $P_{ET}CO_2$ recorded in the control period when the subject was breathing air. Although there may be minor differences in control $P_{ET}CO_2$ from day to day it is, nevertheless, a consistent reference point. Data are available to allow calculation of this control $P_{ET}CO_2$ for all the

studies with the exception of one hypoxic study in subject
III. The control values of $P_{ET}CO_2$ and the calculated ven-
tilations with their means are shown in Table 30. The
difference between the hypoxic and hyperoxic ventilations
at control $P_{ET}CO_2$ is taken to be an index of hypoxic drive
in these steady state studies. The differences between the
control $P_{ET}CO_2$ values for different studies in each subject
are small (Table 29).

   i) Rest

The ranking order of the intensity of the hypoxic drive
in the four subjects as assessed by these three different
methods at rest is shown in Table 31. The overall ranking
is also shown on a simple points basis for the three methods
taking parameter A as the index of steady state hypoxic
drive, parameter 2 as the index of hypoxic drive in progres-
sive hypoxia and the slope of the line relating lowest $P_{ET}O_2$
to VE_{inst} (Table 22) as the best index (since it includes
the stimulus as well as the response and the measurements
are made over the same range of $P_{ET}O_2$) for assessing response
to transient hypoxia.

On this basis, subject III has the greatest hypoxic
drive with all three methods and subject II the lowest hy-
poxic drive with all three methods. Subject I and subject
IV occupy intermediate and equal positions, the only inter-
esting observation here being that subject IV did occupy
equal first position with regard to the transient stimulus.

If the ranking is done on the basis of the ratio of

the slopes of the steady state CO_2 response at $P_{ET}O_2$s of 6.67 kPa and 5.33 kPa to those at 30 kPa and the mean highest breath values with 5 and 7 breaths of nitrogen are also included (Table 31), the ranking order is unchanged. Nevertheless, it is clear that, if the ratio of slopes at $P_{ET}O_2$s of 6.67 and 30 kPa had been used as the only index of hypoxic drive, subject II, who clearly ranks last in the overall picture in Table 31, would have been on that account alone ranked second in order of intensity of his hypoxic drive.

ii) Exercise

Table 32 shows the ranking for the different methods of assessing hypoxic drive on exercise. The steady state drive is measured as described above, the progressive hypoxia drive as parameter 2, and the transient drive again on the basis of the slopes relating lowest $P_{ET}O_2$ to $\dot{V}E$ (Table 22). The transient response is more difficult to evaluate on exercise for the range of $P_{ET}O_2$ over which slopes were measured was not necessarily the same for all subjects. However, the ranges for subjects II and IV are clearly similar and the ranking for subjects I and III has been derived from the slope over the lower of the two $P_{ET}O_2$ ranges available. Had the alternative slopes been used for these subjects, the overall ranking for hypoxic drive on exercise would have been unaffected.

As at rest, subject III clearly has the overall greatest hypoxic drive on exercise, and subject II has the lowest drive with the others occupying intermediate positions.

The most striking observation is that subject IV ranks
second for the steady state hypoxic drive and lowest for
the transient hypoxic drive. Even allowing for possible
sources of error in making comparisons for the steady
state between different days, the steady state drive is
clearly so much more obvious in subject IV than the tran-
sient drive that it is difficult to gainsay.

With progressive hypoxia the ranking at rest and on
exercise was almost identical (the two subjects ranked
1 and 2 had almost identical values on both occasions).

In the transient studies, subjects I, III and IV were
all very similar at rest but exercise produced marked in-
creases in slope in subjects II and III, allowing improve-
ment and maintenance of their ranking respectively, where-
as little or no increase in slope respectively was seen in
subjects I and IV.

Comparison of the mean HBV with 3 breaths of N_2 with
the ratio of slopes in steady state at $P_{ET}O_2$s of 6.67 and
30 kPa, as was done for the miners, shows identical placing
in the ranking order of the highest (III) and lowest (II)
responders with each method with the other two exchanging
positions.

4.   Studies of the Ventilatory Response to Exercise

The ventilatory responses to exercise in hypoxia, nor-
moxia and isocapnic hypoxia for the four subjects are shown
in Fig. 46 as the linear relationship between minute venti-
lation and oxygen uptake. The oxygen uptake, ventilation and
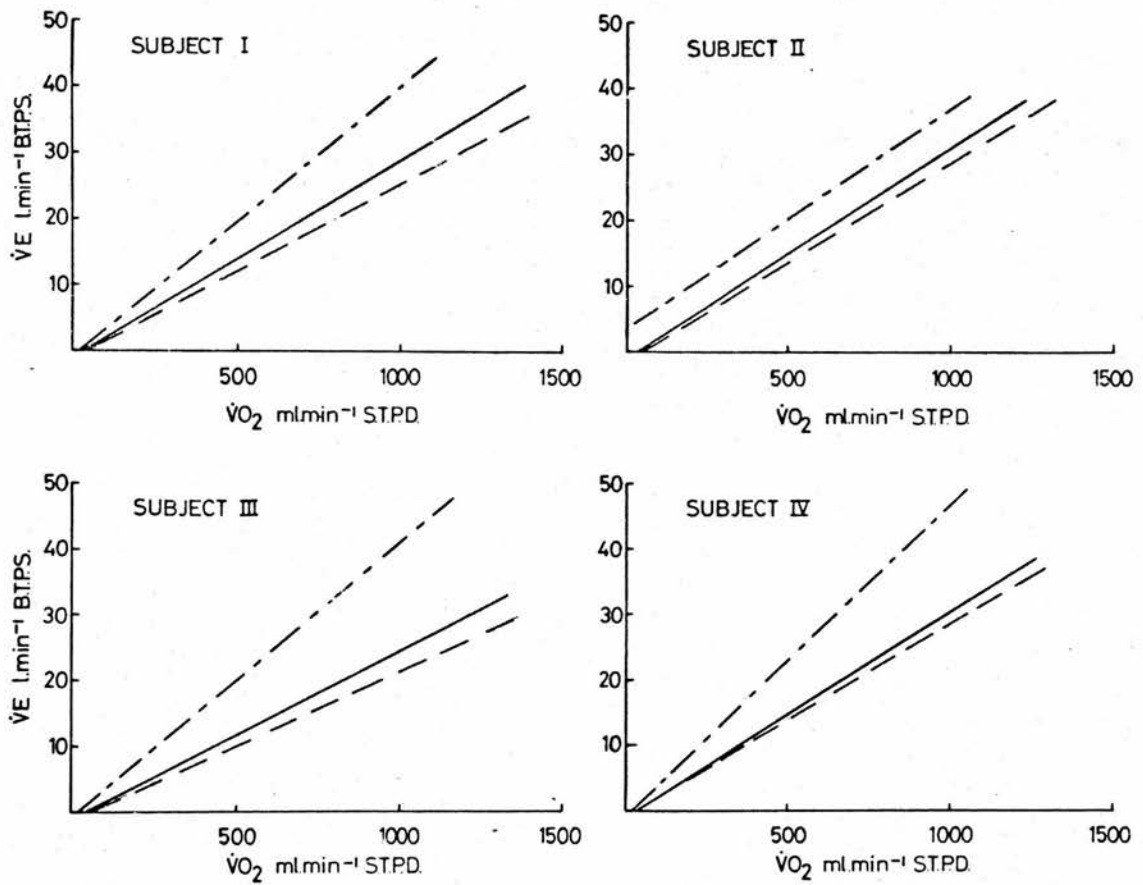
FIGURE 46   The steady state relationships between venti-
lation and oxygen consumption in subjects
I-IV in normoxia (— — —) hypoxia (————)
(PETO2 ~ 6.67 kPa) and isocapnic hypoxia
(— _ — _) (PETO2 ~ 6.67 kPa)

$P_{ET}CO_2$ at which the ventilation was measured at rest and on exercise are shown in Table 33. The $P_{ET}O_2$s at which ventilation was measured are shown in Table 34. Table 35 gives the slopes and intercepts of the $\dot{V}E/\dot{V}O_2$ line. The $\dot{V}E/\dot{V}O_2$ ratio calculated only from the exercise point has been selected as the most reliable index of the ventilatory response to exercise since it was shown in the miners' study that it was highly reproducible.

Comparison of the $\dot{V}E/\dot{V}O_2$ ratios in hypoxia and normoxia shows that there is little increase in ratio in hypoxia when $P_{ET}CO_2$ is allowed to fall. The slope increases by 14 and 12% in subjects I and III respectively, by 6% in subject IV and by 5% in subject II. However, when $P_{ET}CO_2$ is kept constant at "normoxic $P_{ET}CO_2$" during the hypoxic studies, i.e. in isocapnic hypoxia, differences between the $\dot{V}E/\dot{V}O_2$ ratios in normoxia and hypoxia are more obvious. The $P_{ET}O_2$ was well controlled in all studies (Table 33).

When $P_{ET}CO_2$ was kept constant, the increase in the $\dot{V}E/\dot{V}O_2$ ratio was more marked, ranging from a 23% increase in subject II to a 74% increase in subject III, with subjects I and IV having 50 and 45% increases respectively (Table 35). The ratio of the ventilatory response to exercise in isocapnic hypoxia to that in normoxia clearly relates to a subject's hypoxic drive. The ratio is highest in subject III and lowest in subject II, who had the highest and lowest overall hypoxic drives respectively in the earlier studies, with subjects I and IV occupying intermediate positions.

CHAPTER 8   COMPARISON OF METHODS OF MEASURING THE
            HYPOXIC DRIVE TO BREATHING : DISCUSSION

The values for the ventilatory response to CO_2 at rest
in the four subjects were in the established normal range for
this variable (Rebuck and Read, 1971) and as reproducible as
when measured by the rebreathing method (Lyall, Bourne and
Cameron, 1975). The slopes of the CO_2 response lines in
hypoxia were much more variable - a phenomenon which has
plagued respiratory physiologists for many years but which
none of them have ever studied. Anderton, Harris and
Slawson (1964) demonstrated small differences between hy-
poxic CO_2 responses done in series on the same day in normal
man but no-one has provided data on the day to day variabi-
lity of this response in individual subjects. The marked
differences in slope of the CO_2 response line at any low
PO_2 in a given subject are much greater than the variabi-
lity recorded in measuring the hyperoxic CO_2 response line.
Differences in PO_2 or procedure from day to day were not
responsible for the differences, which must be attributed
either to day to day variation in chemoreceptor response to
hypoxia or to differences in the CNS response to a given
chemoreceptor input. In view of the known depressing effect
of hypoxia on CNS function (Kronenberg, Hamilton, Gabel,
Hickey, Read and Severinghaus, 1972) in steady state studies,
it is tempting to assume that variation in the balance be-
tween hypoxic stimulation and depression from day to day is
responsible for the differences observed. The differences
in slopes of hypoxic CO_2 response lines from study to study

are responsible for the differences observed in Cunningham's parameter A in each subject. These differences were considerable with the tightest range for A being 2.11-2.70 in subject IV and the loosest range being 2.18-6.06 in subject III. The values recorded for parameter A in all four subjects are similar to values recorded by others in sea level man (Michel and Milledge, 1963; Milledge and Lahiri, 1967; Lloyd and Cunningham, 1963) and none was as low as the mean values found in high altitude native Sherpas with diminished hypoxic drive to breathing (Milledge and Lahiri, 1967).

The effect of exercise on the ventilatory response to CO_2 in hypoxia and hyperoxia was similar to that reported by other workers. In hyperoxia, the $\dot{V}/PCO_2$ line shifted in parallel fashion to the left with no significant change in slope in all four subjects and a decrease in the intercept of the line on the PCO_2 axis as previously reported by others (Nielsen, 1936; Asmussen and Nielsen, 1957; Bhattacharyya, Cunningham, Goode, Howson and Lloyd, 1970). In hypoxic exercise, the relationship between $\dot{V}E$ and PCO_2 was linear with no evidence of the decrease in slope found at higher ventilation by Bhattacharyya, Cunningham, Goode, Howson and Lloyd (1970). Two patterns of response were observed (Figs. 47-50). In subjects I and III there was a shift to the left of the hypoxic CO_2 response lines compared with rest, with a decrease in both the intercept and the slope of the lines, the hypoxic intercept being less than the hyperoxic intercept.
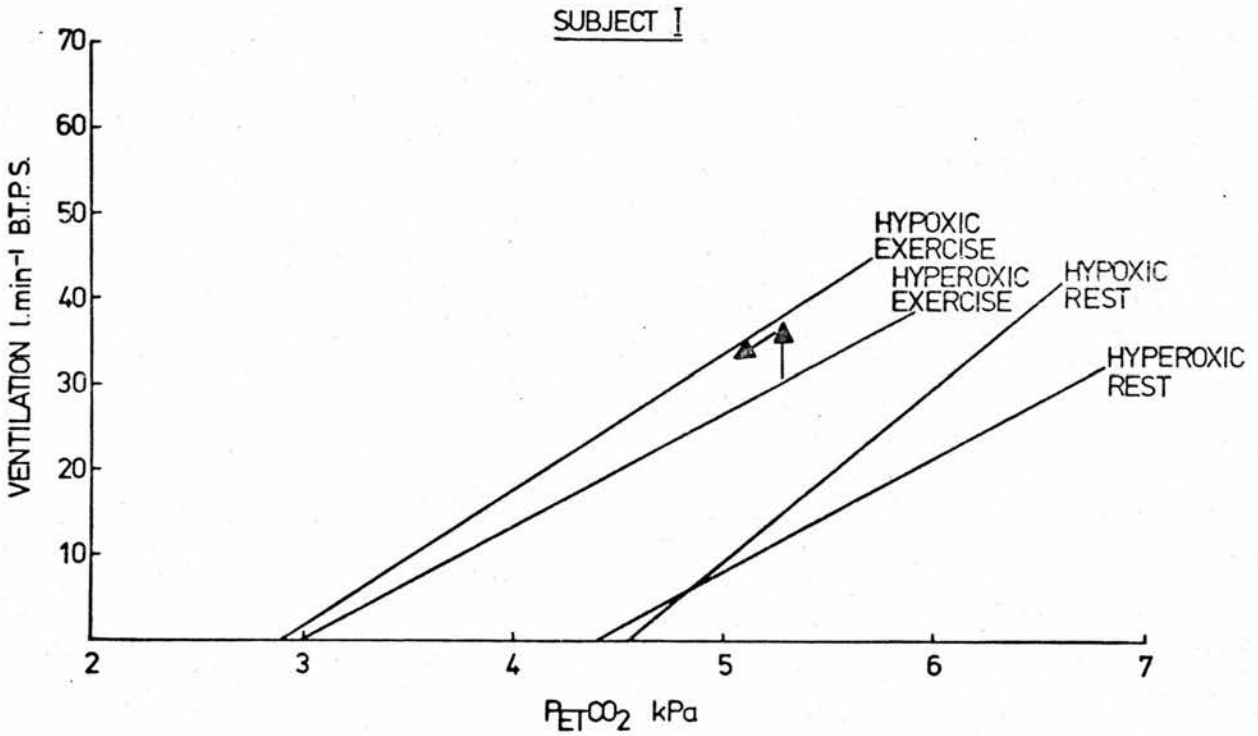
SUBJECT I

FIGURE 47 The mean CO_2 response lines in hypoxia ($P_{ET}O_2$ ~̃ 6.7 kPa) and hyperoxia ($P_{ET}O_2$ ~ 30 kPa) derived from 3 studies at rest and 2 studies on exercise in Subject I. The vertical arrow indicates the increase in ventilation to be expected for a fall in PO_2 on exercise if PCO_2 remains constant at control levels. The oblique arrow indicates the ventilation expected at the same PO_2 for a fall in PCO_2 such as is found by the third breath of N_2 in transient hypoxic studies in this subject (see Fig. 51 and text).

SUBJECT II

VENTILATION l.min⁻¹ B.T.P.S.

HYPOXIC EXERCISE

HYPEROXIC EXERCISE

HYPOXIC REST

HYPEROXIC REST

$P_{ET}CO_2$ kPa
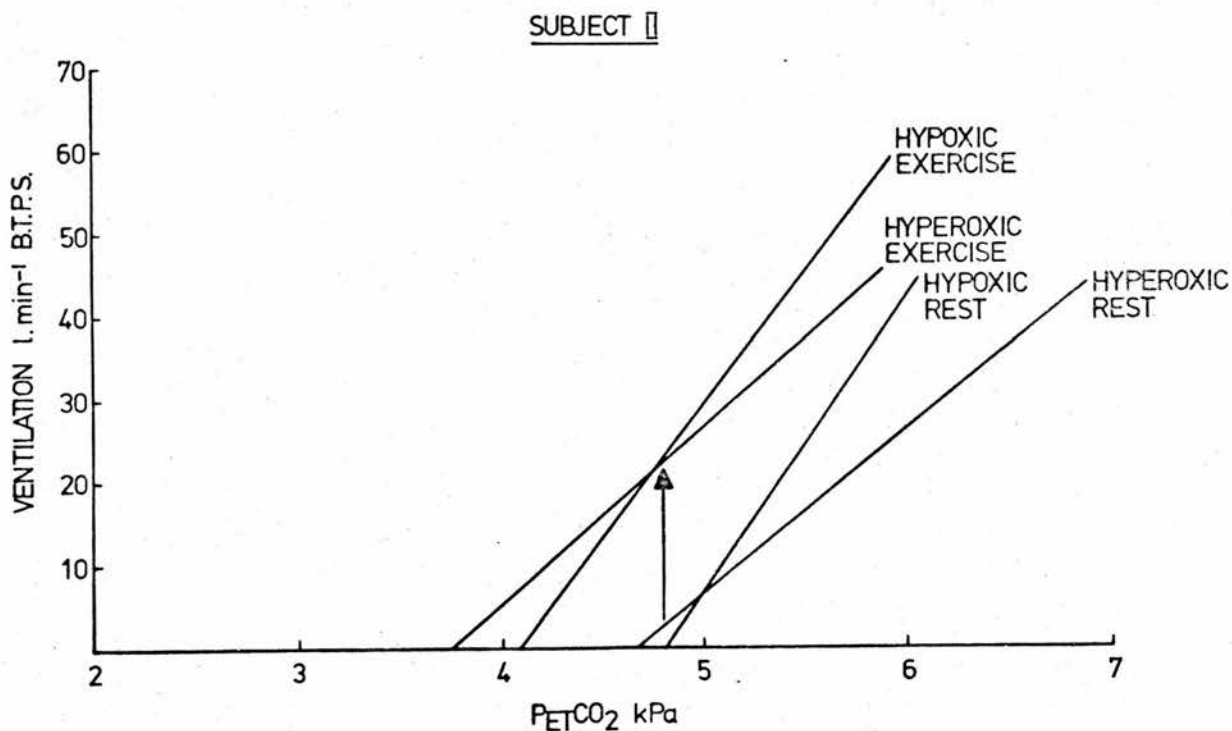
FIGURE 48   The mean CO_2 response lines in hypoxia
($P_{ET}O_2 \sim 6.7$ kPa) and hyperoxia ($P_{ET}O_2 \sim$
30 kPa) derived from 3 studies at rest and
2 studies on exercise in subject II.   The
vertical arrow indicates the control PCO_2
during exercise in this subject.   An analy-
sis similar to that in Figure 47 is diffi-
cult to depict diagrammatically, but can be
pursued using data from Figure 52.
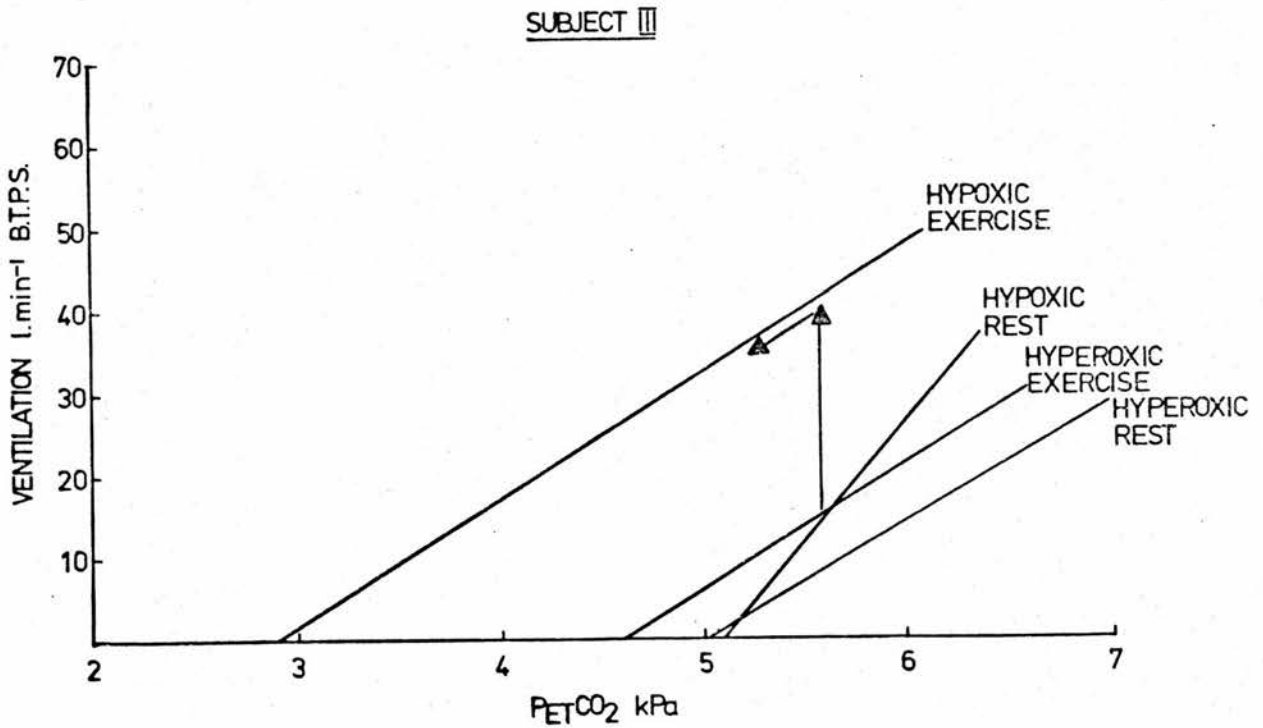
SUBJECT III

FIGURE 49   The mean CO_2 response lines in hypoxia ($P_{ET}O_2 \sim$ 6.7 kPa) and hyperoxia ($P_{ET}O_2 \sim 30$ kPa) derived from 3 studies at rest and 2 studies on exercise in subject III. The vertical arrow indicates the increase in ventilation to be expected for a fall in PO_2 on exercise if PCO_2 remains constant at control levels. The oblique arrow indicates the ventilation expected at the same PO_2 for a fall in PCO_2 such as is found by the third breath of N_2 in transient hypoxia studies in this subject (see Figure 51 and text).
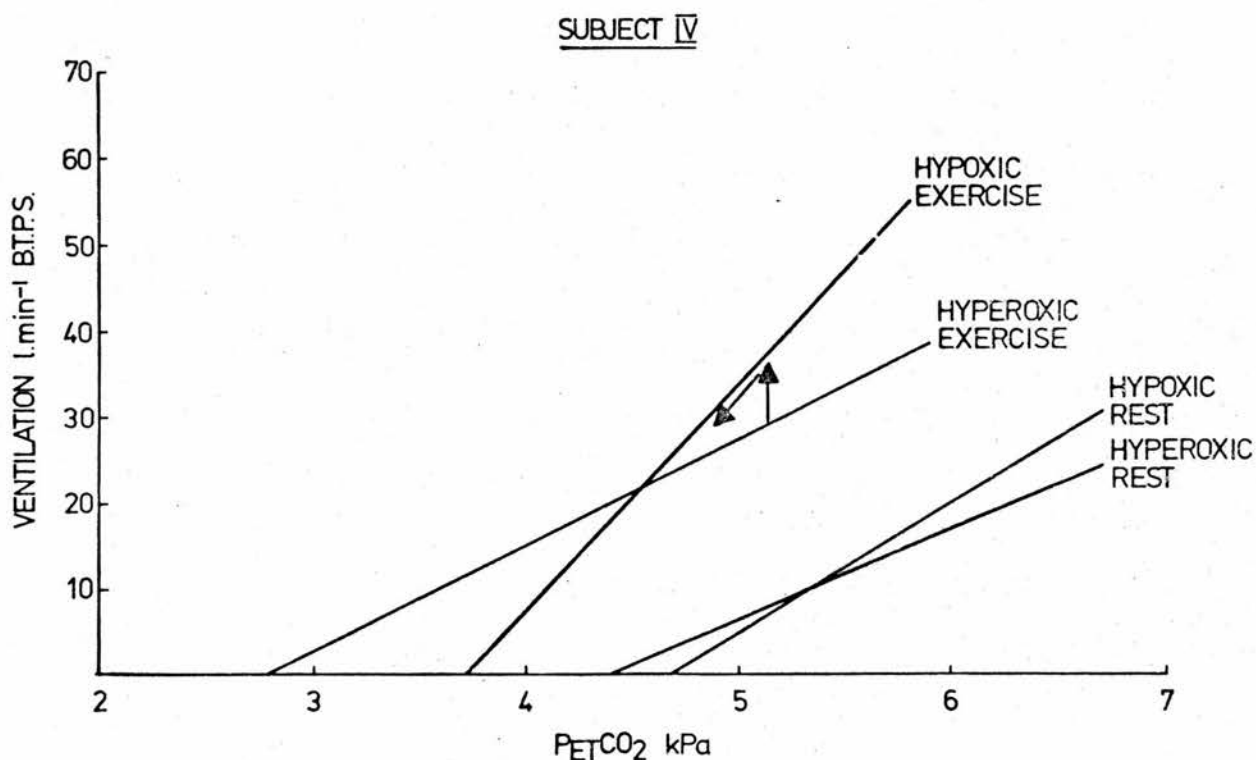
SUBJECT IV

FIGURE 50   The mean CO_2 response lines in hypoxia ($P_{ET}O_2 \sim$
6.7 kPa) and hyperoxia ($P_{ET}O_2 \sim$ 30 kPa) derived
from 3 studies at rest and 2 studies on exercise
in subject IV. The vertical arrow indicates the
increase in ventilation to be expected for a fall
in PO_2 on exercise if PCO_2 remains constant at
control levels. The oblique arrow indicates the
ventilation expected at the same PO_2 for a fall
in PCO_2 such as is found by the third breath of
N_2 in transient hypoxia studies in this subject
(see Figure 51 and text).

In subjects II and IV, however, the slope of the hypoxic
CO_2 response line was similar to or greater than that
found at the same PO_2 in the rest studies and, although
the hypoxic intercept was less on exercise than at rest,
it was not less than the hyperoxic intercept on exercise.
As a result, the hypoxic and hyperoxic CO_2 response lines
in these subjects crossed each other at a ventilation of
about 20 $\ell.min^{-1}$. The "cross-over" effect is also seen in
the studies of Bhattacharyya, Cunningham, Goode, Howson
and Lloyd (1970)on subject 204. The effect of exercise on
the hypoxic CO_2 response lines was similar to that found in
the subjects studied by Masson and Lahiri (1975), who also
found a linear relationship between ventilation and PCO_2
in ranges similar to those of the present study.

The progressive hypoxia studies at rest demonstrated
a similar variability in response. Although in subject I
the hypoxic drive parameter2(Weil's parameter A) was very
reproducible, in the least reproducible subject, subject
II, the value for parameter 2 ranged from 2.46 to 5.82 kPa,
indicating considerable day to day variation. The values
for parameter 2 found in these studies were, for all four
subjects, less than the lowest normal value reported by
Weil and his colleagues (Hirshman, McCullough and Weil, 1975).
This difference is probably related to slight but significant
differences in techniques. Weil, Byrne-Quinn, Sodal, Friesen,
Underhill, Filley and Grover (1970) lowered the $P_{ET}O_2$ from
a level of 16 kPa to 5.3 kPa keeping the $P_{ET}CO_2$ constant at

the levels found at a $P_{ET}O_2$ of 16 kPa. In the present study,
the $P_{ET}CO_2$ was kept constant at the level obtaining in nor-
moxic ventilation with a $P_{ET}O_2$ of about 13 kPa. The small
differences in $P_{ET}CO_2$ which would result from the fact that
there would be depression of hypoxic drive in Weil's studies
with the higher starting $P_{ET}O_2$ would explain the differences
found, since elevation of the $P_{ET}CO_2$ at which the measurement
of 2 is made is known to produce significant increases in
the value for 2 (Weil, Byrne-Quinn, Sodal, Friean, Underhill,
Filley and Grover, 1970).

Similarly, the values for parameter 2 found on exercise
in the present studies are less than those reported by Weil,
Byrne-Quinn, Sodal, Kline, McCullough and Filley (1972).
However, the effect of exercise in the present studies is,
as reported in the above study, to increase the value of
parameter 2. Considerable variability in the values for
parameter 2 was again found, this being most marked in sub-
ject II. Although Hirschman, McCullough and Weil (1975)
have repeated studies on the same subject on as many as
fifteen occasions using this technique, there is no published
information on the reproducibility of parameter 2. The source
of the variability is again open to speculation, but it may
be significant that marked hypoxic depression of ventilation
has been detected in progressive hypoxia studies conducted
over only four minutes (Kronenberg, Hamilton, Gabel, Hickey,
Read and Severinghaus, 1972). It does not seem unreasonable,
therefore, to speculate that an imbalance between stimulation
and depression of ventilation by hypoxia may again be res-

ponsible for this effect.

In the studies reported by Weil and his co-workers, the $P_{ET}O_2$ at which ventilation tended to infinity was fixed at 4.27 kPa for all curve fitting procedures at rest and on exercise. In the current studies the computer was pro- grammed to fit a curve of best fit by least squares regres- sion techniques, without restriction of any of the para- meters. Some support for Weil's curve fitting technique is to be found in the close correspondence of the values for this parameter found in the present studies with the empirical value which he selected.

There is little information available in the literature with which to compare the results of the transient hypoxia studies at rest and on exercise. Lahiri and Edelman (1969) studied one normal subject at rest and demonstrated that, after 3 breaths of N_2 with a minimum $P_{ET}O_2$ of 7.7 kPa, the mean highest breath value was 207% occurring at the fourth or fifth breath; with 5 breaths of nitrogen with a minimal $P_{ET}O_2$ of 3.8 kPa, the mean highest breath value was 264% at the tenth to twelfth breath. The $P_{ET}O_2$ recorded in this one subject and his response are much lower and higher res- pectively than those found in the present study. However, their subject was a respiratory physiologist with an un- usually slow breathing rate. In the same paper, Lahiri and Edelman report studies on three sea level acclimatised high altitude natives. At rest three breaths of N_2 produced a minimal $P_{ET}O_2$ of 9.0 kPa with no ventilatory response and

five breaths of nitrogen produced a minimal $P_{ET}O_2$ of 6.6 kPa with a mean highest breath value of 115%, considerably less than that seen in the normal for a similar minimal $P_{ET}O_2$. The single breath N_2 test of Girard, Teillac, Lefrancois and Lacaisse (1959) produced an average mean highest breath value of 150% for a $P_{ET}O_2$ of 6.3 kPa in normal subjects, which is not too dissimilar to the values for highest breath value and $P_{ET}O_2$ found with seven breaths of nitrogen in the four subjects of this study (Figs. 37-40).

The results of the studies of ventilatory response to transient hypoxia in exercise can also be compared with Lahiri and Edelman's (1969) work at the same level of exercise. Their one normal subject with three breaths of nitrogen had a mean highest breath value of 173% with a minimal $P_{ET}O_2$ of 2.4 kPa. The highlanders, with five breaths of nitrogen had a similar minimal $P_{ET}O_2$ with a mean highest breath value of only 120%. In the present studies only subject III had a moderate ventilatory response on exercise and, although significant increases in ventilation were seen in all subjects with three or four breaths of nitrogen, subjects I, II and IV would certainly have been classified at the lower end of the response range found in the miners' study with three breaths of nitrogen on exercise.

The major problem in interpreting transient hypoxia studies is in relating the ventilatory responses observed to the stimulus level of minimal $P_{ET}O_2$. Conventional $\dot{V}E/PO_2$ plots, with highest breath value plotted against minimal $P_{ET}O_2$, are shown for all four subjects at rest and on

exercise in Figures 37-40. It is not possible to fit a curve to these plots and derive an index of hypoxic drive (as has been done for steady state and progressive hypoxia) because of the large number of insignificant values at the higher 'minimal $P_{ET}O_2$' levels. An alternative analysis has been attempted in Fig. 41 where only the values of ventilatory response obtained at the lower minimal $P_{ET}O_2$s have been used. Here the mean change in ventilation above control is plotted against the stimulus level of minimal $P_{ET}O_2$ for both the rest and exercise studies - the stimulus levels being roughly comparable. In subjects II and III the slope of the line relating the change in ventilation to the $P_{ET}O_2$ is greater on exercise than at rest. Although the $P_{ET}O_2$ range of the exercise measurements is slightly lower than in the rest measurements, this does suggest that the hypoxic drive to breathing is increased in these subjects on exercise. In subjects I and IV, on the other hand, the slope of the $\dot{V}E/P_{ET}O_2$ lines is identical at rest and on exercise, even although the $P_{ET}O_2$ range of the exercise line is lower than that at rest. These two subjects would therefore appear to have no greater hypoxic drive on exercise than at rest when assessed by transient methods. These statements require two qualifications. Firstly, the time course of the fall in $P_{ET}O_2$ differed in the two studies. On exercise, $P_{ET}O_2$ fell rapidly and was low for a shorter period of time than at rest. From what is known of chemoreceptor physiology, a rapid change of $P_{ET}O_2$ would be a greater stimulus to ventilation than a slow fall to the same $P_{ET}O_2$; conversely a

longer period of hypoxia would be a greater stimulus to the
chemoreceptor than a short period. No allowance has been
made in the analysis for the differential effects of these
two factors in the four subjects studied. Secondly, the
fall in $P_{ET}CO_2$, which inevitably occurs with hypoxic hyper-
ventilation, would also have a different time course and
extent in the two studies and might influence chemoreceptor
activity centrally or peripherally. Iso PCO_2 studies would
be necessary to assess the importance of this factor which
may be an important determinant of the ventilatory response
to transient hypoxia particularly on exercise (vide infra).

The ranking of the subjects by the three different
methods of measuring hypoxic drive at rest and on exercise
was remarkably consistent, clearly identifying subject II
as having the lowest and subject III as having the highest
hypoxic drive. One finding is relevant to the discrepancy
between ventilatory responses to transient and steady state
hypoxia observed in the miners' study. Subject IV, who has
an average hypoxic drive when assessed by all other methods,
has a remarkably low ventilatory response to transient hy-
poxia on exercise, whether this is expressed as the mean
highest breath values achieved after three or four breaths
of nitrogen (Table 16) or as the slope of the $\dot{V}E_{inst}/P_{ET}O_2$
relationship (Table 21). This finding in subject IV may be
due to the physiological effects of the lowered $P_{ET}CO_2$ which
results from the hypoxic hyperventilation. The mean maxi-
mal falls in $P_{ET}CO_2$ from the control value for $P_{ET}CO_2$ for
all four subjects following transient hypoxia are shown in

Text Table 5. In subject IV, $P_{ET}CO_2$ fell by 0.26 kPa with three breaths and by 0.35 kPa with four breaths of nitrogen. If these changes in $P_{ET}CO_2$ are considered in the context of the steady state ventilatory response to CO_2 on exercise in this subject, it is possible to construct an explanation for his minimal ventilatory response to transient hypoxia (Fig. 50). With transient hypoxia, ventilation will increase as indicated by the vertical arrow in Fig. 50. However, the resulting fall in $P_{ET}CO_2$ will tend to lower ventilation (by an action at the carotid body) as indicated by the oblique arrow in Fig. 50. The overall effect will be determined by the configuration of the CO_2 response lines on exercise; in subject IV, the configuration is such that even this small fall in $P_{ET}CO_2$ will effectively "abort" the ventilatory response to transient hypoxia. In subject III, on the other hand, whose response is analysed in a similar way in Fig. 49, even greater falls in $P_{ET}CO_2$ would not produce the same degree of limitation of the ventilatory response to transient hypoxia, for the effect of exercise on the CO_2 response lines in this subject is quite different to that found in subject IV. Similar analyses for subjects I and II (Figs. 47 and 48) indicate, as was the case, that their transient response might also be limited by hypocapnia of the degree found in their transient hypoxia studies on exercise (Text Table 5).

These considerations must remain largely speculative for they are based on hypoxic exercise CO_2 response lines measured at a $P_{ET}O_2$ of 6.7 kPa whereas the $P_{ET}O_2$ fell to

TEXT TABLE 5

To show the mean control $P_{ET}CO_2$s (± SD) prior to inhalation of 3 or 4 breaths of nitrogen on exercise in subjects I-IV. The mean lowest PETCO2 occurring in the five breaths following the switch to nitrogen is also shown with the calculated differences from the control value.

Subject	Three breaths N_2			Four breaths N_2		
	Control $P_{ET}CO_2$	Lowest $P_{ET}CO_2$	Difference	Control $P_{ET}CO_2$	Lowest $P_{ET}CO_2$	Difference
	(kPa)	(kPa)	(kPa)	(kPa)	(kPa)	(kPa)
I	5.27 ± 0.10	4.96	0.31	5.29 ± 0.10	4.79	0.50
II	4.81 ± 0.10	4.66	0.15	4.86 ± 0.11	4.51	0.35
III	5.58 ± 0.09	5.16	0.42	5.53 ± 0.10	4.83	0.70
IV	5.13 ± 0.13	4.87	0.26	5.31 ± 0.12	4.96	0.37

lower levels in the transient hypoxia studies. It would be
dangerous to measure hypoxic CO_2 response lines at a lower
$P_{ET}O_2$ on exercise but, from the observations made on the
available data, it is possible to propose a hypothesis
which explains why a subject, who apparently has an intact
hypoxic drive when this is measured at rest and on exercise
by five other methods, falls at the lower end of a measured
range of hypoxic drive (the miners' study) when transient
hypoxia on exercise is used to measure his hypoxic drive.

The hypothesis is that transient hypoxia on exer-
cise will increase ventilation and lower PCO_2 in subjects
with an intact hypoxic drive. The extent of this increase
in ventilation will be determined by the effect of exer-
cise on the ventilatory response to CO_2 in hyperoxia and
hypoxia in individual subjects, for the fall in PCO_2 will
tend to limit ventilation by diminishing carotid body ac-
tivity. Where the configuration of the hypoxic and hypero-
xic CO_2 response lines is such that both the hypoxic inter-
cept and slope are greater than the hyperoxic (as in sub-
ject IV), the hypocapnia may substantially limit the ven-
tilatory response; where the hypoxic intercept is lower
than the hyperoxic and the hypoxic slope is similar to or
less than the hyperoxic (as in subject III), the effect of
the hypocapnia on ventilatory response will be much less
marked. This effect is most likely to be mediated by the
peripheral chemoreceptors, for the time course of events is
too rapid to implicate the central chemoreceptors. The
effect implies a reduction in the multiplicative interaction

of CO_2 excess and oxygen lack in the carotid bodies. Since
a significant increase in ventilation following three breaths
of nitrogen is usually observed by the time of the second
or third breath of nitrogen, the resultant hypocapnia
(Fig. 51) would be capable of influencing carotid body
activity by the fourth or fifth breath or possibly earlier,
although the minimal PCO_2 would not reach the carotid body
until later. It is, therefore, possible that hypocapnia
could influence ventilation at the time when it is rising
to its maximum which was, on average, in the four subjects
of the present study, at the fifth breath (Table 16). A
similar time course of ventilatory response has been ob-
served in hypoxic, hypercapnic subjects at rest when CO_2
is withdrawn from the inspired air (Miller, Cunningham,
Lloyd and Young, 1974). In Miller et al's study, the sig-
nificant falls in breath by breath ventilation were observed
by the second or third breath after CO_2 had been removed
from the inspired gas. There are no data in the present
study on the lung to carotid body circulation time but,
since the studies were performed on exercise, the circulation
time is unlikely to have been greater than in their study.
It would seem therefore that the recorded fall in $P_{ET}CO_2$
in the present studies could exert a significant effect on
the carotid chemoreceptor and hence the ventilatory res-
ponse to transient hypoxia in the manner described above.

Some support for this hypothesis is to be found in the
studies of ventilatory response to exercise in these four
subjects (Tables 33-35 and Fig. 46). When $P_{ET}CO_2$ was allowed
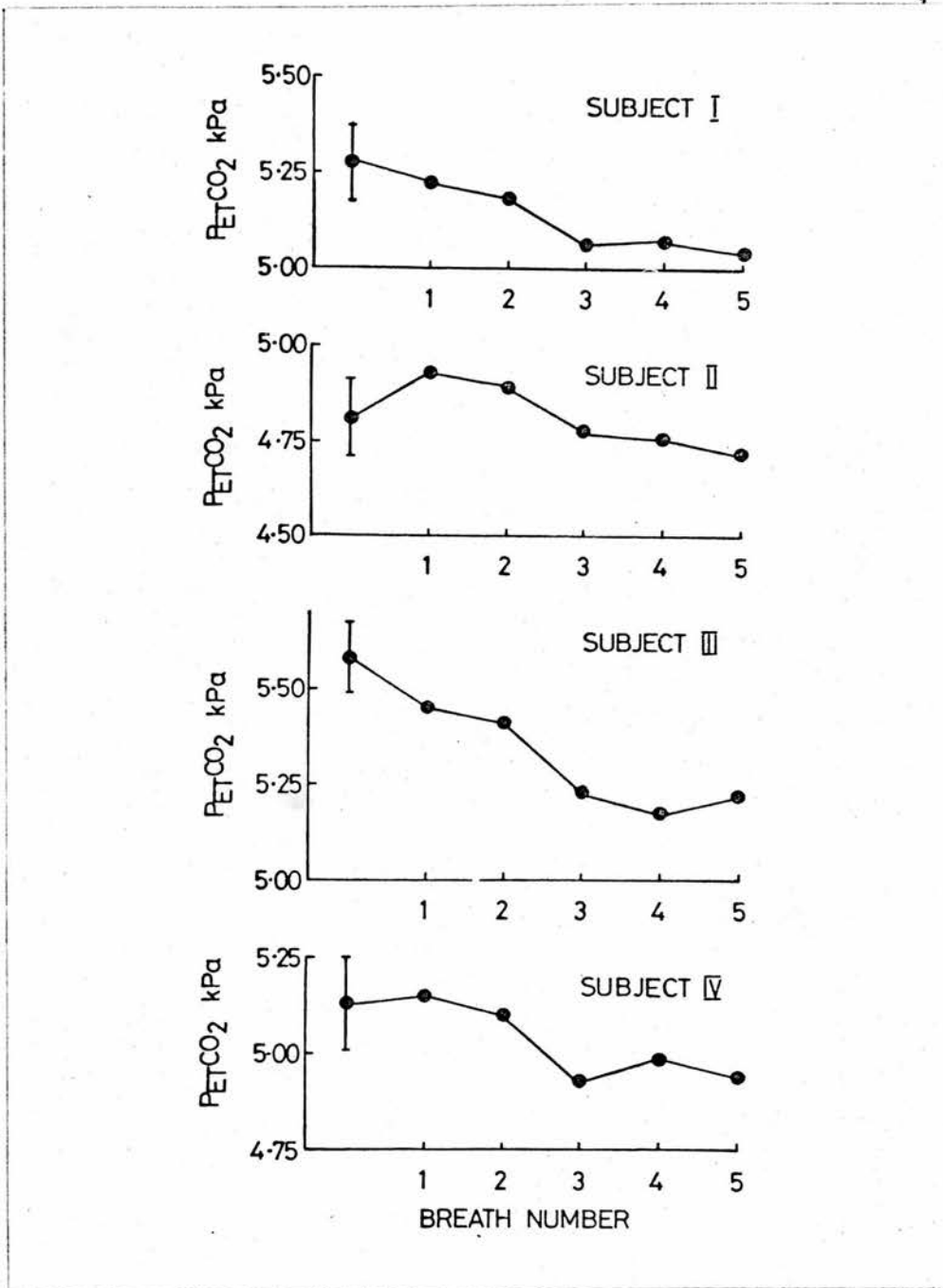
FIGURE 51   The mean breath by breath $P_{ET}CO_2$s in subjects
I–IV derived from 6 studies in which three
breaths of nitrogen were administered to each
subject on exercise. The control PCO_2 is
shown ± 1SD. Breaths 1–3 were the breaths of
nitrogen.

to fall in hypoxic exercise (by amounts not dissimilar to the fall in $P_{ET}CO_2$ following transient hypoxia (Table 33)), the $\dot{V}E/\dot{V}O_2$ relationship only increased by 5 and 6% in subjects II and IV whereas it increased by 12 and 14% respectively in subjects III and I. However, when $P_{ET}CO_2$ was maintained constant in hypoxic exercise, more striking increases in the $\dot{V}E/\dot{V}O_2$ relationship were seen, ranging from 23 - 74% (Table 35), which bore a close relationship to the overall ranking of these subjects on the basis of all the texts of hypoxic drive (Tables 31 and 32). Subjects II and IV were the subjects with less reduction of hypoxic than hyperoxic intercept in the steady state CO_2 response studies on exercise. It seems likely that they were therefore more sensitive to the fall in $P_{ET}CO_2$ induced by hypoxia during exercise for such a fall would act in a similar way to that described in Figs. 47-50 to limit the hyperventilation. Holding $P_{ET}CO_2$ constant allowed the full expression of each subject's hypoxic drive on exercise without the restraints imposed by hypocapnia.

The effect of lowering $P_{ET}CO_2$ on the ventilatory response to transient hypoxia has already been seen in the miners' study where subject 43, who hyperventilated markedly, had no significant ventilatory response. The findings in the present study suggest that there may be individuals with an intact hypoxic drive using conventional methods who, by virtue of the effect of exercise on their steady state hypoxic and hyperoxic CO_2 response curves, have a limited ventilatory response to transient hypoxia on exercise. This

limitation of response is due to the lowering of $P_{ET}CO_2$ consequent on the initial ventilatory response, the fall in PCO_2 restricting, by a carotid body-mediated mechanism, any further ventilatory response. Such individuals would have an intact hypoxic drive when assessed by methods where PCO_2 does not fall, such as isocapnic progressive hypoxia or the steady state ventilatory response to CO_2, either at rest or on exercise. The response to transient hypoxia at rest need not be diminished in such subjects for it is the effect of exercise on the steady state ventilatory responses to CO_2 and hypoxia which is responsible for the limitation of the ventilatory response.

The findings of the present study can be summarised as follows:

1. In general, agreement between measurement of hypoxic drive by transient, progressive and steady state hypoxia at rest and on exercise is good. A single measurement of hypoxic drive using any method is not reliable, and the reproducibility of findings with any one method in any one subject is such that the good agreement between methods mentioned can only be attributed to repeated studies of individual subjects with each method, so that a mean index of hypoxic drive could be obtained for each method.

2. Low values for the ventilatory response to transient hypoxia on exercise in one subject in particular, who appeared to have an intact hypoxic drive when assessed

by other methods at rest and on exercise, can be explained by the effect of exercise on the steady state ventilatory response to CO_2 in hypoxia and hyperoxia in this subject.

CHAPTER 9   THE EFFECT OF CERTAIN DRUGS ON THE STEADY
            STATE VENTILATORY RESPONSE TO INHALED CO_2
            IN HYPOXIA AND HYPEROXIA : INTRODUCTION,
            METHODS AND RESULTS

INTRODUCTION

A number of drugs are known to influence the chemical
control of breathing (Lambertsen, 1964) but the studies to
be reported here are particularly concerned with drugs which
are commonly used in the management of patients with severe
reversible or irreversible obstructive airways disease,
respiratory failure and cor pulmonale. Two separate studies
are reported, concerned with frusemide and bendrofluazide,
the two diuretics most commonly used in patients with cor
pulmonale, and salbutamol, a β_2 adrenergic drug used for
its bronchodilator effect in chronic bronchitis and in asthma.

1.   Frusemide and Bendrofluazide

Both of these diuretic drugs produce a metabolic alka-
losis (Goodman and Gilman, 1965). Some workers (Alexander,
West, Wood and Richards, 1955; Fencl, Muller and Pappenheimer,
1966; Goldring, Cannon, Heinemann and Fishman, 1968; Tunis,
Goldring and Heinemann, 1969; Iff and Flenley, 1972) have
shown that changes in the control of ventilation as assessed
by the ventilatory response to CO_2, can follow in metabolic
alkalosis, while others have been unable to confirm this
(Roberts, Poppell, Vanamee, Beak and Randall, 1956; Stone,
1962). Iff and Flenley (1972) showed that frusemide could
cause hypoventilation with a rise in end tidal CO_2 tension
and an increase in the intercept of the ventilation / PCO_2
response line at high oxygen tensions in normal man. Goldring

et al (1968) had already shown that thiazide diuretics
did not produce hypoventilation in metabolic alkalosis
leading Iff and Flenley (1972) to recommend the thiazide
diuretics as the treatment of choice for domiciliary treat-
ment of cor pulmonale. However, the studies of Goldring
et al (1968) and Iff and Flenley (1972) were made at normal
or raised oxygen tensions. Since patients with cor pulmo-
nale are universally hypoxic, the present study was designed
to assess the effects of bendrofluazide and frusemide on
the ventilatory response to CO_2 during both hypoxia and hy-
peroxia in normal subjects.

2. Salbutamol

The mechanism by which catecholamines stimulate venti-
lation in animals (Young, 1957) and man (Whelan and Young,
1953; Heistad, Wheeler, Mark, Schmid and Abboud, 1972;
Stone, Keltz, Sarkar and Singzon, 1973) is still imperfectly
understood. Noradrenaline has been shown to stimulate ven-
tilation in the cat by an action which is dependent on the
integrity of the peripheral chemoreceptors (Joels and White,
1968). In man, it is known that the potentiating effect
of noradrenaline on the ventilatory response to inhaled CO_2
is dependent on the presence of hypoxia (Cunningham, Hey,
Patrick and Lloyd, 1963; Cunningham, Lloyd and Patrick,
1963) suggesting a similar mechanism. Salbutamol is an
adrenergic agent which differs from noradrenaline in that
its activity is restricted to β receptors (Hartley, Jack,
Lunts and Ritchie, 1968) whereas noradrenaline is predomi-

nantly an $\propto$ adrenergic agent with weak β activity. Although
salbutamol is used clinically for its bronchodilator effect,
it is used in patients with asthma and chronic bronchitis
who already have disturbances in the control of breathing
(Flenley, Franklin and Miller, 1970; Rebuck and Read, 1971)
and effects of this drug on the control of breathing could
be clinically important. β receptors have been implicated
in the respiratory response to both noradrenaline and iso-
prenaline in hypoxia (Heistad, Wheeler, Mark, Schmid and
Abboud, 1972) and the present study was designed to study
the effect of salbutamol on the chemical control of venti-
lation in normal man in hypoxia and hyperoxia using the
steady state ventilatory response to CO_2.

The effect of the drug on heart rate and the plasma
urea and electrolytes was also measured, these results then
leading to further studies in which the serum insulin and
plasma glucose were measured.

METHODS

The breathing assembly used was the same assembly
described in Chapter 4 and the order and timing of admini-
stration of the different gas mixtures was identical. Venti-
lation was measured over three minute intervals in the
steady state using the Parkinson-Cowan CD4 gas meter.
$P_{ET}O_2$ and $P_{ET}CO_2$ were sampled as before using the Varian
M3 mass spectrometer. Recording of the analogue trace for
$P_{ET}O_2$ and $P_{ET}CO_2$ was made on an Elema-Schonander Mingograph
running at a speed of 25 mm.sec^{-1}. The mass spectrometer

was previously calibrated with gases analysed on the Lloyd-
Haldane apparatus so that 7.5 mm on the paper corresponded
to 1 kPa PCO_2 and to 2 kPa PO_2. Control of PO_2 during the
experiment was achieved by reference to the PO_2 meter on
the mass spectrometer where the position of the selected
low end tidal PO_2 of 6.7 kPa had been marked. The end tidal
values for PO_2 and PCO_2 for the 3 minute periods during
which steady state ventilation was measured were determined
by drawing a straight line by eye through the highest points
of the alveolar plateaux for that three minute period. All
lines were drawn by the same observer and measurement of
end tidal PCO_2 by this method was considered to be accurate
to ± 0.07 kPa and that of end tidal PO_2 by ± 0.14 kPa.

SUBJECTS

The subjects for the diuretic experiments were eight
healthy male doctors aged 27-32 years whose height and
weight are shown in Table 36.

The subjects for the salbutamol experiments were seven
healthy male doctors aged 25-35, whose heights and weights
are given in Table 37. Some subjects participated in both
series of experiments and all gave informed consent.

DESIGN OF EXPERIMENTS

Frusemide and Bendrofluazide

Each subject had studies with both diuretics, the order
being randomly allocated, with an interval of at least three
weeks separating the two studies. The subjects took either
frusemide 0.242 mmol (80 mg) or bendrofluazide 0.024 mmol

(10 mg) orally without potassium supplements at 1800 hours on each of four successive days. The isoxic steady state ventilatory response to CO_2 was determined between 1600 and 1800 hours on the first day at an end tidal PO_2 of 6.7 kPa (SEM 0.07 kPa, n = 64) and 29.3 - 33.3 kPa on the first day before taking the drug and again on the fifth day after taking the drug for four days. Plasma urea and electrolytes were measured in venous samples drawn on the first and fifth days immediately before the respiratory studies were performed.

Salbutamol

The isoxic steady state ventilatory response to inhaled CO_2 at an end tidal PO_2 of 6.55 kPa (SEM 0.05 kPa, n = 28) and at a PO_2 of 29.3 - 33.3 kPa was determined 10 minutes after the start of an infusion of either salbutamol 10 µg. min^{-1} or a similar volume of 0.9% saline (40 ml). Studies on each subject were always separated by at least one week. Plasma urea, electrolytes and total CO_2 content were measured in venous samples drawn without stasis immediately before and after the infusion.

As a result of the changes detected in plasma potassium during the main part of the study, three of the subjects were restudied in the fasting state during the infusion of salbutamol at a dose of 10 µg.min^{-1} for one hour while they were breathing air.

The venous plasma potassium, plasma glucose and serum insulin were measured at 10 minute intervals during and after the infusion. The serum insulin was assayed by a

double antibody technique (Hales and Randle, 1963) using
the reagents in the radioimmunoassay kit supplied by the
Radiochemical Centre, Amersham, Bucks.

In one fasting subject potassium excretion in the urine
and venous plasma potassium were also measured, following a
water load at 20 minute intervals before, during and after
an infusion of salbutamol in a dose of 10 μg.min^{-1} while
the subject was breathing air.

RESULTS

Frusemide

a)   Effect of administration of frusemide (0.242 mmol
      (80 mg)) daily for 4 days

Paired comparisons of control and experimental values
in each subject (Table 38) showed the plasma potassium and
chloride values to be significantly decreased (P<0.05) and
the plasma urea significantly increased (P<0.05) by fruse-
mide.   However, the rises in plasma total CO_2 content (P<0.1)
and $P_{ET}CO_2$ (P<0.5) were both insignificant.   Frusemide pro-
duced no significant change in the slope (S) or the inter-
cept (B) of the CO_2 response lines obtained during either
hypoxia or hyperoxia (Table 38, Figs. 52 and 53).

b)   Effect of administration of bendrofluazide (0.024 mmol
      (10 mg)) daily for 4 days

Similar paired comparisons (Table 39) showed a signifi-
cant decrease in plasma potassium (P<0.01) and chloride
(P<0.01) with a significant increase in both plasma urea
and total plasma CO_2 (P<0.01).   There was an insignificant
rise in $P_{ET}CO_2$ when breathing air, and also no significant
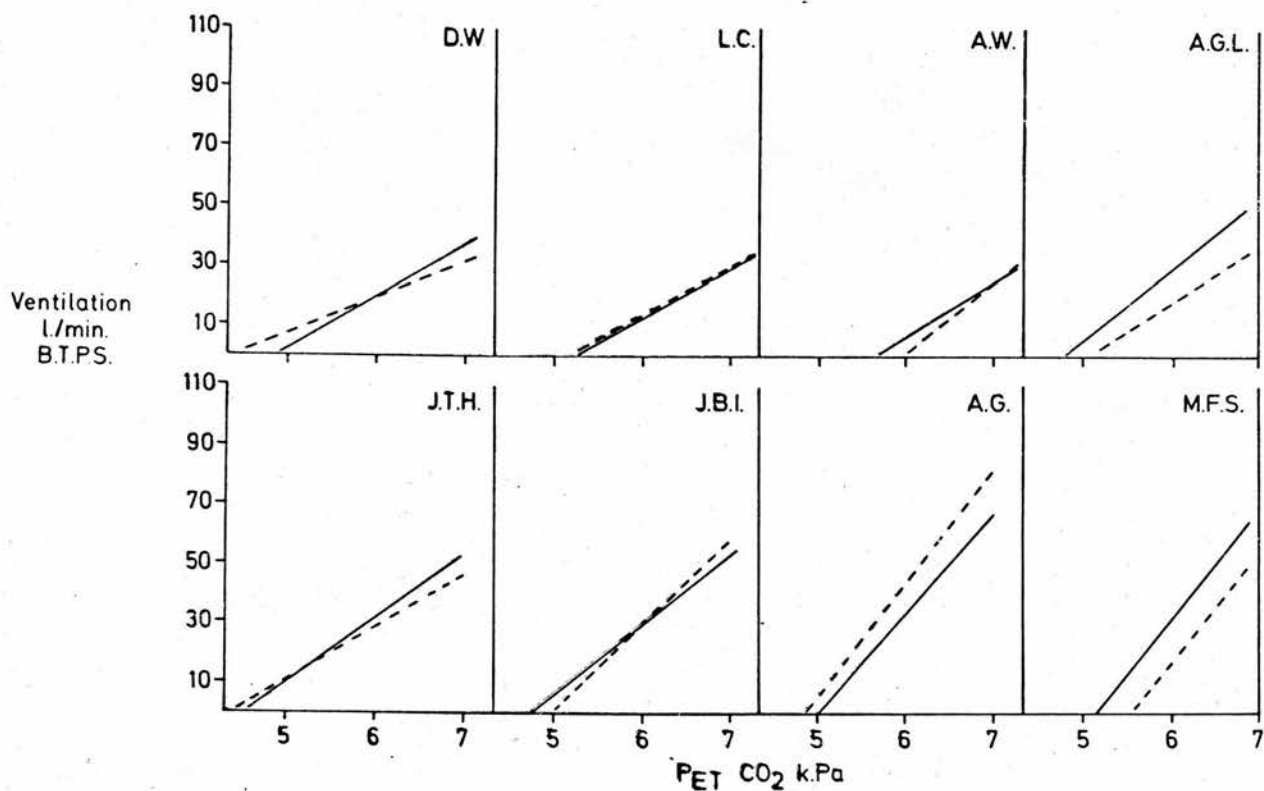
FIGURE 52 CO_2 response lines at an end tidal PO_2 of
            29.3 - 33.3 kPa in eight subjects before
            (————) and after (--------) 0.242 mmol.
            (80 mg) of frusemide daily for four days.
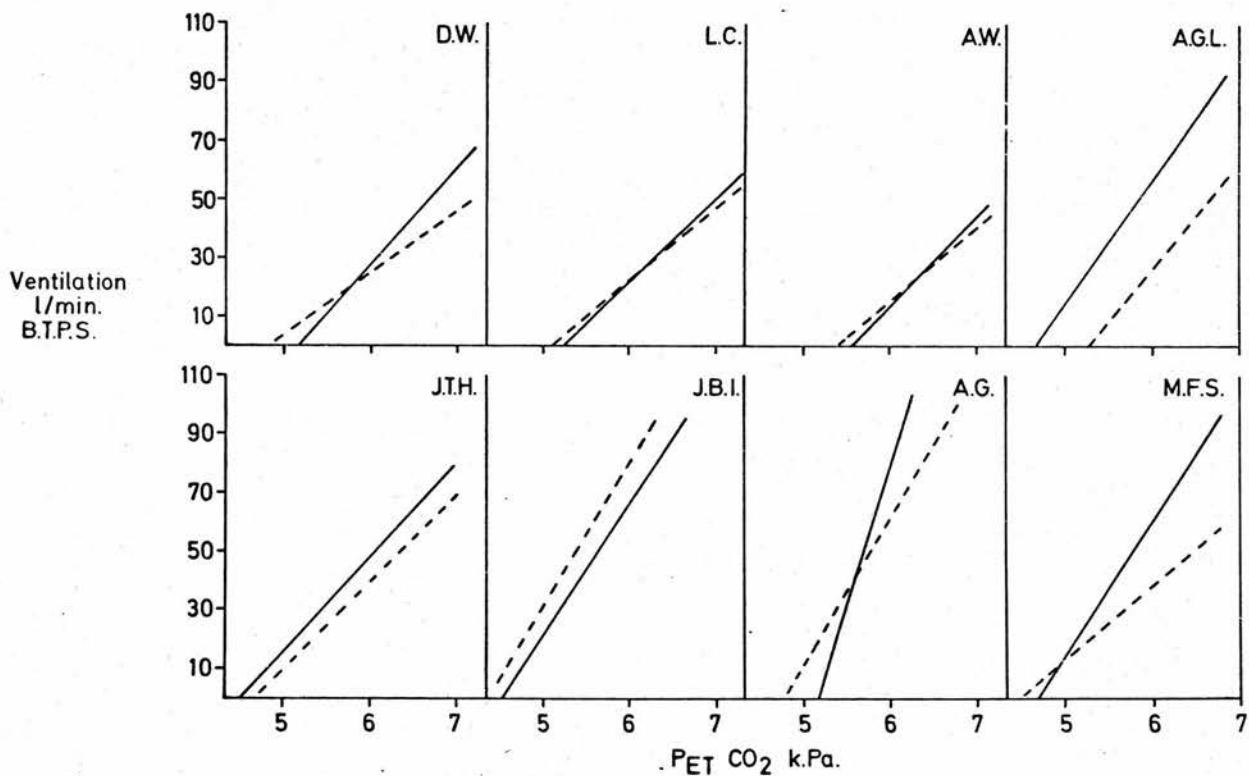
FIGURE 53   CO2 response lines at an end tidal PO2 of
6.7 kPa in eight subjects before (————)
and after (--------) 0.242 mmol (80 mg) of
frusemide daily for four days.

change in the intercept of the CO_2 response line (B) during hyperoxia. However, there was a significant decrease in the slope (S) of the CO_2 response line during hyperoxia (P<0.01) (Table 39 and Fig. 54). During hypoxia, bendrofluazide produced a significant increase in the intercept of the CO_2 response line (P<0.05) but, although the mean value of the slopes of the line was reduced, there was no significant difference on paired t-testing (P<0.1) (Table 39 and Fig. 55).

Salbutamol

a) <u>Ventilatory response to CO_2 and hypoxia</u>

The CO_2 response lines in hypoxia and hyperoxia during the control and salbutamol infusions are shown for all seven subjects in Figs. 56 and 57. The slope of the line increased in all seven subjects with no significant change in intercept in both hypoxia and hyperoxia. The mean increase in slope was 48% in hyperoxia and 44% in hypoxia (Fig. 58 and Table 40) with the former increase being significant at the 5% level on paired t-testing.

b) <u>Plasma biochemistry</u>

The control infusion produced no significant changes in the plasma urea, Na^+, K^+, or total CO_2 content in the five subjects in whom measurements were made. The salbutamol infusion had no effect on plasma Na^+ or total CO_2 content (Table 41) but did produce a highly significant fall in the plasma potassium from a mean value of 3.99 $mmol.\ell^{-1}$ to a mean value of 3.10 $mmol.\ell^{-1}$.
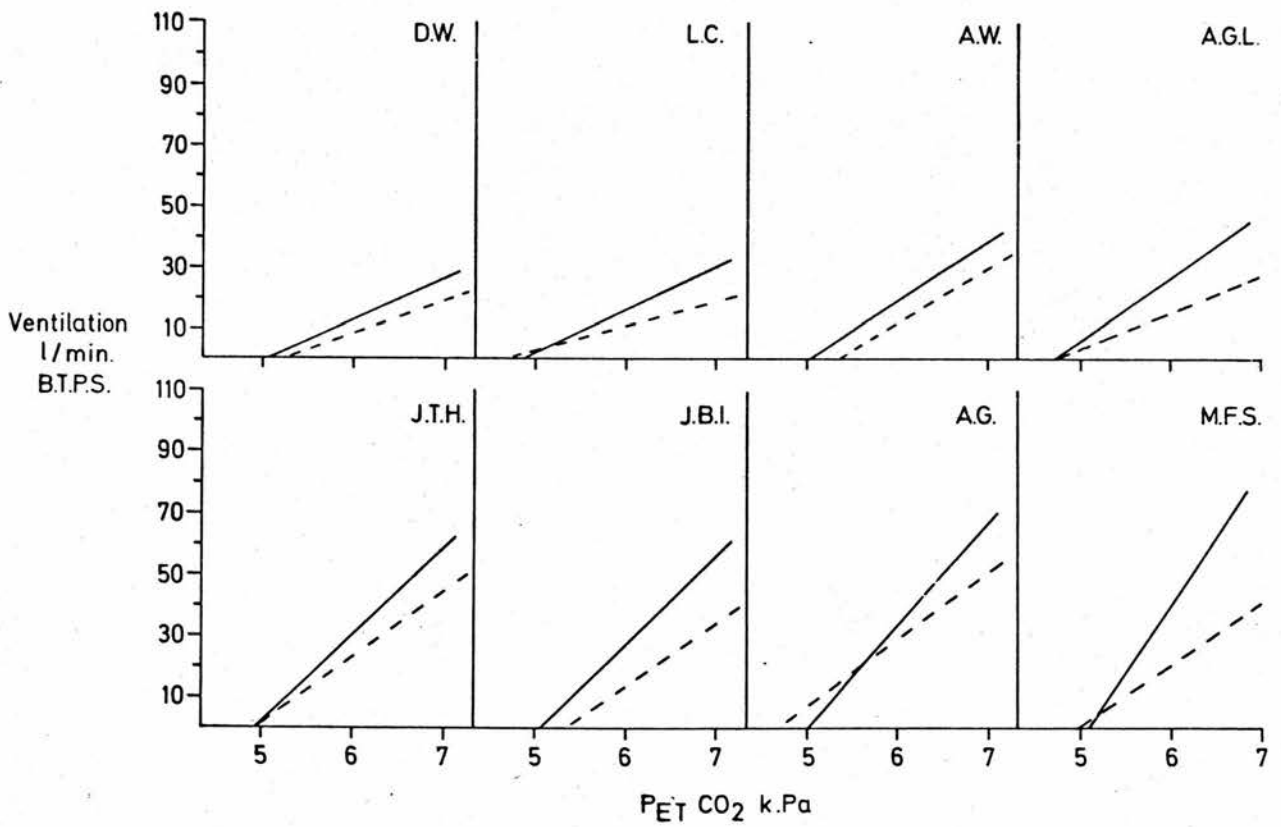
FIGURE 54 CO_2 response lines at an end tidal PO_2 of 29.3 - 33.3 kPa in eight subjects before (————) and after (-------) 0.024 mmol (10 mg) of bendrofluazide daily for four days.
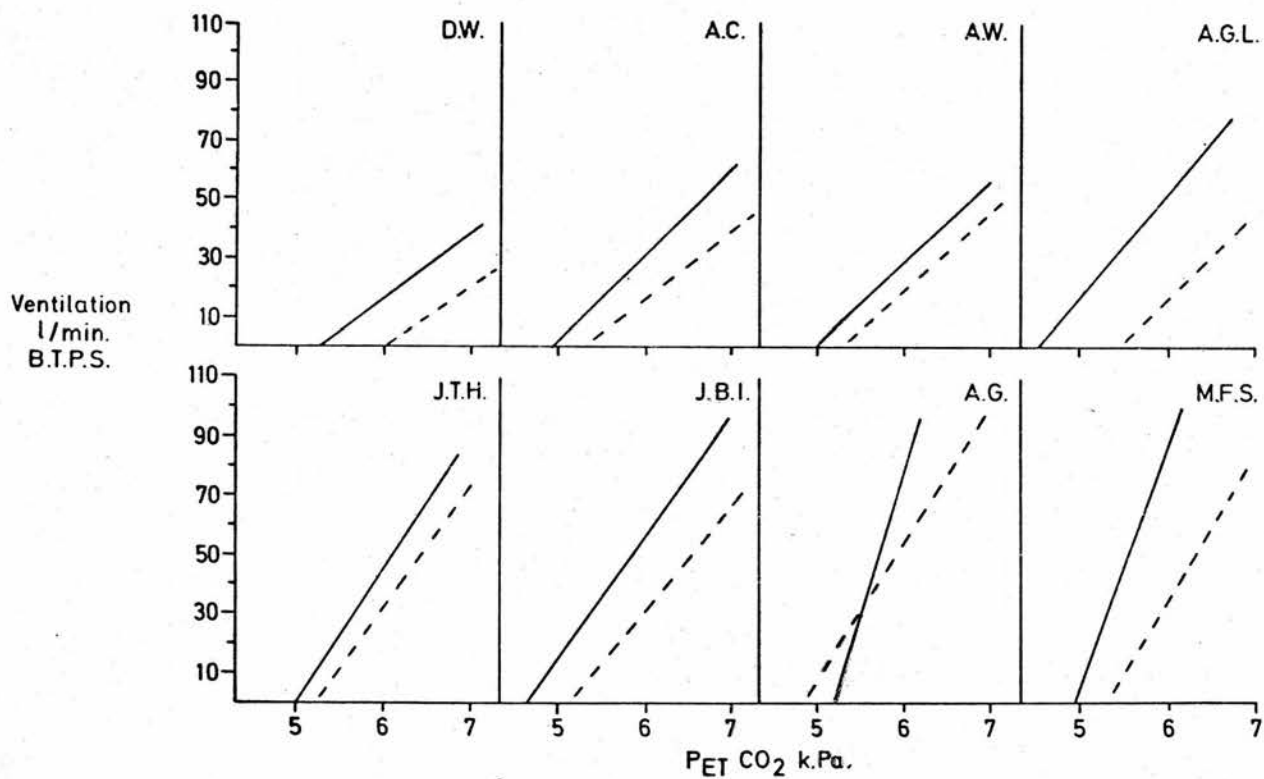
FIGURE 55   CO$_2$ response lines at an end tidal PO$_2$ of
6.7 kPa in eight subjects before (————)
and after (-------) 0.024 mmol (10 mg) of
bendrofluazide daily for four days.
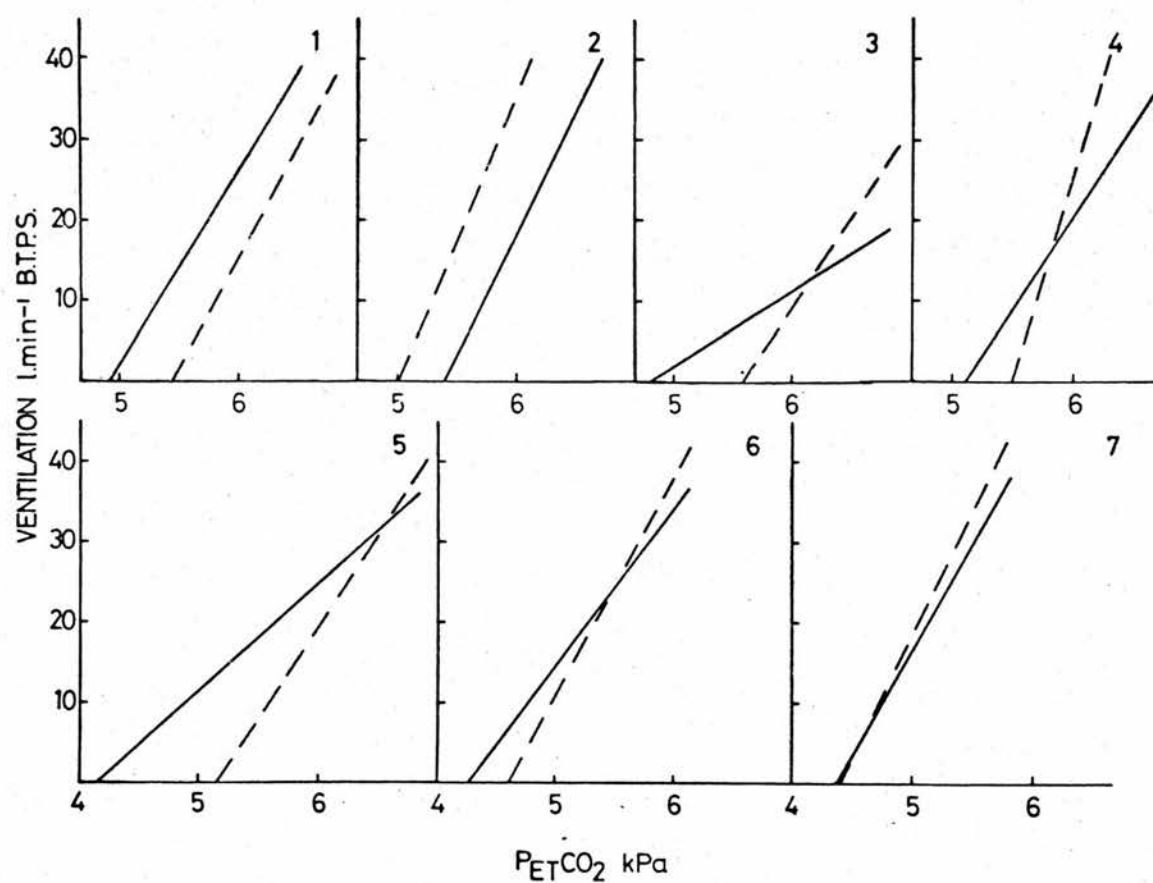
FIGURE 56 CO_2 response lines in seven subjects at an
end tidal PO_2 of 29 - 33 kPa during intra-
venous infusion of normal saline (————)
or salbutamol 10 $\mu g.min^{-1}$ (-------)
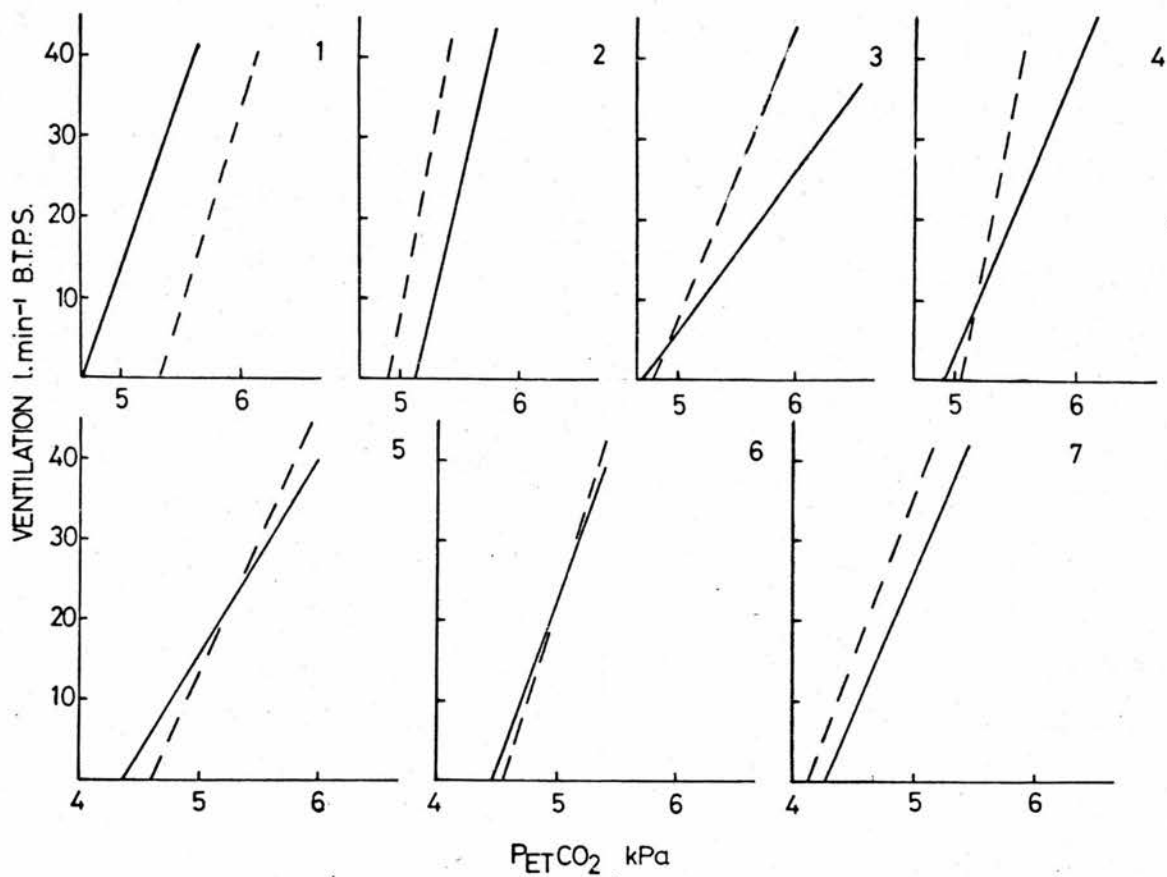
FIGURE 57 CO_2 response lines in seven subjects at an
end tidal PO_2 of 6.7 kPa during intravenous
infusion of normal saline (————) or sal-
butamol 10 $\mu g.min^{-1}$ (-------).
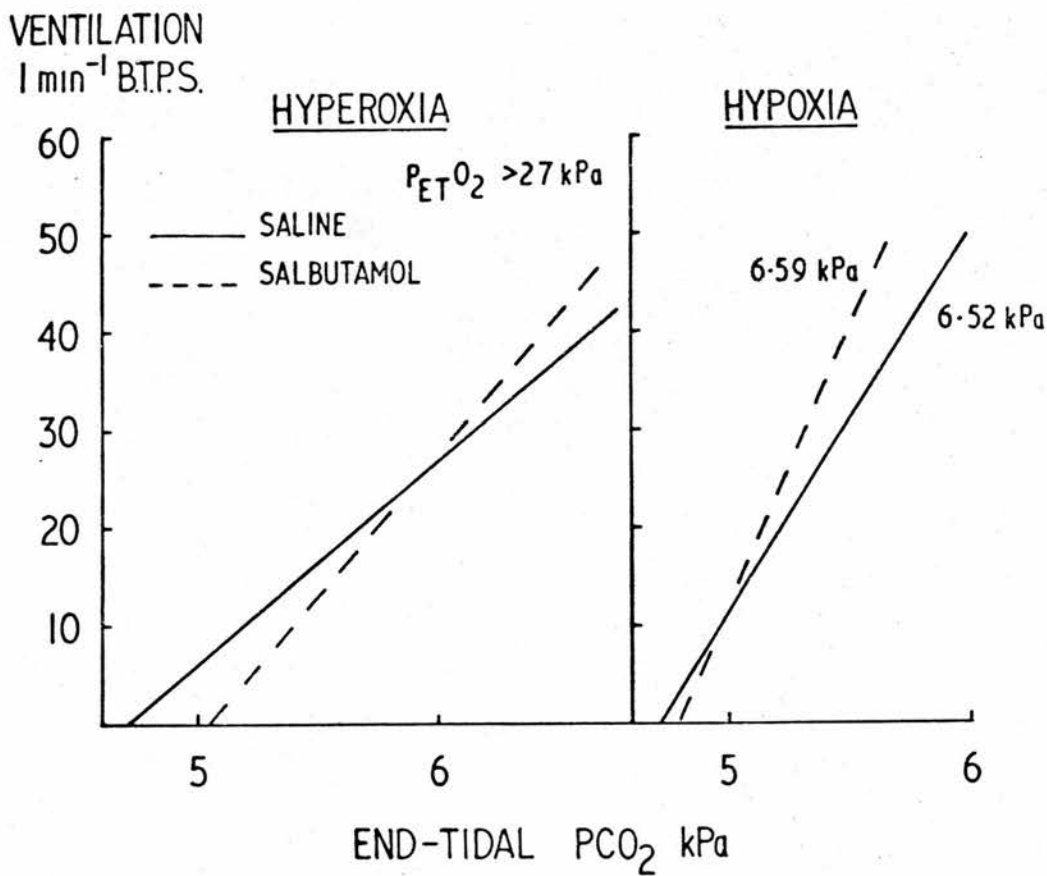
FIGURE 58   Mean CO_2 response lines at end tidal PO_2s of
             > 27 kPa and $\sim$ 6.7 kPa during intravenous in-
             fusion of normal saline (————) or salbutamol
             10 $\mu g.min^{-1}$ (-------).

c)   Heart rate (Table 40)

The drug produced marked increases in heart rate rang-
ing from 25% when the subjects were breathing air to a mean
increase of 50% in combined hypoxia and hypercapnia. For
a given inspired CO_2 concentration the heart rate was sig-
nificantly higher ($P<0.05$) in hypoxia than in hyperoxia.

d)   Plasma potassium, glucose and serum insulin (Fig. 59)

In the three subjects studied plasma potassium fell
progressively after the start of the infusion and began to
return towards normal within 30 minutes of stopping the in-
fusion.

The fall in plasma potassium was associated with in-
creases in plasma glucose and insulin which also returned
towards normal after the end of the infusion.

e)   Urinary excretion of potassium (Fig. 60)

There was a fall in total urinary potassium excretion
during the salbutamol infusion which was closely associated
with the fall in plasma potassium in the one subject studied.
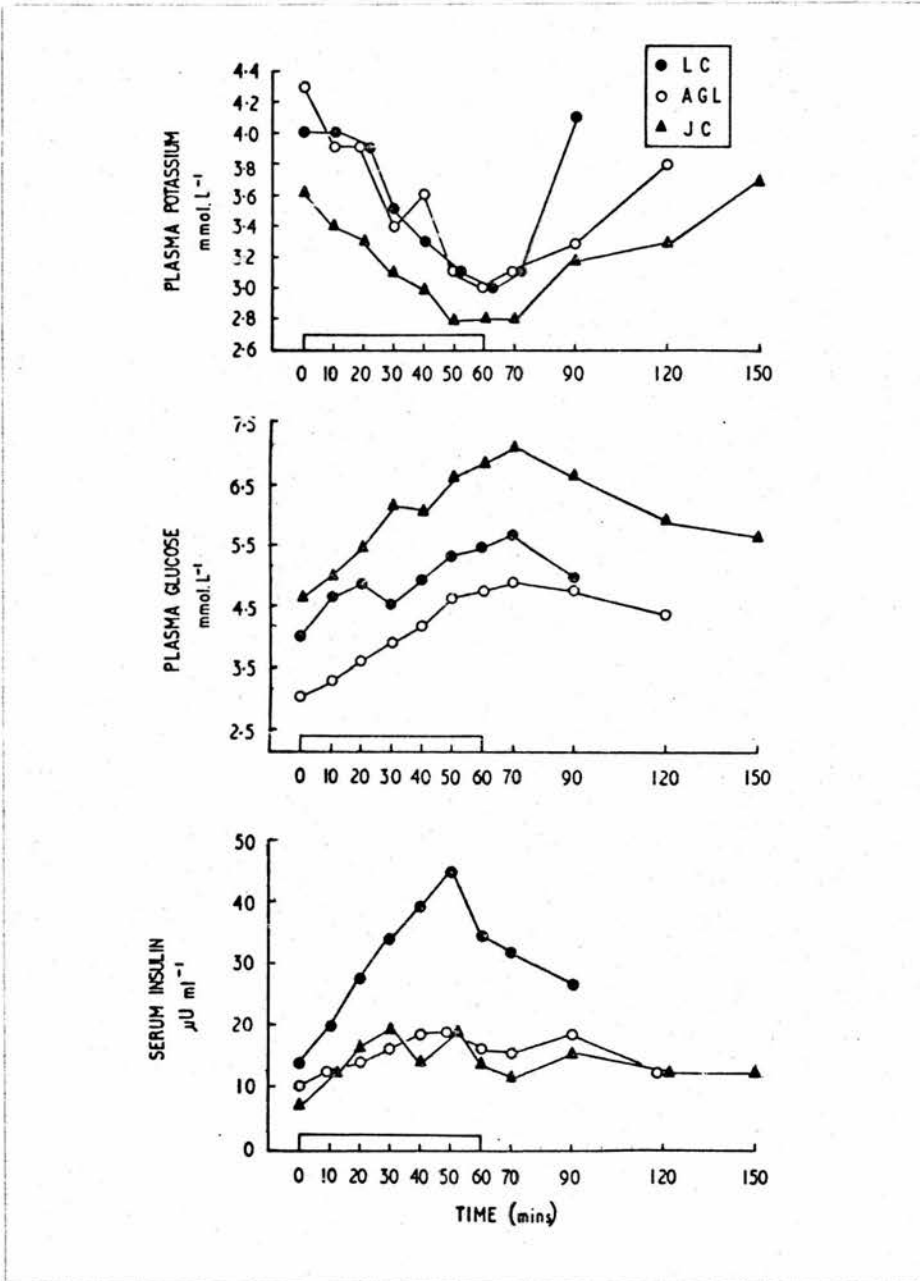
FIGURE 59   Levels of plasma potassium, plasma glucose and
serum insulin during and after intravenous in-
fusion of salbutamol 10 μg.min^{-1}.
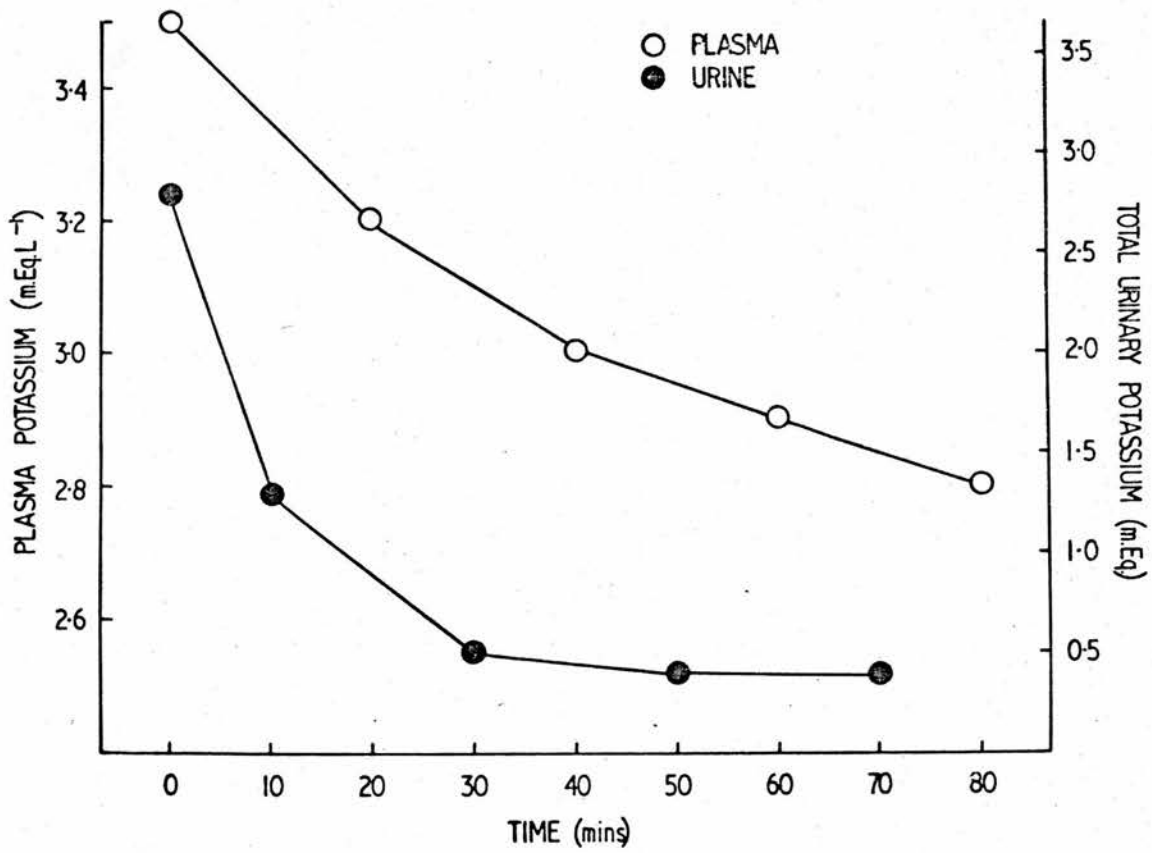
<u>FIGURE 60</u>   Total urinary potassium and plasma potassium
          measured at 20 minute intervals during and
          after intravenous salbutamol 10 μg.min^{-1} in
          one man (AGL).

CHAPTER 10   <u>DRUGS AND VENTILATORY RESPONSE TO CO_2 :</u>
            <u>DISCUSSION</u>

<u>Frusemide and Bendrofluazide</u>

Frusemide had no significant effect on either end
tidal CO_2 tensions ($P_{ET}CO_2$), the intercept (B) or the slope
of the CO_2 response line (Table 37, Figs. 52 and 53) when
the subjects were breathing hypoxic or hyperoxic gas mix-
tures. This result differs from the findings of an earlier
study (Iff and Flenley, 1972) when the $P_{ET}CO_2$ and the inter-
cept of the CO_2 response line were both increased after
frusemide, with the production of a metabolic alkalosis.
However, the metabolic alkalosis encountered in the present
study was less than that found in Iff and Flenley's study.
The absence of significant overall alkalosis on this occa-
sion is probably related to the constant dose of the drug
employed, for if the two heaviest subjects (85 and 95 kg)
are excluded from the analysis, the plasma total CO_2 after
the drug was significantly higher than that before the drug
on paired t-testing in the remaining six subjects (P<0.01).
Further, if the change in plasma total CO_2 is plotted against
the change in intercept of the CO_2 response line incorporat-
ing results from both this and the previous study (Iff and
Flenley, 1972), a significant linear relationship is then
established (Fig. 61).

The shift in intercept of the CO_2 response line after
frusemide therapy (Iff and Flenley, 1972) is probably due
to a rise in cerebrospinal fluid bicarbonate concentration
(CSF HCO_3^-) and fall in hydrogen ion concentration (H^+).
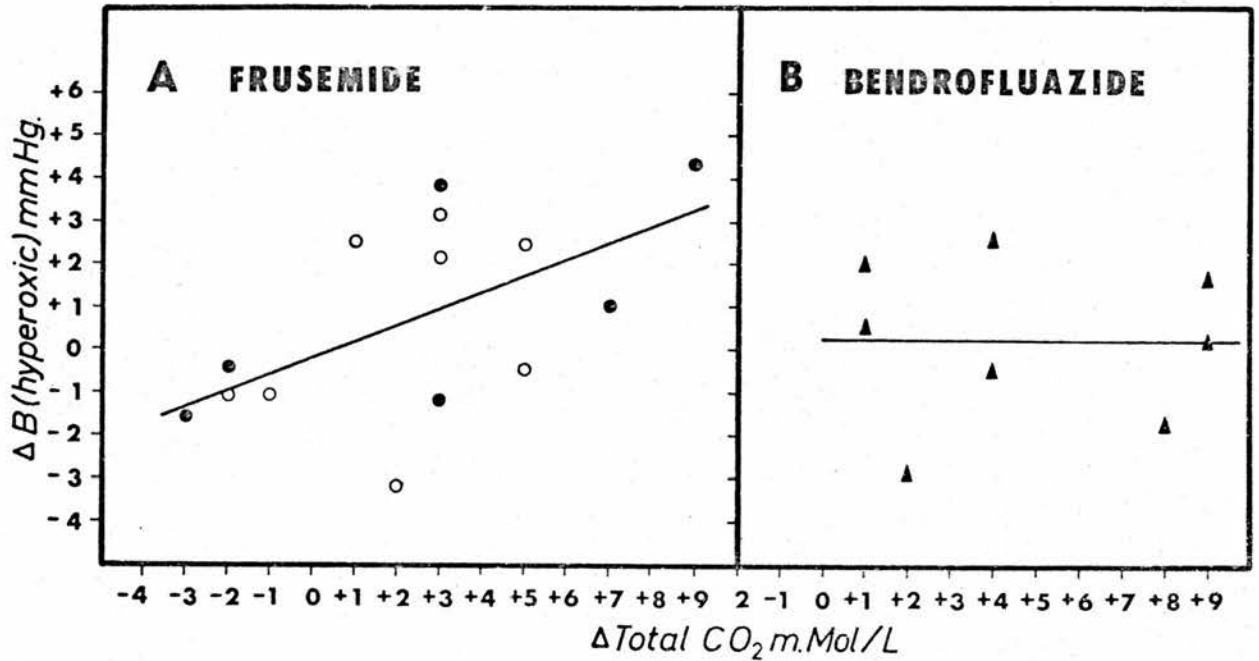
FIGURE 61   Change in the intercept of the CO_2 response
line in hyperoxia (BCO_2) and plasma total CO_2
after   a)   frusemide 0.242 mmol (80 mg) orally
for four days in the subjects of the present
(O) and previous (●) studies (Iff and Flenley
1972) (B = 0.37 CO_2 - 0.18, n = 14, r = 0.5697,
P = 0.05 > 0.02), and   b)   bendrofluazide,
0.024 mmol (10 mg) orally for four days in the
eight subjects of the present study (B = 0.005
CO_2+ 0.261, n = 8, r = 0.0093, P>0.1)

Such changes in CSF are known to shift the intercept to the right, presumably by an action on the central chemo-receptors (Fencl, Muller and Pappenheimer, 1966; Fencl, Vale and Brock, 1969). Although previous studies in man (Bradley and Semple, 1962; Mitchell, Carman, Severinghaus, Richardson, Singer and Schnider, 1965) have suggested that CSF H^+ is remarkably stable, it now seems from studies in rats (Ponten and Siesjo, 1967), goats (Fencl et al, 1966) and man (Fencl et al, 1969) that the H^+ and HCO_3^- of CSF follow changes in the plasma H^+ and HCO_3^- in chronic meta-bolic alkalosis. Case reports (Lifschitz, Brash, Cuomo and Mann, 1972; Oliva, 1972) have confirmed that alveolar hypoventilation can arise in severe metabolic alkalosis, but only when the CSF HCO_3^- concentration is markedly raised. It now appears that even a mild metabolic alkalosis pro-duced by frusemide therapy may cause alveolar hypoventila-tion, as shown by a rise in $P_{ET}CO_2$ and an appropriate shift to the right of the intercept of the CO_2 response line (Iff and Flenley, 1972).

The results after bendrofluazide were surprising and may be summarised as an increase in the intercept of the CO_2 response line in hypoxia with a decrease in the slope of the line, which was only significant when there was no oxygen deficiency (Table 38 and Fig. 62).

If the change in total plasma CO_2 after bendroflua-zide therapy is plotted against the change in the intercept of the CO_2 response line in hyperoxia after this drug, there
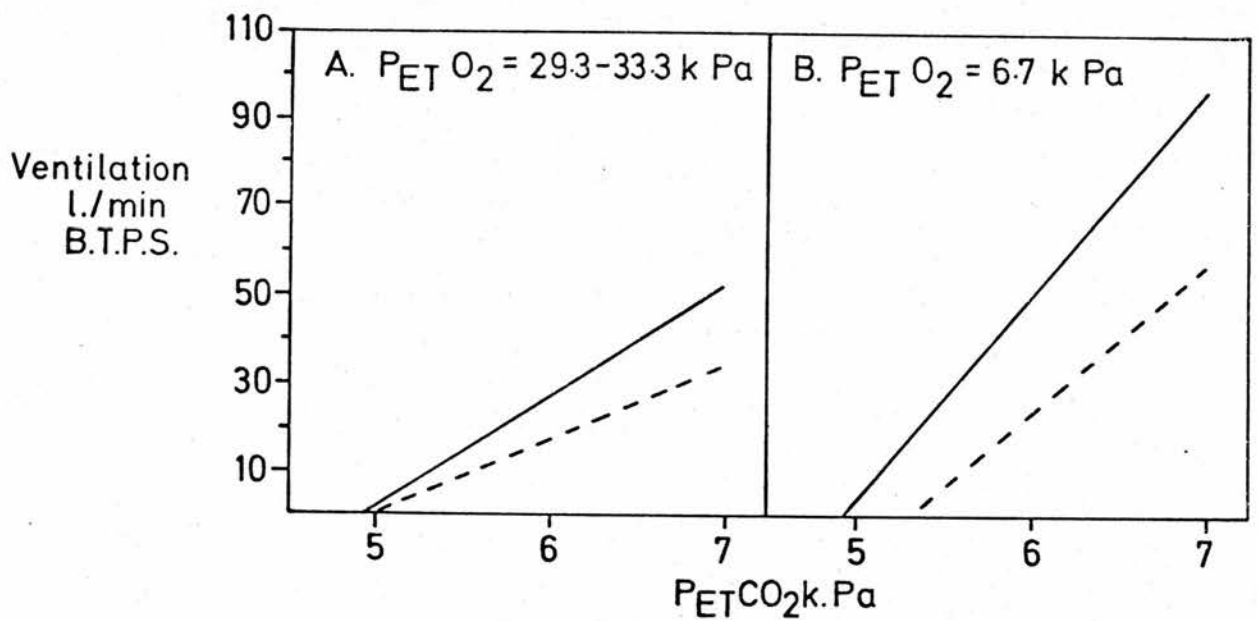
FIGURE 62 Mean CO_2 response lines in eight subjects
before (———) and after (–––––––) 0.024
mmol (10 mg) of bendrofluazide daily for
four days a) at an end tidal PO_2 of 29.3
– 33.3 kPa and b) at an end tidal PO_2 of
6.7 kPa.

is no significant relationship, in contrast to the findings
with frusemide (Fig. 61). Unlike frusemide, bendrofluazide
does not produce a rise in the intercept of the CO_2 response
line in hyperoxia, this being consistent with the unchanged
$P_{ET}CO_2$, and hence P_aCO_2, after the drug. Goldring, Cannon,
Heinemann and Fishman (1968) also found no change in either
the intercept of the CO_2 response line or the arterial PCO_2
in thiazide-induced alkalosis; nor did they show a de-
crease in the slope of the CO_2 response line. However, their
subjects inhaled CO_2 in air and therefore had arterial oxy-
gen tensions of about 13 kPa whereas, in the present study,
there is depression of the slope of the line at a $P_{ET}O_2$ of
30 kPa but not at a $P_{ET}O_2$ of 6.7 kPa. The present results
indicate that, when the peripheral chemoreceptors are in-
activated by a high PO_2, the primary effect of bendroflua-
zide is to depress the response of the central chemorecep-
tors to the rise in H^+ of CSF or brain interstitial fluid,
which follows the inhalation of CO_2.

This depression of central sensitivity to CO_2 by
thiazides could result from changes in the central chemo-
receptor cells after the drug, for it cannot be accounted
for by the increases in CSF buffering. CSF HCO_3^- is raised
after both thiazides and ethacrynic acid (Goldring, Cannon,
Heinemann and Fishman, 1968), yet only thiazides produce
depression of the slope of the CO_2 response. Whether the
effect seen is related to changes in carbonic anhydrase
activity at the central chemoreceptor remains to be es-
tablished. The effect was seen 24 hours after the last

dose of the drug when most of the drug would have been ex-
creted (Goodman and Gillman, 1965) and drugs like bendro-
fluazide have only weak carbonic anhydrase activity (Maren,
1967).

In contrast to the effect of bendrofluazide on the
CO_2 response line in hyperoxia, the drug produces no signi-
ficant change in the slope of the CO_2 response line when
the subjects are hypoxic (Fig. 55). This can be explained
either by suggesting that, in the presence of hypoxia, the
depressant effect of bendrofluazide on the central chemore-
ceptors is overcome by normal peripheral chemoreceptor ac-
tivity, or by suggesting that, for a given degree of hypoxia,
bendrofluazide itself stimulates the peripheral chemore-
ceptors to discharge more frequently, and that this increased
discharge overcomes the central depression. The shift to
the right of the CO_2 response line which is only seen in
hypoxia suggests the former rather than the latter mechanism
to explain the lack of change in slope. Hayes and Torrance
(1974) have shown that acetazolamide shifts the carotid
nerve discharge/PCO_2 relationship to the right at low PO_2
tensions in cats, suggesting that carbonic anhydrase inhi-
bitors may diminish the response of the carotid body to
CO_2, possibly by an action on the postulated H^+ pump (Torrance,
1975). Their findings are in keeping with a shift to the
right of the CO_2 response line in hypoxia only in this
study, and suggest the possibility of significant persis-
tence of carbonic anhydrase inhibition even 24 hours after
the last dose of bendrofluazide.

In both this study, and that of Goldring, Cannon, Heinemann and Fishman (1968), thiazides produced a significant decrease in serum potassium which was greater than that seen after frusemide. Further studies, with oral potassium supplements used to prevent this hypokalaemia, will be required to assess the importance of this factor in determining these ventilatory responses.

Although the mechanisms of the effects on the control of ventilation following bendrofluazide treatment remain open to both speculation and further investigation, the results of this study could have important implications if these findings in normal man can be extrapolated to patients with disturbances of ventilatory control. A patient with acute exacerbation of chronic bronchitis and emphysema, with CO_2 retention and hypoxaemia, is usually treated with controlled O_2 therapy with the aim of relieving hypoxaemia, without further ventilatory depression (Hutchison, Flenley and Donald, 1964). Obviously bendrofluazide is not desirable in such a situation, for it may well potentiate any ventilatory depression from relief of hypoxia, whereas frusemide would appear to carry little risk of such undesirable sequelae.

Salbutamol

The dose of salbutamol used was in the middle of the dose range shown to cause significant bronchodilation in patients with asthma (Warrell, Robertson, Newton Howes, Conolly, Patterson, Beilin, Dollery, 1970; Paterson, Courtenay, Evans and Prime, 1971; Marlin and Turner, 1975)

and smaller than doses currently being evaluated in pre-
mature labour (Davis, 1975). The results with this dose
show a significant increase in the slope of the line re-
lating ventilation to PCO_2 in normal subjects inhaling
CO_2 enriched mixtures in both hyperoxia and hypoxia with
no significant change of the slope of the line.

It is not easy to interpret this finding. Salbutamol
certainly stimulates ventilation when infused in this
dose and lowers PCO_2 as shown in the three subjects who
were studied breathing air (Fig. 63). The drug has a plasma
half life of 2 hours (Martin, Hobson, Page and Harrison,
1971) and it is therefore not surprising that stimulation
of ventilation is more marked at the end of the one hour
infusion when the concentration of salbutamol will be
highest in the blood. This finding, in the context of the
protocol used in determining the CO_2 response lines (Fig.
64), suggests a possible reason for the finding of uniform
increases in slope in hypoxia and hyperoxia. The high
PCO_2 points were determined at the end of the infusion,
when the concentration of salbutamol in the blood would
be higher than at the beginning of the infusion, with pos-
sible consequent greater increases in ventilation at the
high than at the low points, and an apparent increase in
slope of the line. The true effect of the drug may simply
be to produce a parallel shift of the CO_2 response line to
the left. The studies in one subject with infusion of in-
creasing doses of salbutamol at 10 minute intervals, while
PCO_2 was kept constant at a low or a high level, do help to
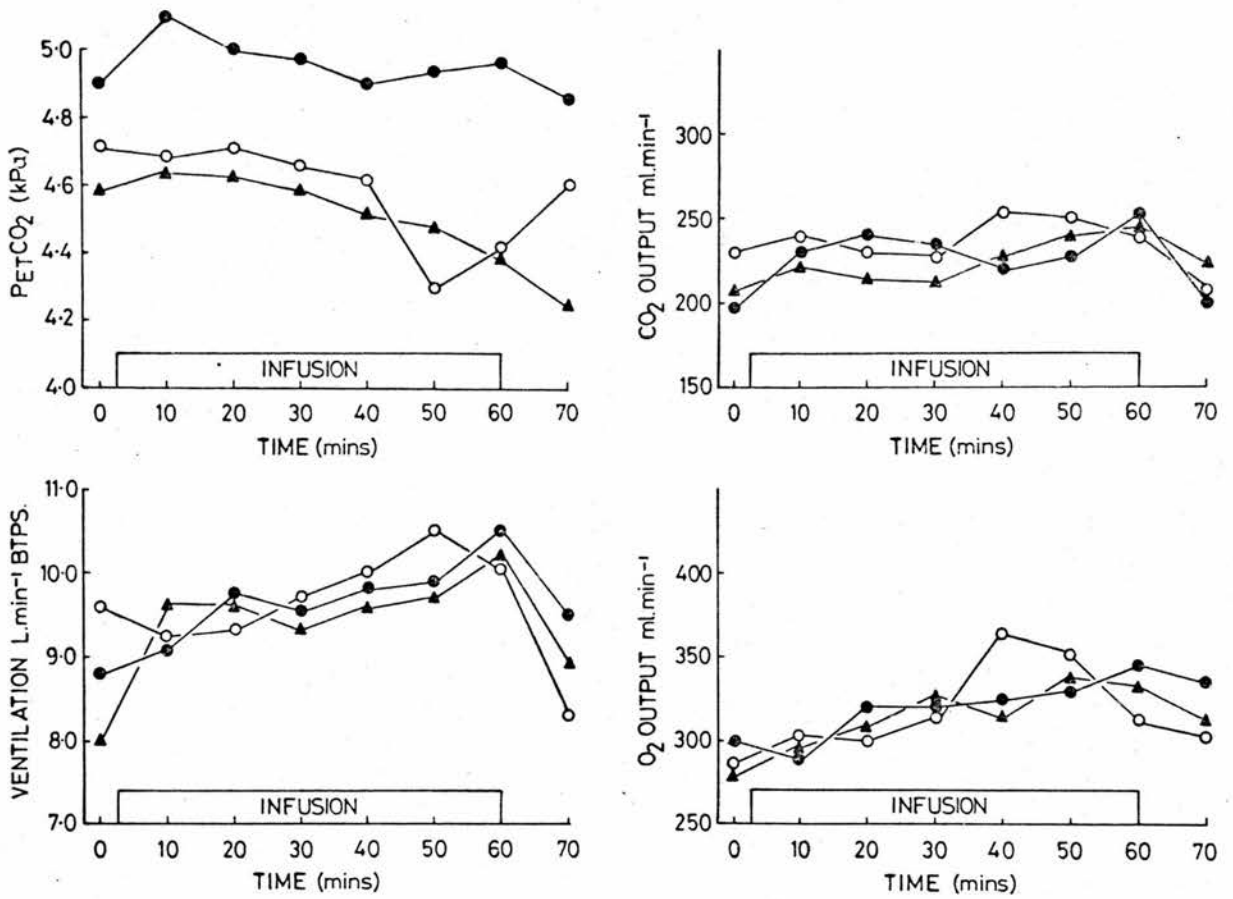
FIGURE 63   Ventilation, end tidal PCO_2, CO_2 output and O_2 uptake in three subjects (the subjects of Fig. 59) during and after infusion of salbutamol 10 $\mu g.min^{-1}$.
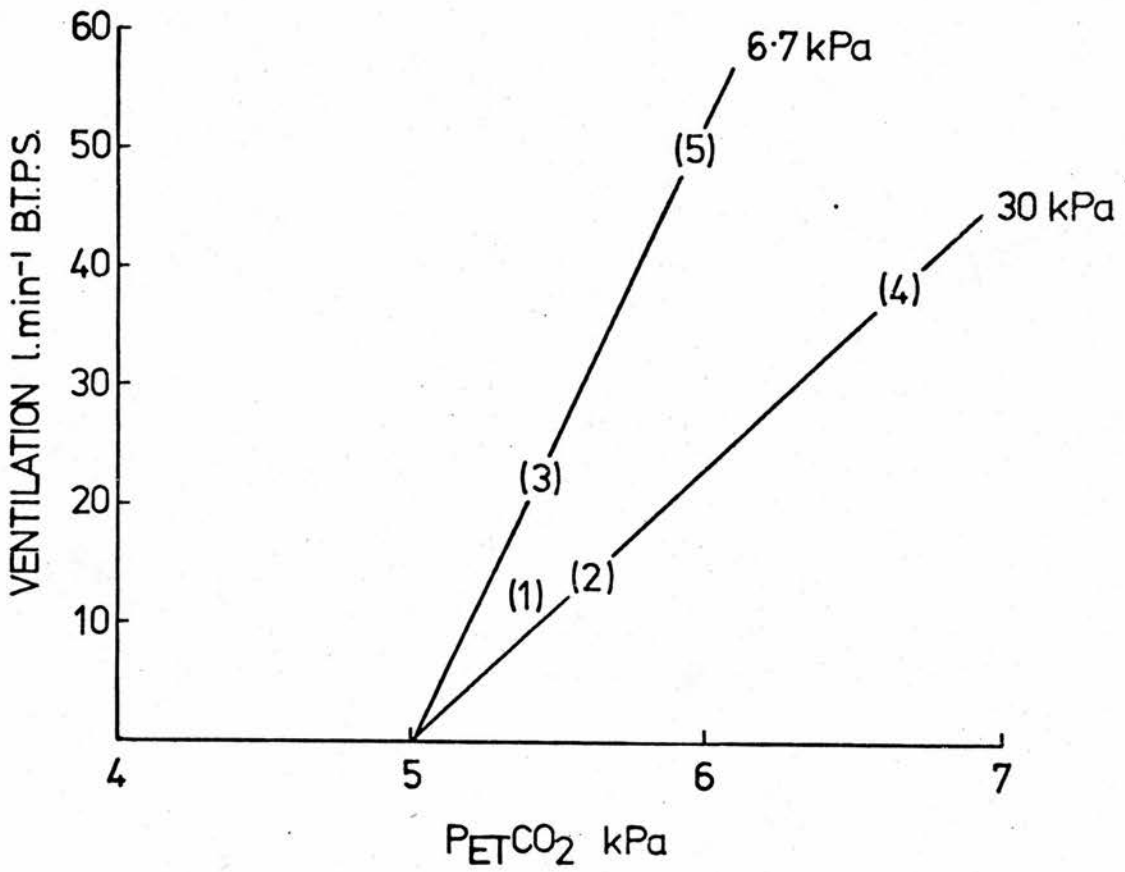
FIGURE 64 To indicate the order in which the points on the $\dot{V}E/P_{ET}CO_2$ line were measured in the sal-butamol infusion experiments. Point (1) is the air point (see text).

resolve this question (Fig. 65). At the two highest dose
levels the slope of the CO_2 response line is still increased,
suggesting that the effect on slope observed in the main
series of experiments is real and not simply a function of
the time during the infusion at which the measurements of
ventilation and PCO_2 were made. Salbutamol would therefore
appear to increase the ventilatory response to CO_2 not only
in hypoxia but also in hyperoxia.

In the cat there is little doubt that the stimulant
effect of noradrenaline on ventilation is dependent on the
peripheral chemoreceptors and is abolished when 100% O_2 is
breathed (Joels and White, 1968). In man, recent observa-
tions have produced conflicting results. Heistad, Wheeler,
Mark, Schmid and Abboud (1972) found that both noradrenaline
and isoprenaline stimulated ventilation and that this ef-
fect was blocked by breathing 100% O_2 or by blockade of β
receptors by propranolol. The ventilatory response to hy-
poxia was not blocked by propranolol. Stone, Keltz, Sarkar
and Singzon (1973) also found that infusion of a similar
dose of noradrenaline stimulated ventilation but they were
unable to inhibit this effect with β blockade using similar
doses of propranolol to those used by Heistad et al and
they did not study the effect of oxygen breathing on the
response. Heistad et al (1971) suggest that catecholamines
stimulate ventilation by an action on β receptors and, since
the effect is blocked by 100% O_2, they implicate the carotid
body in this response. The present study shows nothing to
support this hypothesis. The increase in sensitivity to CO_2
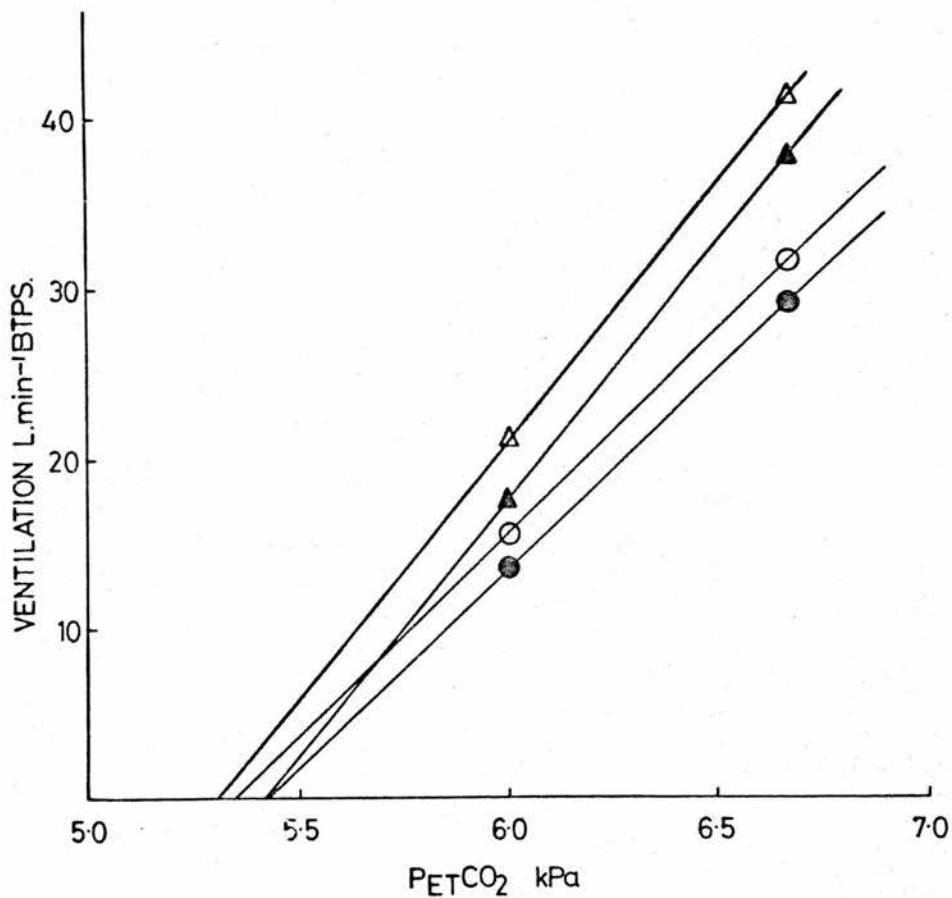
FIGURE 65   Steady state CO_2 response lines measured during
infusion of saline (●———●) and salbutamol 6.4
$\mu g.min^{-1}$ (O———O), 14.6 $\mu g.min^{-1}$ (▲———▲) and
37.6 $\mu g.min^{-1}$ (△———△) in one subject at a
$P_{ET}O_2$ of 30 kPa. These results are derived from
two separate studies at a $P_{ET}O_2$ of 30 kPa in
which $P_{ET}CO_2$ was kept constant at 6.0 or 6.67
kPa while the dose of salbutamol infused was in-
creased at ten minute intervals, the measurements
of ventilation and $P_{ET}CO_2$ being made in the last
three minutes of each ten minute period on both
occasions.

was seen both at low PO_2 and at a level of hyperoxia which is believed to 'block' carotid body mediated responses (Dejours, 1962). If the carotid body is to be implicated in the increased sensitivity to CO_2 during salbutamol infusion, as has been suggested for noradrenaline (Cunningham, Hey, Patrick and Lloyd, 1963), then it is necessary to postulate that hyperoxia of a degree adequate to 'block' stimulation of the carotid body in other circumstances does not do so when salbutamol is infused.

The changes observed in O_2 uptake and CO_2 output with infusion of salbutamol are not great enough to explain the effect on ventilation, which would appear to be independent of metabolism since PCO_2 falls during infusion of the drug when air is breathed. Other metabolic effects of the drug may be responsible for the ventilatory effects. The fall in serum potassium found, as discussed below, is probably related to a shift of potassium from the extracellular to the intracellular spaces. Such a shift would lower cell membrane potential since by the Nernst equation

$$Em = \frac{RT}{F} \ln. \frac{K_o^+}{K_i^+}$$

(Em = membrane potential, K_o^+ and K_i^+ = potassium concentration outside and inside the cell respectively). A fall in membrane potential of the cells of the respiratory centre would render them more excitable and would explain why the increased sensitivity to inhaled CO_2 is seen to an equal degree in both hypoxia and hyperoxia. This hypothesis could be tested by studying the influence of glucose and insulin infusion on the ventilatory response to CO_2.

The marked fall in plasma potassium observed during infusion of salbutamol was associated with rises in plasma glucose and serum insulin. Salbutamol, like other β adrenergic agents, probably stimulated glycolysis (Porte, 1967) and insulin release (Imura, Kato, Ikeda, Morimoto and Yawata (1971) resulting in a shift of potassium from the extracellular to the intracellular space. The fall in urinary potassium excretion observed in one subject is consistent with such an action.

β adrenergic agents increase the heart rate but salbutamol is allegedly a β_2 adrenergic agent with ten times less effect on the heart rate than isoprenaline (Paterson, Courtenay, Evans and Prince, 1971), when given by intravenous infusion to asthmatic patients. Nevertheless, the moderate therapeutic dosage employed in the present experiments produced striking increases in heart rate in normal subjects, with associated palpitations, flushing and tremor.

There is no doubt that intravenous infusion of salbutamol in the dose studied can produce bronchodilation in patients with stable (Paterson, Courtenay, Evans and Prime, 1971) and severe (Marlin and Turner, 1975) asthma. It is unlikely that the effects on the chemical control of breathing demonstrated in this study will be of much benefit when it is used in this situation for, in such patients, the ventilatory drive from non-chemical sources is already markedly increased. The drug may, however, be

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of value in increasing ventilatory drive in bronchitic
patients with the hypercapnia of chronic ventilatory fai-
lure.

The marked tachycardia caused by the drug is disturb-
ing for it is in the context of tachycardia, hypoxia and
acidosis, which may occur simultaneously in status asthma-
ticus, that serious cardiac arrhythmias may result (Collins,
McDevitt, Shanks and Swanton, 1969; Shanks and Swanton,
1971). The hypokalaemic effect of salbutamol is equally
disturbing for falls of potassium of such a degree may also
be associated with cardiac dysrhythmias in digitalised
patients (Lown, 1956). If this drug is to be given by in-
fusion to patients with severe asthma, monitoring of plasma
potassium and electrocardiogram would appear to be neces-
sary precautions.

CHAPTER 11   CONCLUSIONS

The object of the first part of this study was to
detect diminished or absent hypoxic drive to breathing
in normal man. The method selected, namely the ventila-
tory response to transient hypoxia induced by three breaths
of nitrogen on exercise, had been little used previously,
but on grounds of theory and convenience appeared to be a
suitable way of screening a population for the absence of
hypoxic drive.

The results show that the method gives a reproducible
index for hypoxic drive in most subjects when three highest
breath values are measured in each subject on the same day
(Fig. 21). The mean highest breath value, derived from
these three studies, is also reproducible from year to
year (Fig. 22). The method demonstrates a wide range of
hypoxic drive and, particularly relevant to the purpose of
the present study, identified two subjects with reproducibly
low values of mean highest breath value, one of whom had no
significant ventilatory response to transient hypoxia on
exercise on two occasions. The responses in these two sub-
jects were similar to or less than the ventilatory responses
observed in high altitude natives tested in a similar way,
although lower $P_{ET}O_2$s were achieved in the latter study
where five breaths of nitrogen were given (Lahiri and Edelman,
1969).

Assessment of the hypoxic drive to breathing using the
steady state ventilatory response to carbon dioxide at high
and low $P_{ET}O_2$s at rest in nine subjects, with widely differ-

ing ventilatory responses to transient hypoxia on exercise, showed that there was no obvious correlation between the hypoxic drive as assessed by the two methods, subjects with maximal and minimal responses in the transient studies, having identical responses in the steady state studies.

In an attempt to investigate these differences in response the second part of the study investigated the hypoxic drive to breathing using transient, progressive and steady state methods in four subjects at rest and on exercise. These studies show that a single measurement of hypoxic drive using progressive or steady state hypoxia may be misleading, for, in some subjects, considerable variability in the index of hypoxic drive was found. The variability of the ventilatory response to carbon dioxide in hyperoxia was less than that found in hypoxia and it is suggested that this may reflect day to day differences of the known inhibitory effect of hypoxia on central nervous system function, although it may also reflect day to day differences in peripheral chemoreceptor response to hypoxia.

In general, however, when the mean values for hypoxic drive derived from two or more studies, using the three methods at rest and on exercise, are compared, the ranking of the four subjects with each method is remarkably consistent. Nevertheless, one subject had a ventilatory response to transient hypoxia on exercise which was inappropriately low in comparison with the other assessments of his hypoxic drive and certainly as low as the responses found in the

two poorest responders in the miners' study. The effect
of exercise on the steady state ventilatory response to
CO_2 in hypoxia in this subject was to produce an increase
in the slope of the CO_2 response line and less decrease
in the intercept of the line than was found in similar
studies in him in hyperoxia. The configuration of the
steady state CO_2 response lines in this subject is such
that it is possible to postulate that the small fall in
$P_{ET}CO_2$ induced by his initial ventilatory response to
hypoxia would be sufficient to diminish or abolish the
peripheral chemoreceptor contribution to his drive to
breathing and, thus, effectively abort his ventilatory
response to transient hypoxia.

Application of a similar analysis to the steady state
CO_2 response curves of the other three subjects on exer-
cise would be consistent with the effects of a similar
mechanism determining their ventilatory response to tran-
sient hypoxia on exercise. The studies of the ventilatory
response to exercise in normoxia, hypoxia and isocapnia
also point to an important role for CO_2 in determining
ventilatory responses to hypoxia on exercise.

It is possible to conclude from this part of the study
that the differences between the steady state and transient
responses observed in the miners' study may have two ex-
planations. Firstly, estimations of the steady state hy-
poxic drive to breathing are variable from day to day and
it is possible that this variability may play some part
in the poor correlation observed between the transient and

steady state responses observed in the miners. Secondly,

measurements of hypoxic drive made against a background of

normocapnia or hypercapnia correlate well. It would appear,

however, that there may be subjects with a perfectly ade-

quate hypoxic drive when this is measured in normocapnia

or hypercapnia who have a poor response to transient hypo-

xia on exercise. It is suggested that this may be due to

a fall in PCO_2 in these subjects, as a result of their ini-

tial ventilatory response, such that PCO_2 falls near to

or below the threshold for the carotid body in exercise

with effective limitation of the ventilatory response.

Confirmation of this explanation will require much more

detailed studies of the effect of exercise on the steady

state ventilatory response to CO_2 at different PO_2s than

is available in this or in other published work. Correla-

tion of the findings with ventilatory responses to transient

hypoxia in the same subjects will be necessary. Measure-

ment of the lung to carotid body circulation time will be

important to determine if the time course of the suggested

sequence of events is possible and appropriate. It may

well be that a similar mechanism to the above explains

the low responses to transient hypoxia on exercise found

reproducibly in two miners in whom, unfortunately, no data

on the effect of exercise on their steady state ventilatory

response to CO_2 are available.

The ventilatory response to transient hypoxia on exer-

cise would appear therefore not to be, on its own, an ade-

quate test for the detection of normal people with absent

hypoxic drive. Nevertheless, it is simple to apply and could usefully be employed to select individuals for further study using more sophisticated methods although, on the basis of the first and second parts of this study, many of the subjects selected in this way would have a normal hypoxic drive. Apart from the need to investigate further the discrepancies between the transient hypoxia studies on exercise and other indices of hypoxic drive already mentioned, there is clearly also need for a study on the reproducibility of the currently available methods of assessing hypoxic drive and a comparison of the different methods in the same population of normal subjects.

The third part of the study was concerned with the effects of drugs on the steady state ventilatory responses to carbon dioxide in hypoxia and hyperoxia. Frusemide produces a mild metabolic alkalosis with an appropriate shift to the right of the hyperoxic CO_2 response line. Unfortunately, the present studies did not produce the degree of metabolic alkalosis nor the rise in $P_{ET}CO_2$ found in a previous study (Iff and Flenley, 1972) but the results do not contradict their suggestion that frusemide should be the diuretic of choice in hypoxic bronchitic patients receiving controlled oxygen therapy. Frusemide would be a less desirable diuretic for hypoxic bronchitic patients in the absence of controlled oxygen therapy for any rise in alveolar PCO_2 will cause a fall in alveolar PO_2. Such changes were small in the normal subjects studied by Iff and Flenley but could be much greater and of clinical

significance in hypoxic patients receiving larger doses
of frusemide continuously, in whom the metabolic changes
may be greater.

Bendrofluazide depressed the slope of the CO_2 response
line in hyperoxia and increased the intercept in hypoxia,
with no change in the $P_{ET}CO_2$ breathing air. The latter
finding suggests that bendrofluazide may be a more appro-
priate diuretic for domiciliary treatment of hypoxic bron-
chitics for it will not tend, as frusemide does, to lower
the PO_2. The increased threshold to CO_2 in hypoxia and
the decreased sensitivity to CO_2, which was only signifi-
cant in hyperoxia, are the reverse of those to be hoped
for in patients with chronic bronchitis and respiratory
failure where the sensitivity of the ventilatory response
to CO_2 is already markedly reduced. The relevance of the
present findings to the management of such patients re-
mains to be assessed. A double blind cross-over trial with
both drugs, in patients with stable chronic respiratory
failure, to assess the effect of the drugs on arterial
PO_2 and PCO_2, will be needed to clarify the relevance of
the changes observed in normal people to the management of
patients with chronic respiratory failure.

Salbutamol increased the slope of the CO_2 response
lines in hypoxia and hyperoxia. Whether this effect is due,
as discussed, to its metabolic effects, of which the fall
in plasma potassium is the most striking, remains to be
confirmed, as it could be, by studying the effects of a
glucose and insulin infusion on the ventilatory response

to CO_2. The effect on the CO_2 response line would appear
to be independent of the carotid body since it is similar
in both hypoxia and hyperoxia. The importance of the ef-
fect of salbutamol on ventilatory control is also unclear.
In asthma, where the drug is most likely to be used, the
ventilatory drive from other sources is already high and
it will make no further significant contribution to this
drive. In chronic respiratory failure, the side effects
and the availability of more potent ventilatory stimulants,
such as doxapram hydrochloride (Leitch, Clancy and
Flenley - unpublished work), do not indicate that it will
be of much value. The most important finding of the
salbutamol studies is that intravenous infusion of the
drug can produce quite marked hypokalaemia. Since it is
likely to be used by this route in patients with status
asthmaticus, who are already hypoxic, with a tachycardia
and often an acidosis, it seems essential that monitoring
of the serum potassium and electrocardiogram should be
carried out routinely in these patients.

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TABLE 1 Lowest arterial P_{O_2} (P_aO_2) recorded by rapid sampling of arterial blood compared with lowest end tidal P_{O_2} ($P_{ET}O_2$) on computer print out. (1 kPa = 7.5 mmHg)

Subject	Study	P_aO_2 (kPa)	$P_{ET}O_2$ (kPa)
DCF	1	5.47	5.87
	2	6.13	6.40
	3	5.07	6.13
AGL	1	6.93	5.20
	2	4.67	6.80

TABLE 2 To show age, height, weight, haemoglobin concentration, $FEV_{1.0}$, FEV/FVC
ratio and smoking history in the 43 subjects who were studied

SUBJECT No.	AGE (yrs.)	HEIGHT (cm.)	WEIGHT (kg.)	HAEMOGLOBIN CONCENTRATION g.%	$FEV_{1.0}$ ℓ	FEV/FVC %	SMOKER (+ or -)
1	35	166	67	16.4	3.50	84	+
2	41	170	71	14.5	3.80	81	-
3	25	184	83	14.2	4.60	84	+
4	22	174	73	15.0	4.65	85	-
5	29	172	83	15.9	3.80	81	-
6	22	175	61	14.4	4.65	73	+
7	25	-	-	14.6	4.65	84	+
8	44	176	81	15.4	3.40	82	-
9	30	171	72	14.5	4.70	82	+
10	35	171	86	16.1	3.40	82	+
11	34	176	84	13.9	4.35	87	+
12	31	184	79	15.9	4.80	83	+
13	35	182	87	-	4.30	93	+
14	30	172	70	13.7	3.90	75	-
15	37	162	71	15.1	3.90	85	+
16	42	169	74	14.8	3.95	72	-
17	42	171	79	13.7	3.30	65	-
18	34	190	86	15.1	5.00	79	+
19	42	162	82	-	2.60	76	-
20	34	161	66	14.6	3.35	74	-
21	29	167	66	15.9	3.90	92	+
22	35	168	69	14.7	2.90	68	+
23	37	168	66	14.4	5.10	86	+
24	44	177	88	14.6	3.25	71	+
25	22	169	76	14.1	4.50	83	+
26	25	168	61	14.7	3.40	72	+
27	27	169	67	16.1	3.60	71	+
28	35	164	72	14.6	3.90	85	+
29	20	170	64	-	5.00	90	-
30	36	166	64	15.0	4.40	87	+
31	36	164	66	14.4	3.40	81	+
32	34	169	76	14.2	4.20	79	+
33	32	184	96	16.3	4.60	84	-
34	38	177	77	14.2	3.75	60	-
35	38	171	78	14.3	-	-	+
36	35	174	90	15.0	3.00	71	-
37	35	168	73	14.9	3.90	75	+
38	45	168	79	15.2	3.50	78	-
39	31	183	83	15.2	5.60	90	-
40	27	177	78	15.0	4.80	84	+
41	29	175	84	13.7	5.00	89	-
42	32	173	65	14.6	4.55	81	+
43	31	171	69	14.2	4.90	91	-

TABLE 3 To show the exercise ventilation (measured by dry gas meter) ($\dot{V}_E$), the oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide output ($\dot{V}_{CO_2}$), respiratory quotient (RQ), ventilatory response to exercise ($\dot{V}_E/\dot{V}_{O_2}$) and the ratio of ventilation breathing 14% O_2 to that breathing 21% oxygen ($\dot{V}_{E14}/\dot{V}_{E21}$ for all studies in 1971 and 1972.

The results for subject 43 are excluded from the mean value for reasons which will be apparent in the text.

| SUBJECT | $\dot{V}_E$ | | $\dot{V}_{O_2}$ | | $\dot{V}_{CO_2}$ | | R.Q. | | $\dot{V}_E/\dot{V}_{O_2}$ | | $\dot{V}_{E14}/\dot{V}_{E21}$ % | |
| | ℓ/min BTPS | | ml/min | | ml/min | | | | | | | |
No.	1971	1972	1971	1972	1971	1972	1971	1972	1971	1972	1971	1972
1	20.87	23.98	1006	1096	824	995	0.82	0.91	20.7	21.9	104	120
2	29.94	32.25	1255	1373	1031	1217	0.82	0.89	23.9	23.5	104	111
3	27.46	26.46	1264	1195	1069	1051	0.85	0.88	21.7	22.1	113	109
4		30.86		1383		1252		0.91		22.3		115
5	25.5	26.32	1185	1252	964	998	0.82	0.80	21.5	21.0	120	128
6		29.88		1187		1043		0.88		25.2		109
7		25.76		1112		999		0.90		23.2		113
8	43.09	30.2	1252	1040	1047	1040	0.84	0.92	34.4	29.0	93	116
9	20.26	21.7	912	1027	791	892	0.87	0.87	22.2	21.1	125	121
10	30.75	29.41	1419	1323	1206	1204	0.85	0.91	21.7	22.2	104	122
11		28.59		1132		1016		0.90		25.3		112
12		29.11		1170		1029		0.88		24.9		118
13	25.04	27.68	1174	1242	1174	1109	0.79	0.89	21.3	22.3	110	120
14	24.18	25.61	1096	1166	929	1090	0.85	0.94	22.04	22.0	102	110
15	38.55	42.37	1473	1539	1255	1436	0.86	0.93	26.2	27.5	125	106
16	26.77	29.47	1171	1270	978	1074	0.84	0.85	22.9	23.6	105	114
17	36.15	36.39	1330	1227	1163	1248	0.88	1.03	27.2	29.7	108	103
18		32.8		1333		1177		0.89		24.6		117
19	25.46	20.2	1194	956	941	783	0.79	0.82	21.32	21.1	113	124
20	26.32	24.49	1145	1075	1027	1003	0.90	0.94	23.0	22.8	108	116
21		26.5		1143		997		0.87		23.2		112
22		25.95		988		868		0.88		26.3		118
23		25.48		1104		999		0.91		23.1		115
24		31.71		1180		1040		0.89		30.5		104
25		27.4		1185		986		0.84		23.1		110
26	23.71	22.15	946	965	762	826	0.81	0.86	25.1	23.0	108	107
27		29.26		1168		1027		0.88		25.1		105
28	30.77	33.44	1339	1321	1134	1241	0.85	0.94	23.0	25.3	123	119
29	29.89	24.67	1340	1029	1104	911	0.83	0.89	22.3	24.0	117	117
30		27.14		1108		1024		0.93		24.5		112
31		30.15		1044		1044		0.93		28.9		108
32	27.81	26.67	1242	1115	1112	1072	0.90	0.96	22.4	23.9	104	105
33		31.79		1379		1283		0.94		23.1		93
34		29.75		1244		1126		0.91		23.9		112
35	34.3	33.13	1457	1429	1249	1291	0.86	0.91	23.5	23.2	112	118
36		38.45		1498		1297		0.87		25.7		123
37	32.62	35.14	1255	1374	1049	1255	0.84	0.91	26.0	25.6	97	106
38	28.48	25.95	1167	1069	945	977	0.81	0.91	24.4	24.3	107	107
39		42.53		1591		1495		0.94		26.7		108
40	25.44	32.12	1133	1248	980	1095	0.87	0.88	22.5	25.7	102	95
41	28.29	26.93	1367	1212	1179	1084	0.86	0.90	20.7	22.2	118	121
42	30.33	28.45	1062	983	874	910	0.83	0.93	28.6	28.9	108	100
Mean	28.83	29.25	1216	1198	1032	1083	0.84	0.90	23.6	24.4	109.6	112.3
SD	5.33	4.86	148	158	139	153	0.03	0.04	3.0	2.4	8.4	7.6
43	39.04	43.31	1083	1149	964	1054	0.89	0.92	36.04	37.7	-	82

4 To show the control ventilation ($\dot{V}_E$) (measured by pneumotachograph), tidal volume (TV), frequency (f), end tidal PO_2 and end tidal PCO_2 for all studies in 1971 and 1972. Ventilation, tidal volume and frequency are shown ± 95% confidence limits. Subject 43 is excluded from the calculation of means for reasons discussed in the text.

(1 kPa = 7.5 mmHg)

CT	VENTILATION ($\ell.min^{-1}$ BTPS)		TIDAL VOLUME (mls)		FREQUENCY breaths min^{-1}		$P_{ET}O_2$ kPa		$P_{ET}CO_2$ kPa	
	1971	1972	1971	1972	1971	1972	1971	1972	1971	1972
	19.10 ± 3.24	20.65 ± 3.09	1412 ± 415	1488 ± 209	14.2 ± 4.8	14.3 ± 2.4	13.84	12.23	6.21	6.33
	32.81 ± 12.46	25.01 ± 5.25	1559 ± 273	1133 ± 220	21.4 ± 8.8	22.4 ± 4.4	13.47	13.36	5.39	6.23
	24.27 ± 6.06	21.68 ± 3.90	2424 ± 970	1643 ± 619	11.9 ± 6.6	14.4 ± 5.0	12.85	13.27	6.08	6.73
		25.95 ± 4.15		1169 ± 281		22.3 ± 3.9		13.01		5.67
	34.98 ± 10.14	23.1 ± 4.62	2083 ± 790	1480 ± 538	17.8 ± 4.0	16.3 ± 3.2	12.95	12.64	5.40	5.49
		26.25 ± 6.30		1333 ± 397		20.4 ± 5.5		13.88		6.12
		20.64 ± 4.54		1159 ± 480		18.8 ± 4.4		12.51		6.13
	31.53 ± 5.67	25.44 ± 3.30	1027 ± 234	1065 ± 111	31.2 ± 5.5	23.9 ± 2.0	14.59	13.84	4.93	5.80
	19.78 ± 3.16	18.15 ± 2.90	1641 ± 487	1354 ± 222	12.5 ± 3.3	13.4 ± 1.2	12.60	12.63	6.13	6.25
	28.52 ± 6.84	24.73 ± 5.19	1547 ± 340	1410 ± 372	18.8 ± 5.2	18 ± 4.2	14.33	12.91	5.96	6.29
		23.58 ± 4.71		1126 ± 399		21.6 ± 4.2		13.01		5.75
		26.36 ± 5.27		1380 ± 332		19.7 ± 3.5		15.00		5.93
	25.26 ± 7.57	22.42 ± 3.58	1905 ± 677	1521 ± 358	14.8 ± 4.5	17.2 ± 4.9	13.63	13.64	5.67	6.37
	25.66 ± 4.61	23.01 ± 3.91	1507 ± 284	1540 ± 249	17.1 ± 2.0	15.1 ± 1.4	13.32	13.28	5.69	6.59
	28.97 ± 7.24	39.04 ± 6.63	925 ± 257	1276 ± 229	32.7 ± 7.9	31.3 ± 5.2	13.91	14.40	5.44	5.97
	25.09 ± 5.26	25.29 ± 3.28	1344 ± 165	1393 ± 150	19.1 ± 3.7	18.2 ± 1.8	13.75	12.71	5.67	5.77
	31.73 ± 10.78	28.4 ± 3.97	1503 ± 229	1338 ± 211	21.2 ± 5.8	21.4 ± 3.0	12.05	12.71	4.40	5.79
	29.1 ± 7.85	29.98 ± 6.59	1816 ± 462	1805 ± 473	15.6 ± 2.7	16.8 ± 2.7	14.25	14.29	5.27	5.67
	23.53 ± 4.70	22.33 ± 2.90	1291 ± 197	1287 ± 121	18.7 ± 1.9	17.5 ± 1.5	13.37	12.60	5.88	6.07
	23.22 ± 2.32	20.12 ± 2.61	1420 ± 246	1311 ± 384	16.6 ± 2.7	16.5 ± 4.8	13.59	12.53	5.79	6.35
		21.35 ± 4.91		1028 ± 173		21 ± 3.5		12.87		6.45
		23.44 ± 3.75		1065 ± 146		22.4 ± 2.2		12.84		5.41
		21.99 ± 6.15		2162 ± 693		10.4 ± 3.2		13.65		6.07
		26.28 ± 3.15		1266 ± 115		20.3 ± 2.0		13.63		5.08
		25.68 ± 3.59		1483 ± 553		18.4 ± 4.8		13.85		5.55
	29.94 ± 11.37	18.32 ± 2.38	1313 ± 562	727 ± 180	25.3 ± 8.1	25.9 ± 4.9	13.79	13.49	5.08	6.95
		27.60 ± 3.31		1742 ± 460		16.8 ± 4.2		14.39		5.61
	31.32 ± 2.81	27.53 ± 2.47	1489 ± 158	1453 ± 171	21.3 ± 1.8	19.0 ± 1.8	12.93	12.34	5.73	6.35
	23.38 ± 7.48	30.11 ± 3.91	1106 ± 340	1273 ± 266	21.4 ± 7.5	24.1 ± 4.4	13.15	13.07	6.09	6.21
	24.39 ± 6.58	23.78 ± 3.80	1620 ± 392	1475 ± 307	15.8 ± 4.6	16.4 ± 3.0	13.76	14.85	5.77	6.75
		27.16 ± 4.61		1091 ± 183		25.1 ± 3.5		13.40		5.24
	25.12 ± 4.27	21.8 ± 3.48	1514 ± 392	1290 ± 143	17.3 ± 4.6	17.0 ± 2.9	13.01	13.59	5.89	6.56
		26.98 ± 3.50		1382 ± 296		20 ± 3.5		12.57		6.12
		25.9 ± 4.14		1373 ± 315		19.2 ± 3.8		11.95		5.91
	28.13 ± 5.06	31.24 ± 2.49	1340 ± 119	1517 ± 173	21.4 ± 3.5	20.7 ± 2.2	11.85	13.71	4.48	5.92
		33.9 ± 4.74		1587 ± 273		21.6 ± 6.0		13.80		5.51
	38.3 ± 11.1	32.76 ± 4.91	1880 ± 422	1540 ± 229	20.4 ± 4.9	21.3 ± 1.5	14.15	14.35	5.29	5.60
	37.17 ± 5.94	24.33 ± 2.91	2024 ± 371	1738 ± 316	18.5 ± 2.6	14.4 ± 3.3	14.19	13.28	5.37	5.79
		32.19 ± 4.18		1456 ± 170		22.2 ± 2.9		13.51		5.89
	24.46 ± 5.13	23.79 ± 4.75	2034 ± 672	1802 ± 491	12.8 ± 3.2	13.9 ± 3.7	13.88	15.41	5.84	6.51
	25.13 ± 3.51	23.99 ± 2.87	1452 ± 150	1383 ± 129	17.6 ± 1.6	17.6 ± 1.1	12.44	12.67	6.27	6.59
	25.58 ± 5.62	23.9 ± 5.49	915 ± 230	1130 ± 401	29.0 ± 6.5	22.9 ± 4.7	14.72	14.49	4.88	5.80
	27.55 ± 6.30	25.38 ± 4.13	1542 ± 378	1385 ± 298	19.4 ± 4.6	19.3 ± 3.4	13.43	13.39	5.56	6.03
	4.87	4.25	366	255	5.3	3.9	0.71	0.80	0.51	0.43
		38 ± 5.32		1976 ± 316		19.7 ± 3.8		16.14		3.57

Results of 1971 and 1972 transient hypoxia studies in individual subjects. The table shows the 95% confidence limits of the control ventilation expressed as % control, the mean highest breath value and its position and the position of the first breath to achieve significance. Also shown are the highest tidal volume and frequency recorded after the stimulus, the lowest P_{O_2} and P_{CO_2} after the stimulus and the position of the lowest P_{CO_2}

$$(1 \text{ kPa} = 7.5 \text{ mmHg})$$

CONFIDENCE LIMITS OF CONTROL V_E (% control) 1972	MEAN HIGHEST BREATH VALUE (% control) 1971	1972	POSITION OF MEAN HIGHEST BREATH VALUE 1971	1972	POSITION OF FIRST BREATH TO SIGNIFICANCE 1971	1972	HIGHEST TIDAL VOLUME (ml) 1971	1972	HIGHEST FREQUENCY (breaths min^{-1}) 1971	1972	LOWEST $P_{ET}O_2$ (kPa) 1971	1972	LOWEST $P_{ET}CO_2$ (kPa) 1971	1972	POSITION OF LOWEST $P_{ET}CO_2$ 1971
15	178	217	4	5	2	2	2151	2297	21.3	20.7	4.61	2.92	5.31	4.8	4
21	204	211	5	5	2	3	2511	1827	24.7	31.0	3.59	3.31	4.63	4.99	5
18	191	208	5	5	4	2	3279	3262	24.6	20.3	3.11	2.29	4.77	5.17	4
16		207		5		3		2729		30.5		3.35		4.48	
20	183	205	4	5	3	3	3849	2714	19.9	19.8	3.03	2.23	4.35	4.17	4
24		203		4		3		3052		23.3		3.28		5.16	
22		203		4		3		2930		21.6		2.17		4.88	
13	136	203	5	5	5	3	1905	2170	36.6	30.9	6.59	4.19	4.48	4.76	6
16	179	198	5	5	2	4	2305	1988	19.6	19.7	3.25	3.49	5.07	5.13	4
21	155	194	3	4	3	2	2451	2215	23.9	27.4	3.6	2.57	4.83	4.85	4
20		181		4		3		2790		21.4		3.32		4.71	
20		180		5		3		2816		24.4		4.09		4.8	
16	144	169	3	3	3	3	2898	2634	19.9	18.1	3.57	4.93	4.67	5.45	4
17	162	169	4	4	3	3	2640	2679	19.9	17.2	3.41	2.41	4.79	5.41	4
17	127	168	4	5	4	4	1838	2151	39.3	36.8	3.57	3.13	5.07	4.76	4
13	165	166	4	4	2	2	2454	2397	21.5	21.5	4.33	4.15	4.76	4.93	4
14	140	164	5	5	5	3	2407	2185	25.0	25.9	4.59	3.69	3.83	4.81	4
22	147	164	3	5	3	4	3259	2890	19.3	18.8	4.63	3.49	4.68	4.61	3
13	155	161	3	5	3	3	2035	1957	25.2	22.3	4.24	3.56	5.0	5.13	4
13	128	161	5	5	3	3	2111	2239	23.2	21.2	3.04	2.43	5.21	5.11	3
23		156		5		4		1920		26.7		3.25		5.55	
16		155		5		4		1756		26.1		4.45		4.72	
28		155		4		3		2640		17		4.67		5.08	
12		155		5		4		2131		22.1		4.13		4.4	
14		153		4		3		3219		22.7		2.96		4.57	
13	137	151	5	5	-	4	2121	1338	36.4	29.7	7.29	5.39	4.89	6.36	3
12		150		5		4		2258		21.1		3.73		4.76	
9	148	147	4	4	2	2	2510	2689	22.4	19.7	3.45	3.13	4.99	5.45	3
13	150	145	4	5	4	4	2052	1818	28.6	28.9	6.32	7.12	5.23	5.65	4
16	187	142	4	5	3	4	2824	1831	21.1	21.1	3.83	3.68	4.76	5.89	4
17		140		5		5		1623		28.2		4.64		4.48	
16	153	138	5	4	4	3	2048	2053	21.3	19.7	3.79	4.29	5.24	5.97	5
13		137		6		5		1851		23.5		4.51		5.27	
16		133		5		3		2753		22.5		4.36		5.27	
8	127	132	4	4	3	4	2240	2276	24.7	23	3.8	3.89	4.12	5.25	3
14		131		5		5	-	2499		25.8		2.37		4.84	
15	145	129	4	5	4	4	2818	2008	22.2	26.6	5.71	3.55	4.59	4.79	4
12	122	128	3	4	3	3	2796	2180	21.7	20.7	3.49	3.69	4.85	5.07	3
13		122		6		5		1788		29.3		4.03		5.21	
20	149	121	3	5	3	5	3093	1954	21.8	20.5	3.07	4.36	4.84	6.48	3
12	121	117	10	6	-	6	1879	2102	19.8	19.1	4.32	4.37	5.68	6.01	4
23	100	114	3	6	-	-	2326	1546	29.4	25.5	5.29	5.13	4.51	5.45	3
16	151	162	4.0	4.8	3.2	3.5	2492	2289	24.4	23.6	4.21	3.71	4.81	5.11	3.8	4
4	25	29					498	465	5.5	4.4	1.16	1.01	0.39	0.51	0.7	0
14		116		7		7		2267				3.55		3.57	

TABLE 6   Control data for 1974 N_2 transients with $\dot{V}_{O_2}$, lowest $P_{ET}O_2$, mean highest breath value, position of first breath to significance and the ventilatory response to exercise.

(CD4 = dry gas meter;   PT = pneumotachograph measures of ventilation;   1 kPa = 7.5 mmHg)

Subject	Control $\dot{V}_E$ (CD4) $\ell.min^{-1}$ BTPS	Control $\dot{V}_E$ PT $\ell.min^{-1}$ BTPS	Control PCO_2 kPa	Control PO_2 kPa	$\dot{V}_{O_2}$ $ml.min^{-1}$	Lowest PO_2 kPa	HBV %	First breath to sig.	$\dot{V}_E/\dot{V}_{O_2}$ $m/min^{-1}\ell^{-1}$
1	22.67	23.84	6.07	13.15	992	4.33	209	3	24.0
2	25.88	26.79	5.40	13.05	1143	4.35	183	3	23.4
18	37.57	37.89	4.15	14.71	1086	5.07	125	5	34.9
34	26.78	28.88	5.20	13.67	1132	5.80	149	4	25.5
36	31.64	30.84	4.79	14.23	1101	2.99	116	3	28.0
37	26.14	27.10	5.23	13.93	1064	4.31	123	4	25.5
41	26.63	27.30	5.51	13.63	1156	6.27	126	5	23.6
42	23.60	25.10	5.01	13.81	947	6.41	141	4	26.5
43	33.72	36.4	3.57	15.68	987	6.51	108	-	36.8
Mean					1068	38.4			
SD					76	9.1			

TABLE 7   The mean highest breath values in 1971 and 1972
            for subjects who were restudied in 1974

Subject	1971	1972	1974
1	178	217	209
2	204	211	183
18	147	164	125
34		133	149
36		131	116
37		129	123
41	121	117	126
42	100	114	141
43		116	108

Control end tidal P_{O_2}, P_{CO_2}, ventilation, oxygen consumption, carbon dioxide output and respiratory quotient for the CO_2 response studies in 1974

ject o.	$P_{ET}O_2$ kPa	$P_{ET}CO_2$ kPa	V_E (CD4) $\ell.min^{-1}$ BTPS	V_{O_2} m/min^{-1}	V_{CO_2} m/min^{-1}	RQ
1	13.31	5.57	7.46	243	234	0.96
2	12.77	5.65	9.56	264	246	0.93
8	15.21	3.79	13.27	298	232	0.78
4	12.97	5.37	7.32	282	224	0.80
6	14.61	4.32	12.00	394	286	0.72
7	14.36	4.88	8.76	243	234	0.96
1	13.79	4.99	9.16	294	229	0.78
2	13.21	5.37	7.75	268	192	0.71
3	13.69	4.04	10.10	260	162	0.68

TABLE 9 CO_2 response results in 1974. To show the slope (S), the intercept (B) of the hypoxic and hyperoxic lines and also the PO_2 at which they were measured. The ratio of hypoxic S to hyperoxic S, the ΔS and the $\Delta V50$ are also shown (see text for explanation).

($1\ kPa = 7.5\ mmHg$)

Subject No.	HYPEROXIA			HYPOXIA			Hypoxic S / Hyperoxic S	ΔS	$\Delta V50$
	S $\ell.min^{-1}kPa^{-1}$	B kPa	$P_{ET}O_2$ kPa	S $\ell.min^{-1}kPa^{-1}$	B kPa	$P_{ET}O_2$ kPa		$\ell.min^{-1}$	$\ell.min^{-1}$
1	8.42	5.20	26.1	15.22	4.18	6.38	1.80	6.80	18
2	25.61	5.16	26.3	41.01	4.47	6.44	1.60	15.40	36
18	8.26	2.62	25.5	23.78	3.26	6.64	2.87	15.54	2.5
34	9.01	4.21	25.3	16.72	4.27	6.25	1.85	7.71	8
36	7.54	2.77	26.2	13.80	2.81	6.66	1.83	6.26	9
37	23.98	4.75	25.9	65.89	4.83	6.63	2.74	41.81	0
41	7.40	4.21	26.5	17.66	4.44	6.24	2.38	10.26	4
42	14.09	4.47	26.0	22.19	4.20	6.52	1.57	8.10	12.7
43	12.50	4.31	26.5	21.41	3.74	6.48	1.71	8.91	10

TABLE 10   The ages, heights, weights, lung volumes and transfer factor for carbon monoxide in subjects I–IV

Subject	I	II	III	IV
Age (years)	22	29	33	22
Weight (kg)	60	62	82	72
Height (cm)	165	180	174	175
$FEV_{1.0}$ (litres ATPS)	3.35	4.40	4.35	4.60
FVC (litres ATPS)	4.25	5.35	5.30	5.25
FEV/FVC (%)	79	82	82	88
Total lung capacity (litres BTPS)	5.51	7.40	6.79	6.71
Vital capacity (litres BTPS)	4.41	5.90	5.52	5.39
Residual volume (litres BTPS)	1.10	1.50	1.27	1.32
RV/TLC (%)	20	20	19	20
TCO $mmol.min^{-1}$ kPa^{-1}				
Actual	8.59	9.23	11.50	9.97
Predicted ± SD	11.37 ± 1.74	12.19 ± 1.74	10.80	11.98 ± 1.74

TABLE 11 O_2 uptake, CO_2 output and respiratory quotient in transient hypoxia studies at rest and on exercise.

Subject	Study No	VO_2 ml.min^{-1}	VCO_2 ml.min^{-1}	R.Q.
REST				
I	N211	232	184	0.79
	N220	235	179	0.76
II	N206	281	223	0.79
	N207	225	134	0.60
III	N208	297	233	0.78
	N214	271	192	0.71
IV	N213	317	278	0.88
	N223	232	179	0.77
EXERCISE				
I	N226	864	733	0.85
	N212	887	775	0.87
II	N210	890	738	0.83
	N2EXO1	911	729	0.80
III	N209	960	874	0.91
	N215	1095	865	0.79
IV	N2EXO2	1167	896	0.77
	N2EXO4	1111	1025	0.92

TABLE 12   Control ventilation, PO_2, PCO_2 ($\pm$ SD) for individual transient hypoxia studies at rest in subject I. The number of breaths of nitrogen inhaled, the lowest $P_{ET}O_2$ resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position resulting are shown.

For each study the highest $\dot{V}_E$ inst is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ ℓ.min⁻¹ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst ℓ.min⁻¹ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	6.93 ± 0.63	13.39 ± 0.17	4.47 ± 0.07	10.51	7.64	7	110
1	6.89 ± 1.23	13.02 ± 0.75	4.49 ± 0.22	12.01	7.21	1	104
1	6.42 ± 0.67	13.30 ± 0.17	4.30 ± 0.08	11.63	6.98	5	108
1	12.35 ± 0.62	13.82 ± 0.13	5.10 ± 0.06	11.20	12.39	2	100
1	11.32 ± 0.64	13.02 ± 0.18	5.28 ± 0.06	10.65	13.04	7	115 *
1	9.04 ± 0.81	12.69 ± 0.26	5.47 ± 0.07	10.66	9.29	3	102
3	6.50 ± 0.90	13.14 ± 0.63	4.56 ± 0.14	8.42	6.54	6	100
3	6.57 ± 0.69	13.38 ± 0.27	4.39 ± 0.10	8.34	6.84	8	104
3	6.79 ± 0.51	13.52 ± 0.12	4.17 ± 0.05	8.54	7.68	7	113
3	11.91 ± 0.66	13.46 ± 0.11	5.20 ± 0.05	7.81	13.13	7	110
3	12.07 ± 0.78	13.58 ± 0.12	5.14 ± 0.05	7.62	12.82	6	106
3	8.89 ± 0.78	13.38 ± 0.61	5.30 ± 0.15	8.31	9.13	5	102
5	8.12 ± 0.87	13.95 ± 0.33	4.46 ± 0.09	5.78	9.41	7	115
5	6.85 ± 0.53	13.46 ± 0.16	4.31 ± 0.07	6.06	7.98	8	116 *
5	6.66 ± 0.63	13.35 ± 0.25	4.29 ± 0.07	8.85	7.98	7	119 *
5	11.81 ± 0.48	13.42 ± 0.10	5.16 ± 0.03	5.86	13.28	7	112 *
5	11.87 ± 0.81	13.51 ± 0.25	5.10 ± 0.07	5.78	14.69	7	123 *
5	11.17 ± 0.71	12.89 ± 0.09	5.38 ± 0.04	5.53	14.36	5	128 *
7	6.46 ± 0.82	13.18 ± 0.38	4.61 ± 0.12	4.87	8.49	9	131 *
7	5.81 ± 0.61	12.34 ± 0.42	4.66 ± 0.09	4.53	8.28	8	142 *
7	7.03 ± 0.44	13.40 ± 0.14	4.18 ± 0.05	4.23	8.90	8	126 *
7	11.63 ± 1.11	13.02 ± 0.40	5.31 ± 0.10	4.84	15.64	9	134 *
7	11.94 ± 0.64	13.02 ± 0.40	5.20 ± 0.05	4.64	15.26	9	127 *
7	10.81 ± 0.62	13.30 ± 0.17	5.42 ± 0.04	4.73	16.00	9	148 *

TABLE 13   Control ventilation, PO_2, PCO_2 ($\pm$ SD) for individual transient hypoxia studies at rest in subject II. The number of breaths of nitrogen inhaled, the lowest $P_{ET}O_2$ resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position resulting are shown.

For each study the highest $\dot{V}_E$ inst value is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ $\ell.min^{-1}$ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst $\ell.min^{-1}$ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	7.47 ± 0.73	13.14 ± 0.22	5.04 ± 0.08	11.45	7.70	2	103
1	7.20 ± 0.87	12.09 ± 0.30	5.38 ± 0.06	11.06	8.77	6	121
1	7.27 ± 0.90	12.44 ± 0.25	5.07 ± 0.07	10.92	7.60	1	104
1	6.76 ± 0.67	13.40 ± 0.08	5.12 ± 0.03	11.83	8.21	2	121
1	7.66 ± 0.93	13.39 ± 0.43	5.20 ± 0.11	12.21	8.37	2	109
1	7.04 ± 1.24	13.75 ± 0.15	4.95 ± 0.04	11.55	8.16	4	115
3	7.01 ± 0.61	12.38 ± 0.15	5.20 ± 0.07	8.30	9.44	7	134
3	6.88 ± 0.51	12.67 ± 0.21	5.25 ± 0.08	8.39	9.92	4	144
3	7.24 ± 0.90	12.67 ± 0.12	5.01 ± 0.06	8.03	8.62	5	119
3	7.37 ± 1.01	13.40 ± 0.40	5.16 ± 0.09	8.78	8.05	5	109
3	7.36 ± 0.73	13.84 ± 0.15	5.06 ± 0.05	9.07	7.69	3	104
3	7.40 ± 0.69	13.71 ± 0.12	5.02 ± 0.03	8.96	7.84	9	105
5	7.10 ± 0.81	12.18 ± 0.44	4.94 ± 0.14	5.76	11.89	8	167 *
5	7.54 ± 0.72	13.57 ± 0.41	4.89 ± 0.09	6.72	9.69	8	128 *
5	8.53 ± 0.92	13.37 ± 0.55	4.92 ± 0.10	6.64	8.60	8	100
5	7.22 ± 0.62	13.64 ± 0.20	5.06 ± 0.06	6.71	8.95	8	123 *
5	7.56 ± 0.42	14.04 ± 0.19	4.97 ± 0.04	6.10	9.61	7	127 *
5	7.38 ± 1.00	13.60 ± 0.33	5.06 ± 0.10	6.25	9.33	8	126
7	8.06 ± 0.63	13.57 ± 0.09	5.04 ± 0.06	4.93	10.77	9	133 *
7	7.27 ± 0.69	12.85 ± 0.14	5.16 ± 0.05	4.86	10.94	9	150 *
7	7.45 ± 1.01	12.75 ± 0.43	5.00 ± 0.10	5.18	9.13	9	122
7	6.82 ± 0.70	13.50 ± 0.14	5.14 ± 0.07	4.82	9.98	8	146 *
7	6.87 ± 0.67	12.93 ± 0.24	5.23 ± 0.04	4.91	9.39	9	136
7	7.45 ± 0.92	12.40 ± 0.65	5.02 ± 0.09	4.90	8.84	4	118 *

TABLE 14   Control ventilation, PO_2, PCO_2 (± SD) for individual transient hypoxia studies at rest in subject III. The number of breaths of nitrogen inhaled, the lowest P_{O_2} resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position resulting are shown.

For each study the highest $\dot{V}_E$ inst is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ $\ell.min^{-1}$ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst $\ell.min^{-1}$ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	9.03 ± 0.70	13.62 ± 0.24	5.24 ± 0.07	11.40	10.15	3	112
1	8.65 ± 0.35	13.85 ± 0.15	4.99 ± 0.06	11.60	9.27	5	107
1	9.18 ± 0.57	13.82 ± 0.29	5.00 ± 0.08	11.34	8.38	7	91
1	7.98 ± 1.01	13.23 ± 0.27	5.16 ± 0.10	11.47	8.30	2	104
1	8.20 ± 1.70	12.98 ± 0.48	5.16 ± 0.11	11.49	7.88	1	96
1	7.96 ± 0.61	12.69 ± 0.30	5.15 ± 0.09	11.69	11.94	4	150 *
3	8.57 ± 0.56	13.64 ± 0.30	5.28 ± 0.09	9.22	9.55	5	111
3	8.11 ± 1.61	12.89 ± 0.27	5.38 ± 0.09	8.45	11.67	7	143 *
3	6.05 ± 0.72	13.64 ± 0.27	5.01 ± 0.09	9.18	7.84	7	97
3	8.11 ± 0.72	13.54 ± 0.20	5.08 ± 0.06	9.11	8.36	5	103
3	7.43 ± 0.81	12.89 ± 0.23	5.19 ± 0.08	8.28	9.03	5	121
5	8.01 ± 0.94	13.22 ± 0.19	5.26 ± 0.08	6.73	9.66	5	120
5	8.03 ± 2.09	12.63 ± 0.41	5.41 ± 0.18	6.34	12.01	7	149
5	8.75 ± 0.74	14.08 ± 0.19	4.87 ± 0.06	6.72	9.13	4	104
5	3.21 ± 1.06	12.94 ± 0.26	5.21 ± 0.10	6.71	9.92	7	120
5	7.75 ± 0.53	13.33 ± 0.15	5.19 ± 0.06	5.76	9.89	6	127 *
5	8.52 ± 0.54	13.27 ± 0.29	5.17 ± 0.09	7.00	9.25	7	108
7	7.88 ± 0.78	13.25 ± 0.15	5.29 ± 0.06	4.70	12.12	6	153 *
7	9.16 ± 0.91	14.36 ± 0.12	4.95 ± 0.06	5.69	12.87	8	140 *
7	8.98 ± 0.79	13.95 ± 0.23	4.89 ± 0.08	4.65	11.85	8	131 *
7	7.63 ± 0.75	13.30 ± 0.56	5.16 ± 0.10	4.61	11.29	8	147 *
7	8.36 ± 1.07	13.30 ± 0.56	5.16 ± 0.10	5.56	10.59	9	126 *
7	8.09 ± 0.81	13.38 ± 0.17	5.05 ± 0.08	4.66	12.47	8	154 *

TABLE 15   Control ventilation, PO_2, PCO_2 ($\pm$ SD) for individual transient hypoxia studies at rest in subject IV. The number of breaths of nitrogen inhaled, the lowest P_{ETO_2} resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position resulting are shown.

For each study the highest $\dot{V}_E$ inst is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ ℓ.min⁻¹ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst ℓ.min⁻¹ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	8.51 ± 0.67	14.4 ± 0.16	4.96 ± 0.04	11.38	8.56	7	100
1	7.66 ± 1.01	13.90 ± 0.33	4.93 ± 0.10	12.04	9.68	6	126
1	8.32 ± 0.97	13.93 ± 0.29	4.88 ± 0.07	12.50	8.77	1	105
1	8.88 ± 1.42	13.47 ± 0.29	5.66 ± 0.09	10.34	9.76	3	109
1	7.92 ± 1.19	13.53 ± 0.19	5.70 ± 0.07	11.23	7.80	4	98
1	9.28 ± 1.66	13.13 ± 0.53	5.66 ± 0.11	11.28	11.46	6	123
3	7.35 ± 1.12	13.32 ± 1.33	5.00 ± 0.09	8.18	8.56	7	116
3	7.98 ± 0.97	13.81 ± 0.73	4.99 ± 0.19	9.54	9.13	7	114
3	8.86 ± 1.38	-	-	9.11	10.43	8	117
3	8.22 ± 1.27	13.19 ± 0.23	5.77 ± 0.08	7.39	11.16	5	135 *
3	8.28 ± 0.98	13.49 ± 0.23	5.67 ± 0.08	7.77	11.34	7	136 *
3	8.73 ± 1.88	13.46 ± 0.44	5.61 ± 0.12	8.11	12.84	6	147 *
5	9.14 ± 1.32	14.00 ± 0.44	4.85 ± 0.12	7.83	12.60	7	137 *
5	7.75 ± 1.06	13.15 ± 0.24	5.11 ± 0.08	7.45	11.18	6	144 *
5	7.72 ± 0.88	14.01 ± 0.13	4.92 ± 0.05	7.60	9.58	10	124 *
5	8.14 ± 1.28	13.23 ± 0.29	5.69 ± 0.09	5.44	11.00	6	135 *
5	9.85 ± 1.71	14.12 ± 0.41	5.41 ± 0.13	5.93	10.67	5	108
5	8.22 ± 1.12	13.45 ± 0.15	5.54 ± 0.08	6.40	11.41	5	138 *
7	7.82 ± 0.71	14.02 ± 0.32	4.99 ± 0.09	4.52	12.40	8	158 *
7	6.84 ± 0.95	13.30 ± 0.48	5.00 ± 0.08	4.66	12.37	8	180 *
7	7.52 ± 1.41	13.69 ± 0.37	4.89 ± 0.10	5.91	9.81	5	130
7	8.04 ± 2.22	12.95 ± 0.51	5.80 ± 0.17	4.18	13.83	8	172 *
7	8.97 ± 1.11	14.41 ± 0.22	5.67 ± 0.13	4.06	16.59	8	184 *
7	8.67 ± 1.76	14.0 ± 0.26	5.60 ± 0.08	4.91	12.53	9	144 *

...breaths of N2 on exercise. The position of the first breath to achieve significance after the first breath of N2 is also shown.

Subject	REST				EXERCISE			
	No. of N2 Breaths	HBV	HBV Position	First to sig.	No. of N2 Breaths	HBV	HBV Position	First to sig.
I	1	100	3	–	1	105	7	–
	3	103	6	–	2	112	7	3
	5	119	7	7	3	113	5	5
	7	133	9	8	4	117	6	5
II	1	103	1	–	1	102	8	–
	3	115	6	3	2	112	5	4
	5	127	8	6	3	109	5	5
	7	132	9	5	4	127	6	5
III	1	102	4	–	1	108	3	2
	3	107	7	7	2	108	3	3
	5	119	7	4	3	122	4	3
	7	140	8	4	4	137	7	3
IV	1	101	6	–	1	109	4	4
	3	113	6	6	2	105	6	–
	5	119	6	4	3	108	5	5 *
	7	157	8	5	4	113	6	6

* on 95% confidence

TABLE 17   Control ventilation, PO_2 and PCO_2 (± SD) for individual transient hypoxia studies on exercise in subject I. The number of breaths of nitrogen inhaled, the lowest $PETO_2$ resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position resulting are shown. For each study the highest $\dot{V}_E$ inst is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ ℓ.min⁻¹ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst ℓ.min⁻¹ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	23.26 ± 1.93	14.11 ± 0.21	5.25 ± 0.11	9.52	25.57	7	109
1	25.74 ± 1.77	14.57 ± 0.10	5.03 ± 0.06	9.96	27.97	4	108
1	25.08 ± 1.74	14.37 ± 0.19	5.10 ± 0.10	10.28	26.94	7	107
1	22.34 ± 2.58	13.62 ± 0.19	5.48 ± 0.13	9.75	26.23	5	117
1	21.91 ± 2.65	13.40 ± 0.38	5.59 ± 0.15	9.14	25.07	6	114
1	21.98 ± 1.75	13.62 ± 0.24	5.68 ± 0.09	9.45	25.17	3	114
2	23.44 ± 1.59	14.15 ± 0.21	5.22 ± 0.10	6.94	32.00	8	136 *
2	25.15 ± 1.55	14.39 ± 0.15	5.13 ± 0.09	6.83	31.30	7	124 *
2	24.38 ± 1.65	14.29 ± 0.28	5.13 ± 0.11	6.63	28.26	5	115 *
2	24.14 ± 0.97	14.04 ± 0.20	5.29 ± 0.09	6.10	27.63	5	114 *
2	23.98 ± 1.99	13.86 ± 0.19	5.36 ± 0.08	6.70	28.89	5	120 *
2	23.20 ± 1.84	13.76 ± 0.37	5.55 ± 0.12	6.65	27.27	7	117 *
3	24.44 ± 1.47	14.34 ± 0.21	5.21 ± 0.10	5.22	32.10	5	131 *
3	24.99 ± 1.57	14.28 ± 0.23	5.19 ± 0.10	5.07	28.25	5	113 *
3	25.46 ± 1.73	14.48 ± 0.17	5.05 ± 0.09	5.38	28.84	5	113
3	23.45 ± 1.51	13.71 ± 0.20	5.39 ± 0.12	4.63	25.33	5	108
3	24.29 ± 1.22	14.01 ± 0.21	5.41 ± 0.13	4.74	27.31	7	112 *
3	24.10 ± 1.26	14.26 ± 0.22	5.35 ± 0.09	5.17	26.87	9	111 *
4	24.82 ± 2.41	14.14 ± 0.40	5.28 ± 0.16	3.69	32.34	5	130 *
4	24.84 ± 1.43	14.42 ± 0.19	5.10 ± 0.08	4.16	29.12	8	117 *
4	24.42 ± 2.33	14.30 ± 0.29	5.15 ± 0.12	4.34	30.67	6	125 *
4	23.99 ± 2.46	13.93 ± 0.18	5.28 ± 0.08	3.46	30.05	7	125 *
4	21.61 ± 2.11	13.40 ± 0.44	5.52 ± 0.16	3.26	27.18	6	125 *
4	23.83 ± 1.81	14.18 ± 0.17	5.40 ± 0.08	3.79	26.78	5	112 *

TABLE 18 Control ventilation, PO_2 and PCO_2 (± SD) for individual transient hypoxia studies on exercise in Subject II. The number of breaths of nitrogen inhaled, the lowest $P_{ET}O_2$ resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position resulting are shown. For each study the highest $\dot{V}_E$ inst is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ ℓ.min⁻¹ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst ℓ.min⁻¹ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	24.44 ± 1.22	14.43 ± 0.18	4.82 ± 0.09	10.09	27.38	5	112 *
1	23.74 ± 1.65	14.17 ± 0.22	4.73 ± 0.09	9.80	26.03	7	109
1	23.84 ± 1.27	14.31 ± 0.20	4.56 ± 0.12	10.37	22.56	7	95
1	25.28 ± 1.60	14.61 ± 0.17	5.02 ± 0.08	10.65	23.70	4	93
1	23.73 ± 1.91	14.38 ± 0.17	5.04 ± 0.09	10.65	26.07	5	109
1	23.73 ± 1.36	14.43 ± 0.25	4.98 ± 0.10	10.56	24.65	7	103
2	23.71 ± 1.25	14.33 ± 0.26	4.84 ± 0.12	7.80	26.77	7	112 *
2	24.73 ± 1.17	14.36 ± 0.16	4.78 ± 0.09	6.87	28.72	4	116 *
2	23.77 ± 1.48	14.19 ± 0.17	4.63 ± 0.08	6.84	28.48	5	119 *
2	24.48 ± 1.62	14.21 ± 0.25	5.16 ± 0.11	6.69	28.78	6	117 *
2	23.86 ± 2.77	14.59 ± 0.13	4.92 ± 0.09	7.48	27.73	6	116
2	24.01 ± 2.58	14.42 ± 0.16	5.01 ± 0.06	7.60	26.84	5	111
3	22.40 ± 1.99	14.56 ± 0.16	4.76 ± 0.08	5.23	25.98	3	115 *
3	24.23 ± 1.14	14.29 ± 0.21	4.76 ± 0.10	4.93	25.85	5	106
3	23.35 ± 1.32	14.57 ± 0.24	4.61 ± 0.12	5.66	27.36	5	117 *
3	25.54 ± 1.39	14.52 ± 0.15	4.99 ± 0.09	5.31	26.61	9	104
3	24.41 ± 1.66	14.62 ± 0.21	4.93 ± 0.10	6.32	28.08	5	115 *
3	25.91 ± 2.57	14.51 ± 0.13	4.81 ± 0.15	6.21	28.87	6	111
4	24.02 ± 1.41	14.37 ± 0.22	4.80 ± 0.10	4.21	31.87	6	132 *
4	23.59 ± 1.18	14.25 ± 0.15	4.74 ± 0.07	4.25	30.18	6	127 *
4	23.59 ± 2.38	14.25 ± 0.24	4.58 ± 0.09	4.13	32.46	6	137 *
4	24.56 ± 1.50	14.51 ± 0.22	4.99 ± 0.11	3.96	28.62	7	116 *
4	23.96 ± 1.44	14.36 ± 0.21	5.01 ± 0.11	4.22	29.27	6	122 *
4	25.15 ± 2.28	14.33 ± 0.37	5.01 ± 0.15	4.25	32.81	6	130 *

TABLE 19 Control ventilation, PO_2 and PCO_2 ($\pm$ SD) for individual transient hypoxia studies on exercise in subject III. The number of breaths of nitrogen inhaled, the lowest $P_{ET}O_2$ resulting and the highest instantaneous minute ventilation ($\dot{V}_E$ inst) value and position of highest $\dot{V}_E$ inst resulting are shown. For each study the highest $\dot{V}_E$ inst is expressed as a percentage of the control ventilation to give individual highest breath values. Highest breath values outside 2 standard deviations of the control ventilation are indicated by an asterisk.

No. of breaths of N_2	Control $\dot{V}_E$ $\ell.min^{-1}$ BTPS	Control PO_2 kPa	Control PCO_2 kPa	Lowest PO_2 kPa	Highest $\dot{V}_E$ inst $\ell.min^{-1}$ BTPS	Position of highest $\dot{V}_E$ inst	Highest Breath Value % control
1	23.80 ± 1.39	13.04 ± 0.17	5.69 ± 0.08	9.18	25.88	4	108
1	23.75 ± 1.10	12.92 ± 0.19	5.65 ± 0.08	9.32	25.52	5	107
1	23.61 ± 1.62	13.06 ± 0.24	5.58 ± 0.10	8.96	26.56	6	112
1	23.22 ± 1.55	13.59 ± 0.18	5.39 ± 0.07	9.37	25.34	3	109
1	24.31 ± 2.45	13.33 ± 0.21	5.38 ± 0.07	9.23	28.39	3	116
2	22.85 ± 1.27	13.27 ± 0.17	5.79 ± 0.08	5.78	26.39	4	115 *
2	24.19 ± 1.32	13.19 ± 0.20	5.61 ± 0.09	6.36	27.80	4	114 *
2	23.42 ± 1.22	13.15 ± 0.19	5.55 ± 0.07	6.75	25.85	3	110
2	23.46 ± 1.12	13.60 ± 0.18	5.61 ± 0.08	6.39	25.22	5	107
2	23.60 ± 1.28	13.50 ± 0.19	5.44 ± 0.08	6.18	26.20	6	111 *
3	23.60 ± 1.02	13.13 ± 0.22	5.82 ± 0.09	3.99	29.64	4	125 *
3	23.89 ± 1.47	13.14 ± 0.37	5.70 ± 0.14	4.77	32.27	4	135 *
3	23.26 ± 2.16	13.03 ± 0.24	5.55 ± 0.09	4.53	28.36	5	121 *
3	23.69 ± 1.85	13.50 ± 0.16	5.49 ± 0.09	5.32	28.38	5	119 *
3	23.05 ± 1.08	13.52 ± 0.16	5.32 ± 0.07	4.48	28.50	5	123 *
4	22.46 ± 1.86	13.19 ± 0.17	5.72 ± 0.08	2.71	36.41	6	162 *
4	24.72 ± 1.29	13.05 ± 0.24	5.68 ± 0.11	3.14	38.16	7	154 *
4	23.41 ± 2.20	13.05 ± 0.16	5.49 ± 0.07	3.30	37.63	7	160 *
4	24.23 ± 1.26	13.37 ± 0.19	5.60 ± 0.09	3.82	31.88	5	131 *
4	23.44 ± 1.86	13.64 ± 0.22	5.35 ± 0.09	3.86	31.53	6	134 *
4	23.23 ± 1.69	13.31 ± 0.20	5.35 ± 0.08	3.60	29.95	7	128 *

TABLE 21 The table shows the control $P_{ET}O_2$ and ventilation in all 4 subjects for the rest and exercise transient studies. Also shown are the mean lowest $P_{ET}O_2$'s and highest $\dot{V}_E$ inst's obtained with two different stimulus levels of inhaled N_2. The differences between the highest $\dot{V}_E$ inst and the control $\dot{V}_E$ are calculated and shown in the third column for each subject.

	SUBJECT I			SUBJECT II			SUBJECT III			SUBJECT IV		
	$P_{ET}O_2$ kPa	$\dot{V}_E$ ℓ.min BTPS	Difference of highest $\dot{V}_E$ inst from control $\dot{V}_E$	$P_{ET}O_2$ kPa	$\dot{V}_E$ ℓ.min BTPS	Difference of highest $\dot{V}_E$ inst from control $\dot{V}_E$	$P_{ET}O_2$ kPa	$\dot{V}_E$ ℓ.min BTPS	Difference of highest $\dot{V}_E$ inst from control $\dot{V}_E$	$P_{ET}O_2$ kPa	$\dot{V}_E$ ℓ.min BTPS	Difference of highest $\dot{V}_E$ inst from control $\dot{V}_E$
Rest Control	13.26	8.98		13.14	7.32		13.30	8.28		13.64	8.27	
Transient 1	5.81	11.28	2.30	6.36	9.67	2.35	4.97	11.9	3.62	6.77	11.07	2.80
Transient 2	4.64	12.10	3.12	4.93	9.80	2.48				4.70	12.90	4.63
Exercise Control	14.07	23.94		14.40	24.11		13.27	23.55		13.49	30.25	
Transient 1	5.03	28.12	4.18	5.61	27.13	3.02	4.61	29.43	5.88	5.72	34.47	4.22
Transient 2	3.78	29.40	5.46	4.17	30.90	6.79				4.16	36.10	5.85

TABLE 22   The three columns show for all 4 subjects at rest
            and on exercise:

1) the two $P_{ET}O_2$'s at which comparisons of venti-
   latory response to transient hypoxia have been
   made (lowest $P_{ET}O_2$ range).

2) the difference between the mean highest venti-
   latory responses at these $P_{ET}O_2$s.

3) Ratio of the difference in ventilation to the
   difference in $P_{ET}O_2$'s at which the measurements
   of ventilation have been made.

	Lowest $P_{ET}O_2$ Range kPa	Difference in ventilatory response L.min^{-1} BTPS	Ratio $\Delta V_E / \Delta P_{ET}O_2$
REST			
SUBJECT			
I	5.81 - 4.64	1.30	1.11
II	6.36 - 4.90	0.37	0.25
III	6.54 - 4.97	1.78	1.13
IV	6.77 - 4.70	2.33	1.13
EXERCISE			
SUBJECT			
I(i)	6.64 - 5.03	0.85	0.52
I(ii)	5.03 - 3.78	1.82	1.46
II	5.61 - 4.17	3.87	2.69
III(i)	6.29 - 4.61	3.07	1.83
III(ii)	4.61 - 3.40	4.80	3.97
IV	5.72 - 4.16	1.61	1.03

TABLE 23   Values for parameters 1, 2 and 3 from progressive hypoxia studies at rest in subjects I-IV. The mean $P_{ET}CO_2$ ± SD at which the studies were conducted is shown and also the root mean square residual deviation for the best fitting curve. See text for explanation.

	Parameter 1 ℓ.min⁻¹ BTPS	Parameter 2 ℓ.min⁻¹ kPa	Parameter 3 kPa	Mean PCO_2 ± SD kPa	Root Mean Square Residual Deviation
Subject I					
Expt 1	6.54	9.36	3.76	5.17 ± 0.09	0.91
2	7.00	9.22	3.92	5.09 ± 0.10	1.06
3	7.51	9.15	3.59	5.09 ± 0.11	1.02
Mean	7.02	9.24	3.76	5.12	
Range	6.54 - 7.51	9.15 - 9.36	3.59 - 3.92	5.09 - 5.17	
Subject II					
Expt 1	7.40	2.46	4.82	4.68 ± 0.10	0.84
2	8.61	4.13	4.46	4.84 ± 0.06	1.03
3	8.16	5.82	3.62	4.63 ± 0.06	1.20
Mean	8.06	4.15	4.30	4.72	
Range	7.40 - 8.61	2.46 - 5.82	3.62 - 4.82	4.63 - 4.84	
Subject III					
Expt 1	8.42	11.03	4.42	5.30 ± 0.10	1.06
2	8.54	8.53	4.12	5.26 ± 0.09	1.01
3	-	-	-	-	-
Mean	8.48	9.77	4.27	5.28	
Range	8.42 - 8.54	8.53 - 11.03	4.12 - 4.42	5.26 - 5.30	
Subject IV					
Expt 1	7.26	6.24	4.08	5.41 ± 0.09	1.49
2	7.56	3.58	4.01	5.12 ± 0.11	1.19
3	7.57	4.03	4.39	4.93 ± 0.13	1.58
Mean	7.46	4.62	4.16	5.15	
Range	7.26 - 7.57	3.58 - 6.24	4.01 - 4.39	4.93 - 5.41	

TABLE 24   Mean values for oxygen uptake, carbon dioxide output and respiratory quotient during the progressive hypoxia on exercise studies.

Subject	VO_2 $ml.min^{-1}$	VCO_2 $ml.min^{-1}$	R.Q.
I	844	662	0.77
II	831	641	0.76
III	1051	900	0.86
IV	1221	966	0.79

TABLE 25 Values for parameters 1, 2 and 3 from progressive hypoxia studies on exercise in subjects I–IV. The mean $P_{ET}CO_2$ ± SD at which the studies were conducted is shown and also the root mean square residual deviation for the best fitting curve. See text for explanation.

	Parameter 1 $\ell.min^{-1}$ BTPS	Parameter 2 $\ell.min^{-1}$ kPa	Parameter 3 kPa	Mean PCO_2 ± SD kPa	Root Mean Square Residual Deviation
Subject I					
Expt 1	20.53	33.52	4.38	5.35 ± 0.10	3.14
2	19.75	35.00	4.74	5.22 ± 0.11	3.81
3	20.79	41.31	4.83	4.96 ± 0.10	4.17
Mean	20.22	38.27	4.65	5.18	
Range	19.75 – 20.79	35.0 – 41.31	4.38 – 4.83	4.96 – 5.35	
Subject II					
Expt 1	18.05	27.62	4.46	5.07 ± 0.10	2.82
2	8.29	29.43	4.10	4.83 ± 0.09	2.04
3	21.96	30.16	2.41	4.80 ± 0.29	3.09
Mean	16.10	29.07	3.66	4.90	
Range	8.29 – 21.96	27.62 – 30.16	2.41 – 4.46	4.80 – 5.07	
Subject III					
Expt 1	16.25	42.63	4.89	5.82 ± 0.17	2.92
2	22.06	35.09	4.84	6.27 ± 0.20	3.56
3	20.32	36.96	4.36	5.75 ± 0.11	2.81
Mean	19.54	38.22	4.70	5.95	
Range	16.25 – 22.06	35.09 – 42.63	4.36 – 4.89	5.75 – 6.27	
Subject IV					
Expt 1	29.81	22.38	3.37	5.49 ± 0.17	3.68
2	23.19	41.61	4.33	5.37 ± 0.17	5.57
3	31.05	36.37	4.14	5.27 ± 0.13	4.83
Mean	28.02	33.46	3.95	5.38	
Range	23.19 – 31.05	22.38 – 41.61	3.37 – 4.33	5.27 – 5.49	

TABLE 26   Steady state CO2 response at rest in 4 subjects. The results of three studies on each subject are shown with the mean values appended. The columns show the P_{O_2} at which the CO2 response line was measured, the slope of the CO2 response line (S_{CO_2}), the intercept of the CO2 response line (B_{CO_2}) and the ratio of the slopes at low P_{O_2} to the hyperoxic slope. The variability of the measurements of slopes at a given P_{O_2} is shown as the difference between the highest and lowest values for slope expressed as a percentage of the mean value for that P_{O_2}.

Subject	$P_{ET}O_2$ kPa				S_{CO_2} $\ell.min^{-1} kPa^{-1}$				B_{CO_2} kPa				Ratio % hyperoxic				Variability Difference as % mean
	1	2	3	Mean	1	2	3	Mean	1	2	3	Mean	1	2	3	Mean	
I	25.6	25.5	26.0	25.7	12.96	14.16	12.97	13.36	4.10	4.51	4.50	4.37					8.9
	9.37	9.19	9.24	9.26	14.60	19.27	20.18	18.01	4.74	4.38	4.55	4.55	112	136	155	134	31.0
	6.66	6.57	6.59	6.60	17.26	22.79	23.56	21.20					133	160	181	158	29.7
	5.14	5.38	5.24	5.25	20.66	28.73	26.31	25.23					159	202	202	188	32.0
II	30.2	29.8	27.4	29.1	19.82	21.68	20.07	20.52	4.85	4.45	4.84	4.71					9.1
	9.22	9.14	9.20	9.18	32.80	29.14	27.25	29.73	4.99	4.51	4.91	4.80	165	134	135	144	18.7
	6.79	6.63	6.70	6.70	38.97	34.24	34.17	35.79				4.80	196	157	170	174	19.0
	5.27	5.25	5.38	5.30	42.41	36.31	38.33	39.02					213	167	190	190	15.6
III	27.6	26.6	29.5	27.9	16.94	12.50	13.93	14.45	5.48	4.74	4.84	5.02					30.7
	9.45	9.11	9.15	9.23	25.19	17.22	20.91	21.10	5.36	4.93	4.96	5.08	148	137	150	146	37.8
	6.55	6.39	6.56	6.50	35.37	13.58	27.18	27.04					208	148	195	187	62.1
	5.17	5.32	5.36	5.28	43.17	26.78	30.14	33.36					254	214	216	230	49.1
IV	26.5	27.8	27.7	27.3	8.99	11.39	11.57	10.65	4.62	4.27	4.26	4.38					24.2
	9.37	9.20	9.27	9.28	10.47	14.90	16.37	13.91	4.96	4.75	4.33	4.68	116	130	141	130	42.4
	6.61	6.21	6.49	6.43	10.85	18.37	16.84	15.35					120	161	145	144	47.2
	5.19	5.05	5.23	5.15	13.16	24.47	25.32	20.98					146	214	218	196	53.9

TABLE 27   Individual, mean values and ranges for parameters 1, 2 and 3 from the steady state CO response studies at rest in the 4 subjects. Parameter 1 is D in the Cunningham equation; parameter 2 is AD and parameter 3 is C. The calculated values for parameter A and the measured values for parameter B in the Cunningham equation are also shown.

	Parameter 1 $\ell.min^{-1}$ kPa	Parameter 2 $\ell.min$ kPa	Parameter 3 kPa	Root Mean Square Residual Deviation	Parameter A	Parameter B
Subject I						
Expt 1	12.71	55.18	1.28	2.30	4.34	4.10
2	12.35	15.82	3.18	1.67	1.28	4.51
3	13.42	30.71	3.35	2.35	2.64	4.50
Mean	12.83	33.90	2.60		2.75	4.37
Range	12.35 – 13.42	15.82 – 55.18	1.28 – 3.35		1.28 – 4.34	4.10 – 4.51
Subject II						
Expt 1	24.23	52.05	2.56	4.63	2.14	4.85
2	21.78	28.17	3.22	6.01	1.29	4.45
3	24.18	24.86	3.64	5.89	1.02	4.84
Mean	23.40	35.03	3.14		1.48	4.77
Range	21.78 – 24.23	24.86 – 52.05	2.56 – 3.64		1.02 – 2.14	4.45 – 4.85
Subject III						
Expt 1	16.63	62.63	2.84	3.27	3.76	5.48
2	11.39	24.87	3.64	2.15	2.18	4.74
3	11.70	70.93	1.64	1.93	6.06	4.84
Mean	13.24	52.81	2.71		4.00	5.02
Range	11.7 – 16.63	24.87 – 70.93	1.64 – 3.64		2.18 – 6.06	4.74 – 5.48
Subject IV						
Expt 1	10.86	23.31	3.44	2.99	2.14	4.62
2	10.37	28.01	3.16	2.13	2.70	4.27
3	8.07	17.06	1.62	1.35	2.11	4.26
Mean	9.76	22.79	2.74		2.31	4.38
Range	8.07 – 10.86	17.06 – 28.01	1.62 – 3.44		2.11 – 2.70	4.26 – 4.62

TABLE 28   Values for oxygen uptake, carbon dioxide output and respiratory quotient for the studies of ventilatory response to CO_2 on exercise in all 4 subjects.

Subject	VO_2 ml.min^{-1}			VCO_2 ml.min^{-1}			R.Q.		
	1	2	Mean	1	2	Mean	1	2	Mean
HYPEROXIC									
I	881	961	921	794	684	739	0.91	0.71	0.81
II	807	755	831	768	652	710	0.85	0.86	0.86
III	-	1098	-	-	970	-	-	0.88	-
IV	-	1332	-	-	984	-	-	0.74	-
HYPOXIC									
I	896	905	901	887	705	796	0.99	0.78	0.89
II	821	810	816	671	613	642	0.82	0.76	0.79
III	1084	1053	1069	853	903	878	0.79	0.86	0.83
IV	1302	1054	1178	1023	862	943	0.78	0.82	0.80

TABLE 29 Steady state CO_2 response on exercise in subject I–IV. The $P_{ET}O_2$ at which the measurements were made and the slopes (S_{CO_2}) and intercepts (B_{CO_2}) of the best fitting straight line are shown. Results of two studies in each subject in hypoxia and hyperoxia are given with mean values. The $P_{ET}O_2$ of the hypoxic line is shown ± SD.

Hyperoxic

Subject	$P_{ET}O_2$ (kPa)			S_{CO_2} .min⁻¹ kPa			B_{CO_2} (kPa)		
	1	2	Mean	1	2	Mean	1	2	Mean
I	23.05	26.61	24.83	17.49	9.85	13.67	3.61	2.46	3.03
II	24.99	27.28	26.13	22.35	20.33	21.34	3.44	4.06	3.75
III	26.20	30.63	28.41	13.85	16.85	15.35	4.62	4.60	4.61
IV	25.20	24.90	25.10	12.38	12.32	12.35	2.72	2.81	2.77
Mean			26.12			15.68			3.54

Hypoxic

Subject	$P_{ET}O_2$ (kPa)			S_{CO_2} .min⁻¹ kPa			B_{CO_2} (kPa)		
	1	2	Mean	1	2	Mean	1	2	Mean
I	6.75 ± 0.04	6.59 ± 0.14	6.67	15.32	16.40	15.86	2.88	2.96	2.92
II	6.68 ± 0.08	6.63 ± 0.14	6.66	33.51	32.28	32.89	4.14	4.14	4.14
III	6.58 ± 0.11	6.41 ± 0.12	6.50	13.85	16.97	15.41	2.70	3.10	2.90
IV	6.64 ± 0.22	6.28 ± 0.03	6.46	19.24	35.55	27.39	3.42	4.03	3.72
Mean			6.57			22.89			3.42

TABLE 30   To show the individual and mean ventilations derived from the steady state CO_2 response lines on exercise at the control PCO_2. The table lists the control PCO_2 and the derived ventilation for subjects I-IV for the hypoxic and hyperoxic studies. The differences in ventilation at control PCO_2 between the hypoxic and hyperoxic studies are also shown.

Subject	1		2		Mean	
	PCO_2 kPa	V_E $\ell.min^{-1}$ BTPS	PCO_2 kPa	V_E $\ell.min^{-1}$ BTPS	PCO_2 kPa	V_E $\ell.min^{-1}$ BTPS
HYPEROXIC						
I	5.28	29.2	5.31	28.1	5.30	28.7
II	4.82	30.8	5.18	22.8	5.00	26.8
III	-	-	5.99	23.4	5.99	23.4
IV	5.47	34.0	5.24	29.9	5.31	32.0
HYPOXIC						
I	5.37	38.1	4.90	31.8	5.14	35.0
II	5.18	34.9	5.11	31.3	5.15	33.1
III	5.46	38.2	5.90	44.1	5.68	41.2
IV	5.61	42.1	5.44	50.1	5.53	46.1

HYPOXIC - HYPEROXIC V_E

$\ell.min^{-1}$ BTPS

I	6.3
II	6.3
III	17.8
IV	14.1

TABLE 31   Ranking of subjects I-IV for hypoxic drive as assessed by transient, progressive and steady state methods at rest. One point is allocated to the subject with the highest hypoxic drive by a particular method, two points to the second, etc. The subject with the lowest total has the highest hypoxic drive and vice versa. Two totals are shown; the first based solely on one index for each method, i.e. parameter A for steady state, parameter 2 for progressive and the slope $\Delta V_E/\Delta PO_2$ for transient hypoxia; the second total includes points from ranking by other methods in the steady state and transient studies. The values for the different parameters are given in parenthesis.

Subject	I	II	III	IV
Steady State Parameter A	2 (2.75)	4 (1.48)	1 (4.0)	3 (2.31)
Progressive Parameter 2	2 (9.2)	4 (4.2)	1 (9.6)	3 (4.6)
Transient Slope $\Delta V_E/PO_2$	3 (1.11)	4 (0.25)	1 (1.13)	1 (1.13)
Total Points	7	12	3	7
Steady State				
S 6.7/S 26	3 (158)	2 (174)	1 (187)	4 (144)
S 5.3/S 26	4 (188)	3 (190)	1 (230)	2 (196)
Transients				
Mean HBV (5 x N_2)	2 (119)	1 (127)	2 (119)	2 (119)
Mean HBV (7 x N_2)	3 (133)	4 (133)	2 (140)	1 (157)
Grand total points	19	22	9	16

TABLE 32 Ranking of subjects I–IV for hypoxic drive on exercise as described in Table 31. The parameters are given in parenthesis.

Subject	I	II	III	IV
Steady State	3 (6.7)	4 (6.3)	1 (17.8)	2 (14.1)
Progressive	1 (38.3)	4 (29.1)	2 (38.2)	3 (33.5)
Transients slope $\Delta V_E/PO_2$	3 (1.46)	2 (2.49)	1 (3.97)	4 (1.03)
Total points	7	10	4	9
Transients				
Mean HBV (3 x N_2)	2 (113)	3 (109)	1 (122)	4 (108)
Mean HBV (4 x N_2)	3 (117)	2 (127)	1 (137)	4 (113)
Grand total points	12	15	6	17

TABLE 33   Ventilatory response to exercise studies in hypoxia, normoxia and isocapnic hypoxia in subjects I-IV. The table shows the ventilation ($\dot{V}_E$, $\ell.min^{-1}$ BTPS) and the end tidal PCO2 ($P_{ET}CO_2$, kPa) obtaining in the steady state of each condition and the oxygen uptake (VO_2, $ml.min^{-1}$) for the rest and exercise studies in each subject.

Subject	I	II	III	IV
Rest ($\dot{V}O_2$) $ml.min^{-1}$ STPD	236	278	370	264
Hypoxia $\dot{V}_E$	7.55	9.0	9.33	9.59
$P_{ET}CO_2$	4.98	5.16	5.48	5.04
Normoxia $\dot{V}_E$	6.75	8.92	8.78	9.10
$P_{ET}CO_2$	5.31	5.24	5.70	5.30
Isocapnic Hypoxia $\dot{V}_E$	8.91	13.13	12.44	8.86
$P_{ET}CO_2$	5.25	5.20	5.57	5.31
Exercise (VO_2) $ml.min^{-1}$ STPD	868	822	1168	1093
Hypoxia $\dot{V}_E$	26.0	26.32	29.04	34.70
$P_{ET}CO_2$	4.61	5.02	5.30	4.87
Normoxia $\dot{V}_E$	22.84	25.00	25.92	32.82
$P_{ET}CO_2$	5.16	5.18	5.78	5.16
Isocapnic Hypoxia $\dot{V}_E$	34.24	30.74	45.19	47.41
$P_{ET}CO_2$	5.16	5.17	5.75	5.18

TABLE 34 Ventilatory response to exercise in hypoxia, normoxia and isocapnic hypoxia in subjects I-IV. The table shows the end tidal PO_2 values in kPa in each state measured simultaneously with the ventilation and PCO_2 tabulated in Table 33.

Subject	I	II	III	IV
Rest				
Hypoxia	6.27	6.39	6.47	6.48
Normoxia	13.24	12.88	13.15	14.01
Isocapnic Hypoxia	6.56	6.93	6.64	6.62
Exercise				
Hypoxia	6.25	6.61	6.51	6.43
Normoxia	13.49	14.66	12.94	13.71
Isocapnic Hypoxia	6.41	6.81	6.51	6.42

TABLE 35 Ventilatory responses to exercise in hypoxia, normoxia and isocapnic hypoxia in subjects I–IV. The table shows the slope of the line relating ventilation to oxygen uptake (ℓ.min⁻¹ BTPS ℓ⁻¹ STPD) calculated from the rest and exercise measurements. In parenthesis are the values for the ventilation to oxygen uptake ratio from the exercise measurements only. The value of the slopes in hypoxia and isocapnic hypoxia is also expressed as a percentage of the slope in normoxia for each subject.

Subject	I		II		III		IV	
	Slope ℓ.min⁻¹ ℓ⁻¹	Intercept ml. min⁻¹	Slope ℓ.min⁻¹ ℓ⁻¹	Intercept ml. min⁻¹	Slope ℓ.min⁻¹ ℓ⁻¹	Intercept ml. min⁻¹	Slope ℓ.min⁻¹ ℓ⁻¹	Intercept ml. min⁻¹
Hypoxia	29.1 (30)	34	31.8 (32.0)	31	24.6 (24.9)	40	30.2 (31.7)	
% Normoxia	114		105		112		106	
Normoxia	25.4 (26.3)	39	29.5 (30.4)	33	21.4 (22.2)	47	28.6 (30.0)	
Isocapnic Hypoxia	40.0 (39.4)	25	32.3 (37.4)	39	41.0 (38.7)	24	46.5 (43.4)	
% Normoxia	150		123		174		145	

TABLE 36   Heights and weights of subjects
            participating in the diuretic
            study

Subject	Height (cm)	Weight (kg)
JBI	170	60
AGL	180	62
AW	172	71
JTH	183	95
MFS	176	67
DW	173	70
AG	181	85
LC	174	82

TABLE 37   Heights and weights of subjects
            participating in the salbutamol
            study

Subject	Height (cm)	Weight (kg)
JC	178	78
ND	178	70
ADBH	175	77
AGL	180	62
LC	174	82
DJW	173	70
RJEL	180	73

TABLE 38   Carbon dioxide response, plasma urea and electro-
            lytes and end tidal CO_2 tension before and after
            0.242 mmol (80 mg) of frusemide daily for four
            days in eight normal subjects. Values shown are
            means ± SD. *P <0.05. $P_{ET}CO_2$ = end tidal CO_2
            tension; hyperoxic B and hypoxic B = intercept
            of the CO_2 response line in hyperoxia and hypoxia
            respectively; hyperoxic S and hypoxic S = slope
            of the CO_2 response line in hyperoxia and hypo-
            xia respectively; 6.0 mmol/l urea ≡ 36 mg/100 ml.

		Before	After
Urea	(mmol l^{-1})	5.9 ± 0.9	7.6 ± 1.4*
Sodium	(mmol l^{-1})	142.9 ± 2.5	140.5 ± 1.2
Potassium	(mmol l^{-1})	4.20 ± 0.42	3.73 ± 0.37*
Chloride	(mmol l^{-1})	104.6 ± 3.4	99.9 ± 2.8*
Total CO_2	(mmol l^{-1})	27.4 ± 3.4	29.4 ± 3.2
$P_{ET}CO_2$	(kPa)	5.37 ± 0.30	5.42 ± 0.35
Hyperoxic B	(kPa)	5.01 ± 0.34	5.07 ± 0.51
Hypoxic B	(kPa)	4.97 ± 0.39	4.85 ± 0.37
Hyperoxic S	(1 min^{-1} kPa^{-1})	24.23 ± 7.35	24.38 ± 9.82
Hypoxic S	(1 min^{-1} kPa^{-1})	44.86 ±21.90	32.93 ±11.02

TABLE 39   Carbon dioxide response, plasma urea and electro-
           lytes, and end tidal CO_2 tension before and after
           0.024 mmol (10 mg) of bendrofluazide daily for
           four days in eight normal subjects. $P_{ET}CO_2$ = end
           tidal carbon dioxide tension; hyperoxic B and
           hypoxic B = intercept of the CO_2 response line in
           hyperoxia and hypoxia respectively; hyperoxic S
           and hypoxic S = slope of the CO_2 response line in
           hyperoxia and hypoxia respectively; **P<0.01;
           *P<0.05.   6.0 mmol/l urea ≡ 36 mg/100 ml.   **±SD** .

		Before	After
Urea	(mmol l^{-1})	5.4 ± 0.6	6.8 ± 1.00**
Sodium	(mmol l^{-1})	140.9 ± 2.0	139.8 ± 1.7
Potassium	(mmol l^{-1})	3.91 ± 0.19	3.39 ± 0.36**
Chloride	(mmol l^{-1})	104.1 ± 1.5	97.5 ± 0.3**
Total CO_2	(mmol l^{-1})	26.8 ± 1.9	31.5 ± 4.0**
$P_{ET}CO_2$	(kPa)	5.31 ± 0.25	5.49 ± 0.21
Hyperoxic B	(kPa)	4.95 ± 0.11	4.99 ± 0.30
Hypoxic B	(kPa)	4.93 ± 0.23	5.33 ± 0.34*
Hyperoxic S	(1 min^{-1} kPa^{-1})	25.50 ± 10.20	17.10 ± 5.25**
Hypoxic S	(1 min^{-1} kPa^{-1})	47.63 ± 26.93	34.65 ± 10.65

TABLE 40   Mean ventilatory and heart rate responses (± SD) during control (0.9% saline) and salbutamol (10 µg/min) infusion in seven men. (S is slope and B intercept of line relating steady state ventilation to PCO_2 during inhalation.)

	Control	Salbutamol
Ventilatory responses:		
Hyperoxic S (1 min^{-1} kPa^{-1})	20.85 ± 7.28	30.75 ± 9.75*
Hyperoxic B (kPa)	4.71 ± 0.46	5.11 ± 0.47
Hypoxic S (1 min^{-1} kPa^{-1})	38.10 ± 14.7	54.83 ± 22.1*
Hypoxic B (kPa)	4.65 ± 0.31	4.77 ± 0.4
Heart rate (beats/min) breathing:		
Air	63 ± 12	79 ± 14**
2% CO_2 in hyperoxia	65 ± 9	87 ± 18**
2% CO_2 in hypoxia	71 ± 8	103 ± 16**
5% CO_2 in hyperoxia	67 ± 8	97 ± 14**
5% CO_2 in hypoxia	75 ± 9	113 ± 15**

* $P<0.05$

** $P<0.01$

TABLE 41   Plasma sodium, potassium, and total CO2 before and after infusion of salbutamol
(10 µg/min) in seven men.

Subject No.	Sodium (mmol/l)		Potassium (mmol/l)		Total CO2 (mmol/l)	
	Before	After	Before	After	Before	After
1	142	143	3.9	3.2	20	20
2	143	142	4.2	3.2	29	29
3	138	137	3.5	2.9	23	23
4	140	142	4.4	3.4	23	21
5	142	142	3.9	2.9	21	22
6	139	143	3.8	2.7	23	21
7	142	143	4.2	3.4	26	25
Mean (± SD)	140.9 ± 1.9	141.7 ± 2.1	141.7 ± 2.1	3.10 ± 0.27	23.6 ± 3.0	23.0 ± 3.1
P	NS		<0.01		NS	