THE DESIGN AND EVALUATION OF THE $P_{0.1}$ METHOD OF ASSESSING VENTILATORY DRIVE

BY

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Dedicated to

my wife and daughter who make it worthwhile

ABSTRACT

Hypercapnia and/or hypoxia normally cause hyperventilation. The sensitivity to hypercapnia and hypoxia and the resultant hyperventilation is reduced in a patient suffering from damped respiratory centre activity. The $P_{0.1}$ method is a modification of the rebreathing technique where a patient rebreathes from a bag prefilled with a mixture of gases of known concentrations. This modification is not sensitive to airflow obstruction as is the case with the ventilatory response of the rebreathing technique. The $P_{0.1}$ method has been described by several authors during the past 8 years. There is however the need to standardise the technique. This thesis is an attempt to meet this need.

The $P_{0.1}$ method involves the occlusion of the inspiratory airway for a set time after the onset of inspiration of a particular breathing cycle. The pressure ($P_{0.1}$) at this time, generated by the isometric contraction of the respiratory muscles, is recorded together with the end tidal P_{CO2}. The valve is occluded approximately 20 times during a rebreathing trial lasting for 4 minutes. The plot of $P_{0.1}$ versus P_{CO2} is linear and its slope gives an indication of respiratory centre activity. A low slope indicates damped respiratory centre activity. The control electronics was designed using digital logic. The occlusion valve

is closed passively during the expiratory phase and then actively held for a preselected time, most frequently for 100ms, after the onset of inspiration, during the next breathing cycle. The active occlusion period is preselectable between 50ms and 300ms. The inspiratory pressure is recorded at this time, or 10 or 20ms prior to the opening of the valve, by a sample and hold circuit. The occlusion valve can be triggered manually via a push button switch on the front panel, or periodically for preselectable periods every 5 to 30 seconds or pseudo-randomly. Ventilatory phase, pressure preset and autotrigger mode indicators are included as operator aids. In a limited number of clinical trials the equipment worked satisfactorily.

During a hypercapnic study the the CO_2 concentration in the bag progressively increases with a resultant increase in ventilation. The hypercapnic trials carried out yielded encouraging results. The method is simple, rapid and easily reproducible. The regression line plots obtained are linear with correlation coefficients better than those presented in the literature. The sensitivity of the ventilatory drive defined as the slope of the $P_{0.1}$ versus P_{CO2} regression line for a group of 10 healthy adult males tested was 0.79 ± 0.47 $cmH_2O/mmHg$. The device is in clinical use in the Respiratory Clinic at Groote Schuur Hospital. Further work needs to be done to investigate the full meaning of the results obtained and to what extent it can be used as a

noninvasive diagnostic and screening technique for respiratory disorders.

The $P_{0.1}$ method will help the clinician to assess non-invasively the degree of impairment of respiratory centre output in patients suspected of having a damped respiratory centre and who may also suffer pulmonary mechanical defects because the technique is independent of airflow.

ACKNOWLEDGEMENTS

My thanks and appreciation to John Amoore who guided me through this thesis, doctor Steve Louw who proposed and provided the initial guidelines to the thesis, doctor Steve Morrison who provided the force to maintain the momentum of the studies, doctor Ricky Raine who aided me with my clinical trials often under trying conditions, the technologists in the Respiratory Clinic at Groote Schuur Hospital, especially Rodleigh Stevens and Anton Fourie and lastly all the staff at the Department of Biomedical Engineering especially Ted Surgeoner and Horst Kronenberg. A special thanks to the Director of Hospital Services for allowing me to complete the thesis during normal working hours.

And to my parents.

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1 INTRODUCTION

Damped respiratory centre activity is one of the causes that raises the arterial blood carbon dioxide level (hypercapnia). Mild hypercapnia may lead to dyspnea and as the CO_2 level in the body increases further the person becomes lethargic and sometimes semicomatose. Excessively high levels of CO_2 in the body fluids lead to total anaesthesia and death may result. There is a need for a method of quantitative assessment of respiratory centre activity to ascertain whether it is involved in the development of hypercapnia. The method must be simple, rapid, reliable and easily reproducible, and non-invasive.

The $P_{0.1}$ method of assessing respiratory centre activity described here fulfils the needs mentioned above. The method is a modification of the CO_2 rebreathing technique. A subject breathes from a rubber bag prefilled with a mixture of carbon dioxide and oxygen. The initial partial pressure of CO_2 (P_{CO2}) in the bag must be close to that of the mixed venous level of the subject. Rapid equilibrium of the P_{CO2} level is attained between the bag, lungs and the arterial blood due to the size of the bag and the initial concentration of CO_2 in the bag. During selected breathing cycles the inspiratory airway of the rebreathing

circuit is occluded by means of a remotely controlled solenoid valve for the initial phase of inspiration. The valve is occluded for 100 milliseconds after the onset of inspiration. This period is chosen short to ensure that there is no conscious or unconscious response to the occlusion. The pressure generated at 100ms ($P_{0.1}$) due to the respiratory effort is recorded. Simultaneously the end tidal P_{CO2} is also recorded. The plot of $P_{0.1}$ versus P_{CO2} is linear and its slope is used as a ventilatory index in the assessment of respiratory centre activity.

A brief overview of the regulation of ventilatory drive is presented in Chapter 2. Chapter 3 reviews methods of the assessment of ventilatory drive (respiratory centre output) and earlier descriptions of the $P_{0.1}$ method. The development of the rebreathing system is described in chapter 4. The $P_{0.1}$ control unit (chapter 5) is essentially a control device for occluding the inspiratory airway at specific times relative to the breathing cycle. The inspiratory airway is occluded with an occlusion valve during the expiratory phase of a selected cycle and remains closed for 100ms after the onset of the inspiratory phase of the next breathing cycle. It is important to define and detect the onset of inspiration. The pressure signal at the mouth is used and compared to atmospheric pressure. The start of inspiration is defined as the time when the monitored mouth

pressure just goes negative. Expiration is defined as when the mouth pressure is positive. The valve can be triggered manually, by means of a push button switch, or automatically. The autotriggering can be periodic, for example, every 10 seconds, or pseudo random. The solenoid valve is a modification of the inspiratory port of a Collins J respiratory valve.

2 REGULATION OF VENTILATORY DRIVE

The regulation of ventilation is primarily governed by the P_{CO2} level of the blood. The blood P_{CO2} level affects the ventilatory drive which is the total neuromuscular output of the respiratory bellows. This chapter discusses aspects of ventilatory control relevant to this study.

2.1 BACKGROUND PHYSIOLOGY AND ANATOMY

A particular level of respiratory centre output results in a corresponding level of alveolar ventilation. Alveolar ventilation is the gaseous exchange in the alveoli of oxygen from the atmospheric air to the pulmonary blood and the removal of carbon dioxide into the atmosphere. The atmospheric air is transported

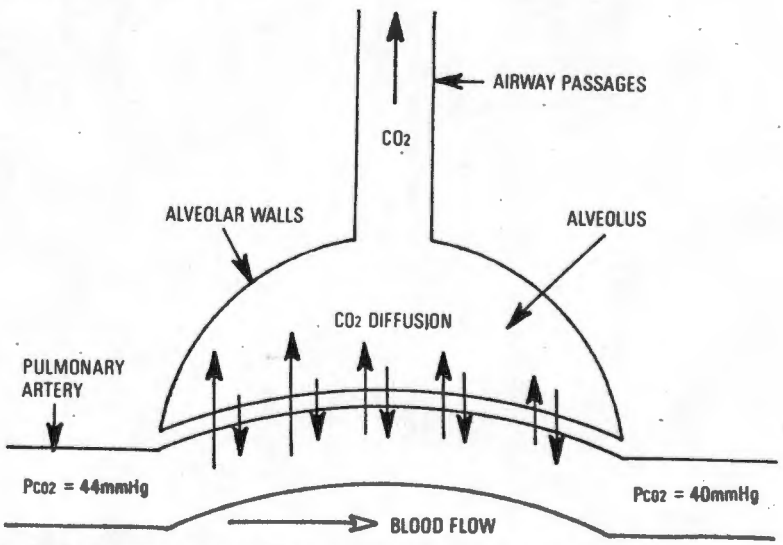


FIGURE2.1 DIFFUSION OF CARBON DIOXIDE FROM PULMONARY BLOOD INTO THE ALVEOLUS.

via the respiratory passages to the alveoli. Carbon dioxide diffuses from the pulmonary blood into the alveoli and out into the atmosphere. The pulmonary capillaries are in close association with the alveolar walls. This is schematically illustrated in figure 2.1.

The rate of alveolar ventilation is adjusted by the nervous system to maintain optimum body O_2 and CO_2 levels. The efferent activity from the respiratory centre automatically controls the ventilation. The respiratory centre consists of a widely dispersed group of neurons located within the brain stem. Voluntary neuronal control of ventilation is located in the cerebral cortex. The drive from these two areas is integrated in the spinal cord together with proprioceptor afferent information from the respiratory bellows. The respiratory centre provides the drive effecting a ventilatory pattern to maintain an optimum carbon dioxide and oxygen homeostasis.

The respiratory neurons that constitute the respiratory centre are grouped together in nuclei in the brain stem. Their anatomical locations have been found by the destruction of selective areas within the medulla oblongata and the pons. For example, transection of the brain stem above the pons does not alter the ventilatory pattern, though all voluntary control of

respiration is lost (Mitchell and Berger 1975). Transection of the brain stem at the border between the medulla and the spinal cord causes respiratory arrest. This indicates that the autonomic control of ventilation is situated between these two borders, namely in the medulla oblongata and the pons. The neurophysiological function of these nuclei are found by electrical or chemical stimulation of these areas and noting the changes in the ventilatory pattern. The exact location of the various nuclei and their neurophysiological functioning has not been conclusively defined (Berger et.al. 1977 and Mitchell and Berger 1975). There is however broad agreement on four major anatomically separate and functionally different groups of respiratory neurons within the brain stem. These are the pneumotaxic centre situated bilaterally in the rostral pons, the apneustic centre (inspiratory area) situated in the medial reticular formation above the pontomedullary border, the medullary centre situated in the substance of the medulla oblongata and a chemosensitive area found superficially on or near the ventrolateral medullary surface (Berger, et.al. 1977, Mitchell and Berger 1975, Trouth, et.al. 1982 and Hendemark, et.al. 1982).

Peripheral arterial chemoreceptors situated in the carotid and aortic bodies respond to acute oxygen lack (Berger et al. 1977).

Receptors in the nasal passages respond to chemical and mechanical stimuli. They cause apnea, bradycardia, cough and sneezing reflexes. Receptors in the pharynx can be mechanically stimulated to cause sniff or cough reflexes. Irritant receptors in the larynx respond to chemical and mechanical stimuli. They cause coughing, slow breathing and apnea reflex effects. Irritant receptors are also found in the trachea which cause coughing reflex effects. Pulmonary stretch receptors are found in the airway smooth muscle of the lungs and respond to inflation of the lung. These receptors send afferent information to the respiratory centre limiting inspiration. Irritant receptors in the lungs responding to mechanical stimuli are found to lie between the epithelial cells. Type J receptors lie in the pulmonary capillary wall and these respond to pulmonary congestion and an increase in pulmonary interstitial-fluid volume.

2.2 PNEUMOTAXIC CENTRE

The pneumotaxic centre modifies the ventilatory pattern by shortening the length of inspiration. It limits inspiration before the lungs become too full of air. Because it regulates the length of inspiration its secondary effect is to regulate the period of respiration and thus the respiratory rate. Strong pneumotaxic signals can increase the respiratory rate to 30 to 40

breaths per minute while weak pneumotaxic signals may reduce the respiratory rate to only a few breaths per minute (Guyton 1981). Afferents from the pulmonary stretch receptors inhibit this centre which in turn applies strong inhibitory signals to the apneustic centre to curtail inspiration. Mitchell and Berger (1975) conclude in their review that the role of the pneumotaxic centre in the regulation of ventilation has still to be uncovered. Berger and co-workers (1977) agree that this centre does not initiate respiratory rhythmicity.

2.3 APNEUSTIC CENTRE

Transection of the brain stem above the apneustic centre causes apneusis (Mitchell and Berger 1975). Thus the function of this centre is to limit inspiration. It is excited by inputs from the lung proprioceptors and the pneumotaxic centre. Its output causes the drive to the inspiratory muscles to appear as a "ramp" during normal respiration. This activity lasts for about 2 seconds after which the expiratory phase begins (Guyton 1981). Mitchell and Berger (1975) suggest that the apneustic centre plays a secondary role in the generation of respiratory rhythmicity.

2.4 MEDULLARY CENTRE

The output from this centre can result in a rhythmic respiratory

pattern in the absence of the pneumotaxic and apneustic centres, though the respiratory pattern is abnormal. The medullary centre is composed of two groups of neurons, the dorsal respiratory group and the ventral respiratory group.

2.4.1 DORSAL RESPIRATORY GROUP

This group is made up of inspiratory cells and is found in the ventrolateral aspect of the nucleus of the tractus salitarius. The neurons project from here to phrenic motorneurons and the ventral respiratory group. Respiratory rhythmicity originates here. Berger, et.al. (1975) conclude that preprocessing of visceral afferent activity, rhythmic drive to the ventral respiratory group and respiratory rhythmicity originate in the dorsal respiratory group.

2.4.2 VENTRAL RESPIRATORY GROUP

This group is made up of inspiratory and expiratory neurons. These are found in the nucleus ambiguus and nucleus retroambiguus. These drive either spinal respiratory neurons or auxillary respiratory muscles.

2.5 CHEMOSENSITIVE AREA

The three areas of the respiratory centre already mentioned do not respond directly to changes in blood P_{CO2}, H^+ and P_{O2}, but are stimulated via a very sensitive chemosensitive area. The chemosensitive area is situated on the ventrolateral surface of the medulla. The sensors are situated superficially 200 to 400 microns below the surface (Berger 1977). This area is highly sensitive to pH. Increased chemosensitive area activity occurs when there is a decrease in brain tissue pH. This results in an increase in both the slope and amplitude of the respiratory ramp. In other words there is an increase in both respiratory rate and tidal volume respectively. This is in order to adjust the respiratory pattern to normalise and maintain CO_2 homeostasis.

This chemosensitive area is stimulated by H^+ concentration (pH). However H^+ cannot move easily across either the brain-blood or the blood cerebrospinal fluid barriers. Carbon dioxide passes easily across these barriers. Carbon dioxide reacts with water to form carbonic acid. The carbonic acid dissociates to form hydrogen ions and bicarbonate ions, thus altering the pH of the tissue medium. Thus the nett result of an increase in blood P_{CO2} is an increase in H^+ concentration around the chemosensitive area and also in the cerebrospinal fluid. It is argued that the H^+

concentration of the cerebrospinal fluid has a greater effect on the chemosensitive area than that of the interstitial fluid. The reasons given are that the concentration of acid-base buffers is much higher in the interstitial fluids than that in cerebrospinal fluid. Therefore the change in cerebrospinal fluid pH is much more significant. Also the cerebrospinal fluid is in intimate contact with a very rich blood supply in the arachnoid plexus. This results in a rapid stimulation, within seconds, to the respiratory muscles via the respiratory centre. The change in brain interstitial fluid pH occurs after a minute or longer.

In the absence of peripheral chemoreceptors the respiratory pattern remains unaltered. This suggests that the chemosensitive area in the medulla oblongata is a primary site for monitoring blood P_{CO2}. Trouth and co-workers (1982) monitored electrical activity of the chemosensitive area and correlated it to phrenic nerve activity on anaesthetised cats. They altered the local pH of the ventral medullary surface with mock cerebrospinal fluid and noted an increase in phrenic nerve activity as the pH was decreased.

2.6 MODEL OF VENTILATORY CONTROL

Several authors have described models of the control of

respiration and they have been reviewed by Grodins and Yomashiro (1977). An early model was described by Gray who in 1945 modelled the system as a controller sensitive to P_{CO2}, P_{O2} and pH. The output of the controller was the alveolar ventilation which controlled the plant. This led to a relationship between alveolar ventilation ($\dot{V}_A$) and P_{CO2}, P_{O2} and pH of the form:

$$\dot{V}_A = a.H^+ + b.P_{CO2} + f(P_{O2}) + c$$

where a, b and c are constants. This describes a linear relationship between ventilation and P_{CO2}. However Grodins and Yamashiro (1977) point out that a number of independant factors affect the relationship, and that the changes in any variable affects the controller constants of the other variables.

Read and Leigh (1967) proposed a theoretical model observing a linear relation between arterial P_{CO2} and brain receptor P_{CO2}. They simulated their model on an analogue computer and the theoretical model agreed well with their experimental observations. Their model holds for the Read rebreathing technique (Read 1967) when rebreathing is initiated with a small bag prefilled with a gas mixture of P_{CO2} above that of the mixed venous level of the subject. This is to allow rapid equilibration of P_{CO2} levels between the bag, lung and arterial blood.

Their model is governed by the following equation;

$$\frac{dC_R(t)}{dt} = M + F.C_a(t) - F.C_v(t)$$

That is, "the rate of change of P_{CO2} level in the receptor tissue (C_R)is equal to the sum of its metabolic CO_2 production rate (M) and the instantaneous CO_2 flow rate in arterial blood (F.Ca(t)) less the instantaneous CO_2 flow rate in venous blood (F.v(t)) from the receptors." (Read and Leigh 1967).

The model is further developed with assumptions on the slope of the CO_2 dissociation curves of the receptor tissue, arterial blood and venous blood and the instantaneous blood flow in the receptor region. From these they solved the linear first order differential equation. Their equation was simulated on an analogue computer and the constants were varied to simulate different physiological states. They plotted curves of brain tissue P_{CO2} at the chemoreceptor against arterial blood P_{CO2}. They found that after 20 seconds of rebreathing, the P_{CO2} difference between brain tissue and arterial blood is relatively constant. Experimentally it has been found that there is a linear relation between arterial P_{CO2} (end tidal P_{CO2}) and ventilation. Read and Leigh (1967) showed that there is a linear relation between arterial blood and chemoreceptor tissue P_{CO2}. From these

observations there exists a linear relation between chemoreceptor tissue P_{CO2} and ventilation.

2.7 SUMMARY

Ventilation has been shown, under rebreathing conditions, to be linearly related to the level of P_{CO2} of the end tidal air. The level of P_{CO2} in the air passages is under these conditions linearly related to the P_{CO2} level in the chemosensitive area of the brain stem.

The regulation of ventilation is summarised in figure 2.2. Carbon dioxide is a waste product of metabolism which increases the interstitial fluid P_{CO2} level. This increase causes a gradient between the interstitial fluid P_{CO2} and the blood which is in close association with the interstitial tissue. CO_2 diffuses from the interstitial fluid into the blood. This tends to increase the blood P_{CO2}. The CO_2 reacts with water to form carbonic acid and is transported in this way by the blood. The respiratory centre senses the increased blood P_{CO2} (as described in section 2.5) and drives the respiratory bellows to remove the excess CO_2 from the blood into the atmosphere. The action of the respiratory bellows moves air to and fro between the lungs and the atmosphere (airflow) and releases CO_2 into the atmosphere during expiration

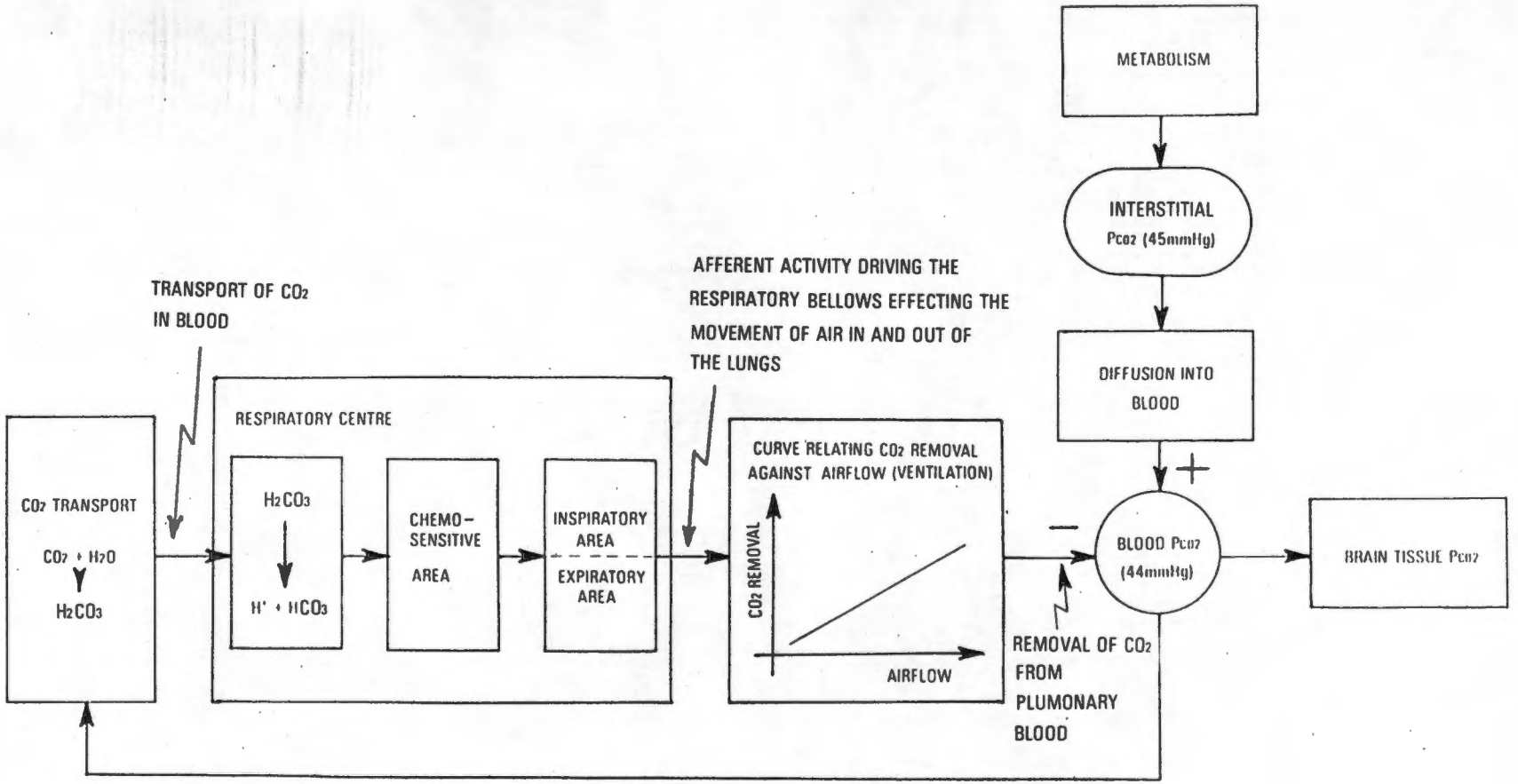


FIGURE 2.2 SIMPLIFIED BLOCK DIAGRAM OF THE REGULATION OF VENTILATION BY THE ARTERIAL P_{CO_2} LEVEL

(CO_2 removal). As airflow is increased, the removal of CO_2 from the blood is increased. The linearity of the relationship between ventilation (airflow) and blood P_{CO2} is an important characteristic of the rebreathing technique which will be described in later chapters.

3 ASSESSMENT OF VENTILATORY DRIVE

3.1 INTRODUCTION

In respiratory disease it is important to assess and monitor ventilation. The ventilatory drive is the efferent output of the respiratory centre effecting ventilation. Brain tissue P_{CO2} level is a potent input to the respiratory centre, affecting its output. The $P_{0.1}$ method, a modification of the CO_2 rebreathing technique of assessing ventilatory drive has been chosen for this study. The $P_{0.1}$ method of assessing ventilatory drive is routinely used in respiratory research laboratories in many major hospitals throughout the world, though the technique is not in widespread clinical use.

The technique of studying the regulation of ventilation has essentially developed over the past 70 years. Ventilation is controlled by the respiratory centre situated bilaterally in the medulla oblongata and the pons. It is made up of widely dispersed groups of neurons. The output of the respiratory centre is the total neuronal discharge which controls the respiratory muscles. This is known as the ventilatory drive and has been estimated by measuring ventilation, the rate of work of the

respiratory muscles, the EMG of the diaphragm, the tidal volume, frequency of breathing and the CO_2 rebreathing method. All of these have certain disadvantages, some of which will be mentioned later, and none of them, except the CO_2 rebreathing method, Read (1967), allow simple, rapidly reproducible serial observations to be made.

Numerous papers are presented in the literature on the development, evaluation, clinical application and the limitations of both the CO_2 rebreathing method - Clark 1968, Dempsey 1976, Fencl 1976, Lederer 1977, Mustchin 1977, Read 1967 and Rebuck 1976 and the $P_{0.1}$ method, Altose 1976, Brayan 1976, Cherniack 1976, Fitzgerald 1976, Gribbon 1982, Jordan 1981, Lederer 1977, Mustchin 1977 and Whitelaw 1976. The papers that cover the technology of the hardware used are limited - Camporesi 1978, Delavault 1980, Jordan 1981, Lederer 1977. This is unfortunate as all the recent papers suggest the need for standardisation of the method. This is not possible because details of the apparatus used and the procedure followed by the various authors are excluded or dealt with in very little detail. This makes it difficult for investigators to compare their results. For example the physical configuration and size of airway tubing used in the respiratory circuit and its dead space should be standardised. All of the papers presented accept the $P_{0.1}$ technique as

theoretically the most accurate and practically the simplest to apply. Whitelaw and co-workers (1975) first presented the $P_{0.1}$ method. It is a modified technique of the CO_2 rebreathing method to aid in the assessment of ventilatory drive in man. The modification allows the already accepted and clinically used CO_2 rebreathing method to be used on patients with defective pulmonary mechanics.

3.2 Development of techniques to assess ventilatory drive

Haldane and Poulton (1908) observed the effects upon the breathing of subjects enclosed in a wooden enclosure. They noted that the subjects hyperventilated as the carbon dioxide level increased within the enclosure and deduced that acute control of ventilation is effected by the P_{CO2} level in the blood. Since this time, techniques for inducing hypercapnia have developed and are today widely used in assessing respiratory function and its control. Many investigations, including those presented by Lopata (1977 and 1978) who attempted to quantitate the ventilatory drive by observing respiratory nerve and muscle activity, are not clinically used because the procedures are time consuming and laborious, afford considerable discomfort to the patients and the results are very unreliable. The steady state CO_2 breathing

method was widely used until Read (1967) presented the simplified rebreathing method. Dempsey (1976) in his presentation to the Symposium on Clinical Methods for the Study of the Regulation of Breathing in Illinois compared the two methods. The steady state method requires typically breathing for between 15 to 25 minutes a gas of known CO_2 concentration and recording the resulting ventilation. This procedure is repeated two to four times using gases of increased CO_2 concentration. The latter technique is obviously time consuming. The results obtained from these two methods agree excellently.

Whitelaw et al (1975) mentioned other methods such as the rate of work of the respiratory muscles, tidal volume and the frequency of breathing. None of these singly represent ventilatory drive. Lopata et al (1977) and Altose et al (1978) used respiratory muscle and nerve activity to evaluate the $P_{0.1}$ method. They found that $P_{0.1}$ relates linearly to phrenic nerve activity and concluded that $P_{0.1}$ can be regarded as an index of total neuromuscular output of the respiratory system. Altose et al (1978) noted that the EMG of the diaphragm is critically dependant upon the position of the oesophageal electrode. The diaphragm is not the only muscle involved in respiration and so measurement of diaphragm EMG is of limited use (Whitelaw et al 1975). Thus it does not reliably reflect ventilatory drive.

The general consensus is that one may now attempt to differentiate between respiratory depression due to effects upon the central nervous system, that is ventilatory drive, and adverse effects principally affecting the lungs, but further work must be aimed at standardising the method so that comparative studies can be done amongst the various researchers.

3.3 CO_2 Rebreathing Method

Read (1967) presented the CO_2 method and it has since been widely applied. In this presentation he establishes the linearity, reproducibility and the normal range of the response curves. His technique involves a subject rebreathing from a small bag, 4 to 6 litres, prefilled with a known mixture of gas of 7% CO_2 and 93% O_2. The initial concentration of the CO_2 is chosen close to that of mixed venous blood. The small size of the bag and the initial P_{CO2} of the gas in it allows a rapid equilibration of the P_{CO2} levels between the mixed venous blood, arterial blood and the gas in the lungs and the rebreathing bag. The 93% O_2 in the bag prevents the patient becoming hypoxic while rebreathing. Figure 3.1 shows a schematic of the respiratory system as described by Read. Rebuck (1976) and Mustchin (1977) say that the effect of the rebreathing technique is to create a physiological "open loop" in the control of breathing. This means that a constant

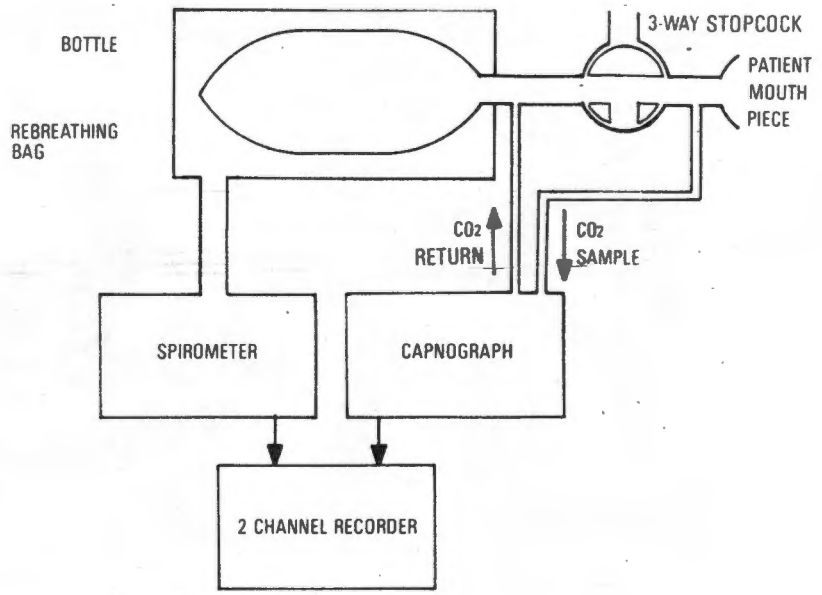
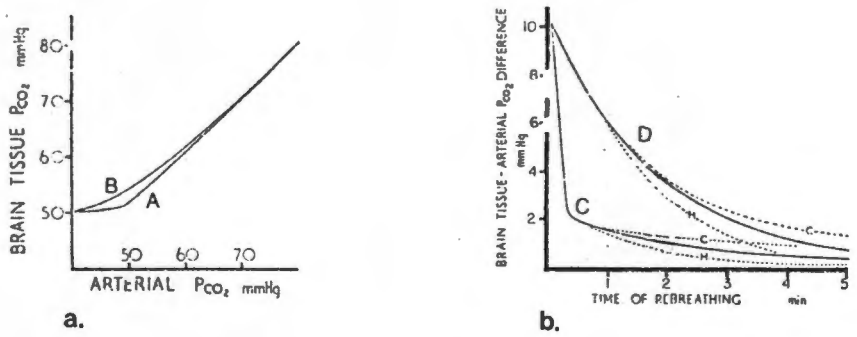


FIGURE 3.1 READ REBREATHING SYSTEM.

relation is established between end-tidal P_{CO2} and the brain tissue P_{CO2} and this is unchanged by the level of ventilation. Read and Leigh (1967) showed that the size of the bag and the initial 7% CO_2 concentration of the gas mixture therein shifted the plot of brain tissue P_{CO2} and arterial P_{CO2} to the right (figure 3.2a). The effect of the 7% CO_2 is to cause a step increase in the arterial P_{CO2} level. The relation between arterial and brain tissue P_{CO2} is linear after this step increase in arterial P_{CO2} (curve A). The relation between brain tissue and arterial P_{CO2} is nonlinear when rebreathing commences without any CO_2 (curve B). Also the difference between brain tissue and

arterial P_{CO2} is relatively constant about 20 seconds after rebreathing has commenced if the bag has an initial 7% CO_2 concentration (figure 3.2b curve C). This difference becomes small only after more than 5 minutes of rebreathing if the initial P_{CO2} of the gas in the bag is zero (curve D).



3.2 A. THEORETICAL CURVES RELATING BRAIN TISSUE P_{CO2} TO ARTERIAL P_{CO2} DURING REBREATHING. B. THEORETICAL CURVES RELATING BRAIN TISSUE - ARTERIAL P_{CO2} DIFFERENCE AT MEDULLARY CHEMORECEPTORS TO THE TIME OF REBREATHING. (REPRODUCED FROM READ AND LEIGH (1967)).

A physiological open loop is described by referring to figure 3.3. Carbon dioxide is a waste product of metabolism and it diffuses into the blood to combine with water to form carbonic acid. This increases the blood P_{CO2}. The carbonic acid dissociates into hydrogen and bicarbonate ions, thus changing the pH of the brain tissue medium. The chemosensitive area in the respiratory centre detects this change in hydrogen ion

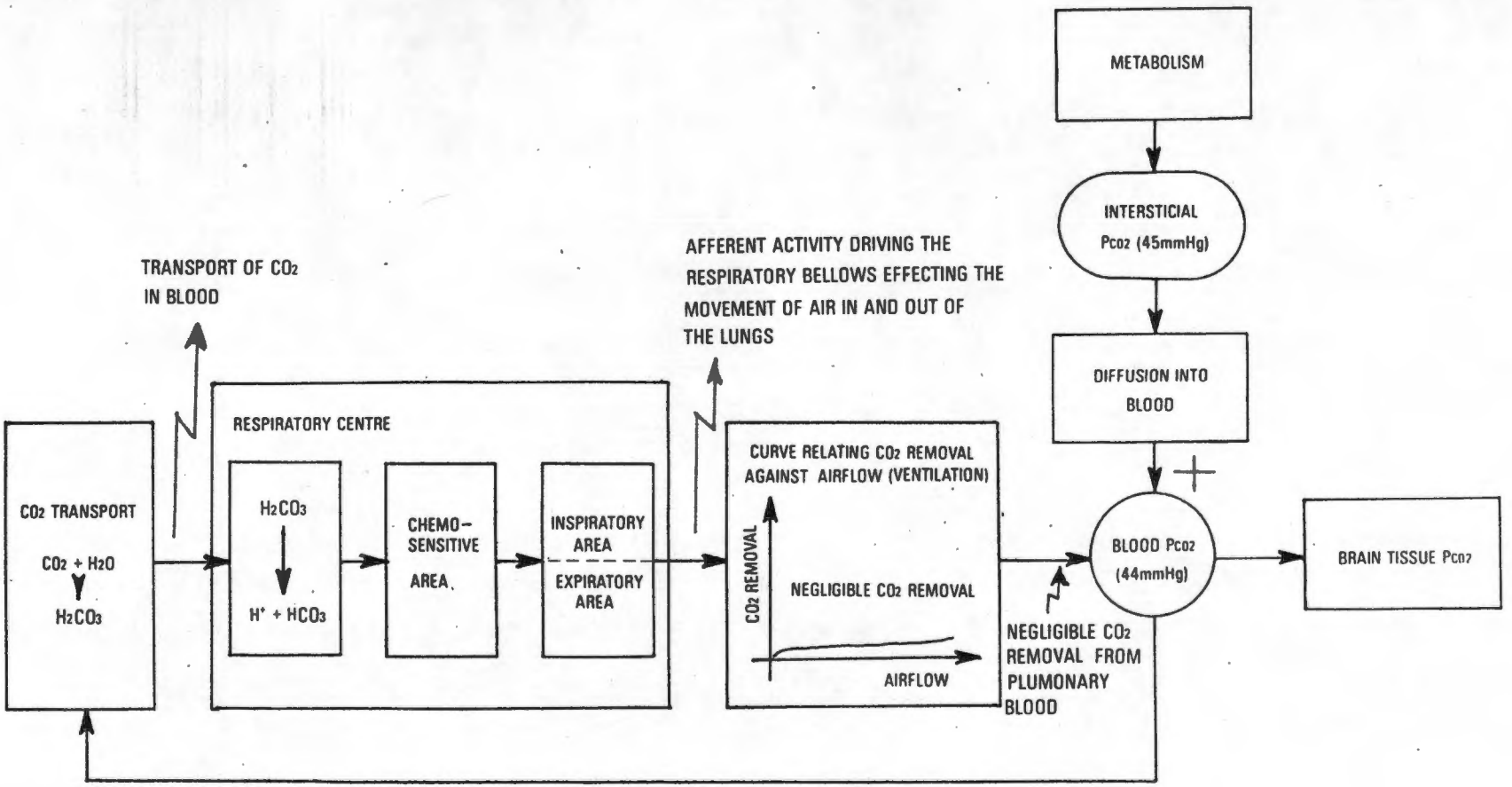


FIGURE 3.3 SIMPLIFIED BLOCK DIAGRAM OF REGULATION OF VENTILATION ILLUSTRATING THE PRESENCE OF PHYSIOLOGIC "OPEN LOOP"

concentration and stimulates the inspiratory and expiratory areas of the respiratory centre. The output from these alter the ventilatory pattern to maintain an optimum brain tissue P_{CO2} level.

Under normal circumstances, the CO_2 is expelled into the atmosphere during the expiratory phase of respiration. The CO_2 concentration of the inspired atmospheric air is virtually zero. The relationship of removal of CO_2 and airflow (expired CO_2) is shown in figure 3.3. There is normally a 4mmHg loss of P_{CO2} as blood travels across a pulmonary capillary. When a person rebreathes from a bag as in the closed circuit illustrated in figure 3.1, the CO_2 is not lost, but builds up in the blood-lung-bag circuit. The rate of loss of P_{CO2} as blood flows across a pulmonary capillary is changed. The plot of the rate of CO_2 removal and airflow becomes flat (constant) under "open loop" conditions. The rate of increase of P_{CO2} in this circuit is constant and is primarily governed by the metabolic rate of the subject. The resultant increase in $P_{0.1}$ and ventilation is linear relative to the increase in P_{CO2} and is governed by the ventilatory drive. Therefore during CO_2 rebreathing, the linear relation between the increase in the circuit P_{CO2} and $P_{0.1}$ and P_{CO2} and ventilation gives an indication of ventilatory drive.

The initial P_{CO2} of the gas in the rebreathing bag must be close to the subject's mixed venous level so that rapid equilibration of the P_{CO2} levels in the blood-lung-bag circuit is achieved by three initial deep and fairly rapid breaths as rebreathing commences. This manifests itself on the P_{CO2} trace as a plateau as shown in figure 3.4. This plateau must be attained within 20 seconds after rebreathing commences. The experiment must be stopped if the plateau is not attained as this indicates that equilibrium has not been set up in the blood-lung-bag circuit.

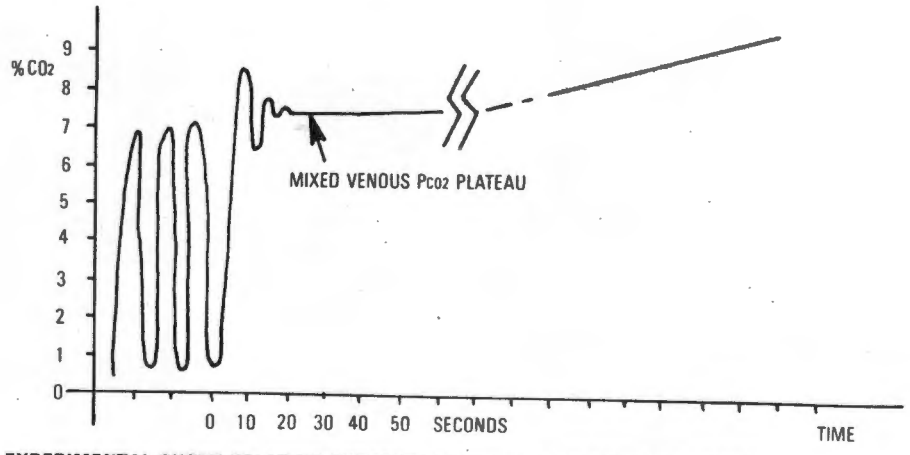


FIGURE 3.4 EXPERIMENTAL CURVE RELATING PERCENTAGE P_{CO2} TO TIME OF REBREATHING

Rebuck (1976) presented a paper in which he describes the ingredients of the rebreathing circuit along with the operating instructions. The most important contribution in his paper is the mentioning of the difficulties experienced by them and other

investigators and the possible ways to avoid them. Precautions must be taken to ensure that the resistance of the circuit is not unreasonably increased while attempting to minimise the dead space. The recording from the dry gas meter may be alinear if the change in potentiometer resistance per angular rotation is not constant and this must be taken into account when calculating minute ventilation. The test must be abandoned if a plateau on the P_{CO2} trace is not attained in the initial stage of the test. His paper comes a long way to the ideal of standardising the technique. Mustchin (1977) noted that both the technical and biological factors seem likely to be responsible for the wide variations of the results; this emphasises the need to standardise the procedure between laboratories. All the investigators found that the normal range of observed slopes is large. Mustchin (1977) quotes that a variation of up to 49 percent was recorded in normal subjects while on the same subject the variability between tests was 7 to 36 percentage. These ranges can be narrowed if the method is standardised. Irsigler (1977) found a mean slope of 2.6 $\pm$ 0.107 liter per minute / mm Hg on 126 normal subjects. He compared his results favourably with those obtained by other workers.

Read (1967) states that when a physiological open loop exists during rebreathing, there exists a constant relation between

changes in arterial blood P_{CO2} level and the medullary chemoreceptor activity (see chapter 2). The stimulant is the affected pH due to the existing CO_2 tension in the blood and not the blood P_{CO2} level. Dempsey (1976) claims that intracranial chemoreceptors are undoubtedly the major site of the stimulus which increases ventilation. These are highly sensitive to local changes of H^+ concentration. But the cell bodies of the medullary neurons with respiratory periodicity are located deep in the medulla and are insensitive, or may even be suppressed by H^+. Also the contribution to the ventilatory response by the carotid bodies is very small or negligible, at least until highly nonphysiological increases in arterial P_{CO2} occur. The ventilatory control via the chemoreceptors is well described by Fencl (1976) who notes that " ...with increase in alveolar P_{CO2}, the pulmonary ventilation increases and minimises the increase in P_{CO2} ".

3.4 $P_{0.1}$ method

The major drawback of the CO_2 rebreathing method is that ventilation is affected by pulmonary mechanics. Examples of abnormalities where ventilation cannot be taken as directly proportional to ventilatory drive are:

(1) airflow obstruction where physical impediment to ventilation

is present, and (2) muscle weakness, where the respiratory muscles are physically unable to generate ventilation.

The $P_{0.1}$ method presented by Whitelaw and co-workers (1975) overcomes at least the first of these two problems - by measuring the force generated by breathing in. The ventilatory drive can be assessed without actually having to generate airflow in this way. The second problem however is not addressed by the $P_{0.1}$ method. The CO_2 method is modified in that the inspiratory airway is occluded for 100ms after the onset of inspiration. This requires a definition of onset of inspiration. Jordan (1981), Camporesi et. al. (1978) and Delavault et. al. (1980) compared the mouth pressure to preset pressure levels to indicate the onset of inspiration. The onset of inspiration is defined as, "When the mouth pressure reaches zero, ..." (Delavault et. al. (1980)), "... usually close to the negative side of zero pressure" (Camporesi et. al. (1978)) and "...a pressure transition to below -0.05k Pa" (Jordan (1981)). The pressure developed due to the isometric contraction of the respiratory muscles reflects the total neuromuscular drive of the respiratory centre. The pressure at 100ms after the onset of inspiration, $P_{0.1}$ is taken as a ventilatory index and it is independent of pulmonary mechanics as there is no flow of air at this instance. Whitelaw found that there are no conscious or unconscious responses to the occlusion

of the inspiratory airway for the first 250ms of inspiration. During this period the pressure increases linearly and the pressure at 100ms was used as it is easy to measure and reproducible.

3.4.1 Correlation to ventilatory response

The correlation between the $P_{0.1}$ response and the ventilatory response to CO_2 is reported to be excellent and the usefulness of the $P_{0.1}$ method is summarised by Lederer (1977). He noted "...that the measurement of $P_{0.1}$ is no better than ventilation in evaluating motor neuron activity in normal subjects. However, in specific circumstances, during anaesthesia or in patients with lung disease, when the mechanical properties of the chest wall of the lung may be altered, measurement of $P_{0.1}$ may be of more value than ventilation".

Altose (1976) and others have confirmed Whitelaw's findings that ventilatory responses correlated best with the changes in pressure early after the onset of inspiration. After about 250ms into the inspiratory phase cortical and/or reflex effects modify the force generated by the inspiratory muscles. Most investigators take the pressure at 100ms, after the onset of inspiration as the ventilatory index. Camporesi et al (1978) and Lopata et al (1978) used the pressure ($P_{0.15}$) at 150ms, after

the onset of inspiration as the ventilatory index. This time interval was taken purely for technical reasons. They claim similar results as the investigators using 100ms after the onset of inspiration.

3.4.2 Response curves

The $P_{0.1}$ response curves observed by Whitelaw (1975) were curvilinear, but later investigators showed them to be linear. Lederer et al (1977) suggest that the curvilinear relation observed by Whitelaw is due to discrepancies in the procedures. He claims that a curvilinear relation can be obtained if care is not taken to allow the CO_2 in the blood, alveolar and the rebreathing bag to reach complete equilibrium before determinations of ventilation or occlusion pressures are made. These regression lines are drawn using the least squares method. Mustchin (1977) suggests the use of a computer to aid in the drawing of the graph and the calculation of the required variables. This he says will increase the accuracy of the test which must only be accepted if a high degree of correlation exists between the two variables.

3.4.3 Effect on timing of total occlusion on breathing

The occlusion of the valve was triggered manually by all the

investigators. Care was taken to avoid the patient anticipating the occlusion to prevent any conscious reaction to the occlusion. The occlusions must not appear periodically as the person will learn to anticipate it. Lederer (1977) claims that intermittent airway occlusion has no significant effect on changes in ventilatory indices. They found that it had no effect on tidal volume to ventilation relationship. The same is observed by other investigators.

3.4.4 Effect of functional residual capacity, FRC

This is claimed to be the chief cause of discrepancies observed inter- and intra-individually. Cherniack (1976) and Mustchin (1977) noted that for any given level of electrical stimulation, the pressure generated by the respiratory muscles, like other striated muscles, will depend on their resting length. It is hoped that correction factors can be developed so that the observed responses are more representable and patients with abnormal FRC can be studied.

3.4.5 Effect of body position

Lederer (1977) observed that if the body position is changed from the sitting to supine position the FRC fell an average of 1.2 litres. The position of the body however had no significant effect on the relationship of the change in P_{CO2} to changes in

minute ventilation, tidal volume or $P_{0.1}$ or any of other ventilatory indices.

3.4.6 Effect of external dead space

Sackner et al (1980) show that external dead space causes an increase in ventilation. It primarily affects the tidal volume and the ventilatory frequency only to a lesser extent. They did not observe any relationship between these effects and dead space volume. The effective dead space is less than the measured values.

3.4.7 Occlusion valve

Very limited information is available on the apparatus used to carry out the $P_{0.1}$ method. Camporesi et al (1978) describes an electromagnetic valve. The essential features of an occlusion valve are:

1. it must be airtight when activated
2. respond rapidly
3. operate silently

and 4. be controlled remotely

They used a commercially available solenoid constructed with a soft iron core and return path. The occlusion was effected by

attracting a black iron sheet disc against a rubber "O" ring. The valve was occluded by different investigators at various times and between various intervals Altose (1976), Lopata (1978), Camporesi (1978) and Jordan (1981). All claim similar results.

3.4.8 Electronic valve control

Delavault and Saumon (1980) presented an electronic control for a solenoid valve. The pressure signal was filtered with a 13Hz cut-off frequency lowpass filter. This actuated a voltage comparator which is used to determine the onset of inspiration. A potentiometer was used to set the reference voltage reflecting the pressure at the onset of inspiration. The rest of the circuitry consists of timing devices. Jordan (1981) presents an automatic method to aid measuring ventilatory drive using the $P_{0.1}$ method. His circuit functions essentially the same. Included are sample and hold facilities to register $P_{0.1}$ and P_{CO2} and these are fed directly into a X-Y recorder. The slope is found graphically.

The onset of inspiration is not defined in any detail by the authors. There appears to be some controversy over the exact point of onset of inspiration. A negative pressure close to zero is taken by the investigators in these two presentations. Even

the presentation titled, " Drive and Timing Components Of Ventilation " by Milic-Emili et al (1976) does not define it.

3.5 Conclusion

The $P_{0.1}$ method if correctly used is a reliable method of assessing ventilatory drive. The method will only become widely used if the procedure is standardised and more accurate results are obtained.

4 P0.1 REBREATHING SYSTEM

4.1 REBREATHING CIRCUIT

4.1.1 CO_2 REBREATHING CIRCUIT

The CO_2 rebreathing system, as introduced by Read (1967), used in the Respiratory Clinic at Groote Schuur Hospital is shown in figure 4.1. The 3-way stopcock enables the subject to breathe either room air or rebreathe from the bag. A nine litre rubber

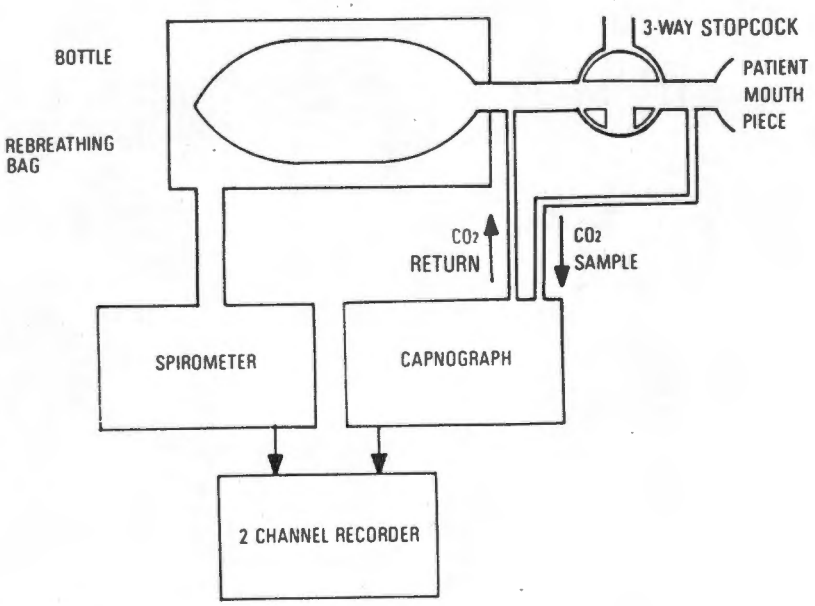


FIGURE 4.1 READ REBREATHING SYSTEM.

bag was used and filled with a mixture of carbon dioxide and oxygen gas of known partial pressures and volume chosen to allow rapid equilibrium of the partial pressure of CO_2 in the bag and the lungs. For example, a patient with a small lung volume requires a smaller bag volume than a patient with a normal lung volume. Rebuck (1976) suggests that the volume of gas in the bag should equal the vital capacity of the subject plus one litre. The P_{CO2} of the gas is chosen close to the mixed venous level so that the P_{CO2} of the bag-lung-blood system can equilibrate within at most 20 seconds after rebreathing commences. The bag was enclosed in an airtight clear-glass bottle so that the movement of the bag could be directly observed. The bottle was attached to a wedge spirometer (570 Wedge Spirometer MED SCIENCE) to measure the volume of gas moving in and out of the bag. The P_{CO2} of the system was continuously monitored by drawing a continuous flow of gas from the mouth-piece through a rapid response infrared CO_2 analyser (Godart Ltd. Capnograph). The sampled gas was returned into the bag to eliminate changes in volume of the system. The volume signal from the spirometer and the P_{CO2} signal from the capnograph were recorded on a 2-channel recorder (Godart Ltd.). The minute ventilation (V_E) was laboriously calculated by measuring the tidal volume (V_t) deflections with a ruler and adding them over approximately half- minute intervals. This sum

of tidal volume was divided by the time interval (half minute) to give minute ventilation. The P_{CO2} was recorded directly off the trace at the point central in the half-minute period. The calculated minute ventilation and the recorded P_{CO2} points were recorded on a work sheet and then fed into a computer which calculated and traced the ventilation versus P_{CO2} regression line, the slope of the line and the coefficient of correlation. Figure 4.2 shows a recorded trace and the calculated regression line.

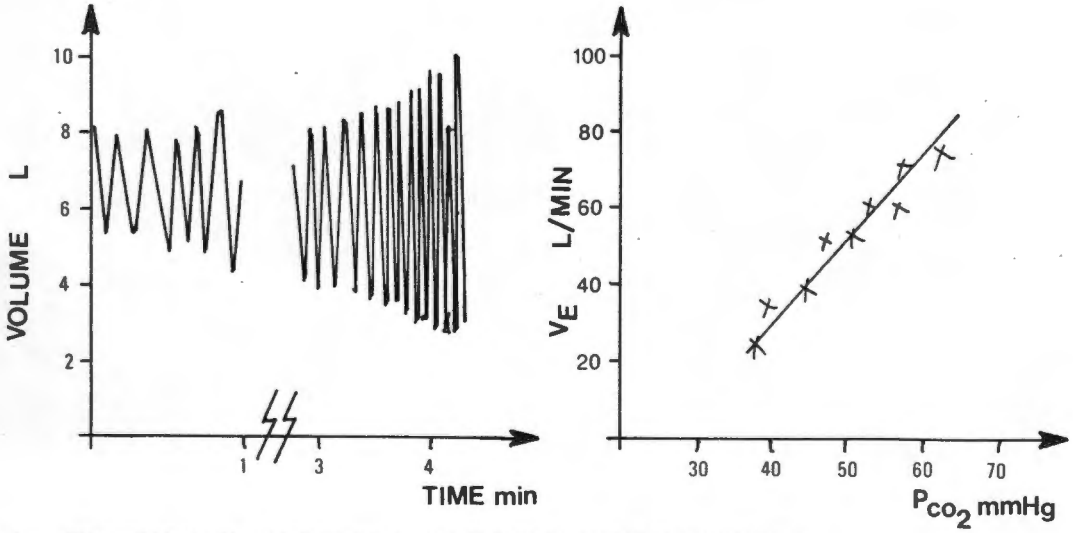


FIGURE 4.2 EXPERIMENTAL TRACE RELATING: A. RESPIRATORY VOLUME (TIDAL VOLUME) TO THE TIME OF REBREATHING. B. CO_2 RESPONSE PLOT.

4.1.2 THE MODIFIED P0.1 / CO2 REBREATHING SYSTEM

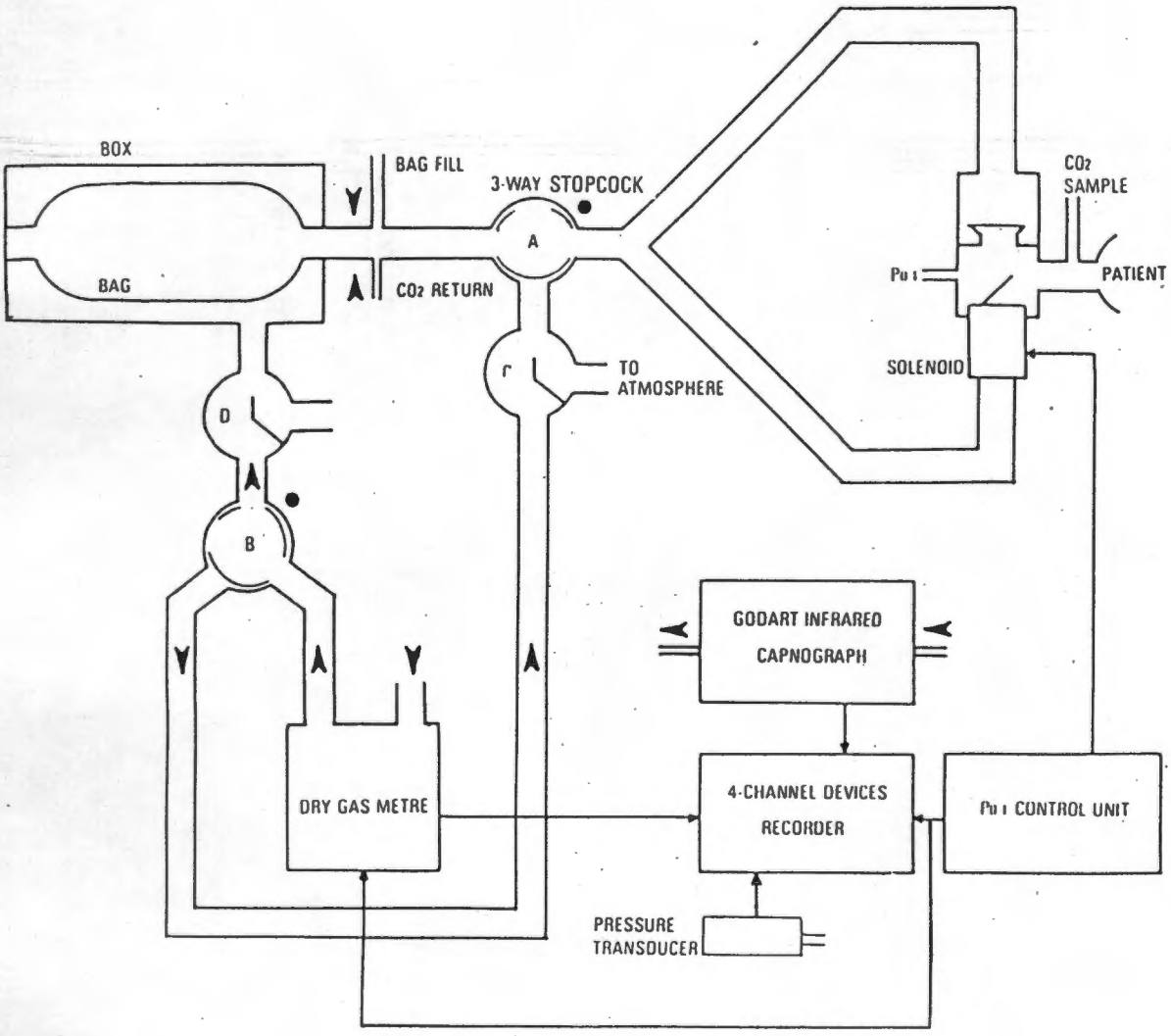


FIGURE 4.3 THE MODIFIED $P_{0.1}$/CO_2 REBREATHING SYSTEM

The $P_{0.1}$ CO_2 rebreathing circuit is the same as explained above except that the inspiratory and expiratory airways to the patient mouth piece are separated by a 2-way valve and an occlusion valve is included in the inspiratory airway. Figure 4.3 shows the modified rebreathing circuit. The bag is enclosed in an airtight perspex box which is connected to a dry gas meter. The 3-way stopcocks A and B and 2-way valves C and D enables ventilation to be monitored when the patient either breathes room air or rebreathes from the bag. When the patient breathes room air, the gas enters through the inlet of the dry gas meter, to the inspiratory airway via stopcock B and valve C and stopcock A. The expired air leaves via stopcock A and into the atmosphere through valve C. While rebreathing, the gas moves to and fro between the bag and the patient via stopcock A . During inspiration the bag collapses and air is drawn into the perspex box through the dry gas meter via stopcock B and valve D. During expiration the gas leaves the box via valve D into the atmosphere. The trace from the dry gas meter enables direct recording of the volume deflection over a period compared to the addition of the measured individual breath by breath volume deflection on the wedge spirometer. The movement of air through the dry gas meter is only during inspiration. A potentiometer turns as the air flows through the meter. The output from the potentiometer changes during inspiration and appears as steps on the volume

trace (figure 4.4).

The pressure generated by the isometric contraction of the respiratory muscles against the occlusion is measured in addition to minute ventilation and P_{CO2}. This pressure is measured at the mouth.

The $P_{0.1}$ control unit controls the occlusion valve and supplies power to the dry gas meter. A 4-channel Devices recorder traces the P_{CO2}, volume deflection and pressure signals as shown in figure 4.4.

4.1.3 HYPERCAPNIC AND HYPOXIC REBREATHING CIRCUIT

This circuit is presently used in the Respiratory Clinic at Groote Schuur Hospital. The circuit has in addition to the $P_{0.1}$ arrangement, a CO_2 scrubber circuit with a pump attached to the rebreathing bag as shown in figure 4.5. For hypercapnic studies, the air in the bag bypasses the CO_2 absorber and is merely circulated by the pump back into the bag. This facilitates mixing of gases in the bag. For hypoxic studies, the air in the bag is circulated through the CO_2 absorber. The CO_2 level in the bag can be maintained constant by controlling the speed of the pump. The percentage saturation of oxygen in the patient's blood is

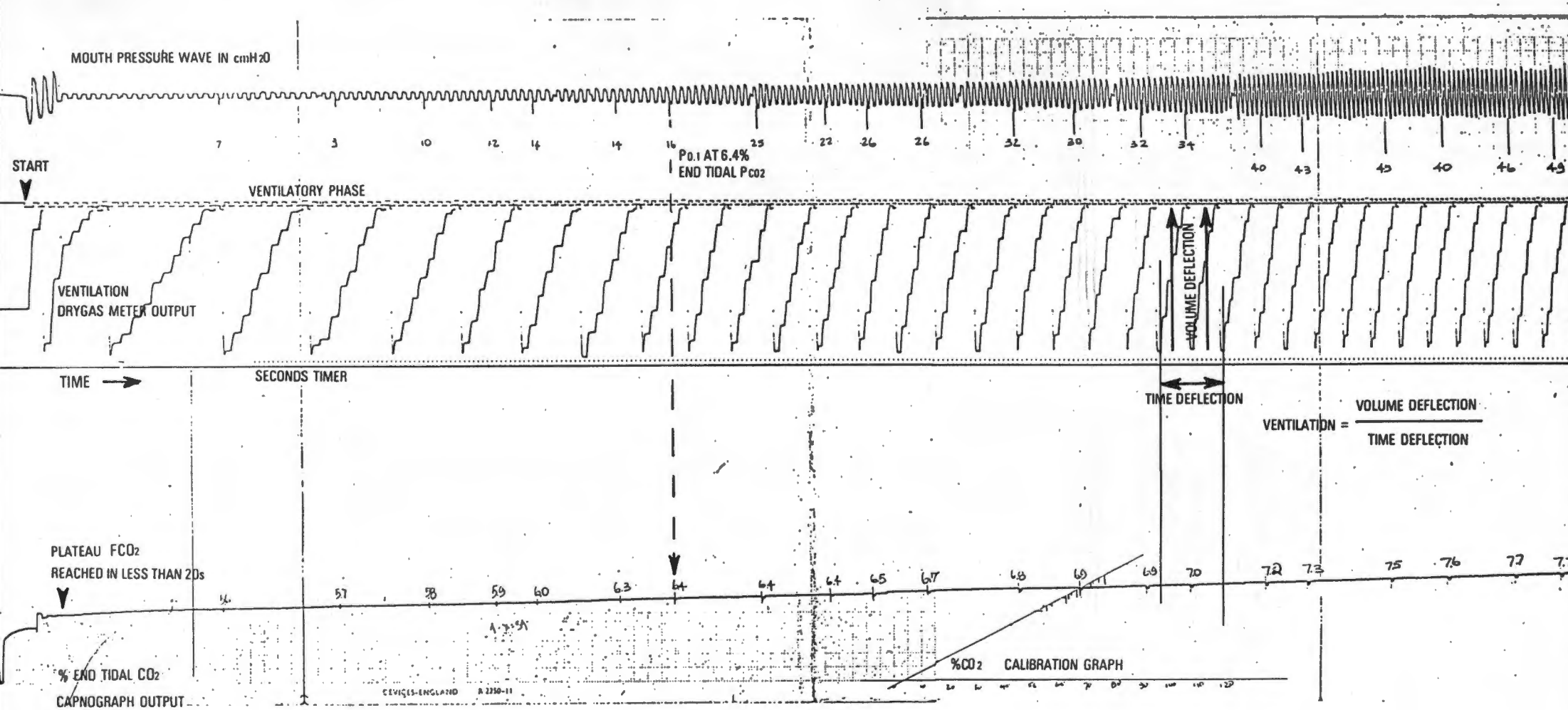


FIGURE 4.4 EXPERIMENTAL TRACE RELATING $P_{0.1}$, P_{CO2} AND TIDAL VOLUME TO THE TIME OF REBREATHING.

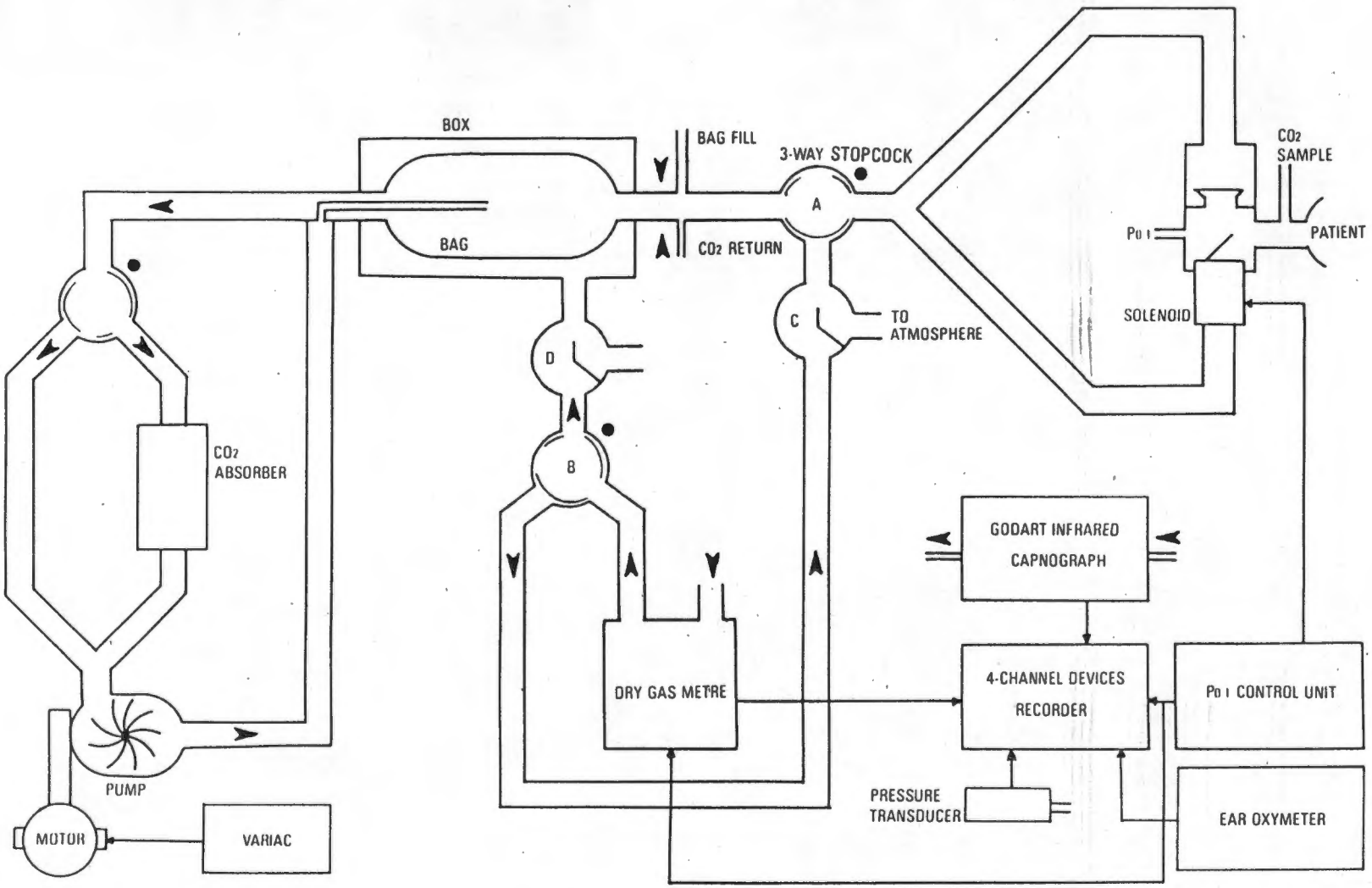


FIGURE 4.5 $P_{0.1}$ - **VENTILATION SYSTEM FOR HYPERCAPNIC AND HYPOXIC STUDIES.**

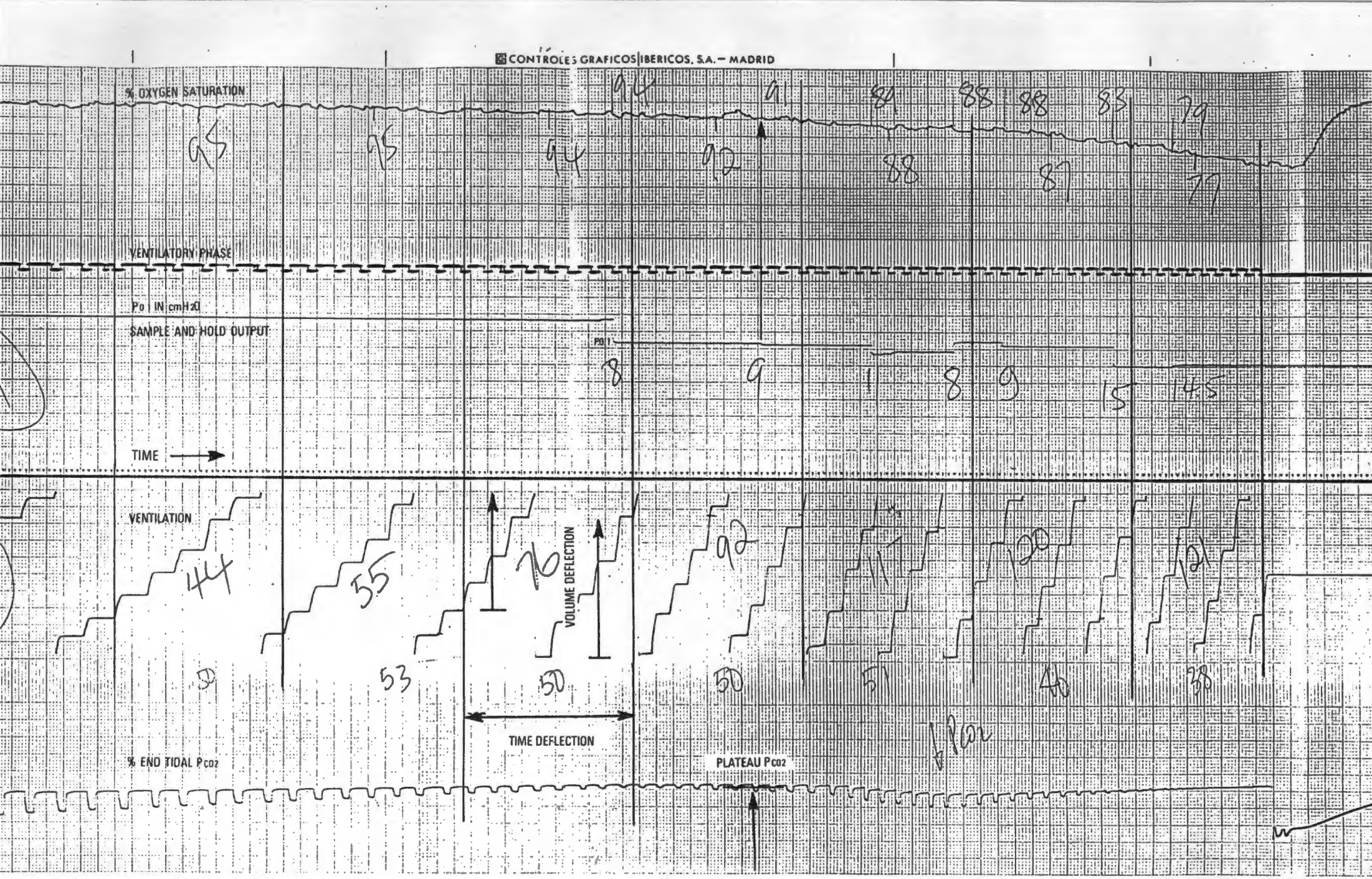


FIGURE 4.6 EXPERIMENTAL TRACE RELATING $P_{0.1}$, P_{CO2}, PERCENTAGE O_2 SATURATION AND TIDAL VOLUME TO THE TIME OF REBREATHING.

continuously monitored using an ear-oximeter (Hewlett Packard). The signal from the oximeter is fed to the fourth channel of the Devices recorder. Figure 4.6 shows a trace of the pressure, P_{CO2}, volume deflection and percentage O_2 saturation as an example.

4.1.4 SYSTEM DEAD SPACE

The dead space of the $P_{0.1}$ rebreathing system was measured by water displacement technique. The dead space of the system is the airway volume from the patient mouth-piece to stopcock A (figure 4.3) and was measured to be 350ml.

4.2. OCCLUSION VALVE

During the $P_{0.1}$ trial, the inspiratory airway of the respiratory circuit must be occluded for a short period in the initial stage of inspiration of a particular breathing cycle. A valve required to do this must fulfil the following criteria;

a. the occlusion be airtight

b. operate silently

c. respond rapidly

d. remote control activation

A suitable valve was not commercially available and an

electromagnetically powered respiratory valve designed and constructed to meet the above specifications is presented here. The valve is essentially a metal disc which is held closed by a solenoid. The valve occludes an opening which is in the inspiratory airway of the respiratory circuit.

4.2.1 DESIGN CONSIDERATIONS

An important design constraint was to minimally modify a low airflow resistance 2-way respiratory valve which is readily available and in everyday use in the Respiratory Clinic. This approach was followed rather than the design of a complete 2-way occlusion valve in order both to minimise the cost and time involved in manufacturing a complete valve and also to maximise on the simplicity and availability of components for such a valve. The Collins J valve as used in the respiratory Clinic at Groote Schuur Hospital was used by Whitelaw (1975) to separate the inspiratory and expiratory airways. The valve is locally supplied and readily available and components such as the diaphragm are amongst the stock items of the clinic. Whitelaw occluded the inspiratory port by manually closing, during expiration, a stopcock in the inspiratory line. This method does not comply with the last two conditions of the criteria mentioned

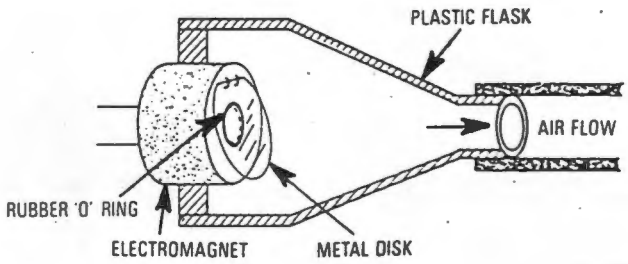


FIGURE 4.7 ELECTROMAGNETIC OCCLUSION VALVE PRESENTED BY CAMPERESI AND CO-WORKERS (1978).

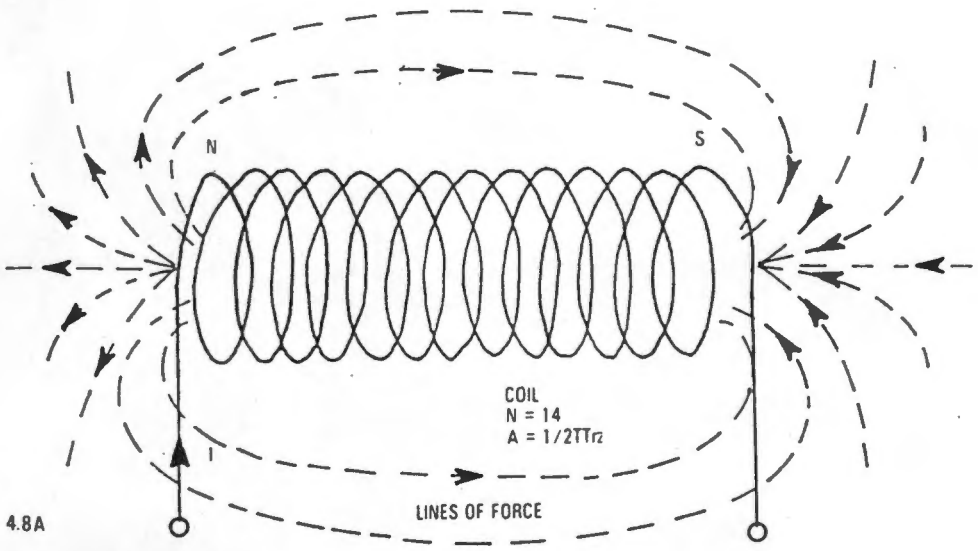
above. Also the timing of 100ms after the onset of inspiration will be inaccurate and inconsistent using this method. Camporesi et al.(1978) used a commercially available solenoid to attract a metal disc against a rubber 'O' ring situated on the body of the solenoid. The disc occluded the air passage through the solenoid. Figure 4.7 shows a schematic of this valve. It does comply with the required design criteria. However, the solenoid is not available locally.

PHOTOGRAPH 4.1 COLLINS J-2 VALVE

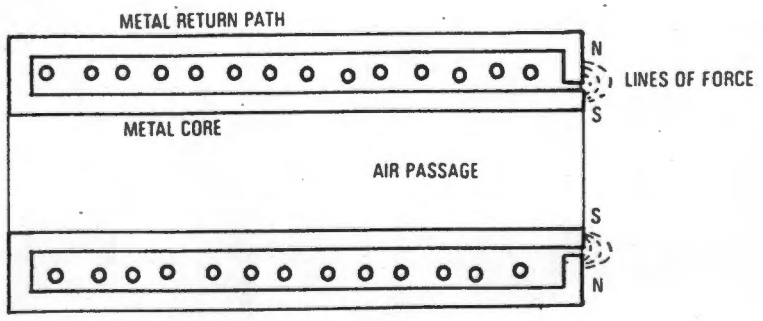
An assembled Collins 'J' valve and one in component form is shown in photograph 4.1. The inspiratory port is a separate component that screws onto the body of the valve. It was decided to modify this component to include a solenoid valve and leave the rest of the valve intact.

4.2.2. OCCLUSION VALVE DESIGN

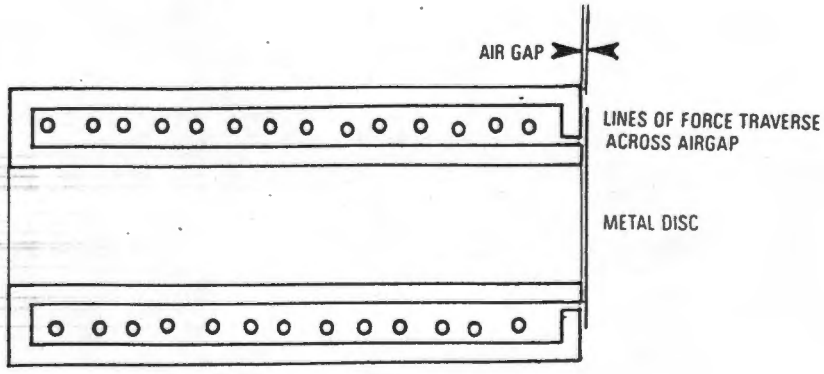
A solenoid (Sears and Zemansky) shown in figure 4.8 is a coil of copper wire consisting of a specific number of turns, N, and having a cross-sectional area A. A current, I, passing through the coil causes it to act like a magnet with a north and south pole, as shown in figure 4.8a, with a magnetic field consisting lines of force traversing from the north to south pole. The lines of force in the field tend to traverse along the shortest distance between the poles. The field is uniform in the centre of the solenoid. If a metal core and a return path made of iron, are included around the solenoid, the lines of force will travel as shown in figure 4.8b. The molecular structure of the metal aligns itself in the direction of the lines of force, affording little resistance. The magnetic field is concentrated in the metal and virtually none through the air as shown in figure 4.8a. The gap between the poles is called the airgap and the force exerted by the field between the poles is inversely proportional to it. A



4.8A



4.8B



4.8C

FIGURE 4.8 THE LINES OF FORCE AROUND A SOLENOID.

metal disc placed over the poles will be attracted strongly to them so as to attempt to bridge the airgap and thus shortening the lines of force even further as shown in figure 4.8c. When the current is switched off, the magnetic field generated by the coil disappears. But because of the hysteresis property of iron, remnant magnetism remains and this is strong enough to attract the disc to the solenoid. Silicon iron has the least hysteresis and is the ideal metal for the valve's construction, but is not available locally. Annealing mild steel reduces its hysteresis. This was used to construct the solenoid.

The design of the valve is shown in figure 4.9. A 120mm long, 50mm diameter mild steel rod was turned into the inner core and outer return path as shown. These were annealed by heating to 2000 degrees Celsius in a laboratory oven and cooled overnight. The metal was then nickel plated to prevent rusting. Imperfections in the nickel plating must be avoided as rust will occur at these points. The figures in brackets on figure 4.9 are those measured after the solenoid was completed. The coil was wound around the core and the components were screwed together. The valve is encased in perspex to afford protection to the metal and to make it compatible to the perspex body of the Collins J valve.

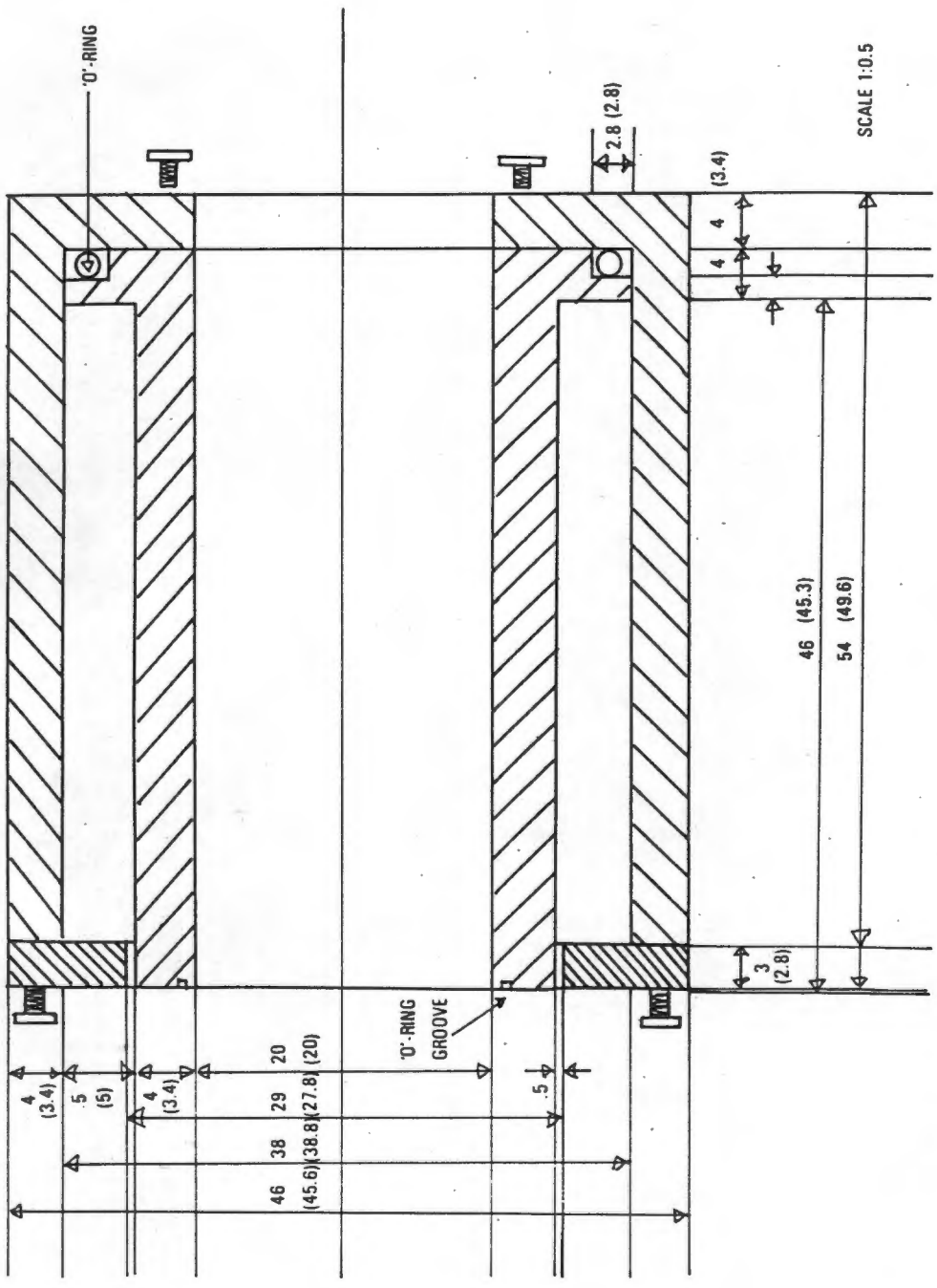


FIGURE 4.9 THE $P_{0.1}$ OCCLUSION VALVE.

The metal disc is attracted by the solenoid against a rubber 'O'-ring placed in a groove in the central core. The 'O'-ring prevents the disc touching the poles of the solenoid and thus acts as a spacer to form the small airgap. It helps to create an airtight seal when the disc is attracted to the solenoid. The metal disc is a telephone earpiece diaphragm and is 34.4mm in diameter and 0.2mm thick. Its mass is 1.2 grams. The diaphragm was obtained from the post office. It was cleaned to remove the original coating and then sprayed with metal primer to prevent rusting. A small model aeroplane plastic hinge (Kavan Hinges Art No. 129) is glued with cyanoacrylate adhesive to the disc. The hinge is attached to the solenoid by clamping it to the perspex casing as shown in photograph 4.2. Spring steel wire, 0.4mm in diameter is placed in the opening path of the disc to limit its movement. A spring is used so that the disc is cushioned when it flaps open, thus preventing excessive force on the hinge and its attachment. Also the disc is pushed closed to some extent by it.

A layer of mylar plastic is attached to the core before the coil is wound onto it. This insulates the coil from the core. The coil is wound with 20 gauge copper wire and is made up of 6 layers with 252 turns (N = 252). The coil has an average cross-sectional area of $33.2cm^2$ ($A = 33.2cm^2$). The total length of wire used is

PHOTOGRAPH 4.2 ATTACHMENT OF METAL DISC TO OCCLUSION VALVE CASING.

approximately 26 meters. The coil was wound by placing the core in the chuck of a lathe and turned manually. The terminals of the coil are channelled out of the metal valve and soldered onto 2.5mm banana sockets fixed into the perspex casing. A 3 meter phillishave flex is used to connect the coil to the $P_{0.1}$ unit via a 6.3mm stereo jack plug.

4.2.3 Occlusion Valve Specifications

a. Coil resistance = 0.8 ohm

b. Coil inductance = 1.1mH @ 16kHz

c. Maximum operating current = 3 amps

d. Mass = 600g

e. Dead space = 175ml = Collins 'J' valve dead space

5 P0.1 CONTROL UNIT

5.1 INTRODUCTION

The $P_{0.1}$ control unit controls the occlusion valve during a $P_{0.1}$ trial. The inspiratory airway must be occluded for a short time after the onset of inspiration. The subject must not anticipate the occlusion and the valve must operate remotely. The $P_{0.1}$ control unit must recognise the onset of inspiration and then after a controlled period, for example 100ms, release the valve. The flow chart in figure 5.1 describes the operational criteria the $P_{0.1}$ unit fulfils. The flow chart is explained below with further reference to figure 5.2.

The $P_{0.1}$ control unit can be divided into 3 functional units. The electronics that fulfil these functions is designed on three separate boards, the $P_{0.1}$ control board, the valve trigger board and the pressure preset indicator and ventilatory phase indicator board. Figure 5.2 shows the functional division of the $P_{0.1}$ Unit.

The mouth pressure, P, is monitored continuously using a Godart Statham PM131 pressure transducer. Channel 1 of the Devices recorder is used to monitor the pressure and the pressure signal

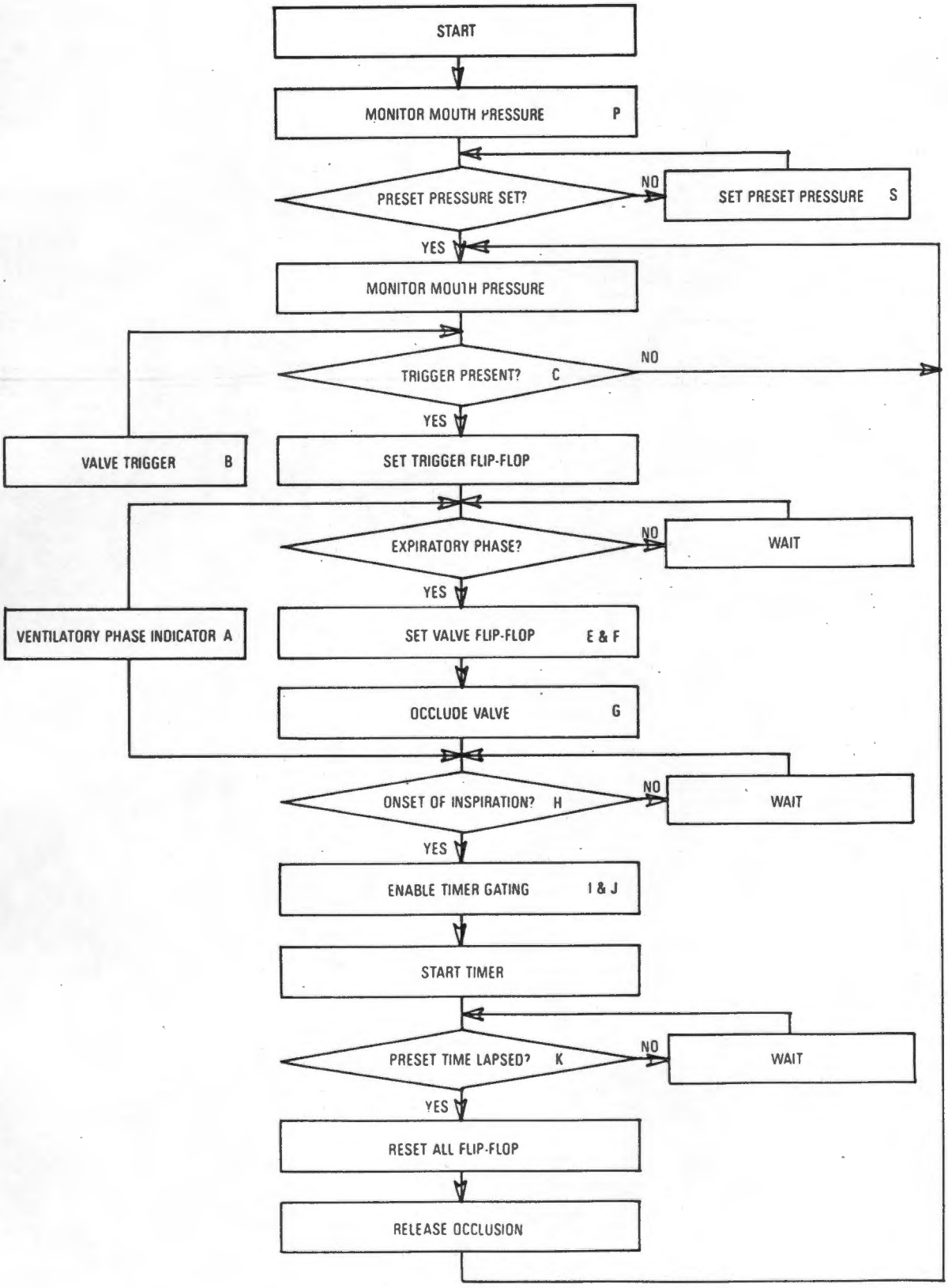


FIGURE 5.1 FLOW CHART DESCRIBING THE CONTROL LOGIC OF THE $P_{0.1}$ CONTROL UNIT

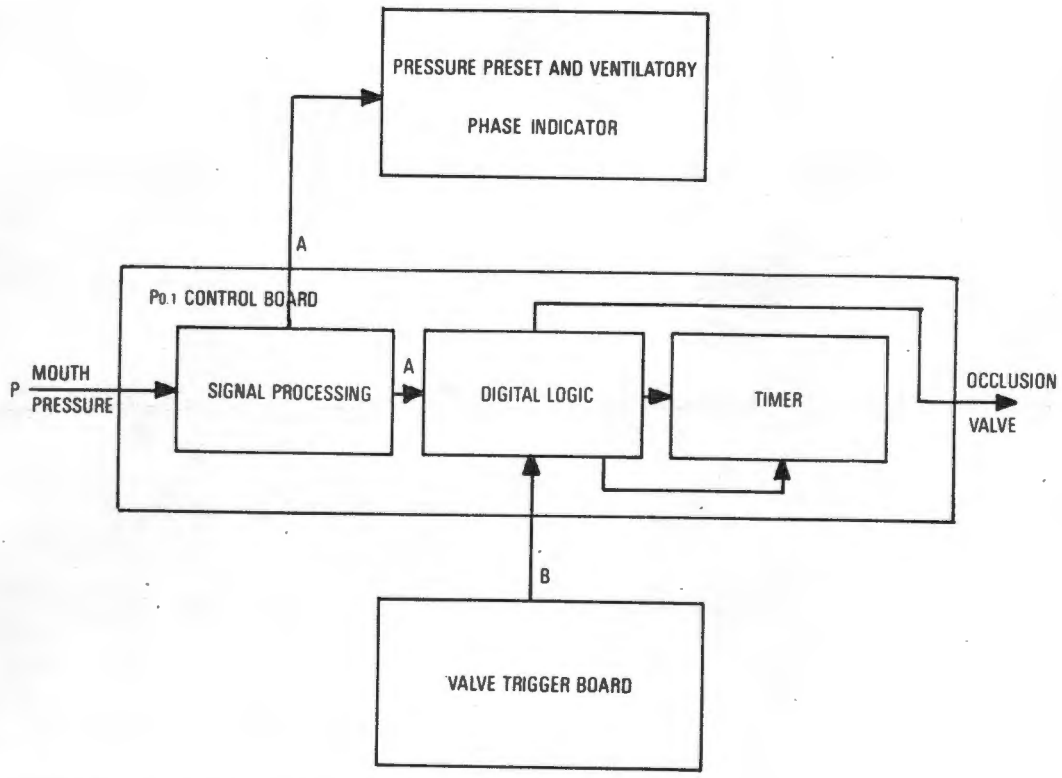


FIGURE 5.2 FUNCTIONAL DIVISION OF THE $P_{0.1}$ CONTROL UNIT.

is zeroed to atmospheric (S) by adjusting the fine offset adjust control on the preamplifier. The pressure signal from the remote meter output of the Devices pressure monitor is led to the $P_{0.1}$ control unit where it is used to detect the onset of inspiration and the inspiratory and expiratory phases (A) of a breathing cycle. The valve trigger board controls the initiation of valve occlusion at preselectable or random times. A command signal (B), to occlude the valve from the valve trigger board sets the trigger flip-flop on the control board. The inspiratory airway is occluded during expiration as there is no flow of air through it during this time. If the trigger signal arrives during

inspiration, the valve is occluded during the subsequent expiratory phase. The timer flip-flop is set at the onset of the next inspiratory phase to start the timer.

After the preset time, for example 100ms, has lapsed, all the flip-flops are reset, the occlusion valve is released and the cycle repeats until the trial is completed. The period when the valve is occluded during the initial stage of inspiration is the active occlusion period (100ms) of the valve. At the end of this period the pressure $P_{0.1}$ is recorded. $P_{0.1}$ can either be recorded on a continuous pressure trace appearing as a "spike" or as a dc value held between occlusions. Figure 5.3 shows a schematic of the control unit. The electronic design of the functional units is described below.

5.2 P0.1 CONTROL BOARD

The functional design of the board is shown in figure 5.1 and discussed above. The criteria for electronic hardware design was local availability of components and simple reliable operation. Digital integrated circuits are used for the latter reason. The control board can be divided into three functional units, the pressure signal processing, digital logic control and the timer.

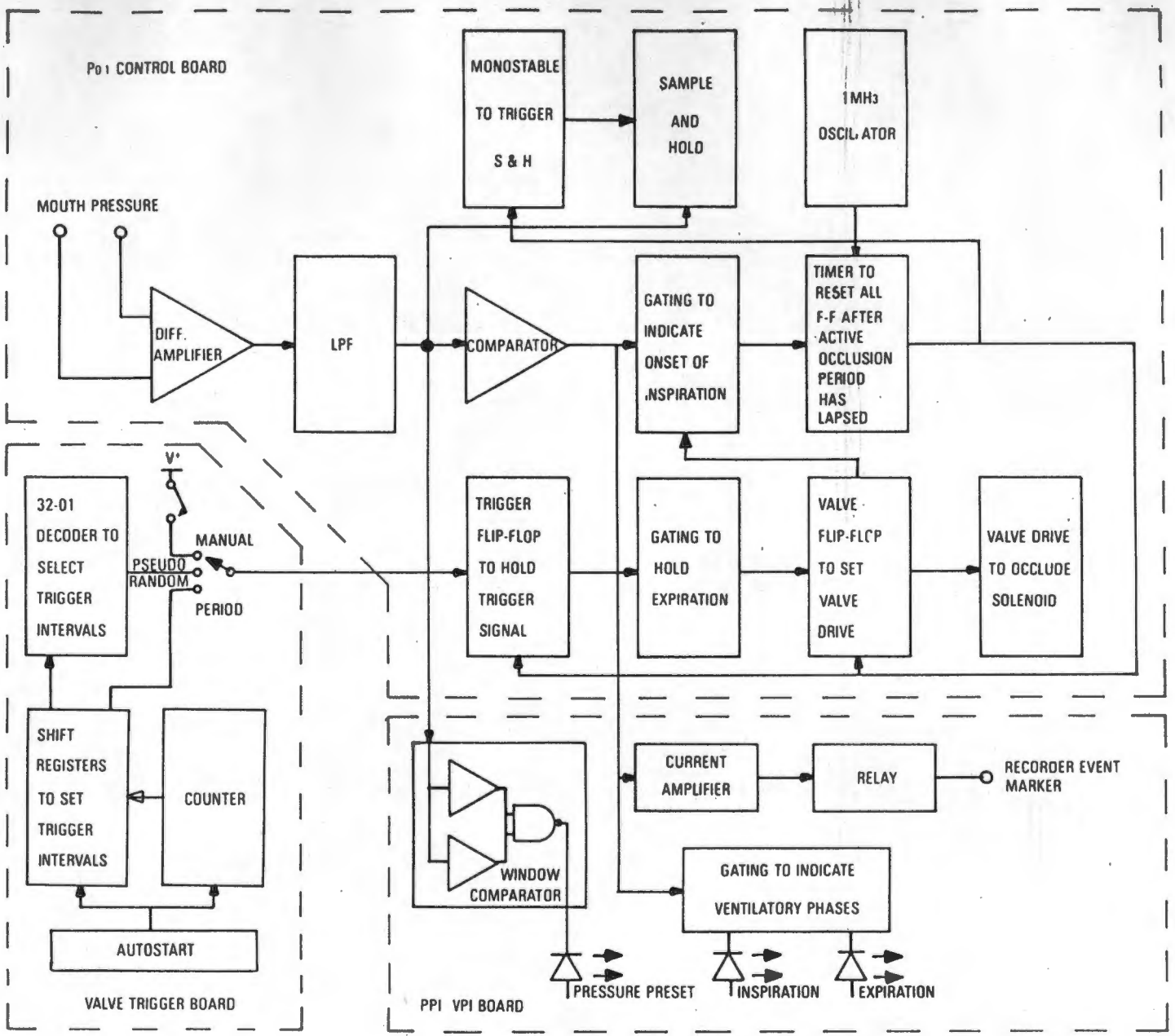


FIGURE 5.3 SCHEMATIC OF THE ELECTRONIC DESIGN OF THE $P_{0.1}$ CONTROL UNIT.

5.2.1 PRESSURE SIGNAL PROCESSING

The pressure signal processing circuitry is shown in figure 5.4. The signal from the remote meter output of the Devices recorder is fed into a differential amplifier (IC1 - LF351) to eliminate common mode signals. The signal is then passed through a second order Salley and Key low pass filter (IC2 - LF351). The filter gives a Butterworth maximally flat response with a 12dB roll off and a 3dB cut-off frequency, f_c, given by:

$$f_c = 1/2TT \quad (C1.C2.R5.R7)^{-1}$$

for $C1 = C2 = C$ and $R5 = R7 = R$

$$f_c = (2TTRC)^{-1}$$

$$= 645 \text{ Hz} \quad \text{for } C = 4.7\text{nF and } R = 330\text{K}$$

The normal respiratory rate is approximately 12 breaths per minute (f = 0.2Hz) and can rise to as high as 40 to 50 per minute (fmax = 0.83Hz). The cut-off frequency of 645Hz allows the pressure signal, P, generated at the mouth to pass through the filter and eliminates all high frequency signals which would constitute noise. The choice of 645Hz cut-off frequency is discussed below. The filtered pressure signal is fed into a voltage comparator, IC3 - LM311. This signal is compared to a

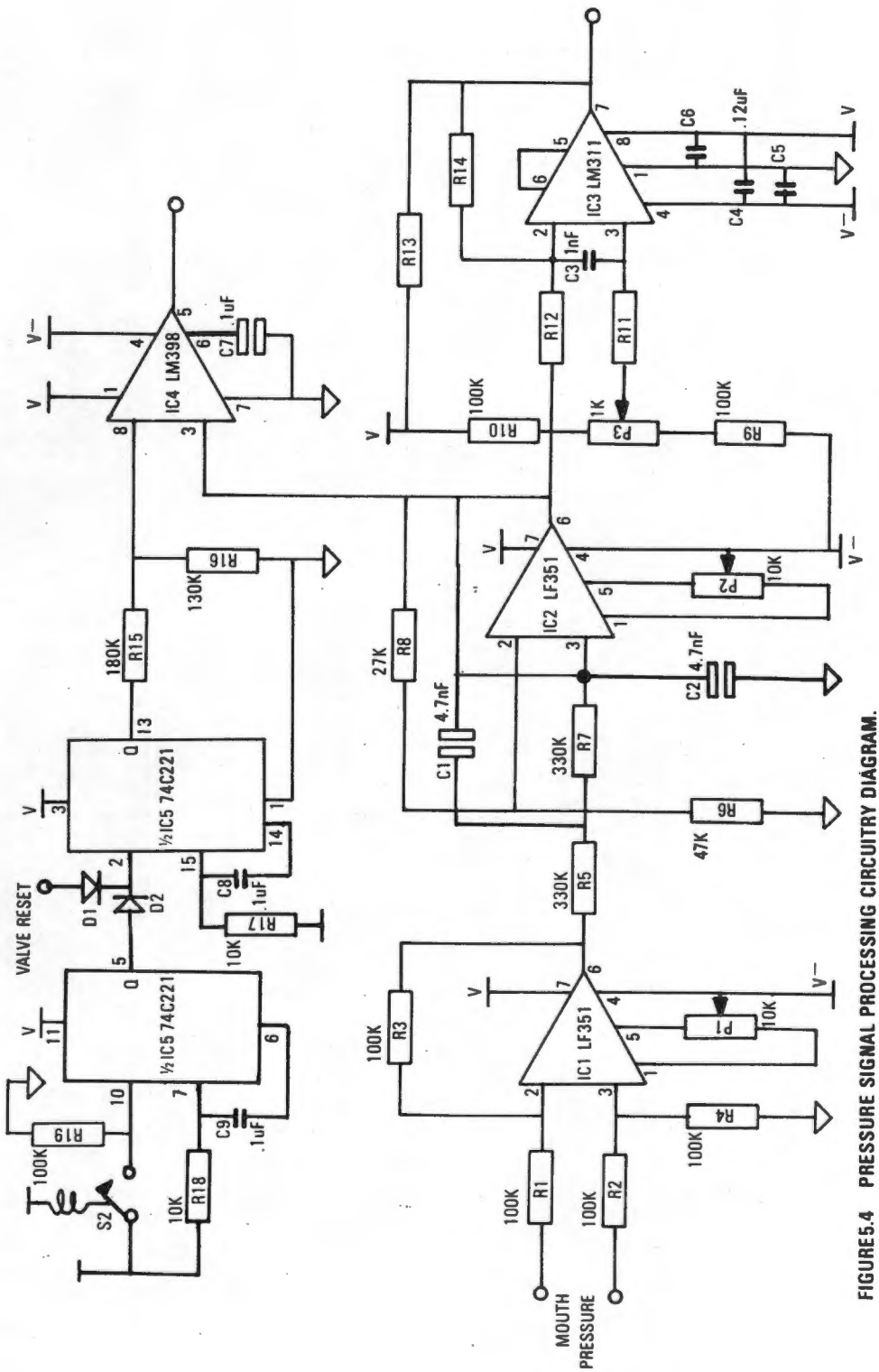
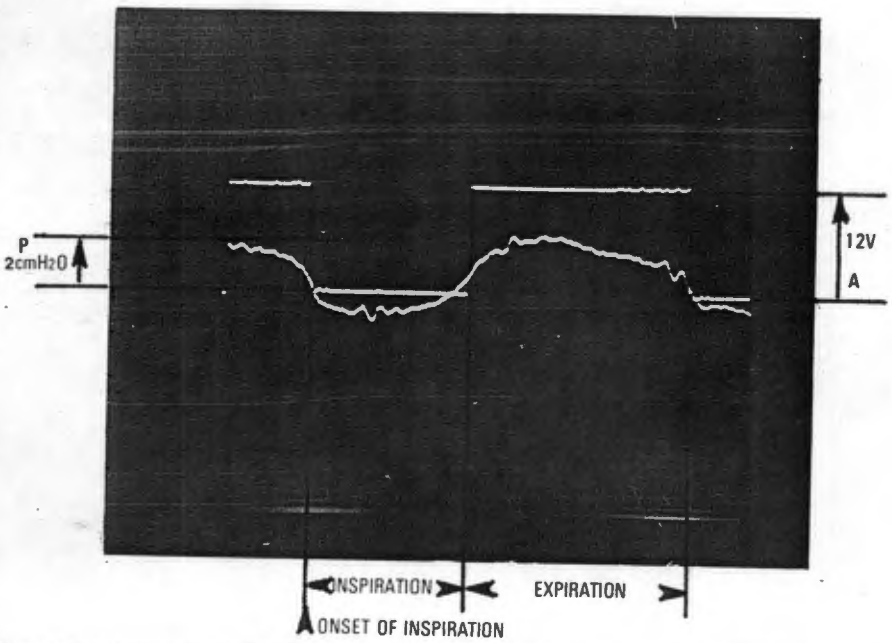


FIGURE5.4 PRESSURE SIGNAL PROCESSING CIRCUITRY DIAGRAM.

voltage reference, V_{ref}, which is derived from a resistor bridge across the positive and negative supplies. V_{ref} is taken as the electrical level at the onset of inspiration on the pressure wave. The comparator output is high when $P > V_{ref}$, indicating expiration and low when $P < V_{ref}$, indicating inspiration. A typical pressure wave and comparator output is shown in photograph 5.1.



PHOTOGRAPH 5.1 EXPERIMENTAL TRACE OF MOUTH PRESSURE WAVE (P) RELATIVE TO COMPARATOR OUTPUT (A).

Hysteresis is introduced into the comparator to avoid oscillations between logic states as the pressure signal approaches Vref. The oscillations are due to noise present in the pressure signal and the high gain and bandwidth of the comparator. Hysteresis, V_h, is introduced by positive feedback of the output signal to the input and is calculated by the following formula:

$$V_h = \frac{2R12}{R12 + R14} \cdot V_o = 43mV$$

$$= 1 \text{ mmHg}$$

This effect is shown in figure 5.5. Bypass capacitors C4, C5 and C6 and C3 are used to further stabilise the comparator.

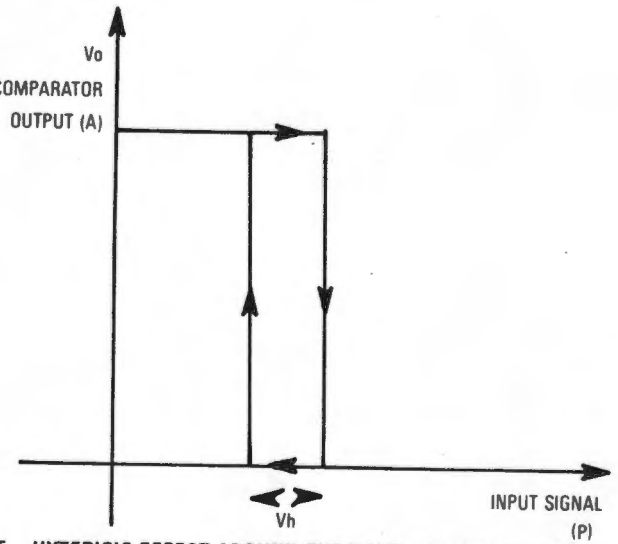


FIGURE 5.5 HYTERISIS EFFECT AROUND THE VOLTAGE COMPARATOR.

The pressure signal from the differential amplifier output is also fed to a sample and hold facility (IC4 - LM398) to hold the $P_{0.1}$ pressure. IC4 is triggered by a monostable (IC5 - 74C221) which goes high at this time. The sample and hold can also be manually triggered via a biased toggle switch, S2. When S2 is activated, it activates the sample and hold via the second monostable on IC5. Manual triggering of the sample and hold allows calibration of the sampled signal. For example, the pressure signal is calibrated against a water manometer in $10cmH_2O$ steps as shown in figure 5.6

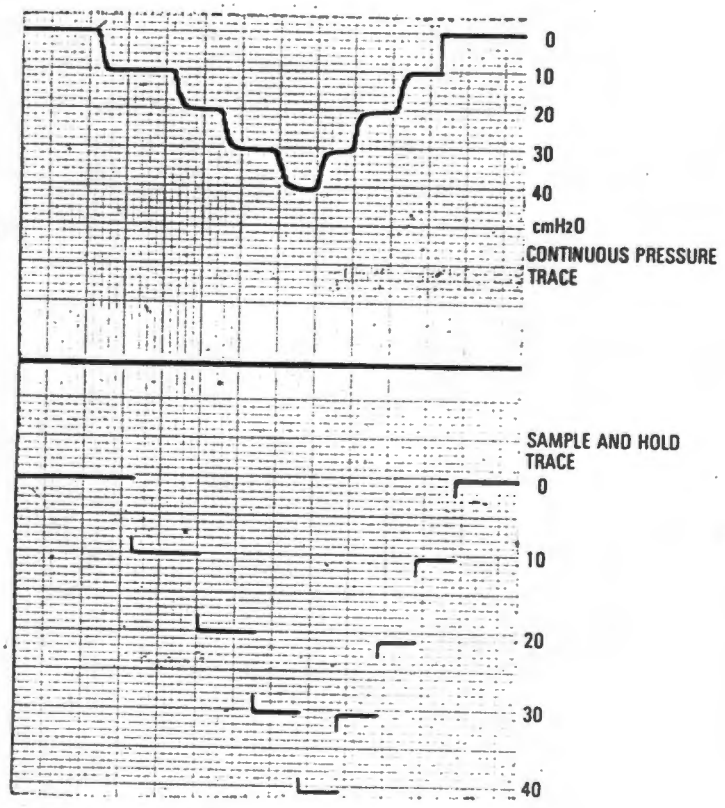


FIGURE 5.6 SAMPLE AND HOLD PRESSURE CALIBRATION TRACE.

A cut-off frequency of much greater magnitude, 645Hz, than the maximum respiratory rate, 0.83Hz, is chosen to minimise the delay (phase shift) at the output from the low pass filter. There must be negligible delay in the pressure signal output from the low pass filter as this signal is used to detect the onset of inspiration. If the signal is noticeably delayed, the detection of the onset of inspiration will also be delayed.

5.2.2 DIGITAL LOGIC CONTROL

The output from the comparator and the valve trigger signal are processed by digital gates (NAND gates - 74C00) and memory elements (D flip-flops - CD4013) so that the valve is actively closed for a preset time after the onset of inspiration. The signal logic is illustrated in figure 5.7 and figure 5.8 shows the electronic circuitry that executes it.

The valve trigger flip-flop (IC7-CD4013) is connected to function as a set-reset flip-flop. The trigger pulse (B) is applied to the reset pin via a current limiting resistor, R20, causing the Q output to be held high. This signal (C) and the pressure comparator output (A) are passed through a NAND gate whose output is inverted (E) to provide the logical AND of the pressure comparator and the valve trigger flip-flop signals. The valve

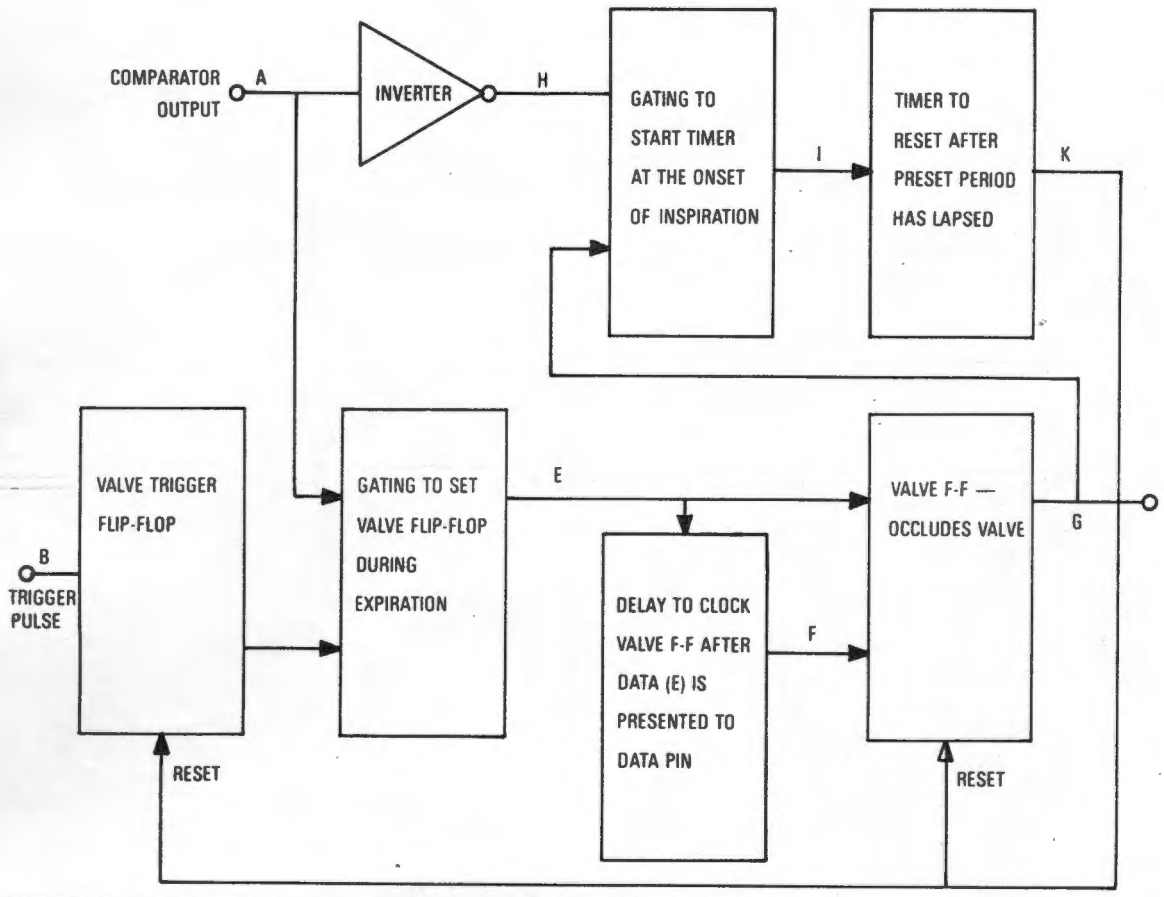


FIGURE 5.7 SCHEMATIC OF THE $P_{0.1}$ CONTROL UNIT DIGITAL LOGIC.

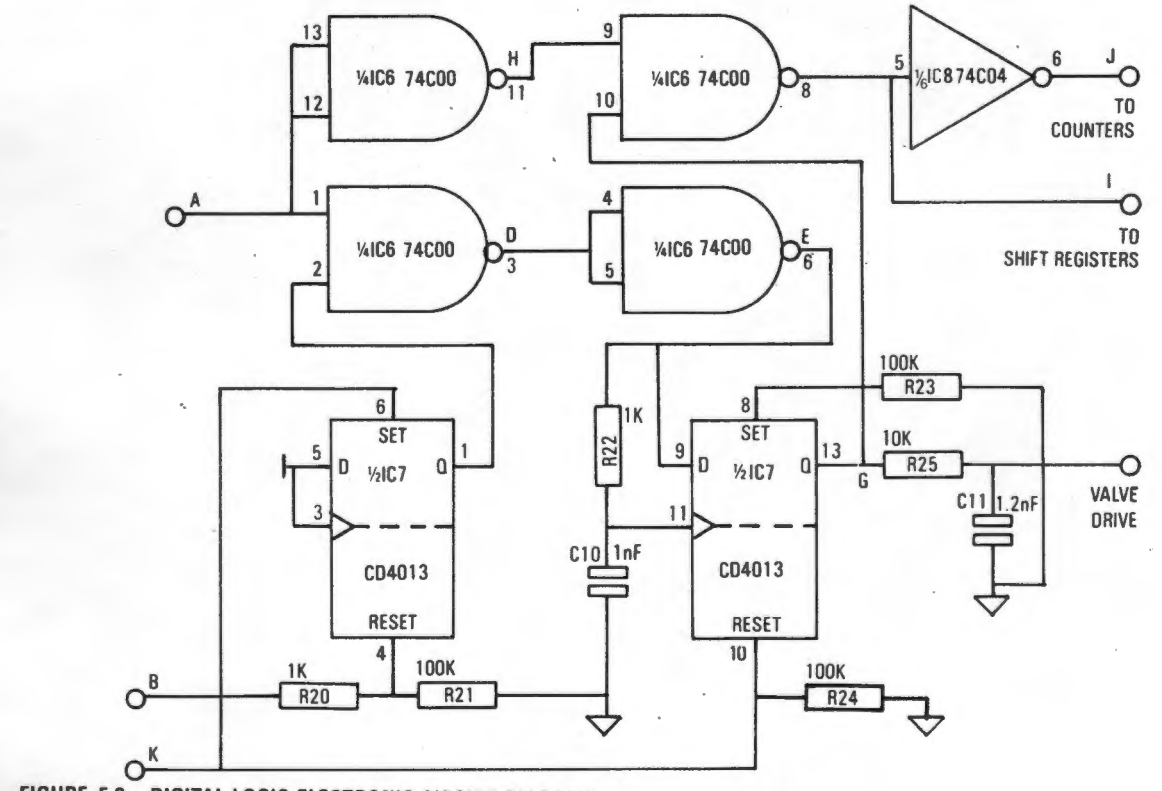


FIGURE 5.8 DIGITAL LOGIC ELECTRONIC CIRCUIT DIAGRAM.

flip-flop is set to allow activation of the occlusion valve when a trigger pulse arrives during an expiratory phase or when the expiratory phase begins while the trigger flip-flop is reset. Signal E is delayed by about 1microsecond (R22.C11 = 1K.1nF) so that the valve flip-flop is clocked after the data is presented to the data input pin. If signal E is presented to the clock and data pin simultaneously, the valve flip-flop output, G, will remain unchanged. The valve is occluded when G is high.

Signal G is passed through a NAND gate together with the inverted comparator signal, H, to enable the timer. The timer is set when signal I goes low and J goes high. This occurs when the valve is occluded and inspiration begins. It runs for a predetermined time, for example 100ms, after which time all the flip-flops are reset. The flow of signals through the digital logic is shown in figure 5.9.

5.2.3 TIMER

Signals I and J enable the timer. The timer schematic is shown in figure 5.10 and the electronic ciruit is shown in figure 5.11.

A 1MHz signal is obtained from the crystal oscillator. The crystal oscillator designed around two CMOS inverters (1/3 IC8-

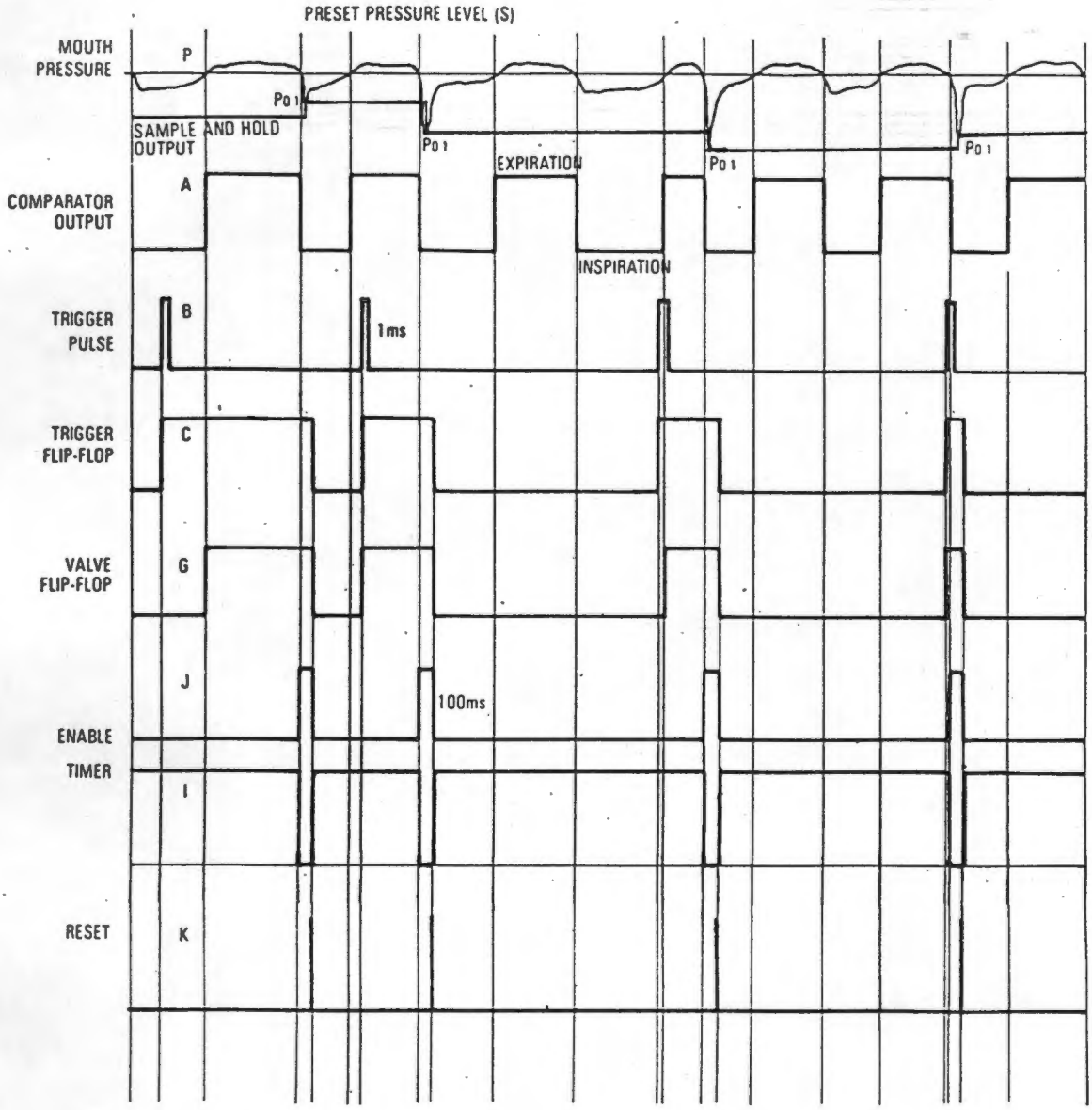


FIGURE 5.9 SIGNAL FLOW THROUGH THE DIGITAL LOGIC CIRCUIT.

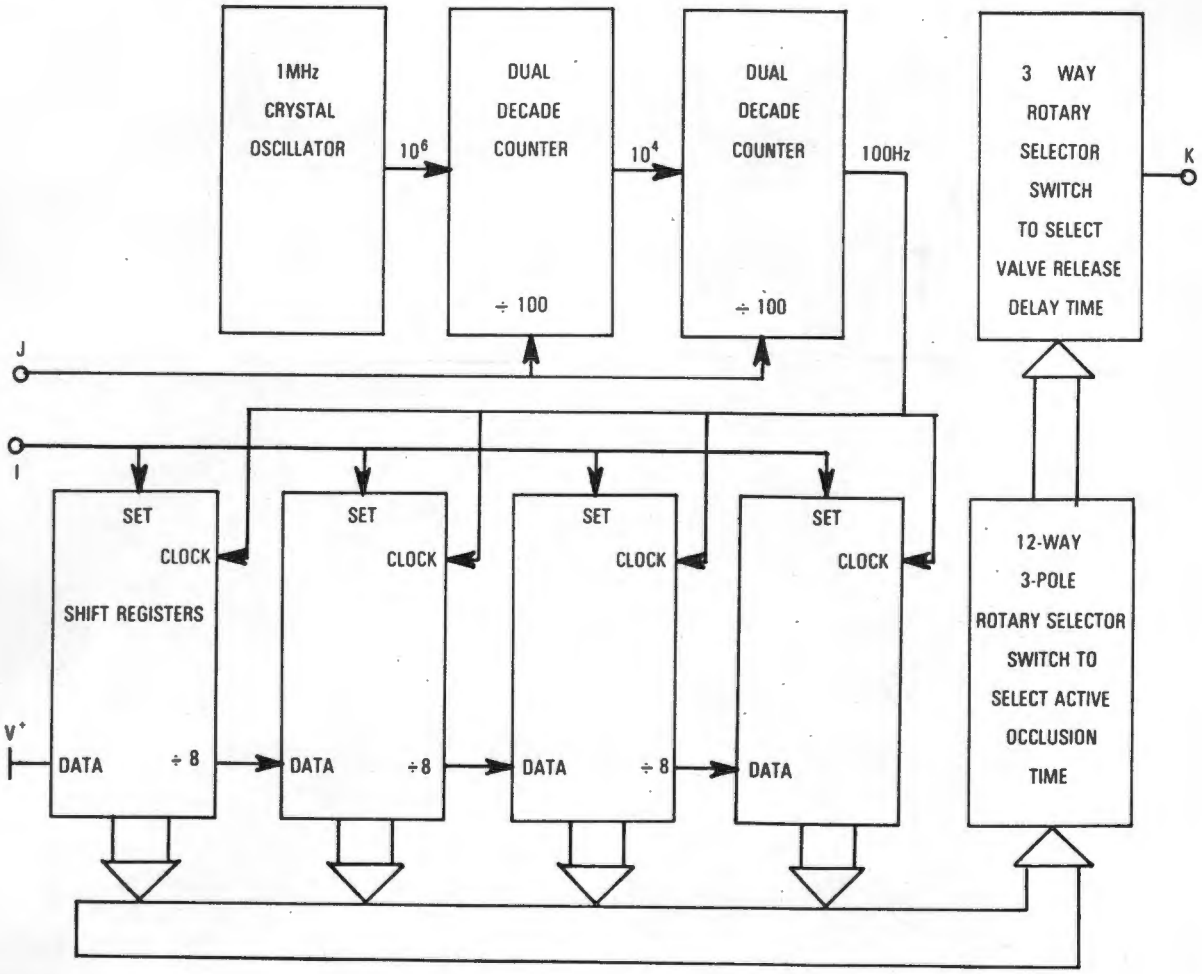


FIGURE 5.10 SCHEMATIC OF THE TIMER CIRCUIT.

(74CO4) is simple, reliable, inexpensive and its power consumption is very little. Two dual decade counters (ICs9 and 10 -CD4518) divide the oscillator frequency to 100Hz. This signal is used to clock four dual 4-stage static shift registers (ICs11, 12, 13 and 14 - CD4015). A clock pulse appears every 10ms and the data presented to the data pins is shifted along the shift registers which are connected serially. The outputs from the shift registers go high sequencially and these are used to

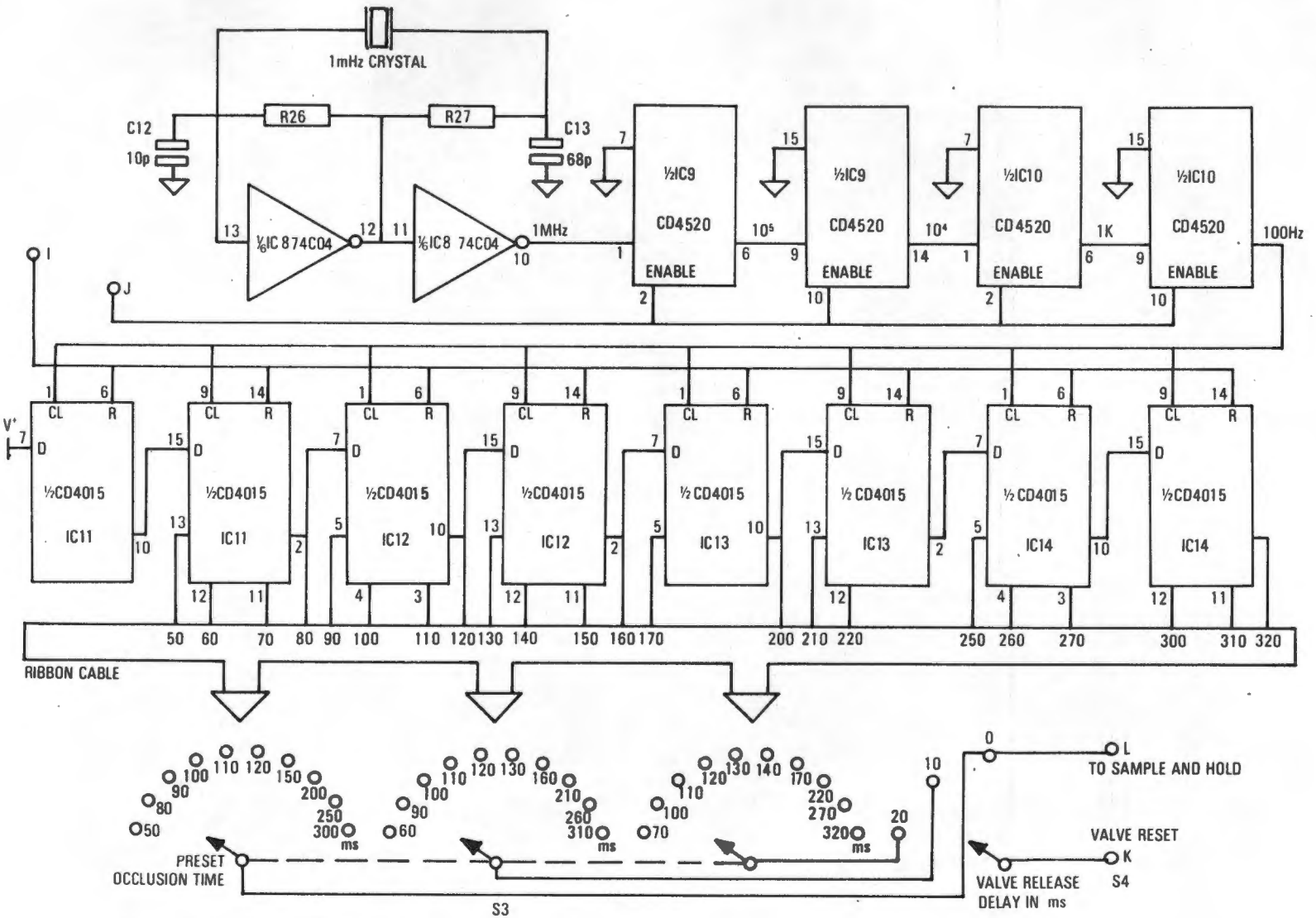


FIGURE 5.11 THE TIMER CIRCUIT DIAGRAM.

accurately reset the occlusion valve. The active occlusion time is preselectable between 10 and 320 milliseconds. The outputs from the shift registers go to a 10-way 3-pole rotary selector switch (S3) which allows the operator to set the period of valve occlusion. The valve release delay period after the $P_{0.1}$ pressure has been measured can be adjusted by turning a rotary switch (S4). The valve can be released immediately or after a delay of 10 or 20ms. The reset signal, K, resets all the flip-flops. Signal L triggers a monostable (IC5-74C221) which activates the sample and hold facility at the instant the active occlusion period ends.

5.2.4 OCCLUSION VALVE DRIVE

The occlusion valve is activated when the valve trigger flip-flop is set (signal G is high). The output from the flip-flop drives the base of a power transistor (T1-LM395) via a 10K current limiting resistor R22 (figure 5.12). The solenoid is in the collector arm of the transistor with a diode, D12, and capacitor, C34, across it to shunt the back emf generated by the solenoid. LM395 is a reliable, fast, high gain, monolithic power transistor with a guaranteed capability of delivering currents in excess of 1A and it can switch 40V in 500ns. The slew rate of the drive to the base is reduced by a RC low pass filter, R25 and C11 with a time constant of 1.2 micro-seconds, to prevent excessive noise

generation when the solenoid is activated. The power transistor is situated on the power supply board to prevent any noise generated by the solenoid activation affecting the digital circuitry.

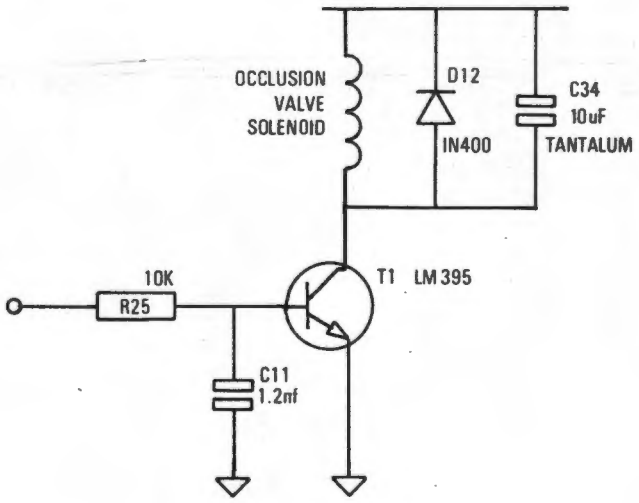


FIGURE 5.12 THE OCCLUSION VALVE DRIVE CIRCUIT.

5.3 THE VALVE TRIGGER BOARD

The occlusion valve can be triggered either manually, periodically or pseudo randomly. Figure 5.13 shows a schematic of the valve trigger board and figure 5.14 shows the circuit diagram. The 1MHz clock signal generated by the crystal oscillator on the control board is divided down to give a 1Hz clock signal using 3 dual decade counters (ICs15, 16 and 17 -

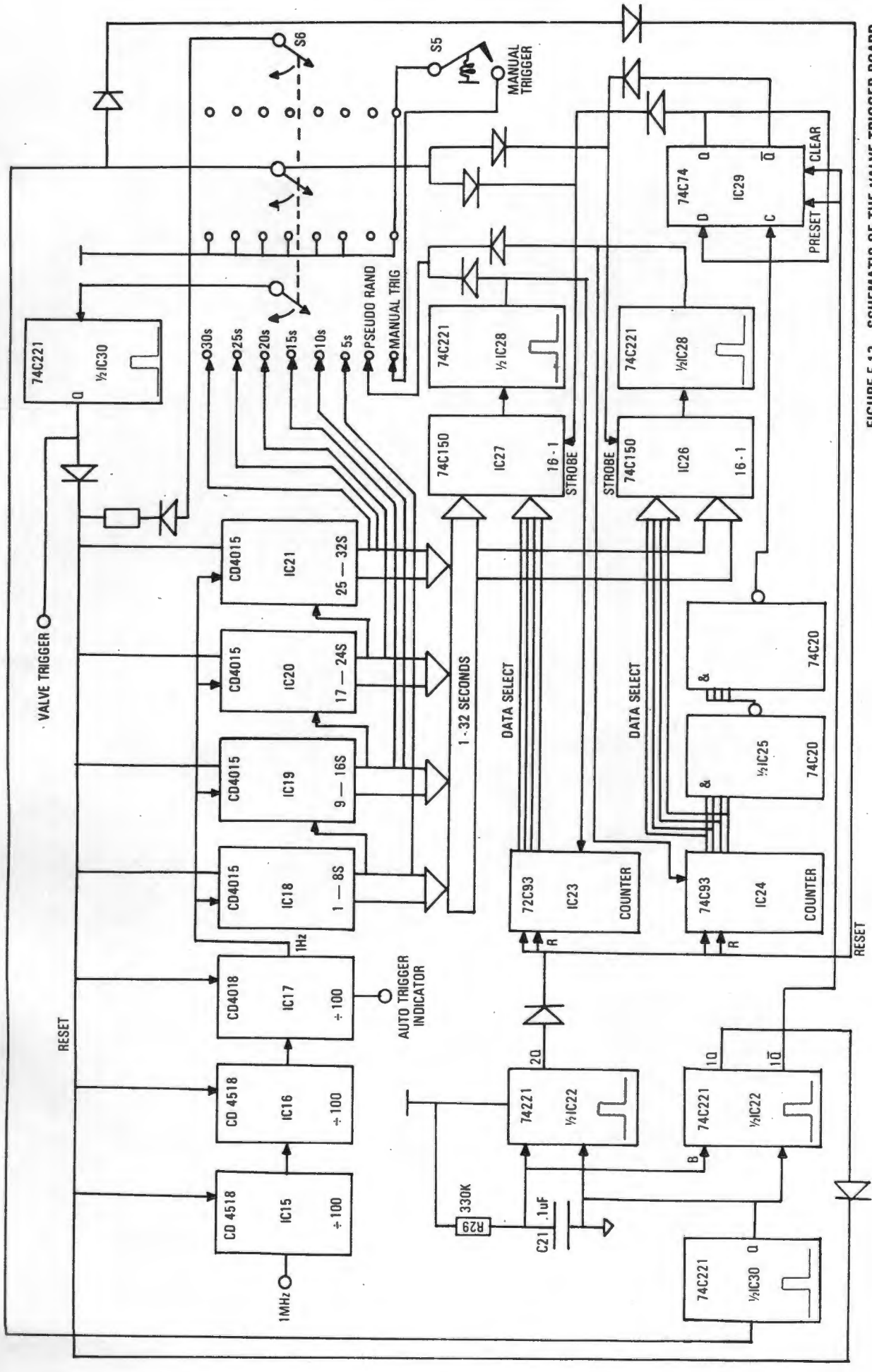


FIGURE 5.13 SCHEMATIC OF THE VALVE TRIGGER BOARD.

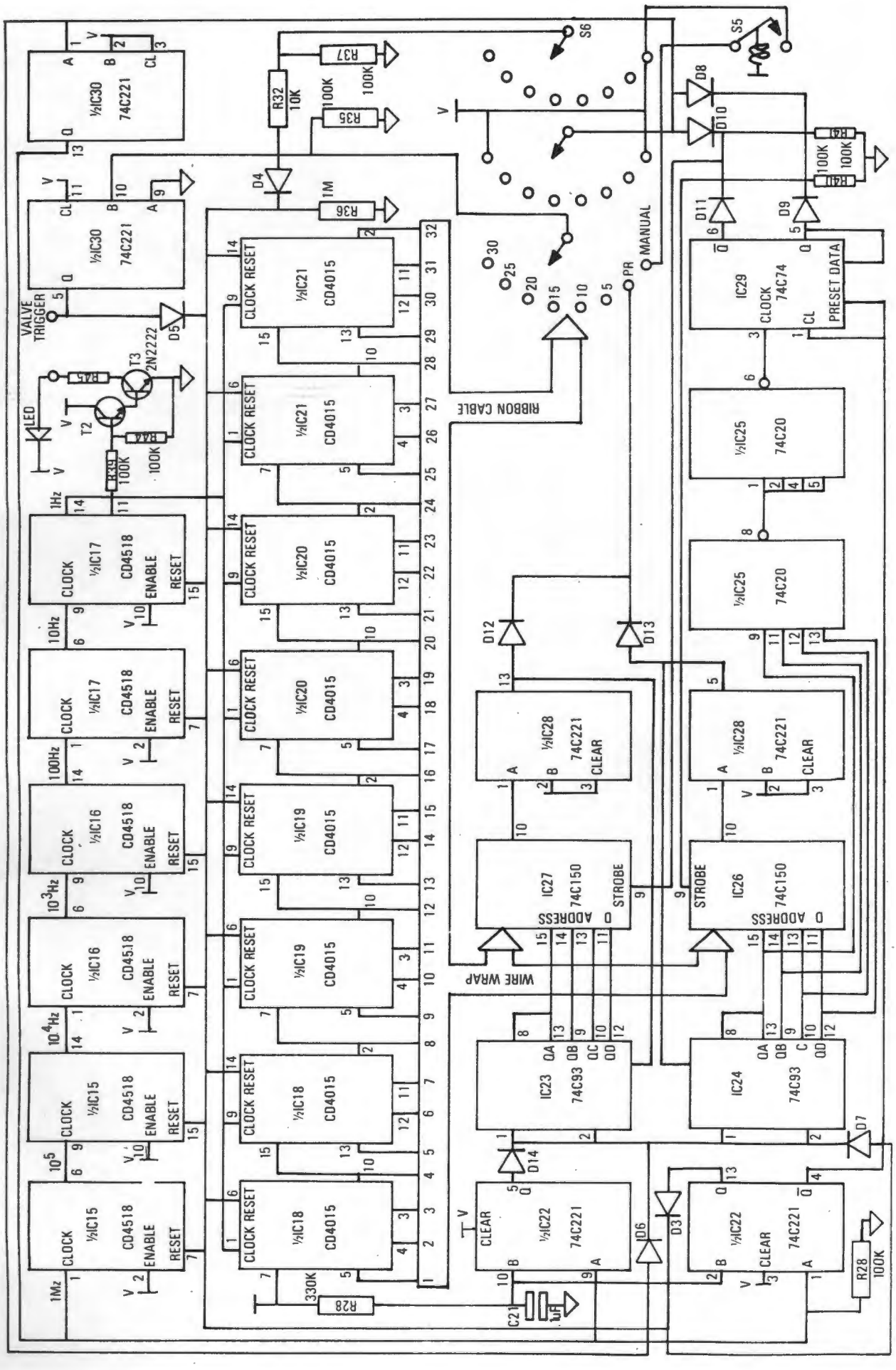


FIGURE 5.14 ELECTRONIC CIRCUIT DIAGRAM OF THE VALVE TRIGGER BOARD.

CD4518). This gives an accurate 1Hz clock pulse to four dual 4 stage static shift registers (ICs18, 19, 20 and 21 - CD4015). The clock pulse appears every second and the data presented to the data pins is shifted along the serially connected shift registers. The outputs from the shift registers go high sequencially and these are used as trigger pulses to the valve trigger flip-flop on the control board. The timing periods are selectable from 1 to 32 seconds.

For periodic triggering of the occlusion valve, the 5, 10, 15, 20, 25 and 30 second shift register outputs are tied to a rotary selector switch, S6. For manual triggering the positive rail is switched via a biased miniature toggle switch, S5, to a point on the same rotary switch. The positive transition, as the switch is depressed, constitutes the trigger signal. For pseudo random triggering, selected outputs from the shift registers are wirewrapped to the inputs of two 16 to 1 decoders (ICs26 and 27 - 74C150). Thirty two intervals between trigger pulses varying between 1 and 32 seconds can be preprogrammed by wire wrapping the particular output pins from the shift registers to the input pins on the two decoders. IC27 is initially enabled by a low signal from the Q output of D flip-flop (IC29 -74C74) and IC26 is disabled by the high (V+) signal from its complementary output. The output from the decoders depend on the data select address

from 4-bit binary counters (ICs23 and 24 - 74C93). The counters are clocked by the outputs from IC28 so that they increment after every valve trigger pulse. When all the outputs from counter IC24 go high (binary code 1111), the D-flip-flop, IC29, is clocked and its output, Q goes high. This enables decoder IC26 and disables decoder IC27. IC26 remains enabled until the autotrigger facility is switched off. The 4 outputs from counter IC24 are fed into a 4 input NAND gate (IC25 -744C20) and inverted to clock the D-flip flop. The pseudo random pulses trigger the occlusion valve with pulses appearing in two cycles. The first being for 32 selected time intervals and thereafter the latter 16 of the first cycle is repeated until the autotrigger facility is switched off. Monostables (IC22-74C221) automatically reset the counters, shift registers and the D-flip-flop when the control unit is switched on. The A-inputs of IC22 are tied to ground via a 100K resistor, R28, and a delayed signal using a low pass filter to the B-inputs to trigger the autoreset facility when the unit is switched on . The monostable sees A as ground and B as a positive transition which triggers it. The autoreset monostables apply a 1ms positive pulse to the reset pins of the counters and shift registers and a negative 1ms pulse to the D-flip flop clear and preset inputs.

When the selector rotary switch, S6, is on manual trigger, the counters and shift registers are disabled by applying a logic

high to the reset line. The decoders are disabled when the switch is set to periodic triggering by applying a logic high to their strobe pins. As the selector switch is turned, a monostable, IC30 resets the counters, shift registers and the D flip-flop. The rotary switch contact point breaks contact between positions. This is seen as a negative transition by the A input of IC30. Diodes are included between outputs to direct the signals from the various points on the board.

5.4 PRESSURE PRESET AND VENTILATORY PHASE INDICATOR BOARD

During a $P_{0.1}$ trial, the occlusion valve must be kept actively closed for a preselected period during the initial inspiratory phase. This period is measured from the onset of inspiration. The onset of inspiration has been defined in section 5.1 and at this point, the comparator output, A, on the main control board changes from a high to a low voltage state. The pressure signal, P, from the Devices pressure monitor is used for this purpose and as in most commercially available equipment, electrical drift is present. This electrical drift is minimised for the Devices by not switching the unit off and the operator has to adjust only the fine offset adjustment control to preset the pressure monitor before a $P_{0.1}$ trial can commence. The PPI (pressure preset

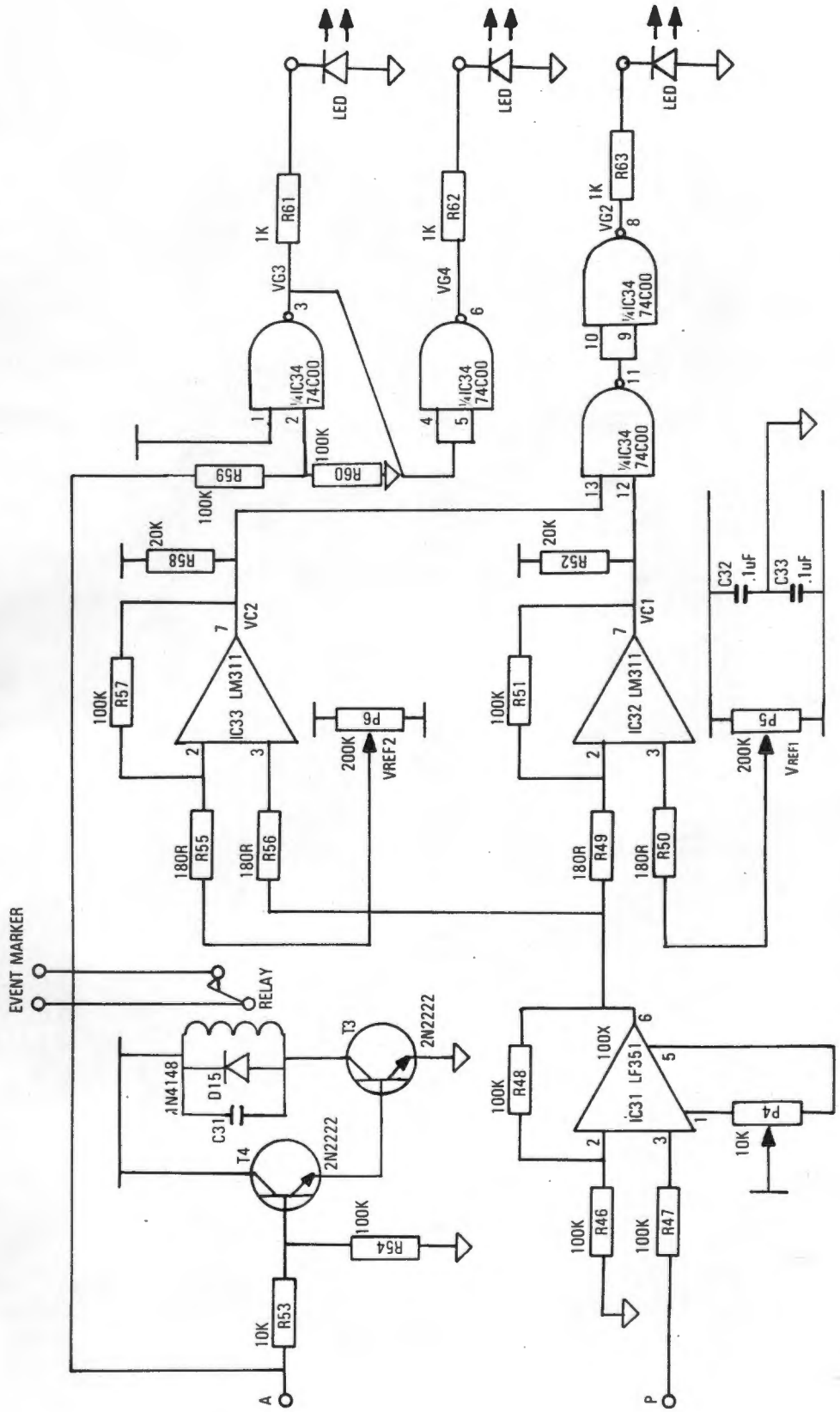


FIGURE 5.15 ELECTRONIC CIRCUIT DIAGRAM OF THE P_{PI} AND V_{PI} BOARD.

indicator) and VPI (ventilatory phase indicator) board is designed as an aid to the operator on the exact setting of the pressure monitor before a trial is commenced. It drives LEDs on the front panel of the unit to indicate that the pressure is preset and also indicates the inspiratory and expiratory phases of ventilation. In addition, a relay is used to operate the event marker of the Devices recorder to indicate the ventilatory phases. A schematic of the pressure preset and ventilatory phase indicator circuit is shown in figure 5.15.

5.4.1 PRESSURE PRESET INDICATOR (FIGURE 5.15)

A narrow window comparator designed around two voltage comparators is used to indicate the recorder preset level. The pressure signal, P, from the low pass filter is fed into the inverting and non-inverting input of two voltage comparators, IC32 and 33 respectively.

The pressure signal is amplified by 100 before it is applied to the window comparator in order to increase the sensitivity of the comparator. This larger swing at the comparator input results in a fast and stable change of state at its output.

The pressure signal is fed into a non-inverting operational

amplifier (IC31-LF351) with a gain of a 100. The LF351 is used for its overall improved characteristics over the more popular LM741. It is a low cost, low current consumption, high input impedance, fast slew rate and low drift JFET operational amplifier. Included externally in the circuit is a 10K trim pot (P4) to zero the output.

The output from the operational amplifier is fed via 180 ohm resistances, R49 and R56, acting as low source impedances, into the inverting and non-inverting inputs of two voltage comparators, ICs33 and 32 respectively. The output is fed back via 10M resistors (R51 and R57) to the non-inverting input to provide hysteresis for the comparator.

The amplified pressure signal is input to either the inverting or the non-invertinginput of the two comparators where it is compared to adjustable reference voltages VREF1 and VREF2 set by trimpots P6 (200K) and P5 (200K) respectively. For Vp > VREF2 the output of the comparator on IC32 is high and for Vp < VREF1 the output of the comparator on IC33 is high. The outputs of the two comparators are logically ANDed and the signal is used (via 1K current limiting resistor R63 to light up a LED on the front panel. This indicates that the pressure monitoring circuit has been zeroed to detect the onset of inspiration. A window width of

2cmH_2O (400mV after the operational amplifier) is found to be adequate to detect the onset of inspiration accurately. P5 is adjusted to give VREF1 = 4.7V to detect the onset of expiration as the pressure becomes positive (1cmH_2O) and P6 to give VREF2 = 4.3V to detect the onset of inspiration as the pressure falls below zero (-0.5cmH_2O).

5.4.2 VENTILATORY PHASE INDICATOR

LEDs are used to indicate the ventilatory phases on the front panel as a simple visual aid to the operator. In addition, the event marker of the devices recorder traces a pulse waveform. The marker is deflected during the expiratory phase. To deflect the marker, the marker input terminals must be shorted together. The comparator output voltage (A) on the main control board is high during expiration and low during inspiration and it is used to drive a reed relay, (Gunther - 3570 1301 121) via a darlington transistor pair (T4 and T5-2N2222) (figure 5.15). The relay is connected between the positive rail and the collector of T5. It is activated through T4 by signal A. A diode (D15-IN4148) and a capacitor (C31-1microfarad) are connected across the relay coil.

Signal A is also used to activate the LEDs on the front panel.

The output of gate 3, VG3, goes high during inspiration and low during expiration. VG3 is inverted using gate 4 whose output, VG4, goes high during expiration. VG3 and VG4 are fed via 1K current limiting resistors R61 and R62 to a red and orange LED respectively. The red LED lights up during inspiration while the orange LED lights up during expiration.

6 CLINICAL TRIALS

The $P_{0.1}$ control unit has been in clinical use for more than six months in the Respiratory Clinic at Groote Schuur Hospital. During this period the functional characteristics, reliability, reproducibility and ease of operation (ergonomic aspects) of the $P_{0.1}$ rebreathing system have been assessed. The first part of this chapter deals with the results obtained during the initial clinical assessment of the $P_{0.1}$ rebreathing system. The $P_{0.1}$ and ventilatory sensitivity to hypercapnia were determined in 13 subjects of whom 5 were patients. This was followed by a trial undertaken to determine the hypercapnic and hypoxic drive in 10 subjects. The subjects were healthy white adult males. They had a physical examination, chest X-ray and pulmonary function tests to confirm that they have normal respiratory function. The controlled clinical trial is presented in the latter part of this chapter.

6.1 CLINICAL ASSESSMENT OF THE P0.1 SYSTEM

6.1.1 METHODS AND APPARATUS

The technique is based on the Read (1967) rebreathing system and the $P_{0.1}$ method presented by Whitelaw (1975). The procedure

followed (for the hypercapnic studies) was as described by Rebuck (1967). The details of the rebreathing system are presented in chapter 4. The hypercapnic and hypoxic rebreathing circuit (section 4.1.3) was used and it is illustrated in figure 4.5. During the assessment of the $P_{0.1}$ rebreathing system, only the ventilatory and $P_{0.1}$ responses to hypercapnia were observed. A 4-channel buffer amplifier was built to interface the various pieces of electronic equipment to the devices 4-channel recorder.

Doctors in the Respiratory Clinic, a member of the Biomedical Engineering Department staff interested in the rebreathing technique, myself and a number of patients were studied during the initial assessment of the $P_{0.1}$ system. The subjects were studied while they were comfortably seated. The procedure was fully explained to the subjects to ensure that they were calm and not apprehensive about the test or the equipment. The subjects were asked to refrain from any respiratory depressants or stimulants at least 2 hours before a trial was commenced.

The pressure channel was calibrated using a water manometer. Subatmospheric pressures in 10cmH_2O steps were applied to the pressure transducer with a glass syringe. These were recorded on the first channel of the Devices 4-channel recorder. A sample and

hold pressure signal was also later introduced and displayed on channel 2. The sample and hold recorded the $P_{0.1}$ signal during a rebreathing trial. The calibration of the sample and hold facility is accomplished by depressing a toggle switch on the front panel to record the 10cmH_2O step changes. The Capnograph was calibrated with 4 standard calibration gases of 2.294%, 6.043%, 7.685%, 9.611% and 12%. This signal was recorded on the 4th channel. The dry gas meter was connected to the third channel.

The Devices recorder pressure channel was preset to atmospheric pressure before a subject commenced to breath from the rebreathing circuit. The subject breathed room air until his or her breathing pattern appeared normal. A normal breathing pattern is defined as a regular breathing rate with relatively constant tidal volume and end tidal P_{CO2}. This normally took about 1 minute. The subject was switched into the rebreathing circuit after expiring to residual volume. They took three steep breaths as the trial commenced to equilibrate the concentrations of the gases between the bag and the lungs and the lungs and arterial blood. The initial concentration of the gas in the bag was 7% carbon dioxide and 93% oxygen. The gas in the bag was circulated using a pump to aid mixing. Rebreathing continued usually for about 4 minutes. However rebreathing was continued until the

subject was exhausted for some of the trials. The CO_2 channel was recalibrated and parts of the respiratory circuit were sterilised in Cidex sterilising medium after the trial was completed. The tracing from the Devices was analysed and the volume and time deflections, the $P_{0.1}$ and the corresponding P_{CO2} levels were entered into a microcomputer to determine the ventilatory and $P_{0.1}$ responses.

6.1.2 RESULTS

The recording of $P_{0.1}$, minute ventilation and the corresponding P_{CO2} levels for a rebreathing study is shown in figure 6.1 and the format presentation of the computed results is shown in figure 6.2. Twenty-two trials were carried out on 8 healthy adults and 5 adult patients. The patients were studied to determine whether a lack of ventilatory drive was the cause of their raised arterial blood P_{CO2}. The results from this study do not represent a typical sample of the population and therefore cannot be used to calculate a population mean. The sample mean and its standard deviation has been calculated and these have been compared to population means presented by Irsigler (1975) (see figure 6.5)

Rapid equilibration of the P_{CO2} levels were attained in all the

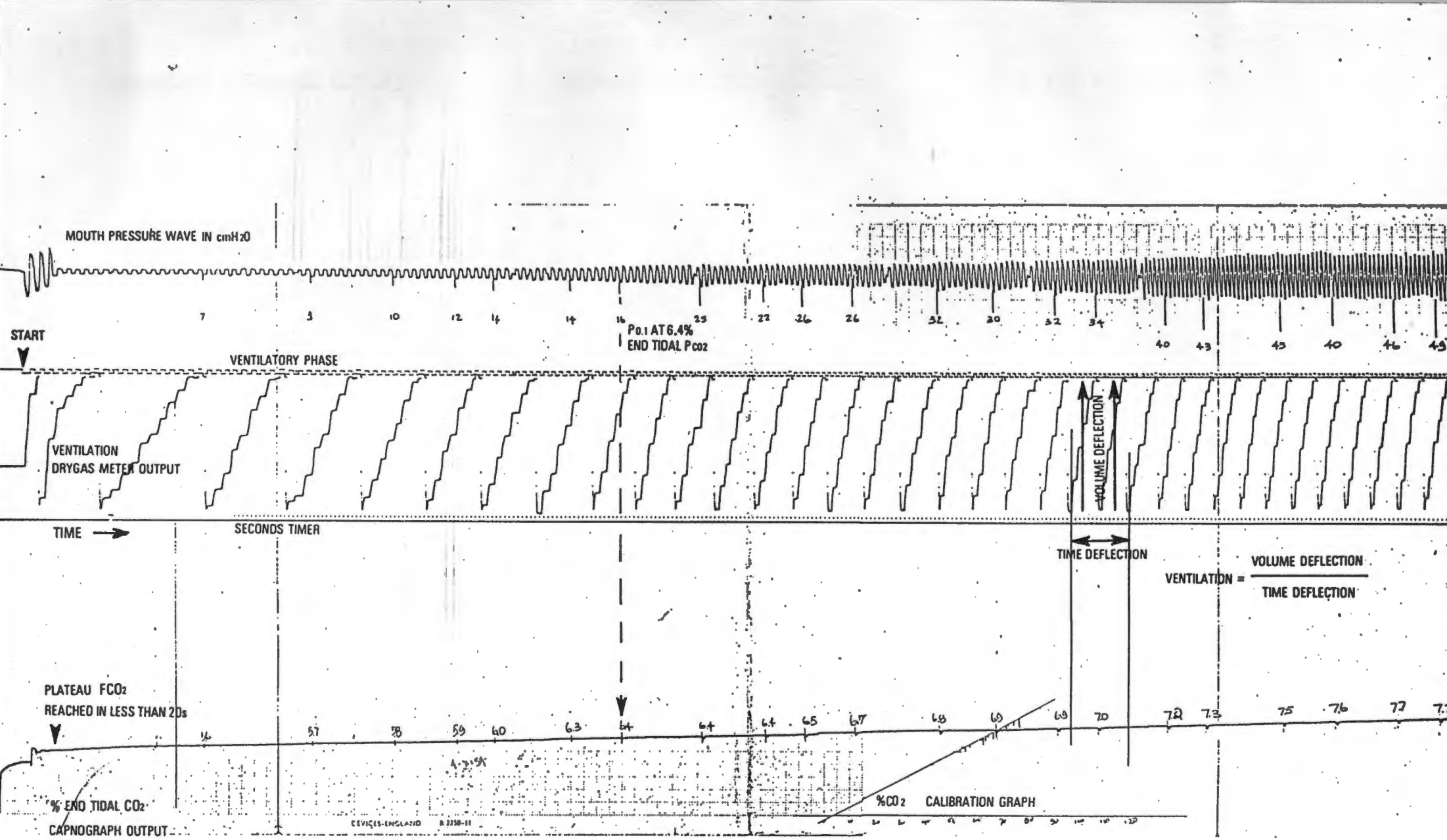


FIGURE 6.1 TRACING OF THE REBREATHING TRIAL OF SUBJECT N.G.

GROOTE SCHUUR HOSPITAL RESPIRATORY CLINIC DEPT.OF MEDICINE

ASSESSMENT OF BREATHING CONTROL

NAME: NG-3-. NAREN GAJJAR FOLDER NO: 000 DATE: 22-FEB-83
SEX: M AGE: 26 yrs HT: 176 cm WT: 80 Kg RACE(1-8): 5
WARD: LAB TECHNOLOGIST: NC CONSULTANT: NCG
REASON FOR TEST: NORMAL - RESEARCH

SPIROMETRY (PREDICTED IN BRACKETS):
FEV1: 1000 ml (4030) FVC: 1000 ml (5080) FEV1/FVC: 100% (80)

HYPERCAPNIC RESPONSE

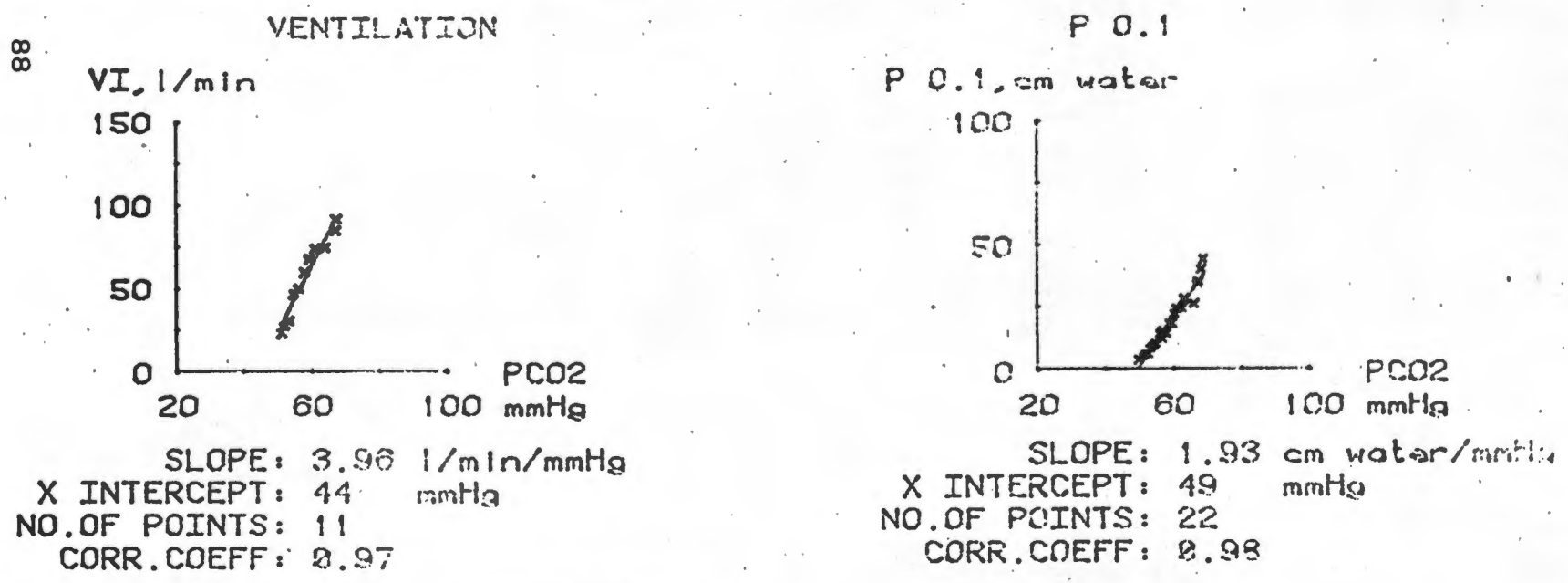


FIGURE 6.2 COMPUTER PLOT OF THE VENTILATORY AND $P_{0.1}$ RESPONSE TO HYPERCAPNIA.

studies. This showed up on the CO_2 trace as a plateau before 20 seconds had lapsed. The minute ventilation increased as the trial progressed as the subject increased his or her tidal volume and frequency. No attempt was made to quantify the relative changes in tidal volume and frequency as past workers did not find a relation between these two variables. Rebuck (1976) notes that the increase in minute ventilation was dependant on three factors. Firstly the size of the respiratory belows, secondly the available volume for respiration and lastly the respiratory rate.

6.1.2.1 VENTILATORY RESPONSE TO HYPERCAPNIA

The results of the ventilatory response are expressed as S_v (l/min/mmHg), defined as the slope of the minute ventilation versus end-tidal P_{CO2} regression line. The ventilatory response for the healthy subjects is 3.21 $\pm$ 1.1 l/min/mmHg (15 studies), for subject NG is 3.21 $\pm$ 0.62 l/min/mmHg (6 studies) and for the patients is 1.37 $\pm$ 0.90 l/min/mmHg (7 studies). The standard deviation is 34%, 19% and 65% of the mean for these respectively. The range is further narrowed when looking at the results of a particular subject. The widest range is for the patients as their responses will vary from patient to patient. The mean for the healthy subjects is higher than that determined for on the trial on10 normal males (figure 6.7). This can be attributed to the

normally high ventilatory responses of 4.16, 5.1, 4.9 and 4.07 l/min/mmHg for three subjects.

6.1.2.2 P0.1 RESPONSE TO HYPERCAPNIA

$S_{P0.1}$ is the $P_{0.1}$ response to hypercapnia and is defined as the slope of the $P_{0.1}$ versus arterial blood P_{CO2} regression line. $S_{P0.1}$ is 1.21 ± 0.74 cmH_2O/mmHg for the total 22 trials, 1.45 ± 0.57 cmH_2O/mmHg for the healthy subjects (14 trials), 1.48 ± 0.68 cmH_2O/mmHg for subject NG (6 trials) and 0.88 + 0.76 cmH_2O/mmHg for the patients (7 trials). The standard deviation is 61%, 52%, 46% and 86% of the mean respectively for the above $P_{0.1}$ responses. The ranges of these responses are wider than that of the ventilatory responses. However the standard deviations decrease similarly in the various groups as for the ventilatory responses.

6.1.3 DISCUSSION

It is not possible to compare the variability of the results for the 8 normals studied compared to those presented by Irsigler (1975). The procedure followed by him vary in detail from that followed for the assessment of the $P_{0.1}$ rebreathing system and even more important, the $P_{0.1}$ rebreathing system is completely different from his. His subjects rebreathed in and out of a Stead

- Wells spirometer Prefilled with 4% CO_2, 60% O_2 and the balance nitrogen compared to the 7% CO_2 and 93% O_2 used here. He changed the CO_2 concentration to about 6% to allow more rapid equilibration of the gases in the rebreathing system.

The correlation coefficients of the regression lines for the ventilatory response are greater and equal to 0.95 for all except 5 of the 22 studies. Only one study, that of a patient, was less than 0.9. For the $P_{0.1}$ response the correlation coeffients are greater and equal to 0.9 for 16 of the 21 studies, greater than 0.82 for 4 studies and 0.75 for one study. It is noted that the correlation coefficient is closer to 1 for the experienced "rebreather" than the one who does it for the first time and even less for patients. It is important for the subject to be relaxed and comfortable.

The relation between the ventilatory response and the $P_{0.1}$ response was analysed. The linear regression of $S_{p0.1}$ versus S_v was calculated. The regression line is defined by the following equation:

$$S_{p0.1} = a.S_v + b = 0.48S_v + 0.58$$

OR

$$S_v = 1/a.S_{p0.1} - b = 2.08S_{p0.1} - 0.58$$

correlation coefficient = 0.86

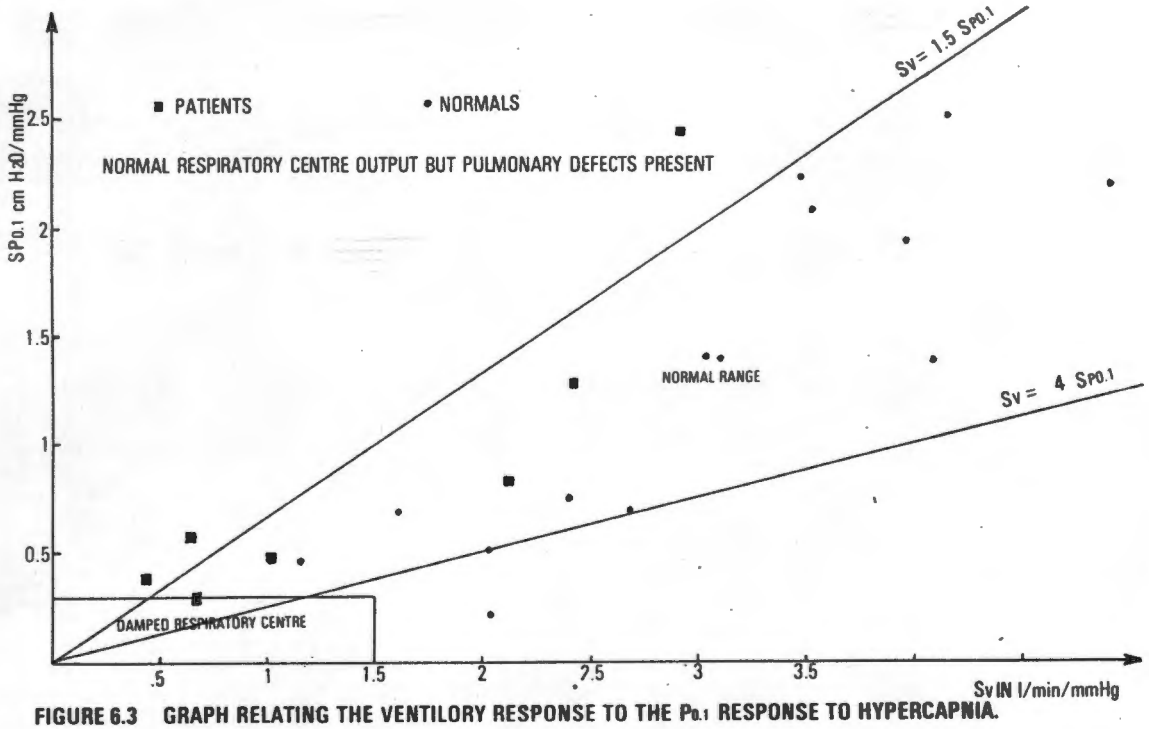


FIGURE 6.3 GRAPH RELATING THE VENTILORY RESPONSE TO THE $P_{0.1}$ RESPONSE TO HYPERCAPNIA.

where a is the slope of the line and b the y-intercept. Note that these results were obtained with a 150ms occlusion time; this is explained later in section 6.2.1. However the graph is still labelled $P_{v0.1}$ which is the terminology for the technique even though the occlusion time is not 100ms. Ideally b is zero. The graph in figure 6.3 illustrates this relation. A hypothetical scoring sheet for assessing ventilatory drive was developed from this relation and is discussed in the following chapter. With

reference to this scoring sheet, the "normal" range for the subjects involved in the clinical assessment of the $P_{0.1}$ appear to lie between the two lines $S_v = 1.5S_{P0.1}$ and $S_v = 4S_{P0.1}$. If S_v = 1,5l/min/mmHg and $S_{p0.1}$ = 0.3cmH_2O are taken as the lower limits of normal ventilatory drive for the ventilatory and $P_{0.1}$ responses respectively then the area bounded by these limits indicates a damped respiratory centre. Points lying in the region above the line $S_v = 1.5S_{P0.1}$ indicate a normal respiratory centre output, but with pulmonary mechanical defects. In this region the $P_{0.1}$ response is normal, but the ventilatory response is reduced for a particular respiratory centre output indicating for example airway obstruction. It is in this region that the $P_{0.1}$ response is of greater value than the ventilatory response as the reduced ventilatory response will falsely indicate a damped respiratory centre output. No points are expected to fall in the region below the line $S_v = 4S_{P0.1}$. In other words the ratio of the ventilatory response to the $P_{0.1}$ response to hypercapnia is not expected to be greater than 4 because if the occlusion time is reduced from 100ms then the slope "a" will reduce. It is important that the onset of inspiration be correctly detected. If it is detected early then it reduces the effective $P_{0.1}$. If a large percentage of the points fall above the line $S_v = 1.5S_{P0.1}$ then it may indicate that the onset of inspiration is detected after it has occurred ie. effectively lengthening the occlusion time and

increasing $P_{0.1}$. It must be noted that the values quoted here for the particular limits are only applicable for this study and not to the general population.

6.2 HYPERCAPNIC AND HYPOXIC TRIAL ON 10 NORMAL MALE SUBJECTS

A formal study involving 10 white adult males was undertaken to obtain a normal range for the $P_{0.1}$ and ventilatory response to hypercapnia and hypoxia. The variables recorded and analysed were the $P_{0.1}$ and ventilatory responses to P_{CO2}, ($S_{P0.1}$ and S_v respectively) and the P_{CO2} at zero ventilation (X intercept), end tidal P_{CO2}, plateau P_{CO2}, minute ventilation and the correlation coefficient of the regression lines.

6.2.1 PROTOCOL FOR THE STUDY

The technique for the study was the same as for the clinical trials for assessing the $P_{0.1}$ system. The subjects were chosen randomly from the hospital and university staff and students. They signed a consent form (Appendix B) after being informed about the test. They were asked to refrain from having any respiratory stimulants or respiratory depressants for at least 12 hours before the test. All the tests were carried out in the morning. The subjects had a chest X-ray and pulmonary function

tests were performed to ascertain that they all have normal respiratory function. The test was repeated after one week.

The detection of the onset of inspiration was checked before the study commenced. The pressure signal from the remote output of the devices was passed through a low pass filter with a cutoff frequency of 5Hz. The signal from the low pass filter is used to detect the onset of inspiration. A 5Hz cutoff frequency delayed the pressure signal by about 50ms and thus the onset of inspiration was being detected 50ms late. The cutoff frequency was increased to 645Hz which delayed the detection of inspiration by about 2ms. This delay is negligible.

6.2.2 RESULTS

The aim of the study was to obtain a normal range for the $P_{0.1}$ and ventilatory response to i) hypercapnia; ii) hypoxia at end tidal P_{CO2}; and iii) hypoxia at mixed venous level (plateau level) P_{CO2}. The results had a large variability as only a small sample of 10 adult males each repeated twice were studied. Also the technique for the hypoxic studies did not allow the drive to be determined at a constant P_{CO2} level. This affected the reliability and reproducibility of the hypoxic drive tests as hypercapnia is a much more powerful respiratory stimulant than hypoxia. The results of the study are presented in the table in

figure 6.4. These results should not be directly compared with the pretrial results. The differences are discussed on page 98.

	SLOPE	CORRELATION COEFFIENT FOR THE LINEAR REGRESSION	NO. OF TESTS
	HYPERCAPNIC RESPONSE		
$S_{PO.1}$ $cmH_2O/mmHg$	0.79 ± 0.47	0.85 ± 0.12	19
S_v $l/min/mmHg$	2.65 ± 0.87	0.96 ± 0.04	18
	HYPOXIC RESPONSE AT END TIDAL PCO2 LEVEL		
$S_{PO.1}$ $cmH_2O/mmHg$	-0.19 ± 0.17	-0.67 ± 0.27	18
S_v $l/min/mmHg$	-0.65 ± 0.26	-0.92 ± 0.1	19
	HYPOXIC RESPONSE AT MIXED VENOUS PCO2 LEVEL		
$S_{PO.1}$ $cmH_2O/mmHg$	-0.67 ± 0.54	-0.79 ± 0.15	18
S_v $l/min/mmHg$	-2.91 ± 1.16	-0.94 ± 0.04	18

FIGURE 6.4 TABLE OF RESULTS FOR THE CLINICAL TRIAL.

6.2.3 DISCUSSION

The mean values for the hypercapnic studies correlate well with the mean values presented in the literature. However the spread of the results is much wider for this study than that presented

in the literature. The hypoxic studies were carried out at the request the respiratory consultant in the Respiratory Clinic. No detailed literature survey was carried out on the hypoxic

AUTHOR	P0.1 SENSITIVITY TO HYPERCAPNIA $cmH_2O/mmHg$	VENTILATORY SENSITIVITY TO HYPERCAPNIA l/min/mmHg
IRSIGLER (1975)		2.60 ± 0.107
HIRSHMAN (1975)		2.69 ± 0.19
READ (1967)		2.65 ± 0.27
ALTOSE (1976)	0.88 ± 0.14	
GAJJAR (1983)	0.79 ± 0.47	2.65 ± 0.87

FIGURE 6.5 TABLE OF COMPARATIVE RESULTS OF VENTILATORY DRIVE.

ventilatory drive and therefore no comparative results are shown. The results of the hypoxic studies can be used to show that the hypoxic drive is a very much less potent ventilatory drive. Results of studies carried out by various investigators are shown in the table in figure 6.5.

6.2.3.1 $P_{0.1}$ RESPONSE TO HYPERCAPNIA

The mean for the $P_{0.1}$ sensitivity to hypercapnia is similar to the mean observed by Altose (1976). The results obtained for the present study are however more widely spread than those presented

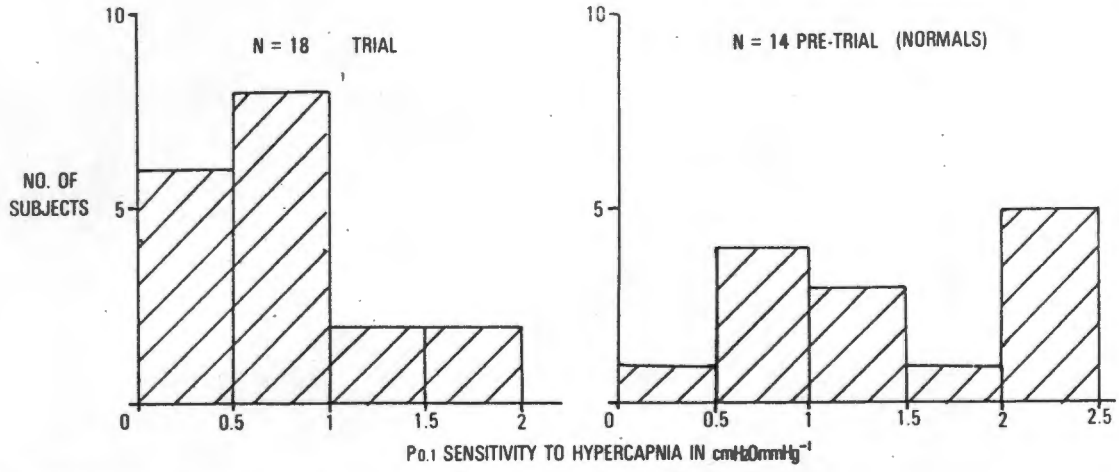


FIGURE 6.6 BAR GRAPH RELATING $P_{0.1}$ SENSITIVITY TO THE NUMBER OF TRIALS.

by Altose. Altose studied 16 subjects compared to 10 (20 trials) presented here. The spread of the results is shown in figure 6.6. and figure 6.7. The spread is the narrower for the trial than the pretrial assessment of the $P_{0.1}$ system. The results obtained for the trial are lower than for the pretrial studies; this is probably because the pretrial study had an effective occlusion period of about 150ms. An important study that needs to be done to confirm the relationship between the occlusion time (t) and

the ventilatory and P_t responses to P_{CO2} with the standardised equipment. The equipment developed allows this to be done and a calibrated range of occlusion times ranging between 60 and 300ms has been provided in the control unit.

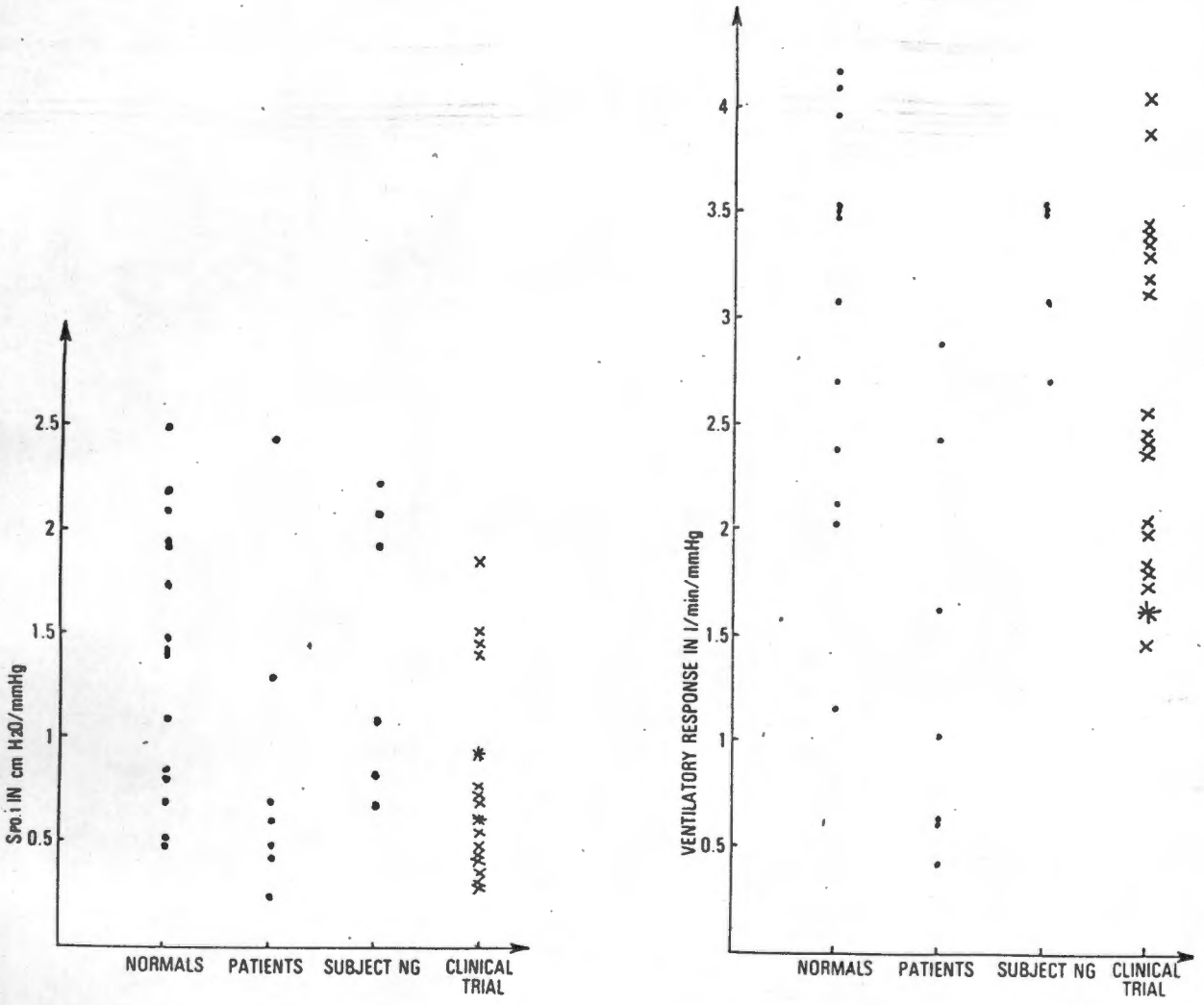


FIGURE6.7 SCATTER DIAGRAM OF $P_{0.1}$ SENSITIVITY TO HYPERCAPNIA AND OF VENTILATORY SENSITIVITY TO HYPERCAPNIA.

The increase in the mean $P_{0.1}$ sensitivity to hypercapnia as the active occlusion period is increased was shown by Altose (1976). His results are reproduced in the table in figure 6.8.

OCCLUSION TIME (t) ms	SLOPE $cmH_2O/mmHg$
100	0.88 ± 0.14
200	1.48 ± 0.21
300	2.12 ± 0.37

FIGURE 6.8 TABLE OF RESULTS RELATING $P_{0.1}$ SENSITIVITY AND VENTILATORY SENSITIVITY TO HYPERCAPNIA. TO DURATION OF ACTIVE OCCLUSION.

With reference to the proposed scoring sheet for the assessment of ventilatory drive, the relation of ventilatory sensitivity (S_v) to $P_{0.1}$ sensitivity ($S_{P0.1}$) to hypercapnia is shown in figure 6.9. More points on the new scoring sheet lie below the $S_v = 4S_{P0.1}$ line compared to figure 6.3. The reason for this is that the occlusion period in the former studies was 150ms compared to the value of 100ms. A "new" set of limits for the normal range are obtained for the clinical study. The slope of this relationship and its correlation coefficient is 0.26 $cmH_2O/l/min$ and 0.72 respectively for the clinical trial. Altose (1976) compared the slopes of the regression line of S_v versus S_{Pt} and a table of his results are shown in diagram 6.10.

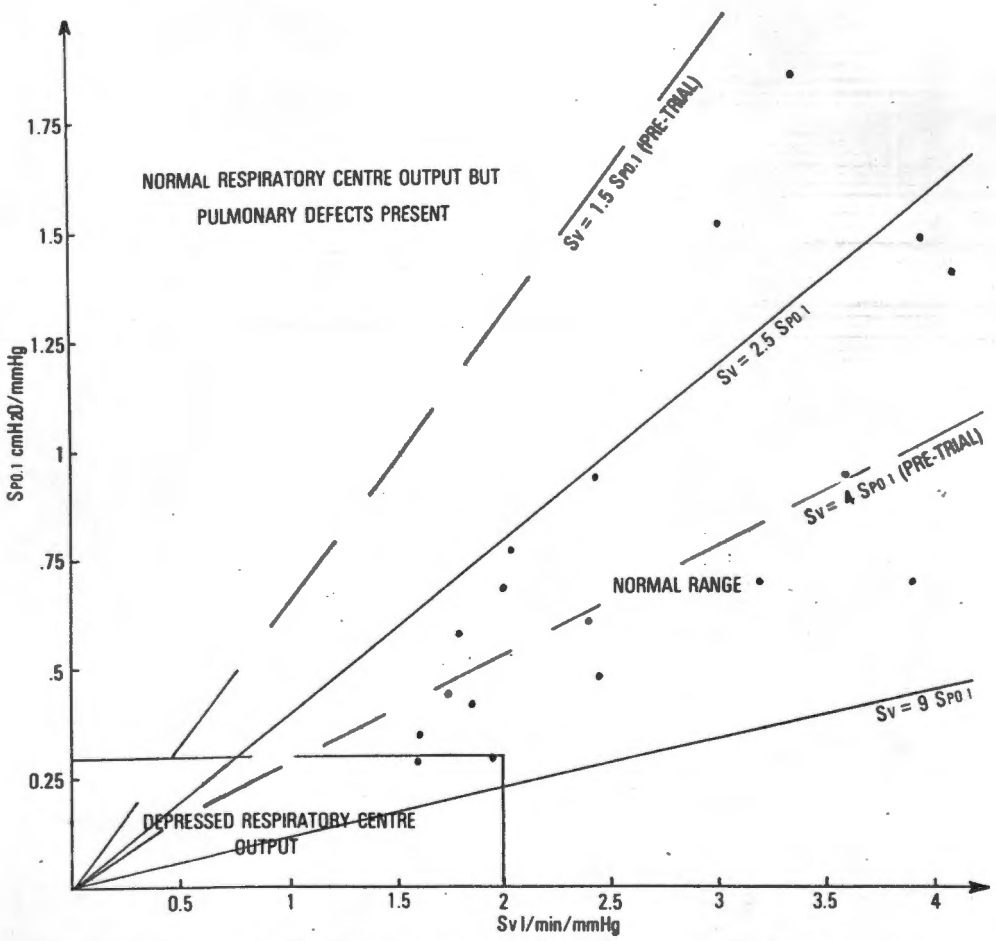


FIGURE 6.9 HYPOTHETICAL SCORING SHEET FOR ASSESSING VENTILATORY DRIVE

The scoring sheet will only be valid if the limits are obtained for a significantly large sample of the population. It is also critically dependant on the length of the occlusion time and the correct detection of the onset of inspiration.

OCCLUSION TIME (t) ms	SLOPE $cmH_2O/l/min$
100	0.36
200	0.55
300	0.91

FIGURE 6.10 TABLE OF RESULTS RELATING $P_{0.1}$ SENSITIVITY TO DURATION OF ACTIVE OCCLUSION

6.2.3.2 VENTILATORY RESPONSE TO HYPERCAPNIA

The ventilatory sensitivity to hypercapnia was 2.65 ± 0.87 l/min/mmHg. This value agrees with those presented by other investigators (see figure 6.5). The plots in figure 6.7 and the bar graph in figure 6.12. illustrate the spread of results. The spread of the results is the narrowest for the trial.

6.2.3 HYPOXIC RESPONSE

Hirshman (1975) found a hyperbolic fit to the relation between minute ventilation and arterial P_{O2}. However the relation between the blood O_2 saturation and ventilation is linear. Unfortunately no comparative results for this relationship were found in the literature. The mean correlation coefficients for the linear regression for this study are presented in figure 6.4. The mean correlation coefficients for the $P_{0.1}$ trials are -0.67 ± 0.27 and

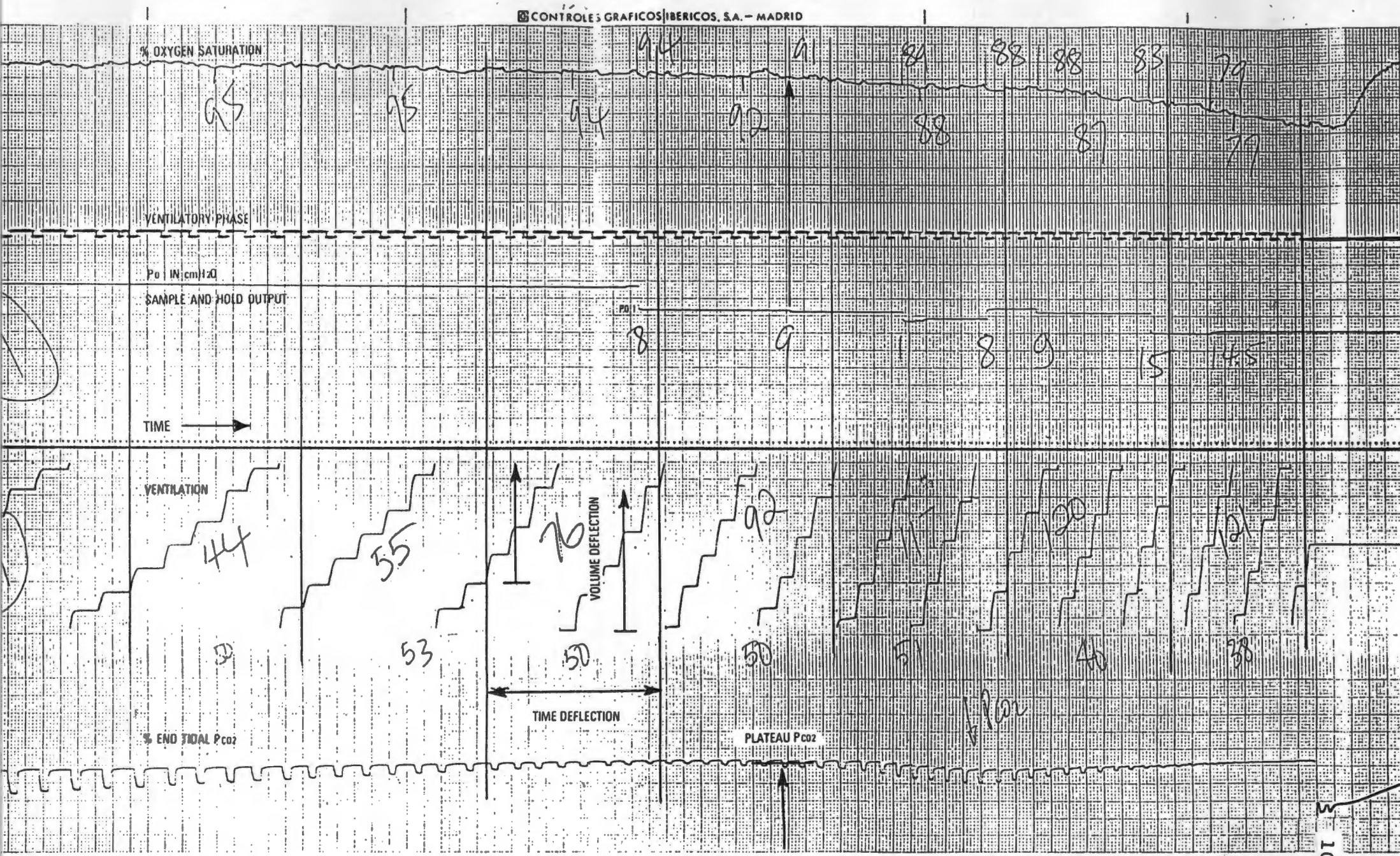


FIGURE 6.11 EXPERIMENTAL TRACE RELATING $P_{0.1}$, P_{CO_2}, PERCENTAGE O_2 SATURATION AND TIDAL VOLUME TO THE TIME OF REBREATHING.

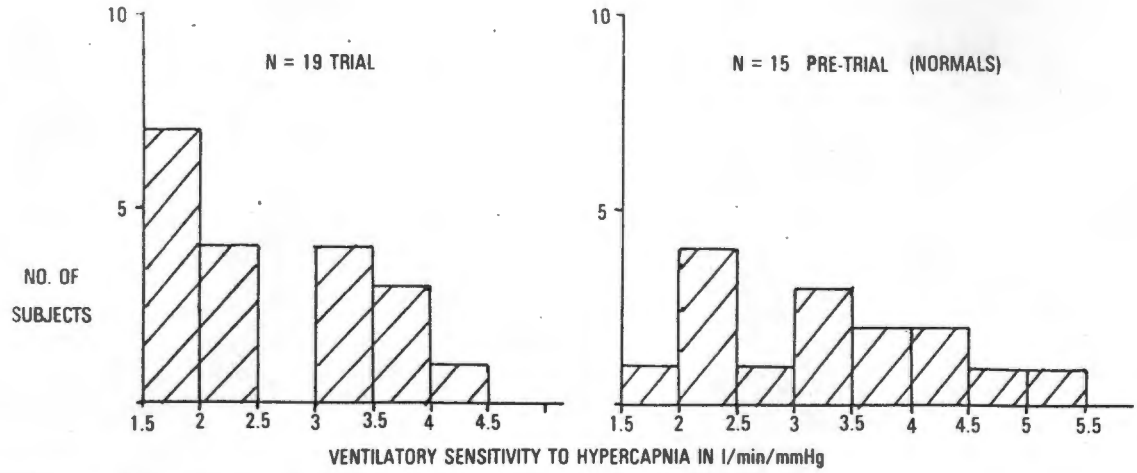


FIGURE 6.12 BAR GRAPH RELATING VENTILATORY SENSITIVITY TO HYPERCAPNIA.

-0.79 ± 0.25 for the hypoxic response at end tidal P_{CO2} level and plateau P_{CO2} level and the standard deviations are 40% and 32% of the mean respectively. The observed results appear nonlinear (low correlation coefficients for a straight line fit) for two reasons. Firstly the hypercapnic drive during rebreathing period was not maintained constant because it was difficult to maintain the rebreathing gas P_{CO2} constant and secondly very few points were taken as the saturation decreased rapidly during the latter part of rebreathing. This is shown in the experimental trace of subject SM1 in figure 11. The subject felt immediate relief when the CO_2 scrubber was turned into the circuit to attempt to maintain the P_{CO2} level at mixed venous level.

6.4 ERGONOMIC ASPECTS OF THE P0.1 SYSTEM

The $P_{0.1}$ control unit was designed with the operator, the clinical technologist, in mind. A minimum number of operator controls are necessary to do a rebreathing trial. Operator aids such as the ventilatory phase indicator and the pressure preset indicator aim to make the unit user friendly. The operator has to switch the control unit on, preset (zero) the pressure signal and then select the valve trigger mode after rebreathing has commenced. Before the trial commences, the sample and hold must be calibrated as explained in section 6.1.1.

The $P_{0.1}$ rebreathing system as a whole requires major rearranging. The system consists of a number of pieces of equipment which are "time shared" with the Respiratory Exercise Laboratory. These tend to be cluttered around the patient during a rebreathing trial. This makes it difficult to reach a number of control points, such as the CO_2 scrubber bypass valve which is situated behind the perspex box containing the rebreathing bag and also the pump speed control which is situated below the box.

These difficulties can be eliminated by rearranging the various pieces of equipment and by obtaining dedicated equipment for the rebreathing system.

7 CONCLUSION

The $P_{0.1}$ and ventilatory sensitivity to hypercapnia can reliably be assessed using the $P_{0.1}$ rebreathing system presented in this thesis. The apparatus is in clinical use in the Respiratory Clinic at Groote Schuur Hospital. A principal technologist in the clinic can operate the system and a medical registrar is using the system for further studies in assessing ventilatory drive. The $P_{0.1}$ control unit functions reliably and no "down time " has yet been experienced due to any electronic faults. The results presented in the previous chapter agree well with those presented in the literature.

7.1 SUGGESTIONS FOR FURTHER STUDY

A study to determine the normal range of the population should be undertaken. The sample must be large so that the results reliably represent the population mean. Also a scoring sheet for the ventilatory drive should be developed to aid the clinician in diagnosing ventilatory dysfunction due to either a damped respiratory centre, pulmonary defects or a combination of both. A hypothetical scoring sheet for the assessment of ventilatory drive is shown in figure 7.1. The limits of the various regions as discussed in section 6.1.3 and 6.3.2.1 can be defined to suit

various sections of the population. It has been found that females have a lower sensitivity (Irsigler (1975)) to hypercapnia and the limits of a scoring sheet for them may be lower.

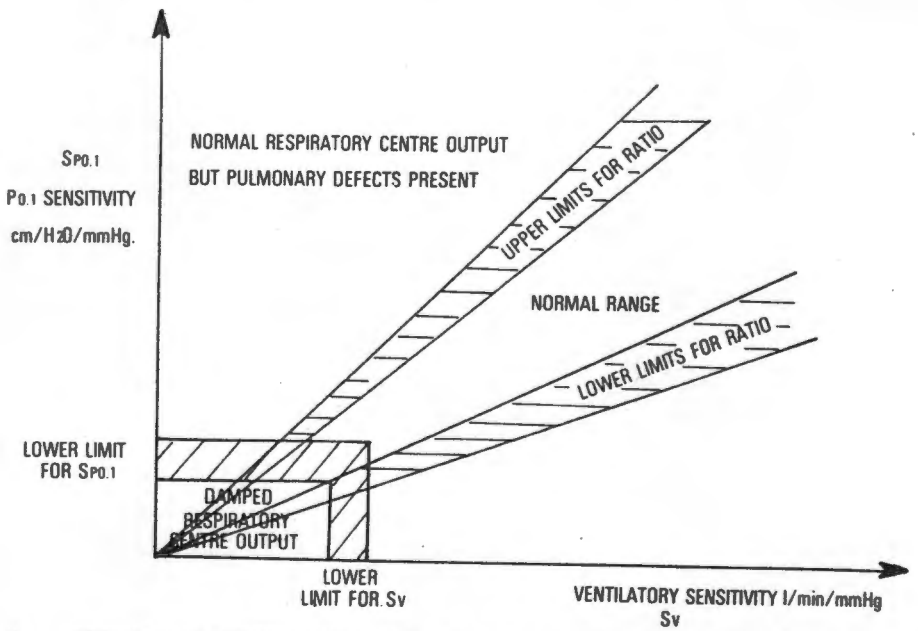


FIGURE 7.1 HYPOTHETICAL SCORING SHEET FOR THE ASSESSMENT OF VENTILATORY DRIVE TO HYPERCAPNIA

The results from the various pieces of equipment must be linked to a computer for on line analysis of the results. This avoids the tedious task of manually calculating the points on the tracing from the recorder, reproducing these points on a work-sheet and then entering the data into a computer to calculate the regression plots. On line analysis of the ventilatory drive must be a prerequisite for a detailed study to find the normal range of the population.

The technique for the hypoxic trials must be changed so that the CO_2 level of the rebreathing system can be accurately maintained. The number of points recorded in the latter third of the O_2 saturation trace must be increased so that the effect of the hypoxic drive can be accurately determined. The dry gas meter output is not linear and this limits the number of points one can take to calculate the minute ventilation. There are linear devices on the market and one of these should be obtained to allow instantaneous measurement of minute ventilation. An attempt must be made to standardise the apparatus so that various investigators can compare their results from the same baseline.

The $P_{0.1}$ response to hypercapnia and the ventilatory response to hypercapnia can be a useful aid in the assessment of ventilatory drive if a reliable population mean is determined and the spread of the results is narrowed. The effect of variations in occlusion time on the responses should also be studied.

BIBLIOGRAPHY

[1] ALTOSE,M.D., KELSEN,S.G., STANLEY,N.N., LEVINSON,R.S., CHERNIACK,N.S.,FISHMAN,A.P.,(1976), Effects of Hypercapnia on the Mouth Pressure during Airway Occlusion in Conscious Man. Journal of Applied Physiology. 40(3):338-344.

[2] BRADLEY,B.L.,MESTAS,J.,FORMAN,J.,UNGER,K.M., (1980), The effect on respiratory drive of a prolong physical conditioning program. American Review Of Respiratory Disease. 122:741-746.

[3] BERGER,A.J.,MITCHELL,R.A.,SEVERINGHAUS,J.W., (1977a), Regulation of Respiration. The New England Journal of Medicine. 297:92-97.

[4] BERGER,A.J.,MITCHELL,R.A.,SEVERINGHAUS,J.W., (1977b), Regulation of Ventilation. The New England Journal of Medicine. 297:138-143.

[5] BERGER,A.J.,MITCHELL,R.A.,SERVERINGHAUS,J.W., (1977c), Regulation of Ventilation. New England Journal of Medicine. 297:194-201.

[6] BRYAN,A.C.,BRYAN,M.H.,KIRKPATRICK,S.M.L.,KNILL,R.L., (1976), The Use of Airway Occlusion in Infants. Chest. 70:142-145. Supplement.

[7] CAMPORESI,E.M., FEEZOR,M., FORTUNE,J., SALZANO,J., (1978), An Electromagnetic Valve for Inspiratory Occlusion Pressures. Journal of Applied Physiology. 45(3):482-483.

[8] CHERNIACK,N.S., LEDERER,D.H., ALTOSE,M.D., KELSEN,S.G., (1976), Occlusion Pressure as a Technique in Evaluating Respiratory Control. Chest. 70:137-141. Supplement.

[9] CLARK,T.J.H., CLARK,B.G.,HUGHES,J.M.B.,(1966), A simple technique for measuring changes in ventilatory response to carbon dioxide. The Lancet. August 13, 2:368-372

[10] DELAVAULT,E.,SAUMON,G., (1980), An Analog Device to Facilitate Occlusion Pressure Measurements. Pflugers Archiv. 138:259-261.

[11] DEMPSEY,J.A.,(1976), CO_2 Response: Stimulus Definition and Limitations. Chest. 70:114-118. Supplement.

[12] FENCL,V.,(1976), Ventilatory Response to Carbon Dioxide in Humans. Chest. 70:113-114. Supplement.

[13] FITZGERALD,R.S., GARFINKEL,F.,SILBERGELD,E.,LOSCUTOFF, S.C.,(1976), Factors in the Interpretation of Mouth Occlusion Pressure during Measurements of Chemosensitivity. Chest. 70:145-149. Supplement.

[14] GANONG,W.F., (1979), Review of Medical Physiology. 9th ed. Sec.VII:497-537. Lange Medical Publications.

[15] GRIBBIN,H.R.,GARDINER,I.T.,HEINZ III,G.J.,GIBSON,G.J., PRIDE,N.B.,(1982), Role of impaired inspiratory muscle function in limiting the ventilatory response to carbon in chronic airflow obstruction. Clinical Science. 64:487-495.

[16] GRODINS,F.S.,YAMASHIRO,S.M., (1977), Control of ventilation. Chapter 7 in Bioengineering aspects of the lung. Edited by WEST,J.B. 515-558. Marcel Dekker Inc.

[17] GUYTON,A.C.,(1981), Textbook of Medical Physiology. 6th ed. Sec.39:476-539. W.B.Saunders Company.

18 HALDANE,J.S.,POULTON,.E.P., (1908), The effects of want of oxygen on respiration. Journal of Physiology. 37:390-

[19] HANCOX,A.J., SCRIMSHIRE,D.A., WARDMAN,R.E., TAYLOR,M.P., (1982), Automatic assessment of respiratory dead-space. Medical and Biological Engineering and Computing. 20:58-64.

[20] HENDEMARK,L.L.,KRONENBERG,R.S., (1982). Chemical Regulation of Respiration. Chest. 82:488-494.

[21] HIRSHMAN,C.A.,McCULLOUGH,R.E.,WEIL,J.V., (1975), Normal values for hypoxic and hypercapnic ventilatory drives in man. Journal of Applied Physiology. 38(6):1095-1098.

[22] IRSIGLER,G.B., (1976), Carbon Dioxide Response Lines in Young Adults: The Limits of the Normal Response. American Review of Respiratory Disease. 114:529-536.

[23] JACOBSON,B.,WEBSTER,J.G.,(1977), Medicine and Clinical Engineering. Prentice-Hall Inc.

[24] JORDAN,C.,(1981), Automatic method for measuring mouth occlusion pressure response to carbon dioxide. Medical and Biological Engineering and Computing. 19:279-286.

[25] LEDERER,D.H., ALTOSE,M.D., KELSEN,S.G., CHERNIACK,N.S., (1977), Comparison of occlusion pressure and ventilatory

responses. Thorax. 32:212-220.

[26] LOPATA,M., EVANICH,M.J., LOURENCO,R.V.,(1975), Relation between the Mouth Occlusion Pressure and Diaphragm Electromyogram in Normal Man. American Review of Respiratory Disease. 111(6):908.

[27] LOPATA,M.,EVANICH,M.J.,ONAL,E.,ZABILLAGA,G.,LOURENCO,R. A., (1978), Airway occlusion pressure and respiratory nerve and muscle activity in studies of respiratory control. Chest. 73:2 February Supplement.

[28] LOURENCO,R.V.,(1976), Clinical Methods for the Study of Regulation of Breathing. Chest. 70:109-112 Supplement.

[29] McKERROW,C.B.,OTIS,A.B., (1956), Low Resistance Valve for Hyperventilation. 9:497-498.

30 MILIC-EMILI,J.,GRUNSTEIN,M.M., (1976), Drive and Timing Components of Ventilation. Chest. 70:131-133. (Suppl.)

[31] MITCHELL,R.A.,BERGER,A.J., (1975), Neuronal Regulation of Respiration. American Review of Respiratory Disease. 111:206-221.

[32] MUSTCHIN,C.P., (1977), Carbon Dioxide Rebreathing and Mouth Occlusion Pressure Measurements. Journal of the Royal College of Physicians. 12(1):87-95

[33] NATIONAL SEMICONDUCTOR. (1980) Linear Databook.

[34] NATIONAL SEMICONDUCTOR. (1978) CMOS Databook.

[35] NATIONAL SEMICONDUCTOR. (1978) Discrete Databook.

[36] READ,D.J.C. ,(1967), A clinical method for assessing the ventilatory response to carbon dioxide. Australian Annals of Medicine. 16:20-32

[37] READ,D.J.C.,LEIGH,J., (1967), Blood-brain Tissue PCO2 Relationships and Ventilation during Rebreathing. Journal of Applied Physiology. 23:53-70.

[38] REBUCK,A.S. , (1976), Measurement of Ventilatory Response to CO_2 by Rebreathing. Chest. 70:118-121. Supplement.

[39] REBUCK,A.S., RIGG,J.A.R.,KANGALEE,M.,PENGELLY,L.D. , (1974), Control of Tidal Volume during Rebreathing. Journal of Applied Physiology. 37(4):475-478.

[40] SACKNER,J.D.,NIXON,A.J.,DAVIS,B.,ATKINS,N.,SACKNER,M. A., (1980), Effects of Breathing Through External Dead Space on Ventilation at Rest and During Exercise. American Review Of Respiratory Disease. 122:933-940.

[41] SCHULTE,F.J.,ALBANI,M.,SCHNIZER,H.,BENTELE,X., (1982), Neuronal Control of Neonatal Respiration - Sleep Apnea and Sudden Infant Death Syndrome. Neuropediatrics. 13:4-14 Supplement.

[42] SEARS,F.W.,ZEMANSKY,M.W. (1973) University Physics 4th Ed. Addison-Wesley Publishing Company.

[43] TROUTH,C.O.,PATRISKSON,J.W.,HOLLOWAY,J.A.,WRIGHT,L.E., (1982), Neurophysiological Studies on the Superficial Medullary Chemosensitive Area for Respiration. Brain Research. 246:47-56.

[44] WHITELAW,W.A., DERENNE,J., MILIC-EMILI,J., (1975), Occlusion pressure as a measure of respiratory centre output in conscious man. Respiration Physiology. 23:181-199.

A $P_{0.1}$ POWER SUPPLY UNIT

The specifications for a power supply unit for the $P_{0.1}$ control unit are:

i. +12V @ 500mA for analog and digital circuitry

ii. -12V @ 150mA for analog circuitry

iii. 1.2A to drive solenoid

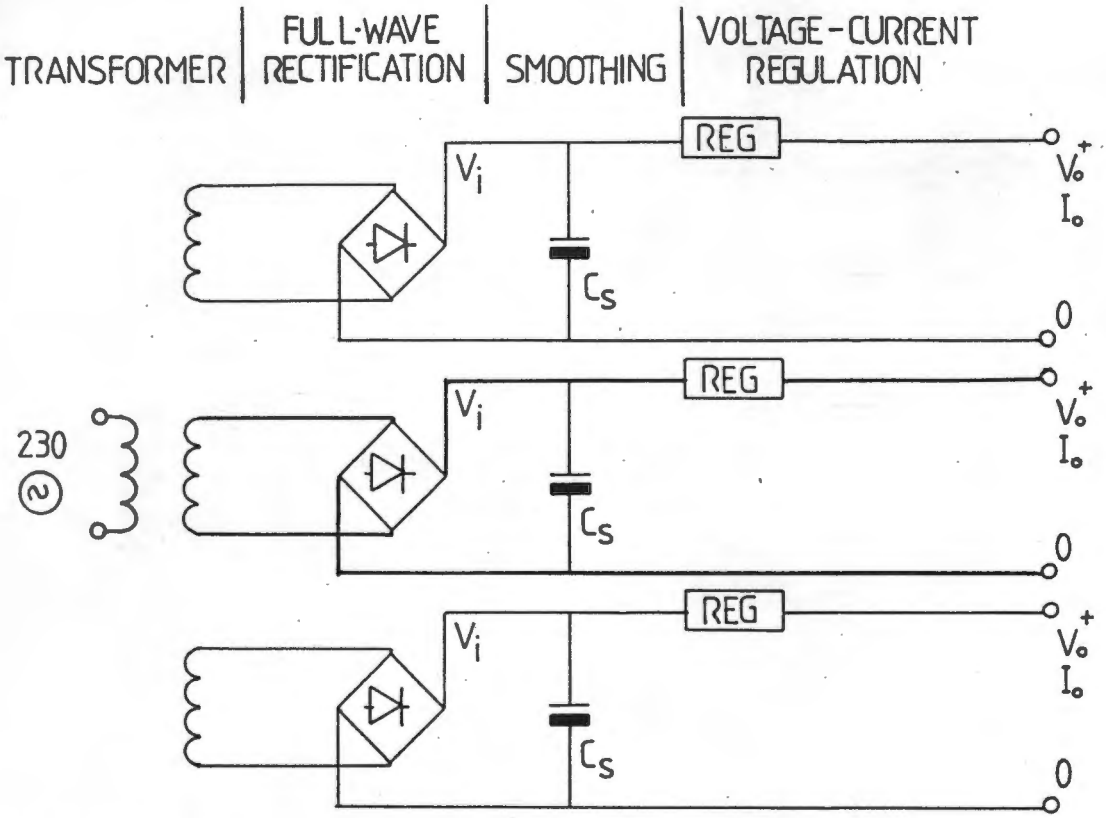
iv. 1.25V @ 1mA for potentiometer on dry gas meter.

It was decided to build a general purpose laboratory power supply as the departmental laboratory had a need for this. The designed power supply has various voltage and current output configurations possible. Three of these units have been built and are used in different applications.

A.1 DESIGN OF POWER SUPPLY UNIT

Figure A.1 shows a schematic of the design configuration and the component layout of the unit. There are three different voltage outputs available and their ratings are primarily dependent on the rating of the transformer. The transformer has to be wound according to the requirements of the particular application.

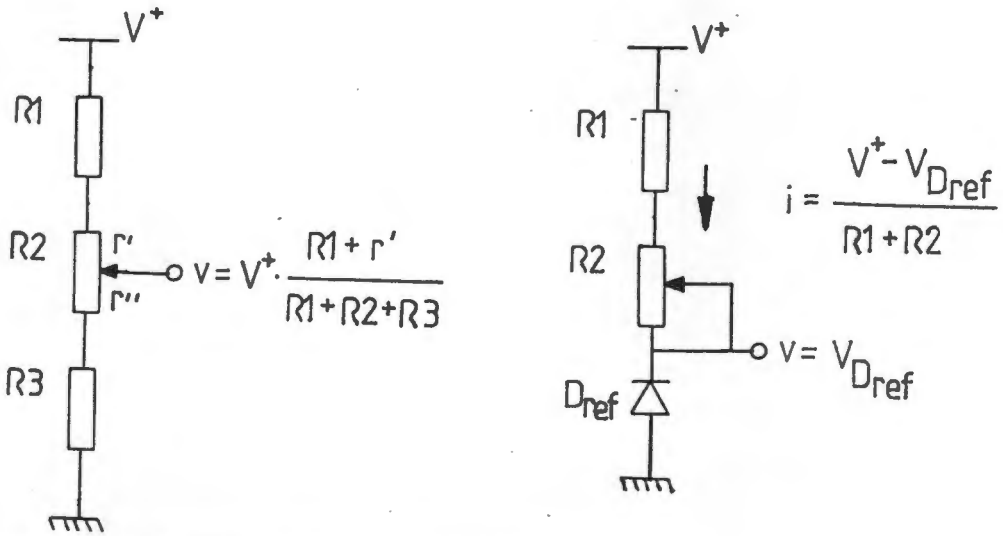
The design is such that low current-rated dual voltage and a



A.1 SCHEMATIC OF POWER SUPPLY DESIGN CONFIGURATION.

high current-rated single voltage supplies are available. The dual supply can typically be of higher voltage, for example 12V at 500mA, while the single supply has a lower voltage, for example 5V at 2A. In addition a voltage output is available from a resistor divider circuit from each output of the dual supply.

To limit power wastage from these, small currents of less than 1mA should be drawn. Figure A.2 explains this circuitry. The input impedance of the equipment supplied by the resistor divider



A.2 SCHEMATIC OF RESISTOR DIVIDER AND REFERENCE DIODE OUTPUT.

circuit will affect the output of the divider. The input impedance (Z_i) of the device is paralleled with (R3 + r") which reduces the resistance at this point. The resistance at this point will become (R3 + r") // Z_i. For example. Let (R1 + r') = (R3 + r") = Z_i = 10K (Z_i = 8K for the Devices recorder), then the output voltage, v, is loaded down from 0.5V to 0.33V. But for, Z_i = 100K, the voltage is reduced to 0.48V. This circuit should thus only be used to supply equipment with input impedances greater than 100K. This can be achieved more efficiently and independent of Z_i by using a reference or a zener diode. The diode acts as a current source and as long as there is sufficient current (0.5mA for the LM313H reference diode), it will maintain its output voltage.

It is possible to use fixed and adjustable voltage regulators. Provision has been made via hard-wire ties to cater for the

different pin configurations of various regulators. The low voltage high current supply can also be connected in the current limiting mode. The board has provision for a transistor switch in the high current circuit. In the $P_{0.1}$ system it is used to drive the solenoid of the occlusion valve. Protection diodes can be used to protect the regulators against capacitive loads. Figure A.3 shows the different configurations for the power supply unit. For further details of the circuit design, see the manufacturers applicaton notes for the particular regulator.

A.2 CIRCUIT MAST AND COMPONENT LAYOUT

Figure A.4 shows the mast of the power supply board. Figures A.5a and A.5b show the component layout for the various voltage output configuration circuits. They should be read in conjunction with figure A.3.

The outputs of figure A.5a are from:

V_1 : Fixed voltage regulator

v_1 : Resistor divider

V_2 : Voltage regulator connected in current limiting mode

V_3 : Fixed voltage regulator

v_3 : Reference or zener diode

the outputs of figure A.5b are from:

V_1 : Adjustable voltage regulator

V_1 : Resistor divider

V_2 : Adjustable voltage regulator

V_3 : Fixed voltage regulator

v_3 : Resistor divider

A.3 CIRCUIT DIAGRAM OF $P_{0.1}$ POWER SUPPLY UNIT

Figure A.6 shows the circuit diagram and component layout of the power supply for the $P_{0.1}$ control unit. The presented format of the circuit is such that it conforms with that of the previous diagrams. The dual supply is obtained using two fixed positive voltage regulators, LM340T12 and LM78L12. When connected, the arrangement supplies +12V at 500mA and -12V at 150mA. A reference diode, LM385Z1.2 is used to supply 1.2V to the dry-gas meter. The current drawn by this circuit is limited by R64 (100R) and trimpot P7(5K) to 2mA.

The LM350K 3A positive voltage regulator is connected in the current limiting mode to supply 1.2A to the solenoid of the occlusion valve when the switching transistor, LM395T, is activated by the main control board. The regulator is placed on the printed circuit board because the heat generated by it is minimal. This is because the valve is activated for short durations of about 2 seconds approximately 20 times during a $P_{0.1}$ trial lasting 4 minutes (approximately 20%).

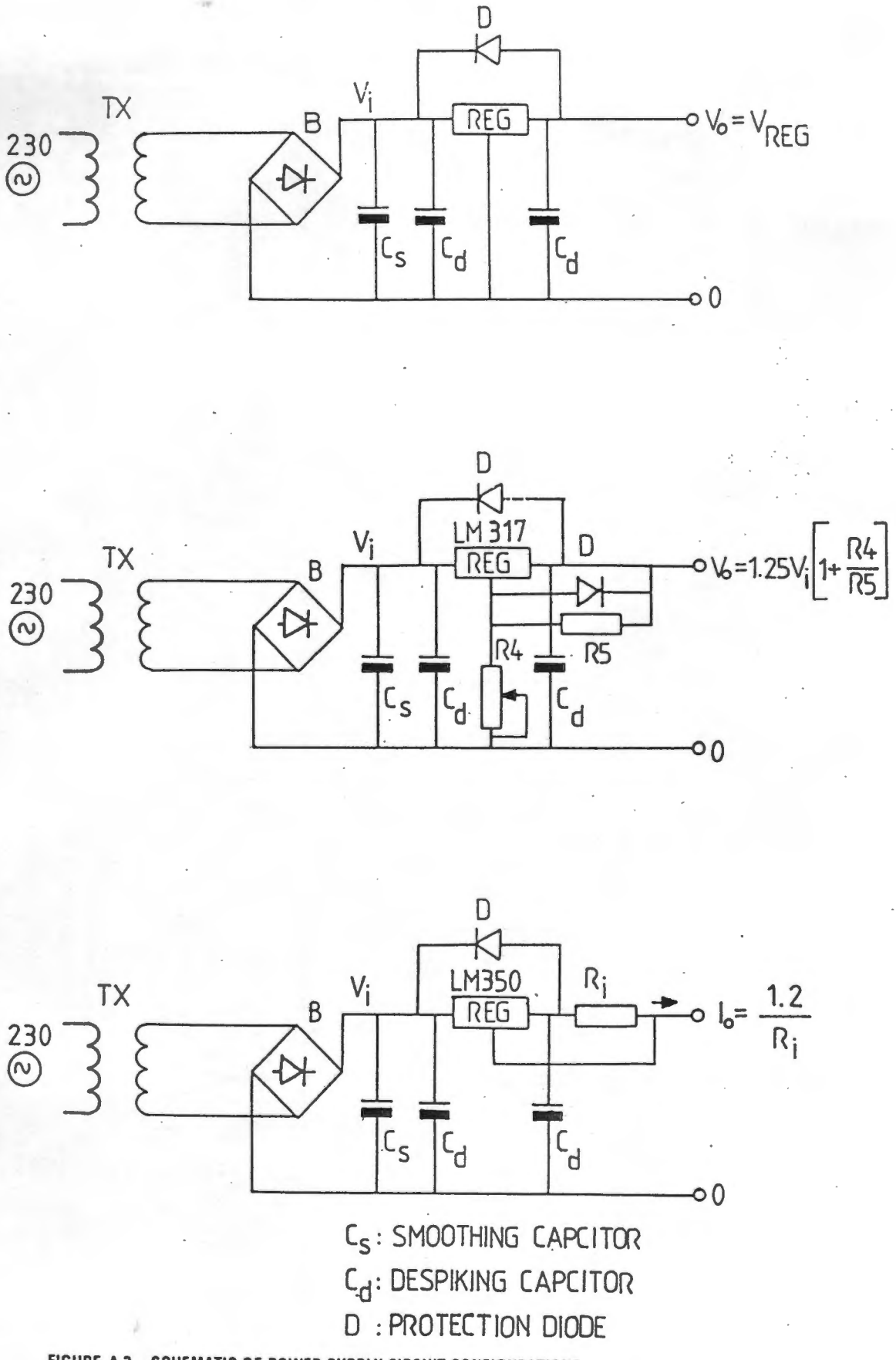


FIGURE A.3 SCHEMATIC OF POWER SUPPLY CIRCUIT CONFIGURATIONS.

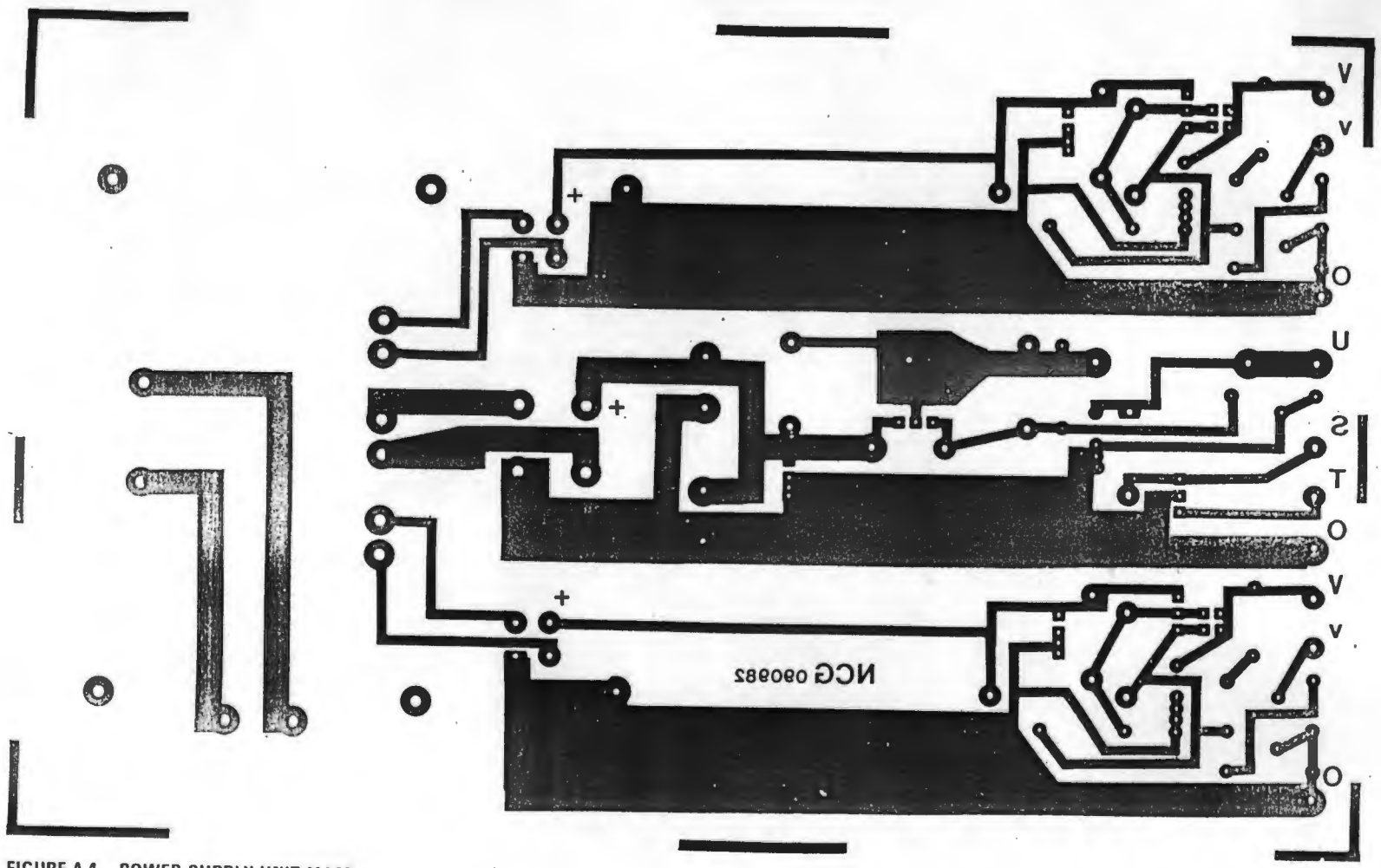


FIGURE A.4 POWER SUPPLY UNIT MAST.

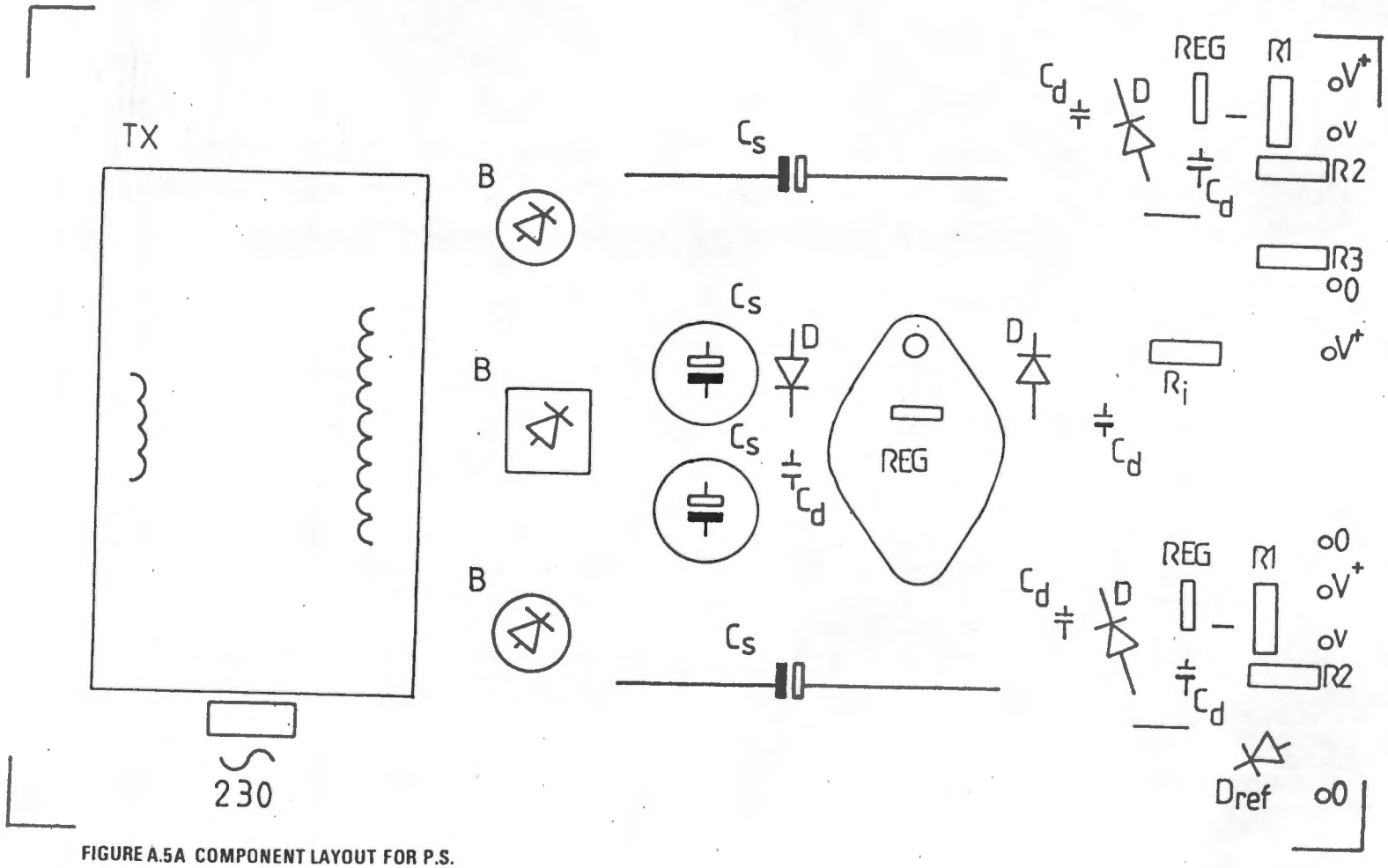


FIGURE A.5A COMPONENT LAYOUT FOR P.S.

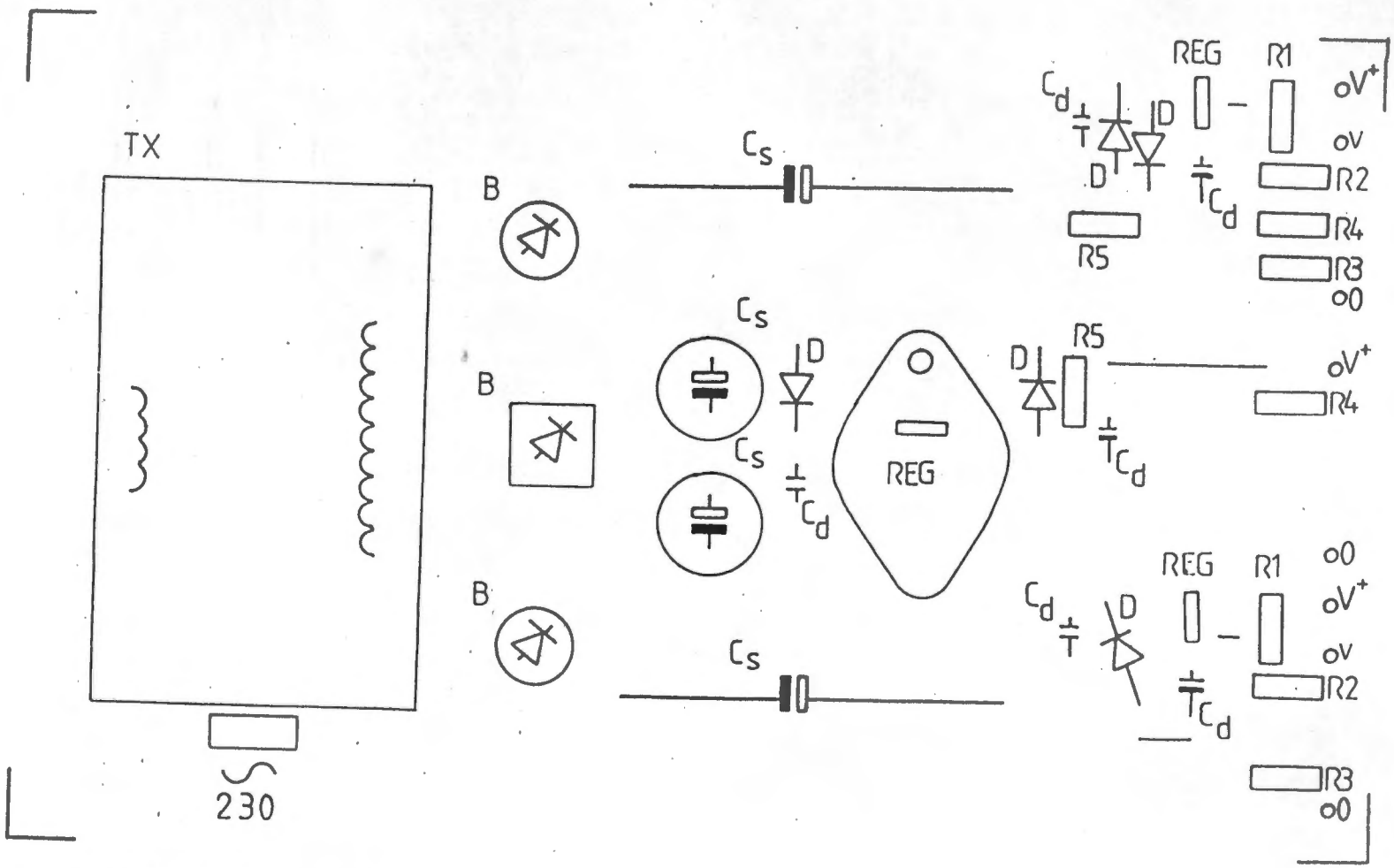


FIGURE A.5B COMPONENT LAYOUT FOR P.S.

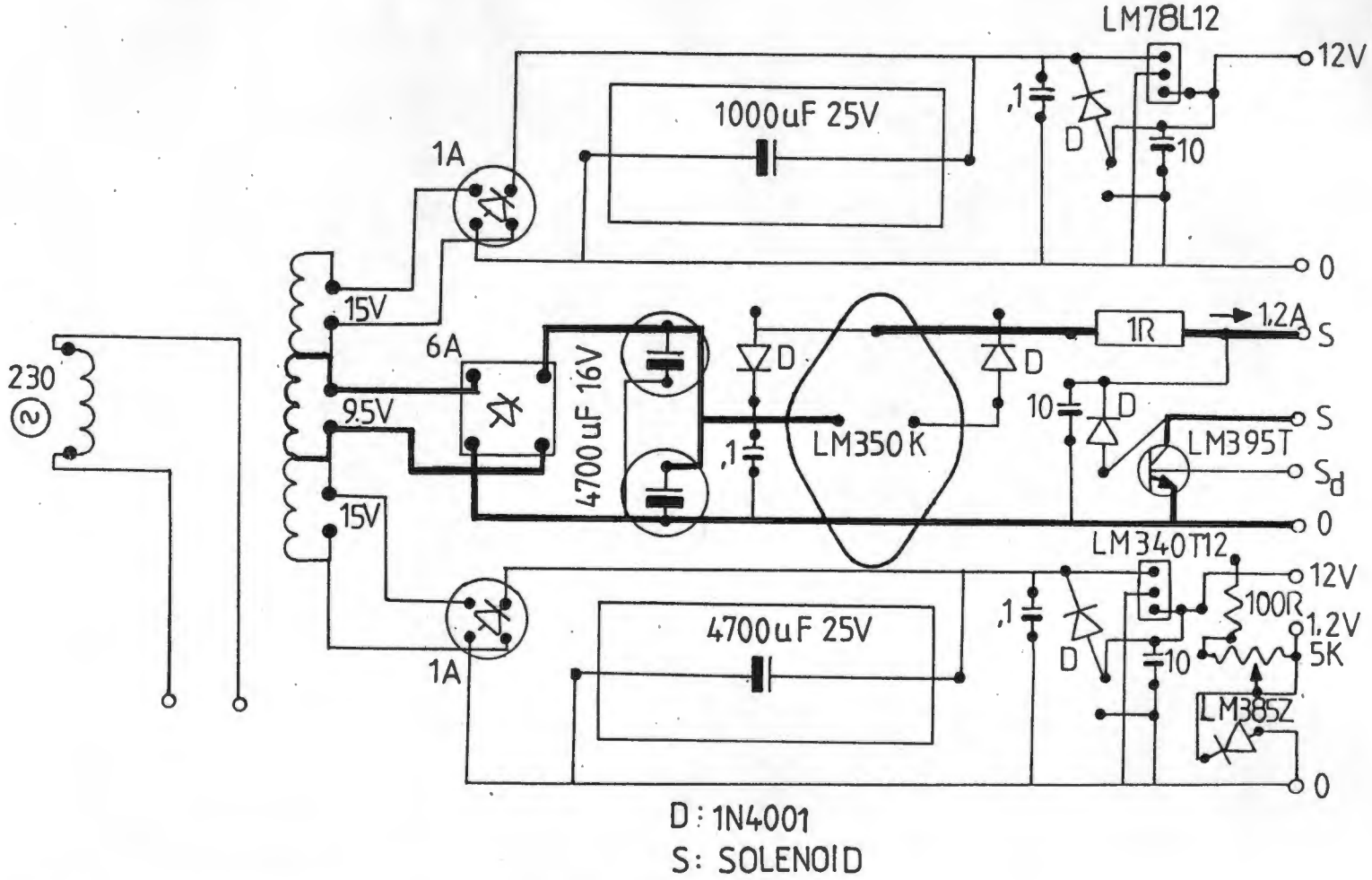


FIGURE A.6 $P_{0.1}$ UNIT POWER SUPPLY UNIT CIRCUIT DIAGRAM AND COMPONENT LAYOUT.

B CONSENT AND DATA LOGGING WORK-SHEETS

RESPIRATORY CLINIC GROOTE SCHUUR HOSPITAL

and

BIOMEDICAL ENGINEERING DEPARTMENT UNIVERSITY OF CAPE TOWN

ASSESSMENT OF VENTILATORY DRIVE : EVALUATION OF THE P0.1 METHOD ON NORMAL SUBJECTS

VOLUNTEER`S INFORMATION AND CONSENT :

We wish to evaluate a new technique of assessing the control of breathing in normal persons. We need volunteers who will undergo a physical examination, pulmonary function tests and have a chest X-ray taken to show that they are normal.

The test protocol involves a subject rebreathing for about 4 minutes from a bag prefilled with a known mixture of oxygen and carbon dioxide. During this time the subject will feel a progressively increasing need to breathe. Three studies will be done. The ECG will be used to monitor the heart for any irregular rhythm. A slight headache lasting for a short time after the tests may be experienced. Some foods like coffee, tea and Coca-Cola affect ones performance during the test and these must be avoided at least twelve hours before the test.

The tests will be repeated one week later. A doctor and a technologist will be present. Volunteers can withdraw from the trial if they wish.

Volunteer's Name : .....

Address : .....

City : ..... Code : .....

Telephone No. : home ..... work .....

SIGNATURE : ..... Date : ...../...../.....

RESPIRATORY CLINIC GROOTE SCHUUR HOSPITAL

and

BIOMEDICAL ENGINEERING DEPARTMENT UNIVERSITY OF CAPE TOWN

ASSESSMENT OF VENTILATORY DRIVE : EVALUATION OF THE P0.1 METHOD ON NORMAL SUBJECTS

Name : ..... Test No. : .... Date : .../.../...

Time : ..... Tech. : ..... Doctor : .....

Phy. Exam. : ..... Chest X-ray : .....

Comments : .....

Sex : ..... Age : .....yrs Ht : .....cm

Wt : .....kg BSA :.....sqm Race : .....

IC : .....ml ERV : .....ml VC : .....ml

FRC : .....ml TLC : .....ml RV/TLC : .....%

FVC : .....ml FEV1 : .....ml FEV1/FVC : .....%

	SLOPE	X-INT mmHg	CORR. COEF.	NO. OF PNTS.	AT PCO2 55mmHg VALUE
HYPERCAPNIC RESPONSE					
Ventilation					
P0.1					
HYPOXIC RESPONSE end tidal PCO2					AT 80% 02 SAT VALUE
Ventilation					
P0.1					
plateau PCO2					
Ventilation					
P0.1.....					

PLATEAU CO2 : .....mmHg END TIDAL PCO2 : .....mmHg

EVALUATION OF THE P0.1 METHOD WORK SHEET

Name: ..... Test No. : .... Date : ..../..../....

TEST# : [ ]HYPERCAP [ ]HYPOX @ END TIDAL PCO2 [ ]HYPOX @ PLAT PCO2

Temperature : ..... Pressure : ..... Humidity : .....

Vol/Rev : ..... Time Sweep : ..... Volume Sweep : .....

Point No.	% CO2	% O2	Time Defln.	Vol. Defln.	P0.1
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

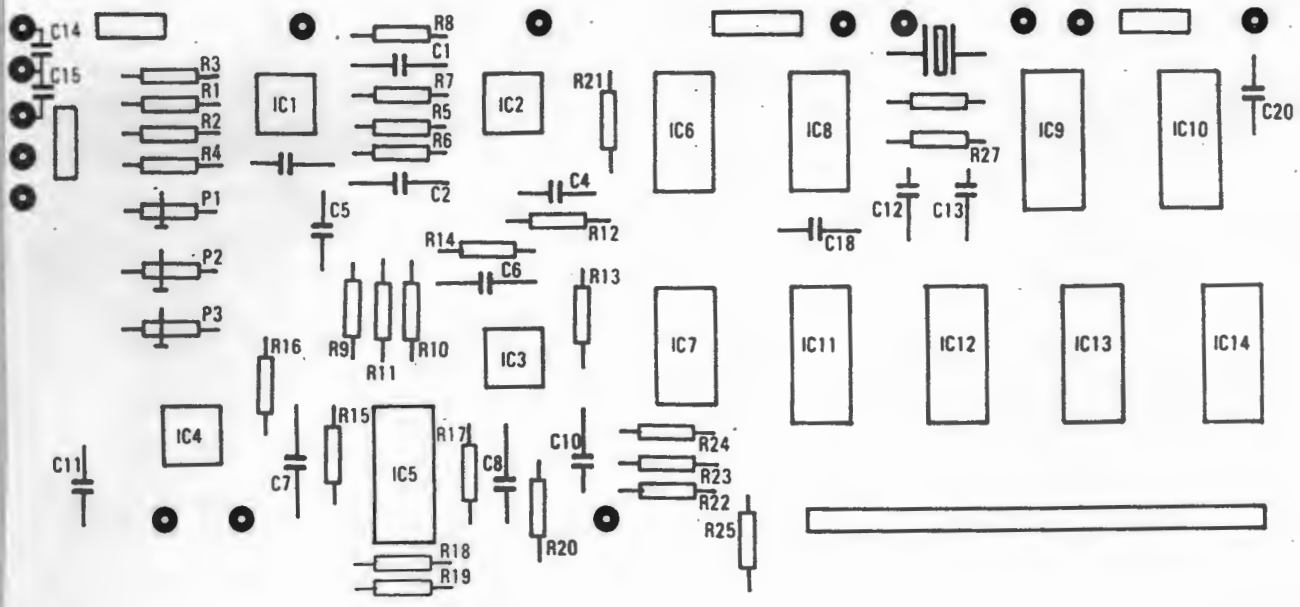
VOL. GAS FILLED IN BAG : .....l INITIAL GAS PCO2 : .....%

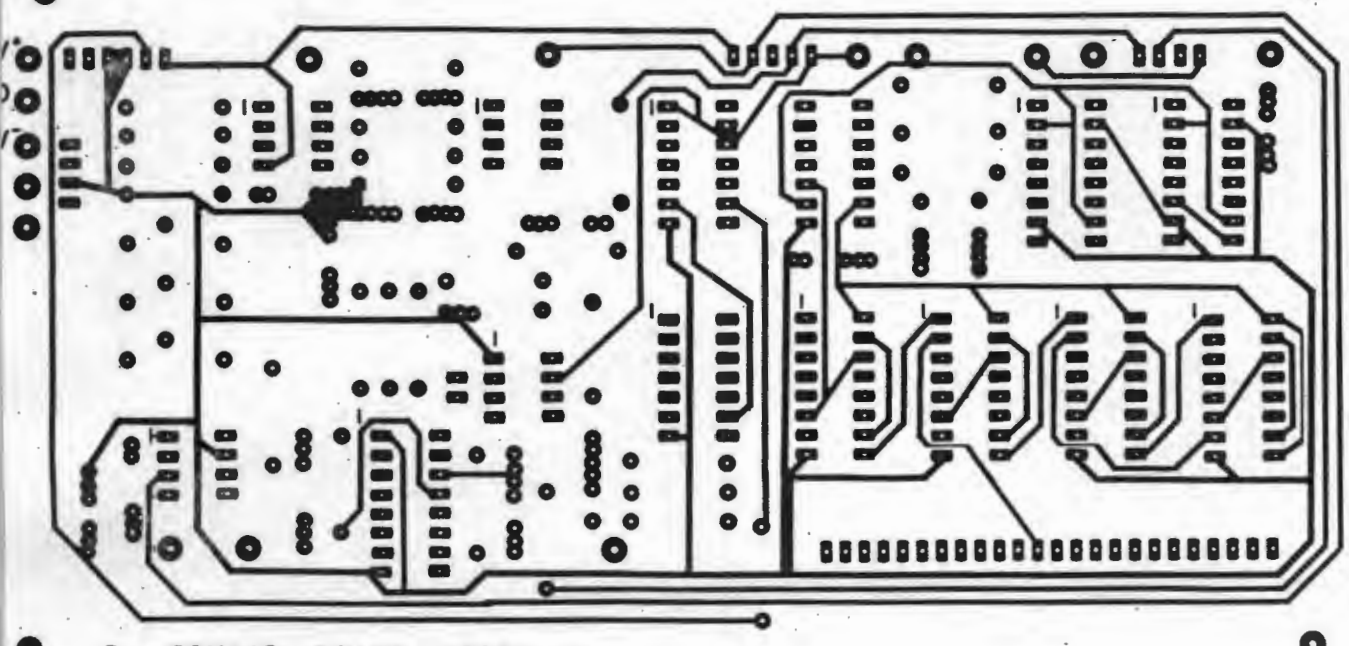
END TIDAL PCO2 : ....% PLATEAU PCO2 : .....% REBR. TIME ....min

C

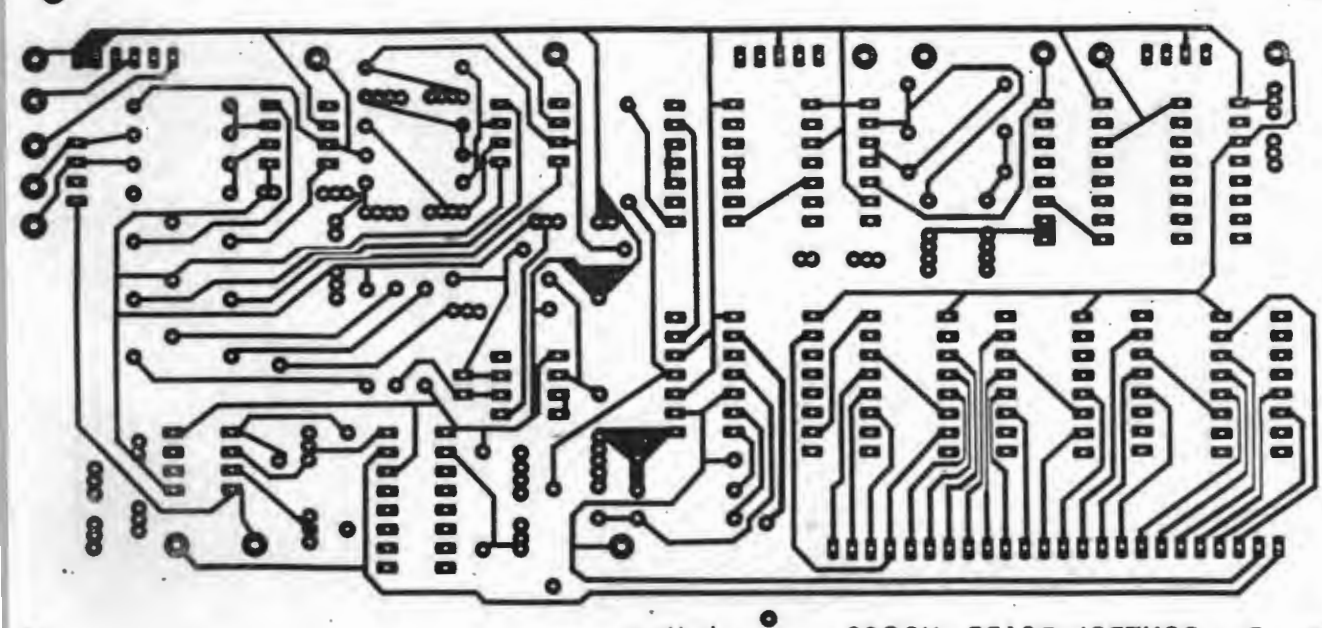
CIRCUIT MASKS AND COMPONENT LAYOUT FOR THE P0.1

CONTROL UNIT





$P_{0.1}$ CONTROL BOARD NCG83 top



$P_{0.1}$ CONTROL BOARD NCG83 bottom

FIGURE C.1 CIRCUIT MASK AND COMPONENT LAYOUT OF THE $P_{0.1}$ CONTROL BOARD.

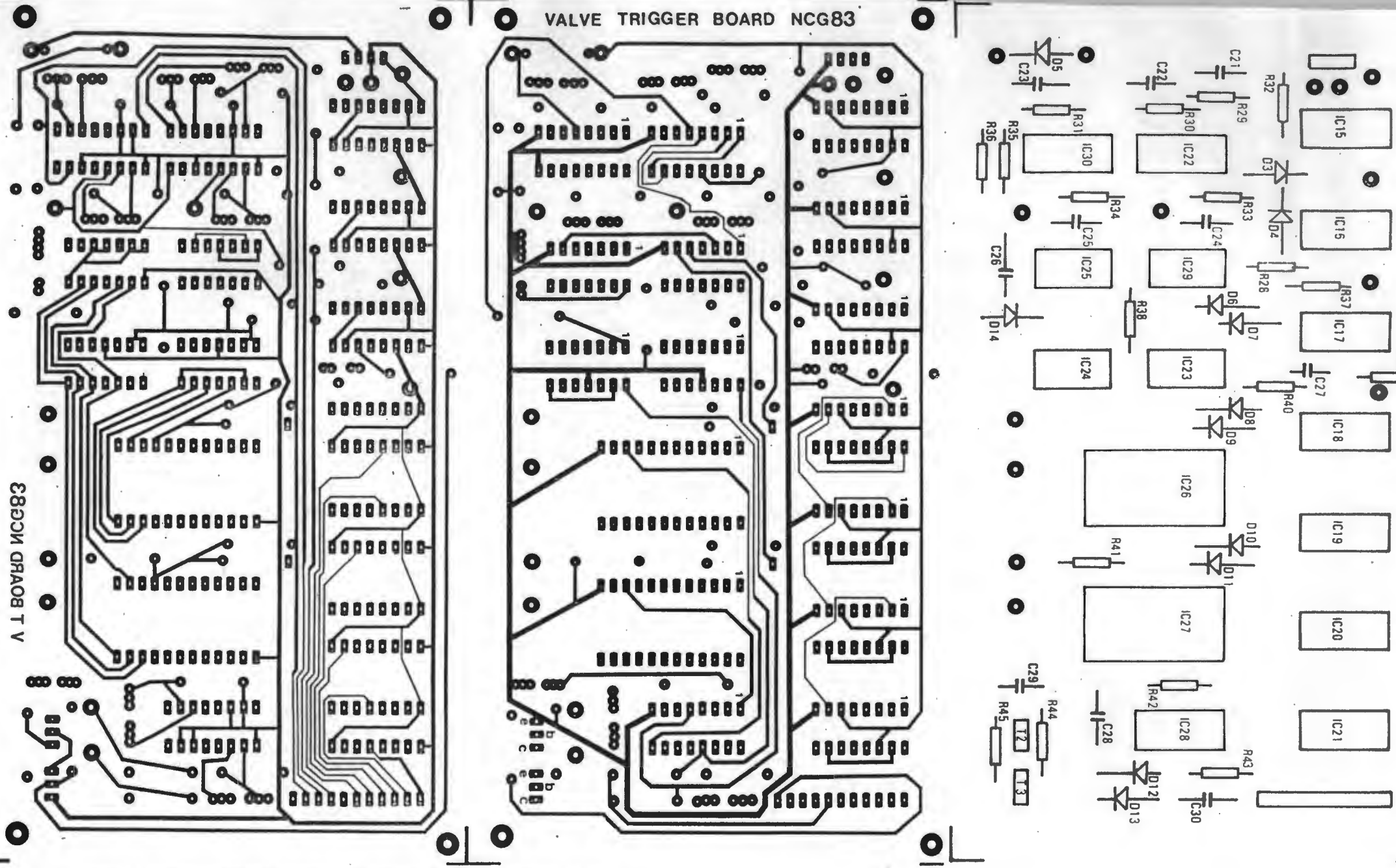


FIGURE C.2 CIRCUIT MASK AND COMPONENT LAYOUT OF THE VALVE TRIGGER BOARD.

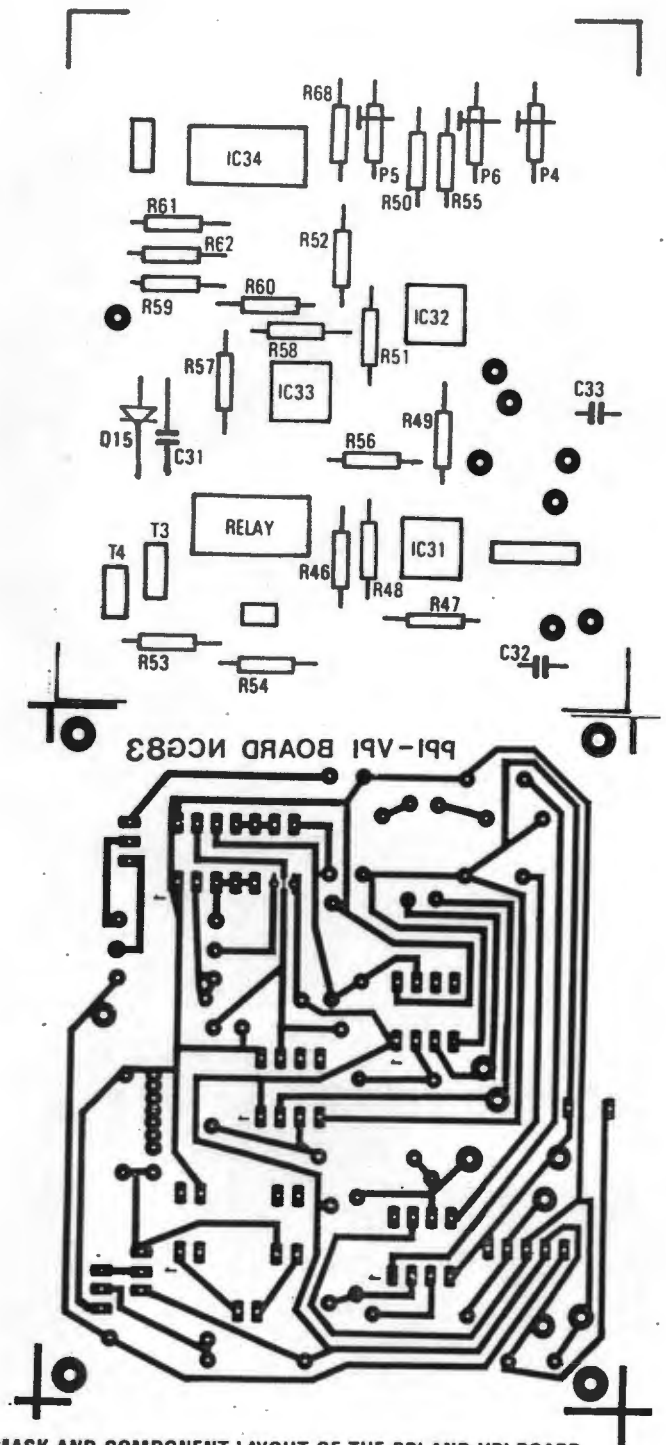
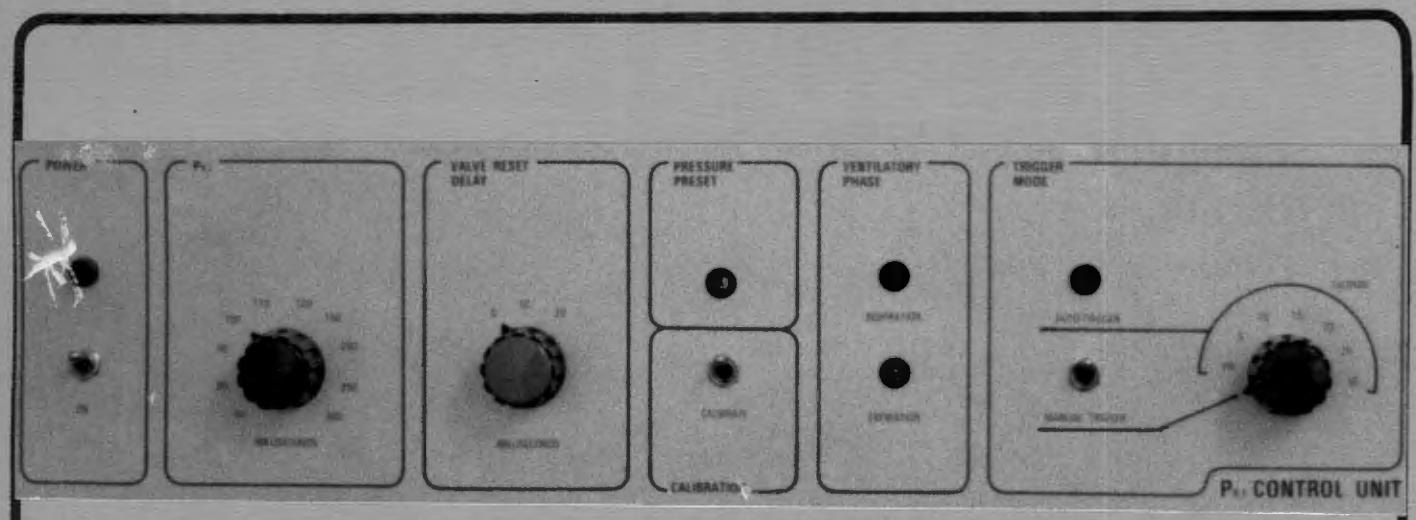


FIGURE C.3 CIRCUIT MASK AND COMPONENT LAYOUT OF THE PPI AND VPI BOARD.



P0.1 CONTROL UNIT