HYPERVENTILATION AND SUBMARINE ESCAPE

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A thesis submitted for the degree of

Doctor of Medicine

of

The University of London

November 1990

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ABSTRACT

The Royal Navy have demonstrated in two sea trials that it is possible for men to make successful escapes from submarines at depths of about 600 ft. However, the outcomes suggest this depth is close to the limit of safe escape under ideal conditions and might be well beyond it in real circumstances. The problem lies in the substantial accumulation of nitrogen which occurs in nervous tissue during all but the last few seconds of the brief escape procedure. As the surface of the sea is approached the nitrogen may evolve destructively as bubbles.

This thesis explores the idea that hyperventilation prior to escape might reduce the risk of bubble formation. Hyperventilation lowers the partial pressure of CO_2 in arterial blood. This is known to constrict cerebrospinal arteries and arterioles and so should restrict the build up of dissolved nitrogen in central nervous tissue. Preliminary experiments by others have indicated that human volunteers can complete the escape procedure successfully after hyperventilating to a $PACO_2$ of 20 mmHg or so. This degree of hyperventilation should halve the inflow of nitrogen.

This thesis :

i) reviews dysbarism

ii) describes the procedures of submarine escape,

iii) develops a mathematical model of inert gas exchange,

iv) predicts the effects of hyperventilation

v) uses a specific task to test psychomotor ability

vi) shows the effect of hyperventilation on ability

vii) uses nitrous oxide anaesthesia to model escape

viii) shows hyperventilation retards anaesthesia, and

viii) concludes hyperventilation reduces the risks of escape.

The findings are also relevant to anaesthesia in neurosurgery.

PREFACE AND ACKNOWLEDGEMENTS

Preface

This thesis was prepared between October 1989 and October 1990 in the Department of Clinical Physiology at the Royal Brompton Hospital. The work was funded by the NHS, and was closely supervervised by Prof DM Denison. It involves a theoretical and experimental study of the use of hyperventilation to manipulate the uptake of inert gas by the brain. The results have implications for submarine escape and the practice of clinical anaesthesia.

Acknowledgements

I am indebted to Profess Denison who conceived this project and kindly allowed me to conduct the experiments. Without his guidance and assistance this thesis would not have been possible.

I would also like to thank the 7 subjects, Professor Denison, Caroline Marshall, Francis Heritier, Peter McNaughton, Tom Sopwith, Eddie Yeo and Benjamin Bridgewater for their patience and acceptance of the unpleasant procedures they underwent.

CONTENTS

SYMBOLS & ABBREVIATIONS

CO_2	Carbon dioxide
PCO_2	Partial pressure of carbon dioxide
PACO2	Partial pressure of carbon dioxide in the alveoli
PICO2	Partial pressure of carbon dioxide in the inspired air
PaCO2	Partial pressure of carbon dioxide in the arterial blood
PN_2	Partial pressure of nitrogen
PAN_2	Partial pressure of nitrogen in the alveoli
PaN_2	Partial pressure of nitrogen in the arterial blood
PO_2	Partial pressure of oxygen
e	Natural logarithim
k	Reciprocal of the time constant
T	Time constant
t	time
Yi	Value of Y at infinite time

Yo	Value of Y at zero time
Y	Value of Y at time t
Pi	Partial pressure of an inert gas at infinite time
Po	Partial pressure of an inert gas at zero time
Pt	Partial pressure of an inert gas at time t.
*	Multiplication
P	Pressure
r	Radius
T	Surface tension
π	Pi
G	Conductance
$\dot{M}CO_2$	Molar flow of CO_2
k	Constant
V_A	Alveolar ventilation
RQ	Respiratory quotient
R	Respiratory exchange ratio
MVV	Maximum voluntary ventilation

$\dot{V}CO_2$	Minute volume of CO_2
PAO2	Partial pressure of oxygen in the alveoli
PIO_2	Partial pressure of oxygen in the inspired air
pH	Negative logarithim of the hydrogen ion concentration
pK_A	Negative logarithim of the dissociation constant of carbonic acid
HCO_3^-	Bicarbonate
N_2O	Nitrous oxide
Vt	Tidal volume
V_D	Dead space volume
FRC	Function residual capacity
Q	Total blood flow
Qd	Pulmonary blood flow through anatomical shunt
Qb	Pathological flow in bronchial circulation
Qtot	Total pulmonary blood flow
FAXn	Fractional concentration of inert gas X in the alveoli at end of n breath

FAX_{n-1} Fractional concentration of inert gas X in the alveoli at end of the previous breath.

FIX Fractional concentration of inert gas X in the inspired air

$ETCO_2$ End-tidal carbon dioxide tension

$PetCO_2$ End-tidal carbon dioxide tension

ICO_2 Inspired carbon dioxide tension

FIN2O Fractional concentration of nitrous oxide in the inspired air

HCT Hypocapnic threshold

NT Normal task

RT Reverse task

TABLES AND ILLUSTRATIONS

1 INTRODUCTION

The Royal Navy requires a method of escaping from submarines that are disabled at depths down to 600 ft. They have demonstrated this can be done successfully, in two trials at sea. However the results of the trials suggest this depth is close to the limit of safe escape under ideal conditions, and might be well beyond it in real circumstances. The problem lies in the substantial accumulation of nitrogen which occurs in nervous tissue in the brief escape procedure. They needed some method of reducing this risk. Denison and Davies(1988) suggested that prior hyperventilation, which constricts cerebrospinal blood vessels, would limit nitrogen accumulation, and so might do the trick. They proposed a three-part investigation to study this.

Firstly a mathematical model was constructed of inert gas exchange in the central nervous system during the escape procedure, (Denison & Bridgewater: in press). The model consisted of a lung ventilated appropriately, with realistic circulatory delays to and from half a dozen body compartments of specific and adjustable gas-exchanging properties. This model confirmed that 600 ft was a likely limit to successful escape under ideal circumstances, and suggested that hyperventilation to an alveolar PCO_2 of about 20 mm Hg, which would roughly halve cerebrospinal blood flow, should limit nitrogen accumulation in nervous tissue significantly.

Secondly, experiments at Brompton Hospital found hyperventilation to this degree could be tolerated by healthy subjects for many minutes, with little deterioration in psychomotor ability. Thirdly studies on 12 Submarine Escape Training Officers and Instructors showed that hyperventilation of this order did not interfere with their ability to complete escape procedures successfully at depths down to 100 ft, (Denison, Bridgewater, Sopwith and Savage: in preparation).

So far, the studies had shown that hyperventilation was safe but not that it was effective. It was clear that it would be unethical to study this aspect by compressing men to 600 ft and counting the heads arriving at the surface, so it was decided to use a short sharp exposure to nitrous oxide as a model of the behaviour of nitrogen in nervous tissue. This thesis explores that proposal.

It begins by reviewing the pathophysiology of acute neurological decompression illness, the problems of submarine escape and the physiology of hyperventilation. Next, it develops the mathematical model of Denison and Bridgwater to compare the build-up and release of nitrogen in nervous tissue during escape, with the accumulation and loss of nitrous oxide in the same tissues which might be achieved in the laboratory at normal atmospheric pressure. The new model is then used to predict the effects of hyperventilation on pulses of nitrous oxide anaesthesia.

Following this, there are descriptions of preliminary experiments carried out to define the equipment that would be needed, the levels of ventilation necessary to sweep nitrous oxide in and out of the lungs quickly, the psychomotor tasks that should be used to demonstrate its effect, and the levels of hypocapnia that were likely influence it.

After this a formal study was conducted on the influence of hyperventilation upon pulses of nitrous oxide anaesthesia, in 7 healthy volunteers. It was obvious that all of the subjects obtained highly significant protection from the pulse of nitrous oxide by prior hyperventilation. The practical interpretation of this finding, and its relevance to the practice of anaesthesia are discussed at the end of the thesis.

2 DECOMPRESSION ILLNESS

2.1 Introduction

Until very recently, diving physicians spoke of most neurological syndromes which occurred within ten minutes of decompression as cerebrospinal arterial gas embolism, and presumed they were secondary to lung rupture (pulmonary barotrauma). Equally, they considered that most neurological syndromes that developed more than ten minutes after decompression were examples of cerebrospinal decompression sickness, which was thought to be due to the generation of bubbles in or very close to nervous tissue. Also if they could identify a segmental level above which neurological signs and symptoms were absent, they tended to label the syndrome as spinal rather than cerebral.

At a consensus meeting held in the Royal Navy Institute of Naval Medicine in Alverstoke in October 1990, a group of diving physicians from many countries agreed that often it was impossible to distinguish cerebrospinal gas embolism from decompression sickness, and not at all easy to locate lesions to the brain or spinal cord, and therefore the phrase acute neurological decompression illness should be used instead, (Francis and Smith 1990) Their practice is followed here.

Decompression illness is a syndrome which occurs if too much inert gas accumulates in tissues and comes out of solution on subsequent decompression, or ruptures through the walls of gas-filled spaces, to damage tissues by its presence as bubbles.

2.2 Inert gas exchange

When the partial pressure of inert gas in the lungs is altered by changing the composition or pressure of the breathing mixture, the inert gas content of body tissues also change. Widely held views of how these occur (e.g Munson & Bowers 1967, Eger 1974, 1982) are summarised in Figure 2.0 which shows the lung processing blood that then passes to various tissues.

Equilibration of inert gas between alveolar gas and blood in the pulmonary capillary is believed to be very rapid, (of the order of 1/40th of a second). As the transit time of blood in the pulmonary capillary is about one second at rest and is very rarely less than one-tenth of a second, even in very heavy exercise, it is supposed that end-capillary blood and alveolar gas are in perfect inert-gas equilibrium, i.e:

$$PAN_2 = PaN_2,$$

(NB please see page 5 for the full list of symbols and abbreviations used in this thesis).

Model of perfusion to body compartments of varying size

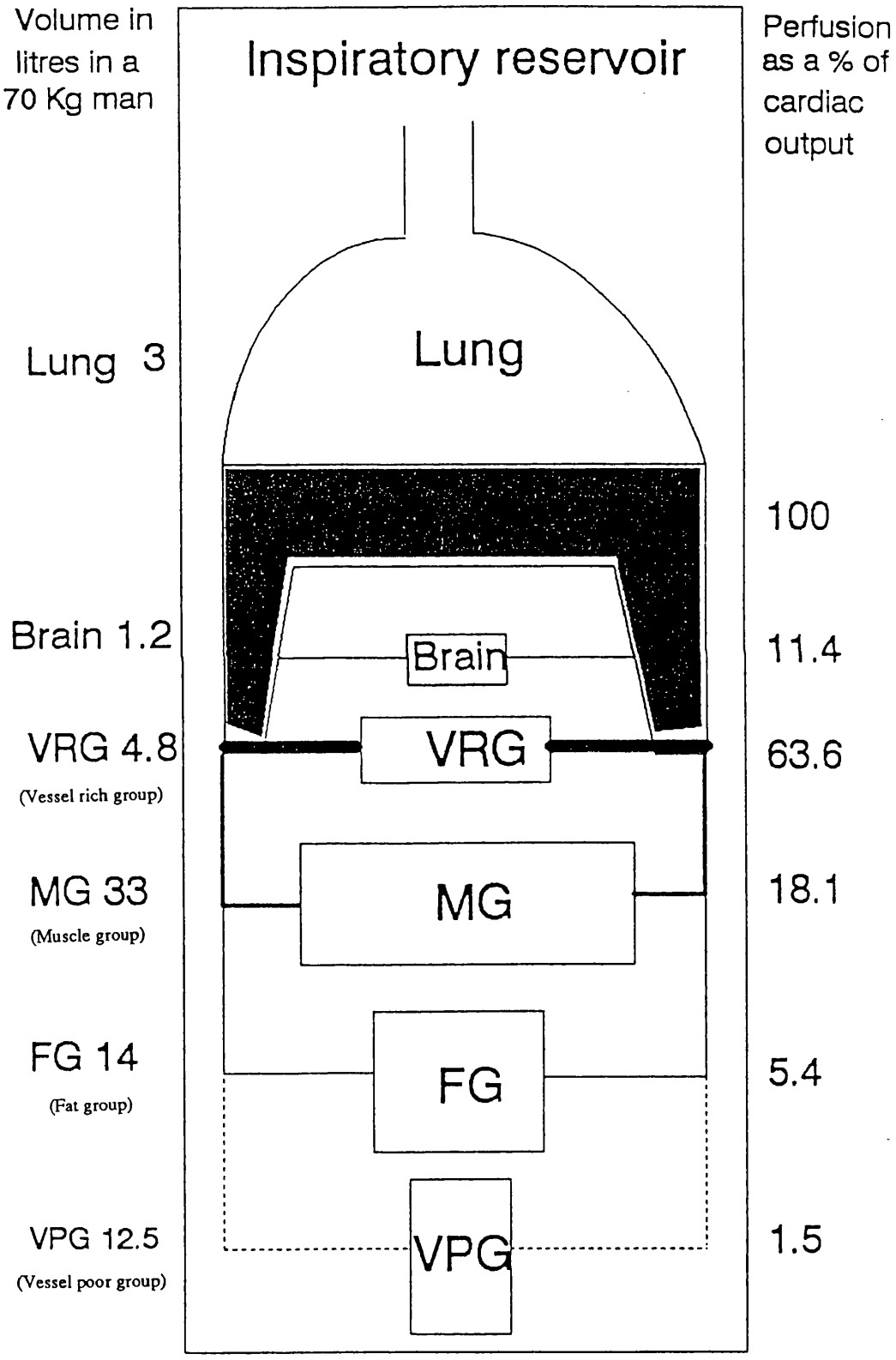


Figure 2.0

The inert gas tension of pulmonary end-capillary blood may be modified by the latter mixing with anatomical shunt blood, but this effect is only significant in the presence of substantial shunts. The mixed arterial blood, with its near-alveolar inert gas tension, then travels to the various tissues, with transit delays varying from a few to many seconds.

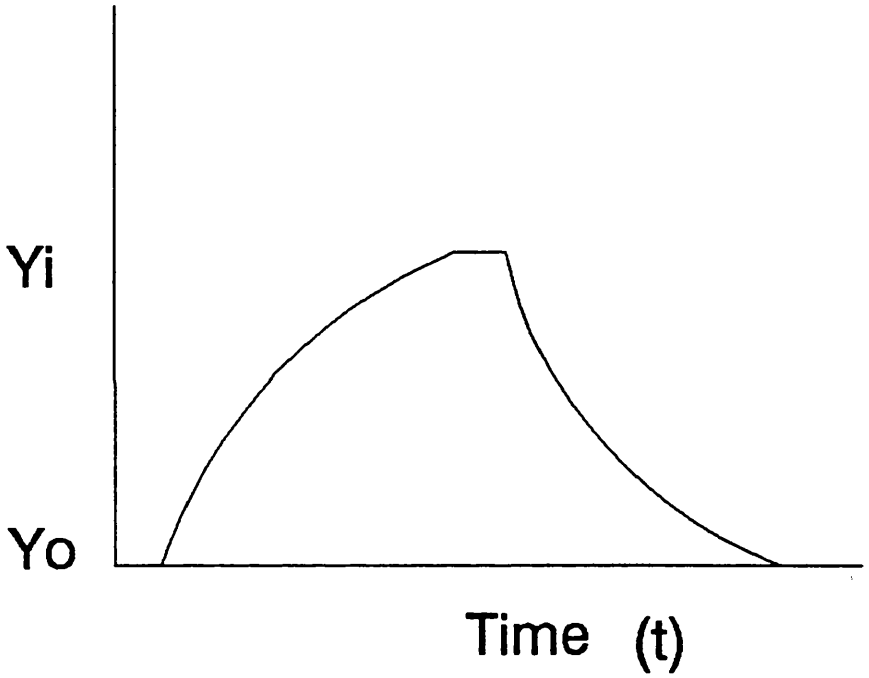
On arrival in the systemic capillary the additional inert gas diffuses into the tissue raising its inert gas content until a new equilibrium is established. This process follows an exponential course, which is thought, in most tissues to be limited by perfusion, i.e the tissue behaves as a rapidly and well-stirred compartment in which delays due to diffusion are trivial compared to those due to the comparatively slow arrival of blood in the capillary.

The time constant of this process is proportional to the volume of tissue and the solubility of the gas in the tissue, and is inversely proportional to the inflow of blood, and the solubility of the gas in the blood, (as indicated by the equation in the Figure 2.1). As the relative volumes, blood flows and solubilities of inert gas vary widely, there is a wide range of time-constants of inert-gas equilibration in the body.

Eger (1982) amongst others, has found it helpful to lump the large family of tissue time constants that exist in real life into four categories, namely the

WASH-IN and WASH-OUT
EXPONENTIAL CURVES

Changes in inert gas tension in the tissues over time



Wash-in	Wash-out
$Y=Yi\ (1-e^{-kt})$	$Y=Yo\ (e^{-kt})$

K = reciprocal of the time constant

$$\text{Time constant} = \frac{\text{Volume of tissue x solubility of inert gas in tissue}}{\text{Blood flow to tissue x solubility of inert gas in blood}}$$

Figure 2.1

vessel rich group, muscle, fat, and the vessel poor group. Representative time-constants of nitrogen exchange for the four groups are a few minutes, less than an hour, several hours and nearly a day; respectively.

The rate at which the venous blood becomes saturated with the inert gas will depend on the speed of saturation of the above four groups, but it will be some 75% saturated within the first few minutes as the vessel-rich group fill. As this occurs, the alveolar-venous difference in inert gas tension will decrease. Thus inert gas uptake by the lung will diminish as the body becomes saturated.

The rate of rise of inert gas concentration in the lungs, arterial blood, the four different tissues compartments of the body, and venous blood follows a roughly exponential time course, as shown by the general formula:

$$P_t = P_i * (1 - e^{-kt})$$

where P_t and P_i are the inert gas pressures at time t and infinate time, k is a rate constant, and t is the elapsed time. When the partial pressure of the inert gas is decreased in the lung, washout of the inert gas from the body occurs in the reverse direction to that described above. As shown by the general exponential washout formula:

$$P_t = P_0 * (e^{-kt})$$

The rate constants may not be the same for the two processes, especially if bubbles form.

2.3 Decompression

When an animal is decompressed it is exposed to several risks. Firstly, those gas-containing spaces that fail to empty fast enough may be distended by the local build-up of relative pressure (e.g sinus barotrauma of decompression) or may burst (e.g the bursting of fish swim bladders or mammalian lungs). Secondly, alveolar gas pressures may fall leading to precipitous hypoxia, compounded by hypocapnic constriction of cerebral vessels. Thirdly, dissolved gas which has insufficient time to escape through respiratory surfaces by diffusion, may come out of solution in the form of bubbles, deforming tissues and obstructing vessels. This evolution of bubbles is one cause of acute decompression illness

Bubbles of inert gas in blood and tissues give rise to a wide variety of symptoms, which depend upon their size and location. Unconsciousness and death can result from bubbles in the brain, dyspnoea from bubbles in the pulmonary artery, paralysis from bubbles in the spinal cord, muscle and joint pains from bubbles in the ligaments, fascia, periosteum, muscle and nerve sheaths, and itching and rashes from

bubbles in skin. The symptoms may appear within a few minutes of decompression or be delayed for several hours.

2.4 Diving, caisson work and flying

For many centuries men and women have dived by breath-holding to harvest pearls, shellfish, sponges and lost valuables. Such dives are necessarily brief, but if they are repeated rapidly enough they can lead to the accumulation of sufficient nitrogen to form bubbles on ascents at the end of the later dives. This was first shown by Paulev (1965), who personally made 60 breath-hold dives to 20 meters in 5 hours and developed what appeared to be decompression sickness, which was relieved by recompression therapy. Rahn (1965) showed that the radiographs of joints of the asymptomatic diving ama of Japan revealed that some of them had punctate areas of dissolution at articular surfaces. These lesions were early signs of dysbaric osteonecrosis, which is one form of chronic bone decompression illness.

The risk of decompression illness is greatly increased by apparatus which allows people to stay at high pressures for longer. Such equipment has been used in salvage operations since Renaissance times. For example, Von Treileben was using a diving bell in about 1640. In 1690 Halley devised a system for dropping lead-weighted barrels containing fresh air, alongside submerged bells. In the 1790's with the

invention of the force pump by Smeaton it became possible to renew bell air continuously. Not long after, Augustus Siebe a German coppersmith working in London fused a copper helmet to a fabric jacket. Uncontrolled amounts of air were pumped into the helmet and escaped via the open waist of the jacket (1819). In 1837 he designed a full suit which was so successful that, in essence, it remains unchanged today. Such suits were generally supplied with air via a hose-pipe, from the surface. This limited the divers movements greatly.

Self-contained underwater breathing apparatus (SCUBA), in which the diver carried a supply of compressed gas with him, was tried out by many people. The invention of the modern form is generally credited to Emile Gagnon and Jacques Cousteau (1943). The endurance of the gas supply of these sets is inversely proportional to depth, but sufficient to allow substantial amounts of nitrogen to accumulate in tissues

In the 1840's compressed air was used to pressurise subterranean and underwater sites to reduce flooding, thus enabling mining and tunnelling in porous soils, and the laying of foundations for bridges. The pressurised sites were known as **caissons**. Many more people experience hyperbaric atmospheres and decompression in these structures, which are widely used today, than in the sea.

Nowadays, almost all sports diving is done on SCUBA systems, commercial divers quite often use surface supply lines or umbilical pipes from submerged static stores of compressed gas, and military divers commonly employ sophisticated SCUBA devices. All of these inventions allow divers to stay down long enough to accumulate large quantities of dissolved inert gas

It is also possible for decompression illness to occur in aviators decompressed to altitudes above 18,000 ft, (Fryer 1969)

2.5 Clinical syndromes

Many divers and caisson workers must have suffered from decompression illness in early times but it was not recognised as a syndrome until Triger (1841) summarised the symptoms he found in a group of caisson workers. At that time he attributed the syndrome to hyperbaric exposure. Thirteen years later, Pol and Watelle (1854) realised that the symptoms of decompression sickness, as it was then called, only occurred on leaving the caissons.

In 1878 Paul Bert recorded similar syndromes in divers and observed that the illness was precipitated by decompression. By then he knew that bubbles were formed on decompression, and that they consisted mainly of nitrogen.

Decompression illness gives rise to a very wide range of symptoms. In the past, these were divided into two types. Type I was mild. It was limited to involvement of skin, lymphatic vessels and joints. Type II was serious, and could involve the brain, spinal cord, vestibular system (the 'staggers') or the pulmonary circulation (the 'chokes'). Nowadays, it is appreciated that Type I can progress to Type II, and labelling it as Type I can give a misleading sense of security.

Cutaneous manifestations are common. They usually present as transient multifocal pruritus after dives in water or in hyperbaric chambers. It is due to solution of blood-borne gas and direct surface absorption of gas, into the sweat glands, hair follicles and sebaceous glands, with resultant local bubble formation upon decompression. This can also occur in subjects under isobaric conditions (Lambertsen et al 1975), if they are in gaseous environments when one inert gas is exchanged for another. Under these circumstances, (isobaric counter diffusion) the novel gas enters the skin more quickly than the old one leaves. This may lead to supersaturation and bubble formation in the skin. Vestibular symptoms also occur with this unusual condition. Patchy pruritus or tender weal-like lesions with central cyanosis may also be caused by intradermal capillary or venule blockade

by bubbles, with local production of bradykinin. Lymphatic obstruction in the skin (peau d'orange) can be found adjacent to painful joints.

Joint pains are also common, especially in caisson workers. The syndrome was frequent in labourers working on the Brooklyn Bridge. At that time a dance known as 'the Bend' was fashionable in New York, so the disabled workers were described as having the 'bends'. This term quickly extended to the similar maladies of divers, and has remained in use ever since. Pain-only "bends" accounted for 70% of the symptoms of decompression illness in a study by Kidd and Elliott 1975. They examined 250 cases that had resulted from a wide variety of pressure-time exposures. Unlike the arthritis of the inflammatory joint diseases, arthritis of decompression is accompanied by little warmth, erythema or swelling. This may be because only a few bubbles need form, in the non-compliant but well innervated tissue in and around the involved joint, to initiate the arthritic pain, which results from the physical deformation of nerve endings. The shoulders and elbows are the common sites of pain in most divers, while in saturation divers and tunnel workers the hips and knees are more frequently affected.

In another, serious, form of decompression illness known as 'the chokes', symptoms include substernal discomfort, coughing and dyspnoea. This can progress

to respiratory failure and death. It is attributed to overwhelming obstruction of pulmonary vessels by bubbles, causing a rise in pulmonary artery and right ventricular pressures and a fall in cardiac output and arterial PO_2.

The most serious form of decompression illness affects the brain and spinal cord. The lesions can occur anywhere and be multifocal. Common early symptoms are dizziness, confusion, disorientation, sensory impairment e.g paraesthesia or hyperaesthesia, motor impairment eg paresis or paralyses, autonomic impairment causing disturbances of bladder, bowel and sexual function, and labyrinthine disturbance ('the staggers') with vertigo, nystagmus, nausea and vomiting. The spinal cord is more often involved than the brain. Spinal lesions generally affect the thoracic, upper lumber, and lower cervical cord. Typically they take several minutes to many hours to develop. However, it is very difficult to demonstrate the sites of lesions ante-mortem, and it is wiser to describe the syndrome by its signs and symptoms without presuming mechanisms or sites.

The time scale is still important. It has been used to distinguish the many manifestations of decompression sickness from those of **decompression barotrauma**. The latter results from the rupture of gas-containing viscera such as the gut, sinuses and lung, when gas trapped within can not escape to the

exterior via the normal route. Thus compressed gas trapped in a sinus, which collapses mucosal vessels, can erupt breaking into intracranial spaces or systemic veins. Similarly gas trapped within the alveoli may rupture into pulmonary vessels, interstitial tissues, pleural spaces or mediastinal planes. Pulmonary venous gas emboli will be taken to the cerebral circulation with severe consequences. These effects generally appear within a **few minutes** of decompression. However, as mentioned earlier, nowadays it is appreciated that silent (i,e subclinical) gas emboli arriving in the vessels of a supersaturated tissue, may later grow to a clinically obvious size in otherwise safe decompressions.

2.6 Mechanisms

By the end of the 17th Century, it was already clear that gases existed, that they dissolved in body fluids, that they were transferred to and from blood by the lung, and that if the pressure about such liquids was reduced the dissolved gas appeared as bubbles. By this time, diving was a common activity. However, the existence of inert gases was unsuspected, so the illnesses produced by diving were unremarked or not understood. When people dive, the surrounding water pressure compresses their compliant chests, raising the alveolar pressure within to ambient levels. As a result, alveolar nitrogen dissolves in pulmonary capillary blood and subsequently all other body tissues. As Boyle (1670) had already

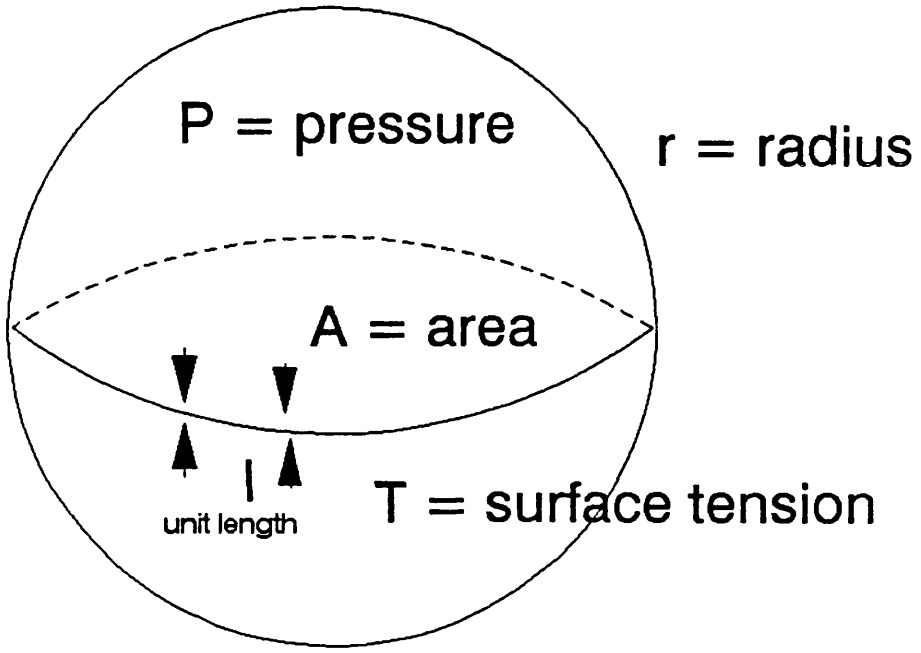
noted, but not in divers, if the ambient pressure dropped too quickly, the dissolved nitrogen came out of solution, forming bubbles in blood and tissues. This is the essential, but as then unsuspected, nature of decompression illness. It is a disease that hinges on the physical properties of bubbles.

The nature of bubbles

Gases dissolve in holes in liquids. Water is a highly organised liquid, its molecules held tightly together by hydrogen bonding. As a result most gases are poorly soluble in water. Organic solvents and lipids are more loosely structured and consequently dissolve more gas. Given time for equilibration to occur, the volumes of gases dissolved in a given liquid are proportional to their partial pressures in the gaseous phase.

At the interface between a pure gas and a pure liquid, the liquid molecules are drawn together by the (gravitational) attraction of the bulk of the liquid phase. This force minimises the interface. Thus under weightless conditions bubbles of gas in liquid, and droplets of liquids in gas are spherical. The force per unit length of a segment of the interface is the interfacial (or surface) tension. As Figure 2.2 shows, this tension is inversely proportional to the radius of curvature of the surface, (Laplace's Law). This implies that minute bubbles are very hard to create and will collapse with great ease. For this

Laplace's Law



At equilibrium (i.e. at a stable volume)
separating force = binding force

$$PA = 2\pi rT$$

$$P\pi r^2 = 2\pi rT$$

$$P = \frac{2T}{r}$$

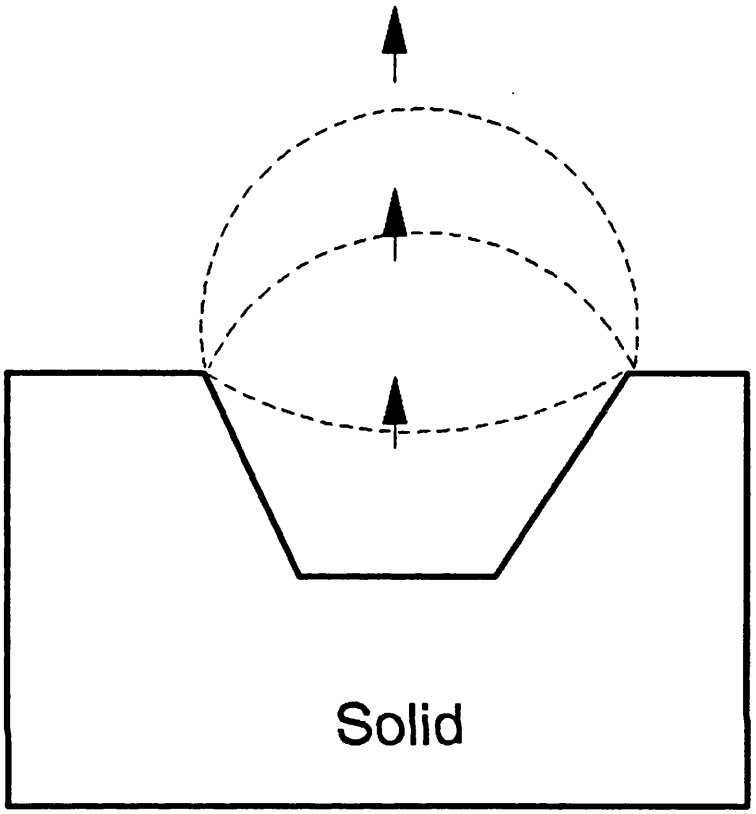
Figure 2.2

reason it is supposed that when the molecules of dissolved gases in super-saturated liquids or solids come out of solution they are much more likely to migrate to pre-existing bubble nuclei, than to form bubbles de novo.

The evidence in favour of this view comes in part from studies of the tensile strength of water. Everyday water drawn up in a column breaks under its own weight when the column is about 30 ft tall. However if the water is compressed to many atmospheres beforehand, it can be drawn up to a height of several hundred feet before it breaks. It is supposed that prior compression crushes pre-existing bubble nuclei. Experiments with transparent shrimps (Daniels et al 1984) have shown similar phenomena in living tissues, so it is supposed that there are many bubble nuclei within us under normal conditions. The very high forces that exist at tightly curved surfaces can contribute to the formation and preservation of bubble nuclei if they are in clefts (Harvey 1944), as shown in Figure 2.3.

When bubbles form in impure liquids, such as biological fluids, their structures are much more complex. Almost all biochemical molecules are amphipathic, that is they have some parts which are polar and prefer to be in water, and other parts which are non-polar and prefer to be out of water. These molecules are attracted to surfaces where they arrange

A crevice nucleus in which a pocket of gas is stabilized in a crack in a hydrophobic solid



The liquid does not advance into the crevice, because the crevice wall is not easily wetted, and a concave gas-liquid interface develops. By Laplace's law the pressure in the bubble is less than the ambient pressure and the gas is stabilized rather than dissolved by surface tension.

During decompression the gas-liquid interface expands from the crevice and its radius decreases, while the pressure due to surface tension increases. This pressure attaints its maximum value when the interface is hemispherical. Further expansion causes the radius to increase and the pressure due to surface tension to fall and a bubble is formed.

Figure 2.3

themselves with the hydrophilic parts directed into the aqueous phase, and the hydrophobic or lipophilic part directed into the non-aqueous (lipid or gaseous) phase. This accumulation of amphipathic molecules gives the bubble a skin (Fox 1954), and often deforms the skin's components. The surface forces and possibly also the deformed molecules also attract white cells and platelets to the interface and activate them (Philip 1972). The bubble has become an inflammatory focus as well as an obstruction.

Likely sites of bubble formation

There are many puzzling features about decompression illness, especially where do bubbles form, and why do they form where they do ? It is helpful, in thinking about this, to consider first the body of a diver who is fully saturated at some high pressure, e.g 6 atmospheres. Let him be breathing air. The pressure in his lungs will be the same as in the water surrounding his chest, i.e 6 atmospheres or 4560 mm Hg. However 47 of these mm Hg will be water vapour and about another 40 will be CO_2, The remainder (4473 mm Hg) will be divided between oxygen and nitrogen. The nitrogen pressure will be close to that in moist ambient air i.e 3567 mm Hg. Arterial blood will have transmitted this tension to all tissues, and over a day or more, tissue tensions will have risen to the same value, i.e the diver is 'saturated' with nitrogen at the depth equivalent to 6 atmospheres.

On rapid decompression the nitrogen molecules will not be able to escape into venous blood and diffuse out through the lungs fast enough to keep pace with the fall in pressure externally. At some critical stage they will accumulate as bubbles. In principle the bubbles would be expected to form in those tissues with the highest residual PN_2 i.e those tissues with high gas solubilities and low blood flows, the so-called slow compartments of the body. However several other factors influence this. Macroscopic bubbles probably develop preferentially by expanding pre-existing gas nuclei. They also form where local hydrostatic pressures are lowest, especially at sites of tribonucleation and cavitation (Ikels 1970). So, patterns of bubble formation are complex even in a saturated diver.

In a diver or caisson worker who has **not** been under pressure long enough for all compartments of the body to become fully saturated, there will be considerable variations in nitrogen tension between tissues. This will bias the distribution of bubble formation towards the slowest of the compartments that are already fully saturated. Concepts of bubble formation are discussed in a little more detail below, and again in the chapter on mathematical modelling.

The formation of bubbles in systemic arterial blood

Blood leaving pulmonary capillaries is completely equilibrated with the inert gas in the lung, and is at a pressure very close to the hydrostatic pressure surrounding the chest. Therefore it has no tendency to form bubbles. As it passes towards systemic tissues several things may happen to alter this. Firstly, it may mix with systemic venous blood with a higher nitrogen tension, that is passing through pulmonary or intracardiac shunts. This will increase its liability to bubble. In the extreme, the venous blood may have already formed bubbles, typically passing through a patent foramen ovale, causing paradoxical embolisation of the systemic arterial tree (Wilmshurst et al 1989). Secondly, on entering the left ventricle, the fluid pressure of the blood will be raised to systemic arterial levels, opposing bubble formation. Thirdly, blood streaming over minor irregularities on valve leaflets or arterial walls may cavitate or tribonucleate (Hennessy 1989). Fourthly, during the several to many seconds in transit from the pulmonary veins to the systemic capillaries, ambient pressure, and so absolute systemic arterial pressure, may have dropped sufficiently for unaided bubble formation to occur. Pressure changes of this magnitude are rare in diving but common in submarine escape, (Ornhagen 1988).

Many animal studies (e.g Lynch et al 1985) have shown that bubbles were only seen in arteries after their appearance in veins. Several studies using the

Doppler ultrasonic probe have confirmed this (e.g Eatock and Nishi 1987). Thus it is supposed that bubbles rarely form in arterial blood, except in very rapid decompressions. The frequency of paradoxical embolism, and the role of the patent foramen ovale, are controversial, but relevant to this thesis. Wilmshurst et al (1989) have argued that patent foramen ovale can be detected in a quarter of the healthy population but are found in some 80% of divers presenting with symptoms of arterial gas embolism. One explanation for this is that paradoxical embolism is responsible for 80% of such incidents. Another is that diving loosens potentially patent foramina, but the clinical pictures are caused by orthodox emboli from ruptured lungs. If the first explanation is true it opens up the possibility of paradoxical transits of silent bubbles from venous blood to supersaturated tissues, producing paradoxical neurological decompression illness.

Arterial gas embolism is an attractively simple explanation for the clinical manifestations of neurological decompression illness, but there are a number of its features that this mechanism fails to explain. Arterial emboli should go to areas of the nervous system with the greatest blood flow. The brain, which weighs some 1300 gm, has an 80% greater blood flow than the spinal cord, which only weighs 40 gm. Also, the grey matter has a greater blood supply than the white matter. But the syndrome affects white

matter more than grey matter, and the cord more than the brain. Also, the histology of the spinal lesions is not typical of arterial embolism.

Mechanism of autochthonous bubble formation

For many years it was supposed that neurological decompression illness was primarily a vascular problem, albeit related more to veins than arteries. Recently that view has been challenged successfully by Francis et al (1990). Using the canine model of spinal decompression sickness developed previously by Hallenbeck et al (1976, 1978) and then Leitch et al (1984,a,b,c) Francis and his colleagues clearly demonstrated that many bubbles form at the concentric aqueous-lipid interfaces of the myelin sheaths, causing them to fragment like shattered onion rings (Fig 2.4). This so called 'autochthonous' bubble formation is now believed to be a contributory cause of neurological syndromes. The extent to which it occurs in other organs is insufficiently studied, but it is commonly seen in adipose tissue, and is clearly a function of the high gas-dissolving power of lipids and the presence of lipid-aqueous interfaces.

Cerebral symptoms are seen more often in aviators and divers who have been decompressed explosively. It is conceivable that bubbles occur as frequently in the brain as in the cord, but are generally silent, due to the greater neuronal redundancy of the brain. There are precedents for this point of view. For

FORMATION OF BUBBLES AT THE CONCENTRIC AQUEOUS-LIPID INTERFACES OF MYELIN SHEATHS

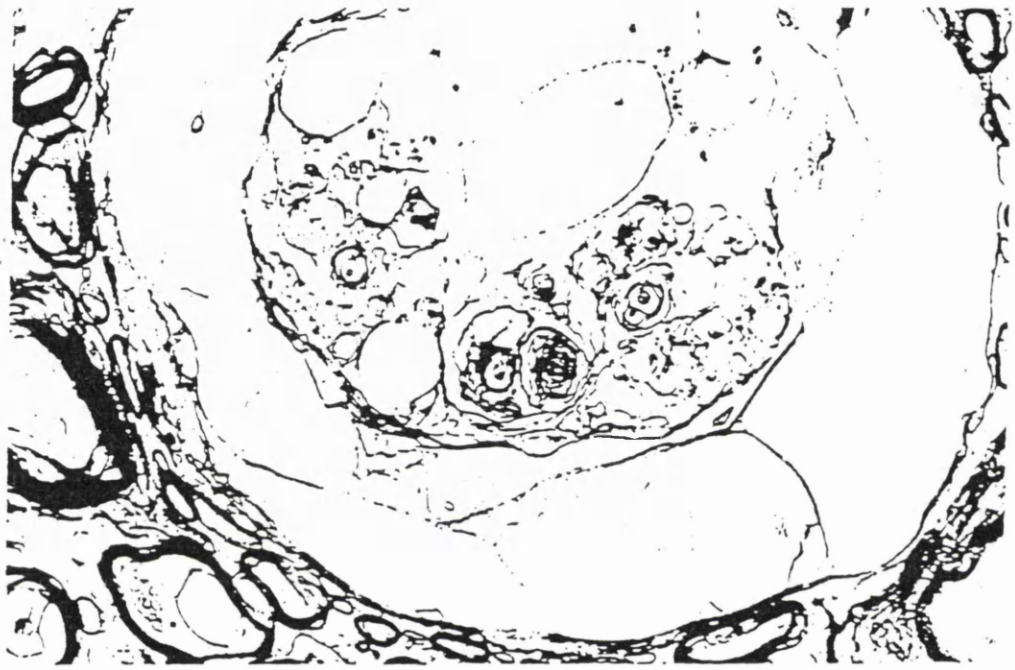


Figure 2.4 Transmission Electron Micrograph of a Non-Staining, Space-Occupying Lesion (x1700, Uranyl Acetate and Lead Citrate)

(reproduction from Francis TJR. (1990). The role of Autochthonous bubbles in acute spinal cord decompression sickness. Ph.D. thesis. University of London.)

example, it is the cerebral rather than the spinal lesions that escape clinical detection in multiple sclerosis. Recently there has been alarming support for this concept from the retinal studies of Polkinghorne 1988, the post-mortem studies of Calder (1986, 1989) and the cerebral isotope scans of Adkisson (1988)

Mechanism of venous bubble formation

Venous blood is fully equilibrated with the inert gas dissolved in the tissues it leaves. The highest PN_2 will be found in a well-saturated tissue with a long time constant. Venous blood leaving this tissue will therefore have the greatest potential to bubble. As this blood mixes with that from other less saturated tissues its PN_2 will fall, so the risk of finding a high nitrogen tension decreases as the venae cavae are approached. But during decompression the inert gas pressure in the alveoli may fall quicker than in the venous blood leaving these tissues, thus increasing the possibility of bubble formation in supersaturated venous blood.

Venous infarction has been thought to account for the predominance of spinal problems in neurological decompression illness. Blood drains from the spinal cord via the epidural vertebral venous plexus, which is a low pressure, valveless, venous lake. Blood flow in this lake is slow and easily hindered by, for example, a slight rise in vena caval pressure.

Bubbles are known to accumulate in the epidural lake. Whether they arise de novo or have come from other tissues which drain into this plexus is not clear. Due to the slow flow in the plexus, bubbles tend to remain for some time. This allows more gas to diffuse into them, oddly leading, it is argued, to venous occlusion and infarction of the cord.

This hypothesis led Hallenbeck and his co-workers (1975, 1976, & 1978) to complete a number of experiments which demonstrated that bubbles did collect in the epidural vertebral venous plexus and that they activated the clotting mechanism he had proposed earlier, (Hallenbeck et al 1973). These effects summate, resulting in a slowing and then a standstill of the blood in the plexus.

However, a number of facts suggest venous infarction is not the sole cause of the spinal syndromes. Large numbers of venous bubbles can be found in asymptomatic divers (Powell 1982). The histology is not typical of venous infarction, as complete obstruction of the plexus would result in a more extensive venous congestion and infarction of the cord. It would seem more likely that the impaired blood flow in these vertebral venous plexus delays diffusion of inert gas from the spinal cord, so encouraging autochthonous bubble formation.

Mechanism of pulmonary vessel obstruction

Whatever the mechanism, bubbles are frequently found in large numbers in the central veins of people who have dived, even after asymptomatic dives (Eatock & Nishi 1987). These bubbles are normally trapped in the lung, where they collapse as gas diffuses away from them into alveoli, leaving the lung unscarred. If the number of vessels involved is large dyspnea develops and respiratory failure may ensue (the 'chokes'). When there is a massive bubble load, pulmonary artery pressure rises, the microvessels expand and some bubbles pass through to the pulmonary veins, travelling on to the systemic tree, which is one form of paradoxical embolism. The rise in pulmonary artery pressure may also open a previously shut foramen ovale, allowing venous bubbles to pass through to the left atrium directly.

Bubbles activate clotting mechanisms, aggravating the pulmonary vessel obstruction. This may be opposed by local vasodilator substances and removal of cellular debris by phagocytic cells, but is made worse by the release of vasoactive amines and prostaglandins and of proteolytic enzymes and toxic oxygen species from activated white cells. Thus, the 'chokes' resembles the adult respiratory distress syndrome.

2.7 Prevention

The principle cause of decompression illness is the evolution of bubbles in fluids and tissues that have

been decompressed too rapidly. It can always be prevented by making the decompression sufficiently slow. In the case of a fully saturated diver this is very slow indeed, i.e roughly 1 to 2 ft/hr. Acceptable patterns of decompression vary with the depth-time profile of the dive. Firstly there are some dives to shallow depths for brief durations for which ascent at a normal rate is allowed. These dives are defined by the 'no stop diving curve' shown in Figure 2.5. All ascents from beyond this limit have to be slowed. Until recently, patterns of acceptable safe ascent could be derived from Diving Tables, themselves based on the outcome of many experimental and actual dives. Nowadays, small wrist-mounted computers serve the same purpose. Both resources are only as safe as the data-bases on which they ride.

2.8 Treatment

One form of serious decompression illness is the 'chokes' which is indisputably due to massive gas embolism in the lung. The other serious forms are neurological. Their true causes are not yet clear. Autochthonous bubble formation may well be common but orthodox or paradoxical arrival of silent bubbles in arterial blood, or even their direct generation in arterial blood by very rapid decompression may also play a part. These points are relevant to treatment.

The aims of treatment are to reduce the volumes of erupted gas as quickly and completely as possible, to

NO STOP DIVING CURVE

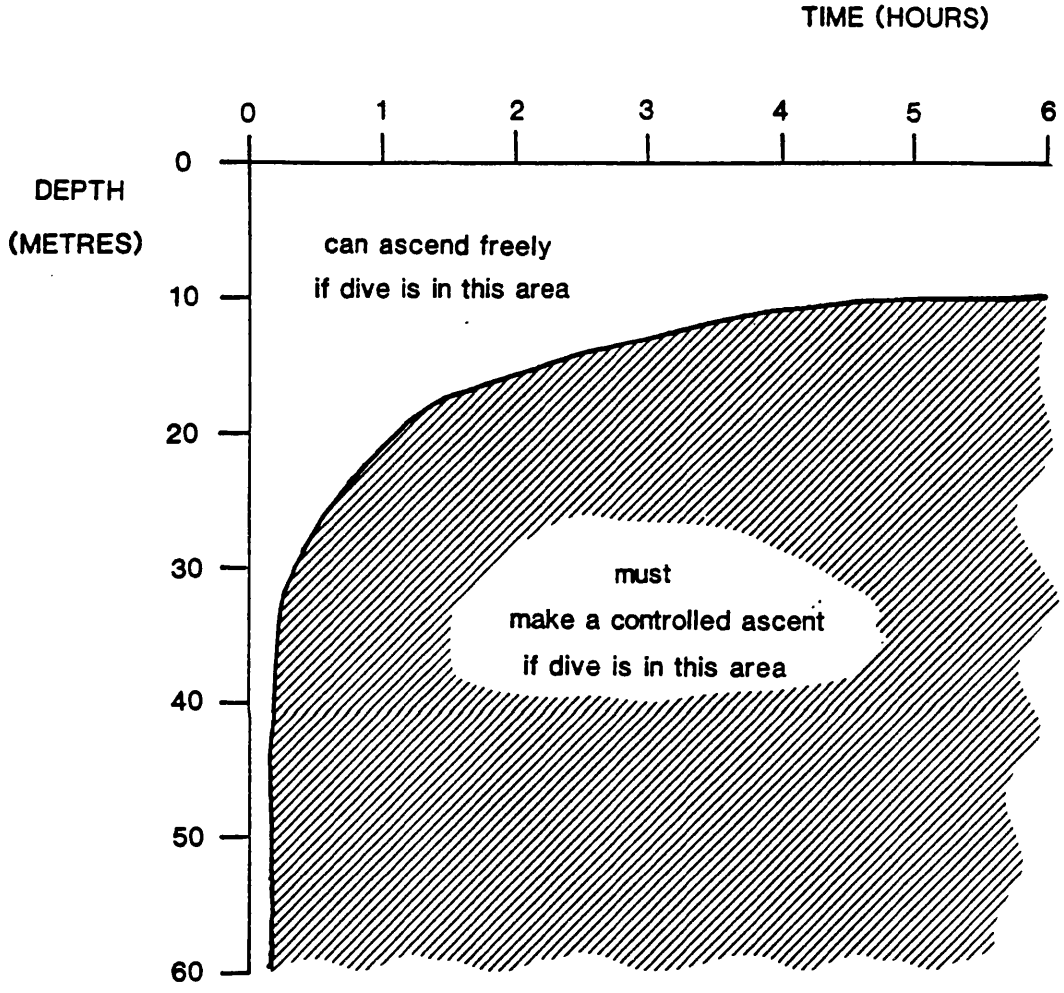


Figure 2.5

optimise oxygenation of compromised tissues, and to limit or reverse the inflammatory and disruptive damage created by the bubbles. The world-wide experience of many workers in many centres has shown that reducing bubble volume by early recompression followed by slow decompression is the only really effective therapy. Typically it takes some hours to organise, except in highly disciplined military and commercial diving operations. Some additional measures are also helpful.

Oxygen. Early administration of oxygen helps in two ways, particularly during therapeutic compression and decompression. It raises the oxygen content of arterial blood. It also accelerates excretion of inert gas by lowering alveolar and arterial inert gas tensions. However oxygen becomes toxic to the lung at partial pressures above 0.5 atmospheres, although this effect takes several hours to develop. More importantly, it becomes toxic to the central nervous tissue if its partial pressure rises above 2 atmospheres. So, oxygen is given continuously immediately it becomes available after a distressed diver surfaces, and is given in controlled amounts for selected periods during therapeutic compression and decompression, according to clear instructions on appropriate diving tables.

Other gases. It is also possible to accelerate inert gas excretion during therapeutic recompression by

switching the diluent from oxygen in the inspirate to a less soluble inert gas. This has to be done with care as it can aggravate the problems of subsequent decompression if provided for too long a time. Again, there are well-established tables for such routines.

Recompression As explained earlier, early recompression is the corner-stone of current therapy. Commonly distressed divers arriving at the surface are recompressed to a maximum of 7 atmospheres in an air-filled chamber. This often produces immediate relief of symptoms. They are held there for an hour or so and then decompressed to sea-level pressure over the next few hours, at rates determined by symptoms. There is plenty of evidence that recompression is more effective the earlier it is given, but also that it is still beneficial if initiated several to many hours after surfacing.

Conventional drugs Heparin, in antilipaemic doses and low dose aspirin with its anti-platelets action have been used in the past, but few doctors would now prescribe either. Both are contraindicated in vestibular and neurological decompression sickness because of the risk of haemorrhage, (Palmer et al 1978). Steroids are undoubtedly effective in reducing the cerebral oedema around malignant tumours, and might mitigate decompression illness in the same way. Bove (1982) suggested the indications for steriods in decompression sickness may be different and is

directed at reducing the inflammatory nature of this disease. Proof of effectiveness is lacking, but steriods have been used in decompression sickness and some reports suggest benefit (Kizer 1981). Although it would be desirable to dilate vessels to compromised cerebral tissue, it has proved to be a difficult task, at least in treatment of the vaso-spasm which accompanies cerebral subarachnoid haemorrhage. Indeed normal areas of brain may 'steal' blood away from compromised tissue when vasodilators are used.

Perfluorocarbons Recently, there has been much interest in the use of perfluorocarbon emulsions as red cell substitutes (Denison 1989a). They also have the potential to resorb inert gas (Denison 1989b). There are encouraging signs from animal studies that they may be effective (e.g Menasche et al 1985, Spiess et al 1988, Bridgewater and Denison - personal communication), but it will be some time before they are accepted into clinical practice. If and when that occurs, it is likely that they will be given by intravenous infusion of about one litre of emulsion, as soon as possible after a disabled diver surfaces, while waiting for the organisation of recompression facilities.

2.9 Summary

When ambient pressure falls well below the partial pressure of inert gas dissolved in tissue, the inert gas may come out of solution in the form of bubbles.

The syndromes that result are known as decompression illness. They may be compounded by gas emboli arriving from sub-clinical or overt lung rupture, or via paradoxical routes that bypass the lung. There are two serious forms. In one there is massive accumulation of bubbles in the pulmonary circulation. This is known as the 'chokes'. In the other bubbles form in the tissue and/or blood vessels of nervous tissue, more commonly affecting the spinal cord than the brain. This is acute neurological decompression illness. If it affects the vestibular system it is known as the 'staggers'. The only really effective treatment for these conditions is early recompression followed by slow decompression. Oxygen is a useful first aid measure because it improves the oxygenation of compromised tissues and accelerates the excretion of inert gas, but it is not a substitute for recompression. Other drugs are also helpful but of minor value.

3 ESCAPING FROM SUBMARINES

Almost all submarines are built to a common plan. In essence they consist of a tubular pressure hull surrounded by various other structures, hidden by an outer casing (Fig 3.0). The crew live inside the air-filled pressure hull at a pressure of one atmosphere. There may be up to 200 men within. Various pressure-tight doors allow men and machinery to move in and out of the pressure hull. The doors are potential sources of inboard leaks.

When the submarine is cruising at the surface, the pressure-tight door on the floor of the conning tower is open. When the submarine dives, the crew return to the pressure hull, the hatch is closed, and the vessel descends. Some research submarines are built to dive to great depths, for example the Bathyscaph Trieste which descended to the deepest point of the ocean (36,000 ft) many years ago. Most submarines are military. They are designed to operate at lesser depths.

Figure 3.1 shows a cumulative depth/area profile of the sea. It illustrates that, on leaving a typical shoreline, the sea-bed will drop gradually to an average maximum depth of 600 ft. This part of the bed forms the Continental Shelf. It has occasional parts that are up to 1000 ft deep. At the edge of the Shelf, the sea-bed descends more deeply, towards vast flat tracts of silt, known as the Abysmal Plains, at depths of 10,000 to 20,000 ft. They are interrupted by occasional chasms

The diagram shows the tubular pressure hull of a submarine.

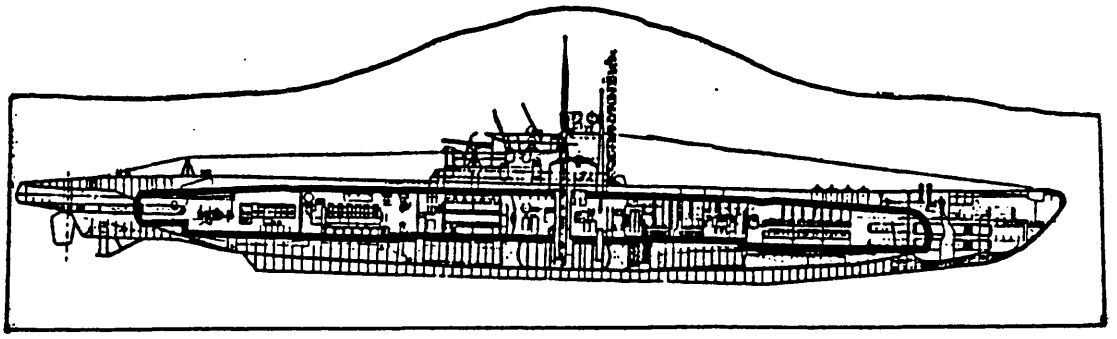


Figure 3.0

CUMULATIVE DEPTH \ AREA PROFILE OF THE SEA

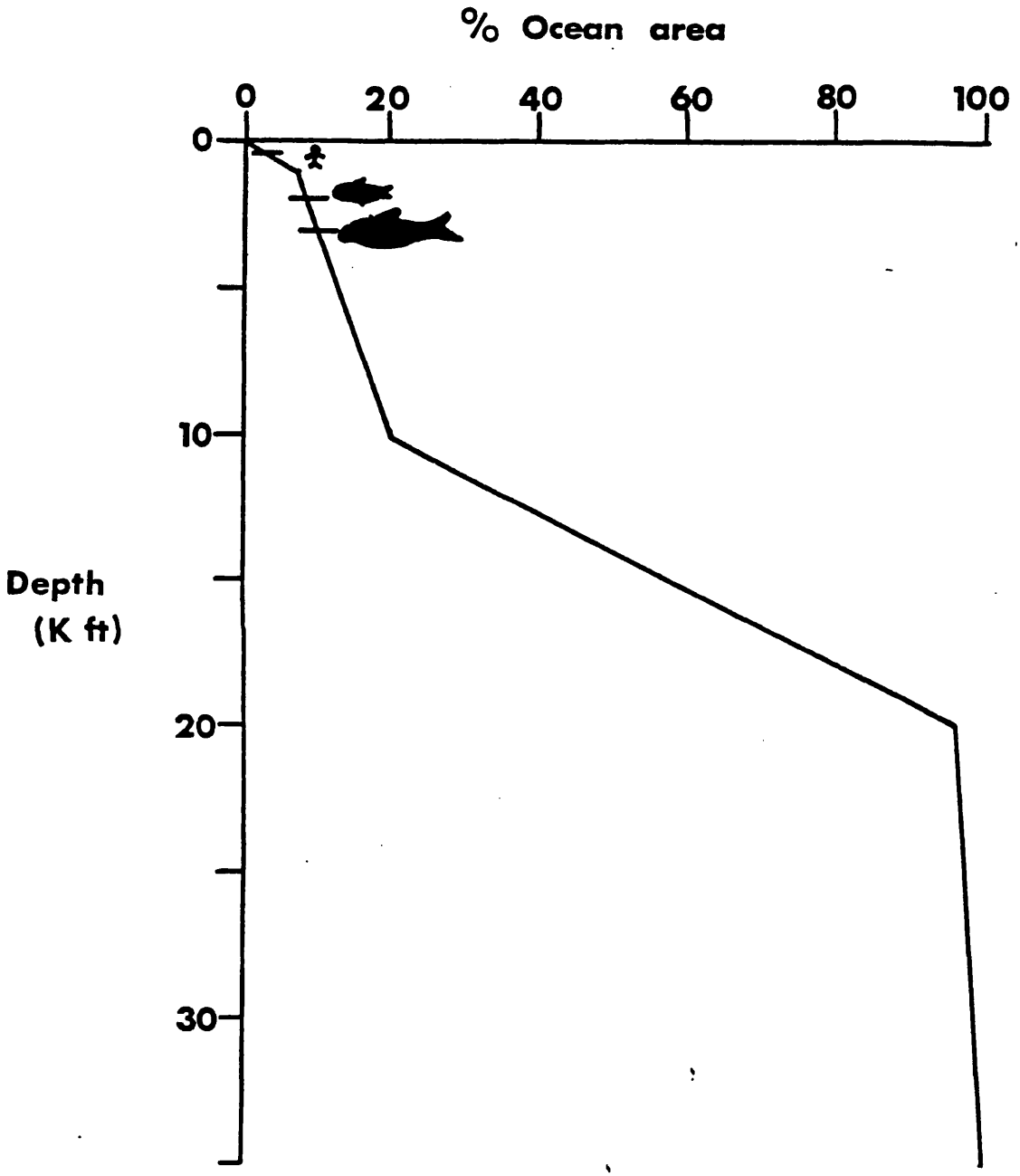


Figure 3.1

and mountain ranges. Ambient pressure increases linearly with depth, by 1 atmosphere per 33 feet or 10 metres.

Pressent day submarines, probably have operating depths of 1000 to 3000 ft. If they decend much lower, they implode. There is no hope of survival in such circumstances.

If a submarine is disabled in shallow waters, e.g by collision, an inboard leak, or a fault in its control system, it will come to rest on the sea-bed, without imploding. The submarine's Commander will prefer to wait for divers and other submarines to come alongside and attempt to lift the vessel. Failing that he would aim to transfer his crew to another submarine via a pressure tight mating ring (submarine rescue). However, this may not be possible. For example, incoming water or loss of atmospheric control may force him to evacuate the vessel before such help arrives. In this caes he has two escape options. Providing there is sufficient time in hand, his men can leave singly or in pairs through the escape tower system. This gives the men the best chance of survival. If time is too short the men can leave en masse in a 'rush escape', but the outcome of this is more problematical.

The Tower Escape System The Royal Navy hold the world record for submarine escape. It was achieved at a depth of 600 ft in a deep fiord off the coast of Norway in 1965, and again in 1987, using the tower escape system shown in Figure 3.2. The escape compartment is a vertical cylinder, the size of a telephone kiosk. It has an inwardly opening pressure-tight entrance hatch as its floor, and an outwardly opening pressure-tight exit hatch as its roof. It usually accommodates one man.

To escape, the man enters by the lower hatch, closing it below him as he does so. At this time the atmosphere in the tower is approximately that of air at one atmosphere. Outside, water is sealing the exit hatch, with a pressure of up to 30 atmospheres (1000 ft). To get out, the pressure within the escape compartment has to be raised to ambient water pressure without damaging the man. This is not a simple task. The man wears an immersion suit to protect him against the cold sea (likely temperature $4^{o}C$). The suit is fitted with a large transparent hood. The pressure in the escape compartment is raised by allowing sea water into it. If nothing else was done this would compress the air in the suit and then the air in the man's lungs, crushing his chest. As water enters the compartment the hood and lungs have to be inflated by air, or some other gas, *pari passu*. If inflation is too slow the hood and lungs collapse. If inflation is to fast the hood and lungs may burst.

TOWER ESCAPE

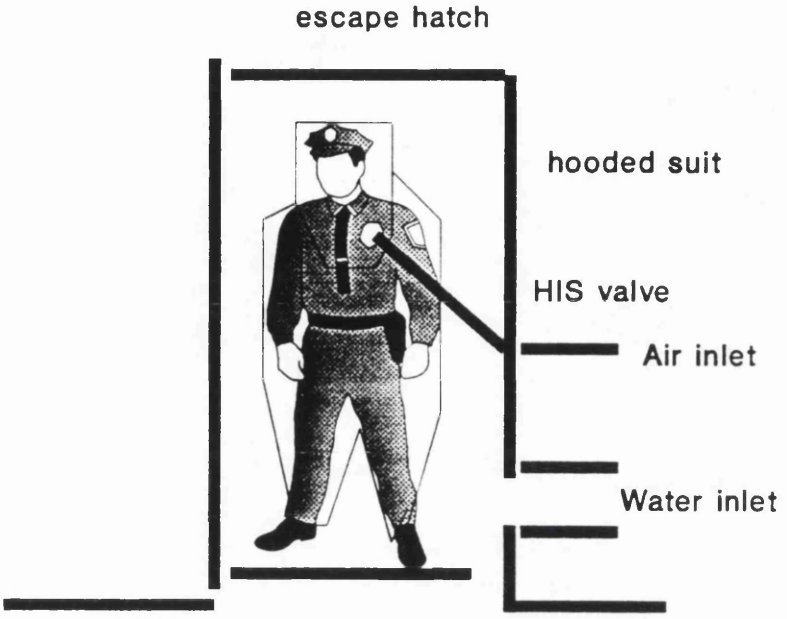


Figure 3.2

At first sight it would seem sensible to compress the man slowly to avoid these risks. However it turns out that this would expose him to high inert gas pressures for long times immediately before a necessarily rapid ascent, ensuring he would get decompressions sickness. In fact, he has to be compressed and ascend, as rapidly as possible, to avoid this. The present procedure is as follows:

The man enters the escape tower, closes the lower hatch and attaches an air hose from his hood to the wall mounted bayonet valve of the Hood Inflation System (the HIS valve). The valve is linked to a pressure demand regulator that delivers air at compartment pressure. Water is then allowed into the tower, displacing tower air back into the submarines pressure hull via a pipe and tap. There is little pressure build up at this time, as the pressure hull has a much bigger volume than the tower. When the water is at about shoulder height this tap is closed. Now the trapped air volume is small and pressure rises rapidly, doubling every 4 seconds until it equalises with that outside, and the upper hatch can be opened. This compression phase takes a maximum of about 20 seconds. There is a few seconds delay while the hatch opens. The man then undoes the bayonet fitting from the HIS valve and begins to ascend due to the buoyancy of his hood, suit and lungs. He quickly reaches a limiting velocity of 10 feet per sec-

ond and arrives at the surface sixty to ninety seconds later. Thus the whole episode, from start to finish, takes about two minutes.

The record escapes at 600 feet were conducted under ideal conditions. The escapees were brave and highly trained escape instructors. The atmosphere in the submarine was air at one atmosphere, with very little if any carbon dioxide to contaminate it. There was no panic as this was an exercise. Nevertheless there were indications that one or two men suffered neurological decompression illness on arrival at the surface. This fitted in with other observations known to the Royal Navy, and suggested that 600 feet was the limit to safe escape under ideal conditions.

In real circumstances, escapes would be made from submarines whose atmospheres were already compressed by inward leaks of water and contaminated with accumulated CO_2; by less practised men, who might well be injured or frightened and so uncoordinated, Under these circumstances, the risks of neurological decompression illness would be much higher.

The same would also be true of 'rush escapes' in which the submarine compartment is deliberately flooded with water, to open the escape hatches permanently so that men can duck into and out of them in a continuous stream, (Fig 3.3). In these circumstances the submarine

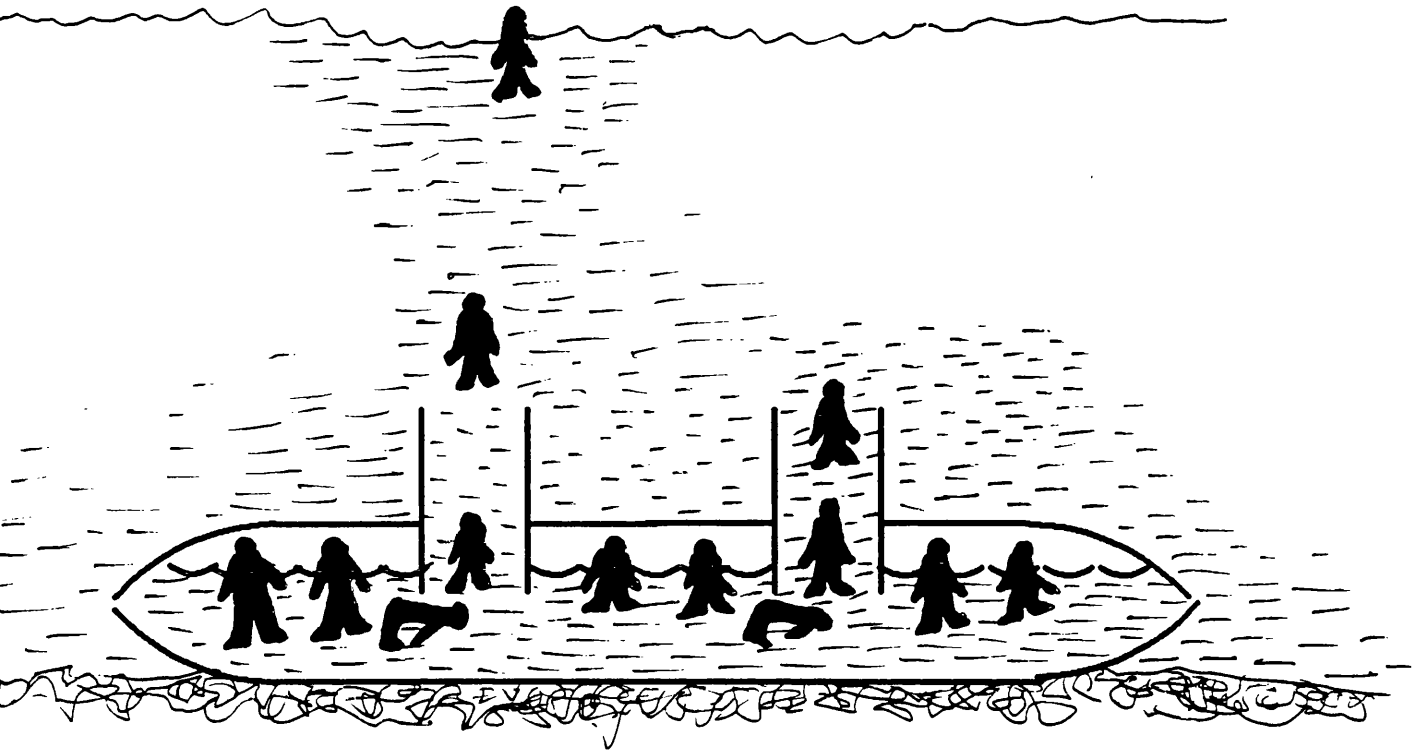


Figure 3.3 The principle of 'rush escape'. An inhabited compartment in the distressed submarine is deliberately flooded, so that hatches can be opened and the crew can escape by ducking under twill trunking to float up through the hatches to the surface. The trunking keeps the air in the compartment, so allowing submariners to breath while awaiting their turn to escape. However, the air is compressed to ambient pressure.

atmosphere is compressed to ambient pressure for the duration of the escape, with proportionate rises in its nitrogen and CO_2 pressures.

For these reasons, and also to consider the possibility of making successful escapes from greater depths, the Royal Navy were anxious to explore ways of reducing the risk of neurological decompression sickness associated with submarine escapes. Denison suggested that prior hyperventilation would constrict cerebral blood vessels and limit nitrogen accumulation during the escape. The background to this is summarised in the next chapter.

4 HYPERVENTILATION

Hyperventilation is ventilation in excess of the metabolic needs. Normally ventilation is set to dilute metabolic CO_2 production eighteen-fold so setting alveolar and arterial PCO_2 at 40 mm Hg and preserving brain pH. Excess ventilation reduces alveolar and arterial $PaCO_2$. As the carbon dioxide tensions fall the pH of nervous tissue rises, peripheral nervous tissue becomes hyperexcitable, cerebrospinal vessels constrict, and central nervous tissue becomes hypoxic and fails. In addition there are some minor circulatory changes elsewhere. The clinical complex that results is known as the hyperventilation syndrome.

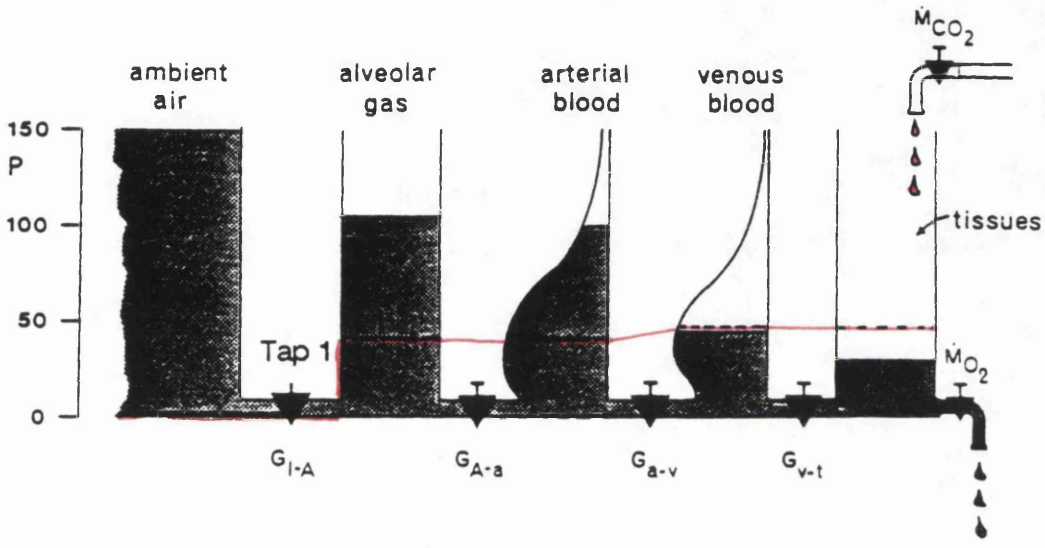
Respiratory aspects

Carbon dioxide is one product of the Krebs cycle, which occurs in mitochondria. The amount produced is determined by the rate of the cycle, and by the nature of the fuel being decomposed. When pure carbohydrate is burnt, each mole of CO_2 that forms releases sufficient electrons to reduce exactly one mole of oxygen, i.e there is a 1:1 exchange rate of oxygen for carbon dioxide in tissues. This ratio is known as the respiratory quotient and refers strictly to events within mitochondria. When pure fat is being burnt the ratio drops to 0.7. When the cycle is running on protein fragments, or on a mixed diet, the ratio is about 0.8.

The carbon dioxide diffuses into cell water, interstitial fluids, red cells and plasma, and escapes through the lung. When the volume escaping from the lung equals the volume produced in the mitochondria, the body is said to be in a respiratory steady state. In these circumstances the respiratory exchange ratio, i.e the ratio of CO_2 excretion to oxygen consumption, at the lips, equals the respiratory quotient. A mental model of this process is shown in Figure 4.0. It consists of a mitochondrial source of CO_2 pouring through a sequence of capacitors and conductors to an infinitely large sink of ambient air. The levels of CO_2 pressure in each capacitor is set by the CO_2 level in ambient air, the CO_2 flux and the sum of the resistances to CO_2 flow that lie downstream.

The principle resistance to the outflow of CO_2 is normally that from the alveolar compartment to ambient air. It is inversely proportional to alveolar ventilation. The resistance to flow from pulmonary arterial blood to the alveolar compartment is rarely large. It is determined by pulmonary capillary transit times, ventilation/perfusion inequality and the size of the anatomical shunt. The fall in PCO_2 from the arterial to venous ends of a systemic capillary is also small. It is determined by the haemoglobin content of blood and the ratio of blood flow to the flow of CO_2. Pressure drops within tissues are very small because the gas is so soluble that it diffuses easily.

MODEL OF CARBON DIOXIDE HOMEOSTASIS



PARTIAL PRESSURE OF CARBON DIOXIDE

PARTIAL PRESSURE OF OXYGEN

Figure 4.0

Because the reciprocal of alveolar ventilation, which is the major resistance to CO_2 outflow, can be varied, it is the main regulator of body CO_2 contents and tensions. Alveolar ventilation needs to be defined quite carefully, because it is a concept rather than a volume which can be easily measured. Figure 4.1 shows another mental model, of a multi-compartment lung perfused by mixed venous blood ($\dot{Q}tot$) of constant composition and ventilated by a fixed tidal volume and respiratory rate ($\dot{V}A$). Let the model belong to a body in a respiratory steady state, so the respiratory exchange ratio (R) equals the respiratory quotient (RQ). Let the anatomical dead space (V_D) take no part in CO_2 exchange. Let the molar flow of CO_2 be $\dot{M}CO_2$. Let the alveolar compartment be ventilated and perfused unevenly (as shown by tubes of varying calibre), so that CO_2 is diluted to different extents in different parts.

As the model is in a steady state the composition of each breath of mixed expirate will be the same. It will consist of a volume V_D that had the PCO_2 of ambient air, and a volume V_T- V_D that is a mixture of the different expirates from each 'alveolus'. This part will be biased toward the composition of the best ventilated compartment. Similarly the mixed pulmonary venous blood will consist of a quantity Qd coming from the anatomical shunt, and another quantity Qtot-Qd that is a mixture of blood from each alveolus. Its composition will be biased towards that of the best perfused space.

Model of a multi-compartment lung

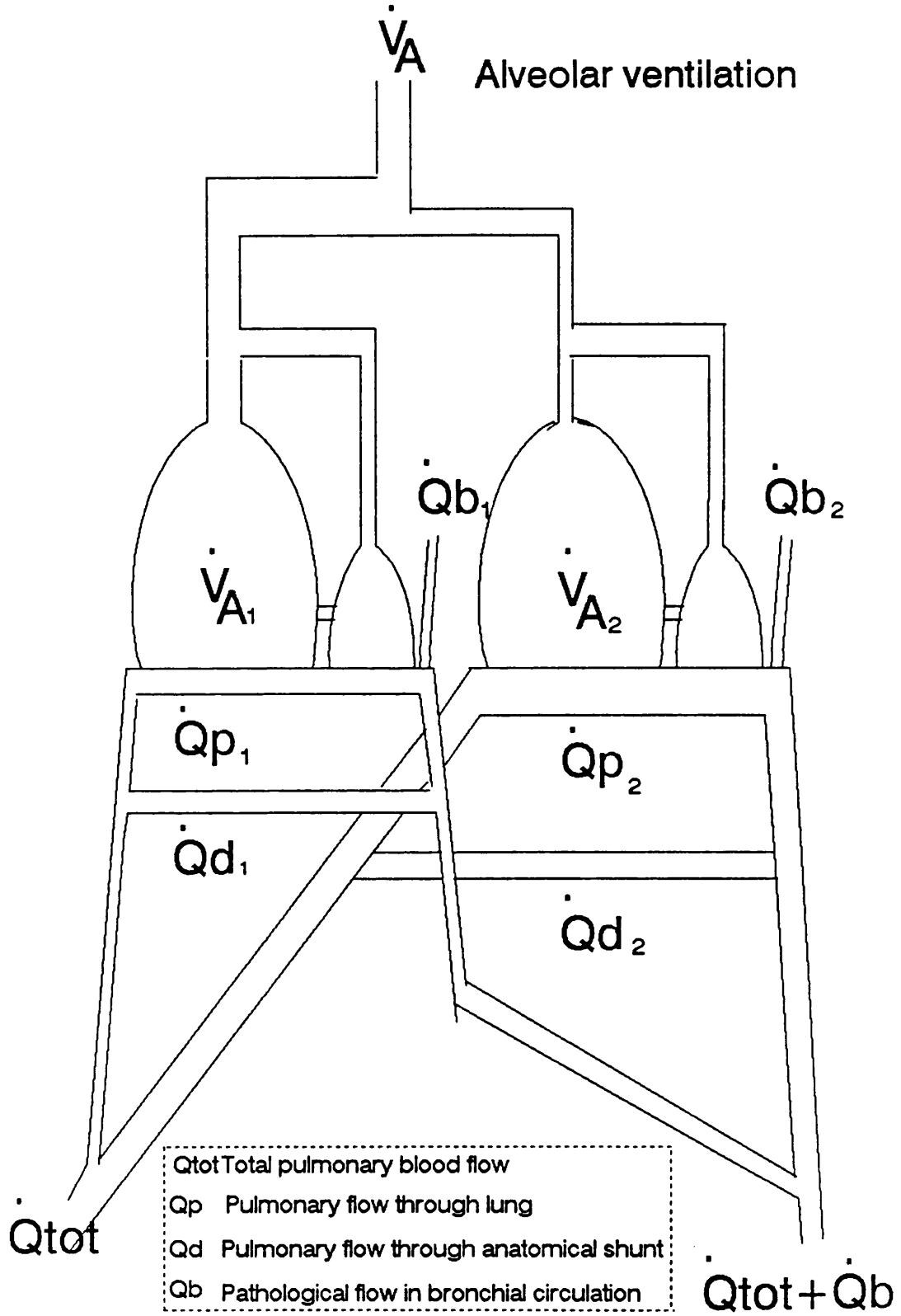


Figure 4.1

Alveolar ventilation (V_A) is that flow of gas responsible for the dilution <u>in alveoli</u> of outflowing CO_2. It is calculated by measuring $\dot{V}CO_2$ and using one of three bases to determine its dilution: end-tidal PCO_2, mixed expired CO_2 with a correction for anatomical dead space, or arterial PCO_2. Each of these will give a slightly different answer, and none of them will equal the actual flow of inspirate into alveoli. It is an 'as if' quantity. In this case it is 'as if the lung were made of a single tubular dead space and a single alveolar balloon, and the balloon was through-flushed by this quantity. The relation used to estimate it is the Alveolar Ventilation equation:

$$PACO_2 = PICO_2 + k(\dot{M}CO_2/\dot{V}_A) \text{ litres BTPS/min}$$

which can be rewritten so:

$$\dot{V}A = k\dot{M}CO_2/(PACO_2-PICO_2)$$

The drive to ventilate comes from the brain stem, which senses arterial PCO_2 and normally adjusts ventilation to maintain it at 40 mm Hg. Increasing alveolar ventilation, has the same effects as opening up the tap 1 in Figure 4.0, i.e there is a temporary increase in the outflow of CO_2 as the tensions in the other compartments fall by almost the same amount as the drop in $PACO_2$. Once this has happened R again equals RQ. However $\dot{V}CO_2$ will have risen because of the increased work of breathing, and some of the other conductances

will have altered slightly because of minor changes in systemic and pulmonary blood flow. The time constants of emptying of various body compartments vary widely. The majority of the changes are complete in about 10 minutes.

The highest ventilation that can be achieved voluntarily (maximum voluntary ventilation MVV) is time-dependant but of the order of 30 times normal resting ventilation, implying that alveolar PCO_2 could be dropped to about 1.5 mm Hg. However, this is not so, because the work of ventilating at this level raises $\dot{V}CO_2$ several fold. However if curarised and anaesthetised patients were ventilated mechanically, it might be possible to drop the CO_2 tensions this low. Such values are sometimes seen in 'brain-dead' patients on ventilators.

Hyperventilation increases the alveolar oxygen tension since, from the alveolar air equation:

$$PAO_2 = PIO_2-(PACO_2)/R$$

(R = respiratory exchange ratio).

Thus a decrease in alveolar PCO_2 will cause an increase in alveolar oxygen tension, but this usually produces little improvement in tissue oxygenation, since arterial blood is already almost fully saturated in people at sea level.

Following a short period of hyperventilation, a period of depressed breathing or apnoea occurs. A phase of periodic breathing commonly sets in, after which respiration gradually returns to normal. A $PACO_2$ of 15 mmHg and PAO_2 of 140 mmHg could be expected after vigorous hyperventilation. The apnoea that results is due solely to the low $PaCO_2$ being below the threshold to stimulate pulmonary ventilation. Over the next couple of minutes PAO_2 will fall to 30 mmHg and the $PACO_2$ will rise to say 36 mmHg. Breathing resumes because the rising $PACO_2$ and the low PO_2 sum to stimulate pulmonary ventilation.

Cardiovascular effects

Hyperventilation has a mechanical effect on the circulation, augmenting blood flow through the increased power of the thoraco-abdominal pump. It also alters the acid-base status of blood according to the Henderson-Hasselbalch Equation :

$$pH = pK + \log_{10} \{[HCO_3^-]/(0.03*PCO_2)\}$$

As crude examples, consider three subjects with a pK of 6.1 and a $[HCO_3^-]$ of 24 mmol but PCO_2 of 20, 40 and 80 mm Hg respectively. The pH of their arterial blood would be 7.7, 7.4, and 7.1. As the altered blood passes through the pulmonary and systemic vessels it causes some changes in calibre directly, but other more substantial ones are produced via central reflexes.

Kety and Schmidt 1946, found cardiac output values of 8-8.5 l/min. in subjects breathing at 25 l/min. In voluntary hyperventilation the blood pressure is rarely reduced, largely owing to this increase in cardiac output. Carbon dioxide has two effects on the peripheral arteriolar resistance, firstly by stimulating the vasomotor centre, and secondly by causing local vasodilatation in the peripheral vessels. In active hyperventilation these two effects caused by a fall in PCO_2 largely cancel each other out, and the commonest effect of voluntary hyperventilation on the blood pressure is a slight rise, due mainly to the increase in cardiac output. The skin is usually pale and moist but not invariably so.

CO_2 has an opposite effect on the pulmonary circulation. For example, Price (1960) has shown excess CO_2 in the fluid perfusing isolated lungs causes pulmonary vasoconstriction. This mechanism would have the beneficial effect of diverting blood from poorly ventilated lung (where the local CO_2 tension will be high) to areas which are better ventilated.

Hyperventilation in anaesthetised patients causes a fall in blood pressure due to depression of the vasomotor centre by the anaesthetic, and mechanical interference with cardiac filling secondary to positive pressure ventilation. (Prys-Roberts et al 1967). The

reduction in cardiac output is considerable, being of the order of 30% of the value obtained in normocapnia when the $PaCO_2$ is reduced to 20 mmHg.

Hypocapnia does not appear to alter myocardial contractility (Foex and Prys-Roberts 1975), but does reduce stroke volume. This may be due to the increase in systemic vascular resistance which also occurs.

Neurological consequences

In the peripheral nervous system hyperventilation often causes paraesthesia of the hands, face and feet. Tetany can develop, characterised by carpopedal spasm (Vernon 1909), stiffness of the face and lips, and increased excitability of motor nerves. This is due in part to a decrease in the ionised calcium concentration of blood. The total blood calcium concentration remains normal, but the alkalosis produced by hyperventilation increases the concentration of plasma protein ions, which mop up more calcium ions from the body pool.

The symptoms of hyperventilation in the central nervous system are dizziness and confusion, which can progress to loss of consciousness. Cerebral hypoxia is probably the main mechanism by which hyperventilation causes this.

Hydrogen ions cannot penetrate the blood-brain barrier but carbon dioxide molecules can. In consequence, brain pH is set, via the Henderson-Hasselbalch relationship,

by the PCO_2 of cerebral end-capillary blood. Hyperventilation lowers cerebral arterial PCO_2. The cerebral circulation responds by vasoconstriction which reduces blood flow, increases the arterio-venous difference in CO_2 content, blunts the fall in cerebral end-capillary and so cerebral PCO_2, and thus reduces the change in cerebral pH. It also widens the arteriovenous difference in oxygen content, lowers cerebral end-capillary and thus cerebral PO_2, and therefore causes cerebral hypoxia.

Many studies have shown there is a nearly linear relation between arterial PCO_2 and cerebral blood flow over the range 20 to 80 mm Hg. They have also shown that hyperventilation can lead to a loss of consciousness, which can be delayed or prevented by the simultaneous administration of oxygen. This implies that the main mechanism for unconsciousness is cerebral hypoxia, and that the brain prefers the preservation of pH to the loss of oxygen. All of these arguments also apply to the spinal cord.

The effect of carbon dioxide on the cerebral vessels was first observed in the late nineteenth century by viewing pia mater vessels directly through a window in the skull. Quantitative measurements of cerebral blood flow were made by Kety and Schmidt (1948) using a nitrous oxide technique. They confirmed earlier work that suggested cerebral blood flow varied with $PaCO_2$. They found that inhalation of 5% CO_2 caused a 50%

increase in flow, and 7% CO_2 a 100% increase. Active or passive hyperventilation caused flow to be reduced progressively until a limit was reached at about 40% of control when $PaCO_2$ was in the low 20's. Similar findings have been obtained in man in studies using Xenon 133 (Oleson et al 1971), and ultrasonic Doppler (Haugh et al 1980) as indicators of blood flow. The Doppler study covered the $PaCO_2$ range 20 to 60 mm Hg.

The response of the cerebral vessels to changes in $PaCO_2$ is very fast. Severinghaus and Lassen (1967) showed that the latent period between alterations in alveolar $PACO_2$ and the resultant changes in calibre of cerebral vessels had a time constant of 20 seconds, barely greater than the lung brain circulation time. This speed of action suggested that the vascular smooth muscle responds directly to changes in arterial PCO_2 rather than tissue or mixed venous PCO_2.

Over the wider range of 15 to 150 mmHg $PaCO_2$ the relation between cerebral blood flow and $PaCO_2$ is sigmoid (Reivich 1964). the greatest variation of flow occurs over the nearly linear segment between 25 and 80 mmHg. Above 100 mmHg and below 20 mmHg the changes in flow are considerably reduced. Over the range of maximum sensitivity the increase in blood flow with $PaCO_2$ is of the order 1.3 ml/100g/min/mmHg $PaCO_2$. Grey matter is more responsive to changes in $PaCO_2$ than white. This was shown by James et al (1969) when they studied the

changes in blood flow over the $PaCO_2$ range of 35 to 65 mmHg, grey matter flow increased at a rate of 1.4 and white matter by 0.46 ml/100g/min/mmHg $PaCO_2$.

Much evidence suggests that hyperventilation causes cerebral hypoxia. Electroencephalographic slowing occurs in man during hyperventilation. This can be reversed by hyperbaric oxygen (Reivich et al 1966). Lactate levels increase in brain tissue and cerebro-spinal fluid during hyperventilation. They can be reduced by hyperbaric oxygen (Plum 1967). Kennealy et al (1980) used intracerebral teflon catheters to measure the CO_2 and O_2 tensions of central neuronal tissue by mass spectrometry in dogs. During eucapnic ventilation cerebral tissue PO_2 was 10.4 mmHg. On changing to hypocapnic ventilation the cerebral tissue PO_2 fell to 5.1mmHg, but on giving 100% oxygen at the same flow it rose to 18 mmHg.

The hypoxia is compounded by a leftward shift of the blood's oxygen dissociation curve, due to the Bohr effect, and also perhaps by some increase in cerebral oxygen consumption in active hyperventilation. Gotoh, Meyer and Takagi (1965) measured jugular venous PaO_2 in subjects who reduced their arterial $PaCO_2$ to 20 mmHg by active hyperventilation. They attributed 75% of the fall in jugular PO_2 to the decrease in blood flow, and the remainder to the Bohr effect.

Hyperventilation has an effect on the rate of induction of anaesthesia. Doubling ventilation may half both arterial CO_2 and cerebral blood flow. The reduction in cerebral perfusion delays the rise of brain anaesthetic partial pressure towards the partial pressure in arterial blood. This opposes the tendency of the more rapid rise in alveolar anaesthetic concentration to hasten it. The balance between these effects depends on the solubility of the anaesthetic. Nitrous oxide is a poorly soluble agent and although hyperventilation causes a modest increase in alveolar concentration this effect is more than offset by the reduction of cerebral blood flow. The result is a small delay in brain partial pressure of N_2O over the first 10 minutes of induction (Eger 1974). These points are clearly relevant to the design of the experiments for the present thesis.

The effects of hyperventilation and psychomotor performance

Many people have shown that psychomotor performance begins to deteriorate when alveolar carbon dioxide tension falls below 25 mm Hg, (e.g Rahn 1946, Balke 1956). Stoddard (1967) examined six subjects, breathing air and hyperventilated at 28 l/min for 10 minutes. A simple psychomotor task was performed during this time. The experiments were done at normocapnic conditions, with the end-tidal CO_2 tensions maintained at resting levels by the addition of carbon dioxide. This was

repeated in a hypocapnic state with no added carbon dioxide, and here the end-tidal PCO_2 fell from 38 to 15 mmHg over ten minutes in an exponential fashion. Mean reaction times were calculated every half minute during all the runs. No significant difference between the control and test experiments were found in two of the subjects, but there was in the remaining four. The level at which this occurred in these four subjects ranged from end-tidal CO_2 tensions of 15 to 19 mm Hg.

Cooper (1988) studied one subject, breathing air and hyperventilated at 35 l/min for 20 minutes while performing the **mannikin** psychomotor task. Three runs were done in normocapnic conditions, here carbon dioxide was added to the fresh air flow to maintain the end-tidal PCO_2 at 38 mm Hg. The same number of runs were done at hypocapnic levels, with no added carbon dioxide, and in these runs the end-tidal PCO_2 fell to between 13 to 18 mm Hg. The response time rose from 0.6 m sec in the normocapnic runs to 1.5 m sec in the hypocapnic runs. The hypocapnic runs were associated with symptoms parasthesia and tetany.

Summary Hyperventilation constricts cerebral vessels and reduces cerebral blood flow. This causes cerebral hypoxia. It should also prolong the time constant for accumulation of inert gas in the brain and spinal cord. These effects appear within one minute and persist for

many minutes. Therefore hyperventilation has the potential to reduce cerebrospinal accumulation of nitrogen during the brief hyperbaric exposure of submarine escape.

5 NITROUS OXIDE

'Anaesthesia' is the Greek word for loss of sensation, but nowadays it is used solely to describe the state of immobility, analgesia, amnesia and lack of awareness that is produced by specific drugs, prior to invasive investigations or surgery. Local anaesthetics act on peripheral nerves and will not be discussed further. General anaesthetics are given systemically and are distributed to the nervous system as a whole. Nitrous oxide is perhaps the oldest and safest of these. Now there are many such agents, that have profound effects which appear to be similar in many ways but differ in some details. Theories of their action have developed along two lines. One supposes that anaesthesia is a unitary phenomenon, fundamentally identical for all agents. The other visualises the action of each anaesthetic varying with its composition and from site to site within the nervous system.

Unlike the pharmacology of other drug classes, structure activity relationships have little to contribute to anaesthetic theory. There is little evidence to support the notion of an anaesthetic receptor. That by itself is remarkable. The diversity of structures among anaesthetic agents suggests that there must be many different ways of producing anaesthesia. However the varying amounts of narcosis, analgesia, excitation,

depression, and convulsive activity produced by anaesthetics implies a great deal of sensitivity and complexity of response and action.

Many common anaesthetic agents are curious as drugs in that they are not metabolised. They behave as if they simply dissolve in tissue and then diffuse out of solution again. In this regard they behave exactly like inert gases, which has led to a general view of anaesthesia. There is a good correlation between anaesthetic potency and lipid solubility. It was first reported by Meyer (1899) and Overton (1901), and is used to support the hypothesis of a single hydrophobic site at which all agents act. Lipid solubility here generally means solubility in olive oil. But anaesthetic agents dissolve in various lipids to different extents, so this theory does not preclude different solubilities in parts of the nervous system with different lipid compositions, (Larson et at 1962). Neurophysiological studies which show that all nerves are affected by anaesthetic agents support the unitary concept of their action but, more recently, experiments on cellular neurophysiology suggests multi-site hypotheses. It is not possible to be precise about the site of action of anaesthetic agents, but it is certain that they are widely dissolved in cerebrospinal nervous tissue, and that nitrous oxide is typical in that respect. This is the purpose of its use in this thesis, as a gas that behaves like nitrogen, dissolving preferentially in the fat of nervous tissue. Like many other

anaesthetic agents it is metabolised to a slight degree, which appears to be unrelated to its anaesthetic properties.

History

Nitrous oxide was studied in an anonymous and impure form by the Oxford physiologist John Mayow around 1680, and again in about 1740 by Stephen Hales the vicar of Teddington who made it from a local outcrop of pyrites. It was first prepared in a reasonably pure form by Priestly in 1772. Its anaesthetic properties were noted by Humphrey Davy. He found that animals died if immersed in it for long, but they stayed alive but insensate for substantial periods if oxygen was added to the gas they breathed. Davy also measured the uptake of nitrous oxide in himself, reporting it to be 2.5 litres per min. when breathing the pure gas (Davy 1800). Soon after this Hickman used nitrous oxide to provide painless surgery on animals. The therapeutic possibilities of the gas were realized by an American surgeon, Horace Wells, in 1844 after he had had a painless extraction of one of his own teeth. Wells' first public demonstration of its use in surgery failed. Shunned by the medical establishment he later committed suicide. It was not until 1863 that Colton began to employ it extensively in dental surgery giving over 120,000 administrations.

Up to this time, the gas was stored in voluminous bags. They probably had some oxygen diffuse into them, improving its safety inadvertently. In 1868 Andrews, a professor of surgery in Chicago, compressed the gas to a liquid at 750 lbs/sq.inch in iron flasks. He also made two important observations, firstly that 21% oxygen should be added to the gas to improve its safety, and secondly that the uncompressed 'pure' gas employed in the current dental practice contained 10 to 25% impurities in the form of free nitrogen and oxygen. These remained in gaseous form on top of the liquid N_2O during compression, complicating the early part of administration.

Although Andrews could provide means of purifying nitrous oxide, and diluting it with 21% oxygen, the quality of his anaesthesia was poor because 79% N_2O is not a potent anaesthetic. This led to the idea that the more potent pure gas acted mainly by inducing hypoxia, but Paul Bert (1878) refuted this convincingly. He successfully anaesthetised animals and people with 21% oxygen in air, in a hyperbaric chamber at 2 atmospheres. However although this proved the anaesthetic power of nitrous oxide it was an impractical way of conducting surgery and was not pursued. For a while nitrous oxide was displaced from favour by the more potent but more toxic agents ether and chloroform. A period of reducing the dose of these by combining them with nitrous oxide followed together with the perfecting of devices for the simultaneous administration of

N_2O and oxygen. Nowadays the limited potency of nitrous oxide is well recognised and it is used to supplement other anaesthetic agents such as halothane, opiates and muscle relaxants.

N2O analgesia

Nitrous oxide is an example of an agent which can produce considerable analgesia in sub-anaesthetic doses. It decreases both the ability to perceive painful stimuli and also the ability or willingness of subjects to report the pain. Analgesic properties start at an inspired concentration of 15%. The relief improves with increasing concentrations of N_2O. This may reflect its weak potency and thus the wide span of sub-anesthetic doses that can be given. But it may also be due to a biased effect on the release of endorphins. These depress the release of neurotransmitter from the terminals of the excitatory neurons facilitating pain pathways in the nervous system. Morphine (or other narcotics) and naloxone (or other narcotic antagonists) act at the same sites, (Berkowitz et al 1979). Naloxone which is a specific opiate antagonist also reverses some of the analgesic effects of nitrous oxide, but has no effect on its anaesthetic properties (Berkowitz et al 1976, Smith et al 1978). It may be relevant that nitrous oxide is known to stimulate the sympathetic nervous system (Price 1970). Cyclopropane and diethyl ether share this property. All these agents have good analgesic properties in sub-anaesthetic concentrations.

The opiate receptor endorphine system may link the two effects. The stimulation of the sympathetic system may explain the low potency of nitrous oxide in relation to its lipid solubility. The minimal alveolar concentration of nitrous oxide required to prevent movement in 50% of patients subject to a noxious stimulus is 1.04 ATA.

Cerebrospinal effects

Since nitrous oxide was initially synthesized by Priestly in 1776, the transient psychotropic effects of this gas have been well described. In addition to inducing euphoria and partial anaesthesia, decrements in cognitive function evolve rapidly, with prolongation of reaction time (the time to choose correctly among several possible answers), worsening of short-term memory and digit span, and poor psychomotor coordination. These psychometric tests of perceptive, cognitive and motor function are subjective and require subject co-operation to obtain reproducibility. There are objective neurophysiological techniques for measuring central nervous function, such as P-300 event-related potentials and other types of evoked potentials on modified electroencephalograms. These are less dependent on patient cooperation but also less sensitive.

The effects of trace levels of nitrous oxide on the function of the central nervous system have shown some conflicting results in the literature. Bruce et al

(1974) suggested that trace levels of N_2O impaired psychomotor performance. They exposed 40 male students to trace concentrations of N_2O (500 ppm) and Halothane (15 ppm) in air, for 4 hours. Immediately following exposure a battery of psychomotor and psychological tests were performed. The most striking decrement in performance was elicited in the psychomotor divided attention audio-visual task. Mean reaction times increased by 0.5 sec. in the combined presence of halothane and N_2O.

On the other hand three other studies (Smith 1977, Cook 1978, Frankhuizen 1978), using similar methods to Bruce, have failed to demonstrate impairment of psychometric tasks with trace levels of N_2O alone or combined with other inhaled agents. Smith found no significant difference in responses to audio-visual reaction time tests in psychological students breathing air as compared with a mixture of 15 ppm of halothane and 500 ppm of N20. Cook, using N_2O alone, found no effect with trace (0.4%) or sub-anaesthetic (10%) levels of N_2O on digit span or the choice reaction time test. Mental impairment was not demonstrated until 20% N_2O was inspired.

Their task consisted of an auditory stimulus (fast or slow clicks) and a visual stimulus (straight or wavy line). The four possible combinations were presented every few seconds. Bruce used 100 responses for each test, and used naive (unpractised) subjects. Cook used

50 responses, and two groups of subjects, one group naive the other were practised subjects who gave consistent scores at the task. The naive group increased their digital span and decreased their reaction time on successive tests. After four to six consecutive tests a learning plateau was reached. It is also of interest to note in this paper the variability of volunteer symptoms, at 30% N_2O some showed little effect, while 2 of the 11 volunteers vomited or became disorientated and could not continue. Frankhuizen studied 24 naive male volunteers, with a complex choice reaction time test. He found no impairment of reaction when they breathed N_2O at 1,600 ppm.

There is a large body of opinion which confirms that psychometric function is impaired at inspired N_2O levels above 20%. Garfielf 1975, Cook 1978, Estrin 1988 and Fowler 1988 all demonstrated that choice reaction times are lengthened in a dose related manner above this level.

Fowler et al (1988) and Estrin et al (1988) also looked at the effects of these levels of N_2O on the neurophysiological test P-300. This is an event-related cortical potential. A microprocessor produces a tone which elicits the P-300 positive cerebral potentials that occur approximately 300 msec after the onset of the tone. The EEG signal is derived from two scalp electrodes. Both studies showed a dose-dependent reduction

of P-300 amplitudes and an increased P-300 latency. However reaction times were slowed more than the P-300 potentials.

Fowler et al (1987) examined the effects of 35% N_2O on learning ability and rehearsal strategy for a given list of words. Learning was slowed and an analysis of the recorded rehearsal protocols revealed a decrease in the overall rate of rehearsal. They also suggested that narcotized individuals can act in an organized and rational manner and are capable of following instructions, even when complex cognitive processes are involved.

Many studies have shown that N_2O produces some increase in cerebral blood flow and intracranial pressure (e.g Laitinin 1967, Sakabe 1976 and 1978, Pelligrino 1984, Todd 1987). These studies were done on man and a variety of animals. In some cases N_2O was the only anaesthetic and in others it was superimposed on steady-state anaesthesia imposed by another inhalational agent. Nitrous oxide at a concentration of 70% caused a 20 to 60% increase in cerebral blood flow. The maximum response occurred with in 15 min of the start of N_2O administration and was maintained at stable levels thereafter.

Unlike the other volatile anaesthetic agents, nitrous oxide does not attenuate the cerebral blood flow response to CO_2 (Todd 1987). In Todd's study, rabbits

anaesthetised with halothane were given N_2O under normocapnic and hypocapnic conditions. Cerebral blood flow increased from 42 to 59 ml/100gm/min during hypocapnia and from 61 to 75 ml/100gm/min during normocapnia.

Uptake of nitrous oxide

Anaesthesia is accomplished by achieving a therapeutic tension of an anaesthetic in the brain. Inhaled anaesthetics cannot be directly presented to the central nervous system, instead they must be administered through the lungs to arterial blood and thence to brain and other tissue.

The alveolar concentration of any anaesthetic results from an interplay of three factors. Namely, alveolar ventilation, uptake and inspired concentration.

Ventilation raises alveolar concentration by bringing anaesthetic into the lungs, therefore increasing ventilation will accelerate the rate of rise and speed up induction of anaesthesia. But doubling ventilation also halves both arterial CO_2 and cerebral blood flow. The reduction in cerebral perfusion delays the rise of brain anaesthetic partial pressure towards the partial pressure in arterial blood. This opposes the tendency of the more rapid rise in alveolar anaesthetic concentration to hasten it. The balance between these effects depends on the solubility of the anaesthetic. Nitrous oxide is a poorly soluble agent and although hyperventilation causes a modest increase in the rate of

rise in the alveolar concentration this effect is more than offset by the reduction of cerebral blood flow. The result is a delay in brain partial pressure of N_2O over the first 10 minutes of induction (Eger 1974).

The build up of anaesthetic in the alveoli is impaired by the rate at which pulmonary blood removes it. Three factors determine how much agent is taken up by blood. Namely, solubility, cardiac output and the anaesthetic tension difference between alveoli and venous blood.

Nitrous oxide is a relatively poorly soluble inhalational anaesthetic, therefore the alveolar concentration of N_2O needed to achieve anaesthesia is quickly obtained, within one minute the alveolar concentration equals 60 to 80% of the inspired concentration. Because N_2O is inspired in large volumes (50% to 75%) the rapid recovery from anaesthesia due to its property of poor solubility presents one major problem. Namely 'diffusional hypoxia'. This is due to the sheer volume of N_2O being dropped into the alveoli from the blood and diluting the available oxygen.

Changes in cardiac output have minimal effects on the anaesthetic partial pressure in the alveoli of poorly soluble agents like N_2O.

The third factor affecting uptake of anaesthetic from the alveoli is the anaesthetic tension gradient from alveoli to venous blood. Uptake increases in proportion to the size of the gradient. This gradient equals zero

after equilibration with all parts of the body. The gradient is greatest at the time of induction. The 'vessel rich group' of the body which includes the brain receives 70 to 80 % of the cardiac output. Because of the high blood flow to mass ratio of this group it rapidly attains equilibration with the anaesthetic tension in the arterial blood. This group of tissues has a low tissue/blood partition coefficient for N_2O which also aids rapid equilibration. With-in the first 10 to 15 minuets of induction 80% of the blood returning to the lungs will be at the same tension as that found in alveoli and arterial blood. The alveolar to venous blood gradient is rapidly reduced to 20% of its initial size. Thereafter the rate of decrease of this gradient is much slower as the three other main body compartments (muscle group, fat group, vessel poor group) become saturated.

In 1954, Severinghaus described the uptake of N_2O in six patients. After denitrogenation the patients breathed 80% N_2O. In the first 2 minutes uptake was less than 1 litre per minute. Subsequently uptake progressive decreased. The rate of uptake being inversely proportional to the square root of time. This has been confirmed by many other workers.

Lastly the inspired concentration of an anaesthetic agent may exert a profound influence on the rate at which the alveolar concentration rises. Eger (1963) demonstrated that the higher the inspired concentration

of an anaesthetic agent the more rapid was the approach of the alveolar concentration to that inspired, he called this the **'concentration effect'**. The concentration effect is of clinical importance for gases such as N_2O that are administered at high inspired concentrations.

When an anaesthetic agent such as halothane (second gas) is administered with N_2O (first gas) the rate of rise of the alveolar halothane concentration is more rapid than when it is given alone. In otherwords the rate of induction of anaesthesia with halothane, a potent agent given in low inspired concentrations, is quicker when given concurrently with high inspired concentrations of the poorly potent agent N_2O. Nitrous oxide is therefore enhancing the effects of halothane. There are two currently accepted explanations for this effect. Firstly the absorption of large volumes of N_2O causes an increase in the inspired ventilation, thereby increasing the rate of delivery of halothane to the lung. Secondly the absorption of large volumes of N2O increases the proportion of the residual gases e.g. halothane, oxygen in the alveoli. These two explanations of the **'second gas effect'** have been confirmed by Epstein (1964) and Stoelting (1969).

Epstein (1964) showed an increased rate of rise of alveolar halothane when administered with 70% N_2O than with 10% N2O. He postulated that the uptake of large volumes of N_2O created a potential subatmospheric

intrapulmonary pressure which leads to an increased tracheal inflow, this inflow adds to the inspiratory ventilation and therefore causes an increased rate of delivery of halothane to the lung.

Stoelting and Eger (1969) demonstrated a **'concentrating effect'** on alveolar gases when N_2O is inspired. In their clinical study, a steady state halothane anaesthesia was obtained, such that the inspired and the alveolar concentrations were equal. Then 70% N_2O was added to the inspired gas. The halothane concentration rose by 0.8% in one minute. They proposed that the second gas is concentrated in the alveoli by the reduction in the alveolar gas volume resulting from N_2O uptake.

When the lung contains a significant ventilation-perfusion abnormality e.g pneumonia, atelectasis, and endobronchial intubation, the arterial rate of rise of N_2O may be slowed considerably (Eger and Severinghous 1964). In contrast such abnormalities would not affect the rate of rise of induction of a highly soluble anaesthetic.

Implications of solubility and the concentration effect on the development and control of anaesthesia

The **alveolar** concentration of N_2O rapidly approaches the **inspired** concentration because the fraction of inspired N_2O taken up into the blood **small** (low blood/gas solubility) and because N_2O **is** usually given in high concentrations (concentration effect). This has

three implications for the fine control of anaesthesia. Firstly, a given inspired concentration achieves its maximal effect in the brain rapidly. This effect being accelerated by the low brain tissue capacity for N_2O, a situation that shortens the half time of equilibration. Secondly, the closeness of alveolar and inspired concentrations means that the precision with which the anaesthetic effect of N_2O may be controlled is great. Thirdly, ventilatory and circulatory changes have minimal effects on N_2O anaesthesia.

Other effects

Nitrous oxide increases both systemic and pulmonary vascular resistance. The mechanism of this effect is not known, but N_2O has been shown to increase noradrenaline release from dog pulmonary artery segments (Rorie 1986), suggesting that vasoconstriction is mediated via the adrenergic system. Although direct myocardial depression is produced by this agent, it is balanced by simultaneous sympathetic stimulation. Thus in intact humans, little cardiovascular depression occurs at analgesic or anaesthetic partial pressures. Nitrous oxide has little effect on the coronary arterioles but does constrict the epicardial arteries (Wilkowski 1987). The latter effect is only of clinical importance in atherosclerotic coronary artery disease.

Although N_2O is a mild respiratory depressant, $PaCO_2$ is usually maintained at normal values. Nitrous oxide does depress the ventilatory response to increased $PaCO_2$ and

to hypoxia. Other respiratory problems are, alveolar collapse due to absorption of gases in an obstructed lung segment, depression of mucocilary flow, expansion of isolated air pockets as in pnemothoraces and lung bullae, and diffusional hypoxia during recovery. These effects increase the incidence of post-operative respiratory complications. Nitrous oxide also seems to produce some respiratory muscle rigidity, generally felt as a 'tight chest', thereby making assisted ventilation difficult unless muscle relaxants are also given.

Toxicity

Nitrous oxide inactivates a B12 component of the enzyme methionine synthetase. Thus by interfering with folate metabolism, DNA synthesis is impaired. A condition similar to B12 deficiency occurs. For example, megaloblastic haemopoiesis and leukopenia follow prolonged inhalation of N_2O in normal subjects (2 to 3 days) or shorter periods in the critically ill patient. Prolonged intermittent administration of N_2O ('Entonox' given for 15 minutes thrice daily) produces megaloblastic changes in man within 24 days. High doses of folinic acid may prevent these changes.

After intermittent exposure to N_2O over several months, a neuropathy is seen which is similar to the syndrome of subacute combined degeneration of the cord in B12 deficiency. Recovery follows abstention.

There is some evidence that N_2O causes an increased incidence of spontaneous abortions and foetal abnormalities among operating theatre and dental personnel, (Cohen et al 1980).

Summary

Nitrous oxide was chosen for this study because it is safe, and has easily measured cerebrospinal effects which have a rapid onset and offset. Also, its anaesthetic effects are relatively independent of slight variations in ventilation and blood flow, and it has quite mild effects on cerebral blood flow, the sensitivity of the cerebral circulation to CO_2, and the control of respiration. These points are described in detail in the chapter on mathematical modelling.

Nitrous oxide is a very safe, weak anaesthetic gas which enters the body and reaches the brain by the same route as compressed nitrogen in diving. It has a rapid onset and offset of action and clear cerebrospinal effects that lend themselves to the modelling of inert gas exchange during submarine escape in man. This concept is explored mathematically in the next chapter.

6 MATHEMATICAL MODELLING

Introduction

The hypothesis that prior hyperventilation should delay nitrogen accumulation in central nervous tissue during submarine escape is not easy to test. At increased barometric pressures nitrogen has a narcotic effect on central nervous tissue. It is detectable in men breathing air at 3 atmospheres (Baddely et al, 1966) and is easily demonstrated in people breathing air at pressures above 5 atmospheres. However the narcosis develops slowly, and is not an obvious feature of the brief exposures of submarine escape. Its time scales are inappropriate. Similarly, looking for evidence of bubble formation in nervous tissue is not practical. The results of any exposure of experimental animals to an appropriate pressure pulse could easily be challenged as unrepresentative of man, and any submission of human subjects to a similar pulse would expose them to unacceptable risks of lung rupture and decompression sickness.

For these reasons it was decided to explore the possibility of mimicking the behaviour of nitrogen with another inert gas, nitrous oxide, which was known to have easily demonstrated effects on nervous tissue, at normal barometric pressures. To do this, it would be necessary to sweep anaesthetic concentrations of nitrous oxide in and out of the lungs, as rapidly as nitrogen moved in and out during escape. Alveolar PCO_2

at the start of the procedure would also have to be controlled precisely. It seemed wise to do some mathematical modelling before designing an experimental protocol.

Many people have made perfusion-limited exponentially filling and emptying models of inert gas exchange in tissues, in the long study of decompression sickness, (e.g Haldane and Priestley 1935, Jones 1950, Roughton 1952, Workman and Bornmann 1975). Some of these have been found wanting because they do not deal with the slow diffusion-limited compartments important in much of diving, (Hempleman 1975). Almost all existing data on decompression sickness in man refers to conventional diving rather than the brief profound compression and decompression of submarine escape in which compartments with rapid time constants are much more vulnerable. Most models do not pay particular attention to breathing patterns, circulatory delays or the rapidly changing arterial PCO_2 levels which are critically important elements of escape procedures.

Denison and Bridgewater think that models of decompression sickness are of two general sorts. One form is based on accumulated statistical data, presumes no underlying mechanisms, and simply calculates the most probable outcome of a specific dive, from its bank of 'real life' data. The best of these is probably the maximum likelihood model of Wethersby (1988). The other sort assumes mechanisms and uses measurable features of

the body and the environment to calculate an outcome. Such models are limited by their assumptions. Denison and Bridgewater felt there was insufficient data to develop a statistical model of submarine escape at present, and that reliable data on prior conditions were unlikely to be forthcoming in the near future, so they designed a mechanistic model.

It consists of a stack of perfusion-limited body tissue compartments, variable blood flows and lung-to-organ delays for each compartment, the mixing of venous streams with variable organ-to-lung delays to produce mixed venous blood, and a lung which can be ventilated to any mixture of breathing patterns, with appropriate gas exchanges between mixed venous blood, alveolar gas and cabin inspirate. The atmosphere of the submarine residence compartment, escape compartment, BIBS supply and HIS supply can be varied, to take account in particular of rising nitrogen and CO_2 levels in the living space and the possible uses of gases other than air to facilitate escape.

This model confirmed that 600 ft was a likely limit to successful escape under ideal circumstances, and suggested that hyperventilation to an alveolar PCO_2 of about 20 mm Hg, which would roughly halve cerebrospinal blood flow, should limit nitrogen accumulation in nervous tissue significantly, (Fig 6.0). Their model is written as a spreadsheet program for Lotus 1-2-3 version 3, and runs on a PC-AT. It was decided to adapt

part of this model to explore the interactions of nitrous oxide and hyperventilation, and so ease the design of an experimental protocol.

It is convenient to begin by considering the way an entirely insoluble gas is washed into and out of the lung. For this purpose the lung could be thought of as a rigid metal box ventilated through a tubular dead space by a piston in the 'lung' substance, as shown in Figure 6.1. Let a rectangular pulse of a novel insoluble gas be introduced into the inspirate for a period of one minute, covering a train of breaths. Assume instantaneous mixing in the alveolar compartment and zero mixing with gas in the dead space. At the end of the n.th inspiration, the mass of of the insoluble gas in the alveolar space would be:

$$FRC \times FAX_n = (FRC + VD) \times FAX_{n-1} + (VT - VD) \times FIX$$

which simplifies to:

$$FAX_n = FAX_{n-1} + \frac{(VT - VD) \times (FIX - FAX_{n-1})}{(FRC + VD)}$$

This relationship can be modelled on a spreadsheet such as Lotus 1-2-3 to plot PAx against time, for any combination of FRC, VT, VD, FIx and respiratory rate, (The mathematical procedures are very simple).

Figure 6.2 illustrates the influence of variations in FRC on the build-up and decay of PAx. It shows that the incoming gas is diluted by the resident gas so that the

monoexponential build up of its concentration in the lung has a time constant that is roughly proportional to FRC. When FRC is held constant and tidal volume is varied the time constant is inversely proportional to VT-VD. When there is almost complete equilibration within the one minute period the washin and washout are symmetrical. By contrast, when the time constant is longer than one minute the washout appears to be much slower than the washin. This illusion which comes from the very different alveolar-inspired gradients in the washin and washout periods is illustrated in Figure 6.3.

To consider the fate of a soluble gas, the model has to be changed, to admit a pulmonary circulation capable of carrying dissolved gas away, (Figure 6.4). In such a model, recirculation has been ignored for the current purpose because the one minute period is too brief for much to occur. The outcomes of respiring one-minute pulses of gases of various solubilities are shown in Figure 6.5. The more soluble the gas, the greater is the steady-state gradient between inspired and alveolar gas, and the more rapid the removal at the end of the pulse. The removal of soluble gas from a single lung compartment during a breathhold is a monoexponential decay with a time constant proportional to alveolar volume and inversely proportional to blood flow and its blood gas partition coefficient

Clearly the faster blood flows through the lungs, the quicker will it carry soluble gas away. This is illustrated for nitrous oxide in Figure 6.6. This graph shows that the treatment of the somewhat soluble anaesthetic gas is almost independent of blood flow and quite like that of nitrogen. It indicates that nitrous oxide is a reasonable model of nitrogen in this regard.

When the blood flows away from the lungs it passes to capillaries serving tissue elements which can be treated as simple containers with perfusion-limited gas exchange characteristics Figure 6.7. Consider the fate of an almost rectangular pulse of nitrogen introduced into the lung of a man by rapidly compressing him and then decompressing him one minute later. With perfect blood-gas equilibration for nitrogen in the lung, this pulse is transported to an element of tissue with a 1 min time constant for blood-tissue nitrogen exchange. Repeat the exposure with alveolar PCO2 reduced from 40 to 20 mm Hg so that blood flow to the element is halved and its time constant rises to 2 minutes. The outcomes of the two exposures are shown in Figure 6.8. Hypocapnia has doubled the time taken for tissue PN2 to reach any given value. The longer the time constant of the tissue, the more nearly is the tissue nitrogen concentration halved, as shown in Figure 6.9

Nitrous oxide dissolves in blood much more readily than nitrogen does, so it is therefore transported to the tissue at a greater rate. Because the blood : tissue

partition coefficient is similar to nitrogen the time constant of the tissues is shorter by a factor of 30 i.e the same as the ratio of the blood : gas partition coefficient of the two gases. In this regard nitrous oxide is not a good model of the behaviour of nitrogen and its exchange might be too swift to show up the protective effects of hyperventilation. Figures 6.10 to 6.15 illustrate this.

Conclusions This mathematical model suggests that hyperpnoea can be used to produce a sharp-edged pulse of nitrous oxide into the lung, and this would be carried to the tissues by the circulation in much the same way as a rectangular pulse of nitrogen. In the tissues halving blood flow (by dropping PACO2 to 20 mm Hg) would almost halve tissue nitrogen content in the elements with time constants brief enough to be important, but nitrous oxide exchange might be too swift to demonstrate a similar effect. Therefore any benefit seen in real life with nitrous oxide would underestimate the benefits of hyperventilation in submarine escape.

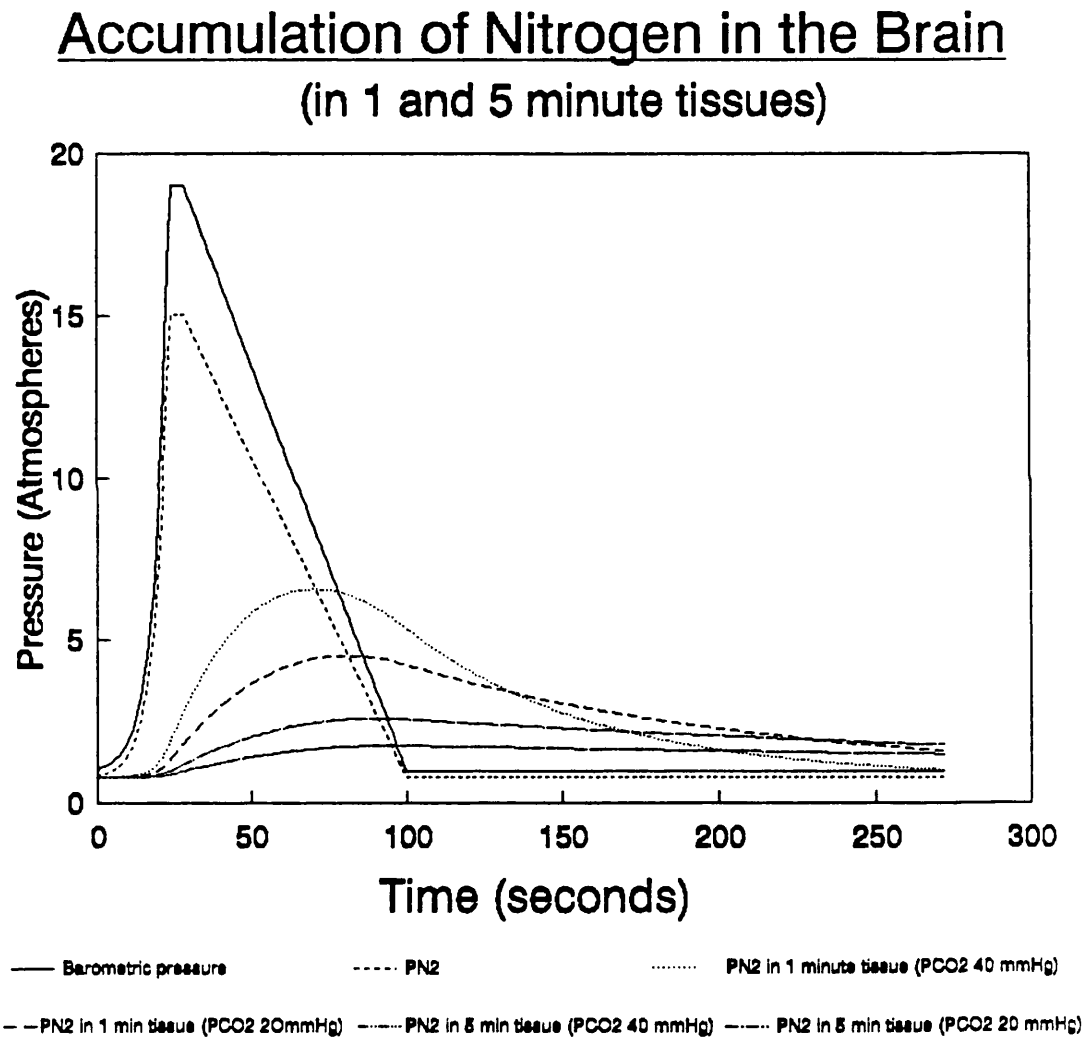

Accumulation of Nitrogen in the Brain
(in 1 and 5 minute tissues)
Pressure (Atmospheres)
20
15
10
5
0
0
50
100
150
200
250
300
Time (seconds)
Barometric pressure
PN2
PN2 in 1 minute tissue (PCO2 40 mmHg)
PN2 in 1 min tissue (PCO2 20mmHg)
PN2 in 5 min tissue (PCO2 40 mmHg)
PN2 in 5 min tissue (PCO2 20 mmHg)

Figure 6.0

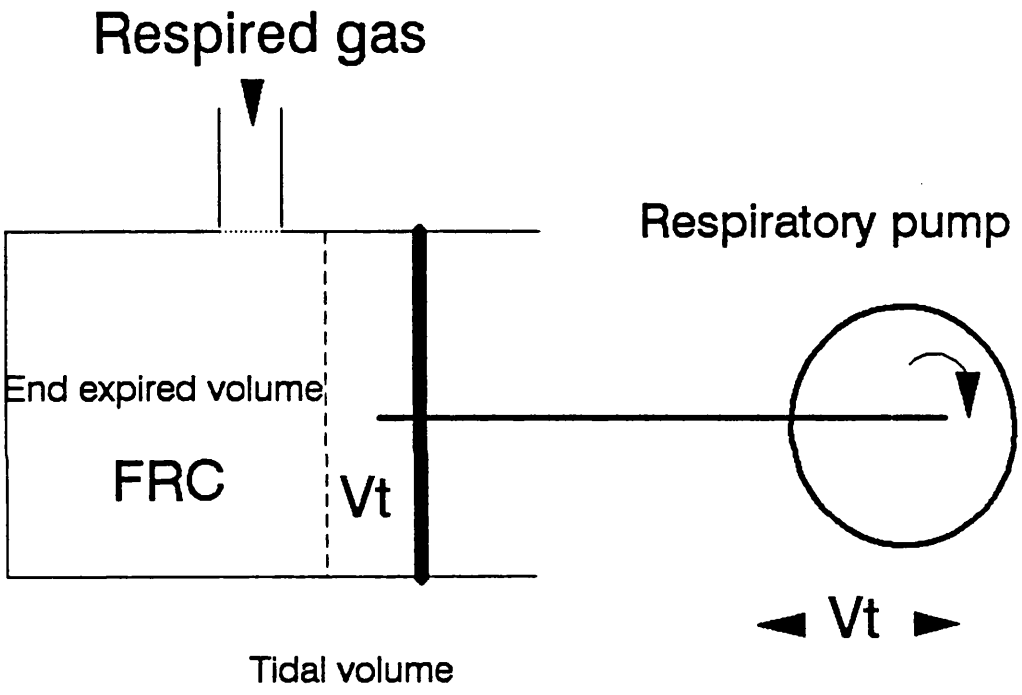

Respired gas
Respiratory pump
End expired volume
FRC
Vt
Vt
Tidal volume

Figure 6.1

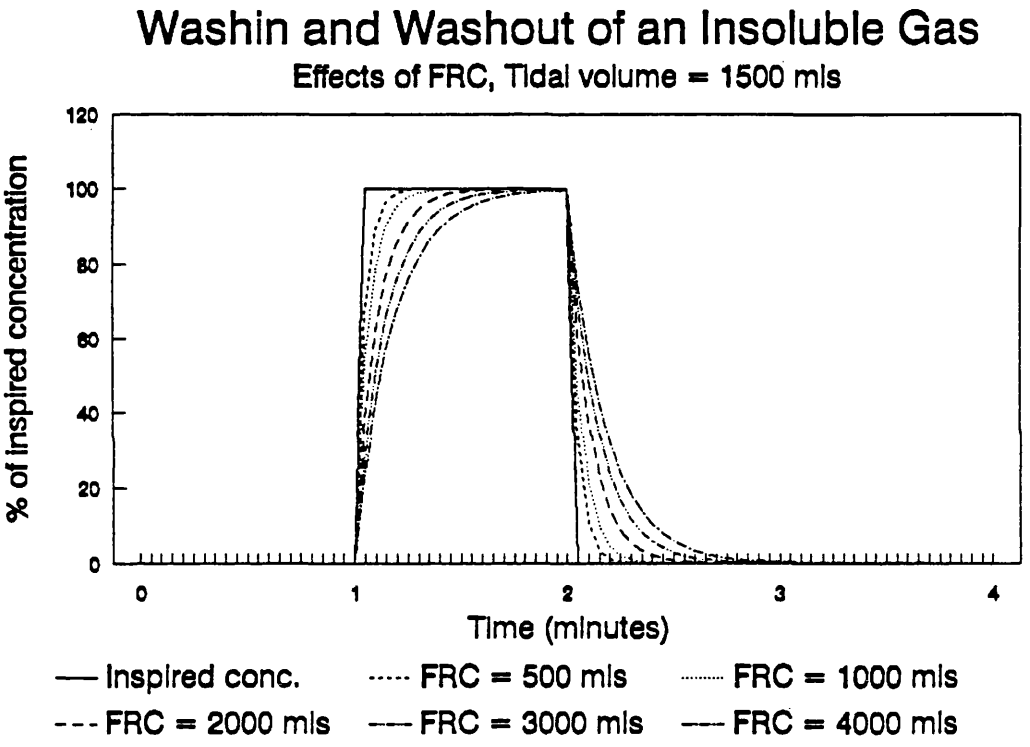

Washin and Washout of an Insoluble Gas
Effects of FRC, Tidal volume = 1500 mls
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
Inspired conc.
FRC = 500 mls
FRC = 1000 mls
FRC = 2000 mls
FRC = 3000 mls
FRC = 4000 mls

Figure 6.2

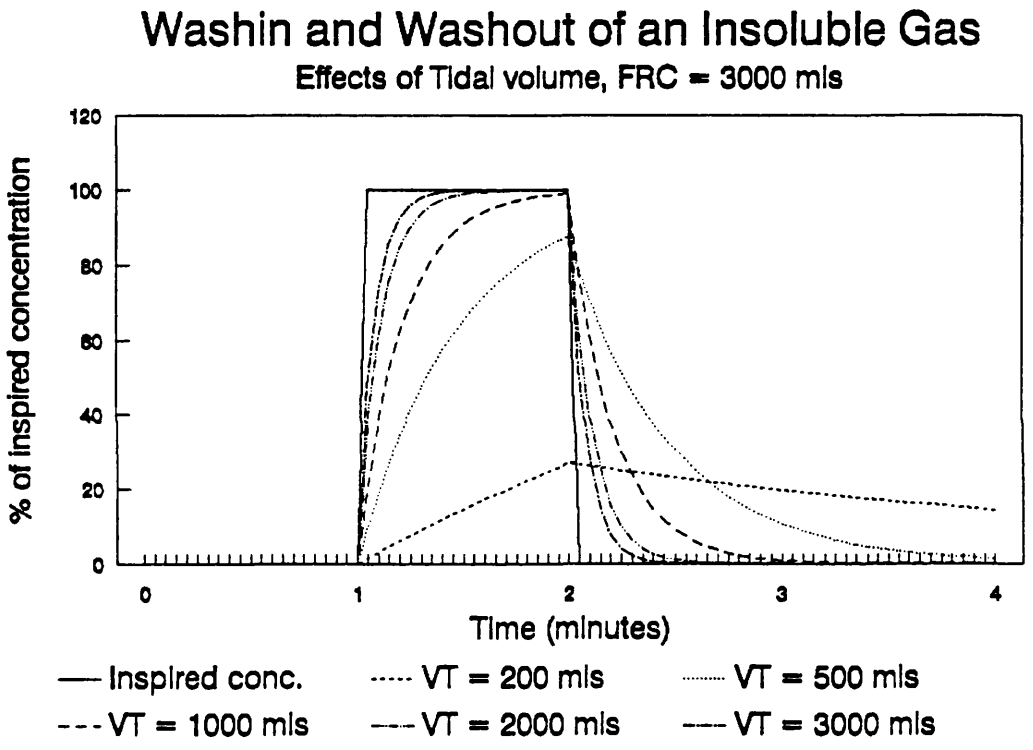

Washin and Washout of an Insoluble Gas
Effects of Tidal volume, FRC = 3000 mls
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
Inspired conc.
VT = 200 mls
VT = 500 mls
VT = 1000 mls
VT = 2000 mls
VT = 3000 mls

Figure 6.3

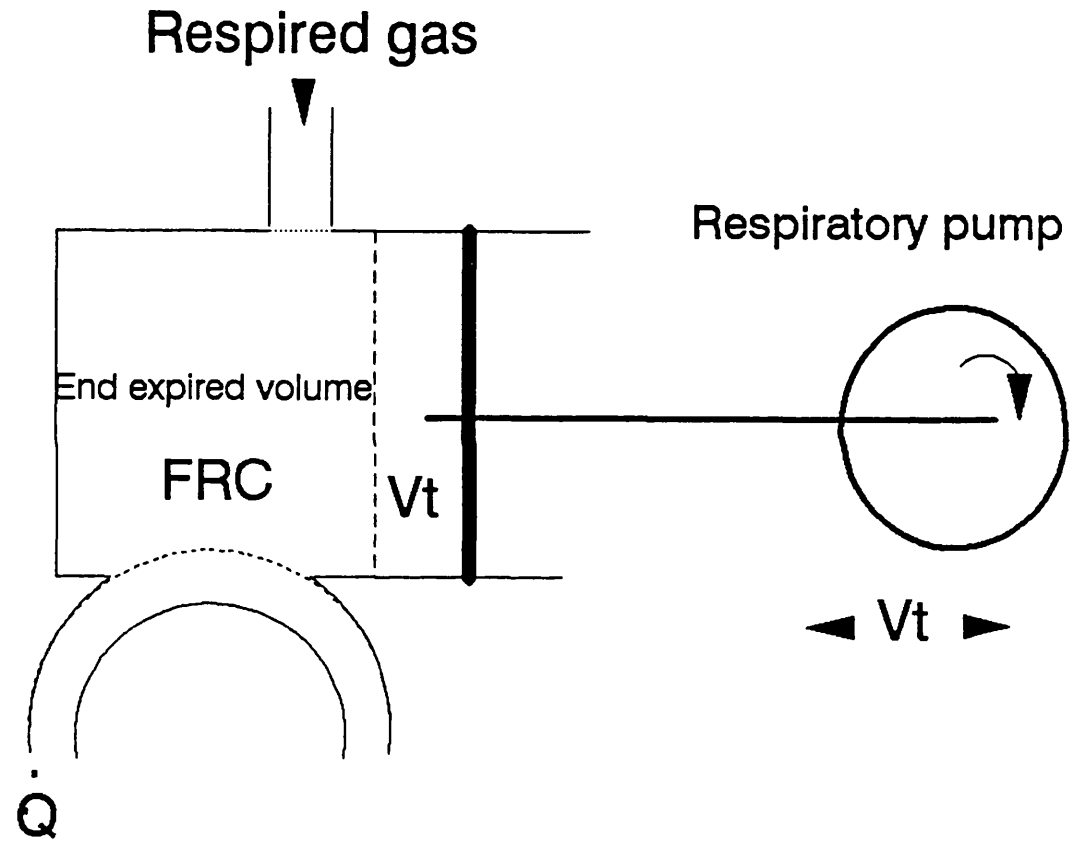

Respired gas
Respiratory pump
End expired volume
FRC
Vt
◄ Vt ►
Q̇
Total blood flow to the lung

Figure 6.4

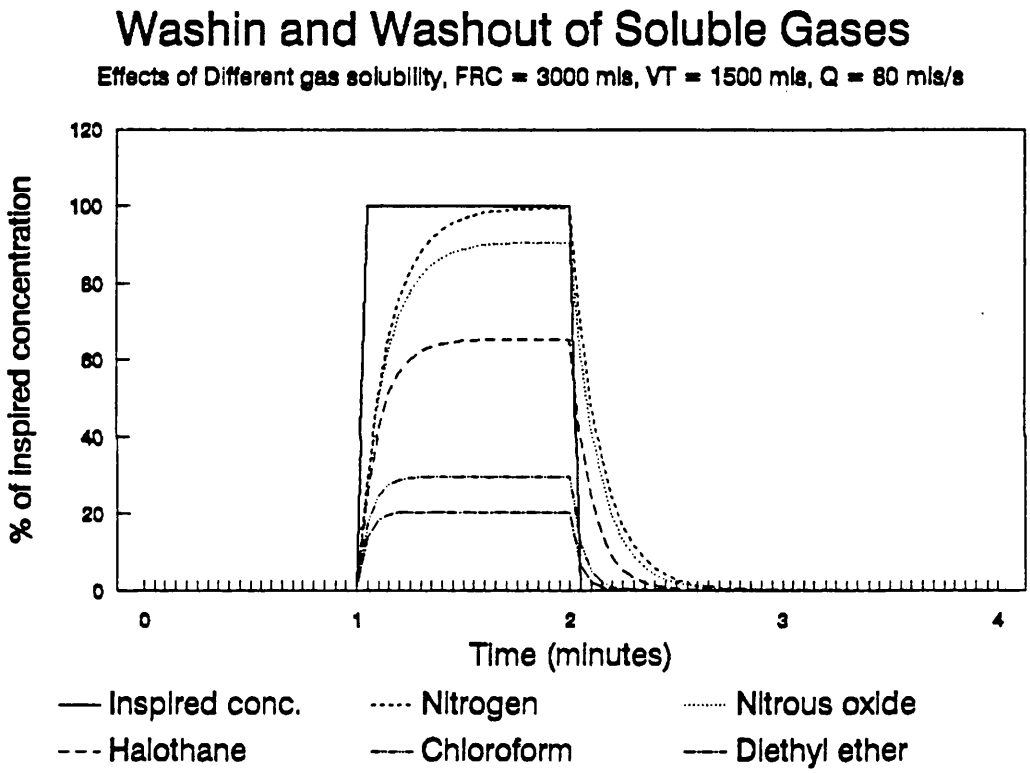

Washin and Washout of Soluble Gases
Effects of Different gas solubility, FRC = 3000 mls, VT = 1500 mls, Q = 80 mls/s
% of Inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
Inspired conc.
Nitrogen
Nitrous oxide
Halothane
Chloroform
Diethyl ether

Figure 6.5

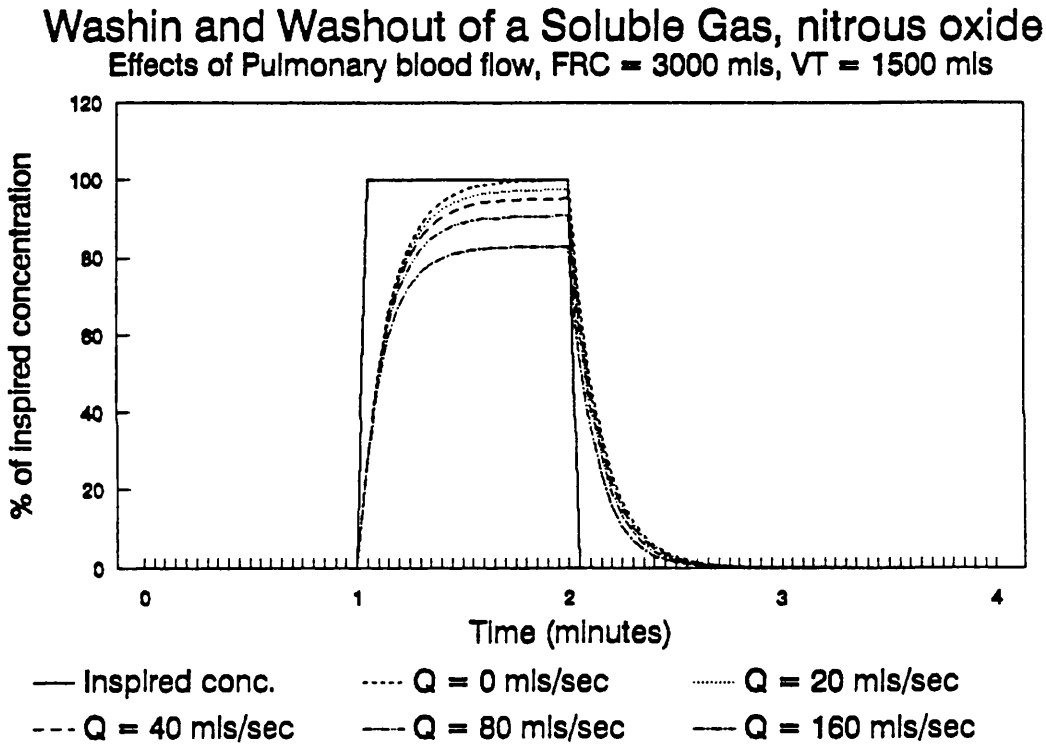

Washin and Washout of a Soluble Gas, nitrous oxide
Effects of Pulmonary blood flow, FRC = 3000 mls, VT = 1500 mls
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
Inspired conc.
Q = 0 mls/sec
Q = 20 mls/sec
Q = 40 mls/sec
Q = 80 mls/sec
Q = 160 mls/sec

Figure 6.6

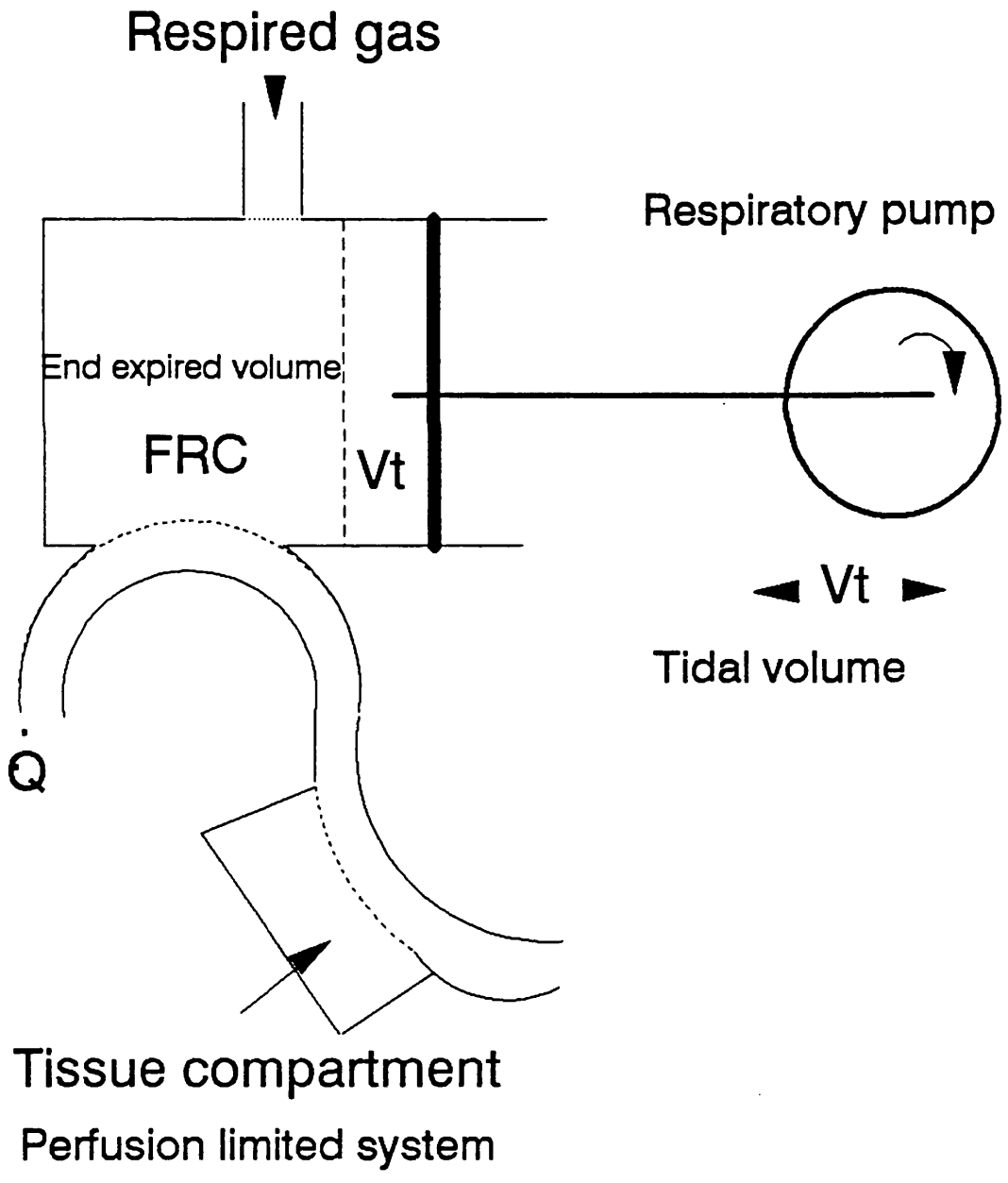

Respired gas
Respiratory pump
End expired volume
FRC
Vt
Vt
Tidal volume
Q
Tissue compartment
Perfusion limited system

Figure 6.7

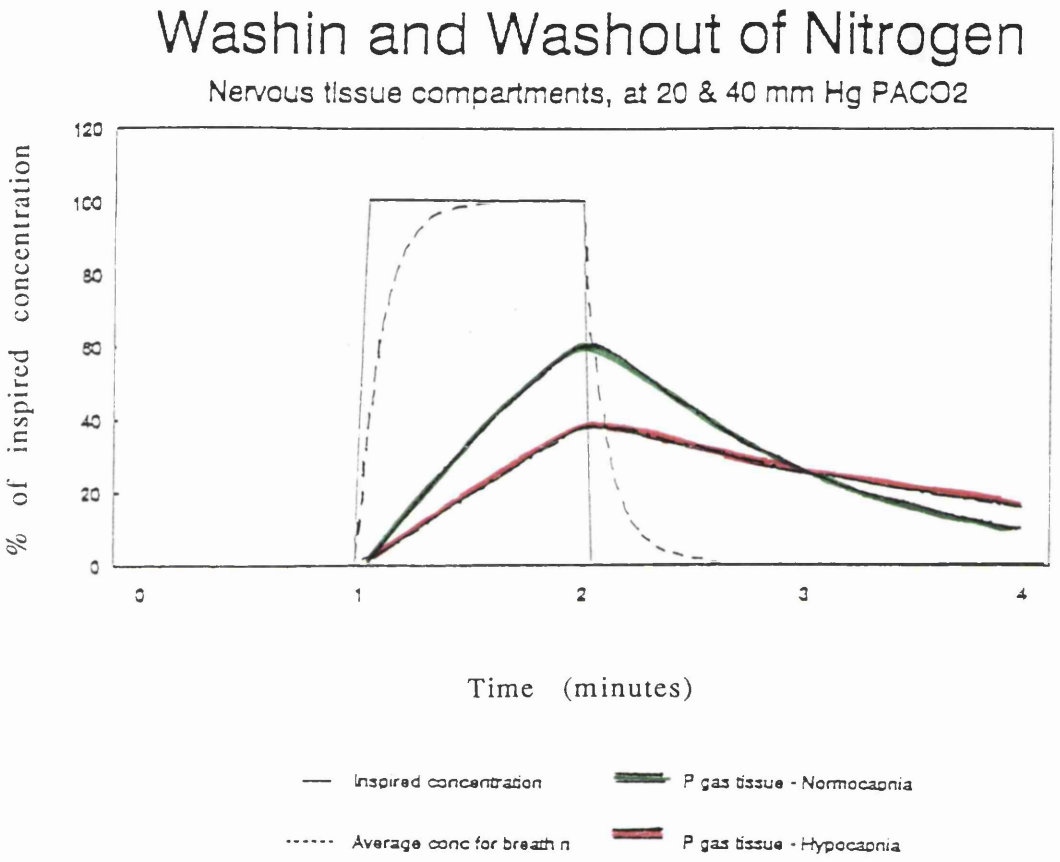

Washin and Washout of Nitrogen
Nervous tissue compartments, at 20 & 40 mm Hg PACO2
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
Inspired concentration
Average conc for breath n
P gas tissue - Normocapnia
P gas tissue - Hypocapnia
1 min nitrogen tissue

Figure 6.8

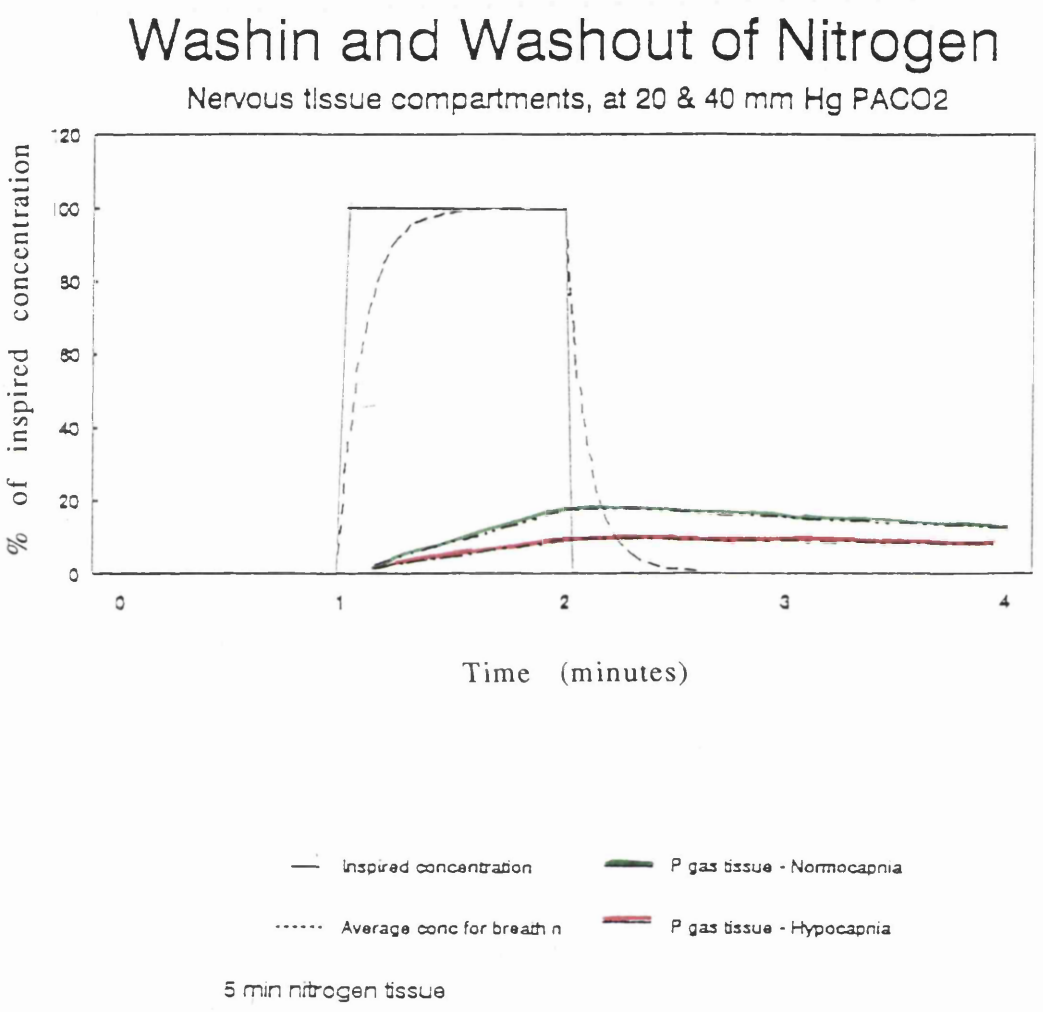

Washin and Washout of Nitrogen
Nervous tissue compartments, at 20 & 40 mm Hg PACO2
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
Inspired concentration
Average conc for breath n
P gas tissue - Normocapnia
P gas tissue - Hypocapnia
5 min nitrogen tissue

Figure 6.9

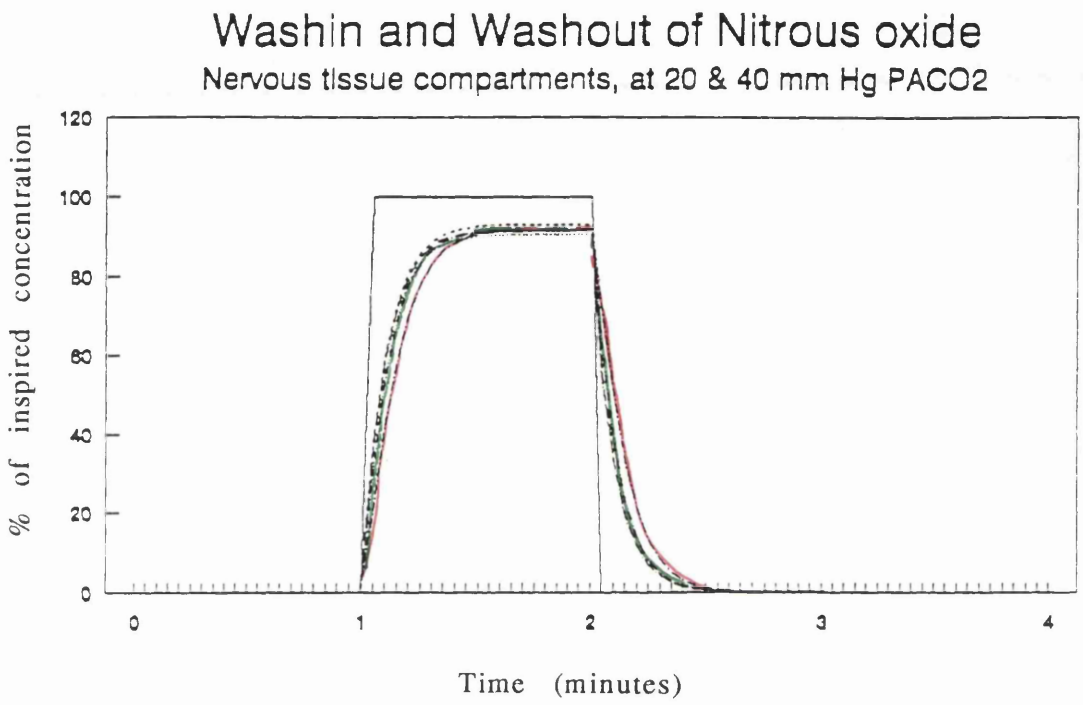
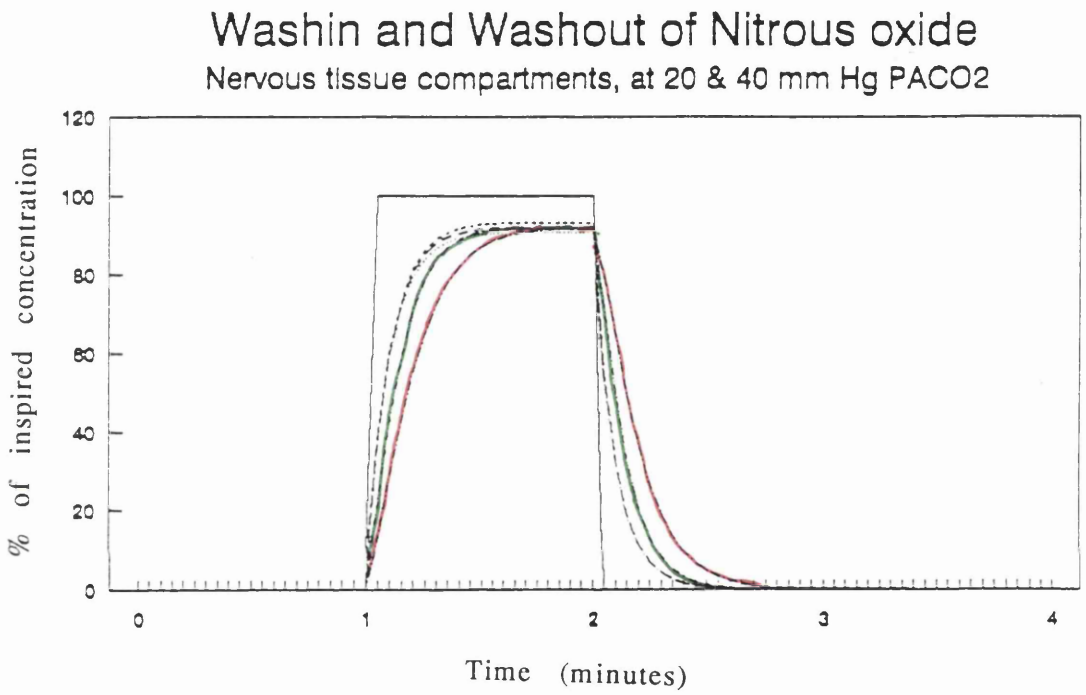
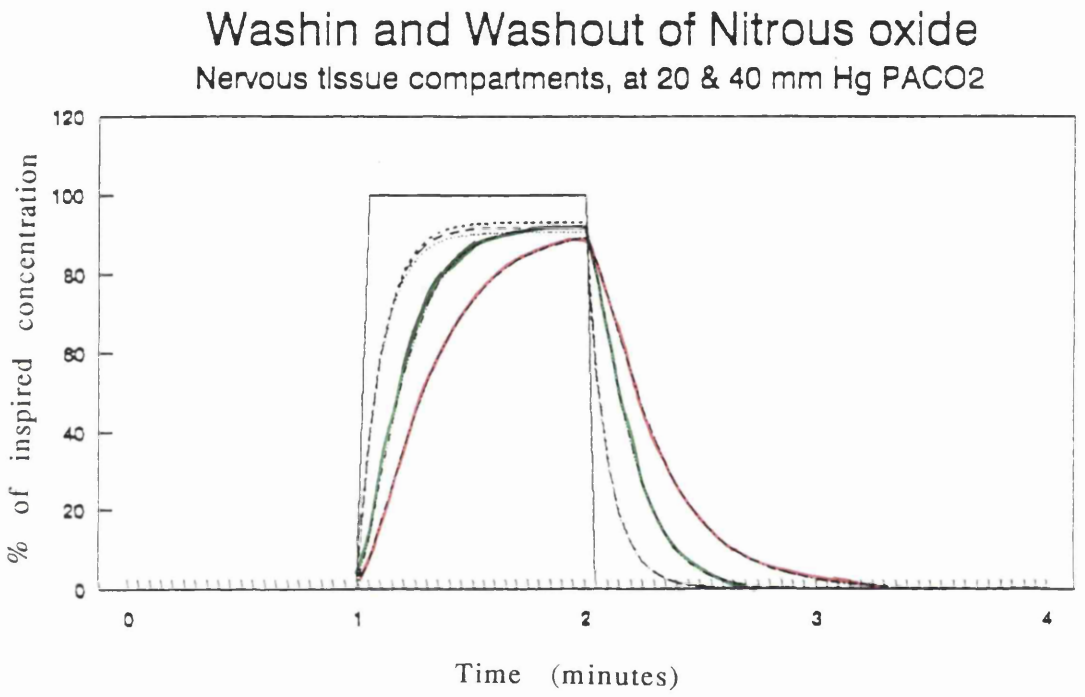

Washin and Washout of Nitrous oxide
Nervous tissue compartments, at 20 & 40 mm Hg PACO2
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
__Inspired concentration
.....Conc at beggining of breath n
.....Conc at end of breath n
----Average conc for breath n
P gas tissue Normocapnia
P gas tissue Hypocapnia
1 min nitrogen tissue

Figure 6.10



2 min nitrogen tissue

Figure 6.11



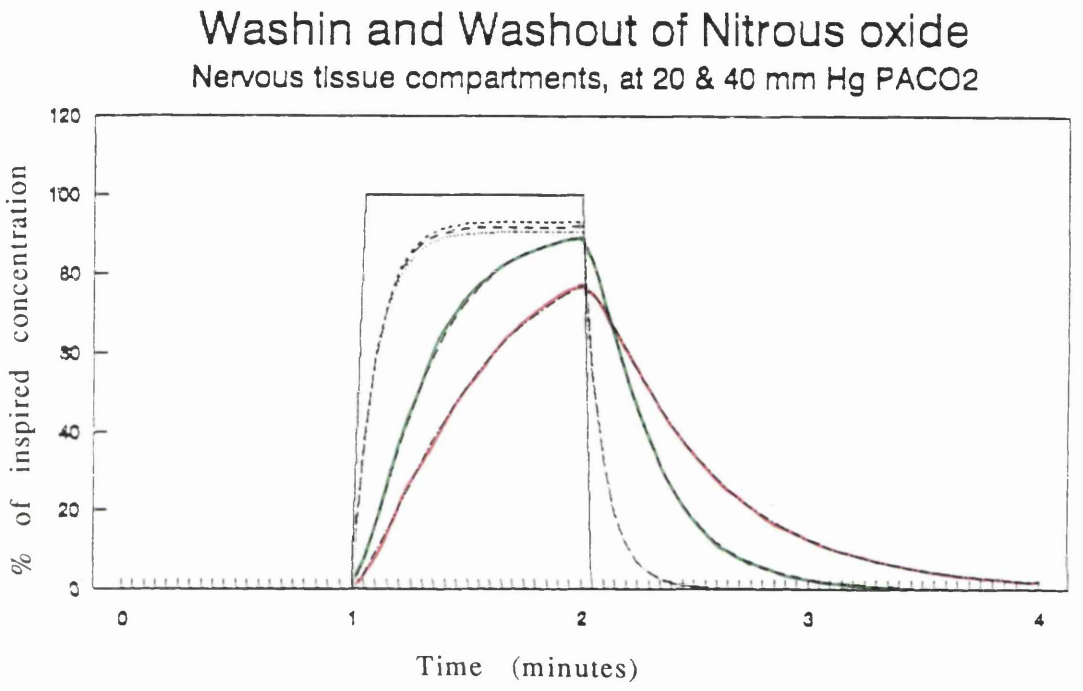
__Inspired concentration .....Conc at beggining of breath n

.....Conc at end of breath n ----Average conc for breath n

__P gas tissue Normocapnia __P gas tissue Hypocapnia

4 min nitrogen tissue

Figure 6.12



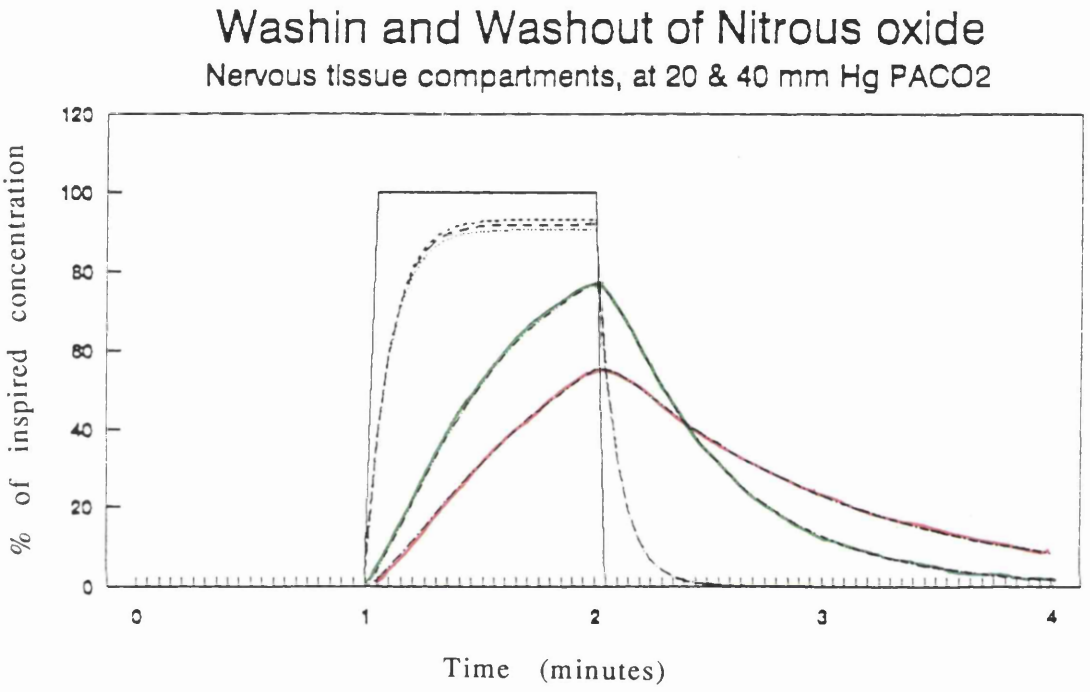
__Inspired concentration .....Conc at beggining of breath n

.....Conc at end of breath n ----Average conc for breath n

_ _P gas tissue Normocapnia _ _P gas tissue Hypocapnia

8 min nitrogen tissue

Figure 6.13



__Inspired concentration .....Conc at beggining of breath n

.....Conc at end of breath n ----Average conc for breath n

==P gas tissue Normocapnia ---P gas tissue Hypocapnia

16 mn nitrogen tissue

Figure 6.14

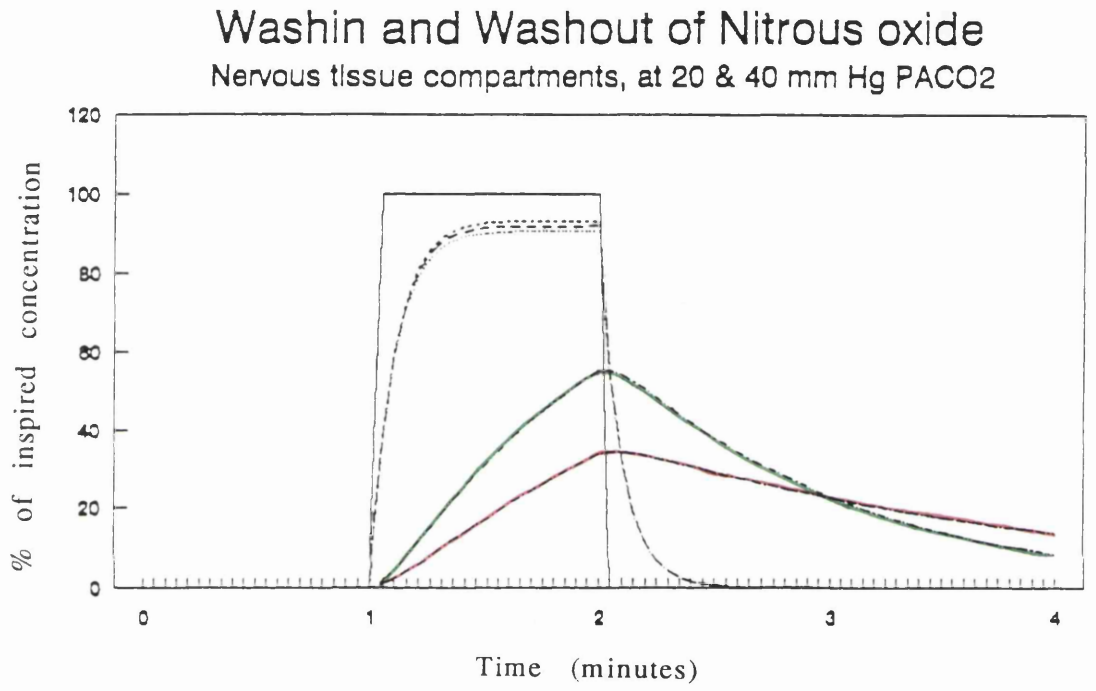

Washin and Washout of Nitrous oxide
Nervous tissue compartments, at 20 & 40 mm Hg PACO2
% of inspired concentration
120
100
80
60
40
20
0
0
1
2
3
4
Time (minutes)
__Inspired concentration
.....Conc at beggining of breath n
.....Conc at end of breath n
----Average conc for breath n
P gas tissue Normocapnia
P gas tissue Hypocapnia
32 min nitrogen tissue

Figure 6.15

7 SELECTING A PROTOCOL

The work that has been reviewed in the previous chapters indicated that the waveform of nitrogen presented to the lungs and so to the body, during unimpeded submarine escape, rises to a maximum over a period of 20 to 30 seconds stays there for a further few seconds and then falls back to atmospheric values over the following minute. It was decided to mimic this with a pulse of nitrous oxide delivered under isobaric conditions at atmospheric pressure, in circumstances which could compare its cerebrospinal effects during normocapnia and hypocapnia, while all other conditions remained constant. Anticipating that there would be some intra- and inter-subject variations in response, it would be necessary to repeat the studies several times on each of several subjects. There would have to be ample time between studies for the effects of any one dose of nitrous oxide to wear off. The dose of nitrous oxide should be sufficient to produce clear-cut effects on cerebrospinal performance, but not so gross that the subject took a long time to recover, or so marked that it was unlikely to be reversed by hyperventilation. Assuming a sigmoid dose-response curve one would need to produce about 80% of a maximum response, under normocapnic conditions.

The level of ventilation would have to be high enough to sweep nitrous oxide into and out of the lungs rapidly, and to drop alveolar PCO_2 to 15 mm Hg. There

should be no change in ventilation between normocapnic and hypocapnic studies because the invasion of the lungs by nitrous oxide had to be the same in the two conditions. Therefore it would be necessary to choose a single level of ventilation in slight excess of all needs, and to add CO_2 to the inspirate to control end-tidal PCO_2 at chosen levels between 15 and 40 mm Hg.

A means of measuring of cerebrospinal performance was needed, that was sensitive to the entry of nitrous oxide into nervous tissue, stable enough to allow comparisons between conditions, and capable of following changes likely to have time constants of about 20 seconds. Therefore one would need to sample performance every few seconds.

With these thoughts in mind it was decided to make the subjects respond to a psychomotor task delivered repetitively at a strict time interval of 3 seconds, and to make them breathe at 38 litres per minute for all experiments so that the mechanical effects of ventilation on chest fatigue, circulation and psychomotor performance would be the same throughout. In addition the respiratory interval would be fixed at 3 seconds. This had two advantages. Firstly it stabilised alveolar ventilation precisely. Secondly it avoided interaction with the psychomotor task. The subjects would be instructed to respond to the task as quickly

as possible, and then to take a breath. Previous experiments of Denison et al (1966) had already shown this was practical.

Before a formal comparison could be made of the effects of a pulse of nitrous oxide on psychomotor performance under normocapnic and hypocapnic conditions, preliminary experiments would have to be done:

1) to discover how quickly nitrous oxide could be swept into and out of the lung, to mimic the rapid rise and fall of nitrogen tension during submarine escape.

2) to find the concentration of nitrous oxide in such a pulse which would produce a clear-cut behavioural effect.

3) to demonstrate that the psychomotor task could follow the evolution and disappearance of this effect adequately.

4) to have the means to apply and monitor the pulse of nitrous oxide safely.

5) to be able to control the partial pressure of CO_2 in alveolar gas accurately.

The next chapter describes how these aims were met.

8 MATERIALS AND METHODS

8.1 Introduction

Previous experience with the psychomotor task of Denison et al (1966) had shown that it could follow rapid changes in consciousness when delivered repetitively at 3 second intervals for four periods of 4 minutes, separated by 2 minute periods of rest. This suggested a basic structure for the preliminary studies in which brief or longer episodes of nitrous oxide breathing could be introduced to explore the onset and offset of its effects over a total time of 22 minutes. Other previous studies (Davies in preparation) had shown that 22 minute periods of normocapnia and hypocapnia could be compared if they were separated by a rest interval of 20 minutes. So an experimental unit of 64 minutes was chosen for all studies. It consisted of an initial 22 minute period containing four 4 minute blocks of the task, followed by a 20 minute period of complete rest and then another 22 minute period for four further blocks of the task. Each block set 80 questions, requiring 320 responses in the first 22 minutes and another 320 in the last 22 minutes, (Figure 8.0). The task acted as a metronome for breathing during the work periods. At first a subdued visual or auditory version of it was used to maintain the same respiratory rate during rest periods, but subjects quickly became so well trained that they kept the rate accurately without aid.

Diagramatical representation of the time course of each experiment

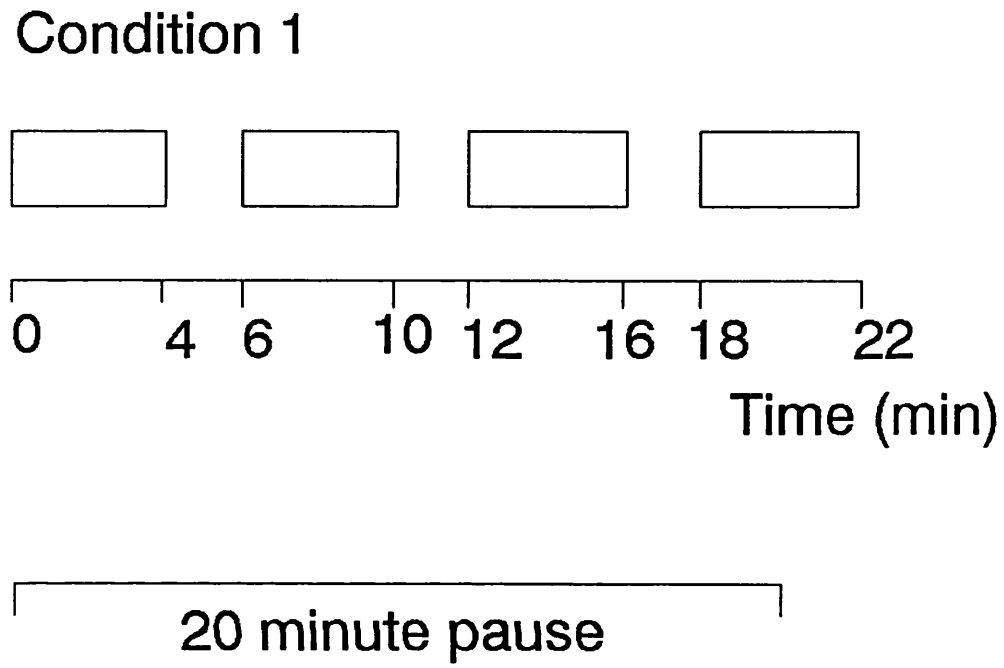


Figure 8.0

All measurements were made on seven medical colleagues of whom one was female. Their ages ranged from 27 to 55 ys. One of the men was of Chinese descent. Five of the others were British. The seventh subject was French. All were in good health with no current respiratory, cardiovascular or cerebrovascular disease. Two had a history of mild asthma and took occasional salbutamol. Details of all seven subjects are summarised in the following table.

Subject number	age Yrs	Height cm	Weight Kg	Mild asthma
1	29	162	54	
2	35	179	76	
3	28	188	105	
4	37	182	73	
5	32	171	64	
6	27	183	73	*
7	55	176	80	*

The volunteers were first asked to learn the psychomotor task. They then became familiar with the respiratory apparatus, which involved hyperventilating at 38 l/min. while performing the task. The subjects were also introduced to a pulse of N_2O, which was given for one minute while hyperventilating. The means of imposing and monitoring the

ventilation, the technique of measuring O_2, N_2O and CO_2, and a description of the psychomotor task are given below. Once they had learnt all these skills and demonstrated a high degree of reproducibility in performing the combination of all three, they were admitted to the preliminary studies. Details of the admission criteria are given later.

8.2 Equipment used

Essentially the same equipment was used for all studies. It is shown in Figure 8.1. It consists of:

1) means of imposing hyperventilation
2) means of imposing a pulse of nitrous oxide anaesthesia
3) means of sampling psychomotor performance every 3 sec.
4) gas monitoring equipment
5) computer hardware and software to run and analyse studies
6) other safety features

These will be described in turn.

8.3 Hyperventilation

Subjects sat in an upright armchair, facing the visual display console of an IBM-compatible PC-AT personal computer. Compressed air, mixed with controlled quantities of carbon dioxide was delivered to them from high pressure gas cylinders. The gases flowed

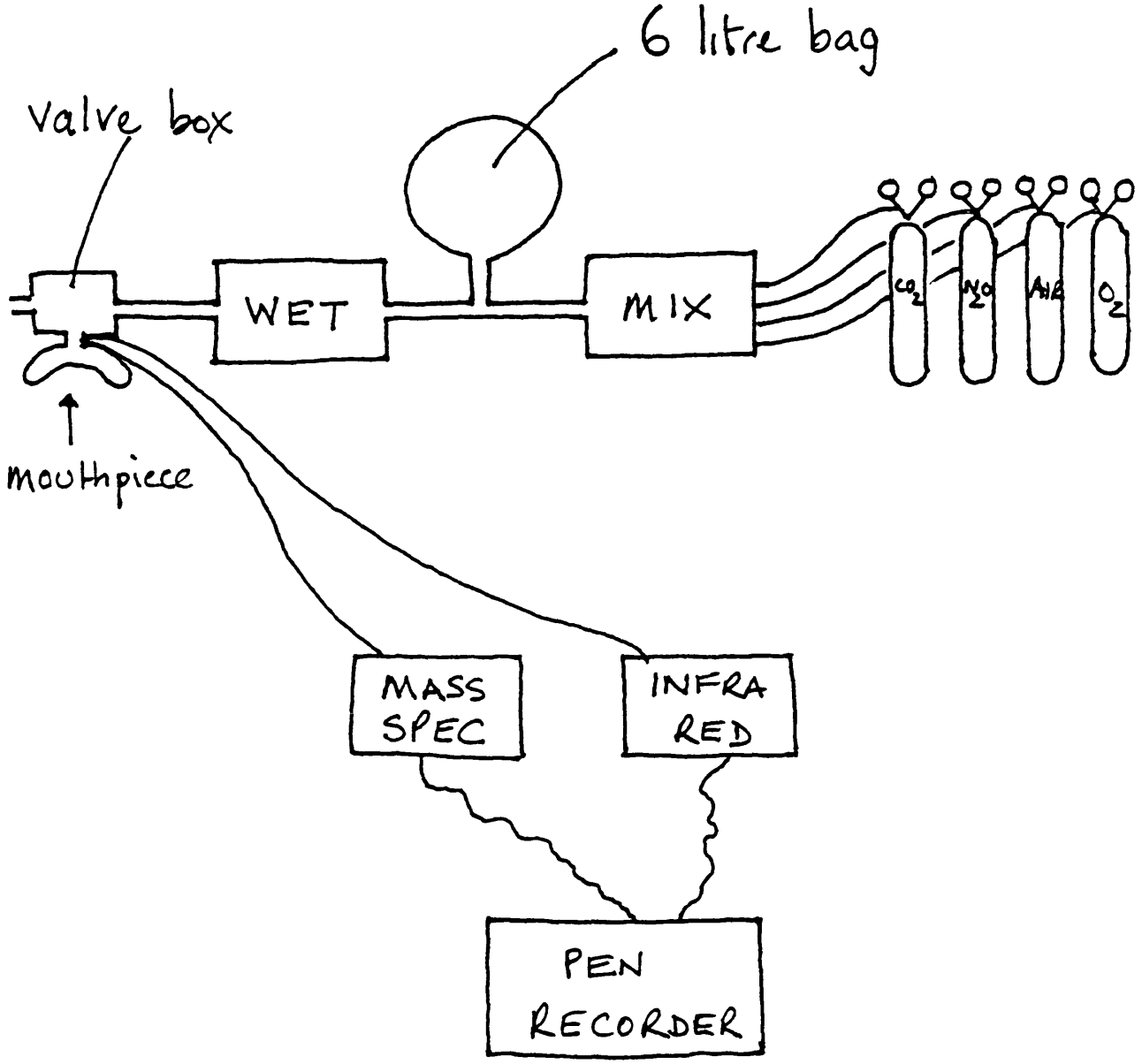

6 litre bag
Valve box
WET
MIX
CO_2
N_2O
AIR
O_2
mouthpiece
MASS SPEC
INFRA RED
PEN RECORDER

Figure 8.1

through precision rotameters, from the cylinders to a mixing box and then to the inspiratory port of a mouthpiece mounted valve box (Hans Rudolph Inc). Between the mixing box and the mouthpiece a 6 litre anaesthetic balloon was added to the circuit on one side-arm, and the output of a temperature-controlled humidifier entered by another. The anaesthetic balloon was placed in the visual field of the subject, close to the display unit, but not obstructing a clear view of it. This arrangement is shown diagrammatically in Figure 8.2.

Total gas flow was set at 38 litres per minute. The subject was instructed to inspire immediately after responding to the task on the display unit. Responses were demanded at strict intervals of 3 sec. The subject was trained to empty the anaesthetic bag on each inspiration. In this way his tidal volume was held very close to 1.9 litres throughout each study.

8.4 Nitrous oxide anaesthesia

Nitrous oxide was stored as pure liquid in high-pressure cylinders. A 120 litre Douglas bag was filled with a controlled mixture of nitrous oxide, carbon dioxide, air and oxygen, to produce an inspirate with the oxygen, carbon dioxide and nitrous oxide pressures appropriate to the experiment in hand. The composition of the bag was determined and adjusted by respiratory mass spectrometry and infrared analyser.

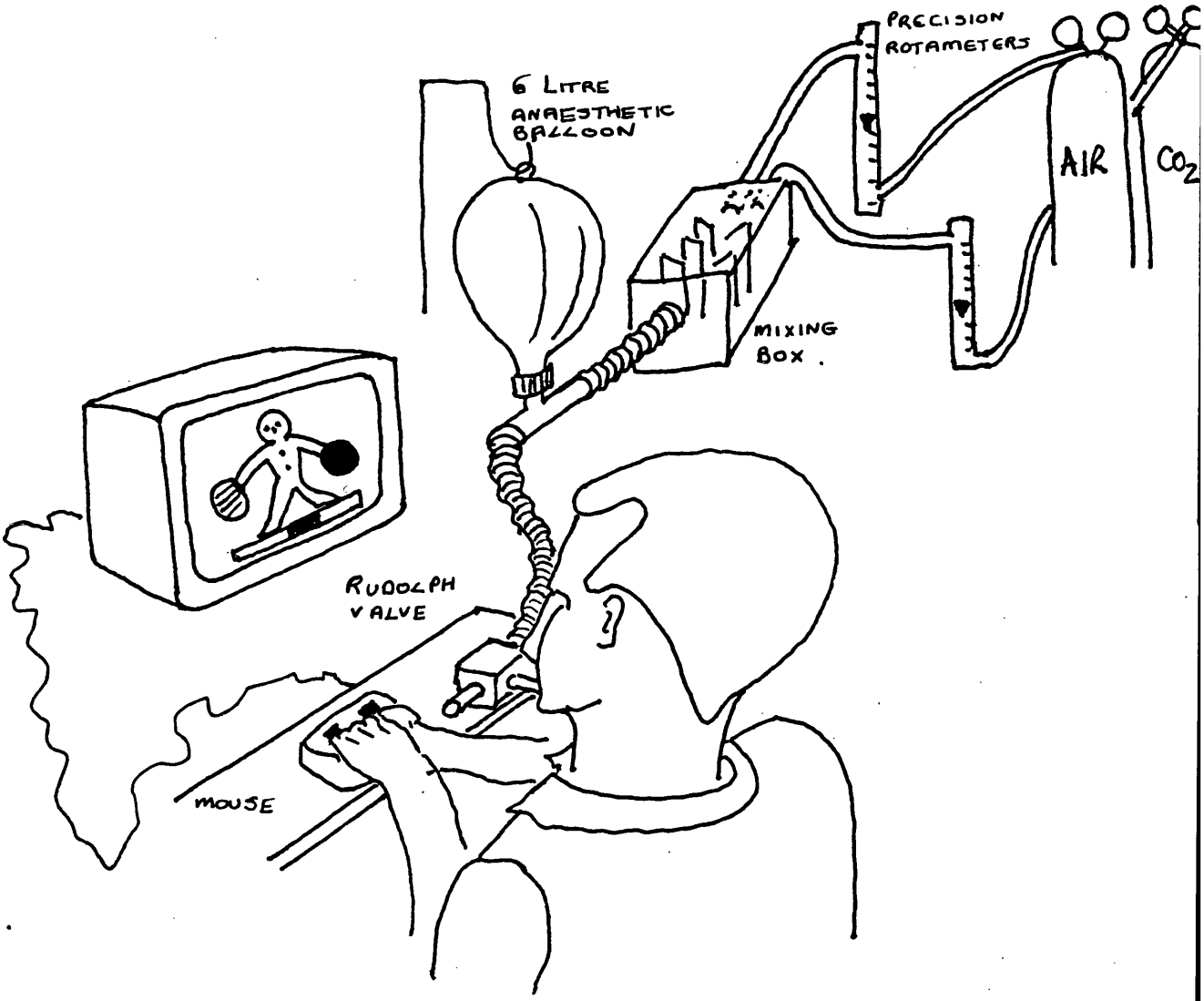

PRECISION
ROTAMETERS
6 LITRE
ANAESTHETIC
BALLOON
AIR
CO_2
MIXING
BOX
RUDOLPH
VALVE
MOUSE

Figure 8.2

Once prepared the bag was added to a third side-arm on the inspiratory circuit, controlled by a wide-bore Douglas tap. The tap was opened to deliver the anaesthetic mixture to the subject, and closed to restore ventilation with the previous nitrous oxide free mixture. This arrangement is shown in Figure 8.3.

8.5 Psychomotor performance

The psychomotor task used was a visual re-orientation task originally designed by Benson and Gedye (1963). In its original form it consisted of a set of 80 randomly shuffled photographic transparencies which were projected onto a screen in front of the subject. All of the slides showed a stylized drawing of a front or back view of a manikin holding a red disc in one hand and a blue disk in the other. The manikin could be upright or inverted. This provided eight variants (four postures, with the red disc in one of two hands), so in a set of 80 slides each variant appeared ten times.

Later Benson and Gedye's preceded each image with another slide showing a red or a blue disc, placed at the centre of the screen, but exactly the same size and colour as one in the hand of a manikin. This disc represented the question 'in which of its hands is the manikin holding the disc of this colour, on the subsequent slide ?'. Thus there was a short-term memory component to the task. The subject faced the screen, without distraction, sitting in armchair with

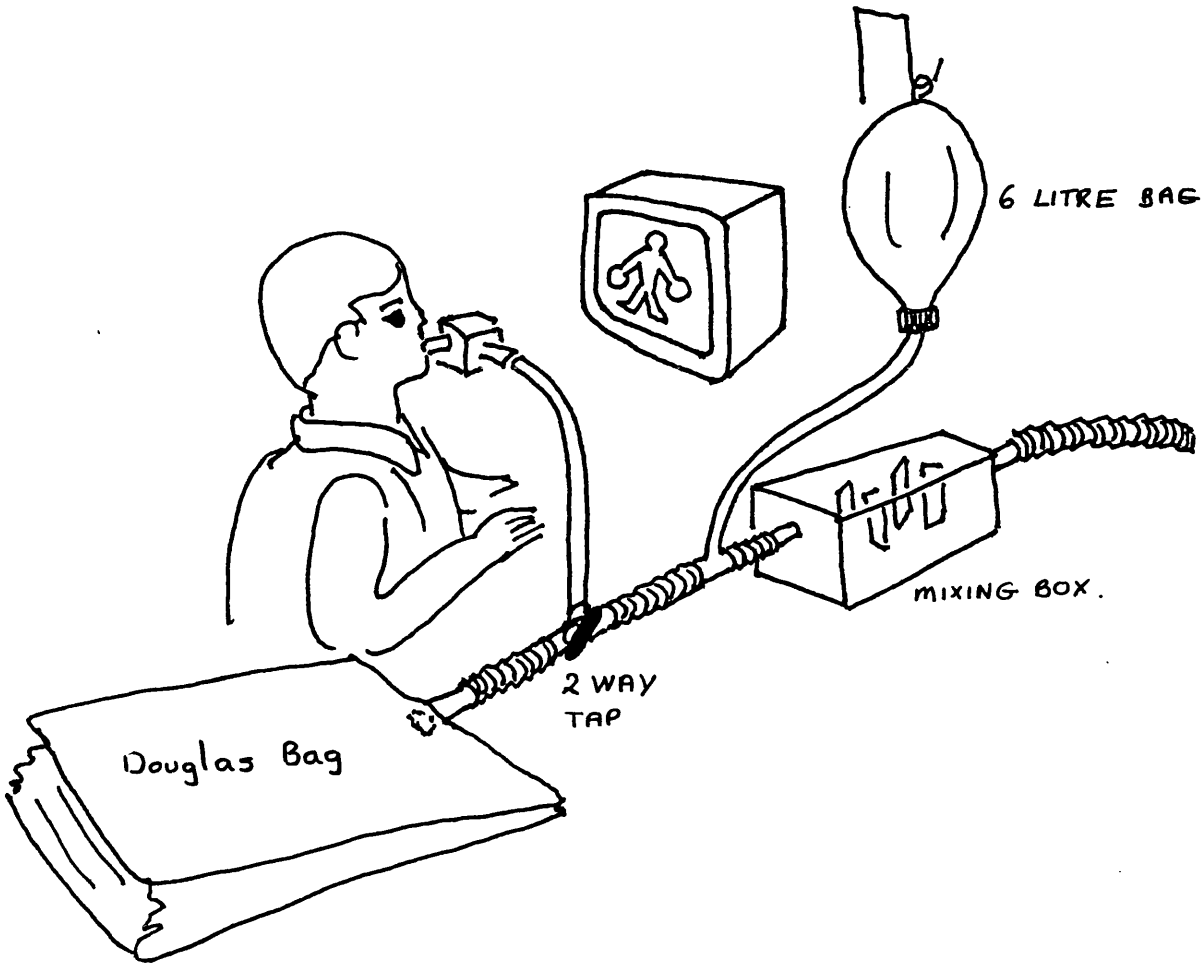


Figure 8.3

a response key mounted on each side. If the subject thought the disc of the nominated colour was in the manikin's left hand, he pressed the left hand key, and vice versa.

Benson and Gedye had chosen this task as a test of visual reorientation, which is an important skill in pilots flying high-performance fighter aircraft that wave and tumble in the sky. They showed that ability to perform this task was related to one aspect of flying ability, as assessed by flying instructors. Later Ledwith and Denison (1964) used the task to study learning impairments associated with mild prolonged hypoxia. To do this the slide projector was automated to deliver the questions at strict intervals of several seconds, and the slide margins were optically coded for easier registration and analysis of image type, question colour and response time.

Later Ernsting et al 1973 studied the rapid losses and recoveries of consciousness associated with rapid decompresion at high altitudes. To do this they needed to deliver the questions more rapidly. So they deleted the question colour slides and therefore the short-term memory component, and coloured the centre third of the ground bar on the manikin slide instead. In this version of the task there are 16 questions (four postures, two hands and two colours) and so five examples of each question in every set of 80

slides. Using this modification and improved automation of scoring Denison established normal values for many subjects and demonstrated that the task was able to follow very rapid alterations in consciousness. Because it could do this, the task was chosen for the earlier studies of hyperventilation related to submarine escape (Cooper 1988).

For that purpose Denison et al automated the task further so that it could be operated and analysed completely by an IBM-compatible PC-AT. They wrote an initial program in Basic and later speeded up the analysis by writing it in Turbo-Pascal with feeder programs to the spreadsheet package Lotus 1-2-3. It was this version of Benson and Gedye's original task that was used to explore the effects of nitrous oxide.

There are four levels of difficulty in this task, each associated with one posture. There is no evidence that handedness or question colour affects response times at all. So, to make consecutive sets of four questions exactly comparable Denison et al decided to include one example of each posture in each set, but to so randomise their order, question colour and handedness , that it would be impossible to discern or be influenced by this hidden structure. In effect the order of each of the four postures is randomized in each set, but question colours and

handedness are randomised through the whole block of 80. These are then presented at strict 3 second intervals, and held on the screen for two seconds precisely. This allows the screen to be blank for one second between images so that the subject has time to release his mind from one question before attempting the next. Subjects respond by pressing the right- or left-hand of a computer 'mouse' mounted on a board across the arms of the subject's chair.

The program records the image number (1-80), image type (1-16), colour (r,b), response made (1.r), response time (0-2000 msec), and correctness (0,1). At the end of the first block of 80 images, results are dumped into a data file, and a two minute blank screen interval is imposed. As this ends a warning note is sounded and the next set of 80 images begins. This sequence is repeated over 22 minutes until four blocks of 80 images have been shown. The experimenter then sets a clock to time a 20 minute rest period, At the end of the rest the experimenter initiates a second 22 minute cycle of images.

Subsequently, data analysis programs normalise response times by posture and print out tables of actual and normalised response times for individual responses and for each set of four. In this way virtually comparable responses are obtained at each 3 sec interval, and strictly comparable responses are collected for each 12 sec interval. When this data is

fed into the Lotus 1-2-3 software, other programs graph the results and do more detailed calculations which will be described later.

8.6 Gas analysis and calibration routines

Respiratory mass spectrometry Mass spectrometers ionise minute quantities of material in a high vacuum, with the aid of an electron gun. The molecules that are ionised lose a single outer shell electron. Some molecules are hit twice, losing two outer shell electrons and becoming doubly charged. Other molecules fragment. When they do so some fragments will already be charged and other uncharged fragments may be hit by the electron beam, acquiring charge. The charged particles are then accelerated and steered in an electromagnetic field in a way which separates them by their mass/charge ratios. The number of ions arriving at each collecting site is directly proportional to the concentration of the mother component in the sample. The degree of ionisation and the degree of fragmentation vary with the intensity of the electron beam. When that is fixed there are constant ratios between the concentration of the mother component and the concentrations of all of the whole and fragmented parts that are ionised.

Respiratory mass spectrometers are designed to sample small flows of gas continuously. The sample is drawn through a fine catheter by a sampling pump. An extremely minute fraction of this flow is admitted

through a molecular leak to the ionising chamber which is evacuated to a pressure of 10^{-7} mm Hg. In the early days of this form of spectrometry the sampling line was heated to prevent water vapour in the sample condensing on its walls, complicating subsequent analysis. Nowadays the sampling lines are made of fine polythene and may be many metres in length. The water vapour dissolves in the polythene and buffers subsequent changes in water vapour pressure. The results derived from long sampling lines are very accurate (Davies and Denison 1979).

The analyser used in these studies was a Centronics MGA 2000 quadripole spectrometer. In this device the charged particles are driven down an electromagnetic helter-skelter created by a rapidly varied voltage pattern imposed on four steel rods that bound the pathway. At the end of the path is a metal disc perforated by a single hole. Only species of a single mass/charge ratio can get through this hole at one time. All other species crash into the disc or escape between the poles. The voltage on the poles is adjusted every 25 msec to admit another mass/charge species through the hole. Up to 8 patterns can be specified in sequence, and the sequence is then repeated, giving the illusion of continuous analysis of up to eight gases at a time. Many experiments with this instrument have shown it has an accuracy of about 0.5 mm Hg and a response time from the 5th to the 95th percentile of the signal of about 100 msec.

Transit times vary with probe length and range from 0.1 sec for a 1 metre probe to 18 sec for a 30 metre probe, (Davies and Denison 1979)

In this experiment the instrument was fitted with a 5 metre polythene probe which could be easily transferred from one to another of the sampling sites. It was a straightforward matter to set the analyser for nitrogen (mass 28) and oxygen (mass 32), but a subterfuge had to be employed to follow carbon dioxide (mass 44) in the presence of nitrous oxide which also has a mass of 44. When nitrous oxide is hit by the electron beam some remains whole (mass 44), some lose one nitrogen atom (seen as mass 14) and can be followed as NO at mass 30. Some lose an oxygen atom (seen as mass 16) and the remnant is nitrogen (mass 28). The concentration time curve of mass 30 was chosen as a measure of PN_2O, because it is the biggest of the peaks and the only one that cannot be confused with single or doubly charged ions of the commonly respired gases. An appropriate multiple of this peak was subtracted from the combined peak at mass 44 to uncover the concentration of CO_2.

The output signals of respiratory mass spectrometers are directly proportional to the partial pressures of each component in the sampled gas. The device is calibrated by exposing the tip to a series of gas mixtures containing accurately known concentrations of each component of interest. The aim is to have a

minimum of three concentrations spanning the range of interest of each component gas. In this way alinearities can be detected. In this case the machine was frequently recalibrated with three reference mixtures. These were:

8% CO_2, 8% Argon, 24% O_2, 60% N_2

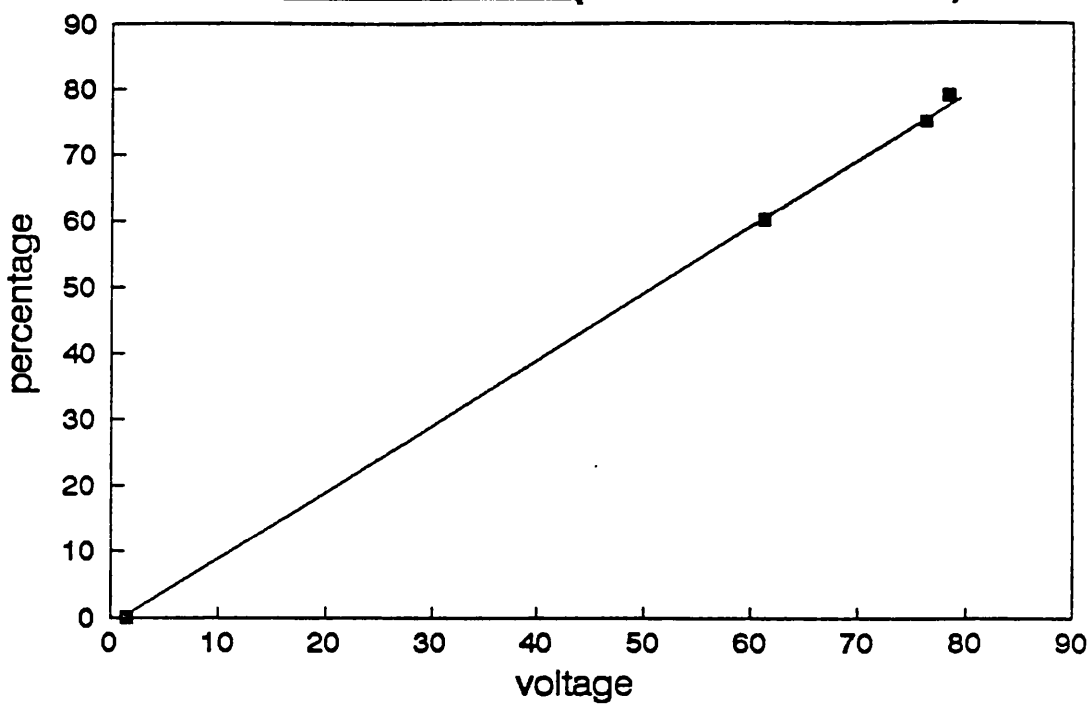
5% CO_2, 5% Argon, 15% O_2, 75% N_2

0% CO_2, 100% Argon, 0% O_2 0% N_2

Between times the sample tip was repeatedly exposed to air and the first reference gas for rapid checks on the instruments stability. A typical set of calibration curves is shown in Figure 8.4 to 8.7. As can be seen, the instrument is linear to $\pm$ 1 mm Hg. There were no significant alterations in the machines sensitivity or stability.

To avoid the considerable expense of having many reference gases made up with various concentrations of nitrous oxide, serial dilutions of the principal reference gas were made to test the linearity of the NO peak at mass 30. The output of this peak bore a constant relation to the equally diluted signals of the oxygen and nitrogen peaks.

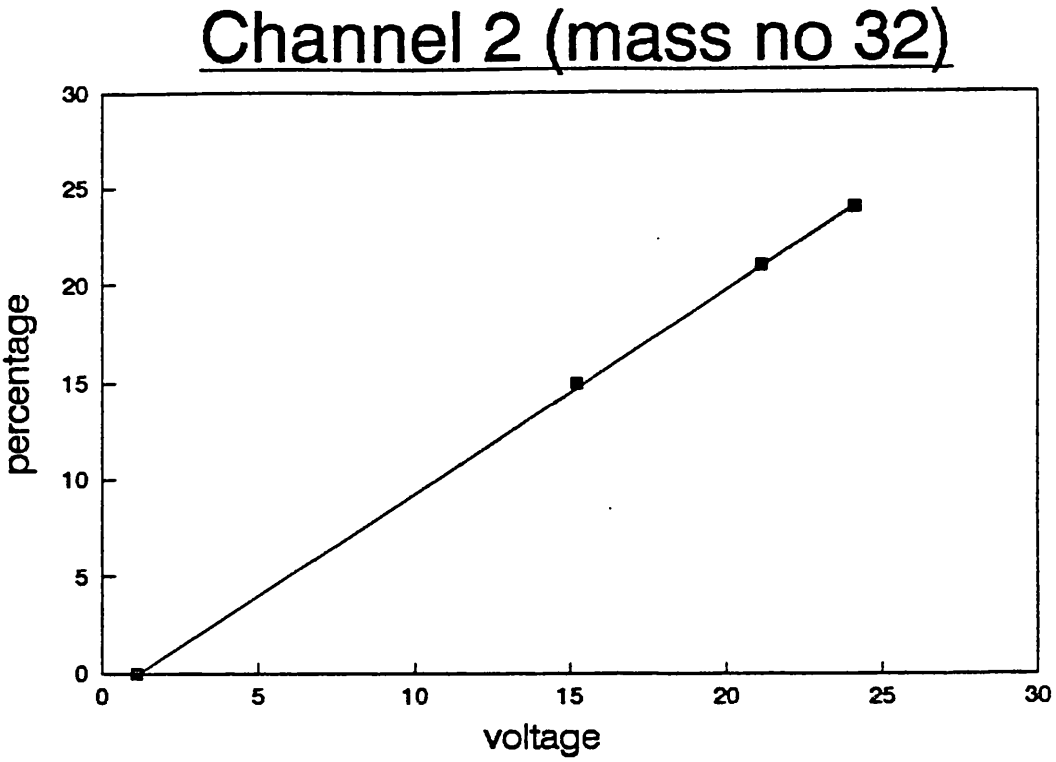
For additional safety an infra-red CO_2 and nitrous oxide analyser was added to the respiratory circuit to follow the concentrations of these two gases at the mouth. The sensing chamber of the device which is



The graph shows the mass spectrometer tracing of four gases, calibration gases 1 and 2, pure argon and air. It demonstrates that channel 1 has a linear calibration curve.

Channel	1	1
mass number	28	28
	Voltage	Percent of N_2
cal gas 1	61.2	60
cal gas 2	76.3	75
argon	1.5	0
air	78.4	79

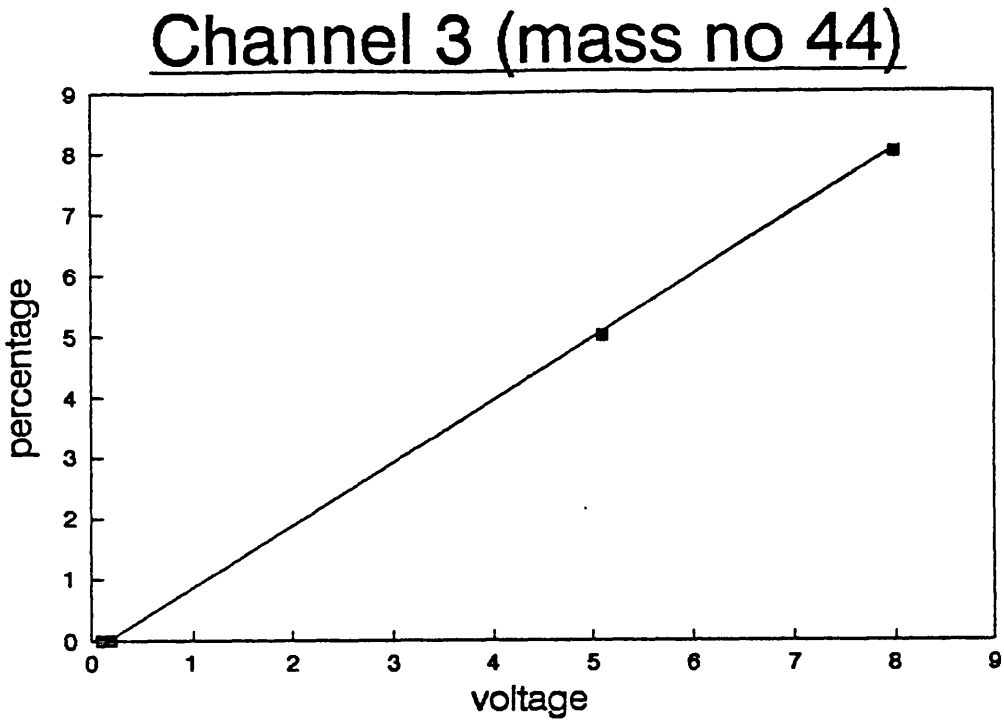
Figure 8.4



The graph shows the mass spectrometer tracing of four gases, calibration gas 1 and 2, pure argon and air. It demonstrates that channel 2 has a linear calibration curve.

Channel	2	2
mass number	32	32
	Voltage	O_2 Percent
cal gas 1	24.1	24
cal gas 2	15.2	15
argon	1.1	0
air	21.1	21

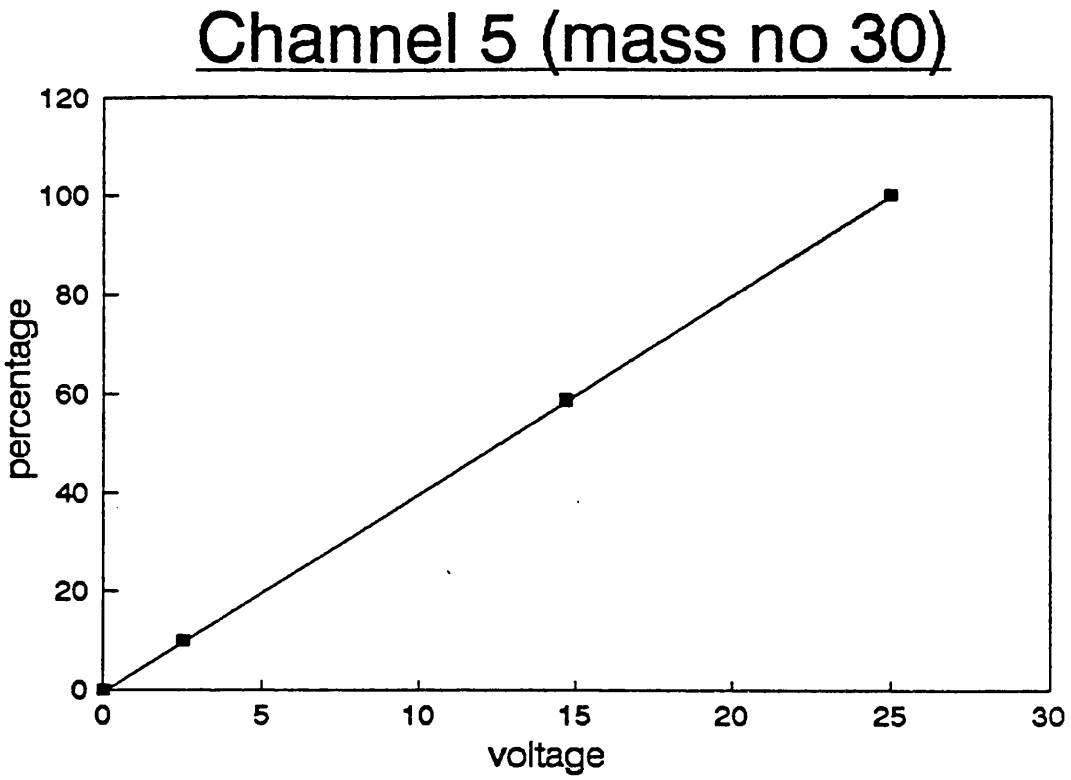
Figure 8.5



The graph shows the mass spectrometer tracing of four gases, calibration gases 1 and 2, pure argon and air. It demonstrates that channel 3 has a linear calibration curve.

Channel	3	3
mass number	44	44
	Voltage	Percent of CO_2
cal gas 1	8	8
cal gas 2	5.1	5
argon	0.1	0
air	0.2	0

Figure 8.6



The graph shows the mass spectrometer tracing of four gases, 100% N_2O, two accurate dilutions of 100% N_2O with air (mix 1 and 2), and 100% O_2. It demonstrates that channel 5 has a linear calibration curve.

Channel	5	5
mass number	30	30
	Voltage	Percent of N_2O
N_2O	25	100
Mix 1	14.7	58.8
Mix 2	2.5	10
O_2	0	0

Figure 8.7

made by Hewlett Packard, (Patient monitor model 78356a) passes an infrared beam across the respired stream at a point where the stream is bounded by two quartz windows. The machine was set to display carbon dioxide tensions having made corrections for the infra red absorption of nitrous oxide in the stream. In this way respired nitrous oxide could be followed at mass 30 by the mass spectrometer, and the compound spectrometric signal of N_2O and CO_2 at mass 44 which was tedious to convert, could be recorded but ignored until after the experiment, while the infra-red meter displayed respired PCO_2.

The infra-red meter was calibrated in the same way as the mass spectrometer. In addition, the correction factor for nitrous oxide was set up using the reference discs provided by the manufacturer. Detailed comparisons between mass spectrometer and infra-red outputs confirmed the meter was satisfactory, for monitoring purposes. The Patient monitor also contains a slowly responding fuel cell for the determination of mean respired PO_2 which gave another easily read check on subject safety.

The flow-meters were checked by setting them to nominated values to fill Douglas bags for known times. The bags were then emptied through rolling-seal spirometers that had previously been calibrated by

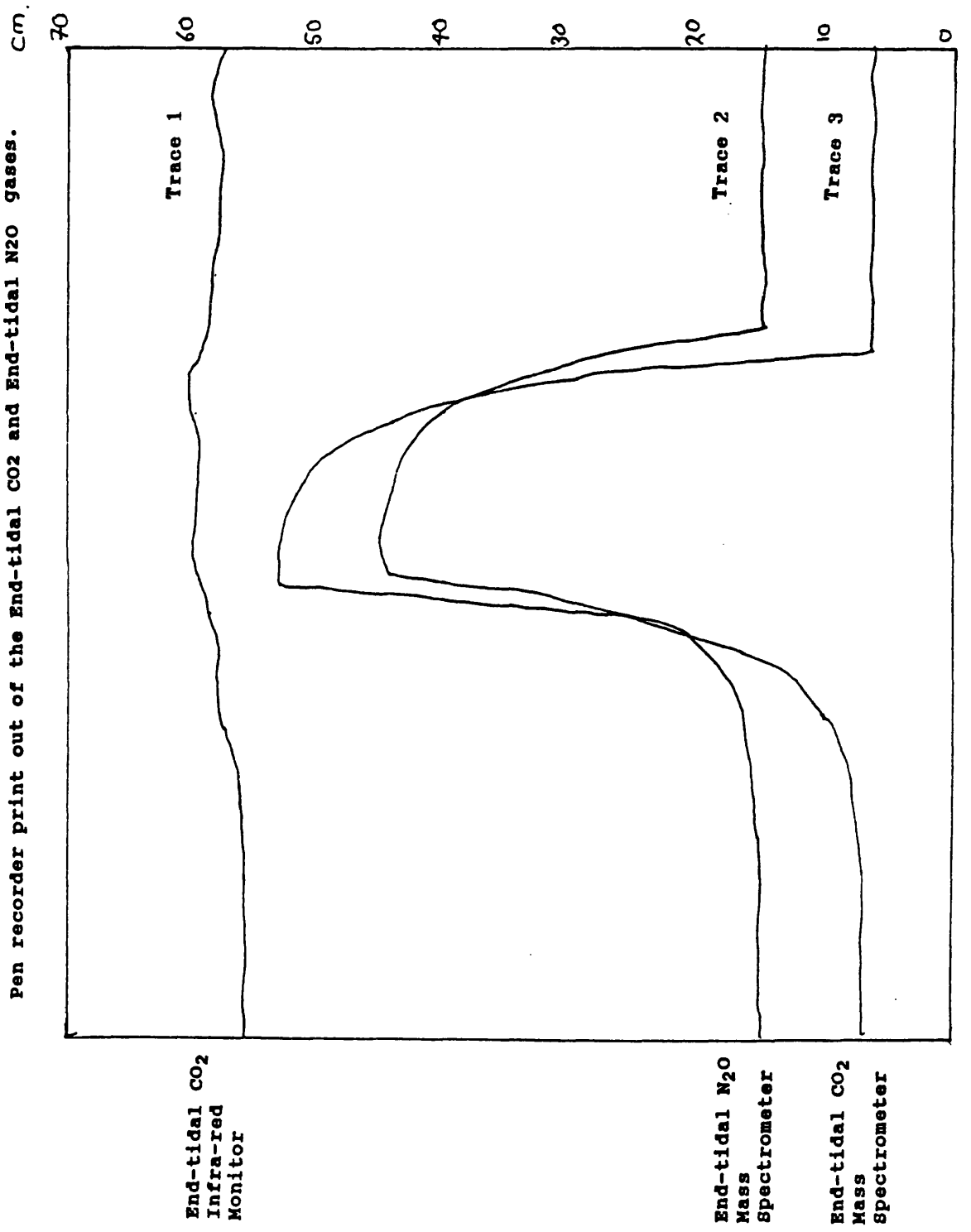
reference syringes with a 6 litre capacity. These tests showed the flow meters were accurate to within 1.0 %.

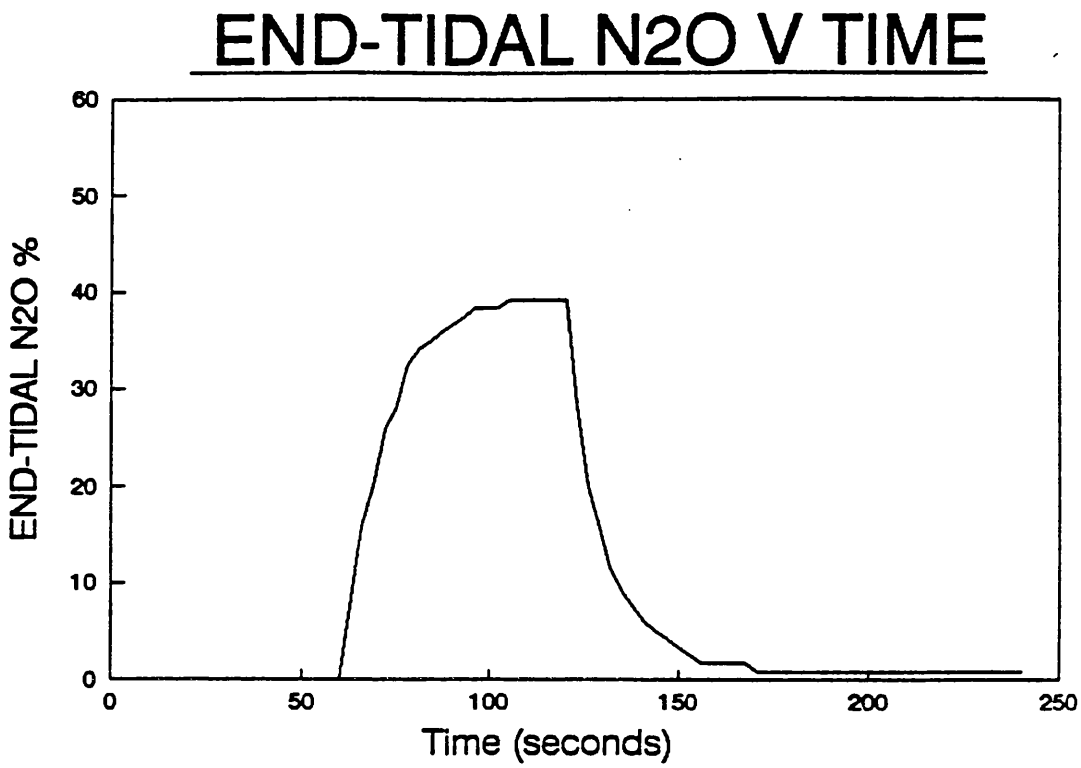
In all of the studies a continuous record of the spectrometer outputs at mass 30 (NO), mass 32 (O_2), and mass 44 (N_2O+CO_2), and of the infra-red output of CO_2, were recorded on a Linseis model LS, flat bed pen recorder, throughout each 22 minute period of study. Smoothed curves were drawn through the end-tidal tensions of each gas, and alveolar tensions were assumed to equal the values of that curve, read at 3 sec intervals. These tensions were typed into a Lotus 1-2-3 spreadsheet for subsequent correlation with the simultaneous psychomotor responses. A typical respired gas trace, and its spreadsheet transcript is shown in Figure 8.8 to 8.10.

8.7 Safety

The concentrations of N_2O employed in these experiments were 30 to 60%. These levels are frequently used in clinical practice to provide pain relief to conscious patients. In the present experiments, the subjects' levels of consciousness were monitored continuously by the psychomotor task. The author of this thesis, a Senior Registrar in Anaesthesia, observed the subjects, noted their respired oxygen, carbon dioxide and nitrous oxide tensions and their psycho-

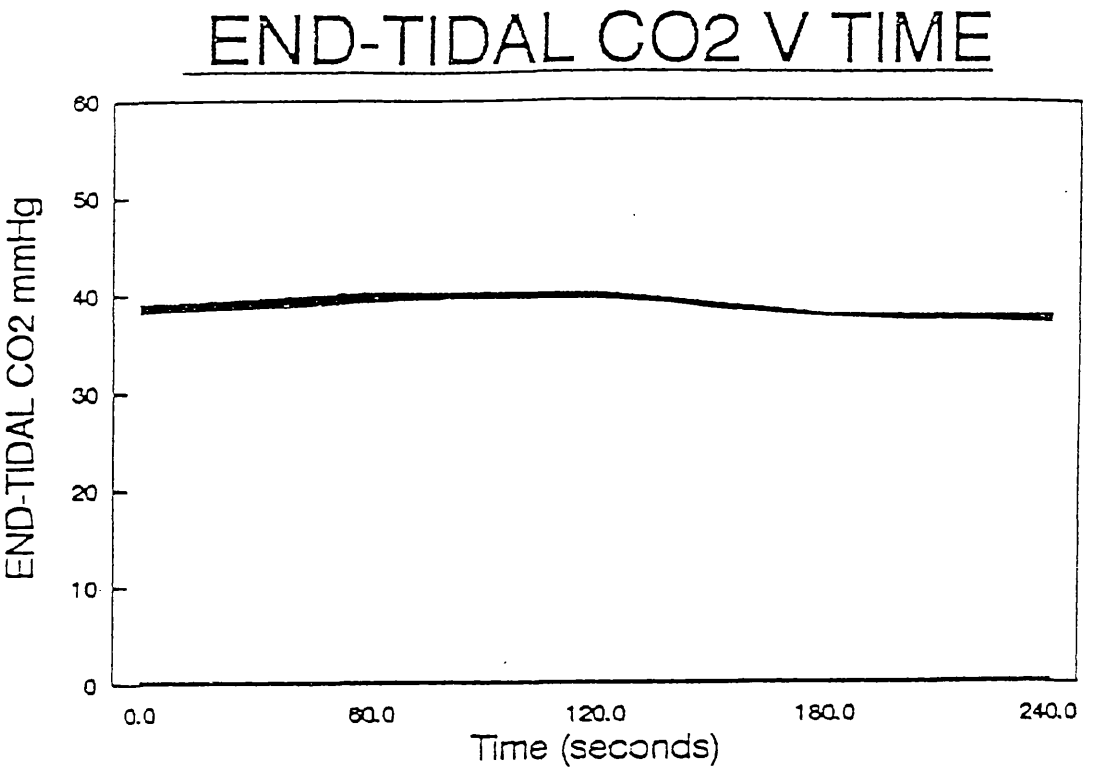
Figure 8.8


Pen recorder print out of the End-tidal CO2 and End-tidal N2O gases.
cm.
70
60
50
40
30
20
10
0
Trace 1
Trace 2
Trace 3
End-tidal CO2 Infra-red Monitor
End-tidal N2O Mass Spectrometer
End-tidal CO2 Mass Spectrometer



The end-tidal print out on the pen recorder (trace 2) was from channel 5 of the mass spectrometer. This channel was calibrated for a mass number of 30, the same as the molecular weight of nitric oxide (NO). Having shown that this channel gave a linear calibretion three calibration marks were made on the paper of the pen recorder (i.e N2O 60%, 10%, and zero %) Thus it was easy to substitute the end-tidal N2O read out in millimetre marks on the paper for an end-tidal N2O percentage.

Figure 8.9



There are two records of end-tidal CO_2 on the pen recorder. One is from the infra-red monitor, the other from channel 3 of the mass spectrometer.

The infra-red monitor records the end-tidal CO_2 with out any compensation for the presence of N_2O, thus it will only give a reliable read out when no N_2O is present, i.e before and after the N_2O pulse. The calibrated infra-red monitor is used to provide two calibration marks on the record paper (zero, 54 mmHg). Thus knowing the monitor gives a linear read-out, it is easy to substitute the end-tidal CO_2 millimetre marks on the paper for an end-tidal CO_2 read-out in mmHg. The result was in agreement with the mass spectrometer.

There is also a mass spectrometer record of end-tidal CO_2 on the pen recorder. This is from channel 3, which is calibrated for a mass number of 44, the molecular weight of CO_2 and N_2O. This channel will only give a linear read-out for CO_2 when the voltage produced by N_2O in this channel is subtracted. There is a fixed relationship between the voltage produced by N_2O in channels 3 and 5. The voltage in channel 5 can be calculated from the pen recorder trace 2. Therefore at each three second interval during the N_2O pulse, the voltage produced by N_2O in channel 3 can be calculated and then subtracted from the voltage found..The mass spectrometer gives a linear read-out for CO_2 in the absence of N_2O. Two calibration marks are made on the paper for a CO_2 of zero and 8% from calibration gases. Therefore the millimeter record on trace 3 can be converted to an end-tidal CO_2 record in mmHg as shown in the graph above.

Figure 8.10

motor responses, throughout each period of hyperventilation and anaesthesia. There were no untoward incidents.

The studies described here were approved by the Ethics Committee of the National Heart and Chest Hospitals.

9 PRELIMINARY EXPERIMENTS

Before a formal investigation of the effects of hyperventilation on nitrous oxide anaesthesia could begin it was necessary to establish the:

i) control and stability of end-tidal CO_2 tensions
ii) control and stability of end-tidal N_2O tensions
iii) relation between end tidal and arterial PCO_2
iv) learning curve of the task
v) performance reproducibility of the fully learnt task
vi) the concentration of N_2O clearly affecting the task
vii) the level of hyperventilation modifying the N_2O effects

The control and stability of end-tidal CO2 tensions

Figure 9.0 shows the outcomes of subject #7 ventilating at 38 litres a minute for 22 minutes. The lowest curve plots the result of adding no CO_2 to the inspirate. There is sharp fall in end-tidal PCO_2 to begin with, that is largely complete in 3 minutes. A gradual fall of about 0.5 mm Hg/min persists to the end of the experiment. This result is typical of unmodified hyperventilation in healthy subjects and reflects the rapid washout of CO_2 from the lungs and circulation accompanied by the much slower elution of CO_2 from other tissues. The intermediate curve illustrates a

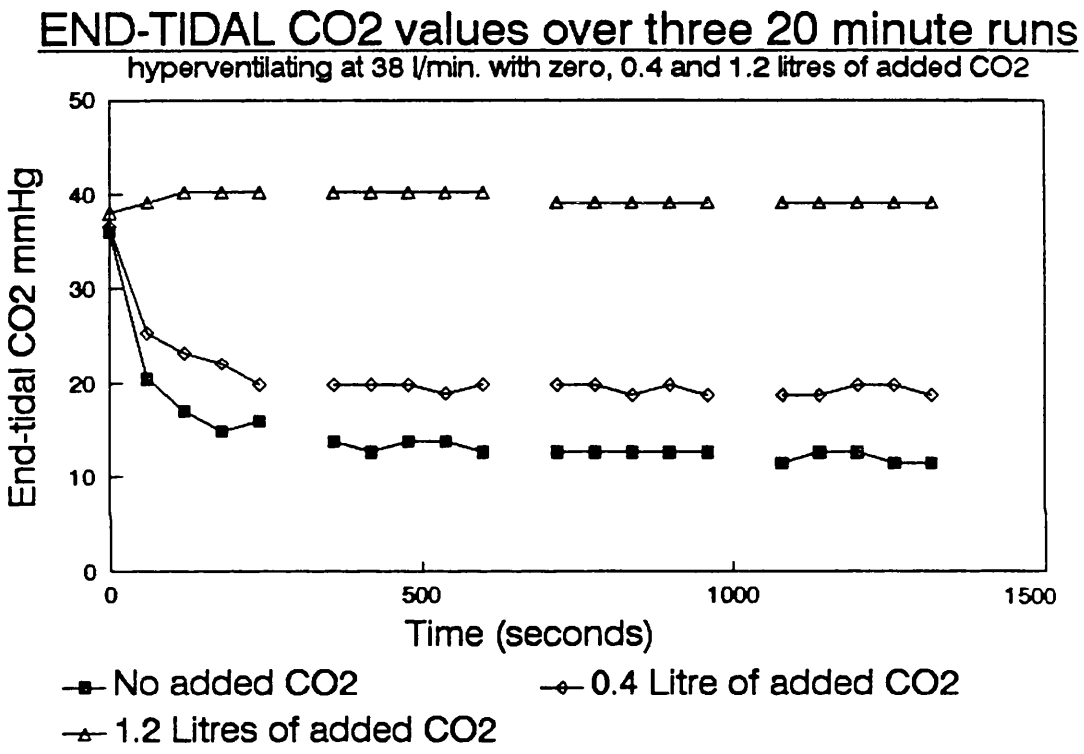

END-TIDAL CO2 values over three 20 minute runs
hyperventilating at 38 l/min. with zero, 0.4 and 1.2 litres of added CO2
End-tidal CO2 mmHg
50
40
30
20
10
0
0
500
1000
1500
Time (seconds)
No added CO2
0.4 Litre of added CO2
1.2 Litres of added CO2

Figure 9.0

consequence of adding 0.4 litres/min of CO_2 to the incoming air, and implies that it is quite practical to select, as here, a desired end-tidal PCO_2 of 20 mm Hg, and hold the expired tension to that value. Similarly, the upper curve, which demonstrates the end-tidal tensions recorded after mixing 1.2 litres/min of CO_2 with inspired air, indicates that it is also easy to hold end-tidal CO_2 tensions at 40 mm Hg.

Figure 9.1 shows the results of a similar experiment in Subject #4. The lowest curve plots the inspired CO_2 tensions when about 0.75 litres/minute of that gas was mixed with the incoming 37.25 litres/min of air, with the intention of holding his end-tidal PCO_2 at 28 mm Hg. As expected, the inspired tension is approximately 760*(0.75/38) i.e 15 mm Hg. To maintain his end-tidal PCO_2 at 40 mm Hg needed the addition of 1.5 litres/minute of CO_2, holding his inspired PCO_2 at 30 mm Hg.

It is impossible to calculate exact CO_2 excretions from this data alone, but simple to make an approximate estimate. In the normocapnic study the PCO_2 gradient between end-tidal and inspired gases is about 10 mm Hg. At a flow of 38 litres/minute this would represent an excretion of 38*10/760) = 500 ml/min but something like a third of the expirate would have been dead-space gas with no CO_2 gradient at all, suggesting a CO_2 excretion of around 330 ml/min. The normal resting excretion is about 200 ml/min. The higher value seen here is reasonably appropriate for subjects sitting upright in

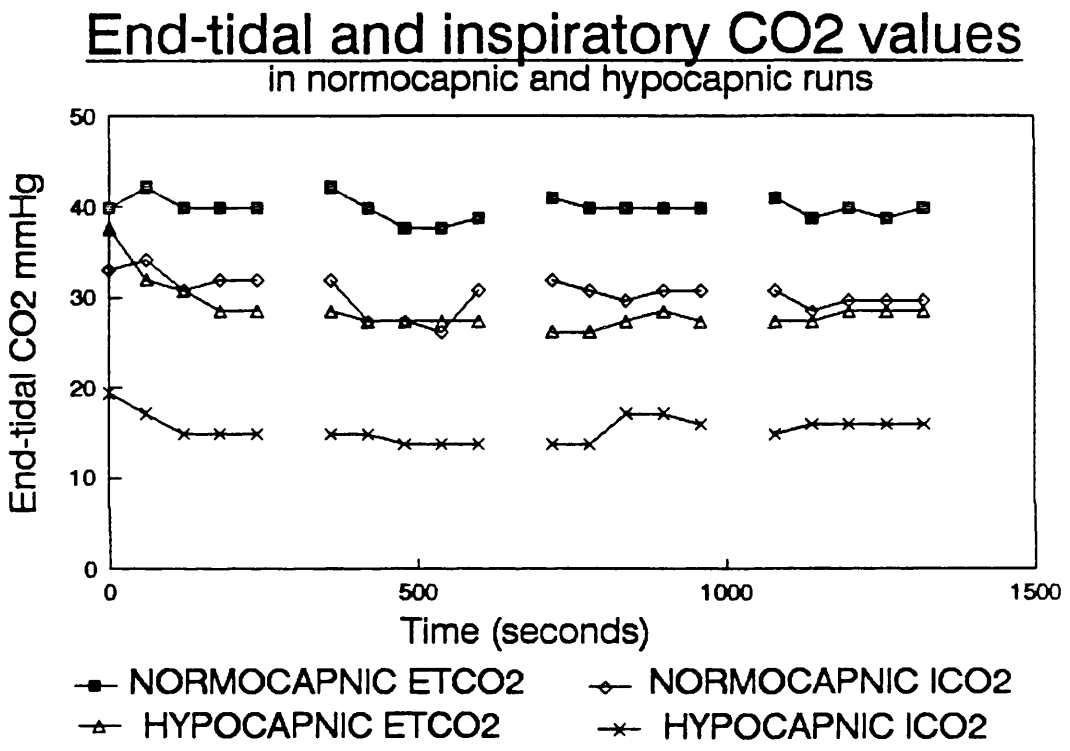
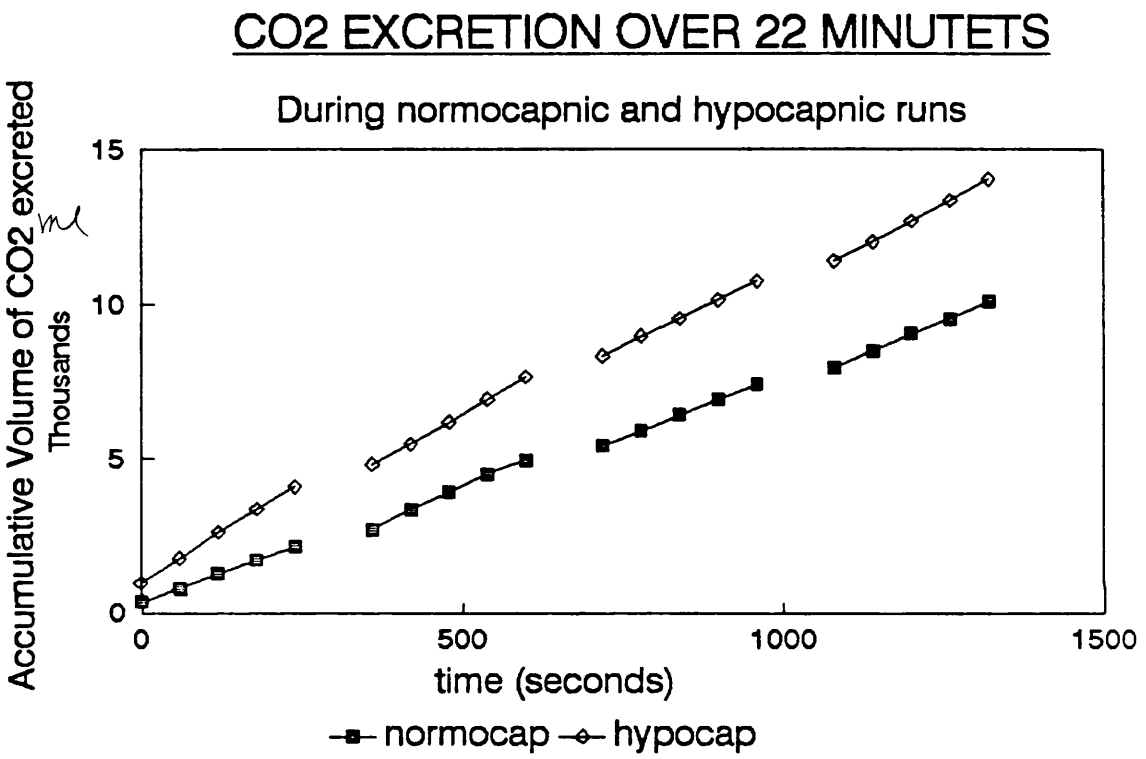

End-tidal and inspiratory CO2 values
in normocapnic and hypocapnic runs
End-tidal CO2 mmHg
50
40
30
20
10
0
0
500
1000
1500
Time (seconds)
NORMOCAPNIC ETCO2
NORMOCAPNIC ICO2
HYPOCAPNIC ETCO2
HYPOCAPNIC ICO2

Figure 9.1

a chair and ventilating at 38 litres/min. It is roughly the same output as is seen in unstressed people driving cars or flying planes. Applying identical assumptions to the two hypocapnic curves suggests an excess excretion of 500 ml, as shown in Figure 9.2. Assuming a functional residual capacity of 3 litres one would expect 3000*(40-28)/760 = about 50 ml to come from the lungs. Assuming that mixed venous and arterial CO_2 tensions have also dropped by 12 mm Hg, and the circulating blood volume is about 5 litres, one would anticipate that about 490 ml had come from blood. It is not worth being too precise about such figures as they involve very crude assumptions, but they do suggest the added excretion is appropriate to the fall in PCO_2 that was achieved.

Figure 9.3 illustrates the maintenance of end-tidal PCO_2 during normocapnic and hypocanic studies in all 7 subjects. The pattern of changes is the same for all of them, i.e the major fall occurs in the first three minutes and is sensibly complete by the sixth minute, which is the beginning of the second 4 minute epoch of the psychomotor task. Because this was so it was decided to use the second and fourth epochs as test periods with the third epoch as an unstressed hypocapnic control period.

The relation between end-tidal and arterial CO2 tensions. Many studies by others (e.g Denison 1967, Piper et al 1974) have shown a close correspondence between



Accumulative total at end of normocapnic run 10090 mls

Accumulative total at nd of hypocapnic run 14040 mls

Figure 9.2

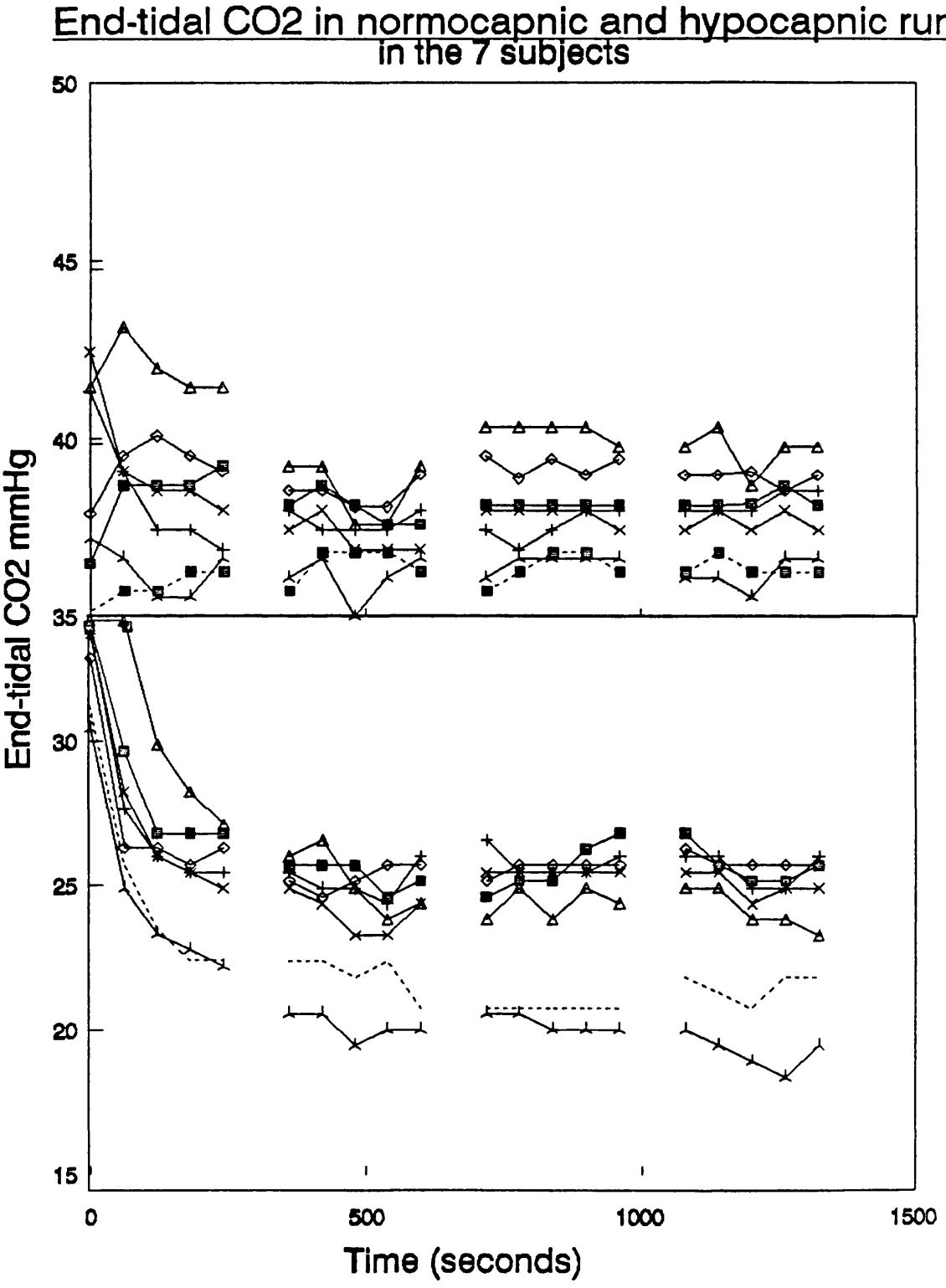

End-tidal CO2 in normocapnic and hypocapnic runs
in the 7 subjects
End-tidal CO2 mmHg
50
45
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

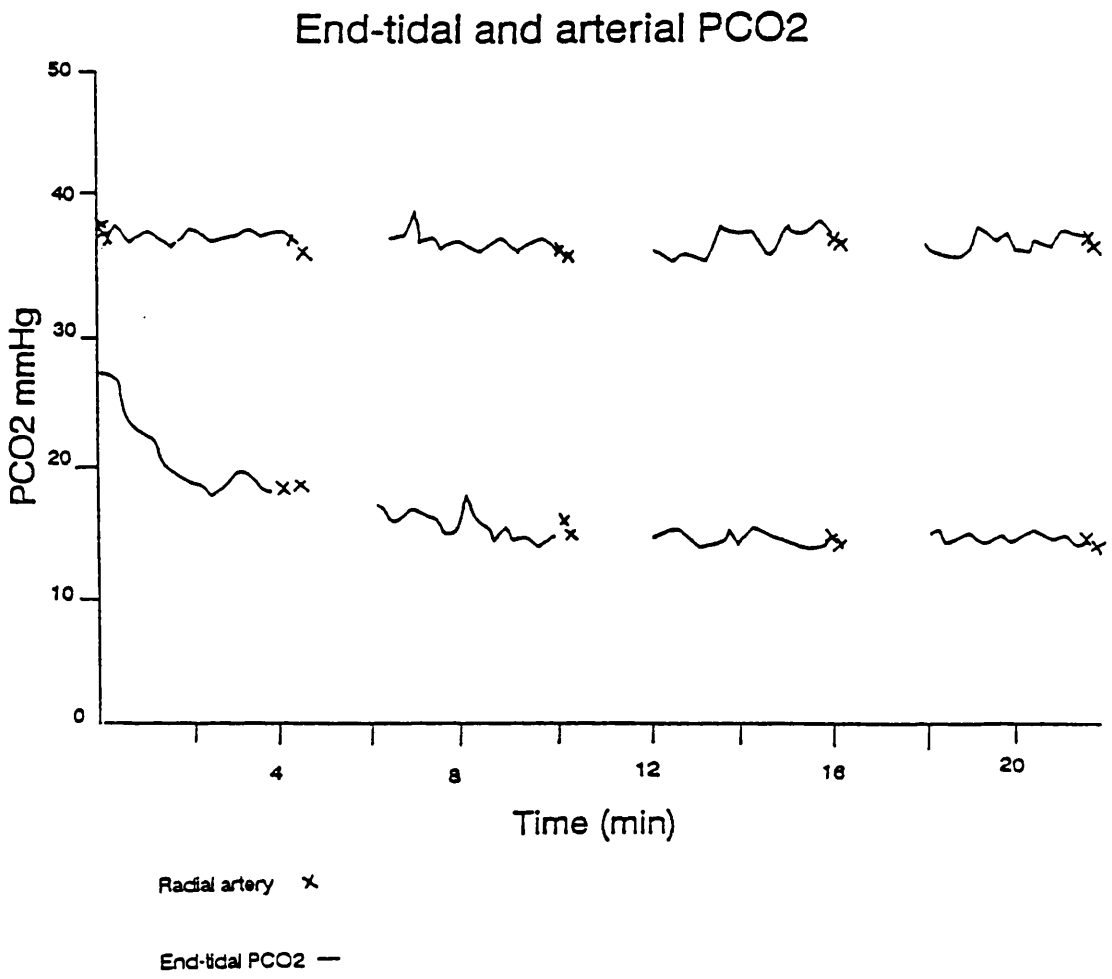
Figure 9.3

end-tidal and arterial CO_2 tensions, so it was decided to demonstrate this in a few of the subjects on one occasion, but not to sample arterial blood regularly. Table 9.0 shows the comparison of duplicate arterial samples with end-tidal gas tensions made on subject #7 during a previous study (Davies et al: in preparation). There is very good agreement.

Table 9.1 shows comparisons of arterial and end-tidal CO_2 tensions at the end of 22 minutes of hyperventilation in 5 subjects (#1, #3, #4, #5 & #6). Again there is good agreement. From these studies it was concluded that it was reasonable to assume close correspondence between the two tensions in the formal study also.

The control and stability of end-tidal N2O concentrations

Figure 9.4 shows the end-tidal nitrous oxide concentrations recorded in subject #7 on four occasions. Time, on the abscissa, spans a four minute epoch in which nitrous oxide was administered from the 60th to the 120th second precisely. In two of the four epochs the subject was ventilating at 38 litres per minute with enough CO_2 added to maintain normocaonia. On the other two occasions no CO_2 was added and his end-tidal PCO_2 had fallen to circa 15 mm Hg. End-tidal N_2O% is on the ordinate. The graph shows this rises exponentially to an asymptote of 47%, with a time constant of about 8 sec. The washout is equally fast. There is very close agreement between the four curves. Figure 9.5 shows the



	PaCO2 in normocapnic runs		PaCO2 in hypocapnic runs	
Time (min)				
0	36.3	36.2	37.8	37.3
4	35.4	34.7	18.1	18.1
10	35.2	35.8	15.8	14.5
16	36.4	36.1	13.7	12.8
22	35.3	35.9	14.1	12.8

Table 9.0

Table 9.1

Blood gases on 5 subjects at the end of 20 minutes hyperventilating at low end-tidal's CO2.

Subject #	1	3	4	5	6
FiO_2 %	0.21	0.21	0.21	0.21	0.21
$ETCO_2$ mmHg	26	25	27	30	22
ICO2 mmHg	16	11	16	18	10
pH	7.52	7.54	7.52	7.48	7.6
$PaCO_2$ mmHg	23.3	24.8	28.5	27.8	21.8
PaO_2 mmHg	134	130	132	133	128
HCO_2 mmHg	18.8	21.3	23	20	22
B.Excess	-3.3	-0.6	2.4	-1.9	0.7
Saturation %	99	99	99	99	99

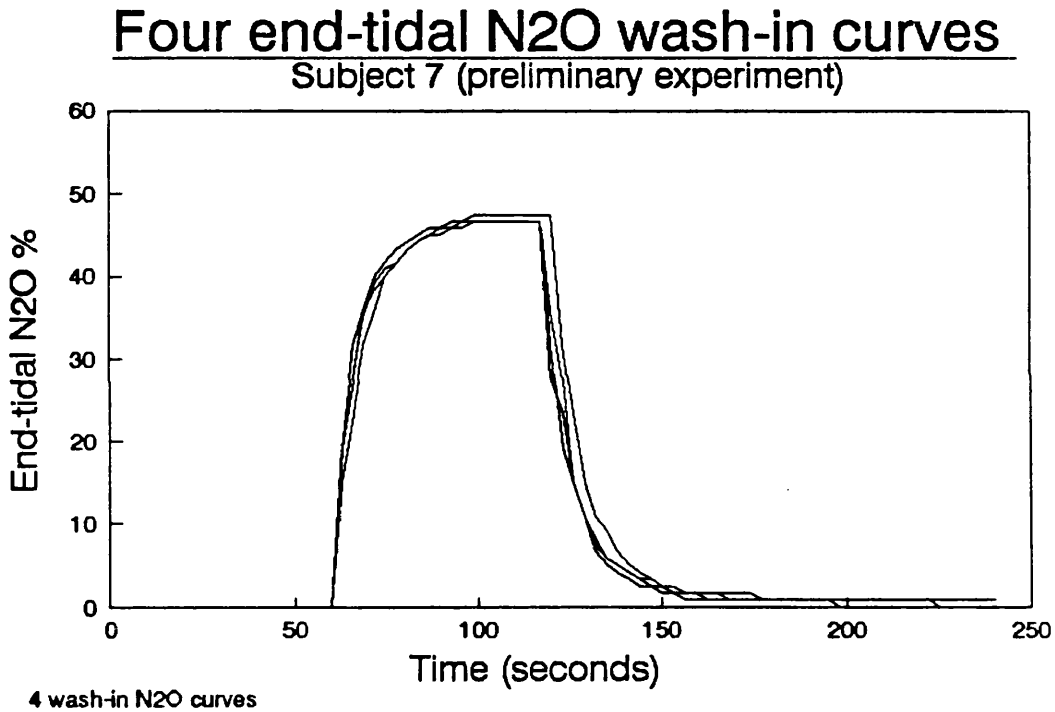
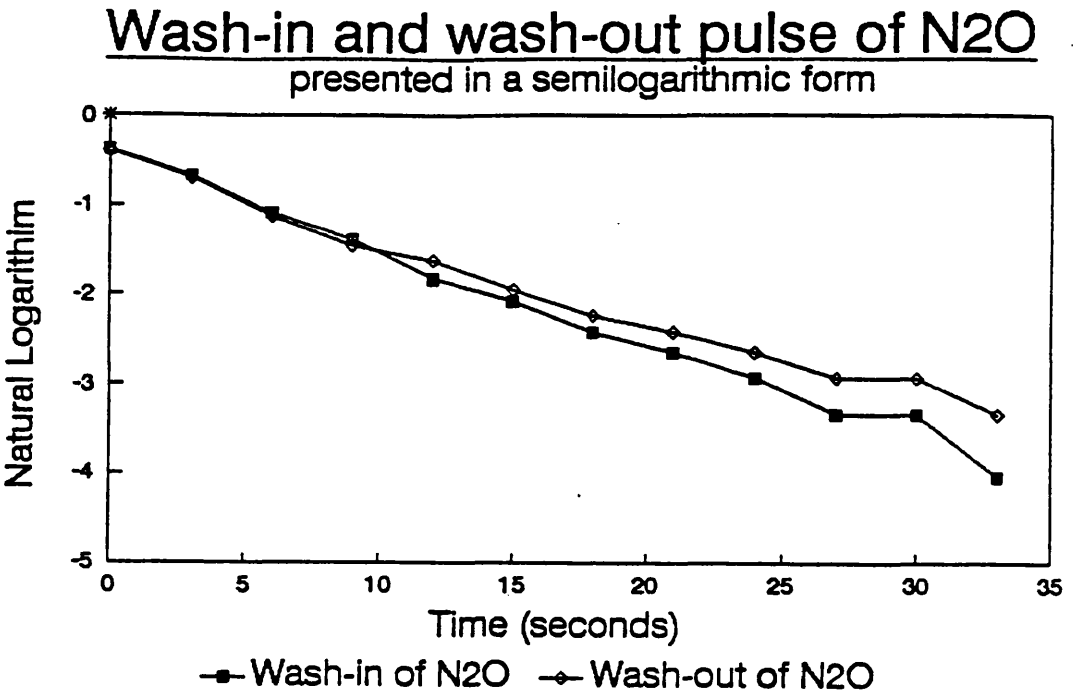

Four end-tidal N2O wash-in curves
Subject 7 (preliminary experiment)
End-tidal N2O %
60
50
40
30
20
10
0
0
50
100
150
200
250
Time (seconds)
4 wash-in N2O curves
2 in normocapnic and 2 in hypocapnic runs

Figure 9.4



Wash-in LN(1-N2O/Aysmtope)

Wash-out LN(N2O/Asymtope)

The natural logarithmic plots for for the wash-in and wash-out curves of N_2O disclose straight lines. Thus confirming their exponential nature. From the slope of these lines it is posible to calculate the time constant and half times.

Equations for wash-in and wash-out curves of N_2O pulses.

Wash-in $Y_1=A(1-e^{-t/Tin})$ $Ln(1-Y_1/A)=-t/Tin$
Wash-out $Y_2=A(e^{-t/Tout})$ $Ln(Y_2/A) =-t/Tout$

A= Asymtope
Ln=Natural logarithm
t=time
T=time constant

At 15 seconds $Ln(1-Y_1/A)=2=-15/Tin$ $Tin =7.5$
$Ln(Y_2/A) =2.1= -15/Tout$ $Tout=7.1$

Half time = Time constant*Ln2.
Therefore at 15 seconds tin=5.2 and tout=4.9.

Figure 9.5

same data on a semilogarithmic scale, with the asymptote for the inspired curve calculated by the procedure of Defares (1958). The time constants of wash-in and washout calculated from these slopes were 7.5 sec and 7.1 sec respectively.

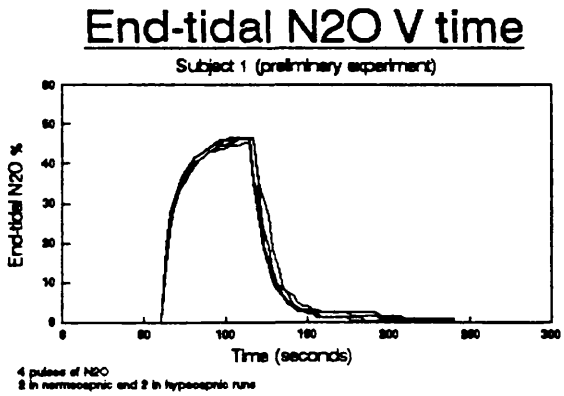
Arithmetic plots of similar data for the other six subjects are shown in Figure 9.6. Again there is close agreement between the four curves. From this it was concluded that it was practical to apply identical and reasonably sharp edged 1-minute pulses of nitrous oxide anaesthesia during hypocapnia and normocapnia in all 7 subjects.

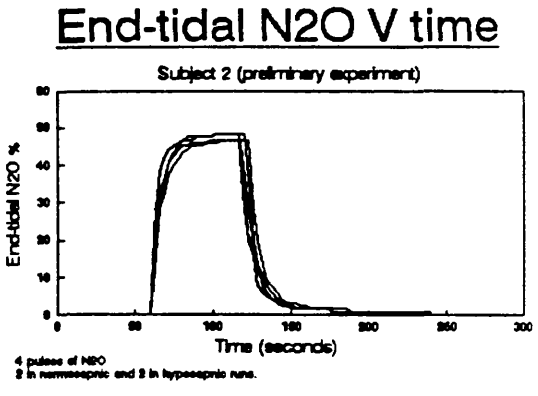
Figure 9.7 shows single curves from subject #5, ventilating at 38 litres per minute, with three different pulse concentrations of nitrous oxide. Semilogarithmic plots of the same data showed that the time constants of wash-in and wash-out are independent of pulse concentration.

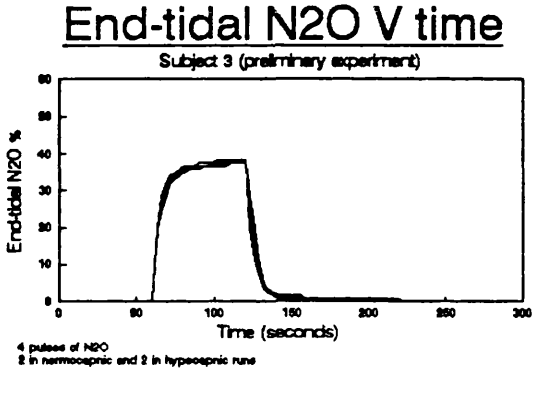
The studies showed it was possible to administer brief pulse of nitrous oxide anaesthesia precisely, with time scales appropriate to submarine escape

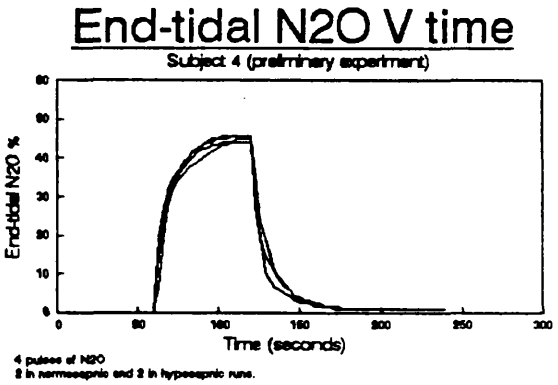
The learning curve of the task

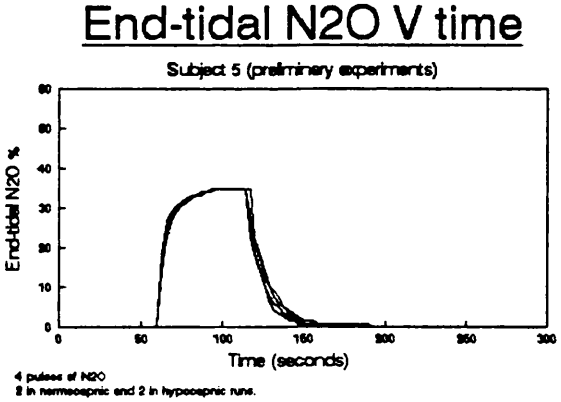
Some of the subjects were already very familiar with the manikin task, but others were not. Figure 9.8 plots the mean response times of five naive subjects learning the task. The numbers on the abscissa refer to consecutive trials of 22 minutes, each contain four 4 minute


End-tidal N2O V time
Subject 1 (preliminary experiment)
End-tidal N2O %
Time (seconds)


End-tidal N2O V time
Subject 2 (preliminary experiment)
End-tidal N2O %
Time (seconds)


End-tidal N2O V time
Subject 3 (preliminary experiment)
End-tidal N2O %
Time (seconds)


End-tidal N2O V time
Subject 4 (preliminary experiment)
End-tidal N2O %
Time (seconds)


End-tidal N2O V time
Subject 5 (preliminary experiments)
End-tidal N2O %
Time (seconds)

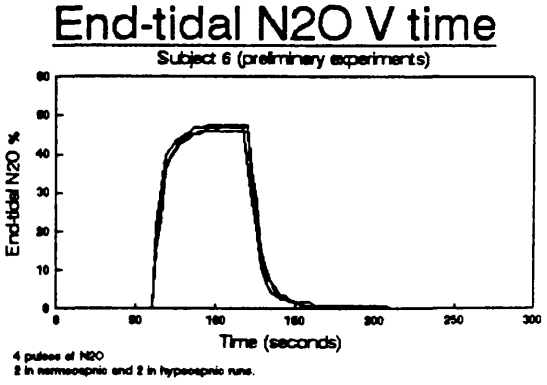
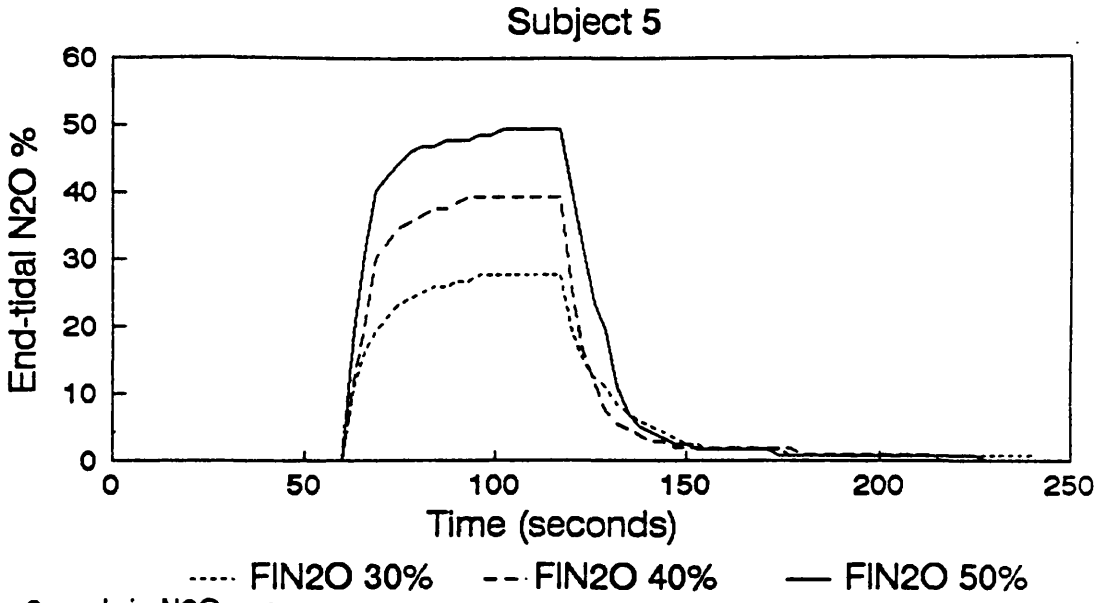

End-tidal N2O V time
Subject 6 (preliminary experiments)
End-tidal N2O %
Time (seconds)

Figure 9.6

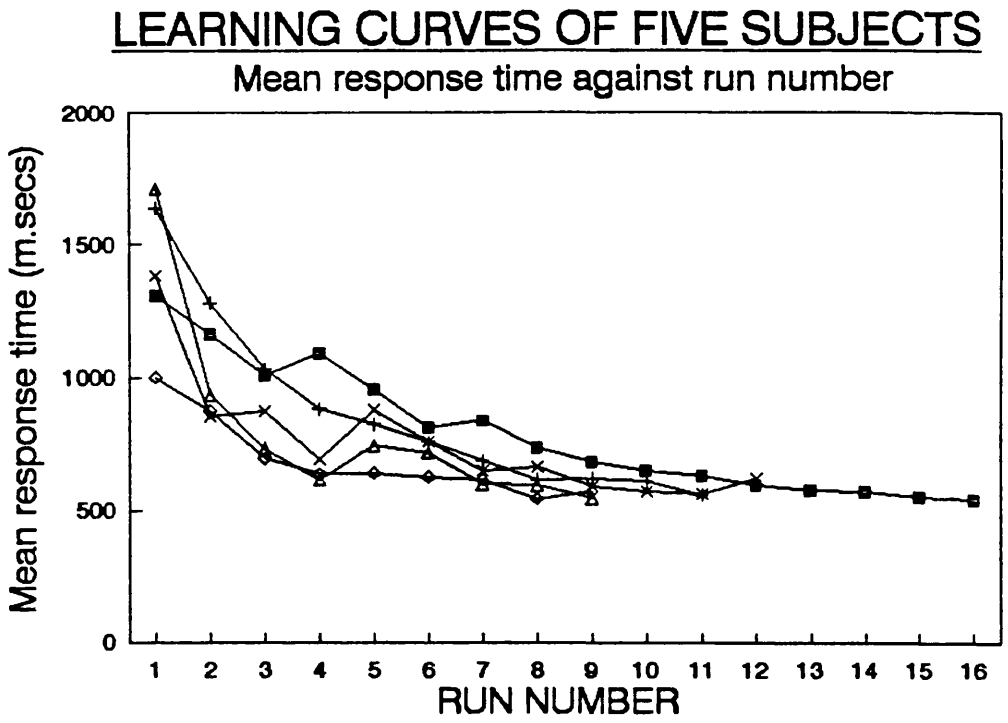
End-tidal N2O V TIME



3 wash-in N2O curves
At N2O inspired levels of 30%, 40%, 50%.

Percent of N2O inspired		Time Constant	Half Time
30%	Wash-in	7.5	5.2
	Wash-out	7.0	4.9
40%	Wash-in	7.1	5.0
	Wash-out	6.5	4.5
50%	Wash-in	7.5	5.2
	Wash-out	6.9	4.8

Figure 9.7


LEARNING CURVES OF FIVE SUBJECTS
Mean response time against run number
Mean response time (m.secs)
2000
1500
1000
500
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
RUN NUMBER

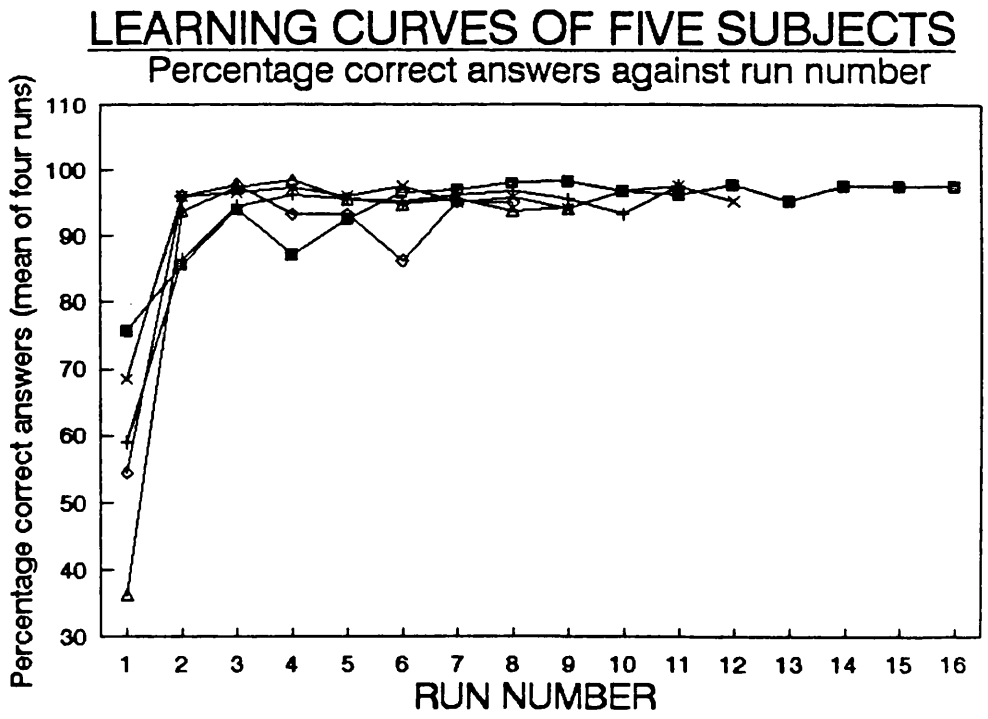

LEARNING CURVES OF FIVE SUBJECTS
Percentage correct answers against run number
Percentage correct answers (mean of four runs)
110
100
90
80
70
60
50
40
30
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
RUN NUMBER

Figure 9.8

epochs of the test. The curves are very similar to each other. The naive subjects appear to require about ten 22-minute exposures to learn how to do the task fast and reproducibly. The lower Figure shows their error rates settled at 2-3% after about four 22-minute exposures. This suggested that error rate would be less sensitive than response time as an indicator of task performance.

The reproducibility of performance of the fully learnt task

Once their response times had settled to a fairly constant value, the subjects were asked to perform two 22-minute sessions of the task. Each session contained four 4-minute test epochs. The subjects breathed spontaneously at this time, performing the task with no distractions. Their times are listed in the Table 9.2. The table shows that on average they achieved a reproducibility of ± 3.4%. Their response times averaged just over half a second. Since the window for recording each response is 2 seconds long (with the third second reserved for a blank screen) it meant that about 1.5 seconds would be available for recording impaired responses. It was thought that this combination of response times and reproducibility was sufficient to justify asking them to combine performing the task with synchronous ventilation at 38 litres/min, hypocapnia and nitrous oxide anaesthesia.

The reverse task

Table 9.2

Stability data on the 7 subjects doing Normal Task breathing spontaneously. Mean results of 8 consecutive epochs for each subject.

Subject #	1	2	3	4	5	6	7
Epoch 1	536	549	525	476	573	505	440
Epoch 2	564	564	580	453	554	489	432
Epoch 3	555	539	533	438	543	489	462
Epoch 4	513	558	579	463	542	485	445
Epoch 5	588	526	561	460	507	485	444
Epoch 6	593	560	507	475	524	479	446
Epoch 7	558	528	520	440	588	482	436
Epoch 8	549	564	576	454	544	496	421
Mean of 8 epochs	557.0	548.5	547.6	457.4	546.9	488.8	440.8
Standard deviation	24.4	14.7	27.7	13.2	23.9	7.8	11.2
Coefficient of Variation	4.4	2.7	5.1	2.9	4.4	1.6	2.5

Average score for the 7 subjects 512

Average % standard deviation of the 7 subjects 3.4

Three of the subjects (#4, #6 & #7) were already very familiar with the task, and in early attempts at combining these insults their performances betrayed little sensitivity to hypocapnia or anaesthesia. It appeared that the task was too simple and too deeply learnt to show impairment except to gross stresses. So it was decided to ask them to perform a variant of the task in which they had to answer every question wrongly rather than correctly. For convenience, this will be referred to as the reverse task. Table 9.3 demonstrates the reproducibility of this task, as performed by the three men. As expected their responses are slower, by about 150 msec, the % variability is slightly greater (4.1%), and the error rate somewhat more. Response times are well below 1 second, leaving at least one further second for impairment to appear.

Analysis of the response times

It was anticipated that hyperventilation might produce a gradual slowing of response times through the 22 minute period of hypocapnia, and that nitrous oxide would certainly produce slowing of about a minutes duration in the middle of the 2nd and 4th forth minute test epochs. As these effects might be slight, they could be lost in the background variability of response times. In addition the gradual slowing induced by hyperventilation might mask the briefer effects of nitrous oxide anaesthesia. We needed some method, of distinguishing the two effects.

Table 9.3

Stability data on the 3 subjects doing the Reverse Task breathing spontaneously. Mean results of 8 consecutive epochs for each subject.

Subject #	1	2	3	4	5	6	7
Epoch 1				668		539	740
Epoch 2				665		578	728
Epoch 3				709		571	792
Epoch 4				723		578	715
Epoch 5				693		517	731
Epoch 6				690		606	789
Epoch 7				712		595	798
Epoch 8				734		577	731
Mean of 8 epochs				699.3		570.1	753.0
Standard deviation				23.2		27.1	31.7
Coefficient of Variation				3.3		4.8	4.2

Average score for the 3 subjects 674.1

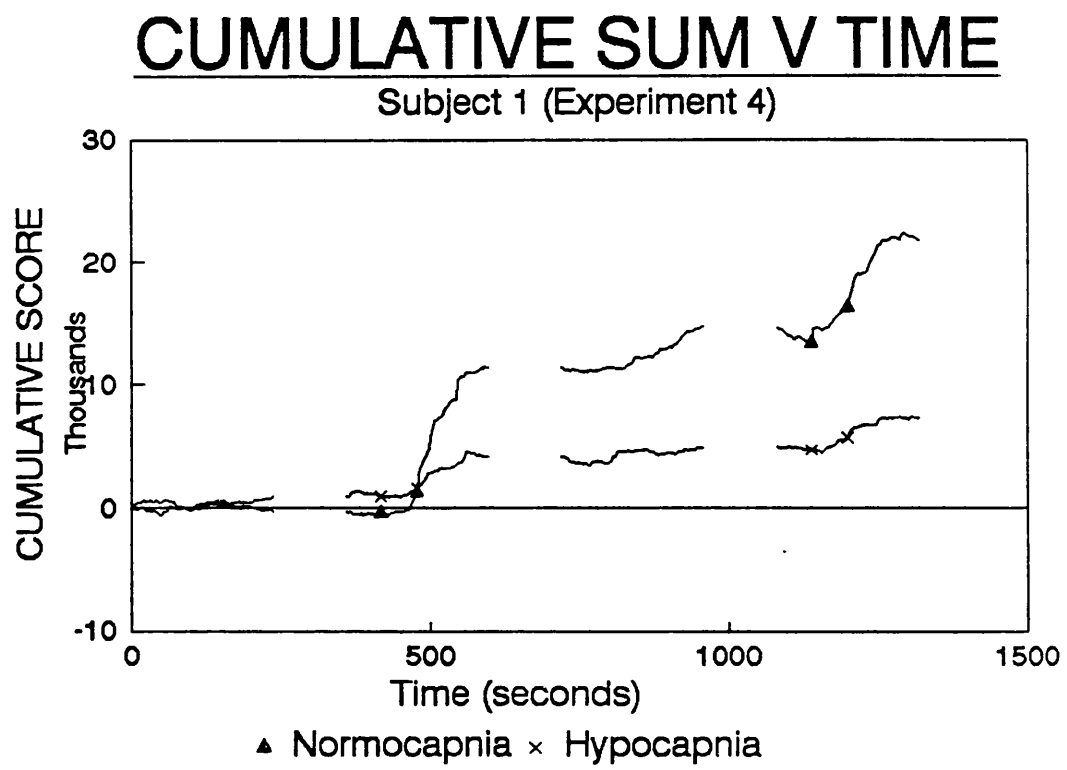
Average % standard deviation of the 3 subjects 4.1

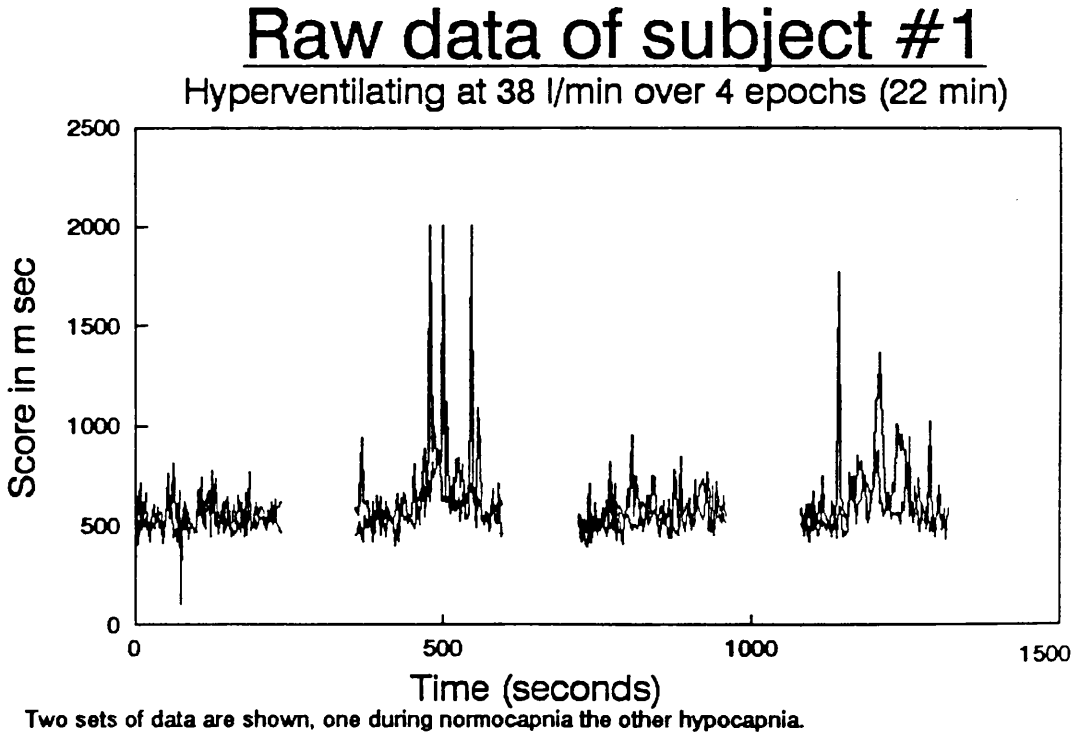
It was decided to average the 30 responses of the first 90 seconds of each epoch, and use each mean as the reference values against which the remaining responses of the epoch would be judged. This was achieved by dumping the raw response times into a Lotus 1-2-3 spreadsheet, calculating the means of the first 30 responses and subtracting them from all 80 responses of the appropriate epoch. Deviations from the means were then accumulated through the whole 22-min period. This procedure takes maximum advantage of the 60 seconds before nitrous oxide is administered (in epochs 2 & 4) and the subsequent 30 seconds before it has any discernible effect, to obtain a reference time appropriate to the subject and state, against which the effects of adding nitrous oxide can be judged.

An example of this is shown in Figure 9.9. The lower panel plots the raw response times. The upper panel plots the accumulated deviation from the reference times. All of the remaining graphs of response times follow this convention, unless stated otherwise.

Effects of hyperventilation on task

At first subjects had slight difficulties synchronising their breathing to the task. They tended to take a breath before responding or to breathe and respond simultaneously. Soon they learnt to respond first and inspire to empty the balloon directly after. Providing they were normocapnic, their response times then became





Two sets of data are shown, one during normocapnia the other hypocapnia.
N2O given in 2dn min of 2nd & 4th epoch

Figure 9.9

at least as reproducible as before, (Table 9.4). Once they had progressed that far they were exposed to hypocapnia at levels down to an end-tidal PCO_2 of 12 mm Hg. It quickly became obvious that some subjects were more sensitive than others to the stress. This manifested subjectively as a sense of tiredness and isolation. Many subjects yawned repeatedly as the 22 minute period of hypocapnia progressed, but had no desire to yawn at all during normocapnia. Objectively, it was detected as a gradual slowing of response times through the period. Examples of this, as seen in subjects #4, #5 and #7, are shown in Figure 9.10 to 9.12. Error rates were less affected.

It was presumed that this effect was due to slowly accumulating consequences of cerebral hypoxia, and supposed that it might sum with or complicate analysis of the effects of nitrous oxide anaesthesia. So it was decided to tailor the level of hypocapnia to that degree that just failed to produce significant slowing of response times in each subject. Interestingly the Chinese subject was most sensitive to hypocapnia, as he was to nitrous oxide anaesthesia. His threshold for slowing was at an end-tidal PCO_2 of 28 mm Hg. Oriental hypersensitivity to the former is well documented. Perhaps the two effects are related. By contrast subjects #6 and #7 had thresholds of 18 and 15 mm Hg. The other four subjects began to slow at 22, 22, 24 and 24 mm Hg.

The concentration of N2O clearly affecting the task

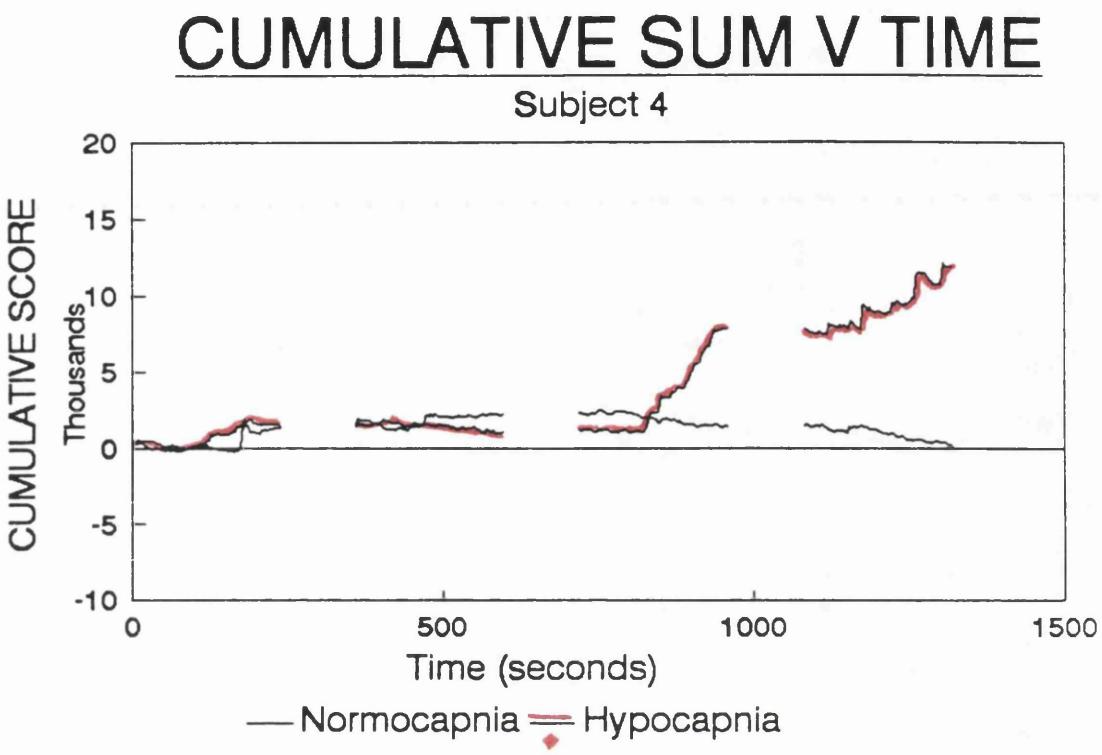
Table 9.4

Stability data on the 7 subjects hyperventilating at 38 litres per minute. Mean results of 8 consecutive epochs for each subject.

Subject #	1	2	3	4	5	6	7
Epoch 1	633	658	502	746	548	550	540
Epoch 2	629	534	515	799	517	589	532
Epoch 3	647	550	525	712	532	568	562
Epoch 4	697	605	541	774	500	589	545
Epoch 5	585	623	541	779	520	585	544
Epoch 6	666	599	499	769	496	536	546
Epoch 7	615	571	473	739	515	577	536
Epoch 8	643	583	530	793	514	575	521
Mean of 8 epochs	639.4	590.4	515.8	763.9	517.8	571.1	540.8
Standard deviation	31.2	37.4	22	27.5	15.5	17.9	11.2
Coefficient of Variation	4.9	6.3	4.3	3.6	3.0	3.1	2.1

Average score for the 7 subjects 591.3

Average % standard deviation of the 7 subjects 3.9


CUMULATIVE SUM V TIME
Subject 4
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

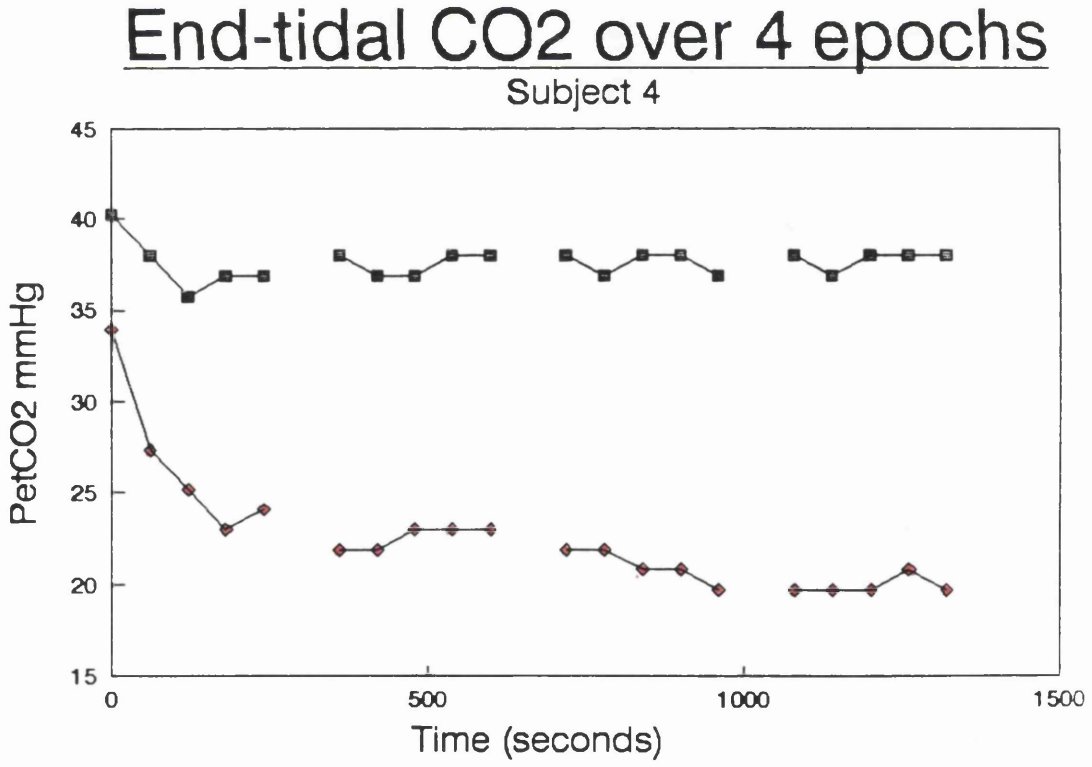
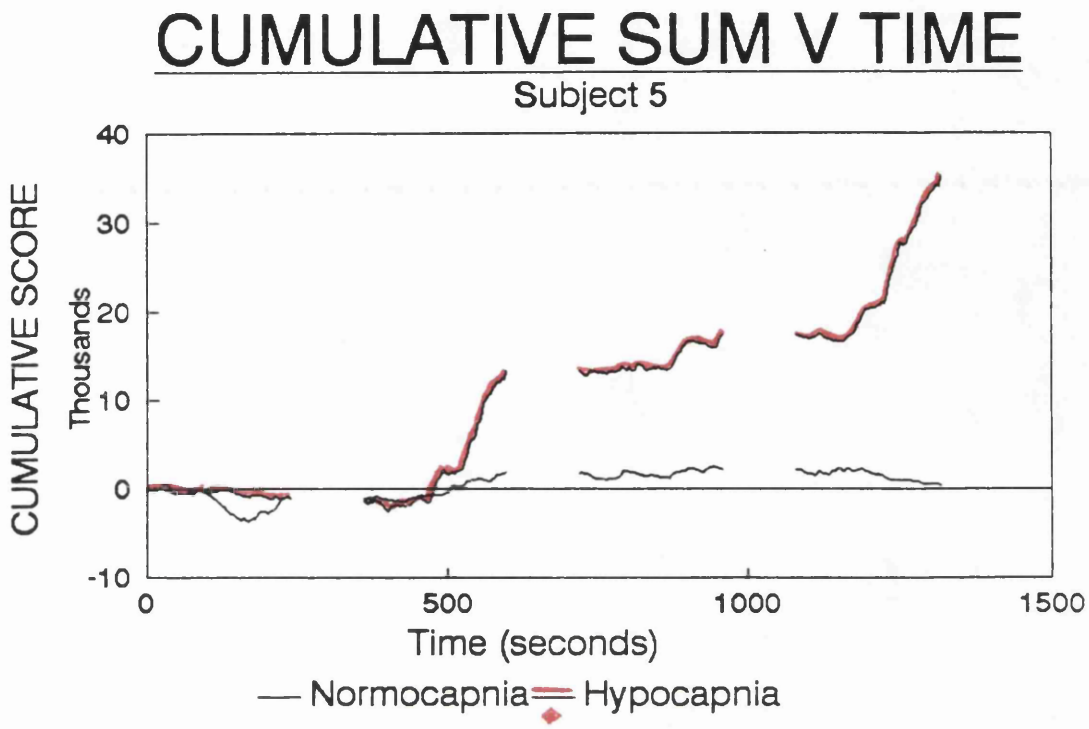

End-tidal CO2 over 4 epochs
Subject 4
PetCO2 mmHg
45
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 9.10


CUMULATIVE SUM V TIME
Subject 5
CUMULATIVE SCORE
Thousands
40
30
20
10
0
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

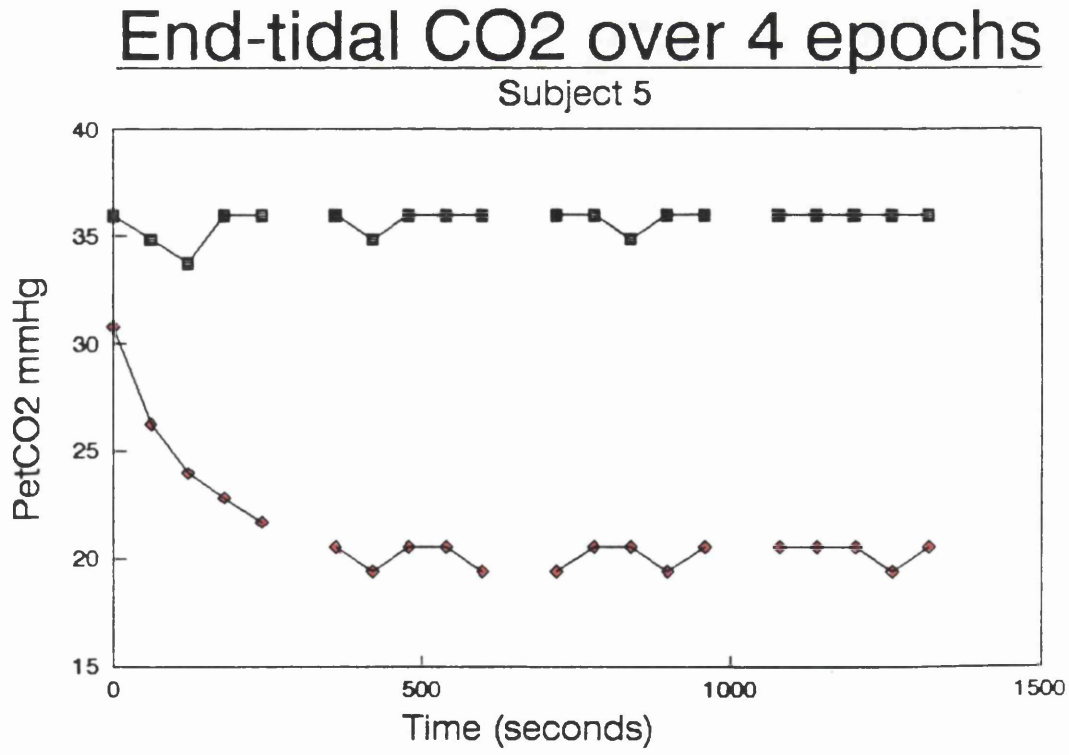
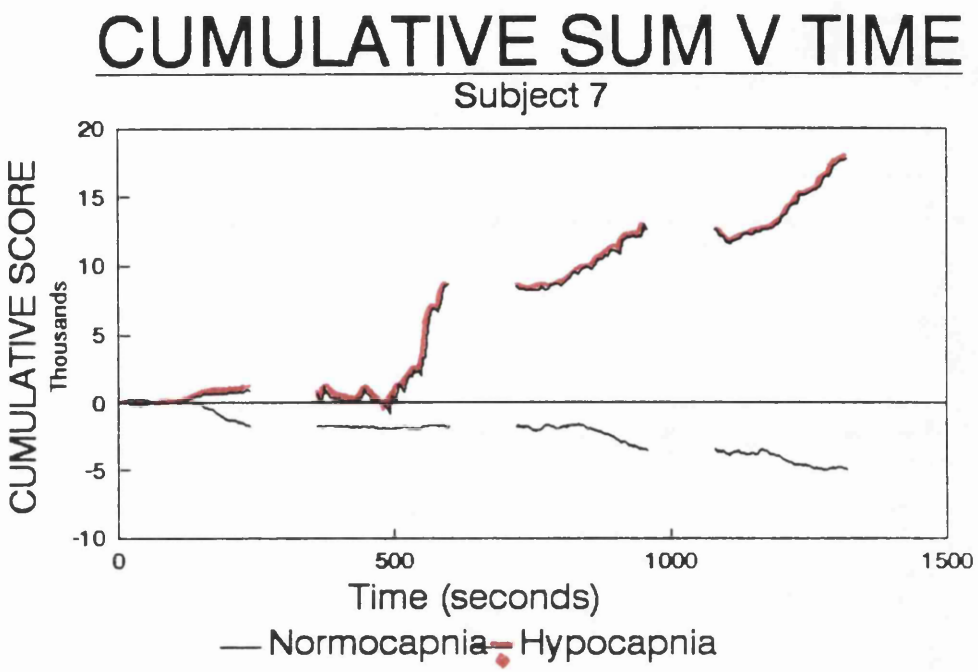

End-tidal CO2 over 4 epochs
Subject 5
PetCO2 mmHg
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 9.11


CUMULATIVE SUM V TIME
Subject 7
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

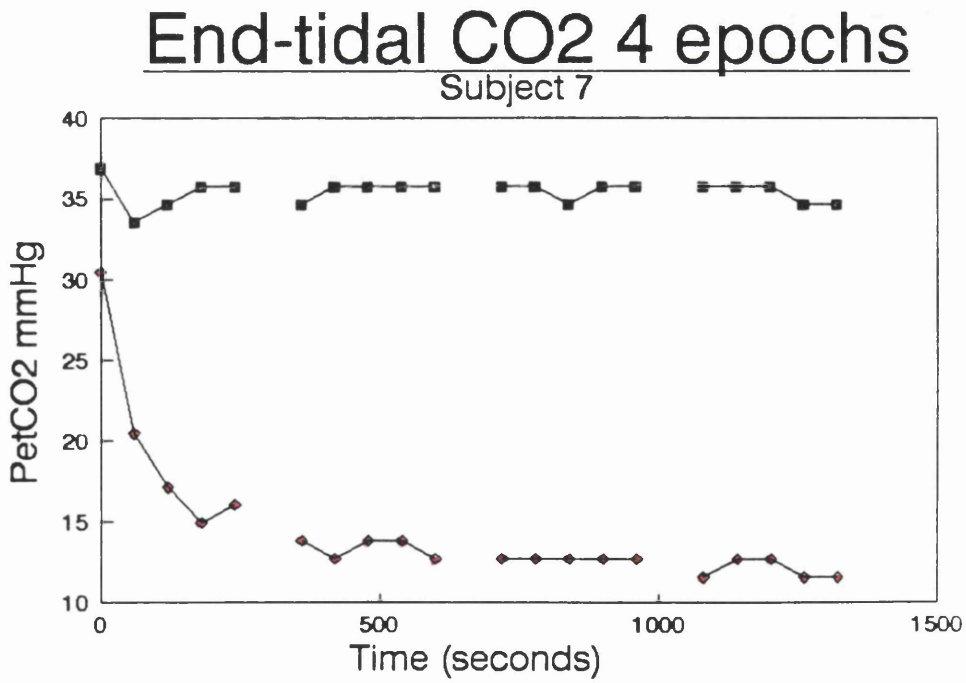

End-tidal CO2 4 epochs
Subject 7
PetCO2 mmHg
40
35
30
25
20
15
10
0
500
1000
1500
Time (seconds)

Figure 9.12

In order to get some feel for the sensitivity of the normal task to nitrous oxide anaesthesia, subject #7 inspired air and then mixtures of 30%, 35% and 50% nitrous oxide for 22 minutes apiece. His mean response times are shown as a bar chart in Figure 9.13. He was breathing spontaneously throughout, so the anaesthetic was slow to invade the lungs and blood stream. His average times rose from 450 msec, to 500, 490 and 550 msec respectively. However he was highly practiced at the task. A cumulative plot of his response times in air and in 50% N_2O is shown Figure 9.14. In this case the mean of the 320 responses in air (i.e 450 msec) was subtracted from both sets of times. This explains why the lower sets of results finish up exactly on the reference line. By contrast, the delays in the responses in nitrous oxide accumulate to almost 32,000 msec, averaging 100 msec per response.

The level of hyperventilation modifying the N2O effects

In the next experiment subject #7 responded through five successive 4-minute epochs separated by considerable rest periods. The results are shown in Figure 9.15. In all of the runs he ventilated at 38 litres/min. In the first trial his end-tidal PCO_2 was held at 40 mm Hg. The mean of all 80 responses was taken as the reference level, which explains why that curve finishes exactly on the reference line. The same reference value is also used for the other four curves. In the second run his end-tidal PCO_2 was again held at

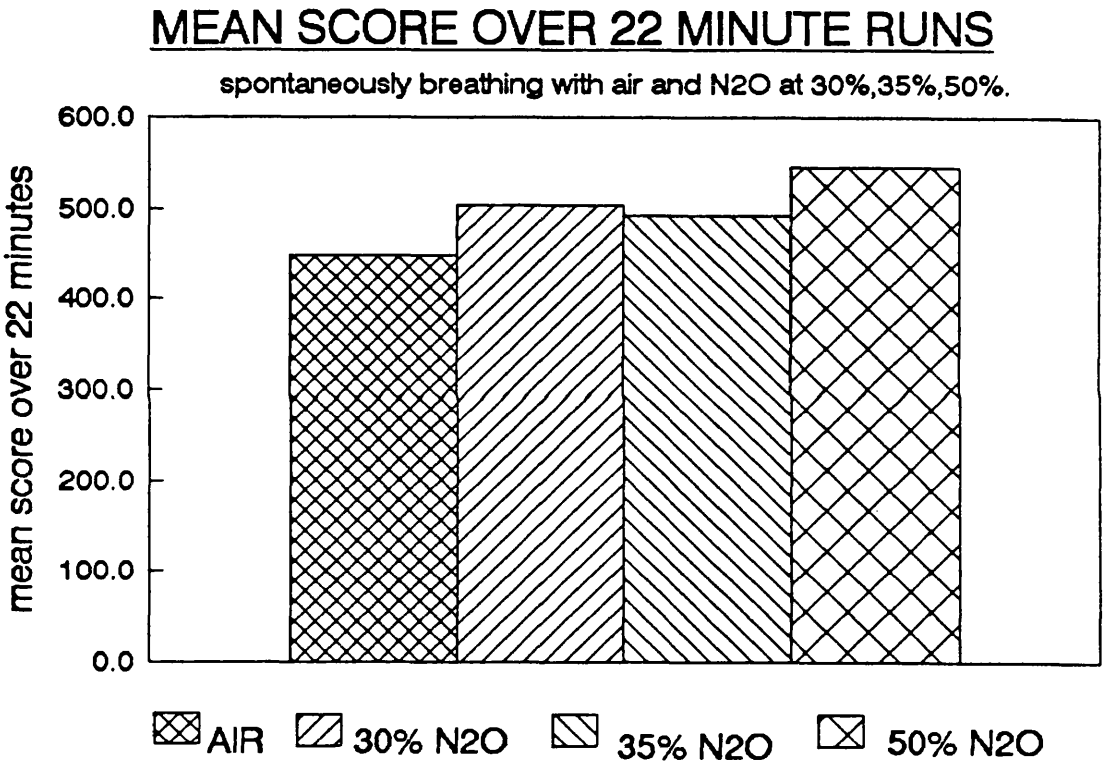
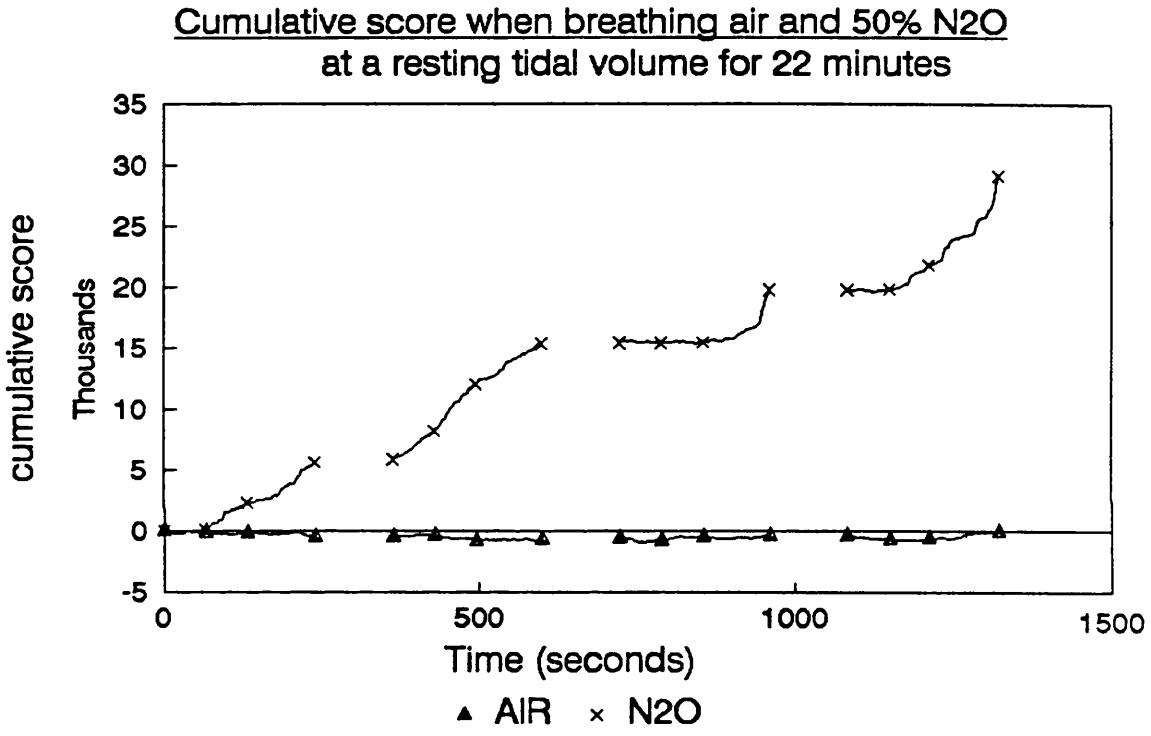
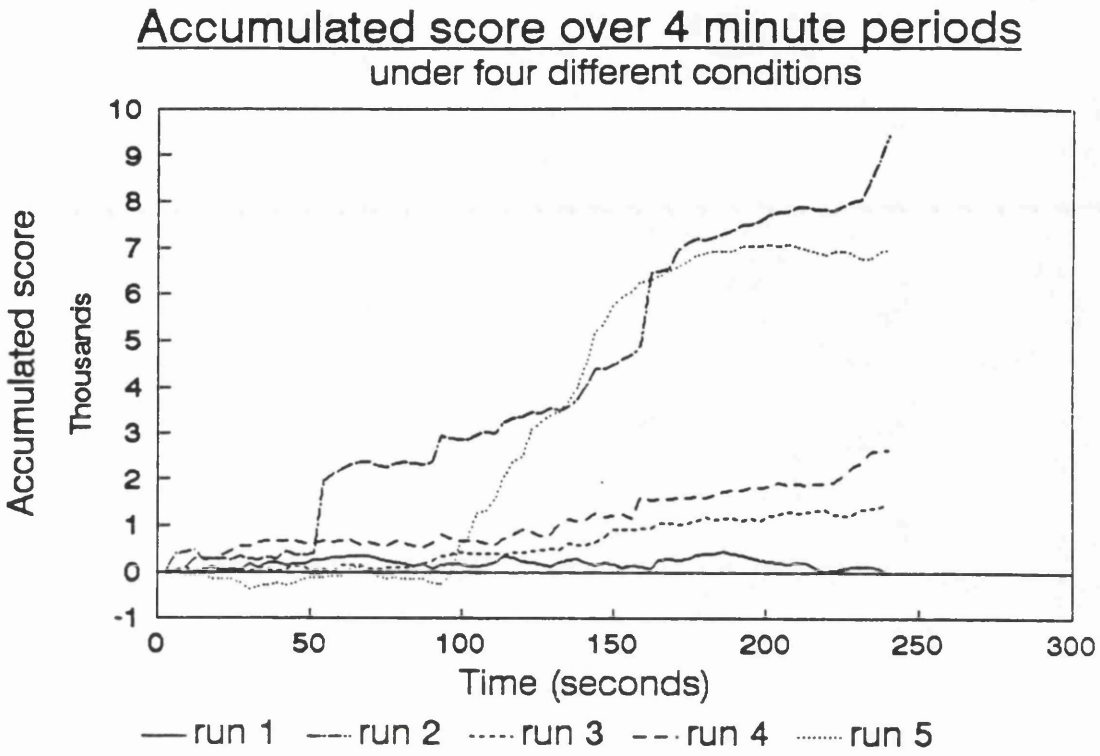

MEAN SCORE OVER 22 MINUTE RUNS
spontaneously breathing with air and N2O at 30%,35%,50%.
mean score over 22 minutes
600.0
500.0
400.0
300.0
200.0
100.0
0.0
AIR
30% N2O
35% N2O
50% N2O

Figure 9.13



Subject 7
Accumulated total for N2O run is 29 seconds

Figure 9.14



The graph shows an accunulated score over a four minute period.
The end-tidal CO_2 was maintained at 40 mmHg in runs 1,2,5. and at 20 mmHg in runs 3,4.
N_2O was inspired in runs 2,3,4,5. but in the first minute only in runs 2,3. and in the second minute only in runs 4,5.

Figure 9.15

40 mm Hg, but 60% nitrous oxide was inspired for the first minute. He accumulated a deficit of 9000 msec. This began to appear after 50 sec, but persisted for the next three minutes. In the third trial he inspired 60% nitrous oxide for the first minute but his end-tidal PCO_2 was held at 20 mm Hg from the start. He gradually accumulated a slight deficit of 1000 sec, i.e about 12 msec per response. Subjectively, he found that 60% nitrous oxide for 1 minute was very unpleasant during normocapnia but barely detectable during hypocapnia. This suggested that the original hypothesis of this thesis had sense. In the fourth and fifth studies he breathed 50% nitrous oxide for the second minute of the run in normocapnic and hypocapnic conditions. In normocapnia he accumulated a deficit of 7000 msec, which began to appear some 30 sec after the start of anaesthesia. In hypocapnia he again only showed a slight and gradual slowing. His subjective impressions were as before.

In subsequent studies all of the subjects became familiar with 1-minute pulses of nitrous oxide anaesthesia, and the threshold concentrations that produced significant slowing in normocapnia were determined. They were 30% in one subject, 40% in two and 50% in 4 of the subjects.

Consequent design of the formal study

On the basis of these preliminary studies it was decided to make a formal comparison of the effects of 1-minute pulses of nitrous oxide anaesthesia on the response times of subjects in normocapnia and hypercapnia. All seven subjects would be studied. The degrees of hypocapnia, nitrous oxide anaesthesia and task difficulty would be tailored to their individual thresholds, and they would all receive nitrous oxide for the 2nd minute of the 2nd and 4th epoch of each 22 minute period. An experiment would consist of two 22-minute test periods separated by a 20-minute interval for rest. Each subject would be normocapnic in one test period and hypocapnic in the other. Each experiment would be repeated in the reverse order to balance out order effects. In one pair of experiments he would receive nitrous oxide, in another pair he would not. In this way the effects of hyperventilation alone could also be determined. Thus each of the seven subjects would perform four 64-minute experiments. Experiments would be separated by recovery intervals of at least three hours, and no more than two experiments would be done in any one day. The outcome of that study is the subject of the next chapter.

10 RESULTS OF THE FORMAL STUDY

For the formal study, seven subjects were asked to complete 4 experiments each of 64 minutes duration. For the first 22 minutes of each experiment, they ventilated at 38 litres per minute. For the next 20 minutes they rested, breathing spontaneously. For the last 22 minutes they ventilated again at 38 litres per minute. Studies were separated by a minimum of 3 hours rest. No more than two experiments were done in a day. Together the four experiments formed a balanced design:

Expt 1	Normocapnia	then hypocapnia
Expt 2	Hypocapnia	then normocapnia
Expt 3	Normocapnia + N_2O	then hypocapnia + N_2O
Expt 4	Hypocapnia + N_2O	then normocapnia + N_2O

The order of the experiments was random. The levels of hypocapnia, nitrous oxide anaesthesia and task difficulty varied with the subject but not with the experiments, as explained in the previous chapter. Two subjects (#2 and #3) were unable to do Experiment 1 . The mass spectrometer developed a fault towards the end of the study. Both subjects are now abroad. The preliminary studies suggested that their responses would have been very similar to those shown in Experiment 2 but as they were still learning to combine

the stresses it would be unwise to include that data in the formal study. Details of the 26 completed experiments are given in Table 10.0.

The results of the experiments are summarised in Tables 10.1-10.4 and Figures 10.1-10.26. These will be described for each subject in turn.

Subject 1

The first subject was noted in preliminary experiments to be moderately sensitive to hypocapnia, showing progressive slowing if her end-tidal PCO_2 fell below 22 mm Hg. So in her hypocapnic runs she was held to end-tidal CO_2 tensions of 25 to 27 mm Hg. The lower panel of Figure 10.1 compares her end-tidal values for Experiment 1. They averaged 39 mm Hg in normocapnia and 27 mm Hg in hypocapnia.

Her response times for Experiments 1 are shown in the upper panel of the same Figure, as accumulated deviation plots. They are sensibly horizontal, the total deviation being less than 2.5 seconds for both runs. In experiment 1 her times gradually reduced through the normocapnic run hence the negative score. In hypocapnia they were constant. Her results for Experiment 2 were almost identical and are shown in Figure 10.2 in Experiment 2.

Her results for Experiment 3 are shown In Figure 10.3. The bottom left panel shows that the four pulses of nitrous oxide were identical (2 in hypocapnia and 2 in normocapnia. The bottom right panel shows her end-tidal CO_2 tensions, which averaged 38 mm Hg in normocapnia and fell to an average of 25 mm Hg in hypocapnia. In the upper panel the fleches mark out the 2nd minute of each epoch and also identify the normocapnic curves. Crosses serve the same purpose for the hypocapnic times. The graph shows that during normocapnia the pulses of nitrous oxide in the 2 minutes of epochs 2 and 4 had clear cut effects. She accumulated a deficit of 11.3 seconds after the first pulse, and added a further 12.8 seconds after the second pulse. On each occasion the nitrous oxide was inhaled from the first fleche to the second fleche. Subjectively and objectively effects appear some 40 seconds after beginning to inhale the gas at this level of ventilation (38 l/min).

The hypocapnic trace, marked by the crosses, shows much less slowing. She accumulated 4.8 sec after the first pulse and 1.3 sec after the second pulse.

Her results for Experiment 4 are plotted and presented in the same way in Figure 10.4. Again the pulses of nitrous oxide inhalation are identical, normocapnic end-tidal PCO_2 was held at 37 m Hg and hypocapnic PCO_2

was held at 26 mm Hg. She accumulated a total deficit of 22 seconds on the normocapnic run and 7.3 seconds on the hypocapnic run.

Subject 2

The second subject slowed progressively if his end-tidal PCO_2 fell below 24 mm Hg so he was run at 25 to 26 mm Hg during hypocapnia and at 38 to 40 mm Hg during normocapnia. He was one of the two who did not complete Experiment 1. His results for Experiment 2 are shown in Figure 10.5. The lower panel shows respired gas tensions. The upper panel shows accumulated times. Graphic conventions are as before. He accumulated trivial deficits in this experiment.

His results for Experiments 3 and 4 are shown in Figures 10.6 and 10.7. Both suggest that the four pulses of nitrous oxide anaesthesia were identical, and that respired gas tensions were well controlled. Also in both experiments deficits in hypocapnia were clearly less than in normocapnia.

Subject 3

The third subject was also prevented from completing Experiment 1. His hypocapnic effect threshold was 22 mm Hg. He was run at 25 mm Hg for Experiment 2, at an average of 22 mm Hg for Experiment 3 and at 26 mm Hg for experiment 4. During the normocapnic episodes he was run at 41 mm Hg. His results for Experiment 2 are

shown in Figure 10.8. The lower panel displays respired gas tensions. The upper panel plots accumulated deficits of response times. They are small, (4-5 sec).

His results for Experiments 3 and 4 are shown in Figures 10.9 and 10.10. Nitrous oxide pulses are identical and control of gas tensions is reasonably good. In both studies he accumulated greater deficits due to nitrous oxide anaesthesia in normocapnia than hypocapnia. Separation of the results was greater where the end-tidal PCO_2 was lower (20 mm Hg at the end of Expt 3 cf 25 mm Hg at the end of Experiment 4).

Subject 4

Subject 4 had a hypocapnic slowing threshold of 24 mm Hg. His hypocapnic studies were run at 25 to 28 mm Hg. He was very familiar with the normal task and was required to do the reverse task instead. Figure 10.11 shows the results of Experiment 1. Gas tensions are steady and accumulated deficits are slight. The same is true of Experiment 2 (Fig 10.12).

In experiment 3 (Fig 10.13) nitrous oxide pulses were identical and control of respired gas tensions satisfactory. The deficit accumulated in normocapnia was 25.1 seconds, and that in hypocapnia was 2.9 seconds. In Experiment 4 the effects of nitrous oxide were not as great and the separation though still present, was marred by a slight loss of attention during the second half of hypocapnic epoch 3 (Fig 10.14).

Subject 5

Subject 5 is of Chinese descent. He had a hypocapnic slowing threshold of 28 mm Hg. His hypocapnic studies were run at 26 to 29 mm Hg. Results of Experiment 1 are given in Figure 10.15. He accumulated a total deficit of 2.4 seconds in normocapnia and 4.9 seconds in hypocapnia. The same was true in experiment 2 (Fig 10.16) where the end-tidal CO_2 during hypocapnia was held at 27 mm Hg.

In Experiment 3 his end-tidal nitrous oxide concentration rose to a maximum of 30% (cf the other subjects at 40-50%), as can be seen in Figure 10.17. The deficit in normocapnia totalled 13.6 seconds but was clearly less in hypocapnia, (8.8 sec). In Experiment 4 (Fig 10.18) the difference was greater (26 sec in normocapnia, 7.5 sec in hypocapnia).

Subject 6

Subject 6 had a hypocapnic slowing threshold of 18 mm Hg. His hypocapnic episodes were held at 18 to 22 mm Hg. He was very familiar with the normal task and was asked to do the reverse task instead. His results are illustrated in Figures 10.19-10.22 Accumulated deficits in Experiments 1 and 2 were very slight. In Experiment 3 he accumulated a deficit of 8.4 seconds in normocapnia, compared with -1.1 seconds in hypocapnia. In Experiment 4 the same was true, (9.2 sec cf -1.1 sec)

Subject 7

The last subject had a hypocapnic threshold of 15 mm Hg. His hypocapnic episodes were run at 19 to 22 mm Hg. He was very familiar with the normal task and performed the reverse task instead. His results are given in Figures 10.23-10.26. In Experiments 1 and 2 the accumulated deficits were very slight. In Experiment 3 he collected a total deficit of 21.4 sec in normocapnia and 4.4 in hypocapnia. In Experiment 4 the corresponding times were 16.7 sec and 3 sec respectively.

Summary of the results of the formal study

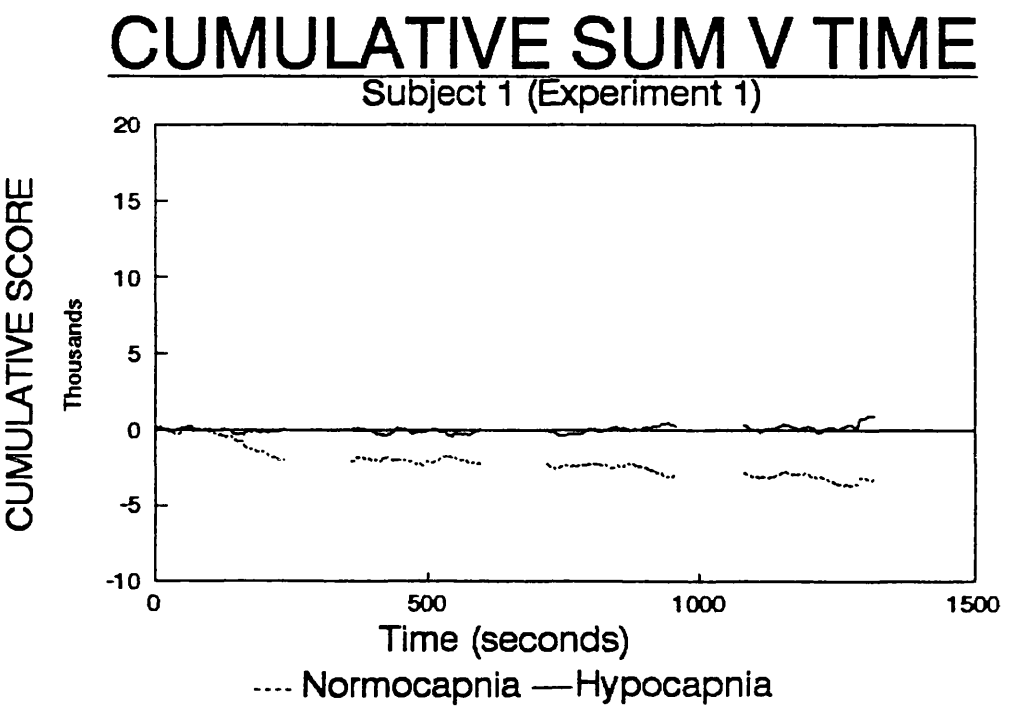
Table 10.1 compares the hypocapnic thresholds with the end-tidal CO_2 tensions at which the subjects were run for their hypocapnic episodes. It shows the end-tidal tensions were held within ± 2 mm Hg of the mean value for any one subject, making Experiments 1 to 4 comparable with each other for all subjects. It also shows that the end-tidal tensions were kept within +5 mm Hg of the threshold tension in all subjects, making the degree of hypocapnia comparable between subjects.

Table 10.2 lists the peak end-tidal nitrous oxide concentrations by subject for each run. Variations over the eight epochs in each subject do not exceed 2.2% i.e roughly 5% of the actual concentration, making the degree of exposure to N_2O comparable from epoch to epoch, within each subject. The variations from subject to subject reflect their sensitivities to the anaesthetic gas.

Table 10.3 lists the accumulated deficits in response times, by subject, for Experiments 1 and 2. The deficits do not exceed 6.2 seconds for the group. The values for the four half-experiments vary from their means by $< \equiv 2.2$ sec within subjects, suggesting that differences in deficits that exceed 5 seconds within subjects should be judged significant. Differences between normocapnia and hypocapnia are less than 3 seconds, in all subjects, and show no constant direction suggesting that any differences between normocapnia and hypercapnia exceeding $\pm$ 6 seconds must have a different cause.

Table 10.4 lists the accumulated deficits by subject for Experiments 3 and 4. The normocapnic totals range from 8.4 to 39.3 seconds. They therefore all exceed the highest deficit seen in Experiments 1 and 2 and must have a separate cause. The hypocapnic totals range from -1.1 to 16.6 seconds, but in every case are less than the corresponding normocapnic value. The hypocapnic values are less than the normocapnic by 14.2 $\pm$ 1.7 sec (mean $\pm$ SEM), i.e they deviate from the null hypothesis by 8.4 SEM, ($P < 0.001$).

The limitations of this study and the significance of the findings are discussed in the next chapter.


CUMULATIVE SUM V TIME
Subject 1 (Experiment 1)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
---- Normocapnia —Hypocapnia

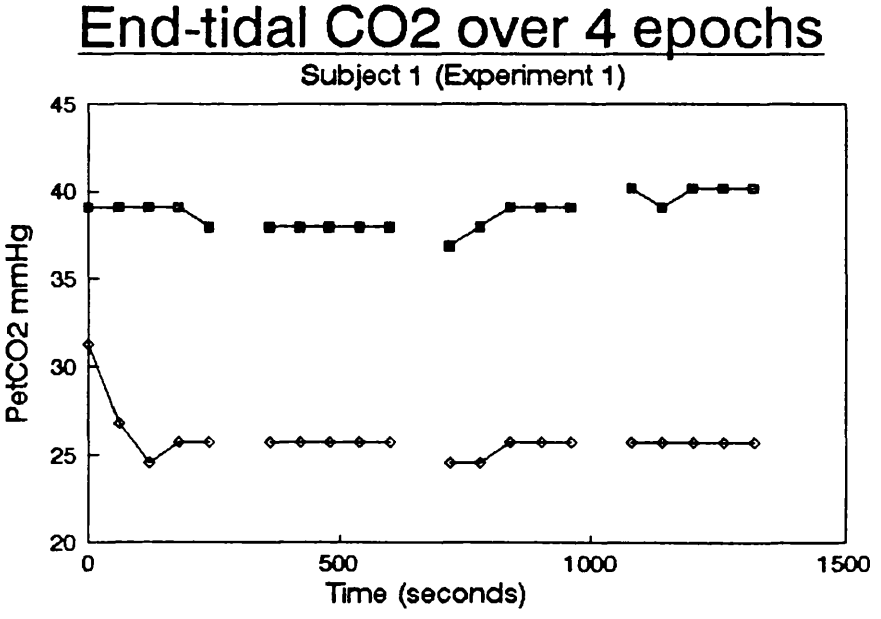
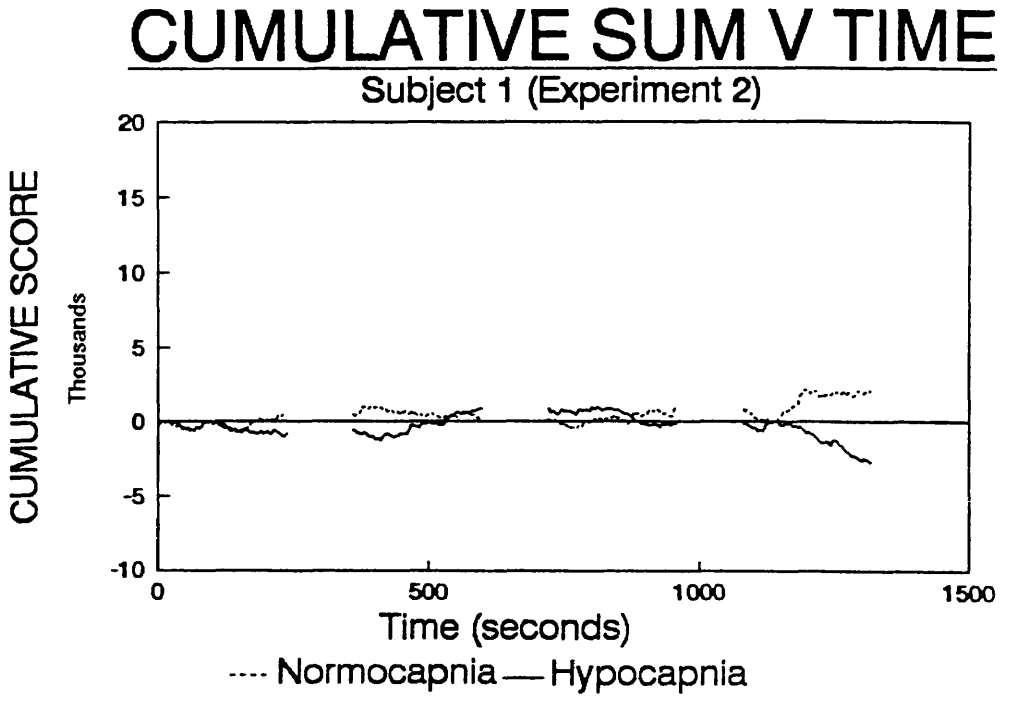

End-tidal CO2 over 4 epochs
Subject 1 (Experiment 1)
PetCO2 mmHg
45
40
35
30
25
20
0
500
1000
1500
Time (seconds)

Figure 10.1


CUMULATIVE SUM V TIME
Subject 1 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
---- Normocapnia — Hypocapnia

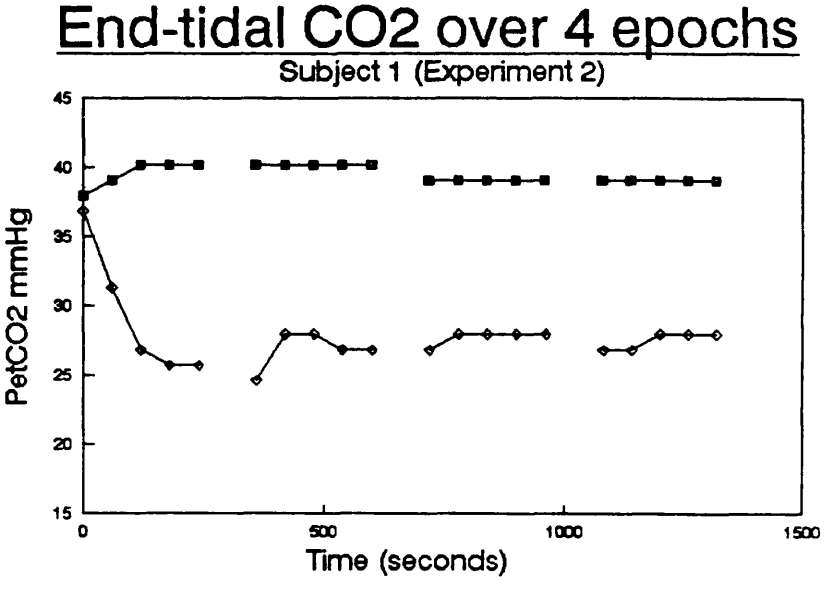

End-tidal CO2 over 4 epochs
Subject 1 (Experiment 2)
PetCO2 mmHg
45
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 10.2

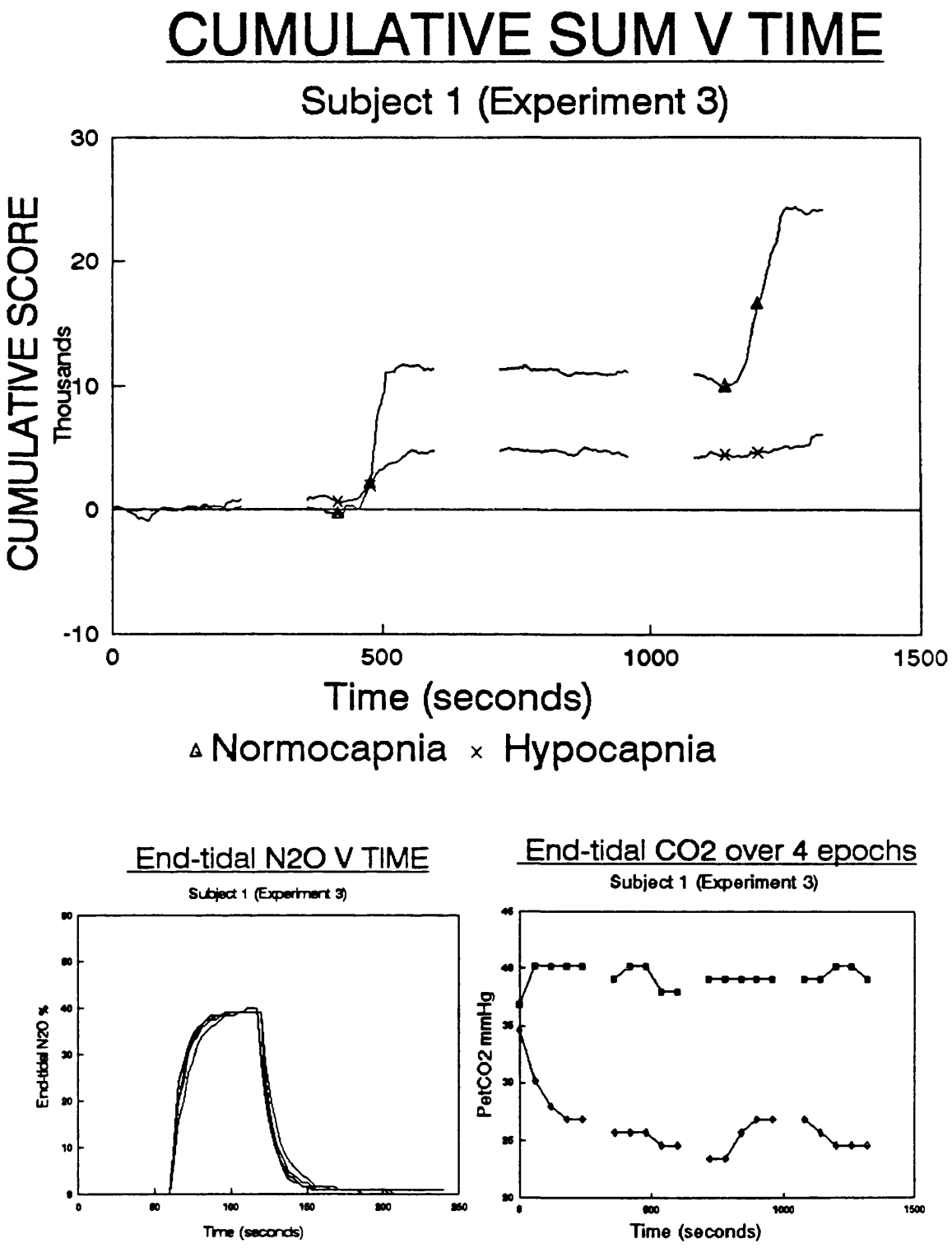
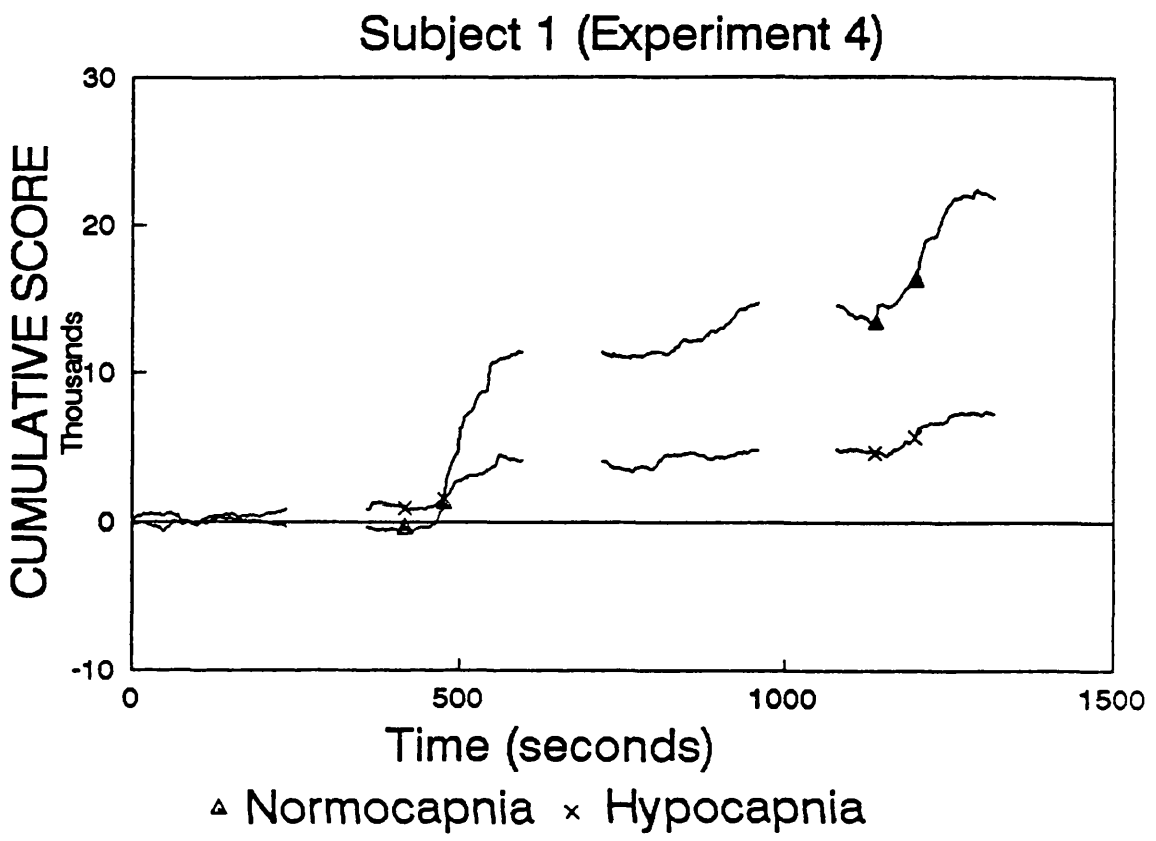
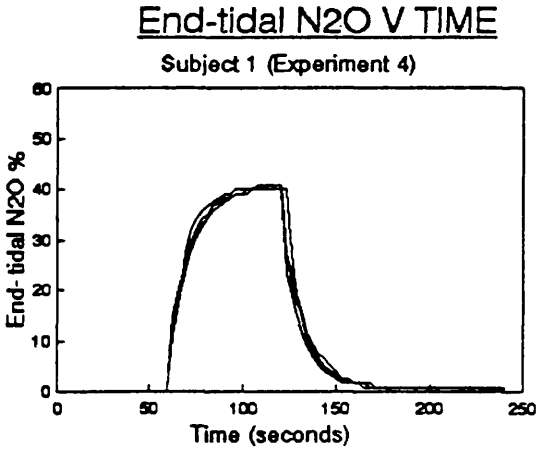
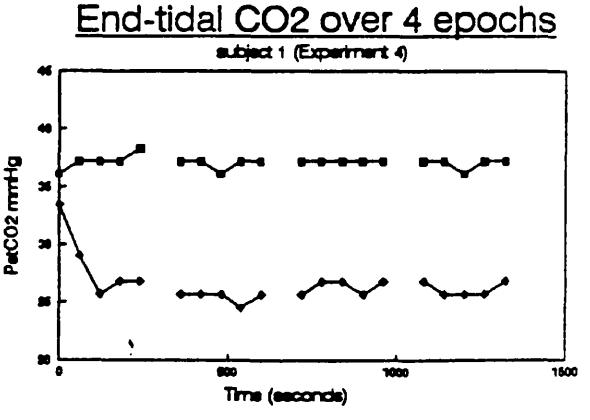

CUMULATIVE SUM V TIME
Subject 1 (Experiment 3)
CUMULATIVE SCORE
Thousands
30
20
10
0
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia
End-tidal N2O V TIME
Subject 1 (Experiment 3)
End-tidal N2O %
Time (seconds)
End-tidal CO2 over 4 epochs
Subject 1 (Experiment 3)
PetCO2 mmHg
Time (seconds)
4 wash-in N2O curves
2 in normocapnic and 2 in hypocapnic runs

Figure 10.3

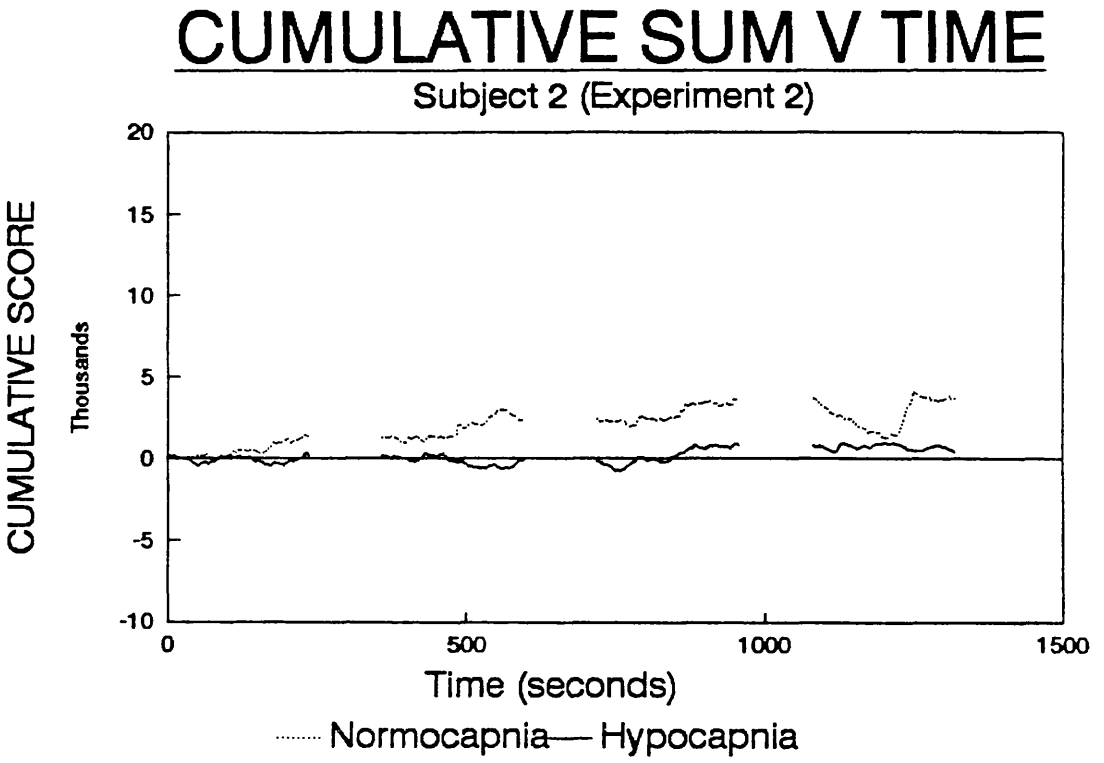






4 wash in N2O curves
2 in normocapnic and 2 in hypocapnic runs

Figure 10.4


CUMULATIVE SUM V TIME
Subject 2 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

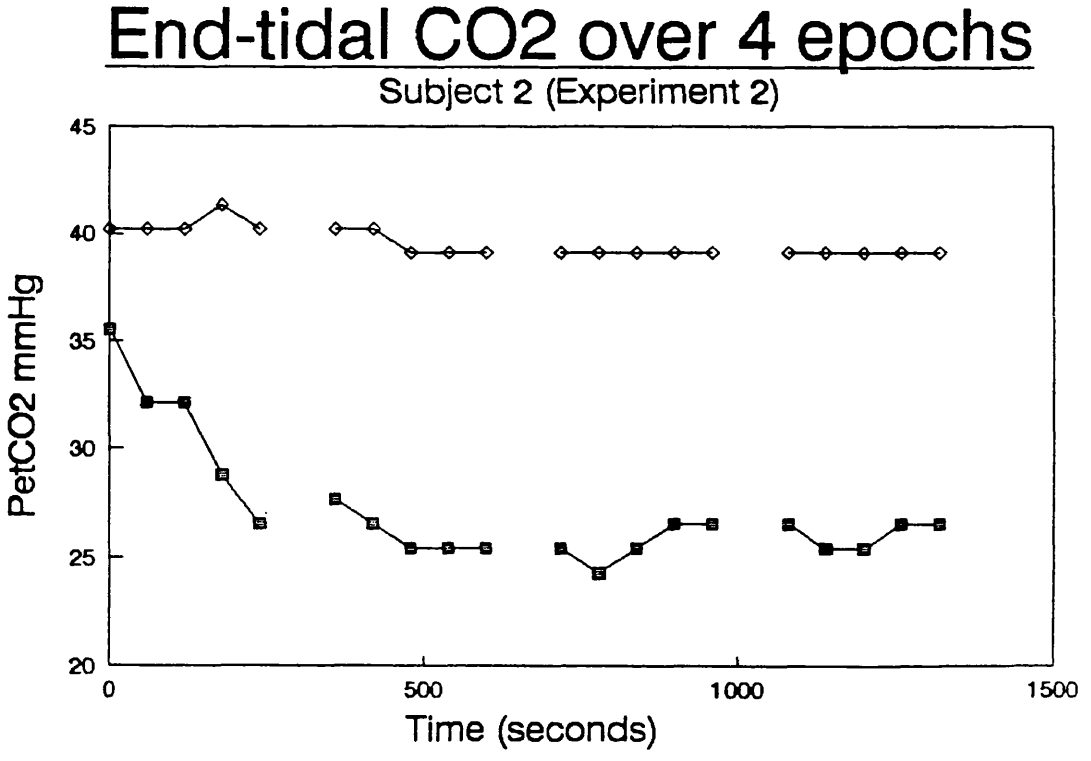
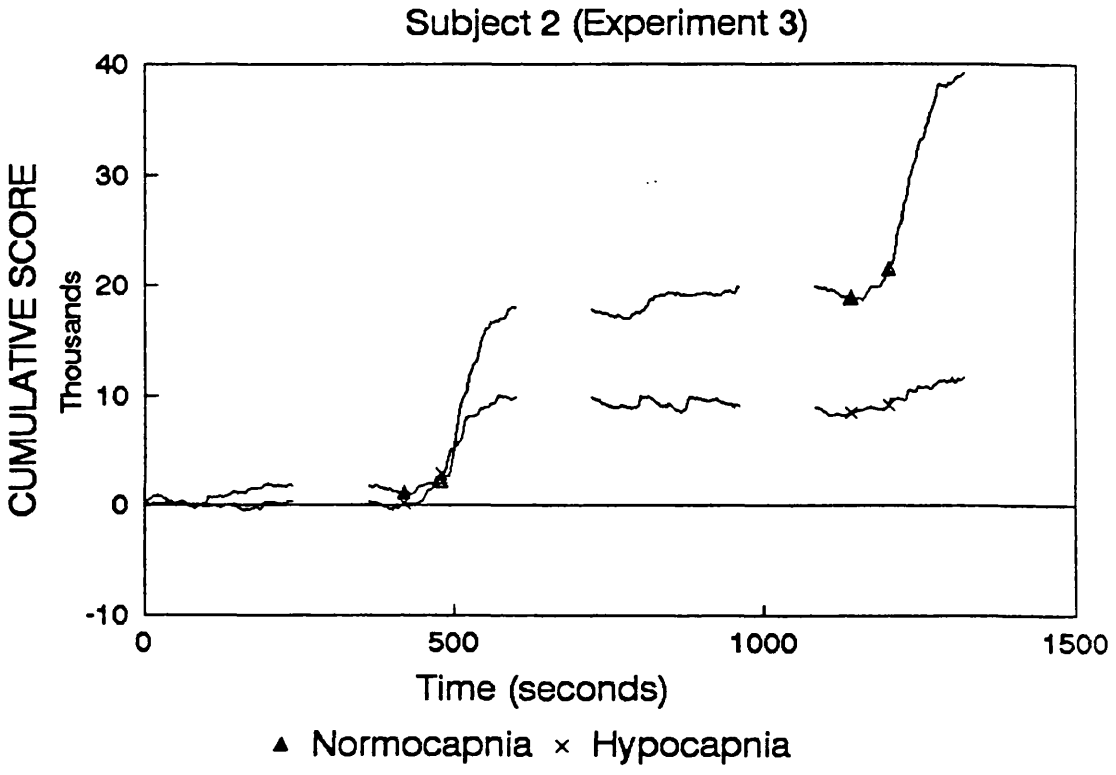
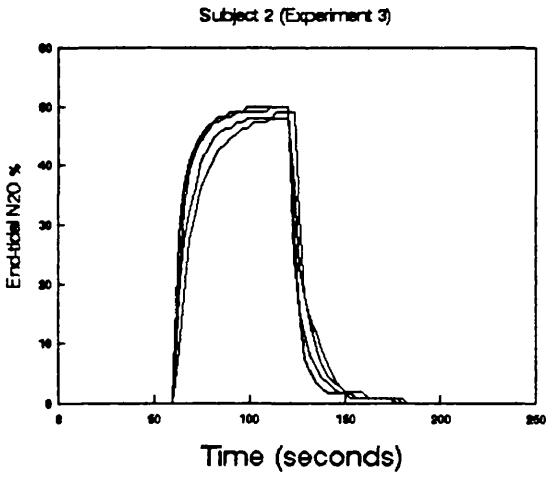

End-tidal CO2 over 4 epochs
Subject 2 (Experiment 2)
PetCO2 mmHg
45
40
35
30
25
20
0
500
1000
1500
Time (seconds)

Figure 10.5

CUMULATIVE SUM V TIME



End-tidal N2O V TIME



4 wash-in N2O curves
2 in normocapnic and 2 in hypocapnic runs

End-tidal CO2 over 4 epochs

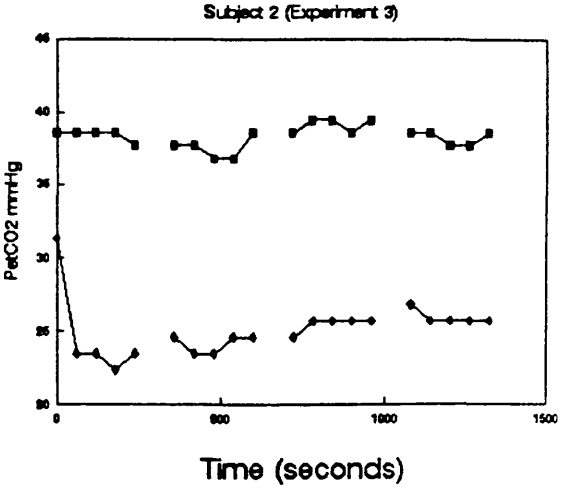
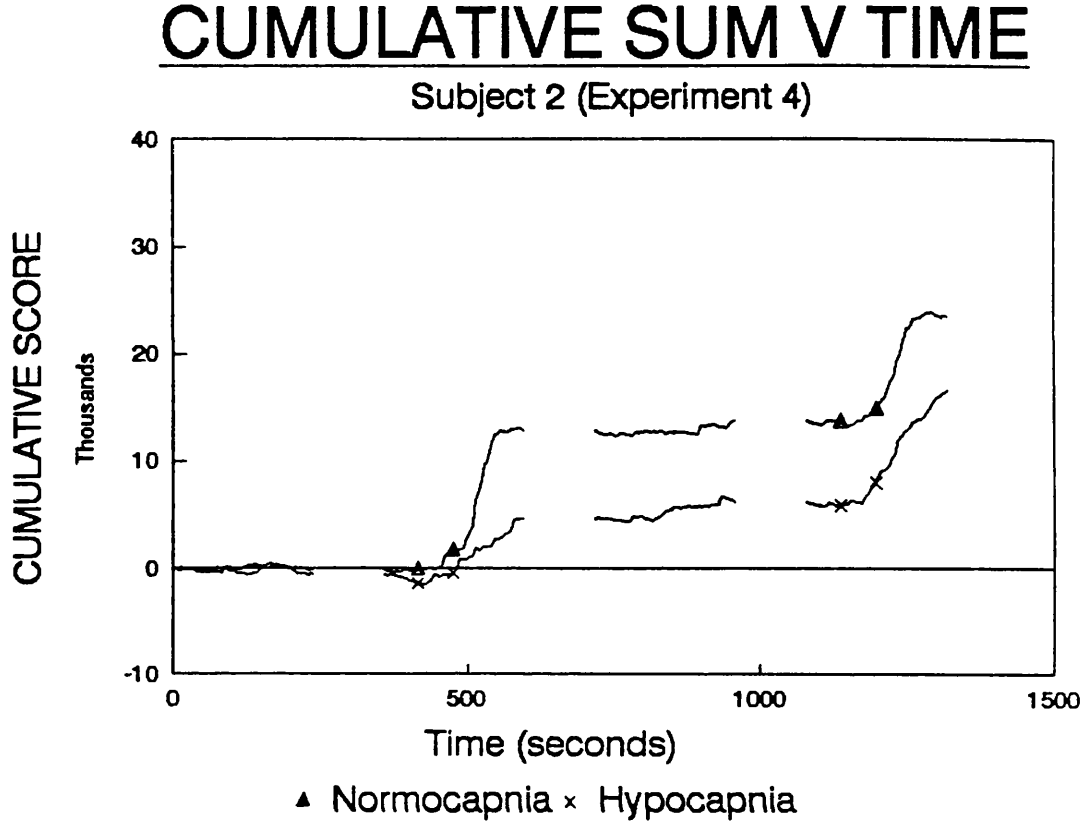
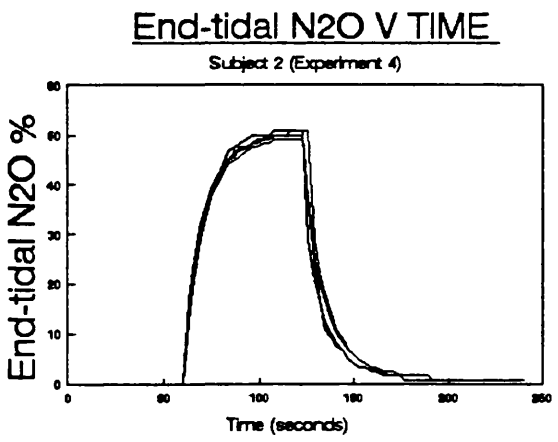
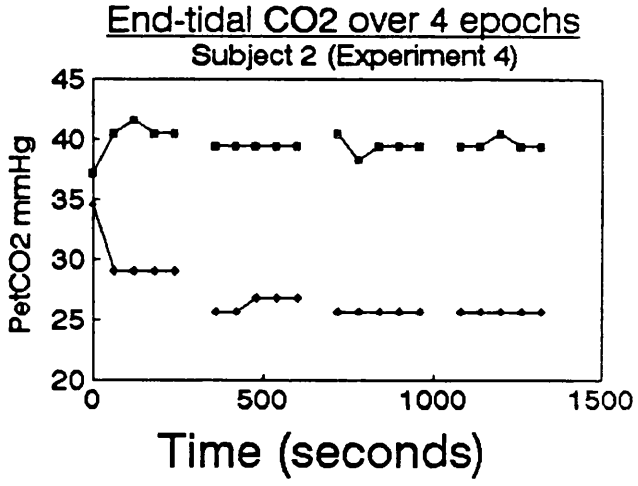


Figure 10.6



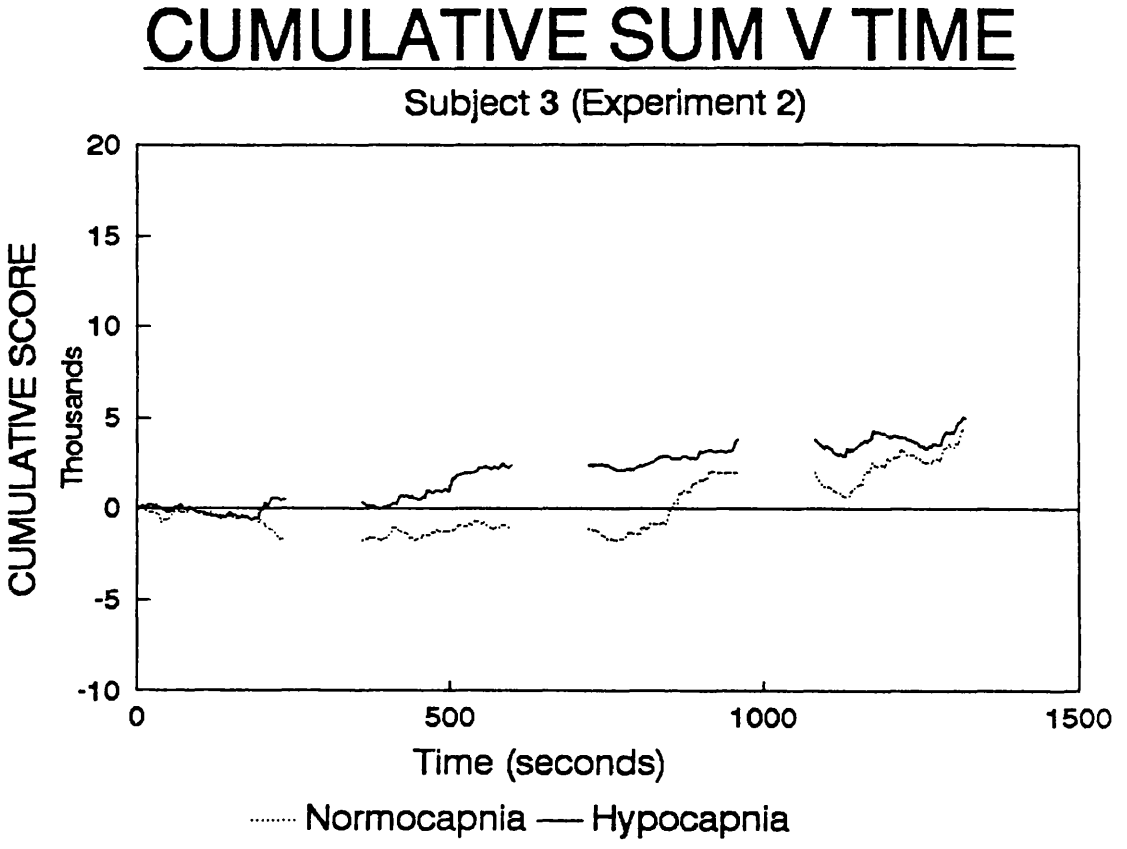




4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

Figure 10.7


CUMULATIVE SUM V TIME
Subject 3 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

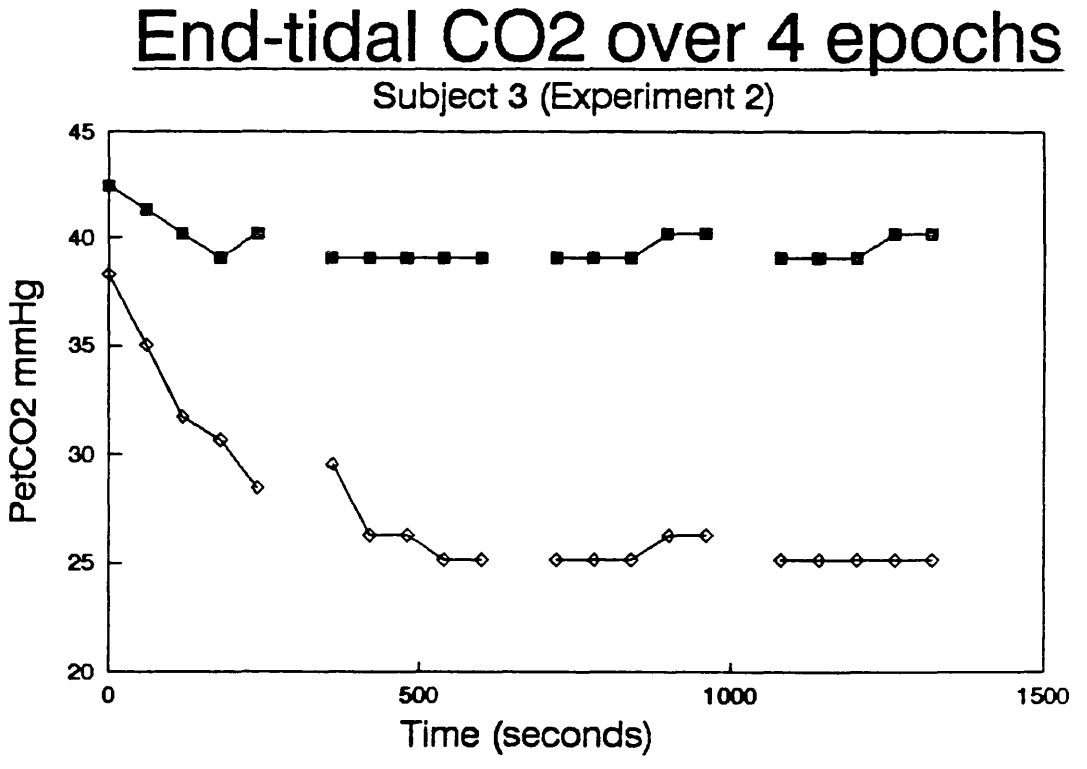
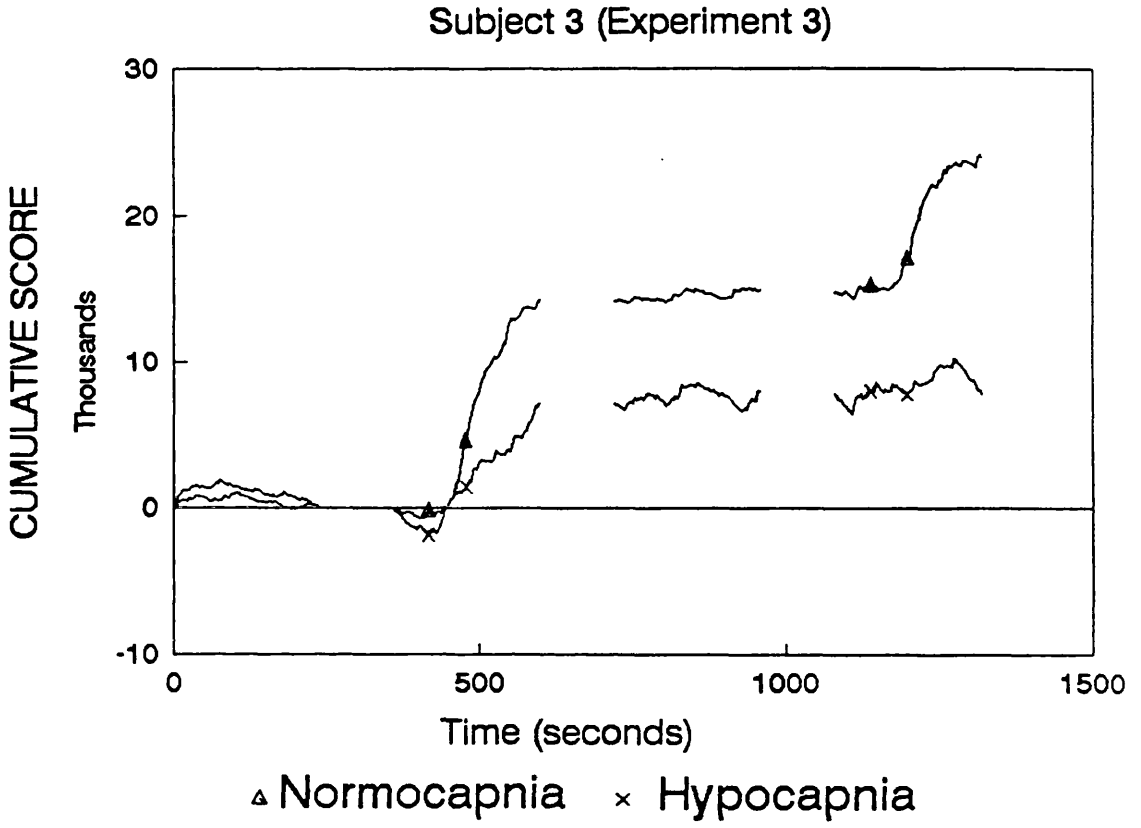
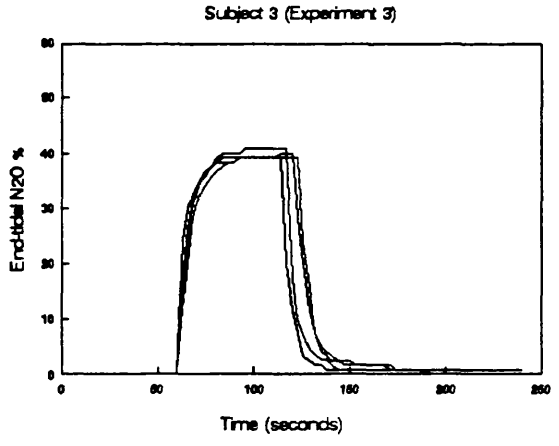

End-tidal CO2 over 4 epochs
Subject 3 (Experiment 2)
PetCO2 mmHg
45
40
35
30
25
20
0
500
1000
1500
Time (seconds)

Figure 10.8

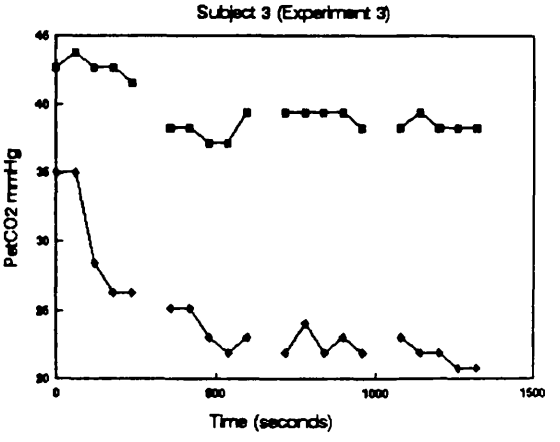
CUMULATIVE SUM V TIME



End-tidal N2O V TIME



End-tidal CO2 over 4 epochs

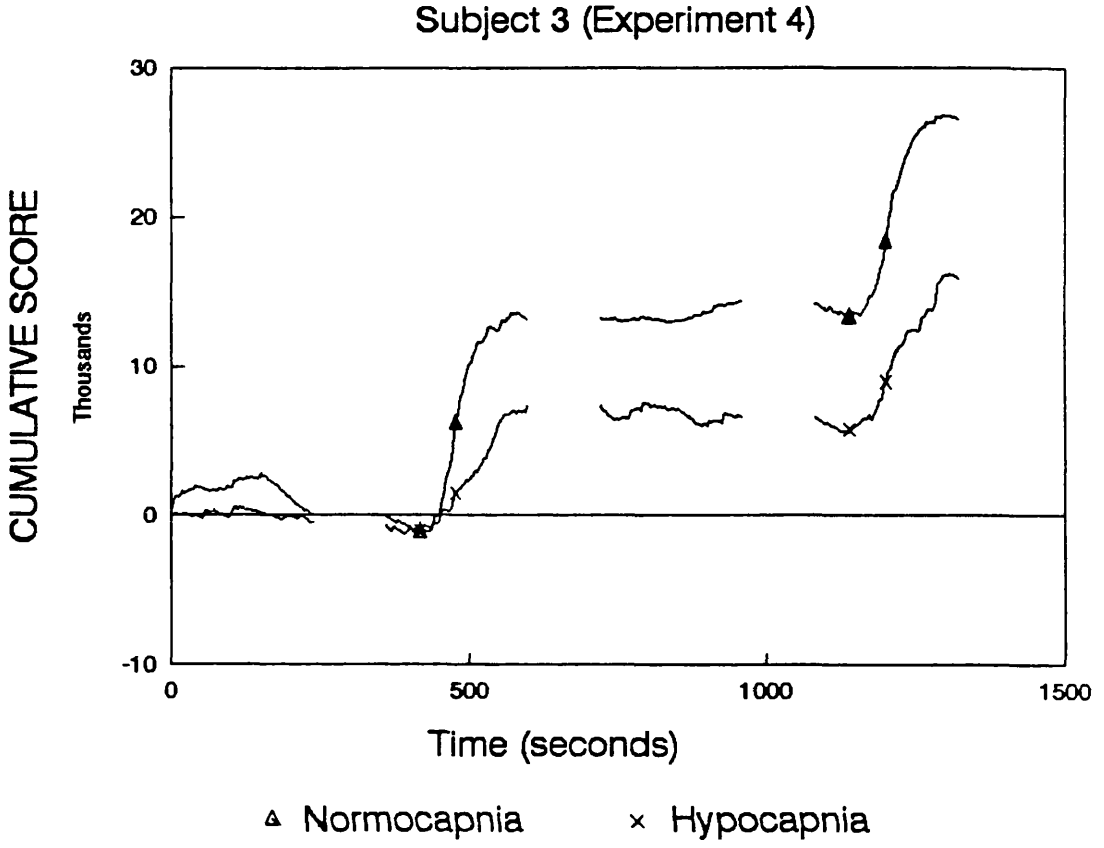


4 wash-in N2O curves

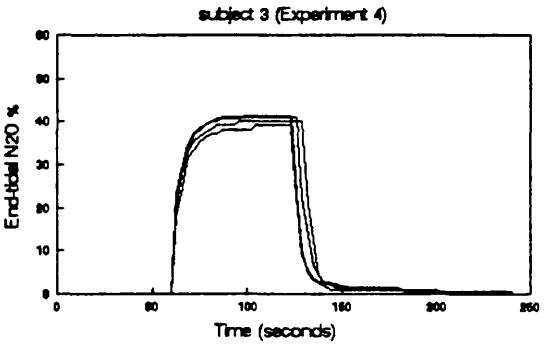
2 in normocapnic and 2 in hypocapnic runs

Figure 10.9

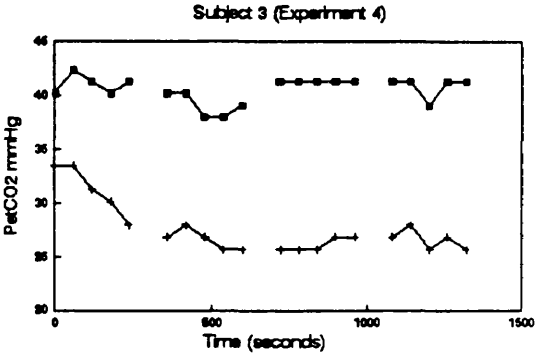
CUMULATIVE SUM V TIME



End-tidal N2O V TIME



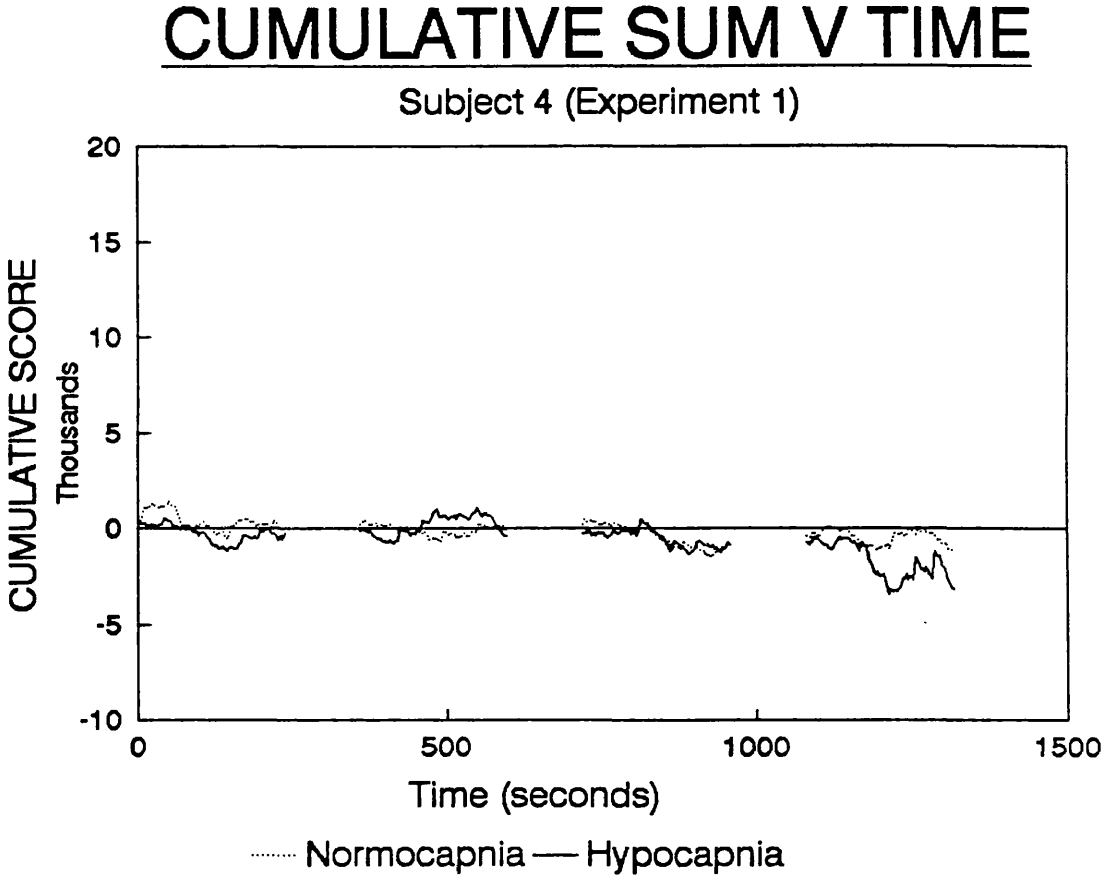
End-tidal CO2 over 4 epochs



4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

Figure 10.10


CUMULATIVE SUM V TIME
Subject 4 (Experiment 1)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

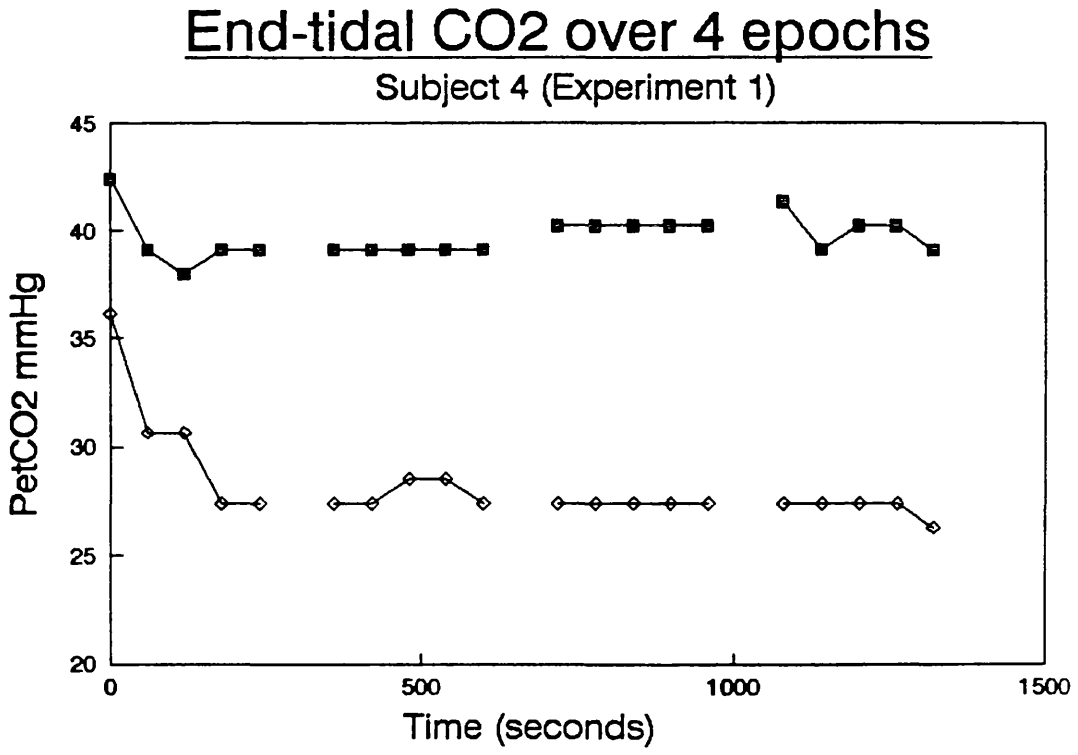
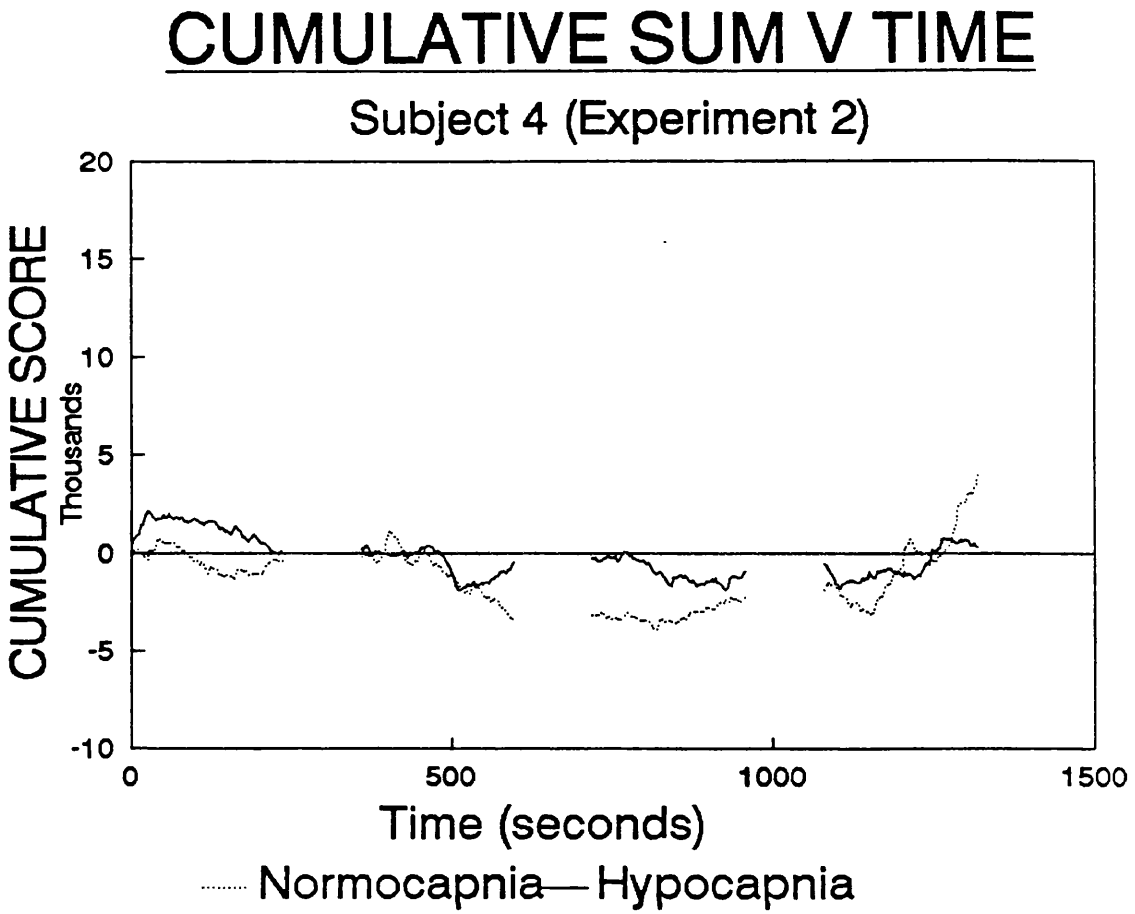

End-tidal CO2 over 4 epochs
Subject 4 (Experiment 1)
PetCO2 mmHg
45
40
35
30
25
20
0
500
1000
1500
Time (seconds)

Figure 10.11


CUMULATIVE SUM V TIME
Subject 4 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

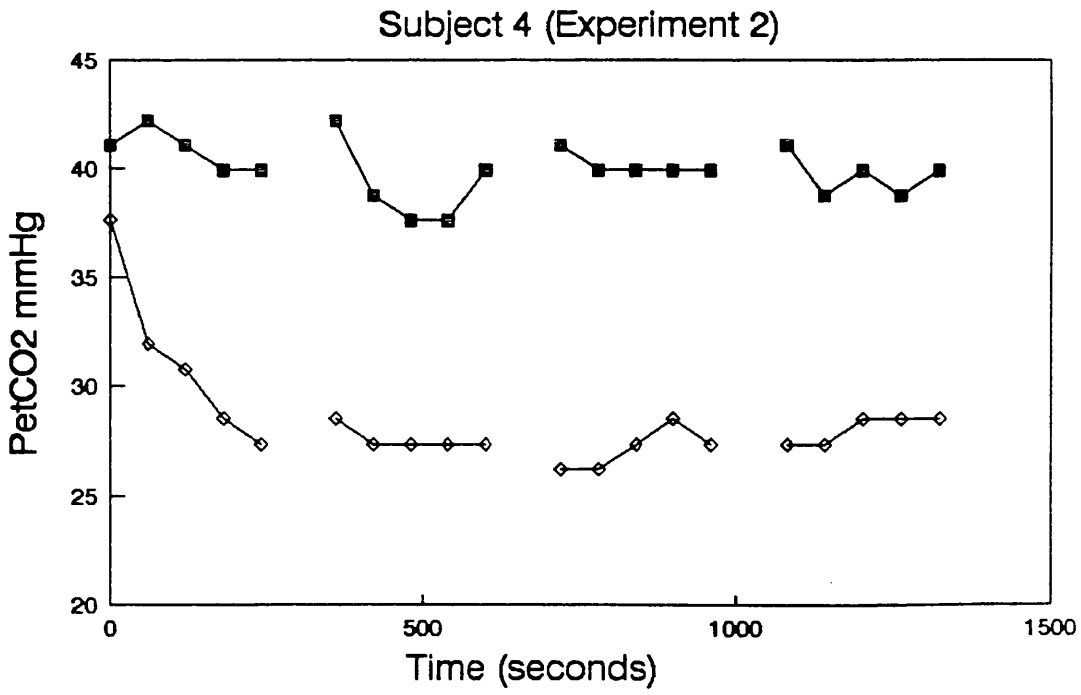
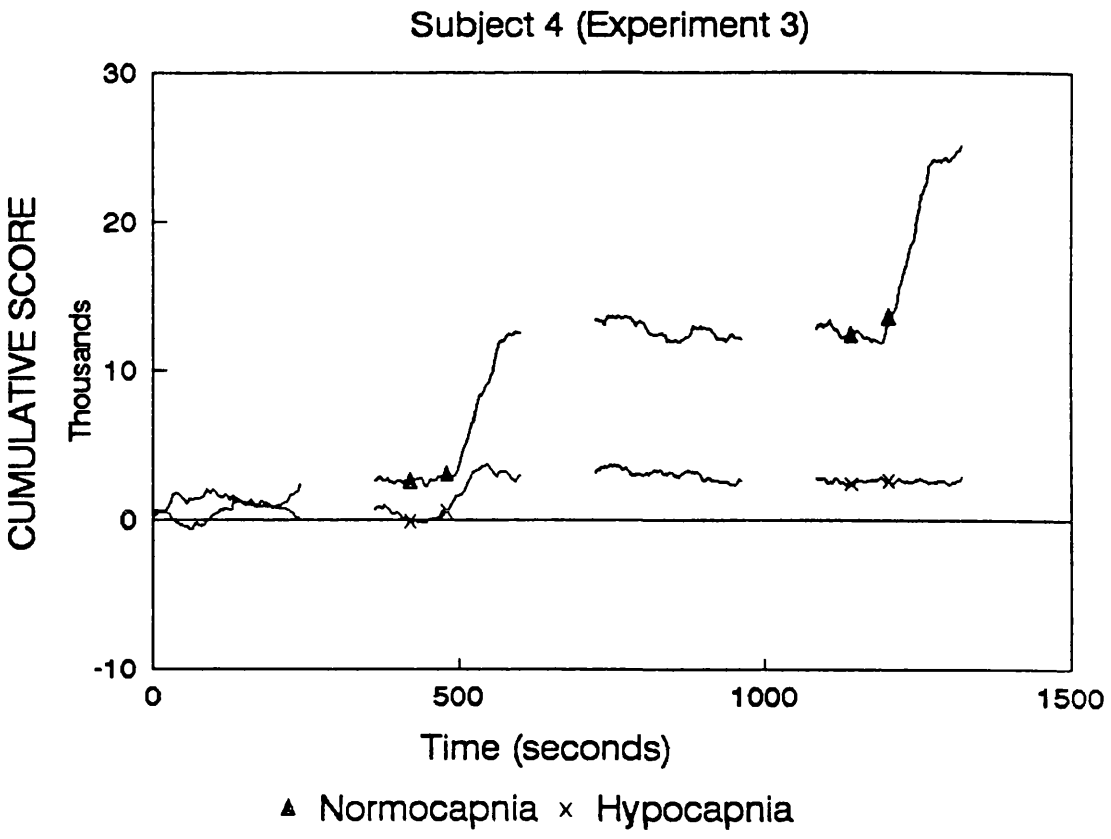
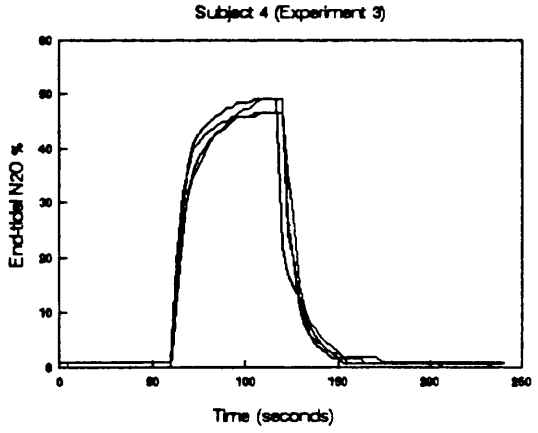

End-tidal CO2 over 4 epochs
Subject 4 (Experiment 2)
PetCO2 mmHg
45
40
35
30
25
20
0
500
1000
1500
Time (seconds)

Figure 10.12

CUMULATIVE SUM V TIME



End-tidal N2O V TIME



4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

End-tidal CO2 over 4 epochs

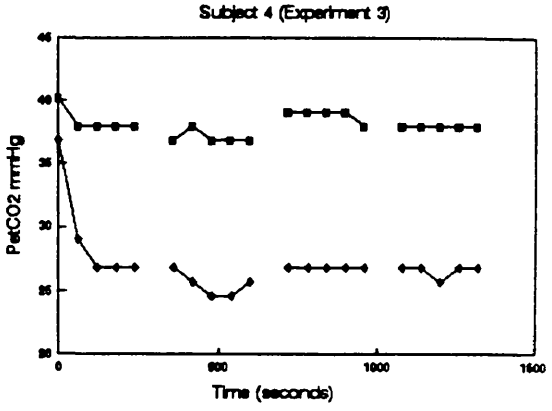
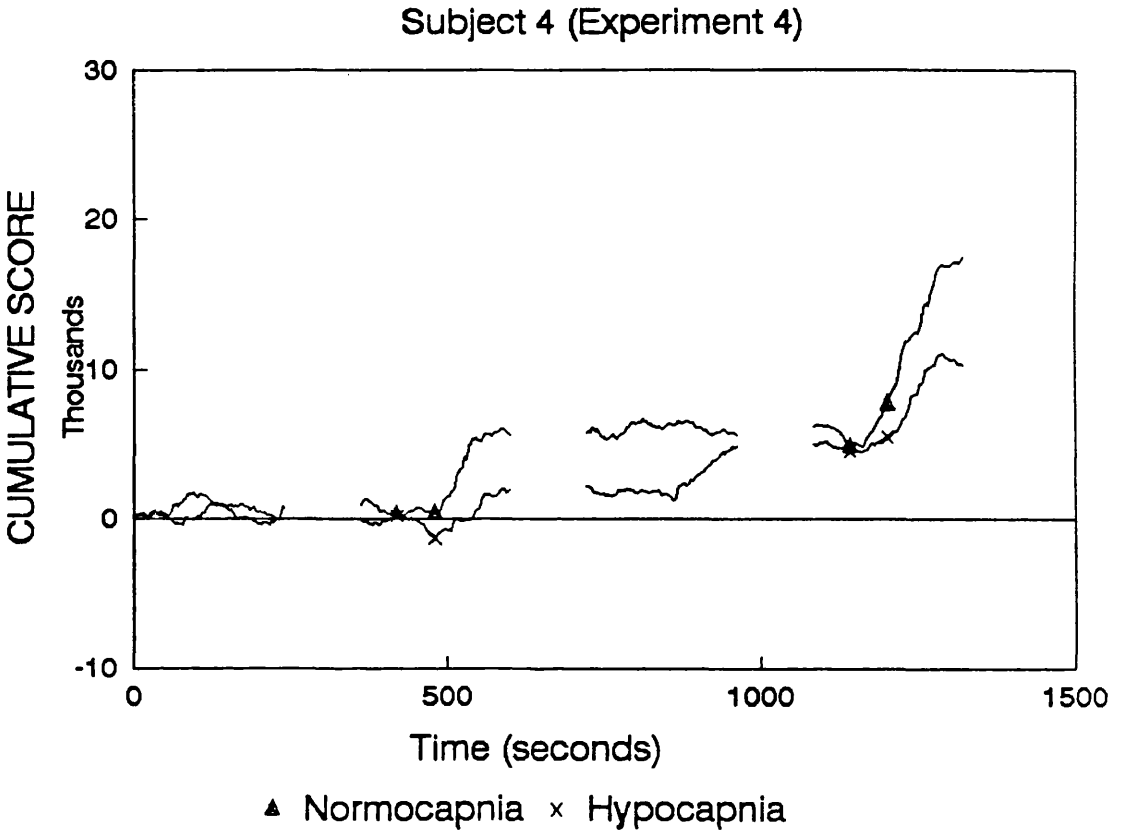
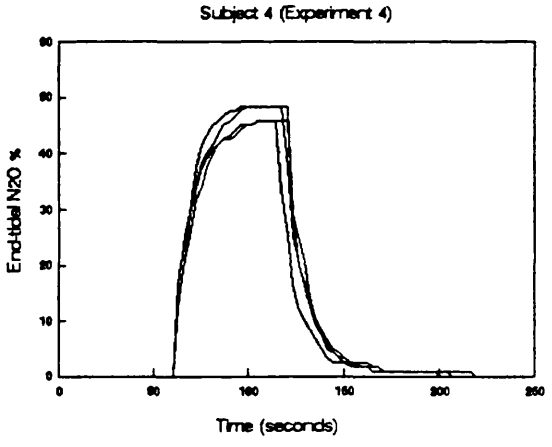


Figure 10.13

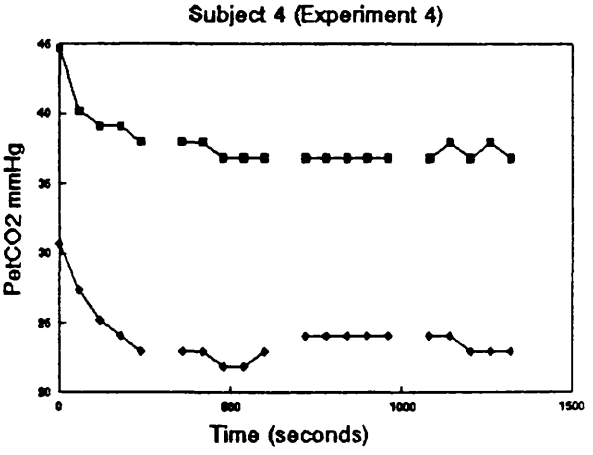
CUMULATIVE SUM V TIME



End-tidal N2O V TIME



End-tidal CO2 over 4 epochs



4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

Figure 10.14

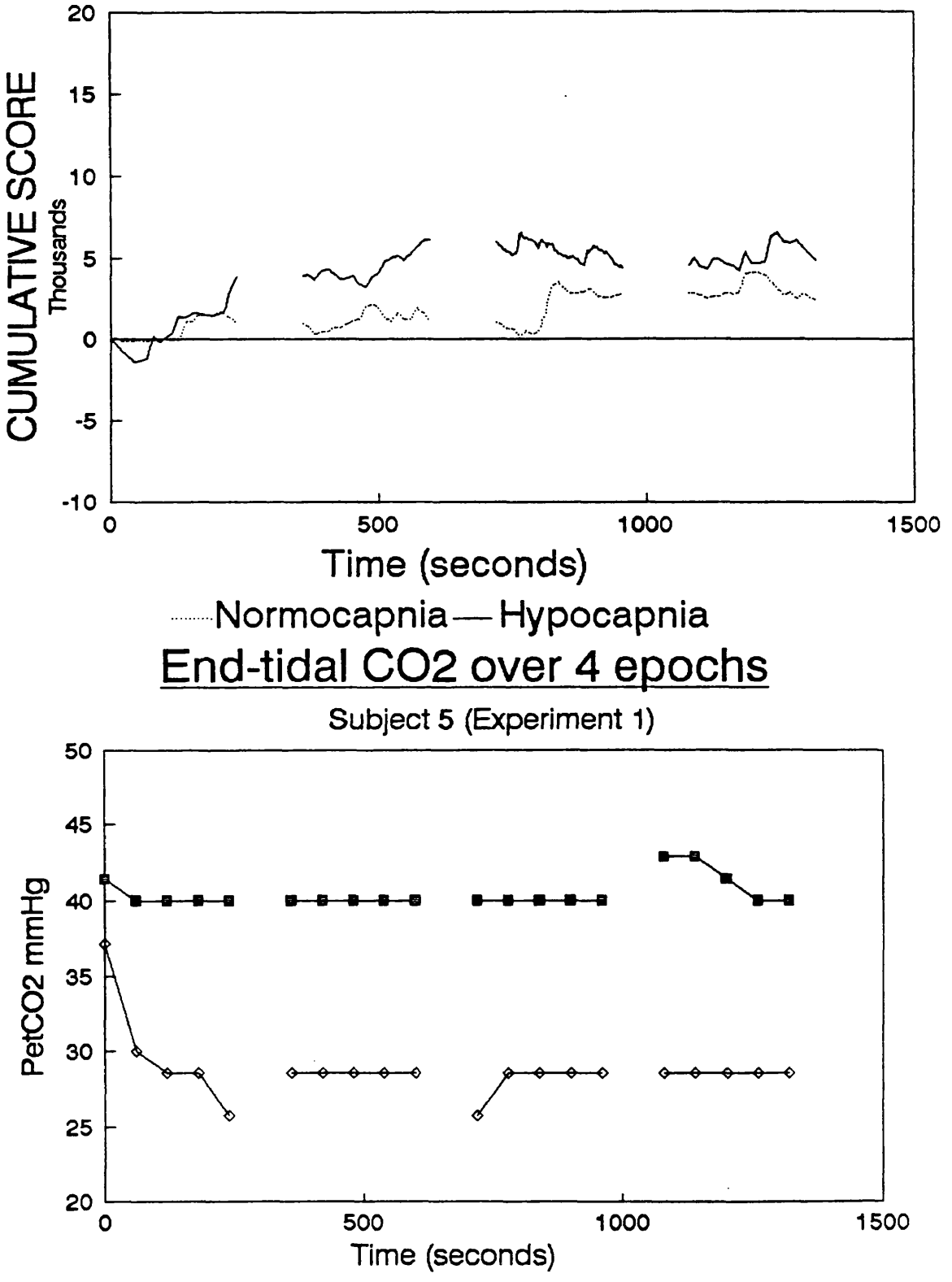
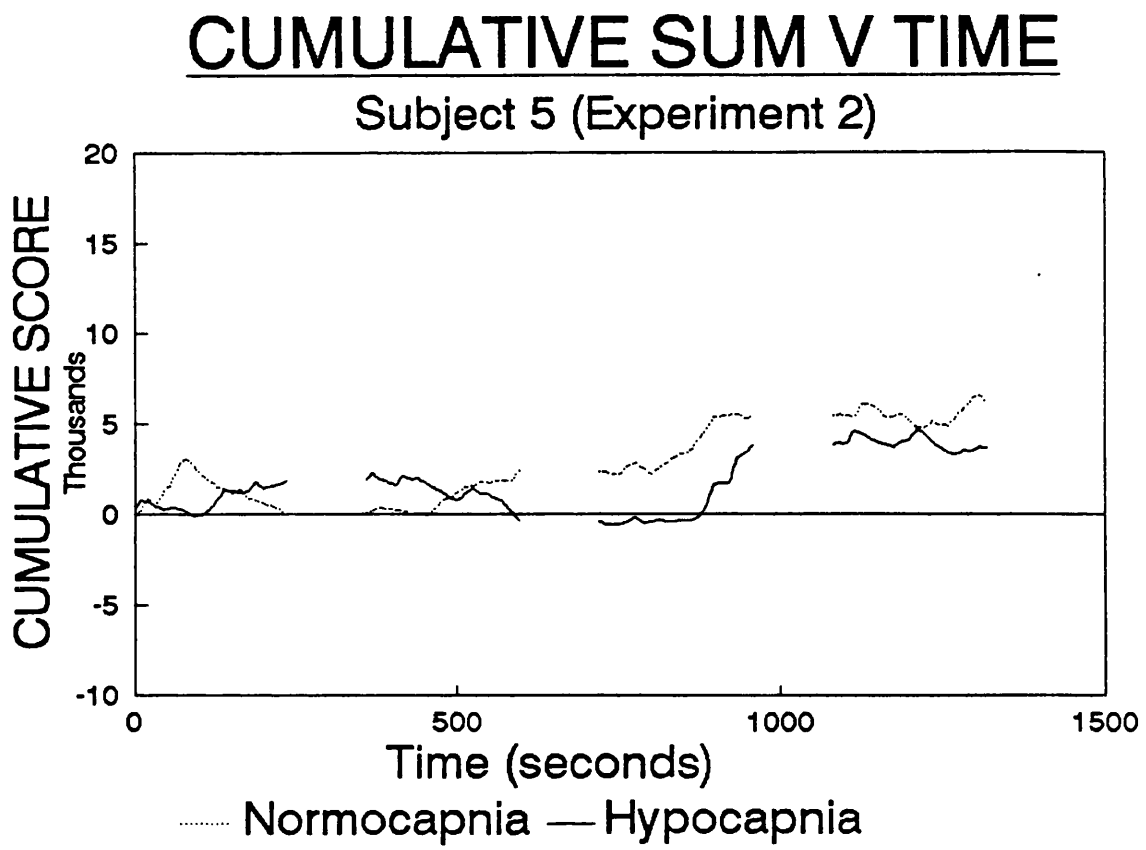

CUMULATIVE SUM V TIME
Subject 5 (Experiment 1)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia — Hypocapnia
End-tidal CO2 over 4 epochs
Subject 5 (Experiment 1)
PetCO2 mmHg
50
45
40
35
30
25
20
0
500
1000
1500
Time (seconds)

Figure 10.15


CUMULATIVE SUM V TIME
Subject 5 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

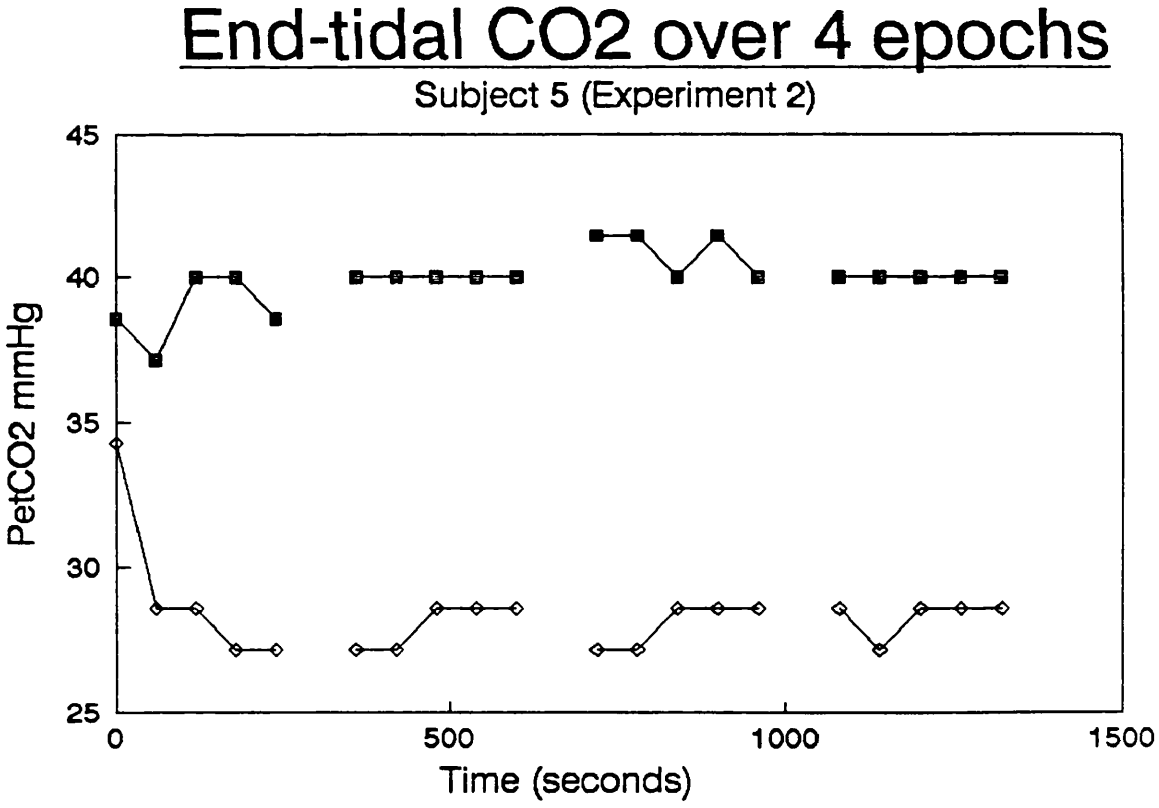
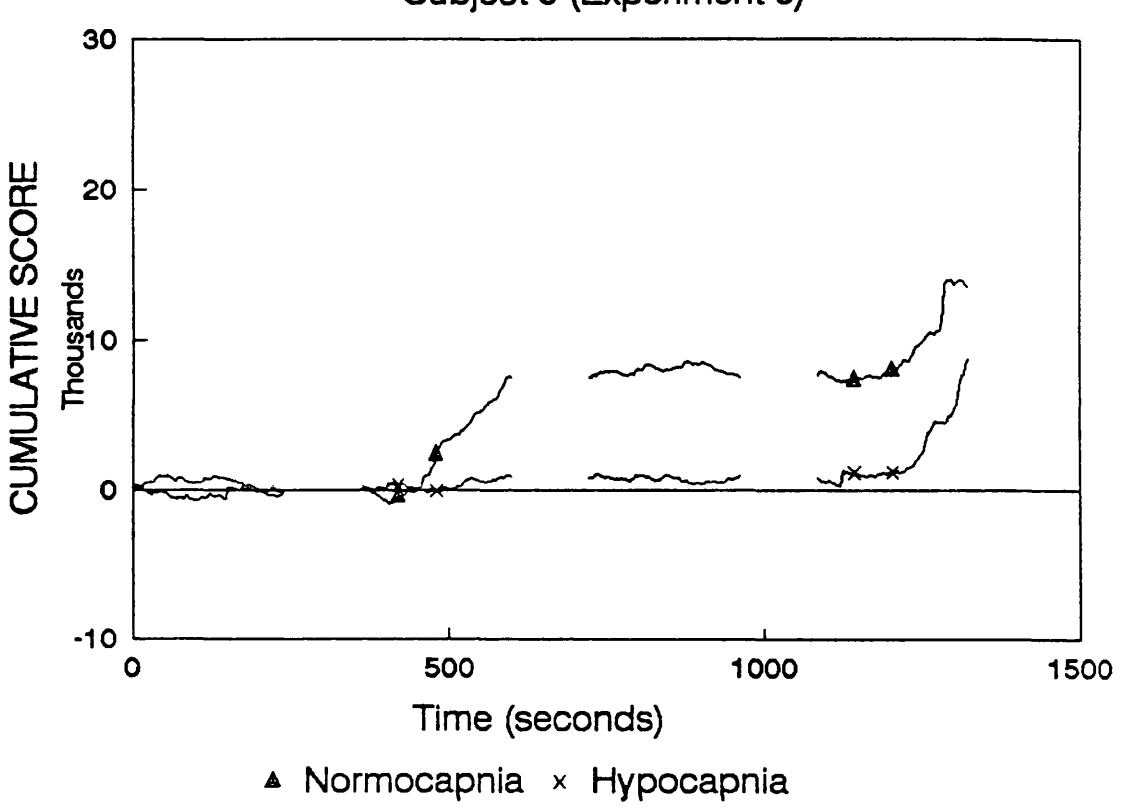
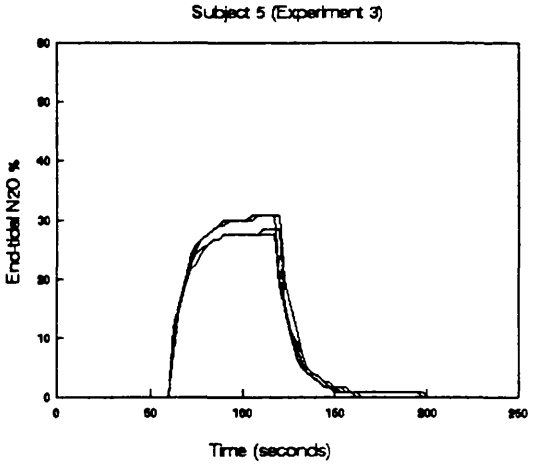

End-tidal CO2 over 4 epochs
Subject 5 (Experiment 2)
PetCO2 mmHg
45
40
35
30
25
0
500
1000
1500
Time (seconds)

Figure 10.16

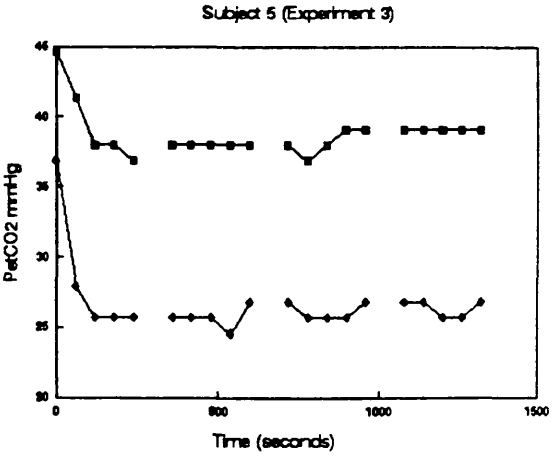
CUMULATIVE SUM V TIME



End-tidal N2O V TIME



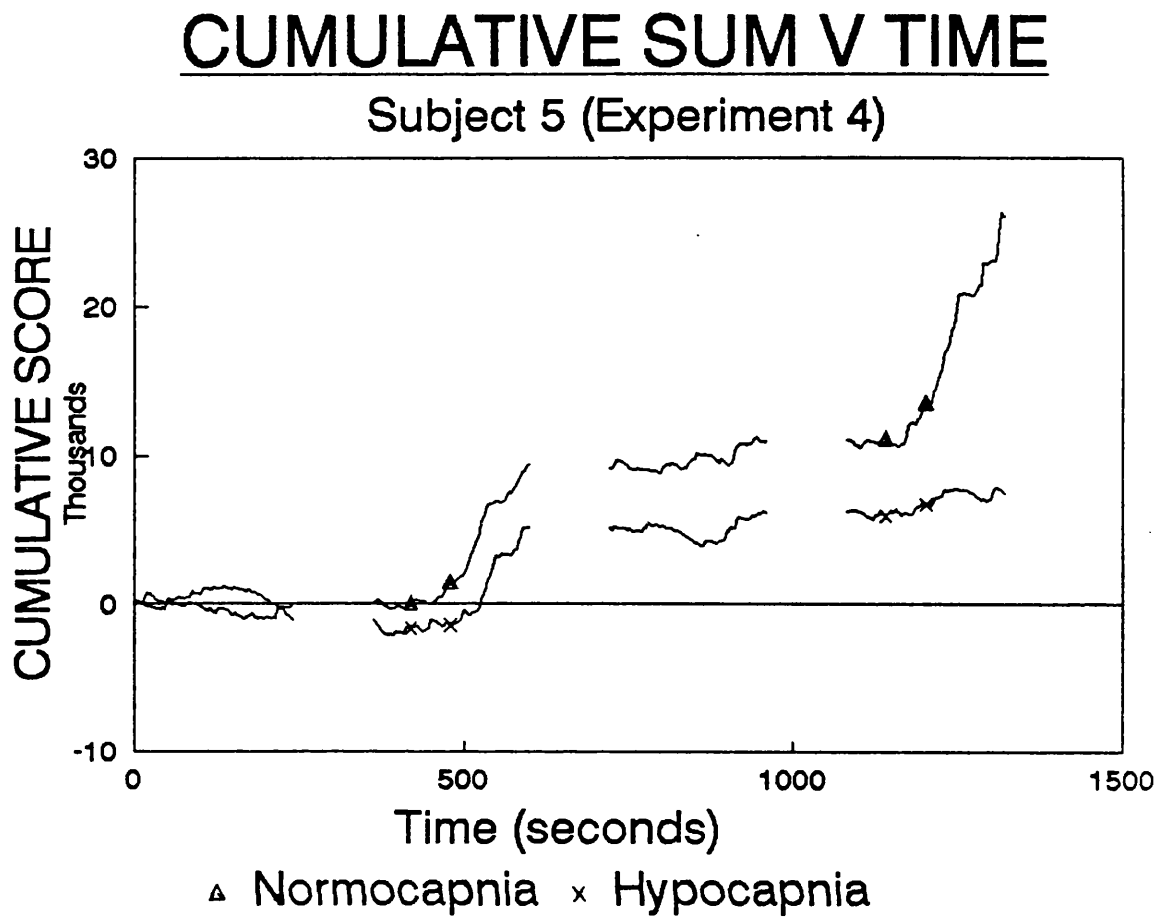
End-tidal CO2 over 4 epochs



4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

Figure 10.17


CUMULATIVE SUM V TIME
Subject 5 (Experiment 4)
CUMULATIVE SCORE
Thousands
30
20
10
0
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

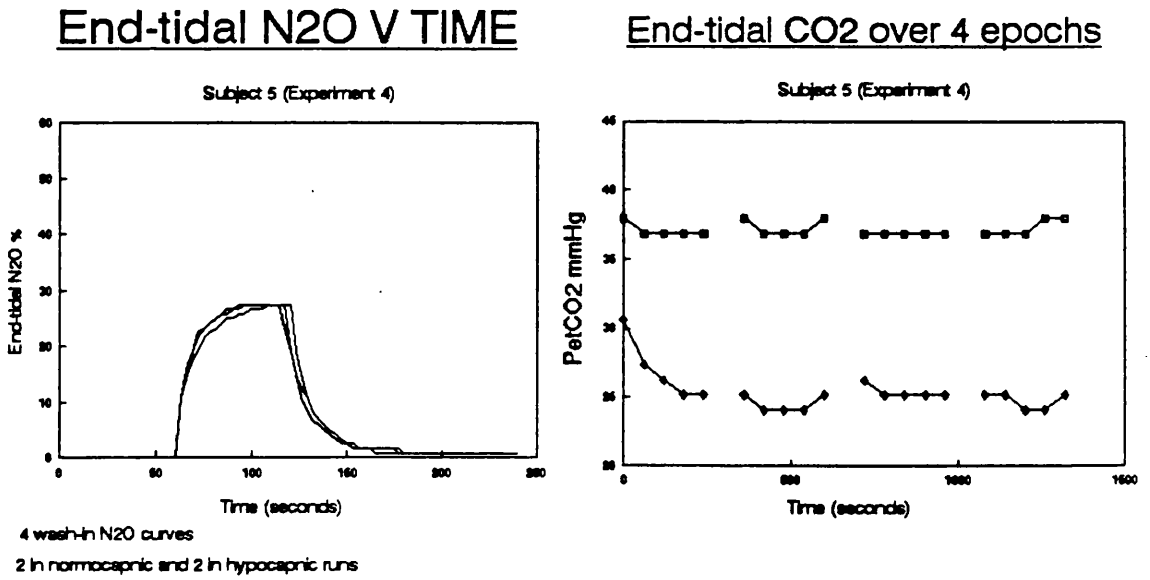
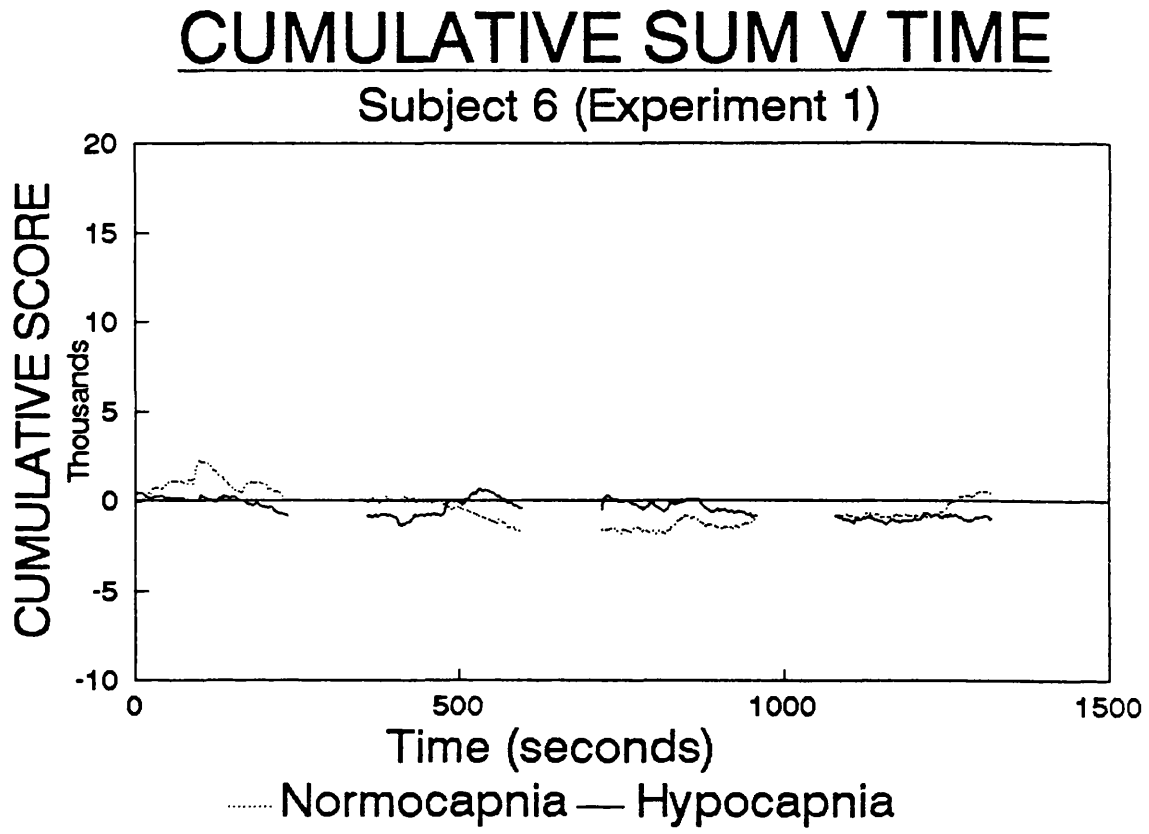

End-tidal N2O V TIME
Subject 5 (Experiment 4)
End-tidal N2O %
Time (seconds)
4 wash-in N2O curves
2 in normocapnic and 2 in hypocapnic runs
End-tidal CO2 over 4 epochs
Subject 5 (Experiment 4)
PetCO2 mmHg
Time (seconds)

Figure 10.18


CUMULATIVE SUM V TIME
Subject 6 (Experiment 1)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

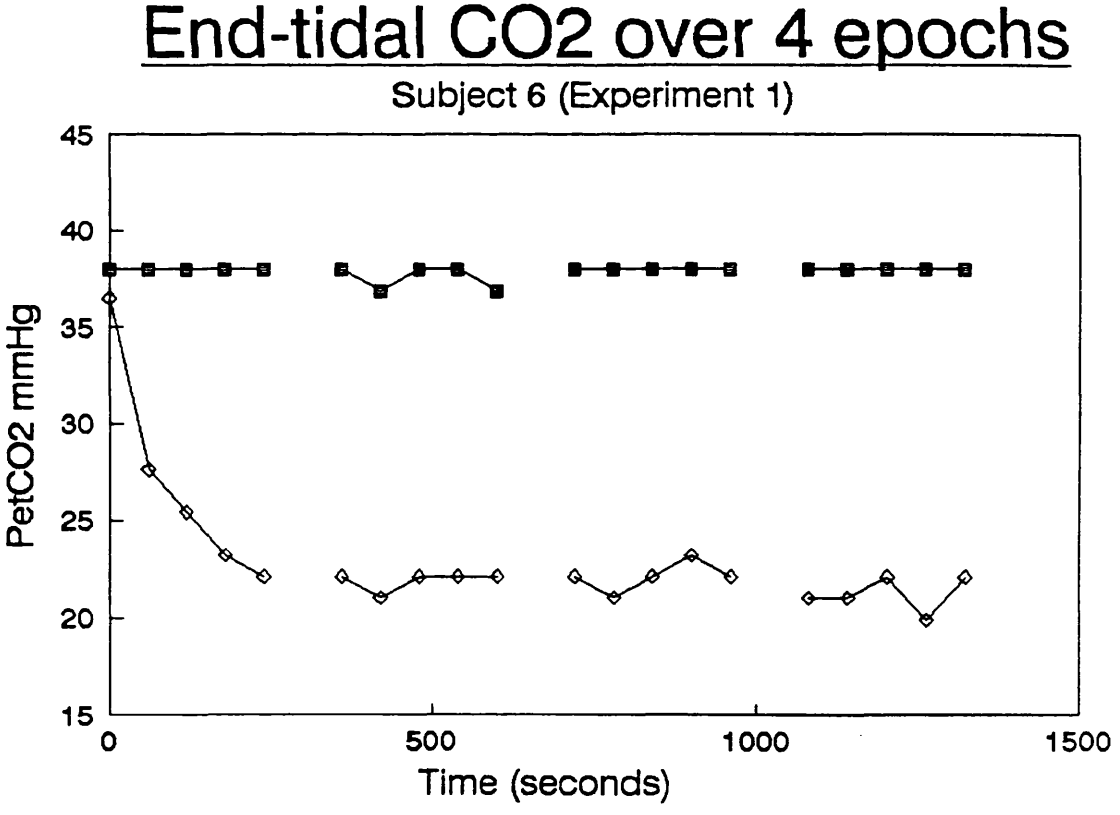
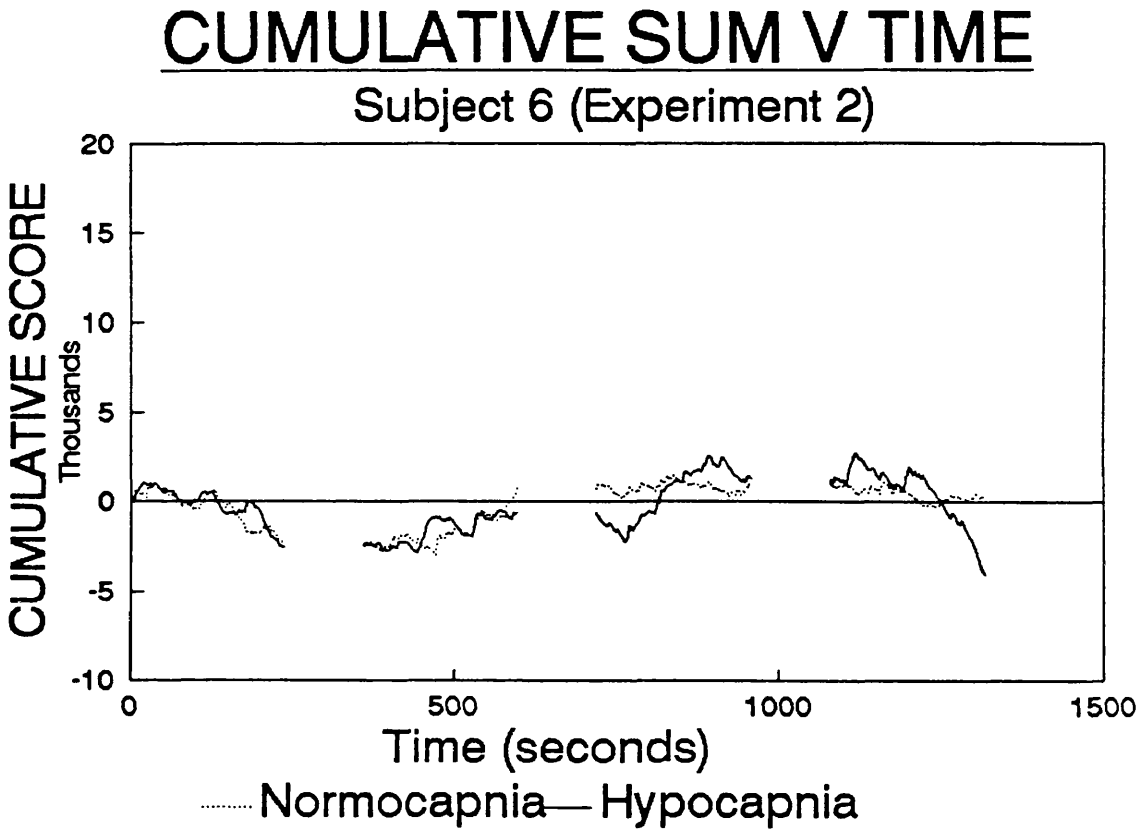

End-tidal CO2 over 4 epochs
Subject 6 (Experiment 1)
PetCO2 mmHg
45
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 10.19


CUMULATIVE SUM V TIME
Subject 6 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

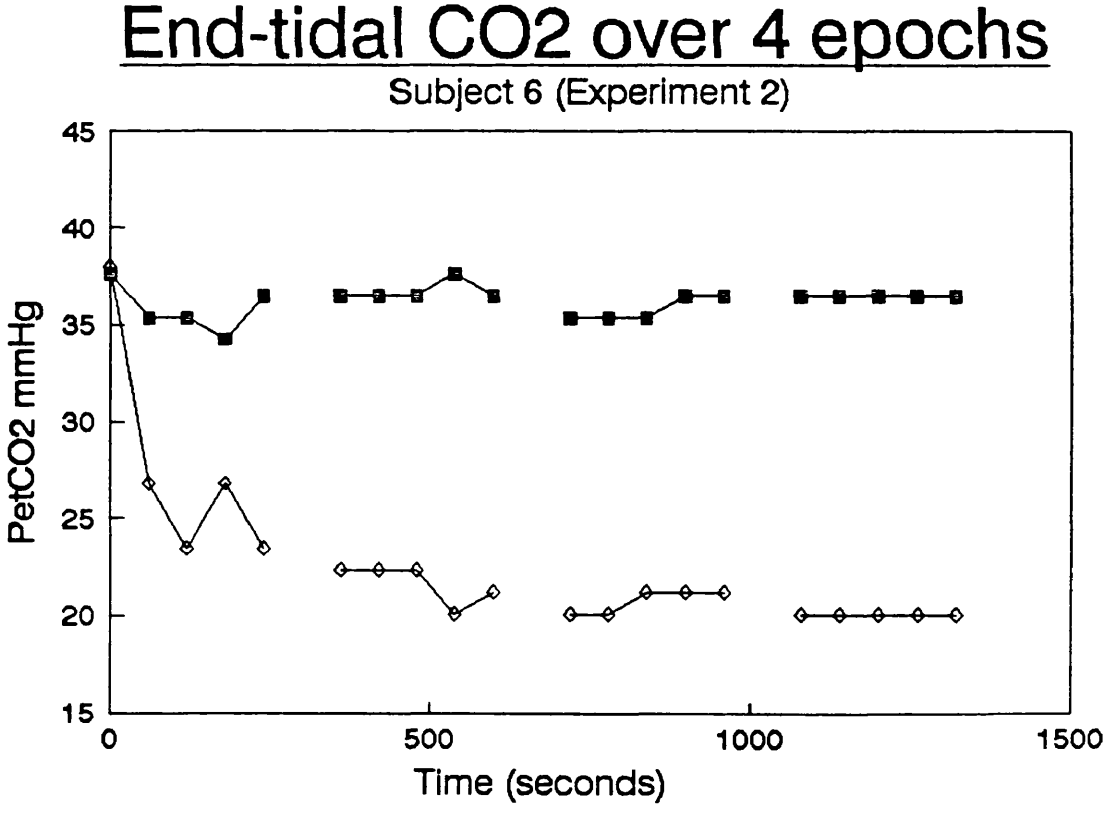
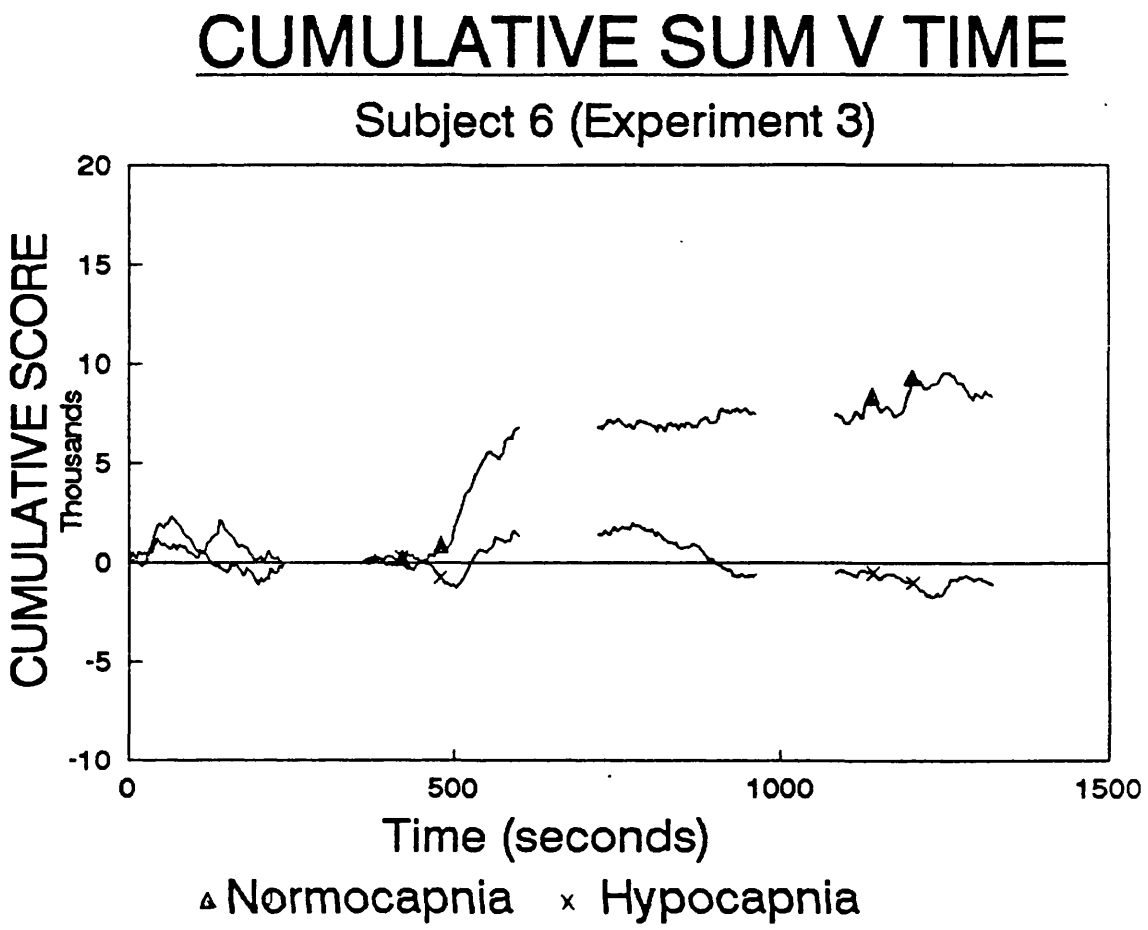

End-tidal CO2 over 4 epochs
Subject 6 (Experiment 2)
PetCO2 mmHg
45
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 10.20


CUMULATIVE SUM V TIME
Subject 6 (Experiment 3)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

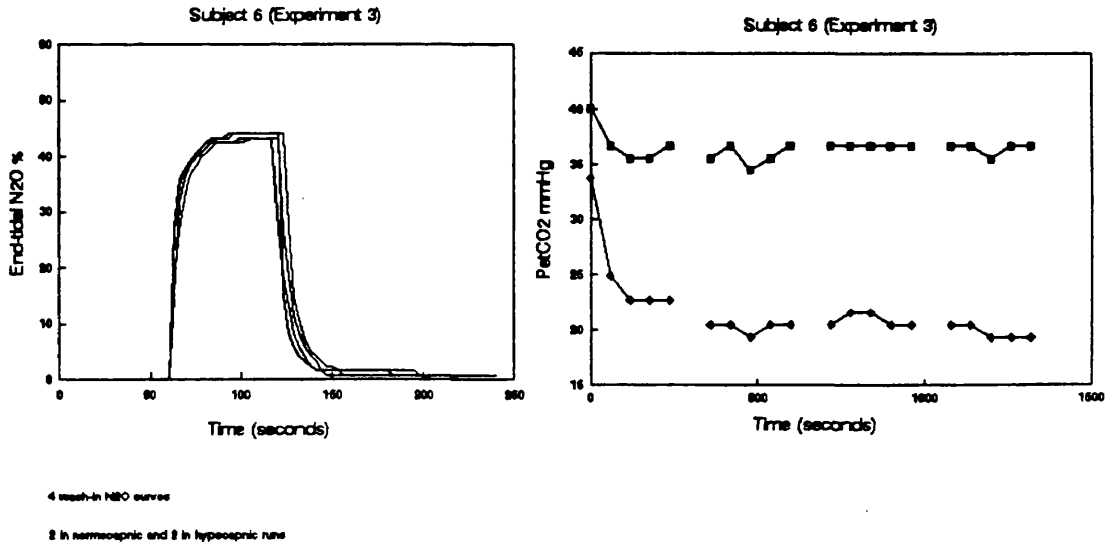
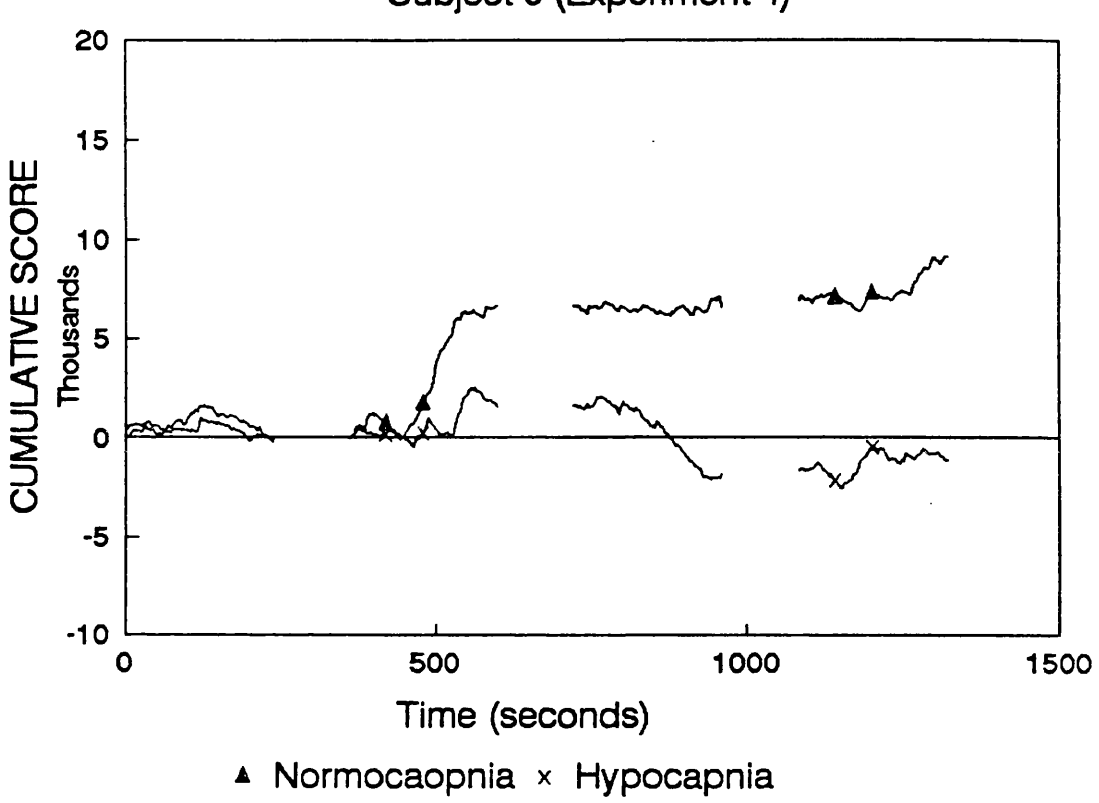
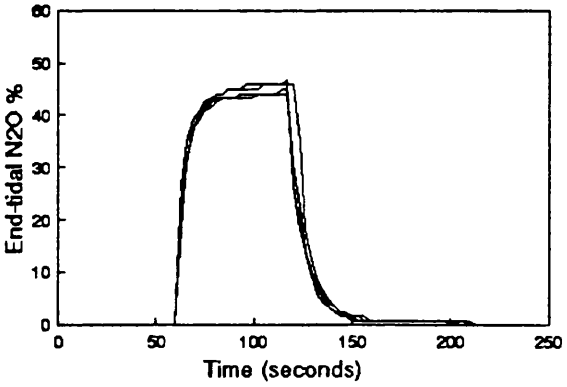

End-tidal N2O V TIME
End-tidal CO2 over 4 epochs
Subject 6 (Experiment 3)
End-tidal N2O %
Time (seconds)
Subject 6 (Experiment 3)
PetCO2 mmHg
Time (seconds)

Figure 10.21

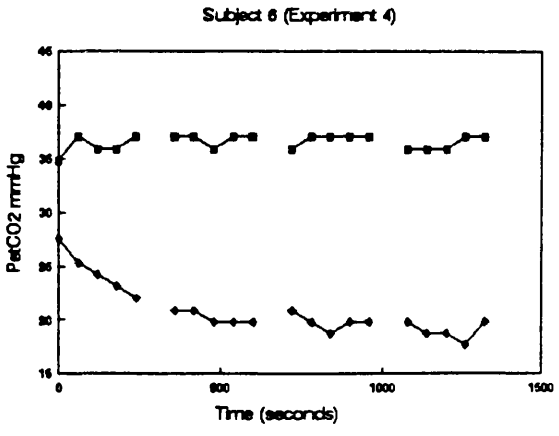
CUMULATIVE SUM V TIME



End-tidal N2O V TIME



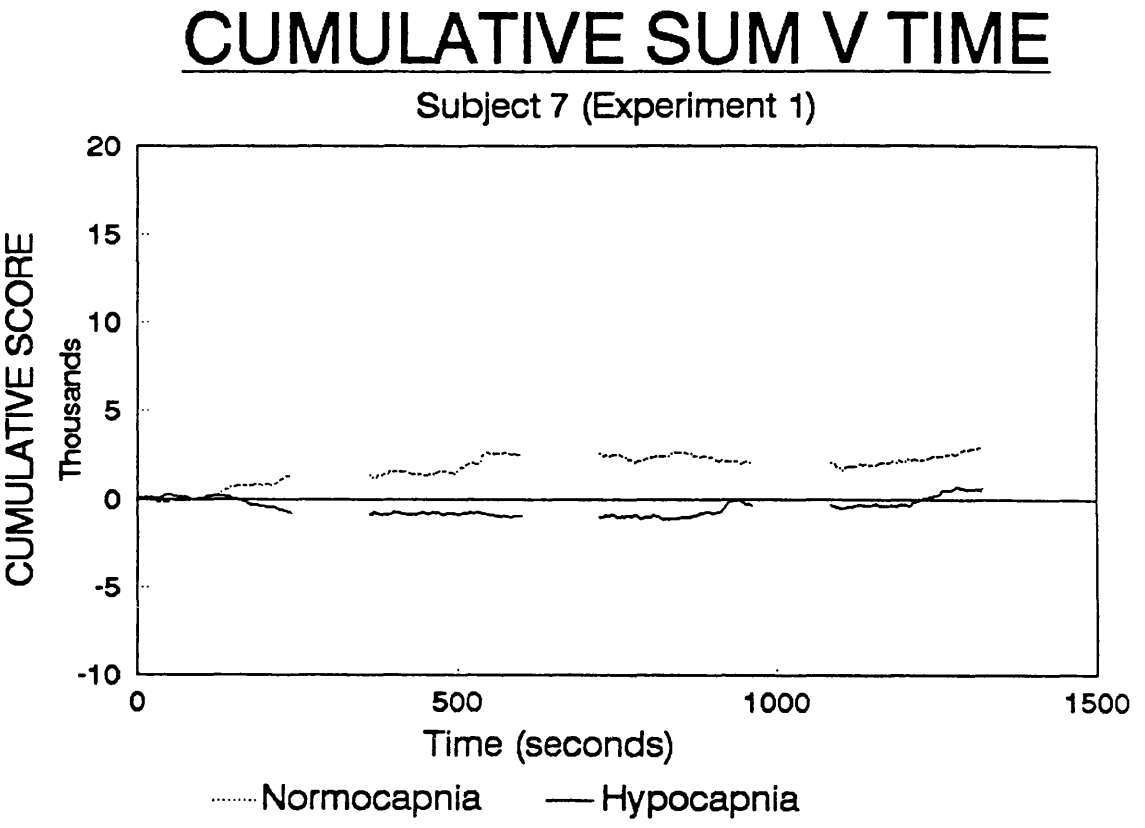
End-tidal CO2 over 4 epochs



4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

Figure 10.22


CUMULATIVE SUM V TIME
Subject 7 (Experiment 1)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

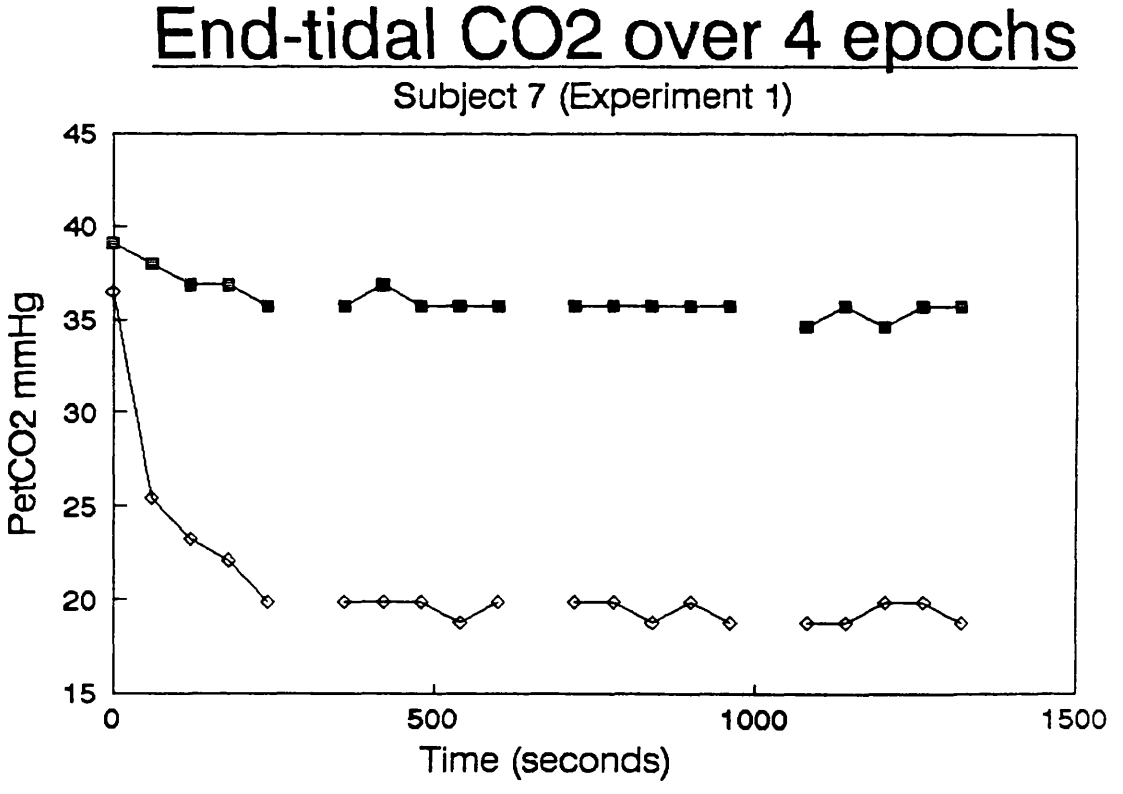
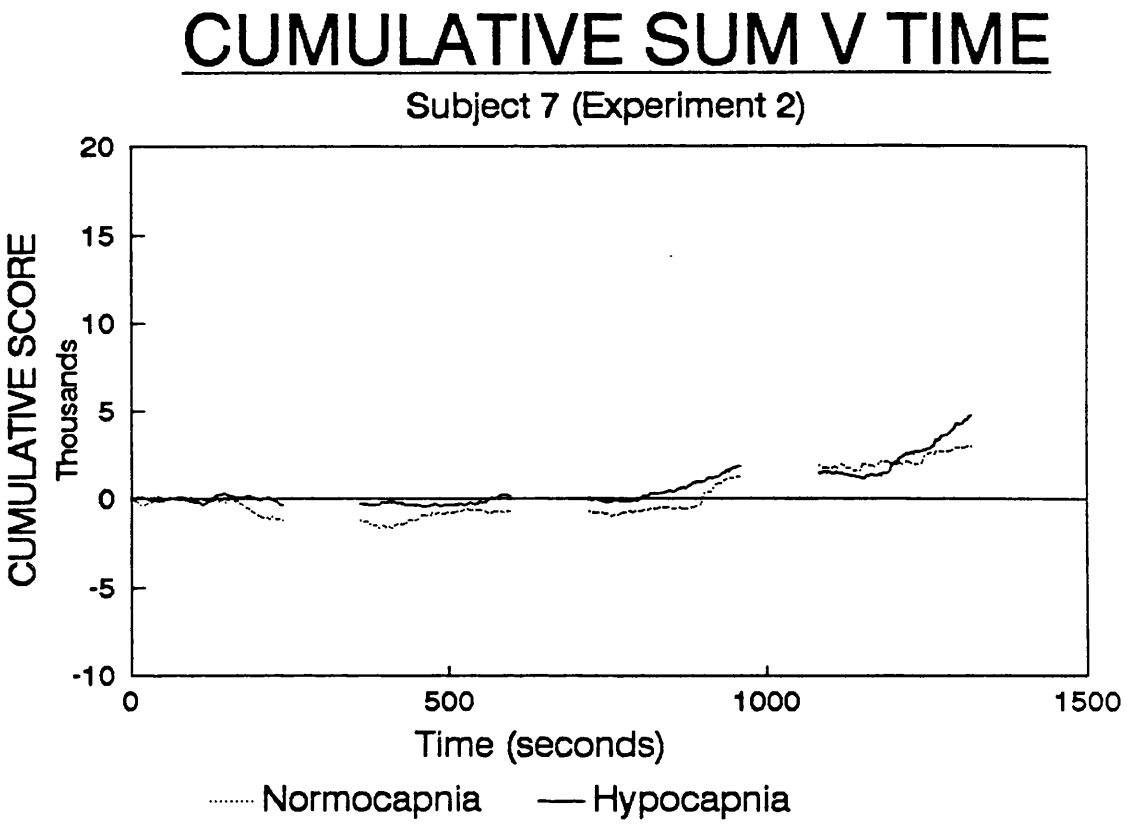

End-tidal CO2 over 4 epochs
Subject 7 (Experiment 1)
PetCO2 mmHg
45
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 10.23


CUMULATIVE SUM V TIME
Subject 7 (Experiment 2)
CUMULATIVE SCORE
Thousands
20
15
10
5
0
-5
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

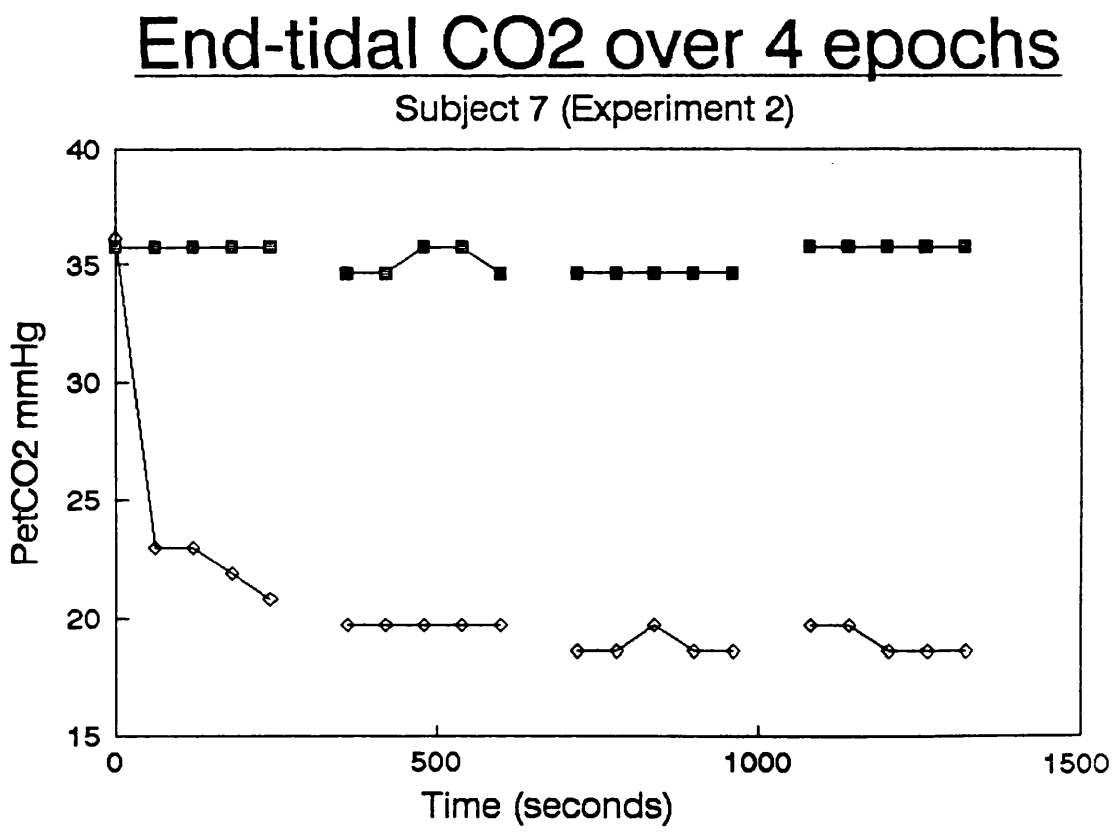
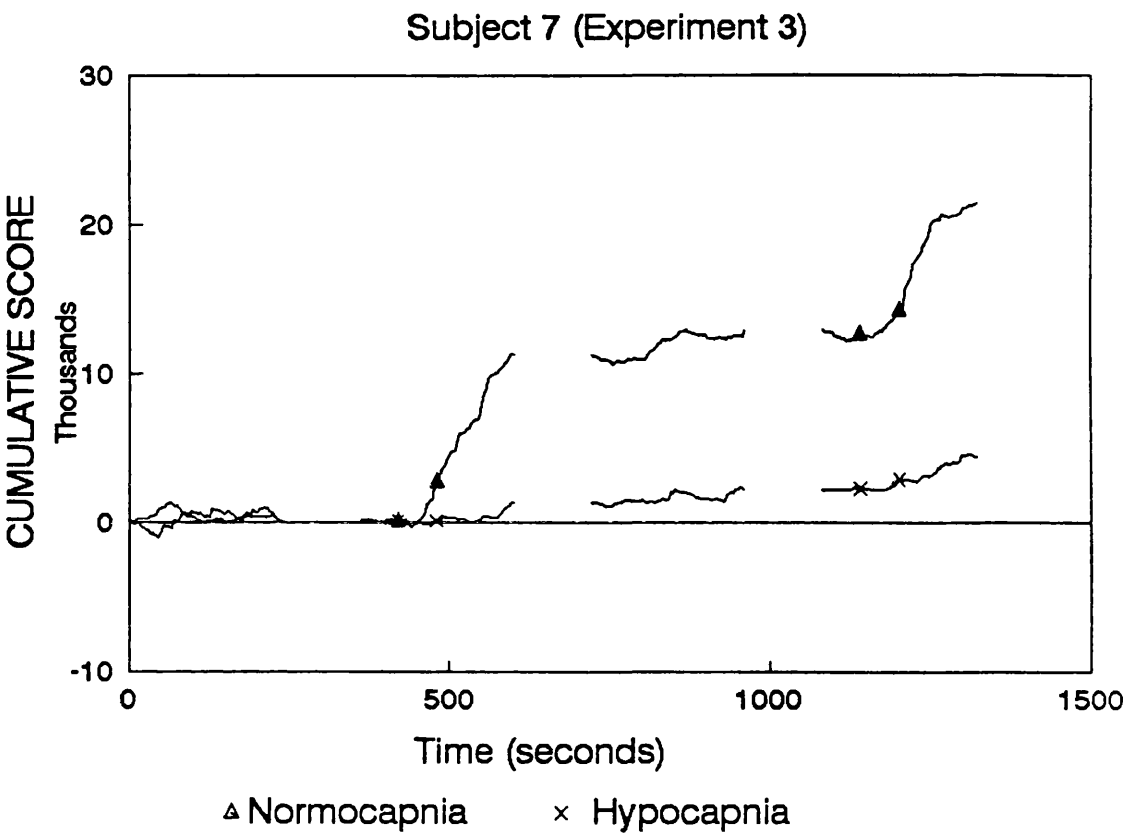
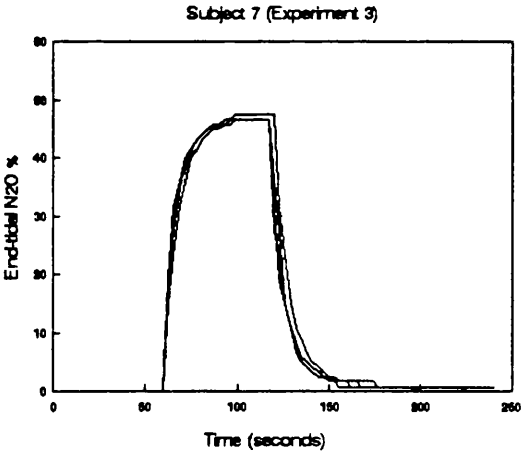

End-tidal CO2 over 4 epochs
Subject 7 (Experiment 2)
PetCO2 mmHg
40
35
30
25
20
15
0
500
1000
1500
Time (seconds)

Figure 10.24

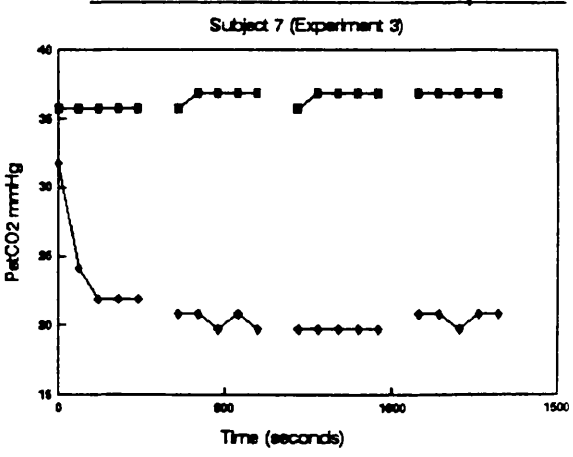
CUMULATIVE SUM V TIME



End-tidal N2O V TIME



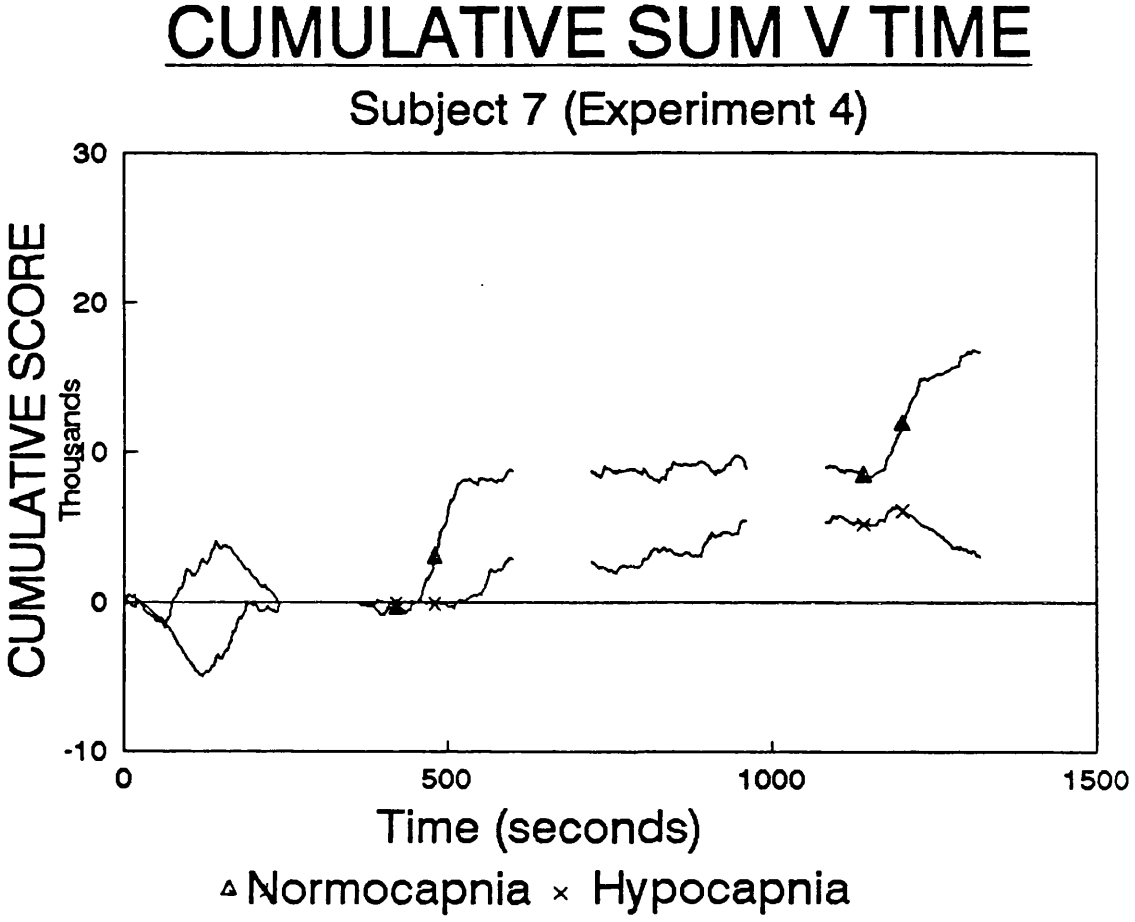
End-tidal CO2 over 4 epochs



4 wash-in N2O curves

2 in normocapnic and 2 in hypocapnic runs

Figure 10.25


CUMULATIVE SUM V TIME
Subject 7 (Experiment 4)
CUMULATIVE SCORE
Thousands
30
20
0
0
-10
0
500
1000
1500
Time (seconds)
Normocapnia
Hypocapnia

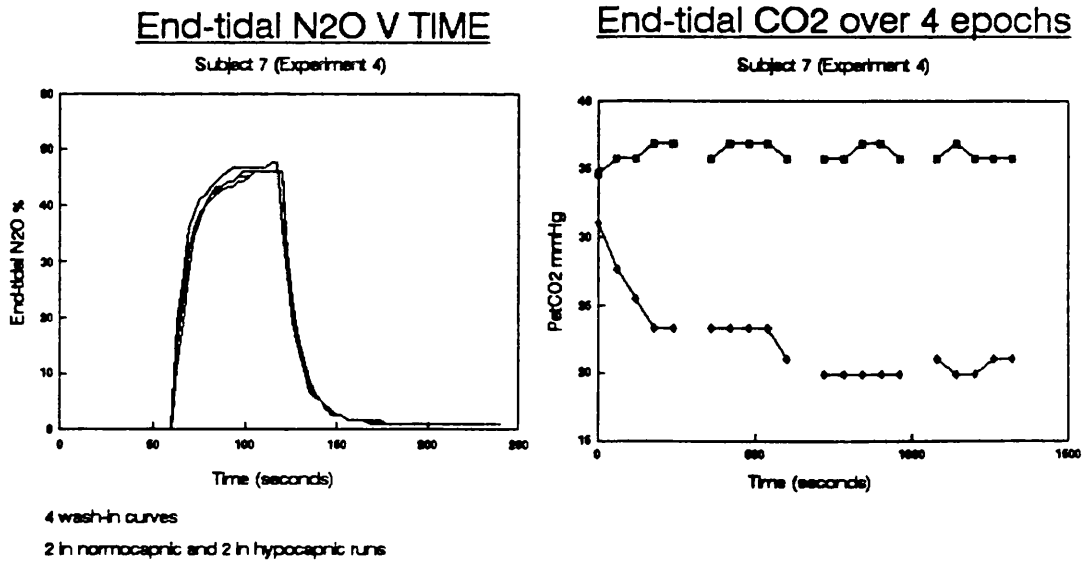

End-tidal N2O V TIME
Subject 7 (Experiment 4)
End-tidal N2O %
Time (seconds)
End-tidal CO2 over 4 epochs
Subject 7 (Experiment 4)
PetCO2 mmHg
Time (seconds)
4 wash-in curves
2 in normocapnic and 2 in hypocapnic runs

Figure 10.26

Table 10.0 to show the design of the formal study

Subject #	1st study	2nd study	3rd study	4th study
1	2	1	3	4
2	--	2	4	3
3	--	4	2	3
4	2	4	3	1
5	1	3	2	4
6	3	2	4	1
7	1	3	4	2

The table lists the order in which experiments were actually done.

Table 10.1 to show the hypocapnic thresholds (HCT) and end-tidal CO_2 tensions of the subjects, for the hypocapnic episode in each experiment. All tensions are given in mm Hg.

Subj.	HCT	Experiment 1	Experiment 2	Experiment 3	Experiment 4
1	22	26	27	25	26
2	24	--	25	25	26
3	22	--	26	22	26
4	24	27	28	27	24
5	28	29	27	26	26
6	18	22	20	22	18
7	15	20	19	19	22

Table 10.2 to show the peaks of end-tidal N2O tensions reached by the subjects in the second and fourth epochs of Experiment 3 and Experiment 4. All values are given as % concentrations at one atmosphere.

Subject #	Expt 3 Normocapnia		Expt 3 Hypocapnia		Expt 4 Normocapnia		Expt 4 Hypocapnia	
1	39.2	39.2	40.0	39.2	40.8	40.0	40.0	40.8
2	50.0	50.0	49.1	48.2	50.8	50.0	50.0	49.2
3	40.0	39.2	39.2	40.9	40.0	40.9	41.3	39.1
4	46.7	46.7	49.2	49.1	48.3	48.3	45.8	45.8
5	30.8	30.0	28.3	27.5	27.5	27.5	27.5	27.5
6	44.2	45.2	43.3	43.0	44.2	44.2	45.8	45.0
7	46.7	46.7	47.5	46.7	45.8	45.8	45.8	47.5

Table 10.3 to show the accumulated deficits in response times, by subject, for Experiment 1 and Experiment 2. All times are given in seconds.

Subject #	Expt 1 Normocapnia	Expt 1 Hypocapnia	Expt 2 Normocapnia	Expt 2 Hypocapnia
1	-3.4	0.9	2.1	-2.7
2	--	--	3.7	0.4
3	--	--	4.3	5.0
4	-1.1	-3.2	4.1	0.3
5	2.4	4.9	6.2	3.8
6	-1.0	0.5	0.3	4.0
7	3.0	0.6	4.8	3.0

Table 10.4 to show the accumulated deficits in response times, by subject, for Experiment 3 and Experiment 4. All times are given in seconds.

Subject #	Expt 3 Normocapnia	Expt 3 Hypocapnia	Expt 4 Normocapnia	Expt 4 Hypocapnia
1	24.1	6.1	21.8	7.3
2	39.3	11.7	23.5	16.6
3	24.0	7.8	26.5	15.9
4	25.1	2.9	17.6	10.3
5	13.6	8.8	26.0	7.5
6	8.4	-1.1	9.2	-1.1
7	21.4	4.4	16.7	3.0

11 DISCUSSION OF THE RESULTS

In all seven subjects, the results of the formal study suggest that:

1) hypocapnia was fully developed within a few minutes of commencing steady increased ventilation

2) the performance of the psychomoter task, when breathing air, was not affected to an appreciable extent by the levels of hypocapnia chosen.

3) the same levels of hypocapnia were used when nitrous oxide was inhaled.

4) nitrous oxide swept into the lung in an identical fashion in normocapnia and in hypocapnia.

5) psychomotor effects of anaesthesia appeared about one minute later.

6) nitrous oxide swept out of the lung in an identical fashion in normocapnia and hypocapnia.

7) psychomotor effects of anaesthesia receded adout one minute later.

8) the psychomotor effects of the pulse of nitrous oxide inhalation was considerably less in hypocapnia that normocapnia.

9) the effects of hypocapnia on nitrous oxide anaesthesia appeared to be fully developed within

seven minutes of the onset of increased breathing, and within two minutes of reaching a steady low end-tidal PCO_2.

However, to obtain these results it was necessary to tailor the degrees of hypocapnia, nitrous oxide anaesthesia and task difficulty to each subject, and to develop a particular way of presenting the effects on response times. Also, all of the studies were conducted on medically qualified people who were aware of the hypothesis to be tested and who could not be blinded to the hypocapnia, the nitrous oxide anaesthesia, the type of task that was testing them, or to subjective interactions between these factors, that they experienced. It could be argued that these factors biased the outcomes of the study in favour of the original hypothesis. These points are discussed below.

The aim of the study was to test the idea that prior hyperventilation would reduce the uptake of nitrogen in nervous tissue during the brief profound compression that inevitably accompanies submarine escape.

That led directly to considering some general points about dose response relationships. Most of these associations are roughly sigmoid, i.e there is a threshold dose below which no effects are seen and another dose above which the system behaves as if it is saturated and no further increases in effects are seen. The greatest sensitivity usually lies midway between the two doses. To show a factor augments an effect of

an agent it may be tested against a constant dose, that is just above the lower threshold, so that most of the usable range above is available to show the increase in response. But use of this dose will conceal any reductions in response that occur. If a factor is expected to diminish a response, that can be shown against a dose of the agent that is just below the saturated upper threshold. But use of that dose will conceal any augmentations that occur. Bias is minimised by working in the middle of the dose-response curve.

Some level of hypocapnia had to be chosen for the design. The choice of degree was complicated by other factors. The purpose of the study was to hunt for the greatest practical benefit, therefore a high dose was needed. Hypocapnia was being used to reduce cerebrospinal blood flow, but that was not being measured. It was known that, in man, vasoconstriction begins to flatten out when the arterial PCO_2 falls below 20 mm Hg (Reivich et al 1964). The study would be irrelevant if the hypocapnia was severe enough to interfere with the escape procedure. Also, the study would be unanalysable if the additional slowing of the response times due to hypocapnia masked any reductions it produced in the concentrations of nitrous oxide in nervous tissue. These points led to the idea that the degree of hypocapnia chosen, should be that which just failed to produce progressive slowing of response times in the absence of nitrous oxide anaesthesia.

Preliminary experiments showed clear-cut and consistent differences between subjects, but it would be wrong to suggest that their hypocapnic thresholds to slowing could be determined very precisely. It was certain that two subjects (#6 & #7) could plough on regardless at surprisingly low end-tidal CO_2 tensions of 15 to 18 mm Hg, on many occasions. It was also definite that the subject from Singapore was much more sensitive, tending to fall asleep and failing to respond at all if his end-tidal PCO_2 dropped below 25 mm Hg. The other subjects were intermediate. Subjects were studied close to their hypocapnic thresholds to get the maximum practicable hypocapnia and to reduce the effects of variations in individual sensitivity. The implications are that they were at roughly similar degrees of cerebrospinal vasoconstriction and, if Reivich's figures are correct they were near-maximally constricted.

Almost identical arguments apply to the degree of nitrous oxide anaesthesia. It was likely that there was a roughly sigmoid relationship between the dose of anaesthesia and slowing of response time, i.e there would be a dose below which there would be no impairment on which to display an improvement of performance, and there would be a higher dose above which the subject would be too deeply asleep for the reduction in cerebral nitrous oxide concentration to be detectable. Again, there were clear and consistent differences in individual sensitivities. The aims were to poise the

subjects towards the top of their individual dose-response curves leaving room to display an effect, and to reduce the effects of individual variations in sensitivity. Doing this would minimise any augmentations of anaesthesia that occurred. These would have been seen as 'absence of effects', but every subject showed a clear benefit so the results have not been biased in this regard.

The psychomotor task was chosen because there was much local experience with it and the task was known to be able to follow changes of consciousness that occurred over periods of a 15 seconds or less. Submarine escape applies a pulse of nitrogen absorption that rises to a peak over about twenty to forty seconds and recedes over the next minute or two. The nitrous oxide pulse follows the same form. Subjectively, effects of nitrous oxide, such as ringing in the ears, coning of vision, loss of peripheral attention and a distorted awareness of time, could be sensed about 30 seconds after the start of inhalation. They built up gradually towards imminent or actual loss of consciousness at about one minute. Task performance was usually well maintained until the end of that minute, suggesting that it was insensitive to amounts of nitrous oxide that were already having other definite effects on the brain.

In retrospect the task may have been too simple to detect some effects, but that illustrates an important dilemma in studies of this sort. We needed a task that

could sample consciousness repeatedly at regular intervals of a few seconds duration. Such tasks must be simple, and therefore less able to show subtle influences. Sophisticated questions take more time to ask and to answer. Preliminary experiments with the reversed task suggested that slight increases in complexity could lead to catastrophic failures of performance, unless the task was very well learnt (i.e had become simple again). One error led to a cascade of others, even in normocapnic air-breathing experiments. When this occurred, temporal resolution and relevance to brief physiological events was lost.

Overtly sudden failures of this sort probably reflect loss of our normal ability to do more than one thing at a time, for example singing while riding a bicycle. When the traffic gets rough the singing stops while cycling continues unimpaired. Singing is a secondary task. Typically, gradual exposures to drugs or other stresses interfere with the performance of secondary tasks long before performance of the primary task is affected but eventually all of the secondary tasks have been sacrificed and then performance of the primary task appears to collapses abruptly. Experimental psychologists often use unannounced measures of secondary task performance as more sensitive indicators of effect. In the present study, breathing regularly and keeping the balloon empty were secondary tasks, which could have been monitored but were not.

Preliminary experiments showed that at least two of the subjects (#6 & #7) could execute the normal task rapidly and without error even on the verge of losing consciousness. The normal task was unlikely to be of any value detecting altered concentrations of nitrous oxide in them. They needed a more difficult test. The object of tailoring task complexity to individual subjects' needs was to present each of them with demands easy enough to only consume 0.5 to 1.0 sec of complex choice reaction time under normal circumstances, so leaving 1 to 1.5 seconds available for impairment to be demonstrated. At the same time the task had to be sensitive to acceptable degrees of hypocapnia and nitrous oxide anaesthesia, but not so difficult that failure led to cascade effects if questions were repeated at 3 sec intervals. Because the experiment was to endure over many 4-min epochs on several days, it was also necessary that learning effects were eliminated. To the extent that the task was too simple, it will have tended to underestimate the influences of nitrous oxide on the brain and of hypocapnia on nitrous oxide anaesthesia.

The preliminary experiments with hypocapnia and nitrous oxide anaesthesia had confirmed previous findings of the use of the task in hypoxia, namely that prior to frank breakdown there was a gradual and slight slowing of response times accompanied by occasional errors and failures to respond at all. These changes were likely

to come at uncertain times that differed with circumstance and would be superimposed on a basic variability in response time of ± 10%. Cutting the total record into fixed blocks of time and comparing means and indices of variability risked losing the signal in the noise. Selecting blocks of time by hand, that varied with subject and circumstance could easily introduce bias. Therefore all response times had to be used. Integrating the times reduces the effects of random variations. Expressing them as deviations from the means of each epoch suppresses effects that persist for more than the duration of an epoch and its subsequent rest interval (4 + 2 = 6 min). This biases the study in favour of detecting non-random changes that develop significantly over the period of an epoch (4 min).

The preliminary studies showed that hypocapnia could produce gradual slowing which might confound the effects of nitrous oxide. The analysis minimises these. The early studies also showed response times usually returned to normal about one minute after the ceasing to inhale nitrous oxide. The design maximises recognition of these. Thus the design is biased in favour of seeing non-random changes over a few minutes, and against the detection of gradual changes over many minutes. However the treatment is the same in normocapnia and hypocapnia. It could only bias the results in favour of the hypothesis if hypocapnia converted the apparently brief effects of the anaesthetic pulse in

normocapnia to a much more slowly developing and persisting change. Such effects would be detected by increased response times rising from the start of one epoch to the start of the next. Table 11.0 show these rarely occurred.

Do the rare occurrences matter ? They would represent an increase in the time constants of cerebral tissues that was sufficient to slow the build-up of significant quantities of nitrous oxide in nervous tissue, but not sufficient enough to suppress it completely. Such changes are still desirable. In addition, in submarine escape, the exposure to hyperbaric nitrogen is shaped like a triangle with a steep leading edge (Fig 11.1). The greatest risk is early on. It diminishes regularly thereafter. The nitrous oxide pulse rises as steeply but is rectangular and so biased towards the development of more prolonged solution. The experimental design is biased <u>against</u> sensing completely the effects of brief triangular exposures.

It was impossible to blind subjects to the hypocapnia and nitrous oxide anaesthesia they experienced. Therefore we needed experienced subjects who could relax. The intention was to study the physiology of submarine escape rather than the psychology of fear. Also, the experiments required informed consent, with an explanation of the potential benefits the procedure might offer to others. For this reason we chose fully rehearsed professional subjects. It is not possible to

Table 11.0 Mean of 4 consecutive epochs in hypocarbic experiments.

Subject Number.	Epoch 1	Epoch 2	Epoch 3	Epoch 4	Mean of the 4 Epochs	Sample standard deviation of the 4 epochs	Coefficient of Variation
1	485	488	485	495	488.3	4.7	1.0
2	526	560	528	564	544.5	20.3	3.7
3	504	486	533	579	525.5	40.6	7.7
4	693	779	694	769	777.8	46.7	6.0
5	643	582	580	610	603.8	29.5	4.9
6	710	709	690	687	698.8	17.1	1.7
7	521	506	500	536	515.8	16.1	3.1

Average % standard deviation of the 7 subjects 4.0

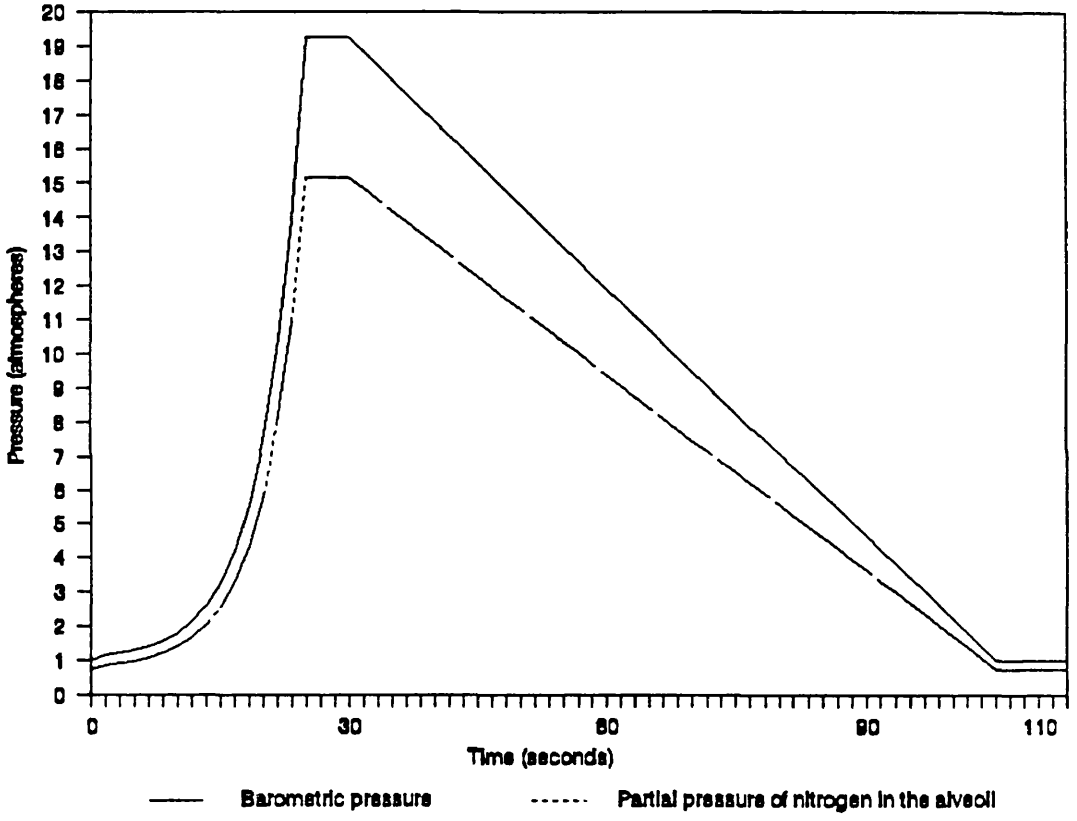

Pressure profile on submarine escape
Pressure (atmospheres)
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0
30
60
90
110
Time (seconds)
Barometric pressure
Partial pressure of nitrogen in the alveoli

Figure 11.1

exclude the chance that they unconsciously willed themselves to provide the results expected, i.e that they allowed themselves to slip into inattention more readily in hypocapnia than normocapnia. However detailed conversations about their expectations and subjective impressions, and the tight reproducibility of effects and timings belie this strongly.

The arguments presented in this chapter suggest that the experimental design reduced variations between individuals and was slightly biased against the outcome that resulted. The chance of unconscious bias in the performance of the unblinded subjects is extremely unlikely but cannot be rejected entirely. It could be excluded if the experiments were repeated on professional subjects, with direct measurements of cerebrospinal inert gas uptake, e.g by Kety's nitrous oxide technique which demands jugular venous blood sampling, by Lassen's xenon techniques which require radio-isotope infusions, or by HMPAO PET-scanning which is still controversial. These alternatives were considered unacceptable for the present study.

Therefore, it is concluded that hyperventilation-induced hypocapnia down to an end-tidal PCO_2 of 15 to 28 mm Hg, consistently blocks some psychomotor effects of a one-minute sharp-edged rectangular pulse of nitrous oxide anaesthesia. Its ability to do this appears to be

fully developed within a few minutes of the commencement of hyperventilation and within two minutes of reaching a specific level of constant low end-tidal PCO_2.

Applications of this finding to submarine escape and neurosurgical anaesthesia are the topics of the last chapter.

12 GENERAL DISCUSSION

The previous chapter concluded that hyperventilation of a few minutes duration induced sufficient hypocapnia to constrict cerebrospinal vessels, and so slow the uptake of nitrous oxide by central nervous tissue and reduce the amount of gas that dissolved in the brain and cord during a brief exposure to nitrous oxide anaesthesia. The paragraphs that follow relate that conclusion to the risk of decompression illness during submarine escape, and to the practice of neurosurgical anaesthesia.

Relevance to submarine escape

It is observed that submariners escaping from depths close to 600 ft sometimes suffer from acute neurological decompression illness. This could arise from several causes. For example, bubbles of gas in venous blood may have by-passed the lung through abnormal routes such as a patent foramen ovale or an unusual pulmonary arterio-venous fistulae; or the lung may have ruptured in the fast ascent, forcing bubbles into the pulmonary veins; or arterialised blood may have bubbled in the few seconds of its journey from lung to brain and cord; or the bubbles may have formed in nervous tissue and local veins. At present, the last explanation is thought to be the most likely cause. If that were so, cerebrovascular constriction would help most obviously by doing exactly as suggested in the opening

paragraph, i.e reducing the amount of gas dissolved in the brain and cord, and so limiting the amount of autochthonous bubble formation.

In all of the other explanations bubbles arrive in the nervous tissue from elsewhere and the outcome is more problematical. Cerebrospinal vasoconstriction should divert bubbles elsewhere, where generally they ought to do less harm. But, cerebrospinal vasoconstriction also obliges incoming bubbles of a given size to lodge in higher orders of the vascular tree, that subtend greater volumes of tissue. This could be more damaging.

The degree of hyperventilation used in these experiments, roughly halved cerebral blood flow. Assuming Poiseuille flow in the vascular bed, this would imply a reduction of one sixteenth in their diameter, which is very approximately the ratio of daughter to mother branches in the medium sized arteries of the systemic bed. Supposing pure dichotomous branching, this degree of vasoconstriction would halve the number of bubbles coming into the bed but would trap the bubbles one generation higher up the tree, so cutting the blood supply to the same total volume of tissue as before. However, if the hypocapnia wore off before the bubble adhered to the endothelium, the trapped bubbles would move distally as the bed dilated, with the end result that there was still less gas trapped in a normally distended bed of vessels. Vasoconstriction might also aggravate the condition by delaying the flow of blood

from the lung to the brain, giving more time for bubbles to form in the incoming blood, in the peculiar circumstances of rapid ascent.

More importantly, any bubbles that arrive in the vessels will be at a pressure close to the absolute pressure of arterial blood, which will be substantially lower than the partial pressure of the gas dissolved in nervous tissue. So, inevitably, the bubbles would grow after arrival. This growth would be reduced by prior hyperventilation. Therefore, prior hyperventilation is likely to mitigate all forms of acute neurological decompression illness developing during submarine escape.

In reality, submarines converge and diverge from their home ports which are in shallow waters. Here risks of colliding with surface vessels or friendly submarines are high. Away from their bases they probably go to deeper waters where the risk of meeting their own kind are much lower, but the hazards of running into an opposing contact or an elaborate but poorly mapped sea floor, though low are still present and would rise in the event of warfare.

In shallow water escapes, made from a submarine compartment that is almost normobaric, the chances of autochthonous bubble formation are low but those of cerebral arterial gas embolism are almost as high as in deep water. Here, hyperventilation may help principally by diverting bubbles of lung gas elsewhere. However, if

the vessel has been holed, and much water has come in, pressure in the living space may already be high and carbon dioxide may have accumulated, dilating cerebral vessels, shortening the time-constants of neural tissues, and favouring the production of bubbles locally. Other neurotoxic containments may also have poisoned the living space atmosphere. In both of these circumstances, hyperventilation ought to be of direct benefit.

Nevertheless, problems remain. In the chapter on mathematical modelling, it was pointed out that in theory, there are a wide range of time constants in nervous tissue. Some of these are so short that they equilibrate with changes in atmospheric pressure almost as rapidly as they occur. In such tissue, autochthonous bubble formation would be rare. At the other extreme are tissues with time constants so long that the occurrence of submarine escape impinges on their bubble content little if at all. When the owner of this galaxy of neural tissues hyperventilates, it is supposed that he reduces the blood supply to all of the components, so prolonging all of their time constants. This will shunt some of the previously vulnerable elements into the 'too slow to be at risk' category, but it will also recruit some of the previously 'too rapid to mount a challenge' regions to vulnerable status.

There is little, if any, accurate information on the time constants of nervous tissue that matter in submar-

ine escape. The effects of hyperventilation on brief profound pulses of nitrous oxide anaesthesia, suggest that the nett effect of hyperventilation will be beneficial, but there is no direct proof that will be so.

Hyperventilation complicates the task of submarine escape, giving the escapee more to think about, when he is already distraught by the principal procedure. It may also impair his ability to escape successfully, perhaps causing him to be slow in escaping; or persuading him to stop breathing on the ascent, favouring subsequent lung rupture.

The original trials of the effects of hyperventilation on the ability to escape, were conducted by highly-trained instructors working in their home environment with minimal stress, secure in the knowledge of excellent medical back up, and of a fine therapeutic hyperbaric oxygen chamber. In a real escape, the situation could be very different, with many submariners trapped in one compartment, away from most, or all support facilities and separated from the officers who could reassure and advise them. Such men would need a very straightforward easily remembered drill, to improve their chances of safe arrival at the surface.

Therefore a final group of practical experiments needs to be done, to establish the appropriate training drill. This raises a tricky ethical point. Suppose hyperventilation interferes with the ability to escape <u>in training</u>, doubling the very low risk of cerebral

arterial gas embolism from say 0.1% to 0.2%, but it promises to reduce the risk of acute neurological decompression in credible scenarios of **real** from, say, 10% to 5%. What course should be adopted then ? In the absence of hard data these are imponderable questions. Therefore it is suggested that a future experiment determines the simplest and most easily remembered and practical advice that can be given to trainee submariners, and that then alternative batches of trainees follow or ignore this advice during the safety of submarine escape training, until say 200 trainees have escaped without serious incident after performing the routine. This would then show that hyperventilation did not produce an unacceptable increase in the risks of escape training, and was therefore unlikely to increase the risks of real escapes. The other arguments, cited previously, would then be acceptable evidence that it was wiser to hyperventilate before escape, than to breathe normally.

Applications in cardiothoracic surgery

Bubbles are commonly introduced into the systemic circulation during cardiothoracic surgery. It is rare for hyperbaric facilities to be available in such circumstances. In this situation, supersaturation of nervous tissues is extremely rare, i.e bubbles are almost always arriving in the cerebrospinal circulation from elsewhere, with no tendency to grow. Hyperventilation is unlikely to be effective retrospectively because it

takes several minutes to deploy, which is many times the duration of the right-heart to brain circulation time. It might be worth considering prospectively, as the way of minimising bubble entry into the cerebrospinal circulation. Thus after de-airing the heart, reducing the $PaCO_2$ before the aorta is unclamped could decrease the number of bubbles reaching cerebral and coronary circulations as the main bulk of them would then be diverted elsewhere. Nitrous oxide is not used at this stage of cardiac surgery because any bubbles that may have been introduced into the circulation would only grow in size in its presence.

Applications in neurosurgery

Venous air embolism is a particular problem in neurosurgery, especially in those operations done in the sitting and reclined but semi-head up positions. These air emboli migrate to the heart and pulmonary circulation and can lead to pump failure in the worst cases. When small emboli are detected by a falling end-tidal CO_2, change in Doppler sound, or increase in pulmonary wedge pressure steps must be taken at this stage to prevent more emboli i.e proper surgical venous stasis and increasing the venous pressure. The nitrous oxide should also be turned off as it will only increase the size of any bubbles present and worsen the situation. Rapidly depressing the arterial blood of nitrous oxide, can be accelerated by hyperventilation. The present

experiments show immediate hyperventilation can reduce alveolar, and thus arterial N_2O tensions may follow, in less than one minute.

The rate of reduction in $PaCO_2$ with hyperventilation and the variable threshold at which hypocapnia induces a deterioration in the psychomotor task performance has a bearing on neurosurgical anaesthesia.

In the normal brain hyperventilation causes vasoconstriction and a decrease in cerebral blood flow and intracranial pressure. In the damaged brain the sensitivity of the cerebral vasculature to changes in $PaCO_2$ is reduced. But beneficial effects are still seen during hyperventilation in the latter situations, because normal areas of brain will still be responsive to hypocarbia. This results in a generalised reduction in intracranial pressure and consequentially there will be a decreased tissue pressure in the oedematous zones will resultant improved perfusion of these ischaemic areas.

Anaesthetic agents such as halothane, ethrane, isoflurane and nitrous oxide can all cause an increase in cerebral blood flow to varying degrees. This can have serious consequences in patients with a raised intracranial pressure. Fortunately the responsiveness of the cerebral circulation to changes in $PaCO_2$ is preserved during anaesthesia with these agents (Drummond & Todd

1985). Although Todd (1987) has recently shown that reductions in $PaCO_2$ did not blunt the cerebrovascular response to nitrous oxide in rabbits.

It was shown in this thesis that it took 4 to 6 minutes of hyperventilation to lower the $PaCO_2$ to a new steady state in hypocapnic experiments. Thus this reinforces the current anaesthetic practice in neuroanaesthesia that volatile agents should not be administered to patients until after 10 minutes of prior hyperventilation. Isoflurane anaesthesia not only has less effect on the cerebral blood flow than other volatile agents but it is also more sensitive to changes in $PaCO_2$ than the others (Drummond 1985). Some authors have reported that, patients with mass lesions and raised intracranial pressure, hyperventilation alone will not prevent profound rises in intracranial pressure during halothane anaesthesia (Stullken 1975). Thus in these patients halothane should not be given until after the brain has been decompressed. Prior administration of barbiturate will prevent the rise in cerebral blood flow induced by nitrous oxide (Sakabe 1978).

Extreme levels of hypocarbia induced by hyperventilation cause cerebral hypoxia (Reivich 1966, Plum 1976, Kennealy 1980). The $PaCO_2$ threshold for inducing deterioration in psychomotor task has been shown by (Rahn 1946, Balke 1956, Stoddard 1967) to be 19 to 25 mmHg. In this thesis there is a variability in this value between the 7 subjects, ranging from 15 to 28

mmHg. One can conclude that during anaesthesia in hypocarbic conditions in order to prevent cerebral hypoxia, extra oxygen should be added to the inspired mixture and the lower limit of the $PaCO_2$ should be 28 to 30 mmHg to provide adequate safety margins. Individually variation in the hypoxic threshold could be picked up by using a cerebral function monitor. Patients with cerebral vascular disease, vasospasm and during induced hypotension will develop cerebral hypoxia much more easily and there $PaCO_2$ should be kept at a higher level during hyperventilation. Concurrent use of volatile anaesthetic agents have been shown to increase the lower safety margin.(Smith & Wollman 1972).

13 SUMMARY AND CONCLUSIONS

It is concluded that prior hyperventilation may be an effective way of reducing the risk of cerebrospinal decompression sickness during submarine escape. In practice it requires submariners to overbreathe to a moderate extent for a few, but not many, minutes before escape. It costs nothing, is simple to apply and occupies no space.

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