The influence of some non-chemical factors on breathing

by

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A thesis presented for the degree of Master of Philosophy at the University of Southampton.

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March 1983

In loving memory of my father FRANCISCO DE PAULA L. BAPTISTA, who would have been very proud to witness this evidence of my efforts and .....

To my husband Flavio and my daughter Carolina

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE

MEDICINE I

Master of Philosophy

THE INFLUENCE OF SOME NON-CHEMICAL FACTORS ON BREATHING

by Ana Maria Baptista Menezes

The influence of some non-chemical factors on breathing was studied in fifteen normal subjects, during CO_2 rebreathing. The variables $\dot{V}E$, dP/dt max, f, VT, Ti and Te were plotted against PCO_2 and correlation coefficient and slopes were measured.

A wide scatter of results was found mainly for the responses of f/PCO_2 and VT/PCO_2 and to a lesser extent for $\dot{V}E/PCO_2$. When f/PCO_2 was studied in terms of Ti and Te, there was a greater variability for Te than Ti. The variable dP/dt max was the measurement with the least scatter in the response.

On the assumption that the influence of psychological factors such as anxiety and unfamiliarity were responsible for the scatter of the results described above it was decided to (i) repeat the measurement on a second occasion and (ii) assess the personality of the subjects through an established questionnaire. This would be compared with the writer's own judgement of the presence or absence of anxiety during the experiment.

The magnitude of these non-chemical influences causing the scatter was quantified by the residual variance $(1-r^2)$. A significant reduction of $(1-r^2)$ was not found on the second occasion of study.

When the residual variance of $dP/dt\ max/PCO_2$ was compared with the residual variance of the other measurements, a significant difference was found, $dP/dt\ max/PCO_2$ having the lowest $(1-r^2)$. It is implicit in the analysis of $(1-r^2)$ that there is a linear relationship between the variables studied. To test this, the Durbin-Watson statistic was applied and many alinear responses were found. As there was no correlation between the magnitude of $(1-r^2)$ and alinear responses I assumed that this factor did not invalidate the use of $(1-r^2)$.

Seven subjects were studied when the respiratory frequency was controlled by a metronome and $dP/dt\ max/PCO_2$ was no longer the measurement with the smallest residual variance.

A model of breathing control is proposed to account for these observations.

Acknowledgements

I am deeply indebted to my supervisor, Professor J.B.L. Howell, for his continued guidance and encouragement throughout the experimental work and the writing of this text.

I would also like to thank Messrs David Cragg, Mark Thomas and John Heath, for their technical assistance in preparing for some of the practical work.

Mr Michael Campbell was indispensable in advising on the statistical analysis, and Angela Taylor, in helping me with my English.

Thanks are also due to Mrs Margaret Dowling for her patience in typing this thesis.

I am very grateful for the financial support from the British Council and to the "University Federal de Pelotas" for allowing me to stay here all this time.

Finally, thanks to my friends who volunteered to be subjects in this study, and to my family who have been a constant source of love and encouragement.

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INTRODUCTION

This thesis describes an attempt to quantify some of the non-chemical factors which influence the mechanisms of ventilatory control in man during increased ventilation induced by CO_2.

I first became aware of the influence of non-chemical factors during pilot measurements of respiratory responses to CO_2 during a standard rebreathing procedure. The problem which I encountered was one of a scatter of results, particularly when untrained subjects were used. This suggested that non-chemical factors were overriding the basic respiratory control mechanisms. Rather than discard these data, I decided to analyse these varying responses to try and estimate, or even measure, the way and the extent to which non-chemical, presumably largely psychological, factors can influence breathing.

The account which follows is organised in VII chapters in which I review relevant aspects of the history of respiratory control, concepts of the "Respiratory Centre" and its organisation and existing methods of measuring the respiratory motor output. The end of the historical review finishes with a model of the control of breathing which includes much information about chemical control, some information about the role of pulmonary afferent nerves, rather less information about the role of afferent nerves from muscles, and very little information about "psychological

factors". Most of the remainder of the thesis concerns my attempts to add to our understanding of psychological factors.

CHAPTER ONE

CHAPTER ONE

HISTORY OF RESPIRATORY CONTROL

The respiratory control system:

- maintains a regular rhythmic breathing pattern by means of involuntary control mechanisms.

- adjusts the tidal volume and the frequency of breathing, so that the minute volume of ventilation is sufficient to meet the demands for gas exchange, with the minimum respiratory effort.

- adjusts breathing so that other activities using the same muscles, such as speech and the control of posture, can occur.

Under most normal circumstances, breathing is controlled so well that the arterial partial pressures of oxygen and CO_2 remain virtually constant, despite different levels of physical activity.

The respiratory system is different from the other gas transporting, i.e., circulatory system, in two ways: first, breathing is totally dependent on intact nervous pathways and second, the respiratory system is under both voluntary and automatic control. The automatic control centre is thought of as originating in the pons and medulla ("Respiratory Centre") and the descending axons are concentrated in the ventral and lateral columns of the cord. The voluntary and behavioural control mechanisms are thought of as starting in the forebrain and descending via the corticospinal or

rubrospinal tracts in the dorsilateral cord. The importance of this system should not be underestimated because many behavioural-related activities involving breathing cause marked changes in ventilation that may override completely the automatic controls which respond chiefly to chemical stimuli.

I Organisation of the "Respiratory Centre"

The three basic elements of the respiratory control system (see fig. 1) are:

sensors - which sense the information and send it to the

central controller - pons, medulla and other parts of the brain which co-ordinate the information and send impulses to the

effectors - these are the respiratory muscles which cause ventilation.

It was only in the beginning of the last century that the location of the respiratory centre was placed in the brainstem. In 1812, LeGallois (quoted by Mitchell and Berger, 1975), studying rabbits reported that when serial slices of the brainstem included a portion of the medulla containing the nerve roots of the vagus respiration had stopped.

The "Respiratory Centre" in the medulla has been studied by many investigators since it was shown that this centre was crucial for rhythmic breathing.

The technique of ablation was subsequently used extensively to study the components of the respiratory

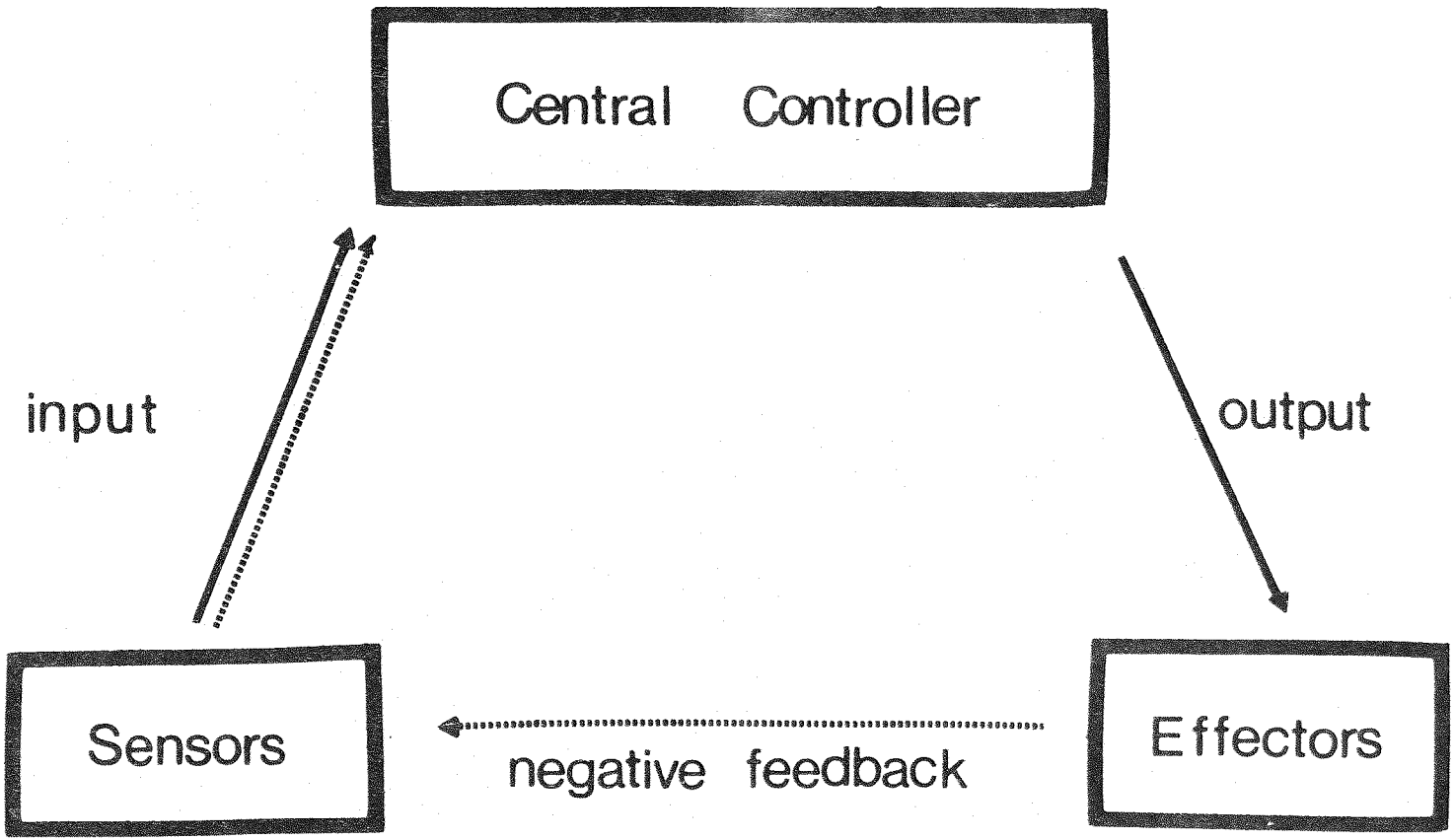


Fig. 1 - "Respiratory Control System". The dotted lines represent inhibitory influences (modified from West, 1979)

centre. In 1923, Lumsden, studying cats, rabbits, dogs and monkeys using brainstem transections, concluded that the respiratory centre could be divided into 3 centres: pneumotaxic, apneustic and medullary centre, the last being divided into an expiratory and an inspiratory gasping centre. He also concluded that the pneumotaxic centre periodically inhibited the apneustic centre leading to normal rhythmic breathing.

After that, many investigators have applied ablation and destruction techniques and it was shown that the vagi must be cut in order for apneusis to occur and that the medulla can generate a rhythmic respiratory pattern (see fig. 2). Thus, transection I alone does not alter the breathing pattern, however, with vagotomy, slow deep breathing results. Transection II causes slow deep breathing with the vagi intact and either apneusis or apneustic breathing when the vagi are cut. Transection III results in a return to rhythmic respiration, in most cases a regular gasping type of respiratory pattern. Transection IV results in repiratory arrest.

Pneumotaxic centre - Since Lumsden's time, many investigators have studied the pneumotaxic centre. Cohen (1971) and Bertrand and Hugelin (1971), using electrical stimulation and neural recording in cats, reported that Lumsden's pneumotaxic centre resides in the region of the nucleus parabrachialis in the dorsolateral rostral pons. In

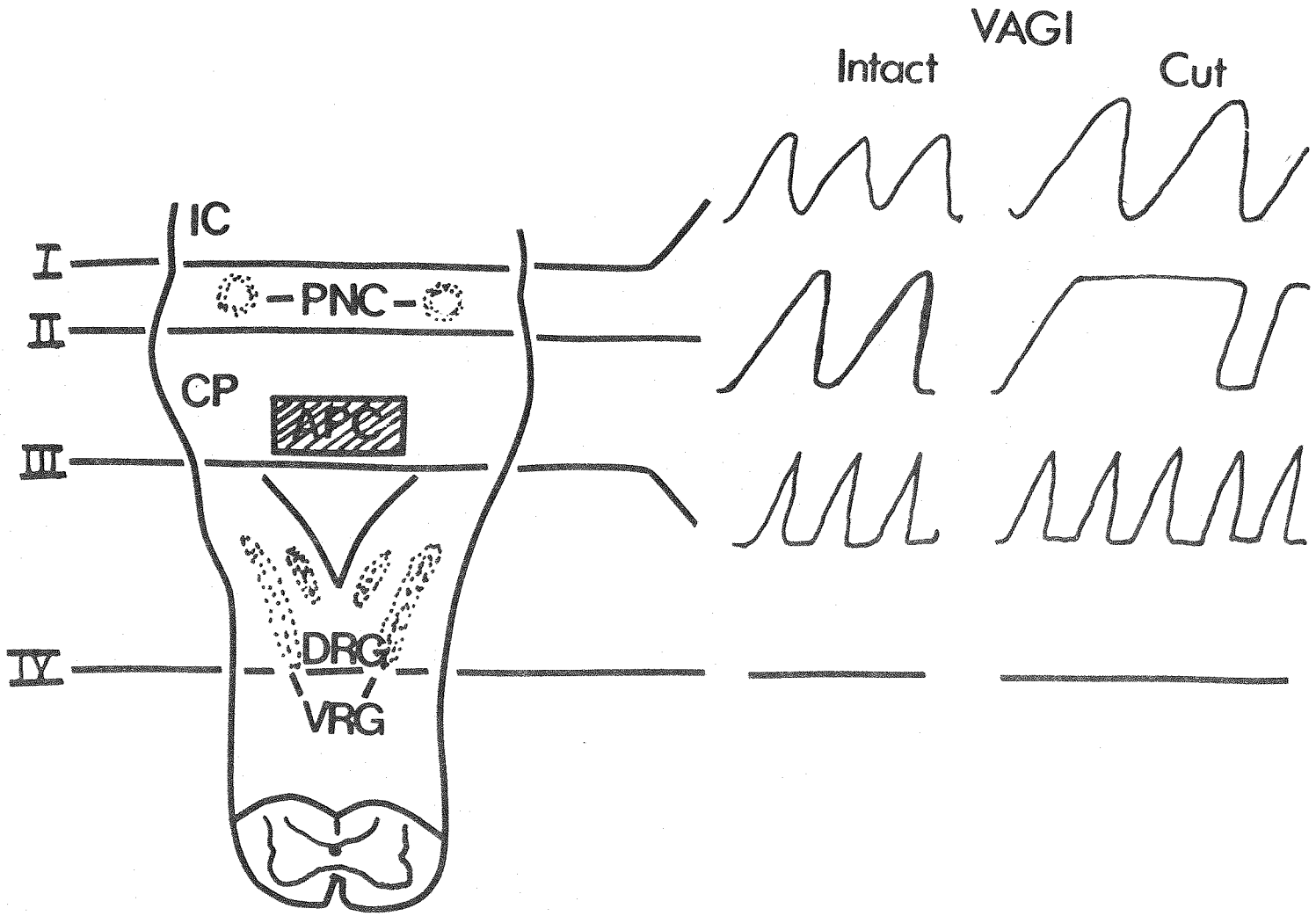


Fig. 2 - Effects of various brainstem and vagal transections on the ventilatory pattern of the anaesthetised animal (redrawn from Berger, Mitchell and Severinghaus, 1977).

1974, Bertrand, Hugelin and Vibert, using neural recordings and histologic marking techniques, found spatially discrete subpopulations of inspiratory, phase- spanning and expiratory neurons in the pneumotaxic centre, and it was suggested that the neurons of the pneumotaxic centre are formed into a self-reexciting network that acts as an oscillator. These authors supported Lumsden's conclusion that the function of the pneumotaxic centre is to modulate the rhythmic respiratory centre in the medulla.

Apneustic centre - Sears (1966) reported that electric stimulation of sites in the medial reticular formation close to the obex led to a tonic contraction of both diaphragm and external intercostal muscles. Andersen and Sears (1970) found that during apneusis there was a tonic activation of both α and γ external intercostal motoneurons with inhibition of the motoneurons of the antagonist internal intercostals. They concluded that the apneustic centre is the site of origin of the long reticulospinal fibres and that the function of these neurons is to set a bias upon the membrane potential of the respiratory motoneurons in the cord.

Berger, Mitchell and Herbert (1976) suggested that the apneustic centre was the location of the normal inspiratory cut-off switch and the site of projection of the various inputs that could terminate an inspiraton. Apneusis would arise from inactivation of this inspiratory cut-off mechanism.

Medullary centre - It is now known that the medulla has 2 aggregations of rhythmic respiratory neurons: the dorsal respiratory group (DRG) which is situated in the ventrolateral portion of the nucleus of the tractus solitarius and a ventral respiratory group (VRG) associated with nucleus ambiguous and nucleus retroambigualis. The former contains chiefly inspiratory neurons and the latter contains both inspiratory and expiratory neurons. The DRG drives the VRG but not vice-versa, and axons from the VRG project to certain spinal respiratory motoneurons or to the accessory muscles of respiration. The inspiratory neurons from the DRG project primarily to the contralateral spinal cord and probably serve as the principal rhythmic respiratory drive to phrenic motoneurons (Cohen, Piercey, Gootman and Wolotsky, 1974). More recently, however, recordings in this region have revealed the presence of expiratory neurons from the VRG that send axons to the contralateral DRG (Merrill, 1981).

Mitchell and Berger (1975) suggested that the DRG is the site of integration and relay for many reflex responses. The respiratory reflex afferents carried in the IX and X cranial nerves are first integrated into the respiratory system in the DRG. Fig. 3 shows a schematic representation of the respiratory control system.

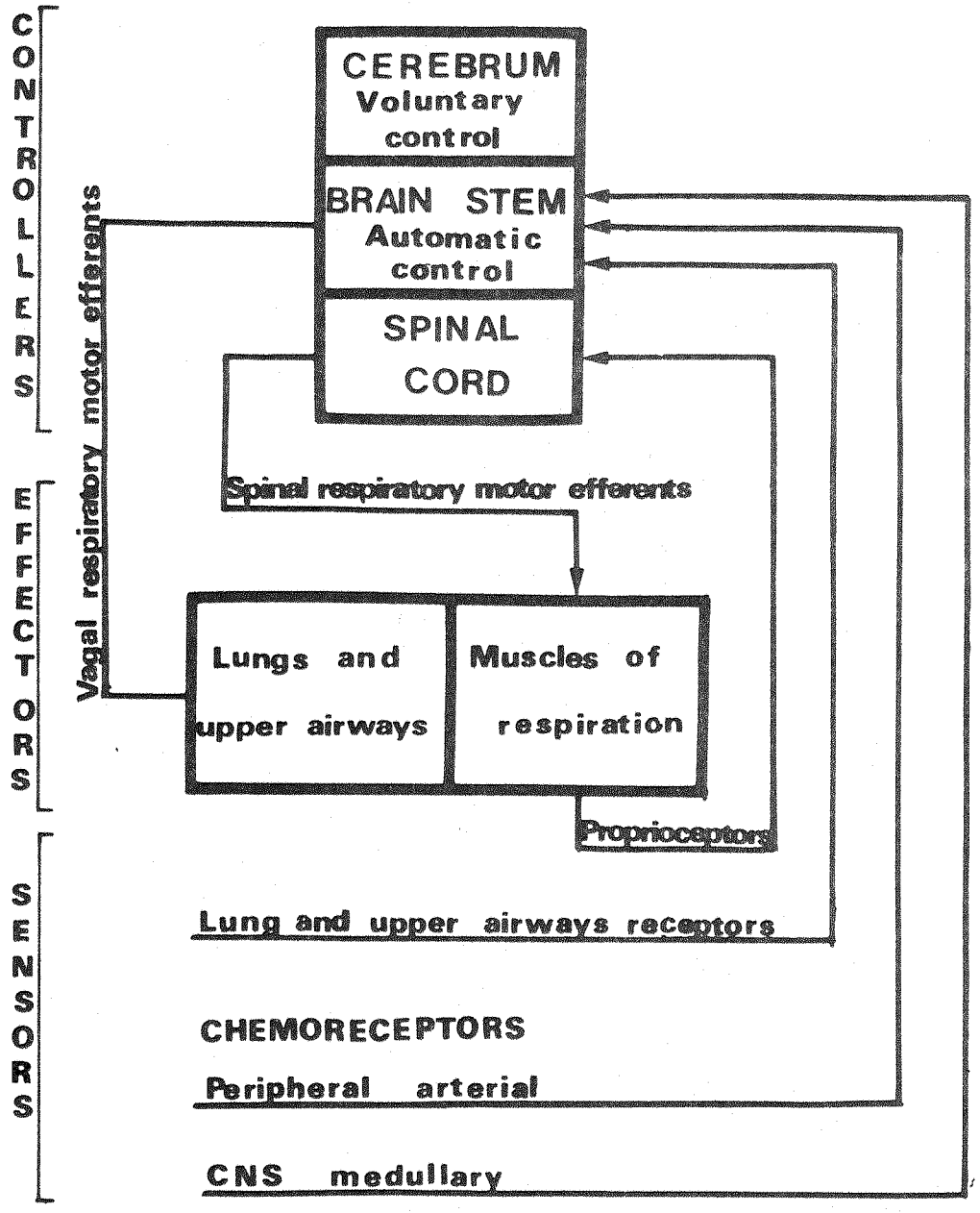


Fig. 3 - Schematic representation of the respiratory control system (redrawn from Berger et al, 1977).

II BEHAVIOURAL SYSTEM

"Breathing, the only autonomic function regulated entirely by skeletal muscle, serves two great homeostatic systems: metabolism and behaviour" (Plum, 1970).

Evidence exists for separate neurological structures mediating behavioural and metabolic influences on the respiratory act at almost every level of the brain, from the cerebral hemispheres to the medulla and even the upper cervical spinal cord. Evidence indicates that the controlling mechanisms for behavioural respiratory function are located largely in the forebrain and the controlling mechanisms for metabolic respiratory regulations lie largely in the hindbrain (Plum, 1970).

Influence from the cerebral hemispheres can profoundly inhibit the behavioural functions of the respiratory act. The results of electrical stimulation of the hemispheres make a strong case for inhibitory influences on respiration arising at this level (Kaada, 1960). Only a limited number of cerebral points, located mainly in the classic somatic motor and premotor areas, facilitate respiration; in contrast to this modest facilitatory influence, large areas of the hemispheres inhibit breathing. The stimulation of some of these areas in experimental animals produces apnoea or respiratory suppression that lasts as long as the stimulus, even though accompanied by severe asphyxia. Taken together, these inhibitory structures comprise most of the contribution of the hemispheres to the limbic system, which is now believed

to mediate the main forebrain contribution to emotional and autonomic behaviour.

According to Kaada (1960) and Nelson and Ray (1968), electrical stimulation of limbic structures in man stops breathing, usually in quiet expiration, with the longest duration of arrest thus far reported being 56s.

A number of authors, including Brown and Plum (1961) have demonstrated that CO_2 responsiveness is greater in patients with bilateral cerebral motor dysfunction than in controls, suggesting that metabolic respiratory functions could be enhanced by the removal of cerebral influences. However, the cerebral hemispheres also normally contribute an important component to the volume of breathing during wakefulness and in most healthy subjects the cerebral drive maintains a rhythm of respiration, even when metabolic stimuli are temporarily removed. This is implicit in the studies by Fink, 1961 (see page 25).

In summary, the act of breathing serves two functions - metabolism and behaviour, and the nervous system regulates these through different pathways. The more primitive metabolic system is located in the reticular formation of the lower pons and medulla, receiving its input from chemoreceptors, vagus nerves and proprioceptive reflexes, and is responsible for blood gas and acid base homeostasis. It automatically regulates its own intrinsic rhythm when stimulated and transmits its impulses to the spinal cord via ventral reticulo-spinal pathways. The behavioural system is

located mainly in somatomotor and limbic forebrain structures, adapts man to speech and complex behavioural acts and conditions him for the expected metabolic demands of activity and exercise. This system is completely functional only when the forebrain is activated by full wakefulness and it transmits its descending impulse, at least partly, to the medullary reticulum, and also partly to the spinal cord via direct corticobulbar and cortico-spinal pathways (Mitchell and Berger, 1975).

III Integration of the behavioural and metabolic systems in respiratory control

Phillipson (1978), in his review of the control of breathing during sleep, has modified the system postulated by Berger et al (1977) in showing how the behavioural and metabolic systems may interact (see fig. 4).

During wakefulness, breathing is governed by both the metabolic and the behavioural respiratory control system; during non REM sleep, breathing is regulated solely by the metabolic control system; and during REM sleep, breathing functions largely independently of the metabolic system and may be considerably influenced by the behavioural system (Phillipson, 1978).

Fink, in 1961, demonstrated in healthy humans that after alveolar hyperventilation (so as to "remove" CO_2 respiratory drive), rhythmic breathing continued if the subjects remained awake, but apnoea developed during sleep or anaesthesia.

In 1978, Phillipson and Sullivan emphasised the importance

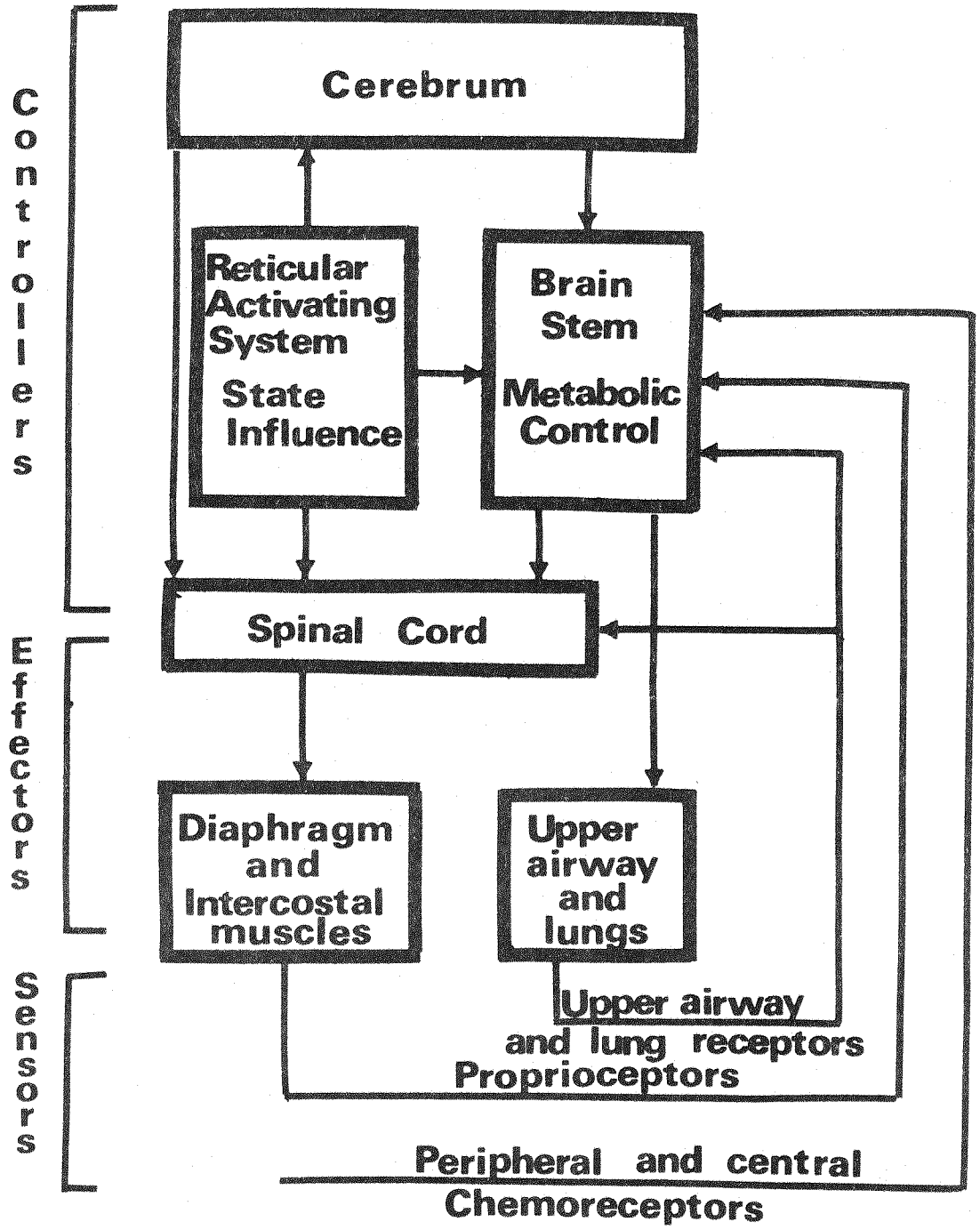


Fig. 4 - Diagram to stress the critical role of arousal (redrawn from Phillipson, 1978).

of arousal which may produce a fundamental change in the nature of the ventilatory response to a respiratory stimulus; arousal permits the initiation of a behavioural and a ventilatory response to the stimulus and it makes possible an appropriate integrated response to respiratory stimuli that includes behavioural as well as ventilatory, cardiovascular and other adjustments.

Phasic behavioural activities that involve the ventilatory apparatus, such as phonation, crying, swallowing and laughing, also exert a profound effect on ventilation through the behavioural respiratory control system. Under such conditions there are marked changes in the pattern of breathing from the regular, cyclic patterns typical of quiet breathing to highly irregular patterns that are dictated by the requirements for the behavioural event. In addition, during such activities, the behavioural control system is capable of overriding completely the metabolic demand for ventilation.

Rigatto, Kalapesi, Leahy, Durand, MacCallum and Cotes, in 1980, studying preterm infants during sleep, not only confirmed the observations of Phillipson et al (1978) who showed that behavioural control can override the chemical control of breathing, but suggested that the opposite is also true, i.e. the chemical control can also override the behavioural control within a certain range. Administration of low inspired CO_2 was enough to change the pattern of breathing of these infants, but not enough to

produce arousal. He also found that, in preterm infants, the hypercapnic response is prompt and effective, both during REM and non-REM sleep.

IV SENSORS

A Lung Receptors

a) Pulmonary stretch receptors - Hering and Breuer (1868) showed in the dog, cat and rabbit, that expansion of the lung reflexly inhibited inspiration and promoted expiration; this effect depended on the integrity of the vagus nerves. The stretch receptors believed to be responsible for this reflex lie predominantly in the bronchi and bronchioles. However, the reflex in man is relatively weak, being elicited only by inflations considerably larger than normal tidal volumes (Widdicombe, 1961; Dejours, 1962; Guz, Noble, Trenchard, Cochrane and Makey, 1964). Bilateral vagal blockade in both anaesthetised and unanaesthetised man does not change the pattern of breathing (Guz, et al, 1964). It has been suggested that the ability of healthy subjects to hold their breath for longer times at higher lung volumes with more asphyxial arterial gas tensions is due to the inhibitory influence of the inflation reflex (Mithoefer, 1959), but Guz's results suggest that this explanation is inadequate since abolition of such a reflex, especially at the high lung volumes when it is active in man, would be expected to shorten rather than lengthen breath-holding time.

b) J receptors - Paintal (1955) has recorded action potential from vagal non-myelinated fibres coming from "specific deflation receptors" in the lungs, the juxta-capillary pulmonary receptors or J receptors. These receptors are close to the pulmonary capillaries and the physiological stimulus for the endings is believed to be the

rise in pulmonary capillary pressure that occurs during muscular exercise. Stimulation of type J receptors was reported to produce reflex inhibition of limb muscles. In the cat the reflex effects of such stimulation are apnoea, hypotension and bradycardia. This effect is called the J reflex and involves the participation of certain cerebral pathways located centrally.

c) Lung irritant receptors - have been studied in rabbits by recording action potentials from the receptors (Widdicombe, 1954). These receptors are stimulated by strong inflations and deflations of the lungs, pneumothorax, pulmonary congestion, the inhalation of ammonia vapour or cigarette smoke, pulmonary micro embolism, anaphylactic reactions, and bronchoconstriction induced by injections of histamine and phenyl diguanide. It was concluded that the reflex action of the receptors is to cause hyperpnoea and probably broncho-constriction and that these receptors may contribute to unpleasant respiratory sensation in human subjects and patients.

Nadel and Gold (1973) suggested that histamine release during an allergic asthmatic attack stimulates irritant receptors, resulting in reflex bronchoconstriction and increased ventilation.

B Peripheral chemoreceptors - the peripheral arterial chemoreceptors are responsible for the immediate increase in breathing produced by lack of oxygen (Biscoe, 1971). They are located in the carotid bodies at the bifurcation of the

common carotid arteries and in the aortic bodies scattered about the ascending arch of the aorta and its branches. Their sensitivity to changes in arterial partial pressure of oxygen (PaO_2) begins around a PaO_2 of 500mmHg, but the ventilatory responses are negligible until arterial unsaturation develops. The relationship between ventilation and arterial oxygen saturations is linear (Rebuck and Campbell, 1974),

Chemoreceptor discharge of the carotid sinus nerve is increased by decreased PaO_2, decreased pH, or increased arterial carbon dioxide partial pressure ($PaCO_2$)(Lahiri and DeLaney, 1975). The aortic body chemoreceptors also respond to decreased PaO_2 and increased $PaCO_2$, but they are not stimulated and sometimes are depressed by decreased pH (Sampson and Hainsworth, 1972).

Increases in chemoreceptor activity in response to decreased PaO_2 are potentiated by increases in $PaCO_2$ or in the carotid body by decreased pH. This potentiation, which is also reflected in the amplified ventilatory response to combined hypoxia and hypercapnia, does not exclude the possibility that part of the ventilatory potentiation is mediated by the respiratory centre (Lahiri and DeLaney, 1975).

C Central chemoreceptors - the ventilatory responses to increases in alveolar carbon dioxide remains almost unaltered after denervation of the peripheral chemoreceptors. In recent years considerable evidence has accumulated that central chemosensitivity does not arise from brainstem respiratory neurons, but from separate chemoreceptor

structures located near the ventral medullary surface. It acts as the primary sensor of the level of carbon dioxide within the body, through the acidification of brain extracellular fluid by carbon dioxide. The chemical environment about the receptors is governed by CSF, local blood flow and metabolism (Mitchell and Herbert, 1974).

D UPPER AIRWAYS RECEPTORS.

The airways of the nose possess receptors whose afferent pathways lie in the trigeminal and olfactory nerves. These receptors are sensitive to various chemical agents and mechanical stimulation.

The trachea also possesses irritant receptors. As with laryngeal stimulation, tracheal stimulation results in coughing, bronchoconstriction and hypertension.

V Control of frequency and tidal volume - Rohrer, in 1925 (quoted by Otis, Fenn and Rahn, 1950 and by Mead, 1960)was the first to show that the respiratory work would be least if a particular frequency of breathing was followed. This was rediscovered by Otis et al in 1950. Mead, in 1960, presented evidence that the respiratory frequency of two species, guinea-pig and man, corresponds more closely to one at which the average force or tension developed by the respiratory muscles rather than the work done by them on the respiratory system, is minimum.

In 1966, Hey, Lloyd, Cunningham, Jukes and Bolton, studied the effects of various respiratory stimuli (changes

in $PACO_2$ and PAO_2, metabolic acidaemia, some drugs, and muscular exercise) on the depth and frequency of breathing in man. The linear relationship between pulmonary ventilation ($\dot{V}E$) and tidal volume (VT) up to a VT equal to about half the vital capacity was unchanged. When the stimulus was a rise in body temperature, however, Hey et al found that it affected the parameters of the $\dot{V}E$-VT relationship.

This work fitted well with the idea that the balance between the depth and frequency of breathing is geared to some principle of minimum force or work.

There are two known mechanisms which determine the tidal volume and frequency for a given ventilation: one is the bulbo-pontine pacemaker (the bulbar apneustic and pneumotaxic centres) and the other is the vagal mechanism. The first one seems to be the main frequency governor, both in eupnoeic man and in various conditions of polypnoea in animals. The vagal mechanism is governed by afferent information on volume, rate of change of volume and transmural pressure of the lungs (Breuer, 1868; Adrian, 1933; Larrabee and Knowlton, 1946; Davis, Fowler and Lambert, 1956). The integrity of the vagus nerves has been reported to be a prerequisite for the increase in respiratory frequency which normally occurs both in man and in animals in response to increased chemical drive of respiration (Scott, 1908; Cohen, 1964; Nesland, Plum, Nelson an Siedler, 1966; Guz, Noble, Widdicombe, Trenchard, Mushin and Makey, 1966; Tang, 1967; Richardson and Widdicombe, 1969).

The studies of von Euler, Herrero and Wexler (1970) in cats, showed that the increase in ventilation in response to CO_2 was achieved by an increase in both tidal volume and frequency. In agreement with the studies obtained by Hey et al (1966), when ventilation was plotted against VT, the relation was found to be roughly linear and above a value of approximately half the vital capacity a further increase in $\dot{V}E$ was almost entirely accomplished by an increase in frequency, while VT remained almost constant.

When the $\dot{V}E$-VT line was extrapolated to zero, the line did not go through the origin but showed an intercept with the VT axis and the $\dot{V}E$-VT relationship was expressed by the equation:

$\dot{V}E = k(VT-Vo)$, where K is the slope and Vo the intercept.

After vagotomy the slope was less steep, the intercept Vo became zero (f remained constant when $\dot{V}e$ increased) and the further increase in f at about half vital capacity was abolished.

When $\dot{V}E$ was plotted against frequency the relation was not linear; on the lower portion $\dot{V}E$ increased faster than f and at about half vital capacity the curve suddenly changed. It was concluded that below this bend a rise in $\dot{V}E$ was effected by increments, both in VT and in f, while at the upper part of the curve, further increases in $\dot{V}E$ were achieved by increasing the frequency.

CHAPTER TWO

CHAPTER TWO

I. EVALUATION OF THE RESPIRATORY CENTRE OUTPUT

Since the early work of Haldane and Priestley (1905) the most commonly used output variable has been pulmonary ventilation, but it has long been recognised that there are some limitations of ventilation as a measure of the motor output of the respiratory centre which relates to its dependence on lung and chest wall mechanics.

Because of this problem other measurements have been used to evaluate the respiratory centre output, such as the oxygen consumption of the respiratory muscles, the mechanical work rate of the respiratory muscles and the diaphragmatic EMG. These methods will be reviewed:

A. Oxygen cost of breathing - if oxygen consumption is measured at rest and again at increased ventilation the excess of oxygen consumed should be due to respiratory muscular activity. Richards, Fritts and Davis (1958) calculated work output by measuring the oxygen uptake at each level of ventilation in response to different inhaled CO_2 concentrations and they concluded that the diminished ventilatory response in patients with emphysema and CO_2 retention was largely due to the increased effort required to ventilate the lungs. But they did not take into account the mechanical efficiency of the respiratory muscles and a reduction in efficiency would require increased oxygen

consumption for the same workload and therefore increased neural drive.

In 1960 Brodovsky, MacDonell and Cherniack calculated total respiratory muscle work from the oxygen uptake and the mechanical efficiency of the respiratory muscles measured separately. Increased levels of ventilation were achieved by interposing dead space consisting of thick-walled rubber tubing. Measurements of ventilation, oxygen consumption and PCO_2 were made at rest and at three levels of increased ventilation. The oxygen cost of increased ventilation was calculated by plotting oxygen consumption against minute ventilation and drawing the best fitting straight line. The efficiency was obtained by measuring the increase in oxygen consumption associated with an added respiratory work load of known magnitude.

work done = efficiency X oxygen consumption
(Campbell, Westlake and Cherniack, 1959).

B. Mechanical work of breathing - another way of measuring work of breathing unrelated to oxygen consumption is by means of a diagram of pressure-volume relationships of the respiratory system (see Fig. 5).

The work done is the product of change in lung volume and the mean pressure during the breath. We have to consider the work done to overcome elastic forces and the work done in overcoming flow resistance.

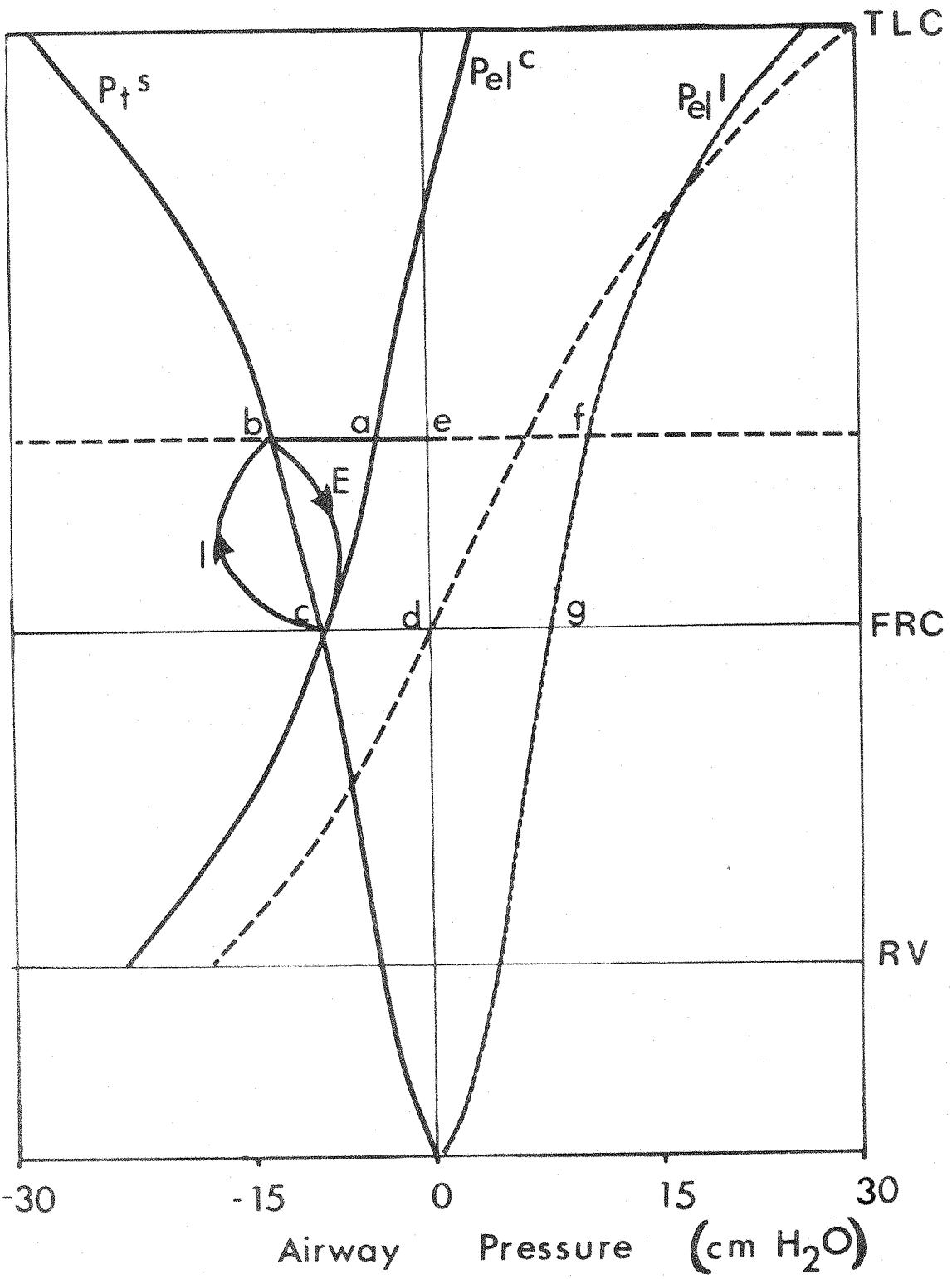


Fig. 5 - Relaxation pressure curve of the whole respiratory system divided into components - relaxation pressure curves of lung ($P_{el}{}^l$) and chest wall ($P_{el}{}^c$). The curve Pt^s is a mirror image of $P_{el}{}^l$. The loop cIbEc represents pressure and volume changes during inspiration in overcoming flow resistance, while the triangular area abc represents work done by the inspiratory muscles on elastic resistance (modified from Campbell, 1958).

Referring to the diagram (Fig. 5), the work done by the chest wall on the lung is the area of the trapezium a,c,e,d. The work done to expand the lung is the area of the trapezium d,e,f,g or e,d,c,b. The nett work done to overcome elastic recoil during inspiration in tidal breathing is the difference between the two trapeziums, the triangle a,b,c. But I already said that we have to consider the work done in overcoming flow resistance during inspiration and therefore a pressure volume loop must be measured dynamically = area c,I,b. Now we can derive the total work done on inspiration.

This analysis is due to Campbell (1958) and was applied firstly by Eldridge and Davis (1959), and further modified by Milic-Emili and Tyler (1963), who confined their measurements to inspiratory work, since they found that expiratory work was not correlated with arterial PCO_2 (see figure 5).

C. Diaphragmatic E.M.G. - Lourenço and Miranda, in 1968, measured the electromyographic activity of the diaphragm. The output from an oesophageal electrode at the level of the diaphragm was integrated electronically and the component derived from cardiac activity subtracted. Although this technique would seem to be independent of lung mechanics it measures the activity of only part of one of the respiratory muscles and uses complicated electronic apparatus. It is also affected in practice by problems of siting the oesophageal electrode.

D. $\underline{P_{0.1}}$ and dP/dt max - in 1973, Grunstein, Younes and Milic-Emili, occluded the airway of anaesthetised cats at FRC and measured the amplitude of tracheal pressure generated in the following inspiratory effort. The maximum inspiratory pressure achieved during inspiration was related to tidal volume and subsequently was shown that the maximum inspiratory pressure on occlusion of the trachea in cats was related to phrenic nerve discharge (Eldridge, 1975).

Clearly, it is impossible to apply this technique directly to conscious humans since voluntary influence interfere with the measurement. Whitelaw, Derenne and Milic-Emili (1975) argued that there would be a delay between the occlusion and the subject's recognition and reaction to it. They suggested the occlusion pressure developed at 0.1 sec after the onset of inspiration (P0.1) as an index of respiratory centre output.

Because the airway is occluded there is no airflow and the occlusion pressure should be independent of flow resistance, and as there is no change in lung volume it should also be independent of the compliance of the lungs and chest wall.

dP/dt max - Matthews and Howell (1975) in this department, measuring from a Y-t record the rate of change of pressure at the mouth when the inspiratory limb of a rebreathing circuit was occluded, at random by a tap, during the previous expiration, found that the spike which represented the differentiated pressure signal (dP/dt) was

occurring with every breath, due to the transient occlusion provided by the inspiratory valve. It was apparent that this spike increased progressively in height with increasing inspiratory effort and that the almost imperceptible transient occlusion of the airway by the inspiratory valve enabled dP/dt max to be recorded with every breath (Matthews, 1975).

dP/dt max represents the rate of isometric force development by the inspiratory muscles before flow occurs and is therefore unaffected by increased flow resistance, reflexes related to increasing lung volume and proprioceptive feedback mechanisms. The response of dP/dt max to CO_2 correlates well with the ventilatory response, but is not reduced by the addition of an external flow resistance (Matthews and Howell, 1975).

II METHODS OF INCREASING RC OUTPUT

A. Steady state method - the subject breathes a gas mixture containing different concentrations of CO_2 to achieve a steady state. After 10 to 15 minutes ventilation is measured and at the same time PCO_2 is measured in arterial blood or alveolar air. The ventilation and arterial blood or alveolar PCO_2 are compared with the values obtained at rest.

The relationship between these variables is shown by curve B in figure 6. Curve B is the typical relationship for a normal man breathing air containing 0%, 3%, 5% and 7% carbon dioxide. Curve B expresses the steady-state relationship between ventilation and $PaCO_2$. Each carbon dioxide mixture was inspired for approximately 10 minutes

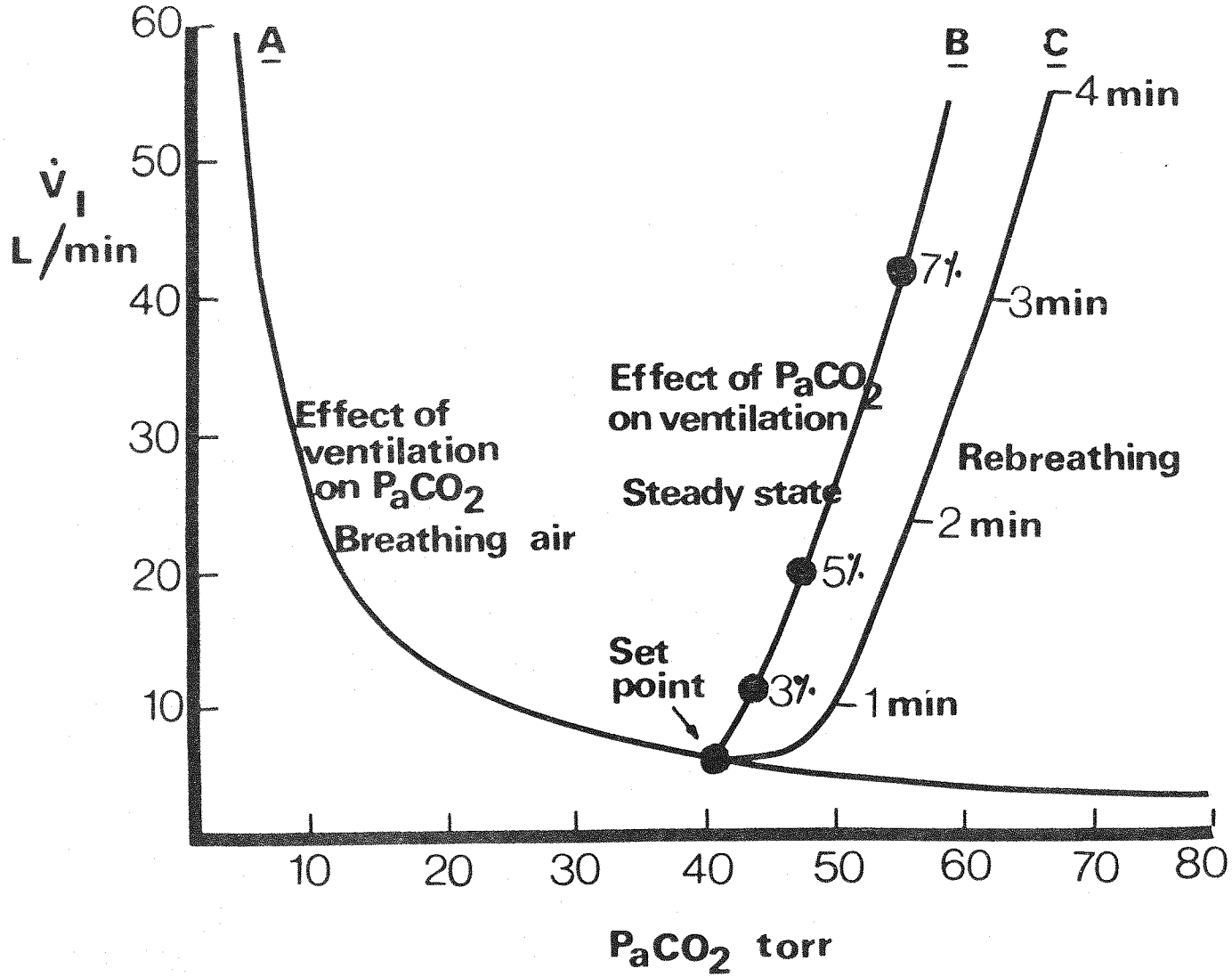


Fig. 6 - Metabolic Hyperbola.
(redrawn from Berger et al, 1977).

before the experimental data were taken. This is sufficient time to permit carbon dioxide to come to its new steady state value at the site of the central chemoreceptors. It is the slope of the ventilatory response in the linear portion of curve B that is conventionally reported as the carbon dioxide sensitivity. This sensitivity may be measured if the subject breathes carbon dioxide in air, but it is probably best to measure this variable with carbon dioxide in a hyperoxic mixture since the slope of the carbon dioxide response curve is increased by hypoxia about doubling at PaO_2 of 40 torr (Kronenberg, Hamilton, Gabel, et al, 1972)(fig 6).

B. Rebreathing Method - a rebreathing method has been developed by Read (1967) which overcomes many of the disadvantages of the steady state method.

Although rebreathing had been used by Haldane at the end of the last century and has been used sporadically since then, it had not been accepted as the method of choice because the patient is not in a steady-state and the relationship between the gas, blood and receptor PCO_2 is uncertain. The latter objection was overcome by Read (1967) who initiated rebreathing with a gas containing CO_2 at a PCO_2 close to the PCO_2 of mixed venous blood. He also provided a small volume of gas (less than 10 litres) for rebreathing and, under these conditions, PCO_2 equilibrium rapidly develops between mixed venous, alveolar gas and rebreathing bag gas. A high initial concentration of oxygen in the rebreathing bag

provides oxygen for metabolism and prevents the development of any hypoxic stimulus to ventilation.

Both the end tidal PCO_2 and ventilation increase continuously and can be plotted against each other at intervals during rebreathing. This produces the conventional plot of ventilation against PCO_2.

The method is rapid and simple, it does not require arterial samples and is therefore suitable for studies made on patients.

It was shown by Read (1967) that the ventilatory responses obtained by rebreathing and by the steady state differed significantly in position but not in slope, and Clark (1968) confirmed the validity of this method for patients with chronic airways obstruction.

The rebreathing method rapidly attains "open loop" conditions; by this it is meant that there is no feed-back from response to stimulus so that the rate of rise of PCO_2 is unaffected by the increased ventilation. On rebreathing ventilation is responding to a rapidly and progressively changing input signal, the magnitude of which is conveniently provided by the end tidal PCO_2.

III REPRODUCIBILITY OF VENTILATORY RESPONSE TO CO_2.

Differences in opinion on this subject are expressed in the earlier literature. Peabody in 1915 (quoted by Schaefer, 1958) and Scott (1920) found that variations can be found in the respiratory responses in any given individual on different days, not only between different individuals. Padget (1928), however, found that the same individual has the same reaction when tested at different times, but different individuals have quite different responses.

Heller, Killiches and Drinker (1929) supported Padget's statement. Their paper demonstrates in several figures the large differences between "high level performers" and "low level performers". They conclude in their paper that "the cause of difference (in the CO_2 responses) resides in some very fundamental feature of the organisation of the individual".

Schaefer (1958) showed that the "fundamental feature" related to the large individual differences in the response to CO_2 is the respiratory pattern of the individual. The respiratory pattern is defined as the relationship between respiratory rate and tidal volume.

When tests were repeated on 8 subjects under the same conditions, after intervals of approximately 4 weeks and 4 months, Schaefer found that the respiratory response to CO_2 was fairly constant during this time.

After that he studied several subjects after an interval of 5-6 years and found that, in general, the subjects remain in their groups.

Read, in 1967, established the reproducibility of the ventilatory response to CO_2. The reproducibility of serial response curves was compared for the rebreathing technique and the traditional steady state method, using the data of Anderton, Harris and Slawson (1964), and he found a similar reproducibility between the two methods.

Clark, in 1968, studying the ventilatory response to CO_2 in chronic airways obstruction measured by the rebreathing method found that this method is repeatable with a coefficient of variation of about 10% in patients.

In view of the suggestion that inter-individual variability in the ventilatory response to CO_2 may be due to genetic differences, Arkinstall, Nirmel, Klissouras and Milic-Emili, in 1974, studied thirty pairs of twins and he concluded that the variability in the ventilatory response to inhaled CO_2 can be attributed to environmental rather than genetic factors. However, the variability in tidal volume response to CO_2 was largely determined by genetic factors. The frequency response to CO_2 appeared to be affected by the personality of the subjects.

In 1976, Irsigler, studying 126 normal young adults, found an excellent short-term reproducibility of results in 111 subjects, and good longer-term reproducibility in most of 10 subjects retested 9 to 27 months later. Rebuck, in 1976, recognised the variability in the ventilatory response among normal human subjects and suggested three factors which could be responsible for this: the first is the size of the

ventilatory pump, as expressed by the vital capacity. The second, and possibly the most important, is the proportion of the available vital capacity which is chosen by the respiratory control system as tidal volume. Third, the influence of increasing frequency on the ventilatory response to CO_2 is also important.

In view of the known influence of wakefulness on respiratory control mechanisms (Bulow, 1963), Rigg, Inman, Saunders, Leeder and Jones, 1977, decided to test the possibility that mental factors may alter the ventilatory response to hypercapnia. Mental arithmetic tasks were performed by healthy adults during air breathing to investigate their effects on ventilation, and the results showed that task performance increased ventilation, both during air breathing and rebreathing, by increasing the frequency of breathing.

CHAPTER THREE

CHAPTER THREE

I The Apparatus for measuring ventilatory and dP/dt max response to CO_2 during rebreathing (see fig. 7).

A 6 litre rubber rebreathing bag was suspended in a perspex chamber. The bag was connected by low resistance tubing to a valve and mouthpiece assembly (see Appendix 1 - Resistance of the circuit). A light spring loaded disc valve (P.K. Morgan 71522) provided a brief occlusion to each inspiratory and expiratory manoeuvre. The opening pressure of the inspiratory and expiratory disc valves was 1 cmH_2O and 0.5 cmH_2O respectively. (This system was based on the apparatus described by Matthews and Howell, 1975).

Changes in mouth pressure were measured using a UP2 transducer. This signal was amplified and differentiated (Robec 7752 dP/dt Amplifier - Robec 7751 Pressure-DC Amplifier), in order to obtain rate of change of pressure during the transient occlusion.

Carbon dioxide (CO_2) levels at the mouthpiece were continuously sampled and end-tidal PCO_2 measured using a rapid reading infra-red CO_2 analyser (Capnograph LB-2 Medical Gas Analyser). The sampled gas was returned from the Capnograph to the rebreathing circuit to prevent loss of

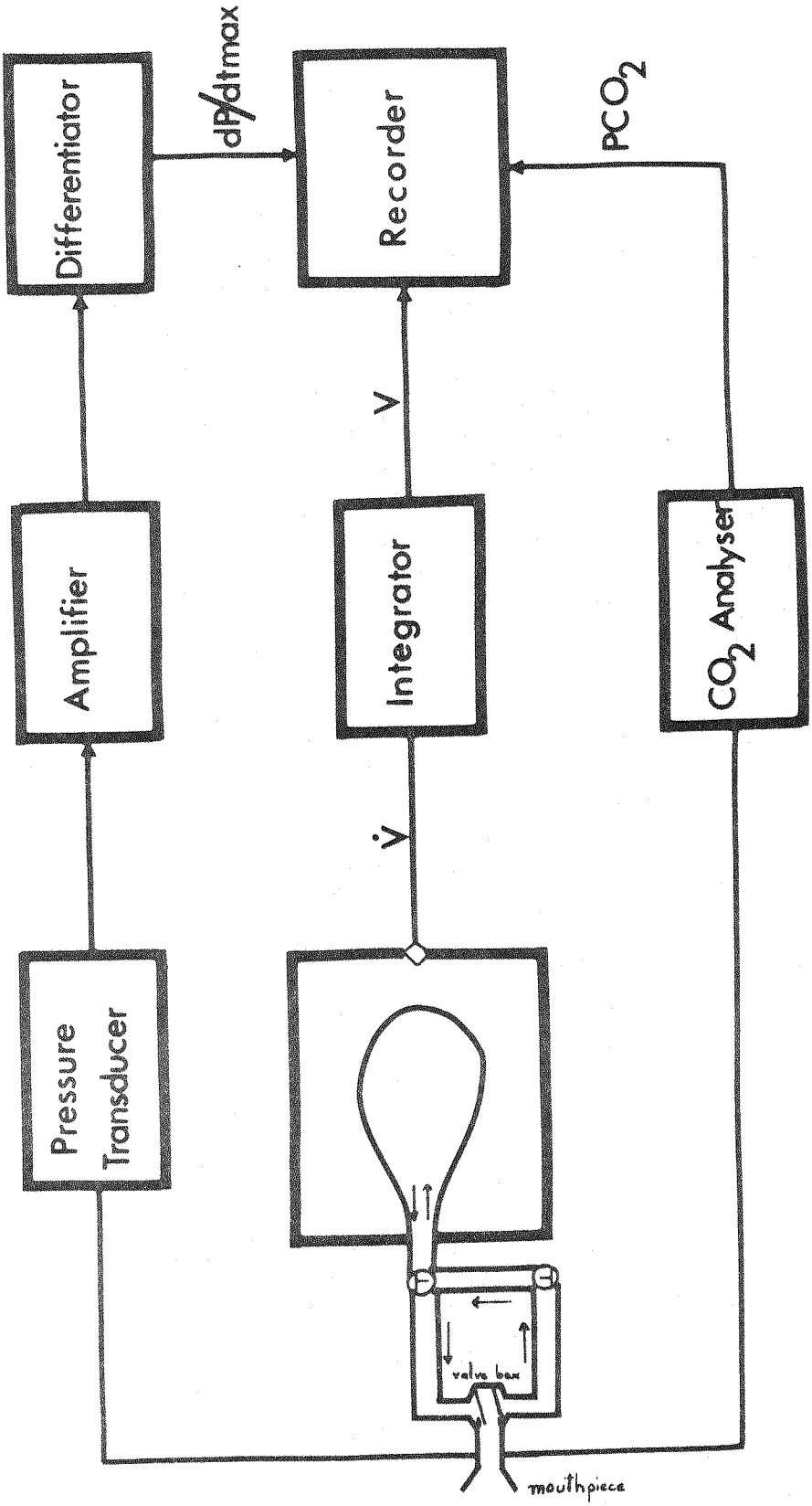


Fig. 7 - Apparatus for CO_2 rebreathing and measurements of the indices of response.

volume. The sampling flow rate used was 0.5 litres/minute.

Ventilatory flow was measured by means of a pneumotachograph fitted into one wall of the perspex chamber. Inflation and deflation of the rebreathing bag inside the chamber resulted in movement of ambient air out of and into the chamber respectively. Tidal volume was obtained by integration of this flow signal (Electro spirometer CS5 Mercury).

Data were recorded using a 4 channel Gould Brush 440 Recorder at a paper speed of 1mm/sec.

CALIBRATION

The mouth pressure transducer was calibrated in cmH_2O by means of an inclinometer (water manometer), before each experiment.

A sinusoidal pressure wave, generated by a piston pump, was then applied to the mouth pressure transducer and the resultant wave form was differentiated giving a trace of rate of change of pressure. By calculating the rate of change of pressure from the pressure trace it was possible to calibrate the differentiated signal (see fig. 8).

The method of this calibration was as follows: from the pressure wave form (a) the maximum rate of change of pressure at the point indicated by line (x) can be related, having previously calibrated the pressure transducer and

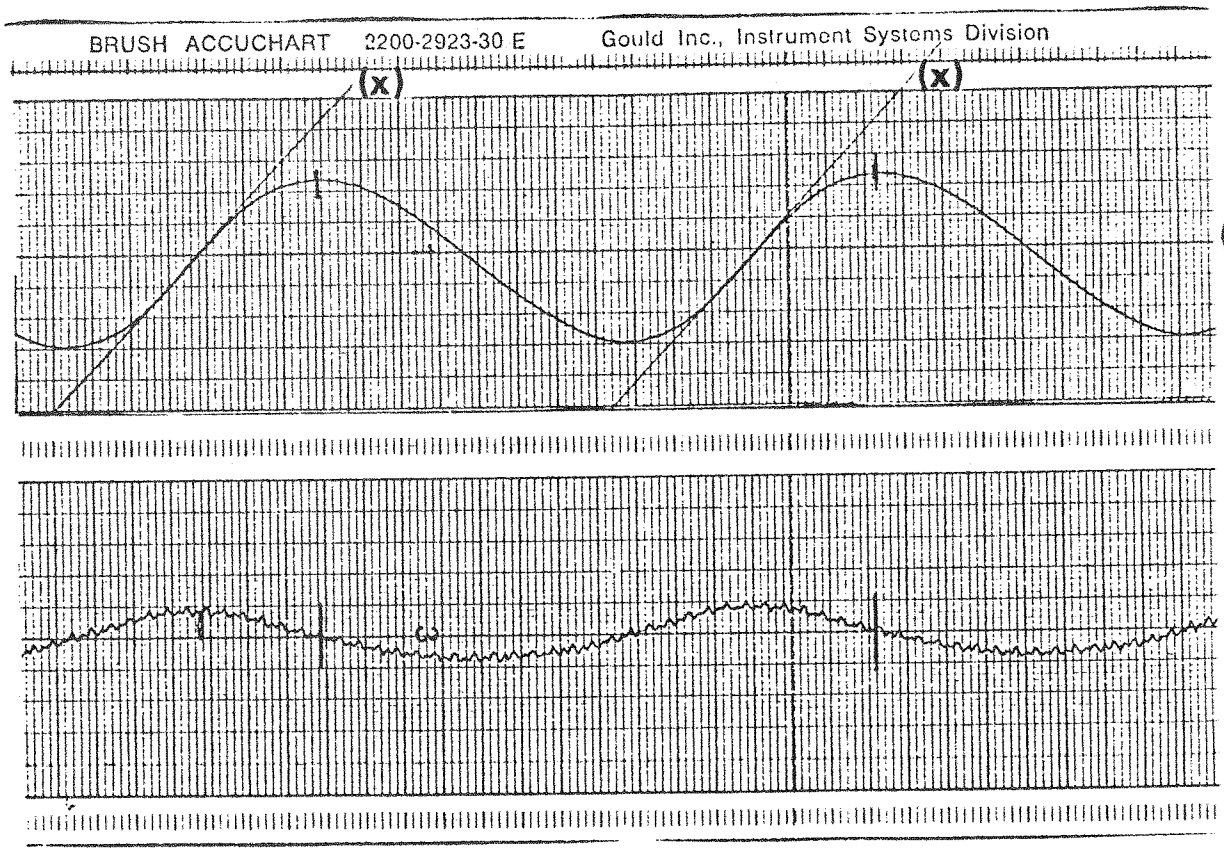


Fig. 8 - Calibration for dP/dt max (see text)

knowing the speed of the paper drive (see Appendix 1 - Frequency response of transducer). The result of this calculation can then be applied to the deflection of the differentiated signal (trace b) and this signal can then be calibrated in terms of cmH_2O/sec^{-1}.

CO_2 Analyser - the Capnograph was calibrated before each experiment using CO_2-free air and three CO_2 concentrations (5%, 7.07%, 9.73%). The CO_2 concentrations were analysed using the Lloyd Gas Analyser apparatus. Replicate measurements were required to agree within 0.05% of error. The response was not linear and for each experiment a graph was plotted as shown below (fig. 9) from which the CO_2 concentration corresponding to a deflection could be determined.

Ventilation - the pneumotachograph was calibrated using a 1 litre syringe, such that the integrated output of flow, i.e. volume, gave a known deflection on the chart recorder. (see Appendix 1 - Calibration for Volume).

II Data Analysis

Ventilation - was measured at approximately 15-20 second intervals by the slope of the volume "staircase".

All results were corrected to body temperature according to the data of Cotes, 1979.

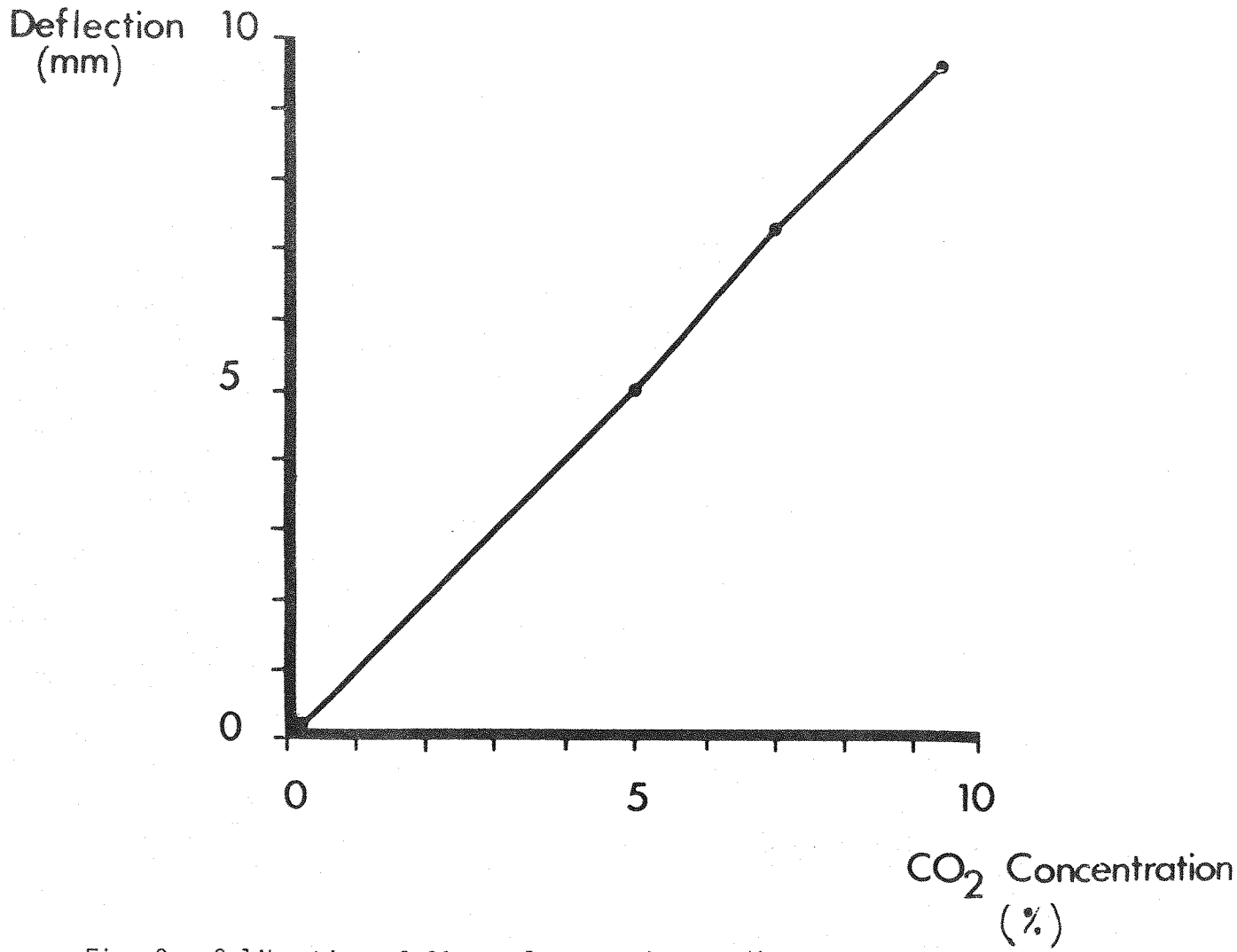


Fig. 9 - Calibration of CO_2 analyser and recording.

The mean dP/dt max - over the same interval as used for the measurement of ventilation (usually 15 to 20 sec), the mean deflection of the trace was calculated by adding the individual deflections and dividing by the number of deflections, and the calibration factor was then applied (see page 53).

Carbon dioxide - CO_2 concentration was measured at 15-20 second intervals by measuring the deflection and reading the corresponding CO_2 concentration from the calibration curve (see fig. 9). This value was converted to partial pressure in mmHg and in kPa.

Respiratory frequency - was calculated by measuring the number of breaths that occurred over the same time interval as for the other measurements.

Mean tidal volume - was calculated by using the equation:

$$\frac{\text{ventilation}}{\text{frequency}}$$ also over the same time interval

Inspiratory and expiratory time (Ti and Te) - was measured directly from the volume trace in breath-by-breath analysis.

III Procedure.

The subject, wearing a nose-clip and breathing through a mouthpiece to air, sat quietly for ten minutes and was then switched into the rebreating circuit which contained

approximately 4-6 litres of 7% CO_2:93% O_2 (Read, 1967).

It is known that the bag size is not critical, but there are limits within which its volume should range (Clark, 1968). Too large a bag delays equilibrium as mixing between bag and lungs is slow, and a too small bag causes the bag to empty during inspiration before rebreathing finishes. Four to six litres of the CO_2 mixture is found to represent a reasonable compromise; the volume being sufficient to allow rapid mixing and equilibration without being exceeded by the tidal volume during hypercapnia (Clark, 1968).

Also, the initial CO_2 concentration in the bag is not critical. A 7% concentration is close to that of mixed venous blood in normal resting subjects and a rapid equilibrium occurs followed by a constant rate of increase of PCO_2 (Fowle and Campbell, 1964).

Recordings were made of ventilation, end tidal CO_2 (PCO_2) and dP/dt max as shown in figure 10.

When the subjects indicated discomfort or when the CO_2 had reached 10%, the experiment was terminated.

IV PRELIMINARY RESULTS AND THEIR CONSEQUENCES

In the initial stage of this study, while becoming familiar with the methodology in making measurements of the ventilatory and other responses to CO_2, measurements were made on 4 subjects: these consisted of 4 individuals (1

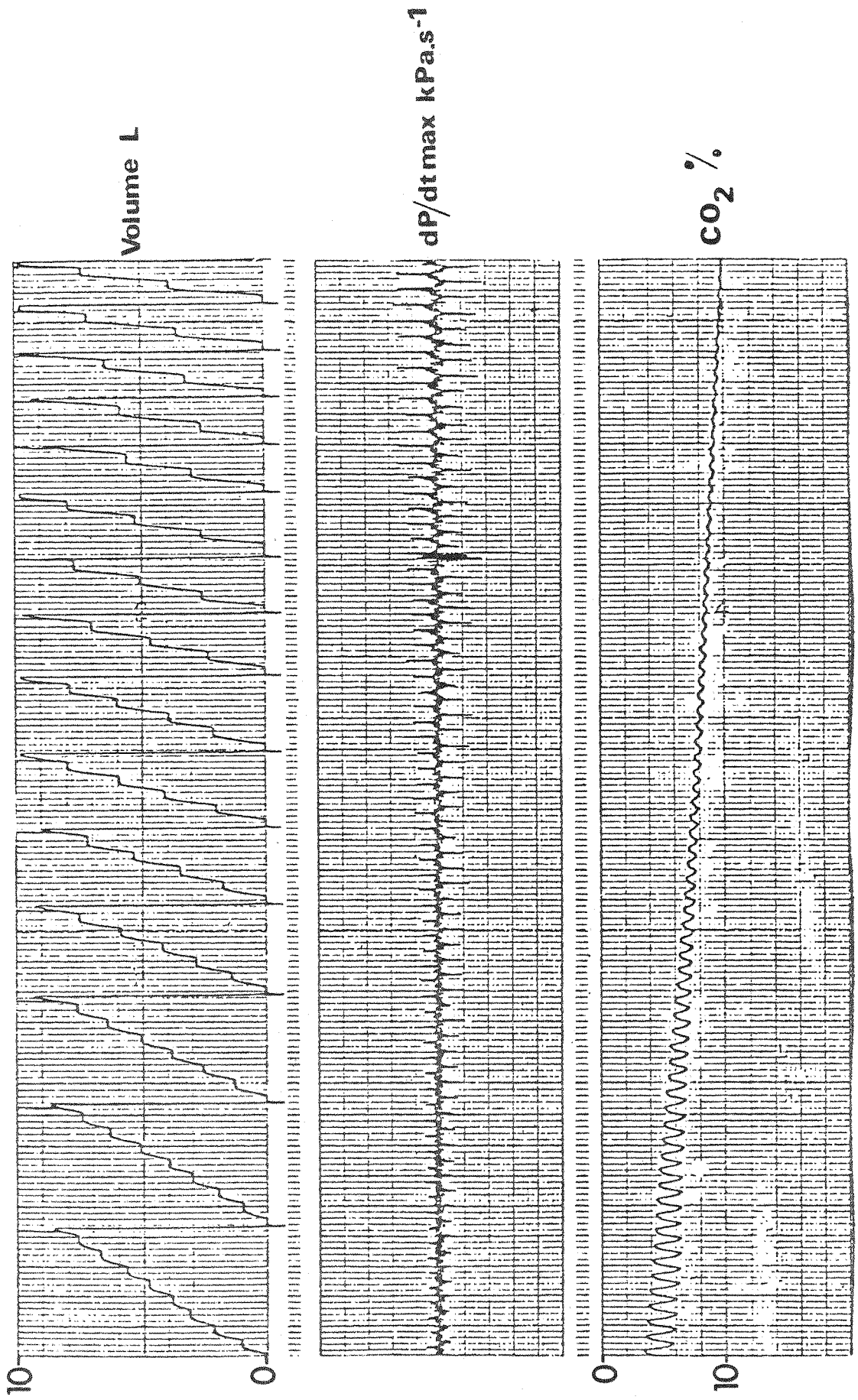


Fig. 10 - Record of CO_2 rebreathing experiment. Stepwise inspired volume is top trace, dP/dt max is the middle trace and end-tidal CO_2 (%) the bottom trace. The trace reads from left to right.

female, 3 male) who were unfamiliar with the procedures involved in respiratory measurements. The results shown in figures 11,12,13 and 14 were obtained.

Compared with results of previous studies in this laboratory, there was a wide scatter of the results relating PCO_2 and the variables of $\dot{V}E$, dP/dt max, VT and f. Because the same equipment was being used and the same procedures were being followed as for the previous studies, the most likely explanation was considered to be that external factors such as anxiety, unfamiliarity etc, were influencing the responses of the untrained subjects.

Because in trained subjects the correlation between these variables was usually much greater, it was hypothesised that measurement of the degree of scatter might provide quantitative information about these external influences. From inspection of the results dP/dt max response appeared to have less variability than the $\dot{V}E$ response.

It was therefore planned to study a larger number of subjects and to repeat the measurement in each subject on at least two occasions.

It had been noted that these four subjects appeared to be anxious to varying degrees during the procedure. It was therefore planned to make an assessment of the mental state of the subject, i.e. did he/she appear to be anxious or relaxed during each subsequent procedure. Because of the

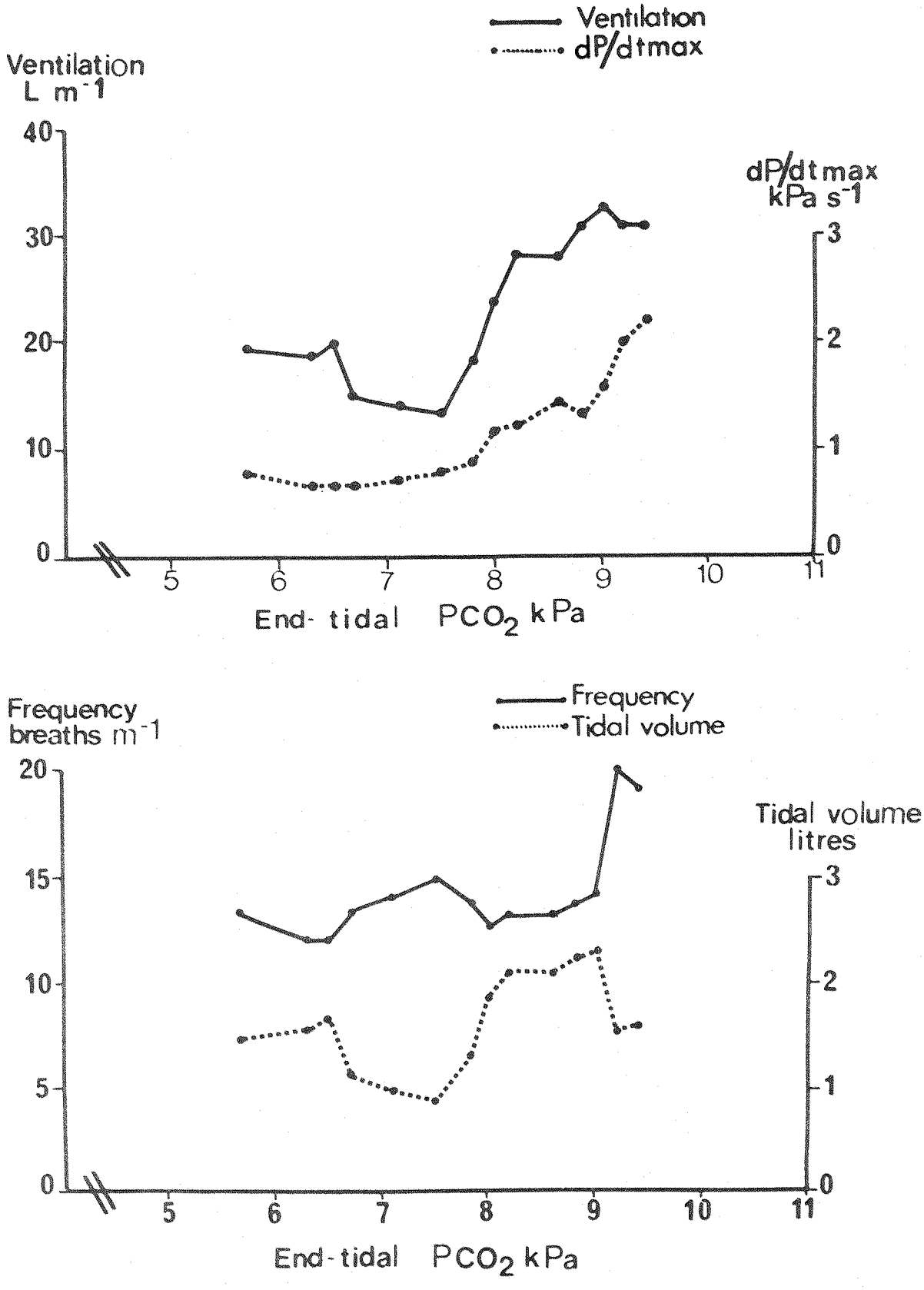
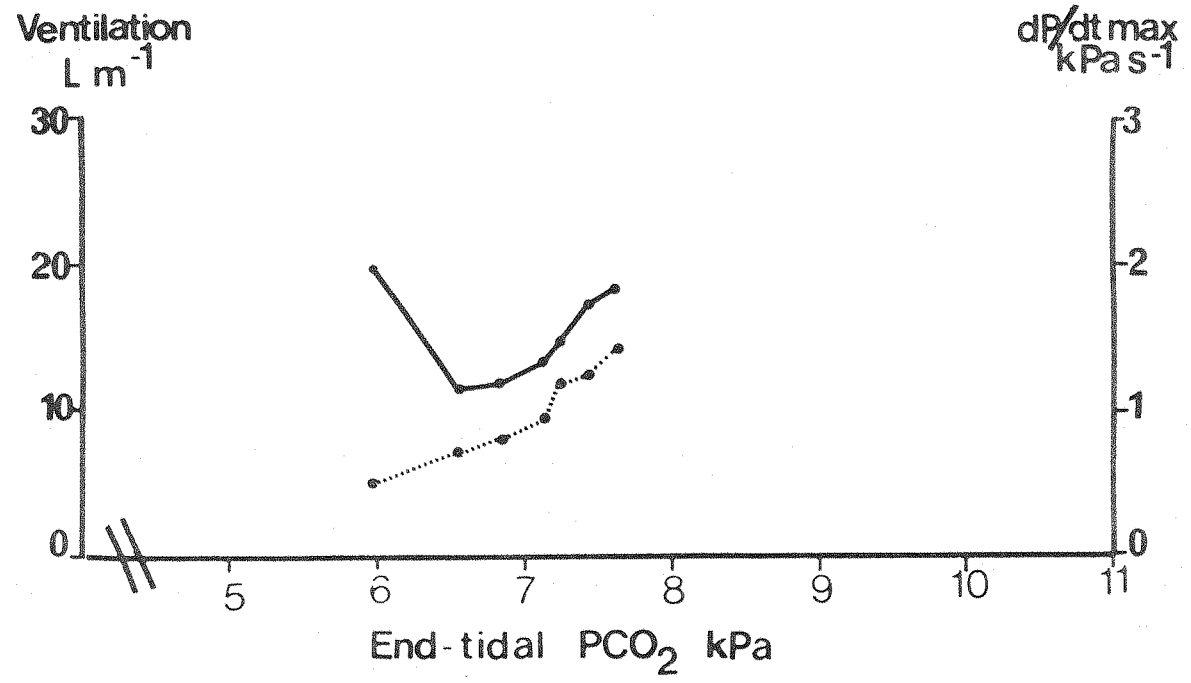


Fig. 11 - Graphs of $\dot{V}E/PCO_2$, dP/dt max/PCO_2, f/PCO_2 and VT/PCO_2. The symbols for $\dot{V}E$, dP/dt max, f and VT are the same for figs. 11, 12, 13, 14.



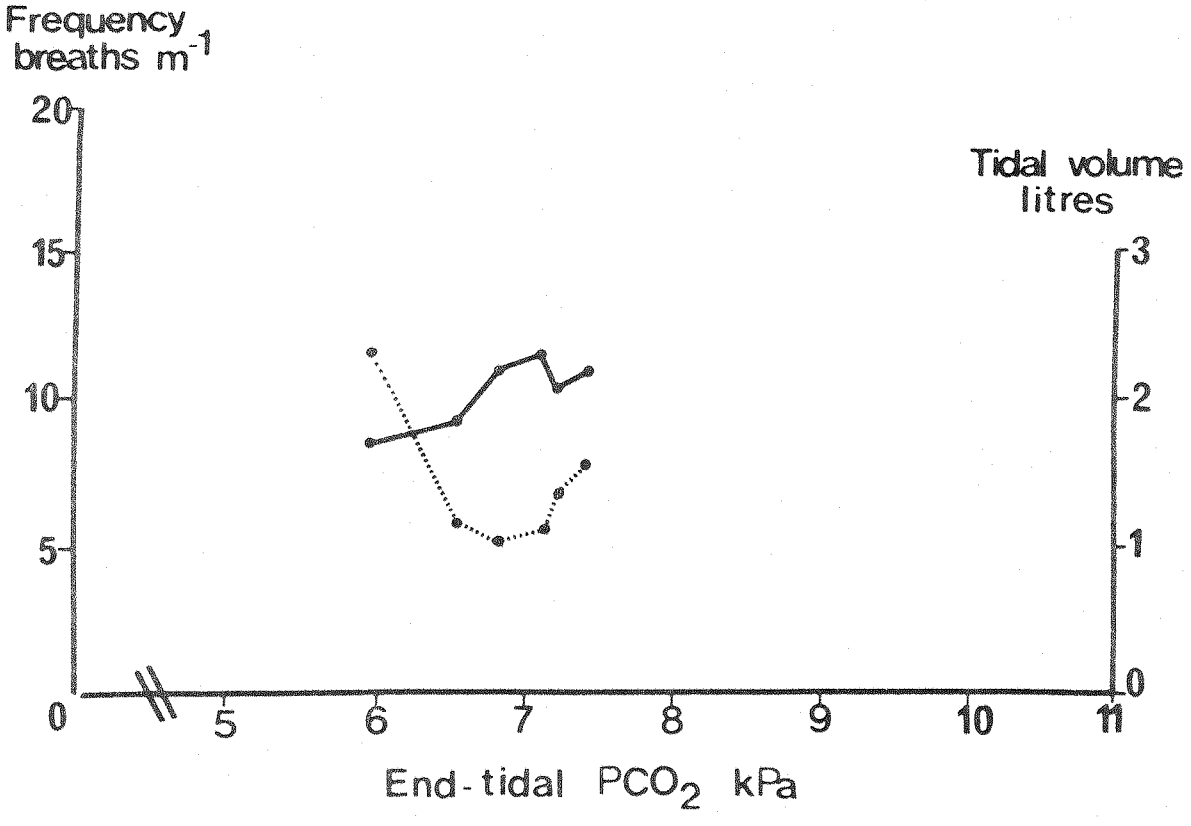
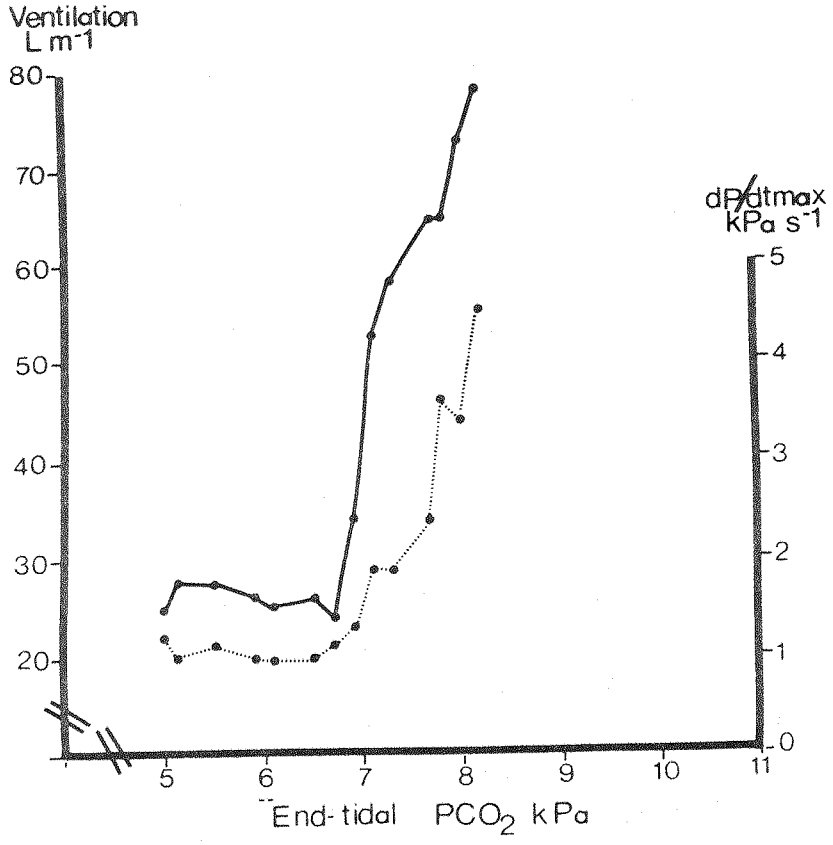


Fig. 12. (see legend page 59).



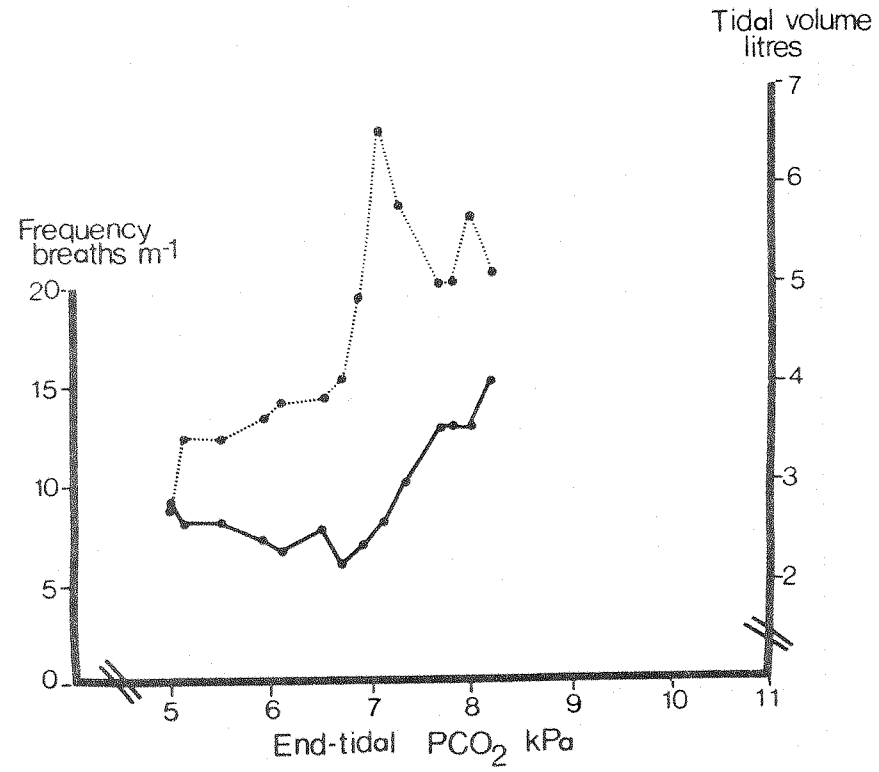
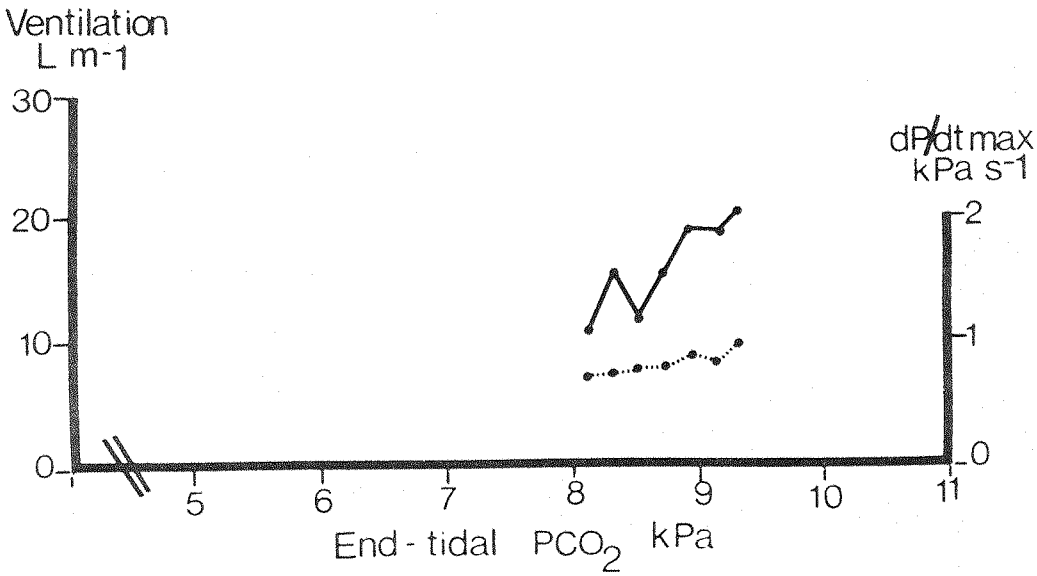


Fig. 13. (see legend page 59).



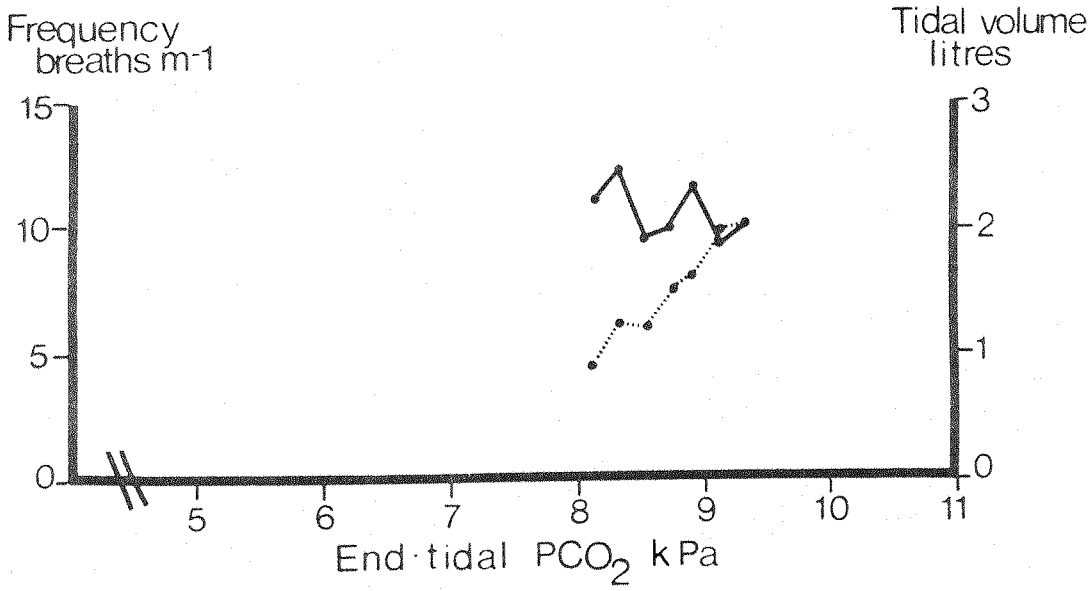


Fig. 14. (see legend page 59).

necessarily subjective nature of this assessment it was later decided to make an objective assessment of the personality of the subject using an established questionnaire (Crown-Crisp Experimental Index, 1979) (Appendix 2), even though it was recognised that this would not necessarily reflect the state of the subject at the time of the experimental procedure.

V MAIN STUDY

The same procedure, as described on page 55 for the preliminary result, was followed for a group of 15 subjects which included the 4 whose results are shown in the "Preliminary Results" above.

Each subject underwent the experiment either on the same day or on different days, according to the availability or personal convenience of the subject. It had been hoped to standardise the replication of the measurements more closely but this proved to be impossible. Table 1 gives details of the 15 subjects studied.

Because of the hypothesis that anxiety or other psychological factors were influencing the results, an attempt was made to assess the mental state of the subjects at the time of the studies. Two types of assessment were attempted. Firstly, my personal judgement of the degree of anxiety or relaxation during the

Table 1 - Details of Subjects

Subject	Age (yrs)	Sex	Weight Kg	Height cm	FEV_1 l	(Pred) *	FVC l	(Pred)	FEV_1/ FVC%	Experience on respiratory measurements	
M.T.	21	M	69.0	1.82	4.68	4.65	5.86	5.90	79.86	-	Technician
M.D.	35	F	68.0	1.64	3.92	2.68	4.35	3.52	79.19	-	Secretary
N.G.	37	M	61.0	1.65	4.05	3.80	4.95	4.35	81.80	-	Oceanographer
O.M.	29	M	67.5	1.73	3.75	3.90	5.40	5.05	69.44	-	Oceanographer
J.A.	36	M	78.0	1.85	4.70	4.72	5.60	5.70	83.90	-	Pathologist
F.M.	40	M	90.0	1.80	3.85	4.35	4.75	5.25	81.05	-	Pathologist
D.G.	31	M	74.5	1.76	3.96	4.05	4.98	5.22	79.51	+	Technician
N.M.	26	F	50.0	1.62	3.45	2.74	3.86	3.62	89.37	-	Engineering
C.G.	34	F	56.0	1.63	2.85	2.90	3.85	3.80	74.02	-	Secretary
T.T.	26	F	55.0	1.60	3.30	3.00	3.80	3.65	78.90	-	Student
P.B.	23	M	76.0	1.82	5.07	4.05	5.73	5.85	88.48	-	Technician
A.A.	31	M	80.0	1.76	3.35	4.40	5.35	5.20	62.61	-	Student
A.R.	20	F	58.0	1.68	3.50	3.45	4.10	4.00	85.30	-	Student
E.G.	26	F	51.0	1.53	3.00	2.78	3.35	3.23	89.50	-	Student
A.M.	28	F	53.0	1.63	3.30	3.74	3.85	3.62	85.70	-	Doctor

* The predicted values were taken out from Kamburoff and Woitowitz (1973)

procedures and, secondly, the objective assessment of the personality of the subject using the questionnaire of Crown and Crisp (CCEI, 1979). This was administered some weeks after the experimental procedure, by sending the questionnaire and instructions for its completion by post to the subjects.

A copy of this questionnaire is given in Appendix 2.

The questionnaire is designed to quantify certain basic personality traits which would not have been expected to change during this time.

The reliability and validity of this questionnaire can be found in detail in the Manual of the CCEI (pages 8 and 9).

My subjects were all well-educated and well-motivated and I consider it reasonable to assume that their reliability in completing the questionnaire was not so different as to make them valueless.

The subjects were required to read the 48 questions in the CCEI, which are expressed in every day, non-specialist, informal, colloquial English, and to select those answers which are relevant to themselves. The questions in the CCEI are purposely not set down in autonomous groups, but split up with the wording and profile on the page varied as much as possible, in order to prevent the subjects seeing them as blocks and skimming through rather than really reading them. This random effect is designed so that each question differs,

at least apparently, from the others to ensure that all of them are read with attention. Restricting the answers to "yes" and "no" only has been avoided as far as possible, as it has been found that some people have a bias towards one or the other (Crown and Crisp, 1979). As many modifications or degrees of response as possible have therefore been introduced into the range of possible answers, such as "frequently", "sometimes", "never", "very", "a little", "not at all", or similar qualified responses. The proximity of extremes is carefully avoided so that answers such as "frequently" or "never" are represented fairly equally on both left and right.

It must be emphasised that according to the authors the CCEI should not be regarded as anything more sophisticated than a simple measurement of personality for use in research and screening. It seemed to be an appropriate test to apply under the circumstances of this study, compared with more complex tests such as the Minnesota Multiphasic Personality Inventory (MMPI).

The total score provided by the CCEI is considered to be a measure of the subject's emotional state, or "level of neuroticism", and includes a profile of six sub-scale scores. These measure, respectively, free-floating anxiety (FFA), phobic anxiety (PHO), obsessionality (OBS), somatic concomitants of anxiety (SOM), depression (DEP) and

hysterical personality (HYS), and each of these sub-scale dimensions is defined by 8 questions. The questions are arranged in such a way as to appear random to the subject who is therefore unable to analyse the aims of the tester to whom, in turn, their arrangement is systematic and meaningful.

The actual definitions of the 6 sub-scale dimensions are given as follows (Crown and Crisp, 1979):

Free floating anxiety (FFA) - the patient is afraid but, unlike normal fear, there is no discernible object of which he is afraid. FFA consists, therefore, of dread, indefinable terror, tension without a cause, or panic. The CCEI asks questions about feeling upset for no obvious reason, feeling faint, unease and restlessness, panicky feelings, worrying, being 'strung-up', 'going to pieces', having bad dreams.

Phobic anxiety (PHO) - the patient feels anxious in specific situations but, if these are avoided, he does not feel anxious. In the CCEI common phobias are asked about, such as of enclosed spaces, illness, going out alone, heights and crowds.

Obsessionality (OBS) - by obsessionality is meant an excessive meticulousness, adherence to routine, punctuality, dislike of sudden change, need to control the environment, tendency to over-check, dislike of dirt. The CCEI asks

questions about common obsessional traits, such as over conscientiousness, cleanliness, recurrence of silly or unreasonable thoughts, love of routine, perfectionism, checking, worry about things that do not matter.

Somatic anxiety (SOM) - the somatic concomitants of anxiety include breathlessness, headaches, other aches and pains. The CCEI asks questions about dizziness, shortness of breath, digestive upsets, bodily tingling or pricking sensations, appetite loss,tiredness and exhaustion, sleep disturbance, sweating and palpitations, alterations of sexual interest.

Depression (DEP) - depression means sadness of mood, difficulty of actions and activity. The CCEI asks about slowing of thinking process, feeling that life is an effort, regret about past behaviour, waking early in the morning, feeling sad, having to make a special effort to cope, the need to cry, loss of interest and sympathy for other people.

Hysteria (HYS) - by hysterical personality traits the CCEI follows the definition in the Glossary of Mental Disorders (1968) - "individuals with shallow, labile, affectivity and over-dependence on others. These individuals crave love and attention, though being unreliable and unsteady in their personal relationships. Under stress they may develop hysterical symptoms. They tend to over-dramatise situations". CCEI questions are about

opinions being easily influenced, enjoyment of acting, excessive displays of emotion, liking of being the centre of attention, tendency to take advantage of circumstances for their own ends, excessive expenditure on clothes, enjoyment of dramatic situations, tendency to pose or pretend (Crown and Crisp, 1979).

VI RESULTS OF PSYCHOLOGICAL ASSESSMENT

The table below (table 2) shows the results of my personal assessment of the degree of relaxation or anxiety of the subjects during the experiment and the results of the Crown-Crisp Experimental Index.

I did not find a correlation between my own judgement about the presence or absence of anxiety and the results obtained by the questionnaire. This was confirmed by a Chi-square test which showed no significant difference at 0.05%, just at 0.5%

The sub-scale of the questionnaire which should correspond most closely to my own assessment was the FFA (free floating anxiety). Only 3 of the 15 subjects analysed by myself as anxious had FFA assessment in the questionnaire.

Four subjects analysed by myself as anxious did not have a high score for FFA in the questionnaire.

On the other hand, 4 subjects whom I had considered as relaxed during the experiment had a high score on the FFA

Table 2.

Results of Crown-Crisp Experimental Index.

Subjects	FFA	PHO	OBS	SOM	DEP	HYS	Personal assessment of the degree of relaxation of anxiety during the experiment.	
							first time	second time
1	No	No	No	No	No	No	anxious	anxious
2	No	Yes	No	No	No	No	relaxed	relaxed
3	Yes	No	Yes	Yes	Yes	Yes	anxious	relaxed
4	No	No	No	No	No	No	anxious	anxious
5	No	No	Yes	No	No	No	relaxed	Not available on this occasion
6	No	No	No	No	No	Yes	anxious	relaxed
7	Yes	No	No	No	Yes	Yes	relaxed	relaxed
8	Yes	No	No	No	Yes	Yes	relaxed	relaxed
9	No	Yes	Yes	No	No	Yes	relaxed	relaxed
10	Yes	Yes	No	No	No	No	relaxed	relaxed
11	No	No	No	No	Yes	No	anxious	relaxed
12	Yes	No	No	No	No	Yes	anxious	anxious
13	No	No	Yes	No	No	No	relaxed	relaxed
14	Yes	No	No	No	Yes	Yes	relaxed	relaxed
15	Yes	No	Yes	No	Yes	Yes	anxious	relaxed

sub-scale.

RESULTS OF THE CO_2 REBREATHING

Graphs of the results of individual subjects are contained in Appendix 3. Tables 3 and 4 summarise the results obtained in the first and second study respectively.

These results were obtained by averaging individual breaths over 15-20 seconds.

Analysis of slopes - most of the authors who have studied ventilatory response to CO_2, and frequency and tidal volume response to CO_2 have assumed a normal distribution for slopes (see references on page 79). On the same assumption, I applied a paired t test to see if there was any significant difference between the slopes of the first and second study. The results showed that there was no significant difference at 0.05% level. For f/PCO, dP/dt max/PCO_2 and VT/PCO_2 the level was: 0.5>P>0,1, and for $\dot{V}E/PCO_2$ the level of significance was just P>0.5.

I also calculated the mean ($\tilde{x}$), standard deviation (SD) and coefficient of variation for these slopes and the results can be seen in Table 5.

Table 3

Subjects performing experiments for the first time.

Records analysed in averaging the results over 15-20 sec.

Values for correlation coefficient and slopes

	$\dot{V}E/PCO_2$	$\dot{V}E/PCO_2$	dP/dt max/ PCO_2	dP/dt max/ PCO_2	Frequency/ PCO_2	Frequency/ PCO_2	Tidal Volume/ PCO_2	Tidal Volume/ PCO_2
Subjects	"r"	"slope" $L.min^{-1}/kPa$	"r"	"slope" $kPa.s^{-1}/kPa$	"r"	"slope" $b.m^{-1}/kPa$	"r"	"slope" l/kPa
1	0.89	6.59	0.89	0.38	0.50	-1.29	0.90	0.90
2	0.80	5.45	0.97	0.36	0.39	0.82	0.65	0.32
3	0.82	5.84	0.96	0.42	0.02	-0.03	0.65	0.29
4	0.02	0.12	0.97	0.57	0.85	1.79	0.58	-0.51
5	0.95	8.18	0.90	0.31	0.07	-0.14	0.85	0.85
6	0.88	16.87	0.82	0.90	0.51	1.21	0.82	0.85
7	0.98	12.95	0.97	0.72	0.94	4.58	0.91	0.38
8	0.93	6.57	0.99	0.56	0.80	1.90	0.94	0.19
9	0.97	8.97	0.99	0.33	0.75	1.39	0.96	0.35
10	0.93	15.78	0.98	1.28	0.72	3.21	0.89	0.79
11	0.79	11.26	0.96	0.42	0.91	1.21	0.75	0.54
12	0.93	15.10	0.93	0.68	0.87	3.59	0.84	0.42
13	0.97	5.45	0.98	0.37	0.71	2.54	0.64	0.17
14	0.92	8.55	0.97	0.49	0.76	2.20	0.89	0.24
15	0.80	4.77	0.89	0.38	0.64	1.30	0.51	0.20

Table 4

Subjects performing experiments for the second time

Records analysed in averaging the results over 15-20 secs

Values for correlation coefficient and slopes.

	$\dot{V}E/PCO_2$	$\dot{V}E/PCO_2$	$dP/dt\ max/PCO_2$	$dP/dt\ max/PCO_2$	$Frequency/PCO_2$	$Frequency/PCO_2$	$Tidal\ Volume/PCO_2$	$Tidal\ Volume/PCO_2$
Subjects	"r"	"slope" $L.m.^{-1}/kPa$	"r"	"slope" $kPa.s^{-1}/kPa$	"r"	"slope" $b.m^{-1}/kPa$	"r"	"slope" $1/kPa$
1	0.59	1.82	0.81	0.27	0.48	-1.26	0.60	0.19
2	0.93	3.48	0.95	0.33	0.38	-0.48	0.90	0.26
3	0.92	11.12	0.94	1.10	0.63	1.69	0.76	0.36
4	0.88	7.98	0.97	0.53	0.77	2.26	0.44	0.33
5	--	--	--	--	--	--	--	--
6	0.77	7.49	0.84	0.47	0.88	1.45	0.50	0.19
7	0.97	8.76	0.92	0.66	0.77	2.97	0.84	0.27
8	0.95	5.89	0.99	0.51	0.79	2.15	0.70	0.14
9	0.98	12.02	0.99	0.73	0.90	4.00	0.97	0.60
10	0.95	14.80	0.98	1.29	0.91	4.71	0.69	0.39
11	0.95	12.32	0.99	0.81	0.95	3.95	0.52	0.17
12	0.91	10.63	0.95	0.26	0.58	1.40	0.91	0.33
13	0.96	6.45	0.99	0.47	0.60	2.52	0.73	0.22
14	0.95	8.43	0.98	0.74	0.81	2.14	0.85	0.28
15	0.99	15.63	0.96	1.25	0.57	1.69	0.83	0.29

Table 5.

Results of SD, $\bar{x}$ and coefficient of variation for the slopes of $\dot{V}E/PCO_2$, dP/dt max/PCO_2, f/PCO_2 and VT/PCO_2 in both studies.

	$\dot{V}E/PCO_2$ L.m^{-1}/kPa		dP/dtmax/PCO_2 kPa.s^{-1}/kPa		f/PCO_2 b.m^{-1}/kPa		VT/PCO_2 L/kPa	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd
$\bar{x}$	8.87	9.05	0.561	0.672	1.744	2.085	0.366	0.287
SD	4.87	3.98	0.264	0.339	1.482	1.617	0.353	0.116
Coef. of var.	54.9%	43.9%	47%	50.4%	84.9%	77.5%	96.4%	40.4%

VII DISCUSSION OF PSYCHOLOGICAL ASSESSMENT

As I mentioned before, I did not find any correlation between my own assessment of the subjects as anxious or relaxed during the experiment, and the results obtained in the CCEI, in the FFA sub-scale. One of the reasons for the lack of correlation between the two methods of assessment may have been due to the fact that the CCEI is analysing general traits of personality in day-to-day life, and I was assessing my subjects over a short period of time, in the specific situation of CO_2 rebreathing. However, this does not explain the discrepancy between my personal assessment of some subjects as being relaxed during the experiment, and their high score for anxiety in the questionnaire. The exception is subject number 7 who had

experience of respiratory measurements and despite having an anxious personality was able to be relaxed during the experiment.

I have to admit that my own assessment was based on overt anxious or relaxed behaviour, and hence my findings could be said to be, to some extent, subjective. The explanation for the high score for hysteria in the questionnaire (8 subjects) is probably related to the fact that this sub-scale also measures the sociability component of extraversion (Crown-Crisp, 1979). This was also found by Howell, Crown and Howell (1973) when studying a normal control group, university students who had a higher score for hysteria than industrial samples.

DISCUSSION OF CO_2 REBREATHING

In Tables 3 and 4, we can see that dP/dt max was the measurement which had the highest correlation coefficient of all the variables, $\dot{V}E$, VT and f when plotted against PCO_2. dP/dt max does not seem to be affected to the same degree as other variables by lack of familiarity with the equipment or by the anxiety displayed by some of the subjects.

Ventilation/PCO_2 had high values of correlation coefficients, but seemed to be more affected by some external factors such as anxiety and familiarity.

There was considerable variation between subjects in the f and Vt responses but the body appeared to be able to "stabilise" the $\dot{V}E/PCO_2$ responses even though f and VT varied widely.

When the subjects performed the experiment the second time, the $\dot{V}E/PCO_2$ relationship seemed to have higher values of correlation coefficient.

The high correlation coefficients which were found in the first study for dP/dt max were again seen in the second study, and for f and VT again there was considerable variation.

All of these comments are based on an impression derived from inspection of these results. A statistical analysis is required to quantify these results and provide support or otherwise for these impressions.

STATISTICAL ANALYSIS

It was not known if correlation coefficients were following a normal distribution. Two possible non-parametric tests of significance were considered, the Wilcoxon and the Mann-Whitney and the latter was chosen. Using this test I compared the "r" values in my data in the following way:

First studies - there was a significant difference at 0.01% level of probability between the "r" values of the regression between $\dot{V}E/PCO_2$ and dP/dt max/PCO_2. This

result supported my initial impression that dP/dt max was the measurement with the least variability. I also found significant results when I compared the "r" values of dP/dt max/PCO_2 with the "r" values of frequency and tidal volume on PCO_2, the "p" value being 0.0001 and 0.001 respectively.

Comparing the "r" values for the regressions of frequency and tidal volume upon PCO_2, using the same statistical method, this "p" value was just over 0.1. Nevertheless, inspection of the two columns (Table 3) shows that there were a greater number of low "r" values for f than for VT which might suggest that if more data were available a significant difference might emerge.

Second studies - analysing Table 4 I found that there was no significant difference between the "r" values of the regression of $\dot{V}E$ and dP/dt max on PCO_2 (p=0.12). When the "r" values of dP/dt max/PCO_2 were compared with the "r" values of f and Vt/PCO_2 the results were similar to the first study (p=0.0001 and p=0.0002 respectively). Inspection of the tables (3 & 4) suggested that this was due to an increase in the "r" values for $\dot{V}E/PCO_2$ in the second study and a decrease in the "r" values for dP/dt max/PCO_2. These impressions were therefore tested by a statistical analysis (see below).

As in the first study, there was no significant difference between the "r" values for the regression of VT

and f on PCO_2, (p=0.1%).

Comparison between the first and second studies - the next comparison to be made was between "r" values on the first and second occasion for each of the following regressions, $\dot{V}E/PCO_2$, dP/dt max/PCO_2, VT/PCO_2 and f/PCO_2. There was no significant difference at 0.05% level between the "r" values for any of these variables. Although I had the impression that $\dot{V}E$ was less influenced by external factors during the second study (page 76), this was not statistically significant at 0.05% level. Similarly, the "r" values of dP/dt max/PCO_2 were not significantly different in the two studies (p=0.8%).

There was an apparent discrepancy in these results because one might have expected that because there was a difference between the "r" values of $\dot{V}E/PCO$ and dP/dt max/PCO_2 on the first occasion and not on the second, there would be a difference between the "r" values of $\dot{V}E/PCO_2$ on the first and second occasions or for the "r" values of dP/dt max/ PCO_2 on the two occasions. That no such differences were found is probably due to the scale of the study being too small to allow differences to emerge statistically. Although it did not reach the level of statistical significance, analysis of individual data for $\dot{V}E/PCO_2$ (Tables 3 & 4)) suggests that differences did exist.

Variability of frequency response- The majority of previous studies quoted in the literature (see below) seems to demonstrate that frequency is the most variable parameter of the ventilatory response to CO_2, although some authors have found more variability in tidal volume. For example, in 1974, Arkinstall et al, studying genetic difference in the ventilatory response to inhaled CO_2 concluded that while the variability in this ventilatory response could be attributed to environmental rather than genetic factors, the variability in the tidal volume response to CO_2 was largely determined by genetic factors. He concluded that the variance in the frequency response to CO_2 was strongly influenced by environmental factors and that this environmental difference obscured the genetic effect on the tidal volume response to CO_2. The frequency response to CO_2 appeared to be affected by the personality of the subjects and this effect of personality, at least partially, would explain the apparent strong influence of environmental factors on the frequency response to CO_2.

Rigg et al, in 1977, studying the interaction of mental stress (mental arithmetic) with hypercapnic ventilatory drive in man, found that these factors caused an increase in ventilation by increasing the frequency of breathing. These conclusions were similar to those of Gautier (1969) who found during steady state measurements of ventilation that

changes in ventilation associated with reading tasks were due to changes in f. By contrast, changes in ventilation associated with chemical stimuli were largely due to changes in VT.

VIII. ASSESSMENT OF NON-CHEMICAL INFLUENCES ON THE RESPIRATORY RESPONSE TO CO_2

There are two variables in each of the indices of sensitivity of response to CO_2 - one is the level of PCO_2 and the other is the measured response $\dot{V}E$, dP/dt max, VT and f. It is reasonable to assume that these latter variables are the dependent variables and the PCO_2 the independent variable because under the circumstances of the experiment, while changing PCO_2 will influence the response, the response will have minimal effect upon the PCO_2.

When the Y values (dependent variable) obtained in an experiment are plotted against the corresponding X values (independent variables), the trend of the plotted points may be linear, but the plotted points will not necessarily fall precisely on any line that we might draw to represent the trend. The problem is to find a line of best fit that relates to Y and X. This line is called the regression line of Y and X. The method of calculating the regression line ensures that it is drawn through the points in such a way as to give the smallest possible value to the sum of the squares of the difference between the actual observations and the corresponding values predicted from the line. No other line drawn through the points could make the sum of the squared errors of the estimates

have a smaller value, so that on this criterion our estimates are the best possible (the method of "least squares"). The equation of this line is:

$$Y' = a + b.X \text{ (regression equation)} \qquad (1)$$

where a = intercept; b = regression coefficient

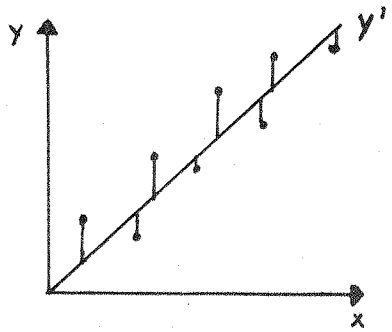
b may be calculated from the formula

$$b = \frac{\Sigma xy}{\Sigma x^2} = \frac{\Sigma(X-\bar{X})(Y-\bar{Y})}{\Sigma(X-\bar{X})^2} = \frac{\Sigma XY-(\Sigma X)(\Sigma Y)/n}{\Sigma X^2 - \frac{(\Sigma X)^2}{n}} \qquad (2)$$

and $a = \bar{Y} - b.\bar{X}$

Then $Y' = \bar{Y}-b.\bar{X} + b.X$ (by subsequent substitution of a in (1)).

Now, looking at the diagram below:



The line Y' will no longer necessarily be equal to the observed value of Y corresponding to an observed value of X, if the relationship between Y and X is not perfect. The value of Y' can be regarded as a prediction of the observed value of Y for the corresponding value of X. Then an error of prediction will be given by:

$$Y - Y' = Y - (a + bX)$$

These deviations of Y from Y' are shown by the vertical lines

in the diagram above.

The residual sum of squares will be:

$$\Sigma (Y-Y')^2 = \Sigma\{ Y-(a+bX)\}^2$$

An error of prediction will also be given by

$$Y-Y' = (Y-\bar{Y}) - b(X-\bar{X})$$

substituting $y = Y-\bar{Y}$

$x = X-\bar{X}$ in the equation above we have:

$$Y-Y' = y - b.x$$

Squaring and summing we have:

$$\Sigma (Y-Y')^2 = \Sigma y^2 - 2b\Sigma xy + b^2\Sigma x^2$$

But $b = \frac{\Sigma xy}{\Sigma x^2}$ (2) and substituting in the equation above we have

$$\Sigma (Y-Y')^2 = \Sigma y^2 - \frac{(\Sigma xy)^2}{\Sigma x^2} \qquad (3)$$

The residual sum of squares measures the variation in Y that cannot be accounted for by a linear relationship. Instead of measuring the variation in Y values in terms of their deviations from the mean of the Y values, the residual sum of squares measures the variation of the Y values from the corresponding predicted values given by the regression equation. The sum of squared deviations from the regression line $\Sigma(Y-Y')^2$ will be smaller than $\Sigma(Y-\bar{Y})^2$ if there is any linear relationship between X and Y. It is the second variable X that makes the regression line and $\Sigma(Y-Y')^2$ meaningful.

If we divide the residual sum of squares by n-2 (degrees

of freedom) we obtain the residual variance:

$$s^2_{Y.X} = \frac{\Sigma(Y-Y')^2}{n-2} = \frac{\Sigma y^2 - (\Sigma xy)^2/\Sigma x^2}{n-2} \qquad (4)$$

The residual variance is a measure of the scatter of the measured values around the regression line. The square root of the residual variance is the standard error of the estimate. This value is a measure of the variability of Y values which are not explained by the regression of Y and X.

But the values for PCO_2 are themselves not fixed but subject to variability, likely to be of a normal distribution, and under these circumstances it is legitimate to express the relationship between the two variables in terms of a correlation cofficient, assuming them to be linearly related. If PCO_2 is plotted on the X axis and the other variables always plotted on the Y axis, the relationship in which we are concerned is the regression of Y on X. It can be shown that the standard error of the estimate of the regression of Y on X

$$= \sqrt{\frac{\Sigma(Y-Y')^2}{n-2}} = S_{Y.X}$$

and X on Y $= \sqrt{\frac{\Sigma(X-X')^2}{n-2}} = S_{X.Y}$

These two regression lines are not the same unless the means and standard deviations of the X and Y variables are identical. The degree of relationship which is present is

given by the correlation coefficient (r). This r is defined as the ratio of the covariance of X and Y ($\Sigma(X-\bar{X})(Y-\bar{Y})/n-1$) and the product of the standard deviations of the X and Y variables

$$r = \frac{C_{XY}}{S_X S_Y} \qquad (5)$$

where C = covariance and S = standard deviation

This can also be expressed by:

$$r = \frac{\Sigma xy}{\sqrt{\Sigma x^2}\sqrt{\Sigma y^2}}$$

or

$$r = \frac{\Sigma(X-\bar{X})(Y-\bar{Y})/(n-1)}{\sqrt{\frac{\Sigma(X-\bar{X})^2}{n-1}}\sqrt{\frac{\Sigma(Y-\bar{Y})^2}{n-1}}}$$

or $$r = \frac{\Sigma XY - (\Sigma X)(\Sigma Y)/n}{\sqrt{\Sigma X^2 - (\Sigma X)^2/n}\ \sqrt{\Sigma Y^2 - (\Sigma Y)^2/n}}$$

It has already been shown that the regression coefficient b can be expressed as

$$b_Y = \frac{\Sigma xy}{\Sigma x^2} \qquad (2)$$

and also $$b_Y = \frac{C_{XY}}{S^2_X}$$

but $$C_{XY} = r.S_X.S_Y$$

Then $$b_Y = \frac{r.S_X.S_Y}{S^2_X} = \frac{r\ S_Y}{S_X}$$

and $$b_X = r\frac{S_X}{S_Y}$$

That is why only if the standard deviations of the X and Y variables are identical we also have $b_Y = b_X$ and then both b_Y and b_X will be equal to r.

When the two regression coefficients are multiplied we obtain

$$b_X b_Y = r \frac{S_X}{S_Y} \quad r \frac{S_Y}{S_X} = r^2$$

and $r = \sqrt{b_X b_Y}$

It was shown before that

$$\Sigma(Y-Y')^2 = \Sigma y^2 - \frac{(\Sigma xy)^2}{\Sigma x^2} \qquad (3)$$

If we multiply both the numerator and the denominator of the last term on the right by ΣY^2 we obtain:

$$\Sigma(Y-Y')^2 = \Sigma y^2 - \frac{(\Sigma xy)^2 \ (\Sigma y^2)}{(\Sigma x^2) \ (\Sigma y^2)} \qquad (4)$$

We know that

$$r2 = \frac{(\Sigma xy)^2}{(\Sigma x^2)(\Sigma y^2)} \qquad (5)$$

Then: $\Sigma(Y-Y')^2 = \Sigma y^2 - r^2 . \Sigma y^2$

or $\Sigma(Y-Y')^2 = \Sigma y^2(1-r^2)$

The residual variance will be:

$$S^2_{Y.X} = \frac{\Sigma y^2(1-r^2)}{n-2} \qquad (6)$$

But Y may be regarded as made up of two components Y' (the predicted component) and Y-Y', the error component.

The variance of the error component Y-Y' is shown above (6) and for the predicted component Y':

$$Y' = \bar{Y} + b_Y(X-\bar{X})$$

But $\bar{Y}' = \bar{Y}$

Then for the variance of Y' we have:

$$\frac{\Sigma(Y'-\bar{Y})^2}{n-1} = \frac{b_Y^2 \Sigma(X-\bar{X})^2}{n-1} = b^2_Y S^2_X$$

or $S^2_{Y'} = r^2 . \frac{S^2_Y}{S^2_X} \ S^2_X = r^2 S^2_Y$

Provided n is sufficiently large for n-1/n-2 to approach 1, then

$$S^2_{Y.X} = S^2_Y (1 - r^2)$$

Thus, if n is large, variance of the observed Y values can be assumed to consist of the sum of variance of the two components Y' and Y=Y' or

$$S^2_Y = S^2_{Y'} + S^2_{Y.X}$$

The sum of the two ratios $\frac{S^2_{Y'}}{S^2_Y} + \frac{S^2_{Y.X}}{S^2_Y}$ will approach 1.

i.e. $\frac{S^2_{Y'}}{S^2_Y} = r^2 =$ proportion of variance predicted from X

$\frac{S^2_{Y.X}}{S^2_Y} = 1-r^2 =$ proportion of variance independent of X

Because $r^2_{XY} = r^2_{YX} = r^2$, the value of r^2 may be interpreted as the proportion of the variance that X and Y have in common and $1-r^2$ as the proportion not shared by X and Y.

r^2 is sometimes known as the coefficient of determination and $1-r^2$ as the coefficient of non-determination (Edwards, 1976).

$1-r^2$ as a measure of external factors would only give a proportion. This would allow comparison of external factors influencing different types of response with different units of measurement (for example, comparison between $\dot{V}E/PCO_2$ response with dP/dt max/PCO_2 response).

$1-r^2$ gives no indication of the magnitude of the influence of external factors upon the variables being studied. This would require inclusion of the actual variance, i.e. $(1-r^2).\Sigma y^2$. Tables 6 & 7 gives such an analysis and while this is of interest when the influence of external factor is being assessed upon the same variable studied on different occasions, i.e. $\dot{V}E/PCO_2$ on first and second time, it would not apply to the comparison between different variables and therefore I have restricted the comparison to that between $1-r^2$ only.

A RESULTS

Table 8 shows the results of this analysis ($1-r^2$) for the variables $\dot{V}E$, dP/dt max, f and VT upon PCO_2 during the first and second occasion of the CO_2 rebreathing.

The differences between the results may be appreciated more easily when they are displayed as frequency-distribution graphs (see figures 15 & 16).

B DISCUSSION

My first hypothesis was that the relationship of dP/dt max on PCO_2 was the least influenced by non-chemical factors. This is confirmed in this analysis of ($1-r^2$) since this variable has the lowest percentage not due to regression when compared with the other variables, i.e. $\dot{V}E$, f and VT. Applying

Table 6.

Results of residual variance for $\dot{V}E$, dP/dt max., f and Vt upon PCO_2 on the first occasion.

Subjects	$\dot{V}E/PCO_2$ $L.m^{-1}/kPa$	dP/dt max/PCO_2 $kPa.s^{-1}/kPa$	f/PCO_2 $b.m^{-1}/kPa$	Vt/PCO_2 L/kPa
1	16.42	0.009	5.4	0.036
2	127.58	0.058	30.3	1.131
3	246.43	0.242	19.5	1.558
4	69.90	0.037	1.6	0.738
5	37.83	0.119	22.5	1.453
6	1232.30	0.473	90.4	5.063
7	28.85	0.128	8.7	0.086
8	108.43	0.141	33.5	0.085
9	25.65	0.017	3.9	0.057
10	369.32	0.621	78.2	1.281
11	301.55	0.056	1.1	0.894
12	151.05	0.370	16.0	0.268
13	12.91	0.061	62.5	0.386
14	216.48	0.211	57.9	0.230
15	225.16	0.691	44.5	1.929

Table 7.

Results of residual variance for $\dot{V}E$, dP/dt max., f and VT upon PCO_2 on the second occasion.

Subjects	$\dot{V}E/PCO_2$ $L.m^{-1}/kPa$	dP/dt max/PCO_2 $kPa.s^{-1}/kPa$	f/PCO_2 $b.m^{-1}/kPa$	Vt/PCO_2 L/kPa
1	26.53	0.161	17.7	0.223
2	25.38	0.202	16.1	0.194
3	432.43	2.708	198.3	1.424
4	75.11	0.075	9.8	1.712
5	-	-	-	-
6	401.30	0.002	4.7	0.879
7	33.43	0.554	32.7	0.163
8	33.87	0.052	21.3	0.145
9	42.99	0.072	4.3	0.181
10	153.62	0.428	23.0	0.811
11	106.79	0.066	8.8	0.429
12	270.54	0.072	36.7	0.199
13	23.53	0.022	82.4	0.403
14	39.87	0.098	10.9	0.242
15	75.97	0.784	79.7	1.487

Table 8.

Results of $(1-r^2)$(proportion of the variance not accounted for by regression) on the first and second occasions, for the variables $\dot{V}E/PCO_2$, $dP/dtmax/PCO_2$, f/PCO_2 and VT/PCO_2.

	$\dot{V}E/PCO_2$		$dP/dtmax/PCO_2$		frequency/PCO_2		tidal volume/PCO_2	
Subjects	first time	second time	first time	second time	first time	second time	first time	second time
1	20.7%	65.1%	20.7%	34.3%	75.0%	76.9%	19.0%	64.0%
2	36.0%	13.5%	5.9%	9.7%	84.7%	85.5%	57.7%	19.0%
3	32.7%	15.3%	7.8%	11.6%	99.9%	60.3%	57.7%	42.2%
4	99.9%	22.5%	5.9%	5.9%	27.7%	40.7%	66.3%	80.6%
5	9.7%	-	19.0%	-	99.5%	-	27.7%	-
6	22.5%	40.7%	32.7%	29.4%	73.9%	22.5%	32.7%	75.0%
7	3.9%	5.9%	5.9%	15.3%	11.6%	40.7%	17.1%	29.4%
8	13.5%	9.7%	1.9%	1.9%	36.0%	37.5%	11.6%	51.0%
9	5.9%	3.9%	1.9%	1.9%	43.7%	19.0%	7.8%	5.9%
10	13.5%	9.7%	3.3%	3.9%	48.1%	17.1%	20.7%	52.3%
11	37.5%	9.7%	7.8%	1.9%	17.1%	9.7%	43.7%	72.9%
12	13.5%	17.1%	13.5%	9.7%	24.3%	66.3%	29.4%	17.1%
13	5.9%	7.8%	3.9%	1.9%	49.5%	64.0%	59.0%	46.7%
14	15.3%	9.7%	5.9%	3.9%	42.2%	34.3%	20.7%	27.7%
15	36.0%	1.9%	20.7%	7.8%	39.0%	67.5%	73.9%	31.1%

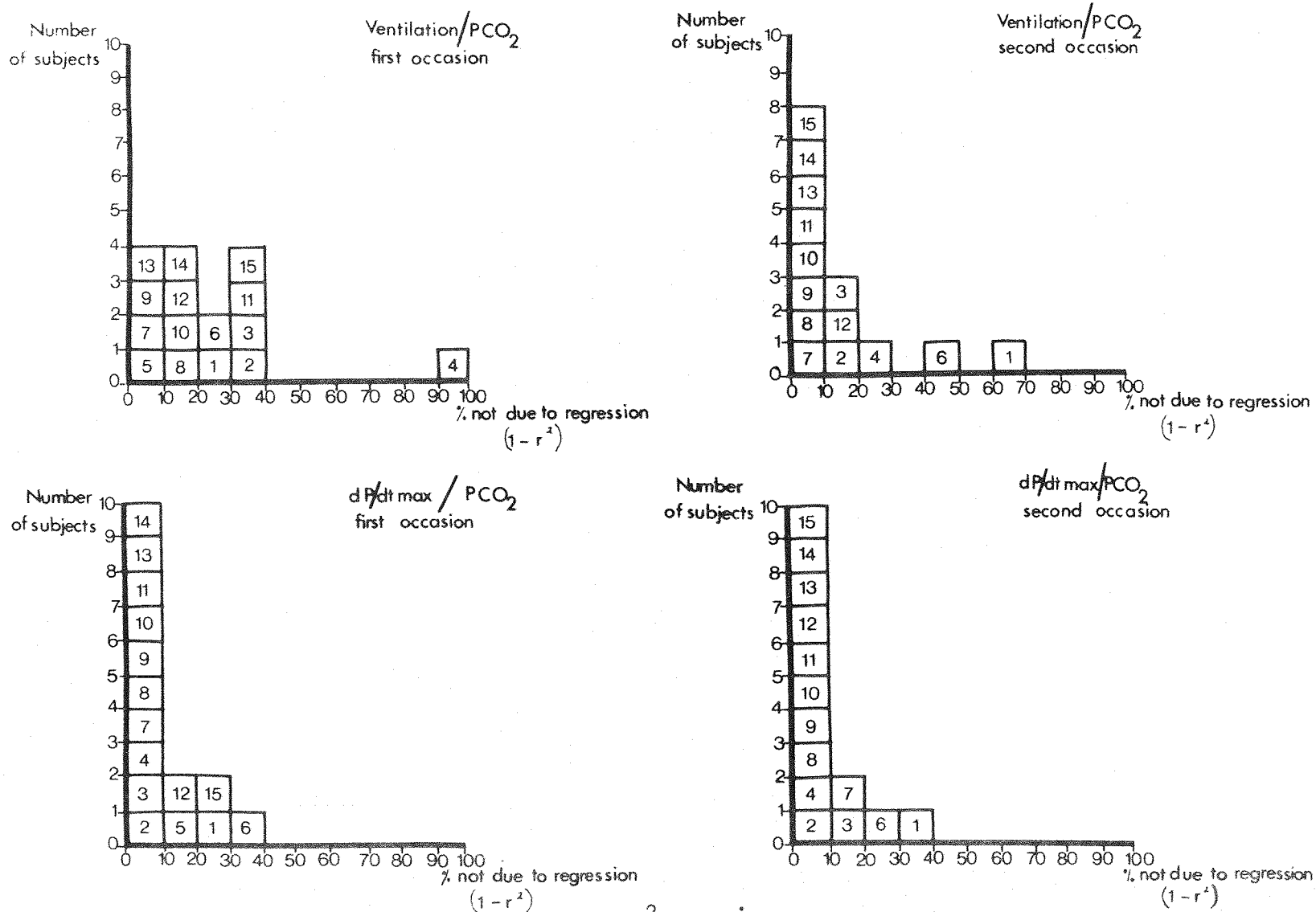


Fig. 15. Frequency-distribution graphs of $1-r^2$ for $\dot{V}E/PCO_2$ and $dP/dt\ max/PCO_2$. The graphs on the left represent the first occasion and the graph on the right, the second occasion.

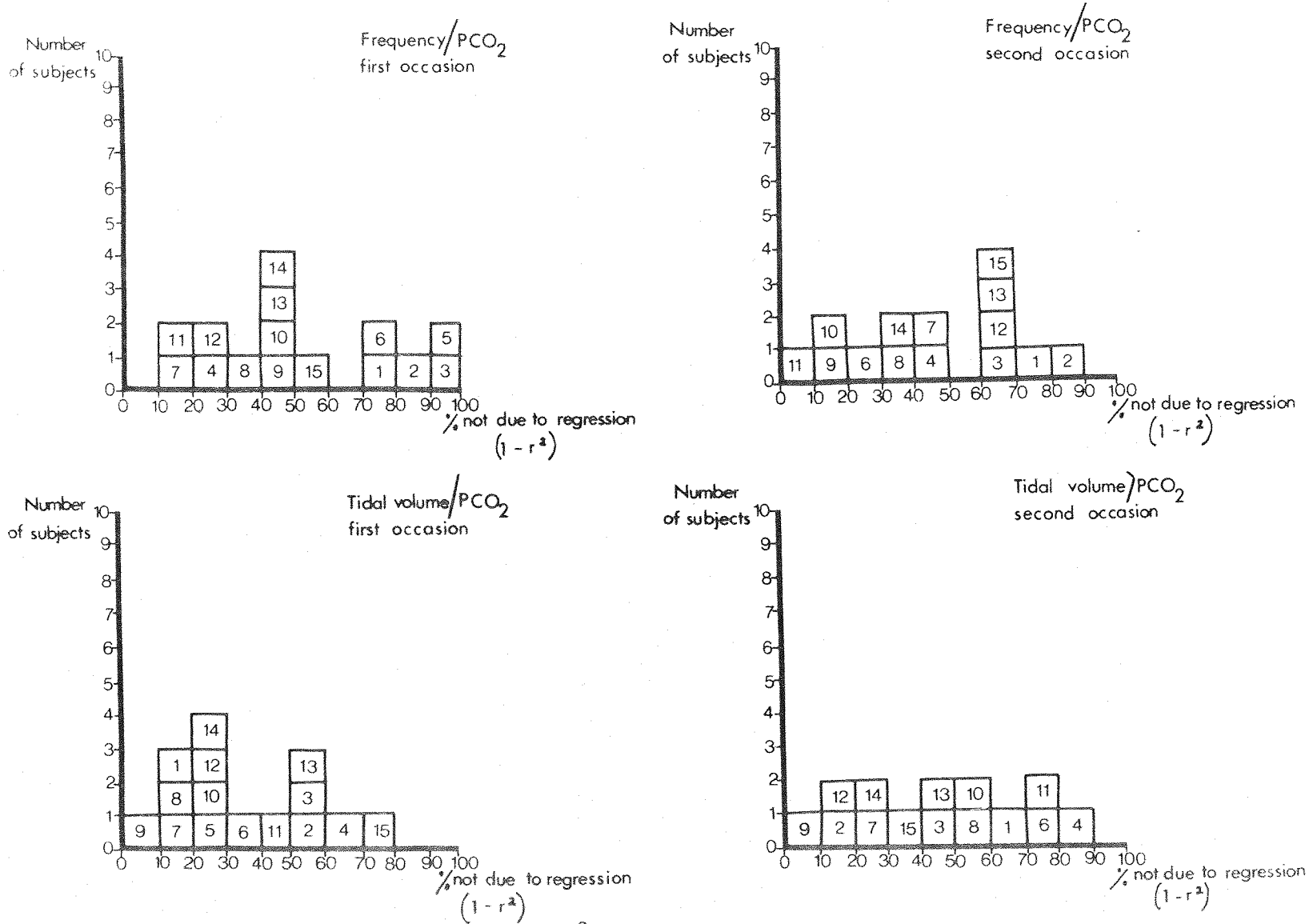


Fig. 16. Frequency-distribution graphs of $(1-r^2)$ for f/PCO_2 and VT/PCO_2. The graphs on the left represent the first occasion and the graphs on the right, the second occasion.

the Mann-Whitney test for the results of $(1-r^2)$, I found significant results between dP/dt max and $\dot{V}E$ on the first occasion and between dP/dt and f and VT on both occasions; in the comparison of dP/dt and $\dot{V}E$ on the second occasion the level of significance was found to be at 0.1%.

There was no significant difference between the results of $(1-r^2)$ for dP/dt max/PCO_2 on the first and second occasion.

In the same way as dP/dt max/PCO_2, the analysis of $(1-r^2)$ for $\dot{V}E$, frequency and VT did not show any significant difference between the first and second time.

The Mann-Whitney test of significance had been applied to the "r" values of these experiments. It was therefore expected that a similar test of the significance of $(1-r^2)$ would give similar results.

My first hypothesis was that familiarity with the experiment would remove some of the external influences occurring during the first occasion. But in view of the lack of significance between the results of "r" for the first and second study and consequently between the results of $(1-r^2)$ for both studies it was not possible to pursue the hypothesis that familiarity with the experiment would reduce the variability of response on the next occasion.

However, it is of interest to explore the data to see if any trends are apparent. The graphs below are the same

frequency distribution as shown before, but now paying special attention to the assessment of the subjects by myself, as anxious or relaxed during the experiment. The cross-hatched symbols represent the anxious subjects (see figures 17 & 18).

There is no suggestion from these graphs that anxiety is correlated with high values of $(1-r^2)$ and even if the subjects are less anxious during the second study this was not followed by a decrease in the proportion of the variance not accounted for by regression.

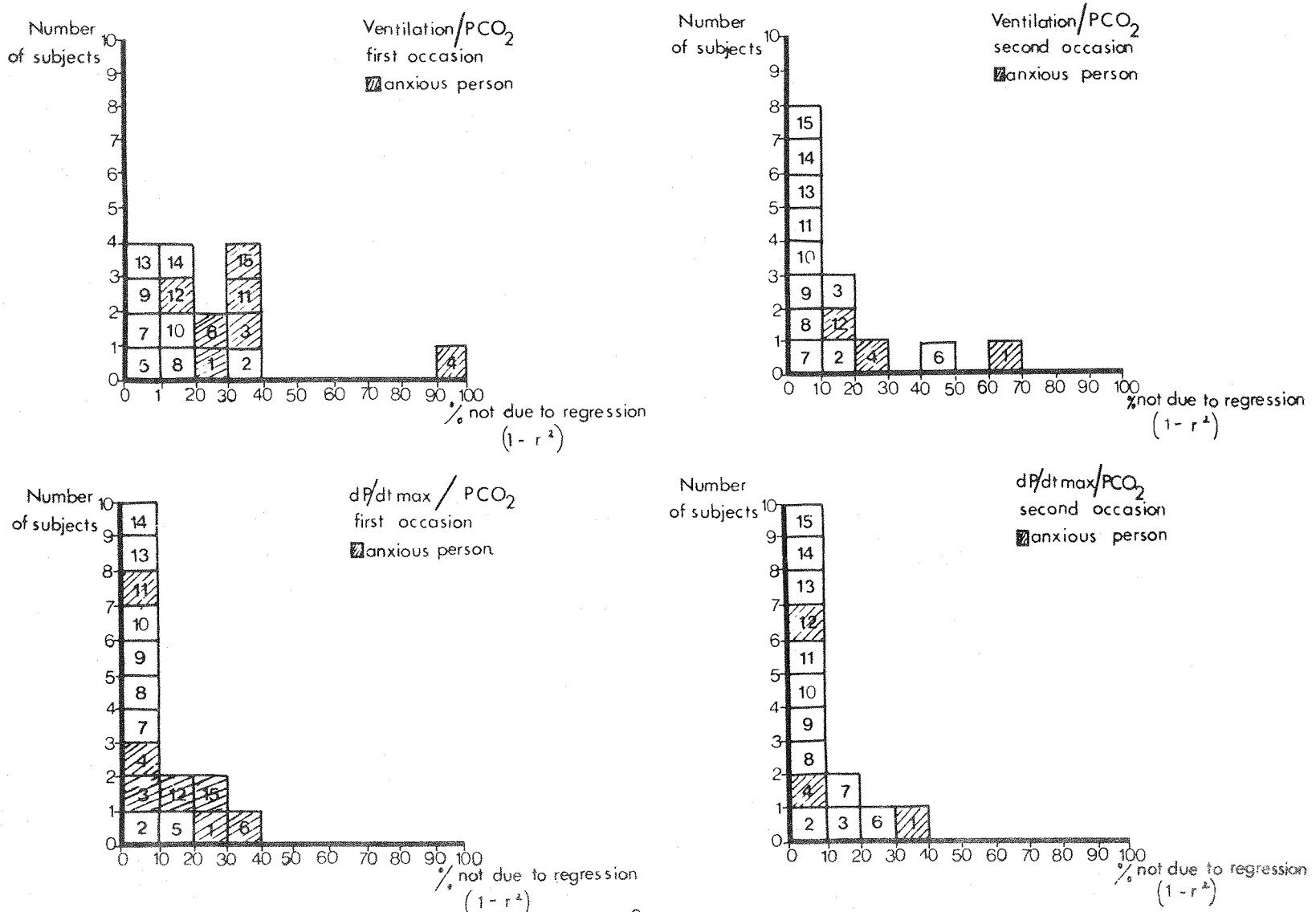


Fig. 17 - Frequency-distribution graphs of $(1-r^2)$ for $\dot{V}E/PCO_2$ and $dP/dtmax/PCO_2$. The cross-hatched squares represent anxious subjects.

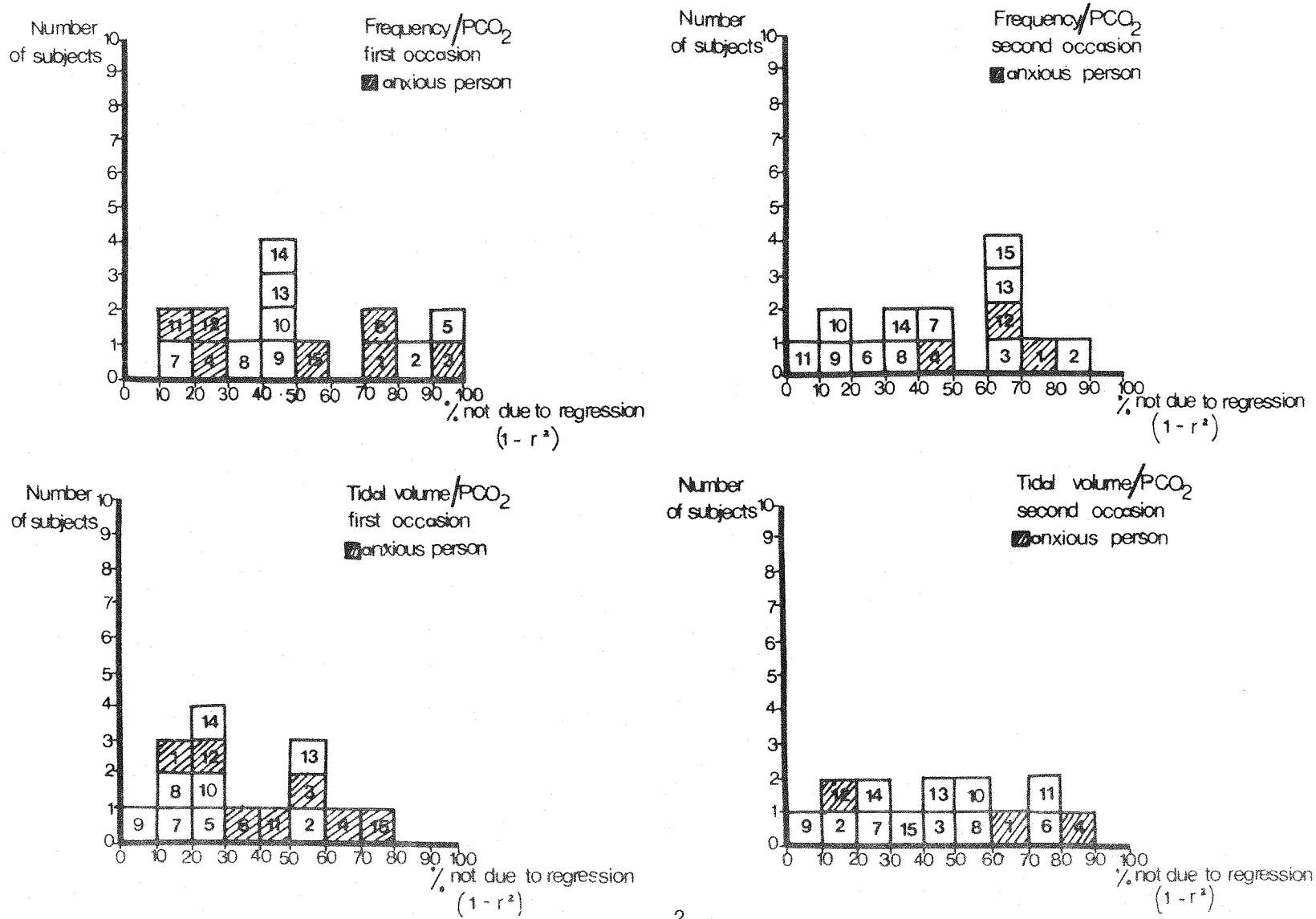


Fig. 18 - Frequency-distribution graphs of $(1-r^2)$ for f/PCO_2 and VT/PCO_2.

The cross-hatched squares represent anxious subjects.

CHAPTER FOUR

CHAPTER 4

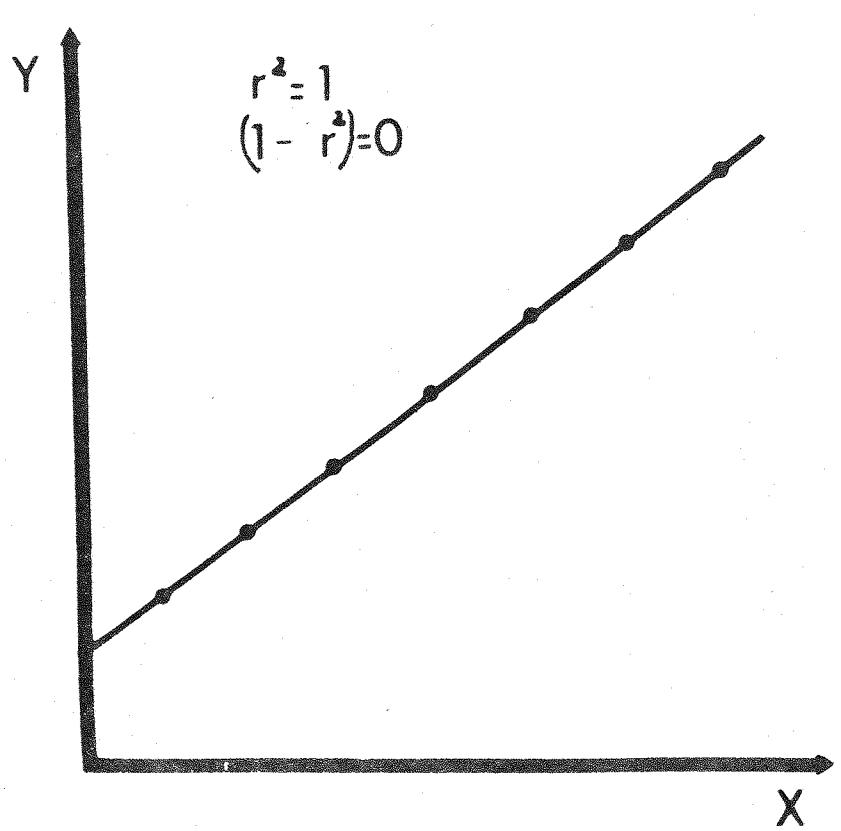
Linearity or non-linearity of regression.

As previously mentioned (page 58), the variation in the scatter of the points around the regression line of the various indices of response to CO_2 were attributed, at least in part, to external factors of which psychological influences were considered likely to be predominant. We decided to analyse the variation not due to regression $(1-r^2)$ as a measure of these external influences, since r^2 measures the part accounted for by regression.

However, when two variables, X and Y, have a curvilinear relationship rather than a linear relationship the correlation coefficient may be low due to this factor alone. Thus, if a low value of a correlation coefficient is obtained and the possibility that a curvilinear relationship exists, it is necessary to examine the plot of Y values on X values in order to determine whether the Y values are linearly or curvilinearly related to the X values.

As may be seen in figure 19, if the points fall on a straight line, there will be a perfect positive relationship between the two variables and in this instance the correlation coefficient is equal to +1. This means that every observed value of Y will be given exactly by Y=a+bX (equation of a straight line).

On the other hand, if the points fall on a curve, as



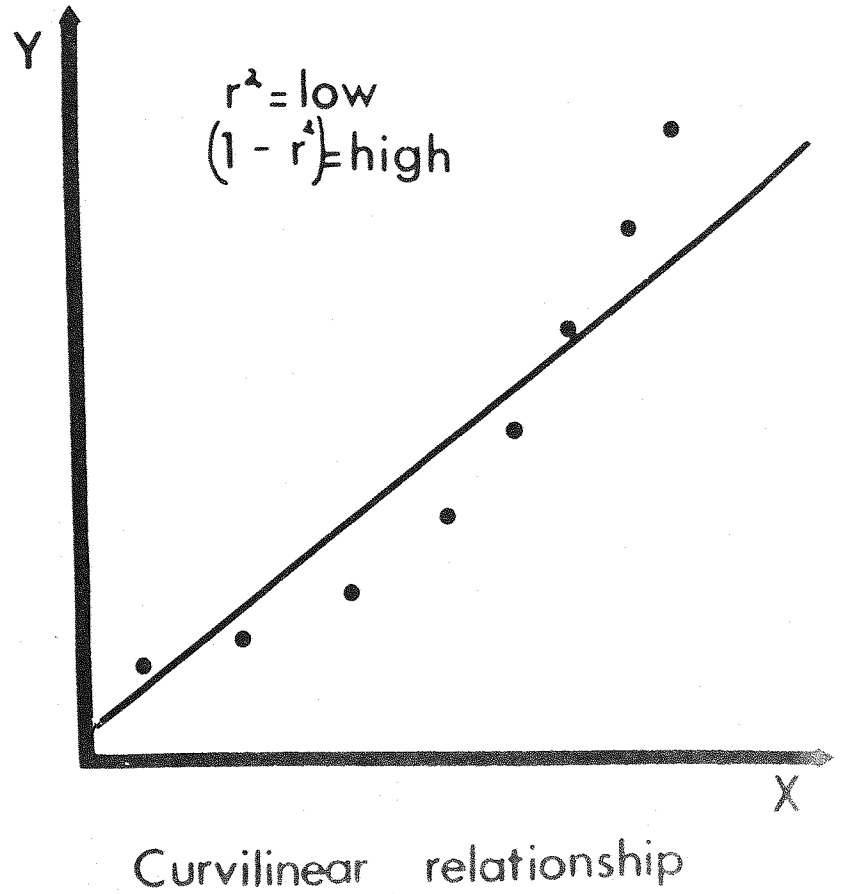


Fig. 19 - Schematic illustration of linear and alinear relationships and the effect upon $1-r^2$.

shown in figure 19, and a linear regression is calculated, it is clear that there will be a scatter of points resulting in an 'r' value less than 1, therefore r^2 will be low and $(1-r^2)$ will be high, not because the variables are not well correlated or because there is a big variation not due to regression, but only because the variables are not linearly related.

In order to determine whether a linear or an alinear relationship existed in the present study, I applied the Durbin-Watson statistic, for the 15 subjects studied during the rebreathing technique on both occasions.

I. The Durbin-Watson test examines whether there is any correlation between adjacent residuals which are the differences between the observations and the fitted values. If the model fits the data the residuals should be randomly distributed, independent of each other, and so adjacent residuals would not be correlated. If the model does not fit the data it is likely that it will depart from the data in a systematic manner, producing correlations between adjacent residuals (Chatfield, 1975).

The results of this test are shown in table 9. In the same table can be seen the results of the significance of "r^2" for each variable ($\dot{V}E$, dP/dtmax, f and VT upon PCO_2) on the first and second occasions of the experiment. This test of the significance of "r^2" is to see whether the result of correlation coefficient had arisen by chance, and then the null hypothesis is confirmed, or whether there is a true correlation between the variables Y and X and then the null

Table 9 - Results of Durbin-Watson statistic and significance of r^2

	Subjects	$\dot{V}E/PCO_2$	$dP/dtmax/PCO_2$	Frequency/PCO_2	Tidal volume/PCO_2	
(1)	First time	0.01>P>0.001 linear	0.01>P>0.001 linear	0.5 >P>0.1 linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.1>P>0.05 linear	0.01>P>0.01 non-linear	0.5>P>0.1 linear	0.5>P>0.1 linear	T value for 'r^2' Durbin-Watson
(2)	First time	0.01>P>0.001 non-linear	0.001 linear	0.5>P>0.1 linear	0.05>P>0.02 linear	T values for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 non-linear	0.5>P>0.1 non-linear	0.001 linear	T value for 'r^2' Durbin-Watson
(3)	First time	0.01>P>0.001 non-linear	0.001 non-linear	P>0.5 linear	0.1>P>0.05 non-linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 non-linear	0.001 non-linear	0.1>P>0.05 non-linear	0.001 linear	T value for 'r^2' Durbin-Watson
(4)	First time	P>0.5 linear	0.001 linear	0.05>P>0.02 linear	0.5>P>0.1 linear	T value for 'r^2' Durbin-Watson
	Second time	0.01>P>0.001 linear	0.001 linear	0.05>P>0.02 linear	0.5>P>0.1 linear	T value for 'r^2' Durbin-Watson
(5)	First time	0.001 linear	0.001 linear	P>0.5 non-linear	0.01>P>0.001 linear	T value for 'r^2' Durbin-Watson

Table 9 cont..

	Subjects	$\dot{V}E/PCO_2$	$dp/dt_{max}/PCO_2$	Frequency / PCO_2	Tidal Volume/ PCO_2	
(6)	First time	0.001 non-linear	0.001 non-linear	0.05>P>0.02 non-linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.01>P>0.001 non-linear	0.01>P>0.001 non-linear	0.01>P>0.001 linear	0.5>P>0.1 non-linear	T value for 'r^2' Durbin-Watson
(7)	First time	0.001 linear	0.001 linear	0.001 linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 linear	0.05>P>0.02 linear	0.01>P>0.001 linear	T value for 'r^2' Durbin-Watson
(8)	First time	0.001 non-linear	0.001 non-linear	0.001 linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 non-linear	0.001 linear	0.01>P>0.001 linear	0.02>P>0.01 linear	T value for 'r^2' Durbin-Watson
(9)	First time	0.001 non-linear	0.001 linear	0.05>P>0.02 linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 linear	0.001 linear	0.001 linear	T value for 'r^2' Durbin-Watson
(10)	First time	0.001 non-linear	0.001 non-linear	0.01>P>0.001 non-linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 linear	0.001 linear	0.05>P>0.02 linear	T value for 'r^2' Durbin-Watson

Table 9 cont...

	Subjects	$\dot{V}E/PCO_2$	$dP/dtmax/PCO_2$	Frequency/PCO_2	Tidal volume/PCO_2	
(11)	First time	0.01>P>0.001 non-linear	0.001 linear	0.001 linear	0.02>P>0.01 non-linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 non-linear	0.001 linear	0.001 linear	0.5>P>0.1 linear	T value for 'r^2' Durbin-Watson
(12)	First time	0.001 linear	0.001 non-linear	0.001 linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 non-linear	0.1>P>0.05 linear	0.001 linear	T value for 'r^2' Durbin-Watson
(13)	First time	0.001 linear	0.001 linear	0.01>P>0.001 linear	0.05>P>0.02 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 linear	0.5>P>0.1 linear	0.02>P>0.01 linear	T value for 'r^2' Durbin-Watson
(14)	First time	0.001 non-linear	0.001 non-linear	0.001 linear	0.001 linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 linear	0.01>P>0.001 linear	0.001 linear	T value for 'r^2' Durbin-Watson
(15)	First time	0.001 non-linear	0.001 non-linear	0.02>P>0.001 non-linear	0.1>P>0.05 non-linear	T value for 'r^2' Durbin-Watson
	Second time	0.001 linear	0.001 non-linear	0.05>P>0.02 non-linear	0.001 linear	T value for 'r^2' Durbin-Watson

hypothesis can be rejected.

II. RESULTS

The Durbin-Watson test shows that 5 subjects had an alinear response for $\dot{V}E/PCO_2$ only in the first study, 4 subjects had an alinear response both in the first and second studies, 5 subjects had linear responses in the first and second studies and none of the subjects had an alinear response in the second study alone.

For dP/dt max/PCO_2, 3 subjects had an alinear response only in the first study, 4 subjects had an alinear response in the first and second studies and 2 subjects had alinear responses on the second study alone.

For f/PCO_2 only 1 subject had an alinear response in the first and second study, 2 subjects had an alinear responses only in the second study and 3 subjects had an alinear response only in the first study.

For VT/PCO_2, 3 subjects had an alinear response only in the first study, 1 subject had an alinear response in the second study alone, and none of the subjects had alinear responses in both studies.

Figures 20 and 21 show the results of $(1-r^2)$ in a frequency distribution curve when the subjects performed the experiment on the first and second occasion and special symbols are used for the subjects who had alinear responses in the Durbin-Watson statistic (square with two dots).

Looking at the results of significance of "r^2" in table 9.

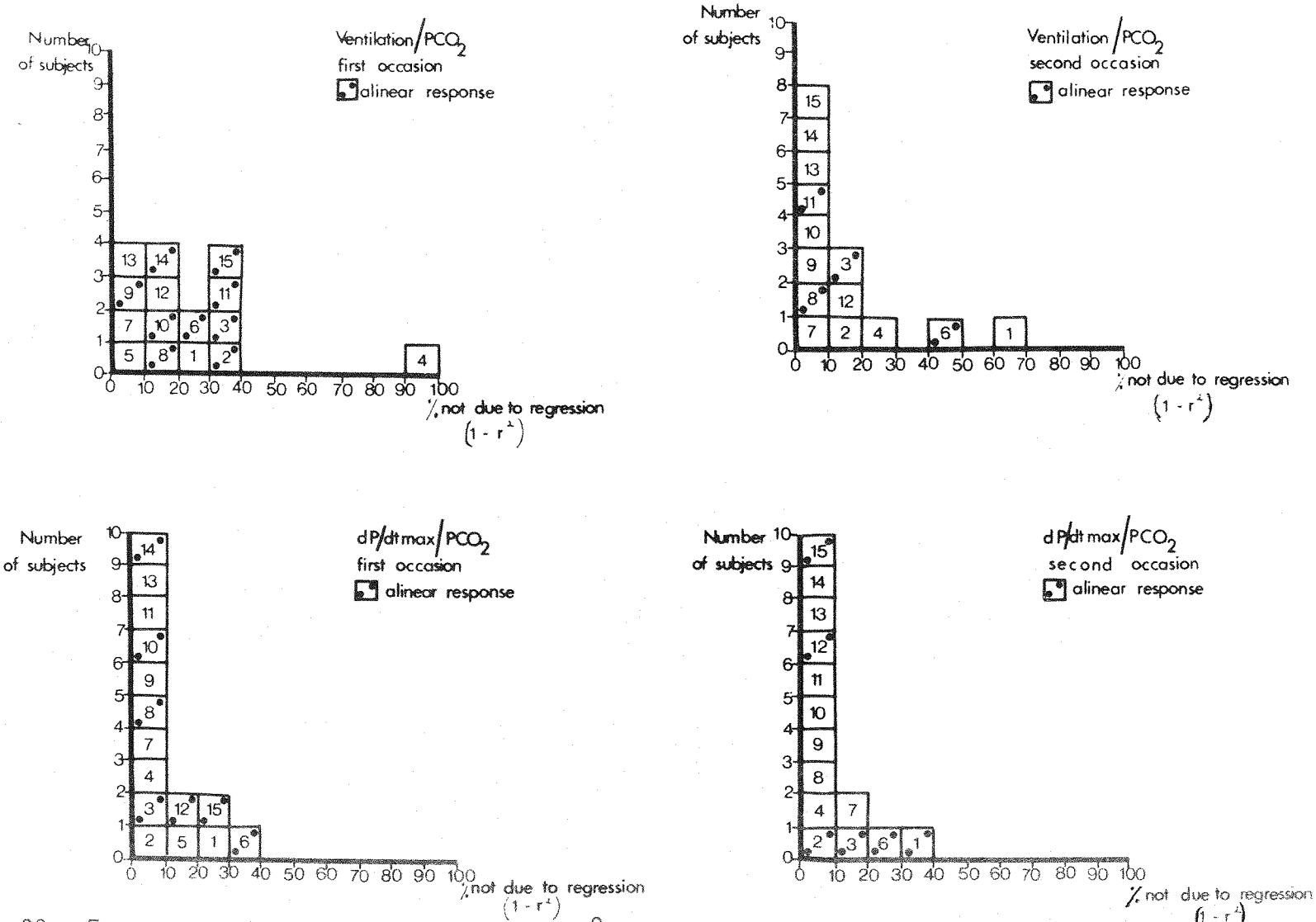


Fig. 20 - Frequency-distribution curves for $(1-r^2)$ for $\dot{V}E$ and dP/dtmax on the two occasions, with those showing alinear responses being identified by

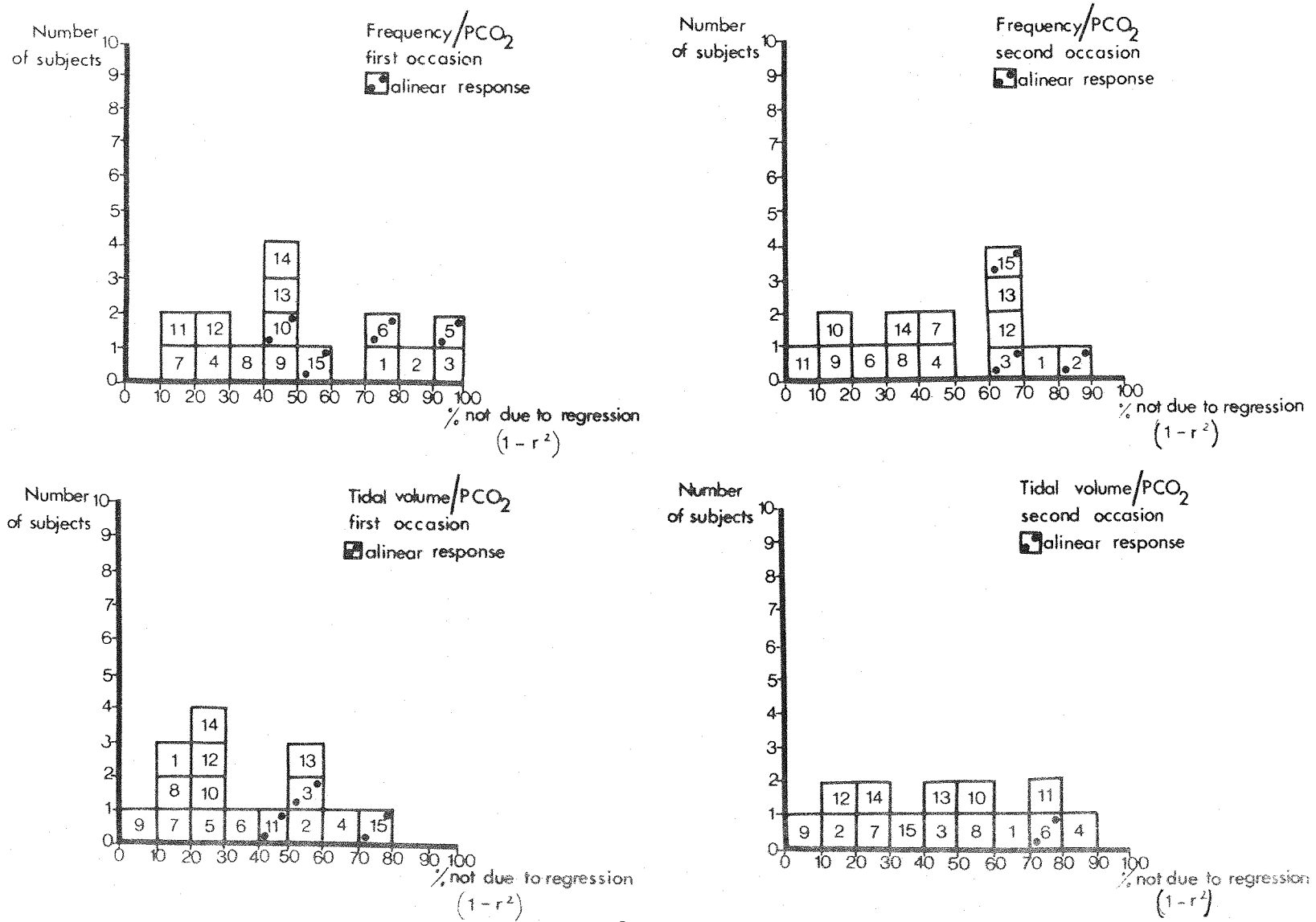


Fig. 21 - Frequency-distribution curves for $(1-r^2)$ for frequency and tidal volume on the two occasions, with those showing alinear responses being identified by [dot]

it can be seen that for $\dot{V}E/PCO_2$ two subjects had a value of "r^2" less significant than 0.05% level (Subject 1 on the second occasion and subject 4 on the first occasion). All the subjects on both occasions had very highly significant results of "r^2" for dP/dt max/PCO_2. As was expected, for f/PCO_2 and VT/PCO_2 many subjects did not have significant values of "r^2" at 0.05% (for f/PCO_2 - subject 1 on both occasions, 2 on both occasions, 3 on second occasion, 5 on first occasion, 12 on second occasion and 13 on second occasion, or for VT/PCO_2 - subject 1 on first occasion, 3 on first occasion, 4 on both occasions, 6 on second occasion, 11 on second occasion and 14 on first occasion).

III. DISCUSSION

We can see that our previous analysis of $(1-r^2)$ (page 91) as a measure of external factors contained a potentially misleading error due to alinearity of some of the regression lines. It seems that some high values of the variation not due to regression in our data, which were attributed to external factors before, now can be attributed to the fact that these subjects had an alinear and not linear relationship in their experiments.

In the diagram of $\dot{V}E/PCO_2$ (fig. 20), on the first occasion we can see that 9 of the 15 subjects had alinear responses. Therefore, $(1-r^2)$ cannot be applied without qualification as a measure of external factors for these experiments, because it may be high, at least partly, due to alinearity.

When $\dot{V}E$ was plotted against PCO_2 on the second occasion, fewer subjects had alinear responses and this alinearity was not confined to those with high values of $(1-r^2)$.

For dP/dt max/PCO_2 I also found many alinear responses and these were not confined to those subjects with high $(1-r^2)$. It is interesting to note that amongst all the indices of response to CO_2, dP/dtmax/PCO_2 was the response with the highest correlation coefficent and the smallest variation not due to regression, but even so I found many alinear responses for dP/dt max using the Durbin-Watson statistic.

For f/PCO_2 and VT/PCO_2, which were the most variable parameters in our experiment with the highest variability not due to regression, few alinear reponses were found to be present in the Durbin-Watson statistic.

It is known that when the points in the data are very scattered the Durbin-Watson test is less sensitive and this could be the explanation for the low number of alinear responses for f and VT upon PCO_2 in my studies, compared with the higher numbers for $\dot{V}E$ and dP/dt max in which the scatter of results is small. dP/dt max/PCO_2 has been described as having a curvilinear relationship mainly in the lower range of PCO_2 (Matthews, 1975) and the Durbin-Watson test in this situation is very sensitive and would detect this as an alinearity in the response; alinear response in this test doesn't mean that the whole relationship between

the X and Y values is a curve and not a straight line. This test does not indicate where the alinearity is occurring and, therefore, I cannot conclude that the alinearity in the $\dot{V}E/PCO_2$ response was due to the so-called "dog leg" or any other reason.

In summary, I think that the variability of some of the responses in this study could be attributed to the alinear relationship between some of the variables, but in view of the poor correlation between alinearity and the magnitude of $(1-r^2)$ it is probable that this alinearity is not the only explanation for the variability found in my results and other causes of $(1-r^2)$ should be looked for.

In addition, the significance and causes of alinearity requires examination.

IV. POSSIBLE CAUSES OF ALINEARITY

During the rebreathing technique, a PCO_2 equilibrium develops between mixed venous blood, arterial blood and gas in the lungs and rebreathing bag after about 15 seconds of rebreathing (Rebuck, 1976). Subsequently, there is a constant increase in end-tidal PCO_2 of approximately 6mmHg (0.8kPa), per minute.

If equilibrium is achieved the mixed venous PCO_2 rises steadily and the end-tidal record is virtually linear. An open loop situation exists, in which the ventilation rate is no longer able to influence the PCO_2. It is therefore possible for non-chemical influences to increase ventilation without inducing an opposing effect from hypocapnia.

There are a number of possible causes for an alinear relationship between $\dot{V}E$ and PCO_2 during rebreathing:

A. Failure to achieve CO_2 equilibrium between the gas in the bag and the blood. It is assumed that if the difference between inspiratory and expiratory PCO_2 in the record is less than 2mmHg there is a CO_2 equilibrium between the gas in the bag and lungs (Rebuck, 1976). To test this possibility I checked all my records and I found that many of my subjects had more than 2mmHg variation in inspiratory and expiratory PCO_2 when they were first switched into the rebreathing circuit.

Could this be the reason for the alinearity of the results?

Two subjects who had less than 2mmHg between inspiratory

and expiratory PCO_2 had alinear responses in the Durbin Watson test and 6 subjects who had a linear response had more than 2mmHg in the beginning of the experiment. I do not think, therefore, that this is the reason for the alinearity of some of the responses.

B. Differences in procedure between subjects - this did not occur in my experiments because I followed the same procedure for all subjects with respect to:

a) size of the rebreathing bag - a 4-6 litre bag was chosen following Read's method (see page 55);

b) initial concentration of CO_2 in the rebreathing bag - a 7% concentration of CO_2 was used (see page 55);

c) initial mixing of gas in bag and lungs - all the subjects were asked to take two deep breaths when connected to the rebreathing circuit, in order to improve the mixing between lungs and bag;

d) analysis of data - the same method of analysis of data was applied. The first 30 seconds of the record after switching the subject into the bag were discarded to minimise the influence of delayed equilibration.

e) all the experiments were done in a quiet room and no coffee or tea was taken by the subjects for two hours prior to the experiment, and no attempt was made to relax the subjects, other than to explain the procedure which would be followed.

C. Faulty techniques - if there was any leak in the equipment which might delay gas mixing or introduce an error into volume measurement our response might not be linear, but this possibility was always checked by paying special attention to the wearing of a nose clip and the position of the mouthpiece. Such fault would be likely to produce a persistent inspiratory-expiratory difference in PCO_2 throughout the study. Such a difference was not seen other than at the beginning of the experiment (point A above).

D. Differences between subjects - it seems clear that some of the variation in ventilatory response to CO_2 is attributable to differences in lung size (Rebuck, 1976). He showed that when tidal volume was constrained to 1L, the wide inter-individual range in ventilatory response was considerably narrowed (Rebuck, Rigg, Kangalee and Pengelly, 1974).

Avery, Cherniack, Dutton and Permut, (1963) showed that the ventilatory response to CO_2 is considerably less in infants than in adults. In the present study there was no apparent correlation between lung size (as reflected through body height) and alinearity of the responses, which would have been expected had this factor been significant.

E. Initial level of ventilation - if the subject had over-ventilated prior to being switched into breathing from the bag, a period of initial compensation by underbreathing might have followed. This would give the initial part of the

response a flatter (lower) slope, until the normal $\dot{V}E/PCO_2$ relationship had been restored.

To explore this possibility, the initial PCO_2 was plotted against response (linear or alinear) as shown in figure 22. The numbers without circles mean the number of the subject when performing the experiment on the first occasion and the numbers with circles mean the number of the subject when the experiment is performed on the second occasion. It will be seen that there was no tendency for the alinear responses to have lower initial PCO_2 than the linear responses. However, it is of interest that the fewer studies with higher initial PCO_2 (subjects 7,4,1) were all linear, but the numbers involved are too small to attach significance to this observation. It is not clear why subject no. 1 had such a high PCO_2 on both occasions.

F. Alinearity may be a normal feature of the $\dot{V}E/PCO_2$ response, i.e., the "dog leg", which many authors have reported. This "dog leg" could be produced for one of the three following mechanisms:

(a) Lack of equilibrium between bag, lungs and arterial PCO_2 - in which case there is no achievement of an "open loop" situation and the PCO_2 is no longer stimulating ventilation.

(b) Neurological mechanism - arousal may produce a fundamental change in the nature of the ventilatory response to a respiratory stimulus and permits the initiation of a

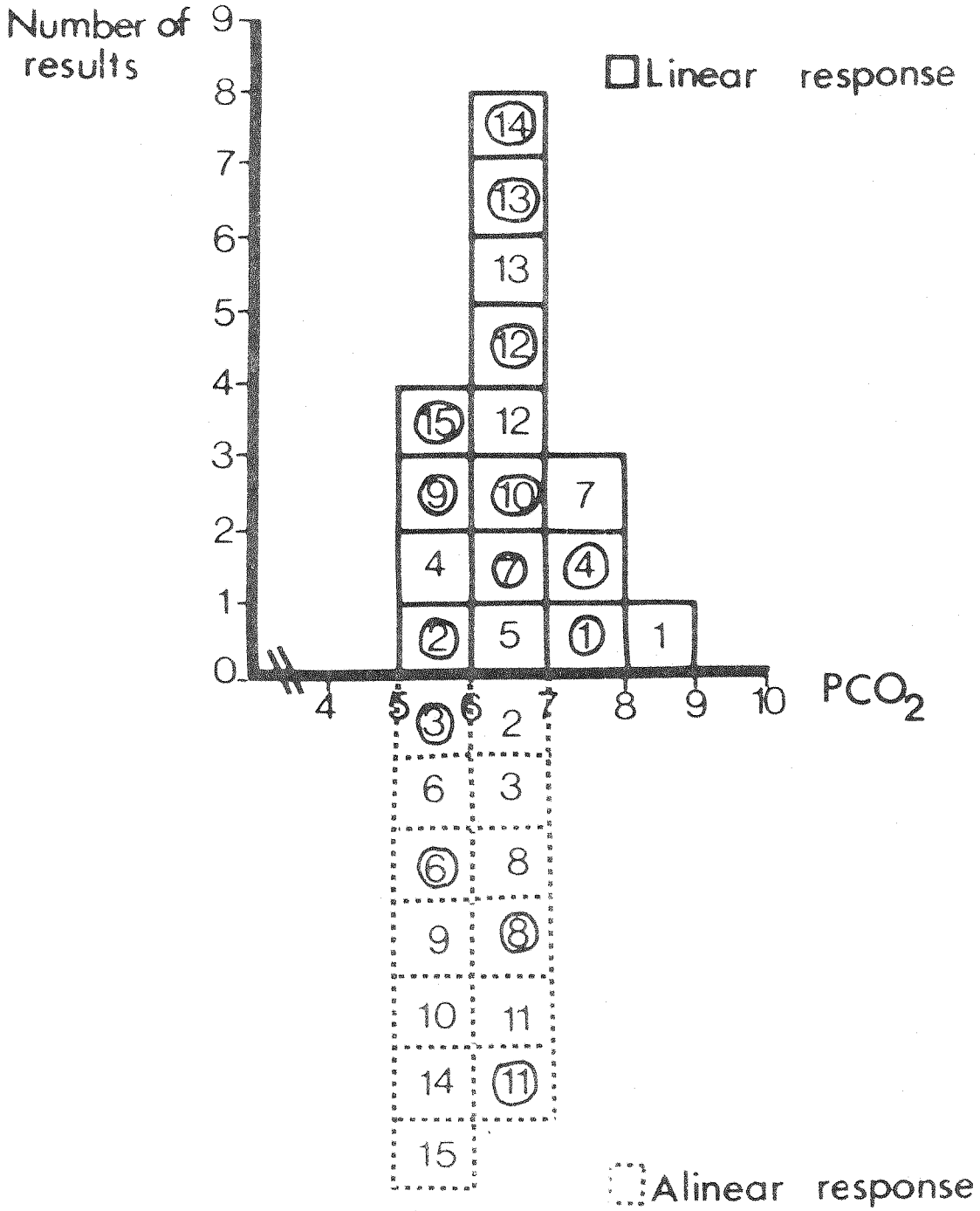


Fig. 22 - Frequency-distribution curve of initial end-tidal PCO_2 values to show no significant difference between those with linear and those with alinear responses.

behavioural and a ventilatory response to the stimulus (Phillipson, 1978). It could be that at low levels of PCO_2, external influences would influence the ventilatory response.

(c) The "dog leg" is the natural shape of the curve. By avoiding the first 30 seconds of the record and having a 7% concentration for CO_2, the "dog leg" should be largely eliminated.

CHAPTER FIVE

CHAPTER 5

METRONOME

I. In the previous studies, the two indices to CO_2 rebreathing with the greatest variability (higher $1-r^2$) were f and tidal volume. Frequency was the technically easier to control by instructing the subjects to breathe according to the frequency set by a metronome.

II. Procedure - Seven subjects from the group of fifteen studied in chapter 3 were chosen according to their availability. The subject, wearing a nose-clip and breathing air through a mouthpiece, sat quietly for ten minutes.

In order to familiarise the subject with the metronome s(he) was given a preliminary run in which s(he) breathed room air at the set frequency. The subject was then switched into a rebreathing circuit as described previously (page 49) and the same measurements of $\dot{V}E$, f, VT and dP/dt max. were made. The only difference from the earlier protocol was that the subject attempted to control the frequency of breathing throughout at that set by the metronome. Three runs at different frequencies were then carried out on separate days. These three different frequencies were not exactly the same for all subjects because I did not set the metronome with the same frequency for all subjects. My interest was to have a controlled frequency during the experiment and not exactly the same number of breaths/minute for every subject. For convenience, when I analysed these data, the subjects were allotted to one of the three frequency ranges, a frequency

controlled by the metronome ranging from 15 to 17 b/min - f_1, f_2- from 18 to 19 b/min and f_3- from 20 to 24 b/min.

The same analysis of data as in chapter 3 (page 53) was used in this study and correlation coefficients and slopes were calculated.

III. RESULTS

The results of correlation coefficient and slopes respectively are shown in tables 10 and 11.

It can be seen that with controlled frequency dP/dt max/PCO_2 was no longer the parameter with the highest correlation coefficient; on the contrary, many of the dP/dt max/PCO_2 results had very low values of correlation coefficient (e.g. 0.46, 0.18, 0.31).

By contrast, it will be noted that ventilation and tidal volume were the measurements with the highest correlation coefficients.

Statistical Analysis - Tables 12 and 13 show the results of "r" values and slopes respectively for the control study on first and second occasions and the metronome study at f_1, f_2 and f_3. The next tables, 14 and 15, show the results of the Mann-Whitney test which was applied for the comparison of both studies.

Description of results

(1) Comparison of r values - in the comparison between "r" values of $\dot{V}E/PCO_2$ in the control study on the first occasion (C_1) and on the second occasion (C_2) with the metronome study at f_1, f_2 and f_3 respectively, I did not

Table 10

Correlation Coefficient Averaged over 15-20 seconds for breathing controlled by Metronome.

Subject	Controlled Frequency	Ventilation/ PCO_2	dP/dt max/ PCO_2	Tidal Volume/ PCO_2
1	15	0.93	0.87	0.93
	18	0.95	0.46	0.93
	22	0.97	0.83	0.97
4	16	0.95	0.66	0.95
	18	0.91	0.18	0.89
	20	0.90	0.76	0.88
6	16	0.86	0.83	0.86
	18	0.90	0.88	0.90
	22	0.82	0.31	0.90
7	16	0.97	0.97	0.96
	18	0.97	0.92	0.97
	21	0.97	0.89	0.97
8	17	0.97	0.95	0.90
	18	0.88	0.86	0.90
	20	0.91	0.88	0.96
13	16	0.93	0.63	0.93
	19	0.84	0.69	0.92
	20	0.90	0.65	0.90
15	17	0.93	0.93	0.93
	19	0.97	0.92	0.96
	24	0.96	0.95	0.96

Table 11

Slopes for $\dot{V}E$, dP/dt, f and VT/PCO_2 for breathing controlled by Metronome.

Subject	Controlled frequency	$\dot{V}E/PCO_2$ $L.m^{-1}/kPa$	$dP/dt/PCO_2$ $kPa.s^{-1}/kPa$	VT/PCO_2 l/kPa
1	15	4.72	0.32	0.30
	18	7.69	0.30	0.43
	22	12.45	0.72	0.49
4	16	6.06	0.12	0.36
	18	7.74	-0.05	0.38
	20	6.75	0.21	0.35
6	16	12.26	0.58	0.78
	18	12.35	1.09	0.75
	22	8.50	0.06	0.36
7	16	14.60	1.09	0.81
	18	20.43	1.57	1.25
	21	16.68	1.23	0.72
8	17	4.69	0.36	0.20
	18	3.11	0.23	0.14
	20	4.90	0.44	0.23
13	16	8.58	0.11	0.42
	19	2.75	0.11	0.14
	20	5.61	0.16	0.32
15	17	11.31	1.06	0.56
	19	17.42	0.87	0.79
	24	20.13	1.28	0.86

Table 12

Results of correlation coefficient in the control study (experiment without the metronome) on the first and second occasion and in the metronome study at f_1, f_2 and f_3.

Subject	Variable	CONTROL		METRONOME		
		1st occasion	2nd occasion	f_1	f_2	f_3
1	$\dot{V}E/PCO_2$	0.89	0.59	0.93	0.95	0.97
	VT/PCO_2	0.90	0.60	0.93	0.93	0.97
	$dP/dTmax/PCO_2$	0.89	0.81	0.87	0.46	0.83
4	$\dot{V}E/PCO_2$	0.02	0.88	0.95	0.91	0.90
	VT/PCO_2	0.58	0.44	0.95	0.89	0.88
	$dP/dtmax/PCO_2$	0.97	0.97	0.66	0.13	0.76
6	$\dot{V}E/PCO_2$	0.88	0.77	0.86	0.90	0.82
	VT/PCO_2	0.82	0.50	0.86	0.90	0.90
	$dP/dTmax/PCO_2$	0.82	0.84	0.83	0.88	0.31
7	$\dot{V}E/PCO_2$	0.98	0.97	0.97	0.97	0.97
	VT/PCO_2	0.91	0.84	0.96	0.97	0.97
	$dP/dtmax/PCO_2$	0.97	0.92	0.97	0.92	0.89
8	$\dot{V}E/PCO_2$	0.93	0.95	0.97	0.88	0.91
	VT/PCO_2	0.94	0.70	0.90	0.90	0.96
	$dP/dtmax/PCO_2$	0.99	0.99	0.95	0.86	0.88
13	$\dot{V}E/PCO_2$	0.97	0.96	0.93	0.84	0.90
	VT/PCO_2	0.64	0.73	0.93	0.92	0.90
	$dP/dtmax/PCO_2$	0.98	0.99	0.63	0.69	0.65
15	$\dot{V}E/PCO_2$	0.80	0.99	0.93	0.97	0.96
	VT/PCO_2	0.51	0.83	0.93	0.96	0.96
	$dP/dtmax/PCO_2$	0.89	0.96	0.93	0.92	0.95

Table 13.

Result of slopes in the control study (experiment without the metronome) on the first and second occasion and in the metronome study at f_1, f_2 and f_3.

SUBJECT	Variable	CONTROL		METRONOME		
		1st occasion	2nd occasion	f_1	f_2	f_3
1	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	6.59	1.82	4.72	7.69	12.45
	VT/PCO_2 (L/kPa)	0.90	0.19	0.30	0.43	0.49
	$dP/dt\ max/PCO_2$ ($kPa.s^{-1}/kPa$)	0.38	0.27	0.32	0.30	0.72
4	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	0.12	7.98	6.06	7.74	6.75
	VT/PCO_2 (L/kPa)	-0.51	0.33	0.36	0.38	0.35
	$dP/dt\ max/PCO_2$ ($kPa.s^{-1}/kPa$)	0.57	0.53	0.12	-0.05	0.21
6	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	16.87	7.49	12.26	12.35	8.50
	VT/PCO_2 (L/kPa)	0.85	0.19	0.78	0.75	0.36
	$dP/dtmax/PCO_2$ ($kPa.s^{-1}/kPa$)	0.90	0.47	0.58	1.09	0.06
7	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	12.95	8.76	14.60	20.43	16.68
	VT/PCO_2 (L/kPa)	0.38	0.27	0.81	1.25	0.72
	$dP/dtmax/PCO_2$ ($kPa.s^{-1}/kPa$)	0.72	0.66	1.09	1.57	1.23
8	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	6.57	5.89	4.69	3.11	4.90
	VT/PCO_2 (L/kPa)	0.19	0.14	0.20	0.14	0.23
	$dP/dtmax/PCO_2$ ($kPa.s^{-1}/kPa$)	0.56	0.51	0.36	0.23	0.44
13	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	5.45	6.45	8.58	2.75	5.61
	VT/PCO_2 (L/kPa)	0.17	0.22	0.42	0.14	0.32
	$dP/dtmax/PCO_2$ ($kPa.s^{-1}/kPa$)	0.37	0.47	0.11	0.11	0.16
14	$\dot{V}E/PCO_2$ ($L.m^{-1}/kPa$)	4.77	15.63	11.31	17.42	20.13
	VT/PCO_2 (L/kPa)	0.20	0.29	0.56	0.79	0.86
	$dP/dtmax/PCO_2$ ($kPa.s^{-1}/kPa$)	0.38	1.25	1.06	0.87	1.28

Table 14.

Results of Mann-Whitney test as N.S. (not significant at 0.05% level) or S (significant at this level) for "r" values between control study, on first occasion, and f_1, f_2 and f_3 respectively in the metronome study and between control study on the second occasion, and f_1, f_2 and f_3 respectively in the metronome study.

Subject	Variable	First occasion and f_1	f_2	f_3	Second occasion and f_1	f_2	f_3
All group of Subjects	$\dot{V}E/PCO_2$	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	VT/PCO_2	S.	N.S.	S.	S.	S.	S.
	$dP/dt\ max/PCO_2$	N.S.	S.	S.	S.	S.	S.

Table 15.

Results of Mann-Whitney test as N.S. or S for "slope" values between control study on first occasion, and f_1, f_2 and f_3 respectively in the metronome study, and between control study on the second occasion and f_1, f_2 and f_3 respectively in the metronome study.

Subjects	Variable	First occasion and f_1	f_2	f_3	Second occasion and f_1	f_2	f_3
All group of Subjects	$\dot{V}E/PCO_2$ $L.m^{-1}/kPa$	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	VT/PCO_2 L/kPa	N.S.	N.S.	N.S.	S.	N.S.	S.
	$dP/dtmax/PCO_2$ $kPa.s^{-1}/kPa$	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

find a significant difference at the 0.05% level. The actual levels of probability can be seen in tables 16 and 17.

When the results of "r" values for tidal volume/PCO_2 were compared in both studies I found significant results at 0.05% between C_1 and f_1 and f_3 respectively and significant results at 0.05% level between C_2 and f_1, f_2 and f_3 respectively (see table 16).

The results for the comparison of r values for dP/dt max/PCO_2 were significant at 0.05% level for C_1 with f_2 and f_3 and for C_2 with f_1, f_2 and f_3.

(2) Comparison of slopes - in the comparison of slopes between the experiment without controlled frequency and the experiment with the metronome I found no significant difference at 0.05% level in the slopes of $\dot{V}E/PCO_2$ (see table 17).

The same lack of significance was found for dP/dt max/PCO_2 and for VT/PCO_2 I found only significant difference at the 0.05% level in the comparison between C_2 (control study on the second occasion) with f_1 and f_3.

(3) Comparison of the variability of f/PCO_2 between the control study and the metronome study - as there was no regression for f/PCO_2 in the metronome study I measured the variance of f/PCO_2 in the control study on both occasions, and in the metronome study at f_1, f_2 and f_3. These variances were then compared using a "paired t test" and a level of significance of $0.01 > p < 0.001$ was found between control studies on both occasions and metronome study at f_1, f_2 and f_3. This difference was to be expected

Table 16.

Levels of significance found by the Mann-Whitney test for "r" values between control study on the first occasion and f_1, f_2 and f_3 respectively in the metronome study and between control study on the second occasion, and f_1, f_2 and f_3 respectively in the metronome study.

Subjects	Variable	First occasion and f_1	f_2	f_3	Second occasion and f_1	f_2	f_3
All group of Subjects	$\dot{V}E/PCO_2$	0.4%	0.6%	0.5%	0.9%	0.9%	0.08%
	VT/PCO_2	0.04%	0.07%	0.04%	0.002%	0.004%	0.004%
	$dP/dt\ max/PCO_2$	0.15%	0.04%	0.02%	0.02%	0.05%	0.008%

Table 17.

Levels of significance found by Mann-Whitney test for "slope" values between control study on the first occasion and f_1, f_2 and f_3 respectively in the metronome study, and between control study on the second occasion, and f_1, f_2 and f_3 resepctively in the metronome study.

Subjects	Variable	First occasion and f_1	f_2	f_3	Second occasion and f_1	f_2	f_3
All group of Subjects	VE/PCO_2 $L.m^{-1}/kPa$	0.7%	0.4%	0.3%	0.7%	0.5%	0.5%
	$dP/dt\ max/PCO_2$ $kPa.s^{-1}/kPa$	0.5%	0.6%	0.8%	0.5%	0.6%	0.6%
	VT/PCO_2 L/kPa	0.2%	0.6%	0.3%	0.01%	0.15%	0.01%

if there was a correlation between frequency and PCO_2.

IV. DISCUSSION

In the present experiment I controlled one of the variables of the following equation: $\dot{V}E=f \times VT$. Since I did not find a significant difference for the "r" values of $\dot{V}E/PCO_2$ between the control and the metronome experiments it follows that I should find a significant difference for "r" values of VT/PCO_2 and such results were confirmed.

The most surprising result in this experiment was $dP/dt\ max/PCO_2$ which was the parameter least influenced by external factors in the experiment without controlled frequency and in the present study is the variable with the lowest correlation coefficient. This was confirmed by a significant difference between the control study and metronome study, although such significance was not found for the comparison of slopes. The possible significance of this observation in relation to the control of breathing will be discussed in more detail in chapter 7.

What is clear from the results of this study is that when we control f the results of "r" values for $\dot{V}E/PCO_2$ and for VT/PCO_2 are much more consistent (page 120); the range of these results is very narrow, while in the experiment without the metronome I found more variability from one day to the other, and from one subject to the other.

CHAPTER SIX

CHAPTER 6

Inspiratory and Expiratory Time

I. I mentioned previously (page 55) that the additional variables, inspiratory and expiratory time, would be measured in this study.

In view of my previous observations, that frequency was one of the most variable measurements I wished to know whether this variability was due to variation occurring during the inspiratory or expiratory phase of breathing.

In order to avoid the loss of sensitivity which would result from averaging breaths over 15-20 seconds, I chose randomly a group of seven subjects from the group of 15 and analysed the results breath by breath.

II. RESULTS

Inspiratory time and expiratory time were plotted against PCO_2 and the correlation coefficients were determined (see analysis of data, page 55). The graphs of individual subjects for Ti and Te are shown in Appendix 4.

The results of correlation coefficient are shown in the table below:

Table 18

Correlation Coefficient for Ti/PCO_2 and Te/PCO_2 regressions.

Subjects	Ti/PCO_2	Te/PCO_2
1	0.69	0.08
4	0.67	0.49
6	0.78	0.49
11	0.49	0.19
12	0.31	0.18
14	0.74	0.05
15	0.74	0.39

Statistical Analysis of Results

I applied the Mann-Whitney test in order to compare the values of 'r' for inspiratory time and expiratory time and I found a significant difference at 0.01% level for this analysis. This indicates that expiratory time, the measurement with the lowest correlation coefficient for all subjects was the phase of breathing where most of the variability was occurring.

One subject had an increase in Ti and two subjects had an increase in Te when these variables were plotted against PCO_2.

This analysis presupposes that the relationship between Ti, Te and PCO_2 are linear. For the reasons explained in detail on page 99, any alinearity would influence the value

of 'r' without carrying the implication that a reduction in 'r' reflected an increase in variance.

I therefore carried out the Durbin-Watson statistic and an alinear relationship was found in three subjects, two for both Ti and Te (6,15) and in one (subject 11) for Te only. The numbers remaining are small, but still there was, in all of them, a greater increase in variability for the Te/PCO_2 relationship.

III. DISCUSSION

Ti and Te versus PCO_2 - in an examination of the literature on respiratory control I have failed to find any data on the relationship between Ti, Te and PCO_2. The results of Ti and Te have largely been related to tidal volume (Clark and von Euler, 1972; Gautier, Remmers and Bartlett, 1973; Gardner, 1977; Gautier, 1980) when a somewhat complicated relationship has often been revealed. For example, Clark and von Euler in 1972 showed, in man, quite different behaviour for Ti vs volume (either Vt or VI) in the lower and upper volume ranges. Along the lower curve, designated range I, Ti remained approximately constant as VI grew in response to the accumulation of CO_2 in the inspired air. At higher volumes, Ti shortened with increasing volumes in the same manner as with the cat. The relative extent of the two ranges varied somewhat between different subjects. At the largest tidal volume, a deviation from the hyperbolic range 2 was often seen. This inspiratory augmentation effect in the high volume range, designated range 3, was variable and usually too limited in extent to be described

accurately. It did seem to be due to an increase in volume in combination with an increase in Ti, in excess of the values predicted from the range 2.

The expiratory time in cats with intact vagus nerves, or with human subjects showing a prominant range 2, was dependent upon Ti in an approximately linear manner.

Gautier et al, in 1973, studying control of the duration of expiration in cats, found that decrease in Te accounted for 65-100% of the total decrease in cycle length. Changes in Ti with hypercapnia were small and variable.

In 1977, Gardner confirmed the curvilinearity of the upper parts of the VI, Ti and the VT, Te relationship and the near constancy of Ti over the lower range of VT. However, he found that Te varies markedly in range 1, while Ti remains nearly constant and so the two ranges were not uniquely related.

The fact that curvilinear relationships were often found for VT/Ti and VT/Te, and in my studies a linear relationship was usually found between VT and PCO_2 (page 105) suggests that a curvilinear relationship might exist between Ti, Te and PCO_2. Such a relationship would contribute to lowering the 'r' value if a linear regression was calculated for these results. The significance of this on the interpretation of the residual variance has already been considered in detail on page 101.

For the reasons which were given in that discussion, I decided to apply the Durbin Watson statistics to the present

results to see whether I was justified in drawing conclusions from a comparison of the residual variances for Ti/PCO_2 and Te/PCO_2.

It will be seen that a linear relationship occurred in 4 subjects and an alinear relationship in 2 and in the Te/PCO_2 only for one further subject. It will be noted that the magnitude of 'r' does not seem to be influenced by whether a linear or an alinear relationship is found, which suggests that alinearity was not contributing to a great extent to lowering the 'r' values.

The aim of this study was to see in which phase of breathing, inspiration or expiration, external influences were interfering. My conclusion, in view of the results shown previously, is that during the expiratory phase of breathing external factors influenced breathing to a greater extent than during the inspiratory phase.

CHAPTER SEVEN

CHAPTER 7.

I. FINAL DISCUSSION

The results described in the preceding sections were designed to test whether, when individuals unfamiliar with the rebreathing procedure are studied, their responses on the first occasion were more variable than on a subsequent occasion. The studies aimed to identify how these changes occurred.

Firstly, on the assumption that anxiety would be an important factor, I tried to assess the mental state of the subjects at the time of study to correlate with the changes in variability.

I also attempted to assess their personality and indices of neuroticism by means of the Crown-Crisp Questionnaire in the hope that this might reflect similar factors. It seems likely that this latter approach was measuring something different from the mental state produced by the situation of the experimental procedure and has not shed light on the reasons for the variability.

The other reasons why I might have obtained such variable results, quite apart from psychological factors, include:

(i) variations in instruments, measurements or procedures (see page 55).

(ii) variations anywhere along the control system including such sites as:

a) peripheral chemoreceptors

b) central chemoreceptors

c) transmission of the neural impulse

d) development of muscular force to power the movement of the lung and chest wall bellows,

but there is no reason to believe that variability at any of these sites would result in changes of the magnitude observed.

It was hypothesised that if the $\dot{V}E/PCO_2$ response reflected solely the chemical control mechanism, we would have a very low variance and any greater variance would reflect the interference from external factors which were thought likely to be due to psychological factors. By repeating the measurements I expected that the psychological factors would be reduced and the variance would be lower. To quantify these external factors it was proposed to measure $(1-r^2)$ and to compare the results of this analysis on first and second occasions for all the indices of response, $\dot{V}E$, dP/dtmax, f and VT.

Although there appeared to be less variance for the $\dot{V}E$ response to CO_2 on the second occasion of the study, this was not statistically significant.

All the results supported the initial impression that $dP/dtmax/PCO_2$ was the most consistent response with the least interference from non-chemical factors.

It was expected that a difference between the first and second occasion would correlate with evidence of changes in overt anxiety, but since there were no significant differences between both occasions of the study for any of the indices of response, this approach did not prove possible. This was despite the obvious reduction in anxiety (from 7 subjects to 3 subjects) as judged subjectively by myself. This suggests that anxiety did not play an important part in the variability of the responses to CO_2 in these subjects, but it is admitted that the method of assessment was crude and opportunity for subconscious bias was possible.

Nevertheless, the magnitude of the scatter which was observed in some subjects on the first occasion was so great that it seems inconceivable that the response reflected solely the influence of chemical factors. It is only reasonable to hypothesise that in individual instances, external factors including anxiety, and unfamiliarity, were interfering with the response. For example, subject no. 4 was so widely variable that it appeared that he had no control mechanism - he was hyperventilating initially and subsequent values were also variable (analysis of the group

with and without this individual did not alter the significance of the results).

The hypothalamus from which originates the sympathetic and parasympathetic nervous systems is known to be closely associated, at least, with the expression of emotional changes in the gut, circulating system, skin and in the control of breathing. The respiratory apparatus is often influenced by the emotional state and extreme examples of respiratory disturbance from this cause are seen in the "hyperventilation syndrome". These influences are not exerted via the chemical control systems, in fact they work in opposition to it, overriding the CO_2 control and leading to hypocapnia.

The precise nervous pathways involved in these non-chemical influences are unknown, but it is possible that the "behavioural pathway" described by Plum (1970) may be involved. Plum based his description of this proposed pathway on studies made in patients with poliomyelitis. It was noted that occasional patients with bulbo-poliomyelitis breathed seemingly normally while awake, but hypoventilated or became apnoeic if they fell asleep. Plum and Swanson (1959) subsequently confirmed this finding and were able to take the observation further in a young woman with polio who breathed quite adequately when she was specifically commanded to do so but became apnoeic whenever the commands were

stopped. It seems possible that this pathway could mediate the effects of anxiety upon the respiratory centre. If the behavioural pathway is involved in my subjects, the possible effects of this mechanism appear to include not only hyperventilation but variations in frequency and tidal volume.

Whereas it was anticipated that these studies would reveal how external factors, mainly psychological, influence the various indices of response, it was not anticipated that the results might shed light on the way in which they affect different stages of an individual breath.

The respiratory cycle consists of an "ascending limb", inspiration, and a "descending limb", expiration. It can be characterised schematically by the tidal volume (VT), duration of inspiration (Ti) and duration of expiration (Te).

For each breath the model proposed by and von Euler (1977) is as follows: - a pool of neurons generate, during inspiration, an increasing activity under the influence of both peripheral and central inputs, especially from the chemoreceptors. The output of these neurons is directed to various respiratory muscles.

Inspiratory activity is terminated at the end of inspiration by another group of medullary (inspiratory off-switch mechanism) which integrates information from the vagus nerves, the pontile pneumotaxic centre, chemoreceptors

and forebrain structures. Once switched off, inspiration is kept inhibited for the subsequent expiration with a delaying power that can be strongly modulated by different reflexes. Thus, it appears that the basic network for respiratory rhythmicity depends on excitation and inhibition between the two basic neural mechanisms: the CIA (central inspiratory activity) generator and the off-switch mechanism. The latter mechanism inhibits the former when the off-switch threshold is reached by the slowly growing activity of the CIA in combination with the likewise slowly increasing activity from the pulmonary stretch receptors.

This model, developed by von Euler (1977), is based upon studies in the cat in which the Hering-Breuer reflex is prominent. Whether it can be applied to man, in whom the Hering-Breuer reflex is virtually absent after the first few days of life (Cross, Klaus, Tooley and Weisse, 1960), must remain doubtful.

It is well known that neurological factors arising from the lungs or elsewhere can influence the timing of the respiratory cycle in a controlled manner, and it is therefore not unreasonable to consider it conceivable that other nervous activity associated with anxiety etc. could influence the respiratory cycle in a more variable manner.

Clark and von Euler (1972) have produced evidence which has been interpreted, quite reasonably, by Remmers, Baker and

Younes (1978) as indicating that inspiratory activity, once initiated, develops in a pre-programmed way appropriate to the particular level of chemical stimulus. This inspiratory programme can be influenced by inhibitory influences arising from the lungs (in cats) but it has to build up to a sufficient degree to inhibit the inspiratory "ramp". The expiratory phase is associated with a rapidly diminishing inspiratory activity and Clark and von Euler showed that this can be readily influenced by pulmonary stretch receptor afferents. Thus, the inspiratory phase appears to be much less readily influenced than the expiratory phase.

In the present study we have a possible way of studying the influence of non-chemical factors upon the stages of the respiratory cycle.

I have observed that of all the variables within a breath dP/dt max is the least variable, Ti the next and Te the most variable. f and VT show similar but largely reciprocal variation and perhaps surprisingly in view of the association of hyperventilation with anxiety, the ventilatory response to PCO_2 shows less variability.

dP/dt max is a measurement made over the first (approximately) 100msec of a breath (Matthews and Howell, 1975) and it is perhaps not surprising that an external factor operating for so short a time upon the beginning of a pre-programmed package when virtually the whole of the

package is still present and unexpended, will have little influence upon it.

Changes in frequency reflect changes in the whole of the breath with ample time for external factors to influence the duration of the respiratory cycle. If chemical ventilatory control is present it would not be surprising if reciprocal changes in VT were present and this is seen in these results. However, the respiratory cycle is in two phases: a usually shorter phase of progressively increasing inspiratory nervous activity (i.e. progressively diminishing nervous activity retained in the pre-programmed package) and a longer expiratory phase in the initial part of which there is rapidly diminishing inspiratory nervous activity as the remainder of the pre-programmed package is expended. It is during this latter phase that external factors might be expected to have the greatest influence on the respiratory cycle.

Examination of the $(1-r^2)$ component of variance (the residual variance) shows some effect from these factors during inspiration, but a much more marked effect during expiration.

Voluntary control of frequency - the small degree of variability of the dP/dt max during rebreathing is in sharp contrast to the large variability which occurred when breathing was made to conform to the timing set by a

metronome. During spontaneous breathing, each breath originates in the respiratory centre and we have already argued that it appears to be a pre-programmed package. By contrast, under the conditions of having to control each breath to begin at a time dictated by the metronome, it seems likely that the breath would be initiated by voluntary control.

The nervous pathways involved in voluntary controlled breathing are not well defined, but the observation in a small number of patients who have lost the ability to maintain adequate alveolar ventilation when asleep (Ondine's Curse)(Severinghaus and Mitchell, 1962) suggests the possibility that the respiratory centre is inactive and alternative pathways leading directly to the spinal motorneurons are involved in the voluntary control (Sears, 1966).

It is also possible that under the conditions of these experiments voluntary control could be operating through an "inactive" or suppressed respiratory centre but would not be utilising a pre-programmed package. In either case, the breath would be expected to be different in its pattern of neurological activity. It is suggested that this is the explanation for the wide variability of the dP/dt max response in the metronome study.

II. SUMMARY

1. Aspects of current understanding of respiratory control, including chemical, neurological and behavioural factors, and methods used for their study are reviewed.

2. Pilot studies of the response to rebreathing CO_2 of four normal subjects, unfamiliar with respiratory measurements, showed a wide scatter of the responses for ventilation ($\dot{V}E$), frequency (f) and tidal volume (Vt). The scatter of response to brief, isometric inspiratory occlusion, measured as the maximum rate of change of inspiratory pressure during occlusion, dP/dt max, appeared to be considerably less.

3. The scatter of these responses was attributed to the influence of non-chemical factors upon the basic chemical control mechanisms, and were thought to be largely due to anxiety and unfamiliarity with the procedure.

4. The magnitude of these influences was quantified by calculation of the residual variance ($1-r^2$) of the relationship between the measured variable and CO_2.

5. It was hypothesised that repeating the measurements on a second occasion would reduce the non-chemical influences and would be quantifiable by the reduction in $(1-r^2)$.

6. A comparison of the influence of non-chemical factors upon each of the different indices of respiratory response to CO_2: $\dot{V}E$, dP/dt max, f and Vt would also be possible, using linear regression analysis and calculation of $(1-r^2)$.

7. Fifteen normal subjects were studied on two different occasions and the initial impression that dP/dt max was the least influenced by non-chemical factors was confirmed. The anticipated reduction in the influence of non-chemical factors on the second occasion was not observed when the values of $(1-r^2)$ for each of the indices of response were compared. The Mann-Whitney test was used to test the significance of differences.

8. In anticipation of finding a difference between the results of the two series of studies, and in the belief that anxiety would be a significant factor, two "psychological assessments" were made. Firstly, a personal subjective assessment of anxiety, based upon observation of the behaviour and appearance of the subject and, secondly, a

personality assessment using the Crown-Crisp Experimental Index. No correlation between either of these assessments, and the results obtained, was observed.

9. The most variable responses to CO_2 rebreathing, measured as the residual variance ($1-r^2$), were the frequency and the tidal volume responses. To study the effect of controlling the frequency response, the measurements were repeated in seven of the subjects when breathing frequency was voluntarily controlled to a predetermined value set by a metronome. Three different frequencies were studied in each subject.

The most striking effect of controlling frequency was that dP/dt max response became markedly more variable. The $\dot{V}E/PCO_2$ response was not significantly affected when frequency was voluntarily controlled.

10. When the variability of frequency was measured in terms of inspiratory time (Ti) and expiratory time (Te) during rebreathing uncontrolled by the metronome, the values of correlation coefficient were significantly smaller for Te.

11. The influence of non-chemical factors was therefore found to be least upon dP/dt max, and greatest upon Te.

12. Although the slopes of all indices of response to CO_2 were variable, there was no significant difference between the responses of the group on the first and second study in the 15 subjects, or when frequency was controlled with the metronome.

13. The use of the residual variance $(1-r^2)$ as a measure of non-chemical factors assumes a linear relationship between CO_2 and the index of response being studied. Linearity was therefore studied for each of the responses using the Durbin-Watson statistic. Alinearity was demonstrated in many responses, but as this did not correlate with magnitude of $(1-r^2)$ it is assumed that this was not an important factor, invalidating the use of residual variance as a measure in this study of non-chemical factors in most instances.

14. Possible reasons for the different susceptibility of the different phases of breathing - initial onset of inspiration, the inspiratory phase and the expiratory phase - are discussed in terms of a neurological model of breathing.

APPENDIX ONE

I.

Resistance of the circuit - the resistance was measured using a water manometer and flow was measured using a rotameter. This was done when flow was both going into the system and out. The resistance found was 0.192 kPa/L at 120 $L.min^{-1}$ of flow in both measurements.

II.

Frequency response of transducer - a sinusoidal signal was applied to a loudspeaker to which was attached an optical wedge linear transducer. Pressure changes were sensed by the pressure transducer, the output of which, and that of the optical wedge, were recorded simultaneously on a Y-t recorder. The graph below (Fig. 23) shows on the abscissa values for log frequency (lnf) and on the ordinate values for the log of the ratio of the transducer output over the loudspeaker deflection (lnA). The response was linear up to 12Hz.

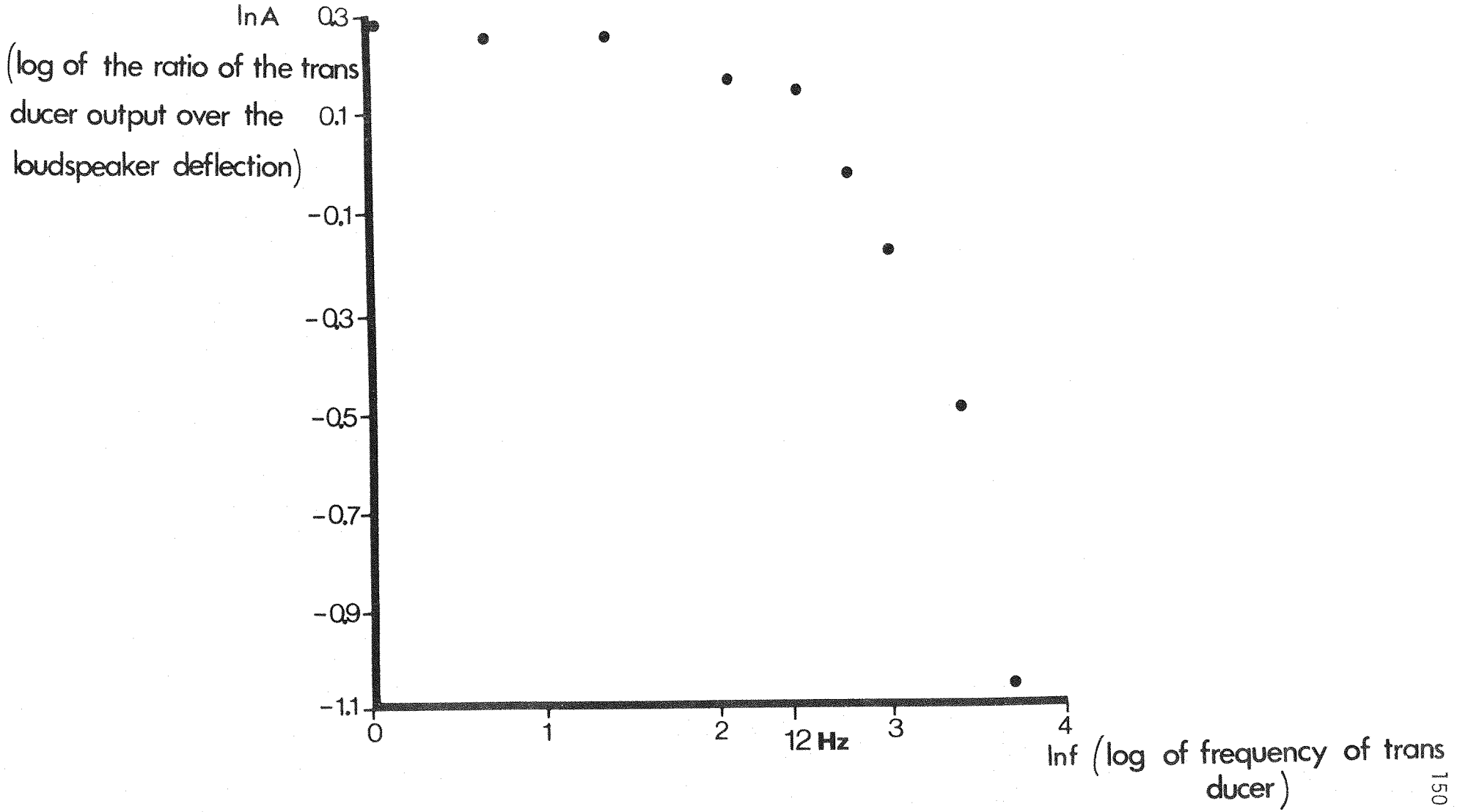


Fig. 23 - Frequency response of transducer (see text)

III. Calibration for volume

The pneumotachograph was calibrated using a 1 litre syringe which was emptied into and filled from a fast recording (60mm/min) water spirometer, at different flow rates. Flow rates were determined from the slope of the volume/time record and the percentage of error was then calculated (see Fig. 24).

It can be seen from this graph that an error of (1-2%) remains constant, except at very high flow rates.

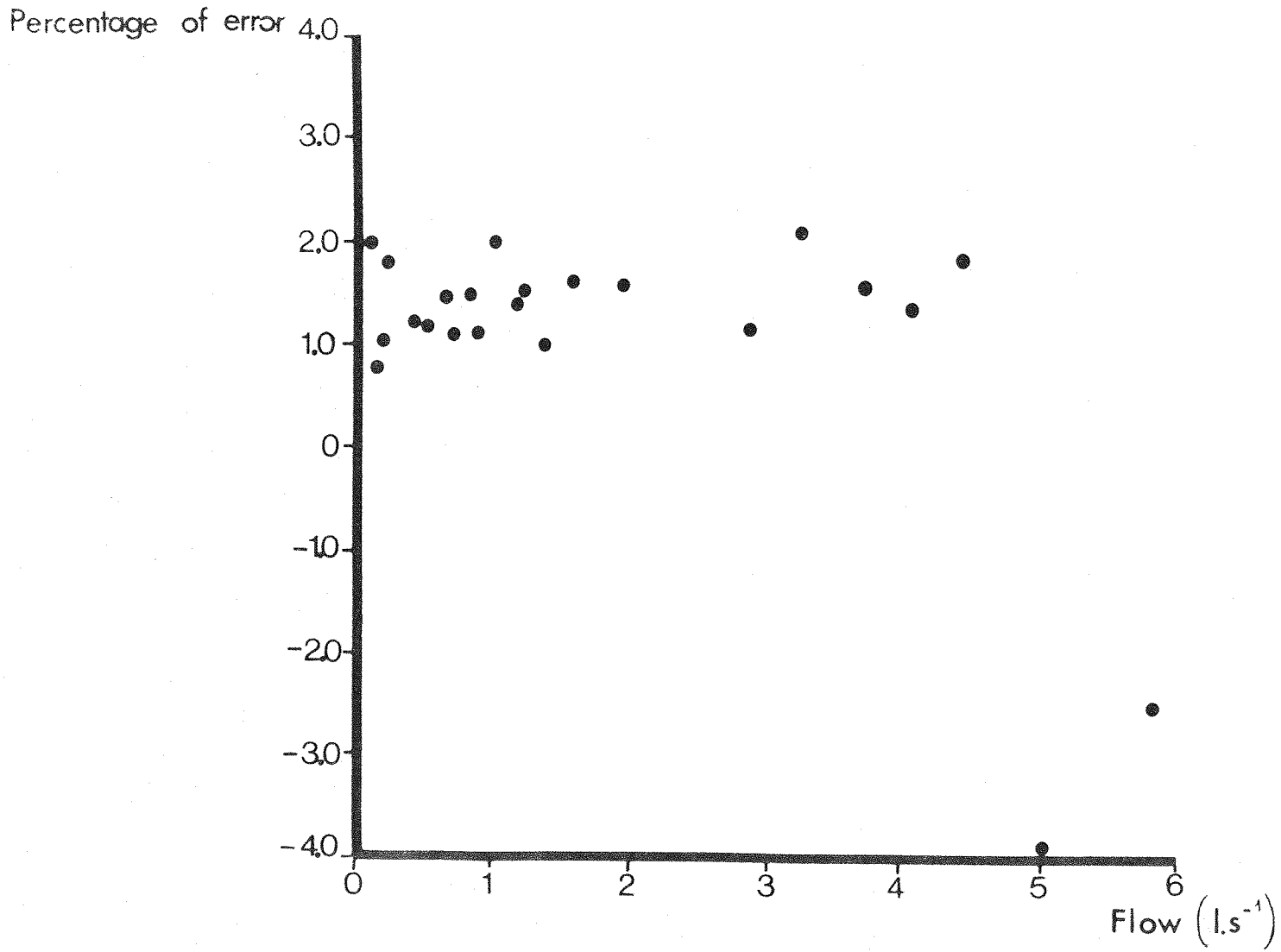


Fig. 24 - Calibration for volume (see text)

APPENDIX TWO

CROWN-CRISP EXPERIENTIAL INDEX

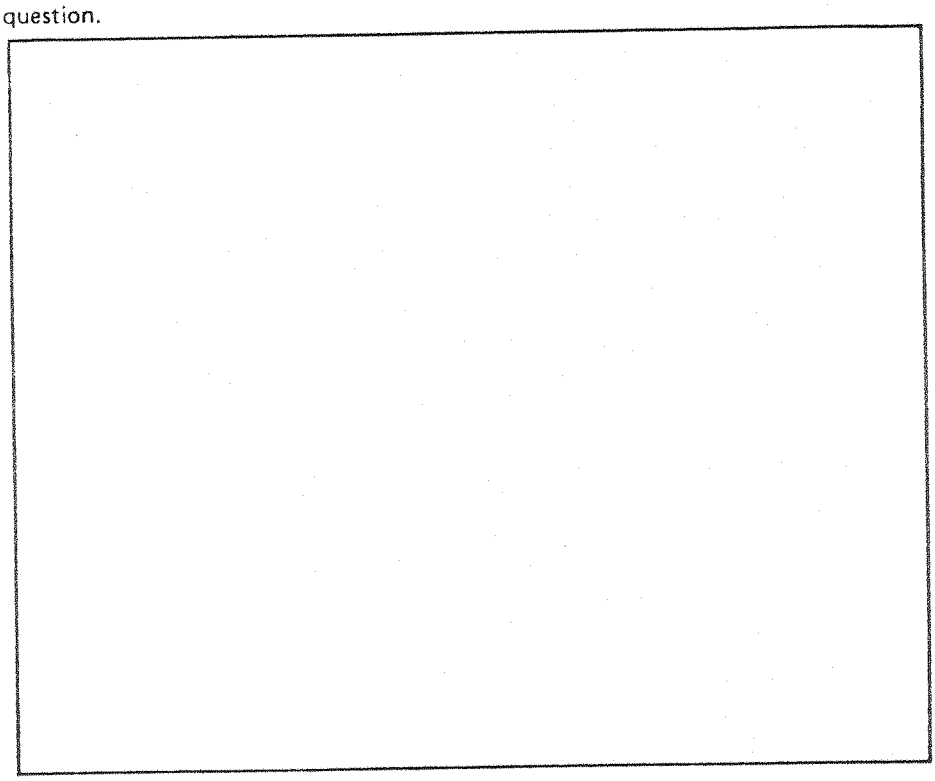
SURNAME ..... AGE.....

FIRST NAME(S) .....

TODAY'S DATE ..... SEX .....

Instructions

The questions overleaf are concerned with the way you feel or act. They are all simple. Please *tick* the answer that applies to you. Don't spend long on any one question.



Hodder and Stoughton

1. Do you often feel upset for no obvious reason? *Yes*..... *No*..... .....
2. Do you have an unreasonable fear of being in enclosed spaces such as shops, lifts, etc? *Often*..... *Sometimes*..... *Never*..... .....
3. Do people ever say you are too conscientious? *No*..... *Yes*..... .....
4. Are you troubled by dizzyness or shortness of breath? *Never*..... *Often*..... *Sometimes*..... .....
5. Can you think as quickly as you used to? *Yes*..... *No*..... .....
6. Are your opinions easily influenced? *Yes*..... *No*..... .....
7. Have you felt as though you might faint? *Frequently*..... *Occasionally*..... *Never*..... .....
8. Do you find yourself worrying about getting some incurable illness? *Never*..... *Sometimes*..... *Often*..... .....
9. Do you think that 'cleanliness is next to godliness'? *No*..... *Yes*..... .....
10. Do you often feel sick or have indigestion? *Yes*..... *No*..... .....
11. Do you feel that life is too much effort? *At times*..... *Often*..... *Never*..... .....
12. Have you, at any time in your life, enjoyed acting? *Yes*..... *No*..... .....
13. Do you feel uneasy and restless? *Frequently*..... *Sometimes*..... *Never*..... .....
14. Do you feel more relaxed indoors? *Definitely*..... *Sometimes*..... *Not particularly*..... .....
15. Do you find that silly or unreasonable thoughts keep recurring in your mind? *Frequently*..... *Sometimes*..... *Never*..... .....
16. Do you sometimes feel tingling or pricking sensations in your body, arms or legs? *Rarely*..... *Frequently*..... *Never*..... .....
17. Do you regret much of your past behaviour? *Yes*..... *No*..... .....
18. Are you normally an excessively emotional person? *Yes*..... *No*..... .....
19. Do you sometimes feel really panicky? *No*..... *Yes*..... .....
20. Do you feel uneasy traveiling on buses or the Underground even if they are not crowded? *Very*..... *A little*..... *Not at all*..... .....
21. Are you happiest when you are working? *Yes*..... *No*..... .....
22. Has your appetite got less recently? *No*..... *Yes*..... .....
23. Do you wake unusually early in the morning? *Yes*..... *No*..... .....
24. Do you enjoy being the centre of attention? *No*..... *Yes*..... .....

25. Would you say you were a worrying person?
Very..... Fairly..... Not at all..... .....

26. Do you dislike going out alone? *Yes..... No.....* .....

27. Are you a perfectionist? *No..... Yes.....* .....

28. Do you feel unduly tired and exhausted?
Often..... Sometimes..... Never..... .....

29. Do you experience long periods of sadness?
Never..... Often..... Sometimes..... .....

30. Do you find that you take advantage of circumstances for your own ends?
Never..... Sometimes..... Often..... .....

31. Do you often feel 'strung-up' inside? *Yes..... No.....* .....

32. Do you worry unduly when relatives are late coming home?
No..... Yes..... .....

33. Do you have to check things you do to an unnecessary extent?
Yes..... No..... .....

34. Can you get off to sleep alright at the moment? *No..... Yes.....* .....

35. Do you have to make a special effort to face up to a crisis or difficulty?
Very much so..... Sometimes..... Not more than anyone else..... .....

36. Do you often spend a lot of money on clothes? *Yes..... No.....* .....

37. Have you ever had the feeling you were 'going to pieces'? *Yes..... No.....* .....

38. Are you scared of heights? *Very..... Fairly..... Not at all.....* .....

39. Does it irritate you if your normal routine is disturbed?
Greatly..... A little..... Not at all..... .....

40. Do you often suffer from excessive sweating or fluttering of the heart?
No..... Yes..... .....

41. Do you find yourself needing to cry?
Frequently..... Sometimes..... Never..... .....

42. Do you enjoy dramatic situations? *Yes..... No.....* .....

43. Do you have bad dreams which upset you when you wake up?
Never..... Sometimes..... Frequently..... .....

44. Do you feel panicky in crowds? *Always..... Sometimes..... Never.....* .....

45. Do you find yourself worrying unreasonably about things that do not really matter? *Never..... Frequently..... Sometimes.....* .....

46. Has your sexual interest altered? *Less..... The same or greater.....* .....

47. Have you lost your ability to feel sympathy for other people?
No..... Yes..... .....

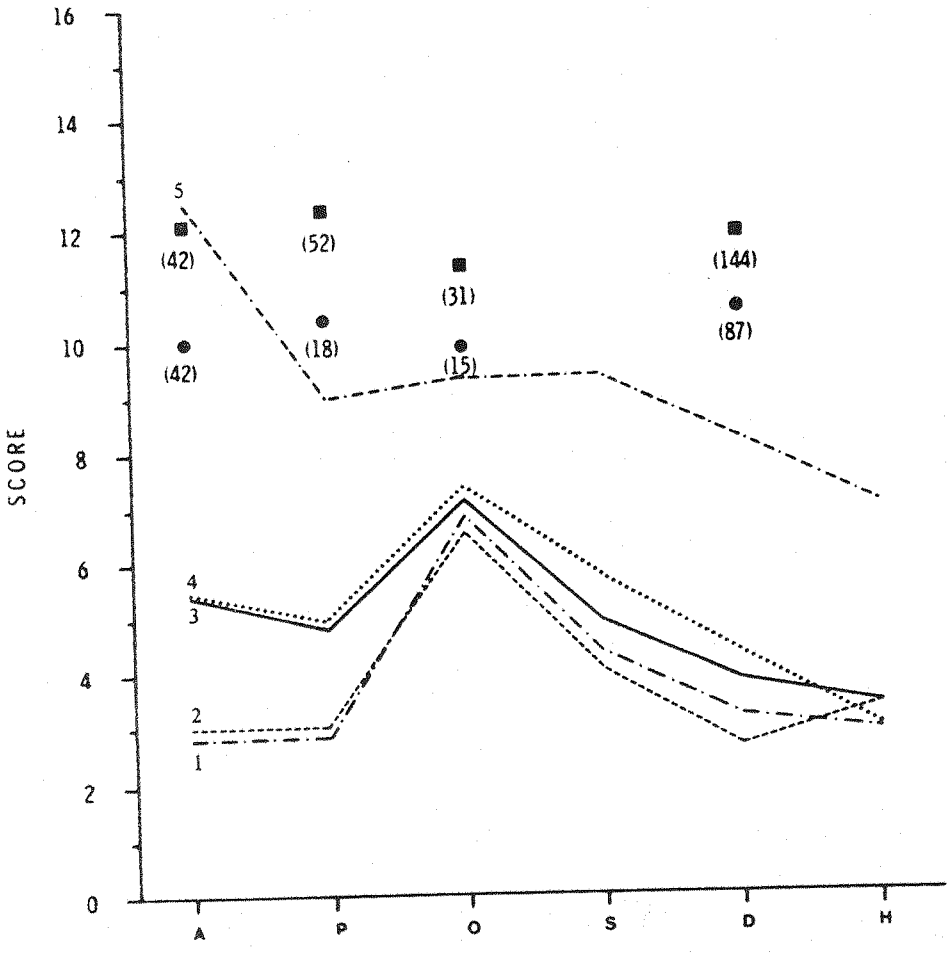
48. Do you sometimes find yourself posing or pretending? *Yes..... No.....* .....

PLEASE CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS

For office use only

A ..... O ..... D .....

P ..... S ..... H .....



Refer to Figure 1 in the Manual (p.10) for profile data

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APPENDIX THREE

Fig. 25 - The graphs contained in this Appendix are the individual graphs for the 15 subjects studied during the CO_2 re-breathing, on the first and second occasion (first occasion is shown on the left and second occasion is shown on the right).

The following symbols apply to all graphs:

●——● ventilation and frequency

●----● dP/dt max and tidal volume

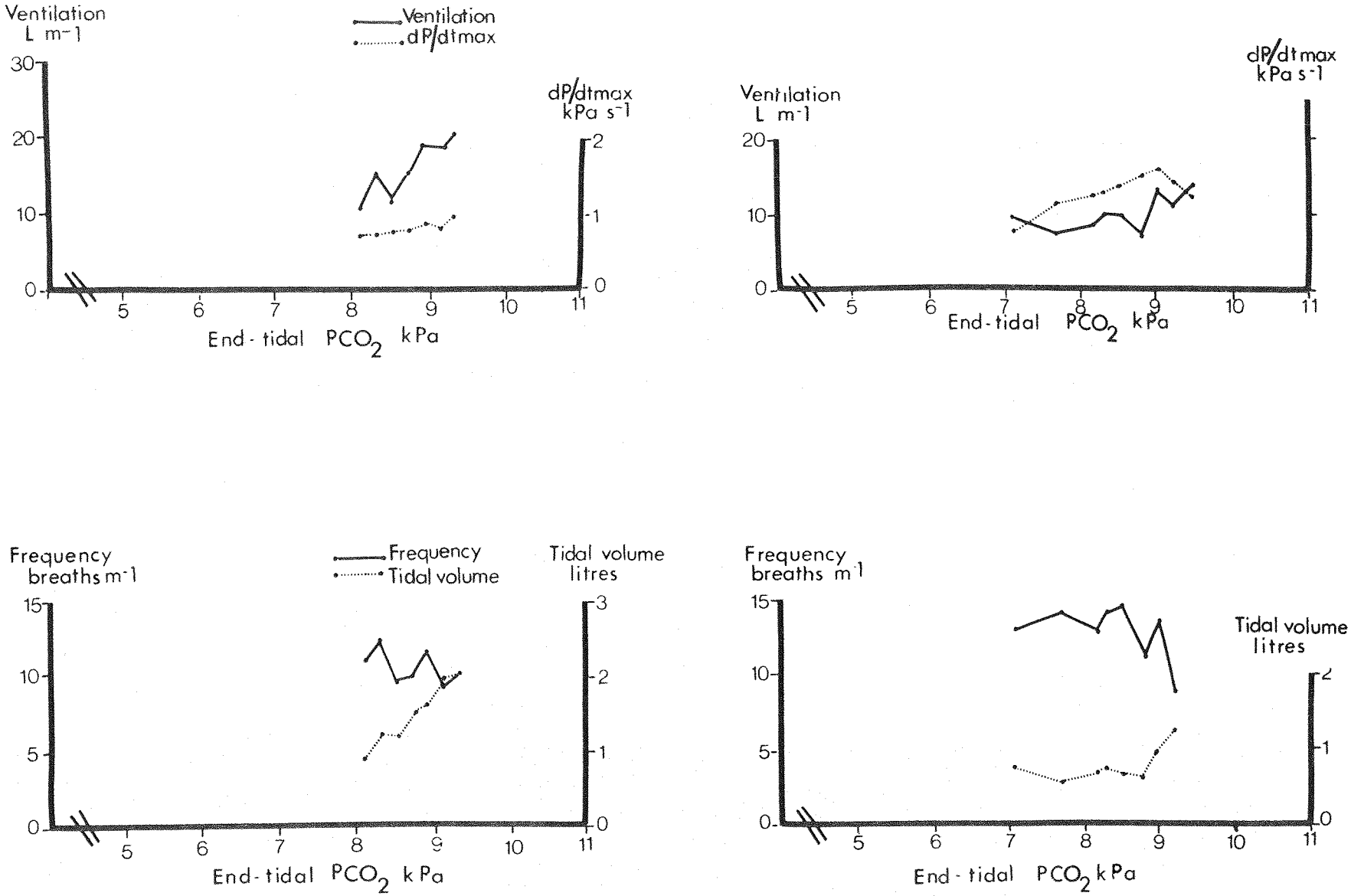
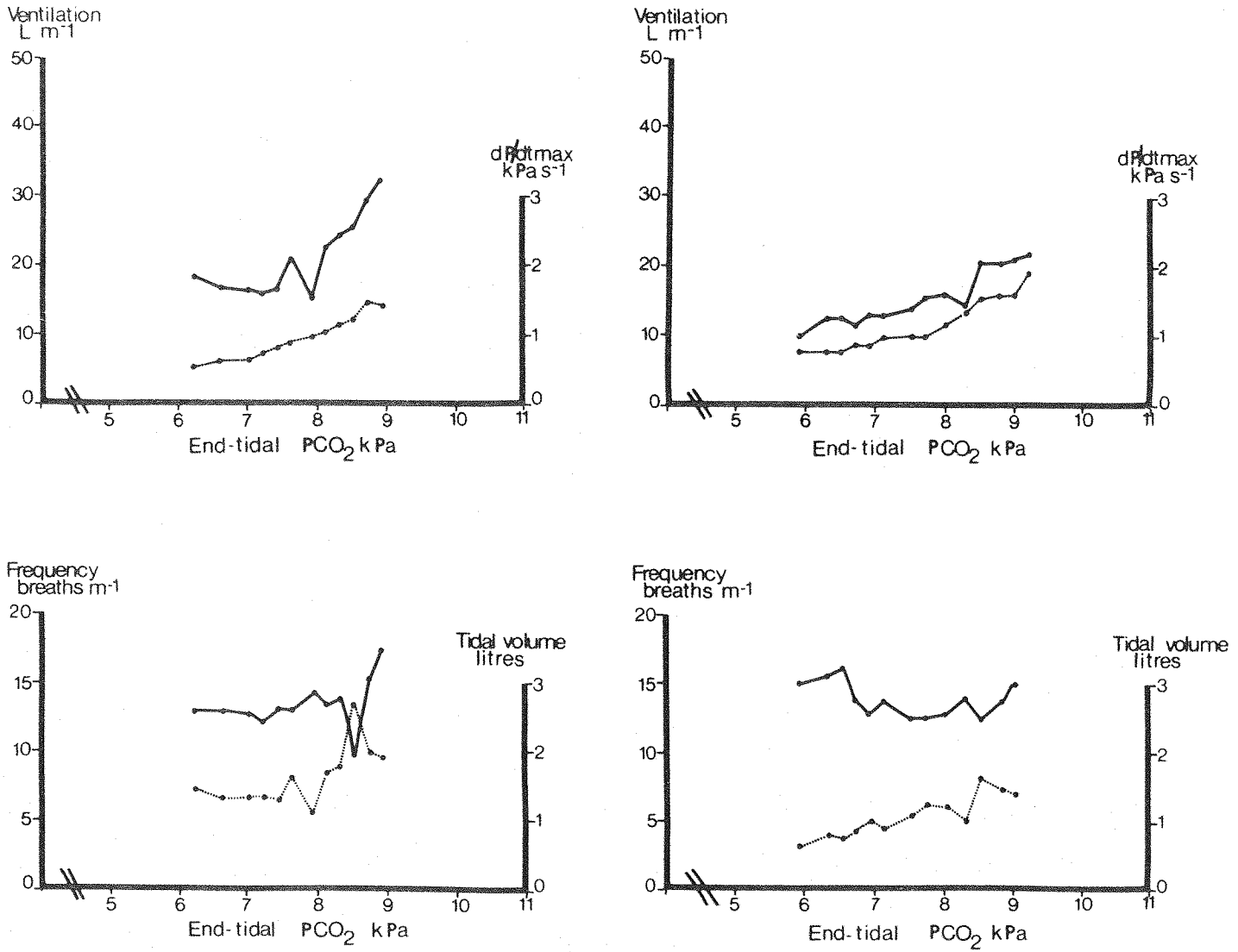
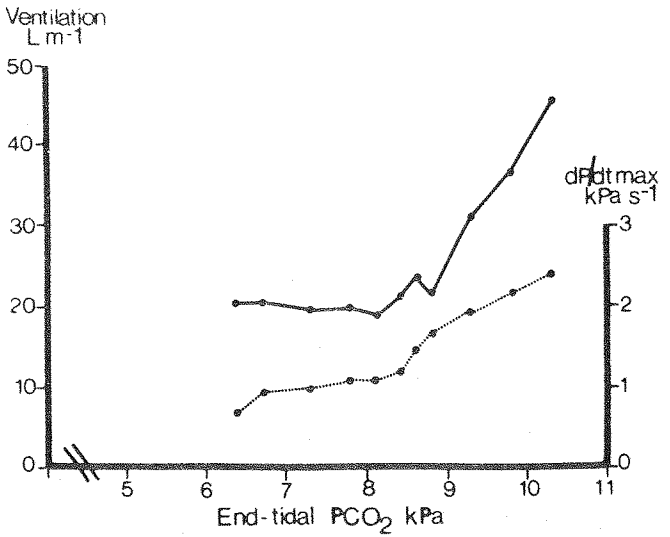


Fig. 25. Subject 1.


Ventilation
L m-1
50
40
30
20
10
0
dP/dtmax
kPa s-1
3
2
1
0
5
6
7
8
9
10
11
End-tidal PCO2 kPa
Ventilation
L m-1
dP/dtmax
kPa s-1
End-tidal PCO2 kPa
Frequency
breaths m-1
20
15
10
5
0
Tidal volume
litres
End-tidal PCO2 kPa
Frequency
breaths m-1
Tidal volume
litres
End-tidal PCO2 kPa

Subject 2.


Ventilation
L m-1
50
40
30
20
10
0
dP/dt max
kPa s-1
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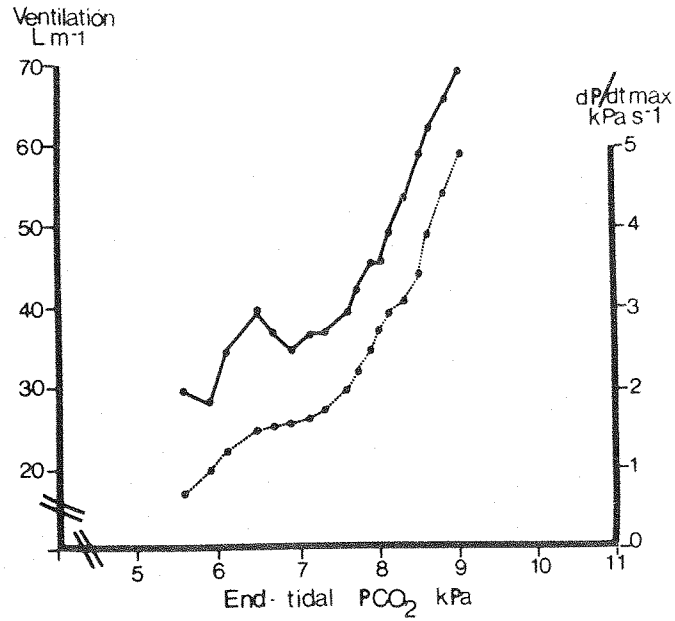
8
9
10
11
End-tidal PCO2 kPa


Ventilation
L m-1
70
60
50
40
30
20
dP/dt max
kPa s-1
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7
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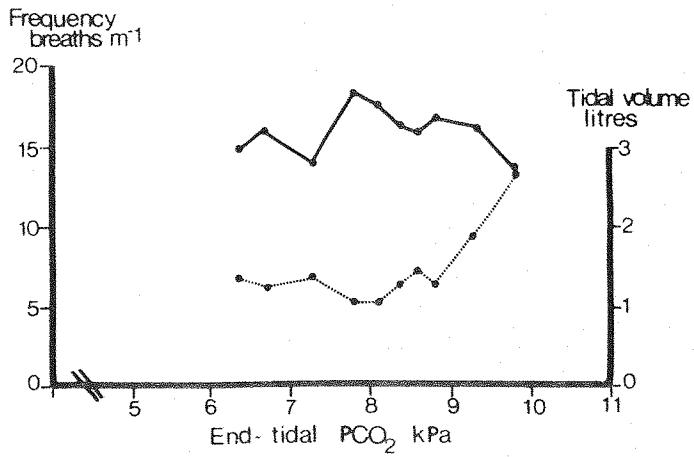
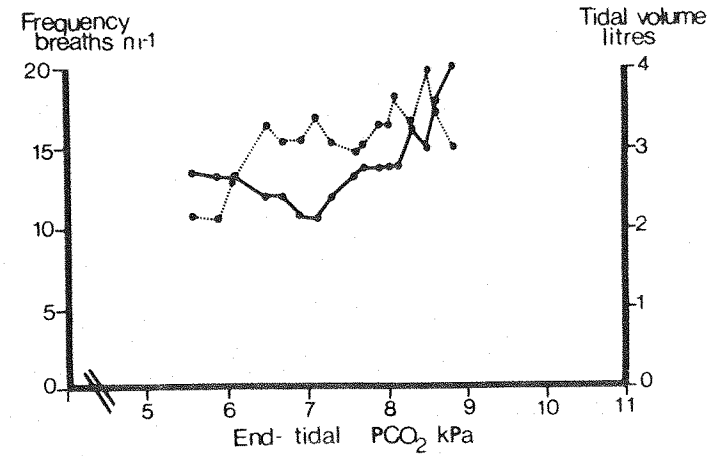
11
End- tidal PCO2 kPa


Frequency
breaths m-1
20
15
10
5
0
Tidal volume
litres
3
2
1
0
5
6
7
8
9
10
11
End- tidal PCO2 kPa


Frequency
breaths m-1
20
15
10
5
0
Tidal volume
litres
4
3
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0
5
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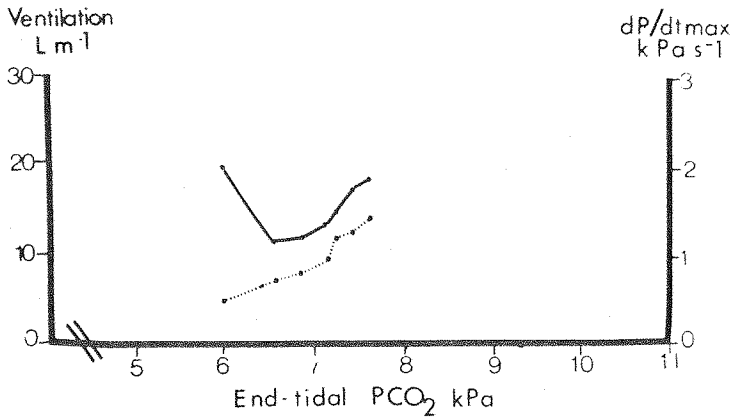
7
8
9
10
11
End- tidal PCO2 kPa

Subject 3.


Ventilation
L m-1
dP/dtmax
k Pa s-1
30
20
10
0
3
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1
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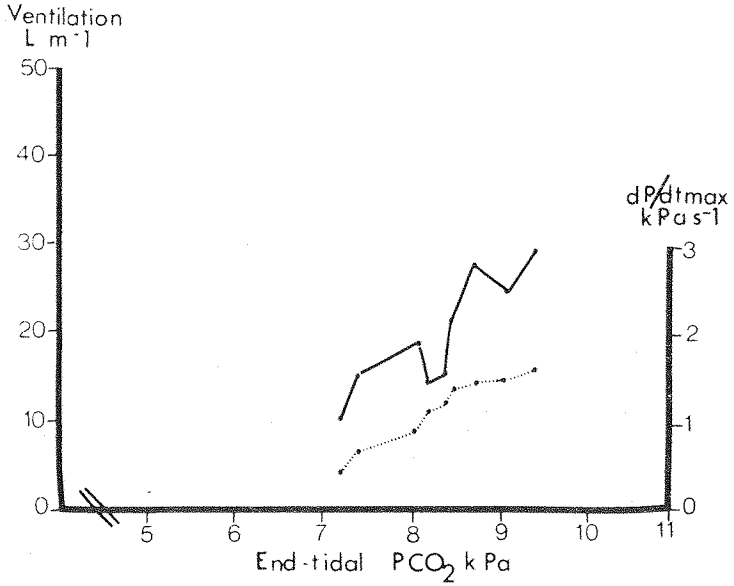
5
6
7
8
9
10
11
End-tidal PCO2 kPa


Ventilation
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dP/dtmax
k Pa s-1
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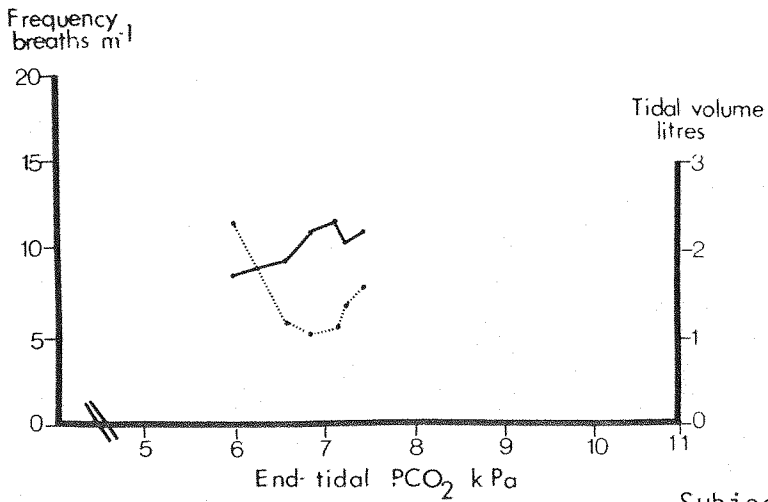
10
11
End-tidal PCO2 k Pa


Frequency
breaths m-1
Tidal volume
litres
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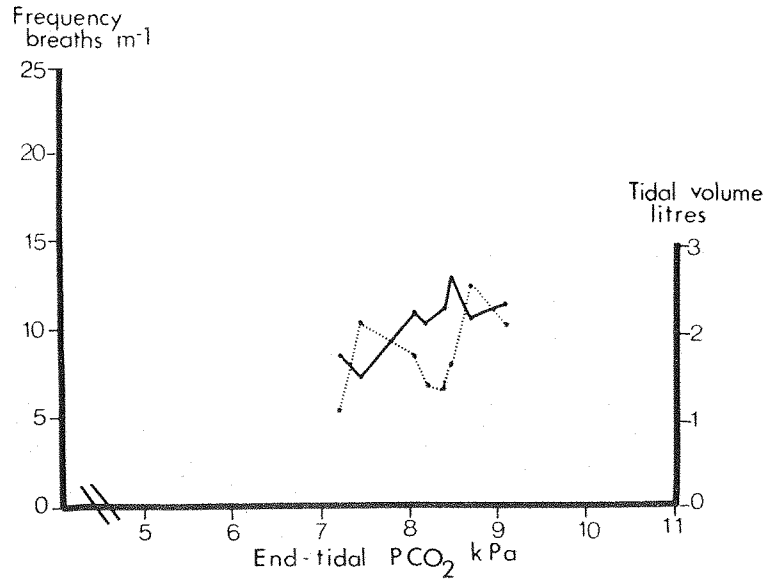
11
End-tidal PCO2 k Pa


Frequency
breaths m-1
Tidal volume
litres
25
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15
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3
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5
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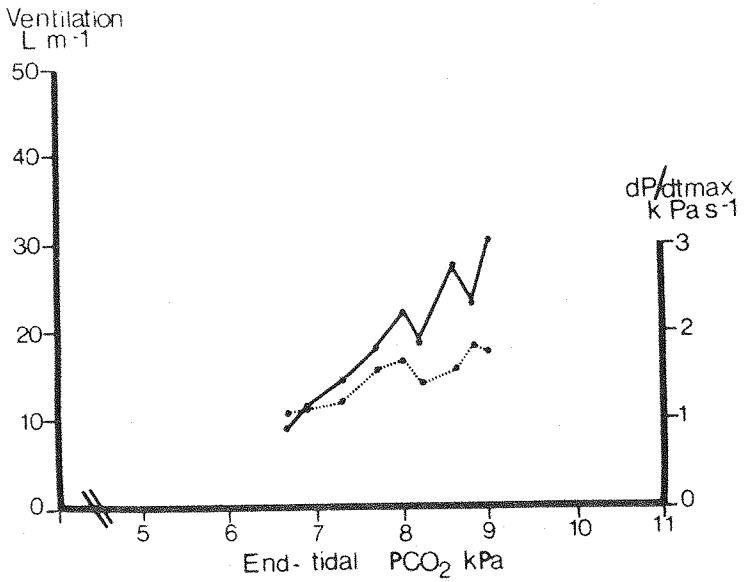
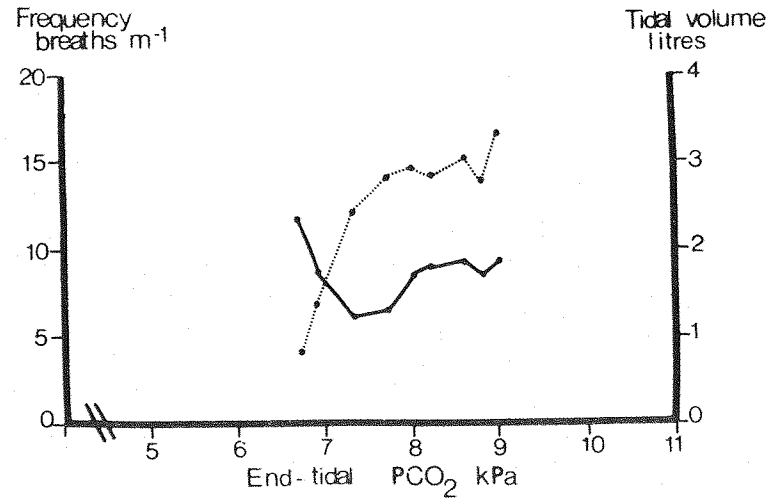
8
9
10
11
End-tidal PCO2 k Pa

Subject 4.



Not available on the second occasion



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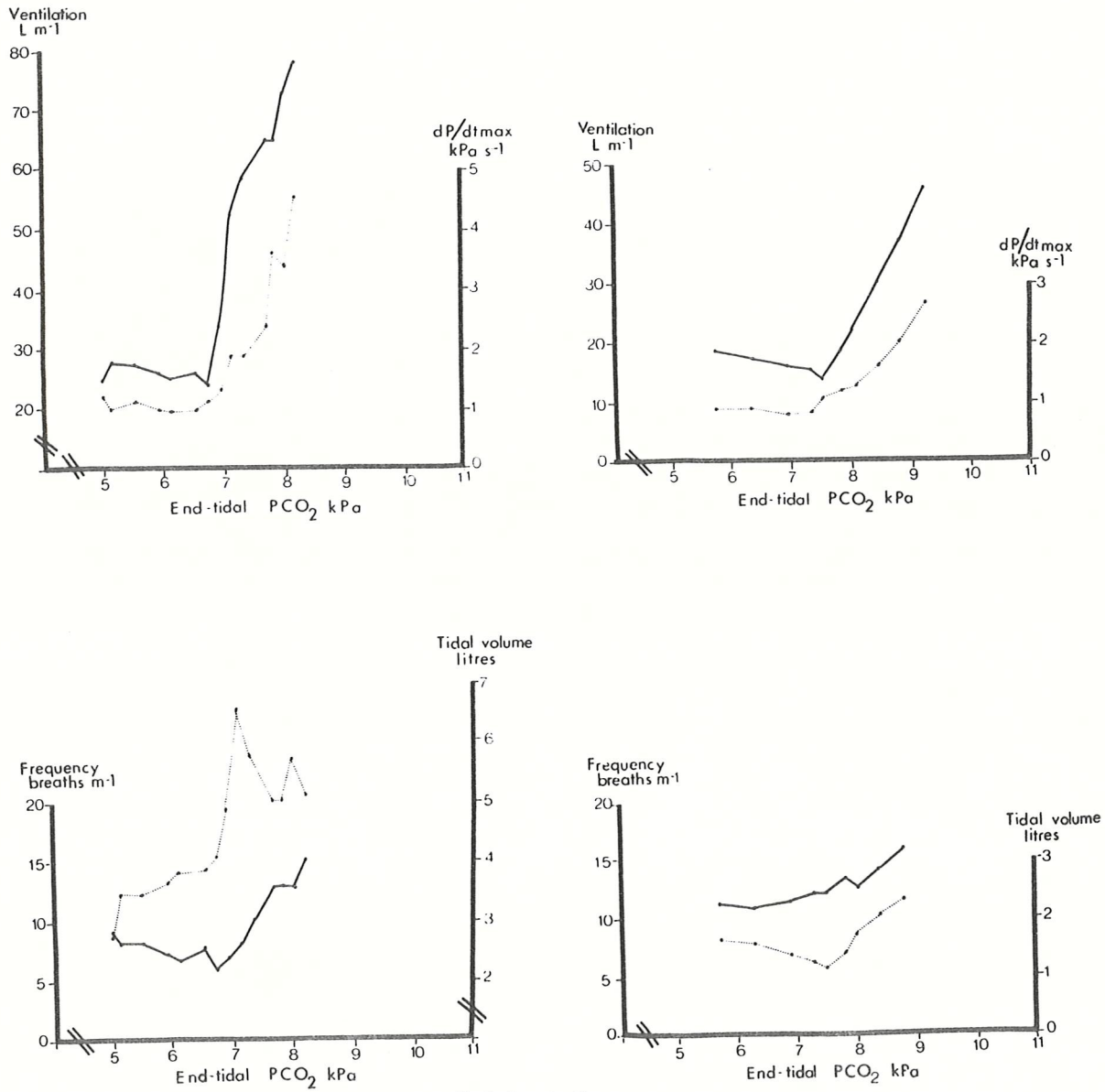
Ventilation
L m-1
80
70
60
50
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dP/dtmax
kPa s-1
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11
End-tidal PCO2 kPa
Ventilation
L m-1
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30
20
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0
dP/dtmax
kPa s-1
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11
End-tidal PCO2 kPa
Tidal volume
litres
Frequency
breaths m-1
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11
End-tidal PCO2 kPa
Frequency
breaths m-1
20
15
10
5
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Tidal volume
litres
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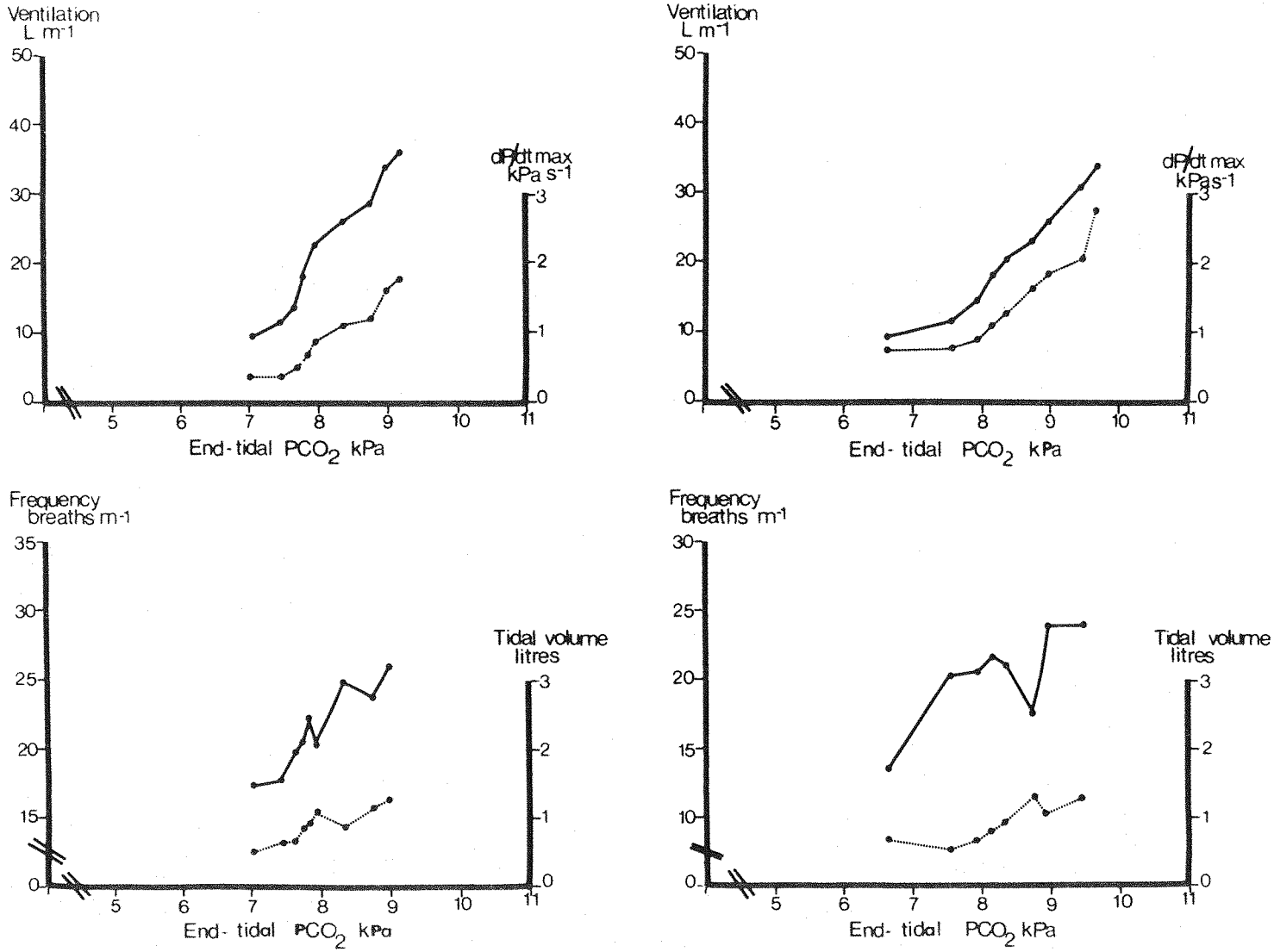
11
End-tidal PCO2 kPa

Subject 6.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20
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dP/dt max
kPa s-1
3
2
1
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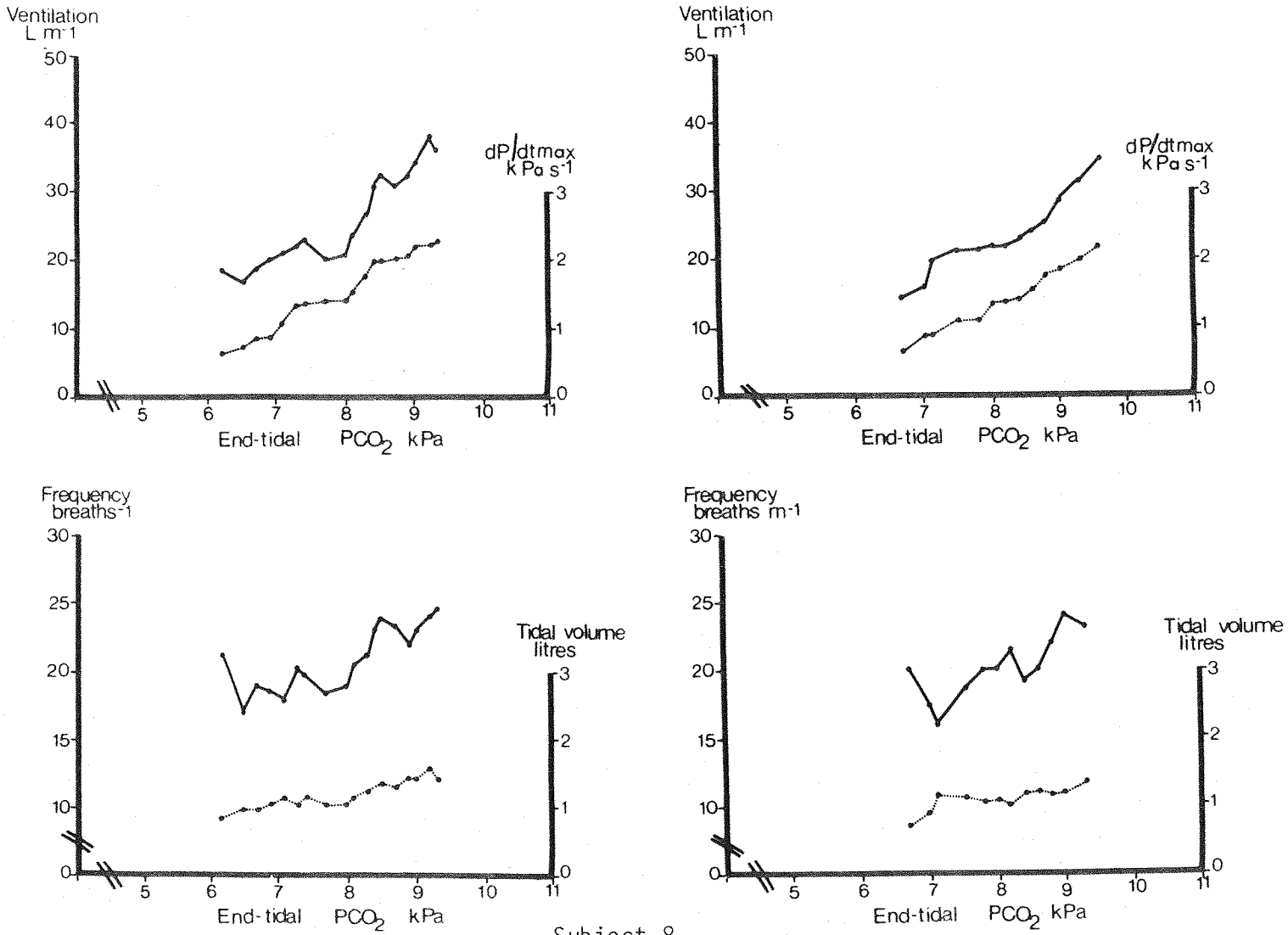
5
6
7
8
9
10
11
End-tidal PCO2 kPa
Ventilation
L m-1
dP/dt max
kPa s-1
End-tidal PCO2 kPa
Frequency
breaths m-1
35
30
25
20
15
0
Tidal volume
litres
End-tidal PCO2 kPa
Frequency
breaths m-1
Tidal volume
litres
End-tidal PCO2 kPa

Subject 7.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30
20
10
0
dP/dtmax
kPa s-1
3
2
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0
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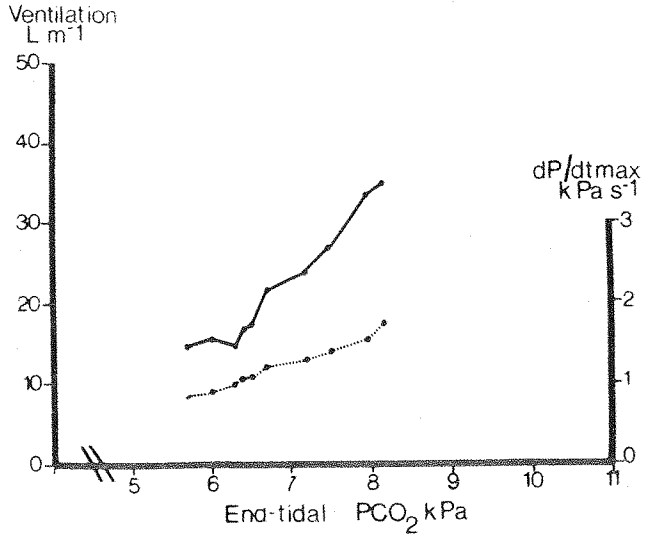
6
7
8
9
10
11
End-tidal PCO2 kPa
Ventilation
L m-1
dP/dtmax
kPa s-1
End-tidal PCO2 kPa
Frequency
breaths-1
30
25
20
15
10
0
Tidal volume
litres
End-tidal PCO2 kPa
Frequency
breaths m-1
Tidal volume
litres
End-tidal PCO2 kPa

Subject 8.


Ventilation
L m-1
50
40
30
20
10
0
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kPa s-1
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8
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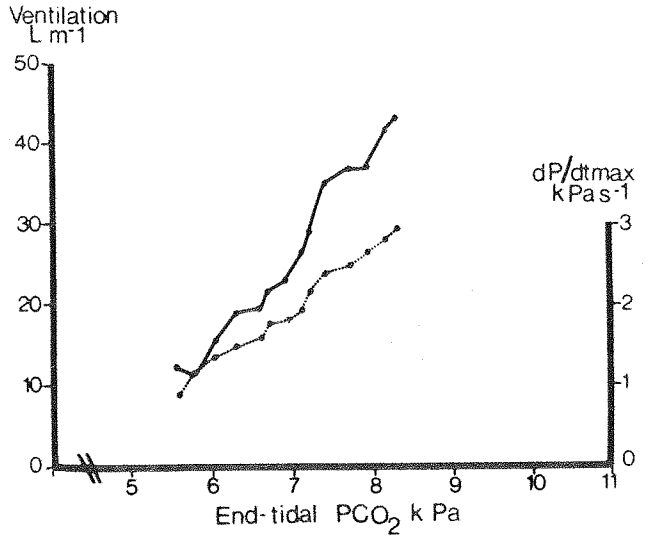
End-tidal PCO2 kPa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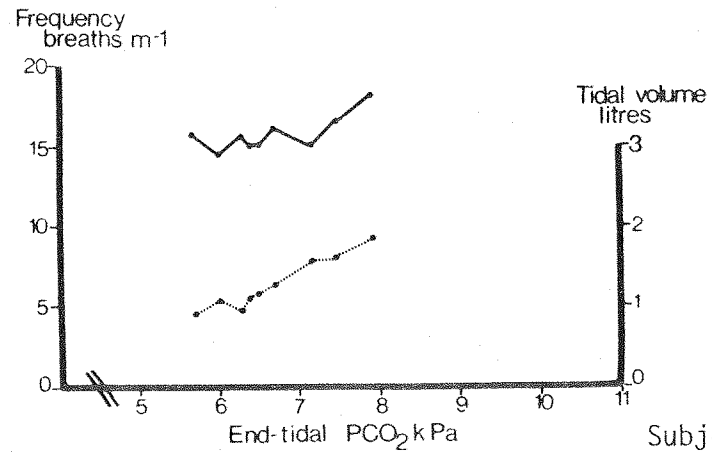
11
End-tidal PCO2 k Pa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Tidal volume
litres
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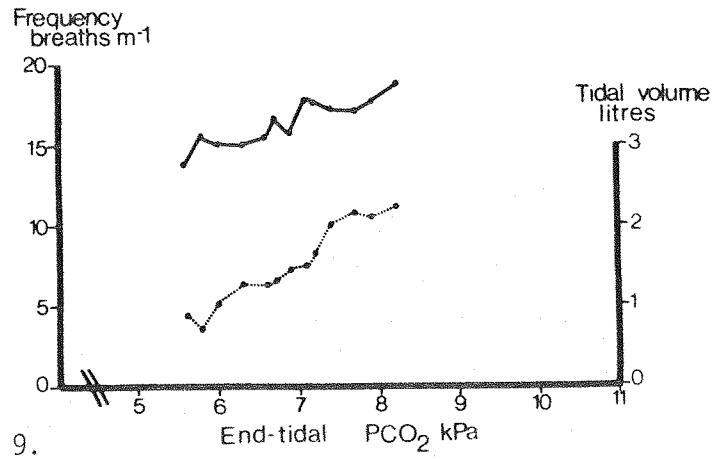
End-tidal PCO2 kPa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Tidal volume
litres
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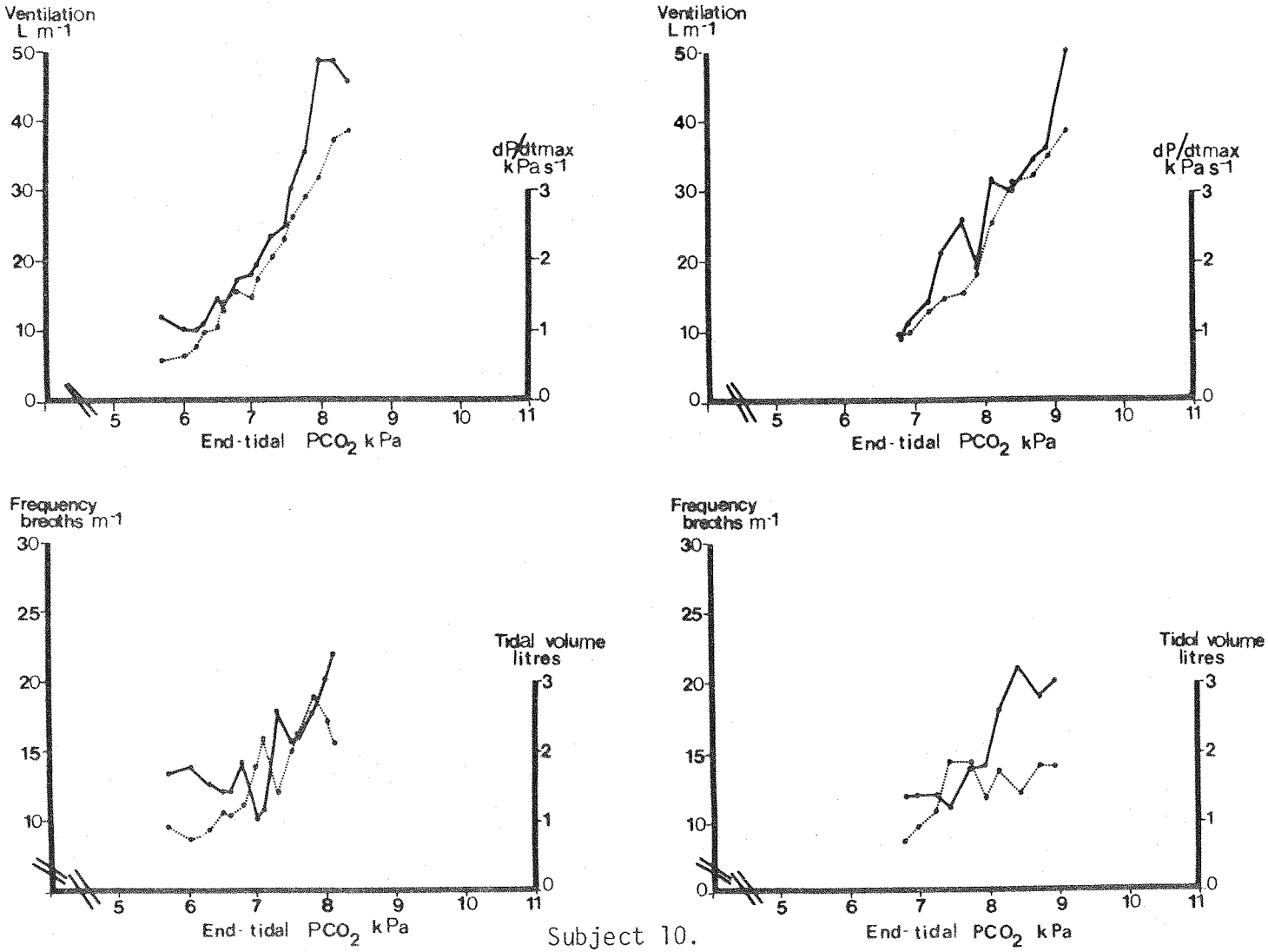
End-tidal PCO2 kPa

Subject 9.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kPa s-1
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7
8
9
10
11
End-tidal PCO2 kPa
Ventilation
L m-1
dP/dtmax
kPa s-1
End-tidal PCO2 kPa
Frequency
breaths m-1
30
25
20
15
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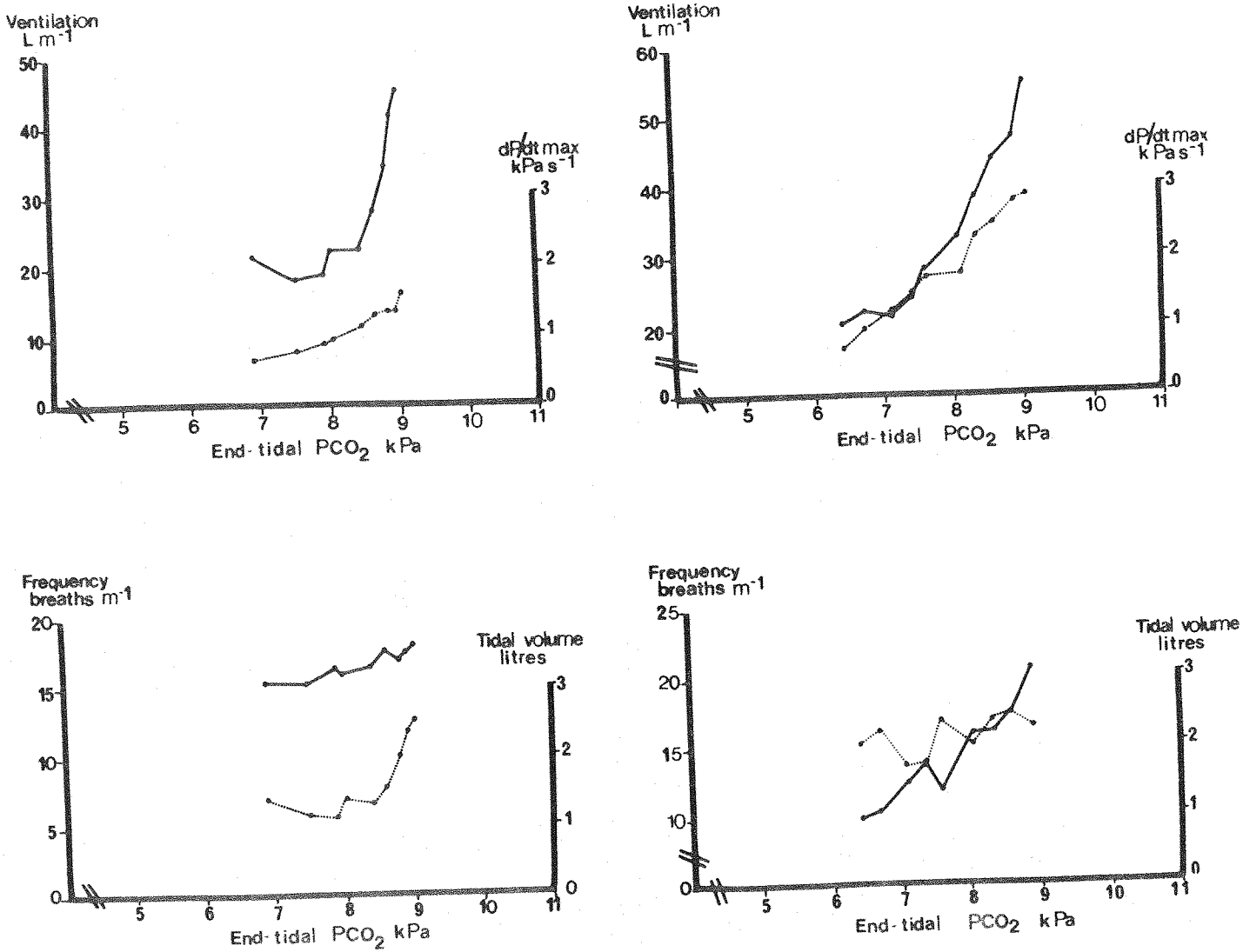
Tidal volume
litres
End-tidal PCO2 kPa
Frequency
breaths m-1
Tidal volume
litres
End-tidal PCO2 kPa

Subject 10.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dP/dt max
kPa s-1
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10
11
End-tidal PCO2 kPa
Ventilation
L m-1
60
50
40
30
20
0
dP/dt max
kPa s-1
3
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1
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9
10
11
End-tidal PCO2 kPa
Frequency
breaths m-1
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0
Tidal volume
litres
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End-tidal PCO2 kPa
Frequency
breaths m-1
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Tidal volume
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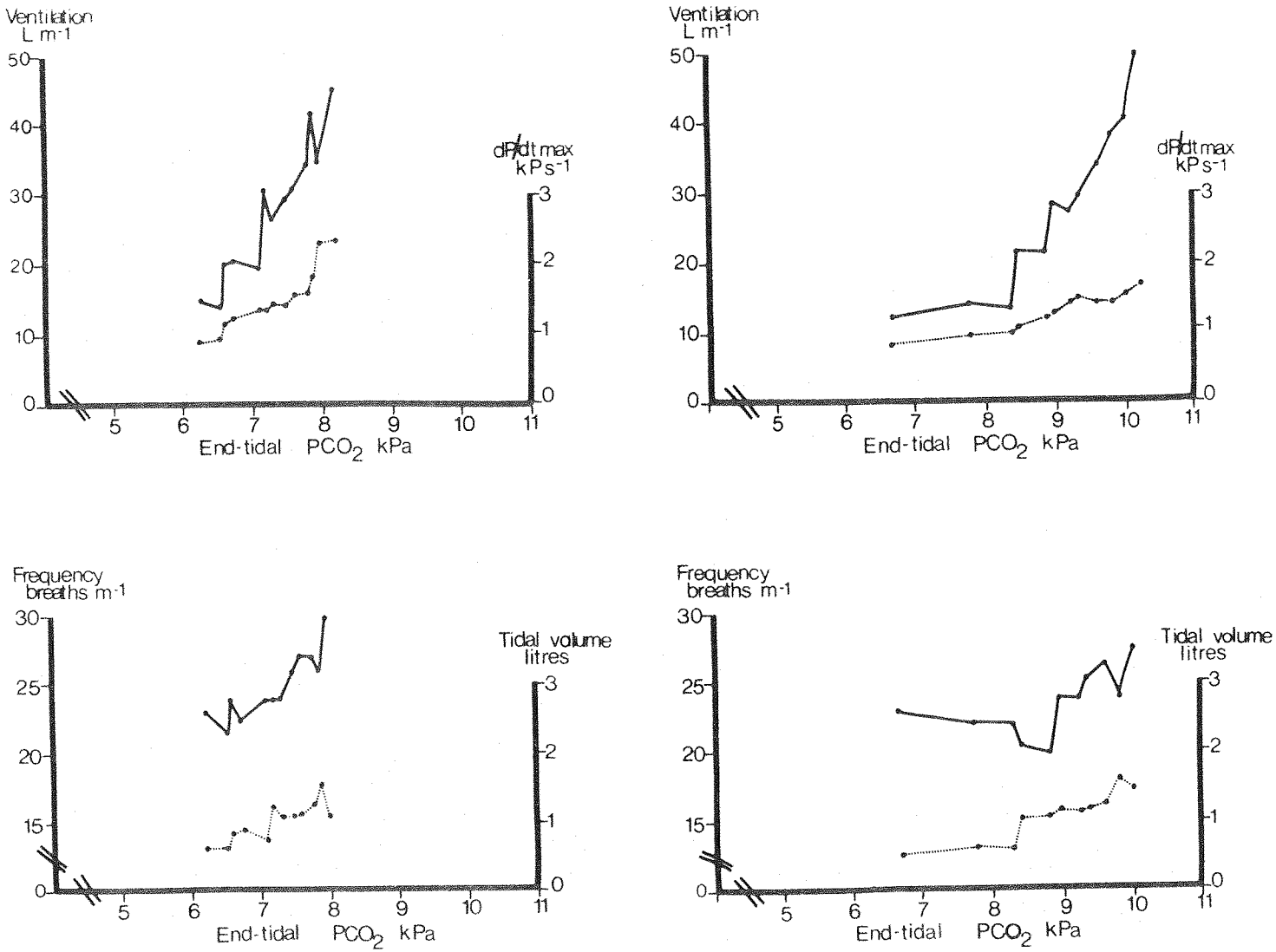
End-tidal PCO2 kPa

Subject 11.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End-tidal PCO2 kPa
Ventilation
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dP/dt max
kPs-1
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End-tidal PCO2 kPa
Frequency
breaths m-1
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Tidal volume
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End-tidal PCO2 kPa
Frequency
breaths m-1
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Tidal volume
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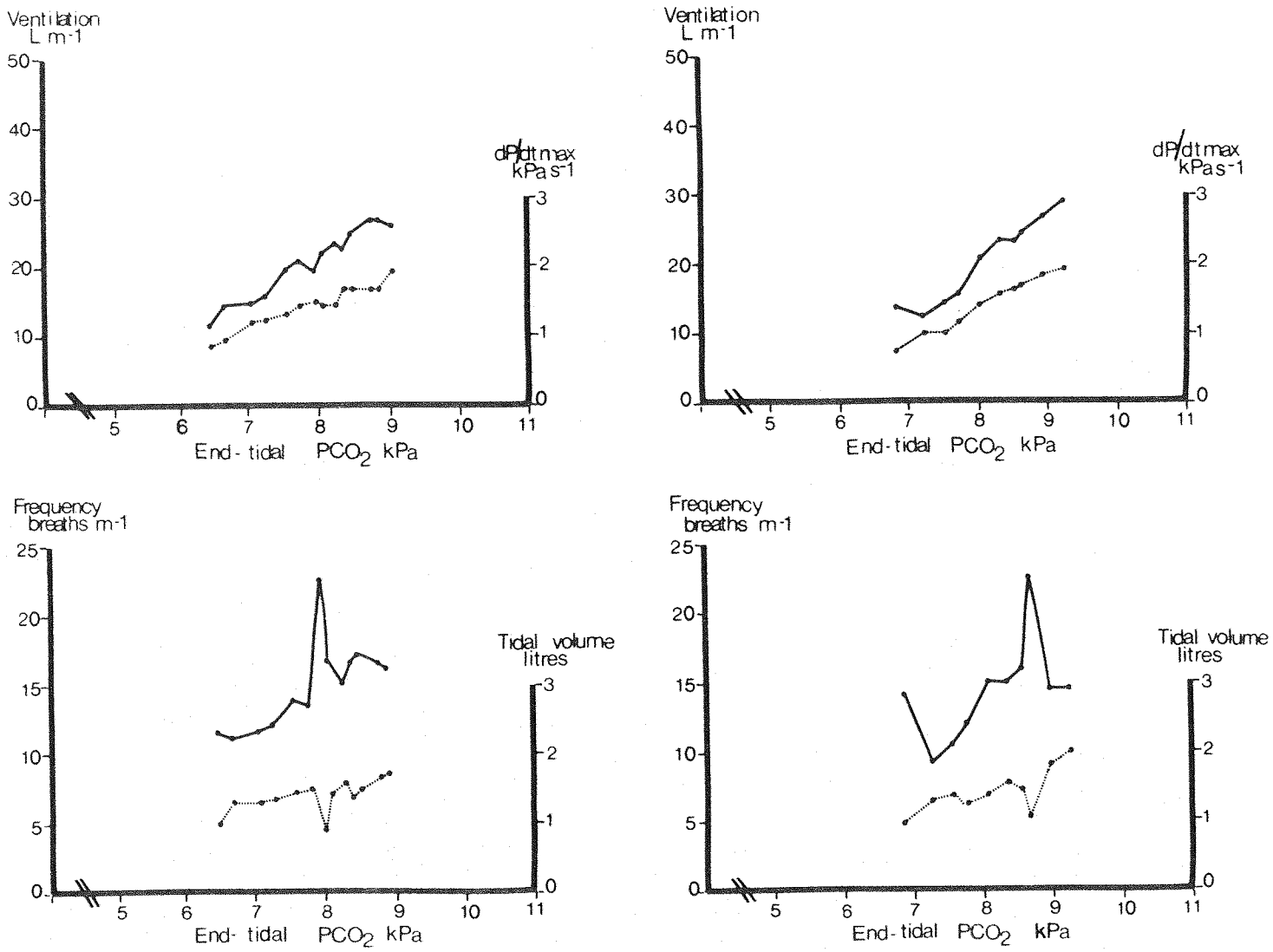
End-tidal PCO2 kPa

Subject 12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End-tidal PCO2 kPa
Ventilation
L m-1
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40
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dP/dt max
kPa s-1
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11
End-tidal PCO2 kPa
Frequency
breaths m-1
25
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Tidal volume
litres
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End-tidal PCO2 kPa
Frequency
breaths m-1
25
20
15
10
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Tidal volume
litres
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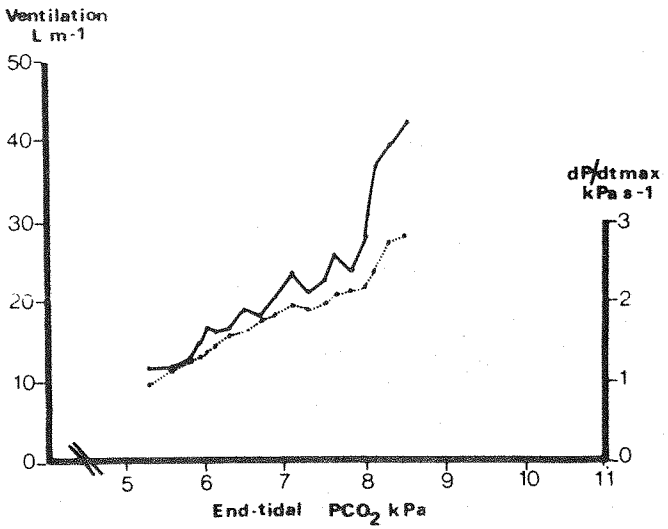
11
End-tidal PCO2 kPa

Subject 13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kPa s-1
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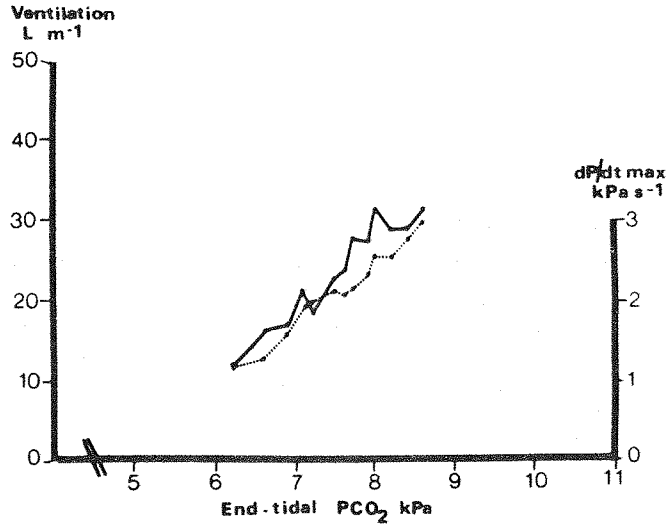
11
End-tidal PCO2 kPa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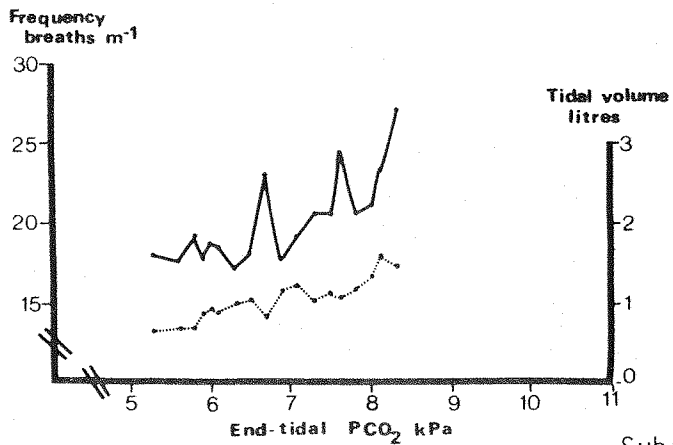
11
End-tidal PCO2 kPa


Frequency
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litres
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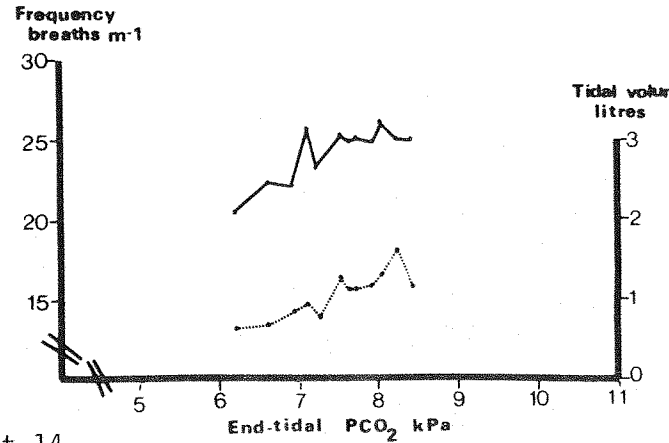
11
End-tidal PCO2 kPa


Frequency
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20
15
Tidal volume
litres
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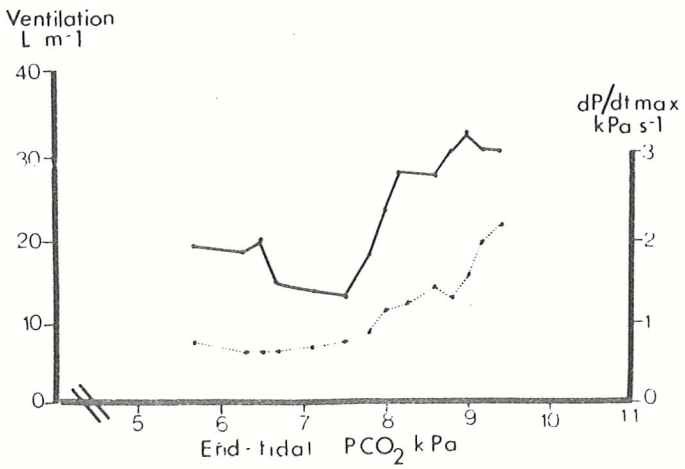
11
End-tidal PCO2 kPa

Subject 14


Ventilation
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40
30
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10
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dP/dt max
kPa s-1
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1
0
5
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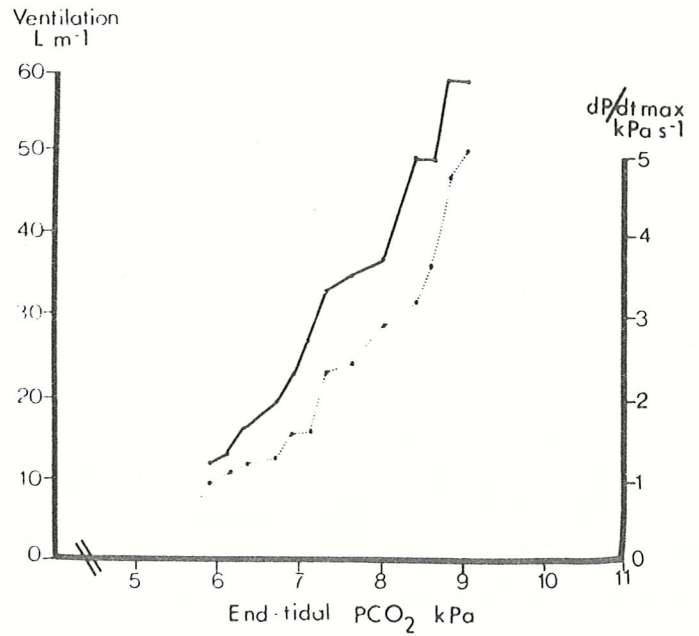
7
8
9
10
11
End-tidal PCO2 kPa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kPa s-1
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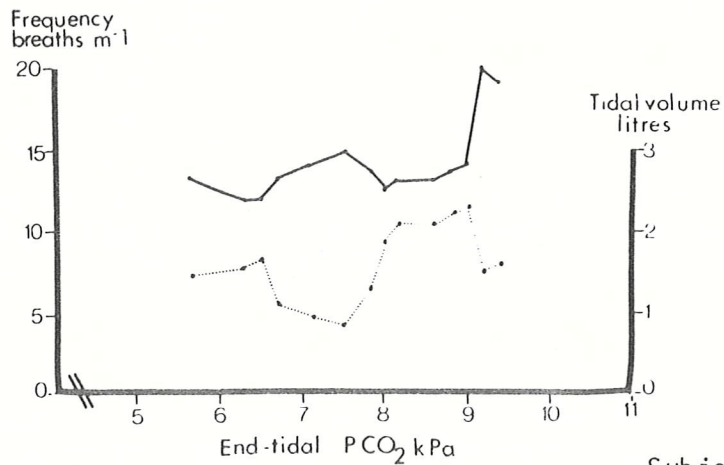
11
End-tidal PCO2 kPa


Frequency
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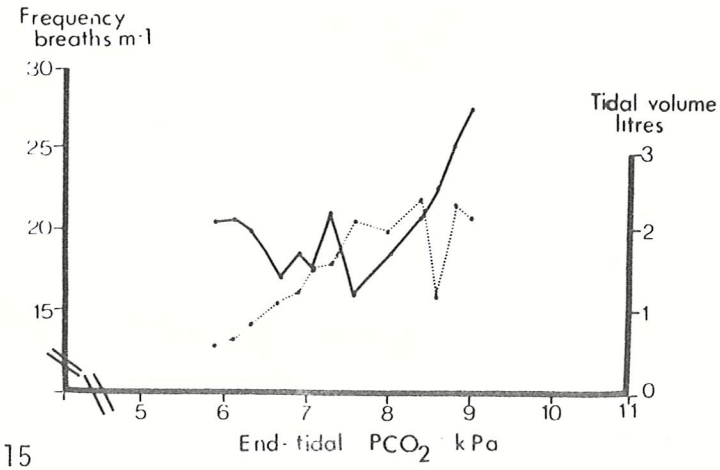
End-tidal PCO2 kPa


Frequency
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Tidal volume
litres
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End-tidal PCO2 kPa

Subject 15

APPENDIX FOUR

Fig. 26 - The graphs which follow are the individual graphs for the seven subjects in whom Ti and Te were measured, in breath-by-breath.

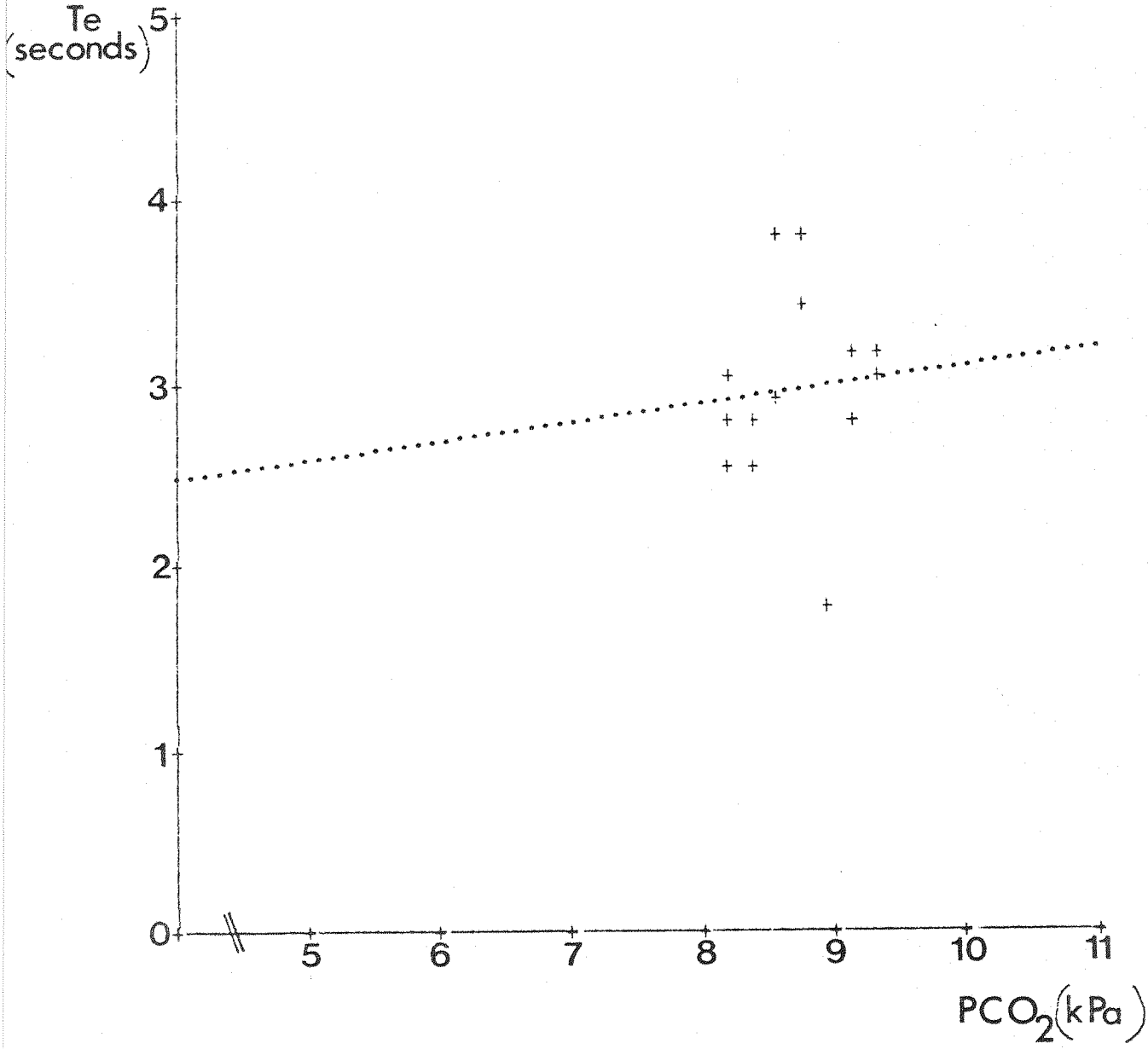
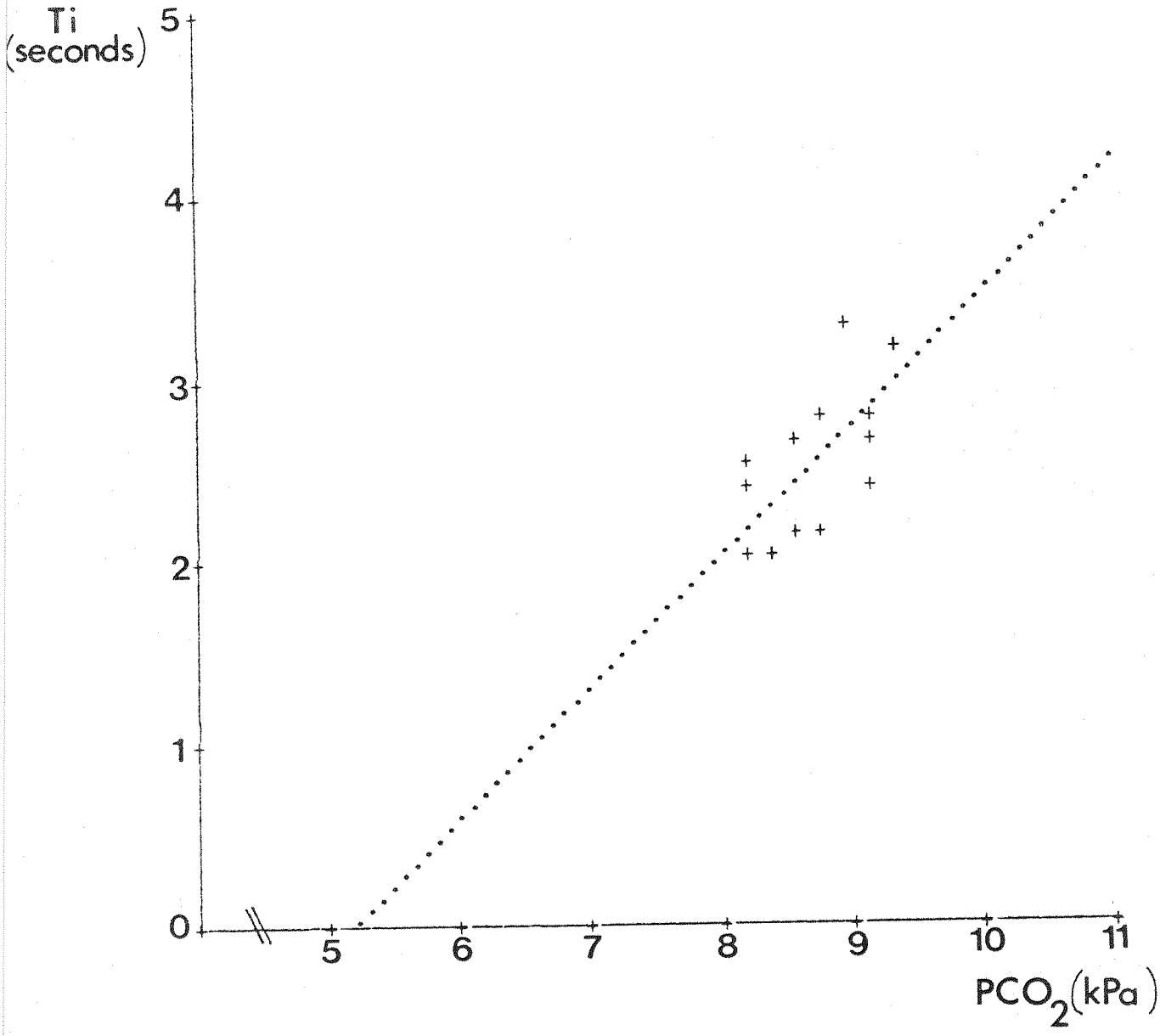


Fig. 26. Subject 1.



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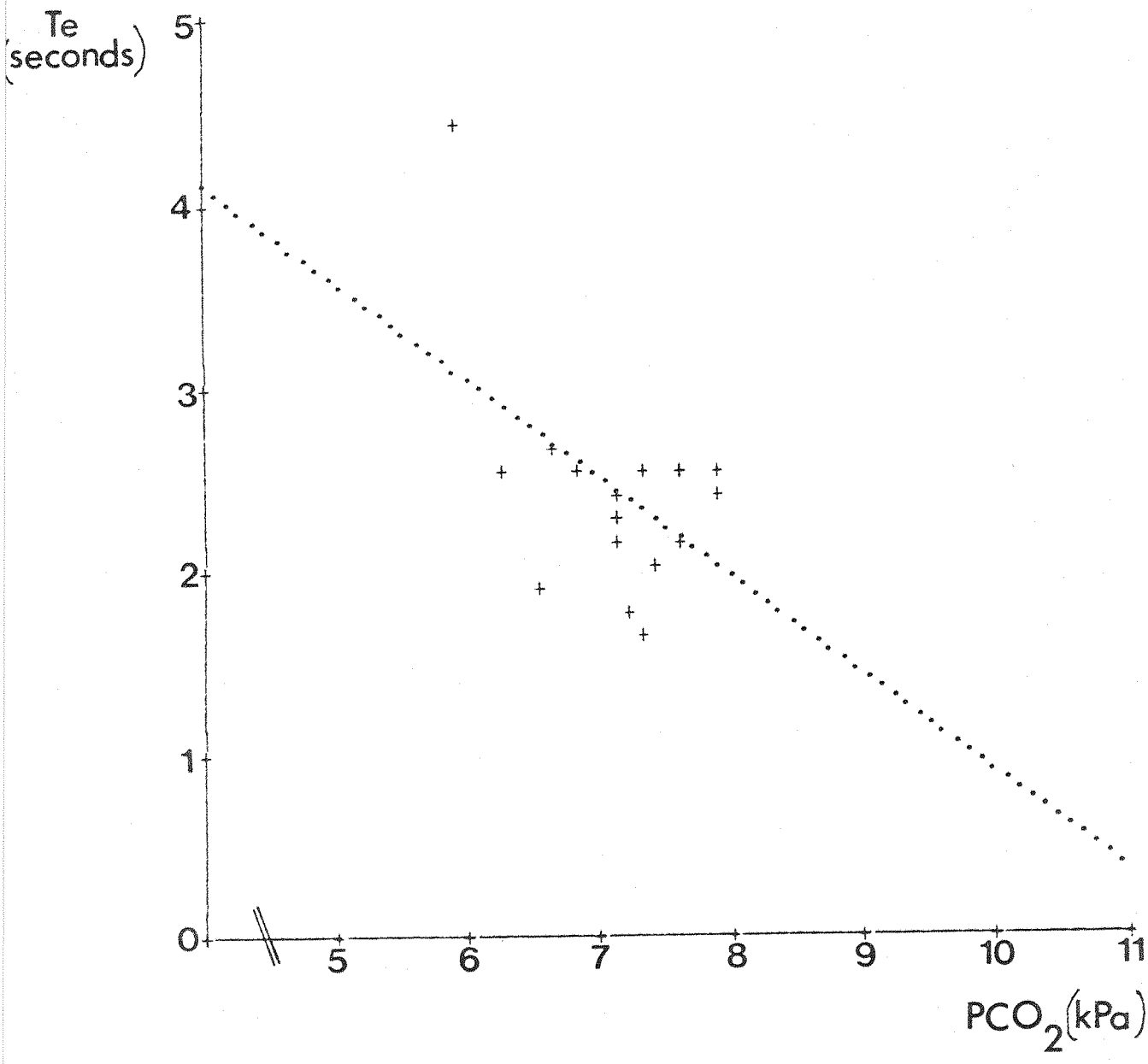

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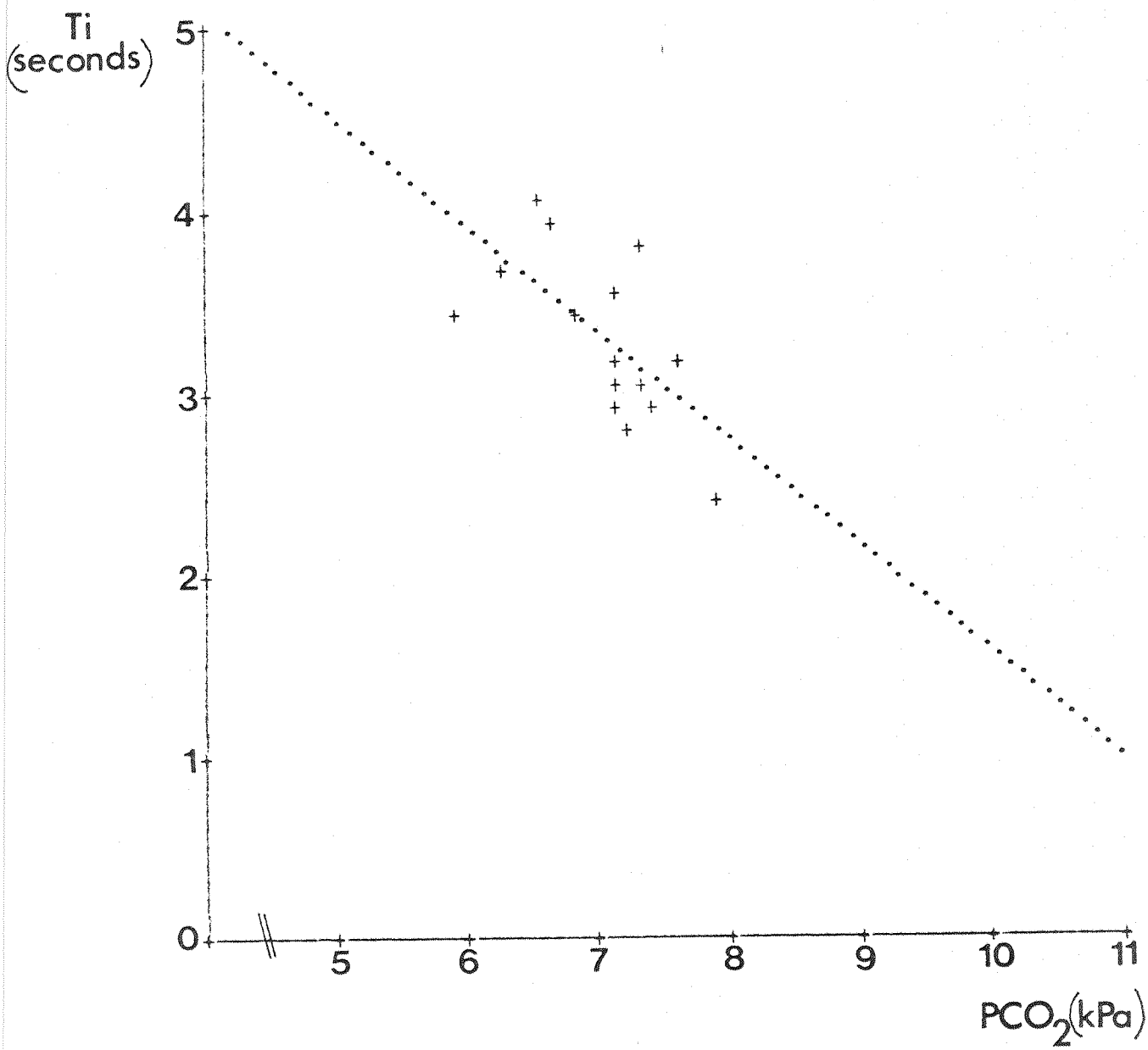

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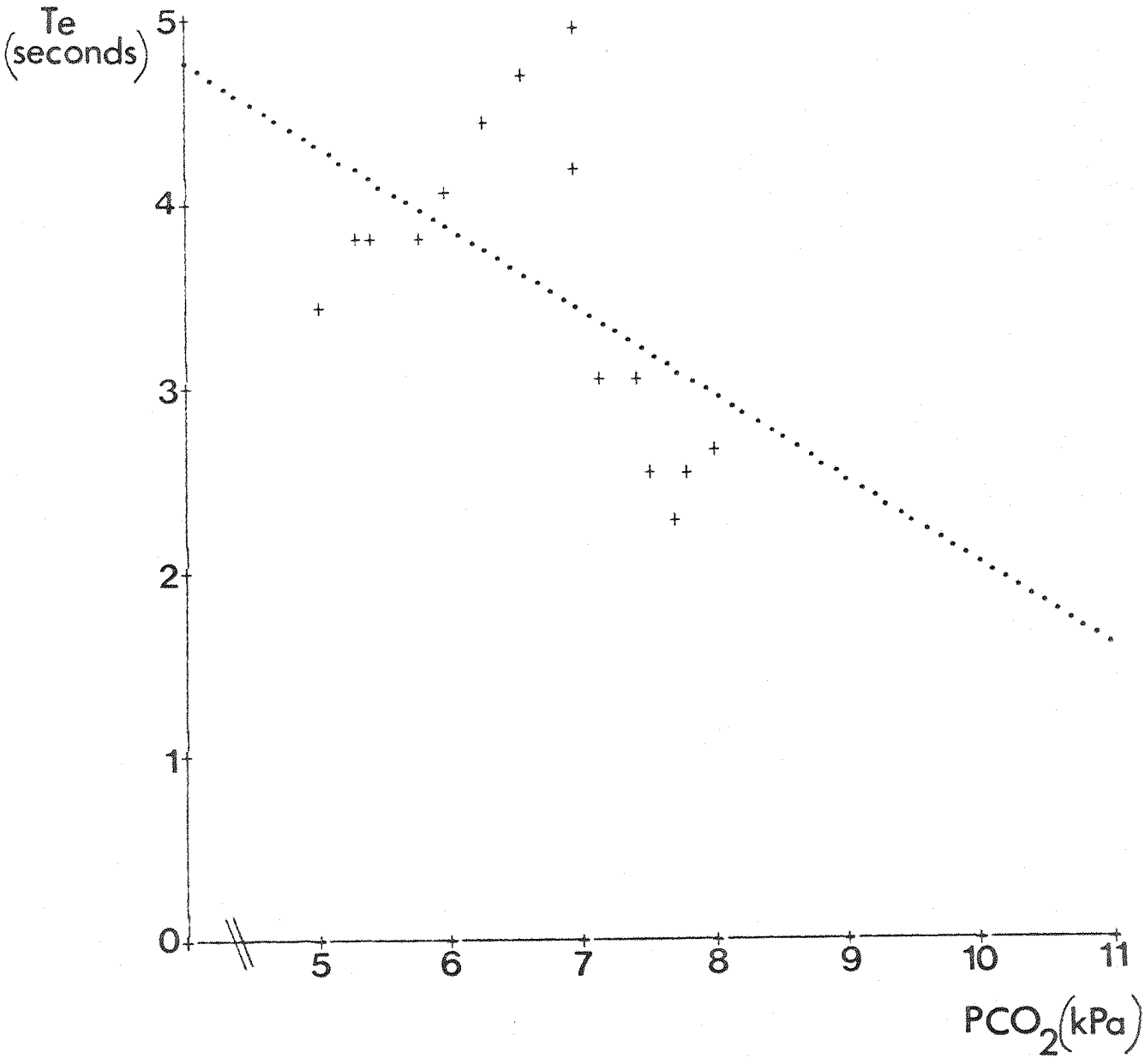

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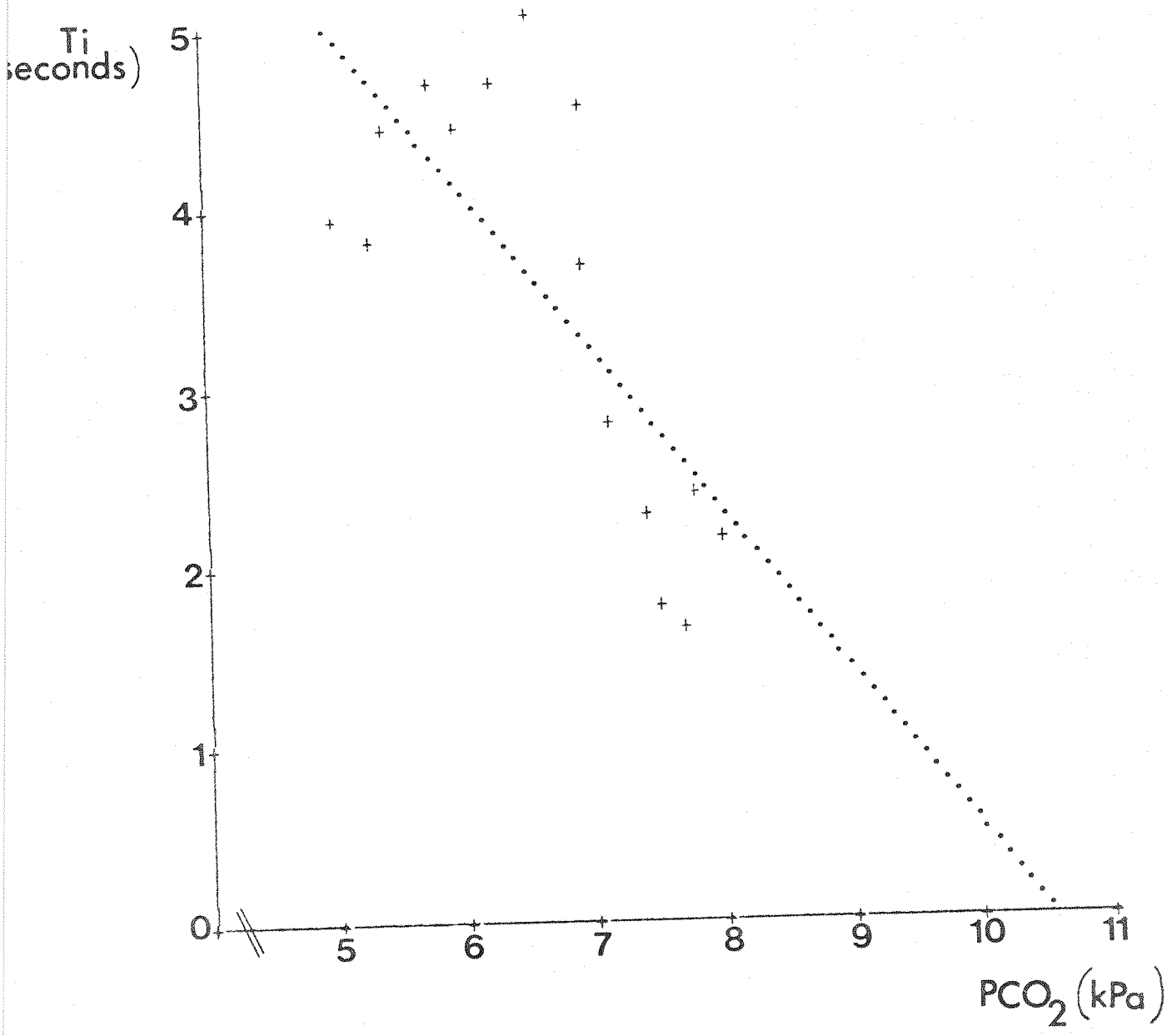

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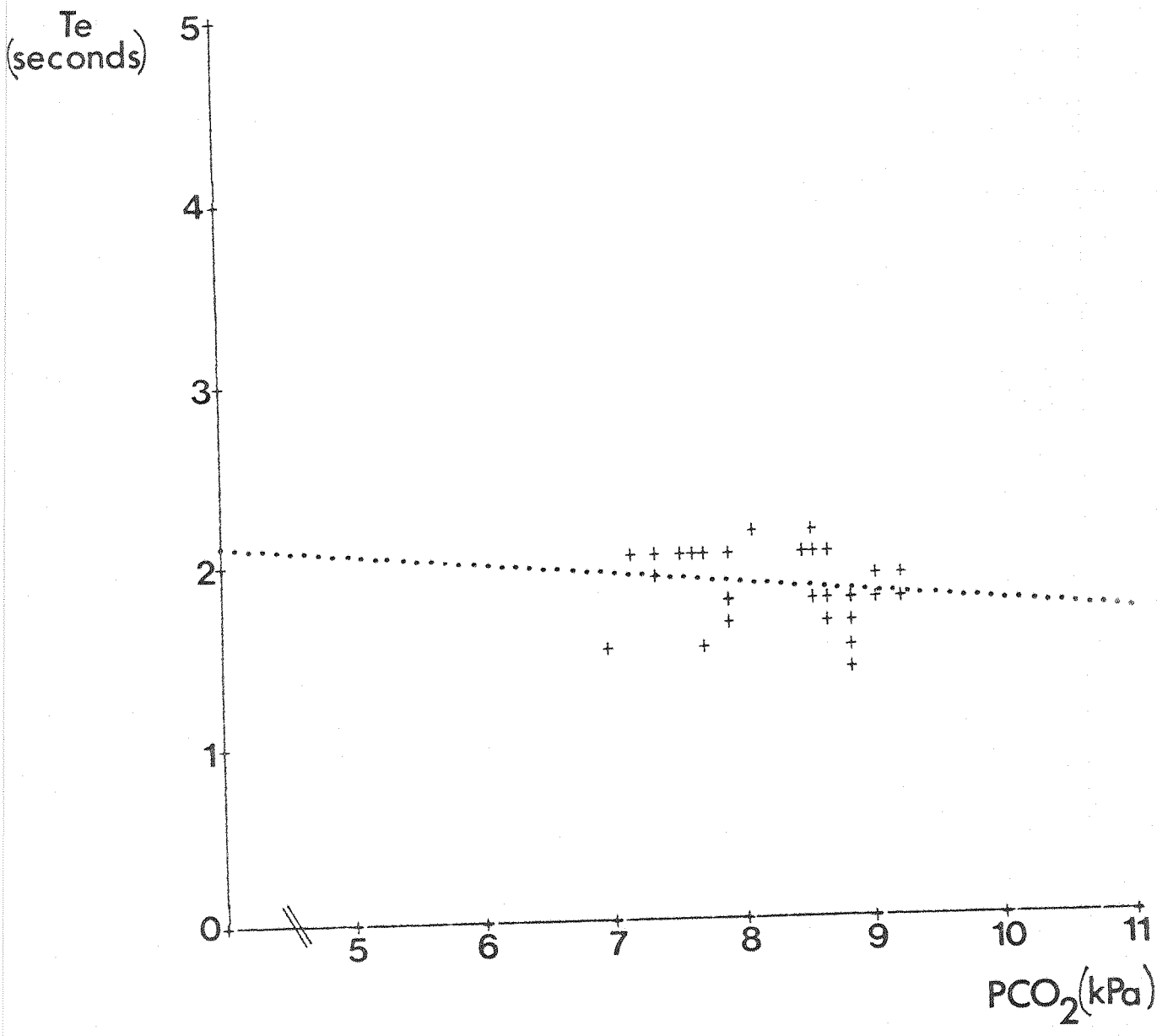

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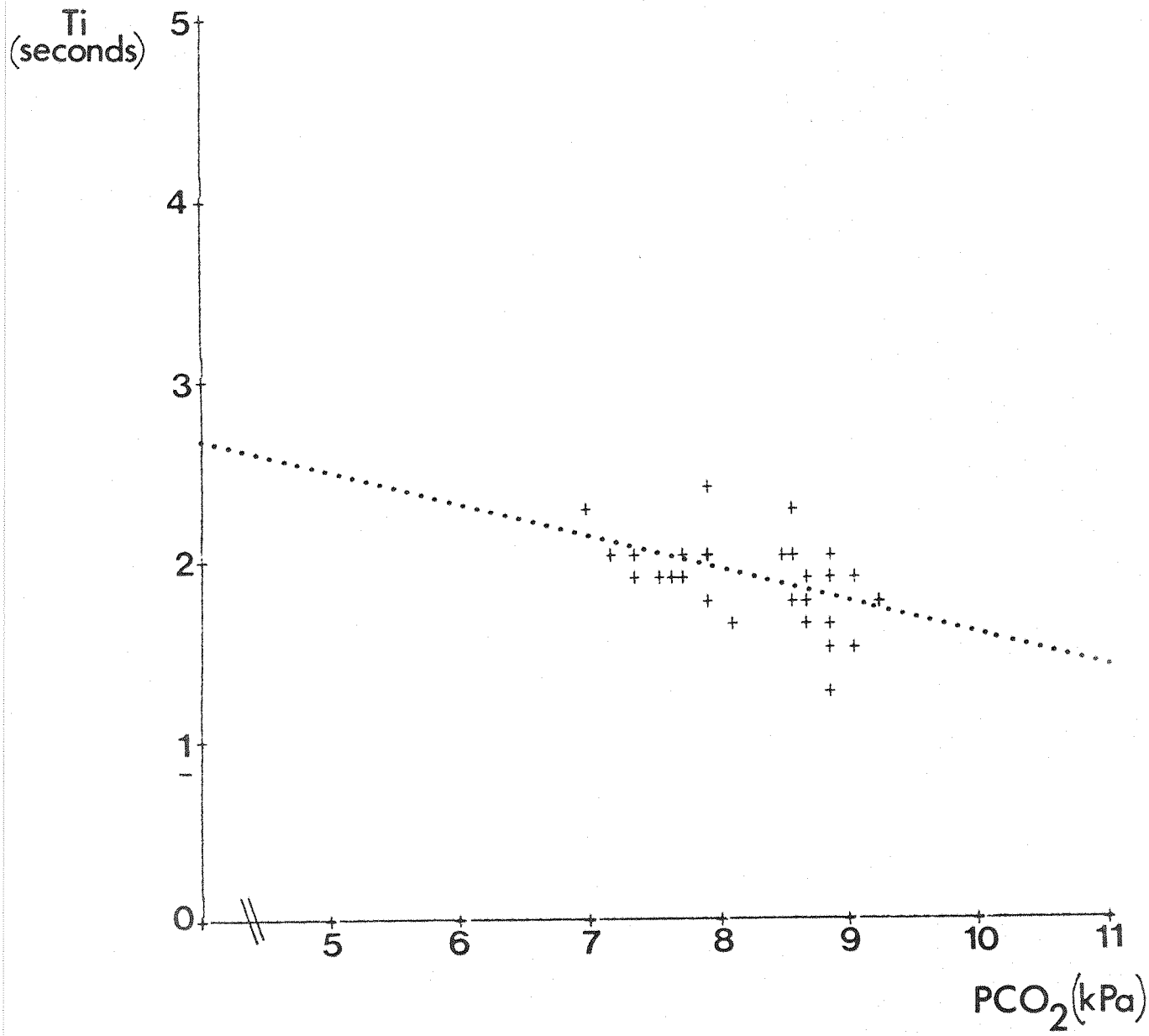

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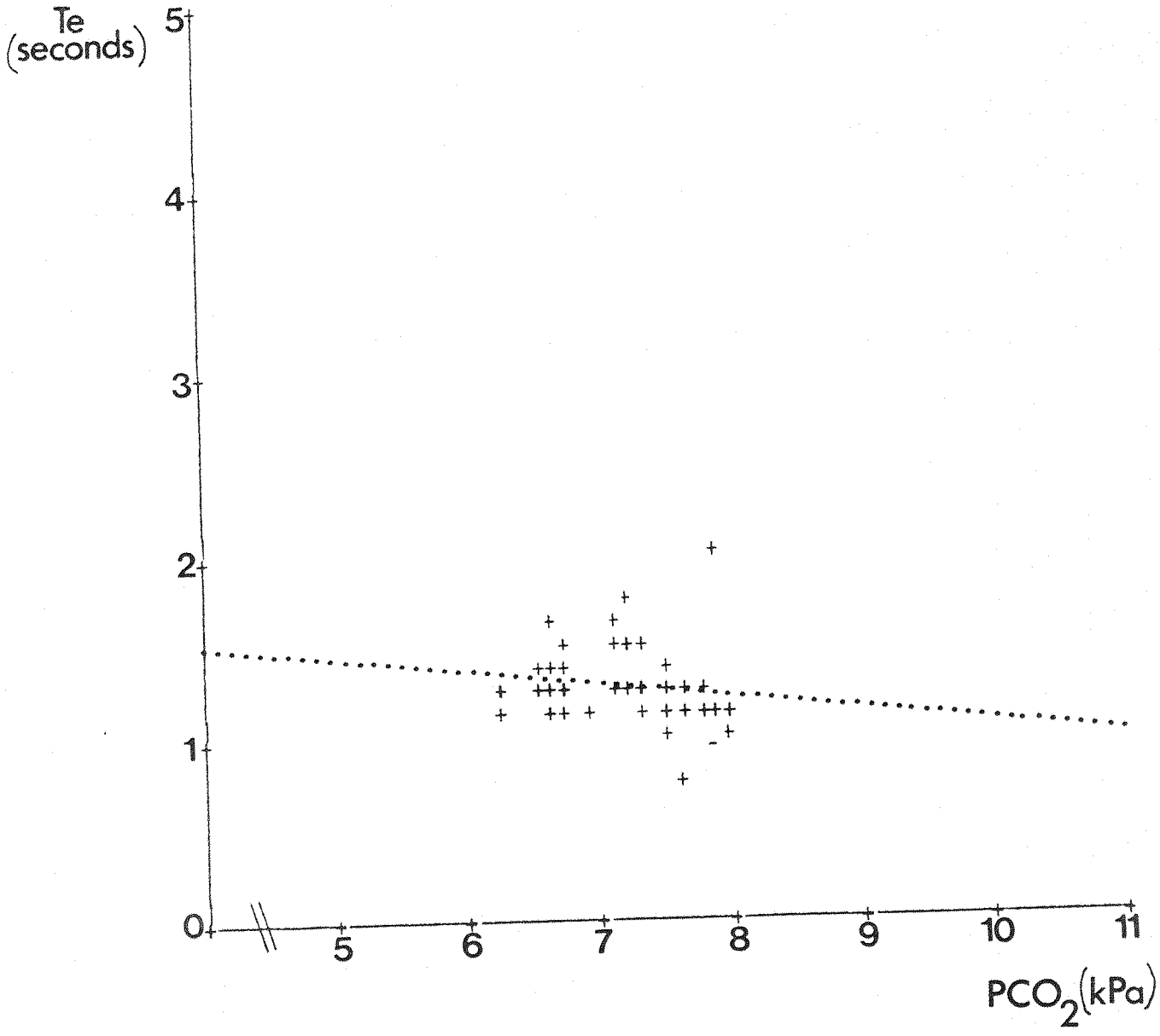

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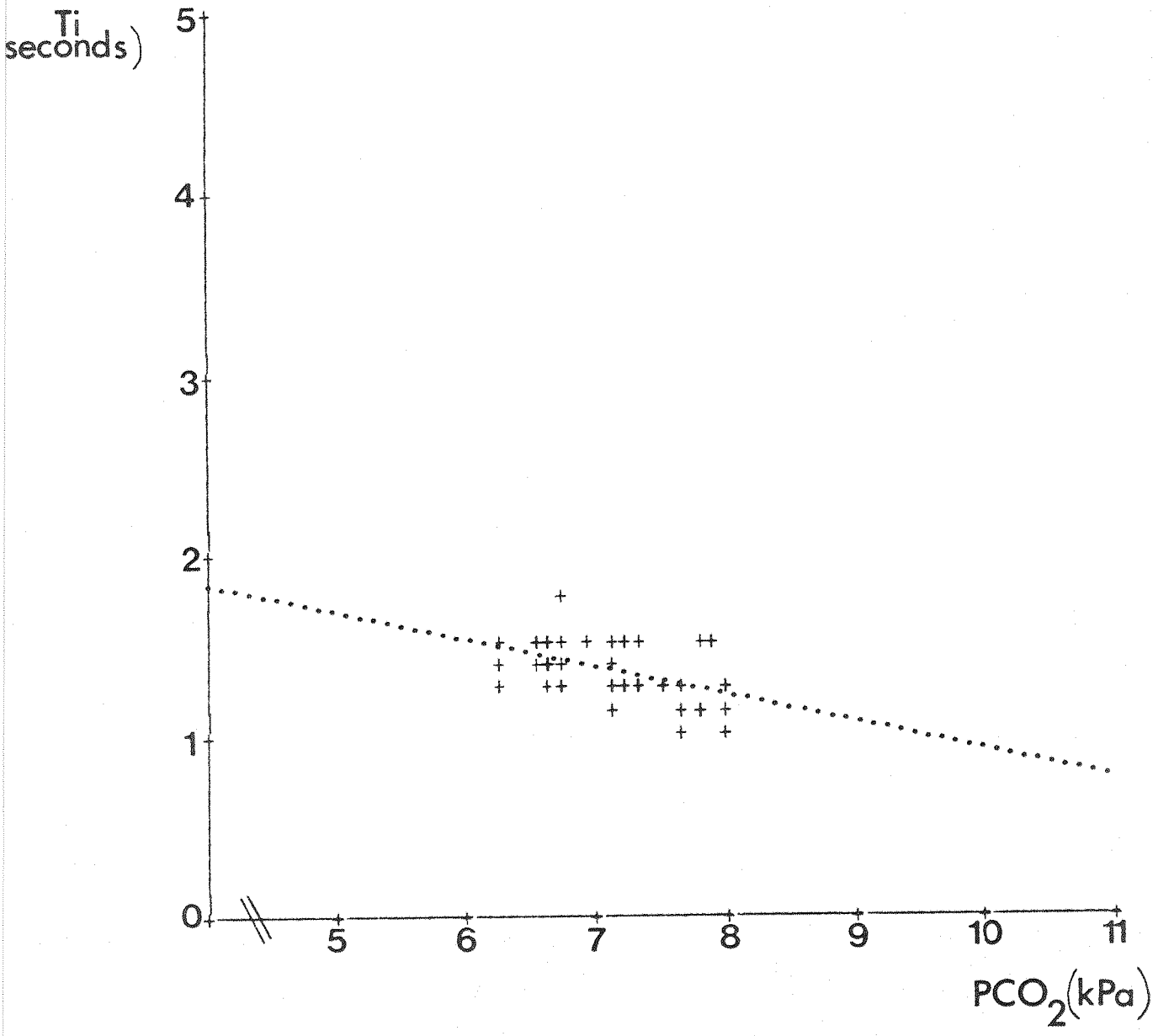

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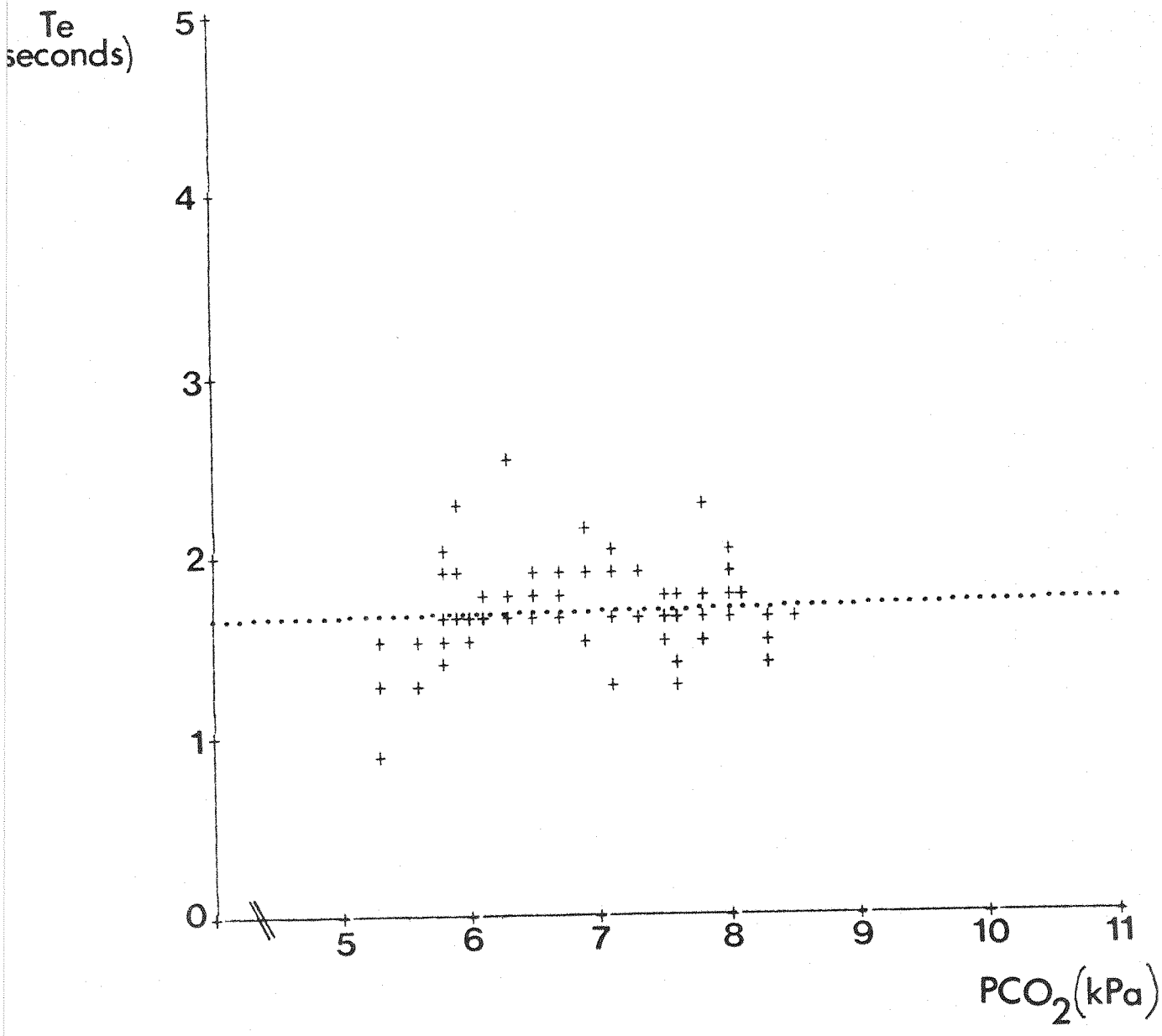

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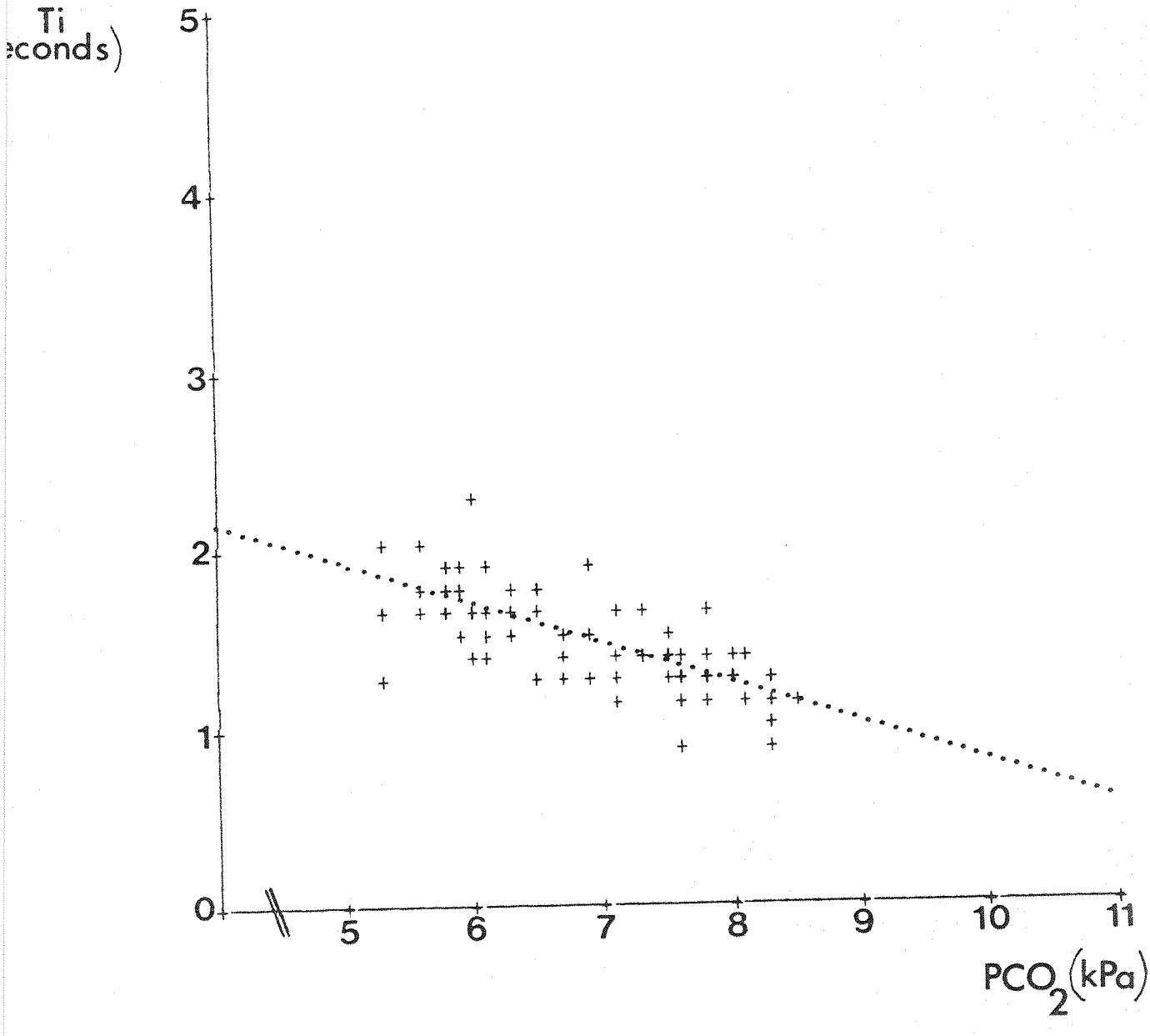

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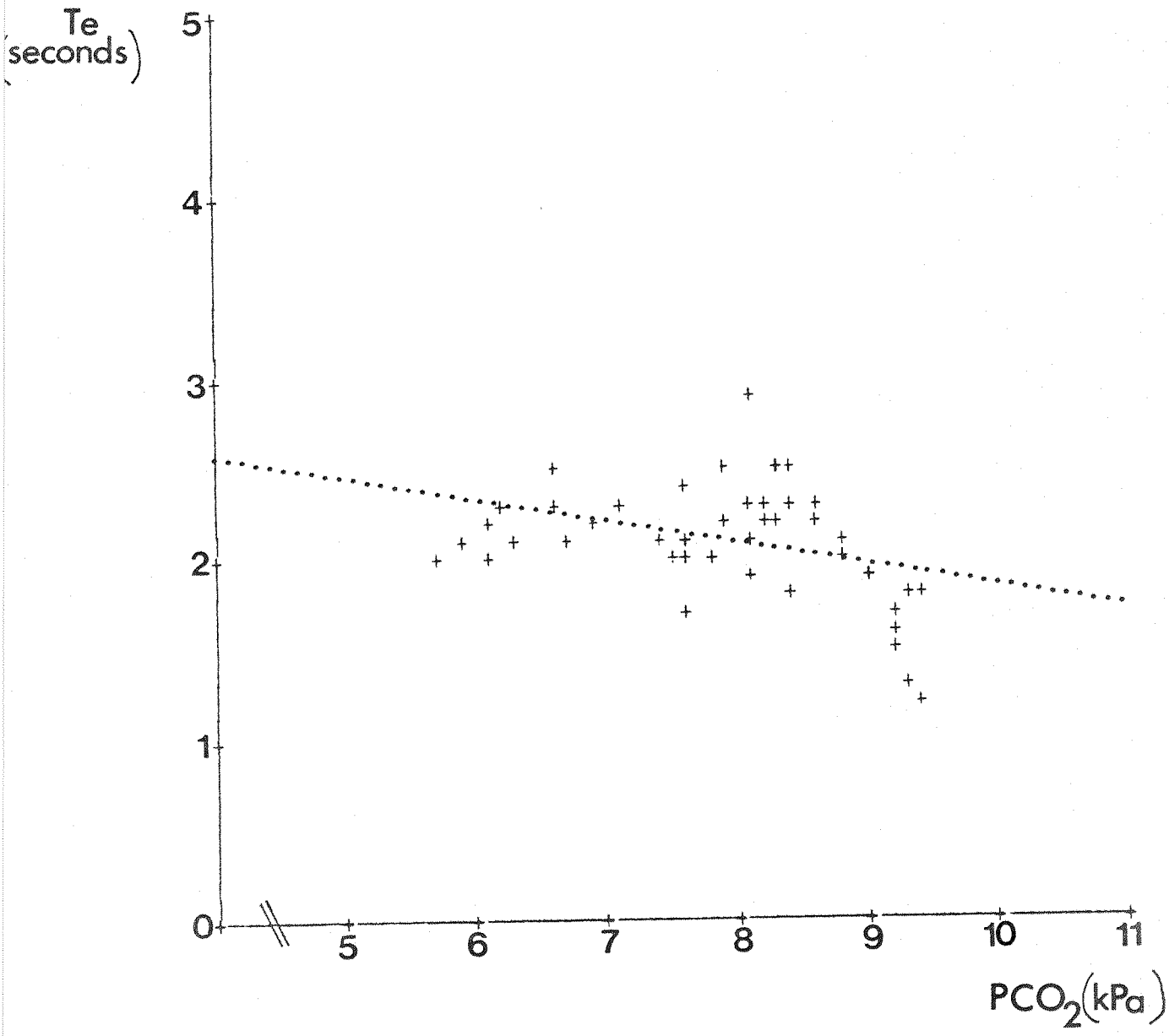

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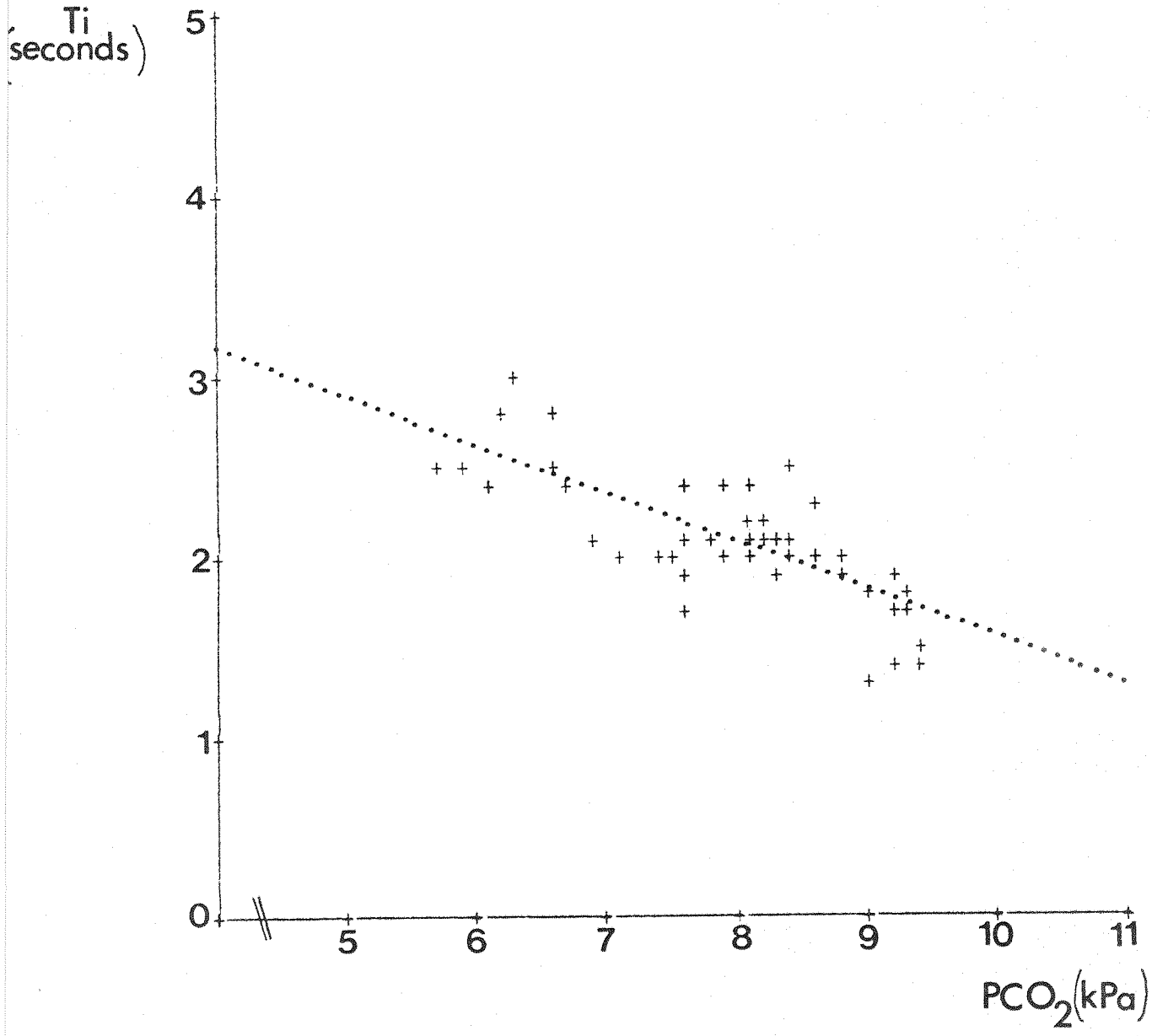

Subject 15.

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