Some Factors Affecting Respiration in Man

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Abbreviations and Symbols

Measured and recorded quantities

T	time	T_T, T_I, T_E	
V_T	tidal volume	$V_{T,I}$, $V_{T,E}$	
$\dot{V}$	ventilation	$\dot{V}_I$, $\dot{V}_E$	
$\dot{v}$	volume flow	$\bar{\dot{v}}_I$	mean inspiratory flow (MIF)
		$\bar{\dot{v}}_E$	mean expiratory flow (MEF)
		$\dot{v}_{I,max}$	peak inspiratory flow (PIF)
		$\dot{v}_{E,max}$	peak expiratory flow (PEF)
$\ddot{v}$	volume acceleration	$\ddot{v}_{I,max}$	peak inspiratory acceleration (PIA)

FRC functional residual capacity

DFRC change in residual capacity $(= V_{T,I} - V_{T,E})$

P pressure, including partial pressure

F fractional concentration

A.T.P.D. ambient temperature and pressure, dry gas

B.T.P.D. body temperature and pressure, dry gas

Suffixes

I	inspired
E	expired
A	alveolar
et	end-tidal
a	arterial
$\bar{v}$	mixed venous

Levels of statistical significance

xxx
+++
●●●

$p<0.001$; xx $0.001<p<0.01$; x $0.01<p<0.05$

ABSTRACT

It has been proposed that the naturally-occurring respiratory oscillation in P_{a,CO_2} carries sufficient information on the rate of metabolism to be implicated in the generation of the hyperpnoea of hypoxic exercise. As a P_{CO_2} signal of this frequency can be transduced by the carotid chemoreceptors but not by those of the medulla, it would be of interest to examine the manner in which hypoxia and a CO_2 transient interact at the carotid body.

In the present study the responses of healthy subjects to an induced P_{A,CO_2} oscillation (of two breaths' period) were examined against a background of graded hypoxia at rest and during moderate rhythmic exercise. The responses were measured on a breath-by-breath basis in a variety of inspiratory and expiratory variables including times, volumes, ventilations and flows.

In brief it was found that:-

(i) oscillating responses were largely confined to P_{A,O_2} less than 72 torr;

(ii) their incidence in hypoxia was potentiated by exercise;

(iii) FRC oscillated, on average, more consistently than any other output variable;

(iv) at times, an inspiratory stimulation occurred on the same breath as an expiratory depression;

(v) a linear multiplication between hypoxia and the P_{A,CO_2} oscillation was occasionally observed, the amplitude of the response increasing as

hypoxia became more intense. Linear muliplication was more frequent in exercise.

The patterns of oscillating responses were interpreted in terms of a carotid body involvement, with hypoxia and the P_{CO_2} oscillation multiplying at receptor level, and a subsequent degree of complexity being introduced by the central timing of the carotid body discharge at the brain-stem. The potentiating effects of exercise may have resulted from a reduced attenuation of the P_{CO_2} oscillation in transit from the lung to the carotid body, and an improved central timing of the carotid body discharge.

Chapter 1

INTRODUCTION

By the end of the nineteenth century, respiratory physiologists were attempting to formulate theories for the unitary action on respiration of hypoxia, hypercapnia and hyperacidity of the arterial blood, Legallois (1812) having focussed attention earlier on an intrinsically rhythmic area of the medulla whose integrity was essential for the act of breathing. It was the insight of J. S. Haldane that paved the way for the elucidation of the chemical regulation of breathing in man, with the development of an accurate, volumetric method for measuring respiratory gases (Haldane & Smith, 1893), and a reliable method for sampling alveolar gas (Haldane & Priestley, 1905).

The importance of P_{A,CO_2} in the regulation of breathing was implied from its constancy over a wide range of barometric pressures, P_{A,O_2} varying considerably (only if the inspired oxygen fell below about 14% was the constancy disturbed); the exquisite sensitivity of the respiratory centre to imposed increases in P_{A,CO_2} was also demonstrated (Haldane & Priestley, 1905). These workers concluded that the P_{CO_2} in the respiratory centres was the primary factor regulating respiration.

The emphasis moved to the arterial pH when Boycott & Haldane (1908) found P_{A,CO_2} to fall during hypoxic hyperpnoea (see also Winterstein, 1910, 1911). This proposal, too, was subsequently modified, Winterstein (1915) having shown that an arterial alkalosis accompanied acute hypoxia. The primary stimulant now became the acidity within the cells of the respiratory centre (Winterstein, 1921). Jacobs' finding (1920) on the ability of CO_2 to penetrate cells, while the passage of fixed acids was prevented, provided strong support for the theory, as it could explain why a given change in pH_a produced by CO_2 had a greater effect on ventilation than did the same change produced by fixed acid in the blood.

With the discovery in the dog of chemosensitive areas in the cardio-aortic region (Heymans & Heymans, 1927) and in the carotid body (Heymans et al., 1930) which elicited a reflex hyperpnoea when perfused with hypoxic or hypercapnic blood, there was no further need to support a central action of hypoxia on the respiratory centres. More recently, however, it has been suggested that hypoxia may stimulate breathing in highlanders and lowlanders at high altitude by lowering c.s.f. pH as a result of an increased anaerobiosis (Lahiri & Milledge, 1967; Sørensen et al., 1969).

In the last 20 years, it has become widely, though perhaps not universally accepted that the site of central chemosensitivity to CO_2 and H^+ is separate from the medullary respiratory centres (cf. Pappenheimer et al., 1965; Lipscomb & Boyarsky, 1972): respiration was stimulated in anaesthetised dogs and cats by perfusion of the 4th ventricle with

artificial c.s.f. having a raised P_{CO_2} or a reduced pH (Leusen, 1954), implying the presence of a superficial site of chemosensitivity (Loeschcke et al., 1958). Areas of chemosensitivity were subsequently located near to the surface of the ventro-lateral medulla (area K: Mitchell et al., 1963; and area L: Schläfke et al., 1970); these would seem to be well placed for responding rapidly to changes in c.s.f. pH, produced either intrinsically or by changes in P_{a,CO_2}. Changes in arterial H^+ or HCO_3^-, however, have little effect because of the poor permeability of the blood-brain barrier to these and other ions (Loeschcke, 1966; Fencl et al., 1969).

Advances have been made in understanding the steady-state integration of the actions of H^+, CO_2 and hypoxia on breathing, it having been appreciated that assessment of the potency of one stimulus necessitated maintenance of the others at constant levels. The theoretical analysis of Gray (1946, 1950), based largely on Nielsen's data in man (1936), predicted that the effects of the three stimuli in the arterial blood were additive on ventilation. The additive interaction of arterial pH and P_{CO_2} has been confirmed in the steady-state, the slope of the $\dot{V}$, P_{A,CO_2} relation being unchanged by metabolic acidaemia or alkalaemia in man (Lerche et al., 1960; Cunningham et al., 1961; Lambertsen et al., 1961) and in the anaesthetised dog (Bonazzi et al., 1959). The relation is displaced to the left in acidaemia and to the right in alkalaemia.

The work of Nielsen & Smith (1952) on man was soon to override Gray's proposition of an additive interaction between hypoxia and CO_2: hypoxia increased the slope of the $\dot{V}$, P_{A,CO_2} relation, implying a

multiplicative interaction between the two stimuli. This observation was subsequently confirmed (Cormack et al., 1955, 1957; Lloyd et al., 1956, 1958; Loeschcke & Gertz, 1958), and led to the formulation of an empirically determined equation of steady-state respiratory regulation which described the multiplicative interaction through the effects of hypoxia on the slope of the $\dot{V}$, P_{A,CO_2} relation (Lloyd et al., 1958; this thesis, p. 72).

The effect of hypoxia on ventilation at P_{A,CO_2} lying below the normal air-breathing level complicates the relatively simple concept of hypoxic stimulation presented above. There is very little evidence of a multiplication by hypoxia, this portion of the $\dot{V}$, P_{A,CO_2} relation approaching the horizontal (Nielsen & Smith, 1952; Loeschcke & Gertz, 1958). Young (1970) reported a small but significant slope on pooling the results of several experiments. The nature of this portion of the $\dot{V}$, P_{A,CO_2} relation is obscure and will not be speculated upon here: suffice it to say that there is evidence of a threshold level for the stimulation of $\dot{V}$ by P_{A,CO_2}, though this is not usually apparent in euoxia or hyperoxia.

The site of the interaction between hypoxia and CO_2 is still a source of discussion, here confined largely to observations on man and the cat (the former being the experimental species in the present experiments, and the latter the species upon which were obtained many observations relevant to this thesis). A review of the evidence in

favour of a peripheral multiplication between hypoxia and CO_2 at the arterial chemoreceptors, and a central addition of the arterial and medullary chemoreceptor drives has been presented by Cunningham (1974a).

There is ample evidence in the anaesthetised cat of multiplication of the two stimuli at the carotid body, from studies on the whole carotid sinus nerve (Hornbein et al., 1961; Eyzaguirre & Lewin, 1961; Fitzgerald & Parks, 1971), from few-fibre preparations (Neil & Joels, 1963), and from single-fibre preparations (Fitzgerald, 1974; Hayes & Torrance, 1974; Lahiri, 1974).

The results obtained from single fibres, and by Fitzgerald & Parks (1971) on the whole nerve, are especially clear: by analogy with whole-body $\dot{V}$, P_{A,CO_2} relations, a series of curvilinear iso-oxic relations between discharge frequency and P_{a,CO_2} was obtained, their gradients rising with increasing hypoxia while their intercepts on the P_{a,CO_2} axis were less affected. Interaction was still present in hyperoxia (P_{a,O_2} ca. 400 torr) (Fitzgerald & Parks, 1971; Lahiri, 1974). This agrees with the earlier demonstration by Cunningham et al. (1964) of there being a residual arterial chemoreflex drive to breathing in man at P_{A,O_2} = 210 torr: "the response to hypoxia accompanied by hypercapnia.... is part of an inverse relation that continues far above the levels of P_{O_2} that could have been encountered before..... the possibility of artificial enrichment with oxygen of the atmosphere breathed."

Multiplication between hypoxia and CO_2 at the arterial chemoreceptors is evident, too, in the reflex respiratory responses. Otey & Bernthal

(1960) found that the ventilation of an anaesthetised dog in which the carotid body was perfused from a donor dog was greater when the donor was subjected to asphyxia than when it was subjected to either hypoxia or hypercapnia.

Biedstra (1963) studied the respiratory effects in the anaesthetised cat of perfusing the arterial and medullary chemoreceptors simultaneously, but separately, with bloods of different P_{CO_2} and P_{O_2}. Lloyd (1966) analysed the results in the manner of Lloyd et al. (1958), and demonstrated the occurrence of a multiplication between hypoxia and H^+ at the arterial receptors, and a central addition of the respiratory drives from these and the medullary receptors.

In man, elucidation of the nature of the interaction between hypoxia and CO_2 is limited to the study of the reflex responses induced by changing the inspired levels of O_2 and CO_2; their interpretation relies on the known properties of the medullary and carotid body chemoreceptors in animals. Dejours (1959) pioneered the approach of using the latency of a reflex respiratory response to distinguish between arterial or medullary chemoreceptor involvement.

Leitner et al. (1965a) showed that sudden breathing of oxygen for 2 or 3 breaths by hypoxic anaesthetised cats caused a transient decrease in the discharge frequency of few-fibre preparations of the carotid sinus nerve with a latency of 3 to 4 seconds; this was accompanied by a change in ventilation with a parallel time course, indicating that most of the

reflex delay is the transport time between the lung and carotid body. A similar reflex result was obtained in euoxia from conscious dogs, being absent after chronic chemodenervation (Bouverot et al., 1965). In man the latency of the reflex response to transient breathing of oxygen in euoxic and hypoxic man is between 6 and 12 seconds (Dejours, 1957, 1962).

There is some more direct evidence in man that the hyperpnoea of hypoxia is mediated by the arterial chemoreceptors, and in particular those of the carotid bodies rather than the aortic bodies. The hyperpnoea was largely abolished after bilateral blockade of the glosso-pharyngeal and vagus nerves in one unanaesthetised subject (Guz et al., 1966). Furthermore, the hyperpnoea of hypoxia was absent in a group of subjects who had undergone bilateral carotid body resection for the treatment of bronchial asthma (Lugliani et al., 1971).

If CO_2 and hypoxia interact multiplicatively at the carotid body, it is predicted that ventilation should change with a short latency in response to a change in P_{A,CO_2} during hypoxia. In hyperoxia, however, the response should be delayed, reflecting the longer vascular and diffusion paths of the medullary chemoreceptors. This presupposes the reflex effects of the carotid body to be generally diminished, if not abolished, by oxygen breathing, as might be expected to occur in man where the signal-to-noise ratio of the respiratory system and the residual hyperoxic activity are both small.

The first prediction was confirmed for conscious, air-breathing dogs that were given two breaths of 7% CO_2 before and after peripheral chemodenervation (Bouverot et al., 1965): the short-latency hyperpnoea was replaced by a slower, less marked response after chemodenervation.

In moderately hypercapnic man, repeated exposure to sudden transient hypocapnia (induced by removal of CO_2 from the inspired air for 2 breaths) induced a depression of ventilation after 2-3 breaths in mild hypoxia (P_{A,O_2} ca. 63 torr) but only after 5 breaths in hyperoxia (P_{A,O_2} ca. 650 torr): Cunningham et al.,(1965a) and Miller et al.,(1974).

Lambertsen et al. (1965) distinguished three components in the "off" transient at the end of CO_2 inhalation in euoxic man. In hyperoxia, the quickest component, which had a latency comparable to that reported above for CO_2 withdrawal in hypoxia, was not seen. Abrupt administration of oxygen at two levels of hypercapnia produced a depression of ventilation after about 5 seconds (Downes & Lambertsen, 1966); the maximal depression of ventilation was greater at the higher level of P_{A,CO_2}. From these results, the multiplicative effects of hypoxia and CO_2 on ventilation must originate from the carotid body and not the brain-stem.

However, evidence for a central multiplication, as well as that occurring at the carotid body, was presented by Edelman et al. (1973) on the basis of finding smaller increases in ventilation during hypoxia when P_{A,CO_2} was increased transiently than when a similar change of P_{A,CO_2} occurred between two steady states. There is an alternative explanation (Cunningham, 1974b): although a predictable relation exists in steady states between the size of a change in alveolar P_{CO_2} (or P_{O_2}) and that occurring at either set of chemoreceptors, the transient state is more

complex. In its passage from the lung to the capillaries in the vicinity of the receptors, an alveolar transient is likely to be attenuated by several factors (Chapter 4, p. 152), the main one being the residual or end-systolic volume of the left ventricle; in the case of a CO_2 transient, the buffering action of the blood and tissues becomes significant. Thus comparisons between steady-state and transient responses are of limited value.

An exception to this criticism is the technique of suddenly and transiently removing a respiratory stimulus (hypoxia, hypercapnia), as practised by Cunningham et al.,(1965a) and Miller et al. (1974). When breathing is driven sufficiently hard, sudden withdrawal of either hypercapnia in hypoxia, or vice versa, is likely to silence the carotid chemoreceptors completely, enabling quantitative comparisons of the ensuing ventilation changes to be made.

More recently, an additional means of separating carotid and medullary chemoreceptor responses has been used, based on the ability of the receptors to respond to $\underline{P_{a,CO_2}}$ oscillations of varying frequency. The limiting frequency to which a chemoreceptor can respond is determined by the length of the diffusion path between it and the nearest capillaries (short for carotid chemoreceptors, long for medullary chemoreceptors), and the ratio of the CO_2 buffering capacity of the tissue to the blood flow per unit volume of tissue (large for medullary chemoreceptors, very small for carotid chemoreceptors); Miller et al., 1974.

Thus the carotid body receptors should be able to transduce much higher frequencies of P_{a,CO_2} oscillation than the medullary chemoreceptors, and these responses should be effectively absent in men breathing oxygen-rich gas (p. 6). The difference between the respiratory response times of the two receptor sites has been shown clearly in anaesthetised dogs: ventilation responded within one breath to a sudden infusion of hypercapnic euoxic blood into the carotid arteries (Dutton et al., 1967), while a similar infusion into the vertebral arteries induced a respiratory response only after a delay of 20 to 30 seconds (Fitzgerald et al., 1968).

In man, alternate breaths of CO_2-free and CO_2-rich gas, sufficient to produce an alternate-breath P_{A,CO_2} oscillation of about 10 torr amplitude, could induce an alternation in the size of breath-by-breath $\dot{V}_E$, $V_{T,E}$ and T_T in hypoxia (P_{A,O_2} ca. 55-65 torr) but not in hyperoxia (P_{A,O_2} ca. 550 torr): Marsh et al. (1973). From the results of Fitzgerald et al. (1968) it is unlikely that an oscillation of 2 breaths' period (5-6 seconds) could reach the medullary chemoreceptors; and the hypoxia-dependency of the responses is more direct evidence for the effect being mediated by the carotid body.

Wolff (1974), using a similar technique on anaesthetised cats in euoxia, observed an alternate-breath oscillation in $V_{T,I}$ which was abolished by prior passage of carotid arterial blood through a mixing chamber.

Using a wider and lower range of stimulating frequencies (period ranging from 10 seconds to 10 minutes) in anaesthetised cats,

Daubenspeck (1973) determined the effects of chemodenervation on the amplitude of the V_T oscillations induced by oscillations of CO_2 ($\Delta F_{I,CO_2}$ ca. 0.02) against a background of mild hypercapnia and euoxia. As the frequency of stimulation rose, so the gain of the response ($\Delta V_T/\Delta P_{A,CO_2}$) decreased, both before and after chemodenervation. Over the higher range of frequencies, the gain after chemodenervation became progressively less than that occurring before chemodenervation.

This was interpreted as a removal of the multiplication between hypoxic and hypercapnic drives at the carotid body. In view of the remarks concerning the quantitative analysis of transient responses (p. 8), one might expect the vascular attenuation of the P_{A,CO_2} signal to increase as its frequency of oscillation rose. Thus, the implied multiplication might have been underestimated.

A similar approach to that of Daubenspeck was used in conscious man during euoxia and hypoxia (P_{A,O_2} = 60 torr) by Swanson & Bellville (1974). Over the same range of frequencies, the increase in gain between euoxia and hypoxia rose with the frequency of P_{A,CO_2} oscillation. The interpretation is again that a multiplication of hypoxia and CO_2 occurred at the carotid body.

Now is a suitable point to consider the significance of an <u>asphyxial oscillation</u> intrinsic to the cardio-respiratory system. Haldane & Priestley (1905) demonstrated that there was a small fluctuation in P_{A,CO_2} and P_{A,O_2} within the respiratory cycle, end-expiratory alveolar gas samples having a more asphyxial composition than those obtained at

the end of inspiration. Krogh & Lindhard (1913) found similar fluctuations on fractionating the expired air, their amplitudes in exercise exceeding those at rest. The form of the fluctuations in P_{A,CO_2} throughout the respiratory cycle was predicted by Aitken & Clark-Kennedy (1928) and DuBois et al. (1952).

The "within-breath" oscillation of P_{A,CO_2} and P_{A,O_2} (ca. 3 torr and 6 torr, respectively, at rest), reflecting the relatively continuous pulmonary perfusion in the face of a discontinuous ventilation, has become the focus of attention in recent years after Yamamoto's proposition (1960, 1962) that the P_{a,CO_2} oscillation, rather than the mean value about which it varies, is the natural error signal of the ventilatory feed-back system. The amplitude and rate of change of the oscillation both increase during exercise as a result of a raised mixed venous P_{CO_2} and an increased cardiac output, and could therefore provide the linkage between ventilation and metabolism, in the face of a relatively constant mean P_{a,CO_2}.

Yamamoto favoured a central site of action for the P_{CO_2} oscillations, but the carotid body would appear to be a more suitable site if one considers the observations presented so far on the frequency responses of the two chemoreceptor areas. Such a hypothesis might therefore be pertinent to the nature of the potentiating action of exercise on the hypoxic drive to breathing that has been observed in man (e.g. Christensen, 1937; Asmussen & Nielsen, 1958; Cunningham et al., 1966; Bhattacharyya et al., 1970).

The within-breath oscillation has been detected intra-arterially in pH and, by implication, P_{CO_2} (Band & Semple, 1966, 1967: man, cat), and in P_{O_2} (Purves, 1964 and 1966a: cat, lamb). The amplitude of the P_{a,O_2} oscillation is decreased by an increased respiratory frequency, a diminished tidal volume and hypoxia (Purves, 1966a); the amplitude of the pH_a oscillation is decreased by hypercapnia (Band et al., 1969b).

The discharge of the carotid body of the anaesthetised cat contains an oscillation with a respiratory period at rest, both in the whole carotid sinus nerve (Hornbein et al., 1961; Biscoe & Purves, 1967a) and in single-fibre preparations (Band et al., 1971; Black et al., 1973; Gehrich & Moore, 1973; Goodman et al., 1974).

The situation during exercise is largely unexplored. Davies & Lahiri (1973) found the mean frequency of carotid body discharge to be unaffected by the imposition of exercise in anaesthetised, hypoxic cats (exercised electrically at an intensity sufficient for hypoxic potentiation of breathing to be demonstrable). These authors made no mention of studying the form of the discharge occurring within the respiratory cycle. Black et al. (1973) observed an increased amplitude of within-breath oscillations in single-fibre discharge from the cat carotid body when whole-body metabolism was increased by dinitrophenol. However, this observation might reflect the effects of D.N.P. acting within the carotid body, its activity being increased as a result of a lowered glomal P_{O_2}.

The available evidence favours the oscillation in P_{a,CO_2} as the agent responsible for eliciting the oscillating discharge from the

carotid body. A general finding is that the cat carotid body responds more rapidly to changes in CO_2 than to changes in hypoxia. McCloskey (1968) and Black et al. (1971) observed that in hyperoxia single carotid chemoreceptor fibres respond with over- and under-shoot to large step-increases and -decreases of P_{CO_2} applied near the carotid body. Large step-changes in hypoxia produced responses that developed more slowly with no over- or under-shoot. Prior infusion of acetazolamide, a carbonic anhydrase inhibitor, abolished the dynamic responses to CO_2 steps, implying the involvement of the enzyme in the dynamic effect.

The cat carotid body responded to the intermittent infusion of euoxic hypercapnic blood into the common carotid arteries at higher frequencies than for infusions of hypoxic eucapnic blood (Fitzgerald et al., 1969). Perhaps the most direct piece of evidence for an involvement of CO_2 in the oscillating discharge comes from the study of Gehrich & Moore (1973) on single fibre preparations from the cat carotid sinus nerve. Euoxic hypercapnia ($F_{I,CO_2} = 0.08$) abolished the oscillating discharge, while in hypoxia ($F_{I,O_2} = 0.1$) the amplitude of the oscillation was little reduced from its air-breathing value.

The response of the carotid body to the P_{a,CO_2} oscillation may be more closely related to the rate of change of PCO_2 with time than to the amplitude of the oscillation. This was first suggested by the results of McCloskey (1968) and Black et al. (1971) described above. Band et al. (1971) observed that, in the spontaneously-breathing, anaesthetised cat, the peak of the oscillating discharge in single carotid chemoreceptor fibres preceded the peak $[H^+]$ in carotid arterial blood, implying that

the receptors had responded to the rate of rise of P_{CO_2}.

Willshaw (1974), using artificially-ventilated, anaesthetised cats, has shown more recently that the amplitude of the oscillation in single fibre discharge frequency was unchanged when the ventilating frequency was doubled and the tidal volume halved: this procedure should have reduced the amplitude of the within-breath P_{a,CO_2} oscillation by a much greater degree than its rate of change. Again, it appears that the cat carotid body responds to a rate of change of P_{a,CO_2}.

It is not clear whether hypoxia multiplies the effect of the within-breath P_{a,CO_2} oscillation on carotid body discharge. Hornbein et al. (1961) found the amplitude of the oscillating discharge in the whole carotid sinus nerve of the anaesthetised cat to be greater at P_{a,O_2} of 70 torr than at either a P_{A,O_2} of 40 torr or 500 torr. Similarly, Biscoe & Purves (1967a) found the amplitude of the oscillating discharge was greatest in euoxia, diminishing in both hypoxia and hyperoxia. Goodman et al. (1974), working on single fibre preparations of the cat carotid sinus nerve, also found a reduction in the oscillation amplitude on passing from euoxia to hypoxia, while Gehrich & Moore (1973) showed there to be little change between euoxia and hypoxia in cats artificially ventilated at a constant frequency.

The hyperoxic results are best explained by assuming the hypoxic drive (see p. 5) at the carotid body to be much reduced, leaving little for the P_{a,CO_2} oscillation to multiply. And in hypoxia, the respiratory frequency of spontaneously breathing cats may well increase, serving to

diminish the amplitude of the P_{a,CO_2} oscillation; thus there would be a diminished CO_2 stimulus for hypoxia to multiply.

However, there was no mention of an increased amplitude of oscillating discharge in hypoxia from the experiments of Gehrich & Moore (1973), which one might have expected as the changes in respiratory frequency had presumably been prevented. It is therefore difficult to infer from these results whether hypoxia and the within-breath oscillation in P_{a,CO_2} multiply their effects on the discharge of carotid chemoreceptors.

By analogy with the observations made on the carotid body of the anaesthetised cat (p.13), there is evidence in man that reflex responses, too, are more easily elicited by quick changes of P_{A,CO_2} in hypoxia than by the corresponding changes in hypoxia. Oscillating respiratory responses were induced by an alternate-breath P_{A,CO_2} oscillation in hypoxia (Marsh et al., 1973; this chapter, p.10) but not by a similar oscillation in hypoxia (Marsh, unpublished results). Respiratory responses were obtained from changes in the within-breath profile of P_{A,CO_2} in hypoxia, but not from corresponding changes in the profile of hypoxia in hypercapnia (Cunningham et al., 1973; this chapter, p.19). The response to transient sudden removal of CO_2 in hypoxia occurs after 2 or 3 breaths (this chapter, p.8), whilst that obtained from the sudden relief of hypoxia had a longer latency of 3 or 4 breaths (Miller et al., 1974).

Therefore, the carotid bodies of both cat and man have the ability to respond to rapid changes of P_{CO_2}, and the within-breath P_{a,CO_2} oscillation in particular, possibly in a rate-sensitive fashion. However,

evidence is equivocal as to whether the P_{a,CO_2} oscillations provide a significant drive to breathing. Support was provided by the experiments of Yamamoto & Edwards (1960): loading the venous blood of anaesthetised, air-breathing rats with CO_2 induced a hyperpnoea but no increase in mean P_{a,CO_2}. The authors concluded that the drive to breathing came from the within-breath P_{a,CO_2} oscillations whose size was presumably increased in proportion to the increases occurring in mixed venous P_{CO_2}. This conclusion was opposed by Lamb (1966) who performed similar experiments on the air-breathing anaesthetised cat and found P_{a,CO_2} to rise during venous loading: in fact, $\dot{V}$ and P_{a,CO_2} were found to be similarly related for both CO_2 inhalation and venous loading.

A second approach has involved abolishing the P_{a,CO_2} oscillations by passage of carotid arterial blood through a mixing chamber before it reaches the carotid body: if the oscillations provide a drive to breathing, then ventilation should fall in their absence. This was confirmed in two air-breathing studies (DuBois & Yamamoto, 1959: rat; Purves, 1966b: cat); in another, ventilation was stimulated (Band et al., 1973: cat); and in one hyperoxic study, ventilation was unchanged, perhaps not unexpectedly in a situation where the hypoxic drive to the carotid body is low (Fenner & Berndt, 1970: cat).

Attractive though Yamamoto's hypothesis on the role of the within-breath P_{a,CO_2} oscillations might be (p. 12), the observations presented above are hardly convincing. As it is the carotid body that transduces

the within-breath P_{a,CO_2} oscillation, the experiments should perhaps have been conducted in hypoxia rather than euoxia to ensure a reasonable mean level of chemoreceptor activity.

Consideration of the role of the oscillations has become complicated by the discovery that the gain of the carotid chemoreflex arc can be varied according to the time within the respiratory cycle a particular signal reaches the brain-stem from the carotid body via the carotid sinus nerve ("central timing").

In anaesthetised, air-breathing cats, injections of saline pulses equilibrated with 100% CO_2 past the carotid body in late expiration and early inspiration (Black & Torrance: 967a; 1971), or only in early inspiration (Band et al., 1968, 1970), can increase the depth of the current inspiration, the following expiration and inspiration being unaffected. If the stimulus is applied early in expiration, it may lengthen the time for expiration, but have no effect on the next inspiration (Black & Torrance, 1967a; 1971). The response appears to be induced by CO_2 rather than H^+, as injections of fixed acid in saline did not affect respiration (Band et al., 1968, 1970). The short latency and memory of this mechanism confer on the respiratory system the ability to discriminate between inputs occurring centrally in adjacent respiratory half-cycles.

Effects obtained by brief electrical stimulation of the carotid sinus nerve were more varied, depending on the strength and duration of the stimulus. Responses similar to those produced above could be elicited if the stimulus strength was relatively low (Black & Torrance, 1967a, 1971; Howard et al., 1969; Eldridge, 1972).

In hypoxic man a small sharp fall of P_{A,CO_2} produced early in inspiration depresses mean ventilation, whereas if it occurs late in inspiration mean ventilation is stimulated, the mean P_{A,CO_2} having been maintained constant (Cunningham et al., 1973). Thus, as in the anaesthetised cat, when the carotid body chemoreceptors are involved, the timing of stimulation in relation to the respiratory cycle is a determinant of the size of the reflex response. This point should be borne in mind when interpreting reflex effects to CO_2 transients that are mediated by the carotid body.

The current status of Yamamoto's hypothesis, which has been extended by Black & Torrance (1967b, 1971) and Cunningham (1974b), is still largely at the speculative stage. Black & Torrance proposed that the central timing of the P_{a,CO_2} oscillation was not optimal at rest, causing very little respiratory stimulation. With increasing intensities of exercise, the amplitude of the oscillation would rise and, in addition, the central timing would approach its optimum (maximal respiratory stimulation). The change in central timing would be achieved as a result of a relatively greater increase in cardiac output (and therefore, presumably, a decrease in the lung-carotid body transit time) than in respiratory frequency.

There is some evidence for the central timing being unfavourable at rest: Cunningham et al. (1973) stimulated ventilation in hypoxic man by changing the central timing of the P_{a,CO_2} oscillation from its usual state and Band et al. (1973) observed an increase in inspiratory tidal volume in the anaesthetised cat when the P_{a,CO_2} oscillation had

been abolished by mixing. Knowledge of the central timing during exercise is lacking but could easily be obtained by simultaneously measuring respiratory frequency and the lung-carotid body circulation time (with an ear oximeter: Lejours et al., 1957).

Cunningham (1974b) has emphasised that, during exercise, a reduced attenuation of the P_{CO_2} oscillation should occur in transit between the lung and the carotid body, largely the result of a reduced end-systolic volume and an increased stroke volume. Thus, the possibility exists in exercise for the effective P_{CO_2} stimulus at the carotid body to be increased, and for its central timing to be enhanced.

In view of the possible importance of the within-breath P_{a,CO_2} oscillation in the regulation of breathing during hypoxia, this thesis was concerned primarily with elucidating, at rest and in exercise, the form of the interaction between hypoxia and a CO_2 transient which, because of its relatively high frequency spectrum, would be detected at the carotid body but not in the medulla. The CO_2 transient was an alternate-breath P_{A,CO_2} oscillation imposed about a constant hypercapnic mean P_{A,CO_2}; its amplitude was constant in the range 10-15 torr, and thus was comparable with that of the within-breath P_{A,CO_2} oscillation occurring in moderate exercise.

This technique was first used by Cunningham et al. (1965a) to study the effects of an oscillating P_{A,CO_2} on mean ventilation during hypoxia.

They concluded that the presence of the oscillation provided no stimulation to the mean ventilation apart from that due to the mean P_{A,CO_2}, and therefore that the stimulating effect of a rapid increase in CO_2 was no greater than the depressing effect of a rapid fall in CO_2.

It was left for Marsh et al. (1973) to demonstrate that the respiratory system could respond on a breath-by-breath basis to the alternate-breath P_{A,CO_2} oscillation during hypoxia (p. 10): significant alternate-breath responses of $\dot{V}_E$ and $V_{T,E}$ were observed in some 60-80% of the runs, and less commonly in V_T.

The hypothesis of the present study was that the respiratory oscillation resulting from the alternate-breath P_{A,CO_2} oscillation would increase its amplitude in response to graded hypoxia, in a fashion analogous to $\dot{V}_E$ in response to steady-state hypercapnia and hypoxia (Cormack et al., 1957; Lloyd et al., 1958). During exercise one might expect the attenuation of the alternate-breath P_{A,CO_2} oscillation to be reduced and its central timing to be improved. Both factors would lead to an enhanced reflex oscillation if the hypothesis of Black & Torrance (1967b, 1971) and Cunningham (1974b) is to have any claim to reality.

An extensive range of inspiratory and expiratory output variables was employed to characterise the oscillating response: for, the comparatively high failure rate of the P_{A,CO_2} oscillation to generate alternate-breath responses in the study of Marsh et al. had led to the idea that some output variable other than $\dot{V}_E$ might bear a closer relation to the output of the brain-stem respiratory centres in the transient state.

Thus, in man, $V_{T,I}$ has been reported to respond more quickly to changes in the chemical drive to breathing than has $\dot{V}_E$ (Loeschcke et al., 1963: step-changes in P_{I,CO_2}; Pearson & Cunningham (1973) and Miller et al. (1974): sudden transient withdrawal of hypercapnia during hypoxia and hyperoxia, and of hypoxia during hypercapnia). However, the behaviour of inspiratory variables is largely unexplored, with the exception of inspiratory duration which is largely unaffected during steady-state CO_2 inhalation (Cunningham & Gardner, 1972).

The presence of a multiplicative interaction between hypoxia and the CO_2 oscillation was confirmed at rest and demonstrated for the first time in exercise, the majority of the oscillating responses occurring at a P_{I,CO_2} of 72 torr or less. The incidence of oscillating responses was generally similar to that found by Marsh et al., and, as predicted, exercise served to increase the incidence of oscillating responses in hypoxia. In some instances, too, the amplitude of the response increased with graded hypoxia.

Thus, despite the increased number of output variables, the relative failure rate of the response observed by Marsh et al. was little affected. However, some unexpected observations were recorded: for example, FRC oscillated, on average, more regularly than any other output variable. This implied an effect of the CO_2 oscillation on lung mechanics, perhaps independently of the carotid body as there have been recent reports of changes in airway P_{CO_2} eliciting reflex respiratory responses. Boushey & Richardson (1973) obtained a reflex slowing of breathing in anaesthetised

cats when 5-10% CO_2 was passed through the larynx. However, the slow response time of the effect precludes it from further consideration in the present study. Bartoli et al. (1974) observed a vagal reflex tachypnoea in anaesthetised dogs when airway CO_2 was increased in hyperoxia independently of changes in P_{a,CO_2} by means of a cardio-pulmonary bypass. Although the reflex was of sufficient rapidity to be considered here, its occurrence in very high levels of oxygen precluded it from involvement here.

Thus a model of carotid body function, including the phenomenon of central timing, was set up to account for the observed reflex responses at rest and in exercise.

Chapter 2

METHODS

This chapter describes the apparatus, experimental procedure, and methods of data collection and processing relevant to the study of the effects of an alternate-breath oscillation of P_{A,CO_2} on respiration.

1. Subjects

The subjects were healthy volunteers who had previously signed a consent form describing the range of experimental conditions to which they might be exposed. Five subjects (3 males, 2 females) participated in the first series of experiments, and 4 subjects (3 males, 1 female) in the second series. Their occupations ranged from that of undergraduate and graduate medical students to one medical graduate. None of them professed a detailed knowledge of respiratory physiology.

The purpose or nature of the experiments was not revealed to the subjects; however, they were informed that they would be made hypercapnic or hypoxic, and would have to exercise on a bicycle ergometer. After each experiment, the subject was asked for his opinion as to the nature of the experiment, and to comment on any unusual sensations experienced (noises; taste of the inspired gas). In no case was the true purpose of the experiments perceived; most often subjects thought that the experiments were of a metabolic nature.

Subjects were selected for participation in the study according to two criteria. First, a fairly regular breathing pattern should be shown during steady-state hypercapnia and hypoxia, with no tendency towards emotional hyperventilation. Secondly, an alternate-breath oscillation in at least one of the recorded respiratory output variables should be exhibited at rest in response to a similar oscillation of P_{A,CO_2} in hypoxia (P_{A,O_2} about 50 torr), but not in hyperoxia (P_{A,O_2} > 200 torr). For this purpose a preliminary experiment was performed on each subject, in which an alternate-breath P_{A,CO_2} oscillation was induced at each of the two levels of P_{A,O_2} (p.26). The size of the alternate-breath oscillations of expiratory ventilation ($\dot{V}_E$), tidal volume ($V_{T,E}$) and time (T_E) and of breath duration (T_T) and inspiratory time (T_I) were estimated by the method used for the Series One experiments (p. 57).

All subjects were in a semi-fasting state during the experiments, having taken only a light meal at least 90 minutes before the start of an experiment.

Relevant information on the subjects is included in Appendix 1, Table 1 (p.161).

2. Apparatus

General description of the apparatus

The arrangement of the apparatus was of open-circuit design (Fig. 1). It was situated behind the subject, as far as possible; any moving parts that were visible were covered so as to mask the movement from the subject. Two inspiratory gas mixtures, differing only in P_{CO_2}, were

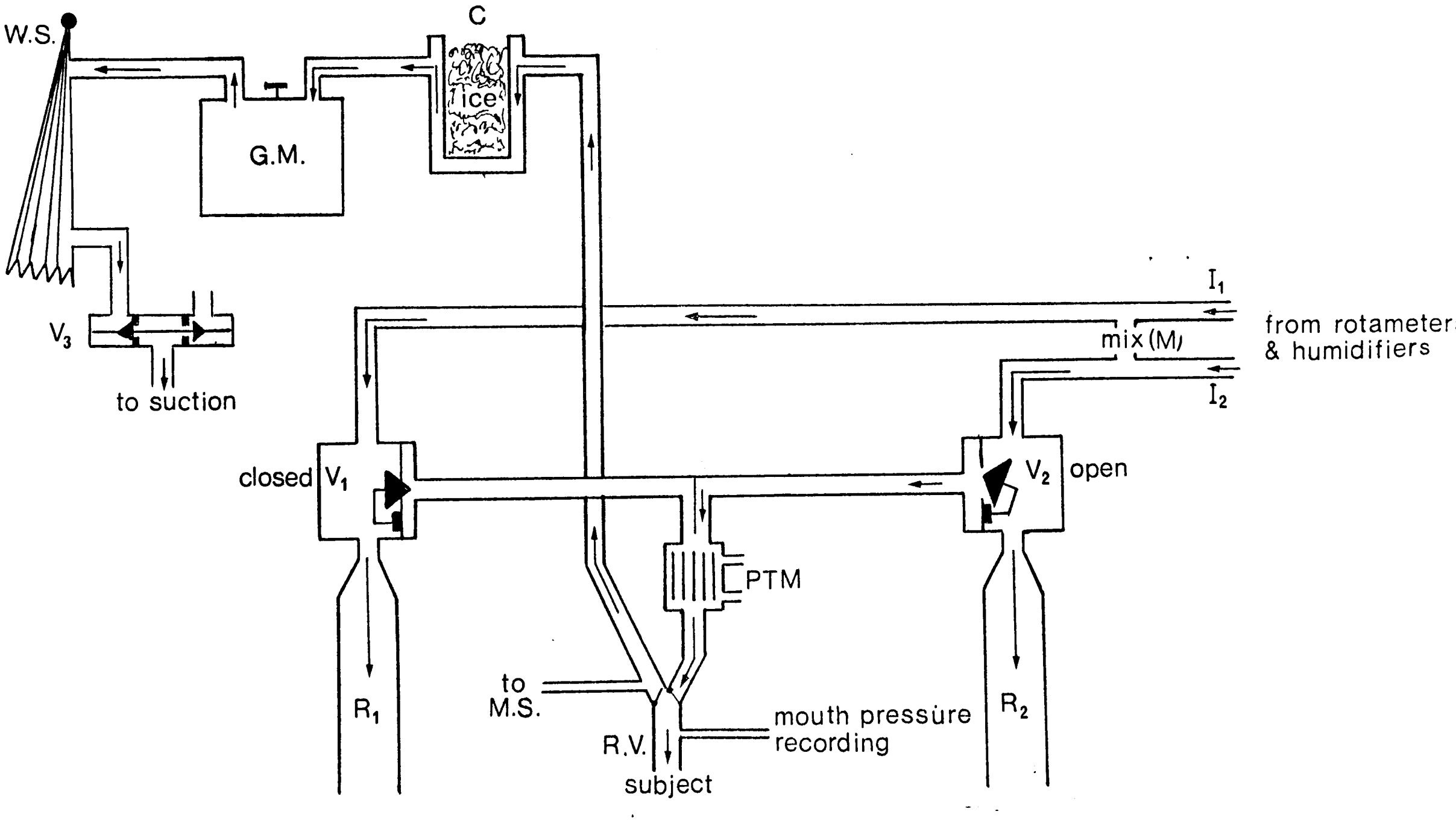


Fig.1 General plan of the apparatus

prepared in each of two banks of flowmeters (Rotameter Manufacturing Co. Ltd, Croydon) by mixing CO_2, air, N_2 and O_2 in suitable flow ratios). O_2, N_2 and CO_2 were supplied from cylinders (British Oxygen Co.), and air was obtained from outside the building by the suction of a domestic vacuum cleaner. A coarse adjustment of air flow was achieved at each flowmeter bank by means of a variable transformer (Variac, Zenith Electrical Co. Ltd, London) attached to the air supply line. Fine adjustment of all gas flows was effected by means of a needle valve at the head of each flowmeter.

The mixtures so produced were directed into 2 inspiratory lines (I_1, I_2) where they were humidified at 40°C. They were then passed into wide-bore, corrugated tubing (reservoir tubes: R_1, R_2) of 10 cm diameter and 40 l. volume, open at the end to the atmosphere. The subject could inspire gas from either inspiratory line through a side-arm situated at the junction of the inspiratory line and the reservoir tube, as long as the solenoid-operated valve (V_1 or V_2) at this point was open. The reservoir tubes served to store excess inspiratory gas, thus preventing room air being pulled back by the subject should his peak inspiratory flow exceed the total forward flow of the inspiratory gas mixture.

The solenoid-operated valves provided the means for imposing upon the subject alternate breaths of high and low P_{CO_2} gas. Each valve was switched, at the start of each expiration, between open and closed positions on alternate breaths; however, the two valves were always of opposing phase, one valve being shut when the other was open and vice

versa. Thus the subject was presented with gas from one or other of the inspiratory lines in sequence, on alternate breaths. Prior passage of the two inspiratory gases through a mixing chamber (M) was employed during control periods when the subject was to be supplied with identical gas mixtures on alternate breaths.

A heated pneumotachometer head (PTM), (Fleisch, Switzerland; distributor: P. K. Morgan, Chatham, Kent), was situated in the common inspiratory line near the respiratory valve (R.V.). The instantaneous pressure difference along the PTM was monitored by means of a micro-manometer (M.D.C. 300, Hilger - I.R.D. Ltd, London) to give instantaneous inspiratory flow ($\dot{v}_I$). Subsequent electrical integration and differentiation of the flow signal gave instantaneous inspiratory volume (V_I) and acceleration ($\ddot{v}_I$), respectively.

Inspiratory and expiratory time (T_I, T_E) and breath duration (T_T) were measured on a breath-by-breath basis from a time-dependent voltage ramp which was interrupted and reset by signals at the start of inspiration and of expiration, respectively. These signals were obtained by differentiation, with a Schmidt trigger, of the mouth pressure waves recorded manometrically (M.D.C. 301, Hilger I.R.D. Ltd) from the common space of the respiratory valve.

Breath-by-breath end-tidal P_{CO_2} and P_{O_2} were measured simultaneously by a dual headed mass spectrometer (M.S.), (VG-Micromass Ltd, Winsford, Cheshire), which sampled expired gas continuously from a point just beyond the expiratory flap of the respiratory valve. The respiratory valve was low in both dead space and resistance.

Expired gas was passed through an ice-filled condenser (C), for drying, and then through a dry gas meter (G.M.), (Parkinson & Cowan Ltd, London) for measurement of mean expired ventilation. Finally, the gas entered a wedge spirometer (W.S.), (SP 70, Cryotech, Wallingford, Berks) where instantaneous expired volume (V_E) was measured. This was achieved by evacuation of the spirometer through a double solenoid-operated valve (V_3) back to a reset position during each subsequent inspiration. The volume signal from the spirometer was differentiated to give instantaneous expiratory flow ($\dot{v}_E$).

Connections between the components of both inspiratory and expiratory lines were made with plastic corrugated tubing (i.d. 3.8 cm). The connections were kept as short as possible so as to minimise the resistance of the apparatus to gas flow.

The various respiratory variables were recorded on a multi-channel hot-stylus recorder (M8, Devices Ltd, Welwyn Garden City, Herts). These were breath-by-breath inspiratory and expiratory times (T_I and T_E), tidal volumes ($V_{T,I}$ and $V_{T,E}$), peak flows ($\dot{v}_{I,max}$ or PIF, and $\dot{v}_{E,max}$ or PEF), peak inspiratory acceleration ($\ddot{v}_{I,max}$ or PIA), end-tidal P_{CO_2} and P_{O_2} (P_{et,CO_2} and P_{et,O_2}), and mean expired volume.

The next section describes in more detail various components of the apparatus. This includes an account of the mode of operation and, where relevant, details of calibrations conducted to determine linearity and of the effect on performance of various interacting factors.

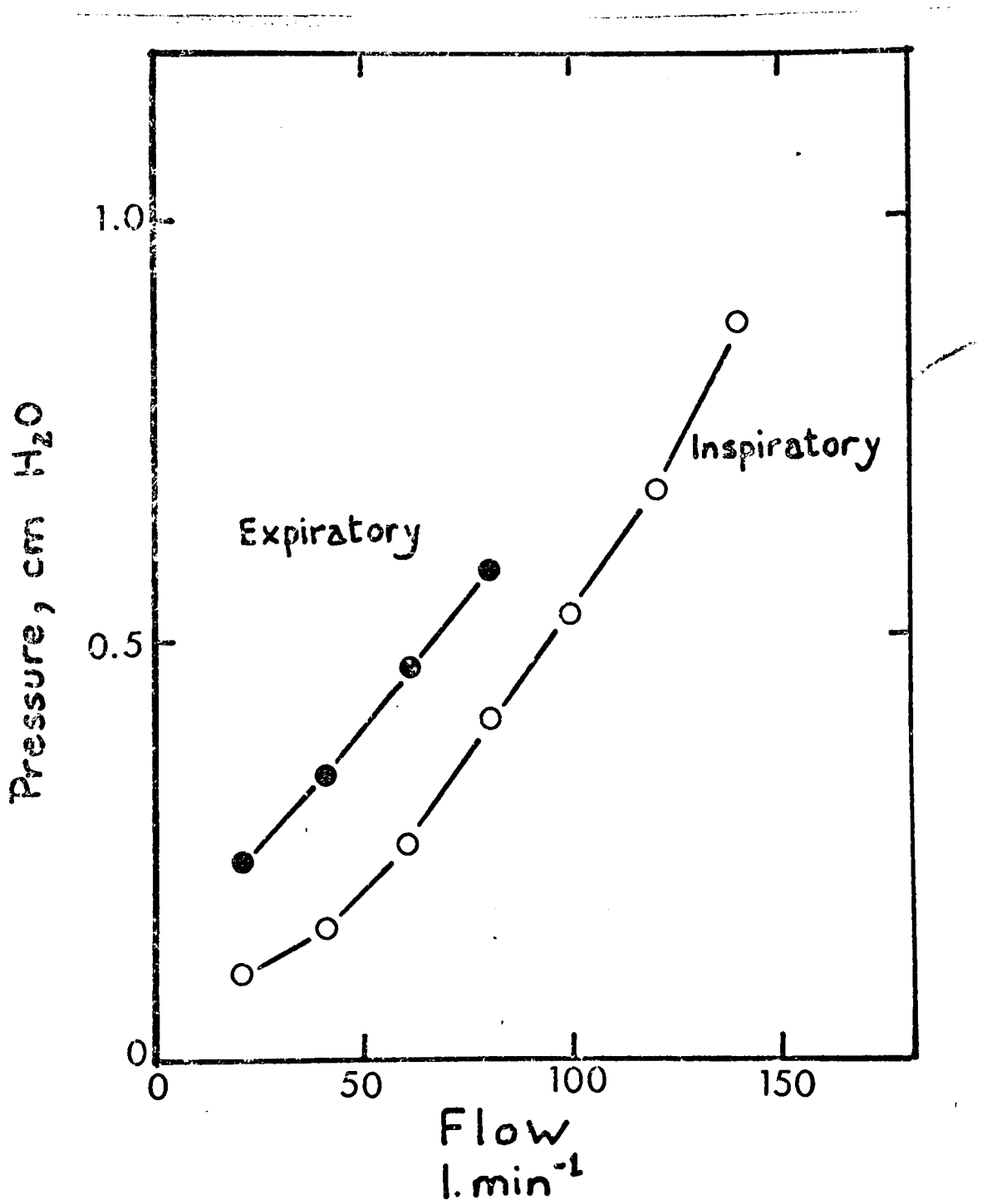
Resistance of the apparatus to flow

The resistance of the apparatus to a steady gas flow may be ascribed to purely resistive elements; however, where the gas flow is changing, the inertia of the gas and any moving parts of the apparatus (flaps of the respiratory valve) may become significant. Thus the resistance of the inspiratory and expiratory lines was estimated under conditions of steady flow (static resistance) and changing flow (dynamic resistance).

The static resistance of the inspiratory line, as far as the subject is concerned, is limited to the demand system, which is that part of the line from just upstream of the inspiratory solenoid-operated valves to the common space of the respiratory valve. Steady air flows (20-140 l. min^{-1}) were passed along this section of the line, and the associated pressure differences were measured (as side pressures) with a strain-gauge manometer (P. K. Morgan Ltd., Chatham, Kent; model 1M15E). From Fig. 2 it is evident that the inspiratory static resistance was not linear: calculated values ranged from 0.23 cm H_2O/l. sec^{-1} at a flow of 40 l. min^{-1} to 0.38 cm. H_2O/l. sec^{-1} at 140 l. min^{-1} (Appendix 1, Table 2, p. 162).

The static resistance of the expiratory line was measured between the common space of the respiratory valve and the sealed outlet of the wedge spirometer. Again, the resistance was found to be alinear

Fig. 2. Static resistance of the circuit.



(ranging from 0.69 cm. H_2O/l. sec^{-1} at a flow of 20 l. min^{-1} to 0.44 cm H_2O/l. sec^{-1} at 80 l. min^{-1}), and of the same order as that of the inspiratory line.

The dynamic resistance of the inspiratory and expiratory lines was then estimated. A sine-wave pump was connected to the common space of the respiratory valve, so that the pulsatile flows of inspiration and expiration could be simulated. The mean flow along each line was 60 l. min^{-1}. Instantaneous flow was measured with the PTM in each case, and displayed on the Devices recorder with the corresponding pressure difference. Resistance was calculated at about 20 points throughout inspiration and expiration.

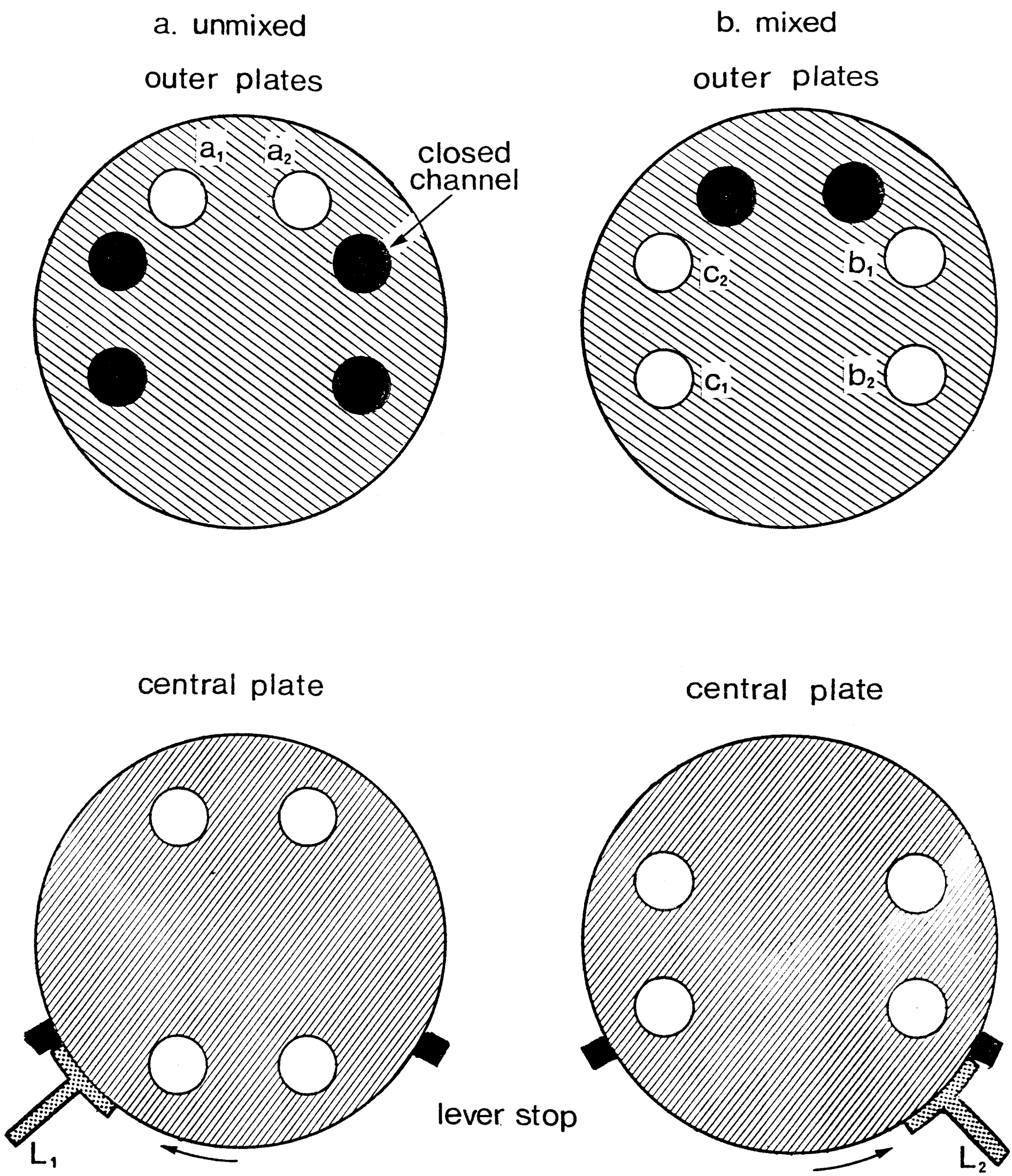
At the start of inspiration and expiration the dynamic resistance was markedly greater than the static resistance for the same mean flow, presumably reflecting the inertia of the gas and the respiratory valve flaps. The dynamic resistance thereafter declined to values of the same order as the static resistance. Even the largest values of dynamic resistance did not approach that of the human respiratory system: a value of about 4 cm H_2O/l. sec^{-1} has been obtained from the data of Mead & Agostoni (1964) for the dynamic resistance of the relaxed respiratory system during mouth breathing.

It was therefore concluded that the estimated dynamic resistance of the apparatus over the range of flows encountered in an experiment was not large enough to influence the mechanics of a subject's breathing. At no time did a subject comment on any undue resistance to breathing.

Mixing chamber and reversing tap

A six-way reversing tap, mounted securely behind the subject and situated upstream of the inspiratory solenoid-operated valves, was used to direct the two inspiratory gases in either of two ways. The gases could pass along the inspiratory lines, making no contact, so that alternate breaths of high and low P_{CO_2} could be imposed upon the subject. The alternative was the direction of the two gases into a mixing chamber for provision of identical gases in each inspiratory line; this procedure simulated the previous condition in all ways but for the occurrence of an oscillation in P_{CO_2}. The flows of the two gases into the chamber were equal, so that the P_{CO_2} of the emergent mixture was the arithmetic mean of the P_{CO_2} of the inflowing gases. The P_{O_2} was unchanged as both inflowing gases had matched P_{O_2}

Fig.3 Six - way reversing tap

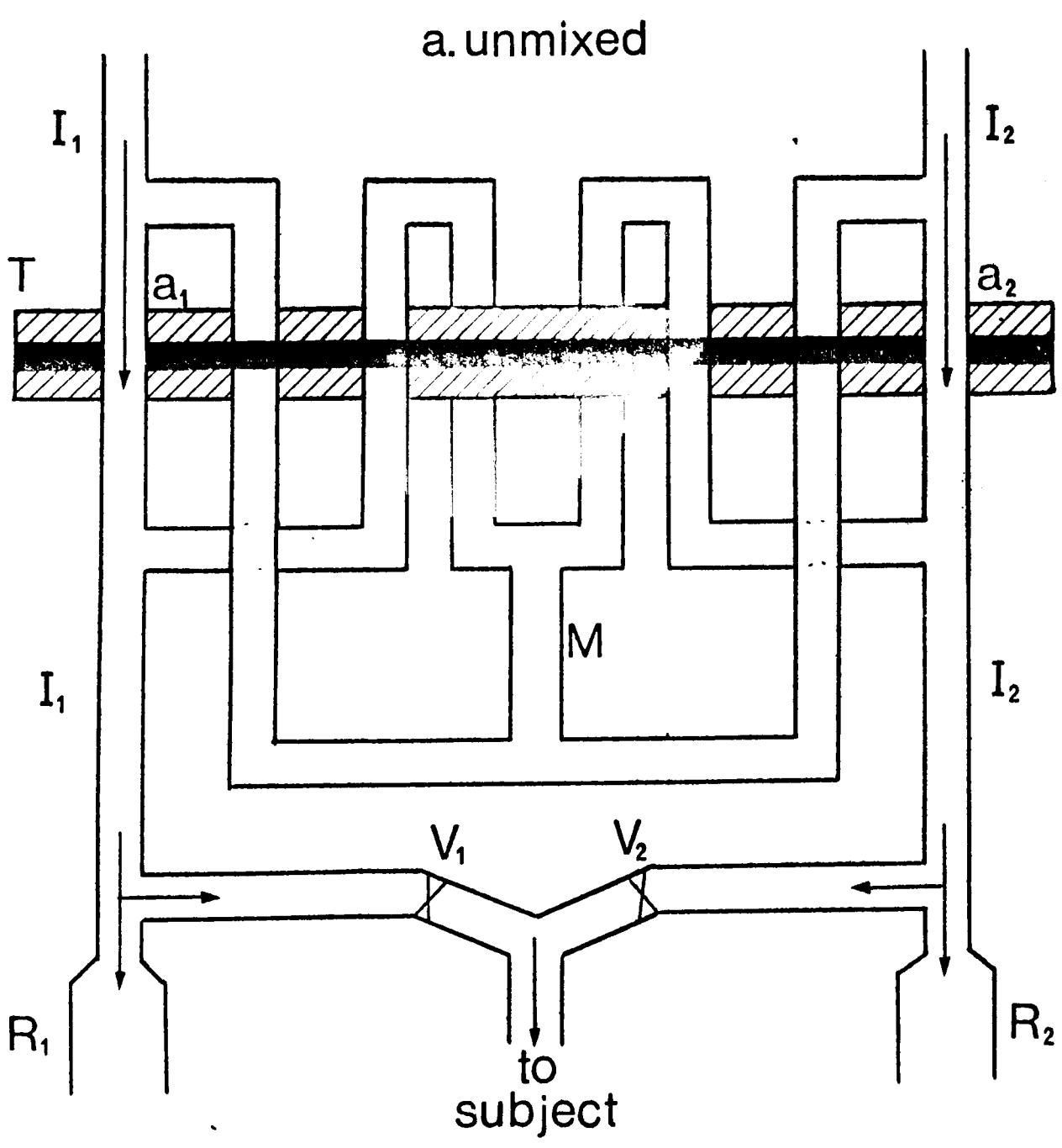


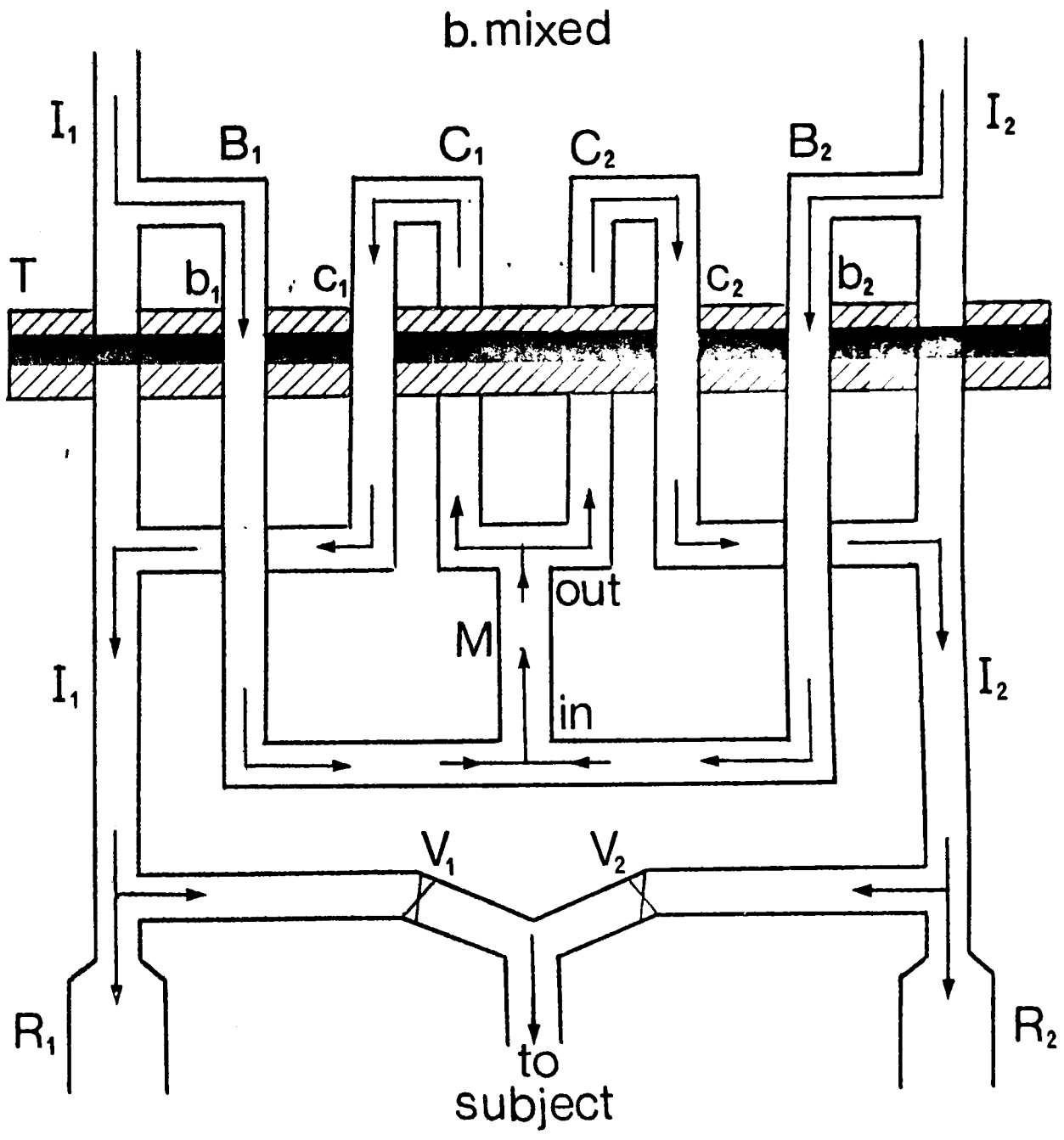
The reversing tap consisted of three superimposed circular plates. Each of the two outer plates (made of duralumin) bore six ports; the plates were fixed with the ports of each aligned to form six channels through the tap. Whether or not a particular channel would be patent was determined by the relative position of a central plate of polytetrafluorethylene (PTFE). The PTFE plate could, by means of a lever, be rotated manually and silently through 90°, relative to the outer plates. The plate was pierced by four ports, arranged so as to produce two patent channels (a_1, a_2) with the lever at L_1 (Fig. 3a), and four patent channels (b_1, b_2, c_1, c_2) with the lever at L_2 (Fig. 3b): hence, the two inspiratory gases bypassed or entered, respectively, the mixing chamber, as described below.

The mixing chamber consisted simply of a piece of perspex tubing (i.d. 3.2 cm.; volume 0.4 l.) which joined the bases of two perspex T-pieces (i.d. 3.2 cm). These served as inlet and outlet for the mixing chamber. Fig. 4 incorporates the mode of operation of the tap (T) and the mixing chamber (M). The tap is shown in cross-section, the outer plates being cross-hatched, and the central PTFE plate shaded. Open channels are indicated by breaks in the PTFE plate, and are labelled according to the convention of Fig. 3. The arrangement for delivery of the separate inspiratory gases to the subject is shown in Fig. 4a, and that for their mixing in Fig. 4b.

Mixing was effected by directing the two gases into the chamber from I_1 and I_2, via lines B_1 and B_2; after mixing, the resulting gas left by lines C_1 and C_2 to rejoin the inspiratory lines downstream of

Fig. 4 Reversing tap & mixing chamber





the tap and mixing chamber. When gases were not to be mixed, closure of both the inlet lines (B_1, B_2) and the outlet lines (C_1, C_2) of the mixing chamber was found to be essential. For not only were the gases prevented from flowing forwards into the chamber along B_1 and B_2, but they were also prevented from mixing by retrograde passage through C_1 and C_2.

Successful operation of the mixing chamber required that the composition of the mixed gas reaching the subject be at its new level on the first inspiration following the introduction of the chamber into the inspiratory lines. The speed with which constancy of composition could be attained was related to the presence and size of various volume capacitances which had first to be cleared of pre-existing gases. The major capacitance was the chamber and its connections leading to the reversing tap. Its total volume was about 7 l., representing a 3.5 l. capacitance for each inspiratory line.

Such capacitances had little effect on the composition of the initial mixed gas, the measured P_{I,CO_2} and P_{I,O_2} of this gas differing little from the expected levels. This is explained by all lever switches being made rapidly and at the start of expiration; ample time was thus available for clearance of residual gas from the inspiratory lines through the reservoir tubes prior to the start of the next inspiration.

Inspiratory solenoid-operated valves

The design and operation of the inspiratory solenoid-operated valves has been described extensively by Pearson (1971), (Fig. 5). The

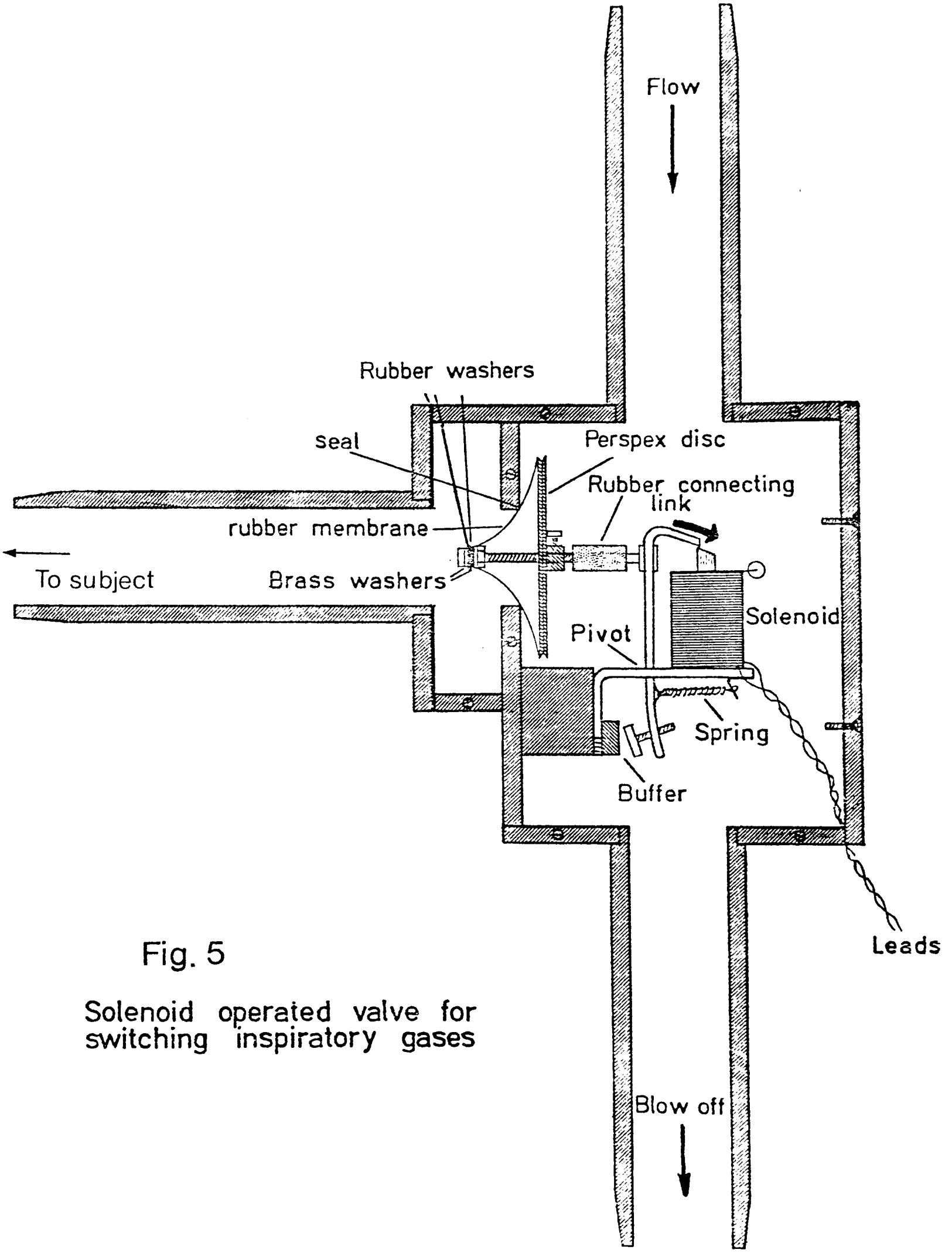


Fig. 5

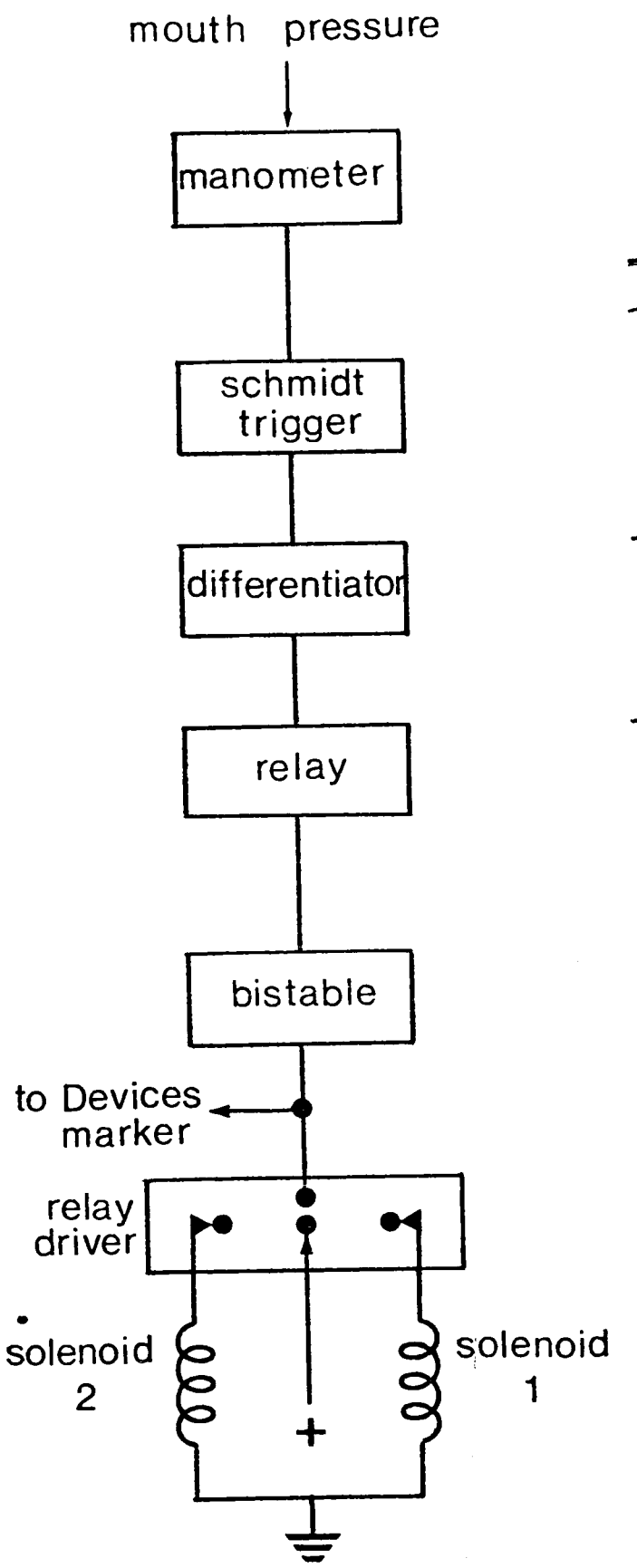
Solenoid operated valve for switching inspiratory gases

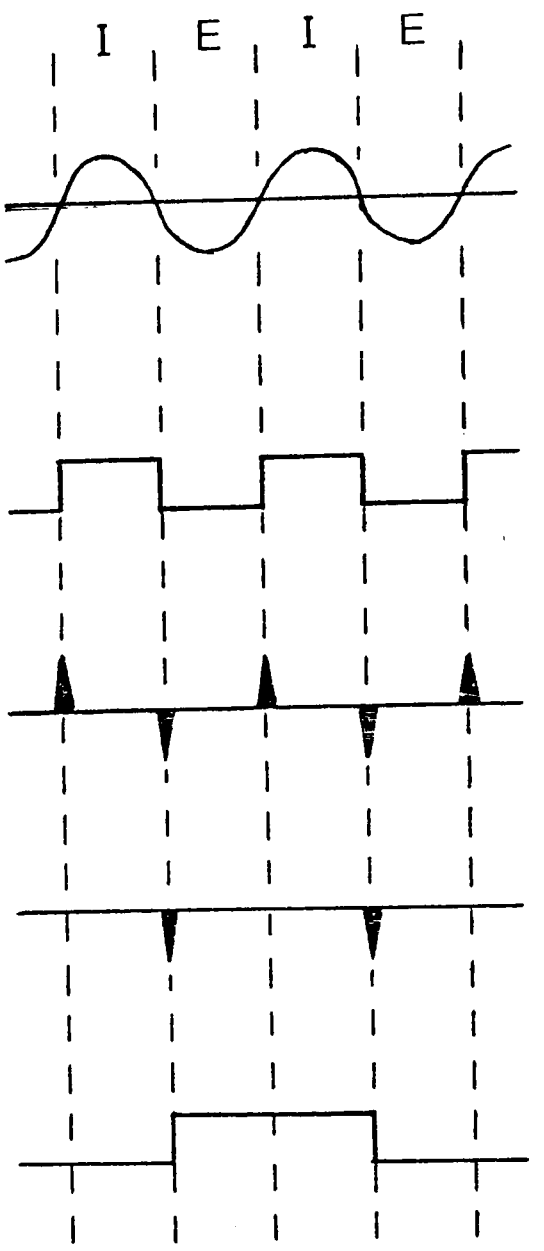
following optimising features existed in the valve design: (i) quick action to provide rapid switching between the two gas mixtures inspired by the subject; (ii) a low resistance of the valve aperture, achieved by making the cross-sectional area of the aperture as large as possible; (iii) silent operation of the valve to eliminate noise having a respiratory rhythm, which might otherwise affect the subject's breathing pattern.

A solenoid (K. A. Williams & Co. Ltd, Solihull, Warwicks) was situated within an expanded T-piece on each of the two inspiratory lines. The pad of the valve sealed the side-arm of the T-piece, thereby closing the demand line to the subject. Each pad consisted of a conical tent-like structure made of toy balloon rubber, attached to a perspex disc at its base. The whole structure was centred on a bolt. By varying the position of the perspex disc on the bolt, the tension in the rubber could be varied. On closure of the valve, the elasticity of its rubber absorbed the impact, minimising noise, and the conical shape of the pad greatly reduced the pressure waves reaching the subject.

The signal for switching the solenoid-operated valves originated from the continuous mouth pressure record, monitored from the common space of the respiratory valve by a micromanometer (M.D.C. 301). The micromanometer output was processed by a Schmidt trigger and a differentiator (Fig. 6). The differentiated signal was passed into a half-wave rectifying circuit which gave a step pulse at the start of each expiration. The output was converted, by passage through a bistable, into a square wave with a period twice that of the previous

Fig.6 Arrangement used for triggering the switching of the inspiratory solenoid - operated valves.





signal (two breaths duration). This signal changed the state of a relay at the start of each expiration, so that one or other of the solenoid-operated valves was activated, and therefore open, for one breath duration (expiration to expiration). In addition, the signal was sent to the devices recorder to provide an indication of which solenoid valve was open at any particular time.

Thus, the facility existed for administering gases of differing P_{CO_2} to the subject, on alternate breaths. Whether or not the subject actually received inspiratory gases possessing the original P_{CO_2} was determined by the size of the common inspiratory dead space. This space represented that volume of the inspiratory demand system which was common to both inspiratory lines. The outlets from the T-pieces containing the solenoid valves were joined by another T-piece, whose stem was divided along its length by a thin perspex partition, so maintaining the integrity of the two inspiratory lines. The space common to both lines therefore lay between the end of the T-piece and the inspiratory flap of the respiratory valve, and was estimated to be 130 ml. It included the pneumotachometer. Each inspiration would therefore consist of 130 ml of high P_{CO_2} gas, for example, mixed with a larger volume of gas having a P_{CO_2} near zero, or vice versa. The actual values of P_{I,CO_2} would thus deviate from the desired values.

Pearson (1971) overcame the problem of a breath-by-breath contamination of inspirates by attaching a suction line to the common inspiratory space near the respiratory valve. This cleared the common space of pre-existing gas and flushed it with the gas about to be inspired.

In the present study this method was not used because the presence of the suction line interfered with the pressure difference generated by flow along the pneumotachometer (the rate of suction varied with the changing pressure during inspiration). Thus, the difference between the P_{I,CO_2} of alternate breaths, recorded at the subject, was somewhat less than the difference existing between the two inspiratory gases in their separate lines. The contamination effect was, in practice, usually insignificant because of the small size of the common space in relation to the recorded tidal volumes.

Pneumotachometer (PTM)

Operation. The principle of the PTM is based upon Poiseuille's law for laminar flow along a cylinder ($R_{PTM} = 8 \eta L/\pi r^4$), where R_{PTM} is the flow resistance; hence, the pressure differential within the PTM (ΔP_{PTM}) is a function of overall gas viscosity (η) and PTM case dimensions (length, L; radius, r). And, flow through the PTM, $\dot{V}_{PTM}$, = $\Delta P_{PTM}/R_{PTM}$. If R_{PTM} is constant, then $\dot{V}_{PTM}$ is linearly related to ΔP_{PTM}. However, such an assumption is an oversimplification (e.g. Blumenfeld et al., 1973): both gas composition and temperature affect η; PTM dimensions are temperature dependent; changes in $\dot{V}_{PTM}$ will affect PTM case temperature. The errors introduced into flow measurement were estimated under conditions similar to those met in the experiments reported in this thesis, where changing gas flow and composition might be expected to influence PTM performance. The nature of such errors is discussed in Chapter 4 (p.138).

Calibration and performance. (i) Effects of gas flow on PTM case temperature: Air was passed through a heated Fleisch PTM head (serial no. 2.1709) from a rotameter, at steady flows in the range of 25-75 $l.min^{-1}$. The air was previously saturated with water vapour. The PTM was heated by a 6-volt A.C. supply. Gas temperatures immediately upstream (T_1) and downstream (T_2) of the PTM were measured by mercury-in-glass thermometers (range 20-40°C). 10 minutes was allowed for stabilisation of gas temperature after a change in flow. Flow through the PTM was not measured, as it was thought that the presence of the upstream thermometer might distort the assumed laminar flow pattern.

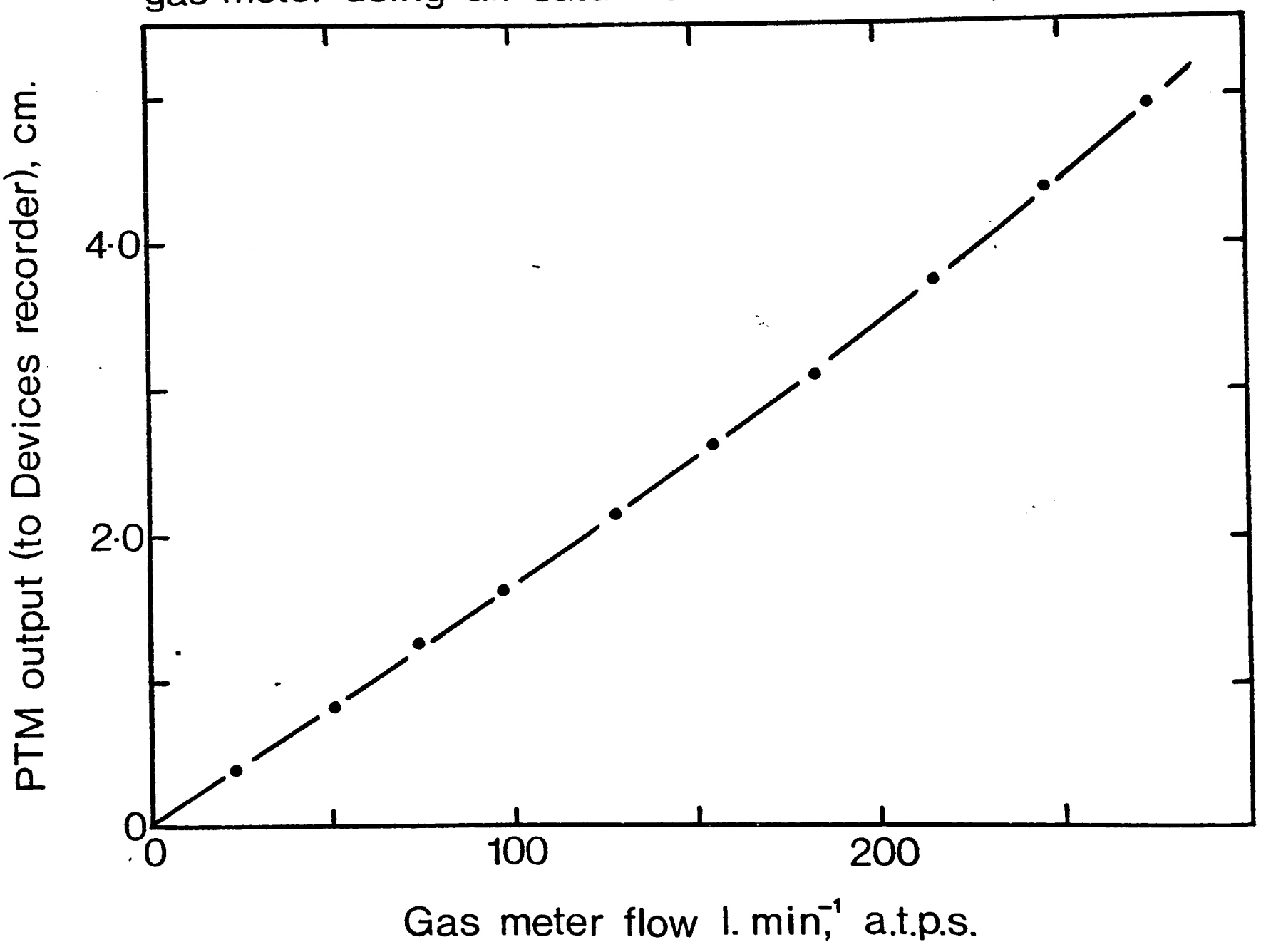
The results are shown in Table 5. As might be expected, T_1 was constant over the flow range, at about 28°C. T_2 was always greater than T_1, a result of the relatively high case temperature. However, as flow rose, so T_2 and the temperature differential across the PTM fell, indicating, albeit indirectly, a fall in PTM case temperature. This would be expected to affect the estimate of flow, through effects on gas viscosity and PTM case dimensions.

(ii) Effects of varying gas composition on steady flow measurement: The apparatus was similar to that of (i) with the following changes: thermometers were omitted; flow was measured both with the PTM and the dry gas meter (Type CD, no. 01334, Parkinson & Cowan Ltd., London), which was put downstream of the PTM; gas was sampled from the gas meter outlet for measurement of P_{O_2} and P_{CO_2} by the mass spectrometer; P_{O_2}, P_{CO_2}, PTM flow, and gas-meter volume (as 10-litre increments) were displayed on

Table 3: The effect of flow on the temperature difference across the PTM.

$\dot{V}$ l. min^{-1}	T_1 °C	T_2 °C	$T_2 - T_1$ °C
25	28.2	34.2	6.0
50	28.1	31.9	3.1
75	28.4	29.3	0.9

Fig.7 Calibration of pneumotachometer (PTM) against a dry gas meter using air saturated with water vapour.



the Devices recorder. The PTM was calibrated for steady flow, over a range of 20-260 $l.min^{-1}$, for various saturated gas mixtures: air, and four mixtures having the following P_{CO_2} and P_{O_2} values:- P_{CO_2} = 0 torr, P_{O_2} = 200 torr; P_{CO_2} = 65 torr, P_{O_2} = 200 torr; P_{CO_2} = 0 torr, P_{O_2} = 40 torr; P_{CO_2} = 65 torr, P_{O_2} = 40 torr. These last four covered the extremes of P_{I,CO_2} and P_{I,O_2} used in the experiments.

PTM output on the Devices recorder (ordinate), was plotted against gas meter flow, for air (Fig. 7). The relation was linear up to about 180 $l.min^{-1}$, having a slightly steeper gradient for higher flows. The PTM outputs for each of the other gases were converted to air flows, using the air calibration curve, then plotted against the corresponding gas meter flow (Fig, 8: hyperoxic gases; Fig. 9: hypoxic gases). Each curve approximated to a linear form, but each of them lay above the line of equality by an amount of 10-15 $l.min^{-1}$, indicating an overestimation of PTM flow. The data upon which the calibration curves were based are presented in Appendix 1, Table 3, p.163.

Calculations were performed to test the hypothesis that the overestimation of PTM flow could be attributed solely to the effects of gas composition on mean viscosity. These were based on empirical expressions of the temperature dependency of viscosities produced by Blumenfeld et al. (1973). For the temperature range of 20-40°C, pure gas viscosities can be expressed as approximations to linear functions of temperature (T):-

$$\eta\, O_2 = 200.0 + 0.299\ T,$$

$$\eta\, CO_2 = 150.7 + 0.465\ T,$$

$$\eta\, N_2 = 167.6 + 0.453\ T,$$

$$\eta\, H_2O = 132.6 + 0.570\ T,$$

Fig.8 Calibration of pneumotachometer against a dry gas meter, for hyperoxic gas with & without CO_2 (saturated with water vapour)

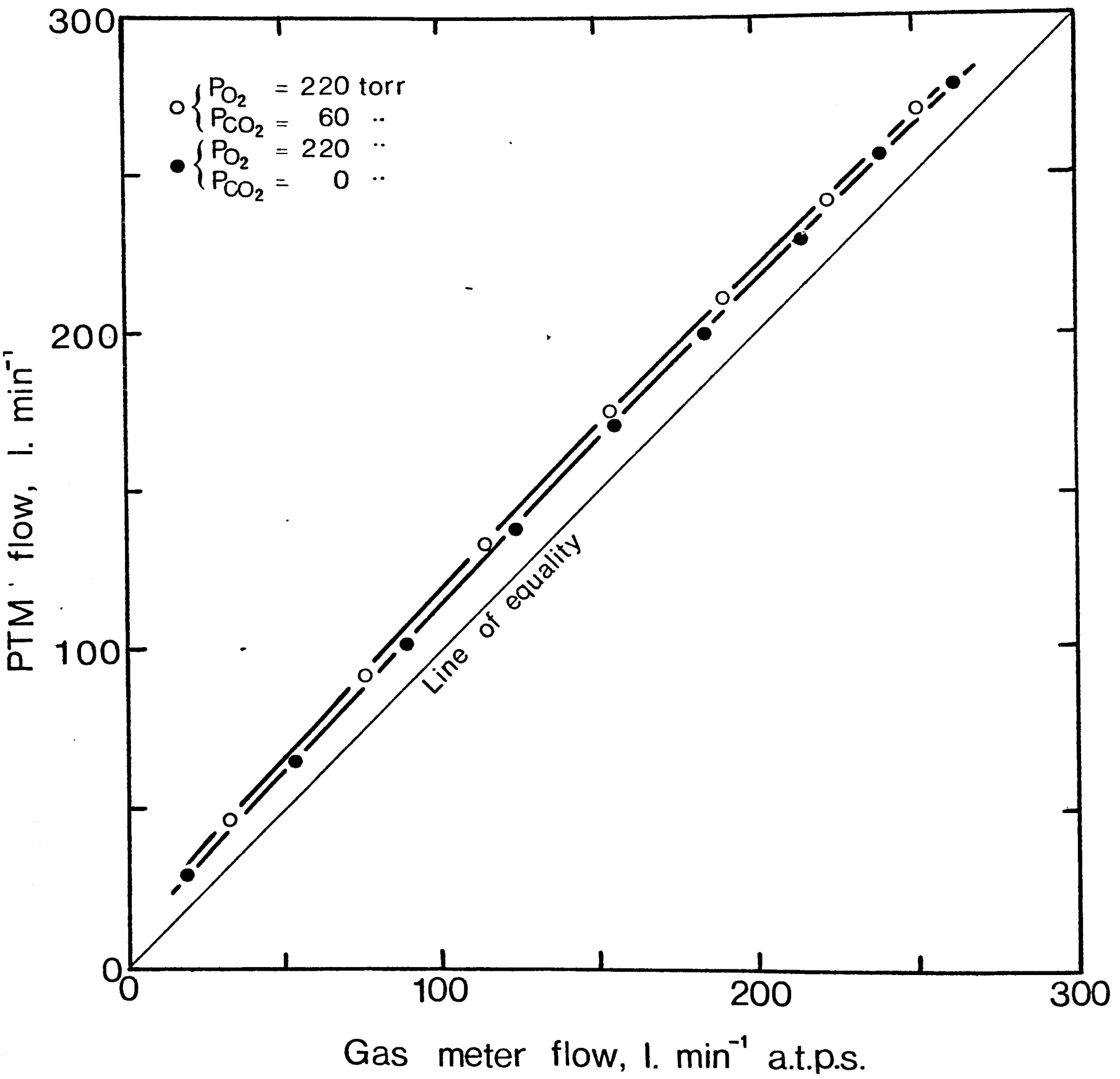
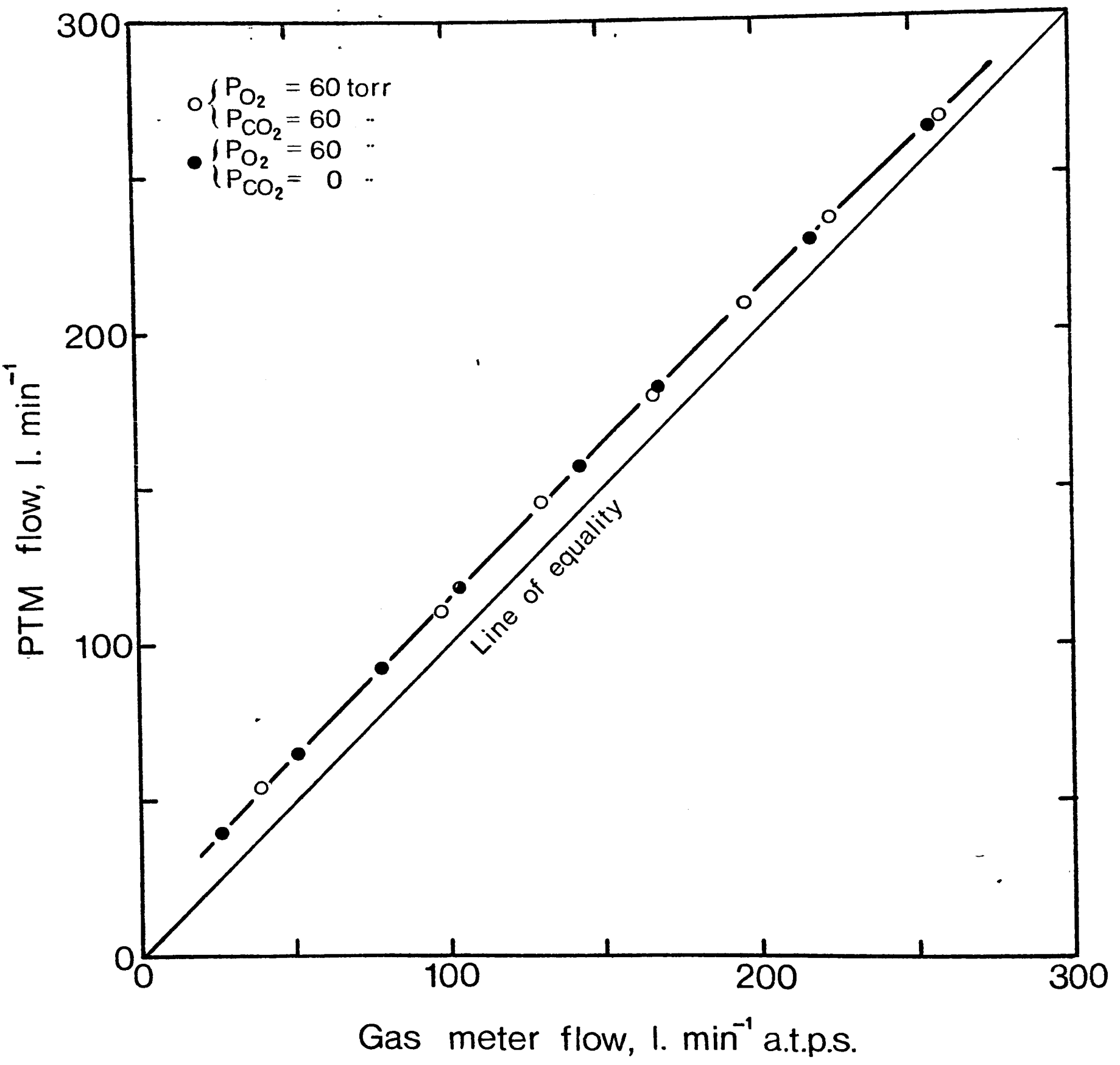


Fig. 9 Calibration of pneumotachometer against a dry gas meter, for hypoxic gas with & without CO_2 (saturated with water vapour)



where η is measured in (deg. C^{-1} x 10^{-6} poise), and T = the average gas temperature along the PTM. It was assumed that the mean gas viscosity of a particular gas mixture was the linear combination of the viscosities of the pure gases, weighted by their fractional concentrations.

The mean gas viscosities were calculated for each of the five gas mixtures used for the PTM calibration, at T = 30°C and 34°C (Appendix 1, Table 4, p.164). The values for the four mixtures were expressed as ratios of the mean viscosity of air at each temperature (Table 4). For a constant PTM flow, the flow recorded by an air-calibrated PTM will be overestimated when the average gas viscosity exceeds that of air.

The following predictions were made. For hyperoxic gas (gases 2 and 3), PTM flow is overestimated; the presence of CO_2 (gas 3) removes some of the discrepancy, by lowering mean η. Hypoxic gas (gases 4 and 5) flow is underestimated; addition of CO_2 (gas 5) increases the discrepancy by lowering mean η further below that of air (gas 1). Increase in PTM temperature from 30 to 34°C, as might occur in an experiment with a fall in mean inspiratory flow, increases mean η by less than 2 deg. C^{-1} x 10^{-6} poise. This increase, though small, shows an oxygen dependency, rising as P_{O_2} falls.

However, there was little agreement between prediction and observation. Although the PTM flow was overestimated in hyperoxia, as predicted, the addition of CO_2 served to enhance this effect rather than to reduce it. In hypoxia, flow was also seen to be overestimated, in contrast to the prediction; furthermore, the addition of CO_2 did not reduce flow.

Table 4: Calculated mean gas viscosities, as ratios of air viscosity (saturated gases).

	Gas mixture		η mixture : η air	
	P_{O_2} (torr)	P_{CO_2} (torr)	30°C	34°C
2	200	0	1.014	1.013
3	200	65	1.007	1.006
4	40	0	0.979	0.980
5	40	65	0.972	0.973

A further factor, not so far considered, is deviation from a condition of laminar gas flow through the PTM. Turbulent flow generates a greater drop in pressure across a tube than does laminar flow, for the same mean flow, reflecting a greater flow resistance. In such a case, the PTM flow would exceed that actually occurring, as was found experimentally in this study. Turbulence could arise from the geometry of the junction of the paired inspiratory lines with the PTM (Fig. 1, p.26), where an asymmetrical increase in cross-sectional area existed:-

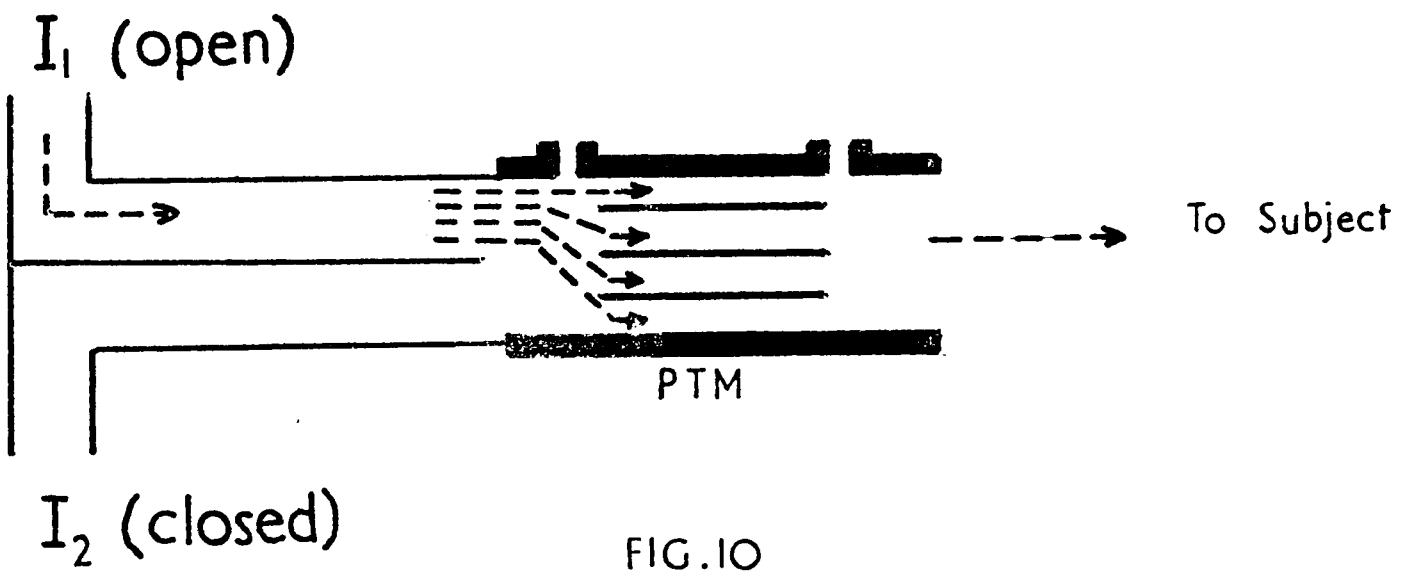


FIG.10

There is no information available as to the existence of such a phenomenon, or what its relative importance might be in accounting for the differences between observed and predicted PTM flow. Thus, it was concluded that the temperature-dependency of gas viscosity could not account for all flow deviations, it being probable that a more complex interplay of gas flow, PTM temperature and case dimensions was involved, with the possibility of a distortion of laminar flow through the PTM.

(iii) Effects of alternate breaths of high and low CO_2 on the breath-by-breath measurement of flow: The theoretical considerations of (ii) led to the possibility of alternate breaths of high and low CO_2, in hypoxia or hyperoxia, inducing a similar oscillation in the PTM output: for the presence of CO_2 is expected to reduce mean V_T, and therefore to reduce the measured PTM flow. Thus, the effects of such an oscillation in P_{CO_2} on breath-by-breath PTM output were examined by driving the apparatus (Fig. 1) with a sine-wave pump, so as to simulate an actual experiment (varying the levels of P_{O_2}, mean flow, and frequency over the required ranges). The peak flow and volume recorded by the PTM during inspiration (peak inspiratory flow and inspiratory tidal volume) were taken as suitable measures of PTM output, being two of the variables monitored during experiments.

Using those methods of measurement and computation employed in the analysis of experiments (p.63, p.67), alternate-breath oscillations in PIF and $V_{T,I}$ could sometimes be detected. However, they were either below the limit of measurement (less than 0.5 mm on the recording paper) or not significantly different from zero (Appendix 1, Table 5, p.165). Thus, it was concluded that effects of alternate breaths of high and low CO_2 had no significant effect on the PTM performance.

(iv) The integration and differentiation of PTM flow: PTM flow was integrated to give a measure of instantaneous inspiratory volume, using an integrator, reset at the start of expiration by a step pulse. The pulse was obtained by passage of the mouth pressure electrical analogue through a Schmidt trigger, a differentiator, and a half-wave

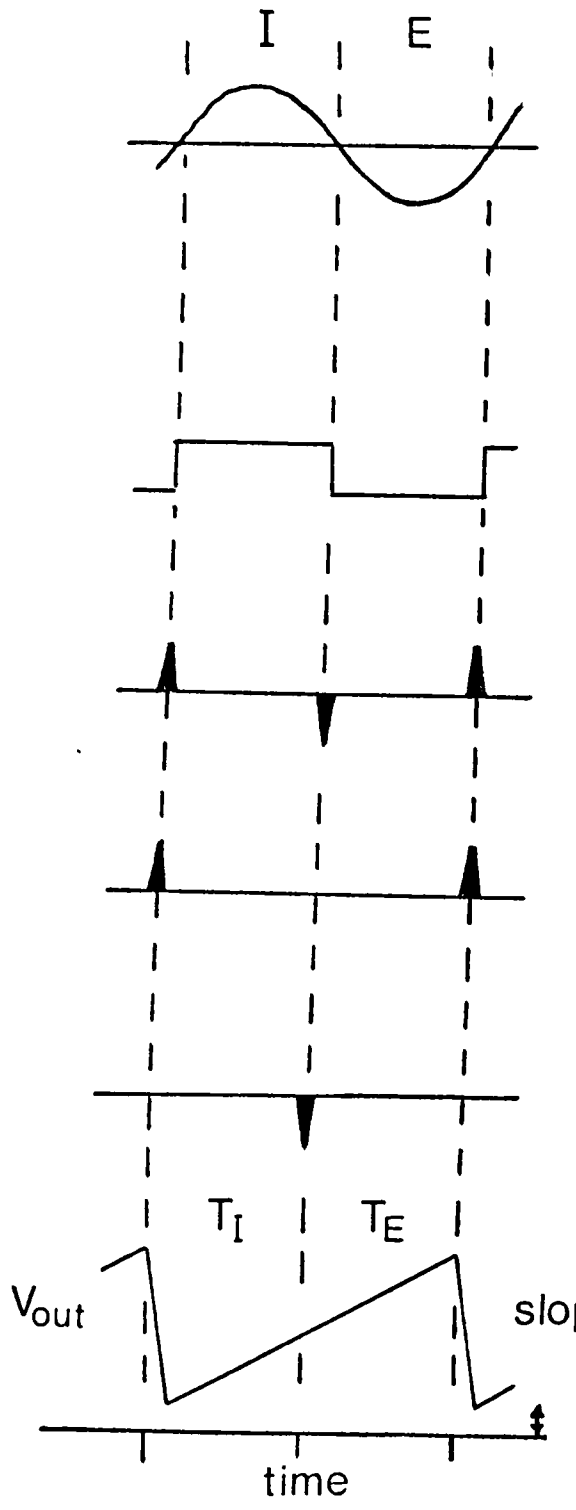
rectifier. Differentiation of PTM flow to give instantaneous inspiratory acceleration was performed by a 0.1 μF capacitor, placed in series.

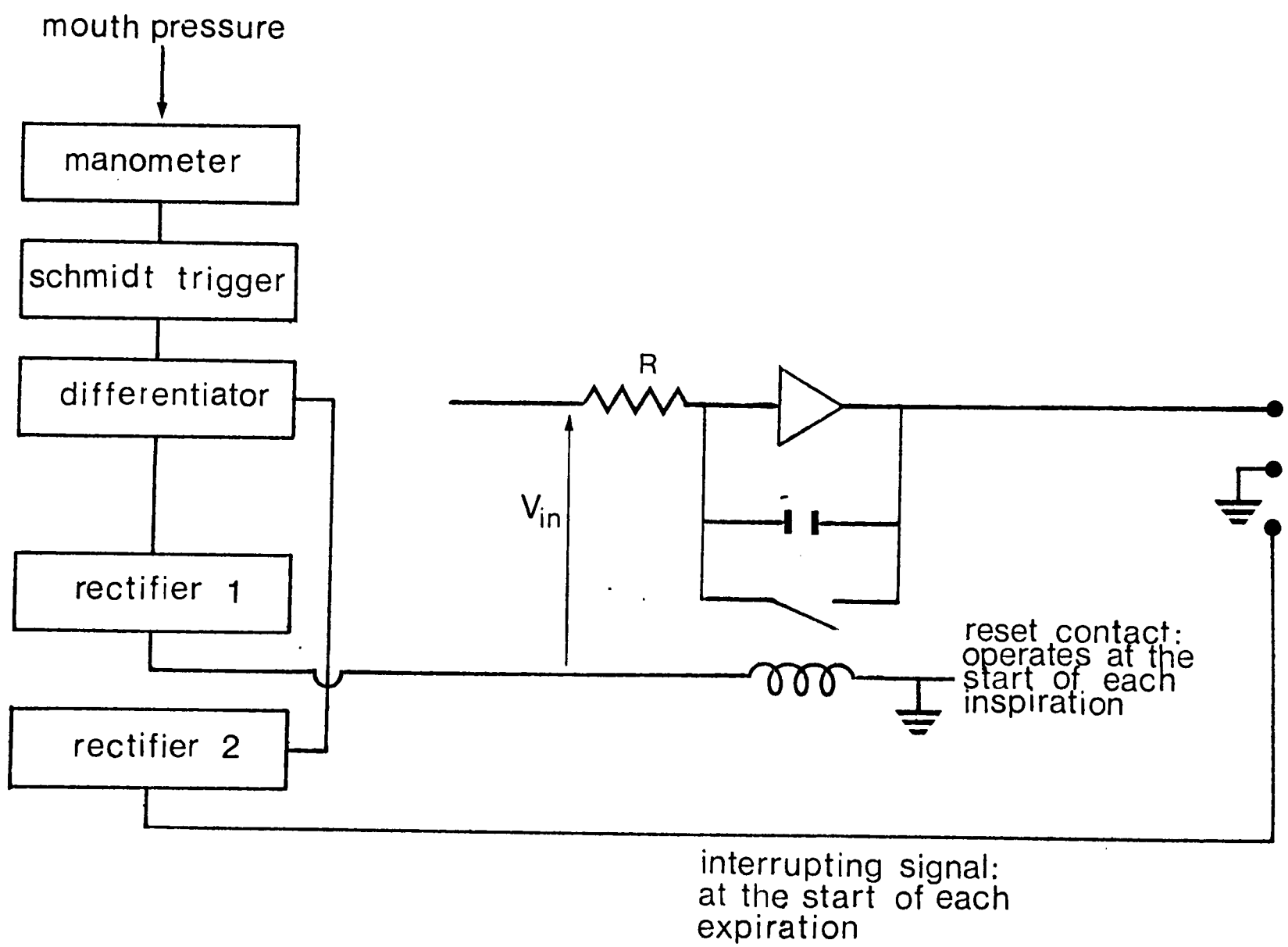
The performance of these circuits was examined by presenting them with an electrical sine-wave, of periods ranging from 1.0 to 4.0 sec. Thus, the range of expiratory times likely to be met in experiments was covered. Differentiation converted the sine-waves to positive cos-waves (approximating to a 270° phase shift), while integration gave negative cos-waves (having a 90° phase shift). The initial and final waves were recorded at fast paper speed on the Devices recorder, and the deviations from the expected phase shifts were estimated.

The greatest deviations observed, expressed as a percentage of the corresponding cycle period, were 2.6% for the integrated wave (period = 1.55 sec) and 5% for the differentiated wave (period = 1.0 sec). All deviations were in the direction of a greater than predicted lag (Appendix 1, Table 6, p.166). Thus, it was concluded that the differentiating and integrating circuits were operating in an acceptable manner. This conclusion, taken with the observation of a nearly linear flow calibration, allowed the deduction to be made that the PTM circuitry was reasonably linear for both inspiratory volume and acceleration.

Calibration during experiments. The PTM was used to measure breath-by-breath inspiratory tidal volume, peak flow and peak acceleration. The PTM was calibrated for flow by passage through it of a steady air flow, humidified at 40°C. The calibration for tidal volume was also performed with air: a manually-operated syringe pump of 1 litre volume

Fig.11 Measurement of T_T, T_I & T_E





$V_{out} = \frac{1}{RC}\int V_{in}$

= 1 volt/sec

passed gas through the PTA. The calibration for inspiratory acceleration was electrical: a ramp of voltage varying with time, at selected constant rates, was fed into the Devices channel normally recording inspiratory flow, at the gain setting to be used in the experiment. The signal was passed simultaneously through the differentiating circuit, and recorded on a separate channel. The amplitude of the differentiated signal was equal to the rate of change of the undifferentiated signal, expressed as a rate of change of flow.

Measurement of breath duration

The mouth pressure signal, converted to an electrical analogue by a micromanometer (M.D.C. 301), was differentiated by passage through a Schmidt trigger and a differentiator. The differentiated signal was passed to two separate half-wave rectifiers; one produced a signal having a step pulse at the start of each inspiration, and the other, a step pulse at the start of each expiration (Fig. 11). The pulse at the start of inspiration closed a relay transiently which resulted in the resetting, at that point, of an integrating circuit (output: 1 volt/sec) in the circuitry of the wedge spirometer.

The rising voltage signal was interrupted at the beginning of expiration by the expiratory pulse (Gardner, personal communication). Thus, measures of breath-by-breath T_T, T_I and T_E could be obtained, by display of the signal on the Devices recorder.

Respiratory valve

The subject breathed through a rubber mouth-piece attached to a perspex respiratory valve. The valve was a Lloyd valve modified by turning the terminal part of the valve through 90° (Gardner, personal communication). Thus, the main body of the valve and most of its connections lay to one side of the subject, allowing him to read a book in relative comfort. This modification increased the valve dead space from about 15 ml to about 35 ml. Gravity-operated hinged perspex flaps closed the inspiratory and expiratory orifices of the valve; the flaps opened in response to the appropriate changes of pressure gradient induced across them by inspiration and expiration.

Mass spectrometer for respiratory gas analysis

Operation. The mass spectrometer analyses vapours at low pressure, according to their molecular weights. For accurate quantitative analysis, the total pressure of the sample should be less than 10^{-5} torr; above this pressure, the spectrometer is non-linear. Therefore, samples of respiratory gas obtained at atmospheric pressure were passed through a pumping system attached to the spectrometer which reduced the total pressure to the required low level. The atoms or molecules of the vapour are first ionised by passage of an electronic beam through the vapour. Electronic bombardment can produce both positive and negative ions, but only positive ions are used for gas analysis. The positive ions are accelerated by a voltage, V_A, and injected at constant velocity

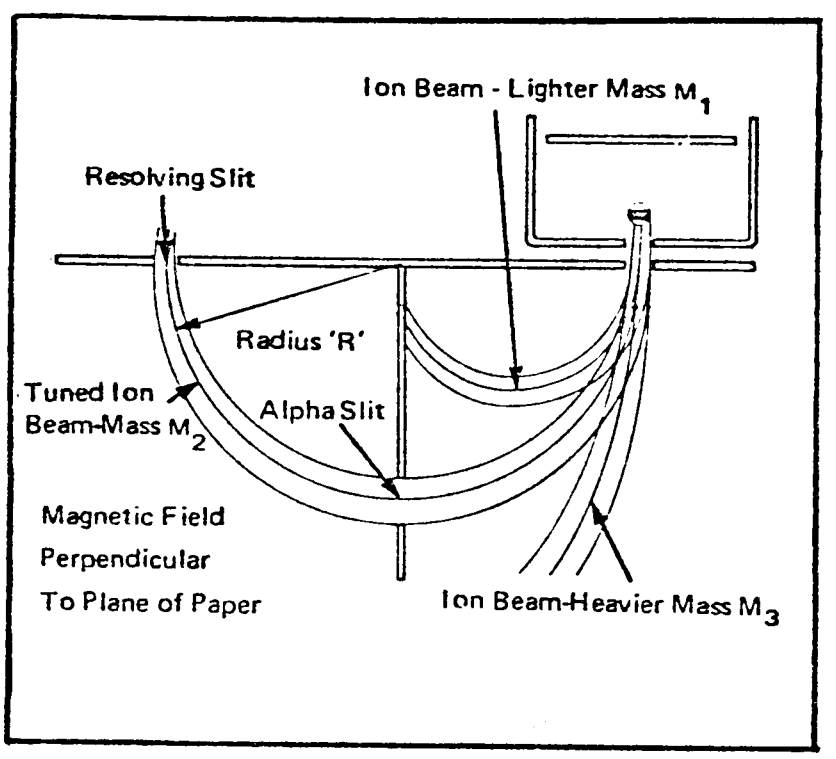


Fig. 12. Mass spectrometer : ion detection in the analyser.

into a chamber (analyser) that is subjected to a magnetic field. Ions are thus caused to orbit in a circular path of constant radius.

The radius of orbit (R) is dependent upon the velocity (which is proportional to V_A), mass (M), and charge (e) of the ion, and the strength of the magnetic field (H):-

$$R^2 = \frac{M.V_A}{H^2.e} \times \text{constant} \qquad (1)$$

In the mass spectrometer, the radius is fixed by limiting the emergence of the ion beam from the magnetic field of the analyser to two slits (the alpha and resolving slits): ions can only emerge through the slits if the correct values of V_A and H are used. The width of the resolving slit determines the ability of the instrument to separate ions of adjacent mass numbers. The Micromass spectrometer employed here is a 1 cm radius, 180° magnetic deflection type, operating with a constant magnetic field which causes ions to orbit through a semi-circle. Only those ions having a 1 cm radius of orbit will emerge through the resolving slit for subsequent ion detection (Fig. 12). Further, from equation (1),

$$\frac{M}{e} . V_A = \text{constant.}$$

Thus, a specific vapour may be located by fixing V_A at a level appropriate to its (M/e) ratio. A fine tuning device allows adjustment of V_A to bring the ion species to peak focussing. Ion detection is achieved by collection from the analyser of emergent ions (collector current, I_c) for amplification.

The size of I_c is a measure of the partial pressure of the vapour in the spectrometer. Factors other than the partial pressure of the vapour may affect I_c, and so distort the true pressure; those relevant to the analysis of respiratory gases will now be considered.

The pressure of the residual gas within the spectrometer influences I_c, since the number of ions produced at the collector depends on the molecular concentration in its vicinity. For this reason, gas samples were freed from water vapour by passage through magnesium perchlorate prior to entry into the spectrometer. Otherwise, water vapour would accumulate in the spectrometer, because, for reasons unknown, its rate of removal from the spectrometer is much slower than those of other respiratory gases.

The composition of the residual gas may also affect I_c. Hydrocarbon contamination, resulting from common oil contaminants, produces CH_2 aggregates (mass = n x 14, where n is the number of aggregates), a major mass peak occurring at mass 41-43, close to the CO_2^+ peak at mass 44. Thus, it is essential to tune the spectrometer carefully. The tuning of each head (for CO_2 and O_2) was checked prior to each experiment, though little adjustment was needed between or during experiments. Moreover, the resolution of the spectrometer heads for O_2 and CO_2 is one unit of mass: thus, peaks of adjacent masses (e.g. 43 & 44) having equal heights will be discrete for all but the first 10% of their height. Hence, it was considered unlikely that hydrocarbon contamination would have a major direct influence on P_{CO_2} readings.

Indirect effects of hydrocarbon contamination, in the presence of O_2, may result from the production of CO_2 from CH_2 units by oxidation. This has been considered as a possible explanation for the observed separation of the calibration curves for CO_2 in O_2 and CO_2 in N_2 (see below).

CO_2 itself may be present in the residual gas, being a fairly common contaminant of ultra-high voltage systems. This effect was minimised by opening the mass spectrometer for sampling at least one hour before starting an experiment. During that time, room air was sampled continuously, in an attempt to clear the endogenous CO_2 that had accumulated. That this was largely achieved was indicated by a decline to near-zero levels of P_{CO_2} in the analyzer from an initial raised level (maximum of 4 torr) with continuous air sampling. The initial clearing operation probably also removed at least some of the hydrocarbon contaminants.

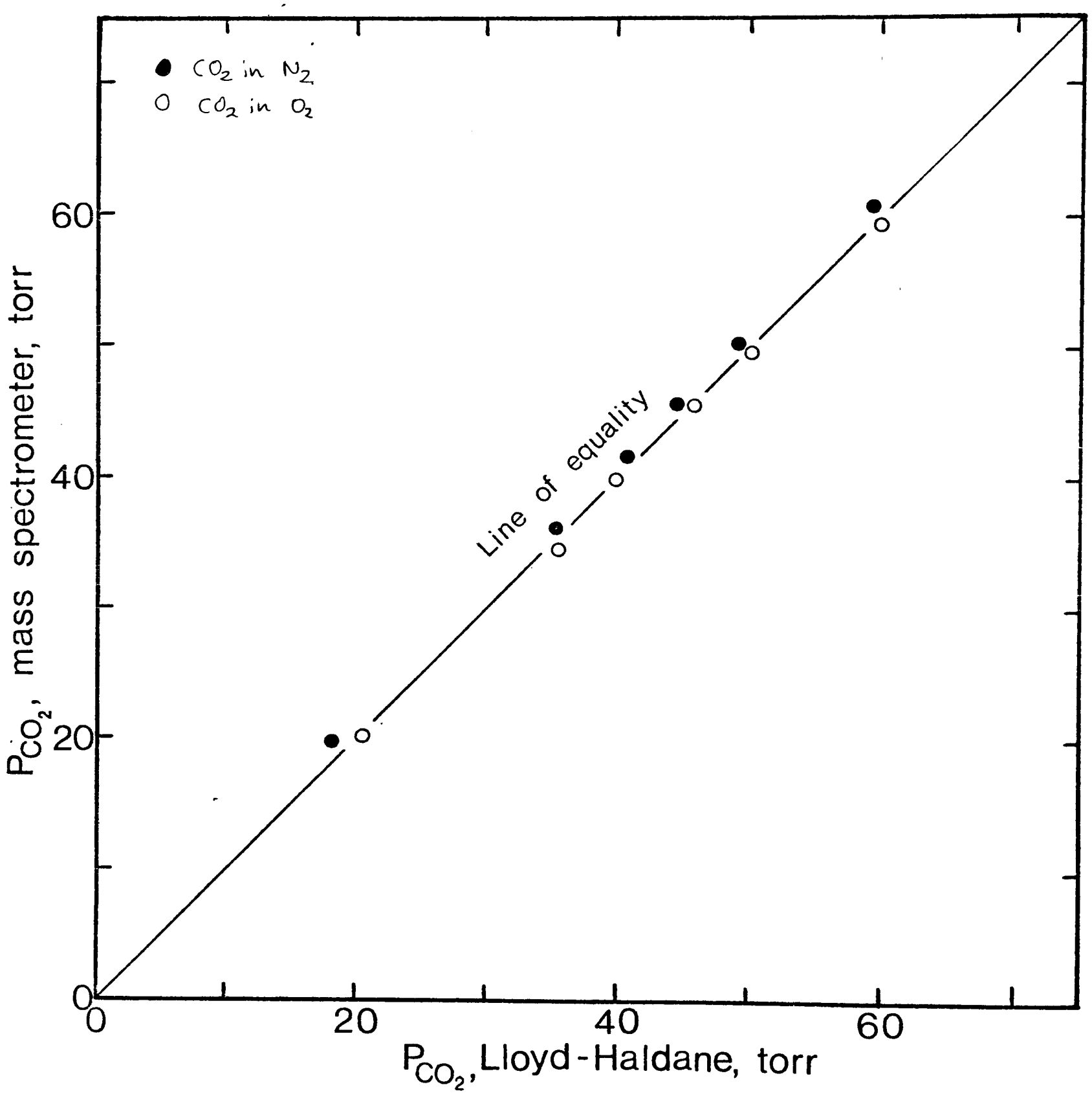
Sampling of respiratory gas. The mode of operation of the mass spectrometer during experiments is now discussed. Two Micromass 2 analyser heads were employed for the simultaneous and continuous monitoring of O_2 (head 1: mass 32) and CO_2 (head 2: mass 44). Respiratory gas was sampled continuously, being drawn by a small pump through a 2.5 ml drying tube, containing magnesium perchlorate, to the start of the spectrometer sampling line. The gas was sampled in one of two ways. In some early experiments, gas was sampled from the common space of the respiratory valve. This gave a record, throughout the respiratory cycle,

of inspired gas, mixed expired gas, and finally end-tidal gas, the last being taken as a reasonable approximation to mean alveolar gas (Fig.23A, p.82). Because of the two extremes of P_{I,CO_2} present on alternate breaths in test runs, it was often difficult to locate precisely the level of P_{et,CO_2} in the low P_{CO_2} breaths, especially during exercise where the alveolar plateau was, in fact, sloping. Thus, for the main series of experiments, sampling of gas from beyond the expiratory flap was performed, giving P_{et,CO_2} and P_{et,O_2} at the end of each expiration. During each experiment the values recorded by each method of sampling showed close correspondence. The sampling rate from the expiratory line was 0.5 $l.min^{-1}$; measured gas meter ventilation was corrected for sampling by adding to it this flow rate.

Calibration during experiments. The spectrometer heads were calibrated during experiments at frequent intervals. The CO_2 head used air for the zero point gas, and, for a span point, a standard gas mixture (containing 6-7% CO_2 and 7-10% O_2), analysed accurately by Lloyd-Haldane analysis. The zero point for the O_2 head was obtained by tuning the head to mass 3 for helium, a gas present in negligible amounts in air. Air and the standard gas mixture provided two span points to cover both hyperoxic and hypoxic ranges.

The various standard gases were directed into the mass spectrometer sampling line via a tap with five inlets and one outlet (Drallim Industries Ltd, Bexhill-on-Sea). The outlet branched into a bubbler and a line leading to the drying tube containing magnesium perchlorate). The bubbler ensured that standard gases were delivered to the start of

Fig.13 Calibration of mass spectrometer (head 2) for CO_2 in O_2 & in N_2



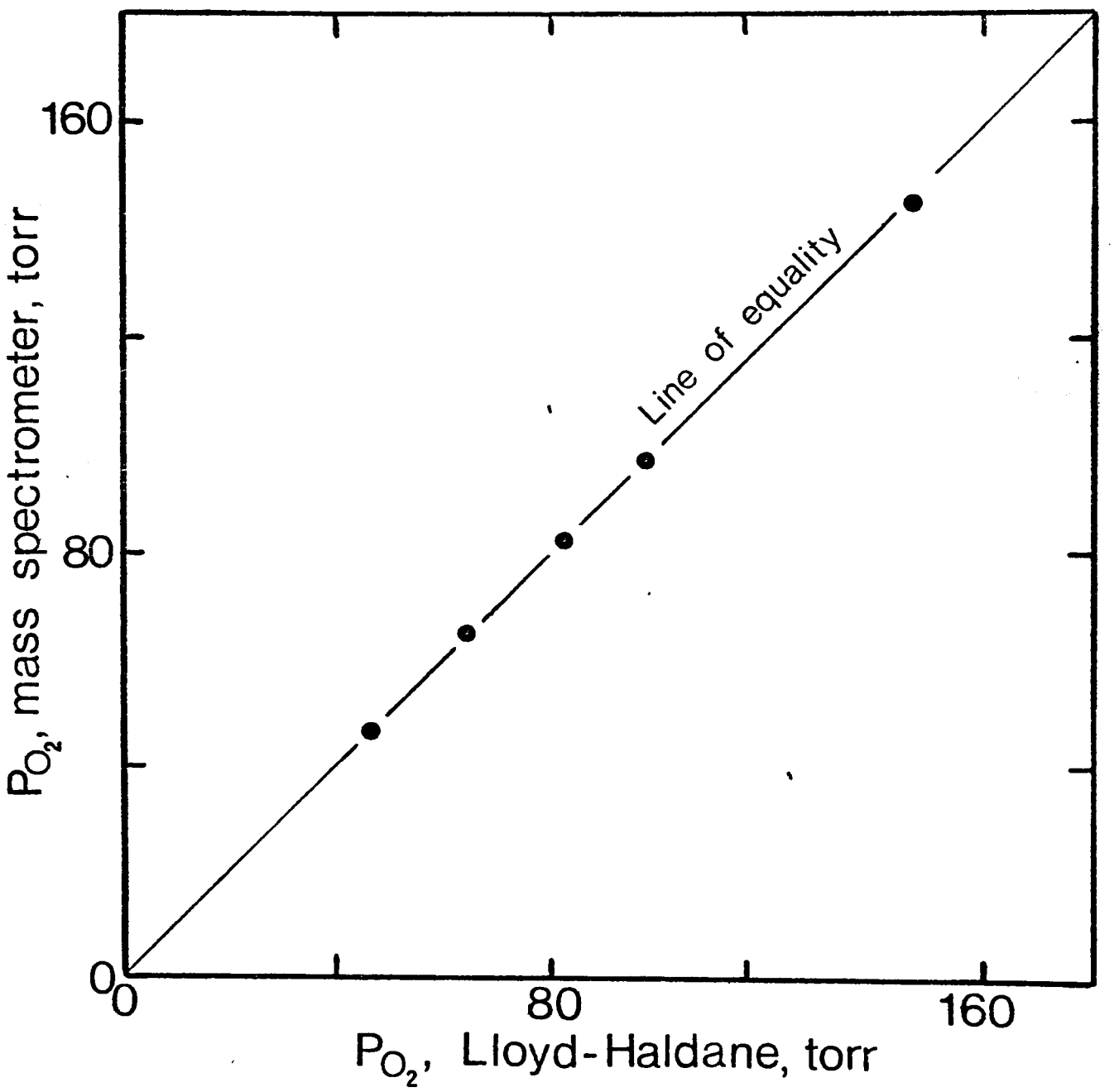
the sampling line at near atmospheric pressure, as was the sampled respiratory gas. A three-way tap which could connect either the standard gas line or respiratory gas line to the drying tube permitted rapid switching between the two gas lines.

Calibration and performance. The 99.9% response time of the mass spectrometer, excluding the attached sampling line and drying tube, was 0.2 sec, at a sampling rate from the expiratory line of 0.5 $l.min^{-1}$. This was in response to square waves of air and 100% CO_2 (head 2), and of 100% O_2 and 100% N_2 (head 1). Inclusion of the sampling line and drying tube increased the response time to 0.7 sec. This speed of response was considered as adequate for the measurement of breath-by-breath P_{et,CO_2} and P_{et,O_2}.

Calibration curves were constructed for each analyser head (Figs. 13 & 14). The ranges of P_{CO_2} and P_{O_2} used were similar to those of the experiments (P_{CO_2} 0-60 torr; P_{O_2} 45-150 torr). The output of the appropriate analyser head was converted to a partial pressure, by the usual experimental calibration method. This was then plotted against the corresponding value obtained by volumetric analysis (Lloyd-Haldane method). The data are presented in Appendix 1, Table 7, p.167. Both the CO_2 and O_2 calibration curves were linear, lying near or on the line of equality.

The CO_2 curve was determined both in pure O_2 and in pure N_2, to assess the possibility of an interaction occurring in the analyser chamber, of CO_2 with either N_2 or O_2. The CO_2-in-O_2 line lay about

Fig. 14. Calibration of mass spectrometer (head 1) for O_2.



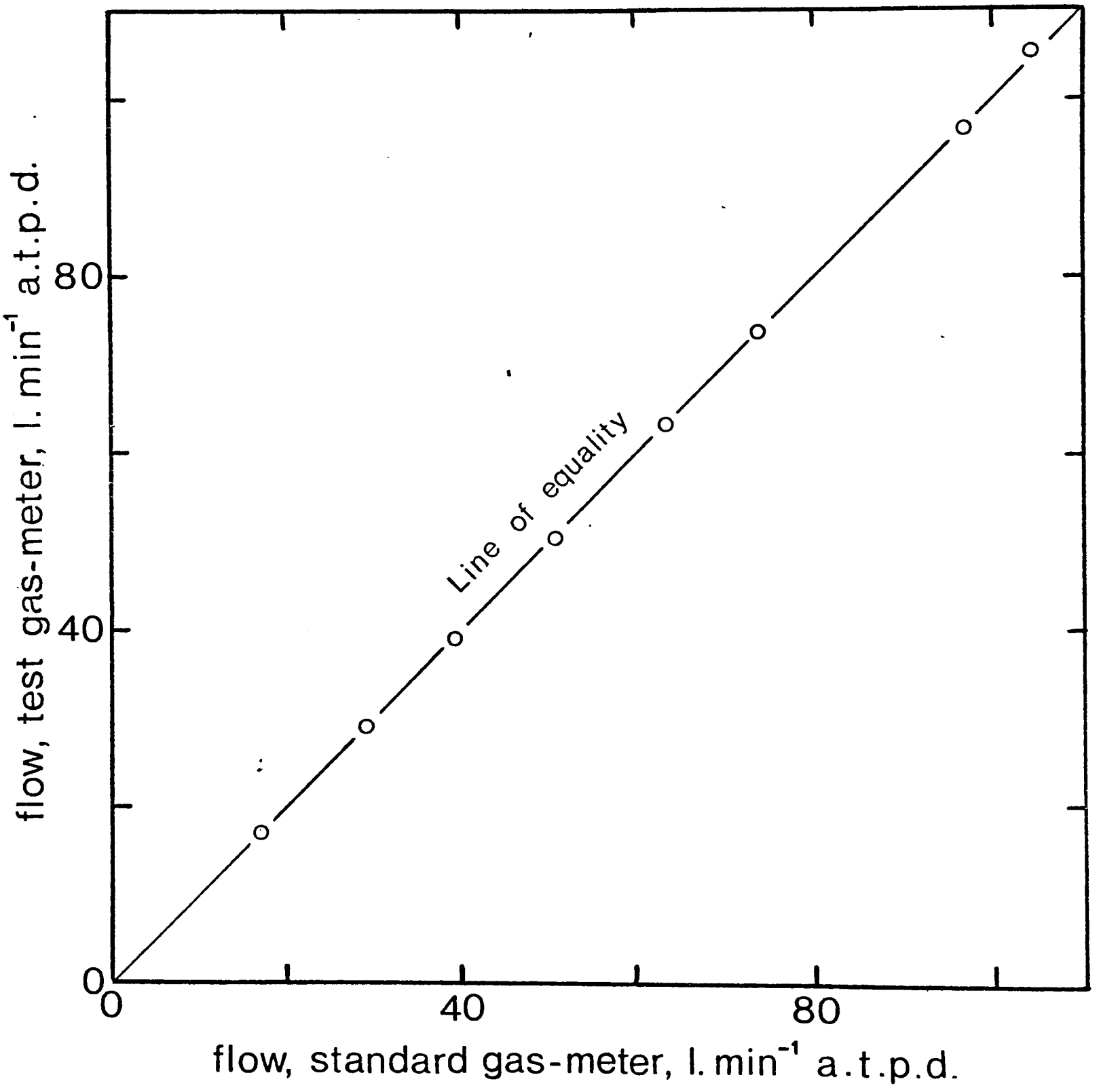
1.5 - 2.0 torr above the CO_2-in-N_2 line; the line of equality lay between the two, being slightly nearer the CO_2-in-N_2 line. From a consideration of mass, there is no reason to suppose that $O_2^+(32)$ or $N_2^+(28)$ could influence CO_2^+ at mass 44. However, as mentioned previously, CO_2 might be produced by the oxidation of contaminating CH_2 units by O_2, causing a greater than expected P_{CO_2} to be recorded. Assuming the effect of O_2 on CO_2 to be a linear function of P_{O_2}, the expected effect over the experimental P_{O_2} range (150 torr) would be 0.5 torr P_{CO_2}, or less. As this approaches the limit of measurement of P_{CO_2}, it has been ignored.

Gas meter

Operation. A dry gas meter (Type CD, serial no. 01334, Parkinson & Cowan Ltd, London) measured expired volume in 10 l. increments. A micro-switch was attached to the 10 l. marker on the face of the gas meter scale. This was closed briefly once every revolution by the passage of the meter needle over it, thus producing an electrical pulse for each revolution (10 l. of gas). The signal was displayed on the Devices recorder. All volumes measured in experiments were at A.T.P.D., gases being previously dried by passage through an ice-filled condenser.

Calibration. The gas meter was calibrated for mean flow by passing a range of steady flows of dry air (15-105 l. min^{-1}) through it and a standard dry gas meter (Type CD serial no. 02011; Parkinson & Cowan Ltd), placed upstream and in series. The standard gas meter had been calibrated for flow previously at Parkinson & Cowan Ltd; it deviated from linearity by only 0.1 $l.min^{-1}$, for increments of 10 $l.min^{-1}$, for air at A.T.P.D.

Fig.15 calibration of dry gas-meter (serial No. 01334)

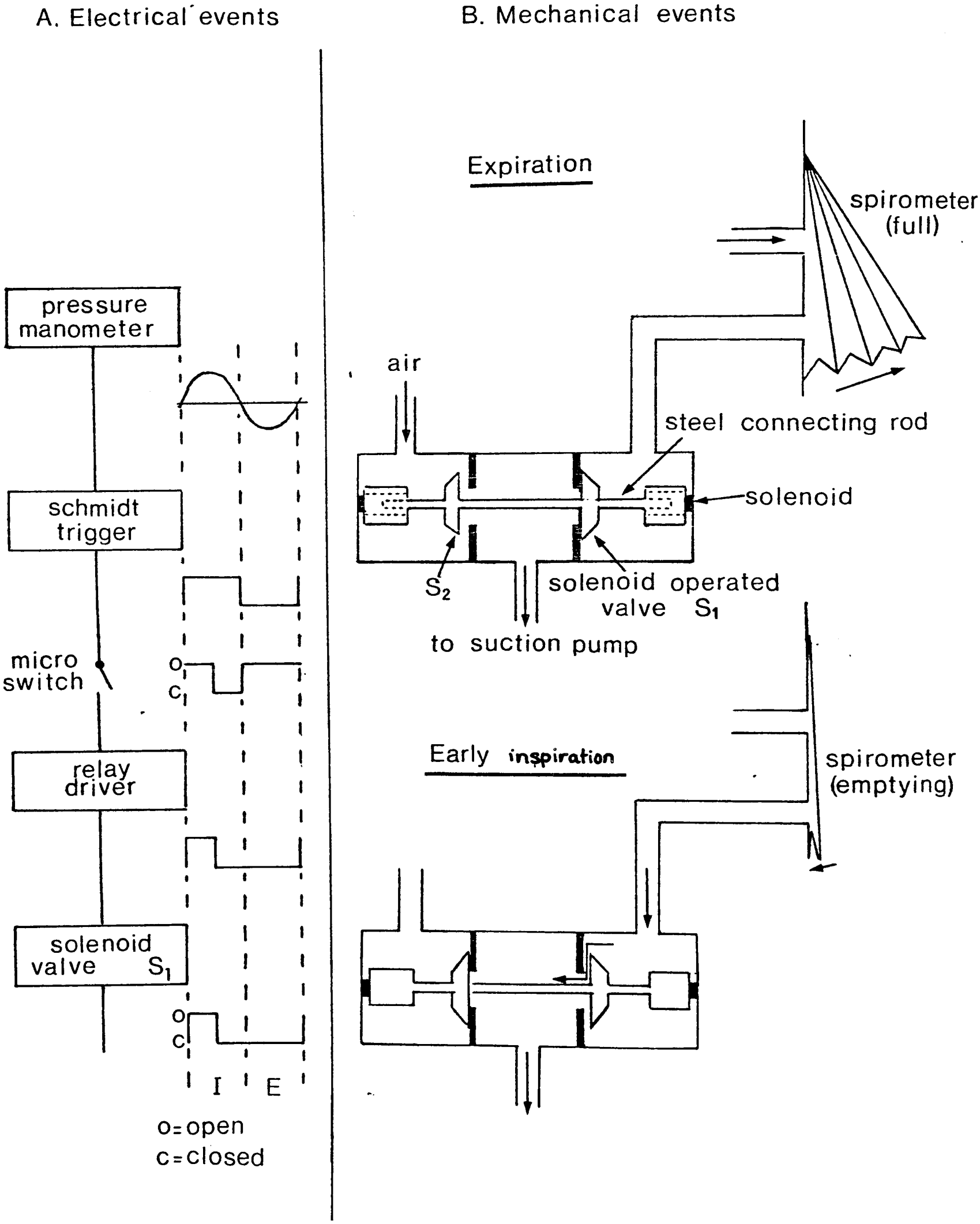


Steady air flows were produced through a flowmeter, as described previously. The time taken for 100 l. of air, at a given flow, to pass through each gas meter was measured with a stop-watch (to the nearest 0.2 sec). In an attempt to minimise errors of time measurement, two or three measurements were made at each flow, for flows of 50 $l.min^{-1}$ or more; the mean time of these was taken for subsequent computation of flow. The temperature of air issuing from the downstream gas meter was found to be invariant (21.5°C) with respect to flow.

Computed mean flows, at A.T.P.D., for the gas meter being calibrated were plotted (ordinate) against the corresponding flows for the standard gas meter (abscissa), (Fig. 15; Appendix 1, Table 8, p.168. The points were scattered closely about the line of equality, the greatest departure of 0.8 $l.min^{-1}$ (0.6%) occurring at the highest flow measured, where the timing error might be expected to be the greatest. Hence, the performance of the dry gas meter (serial no. 01334) for measurement of mean flow and volume was accepted as being both accurate and linear.

During an experiment, the error of time measurement (and hence of mean flow measurement) was greatly reduced from that of the calibration procedure. A timing circuit in the Devices recorder produced a marker at one-minute intervals. This signal, together with the gas meter 10 l. signal, was displayed on the recorder for subsequent computation of mean expired ventilation.

Fig.16 Operation of spirometer for breath-by-breath measurement on open circuit.



Wedge spirometer

Operation. The wedge spirometer (SP 70, Cryotech, Wallingford, Berks) consisted of low compliance bellows, suspended vertically, which could be inflated or deflated in a horizontal plane with a minimal change of cross-sectional area. Its operating volume was 10 l., but it was rarely used beyond 3 l. in the experiments. A Linear Variable Differential Transformer, attached to the moving bellows, provided electrical outputs of instantaneous flow and, by means of an integrator, volume.

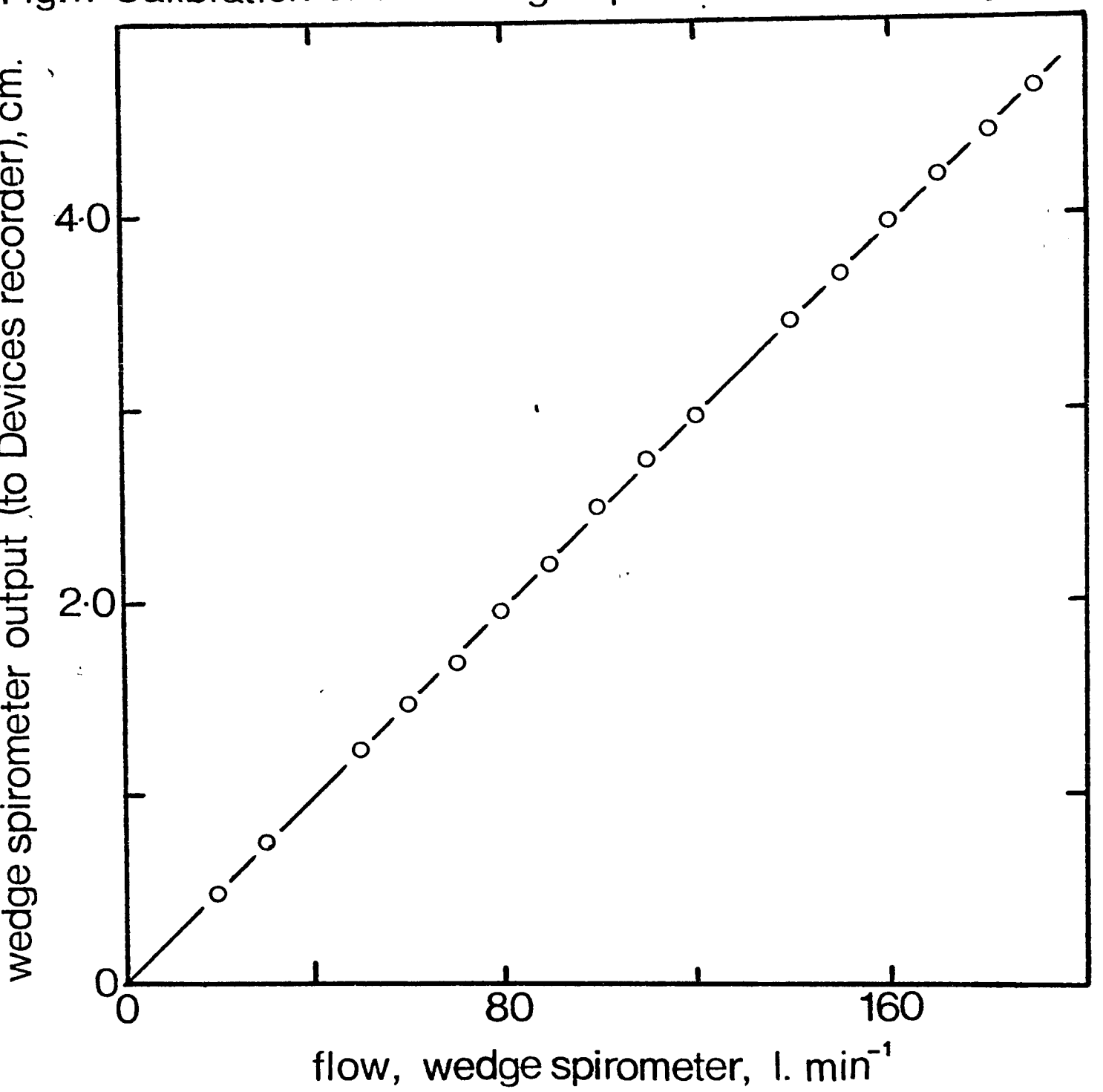
In an open circuit, the spirometer outlet had to be closed during expiration, so as to record the total expired gas volume. During inspiration, the outlet was opened for emptying of the spirometer, by suction, back to a fixed position set by a mechanical stop. A double solenoid-operated valve allowed a suction line to be directed between either the atmosphere (during expiration) or the spirometer (during inspiration). The suction line originated from a domestic vacuum cleaner; a variable transformer (Variac, Zenith Electrical Co. Ltd, London) was employed to regulate the suction rate.

The pair of solenoid-operated valves were connected by a central steel rod, whose ends fitted freely into a solenoid at each end (Fig. 16B). The valve pads were made of truncated cones of perspex which sealed against the circular opening in a disc of hard rubber sheet. As power was switched from one solenoid to the other, the rod moved back and forth between the solenoids, so that the attached cones alternately closed the suction line to the spirometer and to the atmosphere. The solenoids were powered by a 10-volt A.C. supply.

The mouth pressure wave was recorded from the common space of the respiratory valve by a micromanometer (M.M.S. 301, Hilger-I.K.D. Ltd, London). The micromanometer output operated a Schmidt trigger which produced a voltage step lasting for the duration of inspiration. This signal was sent, after amplification, to a relay driver and thence to the solenoid-operated valves, so that the suction line was brought into continuity with the spirometer outlet, causing evacuation of the spirometer (Fig. 16A). The solenoid-energising circuit was broken by the opening of a micro-switch situated at the mechanical stop; this occurred when the spirometer had been evacuated down to the stop. Thus, the spirometer outlet was sealed, and the spirometer was ready to receive gas from the next expiration. Any noise caused by evacuation of the spirometer went unnoticed by the subjects.

Calibration and performance. The spirometer was calibrated for the measurement of breath-by-breath expiratory flow, as follows. A range of dry air flows (20-190 $l.min^{-1}$), set up on an air-calibrated flowmeter, was passed into the spirometer, and its electrical flow output was recorded on the Devices recorder. As the linear range of the spirometer was only 10 l., the time during which continuous air flows could be passed into it was necessarily limited: to 10 sec for a flow of 60 $l.min^{-1}$, for example. A three-way tap was therefore used to connect the evacuated spirometer to the air flow source for short periods, during which the spirometer was assumed to be linear for volume and flow. For the remaining time, the air flow was directed into the atmosphere.

Fig.17 Calibration of the wedge spirometer for steady flow



The air flow through the flowmeter was noted during its passage into the spirometer, and the corresponding flow signal from the spirometer was fed into the Devices recorder. The recording channel, and its gain setting, were those employed for the recording of peak expiratory flow in experiments. A graph of channel deflection (ordinate) versus air flow (abscissa) was plotted (Fig. 17; Appendix 1, Table 9, p. 169). It showed a linear form with a near-zero intercept on the abscissa.

The performance of the integrating circuit for conversion of instantaneous flow to volume was examined by presenting the circuit with an electrical sine-wave, of periods ranging from 1.0 to 4.0 sec. Thus, the range of expired times likely to be met in experiments was covered. Integration converted the sine-waves to negative cos-waves (approximating to a 90° phase shift). The initial and and integrated signal were recorded at fast paper speed on the Devices recorder, and the deviation from the expected phase shift of 90° was estimated. Deviations were all in the direction of a greater than predicted lag. At all frequencies, deviations from the expected result were less than 0.05 sec, which is less than 10% of a 0.5 sec cycle period (Appendix 1, Table 10, p. 170). Thus, the performance of the integrator was considered sound.

It was further concluded that the spirometer must be linear for breath-by-breath expired tidal volume. This was inferred from the precision of the differentiator of the volume signal, and from the demonstrated linearity of the spirometer for breath-by-breath expiratory flow.

As the gas meter was situated upstream of the spirometer, the possibility of it damping the expiratory flow profile was examined. Reduction in the amplitude of breath-by-breath peak expiratory flow, produced by a sine wave pump, was found to be less than 3% of the value obtained in the absence of the gas meter. This was largely invariant for different mean flow rates and frequencies over the experimental range.

Calibration during experiments. Expired tidal volume calibrations consisted of passing 1 l. volumes into the spirometer from a syringe pump of 1 l. capacity. The peak expiratory flow calibration was performed in a similar manner to that used in the complete flow calibration of the spirometer (p. 53).

3. Safety

The following safety precautions were taken in order to ensure the well-being of the subjects:

a). Signature of a consent form (p. 24).

b). Subjects who had suffered any cardio-respiratory illness were rejected.

c). Medical cover: a doctor was present in the room, or an adjacent room, throughout the experiment.

d). A cylinder (BOC Special Cases) of resuscitation gas (95% O_2, 5% CO_2) was available for supply to the subject throughout the experiment. A supply line with a tap from this cylinder allowed rapid provision of the gas to the subject.

e). Checks on the consciousness of the subject were provided in the following manner. At rest, whether seated in a chair or on the bicycle ergometer, the subject was encouraged to read a book which he was required to support by hand. In the absence of conscious motor activity the book would fall from his hand. During exercise, a sufficient check was the subject's ability to keep pedalling.

f). Close scrutiny of P_{A,O_2} and P_{A,CO_2} was made, with frequent calibration of the mass spectrometer.

g). The subject was observed by the experimenter as often as the duties of the experiment permitted.

4. Experimental procedure

Series One

A simultaneous investigation was conducted of the effects of hypoxia and controlled frequency of breathing on the respiratory response to alternate breaths of high and low P_{CO_2}, at rest. Six experiments were performed, two on one subject (368) and one on each of four other subjects (377, 392, 418 and 230). The experimental design was that of a three-way analysis of variance (Sokahl & Rohlf, p. 344), with the three factors each having two states. These were:-

(i) the presence or absence of an alternate-breath oscillation of P_{A,CO_2} (denoted as "OSC" or "STEADY", respectively);

(ii) a steady P_{A,O_2} of 60 torr or of 50 torr (except in experiment 418.1, where P_{A,O_2} s of 65 and 60 torr were used);

(iii) respiratory frequency uncontrolled (NC) or controlled (C) by the experimenter, at a value appropriate to the prevailing level of ventilation.

The order of runs in any experiment was selected randomly. Breath-by-breath P_{et,CO_2}, P_{et,O_2}, $V_{T,E}$, T_T, T_I and T_E were recorded, and $\dot{V}_E$ was subsequently computed; from here onwards P_{et,CO_2} and P_{et,O_2} are assumed to equal P_{A,CO_2} and P_{A,O_2}. The respiratory response used was the mean alternate-breath oscillation of each variable in each run (p. 67).

The subject was seated in a comfortable chair, and breathed through the respiratory valve by means of an attached rubber mouthpiece which was clenched between the teeth. The subject's nose was occluded by a spring clip.

Alternate inspirates of gas containing a high level of CO_2 (8-10.5%; 56-73.5 torr) and a low level of CO_2 (0-1%; 0-7 torr) were administered to the subject by means of the alternate opening and closing of the inspiratory solenoid-operated valves, at the start of each expiration. The P_{I,CO_2} values on alternate breaths were adjusted to produce an oscillation of about 10 torr in the breath-by-breath P_{A,CO_2}. The oscillation lay within a range of P_{A,CO_2} that was well above any presumed

threshold of the $\dot{V}_E$ - P_{A,CO_2} relation. If the P_{CO_2} were allowed to oscillate across the threshold region, then the resulting alternate-breath response might show a positive rectification, its mean value being higher than that predicted by the mean P_{A,CO_2} (Cunningham et al., 1968). Thus, the lower level of P_{A,CO_2} was about 5 torr greater, and the mean P_{A,CO_2} 10 torr greater, than the subject's resting euoxic P_{A,CO_2} (as measured at the start of each experiment). During STEADY runs, identical P_{I,CO_2} values were produced on alternate breaths by mixing the two inspiratory gases in the mixing chamber. The P_{I,CO_2} and P_{A,CO_2} were the arithmetic means of the corresponding pairs of values characterising the P_{CO_2} oscillation. Thus, mean P_{A,CO_2} was constant throughout the course of the experiment ($\pm$1 torr between runs). The levels of O_2 in each inspiratory gas were such that the P_{A,O_2} of alternate breaths was similar ($\pm$1 torr).

Fine control of alveolar gas composition was effected by monitoring breath-by-breath P_{A,CO_2} and P_{A,O_2}, using the results to make appropriate minor and rapid adjustments to the inspiratory gas composition.

After any change in mean P_{A,CO_2} or P_{A,O_2}, no measurements were made until a new steady state had been attained: a minimum of 10 min for CO_2 (Padgett, 1927-28), and 2 min for O_2 (Gee, 1949). As all runs were conducted in at least moderate hypoxia, two precautions were taken to minimise a hypoxic depression of

the respiratory centres (Mitchell et al., 1964; Goode, 1968): each run was preceded by 2 min of hyperoxia (P_{A,O_2} ca. 200 torr; mean P_{A,CO_2} maintained), and the duration of a run was short (3-5 min; 35-97 breaths).

The rhythmic noise produced by closure of the inspiratory solenoid-operated valves being slight, it was unlikely to influence respiration. However, if any respiratory effects were induced, they were assumed to be constant throughout the experiment, as the switching mechanism was always operating. At no time did a subject comment on rhythmic noise, either spontaneously or on being questioned.

The control of respiratory frequency was effected, as required, by means of a signal generator which presented the subject with audible signals at regular intervals. The subject was instructed to change the phase of respiration at each signal; this procedure was expected to furnish similar times for both inspiration and expiration, which was a departure from the spontaneously breathing state where T_I and T_E are rarely equal. The duration of the respiratory cycle approximated to the current mean level of non-controlled breath duration, at the same level of chemical drive.

The duration of an experiment was always less than one hour, and, where possible, experiments were conducted without interruption. The subjects made no complaint of the length or nature of the experiments.

Series Two

A more extensive and quantitative examination was made of the nature of the possible respiratory interaction between steady hypoxia and an alternate-breath oscillation of P_{A,CO_2}, at rest and during mild exercise. The following variables were recorded on each breath:- P_{et,CO_2} and P_{et,O_2}, breath duration (T_T), inspiratory and expiratory times (T_I and T_E), tidal volumes ($V_{T,I}$ and $V_{T,E}$), peak flows ($\dot{v}_{I,max}$ or PIF, and $\dot{v}_{E,max}$ or PEF), and peak inspiratory acceleration ($\ddot{v}_{I,max}$ or PIA). From these were computed inspiratory and expiratory ventilations ($\dot{V}_I$ and $\dot{V}_E$) and mean flows ($\bar{\dot{v}}_I$ or MIF, and $\bar{\dot{v}}_E$ or MEF), and the breath-by-breath change in functional residual capacity (DFRC or $V_{T,I} - V_{T,E}$). Indices of oscillation employed were the mean alternate-breath oscillation and a derivative of an autocorrelation coefficient.

Nine experiments were conducted, two on each of three subjects (409, 455 and 396) and three on another (421). Alternate-breath oscillations of P_{A,CO_2} (ca. 10 torr amplitude) were induced (as before) in subjects seated on a bicycle ergometer, both at rest and during cycling (ca. 30-50 watts), at 4 to 7 levels of P_{A,O_2} within the range 45-200 torr (OSC runs). Control runs, in which the P_{A,CO_2} oscillation was absent, were conducted at similar levels of P_{A,O_2}, also at rest and during exercise (STEADY runs).

The exercise level was intentionally mild, to avoid the complicating effects of lactic acid accumulation and catecholamines associated with

heavy exercise. The same level was used for all experiments conducted on a single subject, being that level which produced a heart rate of about 120 beats/min in euoxia (30, 35, 40, 50 watts for subject 421, 409, 425 and 392, respectively). The pedalling frequency was not controlled.

The order of runs was selected so that corresponding STEADY and OSC runs were adjacent in time. Prolonged exposure to hypoxia was prevented by suitable ordering of the P_{A,O_2} levels, and by brief excursions (ca. 2 min) into hyperoxia (P_{A,O_2} ca. 200 torr). Following the imposition or withdrawal of exercise, five minutes was allowed for the acquisition of a new steady state (Åstrand & Saltin, 1961).

At the end of one experiment on each subject, a series of $\dot{V}_E$-P_{A,CO_2} points was obtained at a lower P_{A,CO_2} (ca. 5 torr above the euoxic P_{A,O_2}), at rest, at each of the levels of P_{A,O_2} used in the experiment. These points were used in conjunction with those of the resting STEADY runs to give 2- or 3-point $\dot{V}_E$-P_{A,CO_2} lines. Thus, an estimate of the steady-state $\dot{V}_E$, P_{A,CO_2}, P_{A,O_2} relations of each subject could be made (p. 72).

The duration of an experiment was of the order of $2\frac{1}{2}$ hours, representing about 20 runs of 5 min maximum duration (41-149 breaths). Each experiment was interspersed with one or two rest periods (5-10 min) during which the subject was free to leave the apparatus.

5. Data preparation and processing

Treatment of data prior to measurement

Runs were marked for subsequent measurement, starting and finishing on a low-P_{CO_2} breath, or its equivalent in the STEADY runs (coming from the same inspiratory line). Any alterations in the two-breath nature of the P_{A,CO_2} oscillation were removed by editing. For example, premature triggering of the inspiratory solenoid-operated valves could be induced by swallowing so that valve switching occurred during inspiration (when swallowing tended to occur) as well as at the start of expiration. This meant that the subject received gas from the same inspiratory line for two consecutive breaths. Thus, starting at the first breath of the disturbance, an odd number of breaths was removed from the run, for all variables, so as to restore the phase of the P_{A,CO_2} signal. Five breaths were usually removed. In the event of the disturbance not altering the phase of the signal, six breaths were removed from the run. This would also largely eliminate any effects the disturbance of P_{A,CO_2} might have had on respiration.

Measurement of data

Breath-by-breath respiratory variables were measured from the paper record of the Devices recorder, using a manually-operated digital data reader (P.C.D. Ltd, Farnborough, Hants) which recorded the magnitude of deflections potentiometrically. Each reading was automatically punched onto digital paper tape, for subsequent analysis by a 1906A computer, a total of 90,000 readings being made.

No attempt was made of reading deflections to less than 0.5 mm. This was converted to absolute units for each of the measured variables in each experiment, at the appropriate gain setting of the signal. A table of measurement limits is presented in Appendix 1 (Table II, p. 171).

Basic data analysis

For each run, breath-by-breath calculation was performed of variables derived from the measured variables. Basic statistics (mean, variance, standard deviation) were computed for all variables, assuming a normal distribution.

In Series Two, a correction was applied to breath-by-breath $V_{T,I}$ and $V_{T,E}$, so as to equate their run-mean values ($\bar{V}_{T,I}$, $\bar{V}_{T,E}$) with the run-mean $V_{T,E}$ obtained from gas-meter ventilation and run-mean T_T, ($\bar{V}_{T,E,G.M.}$). Allowances for changes in the calibration of $V_{T,I}$ and $V_{T,E}$ could thus be made. Discrepancies between run-mean $V_{T,I}$ and $V_{T,E}$ were assumed not to reflect long-term changes in the respiratory quotient (R.Q.) or in functional residual capacity (FRC).

Run-mean values of $V_{T,E}$ differed little from gas-meter $V_{T,E}$, as was expected; the differences were not consistent in either size or direction. However, more obvious differences were seen between run-mean values of $V_{T,I}$ and the corresponding values of gas-meter $V_{T,E}$. These were attributed to the composite effects of gas viscosity, temperature and flow on the performance of the pneumotachometer.

The correction factor for breath-by-breath $V_{T,E}$ was $(\bar{V}_{T,E,G.M.}/\bar{V}_{T,E})$; each $V_{T,E}$ value was multiplied by this factor. The corresponding correction factor for $V_{T,I}$ was $(\bar{V}_{T,E,G.M.}/\bar{V}_{T,I})$. With the run-means for $V_{T,I}$ and $V_{T,E}$ equalised, breath-by-breath changes in FRC could be estimated $(V_{T,I} - V_{T,E}, = DFRC)$.

The runs of data thus obtained were processed in several ways. The data runs of Series Two, and alternate-breath differences arising from them, were tested for the significance of any deviation from a normal distribution. In Series One and Series Two, run-mean alternate breath oscillations were calculated for P_{A,CO_2} and the respiratory output variables, using two slightly different methods. In addition, auto- and cross-circulation analysis was performed in Series Two, on P_{A,CO_2} and the output variables.

Common statistical formulae

The following formulae are employed in this thesis; bracketed numbers are page references to Sokahl & Rohlf.

Weighted average of a statistic "St".

$$\overline{St} = \sum^{n} W_1 \cdot St_1 / \sum^{n} W_1 \qquad (178)$$

where n values of St, each weighted by factor W, are being averaged. The weighting factor for a mean is its sample size, and for a variance, its degrees of freedom.

t-test for the significance of a statistic. The significance of a deviation from a parameter is given by

$$ts = (St - Stp)/ S.E._{St} \qquad (171)$$

where Stp is the parametric value of the statistic, and $S.E._{St}$ its standard error.

t-test for the comparison of 2 means (unequal variances).

$$ts = (\bar{x}_1 - \bar{x}_2)/\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)^{1/2} \qquad (374)$$

where $\bar{x}$, s^2 and n represent mean, variance and size of the sample.

Variance ratio test for the comparison of two variances.

$$F_s = S_1^2/S_2^2 \qquad (183)$$

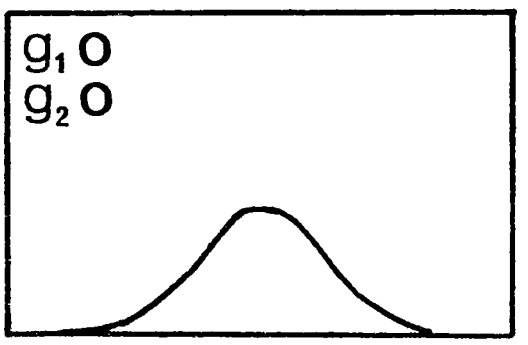
Chi-squared test for the comparison of observed probabilities with expected probabilities. The expected probabilities, p, of events being significant or non-significant are α and $(1 - \alpha)$, where α is conventionally 0.05. The observed probabilities, p', of events being significant or non-significant are the ratios of the number of significant or non-significant events to the total number of events. The significance of the difference between observed and expected probabilities is given by

$$\chi^2 = [(p'_s - p_s)^2/p_s] + [(p'_{ns} - p_{ns})^2/p_{ns}]$$

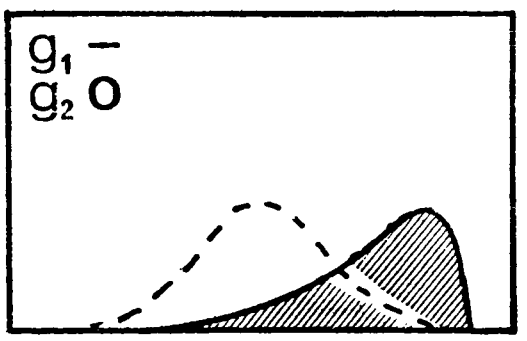
where the subscripts s and ns represent the states of significance and non-significance.

Normality of data

The presence of a normally distributed sample is necessary before certain statistical tests can be performed and conclusions drawn as to



Normal



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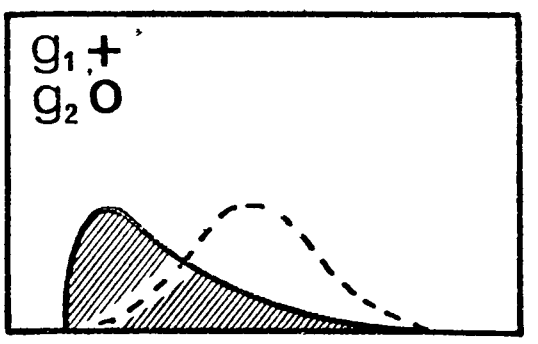

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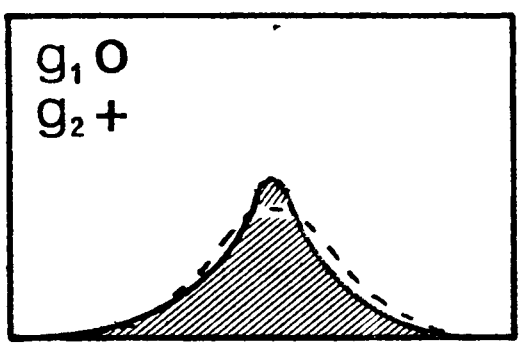
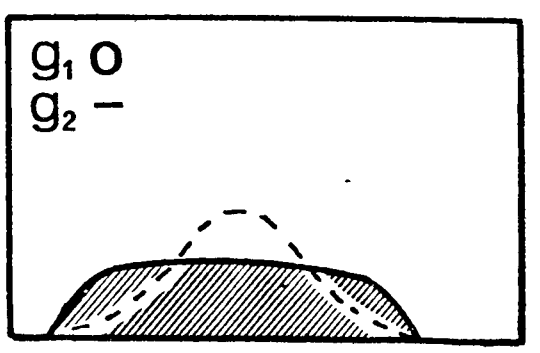


Leptokurtic



Platykurtic

Fig.18 Normal & non-normal frequency distribution.

the nature of the population from which the sample originated.

Therefore, the breath-by-breath records, and the computed differences between alternate breaths of these records, for P_{A},CO_2 and the 13 output variables, were tested for deviation from normality.

A non-parametric test, the Kolmogorov-Smirnov test (Sokahl & Rohlf, p.571), was used to assess the "goodness of fit" of the normal probability density function (the integral of the normal frequency distribution function) to the probability density function of the data. The maximum deviation between the observed and expected cumulative frequencies, d_{max}, was used as the sample statistic. The null hypothesis of normality ($d_{max} = 0$) was rejected at the level of $p = 0.05$ or less. The advantages of the Kolmogrov-Smirnov test are that it is designed for a continuously distributed variable, and is suitable for use with small samples ($n < 100$).

For those sampled variables which showed departure from normality, the nature and degree of the departure were considered in terms of <u>skewness</u> (loss of symmetry about the mean) and <u>kurtosis</u> (maintenance of of symmetry): Sokahl & Rohlf, p.112, and Fig. 18.

The sample statistics for skewness (g_1) and kurtosis (g_2) for the variable, x, represent the population parameters γ_1 and γ_2, and are defined as:-

$$g_1 = \left(\frac{1}{ns^3}\right) . \Sigma (x - \bar{x})^3$$

and $$g_2 = \left(\frac{1}{ns^4}\right) . \Sigma (x - \bar{x})^4 - 3$$

where n and s represent the size and standard deviation of the sample.

g_1 lies within the range of $\pm \infty$, and g_2 is ≥ -2. For a normally distributed variable, g_1 and g_2 both equal zero. Hence, the null hypotheses of "no skewness" and "no kurtosis" were examined by testing the significance of the deviations of g_1 and g_2 from zero, by a 2-tailed t-test (p.65). 95% confidence limits were calculated for g_1 and g_2; values of g_1 or g_2 lying beyond these limits led to rejection of the appropriate null hypothesis.

The calculations for both the parametric and the non-parametric tests were performed using a modified computer program (Sokahl & Rohlf, Program A3.1, p.671).

Computation of mean alternate-breath oscillations

Alternate-breath oscillations were computed for all variables, in all runs, as follows. Each run was first edited so as to remove any obviously large or small events resulting from extraneous interference with the expected response (e.g. sighing, coughing). Such events, if retained in the run, would distort greatly the mean alternate-breath oscillation. Thus, for each variable, any breath having a value of more than 2 standard deviations from the mean of the run was excluded. The breath immediately following the excluded breath was also eliminated, thus retaining the two-breath periodicity of the run. The alternate-breath oscillation could then be calculated.

The expected response to an alternate-breath oscillation of P_{A,CO_2} is a corresponding oscillation in one or more of the measured output variables. Thus, in Series One, for a particular variable, successive

subtraction throughout a run of the response of each breath from that of the immediately preceding breath should give a series of differences exhibiting an alternation of sign, between positive and negative. In Series Two, successive subtraction of each breath from the mean of the run was performed throughout the run. As for the previous method, a series of differences alternating in sign should be obtained. (Fig. 37A, p.124).

An arbitrary convention was followed: the first breath of a run (low P_{A,CO_2}) and the subsequent odd-numbered breaths were classed as "low", i.e. having smaller volumes, flows, ventilations, and longer times than the immediately following even-numbered breaths, which were classed as "high". Thus, odd-numbered differences should be negative in sign, and even-numbered differences, positive. During computation, the sign of each of the odd-numbered differences was reversed, so that those differences which had the sign expected from the hypothesis became positive. Thus, all differences having the sign predicted by the hypothesis were now positive, while those contrary to expectation were negative and would therefore reduce the size of the mean oscillating response.

Basic statistics of the normal distribution (mean, variance, standard deviation) were obtained on the collections of alternate-breath differences for each variable, in each run. The oscillation amplitudes of Series Two were then doubled, converting them from peak-to-mean into peak-to-trough values, thus making them comparable with the peak-to-trough values calculated in Series One. Both methods should yield identical results if the run-mean is stationary (p.125).

Autocorrelation analysis of alternate-breath responses

In Series Two, it was thought necessary to conduct a comparative analysis, between the several output variables, of the mean response to an alternate-breath P_{A,CO_2} oscillation. The alternate-breath oscillation, as just described, gave the response in the absolute units of the variable concerned. In order to standardise the responses an auto-correlation analysis was performed, prior to editing the data for large and small events.

The autocorrelation coefficient of product-moment correlation between the neighbouring members of a series is called the autocorrelation of order 1; and similarly the correlation between members (k - 1) apart is called the autocorrelation of order k. Thus, the estimate, r, of the population autocorrelation coefficient, p, for the variable, u, is

$$r_k = \frac{\text{covariance } (u_t, u_{t+k})}{S_{u_t} \cdot S_{u_{t+k}}}$$

$$= \frac{\text{covariance } (u_t, u_{t+k})}{\text{variance } u_t}$$

$$= \frac{n}{n-k} \cdot \frac{\sum_{t=1}^{n-k} (u_t, u_{t+k})}{\sum_{t=1}^{n} u_t^2}$$

where n is the number of variates of u in the series and S_u is a standard deviation (Yule & Kendall, 1950, Ch. 27). A prerequisite of this method is that the frequency distribution of the population (and therefore the sample) be normal, or nearly normal and single-humped.

The value of r_k can range between ± 1.0. For a random process, r_k approaches zero for any value of k, other than k = 0, where r equals +1. For a periodic function of period, j, r_j is large and positive; and $r_{j/2}$ is large and negative. Thus, for an alternate-breath oscillation (period = 2 breaths), r_2 should be large and positive, and r_1, large and negative. It was predicted that $(z_2 - z_1)$, or ZD, representing the z-transformed values of r_2 and r_1, respectively, would be large and positive if an oscillation was present. In addition, the size of this quantity could be used as a comparative index of the amplitude of the alternate breath response of each of the output variables. However, the autocorrelation functions have no phase component (Bendat & Piersol, p.20). This procedure is depicted in Fig. 37B, p.124.

The significance of ZD tested by means of a one-tailed t-test for the homogeneity of 2 correlation coefficients (Sokahl & Rohlf, p.521).

Cross-correlation analysis for the estimation of latencies

The cross-correlation coefficient, r_k, describes the dependence between two variables, x and y, when they are displaced in time by an amount k, relative to each other:-

$$r_k = \frac{\text{covariance } (x_t, y_{t+k})}{Sx_t \cdot Sy_{t+k}}$$

This expression is analogous to that presented on p.69 for the auto-correlation coefficient. The graphical representation of r_k against the time displacement, k, is known as a correlogram (Fig. 30, p.112).

Cross-correlation analysis was used in Series Two for the estimation of the latency of oscillating responses induced by the alternate-breath P_{A,CO_2} oscillation: a maximum, positive value of r_k should occur at that time displacement between stimulus and response which is equal to the latency of the response (Bendat & Piersol, p.30.).

The correlation between P_{A,CO_2} and each of the output variables was examined for the ten breaths preceding and following a change in the state of P_{A,CO_2} from OSC to STEADY ("off" transient), or vice versa ("on" transient): thus, the sample size, n, was 20 breaths. Time displacements of 0, 1, 2, 3 and 4 breaths were used, larger displacements being excluded because the reliability of r_k is affected if k greatly exceeds 0.1 n, or 2 breaths (Gessner, 1972). The latency of CO_2-induced arterial chemoreceptor effects on $\dot{V}_E$ in man is between 2-3 breaths (Miller et al., 1974), and well within the range of time displacement used here.

If a periodic stimulus elicits a periodic response, then r_k will oscillate between positive and negative amplitude as a function of k (Gessner, 1972). In the present study, where a sizeable portion of the P_{A,CO_2} transient comprised an alternate-breath oscillation, r_k was expected to oscillate with a period of k = 2. This prediction arose from the cross-correlation analysis conducted on a simulated "off" transient (as above), the output of which followed the input function almost faithfully, with a latency of 2 breaths (Appendix 1, p.172). For even values of k, r_k was large and positive, and for odd values,

large and negative; the maximum positive value of r_k occurred at k = 2, which was the latency of the response.

Thus, the maximum positive value of r_k ($r_{k,max}$) of each P_{A,CO_2} transient was obtained by comparing the size of appropriate pairs of r_k, using a 2-tailed t-test for the homogeneity of correlation coefficients (Sokahl & Rohlf, p.521), as follows. When the latency between P_{A,CO_2} and an output variable was an <u>even</u> number of breaths, $r_{k,max}$ was obtained by comparing r_0 with r_2, and r_2 with r_4: in the hypothetical example above, $r_0 < r_2 > r_4$. When the latency was an <u>odd</u> number of breaths, r_1 and r_3 were compared. In the case of T_T, T_I and T_E, however, $r_{k,max}$ should be negative because these variables are inversely related to P_{A,CO_2}.

<u>Determination of respiratory parameters at rest</u>

The steady-state $\dot{V}_E$, P_{A,CO_2}, P_{A,O_2} relation was outlined at rest for each of the experiments of Series Two, using the following assumptions.

(i) Ventilation is linearly related to P_{A,CO_2} at constant P_{A,O_2}, for P_{A,CO_2} greater than the presumed P_{A,CO_2} threshold:-

$$\dot{V}_E = S(P_{A,CO_2} - B) \quad (1)$$

where S (l./min/torr CO_2) is the slope of the line at constant P_{A,O_2}, and B (torr CO_2) is its intercept on the P_{A,CO_2} axis obtained by linear extrapolation.

(ii) B is independent of P_{A,O_2}.

(iii) S and P_{A,O_2} are related hyperbolically:-

$$S = D + AD/(P_{A,O_2} - C) \qquad (2)$$

where C (torr O_2) is the P_{A,O_2} at which S becomes infinite; D is the value of S at infinite P_{A,O_2}; and A (torr O_2) is a hypoxic sensitivity factor.

Thus, $$\dot{V}_E = (P_{A,CO_2} - B) \left\{ D + AD/P_{A,O_2} - C) \right\} \qquad (3)$$

(Lloyd, Jukes & Cunningham, 1958)

In one experiment on each subject, $\dot{V}$ measurements were made at two or more levels of P_{A,CO_2} (at least 5 torr above the resting euoxic value) for about five levels of P_{A,O_2} (range 47-200 torr). A minimum of 16 min. elapsed before measurement of $\dot{V}_E$ after a change in P_{A,CO_2}, and 2 min after a change in P_{A,O_2}.

An estimate of B was obtained from that $\dot{V}_E$, P_{A,CO_2} line which had the smallest standard error of the slope when subjected to a least squares linear regression analysis (Sokahl & Rohlf, p.410). The intercept point ($\dot{V}_E$ = 0, P_{A,CO_2} = B) then became an additional point in the estimation of the regression slopes, S, of the remaining lines. A linear regression of S on $1/(P_{A,O_2} - C)$ was performed, for each value of C in the range 25-40 torr P_{O_2}. C was selected as that value at which the standard error of the slope of the regression line was a minimum, for significant slopes ($p<0.05$) only. Estimates of D (intercept on S-axis) and A (the negative reciprocal of the intercept on the hypoxia axis) were also obtained.

In the second experiment on each subject, $\dot{V}_E$ measurements were made at a single level of P_{A,CO_2} (ca. 10 torr above the resting euoxic value),

for about 5 levels of P_{A,O_2}. The value of D found for the more extensive experiment was used as an estimate of D for the second experiment, as Bhattacharyya (1969) has found D to vary little from day to day, in the same subject. B was estimated from D and the single hyperoxic point (P_{A,O_2} ca. 100-200 torr). $\dot{V}_E$, P_{A,CO_2} lines for the remaining levels of P_{A,O_2} were constructed by joining the single points to B. The remaining parameters were estimated as before.

Where two significant estimates of C were obtained on the same subject, their mean value was used for both experiments, as C, like D, varies little from day to day in the same subject (Bhattacharyya, 1969). Where only one estimate of C was significant, that value was used in both experiments. Where neither estimate was significant, a mean population estimate of 32 was used (Weil et al., 1970). Those estimates of C calculated at rest were assumed to apply to the exercising state: that is, the relation existing between P_{A,O_2} and the P_{O_2} of the carotid body chemoreceptors was assumed to be unchanged by the imposition of mild exercise. It was therefore possible to calculate the hypoxic stimulus to breathing at rest and in exercise as $10^3/(P_{A,O_2} - C)$, Lloyd, Jukes & Cunningham (1958).

In addition, the mean $\dot{V}_E$ of a STEADY run at rest could be compared with that of its corresponding OSC run, under conditions of constant mean P_{A,CO_2} and P_{A,O_2}. Any discrepancy between the mean P_{A,CO_2} values of the two runs was converted into a ventilation term by the $\dot{V}_E$, P_{A,CO_2}

line at the appropriate P_{A,O_2}. This term could then be added to, or subtracted from, the mean $\dot{V}_E$ of the STEADY run, as appropriate.

Similar correction of mean $\dot{V}_E$ in exercise was based on the assumption that any $\dot{V}_E - P_{A,CO_2}$ relation in exercise had a slope which approximated to that at rest, for the same P_{A,O_2}: the assumption is limited to P_{A,CO_2} at least 10 torr above the euoxic value (Asmussen & Nielsen, 1957; Bhattacharyya et al., 1970).

Chapter 3

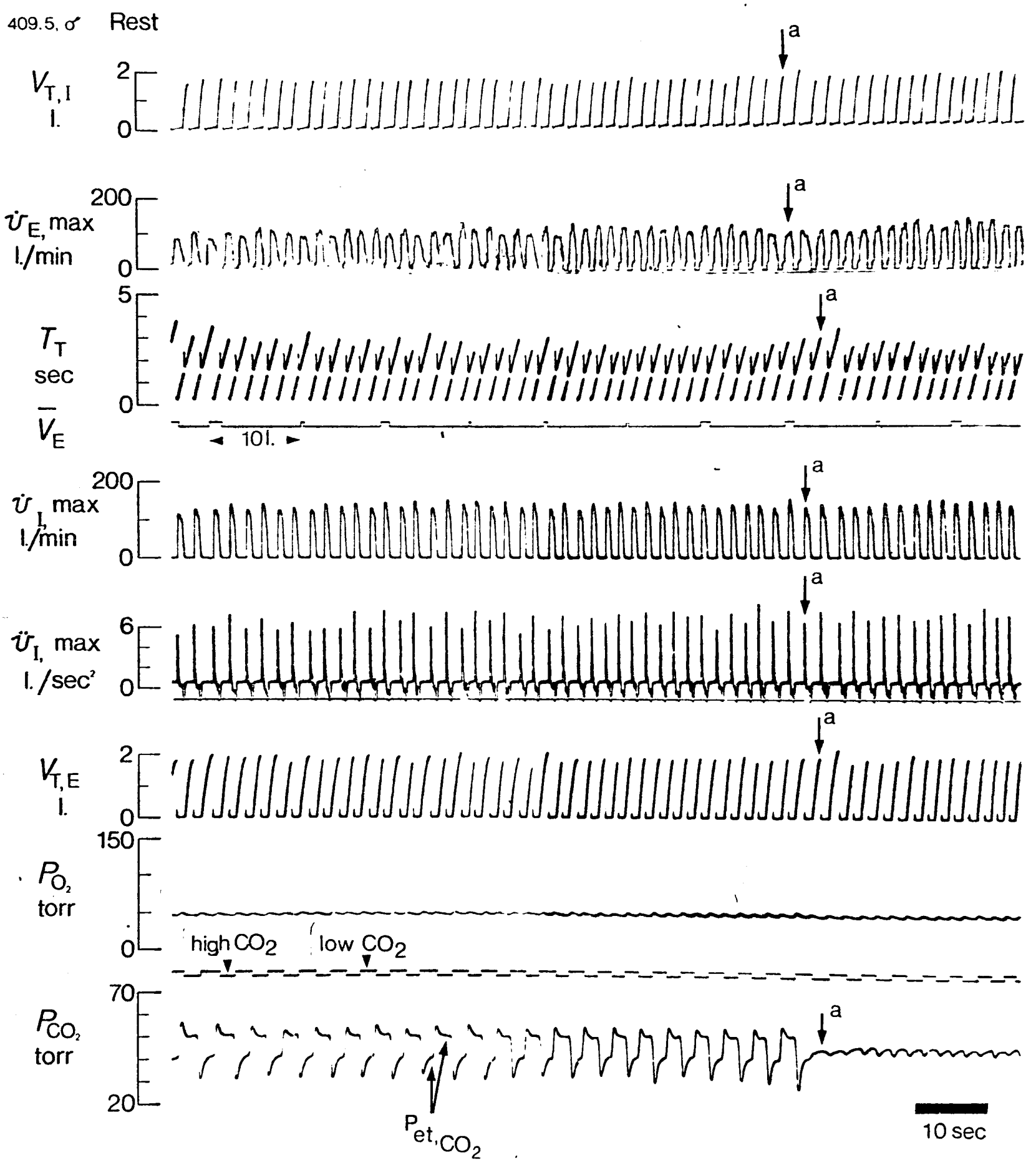
RESULTS

1. Introduction

The experimental results of both Series One and Series Two are presented in this chapter. Figure 19 serves as a useful introduction to the main methodological problem of the thesis: the extraction of an alternate-breath oscillation from the otherwise "noisy" output of the respiratory system. The experimental record illustrated was obtained at rest from subject 409 in Series Two, and is equally applicable to the experiments of Series One, apart from the larger number of recorded variables. An alternate-breath P_{A,CO_2} oscillation of about 10 torr amplitude had been induced, and was subsequently abolished (at "a") by passage of the two inspiratory gases through the mixing chamber (p. 31): that is, an OSC run was converted to a STEADY run. All the while, P_{A,O_2} remained constant at about 48 torr.

Respiratory gas was sampled continuously from beyond the expiratory flap of the respiratory valve. Thus, in expiration, the P_{CO_2} and P_{O_2} profiles represented the progressive washout with time of the dead space and alveolar compartments; during inspiration, P_{CO_2} and P_{O_2} tended to remain at their previous end-expiratory levels. "P_{et,CO_2}" indicates the end-expiratory P_{CO_2} of a high-CO_2 breath and an adjacent low-CO_2 breath. Lying between the P_{CO_2} and P_{O_2} traces is a signal indicating from which inspiratory line gas was being supplied; the signal changed at the start of each expiration (p. 35).

Fig,19 An experimental record



In the presence of an alternate-breath P_{A,CO_2} oscillation, corresponding responses could be detected in breath duration (T_T), expiratory time (T_E), peak inspiratory flow (PIF or $\dot{v}_{I,max}$) and acceleration (PIA or $\ddot{v}_{I,max}$), and less clearly in inspiratory time (T_I), inspiratory and expiratory tidal volumes ($V_{T,I}$ and $V_{T,E}$), and peak expiratory flow (PEF or $\dot{v}_{E,max}$).

The two uppermost traces ($V_{T,I}$ and PEF) were recorded on a separate Devices recorder from the remainder, at a slightly reduced recording speed. Hence, events in $V_{T,I}$ and PEF showed a lack of correspondence with those of the other variables (e.g. at "a"), except at the extreme left of the record. Here it was evident that, on the same breath, T_E and PEF were stimulated (smaller and larger, respectively, than the previous breath), while inspiratory variables such as PIF and PIA were depressed. The phase relations existing between the oscillating output variables are described (p. 92 ; p. 107) and discussed (p. 136) more fully below. Upon removal of the P_{A,CO_2} oscillation, the alternating responses subsided with a latency that was difficult to estimate, but appeared to be less than 6 breaths.

Thus, although a P_{A,CO_2} oscillation of regular amplitude had been imposed, the responses it elicited were, at times, anything but regular. Close attention had therefore to be paid to the two methods of estimating alternate-breath responses: the determination of the mean alternate-breath difference for a particular variable (p. 67) and the auto-correlation function, ZD, (p. 69). A condition common to both methods

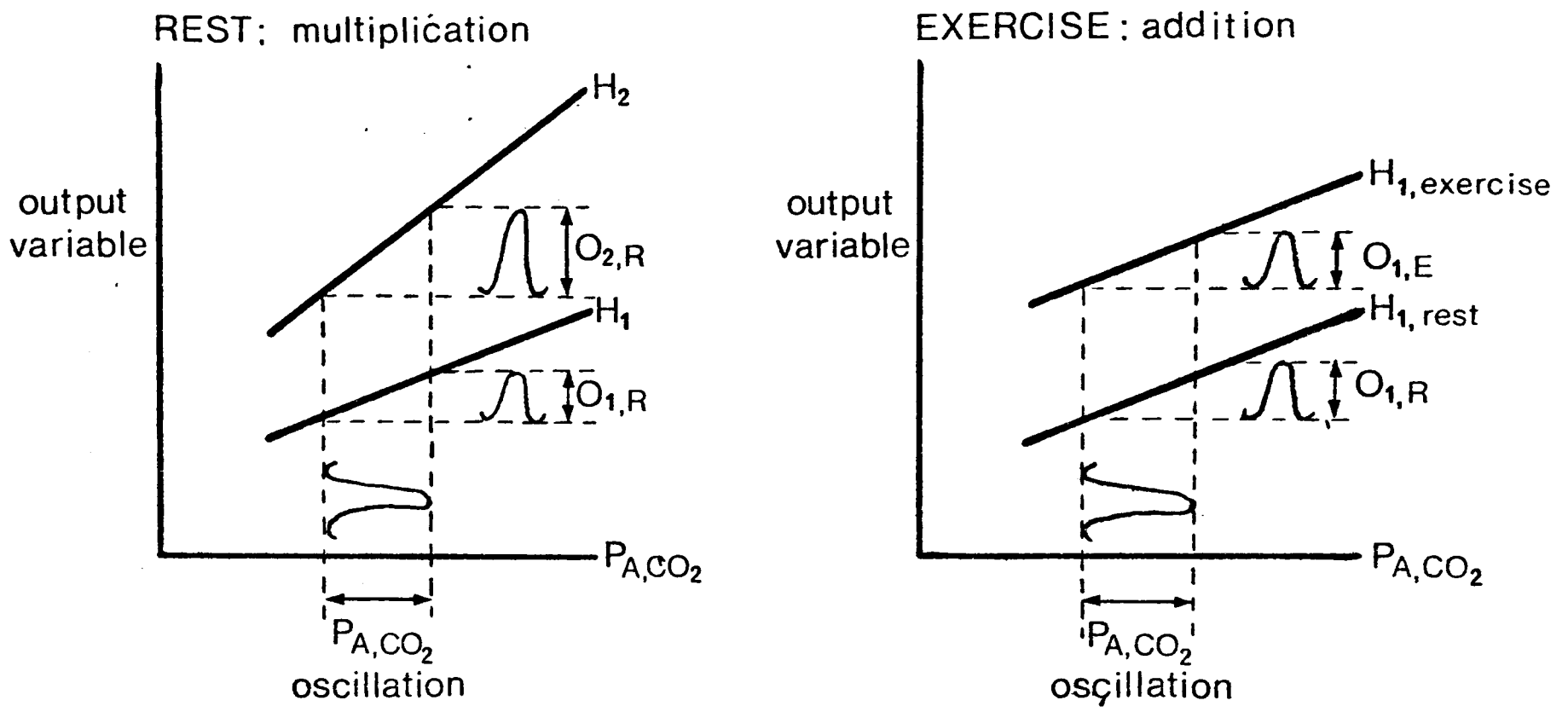
was that the responses should not increase or decrease progressively with time: this is discussed more fully in the next chapter (p.125). The frequency distributions of all data runs have therefore been examined for possible deviation from a normal distribution (p. 80).

An essential prelude to the description of the oscillating responses is a description of the stimulus: this was reconstructed from end-expiratory P_{A,CO_2} values throughout two consecutive respiratory cycles (p. 81). In characterising the responses to the P_{A,CO_2} oscillation, two facets were concentrated upon. First, the pattern of the response was explored for each OSC run in terms of those variables exhibiting a significant alternate-breath response (Series One, p. 87; Series Two, p. 100). Also, an estimation was made by cross-correlation techniques of the absolute latencies of the stimulation of these variables by a CO_2 stimulus (a high-CO_2 breath) in Series Two (p. 111).

In Series One, alternate-breath responses were estimated for expiratory ventilation ($\dot{V}_E$) and its components ($V_{T,E}$, T_T, T_I and T_E). The range of variables was extended in Series Two in an attempt to identify one variable in particular as being a better index than any other of the output from the brainstem respiratory centres. The reasoning which underlay selection of these variables is presented in the next chapter (p. 127).

Secondly, the nature of the interplay between steady hypoxia and the P_{A,CO_2} oscillation on the size of alternate-breath responses was

Fig. 20. The proposed interaction between hypoxia & the P_{A,CO_2} oscillation



H_1, H_2 are hypoxic P_{A,O_2} : $H_1 > H_2$

$O_{1,R}$ and $O_{2,R}$ are the output oscillations at rest, at the 2 P_{A,O_2}s.

$O_{1,E}$ is the output oscillation at H_1 during exercise.

At rest, a multiplication of hypoxia and the CO_2 oscillation gives $O_{2,R} > O_{1,R}$.

In exercise, an addition of a drive to the pre-existing hypoxia-CO_2 drive resets the relation upwards with no change of slope, so that $O_{1,E} = O_{1,R}$.

investigated in different variables, both at rest and in mild exercise. In resting man, the effects of steady hypoxia and steady hypercapnia on $\dot{V}_E$ multiply (Nielsen & Smith, 1952); exercise supplies an additive component to reset the $\dot{V}_E$, P_{A,CO_2} relation upwards at all P_{A,O_2}, certainly within the range of P_{A,CO_2} used in the present study (Asmussen & Nielsen, 1957; Bhattacharyya et al., 1970). In hypoxia, part of the resetting has been attributed to an influence of exercise on the carotid body chemoreflex arc (reviewed by Cunningham, 1974a)

A similar mechanism is proposed here for the interaction between hypoxia and the transient CO_2 signal: that these stimuli would multiply in their effects on the amplitude of alternate-breath responses and that exercise would furnish an extra additive effect on these (Fig. 20). A tentative examination of the proposals was made at rest in Series One (p.95). This was extended in Series Two to include exercise and a wider range of P_{A,O_2}, which enabled a linear regression analysis of oscillation amplitude on hypoxia to be made (p.114).

A final point should be mentioned. It was thought that if much of the breath-by-breath variation in T_T could be eliminated, then the responses to an alternate-breath P_{A,CO_2} oscillation might become more regular. Changes in T_T could affect the alveolar-to-arterial transmission of the P_{A,CO_2} oscillation (Jurves, 1966a) and also its time of arrival at the brain stem in relation to the respiratory cycle, presupposing the latter to determine the degree of respiratory stimulation elicited (Black & Torrance, 1967a, 1971; Band et al., 1968, 1970).

An attempt was therefore made to control T_T in some runs of Series One at a level appropriate to the current level of chemical drive

421·6, Run 1 = rest, P_{A,O_2} = 51 torr, P_{A,CO_2} oscillating

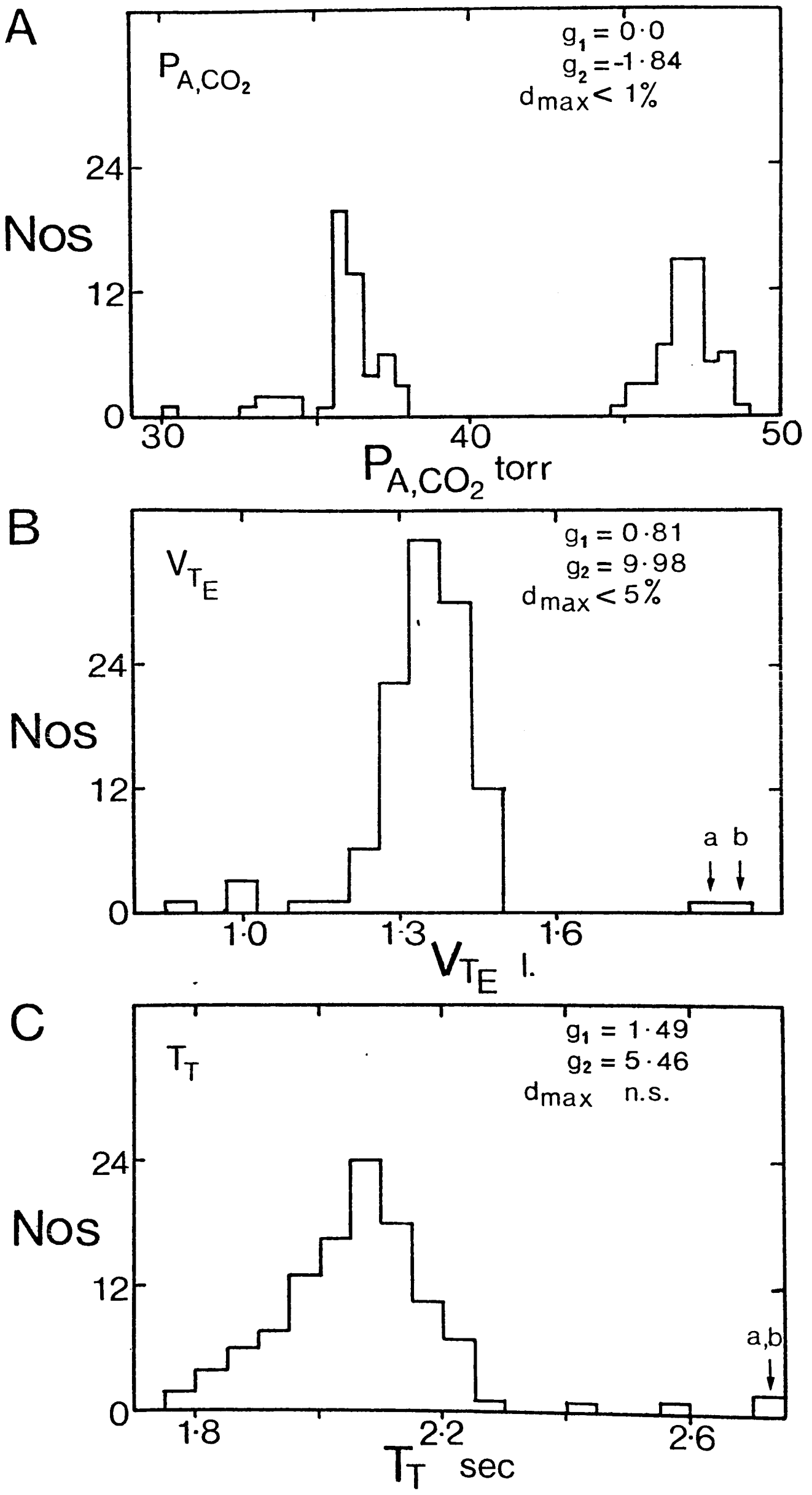


Fig.21 Representative frequency distributions of breath-by-breath data.

to breathing, and so minimise breath-by-breath variation in T_I. However, the procedure proved to be ineffective as the variance of T_I was not consistently reduced by it. The results are reported briefly on p. 86.

2. Normality of data

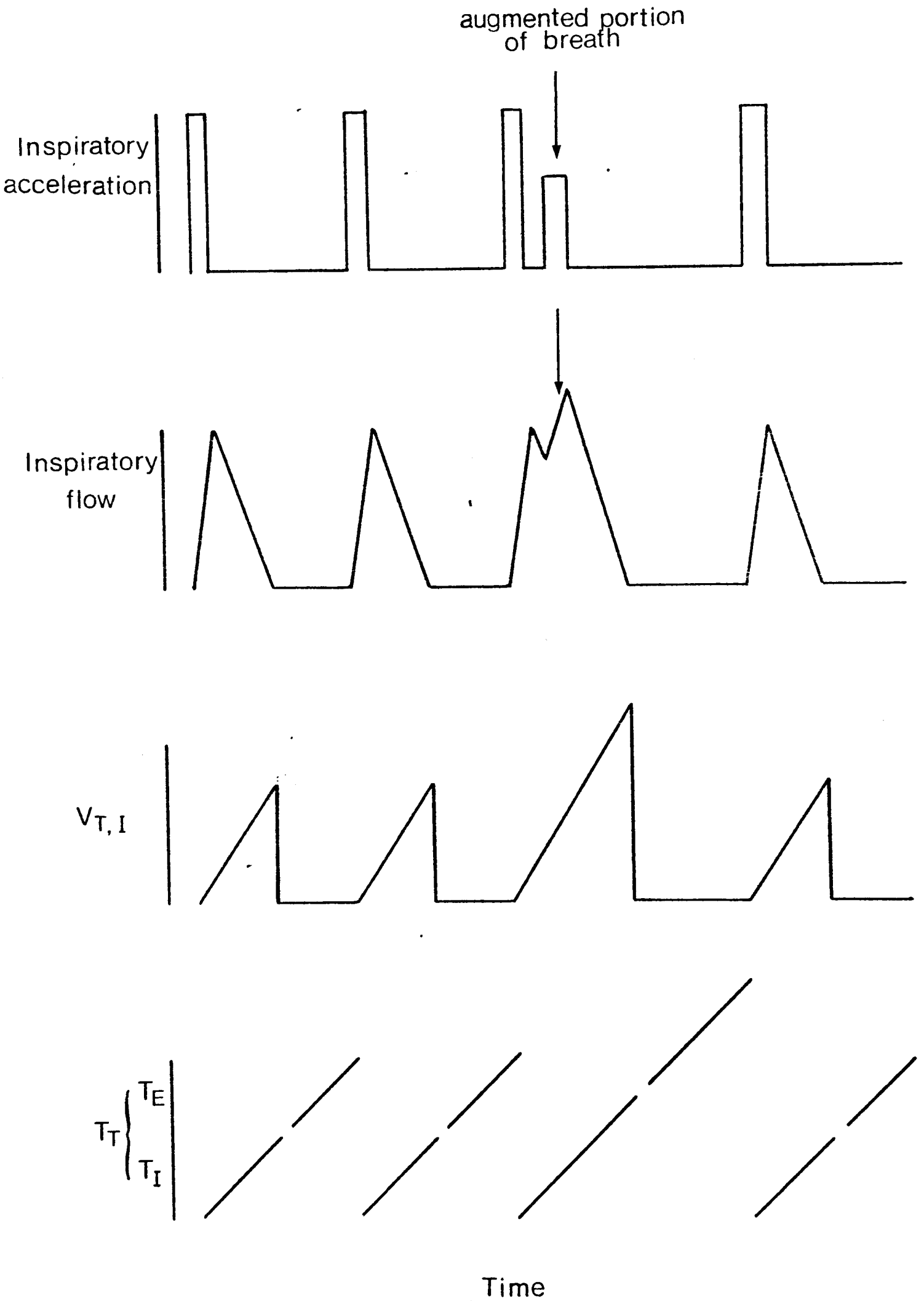
The frequency distributions of all runs in Series Two, and those of their derived alternate-breath differences, were tested for the significance of their departure from a normal frequency distribution. The results are summarised below, being presented in greater detail in Appendix 2 (p. 173).

The distribution of P_{A,CO_2} in OSC runs was predictably non-normal, having a marked bimodal form (Fig. 21A) which was to be expected. In the STEADY runs P_{A,CO_2} was usually distributed normally; any non-normal distributions were always unimodal, usually occurring in runs which showed considerable breath-by-breath variation in their respiratory responses.

Deviations from a normal distribution were infrequent amongst the output variables and always unimodal (Fig. 21B): a normally distributed run has been included for comparison (Fig. 21C). The occurrence of non-normality appeared to be unrelated to the nature of the run (in terms of P_{A,O_2}, the state of P_{A,CO_2}, and whether the subject was at rest or exercising).

The presence of "augmented" breaths (Glogoswka et al., 1972) was noted in some experiments, the criteria for their identification being a large inspiratory tidal volume (greater than 2 standard deviations

Fig. 22. A diagrammatic representation of an augmented breath



above the run-mean), a long breath duration, and a biphasic pattern of inspiratory flow and acceleration (Fig. 22, the arrow indicating the augmented portion of inspiration). Such breaths almost invariably resulted in non-normal distributions for V_T and T_T, and their derived variables. (Fig. 21B, C at "a" and "b").

However, runs previously edited to exclude excessively large and small events (p. 67) gave collections of alternate-breath differences having unimodal distributions which were rarely non-normal.

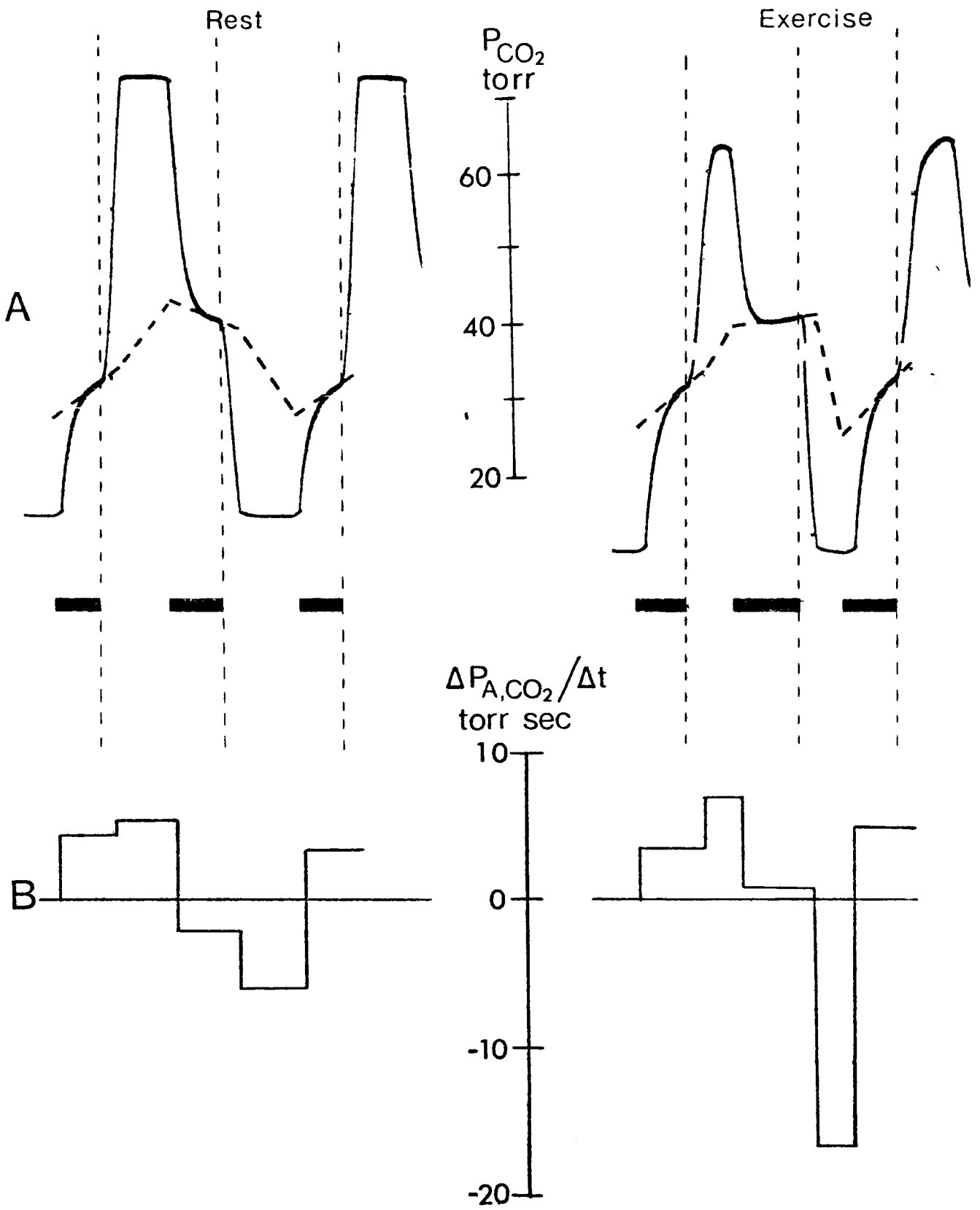
As bimodal distributions were absent from the output variables of OSC runs, it must be concluded that the reflex responses elicited by the alternate-breath P_{A,CO_2} oscillation had been contaminated by the noise of the respiratory system.

In conclusion, the use of statistical methods dependent upon normally distributed data was justified for all frequency distributions examined, with the exception of breath-by-breath P_{A,CO_2} in the OSC runs. These conclusions were applied also to the data of Series One.

3. The form of the alternate-breath P_{A,CO_2} oscillation

This section describes the form of the alternate-breath P_{A,CO_2} oscillation, as computed throughout its 2-breath period. In Fig. 23A is shown the P_{CO_2} profile of one cycle of an alternate-breath P_{A,CO_2} oscillation (solid trace) at rest and in exercise, recorded from the common space of the respiratory valve (P_{A,O_2} ca. 100 torr). Thus, throughout each respiratory cycle, inspired, mixed expired and finally

Fig.23 The form of the alternate breath P_{A,CO_2} oscillations



end-tidal gases were sampled. The period of each expiration is denoted by a solid horizontal bar. As P_{I,CO_2} values were not needed for computing the continuous P_{A,CO_2} oscillation, the P_{CO_2} signal was expanded at their expense to emphasize the alveolar plateaux.

The change in P_{A,CO_2} on successive breaths was 8-9 torr in both records, but the form of their alveolar plateaux differed. The slope of the alveolar plateau in healthy individuals depends on the size and direction of the P_{CO_2} gradient existing between pulmonary arterial blood and alveolar air, and the rate of decrease of lung volume with time (Aitken & Clark-Kennedy, 1928) and the rate of pulmonary blood flow (DuBois et al., 1952).

In exercise, the alveolar plateaux had positive slopes on both the high- and low-CO_2 breaths, implying that mixed venous P_{CO_2} ($P_{\bar{v},CO_2}$) was always greater than P_{A,CO_2}. At rest, alveolar plateaux on the low-CO_2 breaths were also of positive slope, but this was reversed to a negative slope on the high-CO_2 breaths, indicating P_{A,CO_2} to be greater than $P_{\bar{v},CO_2}$ and the CO_2 flux to be temporarily reversed.

The time course of the P_{A,CO_2} oscillation at rest and in exercise was predicted according to the principles of DuBois et al., 1952, assuming the arrival of inspired gas at the alveoli to take 0.4 sec at rest and in exercise (Appendix 2, p.214). The predicted oscillation has been superimposed (dotted line) on the P_{CO_2} profile of both records in Fig. 23A. The peak-to-trough amplitudes are approximately twice the corresponding differences in P_{et,CO_2}: ca. 15 torr at rest and 17 torr in exercise.

The computed alternate-breath P_{A,CO_2} oscillations were differentiated with respect to time (Fig. 23B), there being evidence that the carotid body of the anaesthetised cat may respond to the rate of change of P_{CO_2}, rather than P_{CO_2} per se (McCloskey, 1968; Black et al., 1971; Band et al., 1971).

Differentiation brough out differences between the P_{A,CO_2} signals at rest and in exercise. Thus, the differentiated signal was reasonably symmetrical at rest, but was less so in exercise. The loss of symmetry was largely a result of a shorter time being available in inspiration for P_{A,CO_2} to change from its maximum at the end of a high-CO_2 breath to its minimum at the end of the next (low-CO_2) inspiration, and also of the change in P_{A,CO_2} being greater in exercise than at rest. Depending on the relations between T_I and T_E in exercise, the profile may be more or less symmetrical. Asymmetry might lead to the occurrence of rectification of alternate-breath responses (p.119): that is, the mean response to an oscillating stimulus might be greater (positive rectification) or less (negative rectification) than the mean response obtained from a steady stimulus equal in amplitude to the mean of the oscillating stimulus.

4. The results of Series One

The experimental design of Series One conformed to a three-way analysis of variance for assessing the effects on the reflex transmission of an alternate-breath P_{A,CO_2} oscillation at rest of two levels of

hypoxia (60 torr and 50 torr) and of controlling the respiratory frequency. The form of the analysis of variance was outlined on p.56 .

It became apparent, however, that the aim of reducing the breath-by-breath variation in T_T by controlling respiratory frequency, and thus possibly making alternate-breath responses more regular, was not realised (p.86). Therefore, the study became confined to establishing the nature of the response patterns induced in the output variables ($\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E) by the P_{A,CO_2} oscillation in hypoxia, and whether or not increasing hypoxia interacted multiplicatively with the P_{A,CO_2} oscillation on the size of alternate-breath oscillations.

A convention of Systems Analysis was adopted in this study, whereby the phase and amplitude of oscillations may be analysed separately. Thus, in the amplitude studies, all alternate-breath oscillations were given a positive sign. Tables of alternate-breath oscillations, with their significance levels, are presented in Appendix 2 (Table 16, p.214a). The following nomenclature, bracketed, was employed in characterising the run-types:

——— P_{A,O_2} = 50 torr (50), or 60 torr (60);

——— Respiratory frequency controlled (C), or not controlled (NC);

——— P_{A,CO_2} oscillating on alternate breaths (OSC), or constant on alternate breaths (STEADY).

<u>The variability of oscillating responses in different experiments</u>

A preliminary 2-way analysis of variance was conducted on the collected alternate-breath oscillations of all six experiments, for each variable ($\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E). The intention of this was

to examine the relative variation in the amplitude of oscillating responses, both within the six experiments and the eight run-types, to decide whether or not the experiment could be pooled when exploring the nature of the interaction between hypoxia and the P_{A,CO_2} signal.

The method of analysis is described in Sokahl & Rohlf (p.299): the distribution of the total variance between the experiments and between the run-types was estimated, and the variance-ratio test (p.65) was used to estimate the significance of the contribution of each variance to the total by comparison with the error variance (error variance = total variance minus the sum of the "experiment" and "run-type" variances). The results are presented in Table 5.

For all variables, except T_I, the "run-type" and "experiment" variances were significant ($p<0.05$). The "run-type" variance was more significant than the "experiment" variance for $\dot{V}_E$ and T_E. The converse was true for $V_{T,E}$ and T_T. Neither variance was significant for T_I, an observation which was in keeping with the later observation (p.91) of the paucity of significant alternate-breath oscillations in this variable.

Thus, two conclusions were arrived at. First, the significance of the "run-type" variance in all variables but T_I implied that oscillating responses of varying amplitude must have occurred in at least some of the run-types, a point to be explored in greater detail in the following sections. Secondly, the significance of the "experiment" variance in most variables implied the existence of considerable variation in the

Table 5: The results of the 2-way analysis of variance on the collected experiments.

		Variance		
		Run-type	Experiment	Error
Variable		7	5	35
V_E				
	MS	5.0400	3.0100	0.9400
	F_s	5.36^{xxx}	3.20^{x}	
$V_{T,E}$				
	MS	0.0099	0.0215	0.0015
	F_s	6.40^{xxx}	13.95^{xxx}	
T_T				
	MS	0.0223	0.0391	0.0072
	F_s	2.86^{x}	5.00^{xxx}	
T_I				
	MS	0.0004	0.0007	0.0097
	F_s	N.S.	N.S.	
T				
	MS	0.0156	0.0074	0.0021
	F_s	7.43^{xxx}	3.52^{xx}	

DF = degrees of freedom

MS = mean sum of squares

F_s = variance - ratio test statistic

amplitude of the oscillating responses in different experiments, and therefore in different subjects. Intersubject variation of respiratory responses is certainly not a new phenomenon, and its occurrence in this study precluded any pooling of alternate-breath oscillations from different experiments.

The effects of controlling respiratory frequency on the relations between T_T, T_I and T_E

The method of controlling respiratory frequency, at a level appropriate to the prevailing level of ventilation, was expected to have the following effects:-

(i) The run mean of T_T would be similar in runs having the same P_{A,O_2}, whether the respiratory frequency was controlled or not.

(ii) The run means of T_I and T_E would approach equality in the controlled runs, as the signal controlling respiratory frequency had been arranged to give equal inspiratory and expiratory periods (p.59). This condition would differ from the state of spontaneous breathing in which T_I and T_E are rarely the same.

(iii) The breath-by-breath variations in T_T, T_I and T_E would be less in the controlled runs than in the corresponding runs where respiratory frequency was not controlled. Thus, the variances of these variables would be reduced.

These predictions were examined for each experiment, using 'paired comparisons': each pair consisted of a run with controlled breathing frequency and one in which frequency was not controlled, the two runs

being identical with respect to P_{A,O_2} and the state of P_{A,CO_2}. The results of this study are presented in detail in Appendix 2 (p.215); they were computed from runs of data which had been previously edited to exclude excessively large or small events (p.67).

Of the six experiments examined, in only two was there any indication of the predictions presented above being fulfilled. Thus, in 392.6 a reduction in the difference between mean T_E and T_I occurred consistently when respiratory frequency was controlled; and in 377.5 the variances of T_T and T_E were similarly reduced.

These results pointed to the small degree of success obtained from controlling respiratory frequency by means of a rhythmic audible signal. It seemed that the subjects were, in general, not heeding the imposed signal, though, on questioning at the end of each experiment, the consensus was that respiratory frequency had been matched to the signal in the manner requested by the experimenter.

The occurrence of alternate-breath oscillations in $\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E

Alternate-breath oscillations were calculated for each variable in all runs of each experiment, using the method described on p.67 for Series One. Each oscillation was then tested for the significance of its difference from zero amplitude by a two-tailed t-test (p.65), according to the null hypothesis that the difference was not significant.

In addition, each oscillation (x) was normalised, by expressing it as a percentage of the breath-by-breath mean of the run (x'):-

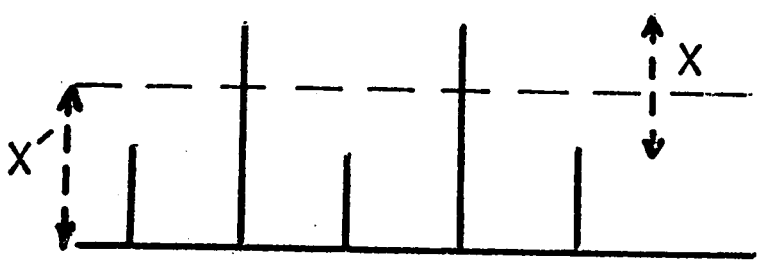


FIG. 24

This enabled comparisons to be made of the relative responses of the five variables to an alternate-breath oscillation of P_{A,CO_2}. Tables of the absolute and normalised oscillations, with their significance levels, are included in Appendix 2, (p.214a).

The distribution of significant alternate-breath oscillations was examined for each variable on the pooled results of the six experiments. The method used a Chi-squared test for the comparison of the observed probabilities of oscillations either differing from, or equalling, zero with the corresponding probabilities expected from a random process ($p = 0.05$ and 0.95, respectively) (p. 65). The null hypothesis was that the corresponding observed and expected probabilities would be equal. Table 6 presents the number of significant alternate-breath oscillations (a) for each variable at the 2 levels of P_{A,O_2} in the OSC runs and in the STEADY runs. The observed probability of a significant oscillation occurring is (a/n), where n is the total of runs being examined. Observed probabilities were only tested for significance in cases of n being greater than 20.

OSC runs. In no variable was a difference apparent between the numbers of significant alternate-breath oscillations occurring at the two levels of P_{A,O_2}.

The combined results at both P_{A,O_2} showed the incidence of significant oscillations to range from 22 out of a total of 24 for T_E to 13 for T_I. $V_{T,E}$, $\dot{V}_E$ and T_T were intermediate, having 17, 20 and 21 significant oscillations, respectively. The total number of significant oscillations was 93 out of a total of 120 (77.5%). Each of these results was shown to be highly significant by the Chi-squared test ($p<0.001$).

Table 6: The distribution of significant alternate-breath oscillations between five variables for all experiments

Variable		No. of significant oscillations (a)					
		$\dot{V}_E$	$V_{T,E}$	T_T	T_I	T_E	Total(a/n)
Run	Total no. runs (n)						
60, OSC	12	10	9	10	6	11	
50, OSC	12	10	8	11	7	11	
All OSC	24	20 xxx	17 xxx	21 xxx	13 xxx	22 xxx	93/120xxx
		83.3%	70.8%	87.5%	54.2%	91.7%	77.5%
60, STEADY	12	1	2	1	4	1	
50, STEADY	12	5	5	3	2	0	
All STEADY	24	6 xxx	7 xxx	4 xx	6 xxx	1 N.S.	24/120xxx
		25.0%	29.2%	16.7%	25.0%	4.2%	20.0%

Thus, in hypoxia, an alternate-breath P_{A,CO_2} oscillation was very effective in eliciting a similarly alternating response from the respiratory system. The occurrence of such responses was little affected by changing the P_{A,O_2} from 60 to 50 torr.

STEADY runs. The total number of significant oscillations occurring in the absence of an alternate-breath P_{A,CO_2} oscillation was 24 out of a total of 120 (20%): $p<0.001$. The distribution of these oscillations between the different variables was significant, with the exception of T_E.

The amplitude of each significant oscillation occurring in a STEADY run was compared with that of the corresponding OSC run (identical with respect to P_{A,O_2} and the state of the respiratory frequency), using a two-tailed t-test which assumed unequal variances (p. 65). The null hypothesis stated that the two oscillations would not differ in amplitude. The results are presented in Table 7.

Significant comparisons ($p<0.001$) occurred in 8 out of 24 instances, the STEADY oscillation always being smaller. The remaining 16 comparisons were not significant; as six of these comparisons concerned OSC values of zero amplitude (shown as N.S.), the corresponding STEADY values were therefore considered, on reflection, not to differ from zero. This anomaly arose because the test which estimated the significance of an oscillation compared it with a constant (zero) rather than with a mean of zero and its attached variance.

Thus, the total number of significant alternate-breath oscillations in the STEADY runs was reduced from 24 to 18 (15%). The incidence of oscillations was of the same order as seen by Marsh et al. (1971), and

Table 7: The results of the amplitude comparisons between paired OSC and STEADY alternate-breath oscillations.

Expt.		$\dot{V}_E$ 60	$\dot{V}_E$ 50	$V_{T,E}$ 60	$V_{T,E}$ 50	T_T 60	T_T 50	T_E 60	T_E 50
368.4$_1$	C					xxx	(N.S.)		
	NC				N.S.				xxx
368.4$_2$	C								
	NC	(N.S.)	N.S.	xxx	(N.S.)		N.S.		
377.5	C		N.S.						
	NC				(N.S.)				
392.6	C		xxx		N.S.		xxx		N.S.
	NC			xxx		N.S.		(N.S.)	
418.1	C		(N.S.)						
	NC							(N.S.)	
230.15	C		xxx		N.S.		N.S.		N.S.
	NC								

Starred runs: OSC > STEADY

N.S. : OSC = STEADY, and OSC > 0

(N.S.) : OSC = STEADY, and OSC = 0, so that STEADY = 0.

was very much less than the 77.5% of the OSC runs. Possible reasons for the occurrence of significant alternate-breath responses in the absence of the P_{A,CO_2} oscillation are discussed in the next chapter (p.138).

The patterns of alternate-breath responses within runs

An investigation was conducted in each run of the relative amplitude of the oscillating responses (using the normalised alternate-breath oscillation) and of the phase relations existing between these responses. Variables were ranked in each run, according to the amplitude of their normalised alternate-breath oscillations (p.87). Ranks of 5, 4, 3, 2 and 1 were applied to the variables, in descending order of oscillation size, starting with that variable having the largest oscillation. Only significant oscillations were ranked. The results are presented in Table 8.

Thus, in experiment 368.4_1, the run "60, NC" had the following ranking order:-

Variable:	T_E	> T_T	> $V_{T,E}$	> T_I
Oscillation size:	(9.60%)	(7.37%)	(4.35%)	(2.99%)
Rank:	5	4	3	2

The oscillation in $\dot{V}_E$ was not significant, and was therefore omitted.

Inspection of Table 8 showed that T_E predominated over the remaining variables in having the largest normalised alternate-breath oscillations. In four of the six experiments (368.4_1, 368.4_2, 377.5, 230.15), T_E was the most highly ranked variable in all the run-types.

Table 8: The ranking order of significant alternate-breath oscillations (normalised) in the OSC runs.

Run	60, NC					60, C					50, NC					50, C				
Rank	5	4	3	2	1	5	4	3	2	1	5	4	3	2	1	5	4	3	2	1
Experiment																				
368.4_1	T_E	T_T	$V_{T,E}$	T_I		T_E	T_T	$\dot{V}_E$	$V_{T,E}$		T_E	T_T	$\dot{V}_E$	$V_{T,E}$	T_I	T_E	T_T	$V_{T,E}$	$\dot{V}_E$	
368.4_2	T_E	$V_{T,E}$	T_T	T_I		T_E	T_T	$\dot{V}_E$			T_E	T_T	$\dot{V}_E$			T_E	T_T	$\dot{V}_E$		
377.5	T_E	$\dot{V}_E$	T_T			T_E					T_E	T_T	$\dot{V}_E$	T_I		T_E	T_T	$\dot{V}_E$		
392.6	$V_{T,E}$	$\dot{V}_E$	T_E	T_T	T_I	$V_{T,E}$	$\dot{V}_E$	T_T	T_E	T_I	T_E	$V_{T,E}$	T_T	$\dot{V}_E$	T_I	$V_{T,E}$	$\dot{V}_E$	T_E	T_T	T_I
418.1	$\dot{V}_E$	T_E	T_T			$V_{T,E}$	$\dot{V}_E$	T_E	T_T		$V_{T,E}$	$\dot{V}_E$				$V_{T,E}$	T_I	T_E	T_T	
230.15	T_E	$\dot{V}_E$	T_I	$V_{T,E}$		T_E	$\dot{V}_E$	T_T	$V_{T,E}$		T_E	$\dot{V}_E$	T_T	$V_{T,E}$		T_E	$\dot{V}_E$	$V_{T,E}$	T_I	T_T

The size of the normalised oscillations in each run decreases from left to right, with the ranking.

Another feature was the near-absence of T_I from the ranking orders. This was to be expected, taking account of the relatively low incidence of significant oscillations in T_I. Where T_I oscillations proved to be significant, their normalised oscillations were usually small, placing them at the lower end of the ranking order.

Average rankings of the five variables were obtained for the pooled experiments and for the individual experiments, irrespective of run-type, (Table 9). The pattern of ranking in the pooled experiments showed the alternate-breath oscillations in T_E to be the largest, in relative terms, having a ranking of 4.5 out of a possible of 5. Oscillations in T_I were the smallest, with a ranking of only 0.5. T_T, $V_{T,E}$ and $\dot{V}_E$ assumed similar intermediate rankings in the range of 2.5 -3. This pattern was almost identical with that reported previously for the occurrence of the oscillating responses in the pooled experiments (p.88). Thus, not only did oscillations in T_E occur more frequently but also they tended to be relatively larger, on average, than the oscillations of the other variables in the same run.

There was variation in the ranking obtained from the individual experiments, two patterns emerging. The first pattern ("T_E-dominant") was present in four of the six experiments (368.4_1, 368.4_2, 377.5, 230.15), and was similar to that obtained from the pooled experiments. The second pattern ("$V_{T,E}$-dominant"), occurring in experiments 392.6 and 418.1, possessed a considerably narrower range of rankings between the five variables, in which the dominance of the T_E oscillations was lost. $V_{T,E}$ was now the most highly ranked variable, followed by $\dot{V}_E$, T_E and T_T, these three variables having rather similar rankings. The ranking of T_I oscillations was again low.

Table 2: The average ranking of significant alternate-breath oscillations (normalised) for each variable in the OSC runs of each experiment.

Variable	$\dot{V}_E$	$V_{T,E}$	T_T	T_I	T_E
Experiment					
368.4_1	2	2.5	4	1	5
368.4_2	2.5	1	3	0.5	5
377.5	2.5	0	3	0	5
392.6	3.5	5	2.5	1	3.5
418.1	3.5	4	2	1	2.5
230.15	4	2.5	2	1.5	5
ALL	3	2.5	3	0.5	4.5

Average rankings are presented to the nearest 0.5 of an integer.

Mention should be made here of the two subjects (377, 392) in whom controlling respiratory frequency was relatively successful (p. 87). There was no difference between the ranking patterns of the runs in which respiratory frequency was controlled or not controlled, in either experiment. Thus, controlling frequency had little effect on the form of the oscillating responses, as judged by the ranking patterns of their normalised alternate-breath oscillations.

The <u>phase relations</u> existing between the alternate-breath P_{A,CO_2} oscillation and the oscillating responses elicited in the several output variables will now be considered. The latency of such a response was taken as the number of breaths elapsing between a high-CO_2 breath and the breath it subsequently stimulated (a stimulated breath having larger volumes, flows and accelerations, and shorter times than an unstimulated breath).

There is a problem associated with the determination of phase differences between a pair of periodic signals: unless the true phase difference (TPD) is less than the period (P) of the signals it cannot be determined, as illustrated below:-

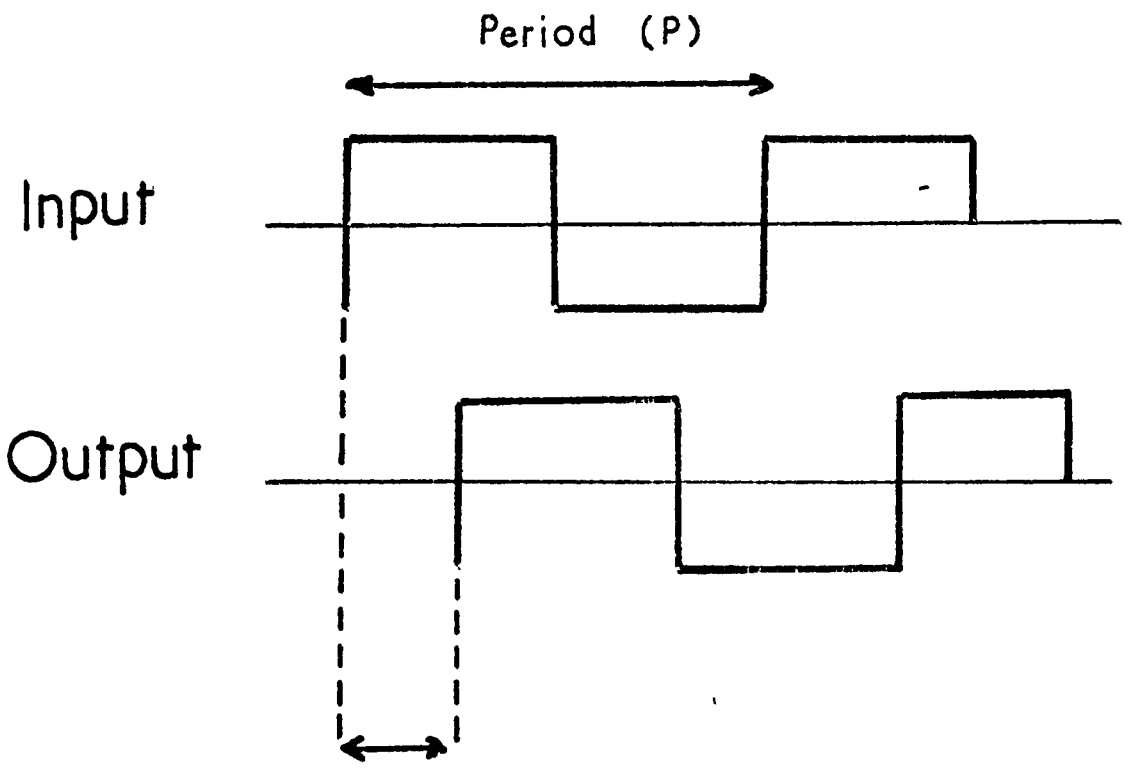
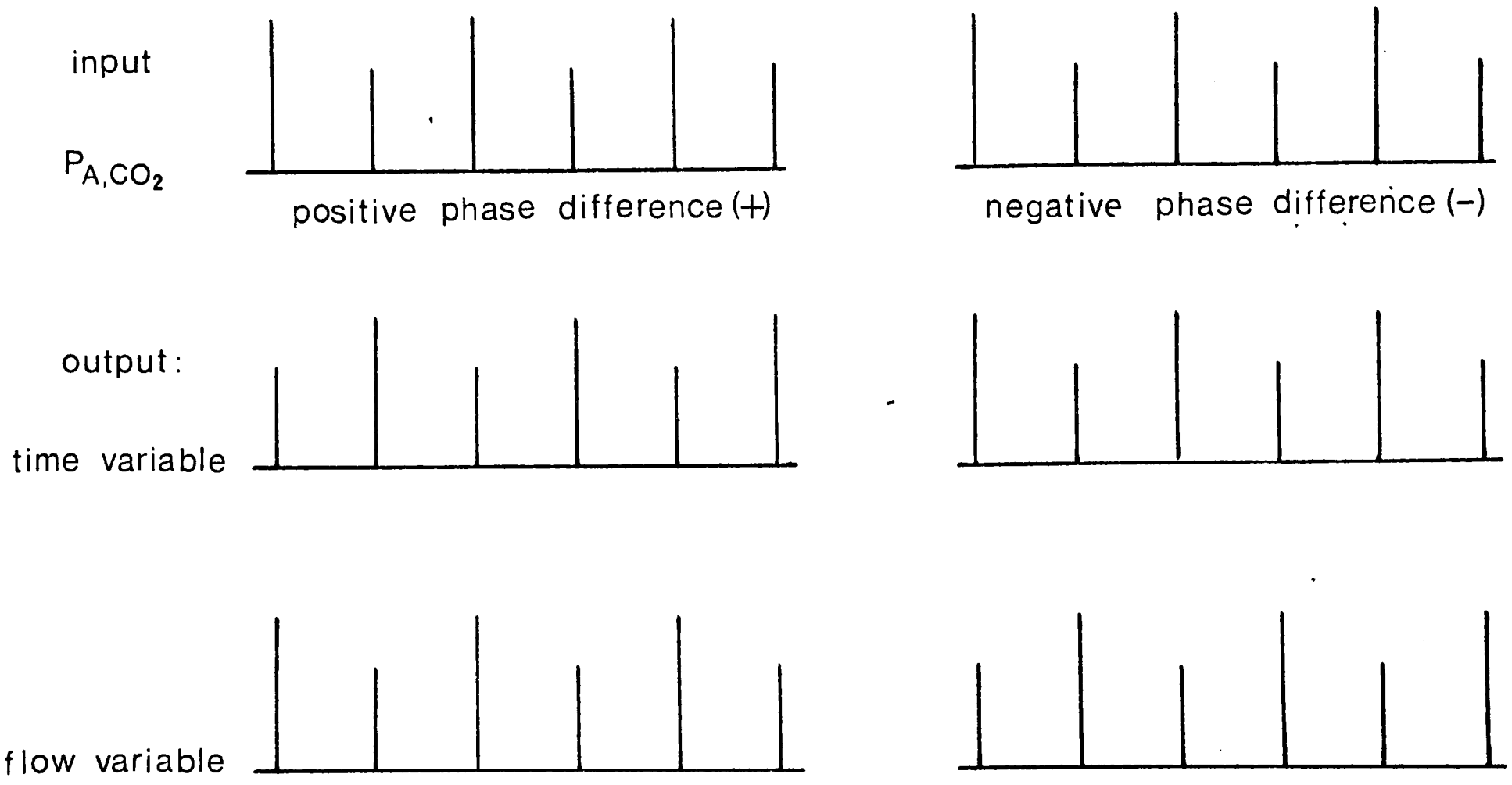


FIG. 25

Fig.26 Diagram of the phase relations that may exist between the alternate-breath oscillations of P_{A,CO_2} & the output variables.



If TPD < P, then TPD = MPD.

If TPD ⩾ P, then TPD = MPD + n. P, where n is an integer.

In the present study, MPDs could not be obtained, as measurements were confined to integral numbers of respiratory cycles (of period, T_T). Thus the only observation that could be made concerning phase differences was that a particular variable had been either stimulated on a high-CO_2 breath (positive phase difference) or on a low-CO_2 breath (negative phase difference). This situation is illustrated in Fig. 26, which shows a simplified alternate-breath P_{A,CO_2} oscillation as an input, and two hypothetical variables (a time and a flow variable) as outputs.

The results on the phase relations of alternate-breath responses in the OSC runs are presented in Table 10, according to the +/- notation described above. Only significant oscillations were included.

A rather consistent picture emerged within most experiments, in which the oscillations of a particular variable had the same phase difference with respect to P_{A,CO_2} for all runs: for example, in experiment 368.4_1 $V_{T,E}$ oscillations always had a positive phase difference, while the phase of T_E oscillations was always negative. There was often consistency, too, in the phase relations existing between the output variables in runs from the same experiment. The phase of oscillations in T_E and T_T from the same run was always the same, as was that of T_I oscillations in all but one case of their being significant. The amplitude and phase of $\dot{V}_E$ oscillations was determined by those of the corresponding oscillations in $V_{T,E}$ and T_T.

Table 10: The phase differences existing between F_{A,CO_2} and the output variables in the OSC runs.

Experiment		368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15
Variable	Run						
$V_{T,E}$	60 NC	+			+		
	60 C	+			+	+	
	50 NC	+			+		
	50 C	+			+	-	
T_T	60 NC	-	-	-	-		
	60 C	-	-		-	-	
	50 NC	-	-		-		
	50 C	-	-		-		
T_I	60 NC	-	-		-		-
	60 C		-		-		
	50 NC	-			-		
	50 C		-		-		-
T_E	60 NC	-	-	-	-	+	+
	60 C	-	-		-	-	+
	50 NC	-	-	+	-		+
	50 C	-	-	+	-		+
$\dot{V}_E$	60 NC			-	+		
	60 C	-	-		+	+	+
	50 NC	-	-	+	+	+	+
	50 C	-	-	+	+		

In the experiments conforming to the $\underline{T_E\text{-dominant}}$ pattern of amplitude response (p. 91), the phase of T_E oscillations determined, through T_T, the phase of $\dot{V}_E$ oscillations. In two experiments (368.4_1, 368.4_2), oscillations in $V_{T,E}$ and T_T were out of phase; in experiment 230.15, these oscillations were in phase; and in experiment 377.5, $V_{T,E}$ did not oscillate, and the variability in the phase of T_E oscillations was reflected in $\dot{V}_E$.

Of the 2 experiments having the $\underline{V_{T,E}\text{-dominant}}$ pattern of amplitude response (p. 91), 392.6 had oscillations in $V_{T,E}$ and T_T that were out of phase, the phase of $\dot{V}_E$ oscillations being determined by the phase of the $V_{T,E}$ oscillations. Experiment 418.1 showed little consistency in the relative influences of $V_{T,E}$ and T_T on the phase of $\dot{V}_E$ oscillations.

In the STEADY runs, there was no consistent pattern to the phase differences of the significant alternate-breath oscillations.

These findings can be summarised in terms of the relative predominance of T_T (itself largely under the influence of T_E) and $V_{T,E}$ in the alternate-breath responses of the various experiments. In the first part of the section, this was considered in terms of the amplitude of the oscillating responses, while the added consideration of the phase relations existing between the variables reinforced the earlier conclusion of the predominance of primary variables such as $V_{T,E}$ and T_E (or T_T), rather than the derived variable, $\dot{V}_E$. This is of interest when one considers the emphasis which is laid upon $\dot{V}_E$ as the controlled variable of the respiratory system.

The effects of increasing hypoxia on the size of alternate-breath oscillations of $\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E

As mentioned on p.93, the original intention of performing a three-way analysis of variance to assess the effects of controlled respiratory frequency and two levels of hypoxia on the amplitude of alternate-breath responses was rescinded. The reason for this action was that the experimental control of respiratory frequency had not been generally achieved in the desired manner (p.87). Respiratory frequency was therefore eliminated from the group of independent variables, only hypoxia and the state of P_{A,CO_2} remaining.

As interest in P_{A,CO_2} was now confined to the oscillating state (the occurrence of significant alternate-breath oscillations being rare in runs where P_{A,CO_2} did not oscillate), the analysis of variance was dispensed with, and the hypothesis of a multiplicative interaction between steady hypoxia and the alternate-breath P_{A,CO_2} oscillation was examined as follows. The average alternate-breath oscillations at P_{A,O_2} = 60 torr and 50 torr were compared, for each variable in each experiment, by a one-tailed t-test which assumed the variances to be unequal (p.65). The null hypothesis stated that no multiplication occurred between hypoxia and the CO_2 oscillation, the oscillation at P_{A,O_2} = 50 torr not being greater than that at P_{A,O_2} = 60 torr. The mean and variance of an average oscillation at a particular P_{A,O_2} represented the weighted average values of the NC and C runs at the same P_{A,O_2} (a formula for the weighted average of a statistic is given

Figs. 27 & 28

The effects of 2 levels of P_{A,O_2} on the response to an alternate-breath P_{A,CO_2} oscillation.

The response is the alternate-breath oscillation: each oscillation is the average value for a pair of NC and C runs. A significant difference between an oscillation at P_{A,O_2} = 50 torr and at 60 torr is indicated by starring in the top right corner of the appropriate box.

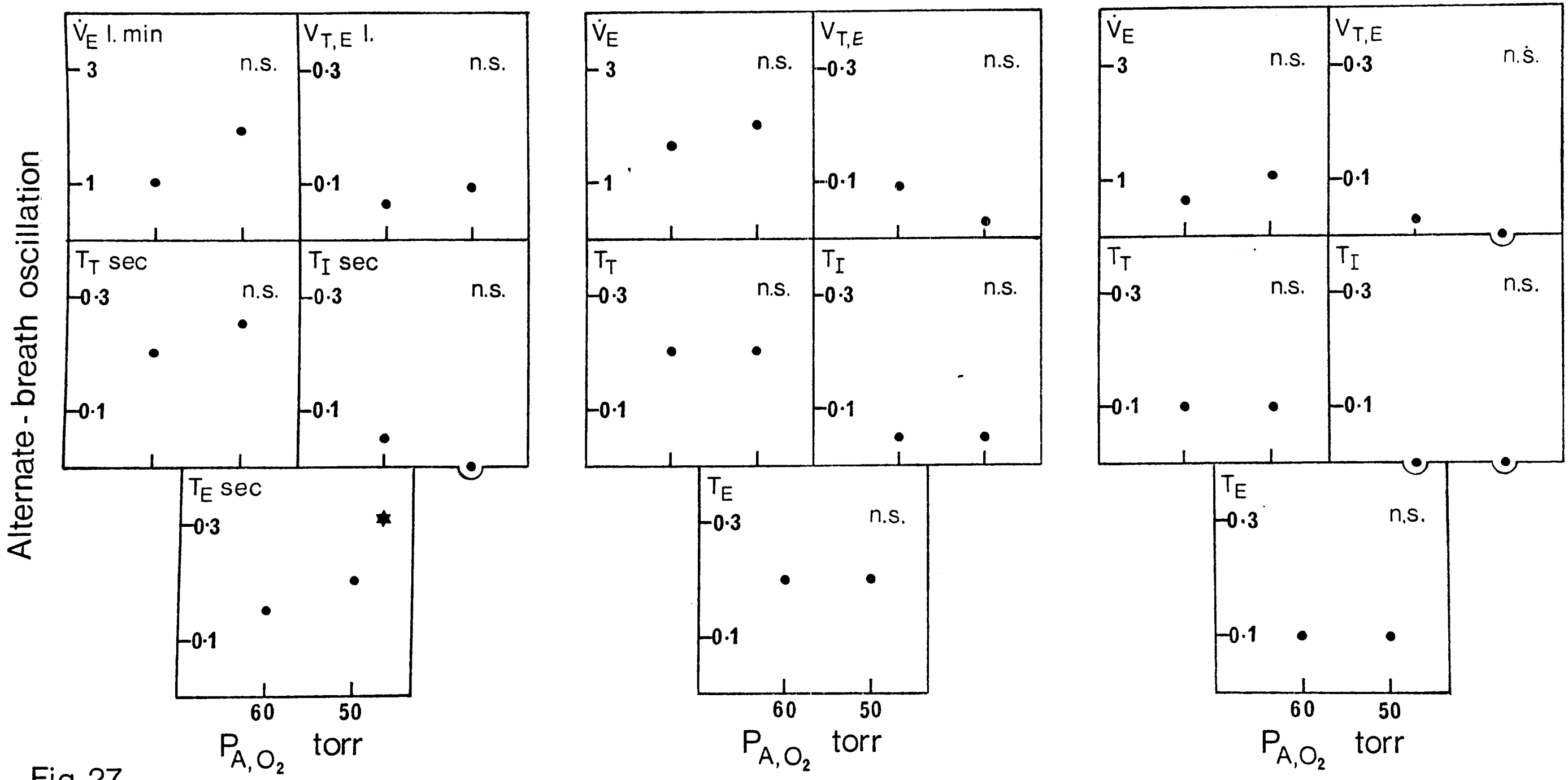

368.4₁
368.4₂
377.5
Alternate - breath oscillation
V̇E l. min
VT,E l.
TT sec
TI sec
TE sec
V̇E
VT,E
TT
TI
TE
3
1
0·3
0·1
n.s.
60
50
PA,O2 torr

Fig. 27

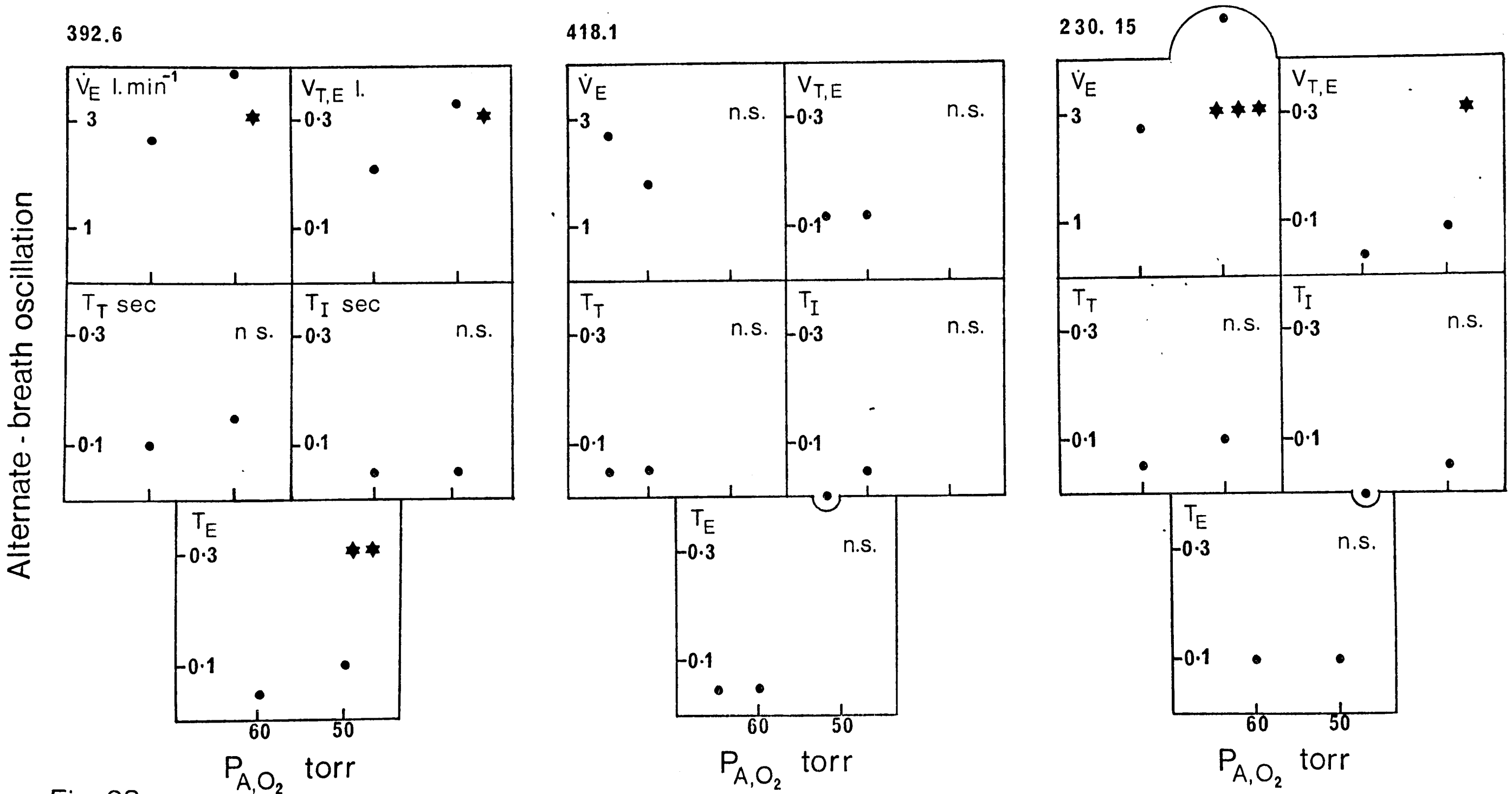

392.6
418.1
230. 15
Alternate - breath oscillation
$\dot{V}_E$ l.min^{-1}
3
1
$V_{T,E}$ l.
0·3
0·1
T_T sec
0·3
0·1
n s.
T_I sec
0·3
0·1
n.s.
T_E
0·3
0·1
60
50
P_{A,O_2} torr
$\dot{V}_E$
3
1
n.s.
$V_{T,E}$
0·3
0·1
n.s.
T_T
0·3
0·1
n.s.
T_I
0·3
0·1
n.s.
T_E
0·3
0·1
n.s.
60
50
P_{A,O_2} torr
$\dot{V}_E$
3
1
$V_{T,E}$
0·3
0·1
T_T
0·3
0·1
n.s.
T_I
0·3
0·1
n.s.
T_E
0·3
0·1
n.s.
60
50
P_{A,O_2} torr

Fig. 28

Table 11: A comparison of the effects of two levels of hypoxia on the amplitude of alternate-breath oscillations.

Variable	$\dot{V}_E$	$V_{T,E}$	T_T	T_I	T_E
Expt					
368.4_1	N.S.	N.S.	N.S.	N.S.	x >0
368.4_2	N.S.	N.S.	N.S.	N.S.	N.S.
377.5	N.S.	N.S.	N.S.	N.S.	N.S.
392.6	x 5>60	x 5<>60	N.S.	N.S.	xx 5 > 0
418.1	N.S.	N.S.	N.S.	N.S.	N.S.
2[illegible].15	xxx [illegible]	x [illegible]	N.S.	N.S.	N.S.

on p. 64). The results of the comparisons are presented in Table 11 and Figs. 27 and 28.

Taking each variable (5) in each experiment (6) together gave 6 comparisons out of 30, as being significant: that is, showing a multiplicative interaction. These were confined to 3 experiments: 368.4_1 (T_E), 392.6($\dot{V}_E$, $V_{T,E}$, T_E) and 230.15 ($\dot{V}_E$, $V_{T,E}$).

The observed probability of multiplication occurring (6/30) was almost significant ($0.05<p<0.10$), by the Chi-squared test (p. 65). The value of χ^2 obtained (3.7) compared favourably with the critical value of χ^2 at $p = 0.05$ for one degree of freedom (3.8).

Thus the possibility of a multiplicative interaction occurring at rest between hypoxia and the P_{A,CO_2} oscillation cannot be ruled out, in some variables at least, and merits further investigation.

Summary

(i) The investigation of the effects of increasing hypoxia and of controlled respiratory frequency on the responses elicited by an alternate-breath oscillation resolved itself into a study solely of the effects of increasing hypoxia, on discovering that controlling the respiratory frequency had been generally unsuccessful.

(ii) In response to the P_{A,CO_2} oscillation, 77.5% of the pooled runs on all variables ($\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E) had significant oscillations. T_E oscillated most frequently, followed by T_T, $\dot{V}_E$, $V_{T,E}$ and lastly T_I. Changing P_{A,O_2} from 60 torr to 50 torr had no effect on

the frequency of occurrence of oscillations in any of the variables. In the absence of the P_{A,CO_2} oscillation only 15% of all the oscillating responses had amplitudes different from zero.

(iii) The average pattern of response within each run for all experiments, in terms of the relative amplitude of oscillations in the different variables, was similar to that for the occurrence of significant oscillations in (ii). Thus, oscillations in T_E were not only the most frequent, but also were, on average, relatively the largest in each run. The runs of individual experiments conformed consistently to one of two response patterns: one was similar to that of the pooled experiments, in which oscillations in T_E predominated (4 experiments), while in the other, oscillations in $V_{T,E}$ predominated (2 experiments).

(iv) The phase relations, with respect to the P_{A,CO_2} oscillation, of oscillations in primary variables such as $V_{T,E}$ and T_E were often consistent within an experiment: $V_{T,E}$ almost invariably had a positive phase difference, while T_E (and T_T) often had a negative phase difference. The phase of $\dot{V}_E$ oscillations depended on the phase and relative amplitude of the oscillations in $V_{T,E}$ and T_T.

(v) In contrast to the <u>occurrence</u> of oscillations, the <u>amplitude</u> of oscillations was sometimes greater at P_{A,O_2} = 50 torr than at 60 torr, demonstrating a multiplicative interaction on respiration of hypoxia and the P_{A,CO_2} oscillation.

5. The results of Series Two

The findings on the reflex transmission of an alternate-breath P_{A,CO_2} oscillation which emerged from Series One produced several alterations in the original experimental design which would permit further examination of these findings in Series Two.

An additional method of estimating alternate-breath responses, based on autocorrelation analysis, was introduced: autocorrelation techniques are particularly appropriate for the detection of oscillating signals which are masked in a background of noise (e.g. Bendat & Piersol, p. 22). The index of oscillation, 2D, was the difference between the Z-transformed autocorrelation coefficients for the sampling intervals of two breaths and one breath (p. 69). It replaced the normalised alternate-breath oscillation (p. 87) as a comparative index of alternate-breath responses in different variables.

The range of output variables was extended to include inspiratory as well as expiratory variables, in an attempt to characterize more completely the patterns of oscillating response. The variables were classed as being either primary (comprising a single measured quantity) or derived (comprising 2 or more measured quantities). The primary variables studied were inspiratory and expiratory times (T_I and T_E), tidal volumes ($V_{T,I}$ and $V_{T,E}$) and peak flows (PIF and PEF), and peak inspiratory acceleration (PIA). The derived variables were breath

duration (T_T), the change in functional residual capacity (DFRC, = $V_{T,I} - V_{T,E}$), inspiratory and expiratory mean flows (MIF and MEF) and ventilations ($\dot{V}_I$ and $\dot{V}_E$).

Greater attention was paid to the latency of the responses induced by the P_{A,CO_2} oscillation. An implication arising from the phase studies of Series One was that the latency of the oscillating response might not be similar for all the participating variables. This was explored further by means of a cross-correlation analysis between P_{A,CO_2} and each output variable in regions of the experimental record where the state of P_{A,CO_2} was changed from OSC to STEADY, or vice versa, against a background of hypoxia.

The implied multiplication between hypoxia and the P_{A,CO_2} oscillation on respiration at rest was re-examined in Series Two. A wider range of P_{A,O_2} (ca. 200-45 torr) and a greater number of P_{A,O_2} levels (4-7) were used for characterising the effects of hypoxia on the amplitude of oscillating responses. A linear regression analysis of oscillation amplitude on hypoxia was performed to examine how closely the effect of hypoxia on the reflex transmission of the P_{A,CO_2} oscillation approached a linear multiplication.

Finally, the effects were explored of moderate rhythmic exercise on the responses outlined at rest: that is, the patterns of oscillating responses and their hypoxic dependency. Also included was an investigation of the possible rectification of the oscillating responses induced in ventilation ($\dot{V}_E$) by the P_{A,CO_2} oscillation, as proposed on p. 83.

The occurrence of alternate-breath responses in 13 output variables in hypoxia and hyperoxia, at rest and in exercise

An alternate-breath oscillation and a ZD value were calculated for each variable in all runs (p.68 and p.69, respectively); these values were then tested for the significance of their differences from zero (p.65 and p.70, respectively). These results are presented in Appendix Two: Table 24 (p.225) for the oscillation, and Table 25 (p.226) for ZD.

The distribution of significant alternate-breath oscillations and ZD values between the 4 subjects (409, 421, 425 and 392) and the 13 output variables was examined, in the OSC runs and in the STEADY runs, the results of the two or three experiments conducted on each subject having been pooled. The incidence of significant events occurring in each subject and in each variable was tested for its deviation from a random event, using a Chi-squared test as in Series One (p.65).

OSC runs. The incidence of alternate-breath oscillations differing from zero in all variables from the pooled runs of all subjects was highly significant ($p<0.001$) by the Chi-squared test (Table 12: "ALL RUNS"): at rest, 38% (range: subject 425, 16.7% to subject 409, 58.5%), and in exercise, 46.6% (range: subject 425, 23.1% to subject 409, 74.8%).

The overall effect of hypoxia was assessed by pooling all runs with a P_{A,O_2} of 72 torr or less. The incidence of significant oscillations

Table 12: OSC runs: the distribution of significant alternate-breath oscillations between subjects.

	Rest					Exercise				
Subject	409	421	425	392	All	409	421	425	392	All
1. All runs										
No. runs (n)	10	17	12	11	50	11	15	11	14	51
No. observations (n x 13)	130	221	156	143	650	143	195	143	182	663
No. significant observations (S)	76^{xxx}	76^{xxx}	26^{xxx}	52^{xxx}	247^{xxx}	107^{xxx}	93^{xxx}	33^{xxx}	76^{xxx}	309^{xxx}
$S \times 100/(n \times 13)$ $\%_S$	58.5	34.4	16.7	36.4	38.0	74.8	47.7	23.1	41.8	46.6
2. Hyperoxia										
n	0	2	2	2	6	0	2	2	2	6
(n x 13)	26	26	26	26	78		26	26	26	78
S		2	1	8	11^{xxx}		4	0	2	6
$\%_S$		7.7	3.8	30.8	14.1		15.4	0	7.7	9.2
3. Hypoxia										
n	7	9	8	6	30	8	6	6	8	28
(n x 13)	91	117	104	78	390	104	78	78	104	364
S	61^{xxx}	68^{xxx}	24^{xxx}	39^{xxx}	192^{xxx}	85^{xxx}	49^{xxx}	29^{xxx}	50^{xxx}	213^{xxx}
$\%_S$	67.0	58.1	23.1	50.0	49.2	81.7	62.8	37.2	48.1	58.5
4. Hypoxia: ZD (for comparison with 3)										
S	49^{xxx}	26^{xxx}	2	20^{xxx}	97^{xxx}	68^{xxx}	34^{xxx}	17^{xxx}	30^{xxx}	149^{xxx}
$\%_S$	53.8	22.2	1.9	25.6	24.9	66.0	43.6	21.8	28.8	40.9

Significance levels (^{x}) are from a Chi-squared test (see text).

here was 49.2% at rest (range: subject 425, 23.1% to subject 409, 67.0%) and 58.5% in exercise (range: subject 425, 37.2% to subject 409, 81.7%),: Table 12, "HYPOXIA".

Replacing the alternate-breath oscillation by ZD consistently reduced the incidence of significant responses in hypoxia, whilst retaining the pattern of the oscillation results (Table 12, "HYPOXIA-ZD": cf. "HYPOXIA"). At rest, 24.8% of the ZD values from the pooled runs were significant, and 40.9% in exercise.

The results obtained in <u>hyperoxia</u> (runs with a $P_{A,O_2} > 180$ torr) were in marked contrast to those just reported for hypoxia. At rest, the incidence of significant oscillations was 14.1% ($p<0.001$ by the Chi-squared test), while in exercise the incidence was 9.2% (not significant): Table 12, "HYPEROXIA". There appeared to be no preferential distribution of the oscillations between variables (Appendix 2, Table 29, p.230). Because of the small number of runs in this group (one per experiment, at most) little statistical weight could be lent to the results.

Having presented a general description of the hypoxic dependency of the oscillating responses, their <u>distribution between the different output variables</u> in hypoxia will now be examined, for both the alternate-breath oscillation and ZD. Rather similar results were obtained from each index of oscillation. A highly significant incidence of oscillations ($p<0.001$) occurred for each variable in the <u>pooled runs</u> at rest and in exercise (Appendix 2, Table 27, p.228).

The pattern for ZD was similar, with only a few variables having an insignificant result: PEF, T_T and T_I at rest, and T_I in exercise (Appendix 2, Table 28, p.229). The results from individual subjects were not tested statistically because of the small numbers of observations.

While T_I evidently responded poorly to the P_{A,CO_2} oscillation at rest and in exercise, it was equally important to establish which variables responded most frequently. Those variables having a high incidence of oscillating responses are presented in Table 13 (alternate-breath oscillation) and Table 14 (ZD), for each subject and for the pooled runs. As before, the study was confined to hypoxic runs.

The identity of these variables for the pooled runs was common to the resting and the exercising states for both indices of oscillation, the ZD result differing from that of the alternate-breath oscillation only by the substitution of PIA for MIF.

Variation was evident in the different subjects. Using the alternate-breath oscillation, the patterns of prominent variables for two subjects (425 and 392) were similar at rest and in exercise, and involved most inspiratory variables (not T_I). Less correspondence between rest and exercise occurred in subjects 409 and 421: for example, in 409, inspiratory variables were dominant at rest, and expiratory variables in exercise.

The results obtained on ZD for the individual subjects were essentially similar to those reported above, the same variables tending

Table 13: The variables in each subject having the largest percentage of significant alternate-breath oscillations in hypoxia.

Subject	No. runs Rest	No. runs Ex.		Rest	Exercise
409	7	8	Variable	$V_{T,I}$, MIF, PIF, PIA, DFRC	$V_{T,I}$, $\dot{V}_E$, MEF, PEF, T_T, T_E
			$\%_s$	100.0	100.0
421	9	6	Variable	$\dot{V}_I$, T_E; $V_{T,I}$, MEF, PEF, PIF, DFRC	$V_{T,I}$, PIF, PIA; MEF
			$\%_s$	77.8 66.7	100.0 83.3
425	8	6	Variable	MIF, DFRC	MIF, PIF; DFRC; $V_{T,I}$, $\dot{V}_I$
			$\%_s$	50.0	83.3 66.7 50.0
392	6	8	Variable	$\dot{V}_I$; $V_{T,I}$, MIF, PIF	$V_{T,I}$, $\dot{V}_I$, MIF, PIF
			$\%_s$	100.0 83.3	87.5
All	30	28	Variable	DFRC; $V_{T,I}$, MIF, PIF	PIF; $V_{T,I}$; MIF; DFRC
			$\%_s$	70.0 66.7	89.3 85.7 78.6 71.4

Table 14: The variables in each subject having the largest percentage of significant ZD values in hypoxia.

Subject	No. runs Rest	Ex.		Rest				Exercise			
409	7	8	Variable	DFRC;	$V_{T,I}$, PIF, T_E;		PIA	$\dot{V}_E$, MEF, V_T, T_E			
			$\%_s$	100.0	85.7		71.4	100.0			
421	9	6	Variable	DFRC;	$V_{T,I}$, $\dot{V}_I$, PEF			PIA, DFRC;	$V_{T,I}$, PIF		
			$\%_s$	55.6	33.3			83.3	66.7		
425	8	6	Variable	DFRC only				DFRC;	$V_{T,I}$;	$\dot{V}_I$;	MIF, PIF
			$\%_s$	25.0				83.3	66.7	50.0	33.3
392	6	8	Variable	MIF				DFRC; $V_{T,I}$, MIF, PIA			
			$\%_s$	50.0				62.5	50.0		
All	30	28	Variable	DFRC;	$V_{T,I}$;	PIF;	PIA	DFRC;	$V_{T,I}$;	PIF;	PIA
			$\%_s$	53.4	36.7	33.3	30.0	75.0	64.3	57.1	46.4

to be prominent for both indices of oscillation, but not always in the same order of prominence, nor with such a high incidence of significant events. There was a tendency for DFIC to be relatively more prominent than was found for the alternate-breath oscillation.

Finally, the incidence in hypoxia of significant alternate-breath oscillations in $\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E at rest was compared between the pooled runs Series One (App. 2, p.213a) and Series Two (Appendix 2, Table 24, p.225). The results are collected in Table 15. It is evident that oscillating responses were generally more prolific in the experiments of Series One than in those of Series Two. T_E was again the most prolific of variables in Series Two (with $\dot{V}_E$) as in Series One; and, in contrast with Series One, T_I had a greater tendency to oscillate.

STEADY runs. Alternate-breath oscillations were computed and tested for the significance of their differences from zero as was done for the OSC runs (p. 68). The amplitude of each significant oscillation was compared with that of the oscillation from the corresponding OSC run, as described for Series One (p. 89). Any STEADY oscillation not differing from the OSC value, when the latter was not different from zero, was not regarded as being a significant oscillation itself.

The distribution of the collected significant oscillations, for all variables, in the individual and the pooled runs was examined for all runs, and for the hypoxic and hyperoxic runs. The incidence of significant oscillations in the pooled runs, irrespective of P_{A,O_2}, was

Table 15: Comparison between Series One and Two: the distribution of significant alternate-breath oscillations between $\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E in hypoxia for all subjects.

		No. of significant oscillations (a)					
Variable	No. runs (n)	$\dot{V}_E$	$V_{T,E}$	T_T	T_I	T_E	Total
+Series 1	24	83.3%	70.8%	87.5%	54.2%	91.7%	77.5%
++Series 2	30	14[xxx]	6[xxx]	8[xxx]	8[xxx]	14[xxx]	50/150[xxx]
(Rest)		46.7%	20.0%	26.7%	26.7%	46.7%	30.0%

Series 1 $T_E > T_T > \dot{V}_E > V_{T,E} > T_I$

Series 2 $\dot{V}_E$ and $T_E > T_T$ and $T_I > V_{T,E}$

2, Table 27 (p.88) (p.228)

+from Table 6; p.88 ++from Appendix 2, Table 27 p.228

3.5% at rest (range: subject 425, 0% to subject 409, 13.1%) and 6.2% in exercise (range: subject 392, 2.8% to subject 409, 16.2%): Table 16, "ALL RUNS". The results from the hypoxic runs were very similar (see also Tables 30 and 31 in Appendix 2, p.231). In hyperoxia, however, none of the oscillations was different from zero.

The results of the comparisons made between the significant oscillations of corresponding STEADY and OSC runs are presented in Appendix 2, Table 32, p.233). Of 21 comparisons at rest and 36 in exercise, 13 and 26, respectively, showed the STEADY oscillation to be significantly less than the OSC value, the remaining comparisons showing insignificant differences between the two. As in Series One, therefore, the incidence of significant oscillations was low in the absence of the P_{A,CO_2} oscillation.

The main observations of this section will now be summarised. In response to an alternate-breath P_{A,CO_2} oscillation, alternating responses were induced almost exclusively in hypoxia ($P_{A,O_2} < 72$ torr); exercise imposed an additional stimulus in hypoxia. There was a tendency for the oscillating responses to occur more frequently in inspiratory variables than in expiratory variables (cf. subject 421 at rest, and subject 409 in exercise), with the change in FRC (DFRC) being the most prominent in this respect.

The examination of the alternate-breath oscillation and ZD as indices of oscillation showed that oscillating responses were more prolific in the former. This appeared to reflect differences in the

Table 16: STEADY runs: the distribution of significant alternate-breath oscillations between subjects.

		Rest					Exercise				
Subject		409	421	425	392	All	409	421	425	392	All
All runs											
n		10	15	10	11	46	110	14	10	11	45
(n x 13)		130	195	130	143	598	130	182	130	143	585
	S	17^{xxx}	2	0	21	21	21^{xxx}	7	4	4	36
	$\%_s$	13.1	1.0	0	1.4	3.5	16.2	3.8	3.1	2.8	6.2
Hypoxia											
n		7	7	6	6	26	7	5	4	5	21
(n x 13)		91	91	78	78	338	91	65	52	65	273
	S	14^{xxx}	1	0	2	18	13^{xxx}	2	1	3	19
	$\%_s$	15.4	1.1	0	2.6	5.3	14.3	3.1	1.9	4.6	7.0
Hyperoxia											
n		0	2	2	2	6	0	2	2	2	6
			NONE					NONE			

Abbreviations are defined in Table 12, p.100.

sensitivity of the two methods, rather than the fact that alternate-breath oscillations had been computed from data runs which no longer contained any excessively large or small events while ZD values had been derived from unedited data. A comparison of significant ZD values obtained from unedited and edited data in the hypoxic OSC runs of experiment 409.5 had shown the general pattern of the size and significance of ZD values to be relatively little affected by the editing procedure (Appendix 2, Table 33, p.234). Despite the difference in the relative efficacy of the two indices, they both appeared to generate qualitatively similar patterns of oscillating response.

Within the range of variables studied in Series One, the relative occurrence of significant oscillations in hypoxia at rest was rather similar for the pooled experiments of Series One and Two, although their absolute incidence was greater in Series One.

The patterns of alternate-breath responses within runs in hypoxia, at rest and in exercise: amplitude

The patterns of oscillating responses induced by an alternate-breath P_{A,CO_2} oscillation were explored with a ranking procedure analogous to that used in Series One (p.90). The analysis was conducted on the hypoxic group of runs, to which most of the oscillating responses were confined. Thus, within each hypoxic OSC run, ranks of 13, 12, 11,..., and 1 were applied to the variables in descending order of ZD size: only those variables having significant ZD values were ranked. Average rankings of the 13 variables were obtained for each subject and for the

pooled subjects at rest and in exercise. The results, expressed to the nearest integer, are presented in Table 17.

At rest and in exercise, all variables but T_I were ranked in the pooled runs, the more prominent variables being:-

Rest: DFRC (7); PIA (4); $V_{T,I}$, MIF, PIF, T_E (3).

Exercise: DFRC (10); $V_{T,I}$ (7); PIF (5).

This pattern of DFRC and inspiratory variables dominating the rankings was similar to the pattern for the occurrence of oscillating responses reported in the previous section, both for the alternate-breath oscillation and for ZD.

The ranking patterns of the individual subjects, certainly for the more prominent variables, were virtually identical with their patterns for the occurrence of oscillating responses (ZD) presented in Table 14 (p.102), and reasonably similar to the patterns for the occurrence of alternate-breath oscillations (Table 13, p.102). The more highly ranked variables are presented below:-

409	Rest	DFRC (13); PIF, T_E (9); PIA (8).
	Exercise	T_E (11); MEF, T_T, DFRC (10).
421	Rest	DFRC (7); PEF (5); $V_{T,I}$, $\dot{V}_I$ (4).
	Exercise	PIA, DFRC (10); $V_{T,I}$, MIF (7).
425	Rest	DFRC (3), only.
	Exercise	DFRC (11); $V_{T,I}$ (8); $\dot{V}_I$ (5).
392	Rest	MIF (6); DFRC (5).
	Exercise	DFRC (8); $V_{T,I}$ (6); PIF (5).

Table 17: The average ranking of significant ZD values for each variable in the OSC runs of each subject (P_{A,O_2} < 72 torr).

	Rest					Exercise				
Subject	409	421	425	392	All	409	421	425	392	All
No. runs	7	9	8	6	30	8	6	6	8	28
Variable										
$V_{T,E}$	2	2	0	3	2	0	4	0	4	2
$V_{T,I}$	7	4	0	3	3	7	7	8	6	7
$\dot{V}_E$	2	3	0	3	2	8	2	0	4	3
$\dot{V}_I$	1	4	0	3	2	2	2	5	4	3
MEF	5	2	0	2	2	10	3	0	4	4
MIF	4	0	0	6	3	2	7	4	4	4
MEP	0	5	0	0	1	7	3	0	0	3
PIF	9	2	0	2	3	7	5	4	5	5
PIA	8	3	0	3	4	4	10	1	2	4
T_T	3	1	0	0	1	10	2	0	0	3
T_E	9	1	0	1	3	11	2	0	1	3
T_I	1	1	0	0	0	1	0	0	1	0
DFRC	13	7	3	5	7	10	10	11	8	10

In contrast, T_I was rarely ranked in any subject: no other variable lacked an oscillating response so consistently.

The patterns of alternate-breath responses within runs in hypoxia, at rest and in exercise: phase

In Series One the phase relations existing between an alternate-breath P_{A,CO_2} oscillation and that of a primary output variable in hypoxia were not necessarily identical in different experiments (p.92): the possibility presented itself that the occurrence of opposite phases for the oscillations in $V_{T,E}$ and T_E might indicate an interplay of more than one mechanism of excitation. With this hypothesis in mind, the phase relations of the several output variables were examined during the OSC runs, as in Series One, and also at the transition between OSC and STEADY runs.

All phase differences related high-CO_2 breaths to stimulated breaths, a stimulated breath having larger volumes, flows and accelerations, and shorter times, than an unstimulated breath (though it was shown subsequently that some variables might be stimulated, and others depressed, on the same breath). An arbitrary convention was adopted for the derived variable, DFRC (= $V_{T,I} - V_{T,E}$), whereby an increase in FRC (DFRC positive) was taken as a stimulation.

P_{A,CO_2} oscillation. As described on p.92 and in Fig. 25, the measured phase difference (MPD) of an oscillating response in relation to the P_{A,CO_2} oscillation was limited to being positive (stimulation

occurring on a high-CO_2 breath) or <u>negative</u> (stimulation occurring on a low-CO_2 breath). Complete results on the phase differences of alternate-breath responses in the OSC runs are found in Appendix 2 (Table 24, p.225): only significant oscillations are examined here. The study was confined to the alternate-breath oscillation, ZD carrying no phase information (p.70).

The data on <u>subject 409</u> were used as a reference with which to compare the less extensive results on the other three subjects. Table 18 presents the phase results of experiments 409.5 and 409.6 at rest and in exercise. Hypoxic runs (P_{A,O_2} < 72 torr) were grouped, while the remainder (P_{A,O_2} > 72 torr) were considered separately.

In hypoxia, a rather consistent pattern of phase relations emerged for each variable, with respect to P_{A,CO_2}. The phase of oscillations in the inspiratory primary variables was always positive, with the exception of T_I which rarely exhibited significant oscillations (these were usually of negative phase). Of the expiratory primary variables, oscillations in $V_{T,E}$ resembled those of the inspiratory primary variables in being positively phased, while oscillations in PEF and T_E were negatively phased.

The phase differences of the derived variables depended on the phase and relative amplitude of the oscillations in their component variables. Thus, oscillations in DFRC ($V_{T,I} - V_{T,E}$) were of positive phase; this reflected the greater influence of the $V_{T,I}$ oscillation, the similarly phased $V_{T,E}$ oscillation being smaller and less frequently

Table 18: The phase differences existing between P_{A,CO_2} and the output variables in the OSC runs of subject 409 at rest and in exercise.

	409.5				409.6					
	Rest		Exercise		Rest			Exercise		
P_{A,CO_2} (torr)	115.5	<72	114	<72	127.5	78	<72	127.5	75	<72
Variable										
$V_{T,E}$		+		+						+
$V_{T,I}$	+	+	+	+	+	+	+	+	+	+
$\dot{V}_E$	-	-		-			-		-	-
$\dot{V}_I$		-		-			+	+		-
MEF		-	-	-			-		-	-
MIF		+	+	+	+	+	+	+	+	+
PEF		-		-					-	-
PIF	+	+	+	+	+	+	+	+	+	+
PIA		+	+	+		+	+	+	+	+
T_T	-	-		-					-	-
T_E		-		-			-		-	-
T_I		-		-			+			-
DFRC	+	+*	+	+	+	+	+	+	+	+

*Negative phase at P_{A,O_2} = 46.5 torr.

significant. The phase of $\dot{V}_I$ and $\dot{V}_E$ oscillations was usually negative as the relative lengthening of T_T outweighed the respective increases in $V_{T,I}$ and $V_{T,E}$. MEF oscillations were also of negative phase, reflecting the phase of the prominent T_E oscillation; and MIF oscillations showed the same phase as the $V_{T,I}$ oscillations.

The phase relations of the remaining runs in experiments 409.5 and 409.6 (P_{A,O_2} > 72 torr) were consistent with the pattern presented above, though significant oscillation was not so common. There were no obvious differences in the phase patterns at rest and during exercise, through the incidence of oscillations was usually higher in the latter condition; this finding was common to the other subjects.

The consistency of the phase relations found in the experiments on the other three subjects (421, 425, 392) were less well defined (Appendix 2, Table 24, p.225). Subject 421 conformed with the phase pattern of the inspiratory primary variables and $V_{T,E}$ exhibited by subject 409. However, differences emerged in the responses of the primary expiratory variables. Oscillations in PEF were invariably positively phased, and could accompany oscillations in T_E of the same phase; however, on occasions, T_E oscillations were negatively phased and were not accompanied by an oscillation in PEF. The phase of oscillations in the derived variables were easily predictable: thus, $\dot{V}_I$ oscillations were often prominent and positively phased in runs where oscillations in both $V_{T,I}$ and T_E (and therefore T_T) were of positive phase. Again, DFRC oscillations showed a positive phase, reflecting

the greater prominence of $V_{T,I}$ oscillations over those in $V_{T,E}$. Those non-hypoxic runs in which significant oscillations occurred tended to resemble the hypoxic responses; however, they were not frequent.

The experiments on subject 425 showed a smaller number of significant alternate-breath oscillations and considerable variation in phase patterns. More often than not in hypoxia, oscillations in the same run showed the same phase, but this often differed between runs. However, consistency was present in experiment 425.2 during exercise, with oscillations in the inspiratory primary variables showing a positive phase (with the exception of T_I).

In subject 392 almost all significant oscillations in hypoxia were of positive phase, involving inspiratory variables and $V_{T,E}$. Significant responses in PEF and T_E rarely occurred. Those non-hypoxic runs having significant oscillations conformed with the hypoxic phase pattern.

Thus, in summary, there was a general tendency for the phase of oscillations in inspiratory primary variables to be positive, with the exception of T_I which rarely oscillated. Oscillations in expiratory primary variables were confined to the experiments of subjects 409 and 421, with the exception of the positively-phased $V_{T,E}$ oscillations: the phase of PEF and T_E oscillations were similar, being positive in subject 421 and negative in subject 409. The phase of oscillations in a derived variable reflected that of the more prominent of its component oscillations.

P_{A,CO_2} transient. As explained on p. 93, measurement of the true phase difference (TPD) between a periodic stimulus and its response is problematic, unless the period (P) of the signal is greater than the TPD. This problem may be overcome by employing a transient stimulus, for then the measured phase difference (MPD) equals the TPD:-

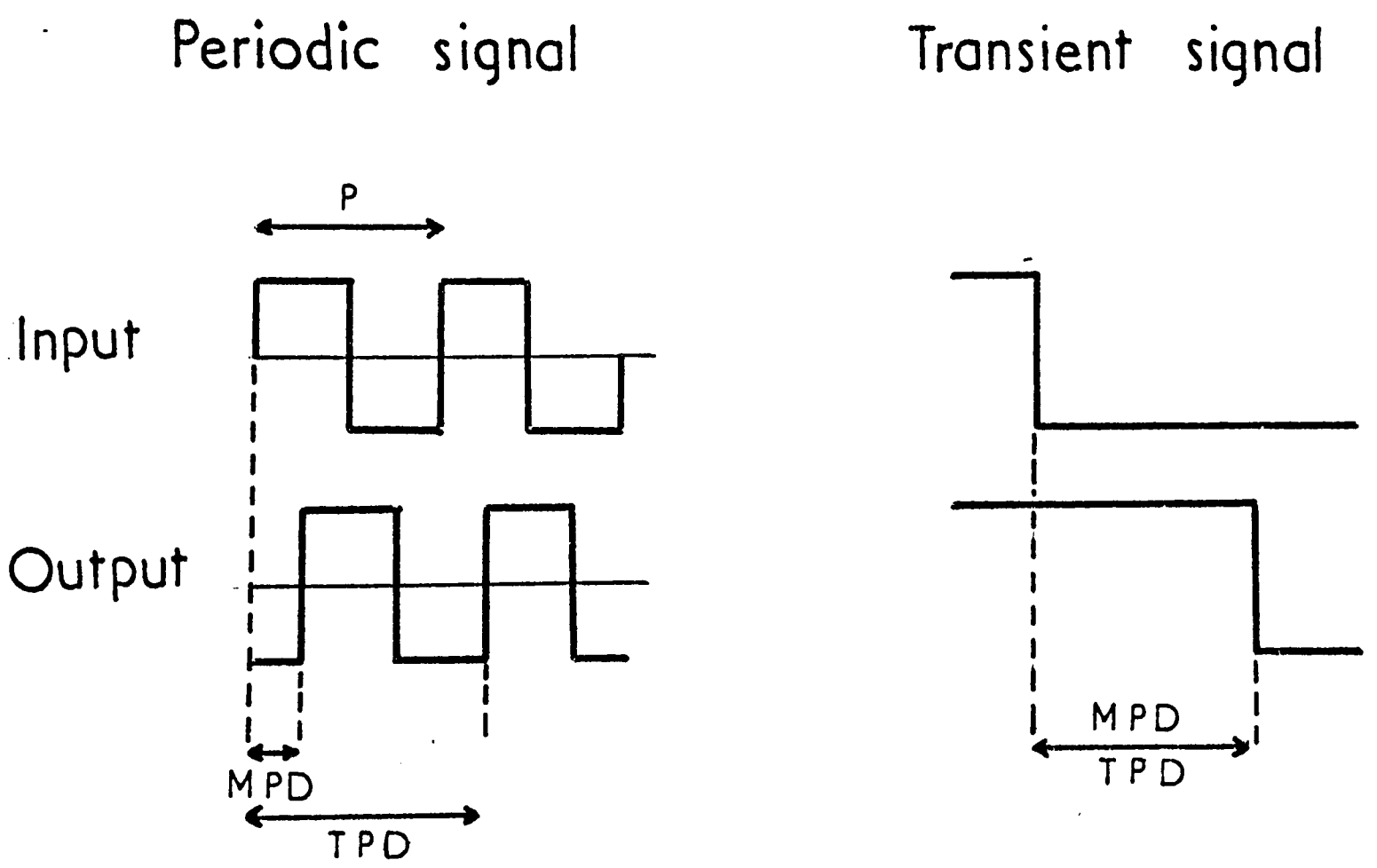
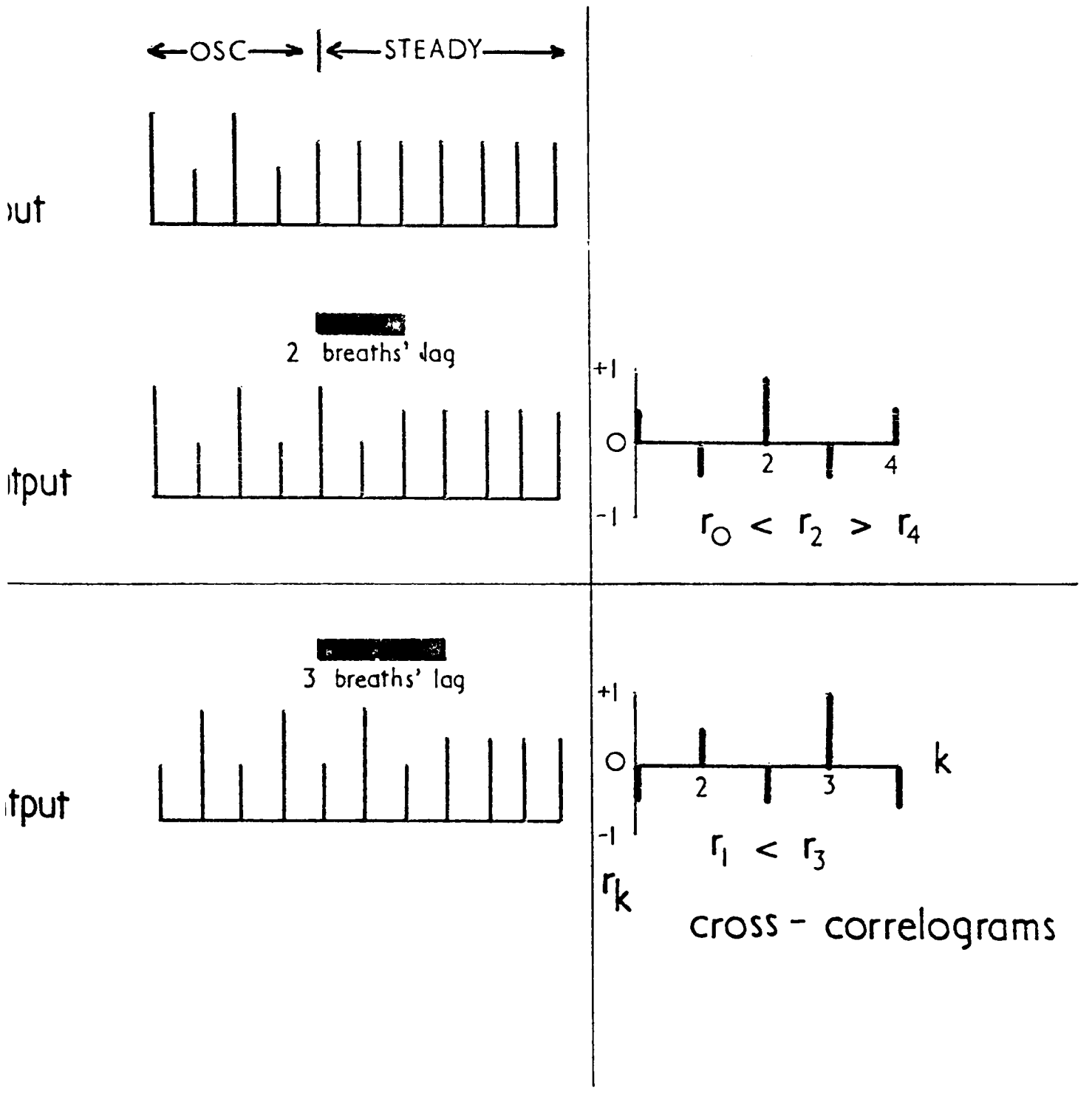


FIG. 29

Thus, the TPD of the responses induced by the P_{A,CO_2} oscillation was estimated in hypoxia by performing a cross-correlation analysis between P_{A,CO_2} and each output variable where the state of P_{A,CO_2} changed from CSC to STEADY ("off" transient) or vice-versa ("on" transient); time displacements of 0, 1, 2, 3 and 4 breaths were used. It was assumed that the TPD equalled the time displacement, k_{max}, at

.30 Diagram of two typical responses occurring at a P_{ACO_2} "off" transient, with their cross-correlograms.



which the cross-correlation coefficient, r_k, was a maximum and positive (with the exception of T_T, T_I and T_E, where the maximum r_k would be negative, these variables being inversely related to P_{A,CO_2}). The method is described in detail in the previous chapter (p.70); and an "off" transient is illustrated in Fig. 19 at "a" (p.77). Transients in which P_{A,O_2} changed by more than ± 2 torr, or in which an excessively large or small event occurred, were not analysed.

Two typical responses are shown diagrammatically in Fig. 30, with their cross-correlograms (p.70). One has a positive (2-breath) phase difference, and the other a negative (3-breath) phase difference; the correlograms are strongly periodic, as predicted (p.172), with $r_{k,max}$ occurring at k = 2 breaths and 3 breaths respectively. Almost invariably, r_k was significant for all time displacements.

In other instances, the periodicity of r_k was not marked: often, only one positive value of r_k would be significant, its time displacement being taken as the latency of the response. In other cases, again, there were no significant values of r_k, presumably indicating a lack of response to the P_{A,CO_2} signal.

Estimation of $r_{k,max}$ by the statistical method of p.72 was unsuccessful for all transients, no value of r_k being <u>significantly</u> greater than any other. However, there was often a value of r_k which was <u>numerically</u> greater than the others, and sometimes with a higher level of significance: the time displacement at which such a value occurred was taken as the latency of the response. The reasons for the lack of success of the statistical test are discussed in the next chapter (p.137).

Complete results on all transients are presented in Appendix 2, Table 34 (p.235); there are four categories comprising "on" and "off" transients at rest and in exercise. Because of the vagaries inherent in the method of latency estimation, only a rather general account of the results is presented. As only one transient was suitable for analysis in the experiments of subject 425, this subject is excluded from the account.

Fairly consistent latency patterns existed for each subject, serving to reinforce the findings reported above on the P_{A,CO_2} oscillation. There was no evidence of a difference between the latency patterns of the four categories of transient in any subject, though the small number of observations may have hindered the detection of changes in latencies.

Latencies of the inspiratory primary variables (excluding T_I) generally tended to be of 2 breaths duration; less often, latencies of 4 breaths or zero (response occurring on the same breath as the stimulus). Responses in DFRC (change in FRC) and in $V_{T,E}$ (rarely significant), as before, responded with the inspiratory variables. Responses in the expiratory primary variables, PEF and T_E, were seen consistently only in subject 409: their latencies were 1 breath shorter than the predominant phase of the inspiratory variables: i.e. 1 or 3 breaths.

The latency of the response in a derived variable was governed by the more prominent of the responses elicited in its components. In subject 409, T_E (and therefore T_T) was especially prominent in this respect, the phase of the derived variables $\dot{V}_I$, $\dot{V}_E$ and MEF conforming to that of T_E.

The effects of graded hypoxia on the size of alternate-breath responses in 13 output variables, at rest and in exercise

The hypothesis of a multiplicative interaction of hypoxia and the P_{A,CO_2} oscillation on respiration was reinvestigated more extensively (p.79 ; p. 99). At rest, there was already some evidence from the experiments of Series One to support this hypothesis: and the results reported so far for Series Two at rest and in exercise support the general notion of a hypoxic dependency of the oscillating responses, with exercise further increasing their incidence.

A linear regression analysis of the oscillating response on hypoxia was conducted for each variable, at rest and in exercise, in each experiment. Three forms of oscillating response were used: (i) the alternate-breath oscillation, for making comparisons on the same variable (e.g. between rest and exercise); (ii) [illegible], for making comparisons between different variables; and (iii) the normalised alternate-breath oscillation, for studying whether the size of oscillations increased with hypoxia more than did the run-mean. The independent variable, hypoxia, was evaluated as $10^3/(P_{A,O_2} - C)$ (Cunningham, 1974b); the value of the constant, C, was determined for each subject (p.72).

Variation in the number and the size of the individual observations which constituted each oscillating response was taken account of by using a regression analysis with replication in the dependent variable (Sokahl & Rohlf, p.428). Thus, for each level of hypoxia, there would be, in effect, many observations of the dependent variable, rather than just one.

The significance of a regression coefficient, b, differing from zero was estimated by a one-tailed variance ratio test (p.65), according to the null hypothesis that the component of the variance due to the regression was no greater than the error component (Sokahl & Rohlf, p.423). The regression coefficient was used as an index of the multiplication occurring between hypoxia and the P_{A,CO_2} oscillation; comparisons between pairs of coefficients, and therefore between degrees of multiplication, were performed by an analysis of covariance (Sokahl & Rohlf, p.448).

Regression analysis: the alternate-breath oscillation. In contrast with the practice of Series One, the amplitude and phase of the alternate-breath oscillations were not dissociated here: this facilitated the interpretation of responses in the derived variables (p.116: experiment 409.6, $\dot{V}_I$ in exercise).

There was no evidence for the existence of a threshold to the generation of an alternate-breath oscillation in the P_{A,O_2} range of 100-200 torr for any variable in any experiment, at rest or in exercise. Pairs of regression lines obtained from all the points, irrespective of P_{A,O_2}, and from points having a P_{A,O_2} of 100 torr or less, had been tested for concurrency: an analysis of covariance had been used to test the null hypothesis that the two regression coefficients of a pair were not different, and in no case was a significant difference obtained.

A study was next made of the occurrence of significant regression coefficients (b) during rest and exercise (Table 19). In all cases but one, values of b were significant, indicating an increase of oscillation amplitude with increasing hypoxia. The exception (experiment 409.6, $\dot{V}_I$ in exercise) had a negative b, with the phase of oscillations changing from positive to negative as hypoxia increased: this reflected a corresponding increase in the prominence of the negatively-phased T_T oscillations over the positively-phased $V_{T,I}$ oscillations (Fig. 32).

In the pooled experiments at rest, a total of 11 regression coefficients out of 117 (13 variables x 9 experiments) or 9.4% differed from zero, which was a significant incidence ($0.01 < p < 0.05$) by the Chi-squared test (p. 65). The regression coefficients were distributed fairly evenly between the group of variables: MEF, MIF, PEF, PIF, PIA, T_T and T_E, with a maximum of 3 occurring in PIF. During exercise the incidence of significant regression coefficients rose to 24 out of 117, or 20.5% ($p < 0.001$). These were distributed over a wider range of variables than at rest, a maximum of 4 occurring in MEF and in PEF, and 3 in PIF. The intercepts of the regression lines on the hypoxia axis were confined to the euoxic-hyperoxic range of P_{A,O_2}, with the exception of the $\dot{V}_I$ run described above.

Of the 33 comparisons made between pairs of regression coefficients at rest and in exercise, where one or both differed from zero, the exercise coefficient was greater than the corresponding coefficient at rest (multiplicative interaction) in 12 instances, or 36.4%: $p < 0.001$

by the Chi-squared test. Only 1 comparison showed the converse result, the remaining 19 not being significant.

The effects of exercise on the hypoxia intercept could only be assessed in the 3 cases where the regression coefficients at rest and in exercise differed from zero. In 2 (experiment 409.5: MEF and PIF), the hypoxia intercept was reduced (to a higher P_{A,O_2}) with no accompanying increase in slope, representing a resetting upwards of the oscillation-hypoxia relation (or an additive interaction). In the third case (experiment 421.4, PIF), the hypoxia intercept was little affected, but the slope was increased (multiplication).

The individual experiments showed considerable variation in the occurrence of significant regression coefficients between rest and exercise. From Table 19 it was evident that most of the significant regression coefficients occurred in experiments 409.5, 409.6 and 423.2: Figs. 31-33 show the relations between the oscillation and hypoxia for each variable, at rest and in exercise.

In the STEADY runs, only 2 regression coefficients out of 117 were significant:-

	b units x 10^2/torr^{-1}	hypoxia intercept torr^{-1}
409.6: Rest, $V_{T,I}$	0.04$^+$	-20.5
421.4: Rest, DFRC	0.04$^+$	12.3

In both cases, the size of the oscillation that would occur at P_{A,O_2} = 50 torr (by prediction from the regression equations) was unlikely to be perceptible. Thus, both relationships were discounted as being physiologically significant.

Table 19: Linear regression of the alternate-breath oscillation on hypoxia, at rest or in exercise (significant results only).

	Rest		Exercise		
	Coefficient (units x 10^2/ $torr^{-1}$)	Hypoxia intercept ($torr^{-1}$)	Coefficient (units x 10^2/ $torr^{-1}$)	Hypoxia intercept ($torr^{-1}$)	Rest v. exercise comparison of coefficients
409.5					
MEF	-26.1 +	8.9	-25.0 +	-3.4	N.S.
MIF	9.3 +	-9.8	N.S.		N.S.
PEF	-20.3 +	15.0	-22.1 +	-6.4	N.S.
PIF	22.6 +	-2.7	N.S.		R > E +
PIA	4.3 +	5.2	N.S.		N.S.
T_T	-0.6 +	0.1	N.S.		N.S.
T_E	-0.8 ++	9.9	N.S.		N.S.
409.6					
$\dot{V}_E$	N.S.		-14.8 +	3.1	E > R +
$\dot{V}_I$	N.S.		-14.9 +++	29.9	E > R ++
MEF	N.S.		-59.0 +	7.2	E > R ++
PEF	N.S.		-59.9 +	9.5	E > R ++
PIF	18.6 +++	-13.9	N.S.		N.S.
PIA	1.4 +	7.9	N.S.		N.S.
T_T	N.S.		-0.6 +	5.2	E > R +
T_E	N.S.		-0.6 +	8.3	E > R ++
421.2					
$\dot{V}_I$	N.S.		9.9 ++	-0.2	N.S.
421.4					
$V_{T,E}$	N.S.		0.4 +	14.7	E > R +
MIF	19.1 ++	10.1	N.S.		N.S.
PIF	19.7 +++	7.9	34.8 +	4.5	N.S.
425.2					
$V_{T,E}$	N.S.		-0.2 +	0.5	E > R +
$V_{T,I}$	N.S.		0.5 +	-8.2	E > R +
MIF	N.S.		23.0 +	5.0	N.S.
PEF	N.S.		25.1 +	19.5	N.S.
PIF	N.S.		42.0 ++	9.6	E > R +
PIA	N.S.		3.6 ++	20.4	E > R ++
DFRC	N.S.		0.6 +	-0.2	E > R ++
425.5					
MEF	N.S.		15.7 +	13.8	N.S.

Table 19 continued:

	Rest		Exercise		Rest - ex. comparison of b
	b (... x 10⁻⁶ ...)	h' ($torr^{-1}$)	b (... x 10⁻⁶ ...)	h' ($torr^{-1}$)	
392.13					
$\dot{V}_E$	N.S.		16.6 +	12.2	N.S.
PEF	N.S.		27.3 +	12.1	N.S.
PIF	N.S.		27.9 +	11.3	N.S.
PIA	N.S.		2.9 +	5.2	N.S.
392.15					
MEF	N.S.		12.0 +	-7.5	N.S.

The distribution of significant regression coefficients between variables.

	Rest	Exercise
$V_{T,E}$		2
$V_{T,I}$		1
$\dot{V}_E$		2
$\dot{V}_I$		2
MEF	1	4
MIF	2	1
PEF	1	4
PIF	3	3
PIA	2	2
T_T	1	1
T_E	1	1
T_I		
DFRC		1
Total	11/117	24/117

The units of the different variables are listed in Appendix 2, Table 24 (p.225).

Figs. 31-33

The relations between the alternate-breath oscillation and hypoxia for each variable at rest (filled circles) and in exercise (open circles). Significant regression lines are present as solid lines (rest) and broken lines (exercise). A solid triangle and a broken horizontal line indicate zero amplitude of oscillation.

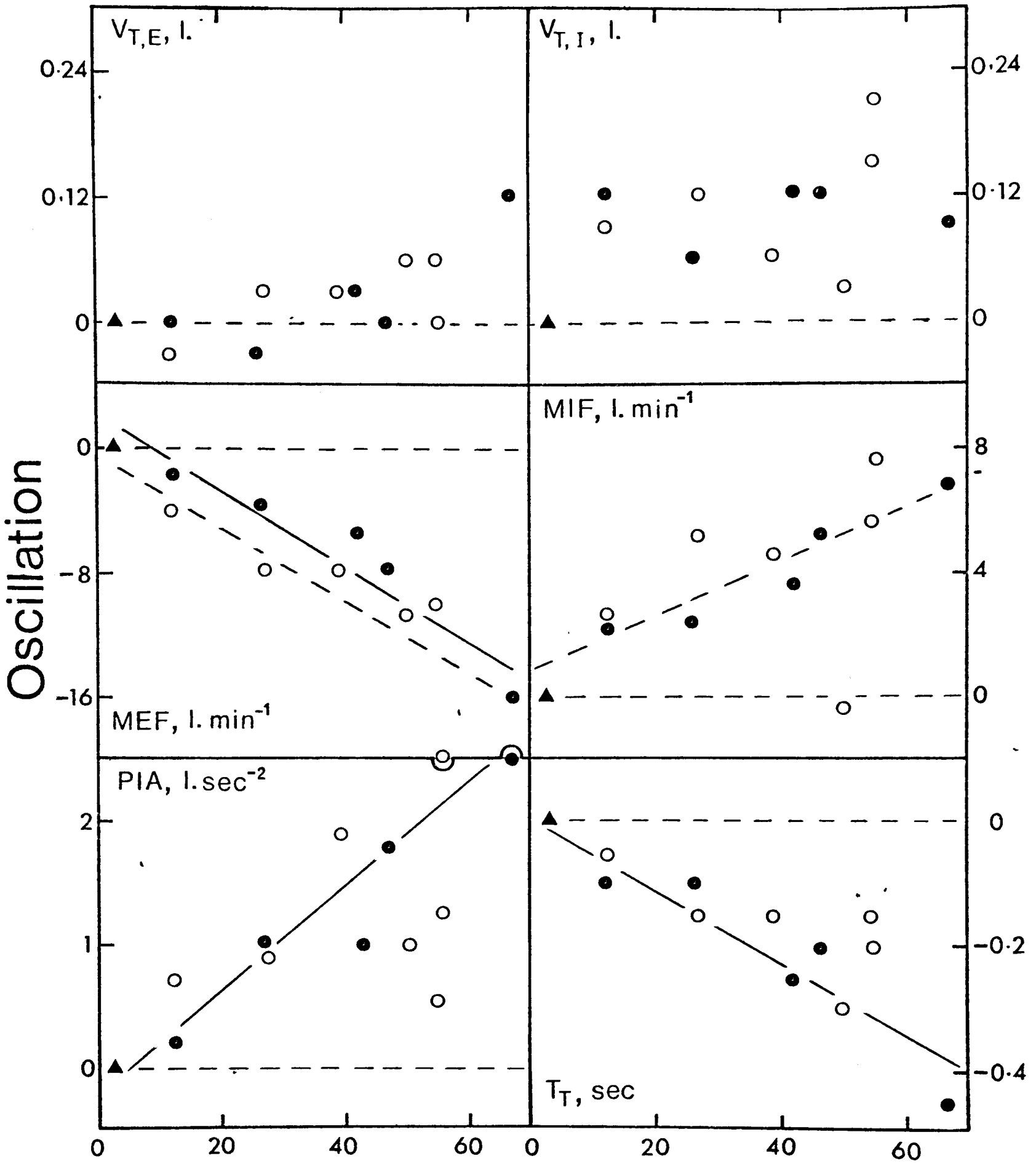
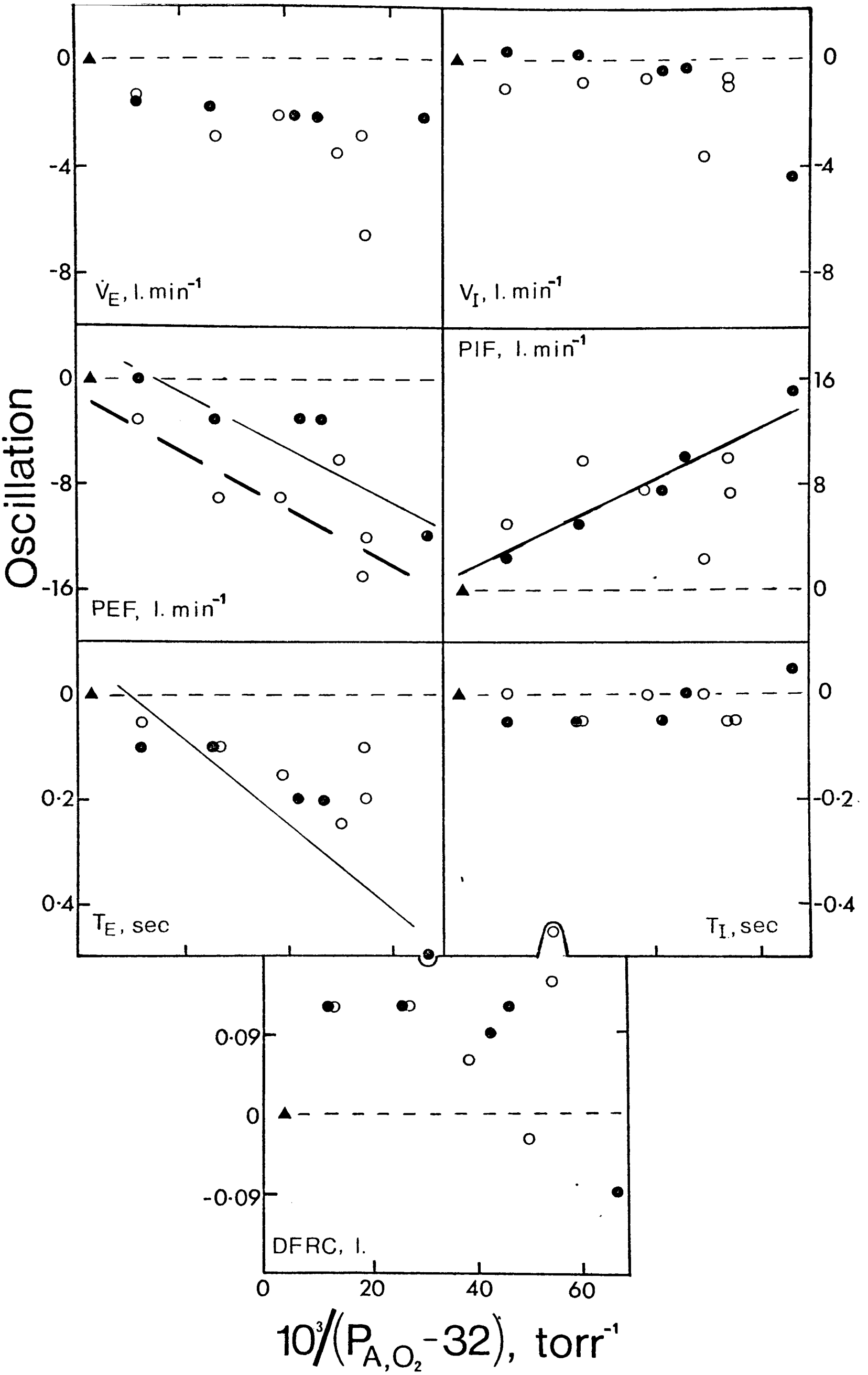

$V_{T,E}$, l.
$V_{T,I}$, l.
0·24
0·12
0
MIF, l. min^{-1}
8
4
MEF, l. min^{-1}
−8
−16
PIA, l. sec^{-2}
2
1
−0·2
−0·4
T_T, sec
Oscillation
0
20
40
60
$10^3/(P_{A,O_2}-32)$, torr

Fig.31 409,5


Oscillation
0
-4
-8
$\dot{V}_E$, l.min^{-1}
V_I, l.min^{-1}
PIF, l.min^{-1}
0
-8
-16
16
8
PEF, l.min^{-1}
0
0·2
0·4
T_E, sec
T_I, sec
-0·2
-0·4
0·09
0
-0·09
DFRC, l.
0
20
40
60
$10^3/(P_{A,O_2}-32)$, torr^{-1}

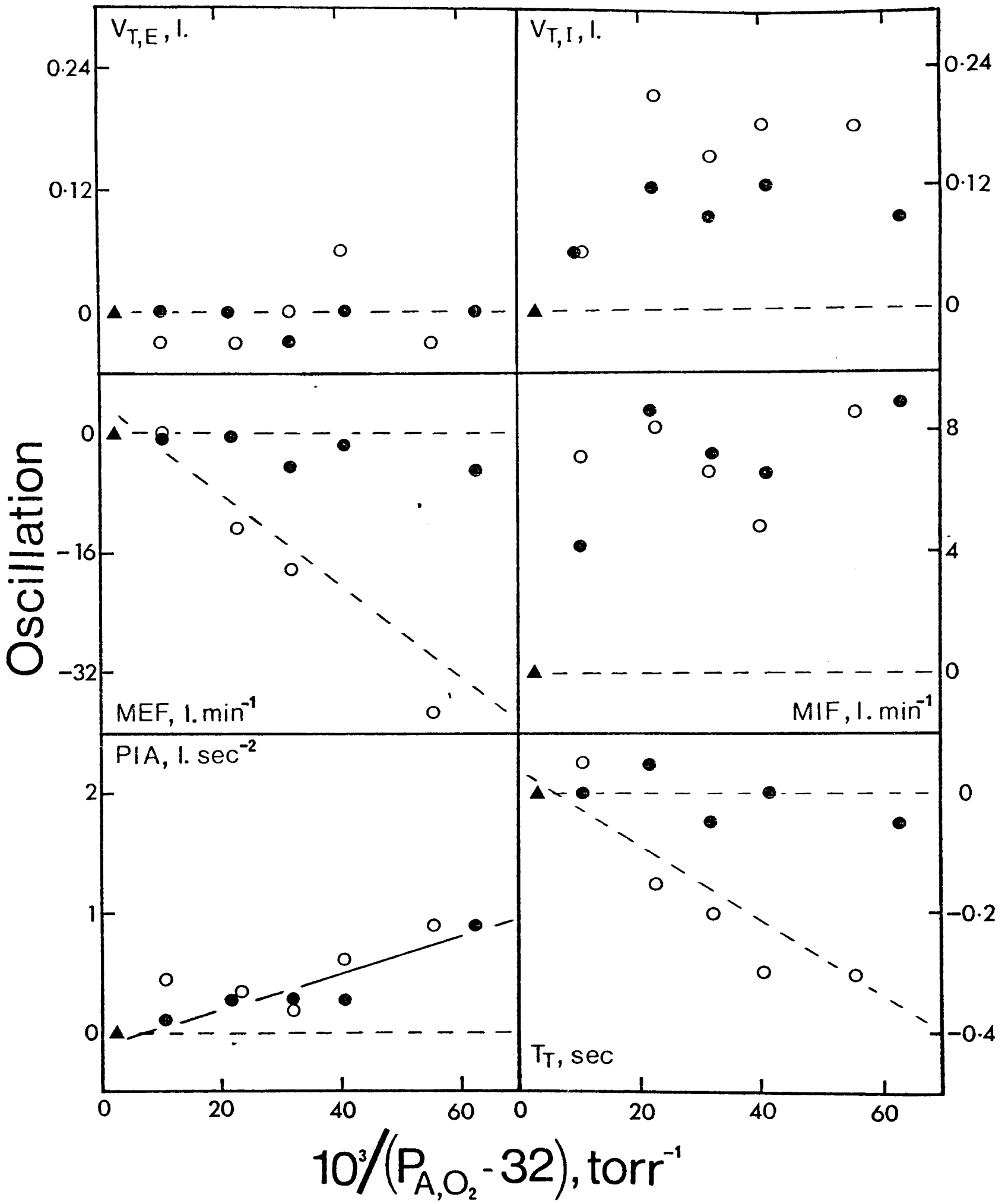
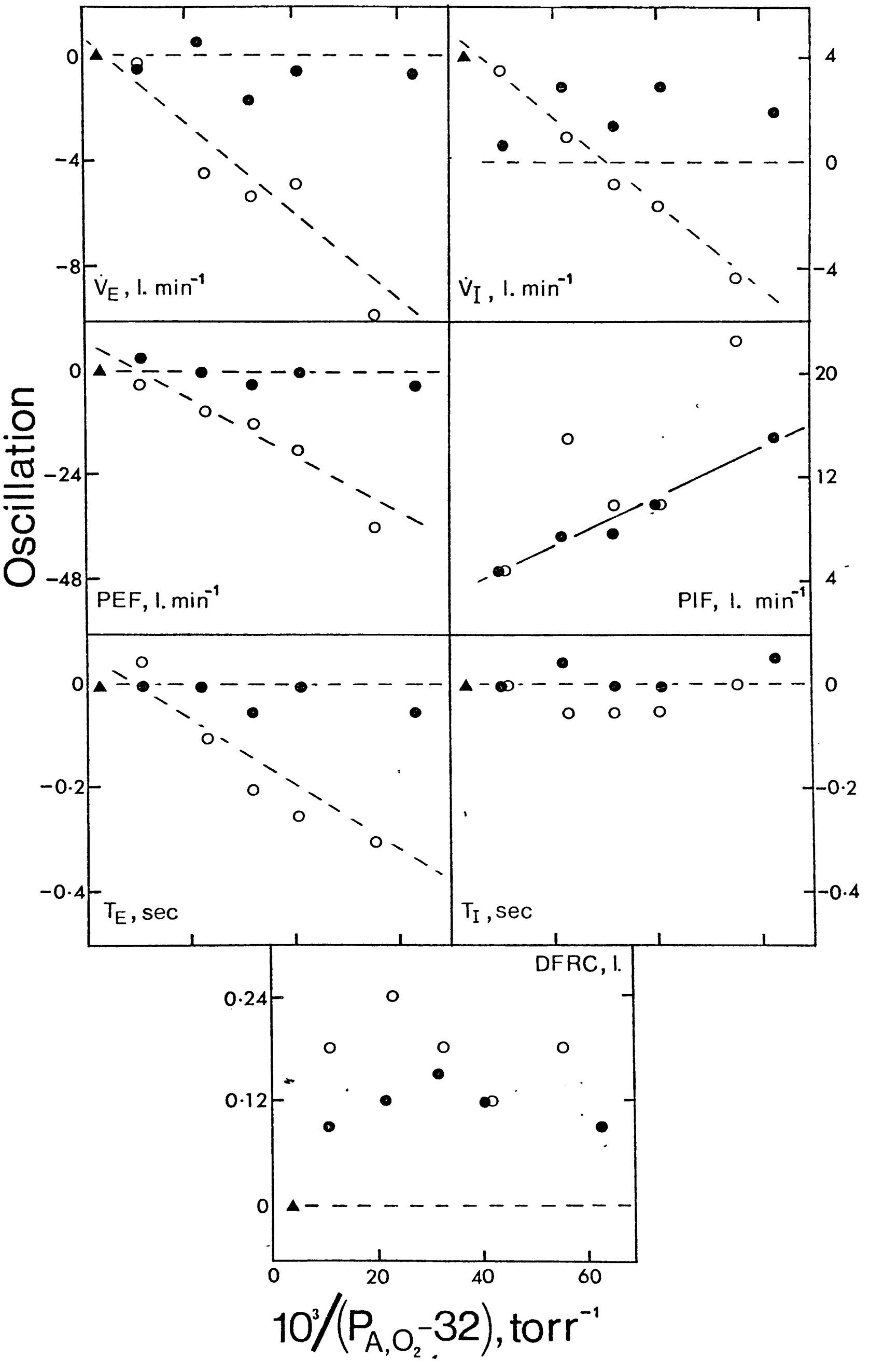

Oscillation
$V_{T,E}$, l.
$V_{T,I}$, l.
0·24
0·12
0
0·24
0·12
0
0
−16
−32
8
4
0
MEF, l. min^{-1}
MIF, l. min^{-1}
PIA, l. sec^{-2}
2
1
0
0
−0·2
−0·4
T_T, sec
0
20
40
60
0
20
40
60
$10^3/(P_{A,O_2}-32)$, torr^{-1}

Fig.32 409,6


Oscillation
0
-4
-8
$\dot{V}_E$, l. min^{-1}
4
0
-4
$\dot{V}_I$, l. min^{-1}
0
-24
-48
PEF, l. min^{-1}
20
12
4
PIF, l. min^{-1}
0
-0·2
-0·4
T_E, sec
0
-0·2
-0·4
T_I, sec
DFRC, l.
0·24
0·12
0
0
20
40
60
$10^3/(P_{A,O_2}-32)$, torr^{-1}

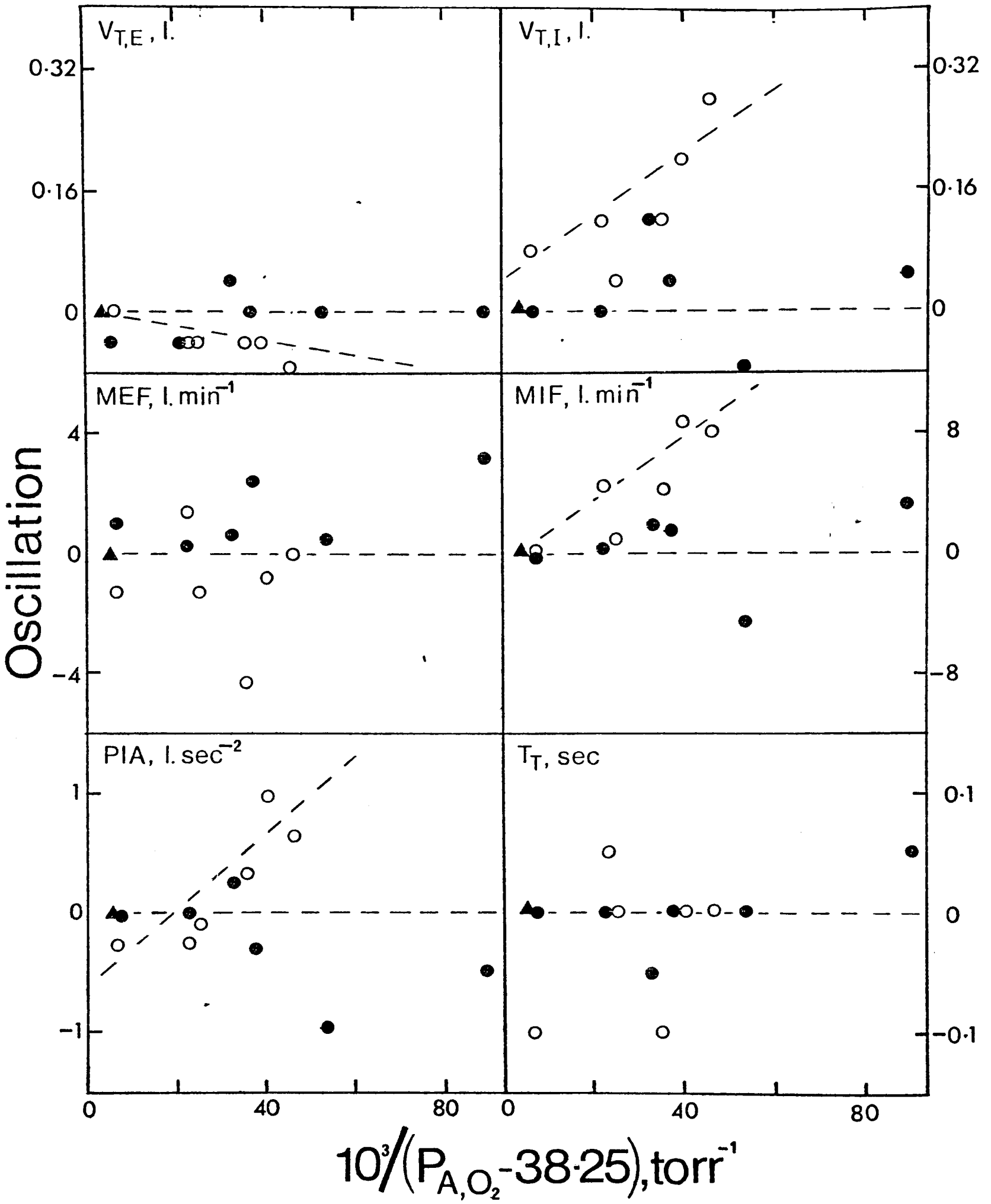
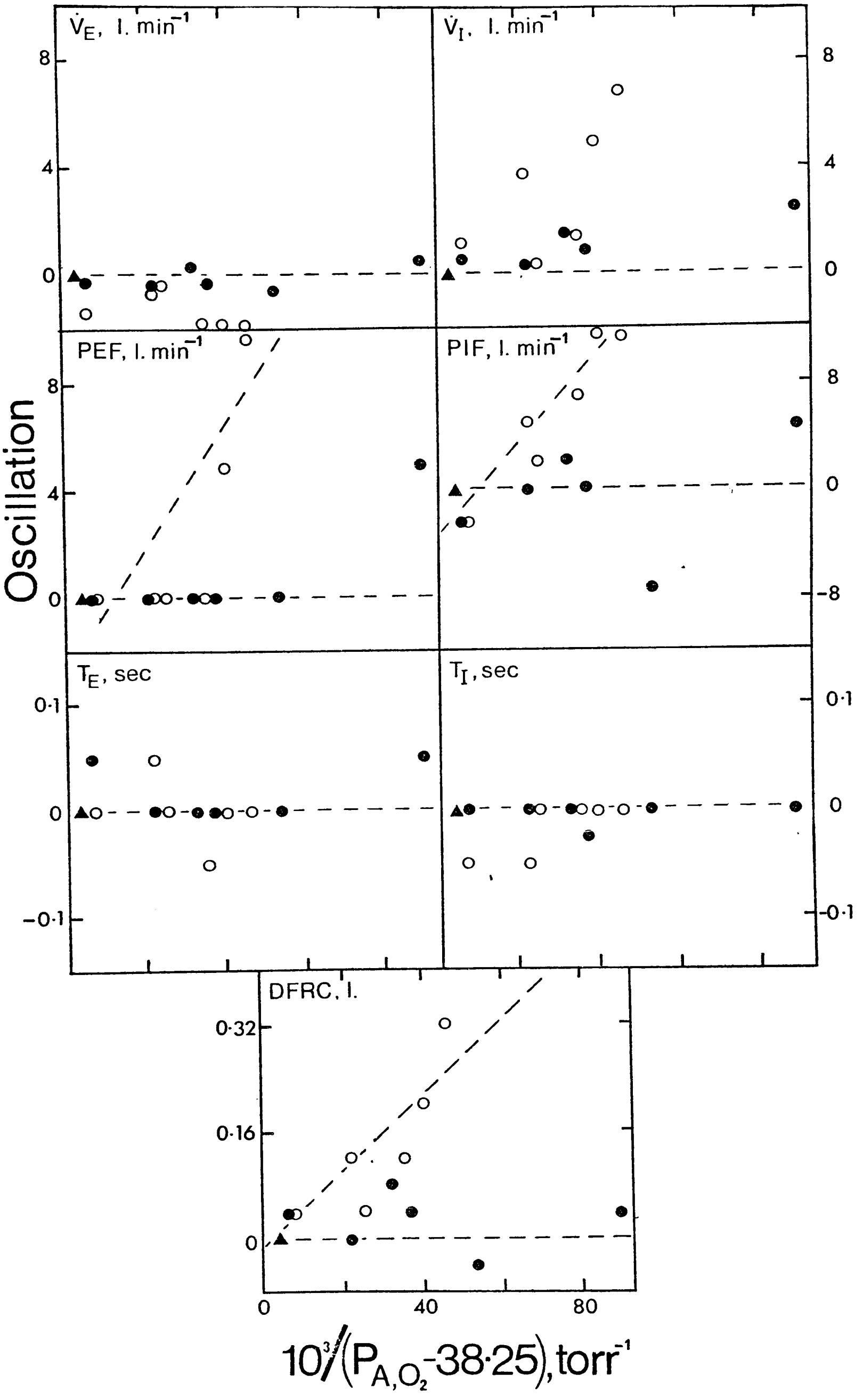

$V_{T,E}$, l.
$V_{T,I}$, l.
MEF, l.min^{-1}
MIF, l.min^{-1}
PIA, l.sec^{-2}
T_T, sec
Oscillation
0·32
0·16
0
4
8
−4
−8
1
−1
0·1
−0·1
0
40
80
$10^3/(P_{A,O_2}-38{\cdot}25)$, torr^{-1}

Fig.33 425,2


$\dot{V}_E$, l. min^{-1}
$\dot{V}_I$, l. min^{-1}
PEF, l. min^{-1}
PIF, l. min^{-1}
T_E, sec
T_I, sec
DFRC, l.
Oscillation
8
4
0
-8
0·1
-0·1
0·32
0·16
40
80
$10^3/(P_{A,O_2}-38{\cdot}25)$, torr^{-1}

Regression analysis: ZD. The regression coefficient of ZD on hypoxia was used as an index of the relative degree of multiplicative interaction of hypoxia and the P_{A,CO_2} oscillation occurring in the different variables. For each experiment the significant regression slopes at rest and in exercise were ordered by size, and are presented in Table 20. The complete results are found in Appendix 2, Table 35 (p.238), and from these the following conclusions were drawn.

Replacement of the alternate-breath oscillation by ZD reduced the incidence of significant regression coefficients, as was found for the occurrence of significant oscillating responses (p.101): at rest 8.5% of the regressions were significant (an insignificant incidence by the Chi-squared test), and in exercise, 13.7% were significant (a significant incidence, $p < 0.001$). The hypoxia intercepts tended to occur at a lower P_{A,O_2} for ZD. In some experiments, the identity of the variables having significant regressions was occasionally altered when ZD was used.

It is evident from Table 20 that several experiments had no significant regressions (experiment 425.5, Fig. 36) while others had very few. Only the experiments on subject 409 had a reasonable occurrence of significant regression coefficients, the larger values being consistently prominent in T_E at rest and in exercise (Figs. 34 & 35). The involvement of T_T and MEF was presumably a reflection of the role of T_E. All the variables listed for 409 were also rather prominent in the incidence of their oscillating responses, both for the alternate-breath oscillation and ZD (Fig. 13 & 14, p.102).

Table 20: The regression coefficients of ZD on hypoxia, ordered by size (largest three only).

Experiment	Rest	Exercise
409.5	T_E > PIA > MEF	T_T > T_E > MEF
409.6	T_E > MIF & PIF	T_E > MEF & T_T
421.2	None	None
421.4	None	MIF only
421.6	T_E only	$V_{T,E}$ > PIF > $V_{T,I}$
425.2	None	DFRC > $V_{T,I}$
425.5	None	None
392.13	None	None
392.15	None	None

Figs. 34-36

The relations between ZD and hypoxia for each variable at rest (filled circles) and in exercise (open circles). Significant regression lines are present as solid lines (rest) and broken lines (exercise). A solid triangle and a broken horizontal line indicate ZD = 0.

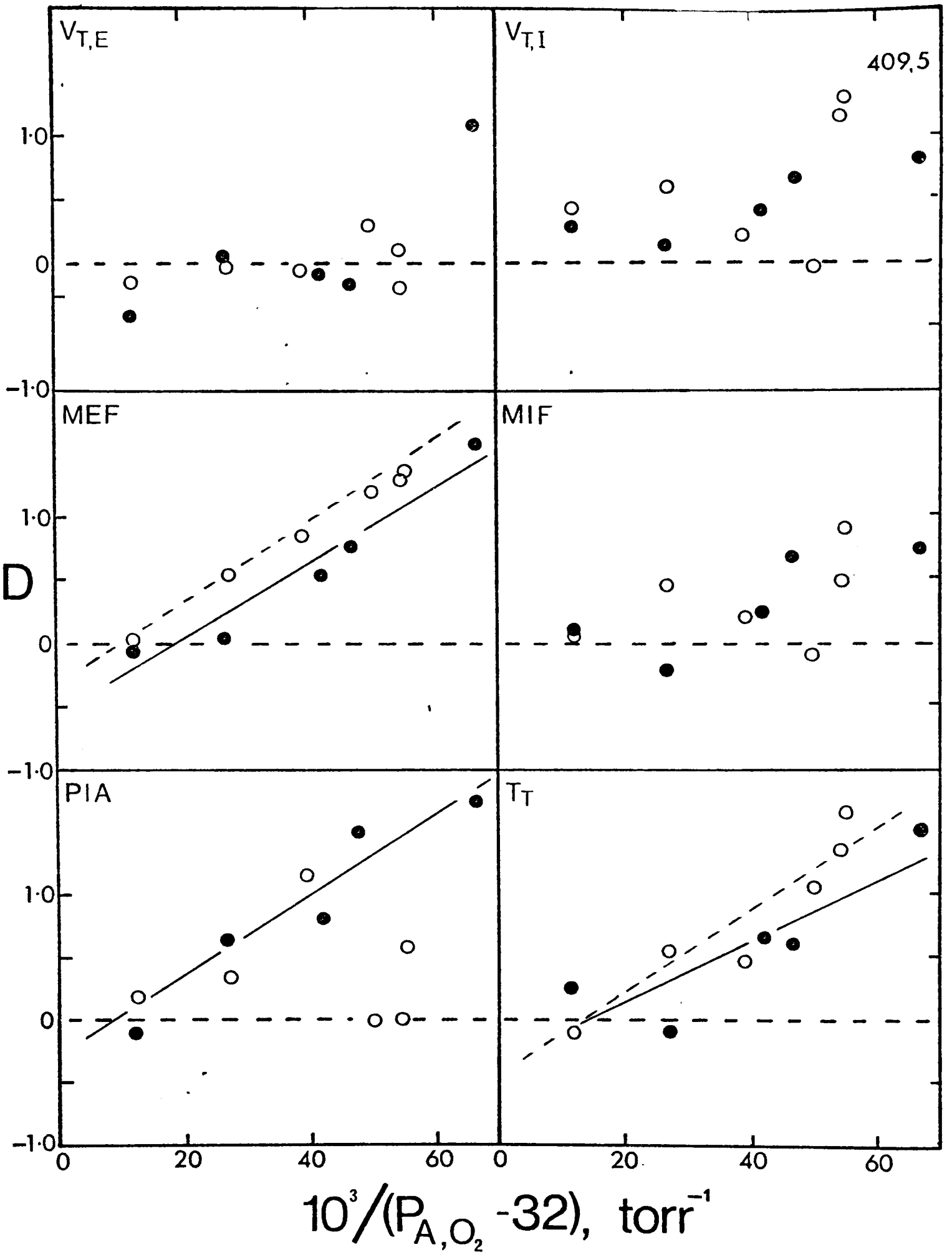
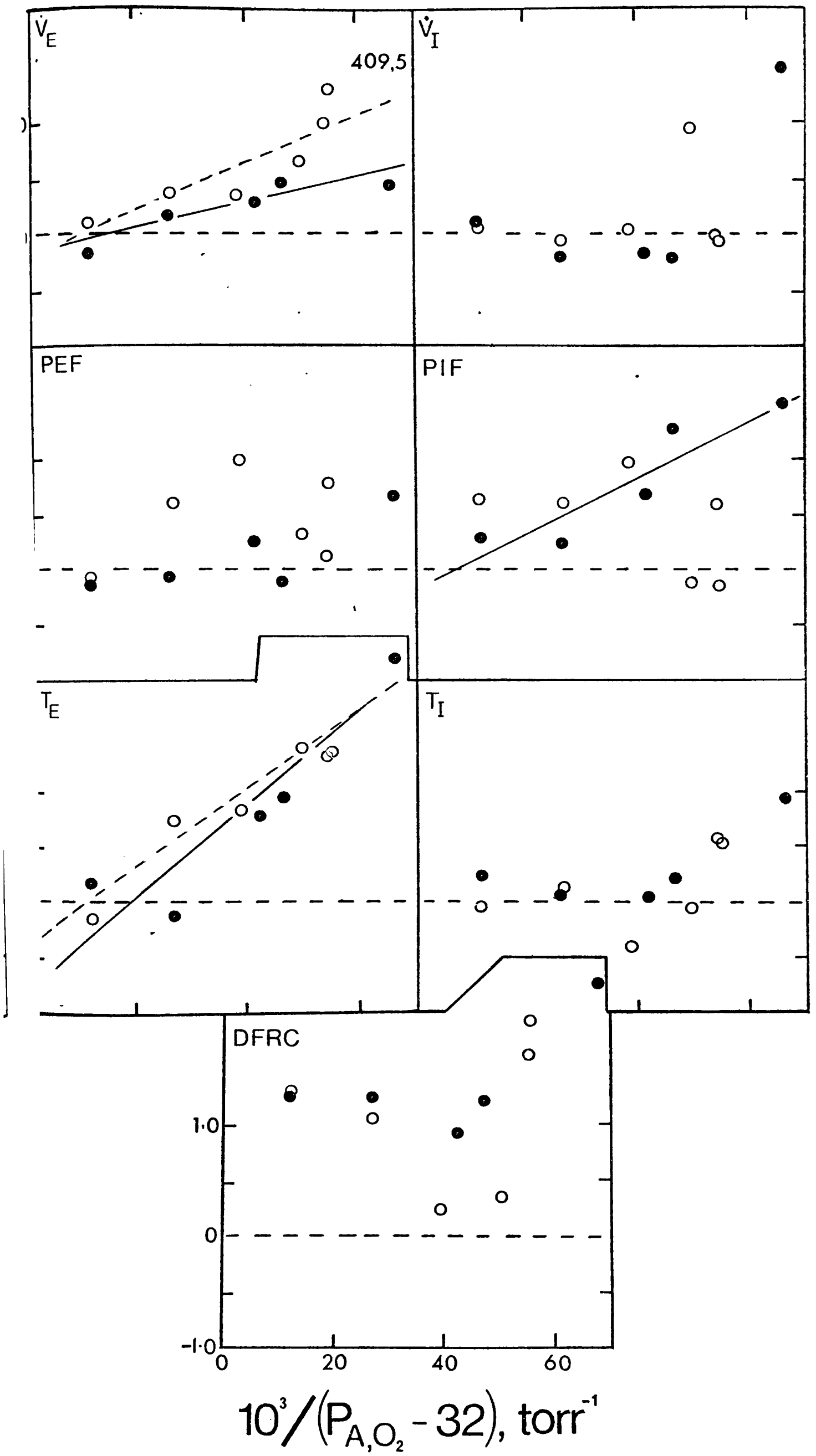


Fig.34 409,5


$\dot{V}_E$
409,5
$\dot{V}_I$
PEF
PIF
T_E
T_I
DFRC
1·0
0
-1·0
0
20
40
60
$10^3/(P_{A,O_2} - 32)$, torr^{-1}

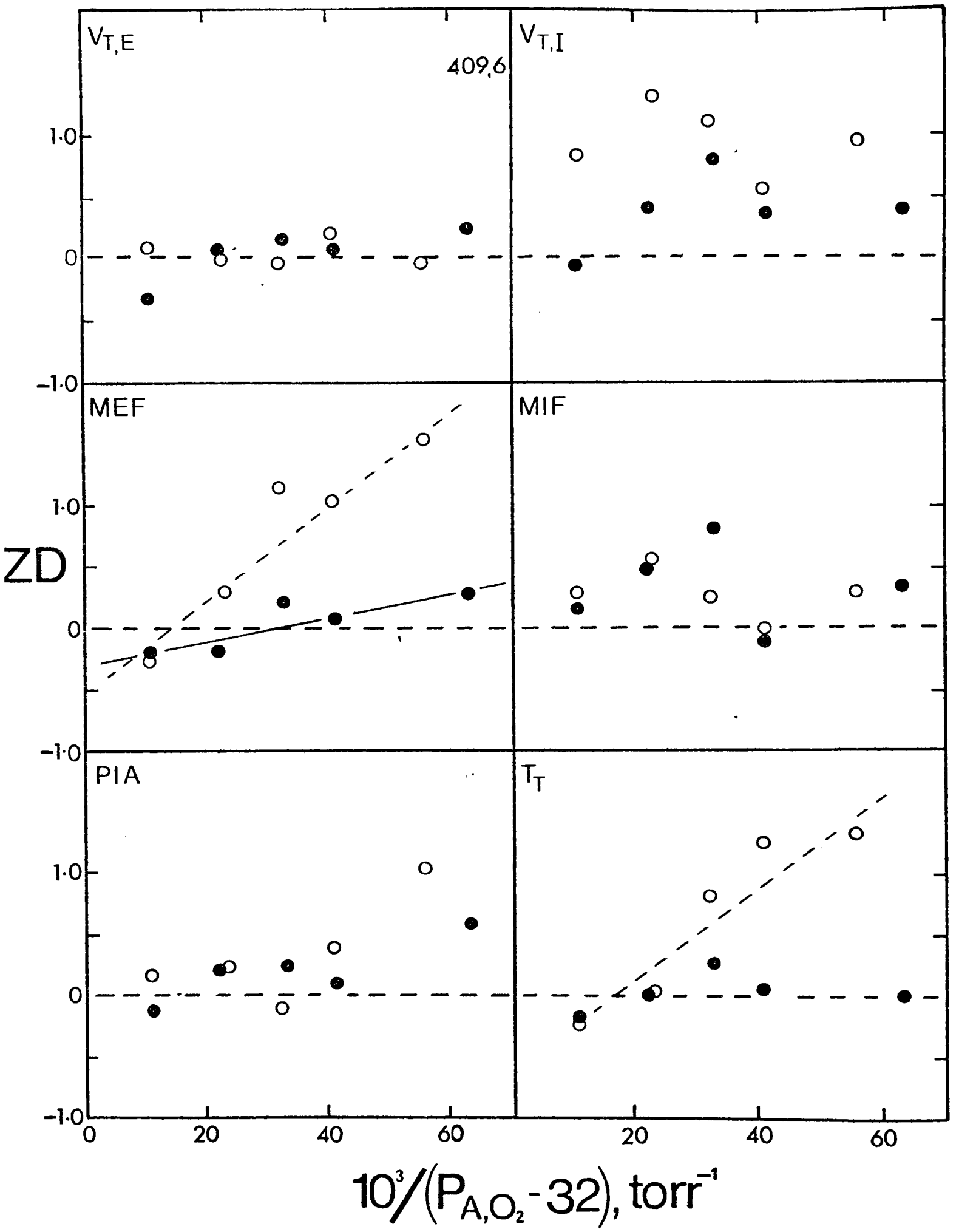
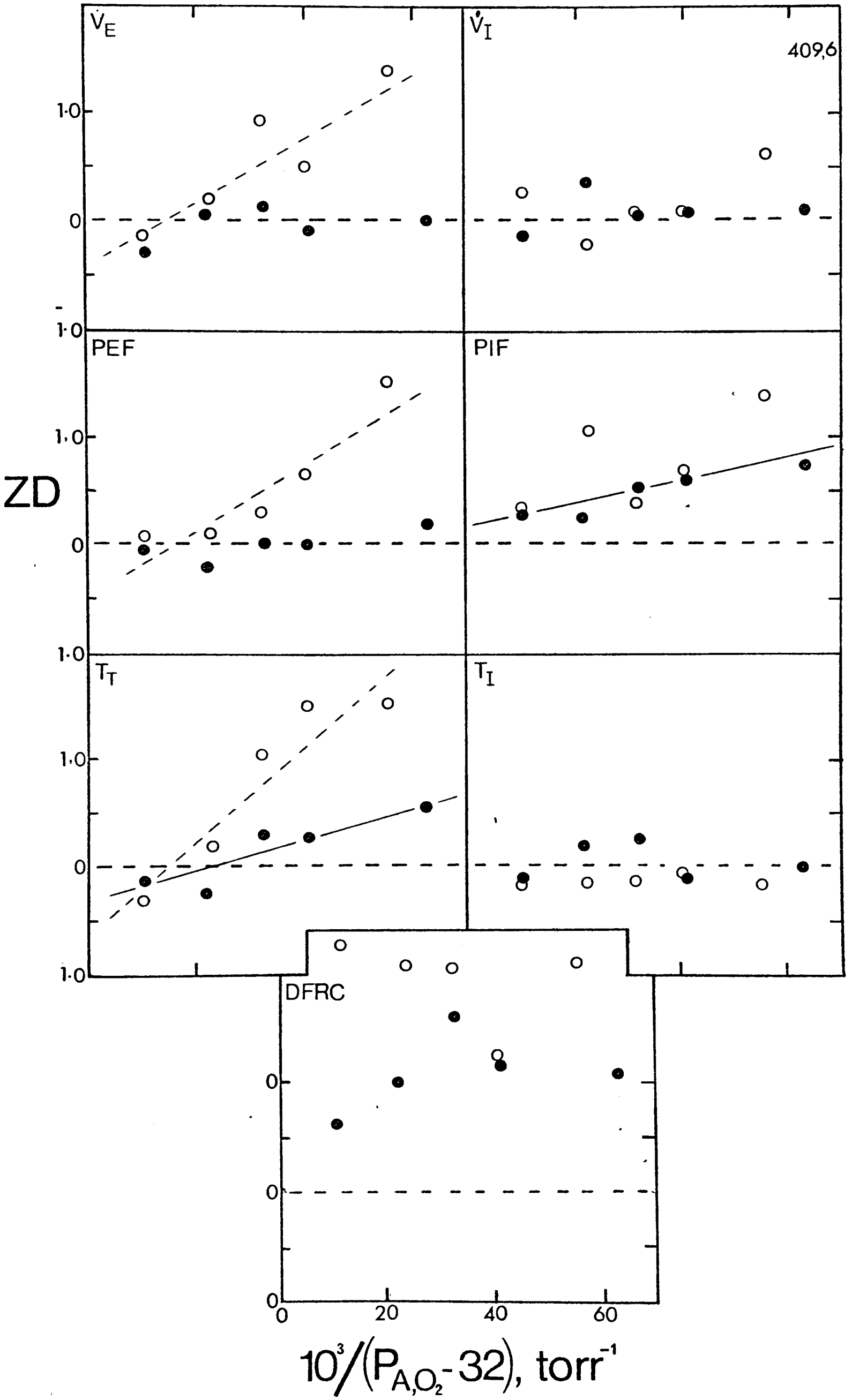


Fig.35 409,6


$\dot{V}_E$
$\dot{V}_I$
409,6
PEF
PIF
T_T
T_I
DFRC
ZD
1·0
0
20
40
60
$10^3/(P_{A,O_2}-32)$, torr^{-1}

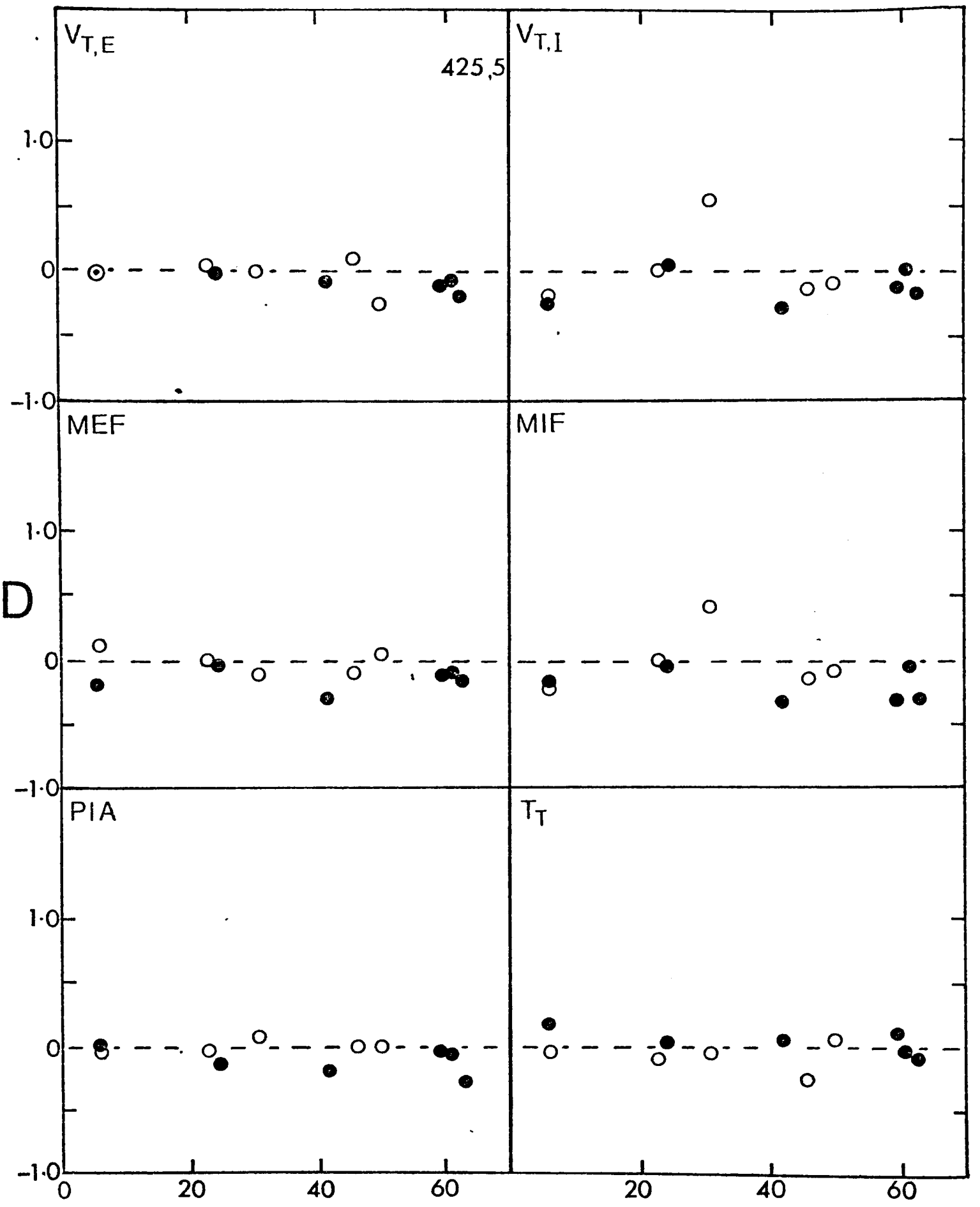
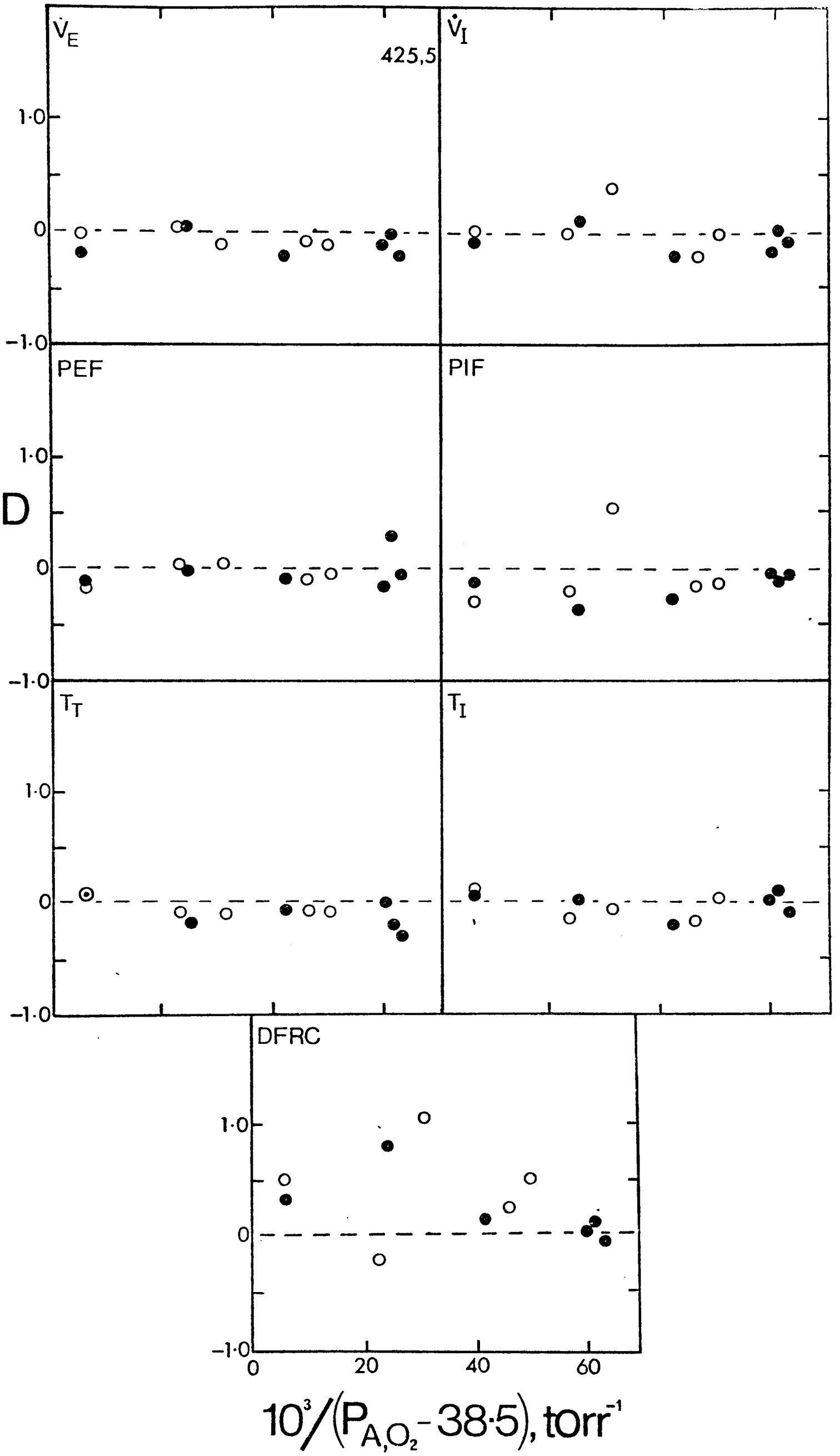

$V_{T,E}$
425,5
$V_{T,I}$
MEF
MIF
PIA
T_T
1·0
0
-1·0
ZD
0
20
40
60
$10^3/(P_{A,O_2}-38·5)$, $torr^{-1}$

Fig.36 425,5


$\dot{V}_E$
425,5
$\dot{V}_I$
PEF
PIF
T_T
T_I
DFRC
1·0
0
-1·0
ZD
0
20
40
60
$10^3/(P_{A,O_2}-38{\cdot}5)$, torr^{-1}

The original intention of using the ΔD regression coefficient for comparative purposes was not fulfilled in the remaining experiments, probably because ΔD was generally a less sensitive index of oscillation than the alternate-breath oscillation.

Regression analysis: normalised alternate-breath oscillation. The results of the regression analysis are presented in Appendix 2, Table 36 (p.).

The incidence and distribution of significant regression coefficients were similar to those of the absolute alternate-breath oscillation (cf. Table 19, p.116). The possible significance of this observation is discussed on p.151.

The effects of an alternate-breath P_{A,CO_2} oscillation on mean ventilation

In 1965, Cunningham et al. concluded that an alternate-breath P_{A,CO_2} oscillation imposed in hypoxia (P_{A,O_2} about 60 torr) had no effect on mean expired ventilation in resting man. This finding was examined in the experiments of Series Two during moderate muscular exercise in hypoxia (P_{A,O_2} < 72 torr): p.74.

A method of paired comparisons was used to estimate the significance of the mean difference in mean $\dot{V}_E$ (mean $\Delta\dot{V}_E$) between paired OSC and STEADY runs in each experiment, at rest and in exercise (the runs were paired

according to P_{A,O_2}). The null hypothesis stating that mean $\Delta\dot{V}_E$ would not differ from zero was tested with a two-tailed t-test (p.65).

Prior to making comparisons of ventilation, any difference in mean P_{A,CO_2} between each OSC and STEADY run was converted into an equivalent ventilation term by means of the $\dot{V}_E$, P_{A,CO_2}, P_{A,O_2} relations of the experiment in question (p.72). This term was then used to correct the mean ventilations to isocapnic conditions. The results are presented in Table 21.

None of the mean $\Delta\dot{V}_E$ values differed from zero at rest. In exercise, one value was significant (experiment 392.15) having a mean $\Delta\dot{V}_E$ of -3.83 $l.min^{-1}$ ($0.01 < p < 0.05$). This represented a <u>negative reflex rectification</u> of the alternate-breath P_{A,CO_2} oscillation. It is possible that the estimation of significance levels for mean $\Delta\dot{V}_E$ was impeded in this study by the small number of observations in each experiment (maximum = 4). With a larger number of observations in each experiment, a somewhat different result might have been obtained. However, the series of experiments was not designed specifically to test this point.

In summary, the conclusions of Cunningham et al.,(1965) were confirmed at rest, and extended to the exercising state, within the limits of the experimental design.

Table 21: A comparison of mean $\dot{V}_E$ in paired OSC and STEADY runs, at rest and in exercise.

	Mean $\Delta\bar{\dot{V}}_E$, ($l.min^{-1}$)	
Experiment	Rest	Exercise
409.5	0.13	-0.38
409.6	1.76	3.83
421.2	3.17	3.99
421.4	0.73	-4.66
421.6	4.45	0.28
425.2	-1.84	1.98
425.5	3.15	-7.64
392.13	3.93	-0.22
392.15	-0.90	-3.83+

Summary

(i) The effects of graded hypoxia (P_{A,O_2} range: 200 to 45 torr) on the responses elicited by an alternate-breath P_{A,CO_2} oscillation were investigated in several inspiratory and expiratory variables, at rest and in moderate rhythmic exercise.

(ii) In response to the P_{A,CO_2} oscillation, significant oscillating responses were confined almost exclusively to hypoxia (P_{A,O_2} < 72 torr). The incidence of these in the pooled runs for all variables was 49.2% at rest, rising to 58.5% in exercise. Oscillations were seen more frequently in the inspiratory primary variables (with the exception of T_I which rarely responded) than in the expiratory primary variables (cf. subject 409): the breath-by-breath change in FRC (measured as DFRC, = $V_{T,I} - V_{T,E}$) responded more frequently than most other variables.

Oscillating responses, estimated by ZD, were less prolific than those estimated by the alternate-breath oscillation, reflecting the different sensitivities of the two methods. However, the occurrence of responses in the different variables was qualitatively similar by both methods, in both the pooled runs and the runs of the individual subjects.

Within the range of variables studied in Series One ($\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E), the relative occurrence of oscillations in hypoxia at rest was rather similar for the pooled runs of Series One and of Series Two, although their absolute incidence was greater in Series One.

(iii) The phase relations, with respect to the P_{A,CO_2} oscillation, of the oscillating responses in the primary variables had similarities in

different subjects; the phase patterns were not altered between rest and exercise. Oscillations in $V_{T,E}$ and the inspiratory primary variables (not T_I) showed a positive phase difference. The remaining expiratory primary variables (PEF, T_E) oscillated in phase: a positive phase difference for subject 421, and a negative phase difference for subject 409. The phase difference of oscillations in a derived variable was that of the most prominent of its component variables.

The phase relations obtained at the P_{A,CO_2} transients confirmed the pattern described above. Latencies for the responses of $V_{T,E}$ and the inspiratory primary variables tended to be of 2 breaths duration, while those of the expiratory primary variables, PEF and T_E, were 1 breath. Variations from this pattern were apparent.

(iv) Interaction between hypoxia and the P_{A,CO_2} oscillation was demonstrated in several variables, using as a criterion the occurrence of a significant linear regression coefficient of oscillation amplitude on hypoxia. Pooling the results gave a greater incidence of interaction in exercise (22.5%) than at rest (9.4%). Considerable variation existed in the individual experiments.

The regression analysis of the amplitude of the normalised oscillation upon hypoxia demonstrated that, often, the amplitude of oscillations increased proportionately more with hypoxia than did the corresponding run-means as the degree of hypoxia increased (or $P_{A_{O_2}}$ fell).

(v) The P_{A,CO_2} oscillation had no effect in hypoxia on mean expired ventilation at rest or in exercise.

Chapter 4

DISCUSSION

This chapter considers first the various methods used in estimating the amplitude of alternate-breath oscillations, and the reasoning behind selection of the extensive range of respiratory output variables in Series Two. There then follows the presentation of a hypothesis of carotid body participation in the generation of alternate-breath responses. Finally the nature of the multiplicative interaction between hypoxia and the P_{A,CO_2} oscillation, and its modulation by moderate exercise, are examined.

Methods of estimating the size of alternate-breath responses

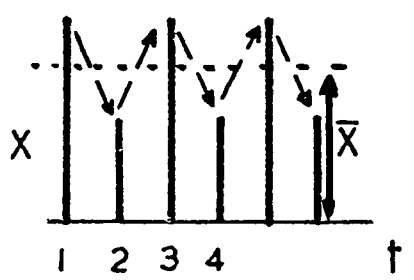
In the experiments of Series One the amplitude of the oscillating response induced by an alternate-breath P_{A,CO_2} oscillation was calculated as the mean alternate-breath difference obtained from successive pairs of breaths in the run (method 1): Fig. 37A and p.67. This method had been used by Marsh et al. (1973), and they had been concerned lest an occasional excessively large or small breath should distort the true estimate of the oscillation amplitude. They therefore preferred to use a method which estimated the regularity of the alternation rather than its amplitude.

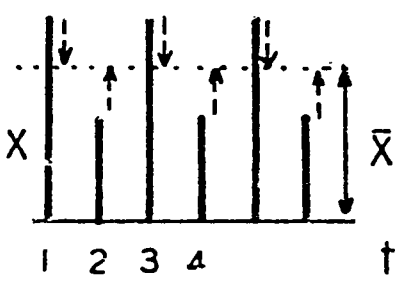
Fig. 37 Computation of alternate-breath responses

A. Alternate-breath oscillation

Method 1 Method 3

Trend absent

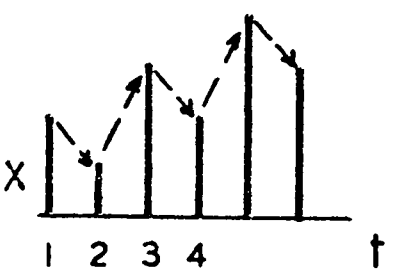


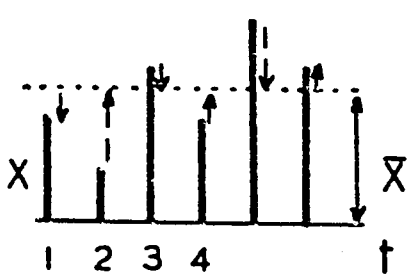


$$OSC_1 = \frac{(x_1 - x_2) + (x_3 - x_2) + (x_3 - x_4) \ldots}{n - 1} \qquad OSC_2 = \frac{(x_1 - \bar{x}) + (\bar{x} - x_2) + (x_3 - \bar{x}) \ldots}{n}$$

$$OSC_1 = 2 \times OSC_2$$

Trend present





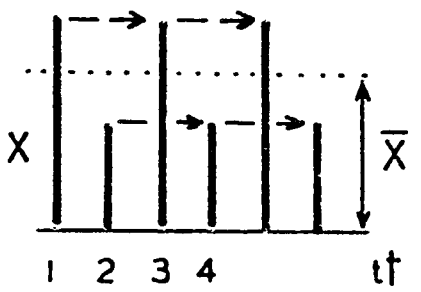
$$OSC_1 > 2 \times OSC_2$$

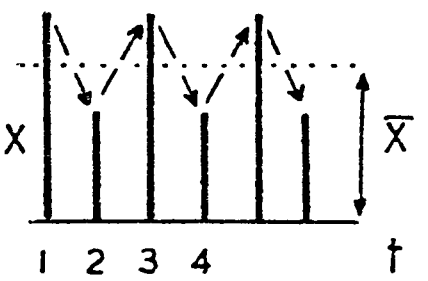
Broken arrows indicate alternate-breath differences in Method 1, differences from the run-mean in Method 3, and pairs of breaths to be correlated in Method 2.

B. ZD

Method 2

Trend absent

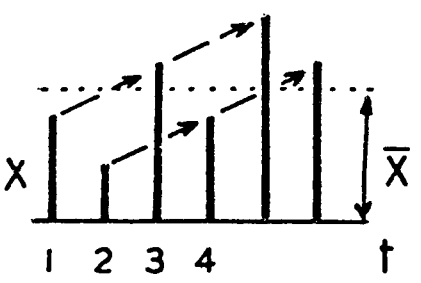


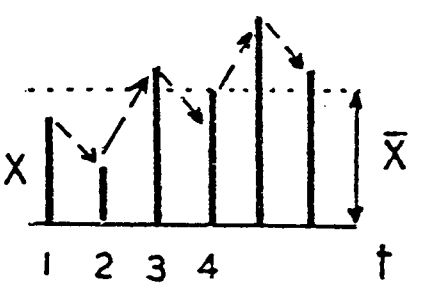


$$r_2 = \frac{\text{covariance}\,(x_t, x_{t+2})}{\text{variance}\,(x)} > r_1 = \frac{\text{covariance}\,(x_t, x_{t+1})}{\text{variance}\,(x)}$$

$$ZD = Z_2 - Z_1$$

Trend present





$$ZD' = Z_2' - Z_1'$$

$$ZD > ZD'$$

An attempt was made in the present study to minimise the distorting effects of extreme-sized breaths by excluding any breath whose size was more than two standard deviations from the run-mean (p.67): it was assumed that such events were not part of the immediate response to the P_{A,CO_2} oscillation.

In Series Two the range of output variables had been extended in an attempt to isolate one variable which might bear a closer relation than any other to the output of the brain-stem respiratory centres. Thus a relative index of oscillation was needed so that the size of the responses in different variables could be compared for each run. It was decided to use the methods of autocorrelation analysis for this purpose: not only could an index of the relative size of oscillations be provided, but also the method is especially suitable for the extraction of a periodic signal (alternate-breath oscillation) from a noisy background. An examination of the frequency distributions of data from the OOC runs (P_{A,CO_2} oscillating) had shown that P_{A,CO_2} was invariably distributed in a bimodal fashion whereas the output variables were distributed unimodally, even when an alternate-breath oscillation was visually apparent (p.80). A considerable degree of contamination of the oscillating outputs therefore must have occurred; whether this reflects the transducing properties of the carotid chemoreflex arc or a less specific effect is considered later (p.158).

The index used was $\underline{Z}$, representing the difference between the Z-transformed autocorrelation coefficients for displacements of two breaths

and of one breath, respectively (method 2): Fig. 37B and p. 69 . ZD was calculated from runs of unedited data so as to assess the degree of distortion introduced into the oscillating responses by occasional very large and small breaths.

Alternate-breath oscillations were calculated in Series Two, using a variant of method 1. As the calculation of a correlation coefficient, and therefore of ZD, involves the processing of the differences of variates from their mean value, the alternate-breath comparisons were related to the run-mean rather than the next breath (method 3): Fig. 37A and p. 68 .

Under steady-state conditions, where the response should not increase or decrease progressively with respect to time, the amplitude of an alternate-breath oscillation obtained by method 1 should be exactly twice that obtained by method 3 on the same data (Fig. 37A: "trend absent"). If a trend were present, this equality would be abolished, and method 3 would then be less sensitive than method 1 (Fig. 37A: "trend present"). However, visual inspection of the runs revealed no obvious trends in the present experiments: this was not unexpected as ample time had always been allowed for breathing to stabilise after imposing changes in the mean stimulus level (p. 58 ; p. 60). Therefore, in the present study, alternate-breath oscillations obtained by either method should have been similar in size.

A comparison between Series One and Series Two of the incidence of oscillations occurring in $\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E during hypoxia showed

the oscillations to be more prolific in Series One (p.103). As different subjects were used in the two studies, it is difficult to conclude whether the difference was due to inter-subject variation or to the method of estimating the oscillation, though the former explanation is favoured.

In Series Two there was a greater incidence of oscillating responses in hypoxia when the alternate-breath oscillation was the index of oscillation, as compared with ZD (p.101). Otherwise, both indices generated qualitatively similar patterns of response, in terms of the relative predominance of oscillations in the thirteen output variables. The difference between the results reflects partly the use of unedited data for the calculation of ZD (and therefore the distorting presence of occasional large or small breaths) and partly the lesser sensitivity of ZD as an index of oscillation. In experiment 409.5 the latter factor accounted for most of the difference, the size and distribution of significant ZD values being changed little when edited data were used instead of unedited data (p.105).

In conclusion, the two methods used for estimating the amplitude of alternate-breath oscillations were comparable in the experiments of this thesis, as the data was free of any obvious trends. In Series Two the autocorrelation function, ZD, was qualitatively compatible with, though less sensitive than, the alternate-breath oscillation; this was a reflection more of method than of the differences between unedited and edited data. Thus, ZD was used as a standardised (or relative) index

of oscillation, while the alternate-breath difference methods were used as absolute indices.

The selection of respiratory output variables

Ventilation ($\dot{V}$) is conventionally regarded as that output variable of the respiratory system through which homoeostasis of P_{O_2}, P_{CO_2} and pH in the body fluids is maintained. Air flow in and out of the lungs is effected by transmission of activity from the brain-stem respiratory centres on to the appropriate sets of respiratory muscles, generating differences in transpulmonary pressure: in inspiration the main effector is the diaphragm (Mognoni et al., 1969; Agostoni & Sant'Ambrogio, 1970), with the external and parasternal portions of the internal intercostal muscles (Koepke et al., 1958; Taylor, 1960); and in hyperpnoeic expiration, the interosseons portions of the internal intercostals (Taylor, 1960) and the abdominal wall muscles (Campbell, 1952).

However, the possibility has already been considered that an output variable other than $\dot{V}$ might bear a closer relation to the output of the respiratory centres during states of changing ventilatory drive from the carotid and medullary chemoreceptors (p.21).

Furthermore, the steady-state proportionality existing between chemoreceptor drive and $\dot{V}$ is maintained only while the resistance to airflow is unchanged. A dissociation of $\dot{V}$ from P_{A,CO_2} occurs in healthy humans when the flow resistance is increased experimentally, whilst the relations between P_{A,CO_2} and inspiratory work (Eldridge & Davis, 1959) and the rate of inspiratory work (Milic-Emili & Tyler, 1963) are little

affected. As airway resistance (R_{aw}) can be influenced by hypercapnia and hypoxia, both locally (Nisell, 1950; R_{aw} decreased) and reflexly (Nadel & Widdicombe, 1962; R_{aw} increased) a search was made for respiratory variables which were measurable and closely related to the outputs of the brain-stem respiratory centres, while being relatively uncontaminated by concurrent changes in the mechanical state of the lungs and airways.

The effects on inspiration of changing the chemical drive to breathing are perhaps more evident in the earlier parts of the phase. The rate of increase of inspiratory volume with respect to time during a breath is unaffected by vagal block or section (Head, 1889: rabbit; Hammouda & Wilson, 1932: dog), the larger tidal volumes which occurred after vagotomy being achieved only as a consequence of the prolonged duration of inspiration. A similar result on the development of efferent phrenic activity was obtained by Larrabee & Knowlton (1946) using experimental pneumothorax in cats.

In addition, Hammouda & Wilson reported an increased rate of change of inspiratory volume in response to asphyxia; and Euler et al. (1970) found the rates of change of the integrated phrenic neurogram, intrapleural pressure and inspiratory volume all to be increased by hypercapnia in cats. Hence, in the present study, mean inspiratory flow (MIF) might serve as an inspiratory index of the chemical drive to breathing, more so than inspiratory tidal volume ($V_{T,I}$).

However, MIF may be less suitable at the higher levels of chemical drive to breathing, for Euler et al. (1970) found the effects of

hypercapnia on the rate of change of inspiratory volume to be confined to the lower levels of stimulation, and to the lower frequencies of breathing for a constant level of stimulation. The increasing hypercapnia may have produced a reflex bronchoconstriction (Nadel & Widdicombe, 1962); and a greater incidence of turbulent flow accompanying increases in instantaneous flow may have further raised R_{aw} (West & Hugh-Jones, 1959; Mead, 1961). In addition, the dynamic compliance of the lung is reduced at high lung volumes (Mead & Whittenberger, 1953). Thus, at high levels of P_{A,CO_2}, MIF may increase less in response to CO_2, and the instantaneous rate of increase in inspiratory volume may decline progressively during inspiration, as pulmonary compliance falls.

Indices of the rate of change of inspiratory volume at the start of inspiration were therefore examined: the peak inspiratory acceleration (PIA) and flow (PIF). These variables may also be influenced by changes in R_{aw}, though not in compliance.

The corresponding expiratory variables (MEF, PEF and PEA, the last not measured here because of a lack of recording space) are the net result of an interaction between at least three factors: a synergism between the forces of passive lung recoil and the expiratory muscles, and an antagonism by post-inspiratory activity in the inspiratory muscles (Green & Howell, 1959; Agostoni et al., 1960; Petit et al., 1960). With increasing chemical drive to breathing, the activity in the expiratory muscles increases, while the post-inspiratory activity of the inspiratory muscles declines; and recoil pressure at the start of expiration will be greater because of the larger end-inspiratory lung volume.

The time for expiration, T_E, is also of interest: Cunningham & Gardner (1972) have shown in man that increases in respiratory frequency accompanying steady-state CO_2 inhalation in both hyperoxia and hypoxia are accomplished by a decrease in T_E, while T_I remains essentially constant.

Finally, changes in FRC were estimated for each breath ($V_{T,I} - V_{T,E}$) as it was thought that the behaviour of FRC might provide an indication of changes in R_{aw} occurring from one expiration to the next. Thus, assuming T_E to be determined by the current level of respiratory drive, an increase in R_{aw} would be manifest as a reduced $V_{T,E}$ and, if $V_{T,I}$ were unchanged, as an increased FRC. As will be recounted later, there was indeed evidence of a participation by R_{aw} in the alternate-breath responses of expiration in some subjects (p.146).

After completing the experiments of this study, two reports were published concerning the use of measures of the isometric activity in the inspiratory muscles at the onset of inspiration as indices of the output from the brain-stem respiratory centres (Milic-Emili, 1973: cat; Howell, 1973: man): thus, the problem of changing lung mechanics during inspiration would be overcome. In man, isometric and isotonic effects were separated by a transient blockade of the inspiratory flap of the respiratory valve (for less than 50 msec) during which time the rate of change of mouth pressure was measured. This quantity correlated well with P_{A,CO_2}. Attractive though the method is in concept and design, it may be invalidated if the subject perceives the momentary impairment of inspiration.

Description of results

The hypothesis presented earlier (p.123) stated that the respiratory effects induced by the alternate-breath P_{A,CO_2} oscillation were mediated by the carotid body. They should therefore be characterised by their hypoxia-dependency and short latency (p.6).

Oscillating responses were estimated in both primary and derived output variables, the primary variables being inspiratory and expiratory times (T_I and T_E), tidal volumes ($V_{T,I}$ and $V_{T,E}$) and peak flows (PIF and PEF), and peak inspiratory acceleration (PIA), and the derived variables being breath duration (T_T), the change in functional residual capacity (DFRC, = $V_{T,I} - V_{T,E}$), inspiratory and expiratory mean flows (MIF and MEF) and ventilations ($\dot{V}_I$ and $\dot{V}_E$).

The condition of hypoxia-dependency demands that the oscillating responses should be present while there is a hypoxic drive to the carotid body (Cunningham et al., 1964). For practical purposes, carotid chemoreflex effects in man usually require a P_{A,O_2} somewhat below the euoxic level for their manifestation. However, this does not preclude the possibility of observing such a response at a higher P_{A,O_2}, but on the basis of steady-state $\dot{V}$, P_{A,CO_2} relations the response should be small.

Thus, in the experiments of Series Two most oscillating responses occurred in hypoxia ($P_{A,O_2} < 72$ torr) with very few apparent in hyperoxia ($P_{A,O_2} > 180$ torr), both at rest and during exercise (p.100). This confirmed the earlier work of Marsh et al. (1973) at rest, and provided the new observation that moderate exercise potentiates the effects of hypoxia.

That the oscillating responses are hypoxia-dependent implies that hypoxia and the alternate-breath P_{A,CO_2} oscillation interact multiplicatively. The form of the multiplication is considered later (p.148), as is the nature of the potentiating action of exercise (p.154).

These results are not incompatible with those of Wolff (1974): anaesthetised euoxic cats responded to similar alternate-breath P_{A,CO_2} oscillations by generating a regular oscillation in $V_{T,I}$. Such regularity was not a feature of the oscillating responses observed in conscious man (p.76); and the responses were not often present in euoxia. This may reflect a higher signal-to-noise ratio of the respiratory system in the anaesthetised cat, or possibly a greater sensitivity to hypoxia, or both.

The hypoxia-dependency of the effects of the alternate-breath P_{A,CO_2} oscillation on mean responses was studied in Series Two, at rest and in exercise (p.119). The study was limited to a comparison of mean $\dot{V}_E$ in paired OSC and ISOCAPNIC runs: only in the case of $\dot{V}_E$ were the steady-state input-out relations sufficiently well characterised to enable accurate comparisons to be made (p.72).

The findings of Cunningham et al. (1965a) were reaffirmed: the effect of the P_{A,CO_2} oscillation on mean $\dot{V}_E$ was not different from that due to mean P_{A,CO_2}. This may reflect that the P_{CO_2} oscillation was equally effective at reflexly stimulating and depressing $\dot{V}$ on alternate breaths, or alternatively that the P_{CO_2} oscillation elicited no breath-by-breath response in $\dot{V}_E$.

Absolute latencies of the oscillating responses were estimated during hypoxia when the alternate-breath P_{A,CO_2} oscillation was either suddenly imposed or suddenly removed (p.111); the techniques of cross-correlation analysis were used and were not entirely satisfactory, as is discussed on p.137. It was concluded that latencies were of four breaths' duration or less, both at rest and in exercise.

In each run of an experiment the oscillating responses in different output variables were examined so that a pattern could be obtained of their relative amplitudes and their phase relations with respect to P_{A,CO_2}. In some experiments the patterns obtained from different runs were rather consistent (subject 409 in Series Two). In other cases there was more variation, and because of the relatively small number of runs performed in each experiment (limited by the time available for experimentation), it was difficult to decide whether the variation was random or the early indication of a mechanism more complex than had been previously envisaged.

At the risk of succumbing to over-generalisation, amplitude and phase patterns were presented in Series One (p.90 and p.92) and Series Two (p.105 and p.107). For the sake of clarity, the description was confined largely to the primary variables, including the derived variables where relevant. These observations are summarised in the following pages as a prelude to the synthesis of a mechanism possessing sufficient flexibility to account for the variations in pattern while retaining a degree of physiological credence.

In Series One ranking the relative amplitudes of oscillation produced two patterns of response: the $\underline{T_E\text{-dominant}}$ pattern, in which T_E oscillations were consistently larger than those in T_T, V_E or $V_{T,E}$, occurred in experiments 368.4_1, 368.4_2, 377.5 and 230.15; and the $\underline{V_{T,E}\text{-dominant}}$ pattern (experiments 392.6 and 418.1) in which the prominence of the T_E oscillations was lost, leaving the four variables, led by $V_{T,E}$, with rather similar relative amplitudes of oscillation. In both patterns T_I was ranked either lowly or not at all, reflecting its infrequent oscillation: this was not unexpected, for T_I in man is hardly changed by CO_2 inhalation during hyperoxia or hypoxia (Cunningham & Gardner, 1972).

The <u>phase relations</u>, with respect to P_{A,CO_2}, of oscillations in the primary variables ($V_{T,E}$ and T_E) were consistent within most experiments. Two phase patterns could be distinguished (Fig. 26, p.93) in 3 experiments (368.4_1, 368.4_2 and 392.6) the T_E oscillations were of negative phase and <u>out of phase</u> with the $V_{T,E}$ oscillations, while in one experiment (230.15) the oscillations of both variables were positive and <u>in phase</u>.

An alternating expiratory stimulation ($V_{T,E}$ larger, T_E shorter) and depression ($V_{T,E}$ smaller, T_E longer), as described for the "in phase" pattern, might have been predicted: for the findings of Cunningham & Gardner (1972) on steady-state CO_2 inhalation, and of Gardner (1974) on step-transients of P_{A,CO_2} have shown $V_{T,E}$ and T_E to respond in this manner.

The "out of phase" pattern was unexpected. It resembles the breath-by-breath positive correlation between V_T and T_T first reported by Priban (1963) during steady-state conditions of respiratory drive.

There appear to be at least two possible explanations for the behaviour of $V_{T,E}$ and T_E: the two variables may be responding to the same signal but by different mechanisms, or one variable may be responding and the other following passively. Judgement on this matter is postponed until the results of Series Two, including both including both inspiratory and expiratory responses, have been reviewed.

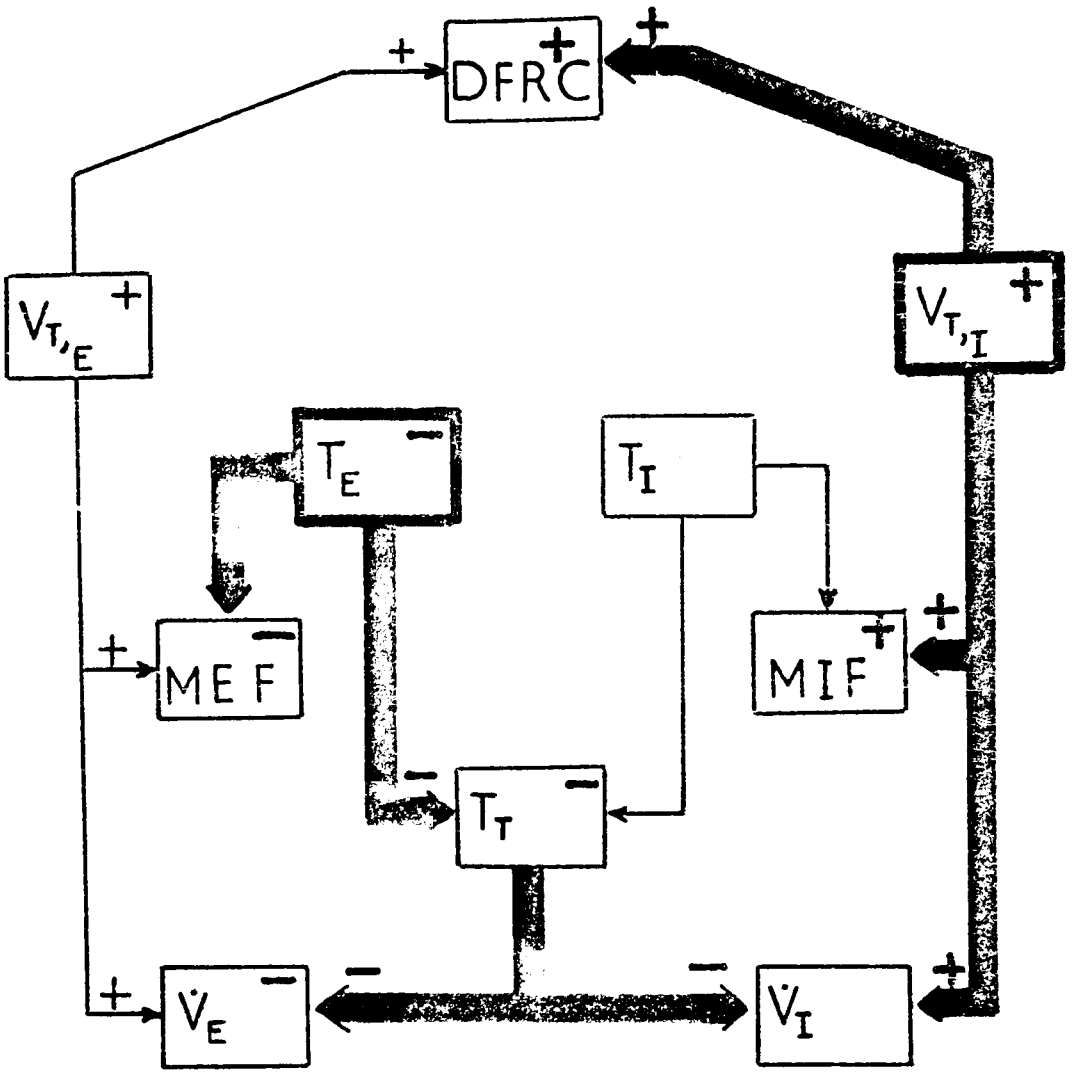
In Series Two, the amplitude patterns (obtained by ranking ZD) and the phase patterns were conveniently classed as <u>inspiratory</u> and <u>expiratory</u>: thus one or both might be present in any experiment. The imposition of moderate exercise had no obvious effect on the patterns, except to increase the incidence of oscillating responses.

The two or three experiments performed on any subject were analysed as one, in an attempt to emphasise any latent patterns of response. This procedure was justifiable as visual inspection of the results had revealed no gross differences in the pattern of response in separate experiments on the same subject, though the incidence of oscillations might have been different.

Perhaps the most surprising finding of the whole study was the ubiquity of the oscillation in EFRC at rest and in exercise: the breath-by-breath oscillation in FRC reflected a difference in the behaviour of $V_{T,I}$ and $V_{T,E}$ This observation is returned to later (p.144).

The <u>amplitude patterns</u> of the primary variables are briefly described. Subjects 425 and 392 had inspiratory patterns only, with oscillations occurring in the inspiratory primary variables ($V_{T,I}$, PIF and PIA) to varying extents. Subjects 409 and 421 possessed both

FIG. 38. Subject 409: phase pattern of the derived variables.



+,− depicts the phase of the oscillation. Thick boxes indicate the prominent primary variables. Thick arrows indicate prominent influences on derived variables.

inspiratory and expiratory patterns, so that oscillations were present in T_E and PEF, as well as in the inspiratory variables. $V_{T,E}$ has been omitted from the expiratory pattern for, as will soon become apparent, its behaviour is more in keeping with an inspiratory primary variable. T_I, as in Series One, responded infrequently.

The phase patterns of the primary variables were rather consistent in subject 409. The inspiratory pattern consisted of positively-phased oscillations in $V_{T,I}$, PIF and PIA. The expiratory phase pattern was manifest as negatively-phased oscillations in T_E and PEF. This implies that an inspiratory stimulation occurred on the same breath as an expiratory depression, and vice versa. Oscillations in $V_{T,E}$ were less frequent and were of positive phase. This pattern corresponds to the "out of phase" pattern for $V_{T,E}$ and T_E in Series One.

The manner in which the oscillating responses in the primary variables interacted in the derived variables is depicted in Fig. 38. The only derived variable relevant to the present discussion is DFRC: it oscillated with a positive phase determined by the $V_{T,I}$ oscillation.

The phase patterns in the remaining subjects were less easily characterised because of a lower incidence of oscillations. The inspiratory phase pattern, together with positively-phased oscillations in $V_{T,E}$ and DFRC, occurred in the remaining subjects to varying extents. An expiratory phase pattern was absent except in subject 421: it differed from that of subject 409, T_E and PEF oscillating with a positive phase in some runs, while in others T_E, only, oscillated with a negative phase.

Thus, a hypothesis of carotid body function is needed which can account for a relatively consistent pattern of response during inspiration and a more labile expiratory response. It had been hoped that estimation of the absolute latencies of the oscillating responses with respect to P_{A,CO_2} might have determined whether the inspiratory primary variables responded ahead of the expiratory primary variables, or vice versa, in those runs where oscillations in T_E and PEF were out of phase with those in $V_{T,I}$, PIF and PIA.

It had been concluded that latencies were of four breaths' duration or less (p.113), but a greater accuracy was not warranted because of the shortcomings of the method. Its weakness lay in the form of the stimulus used. As mentioned on p.92 the latency of an alternate-breath oscillation could not be measured in absolute terms. In retrospect, a similar drawback applied to the CO_2-transient (p.112): the oscillating portion of the transient proved to dominate the single change between the oscillating and steady states of P_{A,CO_2}. As predicted, this resulted in an oscillating cross-correlogram of 2-breath period (Fig. 30, p.112) which precluded a statistical estimation of r_{max}.

Thus, the conclusion that in subjects 409 and 421 the oscillating responses in T_E and PEF tended to lead those in the primary inspiratory variables by one breath can only be tentative (p.113). It would be worthwhile re-investigating the absolute latencies using a more suitable form of CO_2 stimulus: perhaps of a more randomised form, with a frequency spectrum beyond the limits of resolution of the medullary chemoreceptors.

Prior to considering the physiological mechanisms which might have produced these response patterns, the elimination of influences arising from the experimental conduct is discussed. The first influence concerns the effects of changing gas viscosity on alternate breaths on the performance of the pneumotachometer. It was predicted on p. 39 that, on theoretical grounds, inspiratory flow should be overestimated by the pneumotachometer on a high-CO_2 breath, because the increase in mean gas viscosity. As inspiratory volume and acceleration were derived from the flow signal, they should also be subject to overestimation. Conversely, on a low-CO_2 breath underestimation should occur.

As the potential existed for the pneumotachometer to generate an alternate-breath oscillation it was essential to estimate the significance of this effect under the conditions of P_{O_2}, $\dot{V}$, V_T and T_T normally encountered in an experiment (p. 41). It was concluded that the pneumotachometer did not participate in the generation of alternate-breath oscillations in $V_{T,I}$, PIF or PIA.

The other factor that might have induced a spurious oscillation in respiratory output was noise arising from the closure of the inspiratory solenoid valves at the start of expiration. If such noise was perceptible to a subject, persistent alternate-breath oscillations would have been seen in all the STEADY runs: for, the valves operated throughout all experiments. However, the incidence of significant oscillations in the STEADY runs, was very low, so that this effect was discounted.

The incidence of alternate-breath responses occurring in the absence of the P_{A,CO_2} oscillation, although considerably less than in its presence (Series One: 15%, p.89; Series Two: 3.5% at rest and 6.2% in exercise, p.103) may reflect a more general tendency of the respiratory system towards oscillation. Steady-state analysis of the human respiratory system under conditions of constant P_{A,CO_2} and P_{A,O_2} indicates the presence of oscillating responses at several different frequencies (Jensen & Ward, work in progress).

Thus, the patterns of oscillating response that have been described in this section represent the reflex respiratory effects of an alternate-breath P_{A,CO_2} oscillation, presumably emanating from the carotid body. The mechanism inducing these effects has to account for some rather unexpected findings: the possibility of obtaining an inspiratory stimulation and an expiratory depression on the same breath (and vice versa), and of FRC oscillating more regularly, on average, than any other output variable.

The role of the carotid body

It is proposed that the alternate-breath P_{A,CO_2} oscillation is transduced by the carotid body during hypoxia into an oscillating discharge of the same period. This then reflexly affects respiration to produce the observed alternate-breath responses, both at rest and in moderate exercise.

As the within-breath P_{A,CO_2} oscillation can be detected in the brachial artery of man (Band & Semple, 1966, 1967), it is not unreasonable to expect that the alternate-breath P_{A,CO_2} oscillation (half the frequency and about thrice the amplitude of the within-breath P_{A,CO_2} oscillation at rest) is transmitted as far as the carotid body. This has been confirmed for the cat (Band et al., 1969b).

It may be similarly inferred that an alternate-breath oscillation is produced in the carotid sinus nerve discharge (p.13). The peaks and troughs in the discharge frequency might coincide with the maxima and minima of P_{CO_2} or of its rate of change with respect to time. The latter is favoured in the cat (Band et al., 1971; Willshaw, 1974: this thesis, p.14), and possibly also in man, for the human respiratory system resembles that of the cat in responding more easily to quick changes in P_{A,CO_2} during hypoxia than to the corresponding changes in hypoxia (p.16).

The calculated alveolar profile of the alternate-breath oscillation is depicted in Fig. 23 (p.82) for P_{CO_2} and for its rate of change. Allowing for a certain amount of attenuation of the P_{CO_2} oscillation to occur in transit from the lung to the carotid body (p.152), the two

profiles probably do not differ greatly on reaching this point. Thus the basic predictions of the hypothesis are not unduly affected if the carotid body responds to P_{CO_2} or to its rate of change. To simplify the subsequent argument, the alternate-breath profile of the carotid sinus nerve discharge frequency is assumed to be a square wave.

It is further proposed that the variation observed in the pattern of oscillating reflex response represents a variation in the central timing of the alternate-breath oscillation in carotid body discharge in relation to the current respiratory cycle: Black & Torrance (1967a, 1971) and Band et al. (1968, 1970), as described on p.19. The mechanism which mediates the reflex effects of central timing has a sufficiently short latency to enable it to discriminate between adjacent respiratory half-cycles; thus an expiration could be influenced independently of the inspirations immediately preceding it and following it.

The central timing of the carotid body discharge is determined by the ratio between breath duration and the circulation time from the lung to the carotid body (p.19). Two examples are shown in Fig. 39 (p.143): in (a), the carotid body discharge oscillates <u>in phase</u> with the respiratory cycle, being either high or low for a complete inspiration and the following expiration; in (b), the discharge is <u>out of phase</u> by half a respiratory cycle, the period of high or low discharge spanning the expiration of one breath and the inspiration of the next.

A raised level of carotid body discharge arriving centrally early in an <u>inspiration</u> should stimulate that inspiration by increasing $V_{T,I}$ (Black & Torrance, 1967a, 1971; Band et al., 1968, 1970); the absence

of the Hering-Breuer reflex in man, except in extreme hyperpnoea, should preclude T_I shortening in consequence (Crossfill & Widdicombe, 1961; Cunningham & Gardner, 1972). Hence, increases should also occur in MIF, PIF and PIA. Replacing the raised discharge by a diminished discharge in the next inspiration should depress the previously stimulated variables.

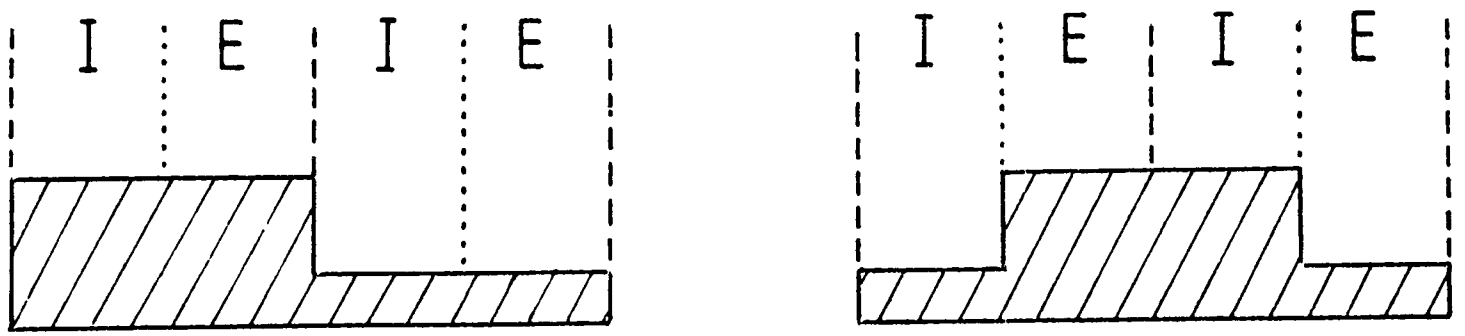
Thus, if the carotid sinus nerve discharge arriving centrally oscillates between these two levels on alternate inspirations, those inspirations may be alternatively stimulated and depressed, generating alternate-breath oscillations in $V_{T,I}$, MIF, PIF and PIA.

The effect of a raised discharge from the carotid body arriving centrally during <u>expiration</u> should be to depress the current expiration by lengthening T_E (Black & Torrance, 1967a, 1971; Howard et al., 1969) and decreasing PEF (Howard et al., 1969). As in inspiration, an alternation in the level of carotid body discharge arriving centrally during successive expirations could alternately depress and stimulate the current expiration, producing alternate-breath oscillations in T_E and PEF.

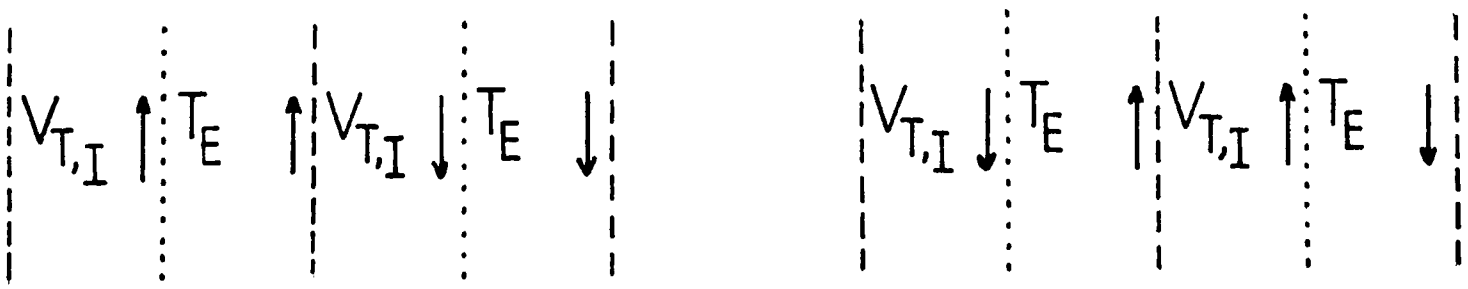
There have been no reports of $V_{T,E}$ responding to central stimulation by the carotid body during expiration. As described earlier (p.136), when $V_{T,E}$ oscillated it was invariably in phase with the oscillations of the primary inspiratory variables, but its relation to the remaining primary expiratory variables (T_E, PEF) was more variable. Integration of the responses of $V_{T,E}$ into the hypothesis of carotid body involvement is therefore postponed until the next section (p.144) where the factors influencing FRC are considered. For present purposes, it is assumed that

Fig.39 Carotid body "timing" hypothesis for eliciting alternate-breath oscillations.

STIMULUS: Carotid body discharge profile arriving at the brain-stem respiratory centres
a) IN PHASE with the respiratory cycle, or, b) 180° OUT OF PHASE with the respiratory cycle.



RESPONSE



I = inspiration; E = expiration

in Series One the occurrence of oscillations in $V_{T,E}$ was an indication that similarly-phased oscillations had been present in the inspiratory primary variables, although these variables had not been recorded.

Thus, depending upon the central timing within the current respiratory cycle of the alternate-breath oscillation in carotid body discharge, the hypothesis predicts that inspiration and expiration may be both stimulated or both depressed on the same breath (Fig. 39b), or one may be stimulated on the same breath as the other is depressed, and vice versa (Fig. 39a).

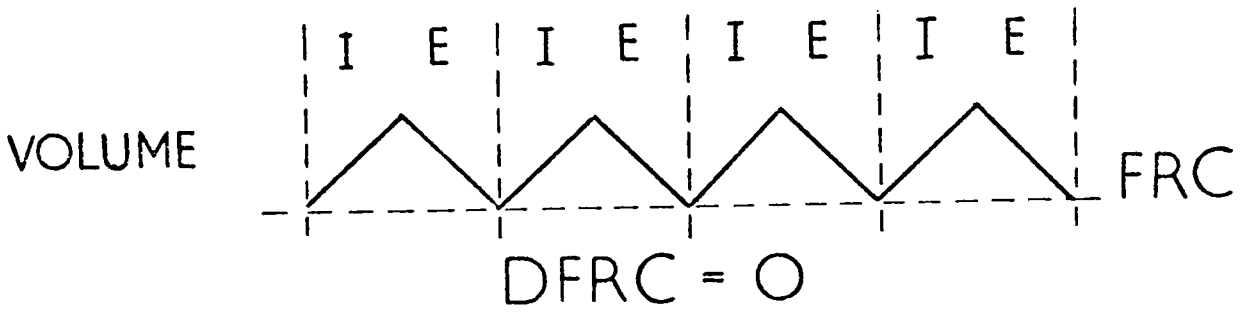
The pattern of central timing depicted in Fig. 39a could account for the "<u>out of phase</u>" patterns of oscillation of $V_{T,E}$ and T_E in Series One (experiments 368.4_1, 368.4_2 and 392.6), and of the primary inspiratory and expiratory variables in Series Two (subject 409, consistently; subject 421, occasionally). The central timing pattern of Fig. 39b could likewise account for the "<u>in phase</u>" oscillations of $V_{T,E}$ and T_E in Series One (experiment 230.15), and of the primary inspiratory and expiratory variables of Series Two subject 421, occasionally).

The observation of Black & Torrance (1967a, 1971) that the effect of CO_2 pulses delivered to the cat carotid body during expiration was more labile than the effect obtained during inspiration might explain the absence of oscillation in T_E and PEF in subjects 425 and 392. Either pattern of central timing in Fig. 39 could account for inspiratory phase pattern in these subjects.

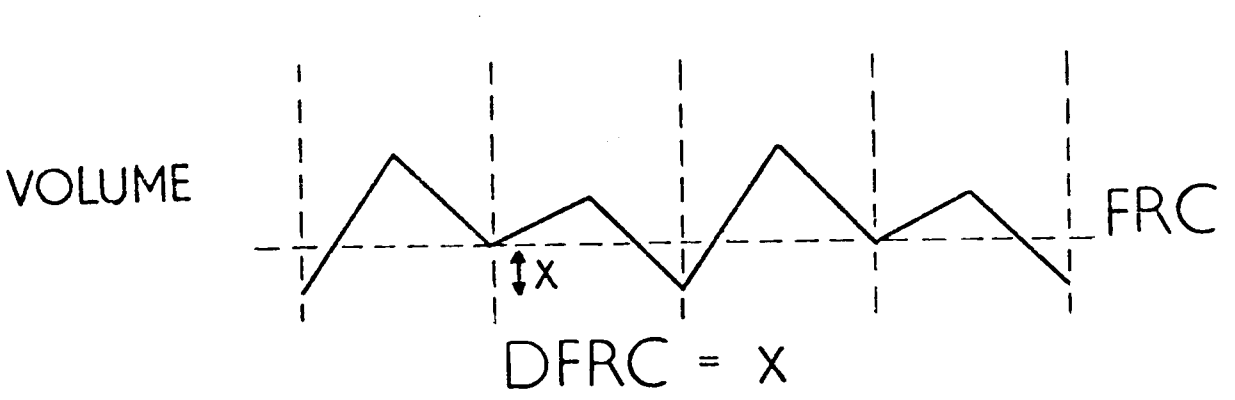
In summary, the response time of the human carotid body (activated by hypoxia) is sufficiently short for a reflex respiratory response to be elicited by the alternate-breath P_{A,CO_2} oscillation. A degree of

FIG.40. Some examples of the relations between $V_{T,I}$ & $V_{T,E}$

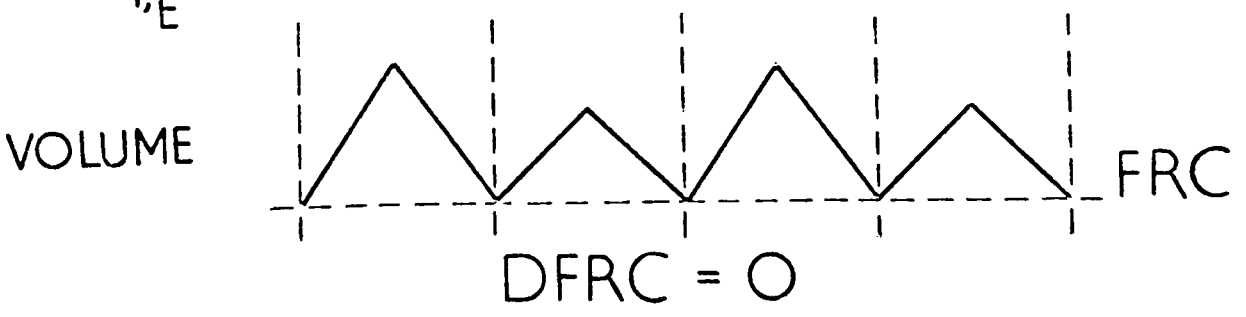
1. $V_{T,I}$ & $V_{T,E}$ not oscillating.



2. $V_{T,I}$ oscillating.



3. $V_{T,I}$ & $V_{T,E}$ oscillating equally.



flexibility may be imposed upon the carotid chemoreflex arc by the timing at the brain-stem of carotid body discharge. Thus it was proposed that the variations observed in the patterns of oscillating responses in different subjects reflect differences in the central timing of the alternate-breath oscillation in carotid body discharge. These differences in timing may arise from differences in the ratio of breath duration to the lung-carotid body circulation time; the means by which these may occur are considered later (p.153).

The alternate-breath oscillation in FRC

The incidence of alternate-breath oscillations in the derived variable, DFRC ($= V_{T,I} - V_{T,E}$) was more widespread than that of the oscillations in either $V_{T,I}$ or $V_{T,E}$, as if the combined effects of these two variables was more uniform than either of them alone. Some examples of the relations occurring between $V_{T,I}$ and $V_{T,E}$ are presented in Fig. 40.

Generally, the DFRC oscillation was positively-phased, and as both the $V_{T,I}$ and $V_{T,E}$ oscillations invariably had the same phase, the amplitude in $V_{T,I}$ was greater than that in $V_{T,E}$. On infrequent occasions, other observations were made: a matching of the amplitude of the $V_{T,I}$ and $V_{T,E}$ oscillation gave no oscillation in DFRC; a greater amplitude of the $V_{T,E}$ oscillation resulted in a negatively-phased DFRC oscillation; insignificant oscillations in $V_{T,I}$ and $V_{T,E}$ produced a significant oscillation in DFRC.

The apparent inability of the changes in $V_{T,E}$ to match those in $V_{T,I}$ has led to a consideration of some factors which might influence

the degree of pulmonary emptying: the breath-by-breath respiratory exchange ratio, the time available for expiration, and the airway resistance.

Respiratory exchange ratio. The breath-by-breath oxygen uptake should be little affected by the presence of an alternate-breath P_{A,CO_2} oscillation. However, the P_{CO_2} gradients between pulmonary arterial blood and alveolar air change on alternate breaths, being about the same as the usual air-breathing gradient on the low-CO_2 breaths, but being diminished (in exercise) or even reversed (at rest) on high-CO_2 breaths (p. 82). The reversal of CO_2 flux on alternate breaths at rest should decrease the volume of gas expired on a high-CO_2 breath. This could generate an alternate-breath oscillation in $V_{T,E}$, negatively-phased with respect to P_{A,CO_2} and therefore out of phase with $V_{T,I}$: such a prediction is, however, contrary to observation.

Even if the rate of CO_2 flux into the blood on a high-CO_2 breath were to equal the normal air-breathing efflux at rest (ca. 240 ml min^{-1}), during a breath of 3 sec duration only 12 ml of CO_2 would enter the pulmonary blood from the alveolar air: this would be imperceptible. Thus, changes in breath-by-breath CO_2 flux are unlikely to affect $V_{T,E}$ or, therefore, FRC.

Expiratory time (T_E). There is little reason to doubt that expiration was an active process in the present study (Campbell, 1952; Taylor, 1960; this thesis, p.129). Thus, the oscillations in T_E which

occurred in several experiments are assumed to reflect the central timing of the alternate-breath oscillation in carotid body discharge (p.142).

The exact nature of the mechanism which determines the level of T_E has not been elucidated. Over a wide range of respiratory stimulation in man, the increase in respiratory frequency accompanying an increase in ventilation is achieved by a shortening of T_E with relatively little change in T_I (steady-state hyperoxic and hypoxic hypercapnia at rest: Cunningham,& Gardner, 1972; step-changes of hypercapnia in hyperoxia at rest: Gardner, 1974; transient removal at rest of hypoxia alone, of hypercapnia in hypoxia, and of hypoxia and hypercapnia together: Drysdale, Jensen & Cunningham, in preparation; in air-breathing exercise: Kay et al., 1974b).

There is evidence in animals that T_E may be modulated by residual inspiratory-inhibiting activity from the previous inspiration (Nadel et al., 1973; conscious dog; Clark & Euler, 1972, and Knox, 1973: anaesthetised cat). In man, however, this effect should be insignificant, if not absent, as the Hering-Breuer inflation reflex can only be demonstrated in excessive hyperpnoea (Crossfill & Widdicombe, 1961; Cunningham & Gardner, 1972).

If the oscillating drive to expiration determines both the amplitude and duration of the expiratory effort, then T_E and $V_{T,E}$ should oscillate in phase, as was found in experiment 230.15 of Series One and, on occasion, in subject 421 of Series Two. If the $V_{T,E}$ oscillation departs from this relation, a change in R_{aw} might be a causative agent.

Airway resistance (R_{aw}). While the oscillating responses in T_E have been shown to satisfy the conditions of hypoxia-dependency and short latency demanded of a carotid chemoreflex (p.6), the implication of reflex changes in R_{aw} being mediated by the carotid body was based upon evidence in the literature from animal experiments.

In animals, CO_2 may dilate the airways locally (Nisell, 1950), and constrict them by a vagal reflex (Einthoven, 1892; Nadel & Widdicombe, 1962). In man there have been conflicting results, perhaps due to varying participation of the local and reflex actions of CO_2: at present, CO_2 is regarded as having a constrictor action (Sterling, 1969; Rodarte & Hyatt, 1973). As CO_2 reduces laryngeal resistance slightly in man (Spann & Hyatt, 1971) by a laryngeal reflex (cat: Dixon et al., 1974), the increase it causes in R_{aw} should reflect a constriction of the lower airways (cf. Sterling, 1969).

In the experiments of Nadel & Widdicombe (1962) on the cat, there was evidence of a multiplicative interaction at the carotid body between hypoxia and hypercapnia on lower airway constriction: the reflex bronchoconstriction produced by hypoxia, and part of that produced by euoxic hypercapnia were abolished by ligating the glossopharyngeal nerves. Exact estimates for the latency of the reflex bronchoconstriction were not available: the neural component from the carotid body to the bronchial smooth muscle should be short, but the limiting factor may be the time taken for contraction or relaxation to develop in the muscle. Nadel & Widdicombe's observations showed R_{aw} to increase within the first 30 seconds after a change in P_{CO_2} or P_{O_2}.

Whether a similar mechanism of bronchoconstriction mediated by increased carotid body drive can occur in man warrants experimental study. At present, however, one is faced with the dangers of over-speculation when invoking an alternate-breath oscillation in lower airway tone and R_{aw} to account for the discrepancies observed between the oscillating responses in $V_{T,E}$ and T_E.

Perhaps the relevant conclusion to be drawn from this section is not so much that FRC oscillated ubiquitously, but that the responses in $V_{T,I}$ and $V_{T,E}$ were rarely matched. If the hypothesis of carotid body function and central timing presented on p.140 has validity, then the mis-matching of $V_{T,I}$ and $V_{T,E}$ would seem to reflect the rather un-natural profile of carotid body discharge (an oscillation with half the frequency of the within-breath oscillation) which makes it possible to stimulate inspiration and depress expiration on the same breath.

The multiplication between hypoxia and the CO_2 oscillation: at rest

Evidence was presented in Chapter 1 of there being a multiplicative interaction between hypoxia and hypercapnia on $\dot{V}_E$ in resting man, mediated by the carotid body (p.21). During steady-state conditions the multiplication is effectively linear: $\dot{V}_E$ increases linearly in response to iso-oxic hypercapnia (Nielsen & Smith, 1952), and to isocapnic hypoxia (Lloyd et al., 1958), where hypoxia is an inverse function of P_{A,O_2} (p.73).

The effects of graded hypoxia on the respiratory responses to CO_2 transients have received less attention. The present study was an

attempt to rectify this situation by examining the hypothesis that the multiplication of the alternate-breath P_{A,CO_2} oscillation by hypoxia is analogous to that of the steady state, so that the amplitude of an oscillating response increases linearly with hypoxia.

In Series One it was tentatively concluded that a multiplication had occurred between the P_{A,CO_2} oscillation and hypoxia within the P_{A,O_2} range of 60 to 50 torr (p.95). The collected results of the Series in all variables ($\dot{V}_E$, $V_{T,E}$, T_T, T_I and T_E) provided 6 instances out of 30 where the oscillation amplitude was greater at the lower P_{A,O_2}; the most marked response occurred in experiment 392.6, with $\dot{V}_E$, $V_{T,E}$ and T_E showing a multiplication (Fig. 28, p.96).

The hypothesis of a linear multiplication between hypoxia and the P_{A,CO_2} oscillation was investigated more fully in Series Two. Because of the extended range of P_{A,O_2} (ca. 200-45 torr) and the greater number of measurements (ca. 4-7), multiplication was assessed by a linear regression analysis of oscillating response (oscillation, %) upon hypoxia (p.114).

The collected results at rest from nine experiments produced 11 regression coefficients out of 117 (9.4%) that were different from zero. In each instance, the oscillation amplitude increased with the degree of hypoxia, as predicted. Although this represented a statistically significant incidence of linear multiplication, it was less than had been hoped for. It should be pointed out that one of the 4 subjects (425) showed very few oscillating responses at rest, and that experiment 421.2 hardly encroached upon hypoxia. The incidence could therefore be

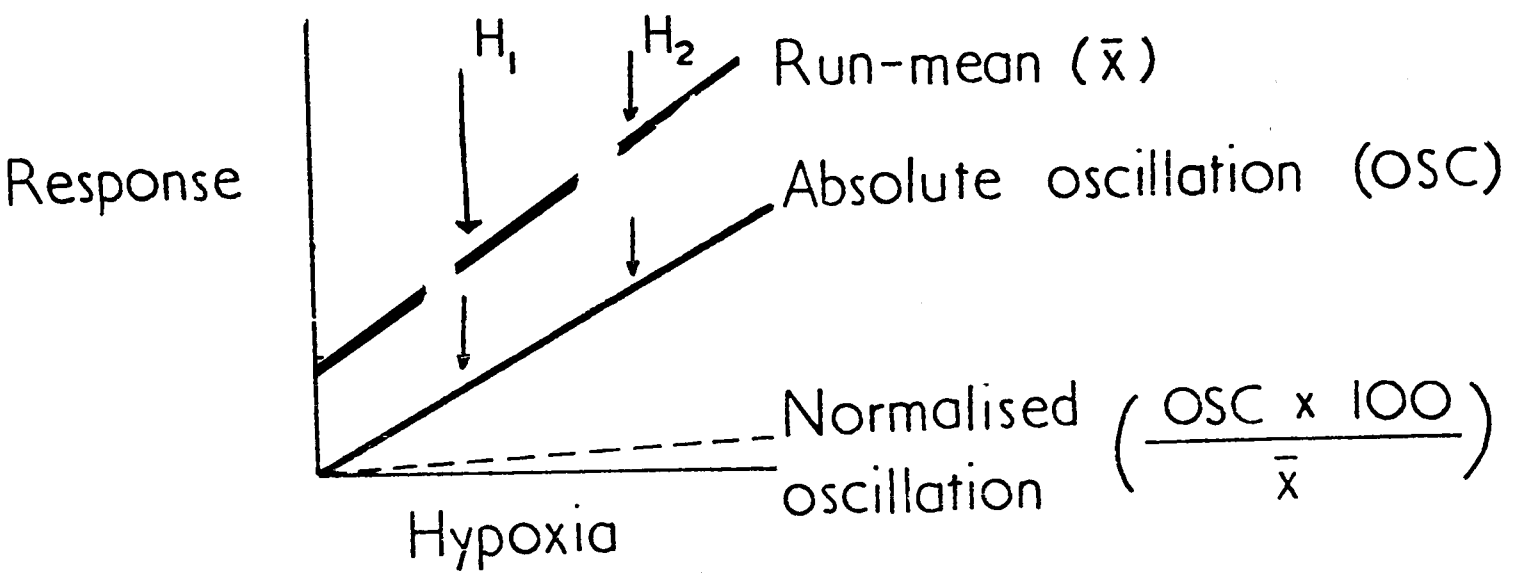
re-expressed for the remaining 6 experiments as 11 out of 78 (14.1%) which is still perhaps rather low.

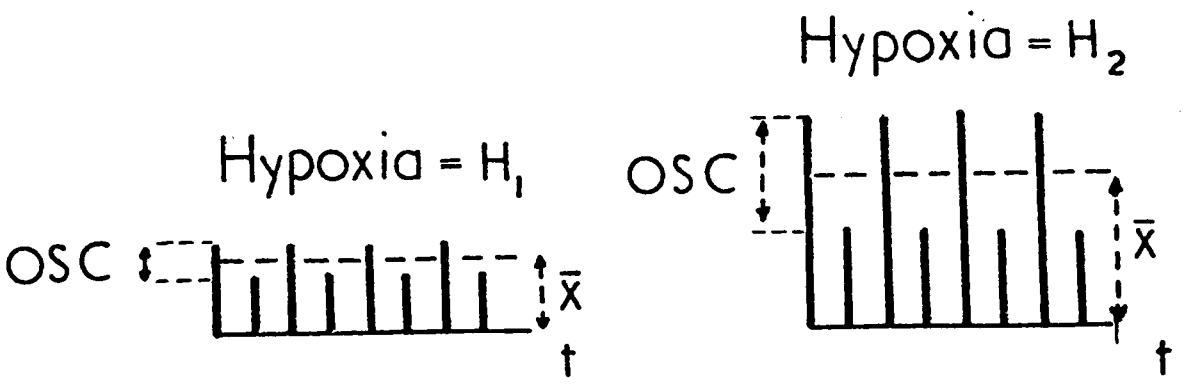
It might be pertinent to compare these results with those of Band et al. (1970) obtained from anaesthetised cats. In 3 cats out of 4, the reflex response ($V_{T,I}$) elicited by a pulse of CO_2 applied to the carotid body at a given point during inspiration was increased when the animal breathed air instead of oxygen; a further reduction in P_{I,O_2} had relatively little effect in 2 cats, but elicited an additional respiratory stimulation in a third. Thus in both conscious man and the anaesthetised cat, multiplication by hypoxia of the respiratory effects of a high frequency CO_2 signal was seen, but by no means invariably.

There was no evidence of a hypoxic threshold for the generation of reflex oscillating responses in the P_{A,O_2} range of 200 to 100 torr (p.115). Cunningham et al. (1964) reached a similar conclusion for steady-state breathing in man: inhalation of pure oxygen at a P_{A,O_2} of 210 torr during hypercapnia produced a small but definite fall in $\dot{V}_E$, implying the existence of a hypoxic drive to the carotid body even at a moderately raised P_{A,O_2}.

The observed multiplication between hypoxia and the P_{A,CO_2} oscillation, although scattered between the different experiments, occurred most often within the group of variables (MIF, PIF and PIA) and to a lesser extent in MEF, PEF and T_E (Table 19, p.116). Multiplication was noticeably absent from the volumes and ventilations. Furthermore, although DFRC oscillated more frequently in hypoxia than any other

FIG.41. The effects of hypoxia on the amplitude of the alternate-breath oscillation and run-mean.





Not drawn to scale.

output variable, graded hypoxia did not systematically increase the amplitude of oscillation.

It is encouraging that those output variables which exhibited the effects of a linear multiplication between hypoxia and the P_{A,CO_2} oscillation were those considered more likely to reflect the reflex effects of a changing drive to breathing (p.127).

Of interest was the observation that linear multiplication was usually still present after the alternate-breath oscillations had been normalised with respect to their run-means (p.119). This implied that the amplitude of the oscillations increased proportionately more with hypoxia than did the corresponding run-means (Fig. 41): for, in all experiments the run-means in the several variables (T_T, T_E, T_I expressed as frequencies for this purpose) increased with hypoxia, with the exception of T_I, though often to a lesser degree at the higher levels of hypoxia.

These observations could imply that the human carotid body is more sensitive to a changing CO_2 stimulus than to a steady CO_2 stimulus. Evidence for the carotid body of the cat responding to the rate of change of P_{CO_2} rather than to P_{CO_2} per se has presented in Chapter 1 (p.14). And, in man, the reflex responses elicited by quick changes of P_{A,CO_2} during hypoxia are elicited more quickly and easily than the corresponding changes in P_{A,O_2} (described on p.16).

The validity of this argument depends on the relation between P_{A,CO_2} and carotid body P_{CO_2} being maintained as hypoxia increases: for, an

"extra" effect of the P_{A,CO_2} oscillation on respiration could result from a reduced attenuation of the CO_2 signal during its passage from the lungs to the carotid body. In addition, as it is the reflex effects of carotid body activity that are being considered, one cannot exclude the phenomenon of central timing: again, an apparent hypersensitivity of the carotid body in the presence of the P_{A,CO_2} oscillation might reflect an improved central timing of the carotid body discharge.

Attenuation of the P_{A,CO_2} oscillation. The two main sites at which the P_{CO_2} oscillation may be attenuated to a greater or lesser degree are the lung and the left ventricle. The mis-matching of alveolar ventilation and pulmonary capillary perfusion and the heterogeneity of pulmonary capillary transit times should both contribute to the attenuation (Yokota & Kreuzer, 1973). Their effects should be lessened with an increased activity of the heart, as occurs in muscular exercise and, to a lesser extent, in hypoxia. A more even perfusion of the lung in exercise reduces the degree of ventilation-perfusion inequality (West & Dollery, 1960). Also there is less variation in the pulmonary capillary transit times during exercise (Knopp & Bassingthwaite, 1969).

In the left ventricle the oscillation is temporally segmented and mixed with the residual blood volume. Therefore, any influence increasing the ratios of heart rate to respiratory rate (f_c/f_v) or of left ventricular end-diastolic to end-systolic volume (EDV/ESV) will limit the distortion of the P_{CO_2} oscillation at this site (Yamamoto, 1962; Yokota & Kreuzer, 1973). And, exercise should decrease the attenuation by effects on both ratios: f_c/f_v is increased in exercise (c.f. Yamamoto, 1962): this thesis,

Appendix 3, p.240 , and although the behaviour of the cardiac residual volumes is lacking in man, EDV/ESV increases during exercise in the conscious dog (Chapman et al., 1959).

The effects of hypoxia are less easy to predict. Asmussen & Nielsen (1955) found that in man the cardiac output (measured by dye dilution using T-1824) was increased during hypoxia (P_{a,O_2} ca. 40 torr) by 10-20% of the control value at rest and during exercise. The increase was due to an increased heart rate, the stroke volume tending to fall slightly.

In the present experiments, at rest f_v rose from ca. 20 min^{-1} to ca. 25 min^{-1}, on average (an increase of 25%). Although the conditions of this study and that of Asmussen & Nielsen are not directly compatible, it does appear that the tendencies for f_c and f_v to increase on exposure to hypoxia are of the same order.

Whether EDV/ESV is affected by the small reduction in stroke volume observed by Asmussen & Nielsen would be difficult to predict.

Thus, the effects of hypoxia on the degree of attenuation undergone by the P_{CO_2} oscillation in transit from the lungs to the carotid body would seem to be minimal.

The timing of the P_{A,CO_2} oscillation. The central timing of the oscillation in carotid body discharge in relation to the current respiratory cycle is determined by the ratio of breath duration and the circulation time between the lung and carotid body. In hypoxia, as discussed above, breath duration is shortened (f_v increased) and cardiac output is raised. An increase in cardiac output is one of the factors which

should decrease the lung-carotid body transit time: during exercise the transit time between the lung and ear lobe capillaries is shortened (Dejours et al., 1957a,b; Drysdale, personal communication), this being considered comparable to the lung-carotid body time (Jain et al., 1972). However, Drysdale (personal communication) found no systematic decrease in the lung-ear lobe circulation time when resting subjects were made hypoxic.

The occurrence of a reduced breath duration in the face of a relatively constant lung-carotid body circulation time must affect the central timing of the oscillating carotid body discharge. However, without prior knowledge of the central timing in euoxia, the effects of a changed timing in hypoxia cannot be predicted: the facility exists for either stimulating or depressing respiration.

Thus, in conclusion, the observed linear multiplication at rest between hypoxia and the alternate-breath P_{A,CO_2} oscillation may represent multiplication at the carotid body, possibly by a mechanism sensitive to the rate of change of P_{CO_2}. In addition, the possibility exists of there being a reflex modulation by changes in the central timing of the oscillating carotid body discharge. The alveolar-arterial transmission of the P_{CO_2} oscillation appears little changed, however.

<u>The multiplication between hypoxia and the CO_2 oscillation: in exercise</u>

In the previous chapter it was proposed that exercise interacted <u>additively</u> with the combined reflex effects of hypoxia and the alternate-breath P_{A,CO_2} oscillation (p.78 and Fig. 20), by analogy with the

steady-state observations of Asmussen & Nielsen (1957) and Bhattacharyya et al. (1970). Although this hypothesis may be a slight oversimplification (the $\dot{V}_E$, P_{A,CO_2} relation during hypoxic exercise is often curvilinear rather than linear), it allows the effects of exercise to be explored by linear regression analysis, as at rest.

At least some of the steady-state "additive" component is hypoxia-dependent (as shown by the rapid fall in $\dot{V}_E$ when oxygen is breathed), the remainder reflecting a neural drive to breathing (Cunningham et al., 1968). The nature of the hypoxia-dependency is not yet clear. Black & Torrance (1967b, 1971) and Cunningham (1974b) have proposed that the increased amplitude of the within-breath P_{A,CO_2} oscillation in exercise provides an increased chemoreflex drive to breathing in hypoxia, and that further modulation may occur as a result of an improvement in the central timing of the carotid body discharge (p.18). Others have proposed a central facilitation of the chemoreflex occurring independently of changes in the arterial blood gases (Hilton & Joels, 1964; Davies & Lahiri, 1973).

In the present study an attempt was made to separate the effects of oscillation amplitude and timing by inducing a P_{A,CO_2} oscillation of constant amplitude at rest and in exercise (the amplitude being comparable to that of the within-breath P_{A,CO_2} in moderate exercise). Therefore the differences observed in the oscillating responses between rest and exercise should principally reflect changes in the central timing of the carotid body discharge. If the major influence of the within-breath P_{A,CO_2} oscillation is exerted through its profile rather than its timing one might expect the effects of exercise in the present study to be of

little consequence in generating more prominent alternate-breath responses. An involvement of the carotid body in exercise was implied from the hypoxia-dependency of the oscillating responses, as at rest. There was a considerable increase in the incidence of oscillating responses (p.100) and of significant regression coefficients (p.114). Linear multiplication was indicated in 24 cases out of 117 (22.5%) from the collected results, representing an approximate doubling of the incidence at rest.

Some features of the hypoxia-dependency were common to the resting and exercising conditions: there was no evidence of a P_{A,O_2} threshold in the range of 200 to 100 torr; linear multiplication was still present in many cases after the responses had been normalised with respect to the run-mean; the most commonly involved variables were rather similar, though the range of involvement was wider.

The hypothesis of addition by exercise predicts that the regression coefficient is unchanged but that the hypoxia intercept occurs at a higher P_{A,O_2}. In only 3 cases did significant coefficients occur both at rest and in exercise: in 2, addition was confirmed (experiment 409.5: MEF, PEF), while in the third, further multiplication was indicated (experiment 421.4: PIF).

The enhanced status of the oscillating responses in exercise may result from a reduced alveolar-arterial attenuation and an improved central timing of the alternate-breath P_{CO_2} oscillation (p.152). Also it is evident from Fig. 23A (p.82) that, although the alternate-breath

oscillation in end-tidal P_{CO_2} is approximately equal at rest and in exercise, the maximum computed oscillation in alveolar P_{CO_2} is larger in exercise, reflecting a greater rate of CO_2 elimination. As the inspiratory and expiratory times are reduced in exercise (Kay et al., 1974b) the P_{A,CO_2} oscillation becomes sharper in profile.

The effects of changes in the central timing of the oscillating carotid body discharge should also be considered (p.153): for, both the lung-carotid body circulation time and breath duration are shortened in exercise. The lack of change in the phase relations of the output variables, both between themselves and with respect to the P_{A,CO_2} oscillation, on going from rest to exercise (p.107) indicates that the ratio of breath duration to lung-carotid body circulation time was not grossly altered. However, smaller significant changes in central timing could have occurred within the respiratory cycle but these would not have been detected by the methods of this thesis.

In conclusion, the observation that moderate exercise can potentiate the incidence of alternate-breath responses in hypoxia may imply that an improvement in the central timing of the carotid body discharge had occurred, and that this effect might provide part of the potentiating action of exercise on hypoxic hyperpnoea under more natural conditions. However, there was no indication of the relative contributions to the oscillating responses in exercise of reduced attenuation and changed central timing of the P_{CO_2} oscillation.

Rarely did exercise modify a pre-existing linear multiplication between hypoxia and the P_{A,CO_2} oscillation at rest. This reflected a rather low incidence of multiplication at rest rather than the absence of a further stimulation in exercise.

Variability of responses

There was considerable variability in the incidence of oscillating responses in different subjects, being especially marked in Series Two. It may be relevant that Band et al. (1970) were unable to elicit a respiratory stimulation in some cats by close delivery of CO_2 pulses to the carotid body. Whether this reflected a depression of chemoreflex activity by anaesthesia or whether the carotid body lacked the ability to transduce high frequency information on P_{CO_2} is not clear. If the latter were the case, one might invoke the phenomenon to account for the poor oscillating responses of subjects 425, 377 and 418.

Alternatively, the efficicacy of the P_{CO_2} at the carotid body might be poor as a result of substantial alveolar-arterial attenuation; or its reflex efficacy may be impaired by the central timing of the carotid body discharge such that the level of activity arriving centrally at sensitive phases of the respiratory cycle was similar on alternate breaths.

Concluding remarks

The ability of the human carotid body to respond to an alternate-breath P_{CO_2} oscillation when activated by hypoxia has been amply demonstrated at rest and during moderate exercise in a wide variety of respiratory output variables. The hypoxia-dependency could take the form of a linear multiplication between hypoxia and the CO_2 oscillation, especially in those variables which had been considered as being suitable indices of respiratory centre output. There were indications that the multiplication might involve a mechanism sensitive to the rate of change of P_{CO_2}.

The reflex effects of the oscillation proved to be more complex than previously imagined, perhaps reflecting the modulating effects conferred on the carotid chemoreflex by changes in the central timing of carotid body discharge. Thus either inspiration or expiration could be excited or depressed independently of the other. It was felt that the ubiquitous oscillation in FRC might reflect this situation, although an additional effect of changing airway resistance has also been considered. The behaviour of FRC and airway resistance in response to changes in carotid chemoreflex drive from one steady state to another warrants attention.

The results obtained during exercise lead to the possibility of a role in hypoxic exercise hyperpnoea of changes in the profile and central timing of the within-breath P_{A,CO_2} oscillation. Rather more specific studies on this point are needed. For example, the degree of alveolar-

arterial attenuation occurring at rest and in exercise could be explored by the techniques of indicator dilution theory: the attenuation undergone by a pulse of nitrogen introduced into the lung could be studied at the ear lobe with an ear-oximeter to record the time profile of the attenuated pulse in arterial saturation.

In addition, rather simple experiments could be performed to examine the relevance of the proposed change in central timing occurring in exercise. The lung-carotid body circulation time could be estimated from the lung-ear time (Jain et al., 1972) at rest and at various levels of exercise; when related to the corresponding breath duration time, this would provide an index of central timing.

Thus, the significance of Yamamoto's hypothesis (1960) concerning the role of the within-breath P_{A,CO_2} oscillation in the hyperpnoea of hypoxic exercise still remains to be established.

A P P E N D I X I

Table 1: Physical characteristics of subjects

Subject	Sex	Age	Height m.	Weight kg	Occupation
230	♂	23	1.77	65	Graduate student in physiology
368	♀	21	1.67	70	2nd year medical student
377	♂	19	1.78	67	1st year medical student
392	♂	23	1.74	70	Graduate student in physiology
409	♂	18	1.75	65	1st year medical student
418	♀	21	1.65	64	3rd year undergraduate in biochemistry
421	♀	20	1.52	51	1st year medical student
425	♂	27	1.78	71	Medical doctor

Table 2: The effects of mean flow on the pressure difference measured along the inspiratory and expiratory lines of the apparatus.

	Inspiratory line		Expiratory line	
Mean flow $l.min^{-1}$	Mean pressure $cm.H_2O$	Resistance $cm.H_2O/l.sec^{-1}$	Mean pressure $cm.H_2O$	Resistance $cm.H_2O/l.sec^{-1}$
20	0.100	0.300	0.230	0.690
40	0.150	0.225	0.330	0.495
60	0.250	0.250	0.460	0.460
80	0.400	0.300	0.580	0.431
100	0.525	0.320		
120	0.675	0.337		
140	0.875	0.375		

Table 3: Calibration of pneumotachometer (PTM) against a dry gas meter (GM) using various gas mixtures saturated with water vapour.

Gas mixture	1		2		3		4		5	
P_{CO_2}, torr	0		0		65		0		65	
P_{O_2}, torr	150		200		200		40		40	
Flow	GM	PTM	GM	PTM	GM	PTM	GM	PTM	GM	PTM
	$l.min^{-1}$	cm	$l.min^{-1}$	cm	$l.min^{-1}$	cm	$l.min^{-1}$	cm	$l.min^{-1}$	cm
	23.6	0.42	18.8	0.48	32.5	0.78	26.4	0.68	38.8	0.92
	50.4	0.83	52.5	1.08	75.9	1.52	50.3	1.07	98.8	1.83
	73.9	1.23	89.0	1.70	114.7	2.22	79.7	1.53	131.2	2.44
	97.3	1.63	124.5	2.32	154.4	2.97	104.0	1.97	166.4	3.03
	129.0	2.15	156.2	2.89	191.1	3.68	142.7	2.64	197.1	3.63
	155.5	2.63	184.4	3.43	223.7	4.28	168.1	3.08	224.3	4.18
	183.3	3.10	215.3	4.03	251.5	4.87	218.1	4.03	260.0	4.83
	216.3	3.73	240.3	4.88			255.6	4.75		
	245.8	4.38	263.3	5.05						
	274.6	4.95								

GM flow: $l.min^{-1}$ A.T.P.S.; PTM flow: cm deflection on Devices recorder.

Table 4: Calculation of some gas viscosities.

Assumptions: (i) P_B = 760 torr.
(ii) Average temperature of the gas in the PTM is 30°C or 34°C.
(iii) The viscosities of O_2, CO_2, N_2 and H_2 may be closely approximated by linear functions of the average temperature of the gas (Blumenfeld et al., 1973).
(iv) The mean viscosity, $\bar{\eta}$, of a mixture of gases is the linear combination of the viscosities of the pure gases weighted by their fractional concentrations, F (Blumenfeld et al., 1973).

a. Viscosities of gases at 30°C and 34°C:

Gas	$^{+}\eta$, deg. C^{-1} x 10^{-6} poise T = 30°C	T = 34°C
H_2O	149.70	151.98
O_2	208.96	210.15
CO_2	164.65	166.51
N_2	181.19	183.00

$^{+}$Data from Blumenfeld et al., 1973.

b. Viscosities of gas mixtures at 30° and 34°C:

Gas mixture	Gas	Partial pressure (torr)	F	T = 30°C η x F	T = 30°C $\bar{\eta}$ deg.C^{-1} x 10^{-6} poise	T = 34°C η x F	T = 34°C $\bar{\eta}$ deg.C^{-1} x 10^{-6} poise
1.	H_2O	47	0.062	9.28	184.707	9.42	186.494
	O_2	150	0.197	41.16		41.47	
	CO_2	0	0.000	0.00		0.00	
	N_2	563	0.741	134.26		135.60	
2.	H_2O	47	0.062	9.28	187.262	9.42	188.924
	O_2	220	0.289	60.39		60.73	
	CO_2	0	0.000	0.00		0.00	
	N_2	493	0.649	117.59		118.77	
3.	H_2O	47	0.062	9.28	185.952	9.42	187.621
	O_2	220	0.289	60.39		60.73	
	CO_2	60	0.079	13.01		13.15	
	N_2	433	0.570	103.28		104.31	

				T=30°C		T=34°C	
Gas mixture	Gas	p.p.	F	$\eta \times F$	$\bar{\eta}$	$\eta \times F$	$\bar{\eta}$
4.	H_2O	47	0.062	9.28	180.890	9.42	182.701
	O_2	40	0.053	11.08		11.14	
	CO_2	0	0.000	0.00		0.00	
	N_2	673	0.886	60.53		162.14	
5.	H_2O	47	0.062	9.28	179.584	9.42	181.398
	O_2	40	0.053	11.08		11.14	
	CO_2	60	0.079	13.01		13.15	
	N_2	613	0.807	146.22		147.68	

Table 5: The size and significance of alternate-breath oscillations in PTM output induced by alternate breaths of high P_{CO_2} (60 torr) and low P_{CO_2} (0 torr)

The results presented below derived from a simulated experiment, in which the subject was replaced by a sine-wave pump. The "tidal volume" and "breath duration" of the pump could be altered to cover the range of values encountered in a typical experiment. The P_{CO_2} and P_{O_2} of inspiratory gas mixtures likewise covered a typical experimental range. Output from the PTM was recorded as flow (PIF), volume ($V_{T,I}$) and acceleration (PIA). Alternate-breath oscillations in these three variables were computed and processed as described in the text, (p.67).

a. The effects of varying inspiratory tidal volume ($\bar{V}_{T,I}$) and breath duration ($\bar{T}_T$) at constant mean flow ($\dot{v}$, = 40 l.min^{-1}) and P_{O_2} (200 torr):

		Alternate-breath oscillation		
$\bar{V}_{T,I}$ l.	$\bar{T}_T$ sec	$V_{T,I}$ l.	PIF l.min^{-1}	PIA l.sec^{-2}
0.5	0.75	N.S.	N.S.	N.S.
1.5	2.25	N.S.	N.S.	N.S.
3.0	4.50	N.S.	N.S.	N.S.

b. The effects of varying mean flow ($\bar{\dot{v}}$) and P_{O_2} at constant $V_{T,I}$ (2.0 l.):

		Alternate-breath oscillation		
P_{O_2} torr	$\bar{\dot{v}}$ l.min^{-1}	$V_{T,I}$ l.	PIF l.min^{-1}	*PIA l.sec^{-2}
200	40	N.S.	N.S.	0.18^{++}
200	50	N.S.	N.S.	N.S.
200	60	N.S.	N.S.	N.S.
100	40	N.S.	N.S.	N.S.
100	50	N.S.	N.S.	N.S.
100	60	N.S.	N.S.	N.S.
50	40	N.S.	N.S.	-0.18^{++}
50	50	N.S.	N.S.	N.S.
50	60	N.S.	N.S.	N.S.
50	70	N.S.	N.S.	N.S.
50	80	N.S.	N.S.	N.S.

*PIA oscillations measured to nearest 0.18 l.sec^{-2}

N.S.: amplitude of oscillation not different from zero.

Table 6: Performance of integrator and differentiator for the pneumotachometer, in response to an electrical sine-wave.

Period	Deviation from predicted lag			
	Integrated wave		Differentiated wave	
sec	sec	% of period	sec	% of period
1.00	0.00	0.0	0.05	5.0
1.55	0.05	2.6	0.10	5.1
1.95	0.00	0.0	0.10	4.1
2.55	0.05	2.0	0.10	3.9
3.15	0.05	1.6	0.15	4.8
3.35	0.00	0.0	0.05	1.5
3.65	0.00	0.0	0.10	2.7

Time measured to nearest 0.05 sec

Table 7

a. Calibration of the mass spectrometer (head 2) for CO_2 in O_2 and in N_2.

CO_2 in O_2 P_{CO_2}, torr		CO_2 in N_2 P_{CO_2}, torr	
Lloyd-Haldane	Mass Spectrometer	Lloyd-Haldane	Mass Spectrometer
18.21	19.30	20.36	19.90
35.28	35.85	35.49	34.35
40.80	41.85	39.94	39.80
44.60	45.85	45.74	45.35
49.26	50.35	50.33	49.35
59.37	60.85	60.01	59.35

Regression equations:-

CO_2 in O_2: $P_{CO_2,M-S} = 1.01\ P_{CO_2,Ll-H} + 0.63$

CO_2 in N_2: $P_{CO_2,M-S} = 1.00\ P_{CO_2,Ll-H} - 0.45$

b. Calibration of the mass spectrometer (head 1) for O_2 in N_2.

P_{O_2}, torr

Lloyd-Haldane	Mass Spectrometer
46.54	45.89
64.04	63.80
80.00	80.33
96.94	96.48
147.21	145.12

Regression equation:-

$P_{O_2,M-S} = 0.98\ P_{O_2,Ll-H} + 0.86$

Table 8: Calibration of Parkinson-Cowan dry gas meter (Type CD, No.01334) with dry air.

Gas flows ($l.min^{-1}$)	
Standard gas meter Type CD, No. 02011	Test gas meter Type CD, No. 01334
17.1	16.9
29.3	29.1
39.6	39.2
50.8	50.6
63.6	63.6
74.1	73.7
82.9	82.6
96.8	96.9
104.7	105.5

Regression equation:-

$$\dot{V}_{TEST} = 0.99\ \dot{V}_{STD} + 0.54$$

Table 9: Calibration of the Wedge spirometer for steady flows of air.

Air flow (37°C, saturated) $l.min^{-1}$	Wedge spirometer output on Devices recorder (cm)
20	0.475
30	0.75
40	1.00
50	1.25
60	1.475
70	1.70
80	1.95
90	2.20
100	2.50
110	2.75
120	2.975
140	3.45
150	3.70
160	3.95
170	4.20
180	4.425
190	4.65

Regression equation:-

Deflection = 0.024. Flow + 0.068

Table 10: Performance of the integrator for the wedge spirometer, in response to an electrical sine-wave.

Period sec	Deviation from predicted lag
0.50	All measured deviations were less
1.00	than 0.05 sec
1.50	
1.95	
2.45	
3.00	
3.30	
3.80	

Time measured to nearest 0.05 sec

Table 11: Measurement limits

Variable / Expt	P_{A,CO_2} torr	P_{A,O_2} torr	$V_{T,E}$ ml	$V_{T,I}$ ml	PEF l/min	PIF l/min	$IPIA_2$ l/sec^2	T_T msec	T_E msec	T_I msec	DFRC ml
368.4 (1 and 2)	0.5	1.5	35					50	50	50	
377.5	0.5	1.5	35					50	50	50	
392.6	0.5	1.5	35					50	50	50	
418.1	0.5	1.5	25					50	50	50	
230.15	0.5	1.5	35					50	50	50	
409.5	0.5	1.5	30	30	3.0	2.5	0.09	50	50	50	30
409.6	0.5	1.5	30	30	3.0	2.5	0.09	50	50	50	30
421.2	0.5	1.5	20	20	1.7	1.4	0.04	50	50	50	20
421.4	0.5	1.5	20	20	2.0	1.7	0.17	50	50	50	20
421.6	0.5	1.5	20	20	1.7	1.8	0.20	50	50	50	20
425.2	0.5	1.5	40	40	4.9	2.4	0.08	50	50	50	40
425.5	0.5	1.5	40	40	5.2	2.4	0.20	50	50	50	40
392.13	0.5	1.5	40	40	5.0	2.4	0.08	50	50	50	40
392.15	0.5	1.5	30	30	4.5	2.4	0.14	50	50	50	30

The prediction of an oscillating cross-correlation function for the P_{A,CO_2} transient.

The P_{A,CO_2} transient was that produced by converting an alternate-breath oscillation of P_{A,CO_2} (OSC) to a steady P_{A,CO_2} (STEADY): it consisted of 10 OSC and 10 STEADY breaths. This transient is simulated below, the output following the input almost faithfully, with a latency of 2 breaths. The cross-correlation function (the variation of r_K with the time displacement, K) was characterised for K = 0, 1, 2, 3 and 4 breaths, with r_K being calculated according to the formula on p.70.

The simulated transient:-

	Data		
	Input	Output	Results
	1.01	1.00	Cross-correlation coefficients
	2.01	1.99	r_0 = 0.911
	1.00	0.99	r_1 = -0.956
	2.02	2.00	r_2 = 1.000
OSC	0.98	1.01	r_3 = -0.953
	1.99	2.01	r_4 = 0.899
	1.00	1.00	
	2.01	1.99	
	1.01	1.01	
	1.99	2.00	
	1.50	1.01	Latency of 2 breaths
	1.49	2.00	
	1.51	1.51	
STEADY	1.50	1.50	
	1.52	1.51	
	1.49	1.52	
	1.51	1.52	
	1.50	1.49	
	1.50	1.50	
	1.49	1.49	

The resulting values of r_k oscillated between positive (even values of k) and negative (odd values of k), being maximum and positive for k = 2 (the latency between input and output).

APPENDIX II

Normality of data in Series Two

This is an account of the results upon which the conclusions concerning normality in Chapter 3 (p. 80) are based. Complete data on non-normality are presented for each experiment at the end of this account (p.180). The terminology used here originates from the statistical account of normality in Chapter 2 (p. 65).

Breath-by-breath non-normality of P_{A,CO_2}

OSC runs. The Kolmogorov-Smirnov statistic, d_{max}, (an index of non-normality) differed from zero in 99 out of 101 runs. The frequency distributions were all bimodal (platykurtotic), having a mean g_2 value of -1.9 (range: -1.4 to -2.0).

STEADY runs. Non-normality, as indicated by d_{max}, occurred in 22 runs out of 91 (15 at rest; 7 in exercise), being distributed fairly evenly between the nine experiments. The nature of the departure from normality had little consistency between runs.

Breath-by-breath non-normality of output variables

The occurrence of non-normality was assessed for the collected experiments as follows. For each run-type (rest OSC and STEADY; exercise OSC and STEADY), the total number of variables not normally distributed (a) was expressed as a percentage of the grand total of variables of all runs concerned (13 x no. of runs, = n); Table 10.

The largest degree of non-normality was found in the STEADY runs at rest (11.2%; experiment range 0-24.4%), followed by the STEADY runs in exercise (8.6%; range 1.3 - 21.5%), the OSC runs in exercise (3.6%; range 0-21.5%), and the OSC runs at rest (0.2%; range 0-15.4%). No statistical test of the difference in the degree of non-normality between run-types was made; however, it seemed unlikely that any significant differences existed. The average degree of non-normality for the pooled run-types of all experiments was 8.1%.

The most common non-normally distributed variable in each of the four run types was T_I, with T_T, T_E, $V_{T,E}$ and $V_{T,I}$ also showing varying degrees of prominence (Table 11). Pooling of the run-types gave a similar pattern. Subsequent inspection of the experimental records showed that many of those runs possessing non-normality in T_T, T_I or T_E contained evidence of interference by events considered extraneous to the expected respiratory response (swallowing, induced by the accumulation of saliva in the subject's mouth; coughing). It was decided to remove the affected breaths from the records of all variables, and then to re-examine their frequency distributions.

Non-normality of output variables, after removal of extraneous disturbances

After removal of disturbances, the occurrence of non-normality was assessed as above. The results are shown in Table 12. The pattern of non-normality was similar to that noted before, the largest degree occurring in the STEADY runs at rest (7.0%; range 0-21.2%). In all

cases the degree of non-normality was reduced, on average, to about 0.5 of its pre-existing level. No significant differences were considered to exist between the four run-types. On pooling the results on the four run-types, the average degree of non-normality was 5.1%, compared with 8.1% prior to the removal of disturbances.

The distribution of non-normality between the output variables for both the individual run-types and the pooled run-types was very similar (Table 12): only the latter will be described. An absolute reduction in the degree of non-normality was seen in all variables, when compared with the unedited data. However, when expressed as a percentage of the total number of non-normal events, the distribution of non-normality was little changed.

The possible effects of hypoxia on the pattern and degree of non-normality were examined by comparing the results obtained from hyperoxic runs (P_{A,O_2} 180 torr or more) with those from hypoxic runs (P_{A,O_2} of 70 torr or less). Taking the pooled results on the four run-types (Table 13), the average non-normality was slightly greater in hyperoxia than in hypoxia, as was the variation between run-types (hypoxia: mean = 5.2%, range = 2.7 - 6.5%; hyperoxia: mean = 8.3%, range = 4.5 - 15.4%). In both hypoxia and hyperoxia, the largest degree of non-normality was present in the STEADY runs at rest.

The distribution of non-normality between the output variables for the pooled runs in hypoxia and in hyperoxia appeared to be similar, when

examined as the percentage degree of non-normality (Table 14), if the small number of hyperoxic runs was taken into consideration.

Relations between the non-normality of breath-by-breath P_{A,CO_2} and output variables

It seemed important to establish whether the observed non-normality in output variables was a direct result of the patterns described for P_{A,CO_2}, or due to other influences.

If some, or all, of the output variables were linearly related to P_{A,CO_2} on a breath-by-breath basis, one might expect the form of their frequency distributions to be similar to that of P_{A,CO_2}. However, the demonstration of such similarity is not sufficient evidence to conclude that P_{A,CO_2} had induced the non-normality.

In none of the OSC runs was the bimodal frequency distribution of P_{A,CO_2} reflected in the frequency distributions of any output variable. In only 10 out of 91 STEADY runs was there any correspondence between the frequency distributions of P_{A,CO_2} and an output variable, as would be predicted if the breath-by-breath variation in P_{A,CO_2} was influencing respiration.

Relations between the non-normality of breath-by-breath output variables

It was considered of no great merit to present a detailed empirical description of the non-normality existing amongst the output variables, unless this would shed light on any mechanism of interrelation between selected variables. The only phenomenon to be studied in this context

was the occurrence of augmented breaths. The presence of one or two augmented breaths in a run could perhaps impose a degree of non-normality on the frequency distributions of breath-by-breath $V_{T,I}$ and T_I, the large values producing a right-skewed distribution (g_1 positive). This prediction was examined for each subject. All runs whose non-normality was thought to be induced by the presence of augmented breaths are marked (A.B.) in the following non-normality tables.

In the experiments performed on subjects 409 and 425, no augmented breaths were apparent, though, on isolated occasions a biphasic profile of inspiratory flow and acceleration was seen in combination with an inspiratory tidal volume and breath duration of more usual dimensions. The occurrence of such a biphasic profile, alone, is not sufficient to classify a breath as being augmented: the corresponding tidal volume must also be considerably greater than the mean.

The other two subjects (421 and 392) both showed consistent but differing patterns of augmented breaths. Subject 421 produced an occasional augmented breath (sometimes two) in most runs, which were otherwise of a fairly regular nature with respect to all breath-by-breath output variables. The peak inspiratory flow and acceleration and peak expiratory flow of augmented breaths did not appear to depart greatly from the mean level.

In <u>experiment 421.2</u>, a total of 10 augmented breaths was recorded from 8 runs out of 19. Of these runs, two ($A.B._1$ and $A.B._2$) were non-normal with respect to $V_{T,I}$, having a positive value of g_1 (skewed

to the right), as would be expected if an augmented breath were contributing to the non-normality. In run A.B.$_1$, $V_{T,E}$, T_I, T_E and T_I were also non-normal (positive g_1). It is reasonable to conclude that the presence of augmented breaths was at least partly responsible for the observed non-normality. Whether this is also the cause of the isolated instances of non-normality of T_I or T_E (positive g_1) is less clear.

In experiment 421.4, 8 augmented breaths were recorded from 8 runs out of 19. Two of the runs (A.B.$_1$ and A.B.$_2$) showed non-normal, right-skewed distributions for $V_{T,I}$. In experiment 421.6, a total of 17 augmented breaths occurred in 14 runs out of 23. Only two of these runs (A.B.$_1$ and A.B.$_5$) showed the appropriate non-normality of $V_{T,I}$, but five runs (A.B.$_1$ to A.B.$_6$, with the exception of A.B.$_5$) showed non-normality of $V_{T,E}$.

The pattern of augmented breaths found in the experiments of subject 392 was more complex, as a result of the large amount of breath-by-breath variation in tidal volume. This was especially marked in runs where the drive to breathing was not too intense. The occurrence of breaths having relatively large tidal volumes and breath durations was quite common, in some cases one every 5-10 breaths. However, by no means all of these breaths could be considered as augmented breaths, there being no evidence of a biphasic pattern in inspiratory flow and acceleration. No analysis of augmented breaths was performed on experiment 392.13, where the occurrence of large breaths was especially frequent.

In Experiment 421.12, 16 augmented breaths were identified in 7 runs out of 22, an average of 2 per run (cf. 421: 1 per run). Two of these runs (A.B.$_1$ and A.B.$_2$) showed a non-normal, right-skewed frequency distribution for $V_{T,I}$.

Thus, it was concluded that augmented breaths could distort the frequency distributions of breath-by-breath $V_{T,I}$, $V_{T,E}$ and T_T so that they were skewed to the right. However, they did not appear to be the sole cause of the observed non-normality.

Non-normality of alternate-breath differences

The samples of alternate-breath differences computed for each variable in each run (Chapter 2, p. 67) were tested for their approximation to a normal distribution, as described previously. The non-normal runs are presented in Table 15 (p.213). All the frequency distributions were unimodal, departing from normality only rarely: for P_{A,CO_2}, 8 runs out of 192 (4.2%) were non-normal, and for the collected output variables, 10 out of 2496 events (13 x 192), or 0.04%.

Table 1

409.5

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	112.5	None			
	69.0	None			
	54.0	None			
	54.0	P_{A,CO_2}	<0.05	-1.78	11.18
	46.5	None			
Rest, P_{A,CO_2} oscillating	115.5	P_{A,CO_2}	<0.01		-1.95
	69.0	P_{A,CO_2}	<0.01		-2.00
	55.5	P_{A,CO_2}	<0.01		-2.00
	54.0	P_{A,CO_2}	<0.01		-1.95
	46.5	P_{A,CO_2}	<0.01		-1.93
Exercise, P_{A,CO_2} steady	117.0	None			
	67.5	None			
	57.0	P_{A,CO_2}	<0.01	-5.67	37.0
	52.5	$\dot{V}_I$	<0.05	-2.57	10.32
		T_E	<0.01	2.97	11.96
	51.0	None			
Exercise, P_{A,CO_2} oscillating	114.0	P_{A,CO_2}	<0.01		-1.96
	69.0	P_{A,CO_2}	<0.01		-1.90
	57.0	P_{A,CO_2}	<0.01		-1.98
	52.5	P_{A,CO_2}	<0.01		-2.02
	51.0	P_{A,CO_2}	<0.01		-2.03
	51.0	P_{A,CO_2}	<0.01		-1.97

Table 2

409.6

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	129.0	None			
	78.0	None			
	63.0	None			
	55.5	None			
	48.0	P_{A,CO_2}	<0.05	0.96	
		T_T	<0.05	0.71	
		T_E	N.S.		
Rest, P_{A,CO_2} oscillating	127.5	P_{A,CO_2}	<0.01		-1.98
	78.0	P_{A,CO_2}	<0.01		-1.96
		T_I	N.S.		
	63.0	P_{A,CO_2}	<0.01		-1.98
	57.0	P_{A,CO_2}	<0.01		-1.92
		T_I	<0.05	0.81	
	48.0	P_{A,CO_2}	<0.01		-1.90
		T_I	<0.02	0.69	0.10
Exercise, P_{A,CO_2} steady	126.0	DFRC	<0.05	3.79	23.01
	75.0	None			
	63.0	None			
	57.0	None			
	51.0	None			
Exercise, P_{A,CO_2} oscillating	127.5	P_{A,CO_2}	<0.01		-1.95
	75.0	P_{A,CO_2}	<0.01		-1.95
	63.0	P_{A,CO_2}	<0.01		-2.00
		PEF	<0.05	0.65	
	57.0	P_{A,CO_2}	<0.01		-1.95
	49.5	P_{A,CO_2}	<0.01		-1.98
		T_E	<0.05	0.60	

Table 3

421.2

		P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	A.B.$_1$	112.5	P_{A,CO_2}	<0.05	0.85	1.23
		76.5	$V_{T,E}$	<0.01	3.54	18.14
			$V_{T,I}$	<0.05	3.32	17.29
			T_T	<0.05	1.25	
			T_E	<0.01	1.69	3.01
			T_I	<0.01	1.62	3.45
		76.5	None			
		66.0	$V_{T,E}$	N.S.		
			$V_{T,I}$	N.S.		
			MEF	N.S.		
			PEF	N.S.		
			T_T	N.S.		
			DFRC	N.S.		
	A.B.$_2$	61.5	$V_{T,I}$	<0.01	1.30	9.52
Rest, P_{A,CO_2} oscillating		112.5	P_{A,CO_2}	<0.01		-1.93
		79.5	P_{A,CO_2}	<0.01		-1.96
		76.5	P_{A,CO_2}	<0.01		-1.92
			T_T	<0.01	3.29	13.71
			T_E	<0.01	4.18	21.62
			T_I	<0.05	2.48	12.00
		67.5	P_{A,CO_2}	<0.01		-1.89
			T_I	<0.01	5.19	39.92
		61.5	P_{A,CO_2}	<0.01		-1.91
			T_I	<0.05	1.64	6.08

421.2 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} steady	120.0	None			
	100.5	None			
	88.5	None			
	70.5	T_E	<0.01	3.32	14.02
Exercise, P_{A,CO_2} oscillating	121.5	P_{A,CO_2}	<0.01		-1.76
	103.5	P_{A,CO_2}	<0.01		-1.83
	102.0	P_{A,CO_2}	<0.01		-1.91
	90.0	P_{A,CO_2}	<0.01		-1.99
	70.5	P_{A,CO_2}	<0.01		-1.94
		$\dot{V}_E$	<0.05	-2.30	10.42

421.4

Table 4

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	193.5	None			
	67.5	P_{A,CO_2}	<0.05	1.07	1.40
		MIF	<0.01	1.52	1.76
		T_I	<0.01	-1.05	1.42
	58.5	P_{A,CO_2}	<0.01	-6.08	50.88
		$V_{T,I}$	<0.01	-1.57	6.75
		PEF	<0.01	0.83	
		T_T	<0.01	2.39	9.65
		T_E	<0.05	4.16	27.67
		T_I	<0.02	-1.17	8.39
		DFRC	<0.01	-3.15	14.20
	51.0	P_{A,CO_2}	<0.01	-7.95	68.82
		$V_{T,E}$	<0.01	-3.02	24.50
		$V_{T,I}$	<0.05	-1.61	15.17
		T_I	<0.01	-0.58	16.60
Rest, P_{A,CO_2} oscillating A.B.1	195.0	P_{A,CO_2}	<0.01		-1.85
		$V_{T,E}$	<0.05	1.95	9.39
		$V_{T,I}$	<0.01	2.61	15.13
		T_T	N.S.		
	97.5	P_{A,CO_2}	<0.01		-1.36
	66.0	P_{A,CO_2}	<0.01		-1.95
	58.5	P_{A,CO_2}	<0.01		-1.90
	54.0	P_{A,CO_2}	<0.01		-1.88
		T_I	<0.01	0.56	

421.4 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} steady	189.0	P_{A,CO_2}	<0.05	1.06	2.87
		$V_{T,I}$	<0.05	2.09	14.65
		$\dot{V}_I$	<0.05	-2.61	13.35
		MIF	<0.01	-0.94	8.67
		PIF	<0.01	-1.65	3.64
		T_T	<0.01	4.05	22.37
		T_I	<0.01	4.25	30.79
	91.5	$V_{T,E}$	<0.05	-0.96	
	76.5	T_I	<0.05	1.67	5.53
	66.0	None			
	58.5	P_{A,CO_2}	<0.01	7.05	56.41
		T_E	<0.01	3.08	12.88
		T_I	<0.01	1.32	3.08
Exercise, P_{A,CO_2} oscillating	189.0	P_{A,CO_2}	<0.01		-1.89
		T_T	N.S.		
		T_I	N.S.		
	91.5	P_{A,CO_2}	<0.01		-1.98
	78.0	P_{A,CO_2}	<0.01		-1.95
	66.0	P_{A,CO_2}	<0.01		-1.90
		T_T	<0.05	3.73	25.06
		T_I	<0.05	2.63	12.41
	57.0	P_{A,CO_2}	<0.01		-1.96

Table 5

421.6

		P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	A.B.$_1$	199.5	$V_{T,E}$	<0.01	2.08	12.90
			$V_{T,I}$	<0.05	2.15	13.04
			MEF	<0.05	0.92	
			MIF	<0.01	-4.14	31.47
			T_I	<0.01	7.58	65.66
		90.0	MIF	N.S.		
			T_I	<0.01	0.95	2.02
	A.B.$_2$	75.0	$V_{T,E}$	<0.05	0.83	6.80
			MIF	N.S.		
			T_I	N.S.		
		57.0	P_{A,CO_2}	<0.05	-2.04	7.63
			$V_{T,I}$	<0.05	-1.06	2.02
			MIF	N.S.		
			T_I	N.S.		
	A.B.$_3$	54.0	P_{A,CO_2}	<0.01	-8.06	66.34
			$V_{T,E}$	<0.02	2.42	11.14
			T_I	<0.01	4.23	27.37
		49.5	$V_{T,E}$	<0.02	-1.27	17.50
			$V_{T,I}$	N.S.		
			MIF	N.S.		
			T_I	N.S.		
			DFRC	<0.01	5.26	42.58

421.6 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} oscillating	199.5	P_{A,CO_2}	<0.01		-1.86
		$V_{T,I}$	N.S.		
		MIF	<0.02	-1.33	11.96
		T_I	<0.01	5.48	43.97
	91.5	P_{A,CO_2}	<0.01		-1.91
		MIF	N.S.		
		T_T	N.S.		
		T_I	N.S.		
	75.0	P_{A,CO_2}	<0.01		-1.90
	58.5	P_{A,CO_2}	<0.01		-1.89
		T_I	<0.01	6.12	57.15
	54.0	P_{A,CO_2}	<0.01		-1.94
		T_T	<0.05	1.73	6.09
		T_I	<0.01	7.28	64.58
A.B.4	49.5	P_{A,CO_2}	<0.01		-1.84
		$V_{T,E}$	<0.02	0.81	9.97
		MIF	<0.05	-2.65	11.10
		T_I	<0.01	4.52	26.24
	45.0	P_{A,CO_2}	<0.01		-1.95
		T_I	N.S.		

421.6 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} steady	199.5	None			
	91.5	P_{A,CO_2}	<0.01	-7.64	63.73
		$V_{T,E}$	<0.01	-0.06	10.50
		$V_{T,I}$	<0.02	-1.09	7.79
		$\dot{V}_E$	<0.01	-4.04	23.40
		MIF	<0.01	-4.46	30.05
		T_T	<0.01	2.24	11.72
		T_E	<0.05	1.38	5.62
		T_I	<0.01	6.07	52.00
A.B. 5	73.5	P_{A,CO_2}	<0.05	1.03	1.38
		$V_{T,I}$	<0.05	0.75	4.74
		T_T	<0.05	1.98	7.14
		T_E	<0.02	1.20	3.90
	69.0	MIF	<0.05	-2.09	10.72
		T_T	<0.02	1.89	6.22
		T_I	<0.01	3.46	19.84
	57.0	T_T	<0.01	1.06	

421.6 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} oscillating	199.5	P_{A,CO_2}	<0.01		-1.95
		T_I	<0.05		
	93.0	P_{A,CO_2}	<0.01		-1.82
		$\dot{V}_E$	N.S.		
		T_I	N.S.		
	72.0	P_{A,CO_2}	<0.01		-1.94
		MIF	N.S.		
		T_T	<0.05	2.27	12.19
		T_I	N.S.		
	69.0	P_{A,CO_2}	<0.01		-1.91
		MIF	N.S.		
		T_T	<0.02	3.33	18.44
		T_E	<0.01	2.87	15.07
		T_I	N.S.		
A.B. 6	57.0	P_{A,CO_2}	<0.01		-1.97
		$V_{T,E}$	<0.05	1.34	4.20
		T_T	<0.01	4.41	26.11
		T_E	<0.01	5.02	36.65
		T_I	<0.02		1.24

Table 6

425.2

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	189.5	P_{A,CO_2}	<0.02	1.24	1.60
	100.5	P_{A,CO_2}	<0.05		
	70.5	None			
	66.0	MEF	N.S.		
		T_T	N.S.		
		T_E	N.S.		
		T_I	N.S.		
	55.5	P_{A,CO_2}	<0.01	0.83	
	51.0	None			
Rest, P_{A,CO_2} oscillating	189.5	P_{A,CO_2}	<0.01		-1.96
	99.0	P_{A,CO_2}	<0.01		-1.74
		PIF	N.S.		
		T_E	N.S.		
	69.0	P_{A,CO_2}	<0.01		-1.97
	64.5	P_{A,CO_2}	<0.01		-1.97
	57.0	P_{A,CO_2}	<0.01		-1.93
		$\dot{V}_E$	N.S.		
		T_T	N.S.		
		T_I	N.S.		
	49.5	P_{A,CO_2}	<0.01		-1.72

425.2 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} steady	189.5	None			
	100.5	None			
	88.5	None			
	66.0	None			
	64.5	None			
	60.0	T_I	N.S.		
Exercise, P_{A,CO_2} oscillating	189.5	P_{A,CO_2}	<0.01		-1.69
	100.5	P_{A,CO_2}	<0.01		-1.79
	88.5	P_{A,CO_2}	<0.01		-1.77
	66.0	P_{A,CO_2}	<0.01		-1.82
	63.0	P_{A,CO_2}	<0.01		-1.66
		T_T	<0.01	1.60	3.16
		T_I	<0.05	1.04	1.99
	60.0	P_{A,CO_2}	<0.01		-1.80

Table 7

425.5

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	202.5	T_E	<0.05	-2.03	11.79
	79.5	None			
	61.5	P_{A,CO_2}	<0.02	1.05	3.08
	54.0	None			
Rest, P_{A,CO_2} oscillating	201.0	P_{A,CO_2}	<0.01		-1.72
	79.5	P_{A,CO_2}	<0.01		-1.83
		T_T	<0.01	2.16	8.19
		T_I	<0.01	4.53	29.9
	61.5	P_{A,CO_2}	<0.01		-1.96
	55.5	P_{A,CO_2}	<0.01		-1.88
	54.0	P_{A,CO_2}	<0.01		-1.86
	54.0	P_{A,CO_2}	<0.01		-1.96
		T_I	<0.01	3.66	20.89
Exercise, P_{A,CO_2} steady	199.5	None			
	82.5	None			
	72.0	PEF	<0.02	-4.73	30.30
	60.0	$V_{T,I}$	N.S.		
Exercise, P_{A,CO_2} oscillating	205.5	P_{A,CO_2}	<0.01		-1.95
	81.0	P_{A,CO_2}	<0.01		-1.88
	70.5	P_{A,CO_2}	<0.01		-1.87
	60.0	P_{A,CO_2}	<0.01		-1.95
	58.5	P_{A,CO_2}	<0.01		-1.91

Table 8

392.13

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady	202.5	$V_{T,E}$	<0.05	1.43	1.62
		$V_{T,I}$	<0.05	1.14	
		MIF	<0.02	1.59	2.34
		PIF	<0.01	1.75	2.47
		T_E	N.S.		
	111.0	None			
	72.0	None			
	57.0	None			
	55.5	P_{A,CO_2}	<0.01	-3.97	27.27
	51.0	DFRC	<0.01		15.81
Rest, P_{A,CO_2} oscillating	202.5	P_{A,CO_2}	<0.05		-1.87
	111.0	P_{A,CO_2}	<0.02		-1.63
	72.0	P_{A,CO_2}	<0.01		-1.90
	57.0	P_{A,CO_2}	<0.01		-1.87
	57.0	P_{A,CO_2}	<0.01		-1.88
	51.0	P_{A,CO_2}	<0.01		-1.92

392.13 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} steady	202.5	None			
	97.5	None			
	87.0	$\dot{V}_E$	N.S.		
		T_I	N.S.		
	76.5	None			
	60.0	P_{A,CO_2}	<0.01	-2.64	20.41
		T_T	N.S.		
		T_E	N.S.		
	60.0	$V_{T,E}$	<0.05	-3.37	13.31
		$\dot{V}_E$	<0.05	-2.08	8.89
		$\dot{V}_I$	N.S.		
		MEF	<0.05	-2.50	8.96
		PEF	<0.01	-2.99	10.41
		T_E	N.S.		
		T_I	<0.02	-1.34	6.82
		DFRC	<0.01		10.32
Exercise, P_{A,CO_2} oscillating	204.0	T_I	<0.01	-2.62	10.11
		DFRC	<0.01		23.49
	100.5	P_{A,CO_2}	<0.01		-1.86
	88.5	P_{A,CO_2}	<0.01		-1.88
	78.0	None			
	60.0	P_{A,CO_2}	<0.01		-1.88
	58.5	P_{A,CO_2}	<0.01		-1.90
	57.0	P_{A,CO_2}	<0.01		-1.89

Table 9

392.15

		P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Rest, P_{A,CO_2} steady		208.5	$V_{T,I}$	<0.01	1.66	2.47
			T_E	<0.05	1.93	6.43
		93.0	P_{A,CO_2}	<0.05	1.54	2.61
			$\dot{V}_E$	<0.05		
			MIF	<0.02	1.70	3.13
		70.5	T_T	N.S.		
			MIF	<0.05	1.01	1.91
	$^{A.B.}_{1}$	60.0	$V_{T,I}$	<0.05	0.79	
		52.5	P_{A,CO_2}	<0.02		
			$V_{T,E}$	N.S.		
			$\dot{V}_E$	N.S.		
			MIF	N.S.		
			T_I	N.S.		
Rest P_{A,CO_2} oscillating		208.5	P_{A,CO_2}	<0.05		-1.65
		91.5	P_{A,CO_2}	<0.01		-1.65
		72.0	P_{A,CO_2}	<0.01		-1.94
			MIF	<0.01	3.07	12.24
			T_E	<0.02	1.61	3.68
		61.5	P_{A,CO_2}	<0.01		-1.85
		52.5	P_{A,CO_2}	<0.01		-1.77
			T_E	<0.05	2.35	10.47

392.15 continued

		P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} steady		201.0	None			
	A.B.2	90.0	$V_{T,I}$	<0.05	0.72	
			T_E	<0.01	3.68	18.17
		60.0	P_{A,CO_2}	<0.01	-7.09	57.41
		52.5	T_T	<0.05	1.31	2.05
			T_I	N.S.		
		49.5	PIA	<0.01	-2.02	5.13

392.15 continued

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
Exercise, P_{A,CO_2} oscillating	202.5	P_{A,CO_2}	<0.01		-1.93
		T_E	<0.05	1.76	4.23
	90.0	P_{A,CO_2}	<0.01		-1.98
	72.0	P_{A,CO_2}	<0.01		-1.95
	64.5	P_{A,CO_2}	<0.01		-1.92
		PIA	<0.05	-1.10	
		T_I	<0.05	1.57	2.48
	63.0	P_{A,CO_2}	<0.01		-1.96
		$\dot{V}_E$	N.S.		
		MIF	<0.05	-1.86	10.57
		PIA	<0.05	-0.98	
		T_T	<0.02	1.98	6.37
		T_E	<0.02	1.10	1.68
		T_I	<0.01	4.56	32.23
	55.5	P_{A,CO_2}	<0.01		-1.99
		$V_{T,E}$	<0.05	-1.85	5.62
		$V_{T,I}$	<0.05	-1.31	3.40
		PIA	<0.01	-1.79	2.86
		T_T	<0.05	1.14	1.33
		T_E	<0.02	0.89	2.57
	49.5	P_{A,CO_2}	<0.01		-2.04
		PIA	<0.01	-1.62	2.53

Table [10]: Non-normality of unedited output variables.

Type of run	Rest, STEADY		Rest, OSC		Exercise, STEADY		Exercise, OSC		Run-types pooled	
Experiment	a/n	%	a/n	%	a/n	%	a/n	%	a/r	%
409.5	0/65	0%	0/65	0%	2/65	3.1%	0/78	0%	2/273	0.7%
409.6	2/65	3.1%	3/65	4.6%	2/65	3.1%	2/65	3.1%	9/260	3.5%
421.2	12/65	18.5%	6/65	9.2%	2/52	3.9%	2/65	3.1%	22/247	8.9%
421.4	12/52	23.1%	5/65	7.7%	10/65	15.4%	5/65	7.7%	32/247	13.0%
421.6	19/78	24.4%	14/91	15.4%	14/65	21.5%	14/65	21.5%	61/299	20.4%
425.2	4/78	5.1%	5/78	6.4%	1/78	1.3%	2/78	2.6%	12/312	3.8%
425.5	1/52	1.9%	3/78	3.9%	2/52	3.9%	0/65	0%	6/247	2.4%
392.13	6/78	7.7%	2/78	2.6%	12/78	15.4%	2/91	2.2%	22/325	6.8%
392.15	11/65	16.9%	4/65	6.2%	5/65	7.7%	17/91	18.7%	37/286	12.9%
Experiments pooled	67/598	11.2%	40/650	6.2%	50/585	8.6%	44/663	6.6%	201/2496	8.1%

a/n = ratio of the total number of non-normal events, in all variables, to the total number of events.

% = a/n expressed as a percentage.

Table 11 : Distribution of non-normality in output variables, according to run-type, before and after editing (pre- and post-edit, respectively).

Type of run	Rest, STEADY		Rest, OSC		Exercise, STEADY		Exercise, OSC		Run-types pooled			
	Pre-edit	Post-edit	Pre-edit	Post-edit	Pre-edit	Post-edit	Pre-edit	Post-edit	Pre-edit		Post-edit	
Variable	a	a	a	a	a	a	a	a	a	% total	a	% total
$V_{T,E}$	8	7	2	2	3	3	2	2	15	7.5%	14	10.9%
$V_{T,I}$	10	9	2	1	5	4	1	1	18	9.0%	15	11.7%
$\dot{V}_E$	3	1	1	0	3	2	3	1	10	5.0%	4	3.1%
$\dot{V}_I$	0	0	0	0	3	1	0	0	3	1.5%	1	0.8%
MEF	3	1	0	0	2	1	1	0	6	3.0%	2	1.6%
MIF	9	5	2	3	4	3	3	1	18	9.0%	12	9.4%
PEF	2	1	0	0	2	2	2	0	6	3.0%	3	2.3%
PIF	1	1	3	0	2	1	1	0	7	3.5%	2	1.6%
PIA	2	0	0	0	1	1	4	4	7	3.5%	5	3.9%
T_T	5	3	7	3	7	6	8	7	27	13.4%	19	14.8%
T_E	7	4	4	3	7	5	7	5	25	12.4%	17	13.3%
T_I	13	7	18	9	8	6	10	7	49	24.4%	29	22.7%
DFRC	4	3	1	0	3	1	2	1	10	5.0%	5	3.9%

a = number of non-normal events. %, total = percentage of total of a.

Table 12 : Non-normality of edited output variables.

Type of run	Rest, STEADY		Rest, OSC		Exercise, STEADY		Exercise, OSC		Run-types pooled	
Experiment	a/n	%	a/n	%	a/n	%	a/n	%	a/n	%
409.5	0/65	0%	0/65	0%	0/65	0%	0/78	0%	0/273	0%
409.6	1/65	1.5%	1/65	1.5%	0/65	0%	0/65	0%	2/260	0.7%
421.2	6/65	9.2%	3/65	4.6%	1/52	1.9%	1/65	1.5%	11/247	4.5%
421.4	11/52	21.2%	3/65	4.6%	10/65	15.4%	2/65	3.0%	26/247	10.5%
421.6	12/78	15.4%	8/91	8.8%	14/65	21.5%	8/65	12.3%	42/299	14.0%
425.2	0/78	0%	0/78	0%	0/78	0%	2/78	2.6%	2/312	0.6%
425.5	1/52	1.9%	3/78	3.8%	1/52	1.9%	0/65	0%	5/247	2.0%
392.13	5/78	6.4%	0/78	0%	6/78	7.7%	2/91	2.2%	13/325	4.0%
392.15	6/65	9.2%	3/65	4.6%	4/65	6.2%	14/91	15.4%	27/286	9.4%
Experiments pooled	42/598	7.0%	21/650	3.2%	36/585	6.2%	29/663	4.4%	128/2496	5.1%

a/n = ratio of the total number of non-normal events, in all variables, to the total number of events.

% = a/n expressed as a percentage.

Table 13: Distribution of non-normality of edited data in hypoxia (i) and hyperoxia (ii).

Type of run		Rest, STEADY		Rest, OSC		Exercise, STEADY		Exercise, OSC		Run-types pooled	
Experiment		a/n	%	a/n	%	a/n	%	a/n	%	a/n	%
409.5	(i)	0/52	0%	0/52	0%	0/52	0%	0/52	0%	0/208	0%
	(ii)	-	-	-	-	-	-	-	-	-	-
409.6	(i)	1/39	2.6%	1/39	2.6%	0/39	0%	0/39	0%	2/156	1.3%
	(ii)	-	-	-	-	-	-	-	-	-	-
421.2	(i)	1/26	3.8%	0/26	0%	1/13	7.7%	-	-	2/65	3.1%
	(ii)	-	-	-	-	-	-	-	-	-	-
421.4	(i)	11/39	28.2%	1/39	2.6%	2/26	7.7%	2/26	7.7%	16/130	12.3%
	(ii)	0/13	0%	2/13	15.4%	6/13	46.2%	0/13	0%	8/52	15.4%
421.6	(i)	5/39	12.8%	6/52	11.5%	4/26	15.4%	2/26	7.7%	17/143	11.9%
	(ii)	5/13	38.5%	2/13	15.4%	0 13	0%	1/13	7.7%	8/52	15.4%
425.2	(i)	0/39	0%	0/52	0%	0/39	0%	2/39	5.1%	2/169	1.2%
	(ii)	0/13	0%	0/13	0%	0/13	0%	0/13	0%	0/52	0%
425.5	(i)	0/26	0%	1/52	1.9%	0/13	0%	0/26	0%	1/117	0.9%
	(ii)	1/13	7.7%	0/13	0%	0/13	0%	0/13	0%	1/52	1.9%
392.13	(i)	1/39	2.6%	0/39	0%	6/26	23.1%	0/39	0%	7/143	4.0%
	(ii)	4/13	30.8%	0/13	0%	0/13	0%	2/13	15.4%	6/52	11.5%
392.15	(i)	2/26	7.7%	1/26	3.8%	2/39	5.1%	5/52	9.6%	10/143	7.0%
	(ii)	2/13	15.4%	0/13	0%	0/13	0%	1/13	7.7%	3/52	5.8%
Experiments pooled	(i)	21/325	6.5%	10/367	2.7%	16/273	5.9%	19/299	6.4%	66/1264	5.2%
	(ii)	12/78	15.4%	4/78	5.1%	6/78	7.7%	4/78	5.1%	26/312	8.3%

Table 14: Distribution of non-normality in edited output variables, according to run-type, in hypoxia and hyperoxia.

Type of run	Rest, STEADY		Rest, OSC		Exercise, STEADY		Exercise, OSC		Run-types pooled			
	(i)	(ii)	(i)	(ii)	(i)	(ii)	(i)	(ii)	(i)		(ii)	
Variable	a	a	a	a	a	a	a	a	a	% total	a	% total
$V_{T,E}$	3	2	1	1	1	0	1	0	6	9.1	3	11.5
$V_{T,I}$	5	3	0	1	0	1	1	0	6	9.1	5	19.2
$\dot{V}_E$	0	0	0	0	1	0	0	0	1	1.5	0	0
$\dot{V}_I$	0	0	0	0	0	1	0	0	0	0	1	3.8
MVE	0	1	0	0	1	0	0	0	1	1.5	1	3.8
MVI	2	2	1	1	2	1	1	0	6	9.1	4	15.4
PEF	1	0	0	0	1	0	0	0	2	3.0	0	0
PIF	0	1	0	0	0	1	0	0	0	0	2	7.7
PIA	0	0	0	0	1	0	1	0	5	7.6	0	0
T_T	2	0	1	0	3	1	5	0	11	16.7	1	3.8
T_E	1	2	1	0	2	0	3	1	7	10.6	3	11.5
T_I	4	1	6	1	3	1	4	2	17	25.8	5	19.2
DFRC	3	0	0	0	1	0	0	1	4	6.1	1	3.8

Table 15: Non-normality of runs of alternate-breath differences.

	P_{A,O_2}	Variable	K-S d_{max}	g_1	g_2
409.5					
Exercise, P_{A,CO_2} oscillating	52.5	P_{A,CO_2}	<0.01	-5.37	32.64
409.6					
Rest, P_{A,CO_2} oscillating	78.0	T_I	<0.01	-4.64	33.12
421.2					
Rest, P_{A,CO_2} oscillating	76.5	T_E	<0.05	3.92	25.17
421.4					
Rest, P_{A,CO_2} steady	67.5	T_I	<0.05		5.38
Exercise, P_{A,CO_2} oscillating	57.0	T_E	<0.05	3.88	24.41
421.6					
Rest, P_{A,CO_2} steady	199.5	$V_{T,I}$	<0.05		
Rest, P_{A,CO_2} oscillating	75.0	P_{A,CO_2}	<0.01	-1.57	
	58.5	T_I	<0.01	6.79	65.37
	49.5	P_{A,CO_2}	<0.01	1.47	6.11
425.2					
Exercise, P_{A,CO_2} oscillating	66.0	P_{A,CO_2}	<0.01	-2.53	7.04
392.13					
Exercise, P_{A,CO_2} steady	60.0	T_T	<0.05	-3.91	22.56
		T_E	<0.01	-4.60	29.62
392.15					
Rest, P_{A,CO_2} oscillating	61.5	P_{A,CO_2}	<0.05	-1.43	2.47
Exercise, P_{A,CO_2} steady	49.5	PIA	<0.05	1.02	3.05
Exercise, P_{A,CO_2} oscillating	64.5	P_{A,CO_2}	<0.05		5.33
	63.0	P_{A,CO_2}	<0.05		4.12
		$\dot{V}_E$	<0.05	-2.60	15.29
	55.5	P_{A,CO_2}	<0.01	-1.45	7.05

An estimate of the time taken for newly inspired gas to reach the alveoli

Assumptions:-

1. The inflow rate of gas in the early part of inspiration approximates to the current value of mean inspiratory flow (MIF, = $V_{T,I}/T_I$).

2. The dead space, V_D, = 0.33 of the tidal volume, V_T: Lambertsen, C. J., 1968, in Medical Physiology, Vol. 1, p.641, ed. Mountcastle, V. B., 12th edn. St Louis: C. V. Mosby.

Data on MIF and V_T were taken from experiment 409.6, at rest and in exercise, over a P_{A,O_2} range of 200 to 50 torr: average values of MIF and V_T were obtained from the values at the two extremes of P_{A,O_2}.

	Rest	Exercise
MIF $l.min^{-1}$	92.5	107.5
V_T (l.)	2.00	2.25
V_D (l.)	0.67	0.75
Time for gas to reach alveoli	0.44 sec	0.42 sec

Therefore, a time of 0.4 sec was presumed to exist both at rest and in exercise.

SERIES ONE.
(5 pages)

EXPIRED VENTILATION (L/MIN., A.T.P.D.)

TABLE 16.
ALTERNATE-BREATH OSCILLATIONS.

RUN DESCRIPTION. PA02	FREQY.	PAC02		EXPERIMENT NO. 368.4,1	368.4,2	377.5	392.6	418.1	230.15
60	NC	CTL	Osc.	-0.37	-1.00*	0.38	-0.74	-0.73	0.19
			%		-2.1				
			SD		3.6				
60	C	CTL	Osc.	-0.56	-0.06	-0.14	-1.09	0.19	-0.37
			%						
			SD						
60	NC	TEST	Osc.	-0.76	1.31	-1.05***	3.33***	0.95***	2.12***
			%			-4.3	7.3	2.5	4.1
			SD			1.9	4.4	2.3	3.3
60	C	TEST	Osc.	-1.36**	-1.86***	0.29	2.30***	4.69***	3.36***
			%	-3.4	-4.4		4.3	11.2	6.8
			SD	3.0	3.3		4.7	4.4	3.8
50	NC	CTL	Osc.	-0.82	1.15*	-0.65	0.51	-0.21	0.60
			%		2.2				
			SD		3.1				
50	C	CTL	Osc.	-0.44	0.31	0.63*	-1.43*	0.85*	-1.63**
			%			1.7	-2.6	1.9	-2.7
			SD			2.0	3.9	3.4	3.5
50	NC	TEST	Osc.	-2.60***	-1.50**	1.40**	2.54***	3.09***	5.13***
			%	-5.6	-3.7	4.2	5.2	7.3	9.8
			SD	3.2	3.4	3.1	3.8	3.5	4.1
50	C	TEST	Osc.	-1.26**	-2.46***	0.87***	4.82***	-0.44	4.52***
			%	-3.0	-4.9	2.5	9.4		8.6
			SD	4.0	3.0	2.1	4.1		4.7

EXPIRED TIDAL VOLUME (L., A.T.P.D.)

TABLE 16.

RUN DESCRIPTION. PA02	FREQY.	PAC02		EXPERIMENT NO. 368.4,1	368.4,2	377.5	392.6	418.1	230.15
60	NC	CTL	Osc	-0.03	-0.06 •	0.03	-0.12 •	0.00	0.00
			%		-2.4		-4.6		
			SD		0.17		0.37		
60	C	CTL	Osc	0.00	0.03	0.00	-0.06	0.00	0.00
			%						
			SD						
60	NC	TEST	Osc	0.09 •••	0.21 •••	0.03	0.24 •••	0.03	0.06 •••
			%	4.4	10.5		9.9		2.9
			SD	0.19	0.3		0.3		0.22
60	C	TEST	Osc	0.06 ••	0.03 •	0.00	0.21 •••	0.24 •••	0.03 •
			%	2.5	1.5		7.8	13.6	1.8
			SD	0.16	0.12		0.26	0.22	0.4
50	NC	CTL	Osc	-0.06 •	0.03 •	0.03 •	-0.06 •	0.00	0.03
			%	-2.8	1.8	2.4	-2.7		
			SD	0.18	0.13	0.11	0.25		
50	C	CTL	Osc	0.03	0.00	0.00	-0.03	0.03	-0.12 •••
			%						5.2
			SD						0.58
50	NC	TEST	Osc	0.06 ••	0.03	0.03	0.24 •••	0.18 •••	0.09 •••
			%	2.5			9.6	11.7	4.5
			SD	0.16			0.3	0.19	0.17
50	C	TEST	Osc	0.12 •••	0.03	0.00	0.36 •••	-0.09 ••	0.09 •••
			%	5.8			14.6	5.2	4.9
			SD	0.2			0.26	0.2	0.19

BREATH DURATIØN (SEC.)

TABLE 16.

RUN DESCRIPTION. PA02	FREQY.	PAC02		EXPERIMENT NØ. 368.4,1	368.4,2	377.5	392.6	418.1	230.15
60	NC	CTL	Osc	0.05	0.00	0.00	0.10•	0.00	0.00
			%				2.7		
			SD				0.26		
60	C	CTL	Osc	0.05	0.00	0.05	0.00	0.00	-0.05
			%						
			SD						
60	NC	TEST	Osc	-0.25•••	-0.25•••	-0.15•••	-0.10••	0.05••	0.00
			%	-7.4	-8.5	-3.9	-2.9	1.5	
			SD	0.2	0.2	0.3	0.17	0.1	
60	C	TEST	Osc	-0.20•••	-0.20•••	0.05	-0.10•••	-0.10•••	0.10•••
			%	-6.2	-6.7		-3.3	-3.1	4.4
			SD	0.2	0.16		0.16	0.4	0.17
50	NC	CTL	Osc	-0.05	0.00	-0.05	0.05•	0.00	0.00
			%				1.7		
			SD				0.15		
50	C	CTL	Osc	0.05•	0.00	0.05	0.00	0.00	0.05•
			%	2.3					2.4
			SD	0.24					0.14
50	NC	TEST	Osc	-0.25•••	-0.20•••	0.15•••	-0.25•••	-0.05	0.10•••
			%	-7.9	-6.3	5.9	-7.5		5.8
			SD	0.17	0.22	0.2	0.32		0.23
50	C	TFST	Osc	-0.25•••	-0.25•••	0.10•••	-0.10•••	0.10•••	0.05•••
			%	-8.1	-8.1	3.4	-3.8	3.6	2.4
			SD	0.19	0.12	0.18	0.17	0.13	0.12

INSPIRATØRY TIME (SEC.)

TABLE 16.

RUN DESCRIPTIØN. PA02	FREQY.	PAC02		EXPERIMENT NØ. 368.4,1	368.4,2	377.5	392.6	418.1	230.15
60	NC	CTL	Osc	0.00	0.05 •	0.00	0.05 •	0.05 •	0.00
			%		2.5		3.6	2.2	
			SD		0.1		0.2	0.1	
60	C	CTL	Osc	0.05 ••	0.00	0.00	0.00	0.00	0.00
			%	2.3					
			SD	0.1					
60	NC	TEST	Osc	-0.05	-0.05 ••	0.00	-0.05 •	0.00	-0.05 •••
			%	-3.0	-4.0		-2.1		-3.9
			SD	0.11	0.12		0.11		0.04
60	C	TEST	Osc	0.00	-0.05 •	0.00	-0.05 ••	0.00	0.00
			%		-2.4		-2.5		
			SD		0.12		0.12		
50	NC	CTL	Osc	0.00	0.00	0.00	0.05	0.00	0.00
			%						
			SD						
50	C	CTL	Osc	0.00	0.00	0.00	0.00	0.00	0.05 •
			%						2.8
			SD						0.09
50	NC	TEST	Osc	-0.05 ••	-0.05	0.05 ••	-0.05 ••	0.00	0.00
			%	-2.3		3.4	-4.3		
			SD	0.10		0.08	0.16		
50	C	TEST	Osc	0.00	-0.05 •	0.00	-0.05 ••	0.05 •••	-0.05 ••
			%		-2.4		-2.6	5.0	-2.8
			SD		0.2		0.11	0.08	0.03

EXPIRATØRY TIME (SEC.)

TABLE 16.

RUN DESCRIPTIØN. PA02	FREQY.	PAC02	EXPERIMENT NØ. 368.4,1	368.4,2	377.5	392.6	418.1	230.15
60	NC	CTL	0.05•	0.00	-0.05	0.00	-0.05	0.00
			3.0					
			0.12					
60	C	CTL	0.05	0.00	0.05	0.05	-0.05	0.00
60	NC	TEST	-0.15•••	-0.15•••	-0.15•••	-0.05•	0.00•	0.05•••
			-9.6	-10.6	-7.8	-3.2	2.1	5.2
			0.12•••	0.11•••	0.14	0.12••	0.07•••	0.08•••
60	C	TEST	-0.15	-0.20	0.05	-0.05	-0.10	0.10
			-9.6	-11.1		-2.9	-6.6	10.6
			0.14	0.18		0.4	0.12	0.09
50	NC	CTL	0.00	0.00	-0.05	0.05	0.00	0.00
50	C	CTL	-0.05	0.00	0.00	0.00	0.00	0.00
50	NC	TEST	-0.20•••	-0.15•••	0.10•••	-0.15•••	0.00	0.10•••
			-11.6	-9.4	9.8	-10.0		10.7
			0.12	0.18	0.12	0.23		0.13
50	C	TEST	-0.25•••	-0.20•••	0.05•••	-0.10•••	0.05•••	0.10•••
			-14.6	-11.8	5.0	-6.6	4.9	8.9
			0.17	0.12	0.13	0.12	0.07	0.11

The effects of controlling respiratory frequency on the relations between T_T, T_I and T_E

This is a description of the results from which the conclusions concerning the effects of controlling respiratory frequency have been drawn: Chapter 3, p. 87. Basic statistics (mean and variance) for the runs of T_T, T_I and T_E are presented at the end of the account (p.). The three predictions of p.86 were tested by a method of "paired comparisons" (each pair consisted of a NC and a C run; the two runs were identical with respect to P_{A,O_2} and the state of P_{A,CO_2}).

Paired comparison: mean T_T

A two tailed t-test (p.65) was used to test the null hypothesis that the NC mean and C mean of each pair were not different. Of 25 comparisons in 6 experiments, 20 were different ($p<0.05$): Table 20, p. 221.

Paired comparison: mean T_I and T_E

The hypothesis to be tested was as follows: within any pair of runs rhe discrepancy existing between mean T_I and T_E would be no less in the C run than in the NC run. Two null hypotheses were employed. First, it was stated that in any run, mean T_E was not significantly different from mean T_I. This was tested with a two-tailed t-test, as used in the previous section. The results presented in Table 21 (p.222).

Combining the results on the 6 experiments, of all the NC runs 22 out of 25 had differences between mean T_E and mean T_I ($p<0.001$). In the C runs, mean T_E and T_I differed in 21 runs out of 25. Thus, the occurrence of significant differences between mean T_E and T_I appeared to be little

affected by controlling respiratory frequency.

The second hypothesis was concerned with making paired comparisons of T' (the difference between mean T_E and mean T_I) in order to assess the probability of T' being lessened when respiratory frequency was controlled (i.e. $T'_{NC} > T'_C$). In 13 comparisons out of 25, T'_{NC} was numerically greater than T'_C (Table22 , p. 223). It is evident that the observed probability of $T'_{NC} > T'_C$ is similar to that of $T'_{NC} < T'_C$, and that a random process is therefore indicated. A similar conclusion was reached in all but one of the six experiments. The exception was 392.6, where all five runs showed T' to be reduced when respiratory frequency was controlled. Thus, subject 392 was the only one to have any success in following the controlling signal.

Paired comparison: variance of T_T

The paired variances were tested according to the following null hypothesis: the variance of the controlled run was not less than that of the uncontrolled run. The hypothesis was tested with a one-tailed variance ratio test (p. 65).

Out of a total of 25 comparisons in 6 experiments, 12 had significant values of F_s, ($p<0.05$), (Table 23 , p.224). Their distribution between experiments showed variation. In 377.5, all 4 comparisons were significant, the situation being less marked in the remaining experiments. Thus, in only one experiment was a consistent reduction in the breath-by-breath variation of T_T observed during the controlling of respiratory frequency.

Paired comparison: variance of T_I and T_E

The paired variances of T_I and of T_E were each tested in a similar manner to the variance of T_T. The null hypothesis for each variable was that the variance of the controlled run of a pair was not less than that of the corresponding uncontrolled run. A one-tailed variance-ratio test was then performed (p. 65). The results on both T_I and T_E are presented in Table 23 (p.224).

The results obtained on the occurrence and distribution of significant F_s values was similar, in both cases, to those obtained on T_T. Thus, for T_I, 9 comparisons out of a total of 25 in 6 experiments had significant values of F_s ($p \leq 0.05$). The significant values were distributed fairly evenly between the 6 experiments. The pattern for T_E was largely similar, with 11 comparisons out of 25 being significant. As was found for T_T, all four comparisons in experiment 377.5 were significant.

Table 17: T_T: mean, variance and number of observations of the edited runs.

P_{A,O_2} (torr)	Type of run Frequency	P_{A,CO_2}	368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15
60	NC	St. Mean	2.90	2.60	3.65	3.00	2.55	2.10
		Var.	0.04	0.03	0.04	0.04	0.04	0.01
		N	63	65	45	55	49	69
60	C	St. Mean	3.10	3.05	2.75	3.15	2.45	2.10
		Var.	0.02	0.02	0.01	0.02	0.01	0.02
		N	61	67	63	57	55	77
50	NC	St. Mean	3.05	2.55	2.25	3.00	2.05	1.95
		Var.	0.02	0.02	0.03	0.01	0.01	0.01
		N	65	65	71	53	53	59
50	C	St. Mean	3.05	3.00	2.80	2.80	2.05	2.05
		Var.	0.03	0.02	0.02	0.01	0.02	0.01
		N	65	55	63	49	73	54
60	NC	Osc. Mean	3.10	2.85	3.60	3.05	3.25 2.00	2.00
		Var.	0.04	0.03	0.07	0.04	0.02 0.01	0.01
		N	71	35	47	37	33 77	79
60	C	Osc. Mean	3.10	3.00	2.80	3.00	2.55	2.05
		Var.	0.03	0.02	0.01	0.02	0.01	0.02
		N	75	65	55	67	49	77
50	NC	Osc. Mean	3.05	3.15	2.35	3.10	2.30	2.05
		Var.	0.04	0.04	0.04	0.06	0.04	0.04
		N	75	37	43	55	61	59
50	C	Osc. Mean	2.95	2.95	2.70	2.95	2.25	2.05
		Var.	0.04	0.03	0.02	0.02	0.01	0.01
		N	89	39	75	75	61	85

T_T measured to the neasrest 0.05 sec.

Table 18: T_I: mean, variance and number of observations of the edited runs.

	Type of run			368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15
P_{A,O_2} (torr)	Freq.^{y}	P_{A,CO_2}							
60	NC	St.	Mean	1.20	1.20	1.70	1.65	1.35	1.05
			Var.	0.01	0.01	0.01	0.02	0.01	0.00
			N	59	57	43	59	49	69
60	C	St.	Mean	1.35	1.25	1.35	1.70	1.30	1.05
			Var.	0.01	0.00	0.00	0.01	0.00	0.00
			N	59	69	63	57	53	75
50	NC	St.	Mean	1.35	1.20	1.10	1.65	1.10	1.00
			Var.	0.00	0.04	0.01	0.01	0.00	0.00
			N	65	59	63	55	51	63
50	C	St.	Mean	1.25	1.30	1.30	1.50	1.20	1.05
			Var.	0.01	0.01	0.01	0.00	0.00	0.00
			N	65	53	65	53	73	54
60	NC	Osc.	Mean	1.35	1.25	1.70	1.65	1.75	1.05	1.05
			Var.	0.01	0.01	0.02	0.01	0.01	0.00	0.00
			N	65	35	49	37	33	81	81
60	C	Osc.	Mean	1.30	1.25	1.40	1.60	1.35	1.05
			Var.	0.00	0.01	0.00	0.01	0.00	0.01
			N	73	77	45	67	45	79
50	NC	Osc.	Mean	1.30	1.45	1.20	1.65	1.25	1.00
			Var.	0.01	0.01	0.01	0.01	0.01	0.01
			N	73	39	27	53	49	67
50	C	Osc.	Mean	1.30	1.25	1.30	1.55	1.20	1.10
			Var.	0.01	0.00	0.01	0.01	0.00	0.01
			N	87	31	81	73	59	85

T_T measured to the nearest 0.05 sec.

Table 19: T_E : mean, variance and number of observations of the edited runs.

Type of run				Experiment					
				368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15
P_{A,O_2} (torr)	Freq.[y]	P_{A,CO_2}							
60	NC	St.	Mean	1.70	1.40	1.95	1.35	1.20	1.05
			Var.	0.02	0.02	0.02	0.01	0.01	0.00
			N	61	63	47	57	43	63
60	C	St.	Mean	1.75	1.80	1.40	1.45	1.15	1.05
			Var.	0.02	0.01	0.01	0.01	0.05	0.01
			N	61	69	59	55	57	69
50	NC	St.	Mean	1.70	1.35	1.15	1.35	0.95	0.95
			Var.	0.02	0.01	0.02	0.01	0.00	0.00
			N	67	59	73	55	73	61
50	C	St.	Mean	1.80	1.70	1.50	1.30	1.85	1.00
			Var.	0.02	0.01	0.01	0.01	0.00	0.00
			N	65	53	63	49	51	50
60	NC	Osc.	Mean	1.75	1.60	1.90	1.40	1.50	0.95	0.95
			Var.	0.02	0.01	0.04	0.01	0.01	0.00	0.01
			N	69	37	51	35	33	73	79
60	C	Osc.	Mean	1.80	1.75	1.40	1.40		1.20	1.00
			Var.	0.02	0.03	0.01	0.01		0.01	0.01
			N	67	77	45	71		51	79
50	NC	Osc.	Mean	1.75	1.70	1.15	1.45		1.05	1.05
			Var.	0.03	0.03	0.02	0.03		0.01	0.02
			N	75	37	43	53		59	67
50	C	Osc.	Mean	1.65	1.70	1.40	1.40		1.05	1.00
			Var.	0.03	0.02	0.01	0.01		0.01	0.01
			N	97	39	77	75		61	83

T_E measured to the nearest 0.05 sec.

Table 20: The significance of the differences in mean T_T between NC and C runs.

Type of run		Experiment					
		368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15
P_{A,O_2} (torr)	P_{A,CO_2}	ΔT_T (NC-C) (sec.)	ΔT_T (NC-C) (sec.)	ΔT_T (NC-C) (sec.)	ΔT_T (NC-C) (sec.)	ΔT_T (NC-C) (sec.)	ΔT_T (NC-C) (sec.)
60	Steady	-0.15^{xxx}	-0.45^{xxx}	0.90^{xxx}	-0.15^{xxx}	0.10^{xxx}	0.00
50	Steady	0.00	-0.45^{xxx}	-0.55^{xxx}	0.25^{xxx}	0.00	-0.10^{xxx}
60	Osc.	0.00	-0.15^{xx}	0.80^{xxx}	0.05^{xx} 0.25^{xxx}	-0.55^{xxx}	-0.05^{xx}
50	Osc.	0.10^{xx}	0.20^{xxx}	-0.35^{xxx}	0.15^{xxx}	0.05^{xxx}	0.00

Measurements to the nearest 0.05 sec

Table 21: The significance of the differences between mean T_E and T_I.

			Experiment					
			368.4_1	368.4_2	377.5	392.6	418.1	230.15
Type of run								
P_{A,O_2} (torr)	Freq.[y]	P_{A,CO_2}	(T_E-T_I) (sec)	(T_E-T_I) (sec)	(T_E-T_I) (sec)	(T_E-T_I) (sec)	(T_E-T_I) (sec)	(T_E-T_I) (sec)
60	NC	Steady	0.50^{xxx}	0.20^{xxx}	0.25^{xxx}	-0.30^{xxx}	-0.15^{xxx}	-0.05^{xxx}
60	C	Steady	0.40^{xxx}	0.35^{xxx}	0.05^{xxx}	-0.25^{xxx}	-0.55^{xxx}	0.00
50	NC	Steady	0.35^{xxx}	0.05^{xxx}	0.05^{xxx}	-0.30^{xxx}	-0.95^{xxx}	-0.05^{xxx}
50	C	Steady	0.55^{xxx}	0.40^{xxx}	0.20^{xxx}	-0.20^{xxx}	-0.55^{xxx}	-0.05^{xxx}
60	NC	Osc.	0.40^{xxx}	0.35^{xxx}	0.20^{xxx}	-0.25^{xxx} 0.25^{xxx}	-0.10^{xxx}	-0.10^{xxx}
60	C	Osc.	0.50^{xxx}	0.50^{xxx}	0.00	-0.20^{xxx}	-0.15^{xxx}	-0.05
50	NC	Osc.	0.45^{xxx}	0.30^{xxx}	-0.05	-0.20	-0.20^{xxx}	0.05
50	C	Osc.	0.35^{xxx}	0.45^{xxx}	0.10^{xxx}	-0.15	-0.15^{xxx}	-0.10^{xxx}

Measurements to the nearest 0.05 sec.

Table 22 : Paired comparisons between $(T_E-T_I)_{NC}$ and $(T_E-T_I)_C$.

Type of run		Experiments						
		368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15	
		$(T_E-T_I)_{NC} - (T_E-T_I)_C$, sec						
P_{A,O_2} (torr)	P_{A,CO_2}							(a/n)
60	Steady	0.10	-0.15	0.20	0.05	-0.40	0.05	4/6
50	Steady	-0.20	-0.35	-0.15	0.10	0.40	0.00	2/6
60	Osc.	-0.10	-0.15	0.20	0.05	0.05 -0.05	0.05	4/6
50	Osc.	0.10	-0.05	-0.05	0.05	0.05	-0.05	3/6
(a/n)		2/4	0/4	2/4	5/5	2/4	2/4	13/25

(a/n) = the ratio of the number of positive differences to the total number of differences. Measurements to the nearest 0.05 sec.

Table 23: T_T, T_I and T_E variances: significance of F_S values for the paired comparisons (NC-C).

Type of run		368.4$_1$	368.4$_2$	377.5	392.6	418.1	230.15	
P_{A,O_2} (torr)	P_{A,CO_2}	F_S	F_S	F_S	F_S	F_S	F_S	(a/n)
T_T								
60	Steady	1.76^{x}	1.87^{xx}	2.57^{xx}	2.80^{xx}	4.38^{xx}	N.S.	5/6
50	Steady	N.S.	N.S.	2.00^{xx}	N.S.	N.S.	N.S.	1/6
60	Osc.	N.S.	N.S.	5.30^{xxx}	2.47^{xx}	N.S.	N.S.	N.S.	2/7
50	Osc.	N.S.	N.S.	2.59^{xxx}	4.00^{xxx}	4.20^{xxx}	2.92^{xxx}	4/6
(a/n)		1/4	1/4	4/4	3/5	2/4	1/4	12/25
T_I								
60	Steady	N.S.	N.S.	3.67^{xxx}	3.29^{xxx}	4.33^{xxx}	N.S.	3/6
50	Steady	N.S.	N.S.	N.S.	2.33^{xxx}	N.S.	N.S.	1/6
60	Osc.	2.33^{xx}	N.S.	7.33^{xxx}	N.S.	N.S.	N.S.	N.S.	2/7
50	Osc.	N.S.	2.67^{xxx}	N.S.	2.33^{xxx}	1.75^{x}	N.S.	3/6
(a/n)		1/4	1/4	2/4	3/5	2/4	0/4	9/25
T_E								
60	Steady	N.S.	1.54^{x}	2.86^{xxx}	2.17^{xx}	2.80^{xxx}	N.S.	4/6
50	Steady	N.S.	N.S.	1.90^{xx}	2.17^{xx}	N.S.	2.00^{xx}	3/6
60	Osc.	N.S.	N.S.	6.00^{xxx}	N.S.	N.S.	N.S.	N.S.	1/7
50	Osc.	N.S.	N.S.	2.44^{xxx}	3.50^{xxx}	N.S.	2.43^{xxx}	3/6
(a/n)		0/4	1/4	4/4	3/5	1/4	2/4	11/25

(a/n) = the ratio of the number of significant F_S values to the total number of F_S values.

TABLE 24. ALTERNATE-BREATH OSCILLATIONS.

SERIES TWO

'OSC' RUNS.

(18 pages: 225_{1-18})

409.5

REST : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
torr.	$torr.^{-1}$		torr.	l.	l.	$l.min.^{-1}$	$l.min.^{-1}$	$l.min.^{-1}$	$l.min.^{-1}$	$l.min.^{-1}$	$l.min.^{-1}$	$l.sec.^{-2}$	sec.	sec.	sec.	l.
54.0	46.5	81	9.0	0.00	0.12***	-2.30***	-0.33	-7.75***	5.16***	-3.00	10.00***	1.80***	-0.20***	-0.20***	0.00	0.12***
	% ØSC		18.9	0.2	7.1	-6.5	-0.9	-12.1	6.4	-4.0	9.6	18.0	-7.7	-14.1	1.2	
	S.D.		1.3	0.2	0.2	4.6	5.3	10.4	8.2	15.3	9.2	1.4	0.4	0.3	0.2	.106
55.7	42.1	65	9.0	0.03	0.12***	-2.08***	-0.37	-5.59***	3.66**	-3.00**	7.50***	0.99***	-0.25***	-0.20***	-0.05*	0.09***
	% ØSC		18.5	2.0	7.3	-6.3	-1.1	-10.2	4.4	-6.0	6.3	11.3	-7.5	-11.5	-2.4	
	S.D.		1.1	0.2	0.2	4.1	4.4	8.3	10.1	12.4	9.0	1.3	0.3	0.3	0.1	.123
47.0	66.7	71	9.0	0.12***	0.09*	-2.13**	-4.44***	-15.96***	6.56***	-12.00***	15.00***	2.52***	-0.45***	-0.50***	0.05	-0.09***
	% ØSC		21.0	6.6	4.2	-4.9	-10.2	-20.2	6.7	-11.4	10.6	20.8	-15.7	-31.0	2.5	
	S.D.		1.7	0.2	0.3	5.7	6.6	13.0	8.2	15.4	10.9	1.7	0.3	0.3	0.2	.287
70.0	26.3	59	9.0	-0.03	0.06***	-1.84*	0.13	-3.67*	2.46*	-3.00	5.00***	0.99***	-0.10	-0.10	-0.05	0.12**
	% ØSC		20.9	-1.7	3.9	-5.0	0.4	-5.8	2.9	-4.0	4.9	9.8	-3.7	-4.9	-2.1	
	S.D.		1.2	0.1	0.1	5.3	5.3	13.1	6.3	17.7	9.6	1.5	0.4	0.4	0.1	.123
116.0	11.9	51	9.0	0.00	0.12***	-1.55*	0.90	-2.67	2.22	0.00	2.50*	0.18	-0.10*	-0.10	-0.05	0.12***
	% ØSC		20.0	0.6	6.8	-4.0	2.3	-3.9	2.4	0.3	2.8	1.8	-4.7	-4.9	-4.4	
	S.D.		1.6	0.2	0.2	4.4	4.9	12.9	8.8	12.9	10.1	1.5	0.3	0.3	0.1	.092

409.5

EXERCISE : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VIE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
52.5	50.0	43	7.5	0.06**	0.03*	-3.25***	-3.63***	-10.79***	-0.38	-6.00**	2.50	0.99*	-0.30***	-0.25***	0.00	-0.03
	% ØSC		16.7	3.5	2.1	-7.1	-7.9	-13.2	-0.4	-6.0	1.9	9.7	-10.3	-16.8	1.7	
	S.D.		3.0	0.2	0.1	3.9	3.8	9.2	11.5	12.9	12.2	2.9	0.3	0.2	0.2	.136
57.5	39.2	61	7.5	0.03	0.06**	-2.13***	-0.74	-7.79***	4.63***	-9.00***	7.50***	1.89***	-0.15***	-0.15***	0.00	0.06***
	% ØSC		16.5	1.5	2.7	-4.7	-1.6	-9.9	4.2	-8.8	5.3	14.6	-5.5	-10.8	1.2	
	S.D.		1.1	0.1	0.1	4.4	3.6	10.4	8.3	9.9	8.3	1.7	0.3	0.2	0.1	.114
50.4	54.4	47	10.5	0.06*	0.15***	-2.83***	0.79	-10.21***	5.66**	-15.00***	10.00***	0.54	-0.15***	-0.10***	-0.05***	0.15***
	% ØSC		23.6	2.2	6.9	-4.5	1.3	-8.2	4.5	-9.3	5.5	3.5	-6.0	-8.9	-4.0	
	S.D.		1.2	0.1	0.2	3.6	4.3	8.4	10.3	14.6	11.8	2.1	0.1	0.1	0.1	.119
50.2	54.8	45	10.5	0.00	0.21***	-6.55***	-0.98	-20.54***	7.66***	-12.00***	7.50*	1.26***	-0.20***	-0.20***	-0.05***	0.21***
	% ØSC		23.7	-0.2	7.9	-9.3	-1.4	-15.0	5.2	-7.4	3.1	6.9	-9.3	-15.2	-2.7	
	S.D.		1.8	0.2	0.2	5.0	4.9	14.7	8.3	14.5	18.5	2.2	0.1	0.1	0.1	.142
69.2	26.9	75	10.5	0.03	0.12***	-2.76**	0.74	-7.83***	5.18***	-9.00***	10.00***	0.90***	-0.15***	-0.10***	-0.05*	0.12***
	% ØSC		23.1	0.9	5.7	-5.0	1.3	-7.3	4.5	-6.9	5.9	6.0	-5.3	-6.7	-2.6	
	S.D.		2.0	0.2	0.2	5.9	6.1	16.8	8.6	20.0	14.4	1.9	0.2	0.2	0.1	.190
114.0	12.2	65	9.0	-0.03	0.09***	-1.37	1.08	-4.03*	2.69*	-3.00	5.00***	0.72*	-0.05	-0.05	0.00	0.12***
	% ØSC		20.6	-1.0	5.2	-2.8	2.2	-4.3	2.6	-2.0	3.6	5.2	-3.0	-3.5	1.4	
	S.D.		1.5	0.2	0.2	5.6	5.8	14.9	8.6	14.7	10.8	2.1	0.4	0.3	0.2	.129

409.6

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	ALTERNATE-BREATH ØSCILLATIØN. PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
127.5	10.5	75	10.5	0.00	0.06**	-0.44	0.74	-0.76	4.34***	3.00	5.00**	0.09	0.00	0.00	0.00	0.09***
	% ØSC		21.1	-0.7	3.9	-1.2	2.0	-1.2	4.9	2.2	3.6	2.9	0.3	0.1	2.0	
	S.D.		1.4	0.2	0.2	5.4	4.4	14.4	10.7	16.0	9.6	0.6	0.4	0.3	0.1	.143
77.7	21.9	81	10.5	0.00	0.12***	0.65	2.91***	-0.55	8.66***	0.00	7.50***	0.27*	0.05	0.00	0.05	0.12***
	% ØSC		22.4	0.4	7.2	1.6	7.3	-0.8	9.2	1.2	5.8	5.7	1.6	1.1	3.3	
	S.D.		1.5	0.2	0.2	6.3	6.6	16.5	16.7	21.1	12.5	0.8	0.4	0.3	0.3	.130
63.0	32.3	75	9.0	-0.03	0.09***	-1.58*	1.40*	-4.40**	7.34***	-3.00	7.50***	0.27**	-0.05	-0.05*	0.00	0.15**
	% ØSC		20.8	-1.5	5.2	-3.7	3.2	-5.7	7.3	-3.2	6.1	5.8	-2.1	-4.3	1.7	
	S.D.		1.4	0.1	0.1	4.9	5.2	13.0	7.7	13.6	8.1	0.8	0.3	0.2	0.1	.117
47.9	63.0	121	10.5	0.00	0.09***	-0.58	1.87	-4.96	8.94***	-3.00	15.00***	0.90***	-0.05	-0.05	0.05	0.09**
	% ØSC		22.0	0.4	4.3	-0.9	3.0	-4.2	7.0	-2.1	8.7	13.0	-1.7	-5.8	3.1	
	S.D.		2.0	0.2	0.2	12.0	11.9	27.3	20.3	36.5	26.1	1.6	0.3	0.2	0.1	.142
56.2	41.2	131	10.5	0.00	0.12***	-0.37	2.87***	-1.73	6.62***	0.00	10.00***	0.27***	0.00	0.00	0.00	0.12***
	% ØSC		21.1	-0.3	6.2	-0.8	5.7	-1.9	6.0	-0.7	6.5	6.0	0.6	1.2	0.4	
	S.D.		1.6	0.2	0.2	5.9	5.5	13.4	10.0	19.6	10.6	0.9	0.3	0.2	0.1	.157

409.6

EXERCISE : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
127.5	10.5	75	10.5	-0.03	0.12***	-0.26	3.51***	-0.61	7.19***	-3.00	5.00**	0.45**	0.05	0.05	0.00	0.18***
	% ØSC		23.8	-1.9	6.4	-0.5	6.9	-0.6	6.6	-1.3	3.5	7.5	1.2	2.1	0.9	
	S.D.		1.8	0.2	0.2	6.9	7.6	19.2	15.1	24.2	11.3	0.9	0.3	0.2	0.2	.085
75.3	23.1	93	10.5	-0.03	0.21***	-4.42***	0.96	-12.87***	8.20***	-9.00**	15.00***	0.36*	-0.15**	-0.10**	-0.05	0.24***
	% ØSC		22.3	-1.4	9.3	-8.0	1.7	-12.4	7.0	-6.6	8.9	5.4	-6.3	-8.7	-2.5	
	S.D.		1.7	0.2	0.2	9.3	8.5	25.7	13.8	30.5	17.8	1.2	0.4	0.3	0.1	.132
63.5	31.7	73	10.5	0.00	0.15***	-5.23***	-0.83	-17.63***	6.72***	-12.00	10.00***	0.18	-0.20***	-0.20***	-0.05*	0.18***
	% ØSC		24.1	-0.1	6.8	-8.9	-1.4	-16.3	5.3	-8.7	5.6	3.0	-8.9	-15.6	-2.5	
	S.D.		1.3	0.1	0.2	7.6	7.6	19.9	11.7	25.1	15.6	1.1	0.3	0.2	0.1	.116
50.0	55.6	69	12.0	-0.03	0.18***	-9.85***	-4.42***	-37.09***	8.63***	-36.00***	22.50***	0.90***	-0.30***	-0.30***	0.00	0.18***
	% ØSC		25.7	-1.1	6.7	-14.3	-6.4	-27.7	6.0	-17.9	11.1	11.9	-13.8	-26.6	0.7	
	S.D.		1.7	0.2	0.2	9.4	9.2	30.2	15.9	33.1	19.0	1.3	0.3	0.2	0.2	.115
56.7	40.6	101	10.5	0.06*	0.18***	-4.79***	-1.61	-17.00***	4.98***	-18.00***	10.00***	0.63***	-0.30***	-0.25***	-0.05**	0.12***
	% ØSC		23.6	2.5	8.0	-8.2	-2.8	-14.9	4.2	-11.7	6.5	10.4	-11.9	-18.7	-3.3	
	S.D.		1.7	0.3	0.3	8.1	8.1	22.1	12.9	32.9	18.6	1.1	0.3	0.2	0.1	.129

421.2

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	ALTERNATE-BREATH ØSCILLATIØN. PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TI	TE	TI	DFRC
76.5	22.5	95	10.5	0.06**	0.10***	1.15	3.03***	3.93**	4.33***	5.10**	7.00***	0.44***	0.00	0.00	-0.05*	0.06**
	% ØSC		21.8	5.0	8.1	3.5	9.3	6.2	6.4	5.4	8.1	9.1	0.4	0.5	-2.6	
	S.D.		1.8	0.2	0.2	5.3	4.8	12.7	8.4	14.4	9.8	0.7	0.2	0.2	0.1	.087
113.0	12.3	103	9.0	-0.02	-0.02	-0.45	-0.29	-0.25	-1.20	-1.70	-1.40	-0.08	0.00	0.00	0.00	0.00
	% ØSC		20.4	-1.7	-1.3	-1.3	-0.8	-0.4	-1.6	-1.5	-2.3	-1.8	0.8	1.7	0.0	
	S.D.		1.5	0.1	0.1	4.4	4.6	10.8	8.0	15.8	13.1	0.9	0.2	0.2	0.1	.066
79.0	21.3	81	9.0	-0.02	-0.02	-1.02	-0.82	-1.96	-2.00	-3.40	-1.40	-0.08	0.00	0.00	0.00	0.00
	% ØSC		19.1	-2.0	-1.2	-2.0	-1.6	-1.7	-2.1	-1.0	-1.8	-0.9	0.4	1.4	0.4	
	S.D.		1.3	0.1	0.1	4.6	5.0	10.4	9.4	24.8	13.8	1.2	0.1	0.1	0.1	.077
67.2	28.4	101	10.5	0.00	0.02	0.62	1.57**	3.86**	0.98	3.40	-2.80	-0.08	0.05*	0.05**	0.00	0.02
	% ØSC		22.9	-0.2	1.0	1.4	3.6	4.3	1.2	2.7	-2.1	-1.5	2.4	4.7	0.7	
	S.D.		2.0	0.2	0.2	4.9	5.6	13.3	9.7	19.6	12.8	1.0	0.2	0.1	0.1	.075
61.5	33.9	83	10.5	0.04**	0.06***	1.89***	2.24***	5.67***	2.47**	6.80***	4.20***	0.28***	0.05*	0.05**	0.00	0.00
	% ØSC		21.0	3.8	4.3	5.3	6.3	7.6	3.6	8.1	4.8	5.5	1.7	3.6	0.2	
	S.D.		1.8	0.1	0.1	3.6	3.5	7.8	7.1	10.8	10.9	0.7	0.1	0.1	0.1	.056

4 21.2

EXERCISE : PAC02 OSCILLATING.

PA02	HYP	N	ALTERNATE-BREATH OSCILLATION. PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
121.5	11.2	75	9.0	0.00	0.08*	-0.82	0.95	-3.71**	3.73***	0.00	4.20***	0.52***	-0.10*	-0.10***	0.00	0.06***
	% OSC		20.4	-0.0	4.6	-2.2	2.6	-4.9	5.2	-0.2	5.3	9.7	-3.7	-7.2	0.3	
	S.D.		2.4	0.2	0.2	4.5	4.1	9.7	8.6	15.4	12.0	0.8	0.4	0.2	0.2	.074
103.0	14.1	65	9.0	0.04	0.06	0.62	1.24	1.40	2.54	1.70	2.80	0.28	0.00	0.00	0.00	0.04**
	% OSC		17.9	2.4	3.7	1.4	2.9	1.6	3.1	1.1	2.3	5.0	0.2	1.4	0.8	
	S.D.		2.0	0.3	0.3	6.0	7.3	14.9	13.7	24.2	12.5	1.2	0.3	0.2	0.2	.090
102.0	14.3	65	7.5	0.02	0.06***	0.14	1.19**	1.31	1.52	3.40	4.20***	0.24*	0.00	0.00	0.00	0.04***
	% OSC		15.8	1.4	4.1	0.4	2.9	1.5	2.0	2.7	3.8	3.9	0.7	1.4	2.2	
	S.D.		1.5	0.1	0.1	3.4	3.3	9.4	6.1	14.9	8.1	0.9	0.2	0.1	0.1	.065
90.5	17.1	61	9.0	0.04*	0.06***	0.15	1.39***	1.33	1.43	3.40	2.80**	0.20	-0.05*	0.00	-0.05**	0.04**
	% OSC		17.8	2.9	5.1	0.3	3.2	1.4	1.7	2.4	2.6	2.9	-2.4	0.2	-3.0	
	S.D.		1.0	0.1	0.1	3.3	2.8	8.7	7.3	12.5	7.5	0.8	0.1	0.1	0.1	.069
70.9	25.7	67	9.0	0.04	0.08*	0.42	2.34***	1.71	3.78***	3.40	7.00**	0.52***	-0.05	0.00	0.00	0.04*
	% OSC		20.0	3.3	5.6	0.9	5.1	1.7	4.4	2.7	5.0	6.7	-2.0	1.3	1.1	
	S.D.		1.6	0.2	0.2	3.2	3.6	9.1	7.9	14.9	15.2	1.1	0.3	0.1	0.1	.098

421.4

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	ALTERNATE-BREATH ØSCILLATIØN. PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
97.5	15.3	71	9.0	0.02	0.02	1.00	1.16	3.17	0.75	4.00	1.70	0.00	0.05	0.05	0.00	0.02
	% ØSC		20.0	1.4	2.0	3.5	4.0	5.8	1.2	6.5	1.7	-0.8	2.3	5.3	0.5	
	S.D.		2.1	0.1	0.2	6.1	7.4	16.1	12.7	21.9	12.1	1.3	0.3	0.2	0.1	.078
54.2	45.1	113	10.5	0.04	0.08	2.99	4.49	7.26	7.30	14.00	6.80	0.34	0.05	0.05	0.00	0.06
	% ØSC		24.5	2.9	6.8	6.9	10.4	9.4	7.3	13.0	6.9	3.5	2.9	7.2	1.0	
	S.D.		2.0	0.2	0.2	5.9	7.8	17.7	25.6	20.0	12.6	1.6	0.2	0.2	0.2	.084
66.0	29.4	77	9.0	0.02	0.04	1.56	1.59	4.82	2.44	8.00	3.40	0.00	0.05	0.05	0.00	0.02
	% ØSC		21.3	1.7	3.4	4.7	4.7	7.8	3.3	10.8	3.4	0.6	2.3	5.9	2.2	
	S.D.		1.5	0.1	0.2	7.6	7.6	17.5	10.2	17.7	9.2	1.1	0.3	0.3	0.1	.087
195.1	6.1	65	7.5	0.00	0.00	0.21	0.31	0.44	-0.17	2.00	0.00	0.00	0.05	0.05	0.00	0.00
	% ØSC		16.7	-0.9	1.3	1.3	1.8	1.5	-0.4	4.1	-0.1	-0.5	1.6	3.5	0.7	
	S.D.		1.5	0.1	0.1	2.7	2.9	6.1	5.7	8.6	6.4	0.6	0.3	0.2	0.1	.070.
58.0	38.5	113	9.0	0.06	0.14	-0.58	1.84	-1.31	5.24	2.00	6.80	0.85	-0.15	-0.10	-0.05	0.10
	% ØSC		22.0	5.4	13.3	-2.0	6.2	-2.6	7.5	2.7	8.8	12.8	-7.4	-9.0	-6.2	
	S.D.		1.6	0.2	0.2	5.0	5.6	10.3	12.6	16.8	12.8	1.3	0.2	0.2	0.1	.107

421.4

EXERCISE : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
78.0	22.0	89	12.0	0.02	0.10***	1.27*	4.78***	3.58*	7.27***	8.00***	6.80***	1.02***	0.00	0.00	0.00	0.06**
	% ØSC		26.2	0.7	6.4	2.3	8.6	3.3	6.4	4.9	5.3	7.9	0.8	2.5	0.6	
	S.D.		1.8	0.2	0.2	5.4	5.9	14.4	14.2	18.4	13.7	2.1	0.2	0.1	0.1	.101
91.2	16.9	73	9.0	0.02	0.04***	0.86	1.94**	3.27*	1.62	6.00**	1.70	0.00	0.00	0.00	0.00	0.04**
	% ØSC		22.1	1.2	3.9	1.8	4.1	3.6	1.7	5.8	1.6	-0.5	0.5	2.9	1.5	
	S.D.		1.3	0.1	0.1	3.9	4.7	10.2	8.1	14.2	7.5	1.4	0.1	0.1	0.1	.043
66.0	29.4	87	7.5	0.04**	0.14***	2.49***	5.94***	10.27***	7.71***	16.00***	8.50***	0.85***	0.00	0.00	-0.05**	0.08**
	% ØSC		20.7	3.5	10.4	4.8	11.2	9.8	7.2	11.0	6.4	5.9	1.1	3.0	-3.9	
	S.D.		1.5	0.1	0.1	3.5	5.5	10.6	10.3	16.7	10.1	2.0	0.1	0.1	0.1	.070
189.0	6.4	89	7.5	-0.02	0.02	-0.41	0.83	0.31	1.08	0.00	1.70	0.34	0.00	0.00	0.00	0.04**
	% ØSC		17.9	-1.6	1.1	-1.1	2.3	0.4	1.5	0.9	1.0	3.1	0.5	2.0	0.6	
	S.D.		1.5	0.1	0.1	5.0	4.0	12.8	9.1	15.1	10.8	1.3	0.2	0.1	0.1	.103
57.7	38.9	81	10.5	0.12***	0.10***	0.48	-0.41	-6.40***	7.52***	0.00	11.90***	2.55***	-0.15***	-0.15***	0.00	-0.02
	% ØSC		23.6	7.7	6.4	0.9	-0.7	-6.0	6.3	0.3	8.1	17.6	-8.1	-15.9	0.9	
	S.D.		1.5	0.2	0.2	6.0	6.3	13.8	13.5	17.3	19.5	1.9	0.3	0.2	0.1	.074

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	ALTERNATE-BREATH ØSCILLATIØN. PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
54.0	46.5	101	9.0	0.00	-0.02	-1.98*	-2.19*	-6.52**	-0.46	-5.10*	0.00	0.20	-0.05	-0.05	0.00	0.00
	% ØSC		23.2	-0.1	-0.8	-4.3	-4.7	-7.6	-0.5	-4.1	-0.8	2.2	-2.0	-4.8	0.2	
	S.D.		1.4	0.1	0.1	8.8	8.6	20.4	15.3	20.1	19.9	2.1	0.3	0.2	0.1	.079
44.2	81.6	87	10.5	0.04	-0.02	1.17	-1.97	-1.91	1.43	-3.40	3.60	1.20*	-0.05*	-0.05***	0.00	-0.06**
	% ØSC		26.6	2.8	-0.7	1.9	-3.2	-1.6	1.1	-2.6	1.9	6.3	-2.2	-5.6	1.5	
	S.D.		1.6	0.3	0.1	9.7	9.2	21.4	18.9	33.7	25.5	4.4	0.1	0.1	0.1	.137
200.0	6.0	91	9.0	0.02	0.00	-0.32	-0.50	-1.43	0.40	-1.70	1.80	0.20	-0.05	-0.05*	0.00	-0.02*
	% ØSC		23.5	1.4	-0.1	-1.1	-1.7	-2.5	0.6	-2.9	1.9	2.5	-2.7	-6.2	0.1	
	S.D.		2.0	0.1	0.1	5.2	4.6	14.2	7.8	19.4	10.1	1.3	0.3	0.2	0.1	.055
91.4	16.8	101	10.5	0.00	0.00	-1.27*	-1.19*	-4.94***	0.38	-6.80***	0.00	0.20	-0.05*	-0.05**	0.00	0.00
	% ØSC		25.9	-0.5	-0.7	-3.2	-3.0	-6.6	0.5	-6.3	-0.7	1.8	-3.2	-6.3	0.8	
	S.D.		1.8	0.1	0.1	5.2	5.3	13.3	8.9	17.0	10.0	1.5	0.3	0.2	0.1	.069
75.7	22.9	103	12.0	0.00	0.06***	-0.11	1.15	-0.26	3.72***	5.10**	7.20**	1.40***	0.00	-0.05	0.00	0.04**
	% ØSC		27.6	0.5	4.7	-0.3	3.1	-0.4	4.5	4.7	7.0	14.3	0.9	-3.0	0.0	
	S.D.		2.2	0.1	0.1	6.0	6.3	15.1	9.7	15.1	12.6	1.5	0.4	0.3	0.1	.073
50.0	55.6	113	10.5	0.04*	0.08***	0.77	1.37**	0.71	3.58***	5.10**	5.40***	0.80***	-0.05	0.00	0.00	0.04**
	% ØSC		27.1	2.5	5.2	1.9	3.4	0.9	4.3	5.8	5.1	8.4	-2.2	2.1	1.5	
	S.D.		2.1	0.1	0.1	5.1	4.7	12.8	9.4	15.9	11.1	1.5	0.2	0.2	0.1	.082
59.0	37.0	149	12.0	0.02	0.04***	1.65***	1.97***	6.15***	1.31	10.20***	3.60**	0.40**	0.05	0.05**	-0.05*	0.02*
	% ØSC		27.7	2.0	3.3	4.2	5.0	8.3	1.6	10.0	2.9	4.2	1.4	4.2	-3.5	
	S.D.		1.9	0.2	0.1	5.5	5.2	13.5	8.6	15.3	9.0	1.7	0.3	0.2	0.2	.066

421.6

EXERCISE : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
199.5	6.0	83	7.5	0.04	0.02	0.88	-0.34	-0.24	1.81	0.00	3.60	0.20	0.00	0.00	0.00	-0.02
	% ØSC		19.7	2.4	1.2	1.8	-0.7	-0.3	1.7	-0.0	2.2	1.3	1.3	2.4	0.4	
	S.D.		1.3	0.1	0.1	4.1	3.4	9.9	7.3	12.9	10.4	2.0	0.1	0.1	0.1	.078
93.7	16.2	129	9.0	0.00	-0.04	-0.13	-1.61	-3.38	-0.49	-3.40	0.00	0.00	0.00	0.00	0.00	-0.04
	% ØSC		22.7	-0.3	-3.0	-0.2	-3.1	-3.3	-0.5	-2.1	-0.6	-0.4	0.2	2.2	3.2	
	S.D.		3.0	0.2	0.1	4.5	6.1	11.3	12.2	15.8	12.6	2.0	0.2	0.1	0.1	.098
71.5	25.3	115	10.5	0.04	0.04	0.80	1.86	2.74	1.47	3.40	5.40	1.20	0.00	0.00	0.00	0.02
	% ØSC		25.6	2.0	3.1	1.3	3.0	2.2	1.2	2.0	3.1	6.3	0.6	0.4	1.5	
	S.D.		1.6	0.2	0.1	4.9	5.0	11.3	11.7	11.7	10.7	2.6	0.1	0.1	0.1	.126
56.3	41.1	105	10.5	0.10	0.06	2.96	1.56	6.05	2.33	10.20	7.20	1.40	0.00	0.00	0.00	-0.04
	% ØSC		28.0	6.3	4.2	4.8	2.5	4.9	1.9	6.2	5.6	7.4	1.2	0.9	1.4	
	S.D.		1.3	0.2	0.1	4.5	5.5	16.1	11.7	14.8	10.6	1.9	0.1	0.1	0.1	.114
68.4	27.5	111	10.5	0.06	0.06	1.36	0.86	2.90	1.37	6.80	5.40	0.40	-0.05	0.00	0.00	-0.02
	% ØSC		25.1	4.1	4.0	2.5	1.6	2.6	1.3	4.9	3.9	3.4	-2.0	2.0	2.4	
	S.D.		1.7	0.1	0.1	5.2	5.4	13.0	10.9	19.6	13.7	1.9	0.2	0.1	0.1	.078

425.2

REST : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.5	6.6	73	7.5	-0.04	0.00	-0.24	0.64	1.00	-0.55	0.00	-2.40	0.00	0.00	0.05	0.00	0.04
	% ØSC		17.3	-1.9	-0.6	-0.6	1.7	1.4	-0.7	0.6	-1.9	0.4	0.4	2.5	1.9	
	S.D.		1.3	0.2	0.2	3.5	5.0	10.8	9.6	16.1	12.8	1.2	0.2	0.1	0.1	.119
57.0	53.3	63	9.0	0.00	-0.08*	-0.48	-2.05*	0.41	-4.83*	0.00	-7.20**	-0.96**	0.00	0.00	0.00	-0.04
	% ØSC		19.0	-0.9	-3.0	-0.7	-3.0	0.3	-3.8	-0.8	-3.8	-8.6	0.5	0.9	0.6	
	S.D.		1.7	0.2	0.2	6.6	7.5	15.7	14.2	21.7	17.4	2.2	0.2	0.1	0.1	.192
69.3	32.0	59	9.0	0.04	0.12**	0.31	1.65**	0.61	1.77**	0.00	2.40	0.24	-0.05	0.00	0.00	0.08**
	% ØSC		19.8	1.3	5.5	0.8	4.6	0.9	2.4	1.3	2.2	4.2	-1.0	0.0	0.3	
	S.D.		2.1	0.2	0.3	4.6	4.5	11.2	8.5	14.1	12.4	1.1	0.5	0.3	0.2	.125
49.5	88.9	69	9.0	0.00	0.04	0.55	2.52**	3.16	3.55*	4.90*	4.80	-0.24	0.05	0.05*	0.00	0.04
	% ØSC		17.6	-0.8	2.3	0.9	4.2	2.3	3.3	3.4	2.4	-2.8	1.3	3.2	0.3	
	S.D.		2.4	0.2	0.2	5.4	6.1	14.1	11.1	18.4	16.9	1.3	0.1	0.1	0.1	.180
65.0	37.4	65	7.5	0.00	0.04	-0.02	0.93	2.41	1.36	0.00	0.00	-0.32	0.00	0.00	-0.05	0.04*
	% ØSC		17.2	-0.6	2.1	-0.0	1.8	2.0	1.4	1.0	-0.5	-3.7	0.3	2.1	-2.3	
	S.D.		1.3	0.1	0.1	8.3	7.7	20.7	12.8	19.3	15.7	1.9	0.3	0.2	0.1	.099
99.5	16.3	97	9.0	-0.04	0.00	-0.34	0.40	0.14	0.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% ØSC		17.7	-1.4	1.2	-0.7	0.8	0.1	0.3	-0.0	0.2	0.0	0.3	1.2	0.2	
	S.D.		2.4	0.2	0.2	6.1	5.9	15.8	10.1	14.9	14.2	1.1	0.1	0.1	0.1	.141

425.2

EXERCISE : PAC02 OSCILLATING.

ALTERNATE-BREATH OSCILLATION.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.5	6.6	61	7.5	0.00	0.08	-1.39	1.25	-1.28	-0.12	0.00	-2.40	-0.24	-0.10	0.00	-0.05	0.01
	% OSC		15.7	0.3	3.6	-3.2	2.9	-1.5	-0.1	-0.6	-2.4	-3.8	-3.4	0.1	4.1	
	S.D.		2.4	0.4	0.4	7.3	5.5	17.0	10.5	21.6	20.2	1.7	0.6	0.4	0.3	.255
89.0	19.7	71	7.5	-0.04	0.04	-0.33	0.46	-1.33	0.75	0.00	2.40	-0.08	0.00	0.00	0.00	0.04
	% OSC		16.6	-2.0	1.7	-0.6	0.9	-1.2	0.7	-0.0	2.3	-1.4	0.3	1.9	0.8	
	S.D.		2.3	0.2	0.3	5.3	5.4	15.8	9.5	27.3	16.0	1.5	0.3	0.2	0.1	.190
63.0	40.4	75	9.0	-0.04	0.20	-1.91	5.05	-0.84	8.60	4.90	12.00	0.96	0.00	0.00	0.00	0.20
	% OSC		18.4	-1.7	8.6	-3.2	8.4	-0.7	7.3	1.9	7.3	10.0	0.7	0.8	1.5	
	S.D.		2.6	0.2	0.2	7.4	7.8	15.8	11.3	23.8	22.7	1.7	0.3	0.2	0.1	.239
66.5	35.4	61	6.0	-0.04	0.12***	-1.78*	1.52***	-4.35	4.19***	0.00	7.20***	0.32***	-0.10	-0.05	0.00	0.12**
	% OSC		13.8	-1.4	5.8	-3.6	3.1	-4.5	4.1	1.3	4.8	3.9	-2.9	-3.2	1.5	
	S.D.		4.3	0.3	0.3	7.4	6.1	16.8	11.6	21.0	24.2	1.6	0.3	0.2	0.1	.257
101.0	15.9	59	7.5	-0.04	0.12*	-0.65	3.79***	1.35	4.32	0.00	4.80	-0.24	0.05	0.05	-0.05	0.12**
	% OSC		15.5	-1.0	6.0	-1.3	7.8	1.4	4.3	-1.7	3.3	-3.0	1.5	5.5	-3.2	
	S.D.		2.0	0.3	0.3	7.0	7.1	16.7	11.5	20.2	18.5	1.9	0.5	0.3	0.2	.235
60.0	46.0	67	9.0	-0.08*	0.28***	-1.80	6.93***	-0.01	8.02***	9.80**	12.00***	0.64	0.00	0.00	0.00	0.32**
	% OSC		19.1	-2.8	10.2	-2.6	10.2	-0.0	6.0	4.9	6.1	5.6	0.3	1.3	1.9	
	S.D.		2.3	0.3	0.2	8.4	8.6	19.7	13.4	22.5	26.4	2.6	0.2	0.2	0.1	.274

425.5

REST : PAØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFR
201.0	6.1	69	10.5	-0.04	0.00	0.03	0.38	1.67	-1.65	-5.20	-2.40	0.00	0.05	0.05	0.00	0.04
	% ØSC		21.0	-1.5	-0.7	0.1	0.9	1.9	-2.1	-2.1	-2.2	-0.4	1.7	3.5	1.0	
	S.D.		2.8	0.3	0.3	6.2	6.8	15.8	12.4	29.7	23.2	2.0	0.4	0.2	0.2	.176
79.0	24.5	75	9.0	-0.04	0.04	-0.62	1.70	2.02	1.29	0.00	0.00	0.00	0.00	0.00	0.00	0.04
	% ØSC		20.0	-1.5	2.4	-1.1	3.2	1.7	1.3	-0.5	0.6	-0.8	0.5	1.9	1.3	
	S.D.		2.1	0.2	0.2	6.6	7.2	17.9	15.1	22.0	16.3	2.1	0.2	0.1	0.1	.106
62.0	42.1	85	10.5	-0.04	0.00	-0.63	0.73	0.91	0.89	-5.20	-4.80	0.00	0.00	0.00	0.00	0.04
	% ØSC		22.0	-1.5	0.2	-1.0	1.2	0.7	0.8	-1.4	-2.1	-0.5	1.1	2.4	0.1	
	S.D.		1.4	0.2	0.2	6.6	8.9	16.1	18.6	21.0	37.1	3.5	0.2	0.1	0.1	.121
54.3	62.4	81	10.5	0.08	0.00	1.30	0.52	3.83	0.85	5.20	-4.80	-0.40	0.00	0.00	0.00	-0.04
	% ØSC		22.2	2.7	0.5	2.5	1.0	3.7	0.8	2.2	-2.3	-3.1	0.3	0.2	0.1	
	S.D.		1.5	0.3	0.3	6.5	5.6	14.1	14.0	20.6	27.3	2.4	0.3	0.2	0.1	.166
54.6	61.2	49	10.5	-0.04	0.00	-1.51	-0.19	2.56	-4.20	0.00	-9.60	-0.60	0.00	0.05	-0.05	0.04
	% ØSC		21.6	-2.1	0.4	-2.4	-0.3	1.8	-3.6	0.9	-4.8	-5.3	0.3	3.8	-3.5	
	S.D.		2.4	0.2	0.2	6.1	6.2	15.6	13.9	23.9	20.9	2.1	0.1	0.1	0.1	.168
55.0	59.6	83	10.5	-0.04	0.00	-2.23	-0.19	-3.84	-1.81	-5.20	-2.40	-0.40	-0.05	0.00	0.00	0.04
	% ØSC		22.2	-1.4	0.1	-3.1	-0.3	-2.6	-1.3	-2.1	-1.0	-2.6	-1.5	0.0	1.8	
	S.D.		2.1	0.3	0.3	7.8	8.2	20.7	17.5	23.9	24.8	2.9	0.1	0.1	0.1	.172

425.5

EXERCISE : PAC02 OSCILLATING.

ALTERNATE-BREATH OSCILLATION.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
205.5	6.0	55	10.5	-0.04	0.00	-0.26	1.30	0.24	1.63	0.00	0.00	0.20	0.10	0.05	0.00	0.04
	% OSC		21.9	-1.3	0.7	-0.6	3.0	0.3	1.8	0.4	-0.4	1.7	2.4	2.1	1.2	
	S.D.		1.8	0.3	0.2	5.2	5.0	13.2	9.3	18.5	15.0	1.6	0.4	0.2	0.2	.152
81.7	23.0	69	10.5	0.00	-0.04	0.47	-0.44	-0.12	-1.46	0.00	-7.20	-0.60	0.00	0.00	0.00	-0.04
	% OSC		21.7	0.7	-0.8	0.8	-0.7	-0.1	-1.2	1.1	-4.1	-5.5	0.0	0.3	0.2	
	S.D.		2.1	0.4	0.4	10.8	10.6	24.4	20.1	34.7	32.0	2.6	0.2	0.2	0.1	.188
70.5	31.0	83	9.0	0.04	0.20***	0.95	3.59***	1.94	6.85***	5.20	12.00***	0.60	0.05	0.05	0.00	0.16***
	% OSC		20.8	2.3	8.0	2.0	7.6	2.2	6.6	3.5	7.5	5.8	1.0	2.1	0.3	
	S.D.		2.1	0.3	0.3	5.3	6.1	13.5	11.1	28.7	18.4	2.4	0.4	0.3	0.2	.228
60.0	46.0	63	10.5	0.00	-0.04	-0.69	-1.25	6.79**	-9.19**	0.00	-9.60	-0.80	0.00	0.05*	-0.05*	0.00
	% OSC		22.0	-0.7	-1.5	-0.8	-1.5	4.2	-5.5	-0.1	-3.2	-3.9	0.4	3.6	-4.0	
	S.D.		1.8	0.3	0.3	9.0	11.2	16.5	27.2	27.8	36.7	3.4	0.1	0.1	0.1	.226
58.2	50.0	99	10.5	0.00	-0.04	1.57	-0.37	5.60*	-3.57	5.20	-9.60*	-0.80	0.05	0.05**	0.00	0.00
	% OSC		22.5	0.0	-0.7	1.8	-0.4	3.0	-2.3	1.9	-3.6	-4.4	1.4	3.9	1.1	
	S.D.		1.9	0.3	0.4	10.1	11.3	21.1	23.3	30.4	36.7	4.4	0.1	0.1	0.1	.191

EXERCISE : PAC02 OSCILLATING.

ALTERNATE-BREATH OSCILLATION.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
205.5	6.0	55	10.5	-0.04	0.00	-0.26	1.30	0.24	1.63	0.00	0.00	0.20	0.10	0.05	0.00	0.04
	% OSC		21.9	-1.3	0.7	-0.6	3.0	0.3	1.8	0.4	-0.4	1.7	2.4	2.1	1.2	
	S.D.		1.8	0.3	0.2	5.2	5.0	13.2	9.3	18.5	15.0	1.6	0.4	0.2	0.2	.152
81.7	23.0	69	10.5	0.00	-0.04	0.47	-0.44	-0.12	-1.46	0.00	-7.20	-0.60	0.00	0.00	0.00	-0.04
	% OSC		21.7	0.7	-0.8	0.8	-0.7	-0.1	-1.2	1.1	-4.1	-5.5	0.0	0.3	0.2	
	S.D.		2.1	0.4	0.4	10.8	10.6	24.4	20.1	34.7	32.0	2.6	0.2	0.2	0.1	.188
70.5	31.0	83	9.0	0.04	0.20***	0.95	3.59***	1.94	6.85***	5.20	12.00***	0.60	0.05	0.05	0.00	0.16***
	% OSC		20.8	2.3	8.0	2.0	7.6	2.2	6.6	3.5	7.5	5.8	1.0	2.1	0.3	
	S.D.		2.1	0.3	0.3	5.3	6.1	13.5	11.1	28.7	18.4	2.4	0.4	0.3	0.2	.228
60.0	46.0	63	10.5	0.00	-0.04	-0.69	-1.25	6.79**	-9.19**	0.00	-9.60	-0.80	0.00	0.05*	-0.05*	0.00
	% OSC		22.0	-0.7	-1.5	-0.8	-1.5	4.2	-5.5	-0.1	-3.2	-3.9	0.4	3.6	-4.0	
	S.D.		1.8	0.3	0.3	9.0	11.2	16.5	27.2	27.8	36.7	3.4	0.1	0.1	0.1	.226
58.2	50.0	99	10.5	0.00	-0.04	1.57	-0.37	5.60*	-3.57	5.20	-9.60*	-0.80	0.05	0.05**	0.00	0.00
	% OSC		22.5	0.0	-0.7	1.8	-0.4	3.0	-2.3	1.9	-3.6	-4.4	1.4	3.9	1.1	
	S.D.		1.9	0.3	0.4	10.1	11.3	21.1	23.3	30.4	36.7	4.4	0.1	0.1	0.1	.191

392.13

EXERCISE : PACØ2 ØSCILLATING.

PAØ2	HYP	N	ALTERNATE-BREATH ØSCILLATIØN. PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
204.0	5.8	57	10.5	-0.04	0.00	-2.45	-0.44	-5.41	0.21	-5.00	2.40	-0.16	0.00	0.00	0.00	0.08***
	% ØSC		22.1	-1.6	0.1	-4.1	-0.7	-3.9	0.2	-2.2	1.8	-2.1	0.3	1.3	0.7	
	S.D.		3.9	0.6	0.6	11.4	11.8	33.4	18.4	35.1	23.1	1.7	0.3	0.2	0.2	147
77.7	22.1	47	9.0	0.36**	0.32**	4.84*	4.90*	8.14	10.79**	5.00	14.40**	0.64*	-0.15*	-0.05	-0.05	0.04
	% ØSC		20.9	12.3	12.3	7.6	7.7	6.0	9.0	2.9	8.3	7.1	-5.6	-4.0	-4.6	
	S.D.		4.0	0.8	0.8	16.4	15.4	42.3	24.3	53.4	33.0	1.8	0.4	0.3	0.2	241
60.2	36.7	55	10.5	0.12*	0.20***	1.39	3.00*	-0.45	5.97**	5.00	12.00***	0.80*	0.00	0.00	0.00	0.04
	% ØSC		21.3	3.7	6.0	1.8	4.0	-0.3	4.2	2.4	6.9	7.1	0.9	0.2	0.5	
	S.D.		1.9	0.4	0.4	9.3	10.3	27.6	15.1	29.3	17.9	2.1	0.3	0.2	0.1	242
88.0	18.0	51	9.0	0.12*	0.28***	2.04	4.94***	5.55	8.76***	5.00	12.00***	0.64***	0.00	0.00	-0.05	0.08***
	% ØSC		18.7	4.3	9.2	3.1	7.5	4.0	6.9	1.9	6.9	7.3	0.9	0.2	-3.0	
	S.D.		1.8	0.4	0.5	8.3	9.3	22.1	15.9	33.9	18.5	1.3	0.3	0.2	0.1	180
57.2	41.2	83	9.0	0.20**	0.24***	4.02**	3.24*	10.23**	8.79***	5.00	14.40***	0.80*	0.00	0.05	0.00	0.04
	% ØSC		20.4	5.9	7.6	5.1	4.1	6.1	5.8	1.4	7.2	6.7	0.6	2.9	0.5	
	S.D.		1.9	0.5	0.5	10.4	9.9	24.2	18.3	29.4	25.8	2.5	0.2	0.2	0.1	194
100.0	14.8	61	9.0	0.04	0.04	-0.41	1.35	-0.32	-0.39	0.00	2.40	0.08	-0.05	0.00	-0.05	0.04
	% ØSC		19.0	1.0	1.9	-0.6	2.0	-0.2	-0.3	-0.2	1.9	0.8	-1.8	0.0	-2.2	
	S.D.		2.0	0.5	0.6	9.8	10.7	25.4	16.2	40.0	24.2	1.5	0.3	0.1	0.2	180
59.0	38.5	95	9.0	0.12***	0.24***	5.02***	7.65***	17.03***	7.96***	10.00*	12.00***	1.04***	0.00	0.05	0.00	0.12***
	% ØSC		21.6	4.3	7.9	6.1	9.3	9.7	5.1	3.0	5.7	9.3	0.0	3.5	1.4	
	S.D.		1.8	0.3	0.4	8.7	11.8	33.6	18.2	34.5	18.4	2.2	0.2	0.2	0.1	213

392.15

REST : PACØ2 ØSCILLATING.

-225,17-

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
72.0	25.2	71	10.5	0.03	0.09	0.52	0.99	3.29	1.68	9.00	2.40	0.00	0.00	0.05	0.00	0.03
	% ØSC		22.9	2.0	4.4	1.3	2.4	4.7	1.6	4.6	1.6	-0.2	>0.2	3.2	1.7	
	S.D.		1.8	0.6	0.6	14.0	14.2	25.7	36.3	62.9	32.1	1.3	0.5	0.4	0.3	.215
91.0	17.0	73	9.0	0.03	0.15*	1.51	2.44*	3.89	5.50*	0.00	4.80*	0.28	-0.05	0.05	-0.05	0.03
	% ØSC		21.7	2.3	9.2	4.8	7.7	6.3	8.3	0.1	6.9	5.8	-1.1	2.1	-2.9	
	S.D.		2.2	0.5	0.4	9.2	8.0	17.6	17.3	38.7	19.3	1.5	0.5	0.4	0.3	.163
52.1	50.1	89	10.5	0.09	0.15*	3.60**	3.80**	6.98**	10.44***	13.50	14.40***	0.70*	0.05	0.00	0.00	0.06
	% ØSC		23.7	4.2	6.4	7.0	7.4	7.7	8.8	6.3	10.6	9.4	2.0	0.3	2.2	
	S.D.		2.6	0.4	0.5	9.7	11.1	20.1	20.5	62.8	31.0	2.5	0.3	0.3	0.2	.256
61.5	34.1	89	10.5	0.09	0.18***	1.83	3.21**	3.97	6.59**	4.50	9.60***	0.14	0.00	0.00	0.00	0.06***
	% ØSC		23.3	4.5	9.2	4.1	7.2	4.4	7.3	3.1	9.4	1.2	0.7	1.0	1.7	
	S.D.		2.7	0.4	0.4	10.3	8.9	17.7	18.1	48.9	21.1	1.9	0.3	0.2	0.2	.103
209.0	5.7	49	9.0	0.09	0.12*	2.69	4.38**	5.55	7.35**	22.50**	4.80	0.42	-0.05	0.00	-0.05	0.00
	% ØSC		17.1	6.2	7.8	7.0	11.6	7.7	9.0	17.0	4.2	6.9	-2.3	1.4	-2.8	
	S.D.		3.1	0.4	0.3	9.8	7.8	22.0	16.0	44.6	19.5	1.8	0.4	0.3	0.2	.118

EXERCISE : PACØ2 ØSCILLATING.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
90.0	17.1	55	9.0	0.21***	0.30***	2.36**	4.99***	3.21	12.07***	9.00	12.00***	0.56*	-0.15**	-0.05	-0.05	0.06
	% ØSC		20.5	8.5	12.1	4.4	9.2	3.3	9.9	4.4	8.9	7.3	-5.3	-4.6	-3.1	
	S.D.		1.3	0.3	0.4	5.4	6.4	13.9	14.1	33.6	15.3	1.8	0.3	0.2	0.1	.238
63.7	31.7	117	10.5	0.06**	0.12	1.62***	3.97	4.21***	6.84*	9.00**	7.20	0.28	0.00	0.00	0.00	0.03
	% ØSC		22.4	3.2	4.5	2.4	5.8	2.9	5.2	4.1	4.5	2.0	0.2	1.0	0.7	
	S.D.		1.3	0.4	0.4	12.0	9.5	24.4	16.9	35.8	20.3	1.8	0.3	0.2	0.2	.178
55.4	43.0	93	10.5	0.03	0.18***	3.36**	5.06***	5.42	9.83***	4.50	14.40***	0.28	0.05	0.00	0.00	0.09***
	% ØSC		23.9	0.7	6.9	4.3	6.5	3.2	6.7	0.8	8.2	1.6	1.4	1.2	0.0	
	S.D.		1.2	0.2	0.3	10.4	12.2	26.8	19.2	39.7	20.5	1.0	0.2	0.2	0.1	.190
64.1	31.3	59	10.5	0.06	0.12*	0.97	3.82**	4.09	6.67*	0.00	12.00**	0.00	0.00	0.00	-0.05	0.12***
	% ØSC		22.9	3.0	5.5	1.4	5.5	2.7	5.2	0.3	7.9	0.5	0.3	0.2	-3.5	
	S.D.		2.0	0.3	0.3	10.2	10.5	29.8	22.3	39.6	28.8	2.2	0.2	0.1	0.2	.234
49.7	56.8	69	10.5	0.06*	0.15***	2.52*	5.92***	10.30*	13.73***	-4.50	16.80***	0.00	0.00	0.00	0.00	0.06**
	% ØSC		25.0	3.1	7.1	3.1	7.2	5.9	8.8	-1.4	9.1	0.3	0.5	0.6	0.2	
	S.D.		0.8	0.2	0.2	9.5	10.9	29.0	18.0	38.8	18.6	0.3	0.3	0.2	0.1	.193
71.3	25.6	113	10.5	-0.03	0.03	-0.23	1.60	3.21	0.45	-4.50	2.40	-0.28	0.00	0.05	0.00	0.06***
	% ØSC		23.0	-2.0	2.2	-0.3	2.3	2.1	0.4	-1.5	2.4	-2.0	0.7	4.7	1.6	
	S.D.		1.4	0.3	0.3	11.0	10.2	37.5	15.2	37.7	19.3	2.2	0.2	0.2	0.1	.125
202.0	5.9	63	10.5	0.03	0.09	0.45	2.16	2.94	3.03	-4.50	4.80	0.00	0.00	0.00	0.00	0.06***
	% ØSC		22.3	2.1	5.2	0.7	3.3	2.0	2.5	-1.2	3.1	-0.6	0.5	1.4	0.7	
	S.D.		2.0	0.4	0.4	11.9	11.1	35.4	16.8	56.0	20.0	2.2	0.3	0.2	0.2	.094

'STEADY' RUNS.
(18 pages: 225_{19-36})

409.5

REST : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2 torr.	HYP torr⁻¹	N	PACØ2 torr.	VTE L.	VTI L.	VE l.min.⁻¹	VI l.min.⁻¹	MEF l.min.⁻¹	MIF L.min.⁻¹	PEF l.min.⁻¹	PIF l.min.⁻¹	PIA l.sec⁻²	TT sec	TE sec	TI sec	DFRC L.
54.0	44.4	49	0.0	0.03	0.06*	0.14	0.05	0.41	0.88	-3.00	2.50	0.27	0.00	0.00	0.00	0.03
	% ØSC		-0.3	1.5	3.3	0.4	0.1	0.7	1.1	-1.6	1.9	2.5	0.0	0.2	1.3	
	S.D.		0.7	0.1	0.1	4.2	3.7	8.5	9.2	14.8	9.0	1.8	0.4	0.2	0.2	.089
54.5	44.4	61	0.0	0.03	0.03	-0.02	0.48	0.01	1.52	0.00	0.00	0.09	0.00	0.00	-0.05	0.03
	% ØSC		-0.3	1.2	2.4	-0.1	1.5	0.0	1.8	-0.5	0.9	0.6	0.3	0.1	-2.7	
	S.D.		0.9	0.1	0.2	3.0	2.8	6.6	5.8	10.4	7.1	1.0	0.3	0.2	0.1	.123
47.0	66.7	61	0.0	-0.03	0.03	-0.80	0.96	-0.20	1.98	-3.00	2.50**	0.36	0.00	0.00	0.00	0.06**
	% ØSC		-0.3	-1.8	2.1	-1.9	2.3	-0.3	2.0	-1.6	2.8	2.9	0.6	0.1	1.0	
	S.D.		1.1	0.2	0.2	4.0	4.2	15.3	14.5	15.0	6.9	1.9	0.5	0.4	0.2	.107
68.7	27.2	63	0.0	0.00	0.00	1.13	0.84	1.69	1.70	0.00	0.00	0.36*	0.10	0.05	0.00	-0.03
	% ØSC		-0.4	-0.1	0.8	3.0	2.3	2.6	1.9	-0.5	-0.8	3.8	2.8	3.8	1.4	
	S.D.		1.3	0.2	0.2	6.6	7.8	15.3	13.0	19.0	8.2	1.3	0.4	0.4	0.1	.235
113.0	12.3	65	0.0	0.00	0.03	0.20	1.05	0.28	1.94	0.00	2.50	0.27*	0.00	0.00	0.00	0.03**
	% ØSC		-0.7	-0.5	1.9	0.5	2.6	0.4	2.2	-0.4	2.1	2.2	0.5	0.2	0.9	
	S.D.		1.0	0.2	0.2	5.4	5.6	12.8	8.5	13.1	7.4	1.3	0.6	0.4	0.2	.092

CUTIØN ERRØR 105 PRØGRAM TERMINATED

EXFRCISE : PAC02 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
52.5	48.5	61	0.0	0.00	0.06	0.94	2.44***	2.64	4.42***	3.00	5.00**	0.18	0.00	0.05	0.00	0.03*
	% ØSC		-0.5	0.2	2.2	2.0	5.3	3.2	4.2	1.6	3.0	1.4	0.8	2.0	0.8	
	S.D.		0.9	0.2	0.2	4.9	4.5	13.0	8.4	13.7	10.1	2.2	0.4	0.3	0.1	.141
57.5	39.2	51	0.0	0.03	0.03	0.10	0.07	-1.28	1.67	-3.00	2.50*	0.36	-0.05	-0.05	0.00	0.03
	% ØSC		-0.2	0.8	2.3	0.2	0.2	-1.7	1.5	-1.8	2.6	3.3	-2.2	-2.2	0.4	
	S.D.		0.8	0.1	0.2	5.1	4.3	13.2	6.9	12.9	9.7	1.9	0.3	0.3	0.1	.093
50.5	54.1	71	0.0	0.00	0.06*	0.69	1.81**	2.55	1.84	0.00	5.00**	0.36	0.00	0.05	0.00	0.06***
	% ØSC		-0.8	-0.1	1.8	1.1	2.8	2.0	1.4	0.0	2.0	2.1	0.4	2.3	1.2	
	S.D.		0.8	0.1	0.1	3.9	4.8	12.9	9.0	18.3	9.8	1.8	0.1	0.1	0.1	.116
67.9	27.9	61	0.0	0.00	0.00	0.65	1.21	1.95	1.71	0.00	2.50	0.27	0.05	0.00	0.00	0.00
	% ØSC		-0.3	-0.6	0.4	1.2	2.3	2.0	1.5	-0.1	1.3	1.8	1.6	1.2	1.2	
	S.D.		1.1	0.2	0.2	6.1	5.5	13.0	11.4	17.0	8.6	1.8	0.3	0.2	0.2	.167
117.0	11.8	61	0.0	0.00	0.06*	-1.14	1.39	-0.46	1.54	-3.00	5.00*	0.45	0.00	0.00	0.00	0.09**
	% ØSC		-0.3	-0.7	3.2	-2.0	2.5	-0.4	1.4	-1.5	2.4	3.0	0.1	1.2	0.4	
	S.D.		1.1	0.2	0.2	6.0	5.5	13.0	12.7	16.3	11.6	1.6	0.2	0.1	0.1	.081

REST : PAC02 STEADY.

ALTERNATE-BREATH OSCILLATION.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
129.0	10.4	71	0.0	0.00	0.03	1.76	2.08	3.49	2.35	3.00	2.50**	0.18	0.10	0.05	0.00	0.03
	% OSC		-0.4	-0.1	1.7	4.5	5.3	5.1	2.5	1.9	3.1	4.4	3.8	4.2	1.3	
	S.D.		1.0	0.2	0.2	6.9	6.6	17.4	9.9	19.2	9.8	0.8	0.6	0.4	0.2	.153
78.5	21.5	47	0.0	0.00	0.03	-0.51	0.78	-0.61	1.95	0.00	2.50*	0.18	-0.05	0.00	0.00	0.03
	% OSC		-0.3	-0.8	1.5	-1.2	1.9	-0.8	2.0	0.2	2.8	4.0	-1.0	0.6	1.0	
	S.D.		1.1	0.1	0.1	5.5	5.1	13.7	9.0	17.7	9.7	1.2	0.3	0.3	0.1	.104
63.5	31.7	67	0.0	0.00	0.06	1.01	1.36	1.86	1.82	3.00	5.00***	0.18*	0.00	0.00	0.00	0.03**
	% OSC		-0.4	0.6	2.7	2.4	3.2	2.5	1.8	3.2	3.3	4.5	1.0	1.4	0.3	
	S.D.		0.8	0.2	0.2	5.4	6.7	14.5	11.9	16.7	9.0	0.8	0.3	0.3	0.1	.134
48.3	61.2	77	0.0	0.00	0.06***	-0.29	1.57	-0.43	2.69	0.00	2.50	0.27*	0.00	0.00	0.00	0.03**
	% OSC		-0.2	0.7	3.5	-0.5	2.7	-0.4	2.3	-0.5	2.2	4.5	0.8	0.4	1.0	
	S.D.		1.2	0.2	0.2	7.7	8.1	17.6	16.6	27.3	15.1	1.1	0.3	0.2	0.2	.102
56.0	41.7	71	0.0	0.03	0.03*	0.04	1.50*	1.13	2.36	0.00	5.00**	0.27**	0.00	0.00	0.00	0.03
	% OSC		-0.3	0.9	2.0	0.1	3.0	1.2	2.2	0.5	2.6	5.5	0.7	1.7	0.4	
	S.D.		0.6	0.2	0.1	5.0	6.0	11.6	11.7	16.9	9.7	0.9	0.3	0.2	0.1	.137

EXERCISE : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTF	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
126.0	10.6	63	0.0	0.03	0.00	0.14	0.68	1.52	1.89	3.00	0.00	-0.18	-0.05	0.00	0.00	0.00
	% ØSC		0.2	1.2	0.3	0.3	1.4	1.7	1.8	3.0	0.9	-3.0	-1.1	0.7	0.4	
	S.D.		2.1	0.2	0.2	8.9	8.6	18.7	18.4	20.6	12.9	1.2	0.6	0.3	0.2	.112
75.5	23.0	71	0.0	0.00	0.06***	0.96	3.18	3.47	4.30*	0.00	5.00**	0.27	0.05	0.05	0.00	0.09***
	% ØSC		-0.9	-0.7	3.6	1.7	5.8	3.3	3.7	0.6	3.1	3.9	2.9	5.1	0.6	
	S.D.		1.6	0.2	0.2	8.1	8.5	20.4	15.2	30.6	13.5	1.1	0.4	0.3	0.2	.123
63.0	32.3	69	0.0	0.00	0.06**	0.87	2.45	0.74	5.32***	0.00	2.50	0.45	0.05	0.00	0.05	0.06***
	% ØSC		-0.0	-0.5	2.5	1.5	4.3	0.7	4.3	0.6	1.3	7.0	1.2	1.2	2.5	
	S.D.		1.0	0.1	0.2	4.6	5.5	13.2	10.8	24.1	12.7	1.1	0.2	0.2	0.1	.125
50.2	54.9	73	0.0	-0.03	0.06*	-0.74	2.11*	0.04	3.48	-3.00	5.00	0.00	0.00	0.05	0.00	0.09***
	%.ØSC		-0.9	-1.1	2.9	-1.2	3.4	0.0	2.7	-1.1	2.9	0.0	0.2	2.3	1.3	
	S.D.		1.0	0.3	0.3	8.7	8.7	18.4	18.0	25.1	23.5	1.2	0.3	0.2	0.1	.137
56.7	40.4	61	0.0	-0.03	0.06	-0.22	1.25	0.82	3.55**	3.00***	5.00	0.09	0.05	0.00	0.00	0.06**
	% ØSC		-0.4	-1.0	2.3	-0.4	2.2	0.8	3.0	2.4	2.6	0.8	1.2	0.5	0.7	
	S.D.		1.1	0.2	0.2	6.6	4.8	16.2	9.1	18.8	7.6	0.8	0.2	0.2	0.1	.138

REST : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N		PACØ2	VTF	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
76.5	22.7	85		0.0	0.00	-0.02*	0.29	-0.07	0.61	-0.30	0.00	-1.40	0.00	0.05	0.00	0.00	0.00
	% ØSC			-0.6	-0.2	-1.4	0.9	-0.2	1.0	-0.4	0.6	-2.0	0.2	1.3	1.5	1.1	
	S.D.			0.7	0.1	0.1	2.9	2.8	7.5	5.9	12.1	6.3	0.4	0.2	0.1	0.1	.066
112.0	12.5	79		0.0	0.00	0.02	-0.15	0.19	0.55	-0.21	1.70	0.00	0.00	0.00	0.00	0.00	0.02
	% ØSC			0.4	0.1	1.1	-0.5	0.6	0.9	-0.3	1.4	-0.1	-0.2	0.4	0.3	1.6	
	S.D.			0.6	0.1	0.1	3.4	3.2	7.2	6.4	14.7	10.1	0.5	0.1	0.1	0.1	.072
76.7	22.3	59		0.0	0.02	0.04	0.49	0.65	1.14	1.41	1.70	1.40	0.00	0.00	0.00	0.00	0.02
	% ØSC			0.5	1.7	2.9	1.3	1.7	1.4	1.9	1.9	0.9	0.3	0.2	0.7	0.8	
	S.D.			0.4	0.1	0.1	5.7	6.0	14.9	10.0	10.8	12.8	0.7	0.3	0.2	0.1	.068
66.2	29.2	79		0.0	-0.02	0.00	-0.18	0.09	-0.38	0.46	0.00	1.40	0.08	0.00	0.00	0.00	0.02
	% ØSC			0.3	-0.9	0.5	-0.4	0.2	-0.4	0.6	-0.1	1.0	1.7	0.2	0.3	0.0	
	S.D.			0.6	0.2	0.2	5.1	4.8	10.7	11.2	24.7	15.8	0.8	0.1	0.1	0.1	.068
61.0	34.5	57		0.0	0.00	0.02	-0.06	0.37	-0.39	0.98	0.00	2.80	0.00	0.00	0.00	0.00	0.00
	% ØSC			0.2	0.2	1.4	-0.2	1.0	-0.5	1.4	0.9	2.5	0.0	0.2	0.1	0.9	
	S.D.			0.4	0.1	0.1	5.5	4.3	14.6	7.3	16.1	11.3	0.8	0.2	0.1	0.1	.088

421.2

EXERCISE : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
120.0	11.4	75	0.0	0.04	0.06	0.13	0.79	1.37	0.82	0.00	0.00	0.00	-0.05	0.00	-0.05	0.04
	% ØSC		0.2	3.1	4.8	0.4	2.3	2.0	1.2	0.3	0.5	-0.2	-2.2	0.7	-3.8	
	S.D.		1.0	0.3	0.3	3.5	3.3	8.9	6.0	13.5	7.0	0.7	0.4	0.2	0.2	.095
101.0	14.5	63	0.0	0.00	0.00	-0.35	-0.61	-0.30	0.17	0.00	-1.40	-0.04	0.00	0.00	0.00	-0.02
	% ØSC		0.2	0.0	-0.5	-0.9	-1.6	-0.4	0.2	0.5	-0.8	-1.0	0.1	1.9	1.7	
	S.D.		1.8	0.2	0.1	6.5	6.0	9.3	15.1	13.1	15.8	0.9	0.3	0.1	0.2	.077
88.0	17.9	69	0.0	0.02	0.02	-0.00	0.35	0.13	1.49	-1.70	0.00	0.00	0.00	0.00	0.00	0.00
	% ØSC		0.4	0.9	2.0	-0.0	0.9	0.1	2.0	-1.6	0.3	-0.1	0.6	0.4	1.0	
	S.D.		1.2	0.2	0.2	6.6	6.5	14.2	14.0	15.3	23.1	0.7	0.2	0.1	0.1	.073
70.0	26.3	57	0.0	0.00	0.00	-0.33	-0.27	-1.01	0.16	0.00	0.00	-0.20	0.00	0.00	0.00	0.00
	% ØSC		0.3	0.3	-0.2	-0.7	-0.6	-1.0	0.2	-0.2	0.5	-2.5	0.9	1.6	0.3	
	S.D.		1.1	0.2	0.2	7.5	8.1	17.8	14.8	22.2	19.4	1.2	0.2	0.1	0.1	.104

REST : PAØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
51.0	54.8	81	0.0	0.00	0.04	0.27	1.44	1.15	1.99	0.00	3.40	-0.17	0.05	0.05	0.00	0.04
	% ØSC		-0.7	-0.5	2.7	0.7	3.5	1.7	1.9	-0.2	2.5	-1.3	2.1	2.7	0.7	
	S.D.		1.0	0.1	0.1	5.0	6.4	11.3	10.1	17.9	12.6	1.5	0.2	0.2	0.1	.072
67.1	28.5	91	0.0	0.00	0.02	-0.32	-0.08	-1.54	0.47	0.00	1.70	0.17	0.00	0.00	0.00	0.02
	% ØSC		-0.5	0.3	1.0	-1.1	-0.3	-2.8	0.8	-1.3	1.6	2.6	0.6	1.4	0.4	
	S.D.		1.1	0.1	0.1	5.5	5.6	9.3	17.0	17.4	14.1	1.4	0.3	0.2	0.2	.078
193.5	6.2	59	0.0	0.00	0.02	-0.30	-0.12	-0.62	0.79	0.00	0.00	0.17	0.00	0.00	0.00	0.00
	% ØSC		-0.2	0.0	1.6	-1.6	-0.7	-1.9	1.9	-2.1	1.5	2.2	0.1	0.9	0.3	
	S.D.		1.0	0.1	0.1	3.2	3.7	7.8	4.8	7.9	6.4	0.7	0.4	0.3	0.1	.053
58.2	38.1	91	0.0	0.00	0.00	-0.16	0.23	-0.26	0.34	0.00	1.70	0.17	0.00	0.00	0.00	0.02
	% ØSC		-0.5	-0.3	0.7	-0.6	0.8	-0.6	0.5	-1.2	2.2	1.9	0.6	0.8	0.8	
	S.D.		1.7	0.1	0.1	3.1	3.7	8.1	8.5	11.6	10.6	1.0	0.2	0.2	0.1	.087

EXERCISE : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
76.5	22.6	65	0.0	0.00	-0.04**	-0.09	-1.76	-0.03	-7.98**	-2.00	3.40	0.85**	0.00	0.00	0.00	-0.04
	% ØSC		-0.4	0.3	-3.1	-0.1	-3.1	-0.0	-6.1	-1.1	2.3	5.6	0.1	1.4	0.3	
	S.D.		1.3	0.1	0.1	4.5	9.2	8.8	19.9	17.3	17.0	2.0	0.2	0.1	0.1	.174
90.8	17.0	93	0.0	0.00	0.04	0.38	1.13	0.63	2.90	0.00	1.70	0.17	0.00	0.00	0.00	0.02**
	% ØSC		-0.6	0.7	4.0	0.9	2.8	0.8	3.2	0.3	2.1	1.2	0.3	1.1	1.1	
	S.D.		1.4	0.2	0.2	6.8	9.3	19.8	14.3	22.3	18.7	1.4	0.2	0.2	0.1	.082
65.7	29.6	73	0.0	0.00	0.02	-0.17	0.79	-0.15	1.78	0.00	1.70	0.34*	0.00	0.00	0.00	0.02
	% ØSC		-0.5	0.4	1.5	-0.3	1.5	-0.1	1.7	-0.1	1.6	3.0	0.2	0.1	0.6	
	S.D.		1.1	0.1	0.1	3.9	4.6	8.8	8.9	17.6	8.8	1.3	0.1	0.1	0.1	.070
188.4	6.4	89	0.0	0.02	0.04	-0.00	0.63	-0.06	1.88	0.00	3.40	0.17	0.00	0.00	0.00	0.02
	% ØSC		-0.5	1.1	3.0	-0.0	1.8	-0.1	2.6	-0.2	3.0	2.1	0.7	2.4	1.2	
	S.D.		1.2	0.1	0.1	3.9	3.6	9.2	8.3	14.4	11.4	1.2	0.2	0.1	0.1	.071
58.2	38.1	75	0.0	-0.04	0.00	0.01	1.26	-1.88	4.97	2.00	5.10	0.68*	0.05	0.00	0.00	0.04**
	% ØSC		-0.2	-2.4	0.4	0.0	2.4	-1.8	4.4	1.1	4.5	5.6	2.2	0.0	2.9	
	S.D.		1.1	0.2	0.2	11.1	11.9	22.8	24.8	17.4	31.4	2.9	0.2	0.1	0.1	.104

REST : PAØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PAØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	IT	TE	TI	DFRC
54.0	45.5	69	0.0	0.02	0.02	-0.31	-0.20	-1.74	0.07	0.00	0.00	0.00	-0.05	0.00	0.00	0.0
	% ØSC		0.0	1.9	1.8	-0.7	-0.4	-2.1	0.1	0.1	-0.3	0.3	-2.1	2.3	0.2	
	S.D.		0.7	0.1	0.1	4.8	4.9	12.9	12.1	13.3	16.7	1.9	0.2	0.1	0.1	.084
200.0	6.0	93	0.0	0.00	0.00	-0.02	-0.20	-0.29	-0.22	-1.70	0.00	0.00	0.00	0.00	0.00	0.00
	% ØSC		0.4	0.5	-0.4	-0.1	-0.7	-0.5	-0.3	-1.2	0.1	0.6	0.1	0.3	0.2	
	S.D.		0.8	0.1	0.1	4.2	3.0	9.7	5.0	17.2	7.1	1.1	0.2	0.2	0.1	.053
90.5	17.1	91	0.0	0.00	0.00	0.28	-0.10	0.26	-0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% ØSC		0.2	-0.1	-0.3	0.8	-0.3	0.4	-0.0	0.8	-0.6	0.8	0.1	0.7	0.4	
	S.D.		0.8	0.1	0.1	4.8	4.7	11.2	7.4	13.1	8.0	1.9	0.3	0.2	0.1	.075
75.0	23.3	97	0.0	0.02	0.00	0.07	-0.34	-0.14	0.44	-1.70	1.80	-0.20	0.00	-0.05	0.00	0.00
	% ØSC		0.3	1.5	-0.3	0.2	-0.9	-0.2	0.6	-1.7	1.0	-1.1	0.6	-2.8	0.0	
	S.D.		1.4	0.2	0.1	5.8	6.3	14.3	9.7	16.3	9.7	2.0	0.5	0.3	0.1	.088
57.2	39.6	105	0.0	0.00	0.00	-0.83	-0.70	-2.01	-0.91	0.00	0.00	0.20	0.00	0.00	0.00	0.00
	% ØSC		0.4	-0.4	-0.2	-2.1	-1.7	-2.6	-1.1	-0.8	0.2	1.3	0.8	1.1	0.2	
	S.D.		0.7	0.2	0.1	6.2	6.1	14.7	12.4	15.5	13.3	1.5	0.3	0.2	0.1	.078
49.5	57.1	97	0.0	-0.02	0.02	-0.25	0.17	0.02	0.85	-1.70	0.00	0.20	0.00	0.00	0.00	0.02
	% ØSC		0.0	-1.4	1.1	-0.7	0.5	0.0	1.1	-2.8	0.4	2.6	0.1	0.1	0.6	
	S.D.		0.5	0.1	0.1	5.9	5.6	14.3	8.3	18.6	9.0	1.2	0.4	0.2	0.1	.084

EXERCISE : PAC02 STEADY.

ALTERNATE-BREATH OSCILLATION.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
199.5	6.0	87	0.0	0.00	0.00	0.50	0.47	1.13	1.92	-1.70	0.00	0.20	0.00	0.00	0.00	0.02
	% OSC		-0.3	-0.4	0.5	1.0	0.9	1.1	1.9	-1.8	0.3	2.0	0.8	0.2	0.4	
	S.D.		1.0	0.2	0.1	3.6	5.8	11.3	11.8	13.7	11.8	1.5	0.2	0.2	0.1	.112
91.1	16.9	105	0.0	0.00	0.00	0.14	-0.20	-0.54	-0.01	-1.70	-1.80	-0.20	0.00	0.00	0.00	-0.02
	% OSC		0.2	0.0	-0.5	0.3	-0.4	-0.5	-0.0	-1.6	-1.3	-1.7	0.3	0.6	0.2	
	S.D.		1.0	0.2	0.1	4.4	4.6	10.0	11.0	14.4	12.4	1.5	0.2	0.1	0.1	.094
73.5	24.1	103	0.0	0.02	0.00	0.89	0.12	2.46	-0.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% OSC		0.5	1.3	0.2	1.5	0.2	2.0	-0.4	0.1	0.3	0.1	0.1	0.0	0.3	
	S.D.		0.7	0.2	0.1	3.8	4.3	13.6	9.4	15.1	11.3	2.3	0.1	0.1	0.1	.112
68.8	27.2	97	0.0	0.00	0.02	0.20	0.05	0.46	-0.49	0.00	0.00	0.20	0.00	0.00	0.00	0.00
	% OSC		-0.2	0.5	0.7	0.4	0.1	0.4	-0.5	-0.6	-0.5	1.9	0.8	0.0	0.8	
	S.D.		1.5	0.1	0.1	4.5	5.0	10.4	9.9	16.3	10.6	1.6	0.2	0.1	0.1	.090
56.2	41.2	85	0.0	0.00	0.00	-0.72	-0.33	-0.45	-0.99	0.00	-1.80	0.40	0.00	0.00	0.00	0.00
	% OSC		0.6	-0.5	-0.4	-1.1	-0.5	-0.3	-0.8	0.0	-1.1	2.0	0.3	0.0	0.2	
	S.D.		0.9	0.2	0.1	5.5	5.8	12.2	12.4	16.5	17.2	2.4	0.1	0.1	0.1	.118

425.2

REST : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.5	6.6	73	0.0	-0.04	0.00	-0.62	-0.58	-1.82	-0.30	-4.90	2.40	0.16	0.00	0.00	0.00	0.0
	% ØSC		0.3	-2.6	-0.9	-1.5	-1.4	-2.1	-0.4	-2.1	1.6	2.5	0.2	1.6	0.2	
	S.D.		0.8	0.2	0.2	5.0	5.5	11.5	10.9	13.6	15.0	1.3	0.2	0.1	0.1	.114
55.4	58.4	71	0.0	0.00	0.04	0.16	1.94	1.64	3.25	0.00	4.80	0.16	0.00	0.00	0.00	0.04
	% ØSC		-0.3	-0.5	2.4	0.2	2.6	1.0	2.5	0.7	2.8	1.4	0.6	0.3	0.5	
	S.D.		2.0	0.2	0.2	6.3	6.2	13.1	12.8	20.1	21.4	2.6	0.1	0.1	0.1	.145
70.5	31.0	65	0.0	-0.04	0.00	0.04	0.17	0.86	0.37	0.00	0.00	-0.08	0.05	0.00	0.00	0.00
	% ØSC		0.3	-1.6	-0.6	0.1	0.4	1.0	0.4	-1.3	1.0	-1.1	1.8	1.1	1.8	
	S.D.		0.8	0.2	0.2	6.0	5.4	18.2	8.0	19.0	13.3	1.1	0.4	0.3	0.1	.147
50.5	81.6	45	0.0	0.00	0.04	-0.34	1.37	0.18	2.26	0.00	2.40	-0.32	0.00	0.00	0.00	0.08**
	% ØSC		0.0	-0.6	2.8	-0.5	2.0	0.1	1.8	0.1	0.8	-2.8	0.5	0.1	0.8	
	S.D.		0.8	0.2	0.2	8.2	8.9	16.6	17.0	22.7	29.6	2.7	0.1	0.1	0.1	.141
66.0	36.0	79	0.0	0.00	0.00	-0.01	1.30	0.89	1.05	0.00	2.40*	0.24	0.05	0.00	0.00	0.04
	% ØSC		0.2	-0.7	0.6	-0.0	2.5	0.8	1.1	-0.8	2.3	3.1	1.4	2.2	0.7	
	S.D.		0.9	0.2	0.2	5.4	5.4	14.6	7.2	15.0	11.6	1.8	0.1	0.1	0.1	.134
101.0	15.9	73	0.0	0.00	0.04	-0.98	1.84*	0.23	1.89	0.00	2.40	0.24	0.00	0.00	0.00	0.04
	% ØSC		-0.0	-0.4	2.3	-1.6	3.0	0.2	1.7	0.7	1.1	2.4	0.7	2.5	0.0	
	S.D.		0.9	0.2	0.2	4.6	6.0	17.0	9.7	15.0	15.0	2.1	0.2	0.1	0.1	.134

425.2

EXERCISE : PAC02 STEADY.

ALTERNATE-BREATH OSCILLATION.

A02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	IT	TE	TI	DFRC
0.5	6.6	45	0.0	-0.04	0.00	0.07	0.27	-0.05	1.76	-4.90	4.80	0.32	0.10	0.10	0.05	0.00
	% OSC		-0.0	-1.6	0.7	0.2	0.7	-0.1	2.2	-4.1	3.2	5.8	3.3	4.3	3.1	
	S.D.		0.8	0.3	0.3	5.0	4.8	10.4	11.6	18.9	18.6	1.4	0.6	0.3	0.3	.216
89.0	19.7	49	0.0	0.00	0.04	0.69	1.51	0.72	3.12	0.00	4.80	0.24	0.00	0.00	0.00	0.04
	% OSC		0.1	0.6	2.6	1.4	3.2	0.8	3.2	0.3	3.7	3.5	0.1	1.6	0.5	
	S.D.		1.1	0.3	0.2	5.4	6.3	14.9	8.1	24.8	13.0	1.7	0.4	0.3	0.2	.183
64.0	38.8	43	0.0	0.00	0.04	-0.05	0.13	1.68	-1.15	0.00	-2.40	0.00	0.00	0.05	-0.05	0.08
	% OSC		0.5	0.2	0.9	-0.1	0.3	1.9	-1.2	-1.5	-1.3	-0.1	0.0	3.0	-2.9	
	S.D.		1.3	0.2	0.2	7.1	7.4	14.6	17.1	20.9	12.9	1.8	0.4	0.3	0.2	.211
60.5	44.9	43	0.0	-0.04	0.08	0.54	1.19	1.70	3.85	0.00	2.40	-0.32	0.10	0.05	0.00	0.04
	% OSC		0.0	-1.4	3.3	1.0	2.3	1.7	3.5	-1.1	1.1	-3.5	2.8	2.7	0.8	
	S.D.		0.8	0.3	0.3	6.7	5.9	14.8	8.1	27.1	16.6	1.8	0.4	0.3	0.2	.253
101.0	15.9	45	0.0	-0.08	0.12	-0.61	2.16	-1.26	0.80	0.00	2.40	0.16	0.00	0.05	-0.05	0.12
	% OSC		-0.3	-2.7	4.6	-1.3	4.6	-1.4	0.8	-0.3	2.2	1.8	0.6	4.0	-2.9	
	S.D.		0.8	0.2	0.2	6.0	5.9	17.2	7.2	21.0	14.9	1.5	0.3	0.3	0.2	.227
65.4	36.9	67	0.0	0.00	0.00	0.10	1.08	0.53	1.65	0.00	4.80	0.08	0.00	0.00	0.00	0.04
	% OSC		0.3	0.2	0.4	0.2	2.0	0.5	1.5	1.3	2.6	1.0	0.2	0.0	0.9	
	S.D.		1.1	0.2	0.2	7.3	7.0	15.9	14.0	17.6	25.4	2.2	0.2	0.2	0.1	.238

REST : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
202.5	6.1	69	0.0	0.00	0.00	-0.36	-0.52	-1.19	-0.22	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	% ØSC		0.2	-1.0	-0.2	-0.9	-1.3	-1.4	-0.3	-1.2	0.6	0.0	0.6	0.3	0.2	
	S.D.		1.0	0.2	0.2	5.8	5.9	15.5	10.3	20.5	13.0	1.3	0.1	0.1	0.1	.115
79.0	24.5	63	0.0	0.00	0.00	-0.21	0.08	0.45	1.49	0.00	2.40	0.20	0.00	0.00	0.00	0.04
	% ØSC		-0.1	-0.7	0.3	-0.4	0.1	0.3	1.4	-0.3	1.1	1.5	0.5	1.8	1.6	
	S.D.		0.5	0.2	0.2	5.4	5.5	16.8	10.7	15.5	17.4	2.2	0.1	0.1	0.1	.140
61.7	42.6	53	0.0	0.00	0.00	0.52	0.37	1.51	-0.65	-5.20	0.00	0.00	0.05	0.00	0.00	0.00
	% ØSC		-0.1	0.2	0.1	1.0	0.7	1.5	-0.6	-1.7	0.5	0.3	2.1	1.4	0.8	
	S.D.		0.5	0.2	0.2	9.7	8.9	24.9	13.5	17.9	26.7	2.5	0.3	0.2	0.1	.184
53.3	66.3	69	0.0	0.04	0.04	0.00	-0.47	-1.07	0.77	0.00	2.40	-0.20	0.00	0.00	0.00	0.00
	% ØSC		-0.3	2.2	1.2	0.0	-0.8	-0.9	0.7	-0.6	1.7	-1.9	0.6	1.4	0.5	
	S.D.		1.4	0.3	0.3	6.6	7.5	17.5	15.4	28.2	28.3	2.4	0.2	0.2	0.1	.162

425.5

EXERCISE : PACØ2 STEADY.

PAØ2	HYP	N	ALTERNATE-BREATH ØSCILLATIØN. PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
199.5	6.2	57	0.0	0.00	0.00	1.09	1.16	4.26	2.60	-5.20	2.40	0.40	0.10	0.05	0.05	0.00
	% ØSC		-0.0	-0.4	-0.5	2.2	2.4	4.3	2.7	-3.1	1.1	3.6	3.6	2.2	3.2	
	S.D.		1.2	0.3	0.3	6.4	7.3	19.4	13.8	24.1	16.8	2.3	0.4	0.3	0.2	.175
83.0	22.3	65	0.0	0.04	0.08	0.96	1.75	0.29	5.20**	5.20	9.60**	0.80*	0.00	0.00	0.00	0.04
	% ØSC		-0.3	0.9	2.7	1.5	2.7	0.2	4.2	1.4	4.4	6.3	0.1	1.0	1.2	
	S.D.		1.4	0.2	0.2	6.3	7.6	20.1	13.8	21.6	23.9	2.9	0.1	0.1	0.1	.159
71.8	29.8	61	0.0	-0.04	0.00	-1.23	-1.06	-2.81	-0.96	-5.20	0.00	-0.60	-0.05	-0.05	0.00	0.00
	% ØSC		0.1	-0.9	-0.0	-2.1	-1.8	-2.4	-0.8	-2.6	-0.5	-4.1	-2.0	-2.7	1.0	
	S.D.		1.1	0.2	0.2	10.5	11.2	33.0	14.1	25.6	31.2	3.3	0.6	0.5	0.2	.119
59.2	47.8	77	0.0	0.00	-0.04	1.06	1.54	0.29	1.84	0.00	-2.40	-0.40	0.05*	0.05	0.00	0.04
	% ØSC		0.2	-0.5	-0.8	1.3	1.8	0.2	1.1	-0.0	-1.4	-1.7	2.3	3.2	1.8	
	S.D.		0.9	0.3	0.2	9.2	10.6	25.8	17.3	23.0	28.6	3.2	0.2	0.1	0.1	.237

REST : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
57.0	42.6	43	0.0	-0.08	-0.08	-2.83	-2.70	-8.10	-4.02	0.00	-7.20	-0.16	-0.05	-0.05	0.00	0.00
	% ØSC		0.1	-3.1	-2.4	-4.6	-4.3	-6.0	-3.5	-0.7	-3.8	-1.5	-2.5	-3.9	0.8	
	S.D.		0.7	0.2	0.2	7.8	8.0	23.4	12.8	32.6	25.2	1.7	0.2	0.2	0.1	.107
202.0	5.9	45	0.0	0.00	0.16	-0.54	-0.56	-2.09	2.08	5.00	2.40	-0.08	-0.10	-0.10	-0.05	0.00
	% ØSC		0.4	0.5	7.6	-1.2	-1.3	-2.3	2.5	2.8	1.2	-0.7	-3.9	-5.2	-2.7	
	S.D.		0.6	0.6	0.5	8.4	8.4	21.9	14.8	45.0	21.7	1.1	0.4	0.2	0.2	.143
72.7	24.8	41	0.0	-0.04	0.04	-0.78	1.01	-0.02	0.67	-10.00	0.00	0.08	-0.10	0.00	0.00	0.00
	% ØSC		0.0	-2.3	2.3	-1.6	2.1	-0.0	0.7	-5.4	-0.7	1.0	-2.8	0.9	1.2	
	S.D.		0.6	0.6	0.4	11.2	8.5	21.8	17.7	45.6	24.5	1.2	0.3	0.2	0.2	.187
50.0	58.8	45	0.0	-0.08	0.00	-3.42	-1.91	-10.52	0.50	0.00	0.00	-0.08	0.00	-0.05	0.00	0.08
	% ØSC		0.1	-3.0	-0.2	-5.5	-3.1	-7.9	0.4	-0.3	-0.4	-1.2	0.9	2.5	1.1	
	S.D.		1.0	0.4	0.3	13.9	13.9	28.5	20.9	44.4	30.8	2.1	0.3	0.2	0.1	.256
56.2	43.0	61	0.0	0.08	0.08	1.48	1.77	4.89	2.08	5.00	4.80	-0.16	0.00	0.00	0.00	0.04
	% ØSC		0.2	2.3	3.2	2.2	2.7	3.6	1.6	1.8	3.6	-1.8	0.3	0.5	1.4	
	S.D.		0.7	0.4	0.5	8.4	10.1	26.1	15.3	32.9	19.5	1.5	0.2	0.2	0.1	.170
111.0	12.7	53	0.0	-0.04	-0.08	-1.54	-1.63	-4.69	-2.88	0.00	-2.40	0.00	0.00	-0.05	0.05	-0.04
	% ØSC		-0.2	-1.3	-4.1	-2.8	-3.0	-4.3	-2.7	-0.7	-2.6	-0.1	0.3	-3.3	2.2	
	S.D.		1.2	0.4	0.4	6.5	6.9	16.1	14.0	37.9	18.4	1.5	0.4	0.3	0.2	.142

EXERCISE : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N		PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
202.5	5.9	51		0.0	0.00	-0.04	-0.98	-0.92	-2.79	-1.22	-5.00	0.00	-0.08	0.00	0.00	0.00	-0.04
	% ØSC			0.2	0.7	-2.0	-1.8	-1.7	-2.3	-1.2	-1.8	-0.4	-1.0	0.9	0.0	0.7	
	S.D.			0.7	0.6	0.5	7.5	7.7	21.8	12.8	42.5	21.3	1.3	0.4	0.3	0.2	.158
98.0	15.3	55		0.0	-0.08	-0.16	-1.04	-1.51	-6.85	-2.70	0.00	0.00	-0.16	0.05	0.00	0.05	0.00
	% ØSC			-0.1	-3.4	-5.7	-1.4	-2.1	-4.5	-1.9	-0.3	-0.2	-1.2	2.2	0.1	4.7	
	S.D.			1.0	0.5	0.5	11.6	11.5	35.6	18.2	46.8	26.7	1.9	0.3	0.2	0.1	.193
76.5	22.7	49		0.0	-0.12	-0.04	-1.27	0.98	-5.00	2.82	-15.00	2.40	0.00	0.10*	0.05	0.10*	0.08*
	% ØSC			0.3	-4.7	-1.2	-2.0	1.5	-3.9	2.2	-5.4	0.9	0.3	4.9	2.7	6.0	
	S.D.			1.1	0.6	0.6	10.3	10.0	29.2	19.4	61.3	26.1	1.7	0.4	0.3	0.2	.183
59.9	37.0	53		0.0	-0.04	-0.04	-0.99	0.25	3.23	-1.49	-10.00	0.00	-0.08	0.00	0.00	0.00	0.00
	% ØSC			0.4	-1.1	-1.7	-1.3	0.3	2.0	-1.1	-3.9	0.3	-1.1	0.8	0.2	1.6	
	S.D.			1.5	0.5	0.5	16.1	11.9	34.9	22.7	42.2	25.1	2.2	0.3	0.2	0.2	.244
87.5	18.2	53		0.0	-0.04	-0.04	1.03	0.78	4.24	-0.49	0.00	-2.40	-0.08	0.10*	0.05*	0.05	0.00
	% ØSC			0.0	-1.5	-1.8	1.6	1.2	3.2	-0.4	-0.0	-1.4	-0.9	3.6	4.1	2.1	
	S.D.			0.9	0.5	0.6	8.4	9.2	25.3	14.9	33.9	21.2	1.2	0.3	0.2	0.2	.191
60.5	36.4	57		0.0	0.04	0.00	-1.64	-1.58	-4.49	-2.30	-10.00	-2.40	0.08	0.00	0.00	0.00	-0.04
	% ØSC			0.5	0.9	-0.5	-2.0	-2.0	-2.6	-1.5	-2.9	-1.3	0.4	0.5	0.2	0.3	
	S.D.			0.9	0.4	0.3	10.1	9.0	28.5	16.0	37.3	23.8	2.0	0.3	0.2	0.1	.166

392.15

REST : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
70.5	26.2	67	0.0	0.21*	0.24**	1.38	2.59*	1.39	1.52	9.00	0.00	0.00	-0.10	0.00	-0.05	0.03
	% ØSC		-0.2	14.2	16.4	4.7	8.7	2.4	2.5	6.7	0.4	0.2	-2.5	1.3	-4.4	
	S.D.		0.8	0.6	0.5	6.3	6.1	15.8	12.7	37.9	15.4	0.9	0.6	0.4	0.4	.156
92.5	16.6	57	0.0	-0.06	-0.06	-1.43	0.21	-3.19	1.22	-9.00	0.00	-0.14	0.05	0.05	0.00	0.06
	% ØSC		0.0	-3.0	-4.2	-4.4	0.7	-6.1	1.4	-5.9	0.6	-3.2	1.6	1.5	1.6	
	S.D.		0.8	0.5	0.7	6.9	10.4	18.2	9.7	25.0	14.6	1.4	0.6	0.4	0.4	.285
52.2	49.8	67	0.0	0.03	0.03	0.29	-0.13	-0.03	0.68	4.50	0.00	-0.28	0.00	0.00	0.00	0.03
	% ØSC		0.0	0.8	0.9	0.5	-0.3	-0.0	0.6	2.7	-0.8	-3.9	0.1	0.5	0.4	
	S.D.		1.1	0.3	0.3	6.9	7.5	18.0	16.0	33.3	20.2	1.8	0.2	0.2	0.2	.194
60.6	35.1	73	0.0	-0.03	-0.03	1.07	1.48	2.11	2.34	0.00	2.40	-0.14	0.05	0.00	0.05	0.00
	% ØSC		0.7	-0.9	-2.0	2.6	3.5	2.5	2.9	1.3	2.5	-1.8	1.4	1.2	2.8	
	S.D.		1.1	0.4	0.4	8.6	7.4	20.7	14.3	42.3	13.9	1.3	0.5	0.3	0.3	.083
209.0	5.7	55	0.0	0.00	-0.03	-0.03	1.32	0.75	2.20	4.50	0.00	-0.28	0.00	0.00	0.00	0.00
	% ØSC		-0.3	-0.3	-3.1	-0.1	3.7	1.2	2.6	2.6	1.3	-5.9	0.4	0.5	2.5	
	S.D.		0.6	0.3	0.3	10.4	9.6	21.4	18.2	49.4	21.4	1.6	0.5	0.3	0.2	.157

EXERCISE : PACØ2 STEADY.

ALTERNATE-BREATH ØSCILLATIØN.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
90.0	17.2	75	0.0	0.03	0.06	0.26	1.80	1.08	2.53	4.50	2.40	0.42	0.00	0.00	0.00	0.06
	% ØSC		-1.3	0.8	3.4	0.5	3.6	1.2	2.3	2.6	2.9	6.3	0.4	0.0	1.4	
	S.D.		1.6	0.6	0.6	9.1	10.1	19.2	18.1	40.1	16.5	1.6	0.5	0.3	0.2	.198
60.7	35.0	73	0.0	0.06	0.03	0.85	0.69	3.67	0.09	-4.50	0.00	0.14	-0.05	-0.05	-0.05	0.00
	% ØSC		-0.0	2.2	1.1	1.3	1.1	2.7	0.1	-1.3	-0.2	1.3	-2.3	-2.9	-3.0	
	S.D.		1.2	0.5	0.5	9.7	10.9	27.2	19.6	46.6	17.3	1.7	0.3	0.2	0.2	.162
53.0	48.0	77	0.0	-0.03	-0.03	-0.80	0.70	0.72	-0.27	4.50	0.00	-0.14	0.05	0.05	0.00	0.00
	% ØSC		-0.1	-0.8	-0.9	-1.1	1.0	0.5	-0.2	1.8	-0.4	-0.7	2.8	3.6	0.5	
	S.D.		1.3	0.4	0.3	11.8	12.4	33.2	21.8	42.1	23.2	2.1	0.3	0.2	0.2	.168
49.3	58.3	67	0.0	0.00	0.03	0.11	2.47	2.90	4.52	9.00	4.80	0.00	0.00	0.00	0.00	0.09
	% ØSC		-0.3	0.1	1.4	0.1	3.0	1.6	3.1	2.7	3.1	0.3	0.9	1.8	0.0	
	S.D.		0.7	0.3	0.2	10.5	10.2	36.7	16.3	32.6	21.1	0.2	0.2	0.2	0.1	.176
201.0	5.9	63	0.0	0.00	-0.03	0.93	1.32	-1.80	4.24	0.00	4.80	0.14	0.05	0.00	0.00	0.00
	% ØSC		0.5	0.2	-2.1	1.5	2.2	-1.4	3.7	-0.7	4.1	1.8	1.6	1.8	2.4	
	S.D.		1.5	0.5	0.5	11.5	10.5	41.9	15.0	52.1	20.2	2.4	0.3	0.2	0.2	.144

TABLE 25.
SERIES TWO.
'OSC' RUNS.
(9 pages 226_{1-9})

ZD VALUES.

409.5

REST : PACØ2 ØSCILLATING.

				ZD VALUE.												
PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
53.5	46.5	81.	4.80	-.20	0.65***	0.46**	-.21	0.77***	0.67***	-.09	1.27***	1.48***	0.61***	0.96***	0.21	1.20***
55.7	42.1	65.	4.97	-.11	0.41*	0.30*	-.17	0.53**	0.24	0.26	0.68***	0.79***	0.66***	0.79***	0.05	0.89***
47.0	66.7	71.	4.83	1.08***	0.81***	0.45**	1.48***	1.57***	0.73***	0.67***	1.50***	1.74***	1.50***	2.23***	0.96***	2.27***
70.0	26.3	59.	4.87	0.05	0.12	0.16	-.18	0.05	-.22	-.06	0.24	0.62***	-.08	-.09	0.08	1.22***
116.0	11.9	51.	4.57	-.40	0.30	-.18	0.09	-.04	0.10	-.12	0.28	-.09	0.26	0.18	0.24	1.23***

EXERCISE : PACØ2 ØSCILLATING.

				ZD VALUE.												
PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
52.0	50.0	43.	2.63	0.28	-.05	0.65**	0.95***	1.20***	-.09	0.33	-.09	-.02	1.04***	1.38***	-.05	0.35
57.5	39.2	61.	4.84	-.06	0.21	0.36*	0.06	0.86***	0.20	0.98***	0.98***	1.15***	0.47**	0.86***	-.38	0.23
50.4	54.4	47.	5.14	0.11	1.15***	1.00***	0.01	1.30***	0.48*	0.13	0.60**	0.01	1.36***	1.33***	0.58**	1.62***
50.2	54.8	45.	4.63	-.21	1.29***	1.32***	-.05	1.36***	0.89***	0.79***	-.13	0.57**	1.66***	1.36***	0.54**	1.93***
69.2	26.9	75.	4.19	-.03	0.58***	0.37*	-.05	0.53***	0.45**	0.61***	0.62***	0.33*	0.53***	0.76***	0.16	1.04***
114.0	12.2	65.	4.64	-.15	0.42*	0.12	0.06	0.02	0.07	-.04	0.66***	0.17	-.12	-.12	-.02	1.24***

REST : PAØ2 OSCILLATING.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
127.0	10.5	75.	4.93	-.32	-.06	-.28	-.13	-.20	0.16	-.05	0.29	-.12	-.21	-.13	-.09	0.59***
77.7	21.9	81.	4.75	0.06	0.41**	0.04	0.34	-.18	0.49	-.18	0.27	0.22	-.01	-.24	0.18	1.02
63.0	32.3	75.	4.86	0.17	0.78***	0.12	0.04	0.23	0.81***	0.03	0.52***	0.26	0.26	0.31*	0.23	1.59***
47.9	63.0	*121.	4.35	0.24*	0.37**	-.01	0.08	0.30*	0.33**	0.19	0.74***	0.58***	-.01	0.54***	-.00	1.11***
56.2	41.2	*131.	4.60	0.09	0.37**	-.09	0.09	0.07	-.11	0.01	0.62***	0.11	0.05	0.27*	-.11	1.15***

EXERCISE : PAØ2 OSCILLATING.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
127.0	10.5	75.	4.40	0.09	0.82***	-.13	0.27	-.23	0.31*	0.07	0.34*	0.17	-.22	-.29	-.16	2.25***
75.3	23.1	93.	4.37	-.02	1.29***	0.19	-.21	0.30*	0.57***	0.09	1.06***	0.23	0.02	0.18	-.14	2.14***
63.5	31.7	73.	5.18	-.03	1.08***	0.93***	0.08	1.14***	0.26	0.31*	0.41**	-.08	0.82***	1.04***	-.11	2.11***
50.0	55.6	69.	4.92	-.03	0.95***	1.38***	0.63***	1.56***	0.28	1.52***	1.39***	1.04***	1.33***	1.52***	-.15	2.19***
56.7	40.6	*101.	4.46	0.21	0.54***	0.51***	0.11	1.04***	0.01	0.65***	0.70***	0.40***	1.25***	1.49***	-.06	1.23***

421.2

REST : PAC02 OSCILLATING.

ZD VALUE.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
76.5	22.5	95.	4.22	0.14	0.46**	0.48***	0.61***	0.67***	0.31*	0.15	0.26*	0.70***	0.28*	0.42**	0.03	0.71***
113.0	12.3	*103.	4.59	-.04	-.03	-.09	-.07	-.06	-.14	0.03	-.25	-.16	-.07	0.05	-.26	-.16
79.0	21.3	81.	4.77	-.10	0.00	0.09	-.03	-.14	0.05	0.17	0.04	0.16	-.15	-.21	0.17	0.21
67.2	28.4	*101.	4.20	-.15	-.11	-.13	0.00	-.09	-.08	-.14	-.09	-.17	-.00	0.20	-.13	0.33*
61.5	33.9	83.	4.43	0.05	0.15	0.40**	0.49**	0.48**	0.09	0.74***	0.02	0.11	-.17	0.00	-.04	0.35*

EXERCISE : PAC02 OSCILLATING.

ZD VALUE.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
121.0	11.2	75.	3.85	-.27	-.06	0.09	-.10	0.25	0.09	-.26	-.07	0.66***	0.17	0.42**	-.05	0.62***
103.0	14.1	65.	3.55	-.37	-.36	-.27	-.09	-.23	-.13	-.18	-.16	0.07	-.45	-.27	-.57	0.09
102.0	14.3	65.	4.26	-.21	-.02	-.35	-.12	-.36	-.11	0.17	-.01	0.14	-.02	-.12	0.10	0.51**
90.5	17.1	61.	4.75	-.05	0.48**	-.22	0.39**	0.25	-.36	-.03	-.14	0.04	-.13	-.20	0.08	0.75***
70.9	25.7	67.	4.44	0.13	0.32*	-.10	0.15	-.28	0.34*	-.05	0.19	0.39*	0.06	0.09	-.25	0.57***

421.4

REST : PAØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TI	TE	TI	DFRC
97.5	15.3	71.	2.24	-.09	-.29	-.24	-.29	-.19	-.35	-.12	-.35	-.33	-.18	-.11	-.16	-.09
54.2	45.1	*113.	4.15	0.08	0.40**	-.00	0.29*	0.11	0.19	0.74***	0.23*	0.06	0.05	0.11	-.07	0.86**
66.0	29.4	77.	4.43	-.05	0.00	-.04	0.00	0.01	-.08	0.25	0.08	-.06	-.21	-.11	-.23	0.10
195.1	6.1	65.	3.98	-.23	-.11	-.15	-.06	-.22	-.05	-.22	-.02	-.32	0.04	0.06	0.00	0.28
58.0	38.5	*113.	4.22	0.44***	0.75***	-.02	0.08	-.10	0.14	-.16	0.72***	0.67***	0.27*	0.04	0.29*	0.65**

EXERCISE : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TI	TE	TI	DFRC
77.5	22.0	89.	4.73	-.15	0.54***	0.07	0.79***	0.19	0.30*	0.26	0.49**	0.19	-.39	-.18	-.23	1.14***
91.2	16.9	73.	4.91	-.32	0.00	-.02	0.25	0.09	0.01	0.26	0.14	-.12	-.06	0.23	-.25	0.77***
66.0	29.4	87.	4.19	0.11	0.78***	0.34*	1.23***	0.83***	0.35*	0.77***	0.54***	0.32*	-.27	-.03	-.19	1.68***
189.0	6.4	89.	3.89	-.17	-.27	-.28	-.26	-.25	-.27	-.13	-.10	-.04	-.09	-.01	-.10	0.11
57.7	38.9	81.	4.54	0.31*	0.16	-.13	-.13	0.29*	0.38**	-.08	0.35*	1.59***	0.51**	0.79***	-.06	-.03

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
53.5	46.5	*101.	4.65	-.25	-.05	-.09	-.04	-.07	-.14	0.06	-.07	-.11	0.11	0.04	0.04	0.20
44.2	81.6	87.	4.73	0.49***	-.02	0.47**	0.26*	0.03	0.18	0.20	0.07	0.22	-.22	0.40**	-.01	1.04***
200.0	6.0	91.	4.04	-.10	-.17	-.19	-.11	-.01	-.20	-.28	-.21	-.32	-.17	-.11	-.12	0.19
91.4	16.8	*101.	4.30	-.09	-.09	0.12	0.14	0.18	-.01	0.11	0.12	-.02	-.03	-.00	-.03	0.03
75.7	22.9	*103.	4.38	0.18	0.45***	0.01	-.11	-.08	0.15	0.05	0.43***	0.79***	-.26	-.19	-.38	0.82***
50.0	55.6	*113.	4.05	-.13	0.24*	-.35	-.06	-.04	-.17	0.05	0.11	0.61***	0.22	-.00	0.06	0.20
59.0	37.0	*149.	4.40	-.12	0.02	-.15	0.02	0.13	-.24	0.40***	-.14	0.00	0.07	0.01	0.15	0.17

EXERCISE : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
200.0	6.0	83.	4.46	-.10	-.17	-.16	-.09	-.16	-.24	-.16	-.23	0.23	-.22	-.13	-.26	0.05
93.7	16.2	*129.	2.94	-.11	-.01	-.24	-.18	-.23	-.19	0.07	-.14	0.00	-.18	-.26	-.03	0.33**
71.5	25.3	*115.	4.35	0.08	0.06	0.16	-.02	-.05	-.08	0.15	0.29*	0.35**	-.19	-.12	-.03	0.51***
56.3	41.1	*105.	4.95	0.61***	0.43**	0.32*	0.04	0.12	0.08	0.26*	0.44***	0.62***	-.11	-.15	-.08	0.43***
68.4	27.5	*111.	4.24	0.47***	0.42**	-.19	-.36	-.10	-.21	0.24*	0.11	-.06	-.04	0.08	-.02	0.38**

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.0	6.6	73.	4.56	-.11	-.18	-.20	-.10	-.17	-.21	-.22	-.22	-.19	0.00	-.04	0.05	0.08
57.0	53.3	63.	4.19	-.26	0.02	-.51	-.34	-.10	-.26	-.05	-.25	0.04	-.35	-.01	-.10	0.11
69.3	32.2	59.	3.78	-.02	0.30	-.25	0.21	-.06	0.27	-.24	0.27	0.09	0.07	0.22	-.00	0.54**
49.5	88.9	69.	3.75	0.11	0.03	-.16	0.04	-.10	-.03	-.17	0.03	0.05	0.23	0.11	-.02	0.30*
65.0	37.4	65.	4.58	0.10	0.04	-.05	0.03	-.08	0.01	-.12	0.07	-.02	-.02	-.06	0.10	0.27
99.5	16.3	97.	3.73	-.06	0.04	-.18	0.09	-.11	-.13	-.20	-.02	-.07	0.08	0.07	0.14	0.52**

EXERCISE : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.0	6.6	61.	3.51	-.11	-.04	-.17	-.09	-.26	-.24	-.38	-.26	0.01	0.07	0.02	0.06	0.28
89.0	19.7	71.	3.41	-.07	0.01	0.04	0.02	-.05	-.16	-.14	-.09	0.00	-.04	-.09	-.01	0.41**
63.0	40.4	75.	3.62	0.03	0.87***	-.10	0.43**	-.28	0.72***	-.07	0.46**	0.35*	-.12	-.19	0.12	1.42***
66.5	35.4	61.	2.53	-.30	0.41*	-.12	0.02	-.24	0.12	-.17	0.02	0.07	0.03	-.13	0.17	0.62***
101.0	15.9	59.	3.40	-.01	0.04	-.09	0.22	-.08	0.15	0.03	0.13	-.06	-.08	-.12	0.07	0.51**
60.0	46.0	67.	3.90	0.08	0.63***	-.07	0.45**	-.21	0.18	-.01	0.09	0.04	-.14	-.02	0.11	1.45***

425.5

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
201.0	6.1	69.	3.29	-.03	-.23	-.19	-.10	-.20	-.15	-.12	-.12	0.00	0.17	0.08	0.08	0.35*
79.0	24.5	75.	3.98	-.03	0.04	0.06	0.10	-.03	-.03	-.01	-.34	-.16	0.02	-.16	0.02	0.80***
62.0	42.1	85.	4.71	-.09	-.28	-.20	-.23	-.29	-.31	-.08	-.27	-.21	0.04	-.07	-.20	0.15
54.3	62.4	81.	4.64	-.18	-.18	-.18	-.11	-.15	-.29	-.05	-.05	-.28	-.09	-.31	-.09	-.03
54.6	61.2	49.	3.86	-.08	-.00	0.03	0.02	-.10	-.05	0.28	-.08	-.09	-.06	-.19	0.10	0.13
55.0	59.6	83.	3.99	-.10	-.13	-.09	-.18	-.12	-.29	-.16	-.05	-.04	0.09	-.00	0.04	0.06

EXERCISE : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
206.0	6.0	55.	4.32	-.03	-.18	-.00	0.03	0.12	-.19	-.14	-.31	-.04	-.04	0.09	0.09	0.52**
81.7	23.0	69.	4.00	0.05	-.01	0.06	-.01	-.01	0.03	0.04	-.18	-.05	-.10	-.07	-.13	-.19
70.5	31.0	83.	3.95	0.01	0.55***	-.11	0.38**	-.12	0.45**	0.05	0.56***	0.07	-.06	-.09	-.05	1.04***
60.0	46.0	63.	4.08	0.08	-.16	-.07	-.23	-.22	-.13	-.10	-.16	0.00	-.25	-.07	-.14	0.23
58.2	50.0	99.	4.31	-.23	-.11	-.11	-.02	0.05	-.07	-.03	-.12	-.15	0.06	-.07	0.05	0.52***

392.13

REST : PACØ2 ØSCILLATING.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
57.2	40.4	69.	4.06	0.39*	0.62***	0.11	0.25	-.12	0.66***	-.12	0.34*	0.64***	0.04	0.32*	0.17	0.21
202.0	5.9	41.	3.93	0.01	0.19	-.07	0.03	-.09	-.05	0.10	-.13	-.20	0.05	-.20	-.06	0.45*
71.5	25.6	55.	3.96	0.84***	0.72***	0.71***	0.72***	0.40*	0.53**	-.13	0.46*	0.16	0.08	0.11	0.04	-.09
51.2	53.6	47.	4.06	-.01	0.30	-.35	0.18	-.38	0.34	-.37	0.16	0.59**	-.15	-.21	-.27	0.32
57.3	40.3	63.	4.01	0.14	0.13	0.33*	0.54***	0.50**	0.04	-.17	0.01	-.13	-.23	0.01	-.07	0.67***
111.0	12.7	55.	3.48	0.68***	0.55**	0.50**	0.43*	0.63***	0.03	-.10	0.05	0.05	-.16	-.18	0.66***	0.63***

EXERCISE : PACØ2 ØSCILLATING.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
204.0	5.8	57.	2.63	0.74***	0.59**	0.45*	0.49**	0.07	1.01***	0.02	0.44*	0.07	0.25	0.36*	-.07	0.39*
77.7	22.1	47.	2.78	0.72***	0.70***	0.49*	0.50*	0.44*	0.50*	-.08	0.25	0.11	0.03	0.04	-.06	0.23
60.2	36.0	55.	3.87	0.25	0.12	-.04	0.08	-.12	0.13	-.18	0.19	0.28	-.32	-.06	-.43	0.19
88.0	18.0	51.	3.80	0.08	0.44*	0.05	0.39*	0.03	0.35*	0.12	0.42*	0.43*	-.17	-.20	-.08	0.53**
57.2	40.4	83.	3.99	0.77***	0.77***	0.90***	0.87***	0.83***	0.52***	-.13	0.71***	0.40**	-.00	0.13	-.06	0.63***
100.0	14.8	61.	3.56	0.12	0.36*	0.10	0.39*	0.18	0.21	-.22	-.02	-.13	0.15	-.20	0.36*	0.23
59.0	37.7	95.	4.14	0.53***	0.85***	0.54***	0.80***	0.70***	0.31*	-.03	0.48***	0.54***	0.03	0.27*	0.30*	0.72***

REST : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
71.9	25.4	71.	4.47	-.17	-.18	-.04	-.06	-.07	0.07	-.11	-.03	-.19	-.16	-.25	0.12	0.16
91.0	17.1	73.	3.10	0.09	0.20	0.00	0.08	0.03	0.02	-.20	0.06	-.07	0.23	0.07	0.31	0.05
52.1	51.0	89.	4.12	0.14	0.12	0.06	0.14	0.04	0.28*	-.09	0.24	0.09	-.08	0.04	-.20	0.09
61.5	34.5	89.	3.73	0.20	0.20	-.01	0.12	-.06	0.07	-.00	0.22	-.08	0.11	0.05	0.09	0.35*
209.0	5.7	49.	3.01	0.32	0.38	0.18	0.26	0.25	0.17	0.24	-.10	0.16	0.09	0.03	0.28	-.14

EXERCISE : PACØ2 ØSCILLATING.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
90.5	17.2	55.	4.45	0.98***	1.06***	0.27	0.67***	0.15	0.52**	0.27	0.38*	-.08	0.39*	0.12	0.54**	0.49**
63.7	32.1	*117.	4.62	0.02	0.09	-.28	-.26	-.25	-.29	-.17	-.10	0.03	-.12	-.07	-.11	0.63**
55.4	43.7	93.	4.98	0.18	0.49***	-.12	0.23	-.21	0.33*	-.30	0.47***	0.15	-.29	-.27	-.32	0.42**
64.1	31.6	59.	4.00	0.28	0.01	-.05	-.04	-.09	0.08	-.28	0.04	0.00	-.15	-.02	-.35	-.22
49.7	58.0	69.	5.92	0.30*	0.45**	0.26	0.26	0.06	0.32*	-.26	0.52**	-.09	0.05	0.08	-.18	0.17
71.3	25.8	*113.	4.55	-.04	-.01	-.09	0.06	-.17	-.09	-.07	-.02	0.06	-.14	-.22	-.09	0.79***
202.0	5.9	63.	3.91	0.23	0.17	0.23	0.23	0.01	0.20	-.04	0.08	-.03	0.15	0.24	-.18	0.87***

CUTIØN ERRØR 105 PRØGRAM TERMINATED

'STEADY' RUNS.
(9 pages : 226_{10-18})

409.5

REST : PAØ2 STEADY.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
54.5	44.4	49.	0.07	-.11	-.05	-.37	-.22	-.42	-.11	-.30	0.04	0.11	-.08	-.23	0.01	0.39*
54.5	44.4	61.	-.02	0.03	0.27	-.09	-.01	-.07	-.21	-.38	-.27	0.03	0.11	0.04	0.14	0.13
47.0	66.7	61.	0.05	-.14	0.03	-.23	-.03	-.17	-.06	-.07	0.10	-.25	-.36	-.29	-.07	0.40*
68.7	27.2	63.	0.11	-.05	-.26	-.15	-.14	-.17	0.10	-.32	-.13	-.14	-.08	-.03	-.03	-.39
113.0	12.3	65.	0.25	-.24	-.13	-.20	-.12	-.23	-.08	-.07	0.11	-.23	-.31	-.31	-.25	0.32*

EXFRCISE : PACØ2 STEADY.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
52.6	48.5	61.	-.01	-.29	0.02	0.13	0.37*	0.08	0.28	-.23	-.04	-.02	-.06	-.01	-.15	0.16
57.5	39.2	51.	0.00	-.13	-.03	0.26	0.16	0.27	0.09	0.09	0.23	0.21	-.02	-.01	0.07	0.15
50.5	54.1	71.	0.02	0.02	0.15	-.11	0.23	-.02	0.08	0.16	-.02	0.29	0.13	0.12	0.12	0.73***
67.9	27.9	61.	-.08	0.17	0.21	-.12	-.10	-.17	-.37	-.03	0.21	0.12	-.01	0.01	-.00	0.52**
117.0	11.8	61.	-.11	-.22	0.10	0.08	0.04	0.08	0.01	0.13	0.04	0.22	-.12	-.16	0.08	0.83***

REST : PAØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
128.5	10.4	71.	0.06	-.20	0.10	0.18	0.13	0.20	-.09	0.02	0.14	-.19	0.05	0.11	-.04	0.61...
78.5	21.5	47.	0.12	-.10	0.19	-.07	-.28	-.05	-.09	0.24	0.26	-.01	-.25	-.21	-.05	0.99...
63.5	31.7	67.	-.12	0.02	-.01	-.15	-.08	-.08	-.06	-.15	0.19	-.08	-.14	-.09	-.07	0.15
48.3	61.2	77.	-.01	-.15	0.06	-.00	0.04	0.08	-.08	-.15	-.13	-.00	0.05	0.06	-.02	0.20
56.0	41.7	71.	0.11	-.03	-.04	-.18	0.04	-.17	-.18	-.05	0.06	0.01	-.06	-.10	-.10	0.07

EXERCISE : PAC02 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
126.3	10.6	63.	0.04	-.12	-.25	-.08	-.01	0.02	-.14	-.15	0.03	0.21	-.08	0.06	-.14	0.49...
75.5	23.0	71.	0.07	-.17	0.02	-.05	0.14	-.11	0.17	-.15	0.16	0.17	-.22	-.23	-.09	1.14...
63.0	32.3	69.	-.06	-.17	0.04	-.03	0.18	-.17	0.17	-.26	-.02	0.14	0.01	-.12	0.09	0.35...
50.2	54.9	73.	0.32	-.07	0.21	-.09	0.09	0.03	0.01	-.17	0.07	-.14	0.05	0.18	0.13	0.90...
56.7	40.4	61.	-.23	-.21	-.12	-.33	-.33	-.40	0.14	0.15	0.30	-.44	-.24	-.33	-.17	0.54...

REST : PACØ2 STEADY.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VT	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
76.0	22.7	85.	0.29	-.25	-.05	-.33	-.09	-.23	-.22	-.16	0.11	-.27	-.12	-.03	-.16	0.17
112.0	12.5	79.	0.18	-.19	-.13	-.03	-.00	-.03	-.29	-.18	-.31	-.02	-.40	-.35	-.17	0.21
76.7	22.3	59.	0.46	-.23	-.30	-.27	-.24	-.17	-.24	-.15	-.38	-.09	-.07	0.02	-.13	0.19
66.2	29.2	79.	-.14	-.27	-.29	-.20	-.26	-.24	-.26	0.06	-.26	-.15	-.13	-.24	-.08	0.22
61.0	34.5	57.	-.11	-.27	-.24	-.27	-.28	-.28	-.22	-.09	-.06	-.12	-.11	-.15	-.18	0.17

EXERCISE : PACØ2 STEADY.

ZD VALUE.

PAØ2	HYP	N	PACØ2	VTE	VTI	VE	VT	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
120.0	11.4	75.	-.21	-.31	-.19	-.24	-.14	-.11	-.33	-.12	-.26	-.09	-.14	-.17	-.08	-.23
101.0	14.5	63.	-.29	-.07	-.22	-.04	-.08	-.20	0.02	-.09	-.14	-.40	-.37	0.06	-.15	0.01
88.0	17.9	69.	-.28	0.03	-.10	-.05	-.14	-.04	-.19	-.08	-.10	-.20	-.34	-.24	-.28	0.08
70.0	26.3	57.	-.07	-.27	-.17	-.06	-.22	-.02	-.14	-.12	-.16	0.03	-.08	-.04	-.18	0.24

421.4

REST : PAC02 STEADY.

ZD VALUE.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
50.2	54.8	81.	0.05	-.18	-.04	-.15	-.05	-.09	-.36	-.15	-.24	-.14	-.40	-.44	-.13	0.12
67.1	28.5	91.	-.21	-.04	-.17	-.05	-.22	-.21	-.20	-.18	-.05	-.10	-.16	-.21	-.14	0.13
193.5	6.2	59.	-.18	-.49	-.36	-.29	-.24	-.32	-.29	-.22	-.31	-.29	-.40	-.42	-.28	0.27
58.2	38.1	91.	0.02	0.03	-.05	-.11	-.13	-.09	-.16	-.26	-.26	-.08	-.36	-.14	0.22	0.02

EXERCISE : PAC02 STEADY.

ZD VALUE.

PA02	HYP	N	PAC02	VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
76.2	22.6	65.	-.17	0.02	0.12	-.28	0.09	-.24	0.18	-.20	0.00	0.02	-.32	-.32	-.21	0.40*
90.8	17.0	93.	-.05	-.18	-.21	-.31	-.33	-.30	-.30	-.07	-.26	-.05	-.13	-.09	-.18	0.05
65.7	29.6	73.	-.03	-.28	-.12	-.13	-.02	-.16	-.00	0.08	0.09	-.12	-.28	-.09	-.30	0.50**
188.4	6.4	89.	-.28	-.04	-.09	-.27	-.30	-.19	-.36	-.13	-.10	0.07	-.08	-.10	-.16	0.06
58.2	38.1	75.	0.14	0.09	-.06	-.02	-.11	-.02	-.03	-.10	-.05	0.17	-.16	-.18	0.01	0.31*

421.6

REST : PAØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
54.0	45.5	69.	0.01	-.18	-.11	-.21	-.12	0.14	-.10	-.28	-.12	-.16	-.29	-.06	-.07	0.12
200.0	6.0	93.	-.01	0.22	0.00	-.20	-.28	-.40	0.07	-.25	-.19	-.21	-.04	-.19	0.10	0.45**
90.5	17.1	91.	-.15	-.15	-.20	-.25	-.29	-.25	-.17	-.01	-.32	-.21	-.23	-.22	-.08	-.11
75.0	23.3	97.	-.22	-.13	-.30	-.15	-.27	-.28	-.12	-.17	-.24	-.16	-.43	-.26	-.23	0.09
57.2	39.6	*105.	-.08	-.21	-.31	-.09	-.20	-.24	-.16	-.18	-.28	-.23	-.16	-.26	-.04	0.11
49.5	57.1	97.	-.09	-.24	-.20	-.05	-.13	-.18	-.11	-.19	-.21	-.11	-.32	-.22	-.21	0.26

EXERCISE : PACØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
200.0	6.0	87.	-.41	-.23	-.48	-.50	-.37	-.51	-.39	0.12	-.36	-.04	-.40	-.34	-.29	0.17
91.1	16.9	*105.	0.01	0.08	-.09	0.19	-.02	-.09	0.11	-.26	0.06	-.07	-.43	-.06	-.09	0.41
73.5	24.1	*103.	-.15	-.23	-.23	-.15	-.16	0.01	-.12	-.17	-.08	-.14	-.48	-.26	-.29	0.01
68.8	27.2	97.	-.43	-.24	-.26	-.08	-.13	-.10	-.22	-.09	-.30	-.22	-.28	-.28	-.16	0.11
56.2	41.2	85.	-.19	-.23	-.22	-.16	0.03	-.16	-.23	-.16	-.15	0.06	-.43	-.21	-.35	0.37

REST : PAØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.0	6.6	73.	0.02	-.20	-.29	-.18	-.05	-.14	-.26	-.22	-.30	-.20	-.19	-.11	-.33	0.2
55.4	58.4	71.	-.28	-.25	-.08	-.23	-.04	-.20	-.22	-.22	-.10	-.25	-.07	-.11	-.02	0.14
70.5	31.0	65.	-.18	-.07	-.01	-.11	0.01	-.10	-.16	-.02	-.14	-.12	-.20	-.14	-.10	0.99***
50.5	81.6	45.	-.19	-.00	0.18	0.06	0.15	-.10	0.02	-.15	-.17	-.18	-.17	-.12	0.11	0.61**
66.0	36.0	79.	-.18	-.24	-.18	-.10	0.10	0.01	-.05	-.17	0.03	-.25	-.12	-.01	-.29	0.17
101.0	15.9	73.	-.12	0.06	0.05	-.05	0.18	-.11	-.09	0.04	-.28	-.07	-.05	0.05	-.07	0.53***

EXERCISE : PACØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
190.0	6.6	45.	0.04	-.24	-.30	-.10	-.13	-.31	-.04	0.39	-.25	-.21	-.11	-.16	0.17	-.17
89.0	19.7	49.	-.29	-.08	0.09	0.04	0.12	-.04	0.26	0.04	0.14	0.30	-.21	-.13	-.05	0.46*
64.0	38.8	43.	-.07	-.09	0.11	-.03	0.16	0.21	-.23	0.11	-.21	-.09	-.17	0.20	-.13	0.15
60.5	44.9	43.	-.21	0.10	0.07	-.12	0.09	-.14	-.15	-.25	-.27	0.01	-.06	-.05	0.03	0.78***
101.0	15.9	45.	-.21	0.21	0.00	-.14	0.35*	-.31	0.13	-.21	0.50**	0.10	0.10	0.07	-.09	0.70***
65.4	36.9	67.	-.12	0.27	-.20	0.02	0.01	-.12	-.09	-.25	-.20	0.12	-.21	-.10	-.17	0.63***

REST : PACØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
202.0	6.1	69.	-.13	-.15	-.06	-.23	-.14	-.20	-.21	-.09	-.23	-.13	0.17	-.13	-.02	-.22
79.0	24.5	63.	-.15	0.09	0.00	0.10	-.08	-.12	-.07	0.08	-.07	-.09	0.03	-.17	0.10	0.46
61.7	42.6	53.	0.04	-.44	-.03	-.09	0.02	0.09	-.26	-.05	-.01	-.22	0.21	0.31	0.02	0.12
53.3	66.3	69.	-.38	-.31	-.25	-.05	-.02	0.00	-.13	-.24	-.05	-.12	-.01	-.07	-.19	-.14

EXERCISE : PACØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
199.0	6.2	57.	-.25	0.10	0.03	0.36	0.44	0.30	0.15	-.13	-.39	-.19	0.30	0.24	0.13	0.20
83.0	22.3	65.	-.05	-.17	-.07	-.01	0.23	0.15	0.06	-.14	0.13	0.21	0.10	0.18	-.13	0.24
71.8	29.8	61.	-.15	0.05	-.28	-.13	-.12	-.18	-.39	-.27	-.08	-.01	-.03	-.13	-.12	0.37
59.2	47.8	77.	-.14	0.05	-.11	0.17	-.05	0.18	-.29	0.27	-.32	-.30	0.19	-.01	-.18	0.24

REST : PACØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
56.5	41.7	43.	0.14	0.72**	0.66**	0.55**	0.50*	0.23	0.67	-.18	0.20	0.12	-.12	-.14	-.28	0.47
202.0	5.9	45.	-.08	0.52**	0.57**	0.46*	0.51*	0.43*	0.17	0.41*	-.10	-.40	0.10	0.05	0.03	-.06
72.7	24.8	41.	0.09	0.60**	0.01	0.69**	0.03	0.15	0.36	-.06	0.01	-.11	-.12	-.28	-.07	0.75***
50.0	57.1	45.	-.11	-.08	-.01	-.17	0.47*	0.17	-.05	-.45	-.16	-.03	0.83***	0.96***	-.31	0.09
56.2	42.1	61.	0.02	0.36*	0.45**	0.25	0.36*	0.24	0.18	0.21	0.02	-.13	-.04	-.15	0.14	0.39*
111.0	12.7	53.	-.05	-.05	0.11	-.13	0.16	-.04	0.12	-.01	-.20	-.05	-.06	-.14	0.04	0.48**

EXERCISE : PACØ2 STEADY.

PAØ2	HYP	N	PACØ2	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
203.0	5.9	51.	-.15	0.15	0.08	0.38*	0.29	0.48**	-.07	0.41*	-.07	-.07	-.04	0.10	-.03	0.20
98.0	15.3	55.	-.06	-.26	-.16	-.10	-.07	0.15	-.28	-.39	-.01	0.07	0.05	0.19	0.14	0.02
76.5	22.7	49.	-.07	0.35*	0.09	0.27	0.11	0.29	0.04	0.08	0.36*	-.31	0.12	-.02	0.36*	0.60**
59.9	36.5	53.	0.13	0.19	-.14	0.13	-.05	-.03	-.15	-.31	-.10	-.28	-.22	0.02	-.31	0.34*
87.5	18.2	53.	-.16	0.17	0.13	-.07	-.12	-.07	-.15	-.11	0.11	0.21	0.17	-.10	0.13	0.47*
60.5	35.7	57.	-.04	0.32	0.39*	0.12	0.16	0.18	0.12	0.19	0.00	0.07	0.20	0.17	0.32*	0.32

392.15

REST : PAC02 STEADY.

PA02	HYP	N	PAC02	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
70.3	26.4	67.	-.28	-.24	-.24	-.10	-.08	-.11	-.20	-.29	-.33	-.40	-.27	-.27	-.16	-.08
92.5	16.7	57.	-.38	-.18	-.23	-.35	-.33	-.45	-.02	-.29	-.19	-.13	-.08	-.15	-.37	0.11
52.2	50.6	67.	-.33	0.14	-.06	-.05	-.16	-.06	-.12	-.29	0.06	-.07	-.14	0.00	-.19	-.20
60.6	35.5	73.	0.01	0.16	0.12	0.10	0.08	0.05	0.09	0.13	0.29*	-.13	-.12	-.17	0.05	0.38*
209.0	5.7	55.	-.29	0.33*	0.10	-.03	-.24	0.01	-.35	0.01	-.31	-.25	0.41	0.15	0.34	0.06

EXERCISE : PAC02 STEADY.

PA02	HYP	N	PAC02	ZD VALUE. VTE	VTI	VE	VI	MEF	MIF	PEF	PIF	PIA	TT	TE	TI	DFRC
90.2	17.3	75.	0.07	0.42**	0.51**	0.10	0.24	0.13	0.20	-.01	0.33*	-.07	0.11	-.02	0.41**	0.44**
60.7	35.4	73.	-.06	0.22	0.08	0.04	-.07	-.01	-.04	0.07	0.05	-.15	0.25	0.09	0.23	0.11
53.0	48.8	77.	0.01	-.36	-.36	-.30	-.15	-.11	-.17	-.26	-.40	-.15	0.14	0.17	0.04	0.54***
49.3	59.5	67.	-.36	0.32*	-.08	-.21	-.10	-.20	-.19	-.30	-.04	-.04	-.17	0.01	-.23	0.35*
201.0	5.9	63.	-.27	0.31	0.20	-.09	-.14	-.15	0.03	0.01	0.17	-.20	-.04	-.13	0.13	-.12

CUTTIØN ERRØR 105 PRØGRAM TERMINATED

Table 26: CSC runs: the distribution of significant alternate-breath oscillations between variables and subjects, irrespective of P_{A,O_2}.

		Rest					Exercise				
Subject		40 409	421	425	392	All	409	421	425	392	All
No. runs		10	17	12	11	50	11	15	11	14	51
Variable											
$V_{T,E}$	a	1	5	0	1	7^{++}	3	6	1	7	17^{+++}
	%					14.0					33.3
$V_{T,I}$	a	10	8	2	7	27^{+++}	11	12	5	10	38^{+++}
	%					54.0					74.5
$\dot{V}_E$	a	6	5	1	4	16^{+++}	9	4	1	6	20^{+++}
	%					32.0					39.2
$\dot{V}_I$	a	4	9	3	8	24^{+++}	3	9	4	10	26^{+++}
	%					48.0					51.0
MEF	a	5	8	1	3	17^{+++}	10	8	2	3	23^{+++}
	%					34.0					45.1
MIF	a	9	6	4	7	26^{+++}	10	6	6	10	32^{+++}
	%					52.0					62.8
PEF	a	2	10	1	1	14^{+++}	9	6	1	2	18^{+++}
	%					28.0					35.3
PIF	a	10	8	2	6	26^{+++}	10	11	5	10	36^{+++}
	%					52.0					70.6
FI...	a	8	7	2	5	22^{+++}	9	[illegible]	1	6	25^{+++}
	%					44.0					49.0
T_T	a	4	6	0	1	11^{+++}	9	4	0	2	15^{+++}
	%					22.0					29.4
T_E	a	5	9	2	0	16^{+++}	9	2	2	0	13^{+++}
	%					32.0					25.5
T_I	a	2	3	3	3	11^{+++}	5	4	1	1	11^{+++}
	%					22.0					21.6
[illegible]	a	10	9	5	6	30^{+++}	10	12	4	9	35^{+++}
	%					60.0					68.6

a = number of significant observations; % = 'a' as a percentage of the number of runs; significance levels (+) are of χ^2 (p.65), and apply only to the collected experiments.

Table 27: OSC runs: the distribution of significant alternate-breath oscillations between variables and subjects in hypoxia.

		Rest					Exercise				
Subject		409	421	425	392	All	409	421	425	392	All
No. runs		7	9	8	6	30	8	6	6	8	28
Variable											
$V_{T,E}$	a	1	4	0	1	6^{+++}	3	4	1	4	12^{+++}
	%					20.0					42.9
$V_{T,I}$	a	7	6	2	5	20^{+++}	8	6	3	7	24^{+++}
	%					66.7					85.7
$\dot{V}_E$	a	5	4	1	4	14^{+++}	8	3	1	4	16^{+++}
	%					46.7					57.1
$\dot{V}_I$	a	3	7	3	6	19^{+++}	2	4	3	7	16^{+++}
	%					63.3					57.1
MEF	a	5	6	1	3	15^{+++}	8	5	2	3	18^{+++}
	%					50.0					64.3
MIF	a	7	4	4	5	20^{+++}	7	3	5	7	22^{+++}
	%					66.7					78.6
PEF	a	2	6	1	0	9^{+++}	8	4	1	2	15^{+++}
	%					30.0					53.6
PIF	a	7	6	2	5	20^{+++}	7	6	5	7	25^{+++}
	%					66.7					89.3
PIA	a	7	5	2	4	18^{+++}	6	6	1	3	16^{+++}
	%					60.0					57.1
T_T	a	3	5	0	0	8^{+++}	8	2	0	0	10^{+++}
	%					26.7					35.7
T_E	a	5	7	2	0	14^{+++}	8	1	2	0	11^{+++}
	%					46.7					39.3
T_I	a	2	2	2	2	8^{+++}	5	2	1	0	8^{+++}
	%					26.7					28.6
DFRC	a	7	6	4	4	21^{+++}	7	3	4	6	20^{+++}
	%					70.0					71.4

a = number of significant observations; % = 'a' as a percentage of the number of runs; significance levels (+) are of χ^2 (p.65), and apply only to the collected experiments.

Table 28: OSC runs: the distribution of significant ZD values between variables and subjects in hypoxia.

		Rest					Exercise				
Subject		409	421	425	392	All	409	421	425	392	All
No. runs		7	9	8	6	30	8	6	6	8	28
Variable											
$V_{T,E}$	a	2	2	0	2	6^{+++}	0	3	0	3	6^{+++}
	%					20.0					21.5
$V_{T,I}$	a	6	3	0	2	11^{+++}	6	4	4	4	18^{+++}
	%					36.7					64.3
$\dot{V}_E$	a	3	2	0	2	7^{+++}	8	2	0	2	12^{+++}
	%					23.3					42.9
$\dot{V}_I$	a	1	3	0	2	6^{+++}	2	1	3	2	8^{+++}
	%					20.0					28.6
MEF	a	4	1	0	2	7^{+++}	8	2	0	2	12^{+++}
	%					23.3					42.9
MIF	a	4	0	0	3	7^{+++}	3	3	2	4	12^{+++}
	%					23.3					42.9
PEF	a	1	3	0	0	$4^{N.S.}$	6	3	0	0	9^{+++}
	%					13.4					32.1
PIF	a	6	2	0	2	10^{+++}	6	4	2	4	16^{+++}
	%					33.3					57.1
PIA	a	5	2	0	2	9^{+++}	5	5	1	2	13^{+++}
	%					30.0					46.4
T_T	a	3	1	0	0	$4^{N.S.}$	8	1	0	0	9^{+++}
	%					13.4					32.1
T_E	a	6	1	0	1	8^{+++}	8	1	0	1	10^{+++}
	%					26.7					35.7
T_I	a	1	1	0	0	$2^{N.S.}$	2	0	0	1	$3^{N.S.}$
	%					6.7					10.7
DFRC	a	7	5	2	2	16^{+++}	6	5	5	5	21^{+++}
	%					53.4					75.0

a = number of significant observations; % = 'a' as a percentage of the number of runs; significance levels (+) are of χ^2 (p. 65), and apply only to the collected experiments.

Table 29: OSC runs: the distribution of significant alternate-breath oscillations between variables and subjects in hyperoxia.

		Rest					Exercise				
Subject		409	421	425	392	All	409	421	425	392	All
No. runs		0	2	2	2	6	0	2	2	2	6
Variable											
$V_{T,E}$	a		0	0	0	0		0	0	0	0
	%										
$V_{T,I}$	a		0	0	1	1		0	0	0	0
	%										
$\dot{V}_E$	a		0	0	0	0		0	0	0	0
	%										
$\dot{V}_I$	a		0	0	1	1		0	0	0	0
	%										
MEF	a		0	0	0	0		0	0	0	0
	%										
MIF	a		0	0	1	11		1	0	0	11
	%										
TEF	a		0	0	1	11		0	0	0	0
	%		0					1	0		1
PIF	a		0	0	0	0		1	0	0	1
	%										
PIA	a		0	0	2	2		0	0	0	0
	%										
T_T	a		0	0	1	1		0	0	0	0
	%										
T_E	a		1	0	0	1		0	0	0	0
	%										
T_I	a		0	1	1	2		0	0	0	0
	%										
DFRC	a		1	0	0	1		2	0	2	4
	%										

a = number of significant observations; % = 'a' as a percentage of the number of runs; significance levels (+) are of χ^2 (p. 65), and apply only to the collected experiments.

Table 30: STEADY runs: the distribution of significant alternate-breath oscillations between variables and subjects.

		Rest					Exercise				
Subject		409	421	425	392	All	409	421	425	392	All
No. runs		10	15	10	11	46	10	14	10	11	45
Variable											
$V_{T,E}$	a	0	0	0	0	0	0	0	0	0	0
	%										
$V_{T,I}$	a	3	1	0	0	4^{NS}	5	1	1	0	7^{++}
	%										
$\dot{V}_E$	a	0	0	0	0	0	0	0	0	0	0
	%										
$\dot{V}_I$	a	1	0	0	0	1^{NS}	2	0	1	0	3^{NS}
	%										
MEF	a	0	0	0	1	1^{NS}	0	0	0	0	0
	%										
MIF	a	0	0	0	0	0	3	1	1	1	6^{+}
	%										
PEF	a	0	0	0	0	0	0	0	0	0	0
	%										
PIF	a	5	0	0	1	6^{+}	5	0	0	0	5^{NS}
	%										
PIA	a	4	0	0	0	4^{NS}	0	3	0	1	4^{NS}
	%										
T_I	a	0	0	0	0	0	0	0	0	1	1^{NS}
	%										
T_E	a	0	0	0	0	0	0	0	0	0	0
	%										
T_I	a	0	0	0	0	0	0	0	0	0	0
	%										
DPIC	a	4	1	0	0	5^{NS}	6	2	1	1	10^{+++}
	%										

a = number of significant observations; % = 'a' as a percentage of the number of runs; significance levels (+) are of χ^2 (p. 65), and apply only to the collected experiments.

Table 31: STEADY runs: the distribution of significant alternate-breath oscillations between variables and subjects in hypoxia.

		Rest					Exercise				
Subject		409	421	425	392	All	409	421	425	392	All
No. runs		7	7	6	6	26	7	5	4	5	21
Variable											
$V_{T,E}$	a	0	0	0	0	0	0	0	0	0	0
	%										
$V_{T,I}$	a	3	0	0	0	$3^{N.S.}$	3	0	0	0	$3^{N.S.}$
	%	0	0	0	0	0	0	0	0	0	$3^{N.S.}$
$\dot{V}_E$	a	0	0	0	0	0	0	0	0	0	0
	%										
$\dot{V}_I$	a	1	0	0	0	$1^{N.S.}$	2	0	0	0	$2^{N.S.}$
	%										
MEF	a	0	0	0	1	$1^{N.S.}$					
	%										
MIF	a	0	0	0	0	0	2	0	1	1	4
	%										
PEF	a	0	0	0	0	0	0	0	0	0	0
	%										
PIF	a	3	0	0	1	$4^{N.S.}$	2	0	0	0	$2^{N.S.}$
	%										
PIA	a	4	0	0	0	$4^{N.S.}$	0	2	0	0	$2^{N.S.}$
	%										
T_T	a	0	0	0	0	0	0	0	0	1	$1^{N.S.}$
	%										
T_E	a	0	0	0	0	0	0	0	0	0	0
	%										
T_I	a	0	0	0	0	0	0	0	0	0	0
	%										
DFRC	a	3	1	0	0	$4^{N.S.}$	4	0	0	1	5^{+++}
	%										

a = number of significant observations; % = 'a' as a percentage of the number of runs; significance levels (+) are of χ^2 (p. 65), and apply only to the collected experiments.

Table 32: The results of the amplitude comparisons between OSC and STEADY alternate-breath oscillations.

Expt.	Rest P_{A,O_2} (torr)	Rest Variables	Exercise P_{A,O_2} (torr)	Exercise Variables
409.5	112.5	$DFRC^{+++}$	117.0	$V_{T,I}$ N.S. PIF N.S. $DFRC^{+}$
	69.0	PIA^{+}		
	54.0	VT_I^{+}	57.0	PIF^{+}
	46.5	PIF^{+++} $DFRC^{+++}$	52.5	$\dot{V}_I$ N.S.
			51.0	$V_{T,I}^{+++}$ PIF' $DFRC^{++}$
409.6	129.0	PIF N.S.	75.0	$V_{T,I}^{+++}$ MIF N.S. PIF^{+++} $DFRC^{+++}$
	78.0	PIF N.S.		
	63.0	PIF^{++} PIA N.S. $DFRC^{+++}$	63.0	$V_{T,I}^{+++}$ MIF^{++} $DFRC^{+++}$
	55.5	$V_{T,I}^{++}$ $\dot{V}_I$ N.S. PIF^{++} PIA N.S.	57.0	MIF N.S. PIF^{++} $DFRC^{+}$
	48.0	$V_{T,I}$ N.S. PIA^{++} DFRC N.S.	51.0	$V_{T,I}^{++}$ $\dot{V}_I$ N.S. $DFRC^{+++}$
421.2	76.5	$V_{T,I}^{++}$	120.0	$DFRC^{++}$
421.4	51.0	$DFRC^{+}$	90.0	DFRC N.S.
			76.5	$V_{T,I}^{++}$ MIF N.S. PIA N.S.
			66.0	PIA N.S.
			58.5	PIA^{+++}
425.2			100.5	$V_{T,I}$ N.S. $\dot{V}_I$ N.S. DFRC N.S.
			60.0	MIF^{+}
392.13	57.0	MEF N.S.	76.5	T_T N.S.
	57.0	PIF^{+}		
392.15			90.0	PIA N.S.
			49.5	MIF^{++} DFRC N.S.

Starred runs: OSC > STEADY; N.S.: OSC = STEADY, & OSC > 0.

Table 33: Experiment 409.5: a comparison of ZD values obtained from runs of unedited data (1) and edited data (2): significant values only.

		Rest				Exercise				
P_{A,O_2} (torr)		70.5	55.5	54.0	46.5	69.0	57.0	52.5	51.0	51.0
$V_{T,E}$	1				1.08					
	2				0.75					
$V_{T,I}$	1		0.40	0.65	0.81	0.58			1.15	1.29
	2		0.40	0.58	0.77	0.44			0.98	1.29
$\dot{V}_E$	1		0.30	0.46	0.45	0.37	0.36	0.65	1.00	1.32
	2		0.42		0.47			0.92	0.90	1.42
$\dot{V}_I$	1				1.48			0.95		
	2				1.28			1.02		
EEF	1		0.53	0.77	1.57	0.53	0.86	1.20	1.30	1.36
	2		0.68	0.58	1.57	0.39	0.68	1.40	1.47	1.51
EIF	1			0.67	0.73	0.45			0.48	0.89
	2			0.64	0.76				0.61	0.89
PEF	1				0.67	0.60	0.98			0.79
	2				0.70	0.44	0.91		1.14	1.12
PIF	1		0.68	1.27	1.50	0.62	0.98		0.60	
	2		0.70	1.25	1.67	0.60	0.78		0.74	
PIA	1	0.62	0.79	1.48	1.74	0.33	1.15			0.57
	2	0.55	0.80	1.42	1.49		1.04			0.50
T_T	1		0.66	0.61	1.50	0.53	0.47	1.04	1.36	1.66
	2		0.63	0.46	1.50	0.47		1.09	1.05	1.77
T_E	1		0.79	0.96	2.23	0.76	0.86	1.38	1.33	1.36
	2		0.78	0.81	2.23	0.53	0.89	1.44	1.26	1.54
T_I	1				0.96				0.58	0.54
	2				0.57				0.74	0.52
DFRC	1	1.22	0.89	1.20	2.27	1.04			1.62	1.93
	2	0.95	0.93	1.20	2.14	0.97	0.66		1.32	1.93

Significance of ZD values for run sizes ranging from 40 to 80 breaths:-
$0.01 < p < 0.05$: ZD > 0.47 to 0.32; $0.001 < p < 0.01$: ZD > 0.61 to 0.42;
$p < 0.001$: ZD > 0.78 to 0.54.

Table 34: Latencies of the significant responses obtained from the P_{A,CO_2} transient in hypoxia.

Run		P_{A,O_2} (torr)		$V_{T,E}$	$V_{T,I}$	$\dot{V}_E$	$\dot{V}_I$	BP
409.5								
Rest, 'On' transient								
	1	69.0	k_{max}					
			$r_{k,max}$					0.
	2	55.5	k_{max}			1		
			$r_{k,max}$			0.54^{+}		0.
	3	54.0	k_{max}		0	1		1
			$r_{k,max}$		0.52^{+}	0.50^{+}		0. 0.45^{+}
	4	46.5	k_{max}			3	3	3
			$r_{k,max}$			0.55^{+}	0.68^{++}	0. 0.66^{++}
Rest, 'Off' transient								
	5	54.0	k_{max}		0	1		
			$r_{k,max}$		0.63^{++}	0.69^{+++}		
Exercise, 'On' transient								
	6	57.0	k_{max}					
			$r_{k,max}$					0.
	7	51.0	k_{max}		0			
			$r_{k,max}$		0.76^{+++}			0.
Exercise, 'Off' transient								
	8	69.0	k_{max}		2	1		1
			$r_{k,max}$		0.75^{+++}	0.44^{+}		0. 0.73^{++}
	9	57.0	k_{max}		3		1	4
			$r_{k,max}$		0.47^{+}		0.48^{+}	0. 0.78^{+}
	10	51.0	k_{max}			1		
			$r_{k,max}$			0.60^{+++}		

IF	PEF	PIF	PLA	T_T	T_E	T_I	DFRC
		2	0				0
		0.47^{+}	0.46^{+}				0.58^{++}
			0	1	1	1	
			0.57^{++}	-0.49^{+}	-0.47^{+}	-0.43^{+}	
	1	2			1		
	0.45^{+}	0.52^{+}			-0.45^{+}		
	3		2	3	3		
	0.66^{++}		0.48^{+}	-0.69^{++}	-0.83^{++}		
		0	4	1	1		
		0.68^{+++}	0.65^{++}	-0.72^{+++}	-0.67^{+++}		
4			4	3	3		
5^{+}			0.60^{++}	-0.52^{+}	-0.58^{++}		
2				1	1	1	2
1^{++}				-0.88^{+++}	-0.85^{+++}	-0.63^{++}	0.84^{+++}
4	1			1	1		2
1^{++}	0.73^{+++}			-0.59^{++}	-0.65^{++}		0.63^{++}
	4		0		1		
)	0.78^{+++}		0.70^{+++}		-0.53^{+}		
4			4	1	1		0
5^{+++}			0.46^{+}	-0.77^{+++}	-0.65^{++}		0.69^{+++}

Table 34 (continued)

		P_{A,O_2} (torr)		$V_{T,E}$	$V_{T,I}$	$\dot{V}_E$	$\dot{V}_I$	MEP
409.6								
Exercise, 'Off' transient								
	1	57.0	k_{max}	3	0	1		1
			$r_{k,max}$	0.53^{+}	0.45^{+}	0.62^{++}		0.72^{+}
421.2								
Rest, 'Off' transient								
	1	61.5	k_{max}				4	2
			$r_{k,max}$				0.49^{+}	0.64^{+}
Exercise, 'Off' transient								
	2	70.5	k_{max}					
			$r_{k,max}$					
421.4								
Rest, 'On' transient								
	1	58.5	k_{max}			2		2
			$r_{k.max}$			0.46^{+}		0.53^{+}
Rest, 'Off' transient								
	2	58.5	k_{max}					
		[illegible]	$r_{k,max}$					
	3	54.0	k_{max}			2		
			$r_{k,max}$			0.44^{+}		
Exercise, 'On' transient								
	4	57.0	k_{max}	2		2		
			$r_{k,max}$	0.51^{+}		0.53^{+}		
Exercise, 'Off' transient								
	5	56.5	k_{max}	2		2		
			$r_{k,max}$	0.56^{+}		0.59^{++}		

MIF	PEF	FIF	PIA	T_T	T_E	T_I	DFIC
2		2					
2	1	2	2	1	1		
0.60^{++}	0.73^{+++}	0.73^{+++}	0.51^{+}	-0.51^{+}	-0.67^{+++}		
	2	2					3
	0.63^{++}	0.48^{+}					0.61^{++}
			2		1		
			0.64^{++}		-0.48^{+}		
2	2						0
0.58^{++}	0.82^{+++}						0.45^{+}
			4		3		0
			0.52^{+}		-0.54^{+}		0.61^{++}
	2				1		
	0.56^{+}				-0.44^{+}		
	2			1			
	-0.55^{+}			-0.48^{+}			
4	2	4					
0.55^{+}	0.79^{+++}	0.85^{+++}					

Table 34 (continued)

421.6	$P_{...},O_2$ (torr)		$V_{T,E}$		$V_{T,I}$	$\dot{V}_E$	$\dot{V}_I$
<u>Rest, 'Off' transient</u>							
	1	49.5	k_{max}	4	4	0	0
			$r_{k,max}$		0.52^{+}		0.44^{+}
425.2							
<u>Exercise, 'Off' transient</u>							
	1	63.0	k_{max}		2		
			$r_{...,max}$		0.62^{++}		
392.13							
<u>Exercise, 'Off' transient</u>							
	1	60.0	k_{max}		2		
			$r_{k,max}$		0.64^{++}		
392.15							
<u>Exercise, 'On' transient</u>							
	1	54.0	k_{max}	4	2	2	2
			$r_{k,max}$	0.64^{++}	0.59^{++}	0.73^{+++}	0.7^{+++}
<u>Exercise, 'Off' transient</u>							
	2	55.5	k_{max}	2	2	2	2
			$r_{k,max}$	0.63^{++}	0.67^{++}	0.49^{+}	0.50^{+}

F	MIF	PEF	PIF	PIA	T_T	T_E	T_I	DF	exercise .son of ients
			4	0				0	S.
			0.47^{+}	0.65^{+++}				0.71^{+++}	S.
									+
									S.
									S.
	4		4	4					S.
	0.66^{++}		0.48^{+}	0.66^{++}					
									+
									++
									+
			2				3		S.
			0.50^{+}				-0.59^{++}		++
									+
	2		2	4	2		2		
	3^{+++}		0.74^{+++}	0.51^{+}	0.83^{+++}		-0.54^{+}		S.
									S.
			2	2	2				.
			0.59^{++}	0.52^{+}	0.55^{+}				+
									S.
									++
									++

Table 35: Linear regression of ZD on hypoxia: significant results.

	Rest		Exercise		
	Coefficient x 10^2	Hypoxia intercept $torr^{-1}$	Coefficient x 10^2	Hypoxia intercept $torr^{-1}$	Rest v. exercise comparison of coefficients
409.2					
$\dot{V}_E$	1.1 +	16.6	2.2 +	10.6	N.S.
MEF	3.1 ++	20.4	3.0 +++	10.6	N.S.
TIF	2.6 +	7.6	N.S.		R > E +
MIA	3.3 +	10.9	N.S.		N.S.
T_T	2.6 +	16.6	3.5 ++	16.1	N.S.
T_E	4.2 +	19.5	3.3 ++	10.9	N.S.
402.6					
$\dot{V}_E$	N.S.		3.1 +	14.7	E > R +
MEF	1.0 +	30.0	4.0 +	13.5	E > R ++
PEF	N.S.		3.2 +	16.4	E > R +
PIF	1.0 +	-18.0	N.S.		N.S.
T_T	N.S.		4.0 +	16.3	E > R ++
T_E	1.45 +	23.7	4.6 +	14.8	E > R +
421.4					
MIF	N.S.		2.1 +	15.3	N.S.
421.6					
$V_{T,E}$	N.S.		2.4 +	15.6	N.S.
$V_{T,I}$	N.S.		1.9 +	15.5	N.S.
PEF	N.S.		1.2 +	13.1	N.S.
MIF	N.S.		2.1 +	16.6	E > R +
T_E	0.6 +	35.5	N.S.		N.S.
425.2					
$V_{T,I}$	N.S.		2.3 +	13.1	E > R ++
DFRC	N.S.		3.1 +	1.8	E > R ++

Table 36: Linear regression of the normalised alternate-breath oscillation on hypoxia: significant results.

	Rest		Exercise		
	Coefficient x 10^2	Hypoxia intercept $torr^{-1}$	Coefficient x 10^2	Hypoxia intercept $torr^{-1}$	Rest v. exercise comparison of coefficients
409.5					
$\dot{V}_I$	-1.05 +	30.5	N.S.		N.C.
MEF	-1.48 ++	3.2	N.S.		N.S.
PEF	-0.92 +	11.9	N.S.		N.S.
PIF	0.72 +	-10.1	N.S.		R > E +
PIA	1.66 +	0.5	N.S.		N.C.
T_T	-10.24 +	0.77	N.S.		N.S.
T_E	-23.84 +	11.25	N.S.		N.S.
409.6					
$\dot{V}_I$	N.S.		-1.19 ++	31.2	E > R +
MEF	N.S.		-2.03 +	3.0	E > R +
PEF	N.S.		-1.38 +++	4.5	E > R ++
PIF	3.89 ++	-39.8	N.S.		N.S.
PIA	7.57 +	-8.6	N.S.		N.S.
T_T	N.S.		-12.74 +	5.97	E > R +
T_E	N.S.		-24.25 ++	9.31	E > R ++
421.2					
$\dot{V}_I$	N.S.		8.13 ++	-5.7	N.S.
421.4					
$V_{T,E}$	N.S.		12.71 ++	13.3	
$\dot{V}_I$	6.93 +	-7.4	N.S.		
MEF	8.90 ++	9.1	N.S.		
PIF	8.56 +	6.3	10.55 +	4.3	
425.2					
PEF	N.S.		7.38 +	20.4	E > R ++
PIF	N.S.		12.26 +	8.7	E > R +
PIA	N.S.		17.04 ++	21.9	E > R ++
392.13					
PIA	N.S.		12.50 +	3.0	

APPENDIX III

The effects of exercise on the ratio of heart rate (f_c) to respiratory frequency (f_v).

The data were obtained from experiment 409.6. Measurements were made during euoxic hypercapnic runs (mean $P_{\bar{A},CO_2}$ ca. 10 torr above the eupnoeic value), at rest and during moderate exercise (40 watts).

	$\dot{V}_E$ $l.min^{-1}$	$V_{T,E}$ $l.$	f_v min^{-1}	f_c min^{-1}	f_c/f_v
Rest	38.0	1.80	21.1	80	3.8
Exercise	49.5	1.90	26.0	120	4.6

The ratio, f_c/f_v, rose on going from rest to exercise.

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