THE CARDIOVASCULAR CONSEQUENCES OF OBSTRUCTIVE SLEEP APNOEA HYPOPNOEA SYNDROME

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DECLARATION

This thesis is the result of my own work. The material contained in this thesis has not been presented either wholly or in part for any other degree or qualification

The research was performed at the Respiratory Physiology Department, University Hospital Aintree, Liverpool.

The author performed all of the experimental work with the exception of the diagnostic sleep studies, which were performed by the sleep technicians of the Regional Sleep Disorders Unit.

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AHI	Apnoea Hypopnoea Index
AI	Apnoea Index
AHVR	Acute Hypoxic Ventilatory Response
ASDA	American Sleep Disorders Association
BMI	Body Mass Index
CO_2	Carbon Dioxide
CPAP	Constant Positive Airway Pressure
CSF	Cerebrospinal Fluid
DRG	Dorsal Respiratory Group
ECG	Electrocardiograph
EDS	Excessive daytime sleepiness
EEG	Electroencephalograph
EOG	Electrocculogram
ESS	Epworth Sleepiness Scale
$EtCO_2$	End-tidal carbon dioxide
$FiCO_2$	Fraction of inspired carbon dioxide
FiO_2	Fraction of inspired oxygen
LV	Left Ventricle
LVEDP	Left Ventricular End Diastolic Pressure
NREM	Non-Rapid Eye Movement
O_2	Oxygen
OSAHS	Obstructive Sleep Apnoea Hypopnoea Syndrome
PaCO2	Partial Pressure of Arterial Carbon Dioxide
PACO2	Partial Pressure of Alveolar Carbon Dioxide
PaO2	Partial Pressure of Arterial Oxygen
PAO2	Partial Pressure of Alveolar Oxygen
PCO2	Partial Pressure of Carbon Dioxide
PO2	Partial Pressure of Oxygen
PSG	Polysomnography
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement

RV	Right Ventricle
SaO_2	Oxygen saturation
SCN	Suprachiasmatic Nuclei
SD	Standard Deviation
SWS	Slow wave sleep
Te	Expiratory Time
Ti	Inspiratory Time
UAR	Upper-Airway Resistance
V_E	Minute Ventilation
Vt	Tidal Volume
VRG	Ventral Respiratory Group

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Chapter One

Introduction

1.1 GENERAL COMMENTS

The physiological states that accompany wakefulness and sleep are substantially different, and the reduction in input from the cerebral cortex during sleep produces specific and reproducible modifications in the feedback mechanisms that constantly regulate the cardiovascular and respiratory systems. The addition of a pathologically increases upper airway resistance both exacerbates these problems and also produces insight as to how this control system responds to this severe asphyxic stress. Obstructive sleep apnoea hypopnoea syndrome is an important clinical problem where just such a repetitive insult occurs. Interpreting the physiological changes that occur during sleep with this condition and the consequences for cardiovascular and respiratory function during wakefulness is the subject of this thesis. This chapter will review the background to our present understanding of these physiological mechanisms and set the goals which will be explored in the remainder of the thesis, which will initially assess the diagnostic criteria used in OSAHS before investigating the ventilatory and cardiovascular responses to peripheral chemoreceptor stimulation during wakefulness and sleep in healthy subjects and OSAHS patients.

1.2 CONTROL OF VENTILATION

Ventilation is the term given to the process of bulk gas transfer necessary to replenish the alveolar oxygen concentration and remove carbon dioxide in the face of continued alveolar perfusion. It is accomplished by active inspiratory muscle action that changes the configuration of the chest wall and, by generating a negative intrathoracic pressure, produces inspiratory flow. Expiration at rest is usually considered to be a passive process in healthy subjects although post-inspiratory muscle activity persists well into expiration and expiratory flow is modulated by laryngeal braking activity (Savard *et al* 1993). Thus inspiration and to a lesser extent expiration require carefully co-ordinated activity not only of the diaphragm and chest wall muscles but also the muscles controlling the patency of the upper airways; which must be activated sequentially with the diaphragm and other respiratory muscles if inspiration is to occur through a low resistance airway.

The demand for ventilation varies with the metabolic requirements of the body, being minimal at rest and when sleeping, and considerably increased, in terms of oxygen consumption and CO_2 production, during maximal exercise. The ability to tolerate conditions of reduced inspired oxygen tension which occur at altitude and in many lung diseases is also an important evolutionary adaptation and a range of physiological defence mechanisms exist which permit minute ventilation as a whole to be appropriately changed in those circumstances. The onset of sleep poses particular problems for the respiratory control system, particularly in individuals where marked increases in upper airway resistance occur. How the cardiovascular and ventilatory responses to hypoxia are modulated by sleep the consequences of this are the main topic of this thesis.

Most knowledge of the anatomy and cellular basis of respiratory control has been derived from anaesthetised animals, where dissection and denervation of structures have enabled the classification of cell groups and identified their role in ventilatory control. Data from humans demonstrate the integrated behaviour of the whole respiratory system and allow us to observe the sum of the influences from:

- the brainstem which acts as the respiratory pattern generator and is also influenced by sustained changes in gas tensions.

• the cerebral cortex, which can modify respiratory rhythm in response changes in sleep state and mood, and interrupts the respiratory cycle with overriding actions such as vocalisation.

• the peripheral chemoreceptors and mechanoreceptors, which provide a feedback mechanism to the brainstem to modify the respiratory cycle and maintain normal blood gas tensions.

1.2.1 Central Control

The Pons

Animal experiments have shown that the pons influences inspiratory timing. Impulses from the nucleus parabrachialis medialis and kolliker fuse nucleus in the upper pons (Fig 1.1), collectively termed the pneumotaxic centre, influence the termination of inspiration. Cohen and colleagues (Cohen 1979) demonstrated that in cats, stimulation of these centres reduced inspiratory time in. Von-Euler *et al* (von Euler *et al* 1983) developed the inspiratory 'off switch' model that proposes that when collective stimulation from central inspiratory activity and stretch receptors reach a critical threshold, the upper bulbo-spinal inspiratory motor-neurones are inhibited and inspiration will cease. Vagotomy and mid-pontine transection or lesions in the nucleus parabrachialis medialis result in apneusis due to the removal of their inhibitory input. St.John (St.John 1972) demonstrated, in similar work on cats, that eupnoea returned after anaesthesia was stopped, suggesting the pons was not the sole regulator of inspiration.

The Medulla

Experiments with animals have also shown the medulla contains two main groups of neurones that receive afferent stimuli from mechanical and peripheral chemoreceptors.

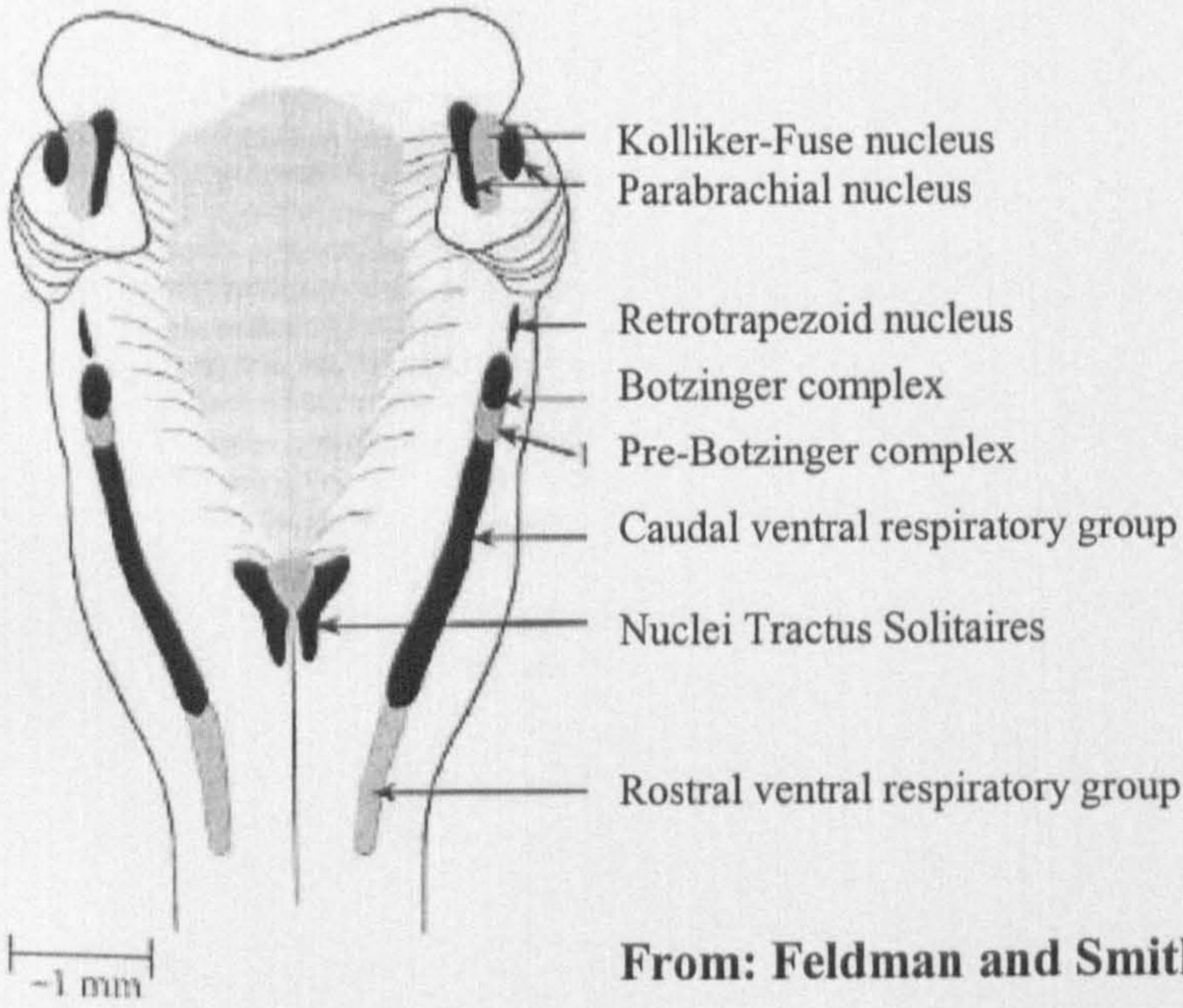
The dorsal respiratory group (DRG) are neurones found in the ventrolateral nucleus of the tractus solaritus (NTS) and were initially suggested to be the origin of the cyclical bursts of inspiratory activity (St.John 1972) DRG neurones receive afferent impulses from the peripheral stretch receptors and chemoreceptors via the

glossopharyngeal and vagus nerves. Type I-beta cells are excited by impulses from chest wall and slowly adapting stretch receptors and are thought to inhibit the Type I-alpha cells which are initiating the lung inflation. Thus the inspiratory rate and cut-off point, collectively termed the 'inspiratory ramp' can be modified.

The ventral respiratory group (VRG) neurones are almost totally inactive during quiet respiration, and thought to play no role in the basic rhythmic oscillations that control ventilation. This group of neurones bring about increases in ventilation when metabolic demands increase, by stimulating both inspiration and forced expiration. Inspiratory ramp time is reduced by stimulation of respiratory muscles via the rostral neurones; expiration is accelerated via the caudal neurones, which stimulate the accessory muscles to generate a forced expiration more rapid than that as phrenic activity declines.

The pre Bötzinger Complex is the most recently discovered sub-region of the brainstem. The work of Smith *et al*, (Smith *et al* 1991), described a small group of neurones in the ventrolateral medulla (Fig 1.1), which, in animals, appear to act as the respiratory rhythm generator. Slices of medulla that contain the complex continue to generate respiratory related rhythmic discharges, and although there are other brainstem sites which have a role in the maintenance of respiratory rhythmicity, such as the retrotrapezoid nucleus and the pontine respiratory group, they propose that the pre-Bötzinger Complex has the bursting pacemaker properties for rhythm generation.

Fig 1.1 - Brainstem Regions of Ventilatory Control



From: Feldman and Smith 1995

This figure shows the brainstem regions that are involved in respiratory control. The Kolliker-fuse and Parabrachial nuclei which regulate inspiration, found in the pons. The rhythm generating pre-Bötzinger Complex and Retrotrapezoid nucleus, thought to be involved in the central chemoreceptor responses, found caudally to the VRG, and the VRG and DRG that modulate responses through peripheral feedback are found in the rostral area of the medulla.

1.2.2 The Central Chemoreceptors

The central chemoreceptors comprise of a number of chemo-sensitive areas located throughout the brain (Nattie 2000). Sites of chemosensitivity include:

- Beneath the ventral medullary surface.
- The ventral medullary raphe.
- The rostral aspect of the VRG.
- The region of the NTS
- The region of the locus ceruleus
- Portions of the hypothalamus.
- The fastigial nucleus of the cerebellum

These areas are highly sensitive to pH and hence indirectly sensitive to CO_2. H^+ ions are formed when an increasing concentration of CO_2 drives the Henderson and

Hasselbach equilibrium in favour of carbonic acid production and dissociation to cause a fall in pH (see Fig 1.2).

Fig 1.2 - The Henderson and Hasselbach Equilibrium.

$$CO_2 + H_20 \quad \Longleftrightarrow \quad H_2CO_3 \quad \Longleftrightarrow \quad H^+ + HCO_3^-$$

This equation demonstrates the equilibrium between CO_2 and H^+. If the CO_2 concentration is increased carbonic acid will form and dissociate, thus reducing the pH. Conversely if the CO_2 concentration falls the equilibrium will be shifted to the right and the H^+ concentration will fall. The balance of the equilibrium can also be disturbed by changes in HCO_3^-; increasing the concentration will see more of the H^+ 'mopped up' and the formation of non-dissociated carbonic acid. A low concentration of HCO_3^- sees more of the carbonic acid buffer dissociating and a rise in pH. Cerebrospinal fluid contains a lower concentration of buffer than does the blood. CO_2 readily passes across the blood brain barrier and blood-cerebrospinal fluid barrier and, due to the poor buffering, almost instantaneously forms dissociated carbonic acid, promptly decreasing pH of the CSF.

Experiments performed on goats, showed acute changes in ventilation in response to small changes in brain fluid pH (Fencl et al 1966). In man, hydrogen ions in the CSF, rather than CO_2 tension or blood pH, act on the central chemoreceptive areas and modulate the ventilatory responses (responses to altered O_2 and CO_2 are discussed later). The exact mechanisms of the central chemoreceptor responses are unclear although all of the chemosensitive sites are adjacent to pre-motor neurones or have anatomical connections with them, and it is suggested the response occurs through excitatory impulses being sent directly from the chemosensitive areas to these pre-motor neurones.

1.2.3 Higher Centers

Ventilation can be consciously and subconsciously modified by the activity of the cerebral cortex. Mood has been demonstrated to affect ventilation in man. Anxiety and fear increase ventilation (Heim *et al* 1968)) via a neural path thought to exist

between mesocortex, the amygdala and the nucleus parabrachialis medialis (NPBM) in the pons (Amorapanth *et al* 2000). The onset of sleep sees an associated reduction in ventilation (Shea 1996) and increase in upper airway resistance through the removal of the wakefulness drive to breathe (Hudgel 1984a and Wiegand 1989). The reduced ventilation during sleep is also, in part, due to the removal of factors such as visual and auditory stimulation that increase ventilation, voluntary respiratory control such as vocalizing, laughing and sniffing, which involve direct efferents from the cerebral motor cortex, as well as non-voluntary respiratory control such as eating, sneezing and coughing. These functions disrupt respiratory cycle timing and depth, and thus sleep onset is also associated with a more regular respiratory pattern than seen when awake (Shea 1996).

1.2.4 Peripheral Receptors

The peripheral receptors include mechanoreceptors and chemoreceptors. Mechanoreceptors in the chest wall, lungs and airways provide a feedback mechanism to the brainstem and facilitate the modification of the respiratory cycle to regulate ventilation and prevent damage to the lung by over-inflation. Peripheral chemoreceptors found in the aortic arch and carotid body also provide afferent feedback to the brainstem and aid the maintenance of blood gas tensions through changes in ventilation.

Mechanoreceptors

There are two main types of stretch receptors,

Rapidly adapting receptors are found in the airway mucosa and are stimulated by both mechanical forces such as increases in lung volume and chemical stimulation such as histamine and prostaglandins. When these peripheral receptors are stimulated they can elicit an array of responses, including cough, bronchoconstriction, and hyperventilation (Petersen 1988).

Slowly adapting stretch receptors are myelinated vagal fibres found in airway smooth muscle. They are stimulated by lung inflation and provoke the Hering-Breuer inflation reflex; a mechanism which limits lung inflation via afferent vagal feedback to the respiratory centers in the DRG.(Knox *et al* 1976) In humans this

reflex is thought to be inactive until the tidal volume is in excess of approximately 1.5 liters. It appears to be a protective mechanism rather than a component of the normal control of ventilation. These receptors may also elicit bronchodilation and tachycardia.

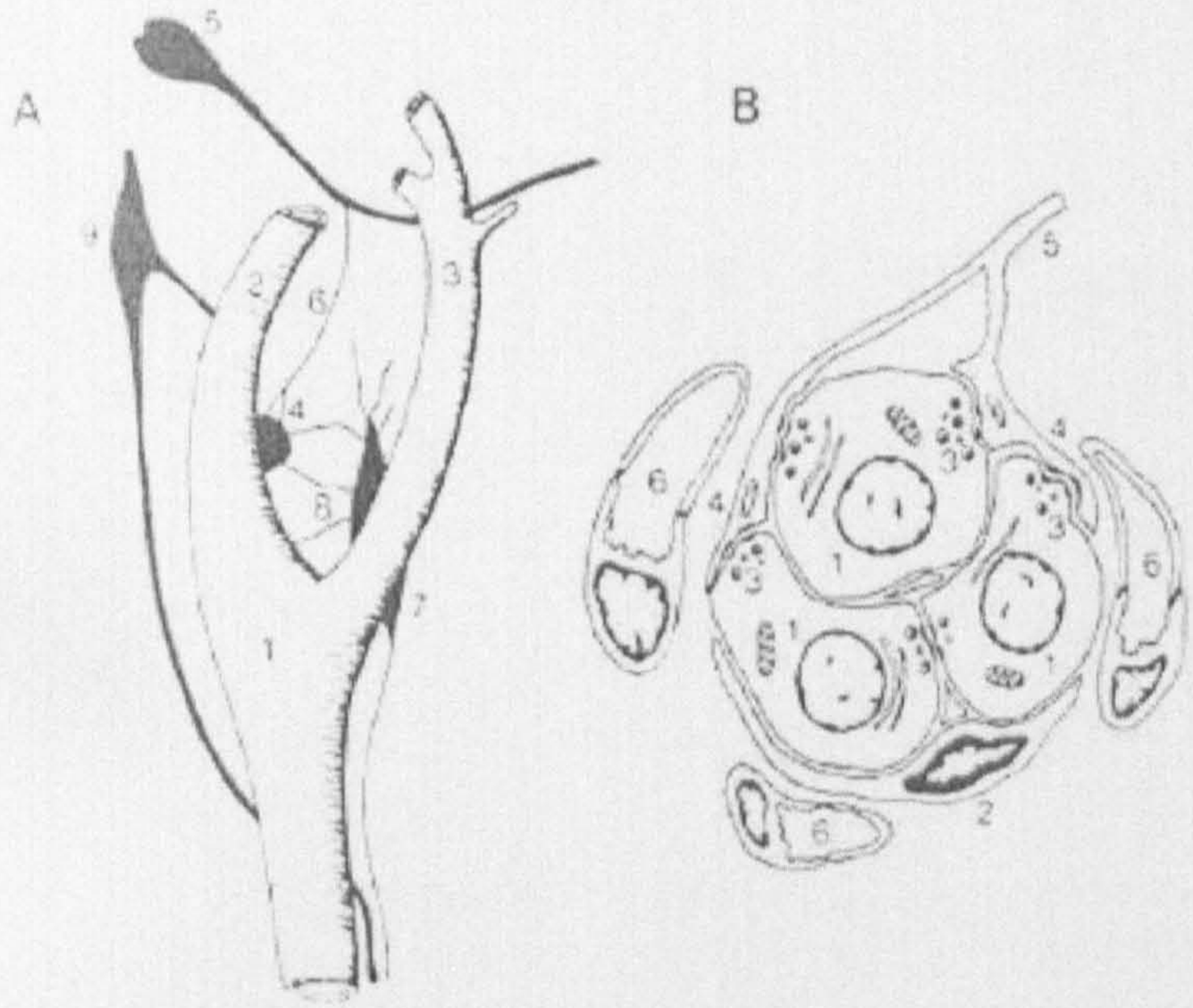
Unmyelinated vagal fibres (C-fibres) are found in pulmonary interstitial spaces, close to pulmonary and bronchial circulation. They respond to lung volume change, and chemical agents such as capsaicin and histamine with a range of responses including cough, hypotension, and apnoea followed by rapid shallow breathing.

Chest wall receptors such as muscle spindles and golgi tendon organs are mechanoreceptors found in muscle fibers of the intercostal muscles and diaphragm. They have a slowly adapting response to muscle stretch; inhibiting homonymous motor neurones via afferent feedback to the DRG, and therefore preventing muscle overload and lung distension (Petersen 1988).

Peripheral Chemoreceptors

Arterial chemoreceptors are discrete structures that respond to hypoxia, hypercapnia, and acidity. They are located adjacent to the aortic and carotid bodies The carotid body chemoreceptors are activated by a reduction in PaO_2 below normal resting levels (80 –100mmHg) and are most active at a PaO_2 of 26 mmHg, thus they have an increasing physiological response and metabolic activity when there is a dwindling supply of O_2 to the tissue. Figure 1.3 demonstrates Type 1A sensory cells, surrounded by a rich capillary network that provides a hugely excessive arterial blood flow per gram of tissue. Therefore, even with the high O_2 consumption of the carotid and aortic bodies, there remains a minimal arterial/venous difference in gas tensions (Gonzalez 1995). This enables the receptors to function in near arterial conditions and thus respond to changes in the arterial blood gas tensions that are being supplied to the brain via the common carotid artery.

Fig 1.3 - Carotid Artery and Carotid body.



Gonzalez et al 1992

(A) Frontal view of rabbits right carotid artery. (1) Common carotid artery, (2) internal carotid artery, (3) external carotid artery, (4) carotid body, (5) Petrosal ganglion, (6) Carotid sinus nerve, (7) Superior cervical ganglion, (8) ganglioglomerular nerve, (9) nodose ganglion.

(B) Lobule of parenchyma cells in the carotid body. (1) Chemoreceptor type I cells, (2) Sustentacular cells, ratio of (1):(2) is approx 4:1, (3) synaptic vesicles, (4) sensory nerve endings, (5) Carotid sinus nerve, (6) Dense capillary bed

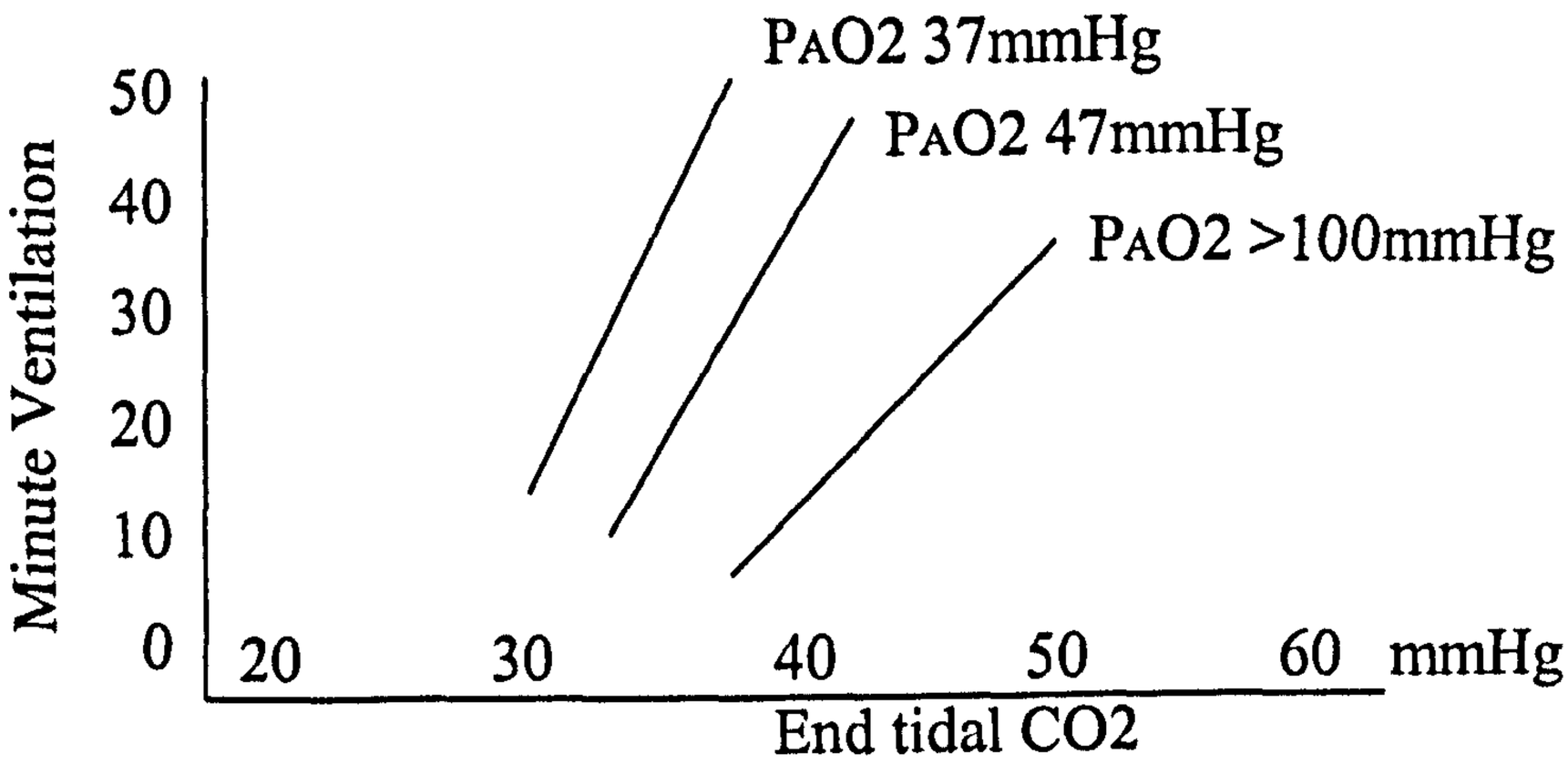
The type-I cell responds to hypoxic and acidic stimuli with a rapid increase in intracellular calcium through the inhibition of a background K-current, leading to membrane depolarization and voltage-gated calcium entry. Carotid body excitation passes via the carotid sinus nerve and glosso-pharyngeal nerve to the DRG in the medulla. Impulses from the aortic body pass via the vagus to the DRG. This peripheral stimulation provides a feedback mechanism for modifying the respiratory cycle as O_2 and CO_2 tensions vary. The effects of these stimuli will be discussed in the next section.

1.2.5 Ventilatory Responses To Hypercapnia

The importance of CO_2 and O_2 in controlling ventilation and blood pressure have been established for many years, yet their exact actions and mechanisms are still not fully understood. Haldane and Priestley (Haldane and Priestly 1905) were among the first to demonstrate the close relationship between alveolar CO_2 ($PACO_2$) and minute ventilation. They noted strong ventilatory responses to small perturbations of inhaled CO_2 tensions, and observed the maintenance of a stable $PACO_2$ when the inspired CO_2 tensions were altered. However, the assessment of these responses was relatively time consuming. Read, in 1967 (Read *et al* 1967), developed a simpler closed circuit rebreathe technique for assessing the ventilatory response to increasing CO_2. Using the assumption that CO_2 rises linearly and proportionately within the circuit, the lungs, and the mixed venous blood, it is possible to assess the ventilatory responses to hypercapnic stimulation of the slope of the VE/CO_2 relationship. It is thought there are at least three components of the hypercapnic ventilatory response. A rapid component with a time constant of 8 –26 seconds occurs through stimulation of the peripheral chemoreceptors, a slower and more acute response with a time constant of 65 – 180 seconds is attributed to the central chemoreceptor response. More recently a very slow component was described by Tansley et al (Tansley *et al* 1998), who observed an increase in ventilation over a 2 hour period when subjects were exposed to euoxic hypercapnia.

A brief (<5 mins) normoxic rebreathe allows the peripheral chemoreceptors to be stimulated and modulate a response via the respiratory centres in the brain stem. Oxygen supplementation during these procedures is necessary, as demonstrated in Figure 1.4, reducing alveolar oxygen greatly increases the ventilatory response to CO_2.

Fig 1.4 - Ventilatory stimulation by CO_2 and Hypoxia



(Calverley. Control of Breathing 1998)

This figure also demonstrates the slope of the Ve/CO_2 relationship is linear, unlike the ventilatory response to hypoxia. During a CO_2 rebreathe there is an initial non-linear response as the CO_2 reaches both circuit/venous equilibrium, and the chemoreceptor response threshold. The CO_2 sensitivity can be calculated by regression analysis to generate the slope of the Ve/CO_2 relationship. Within a normal population CO_2 sensitivity can vary tenfold between individuals even when corrected for body mass (Swanson *et al* 1978)

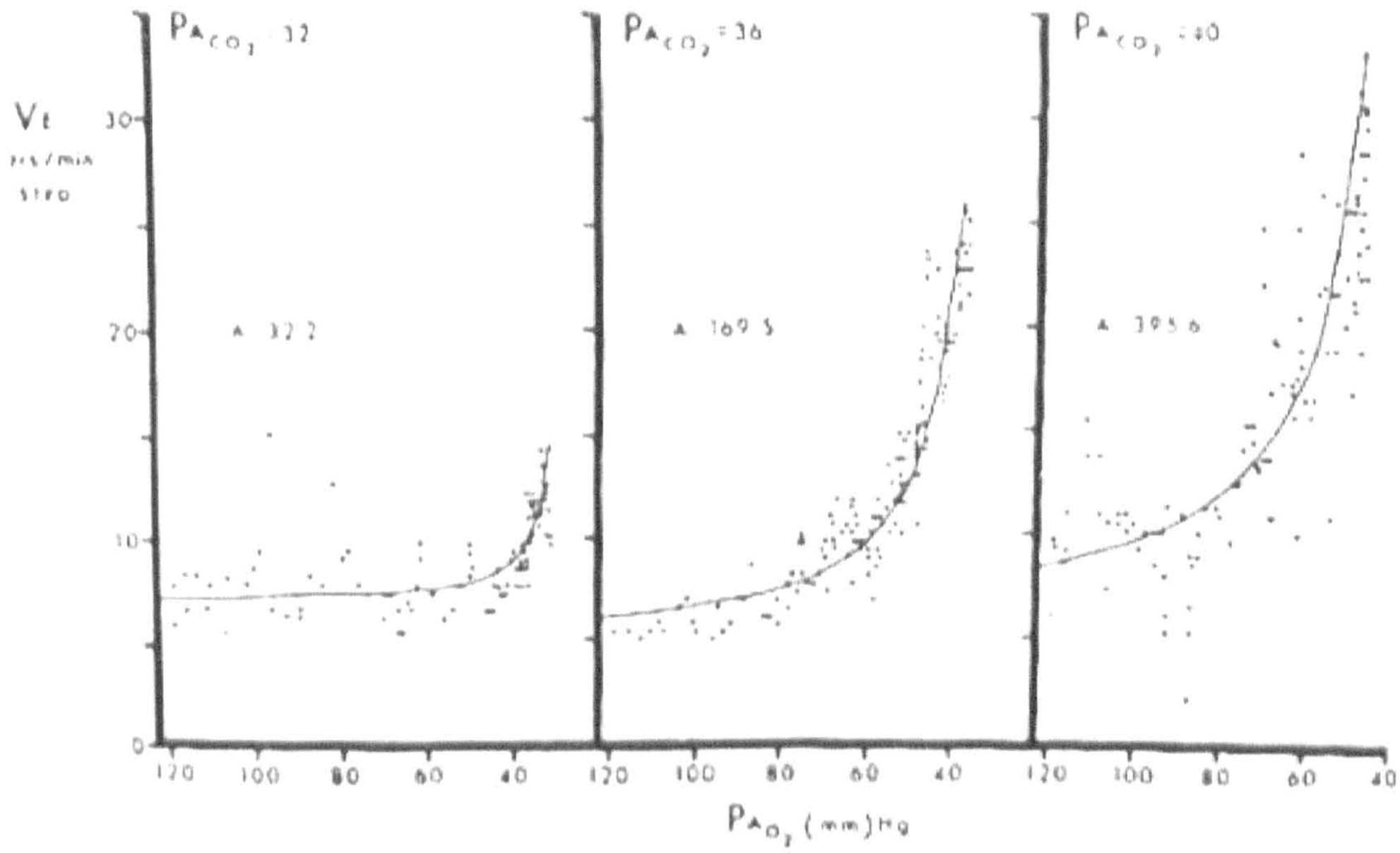
1.2.6 Ventilatory Responses To Hypoxia

Hypoxia occurs at altitude and in conditions such as chronic obstructive airways disease, heart failure and sleep apnoea. In healthy subjects, there is very little ventilatory response to progressive hypoxia under normocapnic conditions, until alveolar oxygen (PAO_2) falls to less than 60 mmHg. The size of this increase varies, in general the lower the PAO_2 the greater the increase in ventilation it produces. However the change in ventilation is less if a static hypoxic stimulus is applied compared to the dynamic stimulus of closed circuit rebreathe. The magnitude of the ventilatory response to hypoxia is considered to be a measure of an individuals' chemoresponsiveness.

Rebuck and Campbell (Rebuck and Campbell 1974) used a closed circuit rebreathing technique, modified from the circuit used by Read et al (Read 1967), to assess the ventilatory responses to progressive hypoxia. Their work demonstrated

that variation in the ventilatory response to hypoxia was significant between subjects but was reproducible for an individual over time. An alternative but equally brief protocol was adopted by Weil (Weil *et al* 1970), who expanded on work done nearly a decade earlier by Lloyd + Cunningham (Lloyd and Cunningham 1963). He analysed the hyperbolic ventilatory responses to hypoxia. This work, which is demonstrated in Fig 1.5, shows an individuals' hypoxic sensitivity was reduced under hypocapnic conditions. The low CO_2 tension was thought to reduce the carotid body firing rate and have a depressant effect on the central chemoreceptors by creating an alkalotic CSF.

Fig 1.5 - Acute ventilatory response to hypoxia in a single individual under hypocapnic, normocapnic and hypercapnic conditions.



Weil *et al.* 1970

Weil also demonstrated that the hypoxic response was significantly increased under hypercapnic conditions and that this increase in ventilation was greater than the arithmetic sum of the hypoxic response and hypercapnic response. This work, reviewed by Rebuck and Slutsky in 1981 (Rebuck and Slutsky 1981) highlighted the augmenting effects of hypercapnia on the peripheral chemoreceptor responses to hypoxia.

Animal studies have shown the carotid body to be the main receptor influenced by hypoxaemia. Lahiri and Gelfand (Lahiri and Gelfand 1981) reviewed work in dogs, that demonstrated that there is very little afferent discharge from the aortic body when stimulated with moderate hypoxaemia. However, when the carotid body was given the same stimulus there was a significant increase in minute ventilation (VE) through a reduction in inspiratory time (Ti), expiratory time (Te) and an increased tidal volume (Vt).

In man local anaesthetic blockade of the IXth and Xth cranial nerves, which blocks the afferent impulses from the carotid and aortic bodies, abolishes the ventilatory response to normocapnic hypoxia (Guz *et al* 1966). Human subjects who have had their carotid bodies denervated or removed demonstrate a 15% reduction in resting ventilation and no ventilatory response to normocapnic hypoxia. However, there is a weak response to hypercapnic hypoxia, which may be elicited by the aortic bodies (Whipp et al 1983).

The ventilatory response to hypoxia is triphasic. A short progressive hypoxic rebreathe, most commonly used to assess hypoxic sensitivity, lasts for only a few minutes and allows the peripheral chemoreceptors to be progressively stimulated and modulate a ventilatory response via the brain stem (Zhang *et al* 2000). If this hypoxia is sustained, the elevated ventilation declines during the following thirty minutes. Initially this was thought to occur as a direct result of hypoxic depression on the aortic and carotid bodies, but it has since been suggested that it occurs through adaptation of the carotid body (Robbins 1995). This hypoxic ventilatory decline is partially reversed after several hours or days and reaches a plateau at a ventilatory acclimatisation to hypoxia, which is a direct result of metabolic hypoxaemia on the CNS, rather than a modification of peripheral hypoxic responses. (Tansley *et al* 1998).

1.3 CONTROL OF BLOOD PRESSURE

The maintenance of at an adequate tissue perfusion pressure is essential for the circulation of the blood, and like ventilation, pulmonary and systemic blood pressures are tightly regulated. Failure to maintain arterial pressure at these levels is an important factor increasing the risk of: stroke, chronic heart failure, ventricular hypertrophy, renal failure and death.

Arterial blood pressure reflects the balance between cardiac output (CO), which is the measure of stoke volume (SV) multiplied by heart rate (HR), and peripheral resistance (PR). These factors are affected by the metabolic needs of the body, external influences such as temperature, and physical influences such as gravity and changes in posture. There are a number of mechanisms that regulate blood pressure including, short-term mechanisms such as the baroreceptor reflex, and long-term regulation such as the renin-angiotensin mechanism. This section will briefly outline the mechanisms that control blood pressure, discuss their responses to hypoxia and hypercapnia, and the implication for the responses seen in patients with OSAHS.

1.3.1 Cardiac Output

Cardiac output in a healthy subject at rest is dependant on body size, and can be normalized using the cardiac index, cardiac output per m^2 of body surface, which has a value of approximately 3.2 L/min/m^2 in healthy subjects. Changes in cardiac output can be produced by changes in heart rate or stroke volume.

Heart rate is influenced primarily by central mechanisms but is also modulated by local influences.

Central mechanisms involve sympathetic stimulation of the sino-atrial node (SAN), atrio-ventricular node (AVN) and the cardiac muscle, where it exerts a positive chronotropic effect. In contrast, parasympathetic stimulation exerts a negative chronotropic effect, reducing the heart rate. The mechanisms of neural control are discussed in the next section.

Local factors include:

- Body temperature: depolarization at the SA node is slower at low body temperature, thus causing a fall in heart rate, at higher temperatures there is a higher heart rate.
- Circulating hormones such as adrenaline and nor-adrenaline released from the adrenal medulla act on the SAN, AVN, and cardiac muscle.

Stroke volume: the volume of blood ejected from the left ventricle during systole is also determined, in part, by neural inputs and local influences, however, muscle loading and unloading also have influences.

Central mechanisms involve sympathetic stimulation of alpha and beta receptors on cardiac muscle cells. The release of nor-adrenaline from post ganglionic fibres causes the myocytes to contract with greater force. This positive inotropic action increases the ejection fraction and reduces end-systolic ventricular blood volume. Parasympathetic stimulation of myocytes by acetylcholine, released from the vagus nerve, results in a reduction in contractility and a fall in cardiac output.

Local effects such as circulating adrenaline from the adrenal medulla alter contractility of the chambers and hence stroke output. In addition the mechanical load on the cardiac muscle, especially in the ventricles has an important effect.

Preload is often represented as the left ventricular end diastolic pressure (LVEDP) which represents the tension created during diastole by blood filling the heart and stretching the myocytes. Starlings law of the heart states that "the energy of contraction is proportional to the initial length of the cardiac muscle fibre". Thus an increase in venous return will increase ventricular distension and increase the LVEDP which results in a contraction with greater force.

There are many factors that affect venous return and preload in healthy humans, such as:

- Blood volume. Reduced blood volume is generally associated with a fall in venous pressure and hence a fall in preload.
- Gravity and posture. Changes in posture alter preload. Gravity causes pooling of blood to occur in the limbs when standing, if there is a change in posture e.g. to the

supine position, gravity will no longer draw blood into the extremities of the limbs and thus venous return and preload will increase.

- Venous tone. Increasing venous tone will increase venous pressure and preload. A reduction in venous tone will see a fall in venous pressure and a fall in preload
- Exercise. During exercise, the contracting muscles pump blood into the venous system and increase preload.
- Filling time. At high heart rates filling time is limited. As a consequence preload may fall.
- Atrial contractility. Increases in sympathetic activity increase cardiac muscle contractility and hence the atria have a greater ejection fraction and increase the ventricular preload.
- Disease. LV and RV functions may differ and hence a dis-equilibrium between the pulmonary and systemic circuits will affect filling and reduce cardiac output.
- Respiration. There are cyclical changes in stroke volume associated with respiration. During inspiration the negative pressure within the thorax is exerted on the heart and causes an increase in atrial filling, thus preload and stroke volume are greatest at end inspiration. During expiration the positive intrathoracic pressure opposes cardiac filling, thus preload and stroke volume are reduced. Respiratory efforts can directly modulate the BP especially when associated with airflow limitation when greater thoracic pressure swings occur and these mechanical effects are exaggerated.

Afterload

Vascular resistance is the result of friction between blood and the walls of blood vessels. The tension that a contracting ventricle must create to open the semi-lunar valves and eject blood against the resistance of the vascular system is termed 'afterload'. Afterload is increased by any factor that restricts blood flow. High peripheral resistance opposes blood being ejected from the left ventricle and hence ejection fraction and cardiac output are reduced. The relationship of the radius and resistance of a vessel can be expressed as

$$R \sim 1/r^4$$

Where R is resistance, and r the vessel radius. This formula demonstrates that if the diameter of a vessel is halved, the resistance will increase 16-fold, thus small changes in vasomotor tone can result in large changes in peripheral resistance. Capillary beds and arterioles are the major component of peripheral resistance. Their vasomotor tone and hence lumen diameter are influenced by local factors, neural mechanisms, and intrinsic mechanisms such as distension of vessels; the myogenic response to distension is to contract to preserve blood flow and capillary filtration properties.

Local factors promoting vasodilation include:

- By-products of metabolism such as acidosis, lactate
- High ambient temperature.
- Chemicals released during inflammation such as histamine and nitric oxide.

Local factors promoting vasoconstriction include:

- Trauma, which sees the release of prostaglandinds and endothelins.
- Low ambient temperature.
- Anti diuretic hormone (ADH), which is discussed in the hormonal control section.

Central mechanisms involve neural connections between the hypothalamus, vasomotor centres in the medulla, neurones innervating blood vessels, baroreceptors and chemoreceptors. These mechanisms are discussed in the next section.

1.3.2 Neural Control of Blood Pressure.

The Hypothalamus and Medulla

Many studies have shown that stimulation of the caudal hypothalamus results in increased systemic arterial pressure, heart rate, myogenic contractility, and tidal volume. Work with animals has shown control of the cardiovascular system centers around the paraventricular nucleus (PVN) in the hypothalamus. It has demonstrated

that the PVN has efferent connections with the cardioacceleratory, cardioinhibitory, and vasomotor centers in the medulla and the NTS in the caudal medulla, the central area known to receive afferent signals from the chemoreceptors and baroreceptors. Cirriello 1980 (Cirriello *et al* 1980) showed in cats that electrical stimulation of the PVN increased heart rate and blood pressure, as well as reducing the bradycardic response to carotid nerve stimulation, thereby demonstrating its potential role as a feedback mechanism between the chemoreceptors and baroreceptors and the cardiovascular vascular system.

In 1986 Porter and Brody (Porter and Brody 1986) demonstrated that there were two groups of neurones in this area with different functions. Electrical stimulation of the PVN magnocellular sites had depressor effects and caused vasodilation, whereas stimulation of the parvocellular PVN resulted in pressor effects and caused vasoconstriction, suggesting there are two distinct sites for modulating positive and negative feedback mechanisms of circulatory control.

Most animal experiments observing how the PVN is affected by afferent feedback have used stimulation of these nerves to simulate both baroreceptor and chemoreceptor activity simultaneously. By injecting saline equilibrated with 100%CO_2 into the carotid body, Banks and Harris 1988 looked at the firing of neurons in the PVN when only the chemoreceptors were stimulated. They demonstrated there was no effect on the PNV firing rate. This lead to speculation that the PVN involvement is limited to modulation of the baroreceptor response and that its role in the chemoreceptor response is minimal.

Innervation of the Heart

The neural connections between the heart and the medulla are: the sympathetic pathway which connects the **cardioacceleratory** center with SA node, AV node, atria and ventricles, via pre and postganglionic fibers. The parasympathetic path which connects the **cardioinhibitory** center to the heart via the vagal nucleus, vagus and cardiac plexus.

Vascular Innervation

The innervation between the vasomotor centers in the medulla and the vascular system, comprises of three types:

Sympathetic vasodilation in skeletal muscle and sweat glands occurs when acetylcholine and vasoactive intestinal peptide are released to cause a reduction in resistance. These nerves are only transiently active for the defence 'fight or flight' response. They have a negligible response to baroreceptor feedback and play little role in the regulation of homeostasis

Sympathetic vasoconstriction occurs in the skin and intestines when nor-adrenaline is released into the circulation and from nerve endings.. These neurones densely innervate large and intermediate arteries, and to a lesser extent, the arterioles and veins of most organs and tissues. The baroreceptors are the major receptors that influence the activation of these neurons, as they are the principal regulators peripheral resistance. This will be discussed later.

Parasympathetic vasodilation occurs with the release of acetylcholine and vasoactive intestinal peptide from the vagal and sacral spinal neurons. Their innervation is generally limited to organs and tissues that intermittently need large increases in blood flow such as sweat glands, the digestive system and genitals.

1.3.3 Cardiovascular Reflexes

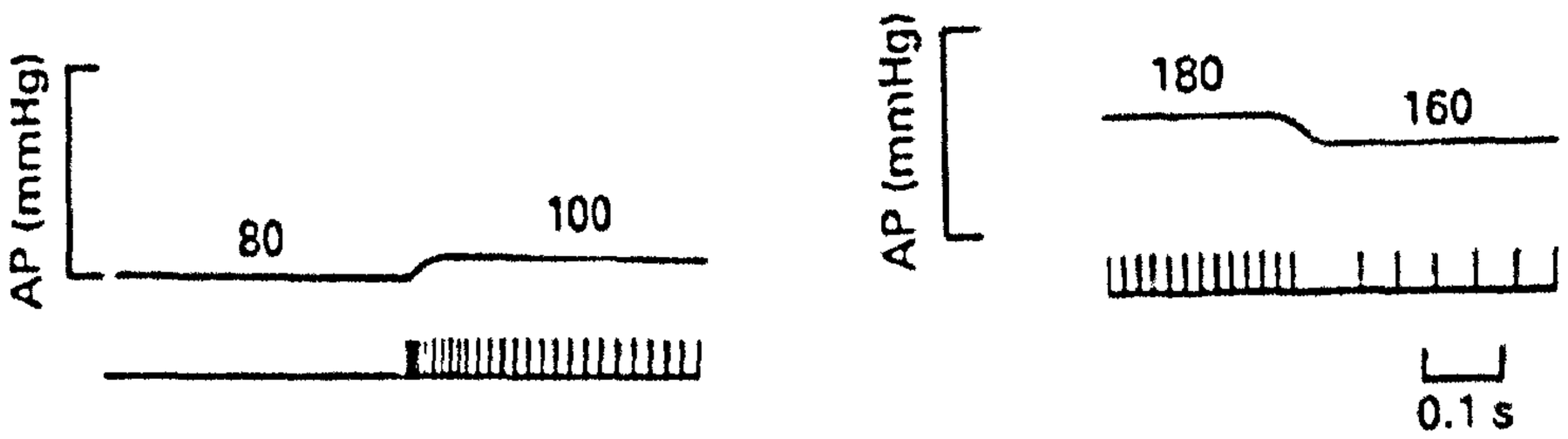
The Baroreceptor Reflex

Baroreceptors are mechanoreceptors that respond to blood vessel stretch and can, therefore, initiate responses to changes in blood pressure. They are non-encapsulated nerve endings in the adventitial layer of the aortic arch and carotid sinus. The aortic baroreceptors, found in the transverse arch of the aorta send afferent signals from the aortic nerve, via the vagus to the NTS. The carotid sinus afferent fibers pass from the carotid sinus nerve via the glossopharyngeal nerve to the NTS. The NTS has interconnections with the PVN in the hypothalamus. In 1988 Bauer (Bauer *et al* 1988) demonstrated that injections of GABA agonist into the posterior hypothalamus reduced baroreceptor response. This suggested that bradycardia from baroreceptor stimulation resulted from cell body activation in the caudal hypothalamus. Dillon in similar experiments in 1991 (Dillon *et al* 1991) produced a fall in tidal diaphragmatic activity and respiratory rate with baroreceptor stimulation, and demonstrated that this response was blocked with injections of GABA into the caudal hypothalamus. He concluded that GABAergic mechanisms in the caudal hypothalamus modulate both the cardiovascular and respiratory responses to baroreceptor stimulation. Barman 1990 (Barman 1990) made recordings from hypothalamic neurones that had sympathetic and/or cardiac related discharge and found that baroreceptor stimulation inhibited their discharge. Thus it appears that activation of baroreceptors depresses the hypothalamic neural activity that provides drive to the cardiovascular and respiratory systems.

There are two classes of baroreceptor fibers. A-fibers are unmyelinated large diameter fibers that have a firing threshold at an arterial pressure of 50-60 mmHg and show a maximum response at around 90mmHg, making them ideally suited to respond to hypotension. C fibers are thinner non-myelinated fibers that have firing thresholds to arterial pressures in excess of 80 mmHg. Individual fibers have a limited range of pressure sensitivity, the mean range being 30 mmHg. However as pressure progressively increases, receptors with higher thresholds are recruited, thus giving the baroreceptors an approximate range from 50 to 200 mmHg. Baroreceptors response to distension is enhanced in the carotid sinus due to the thinness of the

tunica media, allowing large changes in vessel diameter. Reflex responses are initiated to both loading and unloading, and these maintain homeostasis by altering heart rate, cardiac contractility, venous and arterial constriction and dilation as well as hormonal secretion. Individual fibers increase their firing rate as blood pressure increases (see Fig 1.6). If this elevated pressure is sustained the firing rate will plateau at a slower rate than that during the dynamic response, but are still elevated in comparison to the previous resting rate. When there is a fall in pressure, baroreceptors transiently cease firing afferent impulses during the dynamic stage. Activity then resumes but at a slower rate at the reduced static pressure (Fig 1.7).

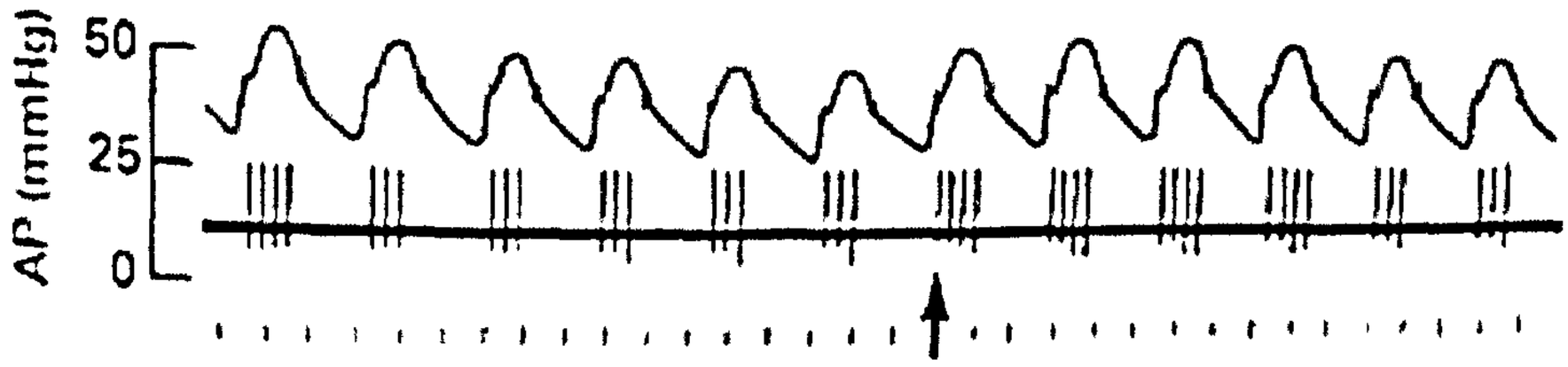
Fig 1.6 - Carotid sinus response to static and dynamic arterial pressures.



(Landgren et al 1952)

This figure shows the firing rate of a single baroreceptor afferent fiber from the carotid sinus of a cat. As arterial pressure (AP) is increased there is a large increase in firing rate. When the pressure plateaus the firing rate slows. The converse is seen during a fall in arterial pressure. There is a cessation of afferent discharge, which resumes at a slower rate when the lower pressure is maintained.

Fig 1.7 - Single baroreceptor afferent fiber of rabbit aortic arch in response to in-vivo dynamic arterial pressures .

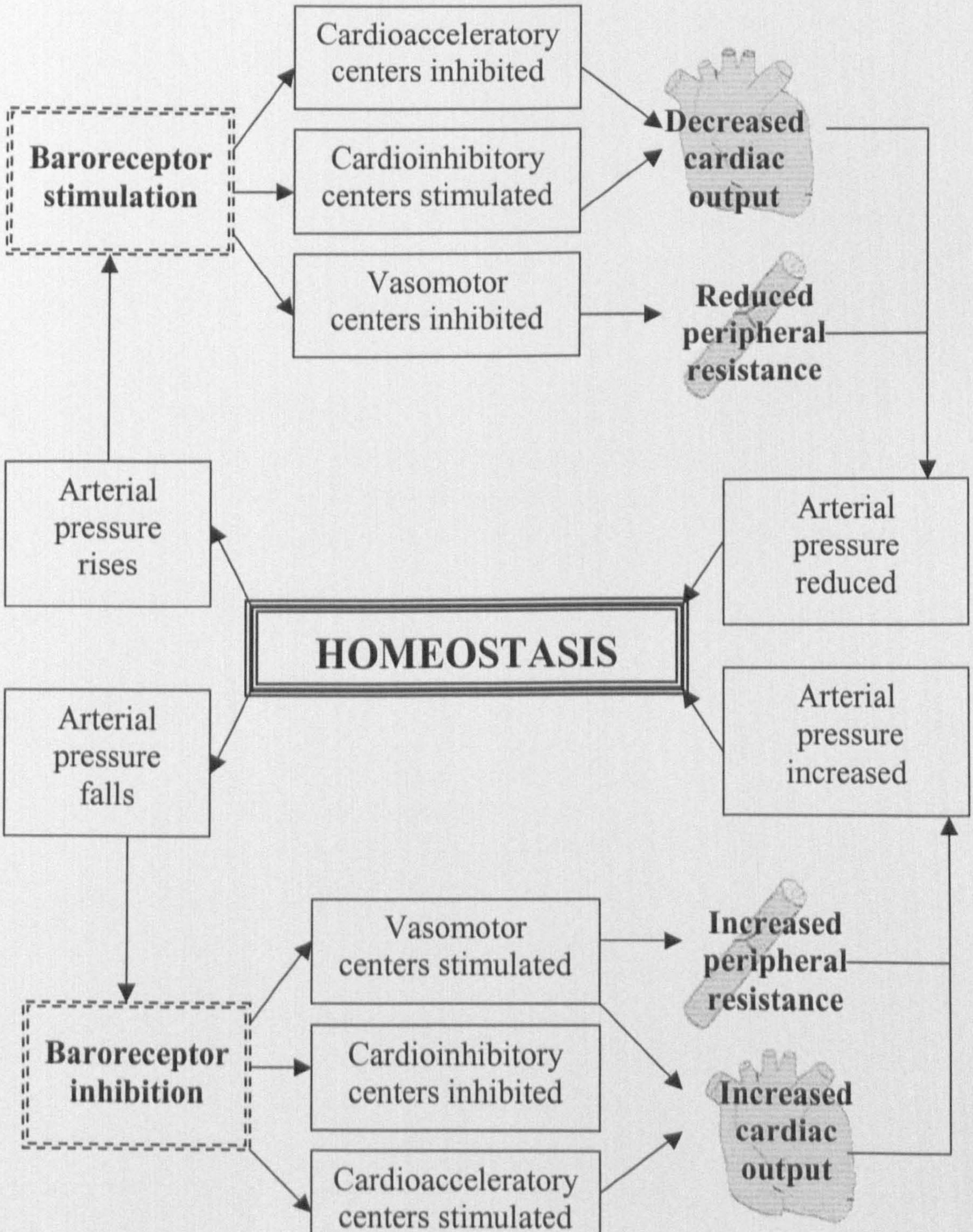


(Downing *et al* 1963)

In vivo, when there is no static pressure, there is intermittent rapid firing following systole, followed by minimal afferent activity during diastole. This figure shows the firing rate of a single afferent fiber from the aortic arch of a rabbit during changes in arterial pressure. The arrow indicates the start of the pressure increase associated with ventricular systole. There is an associated burst of afferent discharge as the pressure increases, followed by a silent phase as the pressure wave diminishes.

In man, baroreceptor stimulation causes an inhibition of the vasomotor and cardioacceleratory centers and activation of the cardioinhibitory center, to produce a fall in blood pressure (see Fig 1.8). A fall in blood pressure has the opposite effects on these centers. There are a number of ways of assessing the baroreflex or baroreceptor sensitivity, some involving invasive procedures such as measurements of muscle sympathetic nerve activity (Carlson *et al* 1996), however the simplest involve recording heart rate intervals and blood pressure changes after a bolus injection of phenylephrine or sodium nitoprusside (LaRovere *et al* 1998, Carlson *et al* 1996). Phenylephrine causes vasoconstriction and an increase in blood pressure, sodium nitroprusside causes vasodilation and a fall in pressure. The baroreflex slope is calculated as the change in heart rate interval versus the change in blood pressure and is approximately 9 (+/-2) ms per mmHg in normal subjects. A low baroreflex sensitivity is seen a predictor of total cardiac mortality and has been exhibited by OSAHS patients (LaRovere *et al* 1998).

Fig 1.8 - The Baroreceptor Reflex



Chemoreceptors

Chemoreceptors and their influence on ventilation were discussed earlier. Peripheral chemoreceptor stimulation, like baroreceptor stimulation, is also modulated in the caudal hypothalamus. Cross and Silver showed, in 1963 (Cross and Silver 1963), that, in cats, systemic hypoxia stimulated caudal hypothalamic neurones and the same neurones were also stimulated with hypercapnia. Further work by Thomas and Calaresu in 1973 (Thomas and Calaresu 1973) demonstrated that carotid sinus nerve stimulation increased medial hypothalamus neurone firing frequency and that selective stimulation of peripheral chemoreceptors and arterial baroreceptors both increase the firing frequency, which in turn increases arterial pressure and heart rate. Hypoxia and hypercapnia initiate a sympathetic constriction of non-dermal resistance vessels and splenic capacitance vessels to increase blood pressure. If ventilation is limited there is modest bradycardia, but if ventilation is allowed to increase, pulmonary stretch receptor stimulation produces a lung inflation reflex, which promotes vasodilation and tachycardia.

In 1992 Dillon and Waldrop (Dillon and Waldrop1992) showed that caudal hypothalamic neurones, in cats, were stimulated by increasing inspired CO_2 and that the activated neurones had a discharge pattern which was related to the cardio respiratory responses. They also went on to show this response persisted in sinoaortic denervated cats, implying that the response was not mediated by peripheral chemoreceptors, but more probably by the dorsal and ventrolateral medulla, or even on the caudal hypothalamus itself. Their experiments with hypoxia showed increased activity in some caudal hypothalamic neurons; almost 50% of which did not change firing frequency in peripheral chemodenervated cats and only 13% responded to both hypoxia and hypercapnia. Thus increases in blood pressure and heart rate, in response to hypoxia and hypercapnia appear to be regulated by separate populations of caudal hypothalamic neurones, which are activated by peripheral chemoreceptor afferents and local influences.

In man the cardiovascular response to chemoreceptor stimulation can be assessed by monitoring heart rate and blood pressure as subjects are exposed to hypoxia and/or hypercapnia, and represented as the change in blood pressure or heart rate per unit change in O_2 or CO_2, usually SaO_2 and end-tidal CO_2 respectively. The few studies

investigating the cardiovascular responses to hypoxia or hypercapnia have demonstrated small increases in heart rate and little or no change in blood pressure when exposed to progressive hypoxia (Laks *et al* 1997). However, a significantly greater heart rate and blood pressure response was observed when subjects are exposed to hypercapnia (Kiely *et al* 1996)

1.4 SLEEP IN HUMAN ADULTS

Sleep can be defined as a promptly reversible state of reduced awareness and responsiveness to internal and external stimuli. The biological functions of sleep remain controversial, but it is accompanied by a series of stereotyped physiological changes that have important consequences for health. Humans have a natural circadian cycle of approximately 24.3 hours, which, using external factors such as clocks, and the day/night cycle, is maintained at 24 hours. The amount of time during the 24 hour day that is spent sleeping generally peaks during adolescence at around 10 hours per night and diminishes to as little as 3 or 4 hours per night during old age (Hume *et al* 1998). Sleep deprivation has severe physical and psychological effects, encompassing changes in mood, cognitive impairment and psychosis (Roehrs *et al* 1994, Poceta *et al* 1992).

Sleep quality is more important than the total time spent in bed. Adolescents and young adults maintain a sleep efficiency, (the percentage of time in bed spent asleep), of over 90%, but this diminishes to 70-80% with old age. Recurrent arousals from sleep decrease cognitive performance. The degree of arousal, which can be classified from modestly elevated autonomic activity to full awakening, also has important consequences, as does the stage of sleep being disrupted. In general the greater the arousal intensity, defined by EEG activity, and the more arousals from stages 3 and 4 sleep, the greater the impact on daytime functioning. This section will describe the measurement of sleep and the physiological changes which are associated with it.

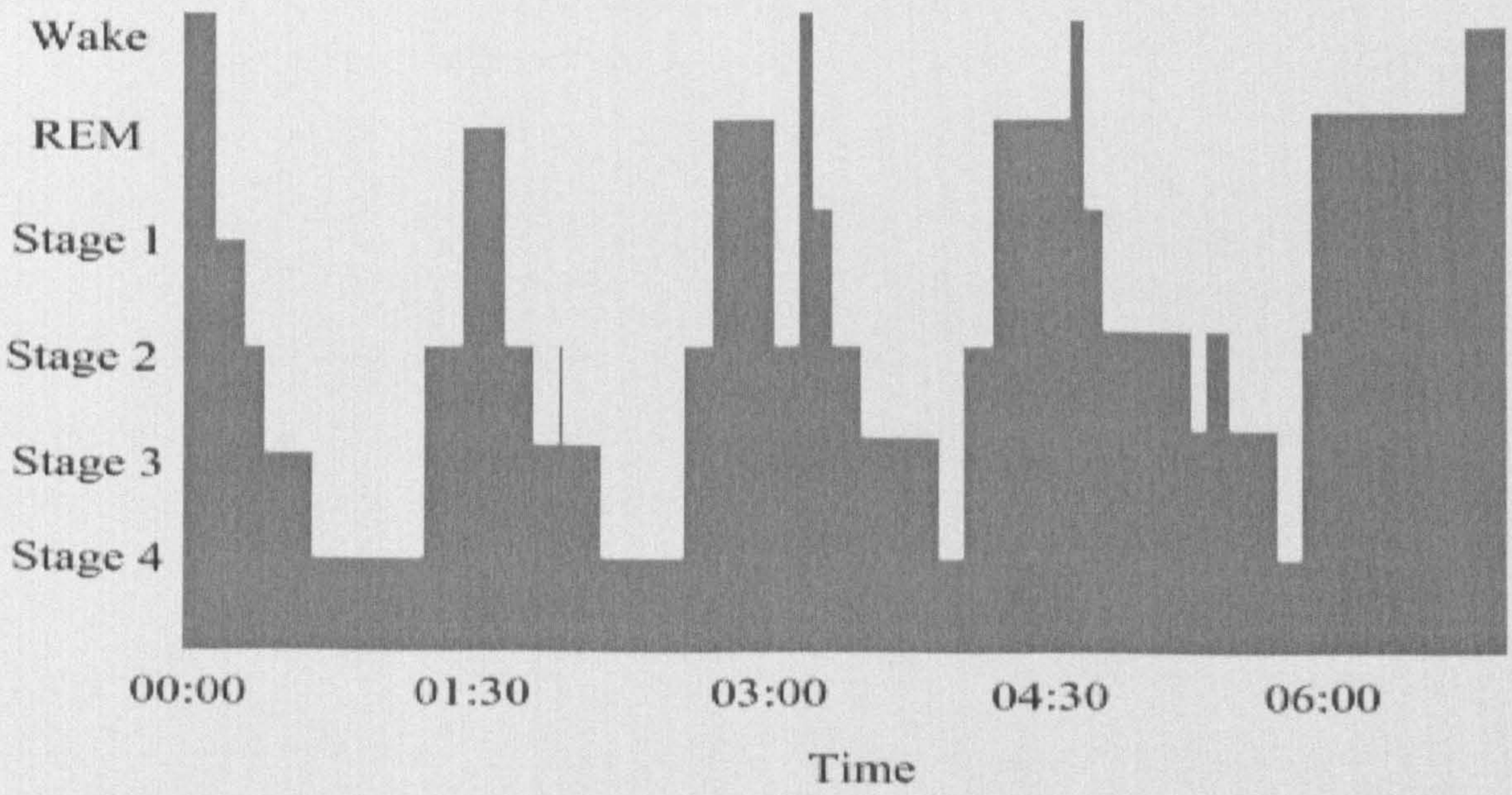
1.4.1 Sleep Architecture

Sleep can be classified into a series of stages depending on changes in EEG. The consensus report published by Rechtschaffen and Kales in 1968 (Rechtshaffen and Kales 1963) remains the most widely used manual for staging sleep. Using EEG techniques they defined methods that could be used to assign sleep stages based on scoring thirty-second epochs. A hypnogram of the consecutive sleep stages during the night can be constructed to demonstrate the gross architecture, and fundamental

measurements can be made, such as sleep onset latency and total sleep time. The hypnogram of a normal night of sleep (Fig 1.9), shows a rapid transition from sleep onset, through stages 1 and 2, into slow wave sleep. After some time in slow wave sleep, there is a transition though stage 2 into REM, each of these complete cycles lasting approximately 90 minutes. As the night progresses the amount of time in SWS decreases and the time in REM increases.

Studies have shown that stages 3 and 4 sleep, (slow wave sleep (SWS)) are important for recovering from sleepiness and restoring normal daytime functioning; repeated arousal from these stages, results in impaired daytime cognitive performance and performance speed (Ferrara 2000). The value of REM sleep remains unclear since antidepressant drugs such as imipramine, a tri-cyclic and dexnafenodone, a phenyl substituted tetrahydro-naphtalenone, suppress REM without any apparent detrimental effects on daytime function (Jobert 1999); thus its physiological value appears minimal. Arousal from REM requires relatively small stimuli, which has led to the suggestion that it may be an alerting stage to enable subjects to awaken when external threats are detected.

Fig 1.9 - A diagrammatic representation of a normal hypnogram.



This figure demonstrates the gross changes in sleep stages between midnight and 7.00 am. Longer periods of SWS, with short episodes of REM are observed in the first part of the night. In the latter half the amount of SWS diminishes and REM increases.

1.4.2 Arousals and Sleep Disruption

Defining an arousal or acute change in the depth of sleep continues to be a source of controversy. The ASDA criteria (Bonnet *et al* 1992) requires scoring of quite dramatic changes in EEG which lasts for a minimum of 3 seconds. These large arousals correlate poorly with measures of daytime symptoms, such as the Epworth Sleepiness Score (ESS) which is a subjective questionnaire to assess daytime somnolence (Johns 1993). There have been many attempts to redefine arousals. Investigators have investigated small events such as micro arousals; EEG changes as brief as 1 second (Cheshire *et al* 1992, Douglas *et al* 1996) and larger ones like movement arousals; abrupt increases in EMG activity and appearance of alpha rhythm in the EEG (Collard *et al* 1996). In each case the correlations with daytime symptoms remain unsatisfactory.

The poor correlation of EEG data and daytime symptoms led to the concept of scoring non visible arousals (Martin *et al* 1997). Increases in ventilation, heart rate and blood pressure are associated with arousal from sleep. They result from a surge of autonomic activity and the associated responses are out of proportion to the physiological needs and in excess of those observed in the proceeding periods of quiet rest (Horner 1996). The function of this excessive response remains unclear. However it provides investigators with a number of potential tools for identifying arousals in the absence of changing EEG frequency.

A single night of experimentally induced disrupted sleep reduces cognitive functions and the ability to resist sleep (Martin *et al* 1997). These can be assessed using such tests as the 'maintenance of wakefulness test' and OSLER, in which subjects are asked to remain awake in a quiet dark room (Poceta *et al* 1992, Bennett *et al* 1997), driving simulators (George *et al* 1996) or reaction speed testing with a psychomotor vigilance test (Jewett *et al* 1999). Reduced functional skills and concentration puts the sufferer of sleep disruption at greater risk of accidents and many publications have now demonstrated patients with OSA are at much greater risk of being in a car accident than a healthy subject (Aldrich 1989, Findley *et al* 1988, Williamson *et al* 2000). The work by Williamson et al has demonstrated that one night of sleep deprivation puts healthy subjects in a worse functional state than if

they had, according to Australian law, too much alcohol to be capable of driving safely.

Sleep 'debt' and poor daytime functioning through intentional sleep deprivation can be quickly rectified with a few hours of undisturbed sleep, but in a disorder such a sleep apnoea, which is characterised by regular sleep disruption on a nightly basis, the consequences become more serious. The sleep debt becomes larger, daytime functioning becomes progressively worse and mood and quality of life can be severely affected.

1.4.3 Physiological Changes During Sleep

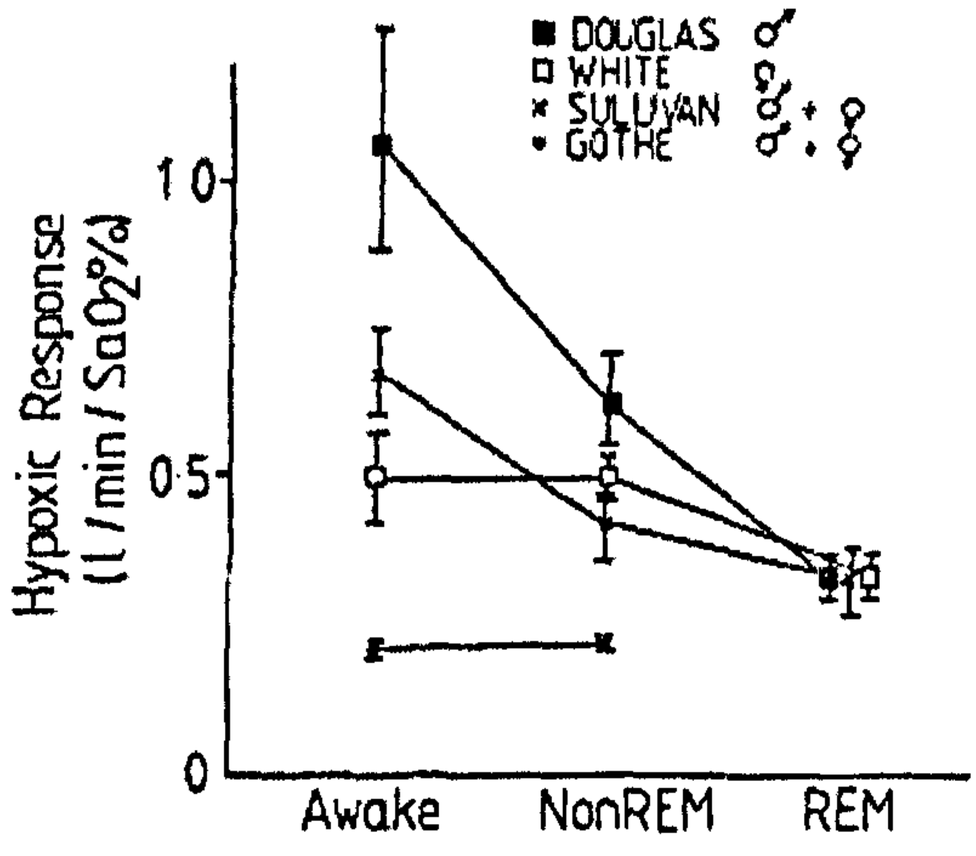
Control of Ventilation

The onset of sleep sees the removal of the wakefulness drive to breathe and a reduction in ventilation. Douglas et al (Douglas *et al* 1982b) found, in a group of 19 healthy adults, that minute ventilation was significantly reduced in all stages of sleep compared to when awake (VE reduced by 6% in NREM and 15% in REM). He noted that breathing pattern was more rapid and shallow during sleep and the mean tidal volume fell by 27% during REM. The fall in ventilation results in an increase in $EtCO_2$, but this rise is not proportional to the fall in ventilation, as there is also a small fall in basal metabolic rate during sleep. There is also a fall in the ventilatory responses to hypoxia and hypercapnia during sleep.

In a review of ventilatory control during sleep, Douglas (Douglas 1985) compared the results from four studies investigating hypoxic responses during wakefulness, NREM and REM (Fig 1.10). The scatter and large confidence intervals demonstrate the large variation in normals hypoxic sensitivity during wakefulness. Some of this variation reflects differences in experimental methods, and some is due to the gender differences, as comparing the single sexed groups, men clearly appear to have a much higher ventilatory response to hypoxia than women. During NREM sleep there was more agreement between the results of the four studies and a general fall in responsiveness, the all male group showing a highly significant fall in response while the all female group showed no change. In REM sleep all groups have very similar

responses, which are all significantly lower than seen during NREM and wakefulness.

Fig 1.10 - Hypoxic ventilatory responses during sleep.



From: Douglas 1985

The ventilatory responses to hypercapnia were studied by Douglas et al and Berthon Jones *et al* (Douglas *et al* 1982c, Berthon Jones et al 1984). Douglas found that the ventilatory response to hypercapnia was reduced during both NREM and REM sleep. This reduced response resulted from the fall in minute ventilation during sleep while the slope of the VE/CO_2 response was not significantly altered suggested an alteration in set-point of the response threshold. Berthon-Jones demonstrated similar responses in females. The ventilatory response to CO_2 during wakefulness (1.39 l/min/Torr (SE 0.14)) was very similar to that during NREM (1.40 l/min/Torr (SE 0.13)), but he observed different levels of minute ventilations at 60 Torr CO_2, (20.7 l/min during Wake vs. 17.1 l/min during NREM). He also demonstrated that males have a significant fall in the VE/CO_2 slope during NREM and REM sleep (Wake 2.52 l/min/Torr, NREM 1.29 l/min/Torr, REM 0.78 l/min/Torr), further emphasizing the influence of sleep and female sex hormones on the control of ventilation.

The Upper Airway

The pharynx has no structural rigidity, being made up of several groups of muscles that perform a number of functions such as swallowing and bracing against the negative pressure occurring during inspiration. As pharyngeal patency is governed by the tonic activity of these muscles, reductions in neural control, e.g. during sleep, can result in increases in airway resistance. The palatal muscles (tensor palatini, levator palatini, palatoglossus, palatopharyngeus, and muscular uvulae) position the soft palate to reduce airway resistance and can adapt to nasal or oral breathing.

During nasal breathing the palatoglossus closes the oral airway as well as keeping the palate from falling onto the posterior pharyngeal wall when the individual is in the recumbent or supine position. Tangel et al (Tangel *et al* 1995) demonstrated that the pharyngeal dilating palatoglossus has an inspiratory related phasic activity, its contraction during inspiration preventing increases in airway resistance. The other muscle important for pharyngeal dilation and patency is the genioglossus. This muscle controls the position of the tongue; it is involved in protruding the tongue and also maintaining the oropharynx by keeping the posterior part of the tongue away from the pharyngeal wall. This muscle also has an inspiratory phasic activity and dilates the pharynx during inspiration or when an intra-pharyngeal negative pressure is applied (White 1999)

Upper airway resistance (UAR) increases in normal subjects during the transition from wakefulness to sleep, and the increase in airway resistance when a resistive load is applied, is significantly greater than that seen during wakefulness (Weigand *et al* 1989). The variability in UAR within this small number of subjects increased five-fold with the onset of sleep, suggesting upper airway collapsibility varies among normal individuals. The UAR during NREM sleep with and without resistive loads correlated well together but did not correlate with wakeful measures of resistance, indicating it would not be possible to define individuals who are likely to experience airway collapse during sleep from daytime measures of resistance. There is also a strong relationship between the increase in UAR and the fall in ventilation with the onset of sleep, further demonstrating that airway resistance and collapse, and the associated flow limitation, are progressive rather than definitive events.

Control of Blood Pressure

Blood pressure has a diurnal rhythm, dipping by around 10% during the night to reach the nadir at approximately 3 am, and peaking in the morning (Millar-Craig *et al* 1978). The mechanisms controlling for this nocturnal dipping are unknown but are likely to be multifactoral. Initial data suggested a neuro-hormonal mechanism, as cerebral and urinary catecholamine secretion is reduced during sleep. The morning peak was attributed to the arousal response, and the day-night difference was enhanced by the removal of wakeful influences that elevate arterial pressure, such as physical activity. More recently, through experiments on rats, it has been suggested the nocturnal blood pressure dip may be directly influenced by the suprachiasmatic nuclei (SCN). Rats with a SCN lesion demonstrated an abolition of the 24-hour blood pressure variability (Janssen *et al* 1994, Stoynev *et al* 1996). However these studies also disrupted many other circadian cycles such as food intake, which can influence blood pressure and this may be the cause of the non-dipping.

Many studies in man have demonstrated the absence of a fall in nocturnal blood pressure is often associated with systemic hypertension or OSAHS, and is an indictor of poor prognosis and increased mortality (Noda *et al* 1993, Pankow *et al* 1997).

As mentioned already, arousal from sleep sees a large surge of sympathetic nerve activity that significantly increases heart rate, blood pressure and ventilation. Davies (Davies *et al* 1993a) demonstrated that, during NREM sleep, transient arousals to external stimuli produce an increase in blood pressure. The degree of arousal was scored according to the change in EEG content, but also included arousals without visible changes in EEG frequency, had a strong relationship with the change in blood pressure. In normal subjects this presents no long term consequences as the arousal response occurs infrequently during the night, but in patients with OSA, repeated sympathetic activation and surges in blood pressure could potentially abolish nocturnal dipping and potentially lead to persistent hypertension and increased cardiovascular morbidity.

1.5 THE OBSTRUCTIVE SLEEP APNOEA HYPOPNOEA SYNDROME

1.5.1 Definition and Epidemiology

Sleep disordered breathing has been noted and described since the early 19th century. In a publication in the Lancet in 1877 (Broadbent 1877), Broadbent describes an elderly gentleman, in the supine position, who snores loudly and experiences 'perfect silence through two or three or four respiratory periods, in which there are ineffectual chest movements; finally air enters with a loud snort', what we now know to be an obstructive apnoea. Broadbent even postulated that the obstruction occurred as a result of 'falling back of the tongue' and pharyngeal resistance, and went on to report central apnoeas He describes 'the pause was so long as to excite attention, and indeed alarm; and I found...actual cessation of all respiratory movements'. Furthermore, several authors noted a strong link between periods of prolonged apnoea when asleep and the so-called Pickwickian syndrome. Little interest or emphasis was placed on the consequences of apnoeas until Lugaresi investigated the cardiovascular responses to apnoeic events during sleep. He published several papers in 1972 (Lugaresi *et al* 1972a,b,c), and was the first to host a conference looking specifically at sleep disordered breathing.

In 1976 a paper by C. Guilleminault titled 'The sleep apnoea syndromes' was published (Guileminault *et al* 1976) and the importance of apnoeas during sleep received widespread acknowledgement as a syndrome worthy of further investigation and treatment. He described 62 patients, the majority (66%) were not obese, did not have craniofacial abnormalities and did not have any respiratory symptoms during wakefulness, the remaining 34% had Pickwickianism; obesity and hypersomnolence. All patients experienced nocturnal apnoeas. He classified the apnoeas as central or obstructive and described how all of the patients experienced respiratory obstruction during sleep and commented on the likelihood of this being a widespread phenomenon.

'The sleep hypopnoea syndrome' published in 1988 by Gould *et al* (Gould *et al* 1988) was an important publication that pointed out that abnormal respiratory events other than apnoeas could be important. He studied 50 patients and analyzed the relationships between reductions in thoraco-abdominal movement and nasal airflow

with 4% oxygen desaturations and EEG arousals. He demonstrated the hypopnoea index derived from looking at a 50% reduction in thoraco-abdominal movement compared best with desaturation and arousal indices. This paper lead to the gradual acceptance of the apnoea hypopnoea index (AHI) as the most appropriate measure of disease severity

OSAHS defined according to the American Sleep Disorders Association (ASDA) consensus report, is a syndrome in which patients experience intermittent upper airway obstruction that results in repetitive flow limitation during sleep and has associated daytime symptoms.

- Apnoeas are classified as the total cessation of ventilation with a 4% arterial oxygen dissociation.
- Hypopnoeas are a 50% reduction in ventilation with an associated arterial oxygen desaturation or cortical arousal.
- Patients must experience a minimum of 15 respiratory events per hour of sleep and have associated symptoms such as excessive daytime sleepiness (EDS) or snoring.

There has been some debate regarding the validity of this empirically derived diagnosis. It is difficult to define what is significantly abnormal and worthy of treatment when the continuum from normal to abnormal ventilation does not correlate well with daytime symptoms. The question arises as to what specific value of AHI should be considered abnormal, should shorter events with milder desaturations be scored or should only longer more severe events be included when scoring the AHI? Some answers have come from The Sleep Heart Health study (Gottlieb *et al* 1999) which looked at 1824 community dwelling adults. They assessed sleepiness using the Epworth sleepiness score (ESS) and classified subjects according to their AHI, (<5, 5 to <15, 15 to <30 or 30+). The study demonstrated there was a relationship between ESS and AHI. However, the percentage of subjects with excessive daytime sleepiness (EDS) varied from 21% in the non-apnoeic group to 35% in the most severe group, demonstrating in a general population that EDS exists without apnoeas and apnoeas without EDS. Young et al (Young *et al* 1993), showed in a random sample of 602 employed men and women aged 30 to 60 years old, that 9% of women and 24% of men had an AHI greater than 5 and an estimated 4% of men and 2% of women, suffered with both sleep disordered breathing and

EDS. OSAHS is also more prevalent in the elderly population; studies have demonstrated a range from 20 – 60% of subjects aged over 50 have an AHI greater than 5 (Ancoli-Israel *et al* 1991 Phillips *et al* 1994). These studies suggest that OSAHS, however defined, occurs as frequently in the population as other common diseases such as asthma and is therefore a major public health problem (National Heart, Lung and Blood Institute 1994, Phillipson 1993).

1.5.2 The Upper Airway

Obstruction of the airway during sleep usually occurs at the pharynx. There are a number of factors that influence upper airway patency and hence the propensity of the upper airway to collapse during sleep. The pharyngeal dilator muscles described earlier have a reduced activity during sleep, compared to wakefulness. This increases upper airway resistance and airway collapsibility (Weigand et al 1989). Upper airway muscle activity in OSAHS patients was increased during both wakefulness and sleep compared to normal subjects, suggesting that their airways are permanently in a high tonic state to protect against their susceptibility to collapse (Surratt *et al* 1985). Martin *et al* demonstrated, using acoustic reflection, that all upper airway dimensions except the oropharyngeal junction decreased with increasing age in normal subjects, and that the decrease in airway size on lying down was greater in men than women. However, in this study, the men had a greater body mass index (BMI) and for any body mass, the men had greater neck circumferences than women (Martin 1997). Trinder *et al* (Trinder *et al* 1997) also showed that men had a greater airway resistance during sleep than women, but again recruited a population where the males were significantly heavier than the females. However, there have been several studies that have demonstrated gender related differences in the size and mechanical properties of the pharynx in normal subjects (Brooks *et al* 1992, Brown *et al* 1986), and a study by Whittle *et al* (Whittle *et al* 1999) demonstrated that, in well matched groups of normal subjects, the volume of fat in the neck did not differ between men and women, but there were differences in the mass of soft tissue and in the deposition of the fat between the sexes.

Many studies using computerized tomography and magnetic resonance imaging (Shepard *et al*1997, Ryan *et al* 1991, Katz *et al* 1990, Anderson *et al* 1991) have demonstrated that OSAHS patients, when awake, have a reduced upper airway volume or cross-sectional area, especially in the hypopharynx and oropharynx areas, compared to normal subjects. Mortimore *et al* (Mortimore *et al* 1998) demonstrated that non-obese OSAHS patients had 30% greater total body fat than matched control subjects, and that neck tissue volume was 10% greater. AHI has been demonstrated to correlate with external neck circumference, BMI and internal circumference of the distal pharynx (Katz *et al* 1990), and Davies et al (Davies *et al* 1992) demonstrated that neck circumference, when corrected for height, is a good predictor of SaO_2 desaturations when asleep.

Patients with increased nasal resistance create greater negative pressures within the airways during inspiration than normal subjects, and are at an increased risk of OSAHS. Studies have demonstrated that chronic nasal resistance is an independent risk factor for OSAHS (Lofaso *et al* 2000), and increased nasal resistance resulting from allergic rhinitis causes sleep disruption and increased risk of apnoeas (McNicholas *et al* 1982).

1.5.3 Risk Factors and Symptoms of OSAHS.

Clinical features and symptoms can aid a physician in their identification of subjects who are likely to suffer with OSAHS, such as:

- **Excessive daytime sleepiness,** which is the symptom that most affects the quality of life of these patients
- **Snoring,** in particular high snoring intensity, rather than the frequency of its occurrence (Kump *et al* 1994).
- **Body proportions,** such as waist circumference, when corrected for age and BMI, or neck circumference when corrected for height, explain some of the variance in AHI or SaO_2 dip rate (Deegan *et al* 1996, Davies *et al* 1992).
- As well as: witnessed apnoeas or choking, sleeping supine, morning headaches, race, and tobacco and alcohol use,

1.5.4 Physiological Responses To Obstructive Events.

In patients with OSAHS the negative intra-luminal pressures created during inspiration lead to increased airway resistance or collapse and flow limitation. An obstructive apnoea is characterized by continuing ventilatory efforts during the airway obstruction

Ventilatory efforts increase during an obstructive apnoea, although inspiratory flow ceases, some expiratory flow may still occur. This reduces the thoracic gas volume and promotes a more rapid arterial oxygen desaturation. A dog model of OSAHS was used to demonstrated that arousals and the termination of obstructive events were triggered primarily by carotid body excitation, and its denervation saw a near abolition of the arousal response (Bowes *et al* 1981). This suggested arousal are modulated via a chemoreceptor response. However Berthon-Jones *et al* demonstrated that under eucapnic conditions in man, the ventilatory response to hypoxia and hypercapnia during sleep is reduced, and that hypoxia is poor arousal stimulus (Berthon-Jones *et al* 1982 and 1984). Using a dog model of OSAHS, Yasuma et al demonstrated that mechanoreceptor stimulation arising from the ventilatory apparatus may contribute substantially to the arousal response to hypoxia (Yasuma *et al* 1991). Berry *et al* (Berry *et al* 1992) found that in normal subjects hyperoxia prolonged the time to arousal after airway occlusion by decreasing the rate of increase in the magnitude of inspiratory efforts, but it did not change the arousal threshold. This group also assessed the effect of hypercapnia on the arousal response to airway occlusion (Berry *et al* 1993). They demonstrated that an increase in inspired CO_2 before airway occlusion resulted in a reduced time to arousal by increasing the rate at which the inspiratory efforts increase. However the inspiratory efforts measured at arousal did not differ between the normocapnic and hypercapnic occlusions. Gleeson *et al* (Gleeson *et al* 1990) demonstrated that, regardless of the ventilatory stimulus (hypoxia, hypercapnia or resistive load), the increasing ventilatory effort was the same at arousal and thus concluded that it was likely that ventilatory effort was the arousal stimulant during an obstructive apnoea. Work by Sforza *et al* (Sforza *et al* 1996) suggested that the degree of ventilatory response during upper airway occlusion in OSAHS may be influenced by the sensitivity of central neural drive to chemical stimuli, as the change in esophageal pressure during

an apnoea, the rate of this pressure change and the maximal esophageal pressure at the end of an apnoea all positively correlate with awake ventilatory responses to hypoxia and hypercapnia.

Heart rate responses to obstructive events are more variable. Two heart rate responses during an apnoea were initially described. In the early phase of the apnoea the diving response elicits peripheral vasoconstriction and bradycardia, following which there is an increase in sympathetic activity and a tachycardia. (Stoohs *et al* 1992) Subsequently the individual heart rate patterns have been shown to depend on their hypoxic chemosensitivity. Some subjects increased their heart rate during an apnoea, in others it falls (Bonsignore *et al* 1997), while some have no response (Stoohs *et al* 1992)) The type of response correlated with breath holding times and the ventilatory response to progressive isocapnic hypoxia (Sato *et al* 1997).

Blood pressure in dogs increases in response to airway occlusion during sleep in the absence of a cortical arousal. Heart rate also increases but stroke volume and cardiac output do not. (O'Donnell *et al* 1996, Schneider *et al* 1997). Okabe *et al* found that, in man, the mean blood pressure increase during an apnoeic episode correlates with the decrease in SaO_2. They also showed that this response was three times greater than the mean blood pressure response to isocapnic hypoxia when awake (Okabe et al 1995). However there were some unusual methodologies employed in this study. The change in blood pressure associated with an apnoea was measured as the difference between the blood pressure 'just before sleep' which was significantly lower than that seen at rest before performing the hypoxic challenges, and 'the peak blood pressure value induced by each apnoeic episode', which may indeed be the arousal response and not the change in blood pressure during the apnoea itself. Their description remains unclear and the blood pressure rises associated with an apnoea were twice the size of the large arousal responses documented by Davies *et al* (Davies *et al* 1993a,b) and Rees *et al* (Rees *et al* 1995). Garpestad *et al* (Garpstead *et al* 1992), used invasive blood pressure monitoring and an ambulatory ventricular function monitor, to show that heart rate and mean arterial pressure (MAP) rise (MAP at start of apnoea 81 +/- 13 mmHg, MAP before apnoea termination 90 +/-8 mmHg). Rees *et al* (Rees *et al* 195) reported that, in OSAHS patients in NREM

sleep, having spontaneous apnoeas, there was a significant increase in pleural pressure, mean blood pressure, and CO_2 tension. These physiological changes as well as the apnoea duration, the numbers of inspiratory efforts made, the peak pleural pressure and the increase in median EEG frequency during the apnoea were not related to the absence or presence of an EEG arousal at apnoea termination. This suggests that the arousal response is continuous and not discrete, and that autonomic and brainstem arousals at apnoea termination, influenced by the multifactoral physiological changes, are more precise measures of sleep disruption.

1.5.5 Arousals

During an obstructive event: hypoxia, hypercapnia and airway occlusion result in an increase in respiratory efforts, these are thought to be the main cause of apnoea termination (Gleeson et a1 1990). Most apnoeas terminate with an associated cortical arousal and a transient surge of sympathetic activity which is thought to be part of a 'fight or flight' defence response ; blood pressure, heart rate and ventilation dramatically increase beyond metabolic demands (Horner 1996). However, autonomic arousal can been seen even in the absence of significant EEG changes, Carley *et al* reported that transient acoustic stimulation during normal sleep evoked a significant increase in ventilation that lasted for 1-4 breaths and was largely unaffected by the presence or absence of an EEG arousal (Carley *et al* 1996). In 1984 Guilleminault el at noted that the abrupt tachycardia associated with the resumption of breathing was minimally affected by administration of O_2 before the obstructive event, suggesting that hypoxia was not the only factor involved in the heart rate response at apnoea termination. (Guileminault *et al* 1984). Ringler and co-workers noted that O_2 supplementation had little effect on the post-apnoeic blood pressure rise (MAP increase 18.8 +/- 7.1mmHg with O_2, 21.3 +/- 9.2mmHg without O_2), adding further evidence that chemoreceptor responses were not the primary factor influencing the sympathetic outflow associated with arousal (Ringler *et al* 1990). Rees *et al* showed that the physiological changes occurring during obstructive events, such as fall in SaO_2, increase in CO_2 and number of attempted respiratory efforts, had little influence on whether an apnoea terminated with an

arousal or not, as similar conditions were seen in individuals when both types of apnoea termination existed. They also noted that the CO_2 tension at apnoea termination and the associated increases in blood pressure during the apnoea were well correlated and similar for events with and without cortical EEG arousal (Rees *et al* 1995). However much of the blood pressure response at arousal appears to be independent of normal cardiovascular control. When acoustic and vibratory stimuli where applied to evoke an arousal in normal subjects during NREM sleep, a blood rise similar to that at the end of and obstructive apnoea was observed (Davies *et al* 1993a). This suggests the relationship between $EtCO_2$ and the blood pressure rise may be coincidental, and that the changes seen with a cortical arousal are independent of the mechanisms employed to maintain homeostasis.

1.5.6 Long-term Physiological Changes Associated with OSAHS.

The association between OSAHS and hypertension has been the subject of much controversy. Identifying OSAHS as an independent risk factor for hypertension is difficult due to the many confounding factors that are strongly associated with both disorders, such as age, sex and BMI. In 1989 Stradling investigated this relationship, and concluded that evidence of causality was lacking (Stradling *et al* 1989). Since then more studies have been published without controlling for these confounding variables (Kiselak *et al* 1993, Lavie *et al* 1993), but more recent data has recognised the importance of doing this. Suzuki *et al* noted 50% of their normotensive and 43% of their hypertensive OSAHS patients did not have a nocturnal dip in blood pressure, and only showed a relationship between AHI and 24-hour blood pressure elevation in the hypertensive non-dipping group (Suzuki *et al* 1996). In 1997 a study by Pankow *et al* concluded that OSAHS was associated with hypertension independent of age and obesity, and that non-dipping is related to apnoea severity (Pankow et al 1997). In 1994 the Wisconsin sleep cohort reported that subjects with an AHI>5 had significantly higher blood pressure than people without sleep disordered breathing, and a dose dependant relationship between AHI and mean blood pressure was observed after controlling for age, sex and obesity (Hla *et al* 1994). Three years later the same investigators published their findings from one of the largest studies to investigate this relationship. They performed polysomnography and blood pressure

recordings on 1060 employed men and women aged between 30 and 60 years. Blood pressure increased linearly with increasing AHI, independent of known confounding factors. The odds ratio, in this overweight middle aged population, for hypertension associated with an AHI of 15 (vs. 0) was 1.8. (Young *et al* 1997).

In 2000, Lavie *et al* published the findings from their 10 year prospective study which added further evidence of a causal relationship. They assessed 2677 adults aged 20 to 85 years and found that blood pressure and the number of patients with hypertension increased linearly with increasing AHI after adjustment for age, BMI and sex. Each apnoeic event per hour of sleep increased the odds of hypertension by about 1%, and each 10% decrease in mean nocturnal oxygen saturation increased the odds by 13%.(Lavie *et al* 2000). The mechanism underlying the development of hypertension is still unknown, although recurrent hypoxia, intrathoracic pressure changes, and recurrent surges in sympathetic activity associated with arousal from sleep may all contribute.

There is controversy about the effects of snoring on hypertension. In 1985 Koskenvou *et al* investigated 7551 subjects aged 40-69 years. Using data collected from a postal questionnaire demonstrated that hypertension was significantly associated with snoring with a relative risk between habitual snorers and non-snorers of 1.94 in men and 3.19 in women (Koskenvou *et al* 1985). Lindberg *et al* showed in a 10 year follow-up study that persistent snoring was an independent risk factor for the development of hypertension among males aged less than 50 years (Lindberg *et al* 1998). However two studies that recognised OSAHS as a confounding factor reported that simple snoring was weakly or not at all related to hypertension (Young *et al* 1996, Hoffstein *et al* 1994). Systolic and diastolic blood pressures, adjusted for age, sex and BMI, increased stepwise across the categories of no sleep disordered breathing, simple snoring, mild moderate and severe OSAHS, emphasising that snoring is at the beginning of the sleep disordered breathing spectrum (Young et al 1996).

Further insight into the relationship between repetitive upper airway obstruction and hypertension has come from animal models of OSAHS. Using a dog model, which has an implanted tracheostomy and occlusions controlled remotely using a telemetry system, and a control model in which arousals were induced by acoustic stimuli, Brookes et al found that OSAHS per se produced sustained daytime

hypertension and that recurrent arousals from sleep cannot account for the daytime hypertension (Brooks *et al* 1997). This implies that the changes during the apnoea, rather than the arousal evoked by them, are responsible for hypertension. Rats exposed to repetitive hypoxia over 35 consecutive days develop chronically elevated systemic blood pressure that is still elevated after hypoxic stimulation has ceased (Bao *et al* 1997a, Fletcher *et al* 1996). The second study demonstrated that eucapnic hypoxia was a more potent stimulus to acute BP elevation than hypocapnic hypoxia (Bao *et al* 1997b). However it might be more useful to assess the effect of hypercapnic hypoxia on blood pressure, as these are conditions that occur during an apnoea rather than hypocapnic hypoxia. Lavie's recent paper (Lavie *et al* 2000) also showed a strong relationship between the levels of hypoxaemia experienced during the night and the development of hypertension.

OSAHS patients have been demonstrated to have high resting muscle sympathetic nerve activity (MSNA), which may, through increasing peripheral constriction and cardiac output, contribute to sustained elevated blood pressure (Narkiewicz *et al* 1998, Hedner *et al* 1988, Somers *et al* 1995). Somers and co-workers demonstrated this increased further during sleep, and Narkiewicz *et al* not only demonstrated that it existed in the absence of obesity, but also that obesity alone, in the absence of OSAHS, was not accompanied by increased sympathetic activity. This elevated activity may result from the repetitive hypoxic episodes that characterise OSAHS.

Sympathetic and blood pressure surges to voluntary apnoea, in normal subjects, are augmented by hypoxia, implying there is some involvement of the carotid body chemoreceptors (Hardy *et al* 1994). Patients with OSAHS demonstrate an increase in sympathetic activity and blood pressure during an obstructive apnoea, but these increases muscle sympathetic nerve activity during the apnoea are blunted by O_2 administration (Leuenberger *et al* 1995). Two recent studies by Narkiewicz and colleagues have demonstrated there may be an increase in the tonic chemoreceptor activity in patients with OSAHS. Deactivation of the peripheral chemoreceptors, by breathing 100% O_2, saw significant reductions in MSNA and mean arterial pressure in OSAHS patients but not in the matched control group (Narkiewicz *et al* 1998). Conversely, he demonstrated greater increases in ventilation, heart rate and mean blood pressure during hypoxia, in OSAHS patients compared to control subjects, suggesting there is a selective potentiation of peripheral chemoreflex sensitivity in

these patients (Narkiewicz *et al* 1999). However these results are controversial, as other studies have demonstrated a depression of peripheral chemosensitivity in these patients (Osanai *et al* 1999, Hedner et al 1992).

1.7 AIMS OF THIS THESIS

As this review of the literature illustrates, there is now a substantial body of data demonstrating that cardiovascular and ventilatory control mechanisms are closely related in their neural connections within the brainstem and both are modulated by higher cortical function which is reduced during sleep. There is a significant amount of variability in these responses, particularly that to hypoxia, depending on how long the stimulus is maintained. The briefer 'defense' responses assessed in terms of increased respiratory center output, increased respiratory muscle activation, or sympathetic activation, are the ones most relevant to upper airway obstruction, which is the defining event in patients with OSAHS.

Study of these patients confers a relatively stereotyped physiological response to upper airway obstruction during sleep, which occurs as a result of a reduction in upper airway muscle activation in a pharynx at risk of collapse. Acute cardiovascular changes result from this, with consistent rises in blood pressure in response to these arousal stimuli, although the heart rate response is more variable. These acute changes may, in part, be chemoreceptor mediated but obstruction with hypoxaemia seems to be needed if prolonged hypertension is to develop.

Despite the significant data from animal studies and healthy adults about the ventilatory and acute cardiovascular responses to repetitive upper airway obstruction, there is little data about how the cardiovascular system response to progressive hypoxia. Given the importance of chemoreceptor stimulation, we postulated that they would be modulated by changes in arterial CO_2. Given the potential for adaptation in the cardio-respiratory control systems, patients with OSAHS may show a blunting of any hypoxia stimulant effect, other influences like age and BMI may also be relevant.

Sleep itself has a powerful influence on these cardiovascular responses, and assessing them during established sleep aswell as wakefulness is necessary. Patients

with reproducible upper airway obstruction provide a medical model of such changes but their 'intrinsic' chemoresponsiveness influencing cardiovascular and respiratory responses can be measured if upper airway patency is maintained by nasal CPAP. A further consideration is to what extent the duration of these respiratory disturbances influence the cardiovascular responses. It is therefore appropriate to assess the diagnostic criteria used in classifying OSAHS. As noted already these are empirically derived arbitrary units, and will be used when recruiting patients to the studies. The first part of the thesis will consider them in terms of the relationship of these criteria to one of the most important factors in OSAHS, excessive daytime sleepiness. It is possible that the duration of events may not only be important in influencing excessive daytime sleepiness, but may also influence the cardiovascular changes seen during and after an event and may even influence the long term cardiovascular changes associated with OSAHS.

Chapter Two

Apparatus and Methodology

2.1 GENERAL COMMENTS

Throughout this thesis several types of investigation were performed, such as polysomnography and hypoxic challenges. In the case of hypoxic challenges, several forms of apparatus and protocol were employed to best suit the circumstances in which we aimed to induce hypoxia. Details of the standard protocols and data interpretation are presented here, with specific modifications commented upon in the chapters where they arise.

2.2 POLYSOMNOGRAPHY

Overnight polysomnography (PSG) was performed in the regional sleep disorders laboratory, at the University Hospital Aintree. The laboratory used was a single patient room specifically designed for PSG recording, situated in the hospital respiratory physiology department. The PSG was performed using a Jaeger/Aequitron-Medical Sleeplab 1000p. This is PC with a Pentium II processor and 32 megabytes of RAM. Studies were archived to 1-gigabyte Optiplex optical disks, which permits uploading data and offline analysis of both sleep and cardiovascular/respiratory data. The standard PSG montage incorporates:

Sleep staging, performed using electroencephalography (EEG), electromyography (EMG) and electrooocculography (EOG).

Respiratory event analysis using a pulse-oximetry, thoracic and abdominal pneumatic plethysmography, an oronasal thermistor and an electrocardiogram (ECG)

Limb activity monitoring using tibial EMG.

The skin was prepared by rubbing with an abrasive solution (Omniprep) to remove oils and dead skin cells from the areas where electrodes were to be placed. The gold stick-on cup electrodes (SLE Diagnostics) were filled with conductive electrode cream (Dracard). The scalp electrodes were glued in place using collodion EEG adhesive (SLE Diagnostics), the remainder of the electrodes being fixed in position with a waterproof adhesive tape (Omega Medical). A maximum impedance of 10 K-ohms was acceptable for acquiring good quality data from the surface electrodes. If

any electrode had an impedance in excess of 10 K-ohms it was removed, the skin prepared again and the electrode then reapplied.

- **EEG** surface electrodes were positioned according to the 10-20 International Placement System (Jasper 1958) (Fig 2.1), to give bipolar measurements between C3 and A2, C4 and A1 and C3 and C4.
- **EMG** surface electrodes were placed in positions F3 and F4 to give a bipolar measure of tonic activity of the platysma; this was used as an indicator of postural muscle tone and employed when differentiating wakefulness and REM sleep.
- **EOG** surface electrodes were attached to positions Sp1 and Sp2, to give opposing deflections from the baselines when eye movements occur.
- **ECG** electrodes were placed above the left and right clavicles and acquire an ECG lead I recording. The heart rate is calculated from the R-R interval.
- **SaO_2** recordings were made using a Datex-Ohmeda 3700 pulse oximeter, set for 3-second data averaging, with a finger probe patient attachment.
- **Oronasal airflow** is a non-quantitative measure of respiratory airflow and was measured using a molded thermistor with three sensors, one at each of the nares and one at the mouth. As exhaled air warms the sensors a downward deflection from the baseline occurs, reversing as the relatively cool room-air is inhaled.
- **Respiratory efforts** were recorded using two elasticated, air filled bands, placed around the thorax and abdomen, and connected to pressure transducers. With inspiration, the bands are stretched, their volume increases and the pressure falls, with expiration, the bands contract and a pressure increase is observed. These indicate the presence or absence of efforts from the chest wall muscles.
- **Limb activity** was monitored from surface EMG electrodes placed on the calf of the patients, and indicates periodic limb movements which may be associated with an arousal.

2.2.1 Sleep Staging

This system utilizes computer-aided sleep staging for semi-automated analysis of EEG, which scores 30 second epochs according to the dominant frequencies. The scorer visually interprets the EEG in accordance with Rechtschaffen and Kales

methodology (1963) and sets the frequency boundaries for each stage. A ten second running average is then calculated by the computer as the local EEG baseline and is used to determine the frequency and amplitude changes associated with an arousal or change in sleep stage. The results for each epoch are then manually validated by the scorer

The automated staging criteria are listed below:

- Spindles must have a maximum average frequency value (AFV) of 6Hz and a minimum duration of 0.5 seconds.
- K-complexes must have a minimum AFV of 2.5Hz and a minimum amplitude of 50% of full scale.
- Delta waves have a minimum amplitude of 50 microvolts.
- Stage 3 sleep requires the presence of 35-49% delta waves
- Stage 4 sleep requires the presence of 50% or greater delta waves
- REM has a minimum AFV of 3Hz and an out of phase deflection ratio between the two EOG channels of 1.7

The manual process involves:

- The average EEG frequency values are set at the boundaries between stages, by the scorer, to enable the automated process to apply these stage/frequency criteria to every epoch.

EOG and EMG comparisons being made by the scorer to differentiate the stages that, when the EEG analysis has been performed, may be REM or wakefulness.

Standard measures of the sleep architecture are made when each 30-second epoch has been assigned a sleep stage these include:

- Sleep onset latency, which is the time in minutes from 'lights out' until the time when the subject is asleep.
- Total sleep time, which is the total time in hours and minutes that the subject spends asleep
- The number of minutes spent in each sleep stage.

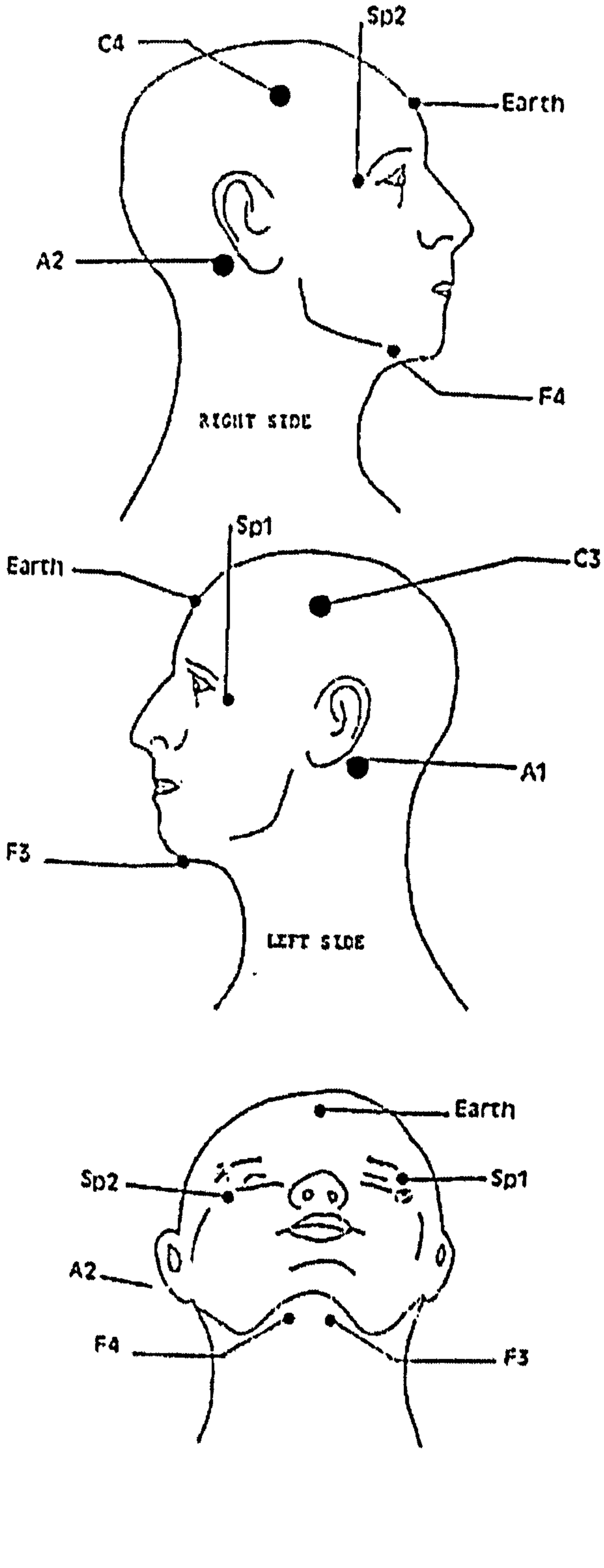
2.2.2 Scoring Arousals

In the standard analysis mode, automated arousal scoring uses the following EEG criteria,

- a minimum frequency change of 2.5Hz from the local baseline
- a minimum frequency level of 6Hz
- a minimum amplitude increase of 50% from the local baseline
- a minimum duration of 3 seconds
- a maximum duration of 15 seconds
- a doubling of the EMG if arousals are to be scored while in REM.

Arousals can also be manually scored, by the user, using the arousal scoring guidelines outlined by ASDA (Bonnett *et al* 1992). Arousals can be represented as the arousal index, which is the mean number of arousals per hour of sleep, and are automatically associated with respiratory or cardiovascular events such as apnoeas or oxygen desaturations if it occurs within a 15 seconds of these events.

Fig 2.1 - The 10-20 International Surface Electrode Placement for PSG (Figures from K.Rees PhD 1995)



2.2.4 Scoring Oximetry Parameters

A desaturation is automatically scored using the criteria of:

- a minimum fall in SaO_2 of 4%
- the fall in SaO_2 occurs over a minimum of 10 seconds
- there is a minimum of 2 seconds between subsequent falls in SaO_2.

The desaturation index is calculated as the number of desaturations per hour and is most commonly expressed as the mean number of desaturations per hour of sleep.

2.2.5 Scoring Respiratory Events

The conventional ASDA criteria for respiratory events were adopted unless otherwise stated.

An apnoea is scored if all of the following criteria are met:

- there is a maximum oronasal flow signal of 12% of the previous 30s baseline
- the absence of flow lasts a minimum of 10 seconds
- there is an associated 4% fall in SaO_2 within a 20 second lag time

An apnoea is scored as

- **obstructive** if there is continuing respiratory effort (a minimum of 12% full scale in either the thorax or abdomen).
- **central** if there is no respiratory effort (a maximum of 11% full scale in either the thorax or abdomen).
- **mixed** if there is the absence of respiratory effort follow by respiratory effort.

A hypopnoea is scored if all of the following criteria are met:

- there is a maximum oronasal flow signal of 50% of the previous 30s baseline
- the flow reduction lasts a minimum of 10 seconds
- there is an associated 4% fall in SaO_2 or a cortical arousal within a 20 second lag time

As with the desaturation data, the apnoea index, hypopnoea index and apnoea hypopnoea index (the sum of the apnoea index and hypopnoea index), are expressed as the mean number of events per hour of sleep.

2.3 HYPOXIC CHALLENGES

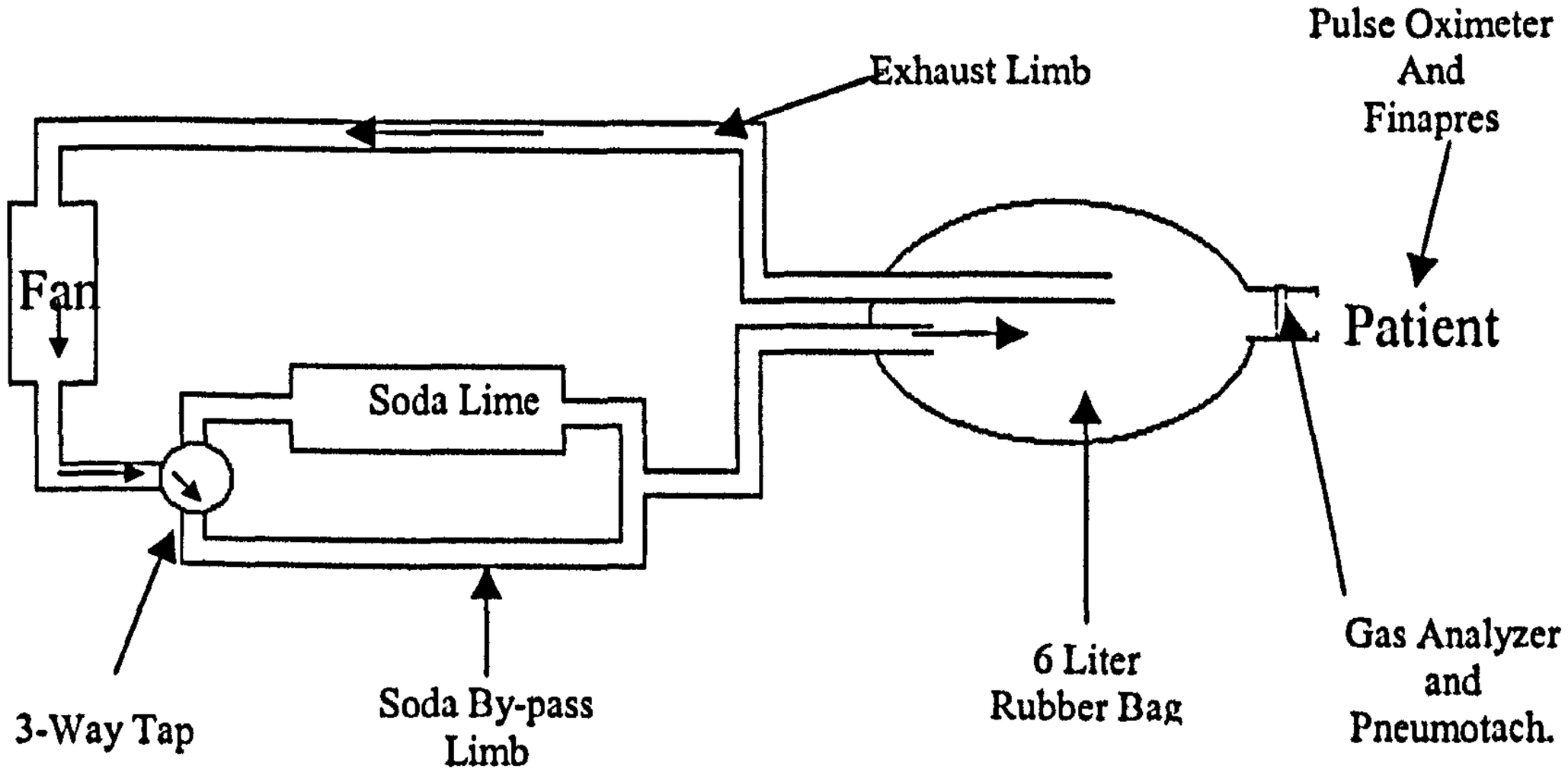
Three different methods of inducing hypoxia are used in this thesis. The rebreathe technique is used for testing healthy subjects and OSAHS patients during wakefulness, as it is the most widely used and simplest method. However, due to the size and weight of this apparatus, it is unsuitable for testing subjects during sleep, and so the smaller light weight 'forced end-tidal' apparatus is used for testing healthy subjects in stable NREM sleep. Patients with OSAHS need constant positive airway pressure (CPAP) to abolish airway obstruction, snoring and desaturations while their hypoxic responses are assessed during NREM sleep. Thus a method of inducing hypoxia and hypercapnia under CPAP conditions is also employed. The next part of this chapter details these three methods.

2.3.1 The Closed Circuit Rebreathe Technique

Apparatus

As discussed in chapter one, this method is used to evaluate ventilatory responses to changing blood gas tensions, and in our studies, the parallel cardiovascular changes. This hypoxic rebreathe apparatus and protocol are similar to that described by Rebuck and Campbell (Rebuck and Campbell 1974), but modified to take advantage of more recent technological changes. Figure 2.2 is a diagrammatic representation of the circuit.

Fig 2.2 - The Closed Circuit Rebreathe System



This system employs four main pieces of apparatus: the rebreathing circuit, the gas analyzers and pneumotach, the pulse oximeter, the Finapres blood pressure monitor.

The Rebreathing Circuit.

The circuit has a volume of 7.3 liters. This air is constantly circulated by the CPAP fan, which has an output of 30 liters per minute. When the exhaust limb is disconnected, room air is drawn in by the fan and inflates the 6l rubber bag. The air in the bag passively flows back into the room via the exhaust limb hence the air in the bag is being constantly flushed with room air. This enables us to acclimatize the subjects to instrumentated breathing on the system before we induce hypoxia or hypercapnia. When the exhaust limb is connected to the fan, the air in the closed circuit is constantly circulated. If the three-way tap directs the air through the soda lime chamber, CO_2 is scrubbed from the circuit and normocapnic conditions are maintained. If the three-way tap directs the flow through the soda by-pass limb, the exhaled CO_2 quickly builds up and the $EtCO_2$ is seen to rise rapidly and progressively rise. Using the real time breath-by-breath gas analysis, it is possible to manually maintain stable CO_2 tensions during the test by opening and closing the soda lime chamber. Regardless of whether the air is directed over the soda lime or through the bypass limb, when the circuit is closed progressive hypoxia is induced, the speed of the fall in SaO_2 is dependant on the individual's oxygen consumption. Using this system, with a circulating volume of 7.3 liters, it takes approximately 5 minutes to see a 20% fall in SaO_2.

The gas analyzers and pneumotachograph

The Medgraphics CPX Cardio-Respiratory system was connected between the subject and the 6l bag. It was used for breath-by breath ventilatory cycle and gas analysis. It utilizes:

- a Pitot tube pneumotachograph (Medgraphics®preVent™) which was validated by Porszasz et al in 1994, and meets American Thoracic Society and European Respiratory Society clinical performance standards. The pneumotachograph is calibrated with a 3-liter syringe and has a flow range of +/- 18 liters per second, a resolution of 8.64 ml/second and a dead-space of 20ml.

- real time O_2 analysis, performed by a Zirconia analyzer with a range from 0.01 to 99.99% O_2, a response time of less than 100msec and an accuracy of +/- 0.1%.
- real time CO_2 analysis, performed by an NDIR analyzer with a range from 0 to 10% CO_2, a response time of less than 100msec and an accuracy of +/-0.1%.

The BreezeEx software calculates breath-by-breath measures that include:

- Minute ventilation (V_E (l/min))
- Tidal volume (Vt (L))
- Inspiratory Time (Ti (s))
- Expiratory Time (Te (s))
- Fraction inspired O_2 and CO_2 (FiO_2 and $FiCO_2$ (%))
- Fraction expired O_2 and CO_2 (FeO_2 and $FeCO_2$ (%))
- End-tidal O_2 and CO_2 (EtO_2 and $EtCO_2$ (mmHg))

This breath-by-breath data was saved as a comma-delimited file and analysed using Microsoft Excel.

The Pulse Oximeter

A Datex-Ohmeda 3700 pulse oximeter was used with a finger probe. This is a non-invasive means of determining arterial oxygen saturation, measured photometrically by the absorption of oxyhaemoglobin and deoxyhaemoglobin at selected wavelengths of light. Measurements are confined to the time when blood vessels are distended by the pulse wave to reduce errors associated with the degree of dilation of blood vessels and the amount of blood in the light path (pulse oximetry). The device was set on the fast averaging response mode, which provides the mean SaO_2 from the previous 3-second period as an analogue output signal every second. The pulse oximeter was connected to the Medgraphics CPX system as an analogue external device and calibrated with 0-1volts representing 0-100% SaO_2. The average SaO_2 during each breath was incorporated in the breath-by-breath data files, and exported to, and analysed using Microsoft Excel.

The Finapres blood pressure monitor

An Ohmeda Finapres 2300 digital plethysmograph comprises of an inflatable finger cuff, fitted with a pump, pressure transducer and photoplethysmograph to measure the diameter of the finger, and measures arterial blood pressure in the finger

using the Penaz technique. The technique is based on the concept that if a force applied around an artery is the same as the arterial pressure, there will be no transmural pressure and no change in the size of the artery. Arterial pressure changes occur with each pulse wave associated with cardiac ejection, the Finapres photoplethysmogram detects the change in volume of the finger. Constant adjustments in the pressure of the finger-cuff are made to maintain a constant finger volume; the pressures that are needed to maintain the constant volume, balance the transmural pressure difference and thus are equal to the arterial pressure. The Finapres has a measurement range of 20-260mmHg and a pulse rate measurement of 12-175 beats per minute. An analogue output signal was used to print the real time pressure waveform at rest and during the hypoxic challenges on a Schwartz Picker 1200 pen recorder. A 0-100mmHg signal was also printed as a calibation reference. Beat-by-beat systolic and diastolic blood pressures were measured manually from the printed data by observing the peak and lowest blood pressures. The mean blood pressure is calculated as the diastolic pressure plus a third of the difference between the diastolic and systolic pressures. These data were associated with ventilation and pulse oximetry data by triggering a time signal indicator on the blood pressure recorder as the breath-by-breath data acquisition was started. The mean systolic, diastolic and mean blood pressures were calculated for each 10 second period and entered into the Excel spreadsheet containing the ventilation and oximetry data.

The Closed Circuit Rebreathe Protocol.

Subjects were asked to abstain from alcohol, caffeine and exercise for four hours prior to testing. They were sat in a comfortable chair facing away from the recording and rebreathing apparatus, and fitted with the finger oximeter probe, finger BP monitor and nose clips. Care was taken to ensure the arm with the blood pressure monitor monitor and oximeter remained rested on the arm of the chair and did not move during the rest period or the hypoxic challenge. Subjects breathed through the mouthpiece attached to the open circuit. Resting data was acquired for 4 to 6 minutes or until a steady baseline ventilation was observed. The circuit was then closed and the hypoxic challenge commenced. The challenges were terminated when the SaO_2 falls below 80% or conditions could no longer be tolerated. Subjects

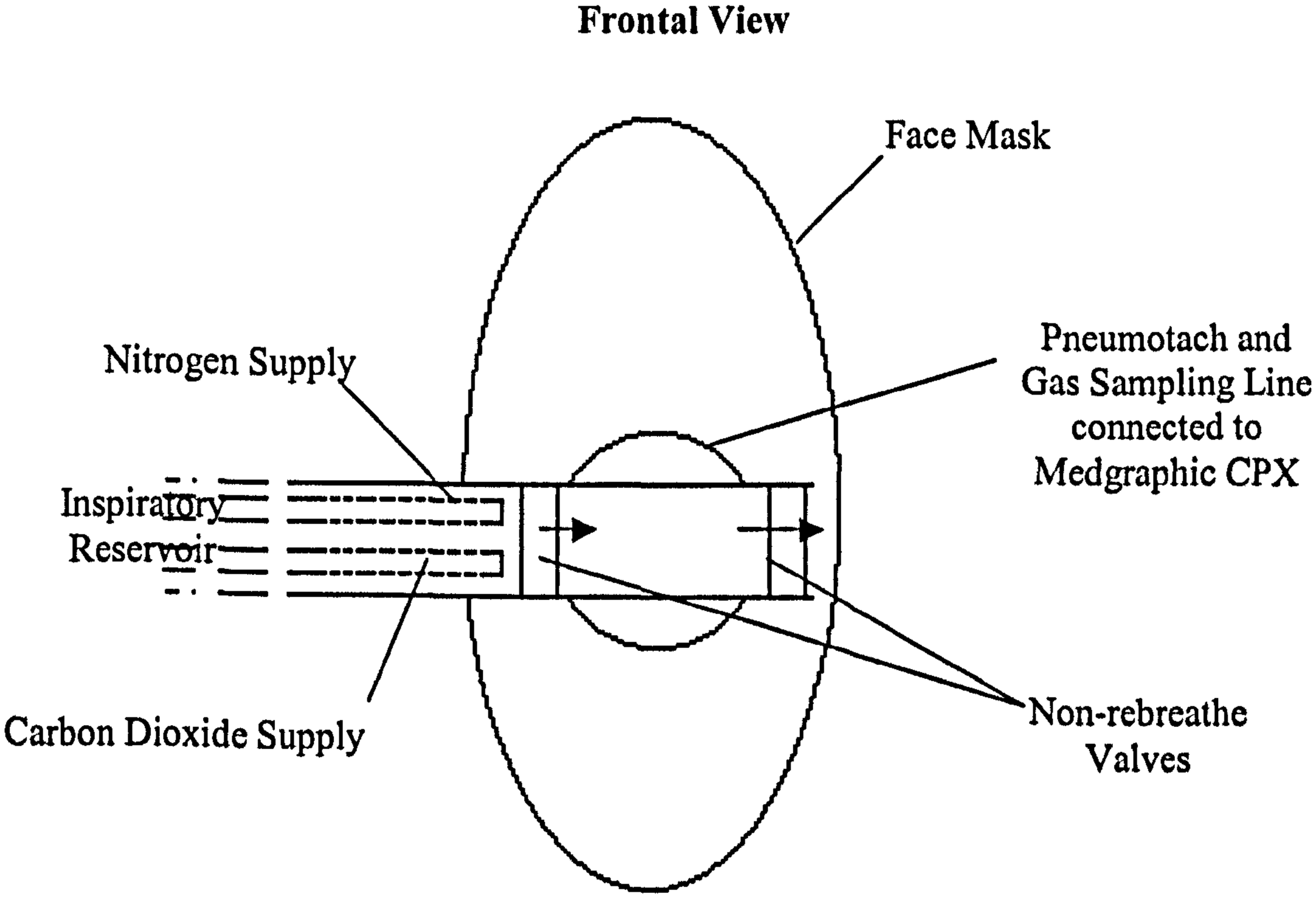
had progressive hypoxia induced under both isocapnic normocapnic and isocapnic hypercapnic conditions. These were performed in a random order, with a 40-minute break between tests.

2.4 THE FORCED END-TIDAL HYPOXIC CHALLENGE

2.4.1 Apparatus

This technique induces hypercapnia and/or hypoxia using a light weight full face mask and manually controlled inspiratory gas mixtures. Fig 2.3 is a diagrammatical representation of the apparatus used to assess ventilatory and cardiovascular responses with this method.

Fig 2.3 - The forced end-tidal technique apparatus.



This utilizes a lightweight non-rebreathing system that can be worn for several hours by subjects who are awake or asleep. The mask is connected to a T piece and two unidirectional valves which only permit inspiration from the inspiratory reservoir and expiration into the local environment. The inspiratory reservoir is a piece of tubing with a diameter of 23mm and a total volume of 8.30 liters, one end is connected to the inspiratory valve on the patient interface, the other end is left open to the atmosphere. Within the whole length of this reservoir tubing are two finer tubes, with a mean diameter of 6 mm, the end that terminates in the reservoir tube is sealed, the other end is connected to an N_2 or CO_2 cylinder. These N_2 and CO_2 supply tubes are perforated to allow the gas in them to diffuse evenly into the reservoir tube. CO_2 can be manually titrated into the reservoir to produce hypercapnic conditions, N_2 can be titrated in to induce hypoxia, which is done by adjusting the flow regulator on the cylinder and observing the real-time inspiratory gas analysis.

In addition to the mask and gas mixture controls, subjects are connected to the Breath-by-breath ventilation analysis equipment, Finapres 2300 blood pressure monitor and an Ohmeda 3700 pulse oximeter which are described earlier in this chapter.

2.4.2 Protocol

This system was used on subjects during wakefulness and sleep. Subjects abstained from alcohol, caffeine and exercise for 4 hours prior to testing. The tight fitting mask, Finapres blood pressure monitor and pulse oximeter are fitted to the subjects when they were ready to sleep with PSG electrodes already attached. Subjects were supine with all monitoring being done from an adjacent room. They breathed room air for 4-6 minutes or until a steady baseline ventilation was observed. If hypercapnic hypoxia was to be induced, the elevated CO_2 environment was created and maintained for 30-60 seconds before the progressive hypoxia was induced. The hypoxic conditions were then created with the intention of reducing the SaO_2 to 80% over a 5-6 minute time period. Both normocapnic and hypercapnic hypoxic responses were assessed in a random order with a twenty minute break between the two. The challenges were conducted during EEG confirmed wakefulness and stable stage two sleep. The challenges were terminated when the SaO_2 fell below 80%, subjects moved or an EEG arousal was detected. Results were discarded if there was

an electrocortical arousal or any movement in the arm with the blood pressure monitored attached. Data was analysed in the same method as described for the closed circuit rebreathe procedure.

2.5 THE CPAP HYPOXIC CHALLENGE.

2.5.1 Apparatus

It is not possible to assess the hypoxic responses in OSAHS patients when they are asleep due to the airway obstruction, disordered breathing and arousal responses. However, it is possible to assess the hypoxic responses if a patient has sufficient CPAP to abolish airway obstruction, snoring and spontaneous desaturations. The Medgraphics CPX pneumotachograph, described earlier, cannot function under CPAP conditions thus an alternative device for breath –by-breath gas analysis was needed.

The Sullivan V CPAP is a flow generation device that can produce a range of flows to create mask pressures between 4 and 20 cmH_2O. These devices are manually set at the pressure required to abolish 95% of the patients obstructive events. The inspired gas concentrations can be adjusted by titrating N_2 or CO_2 into the air inlet of the CPAP device.

The Datex Normocap 200 measures inspired and end-tidal concentrations of CO_2 and O_2. Its measurement range is 0-10% CO_2 and 0-100% O_2 with measurement rise times of <280ms and <450ms respectively. The flow generated by a CPAP device rapidly mixes with the exhaled gas in the mask, and so an accurate end-tidal concentration cannot be measured. However, the device can be attached, via a gas sample line, to a CPAP mask to monitor the inspired gas concentrations. The analogue output from this device was used as an extra channel on the standard PSG montage from which the real time inspired gas tensions can be observed or analysed at a later time.

2.5.2 CPAP Hypoxic Challenge Protocol

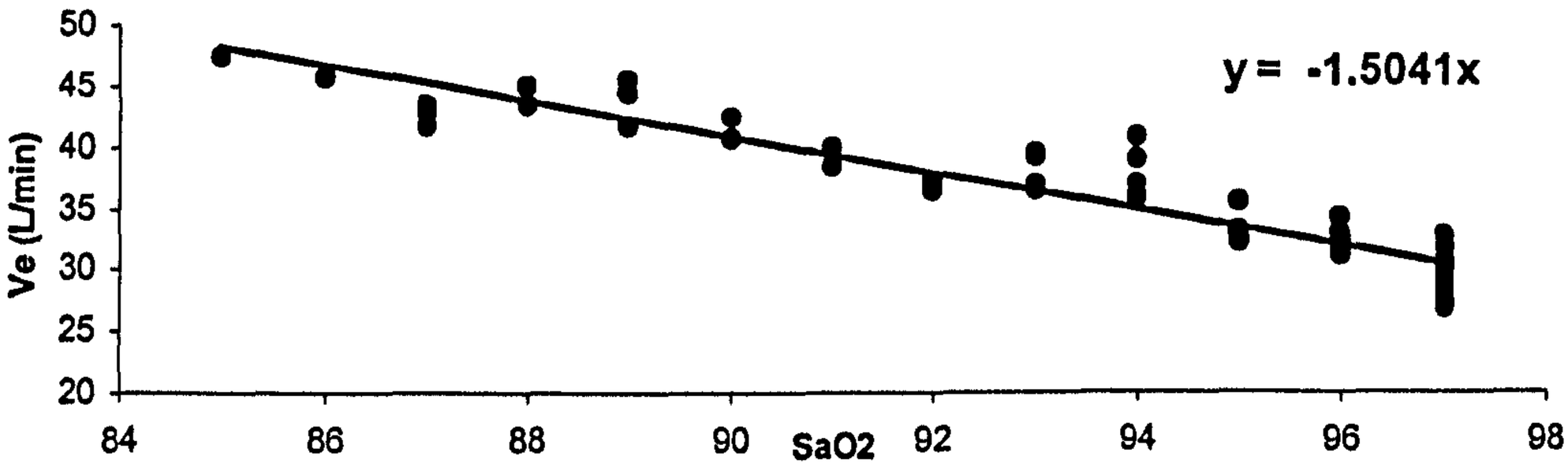
Patients were fitted with a full face mask connected to a CPAP device set at the pressure required to abolish 95% of their obstructive events, and allowed to sleep. The hypoxic challenges were performed during EEG confirmed stage two sleep. If hypercapnic hypoxia was to be induced, the CO_2 was titrated into the device and maintained for 30-60 seconds before the progressive hypoxia was induced. The amount of CO_2 required to increase the end-tidal CO_2 by 5-6 mmHg was estimated from the results obtained during wakefulness. The nitrogen flow was then progressively increased with the intention of reducing the SaO_2 to 80% over a 5-6 minute time period. The challenges were terminated when the SaO_2 fell below 80%, subjects moved or an EEG arousal was detected. Results were discarded if there was an electrocortical arousal or any movement in the arm with the blood pressure monitored attached. The influence of: the apparatus used to measure sleep, the CPAP, to which patients were unfamiliar, and the effects of hypoxia and hypercapnia all combined to increase the arousability of these patients. The results presented in this thesis were obtained from experimenting on a group of patients, some of whom had no valid results due to their inability to sleep with such instrumented conditions, and some were aroused from sleep before their hypoxic responses were properly assessed. This unintentional selection bias will affect the results. Both normocapnic and hypercapnic hypoxic responses were assessed in a random order with a twenty minute break between the two.

HYPOXIC CHALLENGE DATA ANALYSIS

The **acute hypoxic ventilatory response** (AHVR) was calculated using the slope of the increase in minute ventilation during a hypoxic challenge, and expressed as the increase in ventilation per percent fall in SaO_2 (l/min/SaO_2). This is a normalized measure commonly used when expressing responses to hypoxia, (Rebuck and Campbell 1974) which can also be applied to heart rate and blood pressure responses. Fig 2.4 is an example of the ventilatory response to hypoxia. The graph is plotted so the X axis demonstrates the SaO_2, and the y-axis shows the minute ventilation calculated from each breath at each level of SaO_2. The linear regression

shows the AHVR, as the increase in ventilation in response to the fall in SaO_2. In this example the AHVR is an increase in minute ventilation of 1.5 litres/min for each one percent fall in SaO_2.

Fig 2.4 - A Representative Example of an Acute Hypoxic Ventilatory Response



The heart rate and blood pressure responses to hypoxia are measured by plotting them on the y-axis.

This thesis investigates the effects of CO_2 on the responses to hypoxia. Therefore a similar hypoxic stimulus is needed under normocapnic and hypercapnic conditions. The data for each individual were cropped so the lowest SaO_2 reached was the same for both hypoxic challenges.

Chapter Three

Polysomnographic predictors of daytime sleepiness

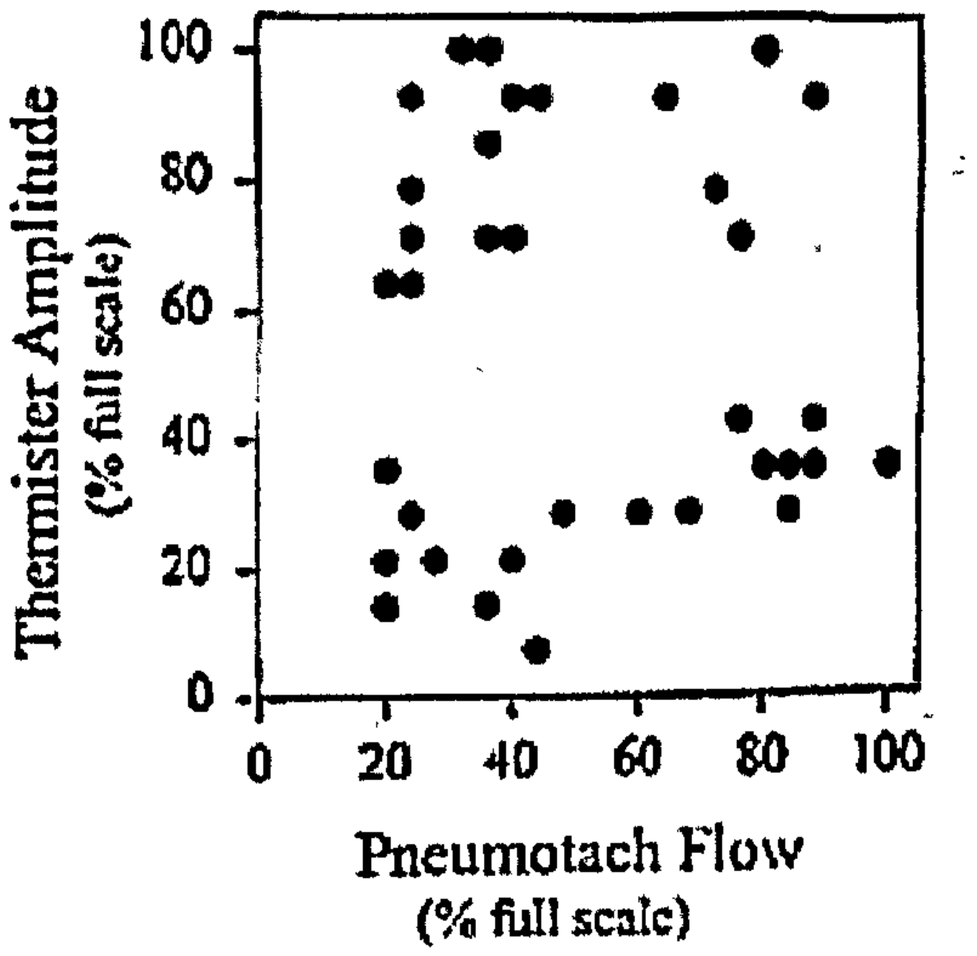
3.1 INTRODUCTION

Respiratory disturbances during sleep define the sleep apnoea and hypopnoea syndrome, but as with any disorder, there must be a threshold value that defines its presence, and a scale to measure disease severity. Since the first papers defined sleep apnoea, the scale has been the number of respiratory disturbances per hour of sleep, initially the apnoea index (Guilleminault *et al* 1976) and more recently the apnoea hypopnoea index (Gould *et al* 1988). However, defining and measuring these events, and defining the threshold of abnormality remains debatable.

Quantifying respiratory events is problematic as there are no guidelines about the use of instrumentation to detect airflow, most of these appliances are not quantitative and potentially do not measure true changes in ventilation. Thus the classification of respiratory disturbance varies enormously between sleep centres (Moser *et al* 1994). As noted previously thermistors are thermosensory devices placed at the nares and mouth that measure the increase in temperature with exhaled airflow and cooling as room air is inhaled. Figure 3.1 demonstrates the poor relationship between this measure and flow measured quantitatively using a pneumotachograph.

Recent work by Montserrat et al (Montserrat et al 1997) has showed that the square root of the pressure signal obtained from cannulae in the nares, correlates well with the flow signal from a pneumotachograph and would be an appropriate device for apnoea and hypopnoea detection. However this technology is yet to be made widely available in commercial polysonographic systems.

Fig 3.1 – The relationship between breath amplitude measured by pneumotachograph and thermistor (Redline+Saunders 1997)



This figure demonstrates no relationship between the thermistor signal (y axis) and flow measured using a pneumotachograph (x axis).

Even if flow quantification instruments were standardized, the definitions of apnoea and hypopnoea, and the threshold for abnormality still remain unclear. Since the publication of the paper by Gould et al in 1988, describing hypopnoeas, there have been many more publications redefining the hypopnoea and sleep disordered breathing. The ASDA consensus report defines

- an apnoea as a 10 second or greater cessation of ventilation with a minimum 4% fall in SaO_2
- a hypopnoea as a 50% reduction in ventilation, lasting for a minimum of ten seconds and having an associated 2% desaturation or cortical arousal.

These have been widely accepted as the standard respiratory event criteria. To be diagnosed with OSAHS patients must experience symptoms of excessive daytime sleepiness as well as one or more other symptom associated with OSAHS, such as snoring or morning headache. However, there is continuing debate about how many respiratory events per hour is clinically significant, as there is a poor correlation between AHI and daytime sleepiness measures such as the maintenance of wakefulness test (MWT) (Poceta *et al* 1992) or Epworth sleepiness score

(ESS)(Johns 1993). Some patients have a very high AHI but remain asymptomatic, while others may have no identified sleep apnoea but score highly in terms of symptoms and EDS measures.

Redline et al (Redline *et al* 2000) looked at the effects of varying approaches to identifying respiratory disturbances on the AHI. They looked at the inter-correlations of AHI scored using eleven different criteria. All changes in flow lasted a minimum of 10 seconds but the associated desaturation and arousal criteria were altered. The highest correlations were seen with AHI definitions that required an associated desaturation. Similar results were published by Tsai et al (Tsai *et al* 1999), who looked at the intercorrelation of AHI when only the hypopnoea definition was varied. They scored a hypopnoea if there was a 10 second or greater reduction in flow with:

- a 4% desaturation,
- a 4%desaturation or EEG arousal,
- an EEG arousal.

They demonstrated a strong correlation between the AHIs scored using desaturation criteria. These data demonstrate that most respiratory events are likely to be associated with desaturations and are less well associated with arousals.

Daytime sleepiness is the symptom that most impairs quality of life in OSAHS. Sleep disruption and deprivation reduce attention span, cognitive function and increases the risk of being involved in a road traffic accident (Strohl and Redline 1996). Hosselet *et al* varied the definition of sleep disordered breathing to identify the optimal respiratory metric that objectively correlates to symptoms of EDS. They used the conventional apnoea criteria, scored hypopnoeas with and without desaturations and arousals, and scored flow limitation events which are identified from a plateau in the nasal cannulae pressure signal. All events lasted a minimum of ten seconds. They demonstrated that, using all the respiratory event indices derived from their analyses, an RDI of 18 events per hour, when including all forms of respiratory disturbance, was the best discriminant for absence or presence of EDS associated with sleep disordered breathing (Hosselet *et al* 2001).

3.2 STUDY AIMS

This study was undertaken to explore the potential of altering the AHI criteria, using standard methodology, to improve the correlation between disease severity and EDS. As most studies have demonstrated respiratory events are strongly associated with desaturations, and most studies have inherently accepted the 10-second minimum event duration criteria, this study will investigate the effects of altering the minimum duration criteria, and the desaturation criteria, on the relationship between AHI and ESS. Reducing the minimum event criteria should incorporate shorter events which are disregarded by the 10 second criteria and which may be responsible for arousal and sleep fragmentation. Increasing the minimum event duration should eliminate shorter events and score only the more severe events where greater falls in SaO_2 occur with potentially larger arousal responses. We have assessed the effect of adjusting the desaturation criterion, which allows us to score events where less marked changes in blood gas tensions occur but which may still cause arousal from sleep.

We hypothesized that:

- Reducing the minimum event duration to less than 10 would increase the number of events scored.
- Increasing the minimum event duration to greater than 10 seconds decrease the number of respiratory events scored.
- Reducing the desaturation requirement would increase the number of respiratory events scored.
- Events other than those identified by the ASDA criteria also have the potential to cause arousals and increase sleep fragmentation, which would see an increase in EDS. Scoring these milder events by reducing the duration and desaturation requirements should improve the correlation between AHI and ESS.
- Increasing the minimum event duration, and hence only scoring more severe events would worsen the relationship between the AHI and ESS.

3.3 STUDY POPULATION

This retrospective study comprised of 47 apnoeic patients (7 female), who had symptoms indicative of OSAHS and had been referred for PSG by the physicians in the University Hospital Aintree outpatient sleep clinics. Patients attended the sleep laboratory for a single night and were diagnosed using a standard PSG montage, Rechtschaffen and Kales sleep staging techniques and the ASDA criteria for scoring arousals and respiratory events. Patients were chosen from the records of all subjects seen in the sleep lab over the previous 6 years, and randomly selected to obtain a population with a wide distribution of AHI, ranging from mild to severe and with a range of ages and body masses. The inclusion criteria required subjects to be aged over 18 years, have an AHI=>10, and a minimum of 4 hours of total sleep time during the diagnostic study.

3.4 METHODS

3.4.1 Polysomnography

After referral to the sleep laboratory, patients attended for a single night diagnostic PSG. Epworth sleepiness scores were completed on the night of the study. PSG was performed using the Jaeger Sleeplab 1000p a standard montage detailed in the methodology chapter (page 48):

- **Sleep scoring** was performed using the EEG, EOG and EMG channels in the Jaeger computer aided mode
- **Arousals** were scored visually according to the ASDA guidelines and automatically by the PSG.

Further analyses of respiratory and desaturation data were only performed if there was a minimum of four hours total sleep time. Pre-determined definitions used in the diagnostic night study were :

- **Desaturations** were scored if a 4% or greater reduction in SaO_2 was seen to occur over 10 seconds or longer.
- **Apnoeas** were scored if the nasoral thermistor flow signal fell below 12% of baseline for a minimum of 10 seconds and if a 4% desaturation occurred within 20 seconds of the apnoea termination.
- **Hypopnoeas** were scored if the nasoral thermistor flow signal fell below 50% of the baseline for a minimum of 10 seconds with an associated 4% desaturation or EEG arousal occurred with 20 seconds of the event.
- **AHI** was defined as the total number of apnoeas and hypopnoeas divided by the total sleep time.

Respiratory Event Analysis

After the initial analysis and diagnosis using the above criteria, the respiratory data were reanalysed a total of 16 times. The AHI was calculated when the:

- **Minimum event duration** for respiratory event inclusion was adjusted from the standard 10 seconds to 6, 8, 10, 12, 15, 20, 25 and 30 seconds.
- **Desaturation requirement** was varied with each of these respiratory event durations, events requiring a fall of 2% SaO_2 as well as the usual 4%, hence giving us 2 analyses for each of the 8 minimum event durations.

This resulted in 16 analyses of respiratory variables per patient. The new criteria included events ranging from the mildest hypopnoeas with a 50% reduction in flow for only 6 seconds and with a 2% desaturation or an arousal, to the most severe apnoea, cessation of airflow lasting a minimum of 30 seconds with a 4% or greater desaturation.

3.4.2 Data Analysis

The study population characteristics defined by conventional criteria, and the effect of changing duration and desaturation criteria on the AI, HI, and AHI are presented as the group mean and standard deviation unless otherwise stated. These data were analyzed to assess the inter-relationships between these modified indices of disease severity and their relationship with ESS. Correlation co-efficients (r) were calculated and the statistical significance of these relationships are presented. Multiple regression analysis was performed to examine the multifactoral relationship between EEG variables, respiratory events and daytime sleepiness. Statistical significance was accepted as a p value equal to or less than 0.05.

3.5 RESULTS

3.5.1 Study Population Characteristics

Table 3.1 presents the group mean data for the 47 (7 female) OSAHS patients. The range and standard deviations show there was a wide distribution of ages, disease severity, subjective sleepiness and body masses.

Table 3.1 – Study Population Charateristics

	mean	SD	SE	Min	Max
Age	54.3	10.4	1.64	29.0	72.0
BMI	33.6	5.6	0.88	22.5	45.0
ESS	13.0	5.5	0.80	2.0	24.0
AHI	39.7	24.6	3.59	10	92

AHI determined using the ADSA definition (see page 54 for details).

3.5.2 Polysomnographic Characteristics of the Study Population

EEG data were analysed for diagnostic purposes and not reanalysed as respiratory event criteria were altered. Data from the poysomnographic EEG analyses are presented in Table 3.2.

Table 3.2 - Sleep and Arousal Data

	Mean	SD	Se	Min	Max
Sleep Onset (mins)	4.39	5.89	0.86	0	16.5
Total Sleep Time (Hours)	5.84	0.69	0.07	4.6	7.6
Arousal Index (events per hour)	53.9	17	2.49	25.5	90.7

Patients had a rapid sleep onset, with a group mean of only 4.4 minutes. All patients had a total sleep time in excess of the minimum 4 hours required for inclusion in the study (mean 5.8 hrs). However, their sleep was very fragmented, the mean 54 arousals per hour indicating significant sleep disruption throughout the night.

3.5.3 Oxygen Desaturation Data

Oxygen saturation data was analysed to identify dips of 4% or greater.. The group mean data is presented in Table 3.3.

Table 3.3 - Oxygen Desaturation Data

	Group mean	SD	SE	Min	Max
4% Desat Index (Dips per Hour)	45	28.4	4.14	4	95
Mean Low SaO_2	84.3	5	0.73	90	70
Mean Duration (sec)	37.5	14.7	2.14	15	90

The group had a mean 45 dips in SaO_2 (4% or greater) per hour of sleep. There was a wide amount of variability between the patients, the range encompassing desaturation indices from 4 to 95. The mean desaturation reached was 84% and the mean duration of a desaturation was 38 seconds.

3.5.4 Standard Respiratory Event Data

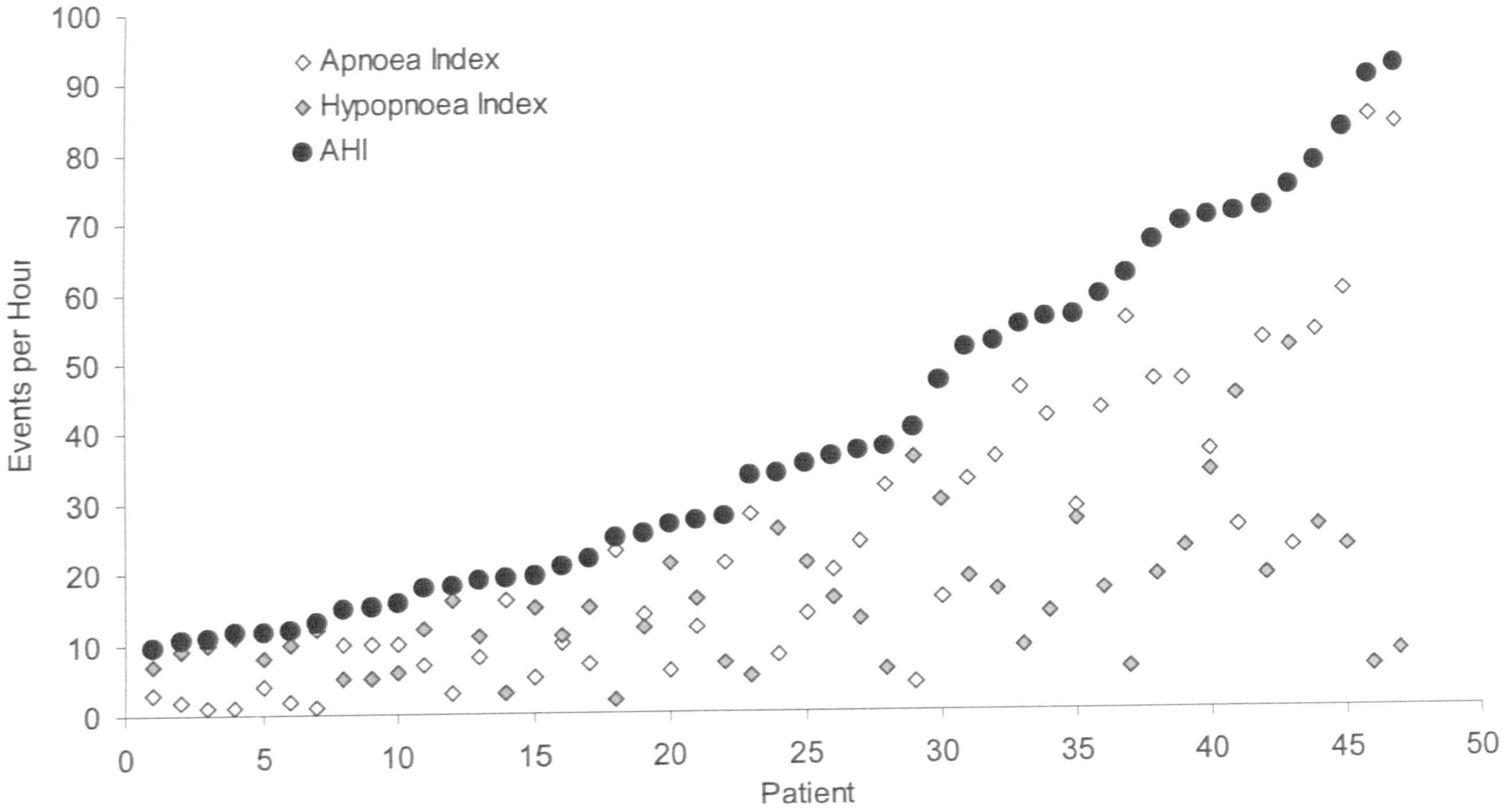
AHI was scored according to the ASDA criteria for diagnostic purposes.

Table 3.4 - Group mean apnoea and hypopnoea indices

	Group mean	SD	SE	Min	Max
Apnoea Index	23.9	21.6	3.15	1	85
Hypopnoea Index	15.7	10.7	1.56	2	52
AHI	39.7	24.6	3.59	10	92

Table 3.4 demonstrates that our chosen population had a range of AHIs from 10 to 92 events per hour. This patient group contains both patients with an AHI comprising primarily of apnoeas as well as a number of patients who experience a majority of hypopnoeas. This is demonstrated in Fig 3.2, which shows individuals AHIs expressed as different ratios of apnoea indices and hypopnoea indices.

Fig 3.2 - Distribution of respiratory events in the study population.

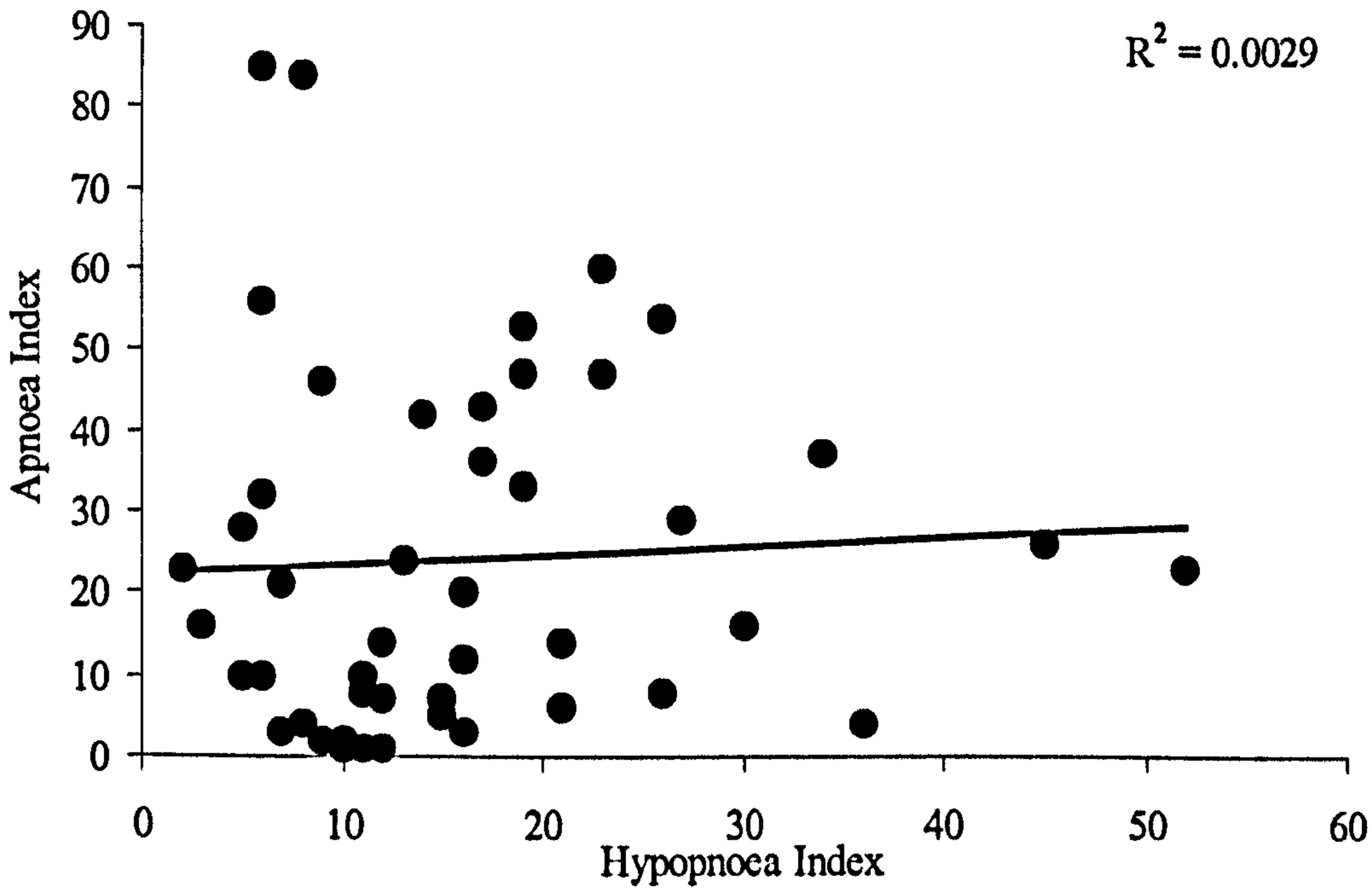


3.5.5 The Relationships Between Standard Respiratory Indices.

The relationship between the apnoea and hypopnoea indices.

Fig 3.3 shows that within this group of patients there was no relationship between the apnoea and hypopnoea indices; some patients experienced many apnoeas and few hypopnoeas, and vice-versa, with a widespread scatter between these two extremes and no significant correlation between the two types of events.

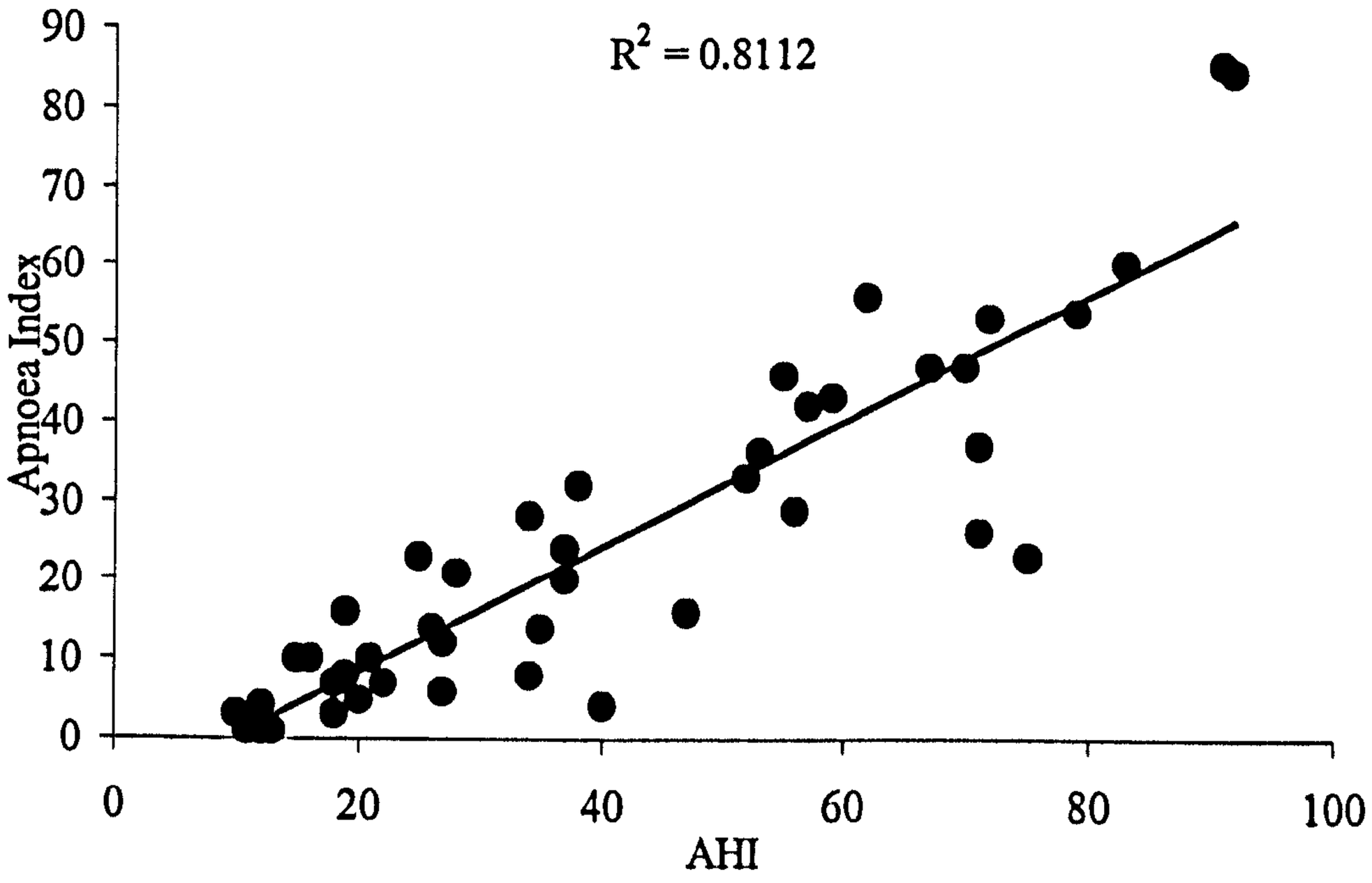
Fig 3.3 - The relationship between the apnoea and hypopnoea indices.



3.5.6 The Relationship Between The Apnoea Index And AHI

Fig 3.4 demonstrates a strong relationship between the apnoea indices and AHI ($p<0.001$). Unsurprisingly, this indicates that the apnoea index strongly influences the apnoea hypopnoea index; individuals who have a high apnoea index are highly likely to have a high AHI.

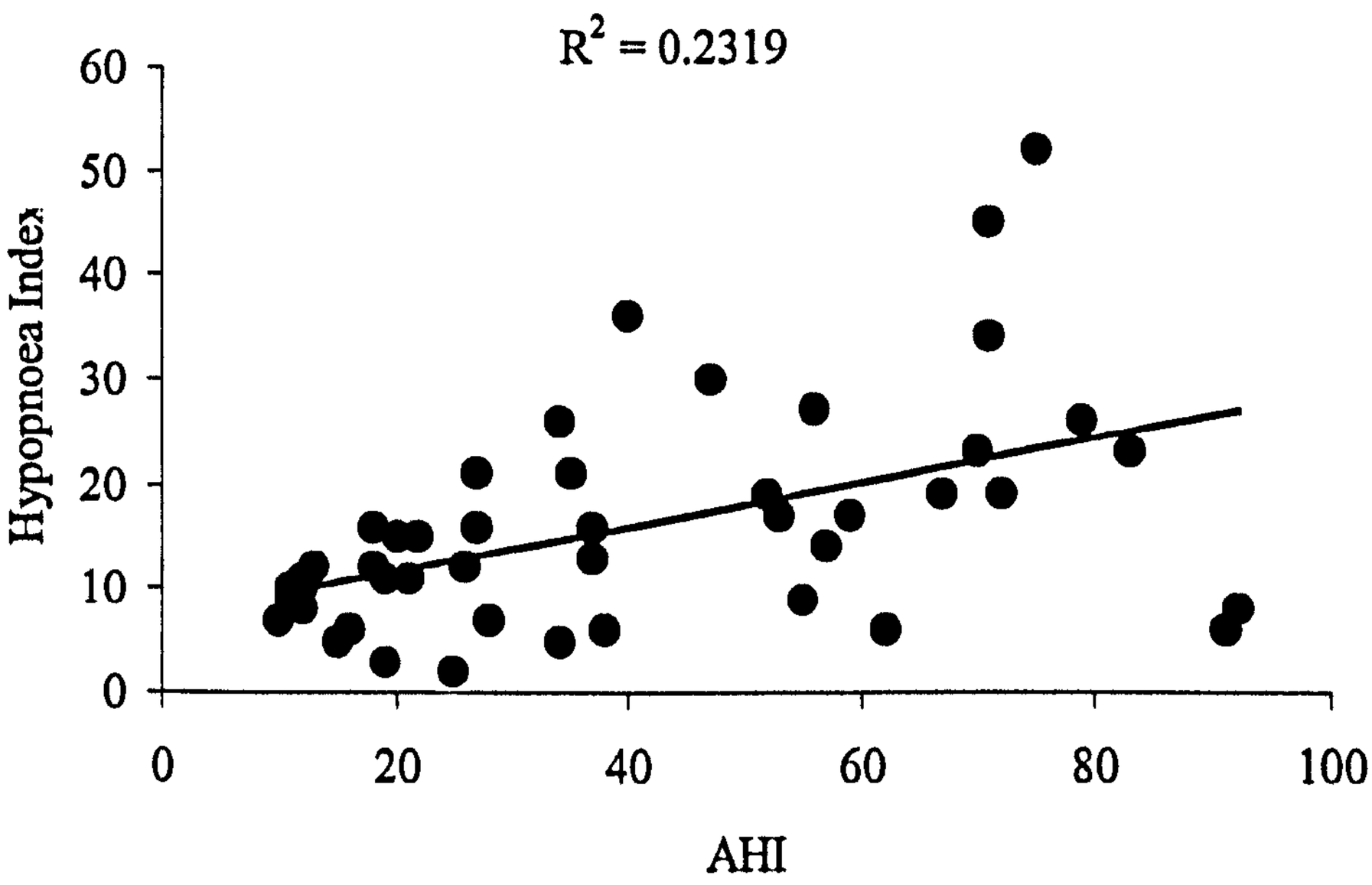
Fig 3.4 - The relationship between the apnoea indices and AHI



The relationship between the hypopnoea index and AHI

Fig 3.5 demonstrates a strong relationship between the hypopnoea index and the AHI ($p < 0.001$). This relationship was weaker than that between the apnoea index and AHI, however the correlation was highly statistically significant and also indicates that patients who have a high hypopnoea index tend to have a high AHI aswell.

Fig 3.5 - The relationship between the hypopnoea indices and AHI



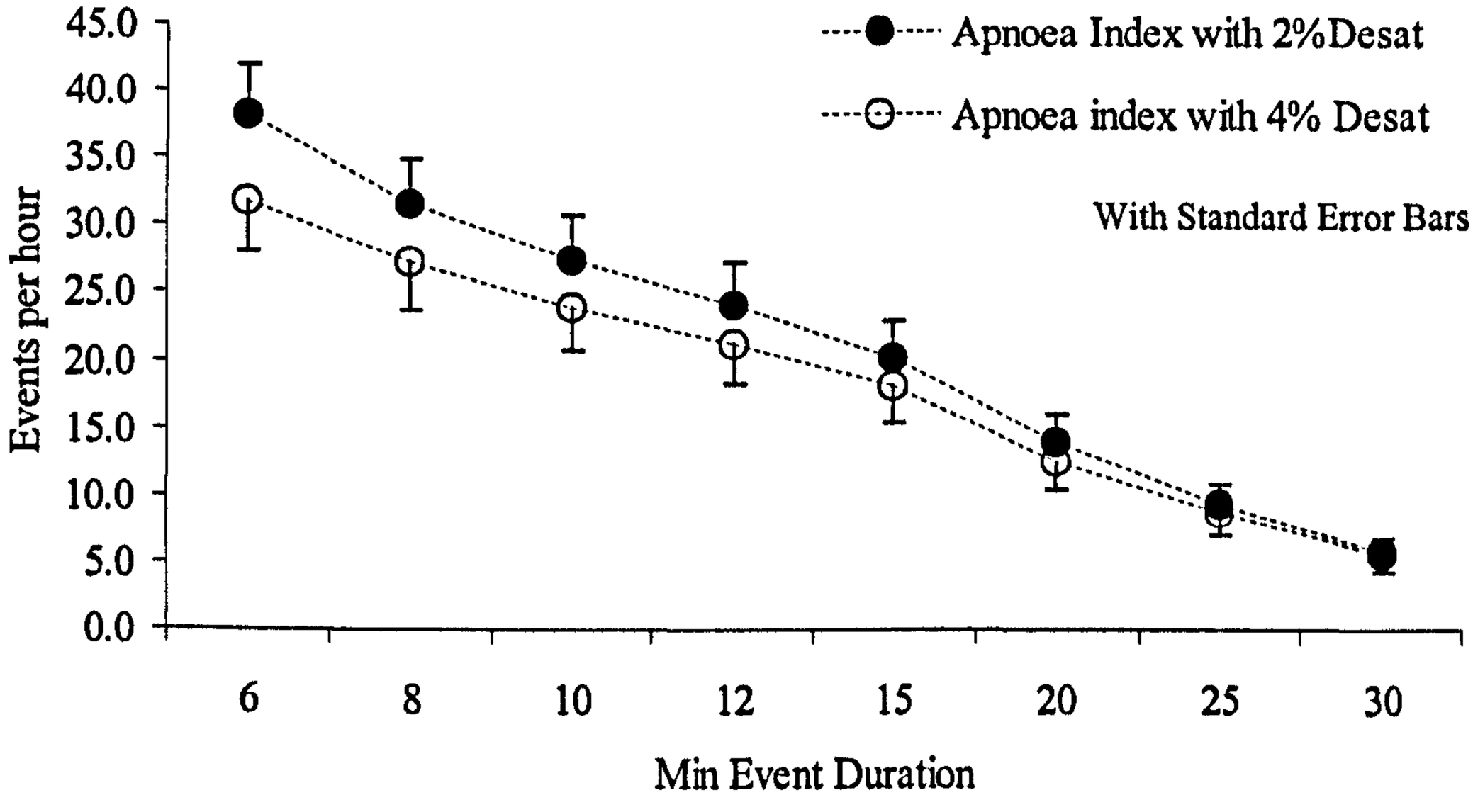
The effects of varying the respiratory event criteria

In this analysis the apnoea index and hypopnoeas index were considered separately as well as the combined apnoea-hypopnoea index to assess their relative diagnostic importance. Varying the respiratory event criteria produced different changes in the apnoea index, hypopnoea index and AHI

The Apnoea Index

The effects of varying the duration and desaturation requirements on the apnoea index are illustrated in Fig 3.6 and table 3.5.

Fig 3.6 - The Apnoea Indices with altered respiratory event criteria.



These data demonstrate that as the minimum event criteria was reduced from 10 seconds to 8 and 6, more apnoeas were scored. Conversely, as the minimum duration requirement increased, an inverse linear relationship was seen between the minimum event duration requirement and the number of apnoeas scored.

Table 3.5 - Group Mean Apnoea Index

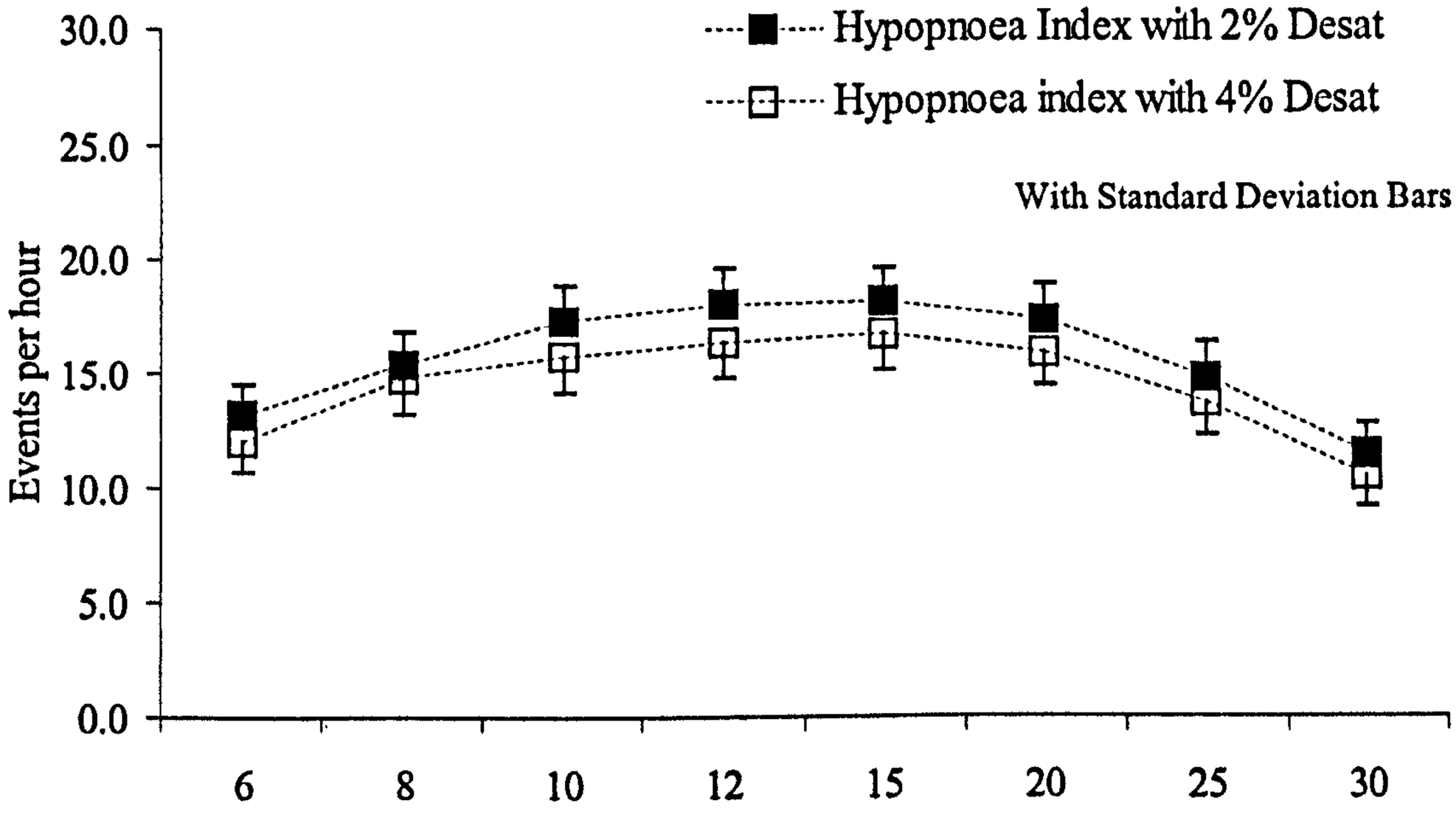
Min Event Duration (sec)	6	8	10	12	15	20	25	30
AI with 2% Desat (SD)	38.2 (25.2)	31.6 (23.4)	27.4 (22.0)	24.1 (20.5)	20.0 (18.6)	13.8 (14.5)	9.3 (10.8)	5.8 (7.87)
AI with 4% Desat (SD)	31.7 (25.2)	27.1 (22.9)	23.9 (21.6)	21.3 (20.3)	18.0 (18.4)	12.4 (14.0)	8.7 (10.8)	5.6 (7.9)

Reducing the desaturation requirement allowed more short apnoeas to be scored, but this effect diminished as the duration requirement was increased and only the longer more severe apnoeas were scored.

The Hypopnoea Index

The changes in the number of hypopnoeas scored when the respiratory event criteria were varied are shown in Fig 3.7 and table 3.6.

Fig 3.7 - The Hypopnoea Indices with altered respiratory event criteria.



As the event duration requirement was reduced below 10 seconds, marginally fewer hypopnoeas were scored. There was also a small fall in the number of hypopnoeas scored as the minimum event duration requirement was increased beyond 15 seconds. There are more hypopnoeas scored when the desaturation requirement was reduced, however the effect of this was small and increased the mean hypopnoea index by just one event per hour regardless of the event duration.

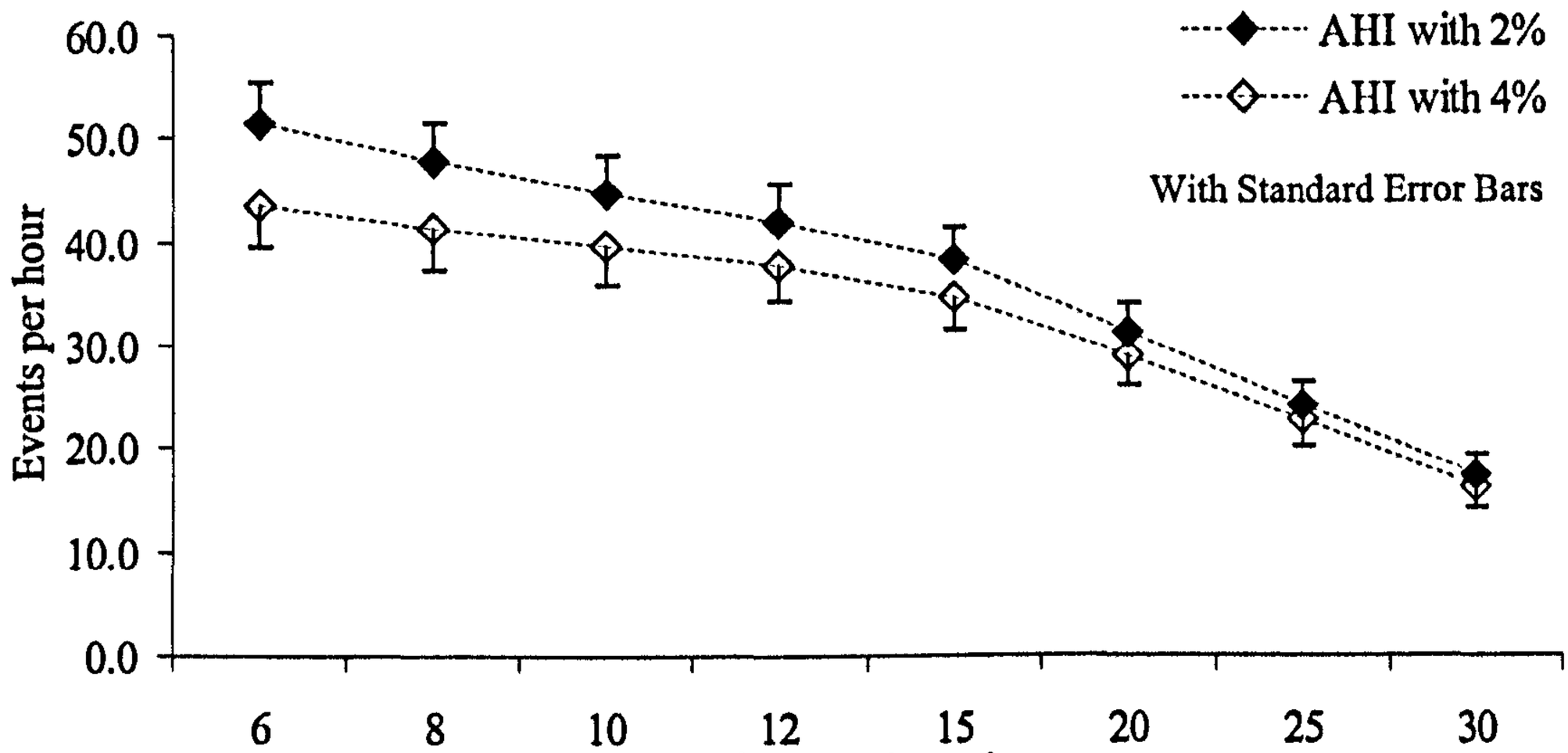
Table 3.6 - Group Mean Hypopnoea Index

Min Event Duration (sec)	6	8	10	12	15	20	25	30
HI with 2% Desat (SD)	13.2 (8.8)	15.4 (9.5)	17.3 (10.8)	18.0 (10.8)	18.1 (10.5)	17.3 (10.3)	14.8 (10.3)	11.4 (9.1)
HI with 4% Desat(SD)	12.0 (8.8)	14.0 (10.4)	15.8 (10.7)	16.3 (10.9)	16.6 (10.6)	15.9 (10.4)	13.7 (10.2)	10.5 (8.8)

The Apnoea Hypopnoea Index

Fig 3.shows that when the apnoea and hypopnoea indices were combined there was an overall increase seen in the number of events scored per hour as the event duration was reduced from 10 to 8 and 6 seconds, and a reduction in the number of events scored when the minimum event duration was extended. When the desaturation requirement was reduced from 4% to 2% more short events were scored

Fig 3.8 - The AHI with altered respiratory event criteria.



These data demonstrate the change in AHI when the minimum event duration is increased from 6 seconds through to 30; there is a linear reduction in the number of events scored. Reducing the desaturation requirement sees a greater number of short events scored, however as the duration of the events increase the desaturation requirement has a diminishing effect on the AHI.

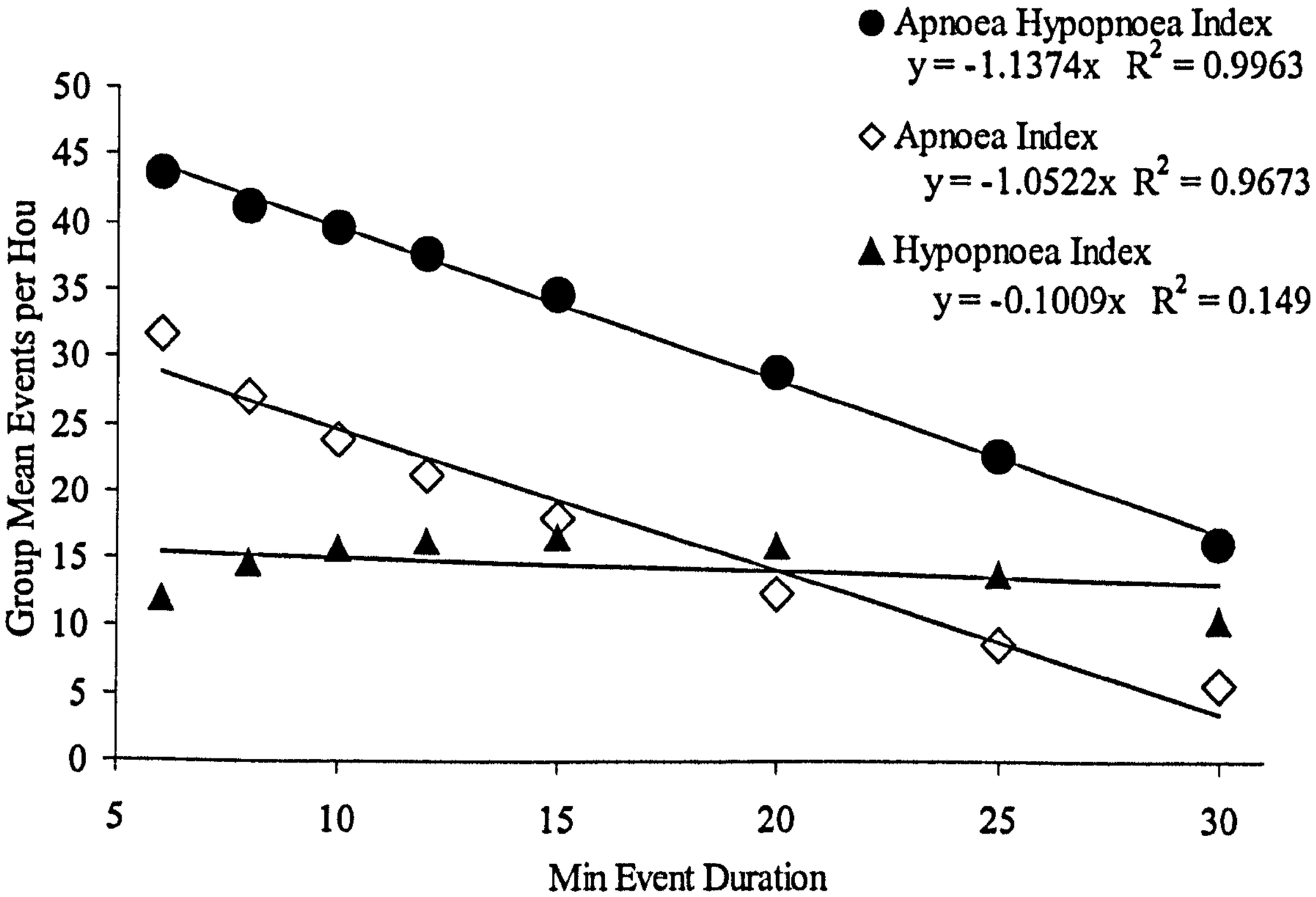
Table 3.7 - Group Mean Apnoea-Hypopnoea Index

Min Event Duration (sec)	6	8	10	12	15	20	25	30
AHI with 2% Desat (SD)	51.5 (27.0)	47.0 (25.7)	44.7 (24.5)	42.0 (24.0)	38.1 (22.8)	31.0 (19.7)	24.0 (16.9)	17.2 (13.7)
AHI with 4% Desat (SD)	43.6 (27.2)	41.2 (25.3)	39.7 (24.6)	37.7 (23.9)	34.7 (22.7)	28.8 (19.6)	22.6 (16.7)	16.0 (13.4)

The relationship between respiratory event indices and the minimum event duration

Fig 3.9 illustrates that there was a strong inverse linear relationship between the minimum event duration and the apnoea and apnoea-hypopnoea indices. However, the minimum event duration had little effect on the number of hypopnoeas scored.

Fig 3.9 - The relationship between the number of respiratory events scored and the minimum event duration



The effect of altering the respiratory event criteria on individuals AHI

Figures 3.9a and 3.9b shows that as the minimum duration and desaturation criteria were varied, a wide distribution of AHI remained throughout the population. There were no subgroups who experience more modest or acute effects than the majority, all individual AHIs undergoing relatively similar modifications as the respiratory parameters were changed.

Fig 3.9a - Individuals AHI with 2% desaturations and varying event durations.

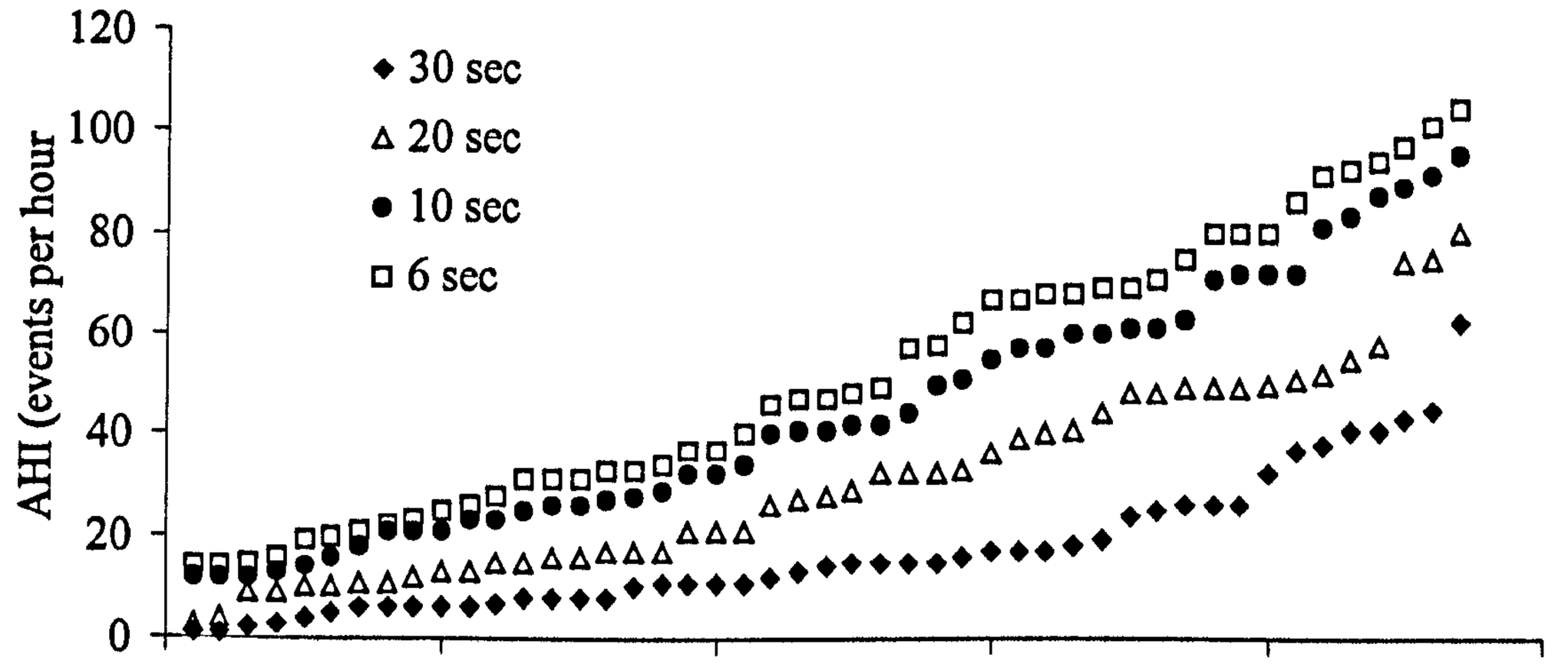
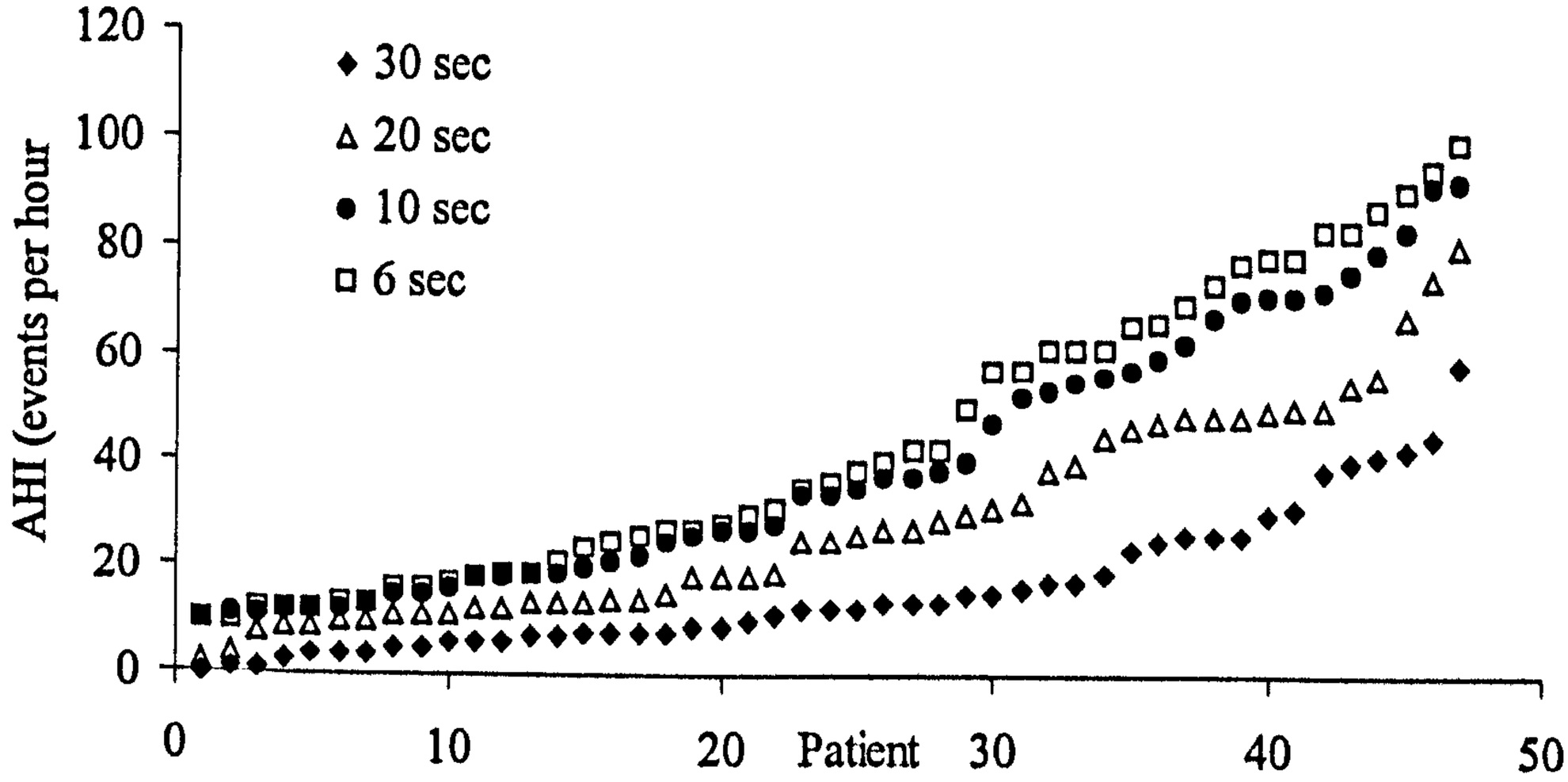


Fig 3.9b - Individuals AHI with 4% desaturations and varying event durations



3.5.7 The Relationships Between Respiratory Events And ESS

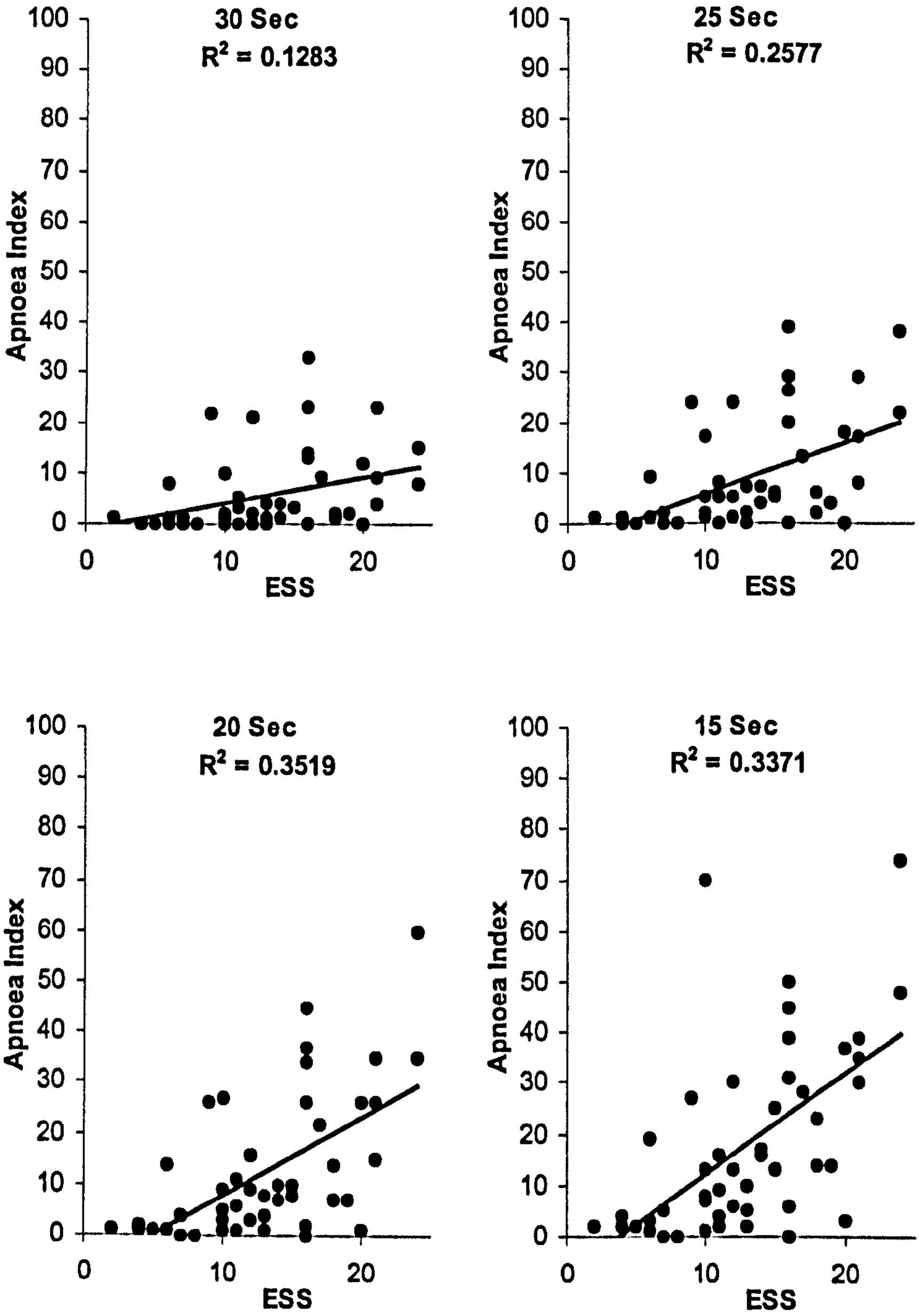
The relationship between the modified Apnoea Indices and the ESS

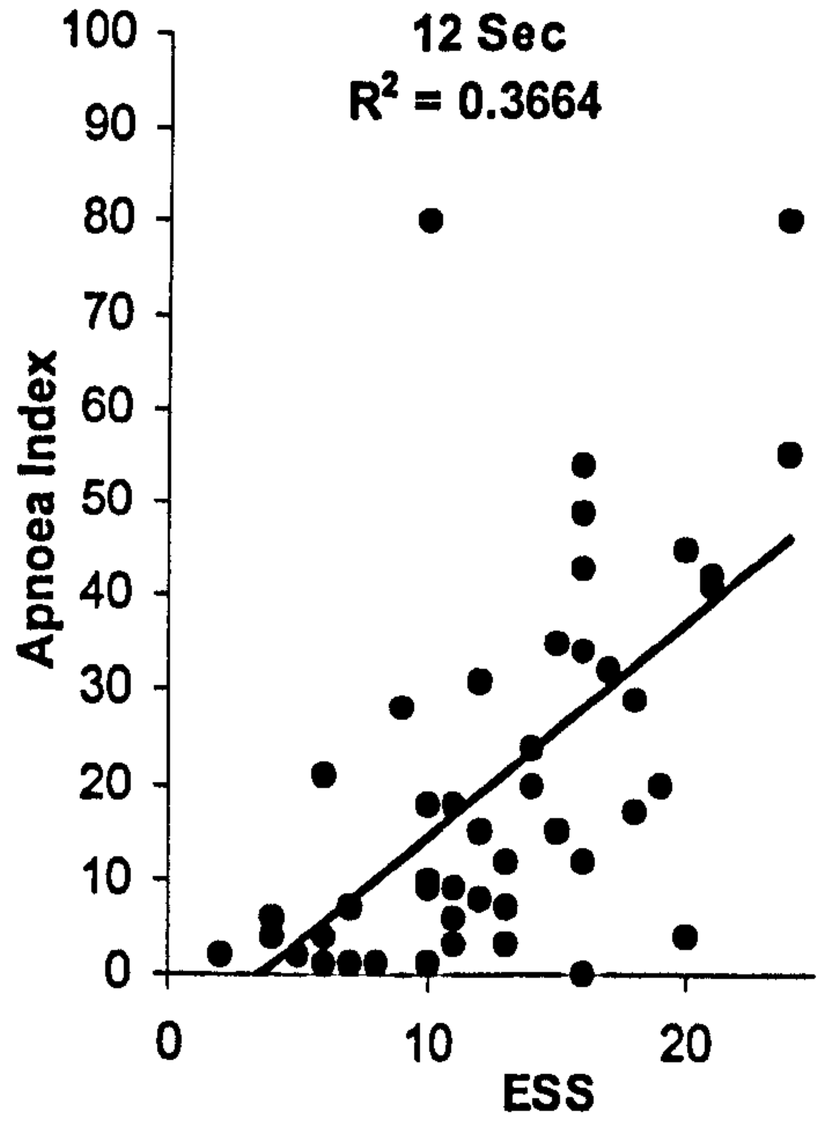
Table 3.8 and the subsequent 8 Figs present the correlations between the ESS and the 8 apnoea indices scored with the 4% desaturation criteria. The correlation coefficient increased as the minimum event durations was reduced from 30 to 6 seconds indicating that when shorter events were scored, the apnoea index and ESS became more strongly associated. However in all cases the association between apnoea index and ESS remain statistically significant.

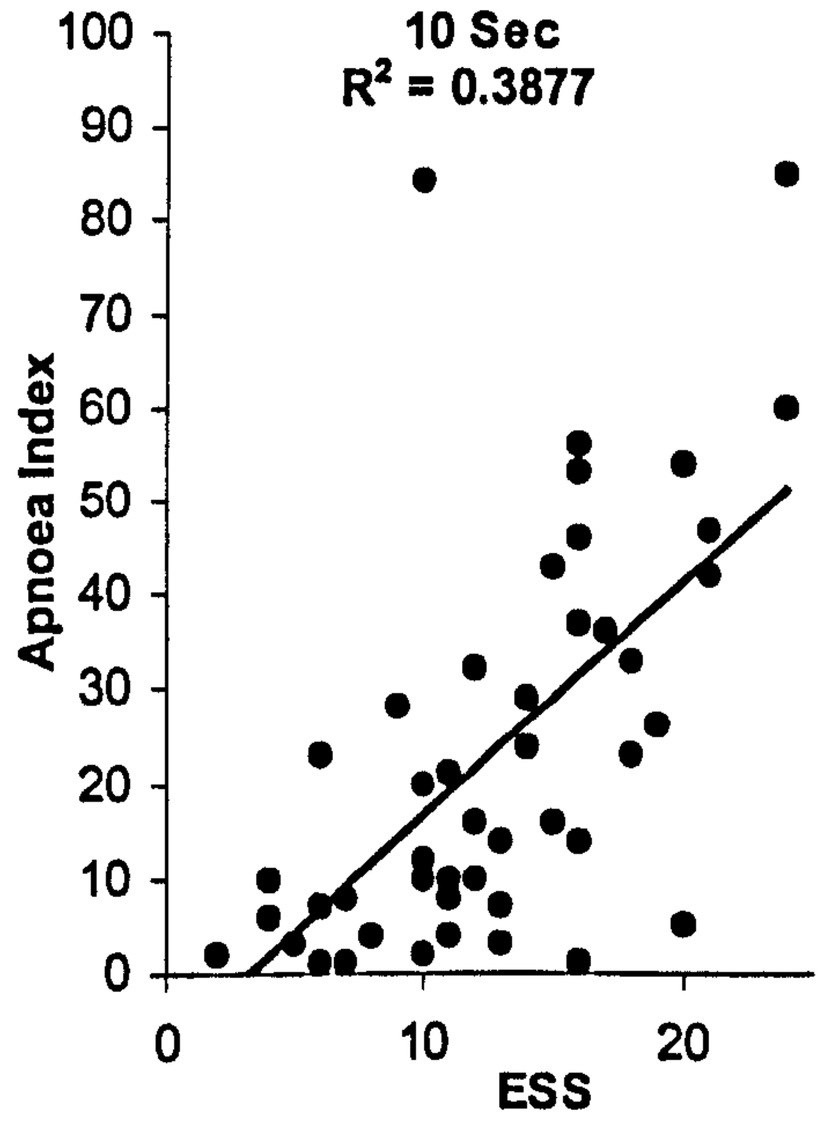
Table 3.8 - The correlation between the apnoea indices and ESS

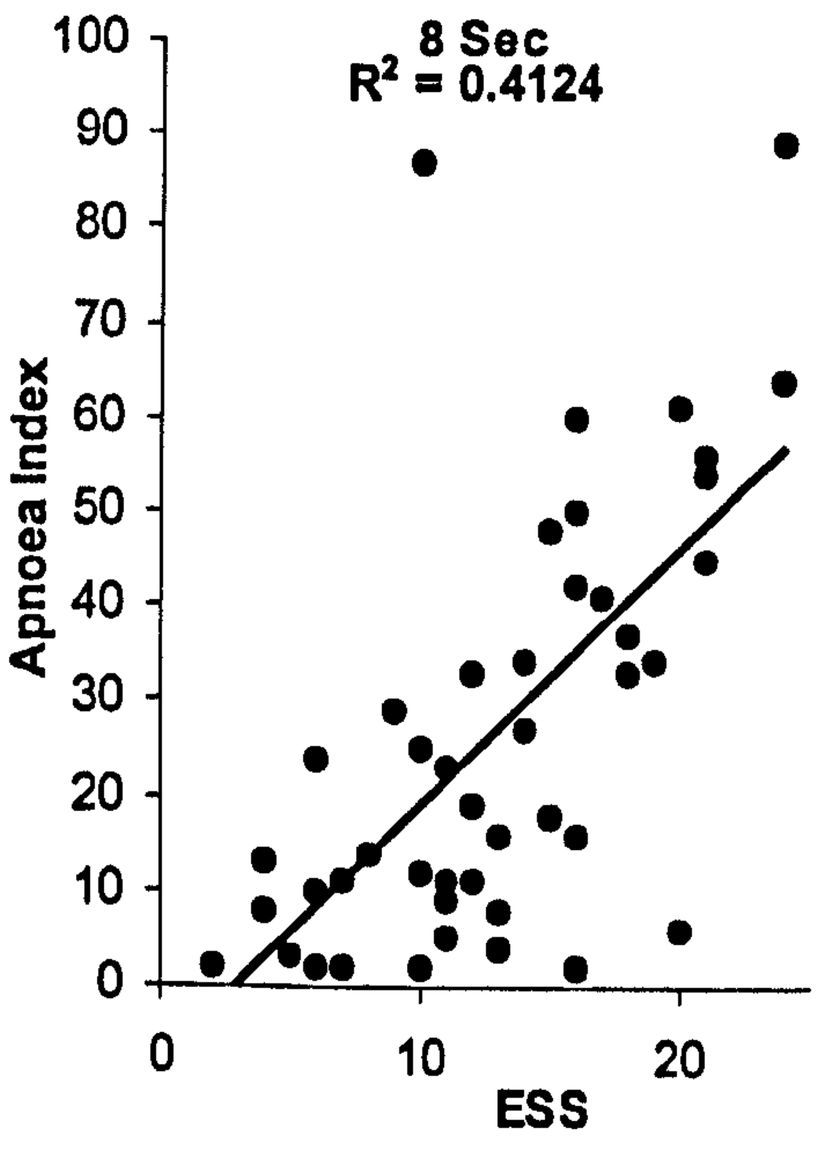
Minimum Duration (sec)	6	8	10	12	15	20	25	30
Correlation Co-efficient (r)	0.66	0.64	0.62	0.60	0.58	0.59	0.51	0.36
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.02

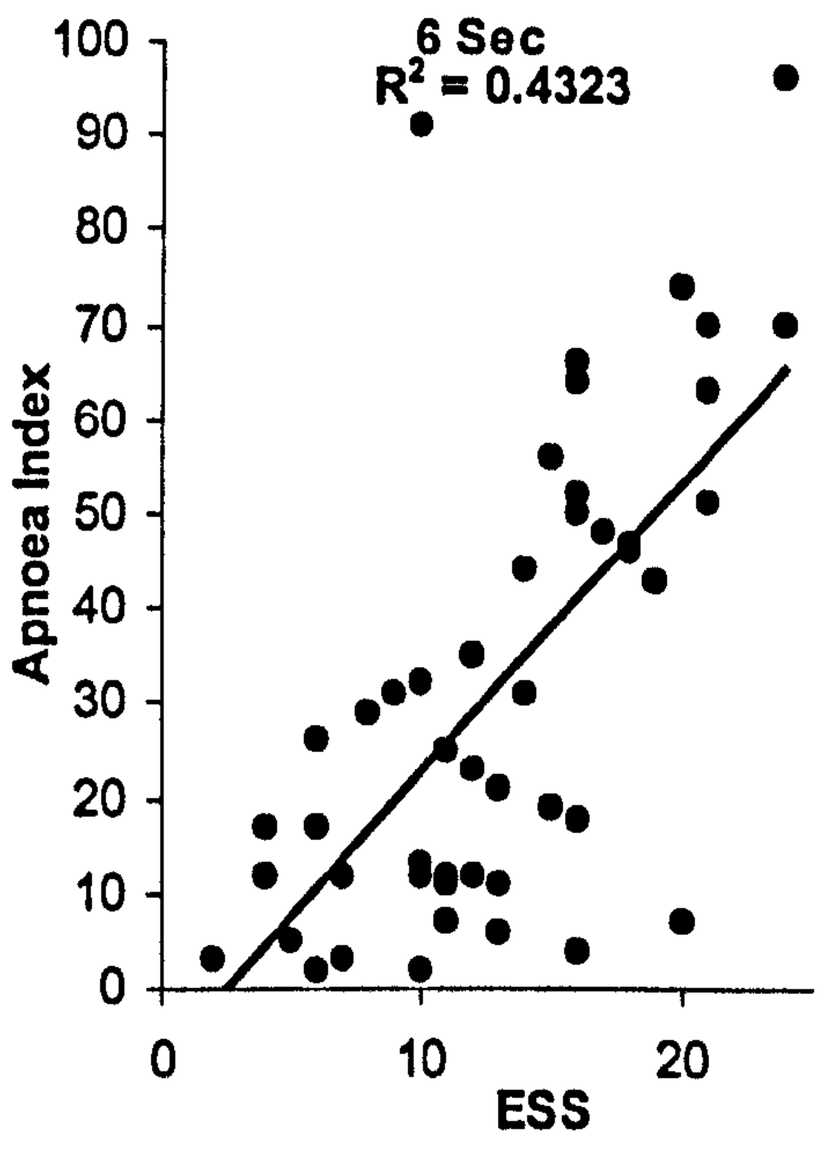
Fig 3.10 - The relationship between Apnoea Index and ESS




12 Sec
R^2 = 0.3664
Apnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100


10 Sec
R^2 = 0.3877
Apnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100


8 Sec
R^2 = 0.4124
Apnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100


6 Sec
R^2 = 0.4323
Apnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100

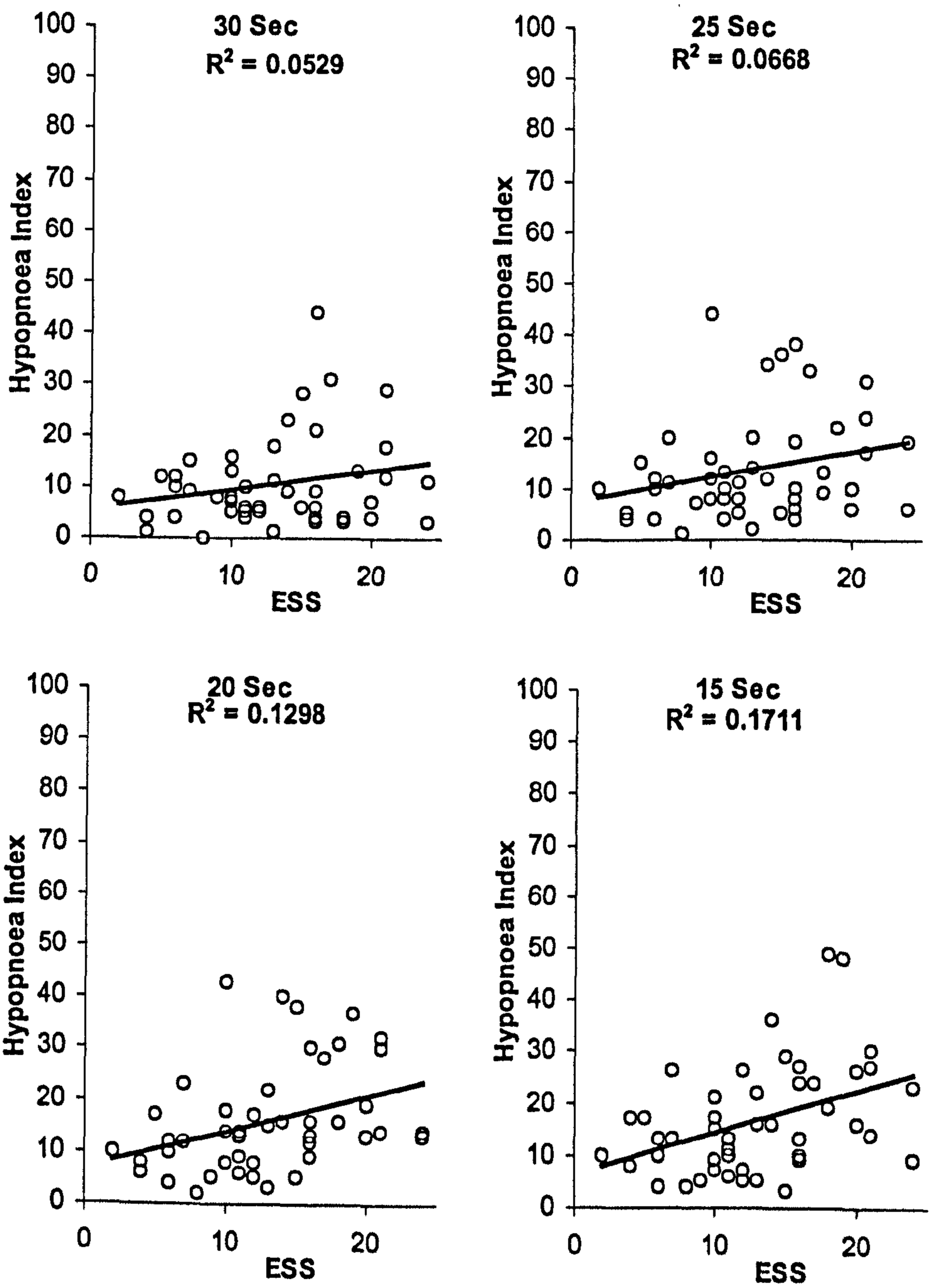
The relationship between the modified Hypopnoea Indices and the ESS

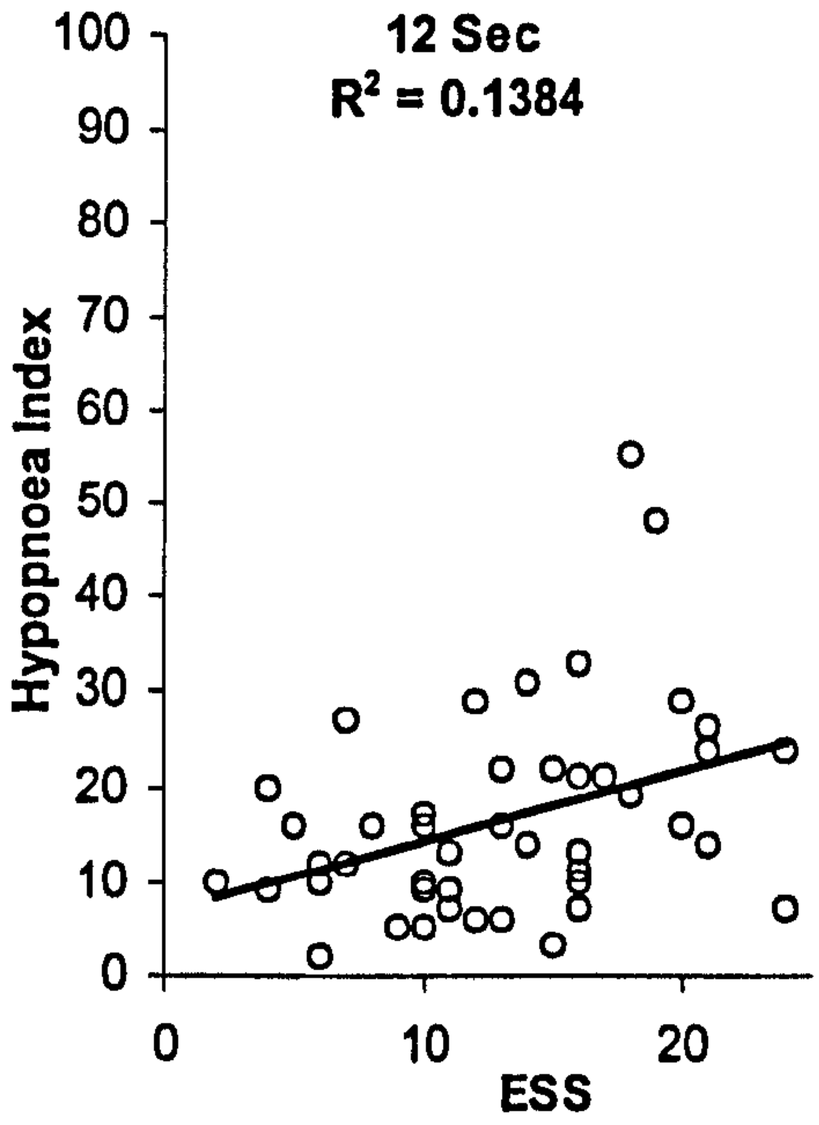
Table 3.9 and the subsequent figures show the correlations between the ESS and the hypopnoea index scored using the 8 minimum event criteria with a 4% desaturation. There was no relationship between the ESS and the hypopnoea index when events shorter than 10 seconds or longer than 20 seconds were scored. The only significant relationships were demonstrated when more than 15 hypopnoeas per hour were scored; when the minimum duration parameter was set between 10 and 20 seconds.

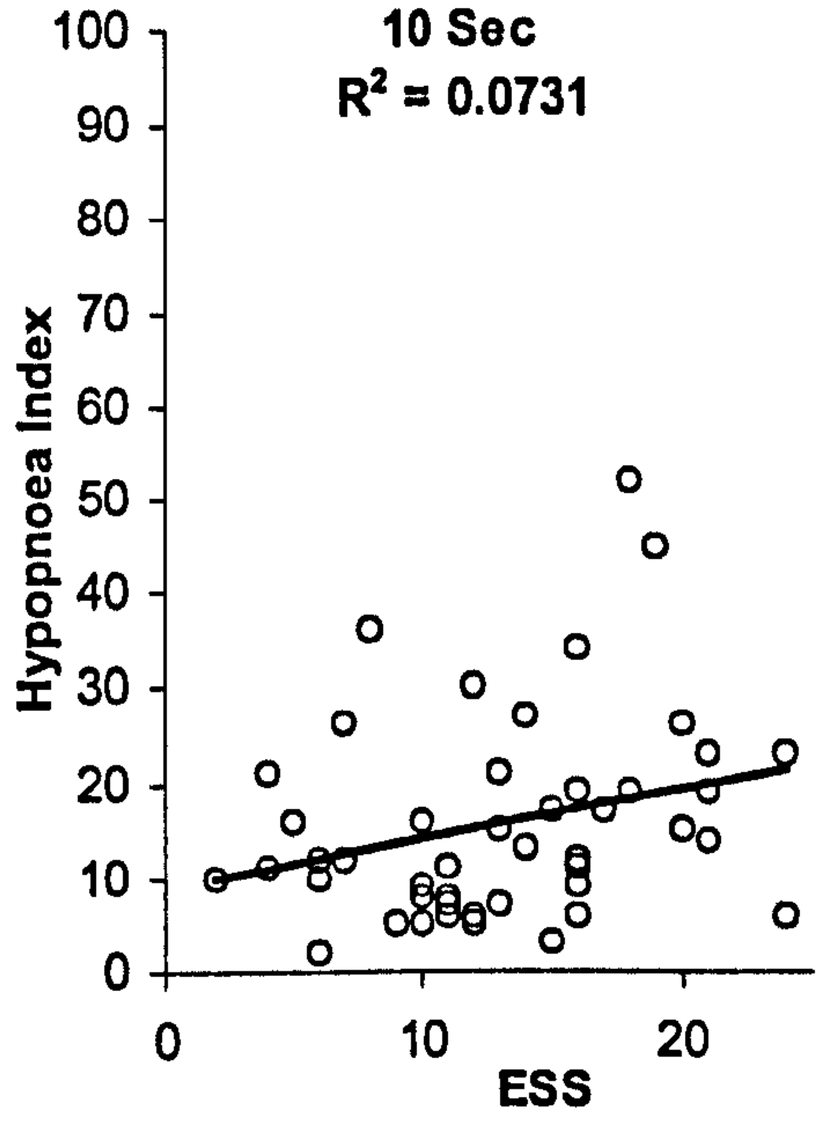
Table 3.9 - The correlation between the hypopnoea indices and ESS

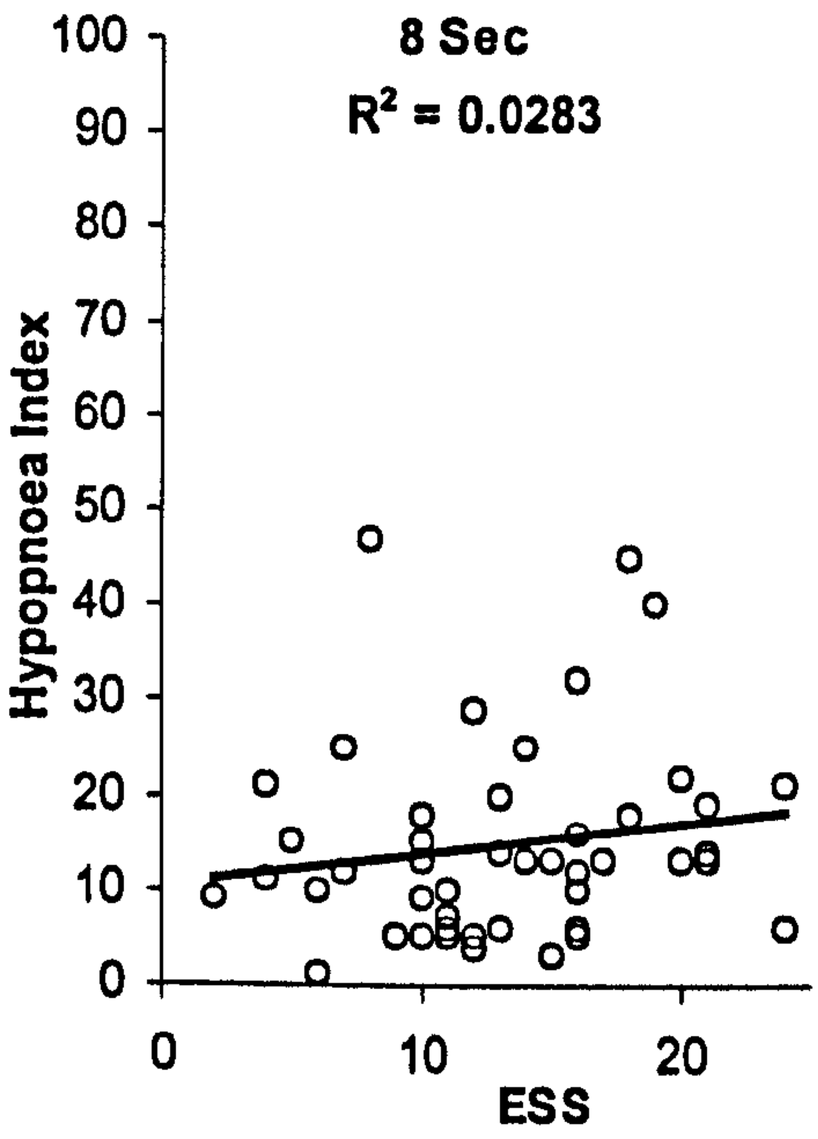
Minimum Duration (sec)	6	8	10	12	15	20	25	30
Correlation Co-efficient (r)	0.12	0.17	0.27	0.37	0.41	0.36	0.26	0.23
p	ns	<0.2	<0.05	<0.02	<0.01	<0.02	<0.1	<0.2

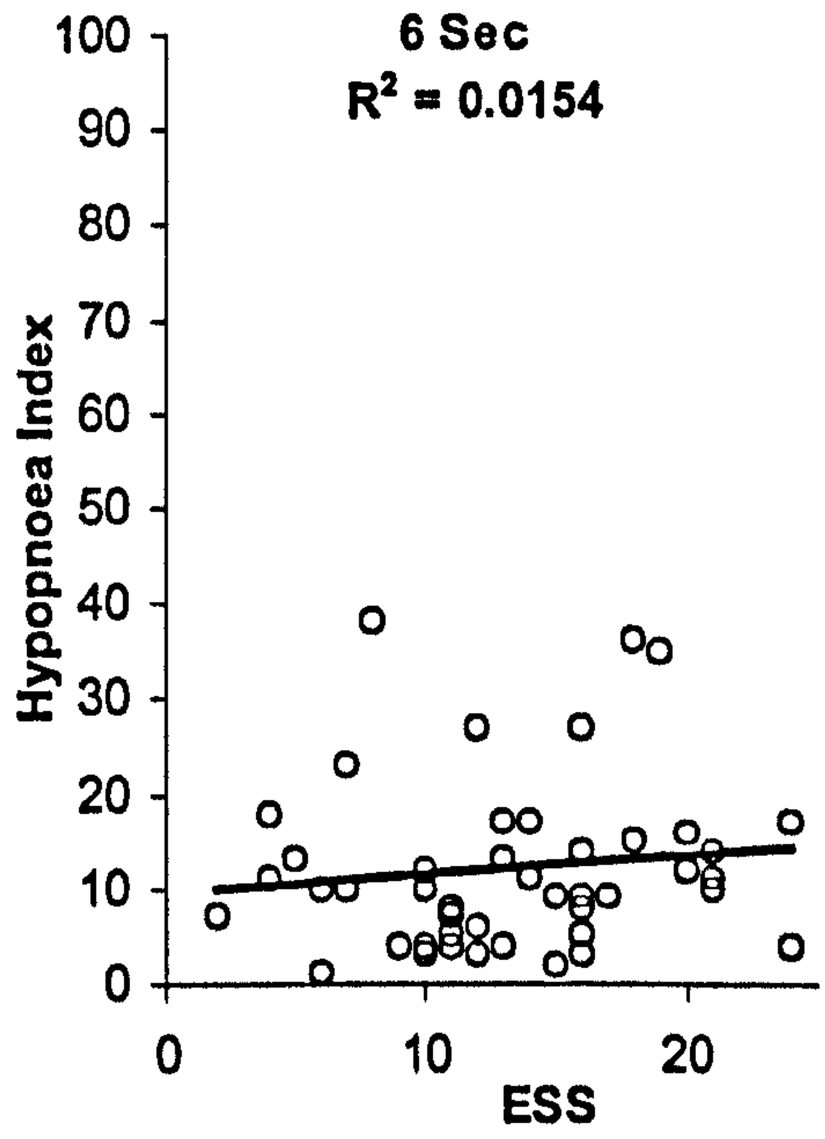
Fig 3.11 - The relationship between Hypopnoea index and ESS.




12 Sec
R^2 = 0.1384
Hypopnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100


10 Sec
R^2 = 0.0731
Hypopnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100


8 Sec
R^2 = 0.0283
Hypopnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100


6 Sec
R^2 = 0.0154
Hypopnoea Index
ESS
0
10
20
30
40
50
60
70
80
90
100

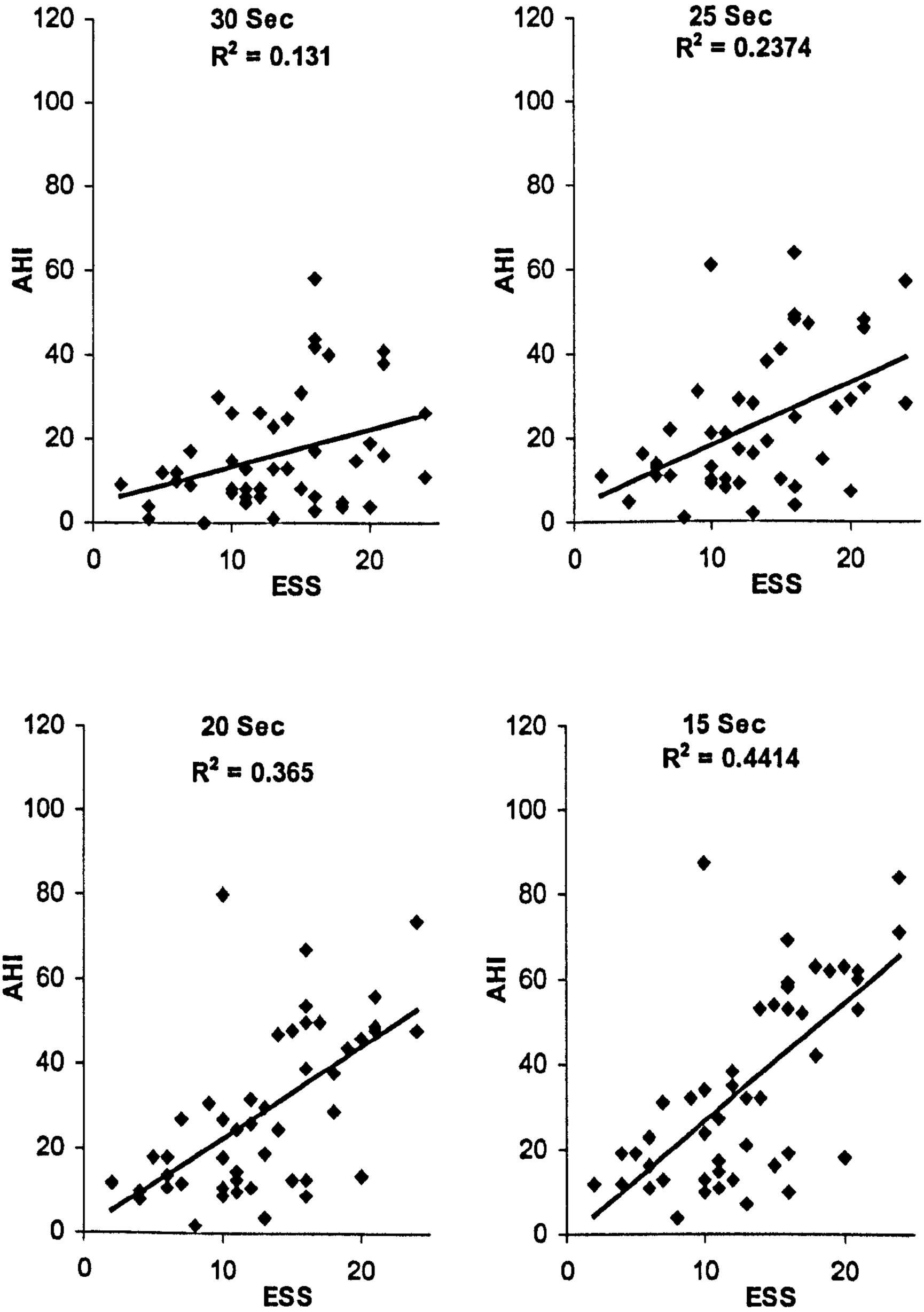
Correlations between the modified apnoea hypopnoea indices and ESS

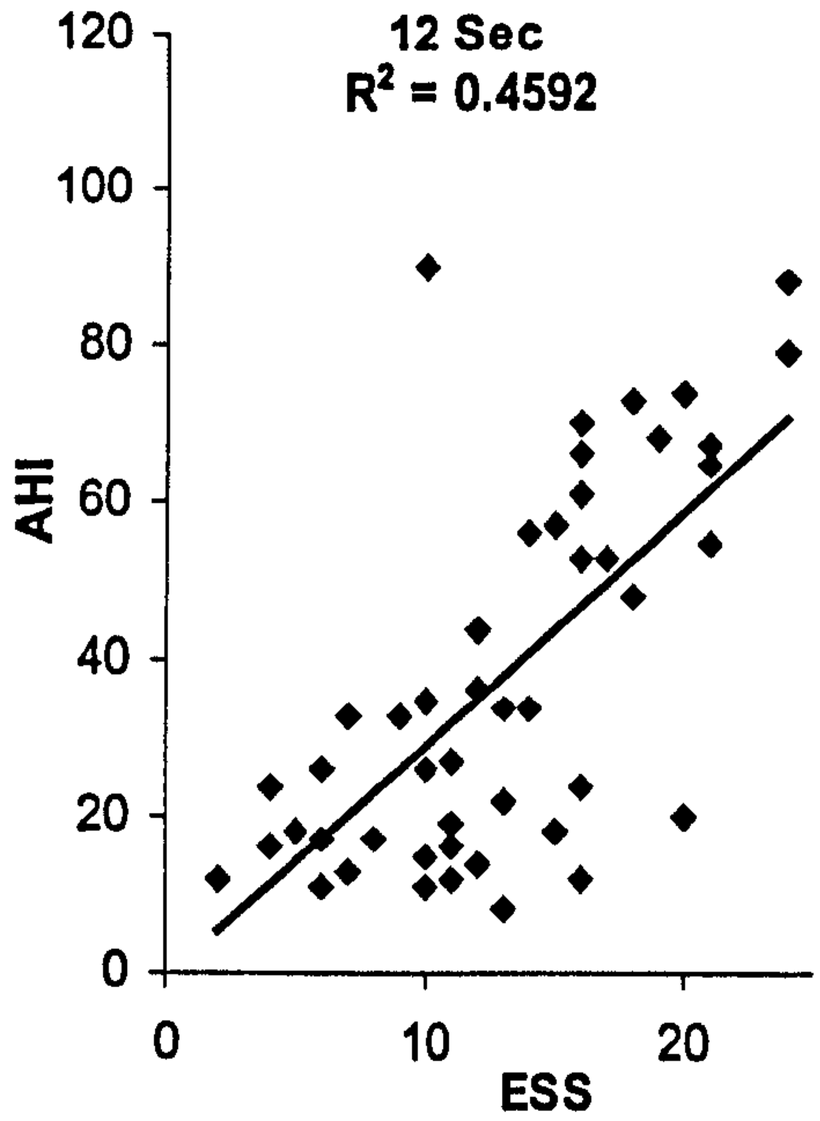
Table 3.10 and the figures on pages 105-106 present the correlation coefficients between the ESS and the AHI for the 8 minimum event criteria with a 4% desaturation. All criteria were strongly significantly related to ESS. Differences between criteria were of only marginal significance until events lasting over 25 seconds were scored, and again, all remained statistically significantly correlated with ESS.

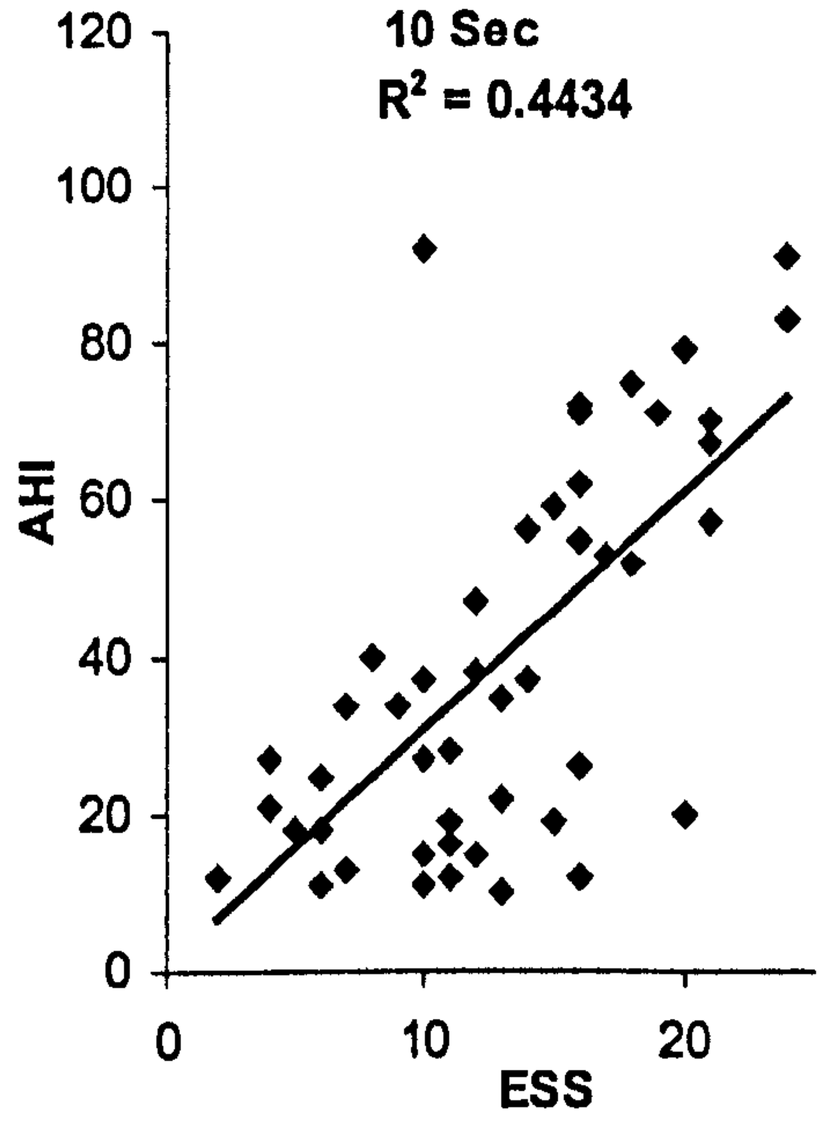
Table 3.10 - The correlation between the AHI and ESS

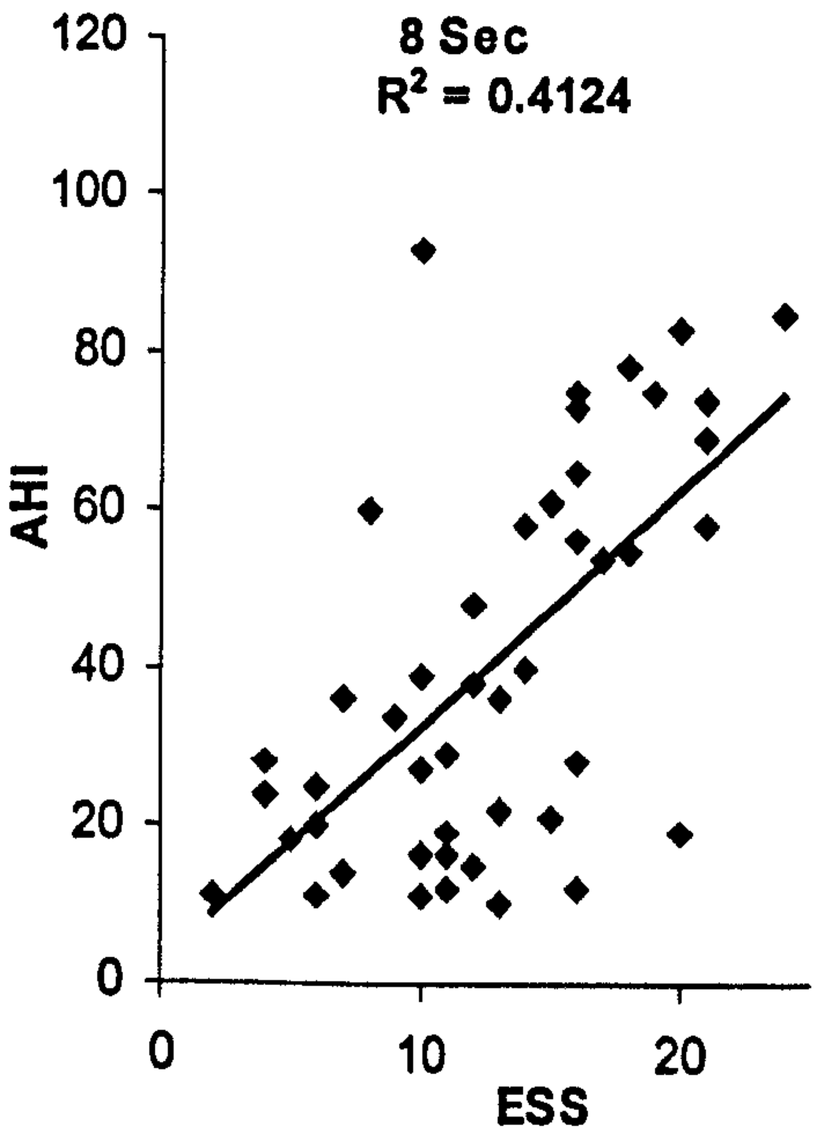
Minimum Duration (sec)	6	8	10	12	15	20	25	30
Correlation Co-efficient (r)	0.65	0.64	0.67	0.68	0.66	0.60	0.49	0.48
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

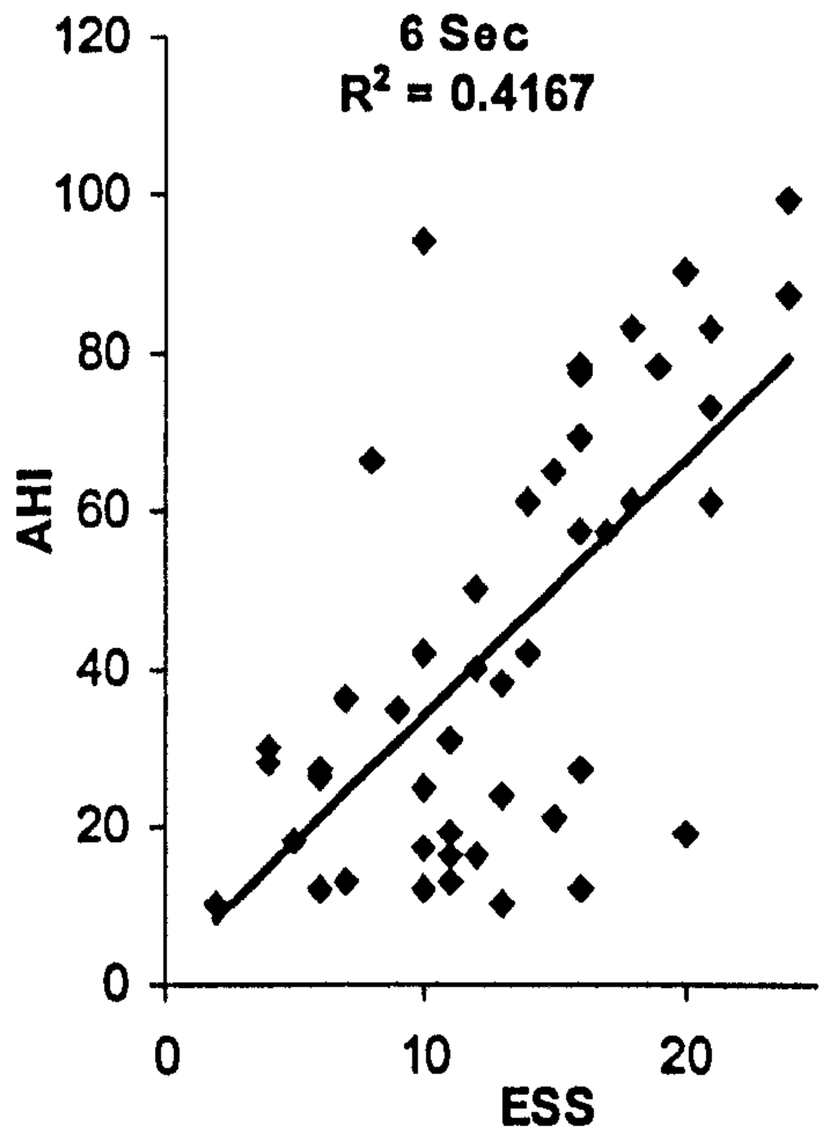
Fig 3.12 - The relationship between AHI and ESS.




12 Sec
R^2 = 0.4592
AHI
ESS
0
20
40
60
80
100
120
0
10
20


10 Sec
R^2 = 0.4434
AHI
ESS
0
20
40
60
80
100
120
0
10
20

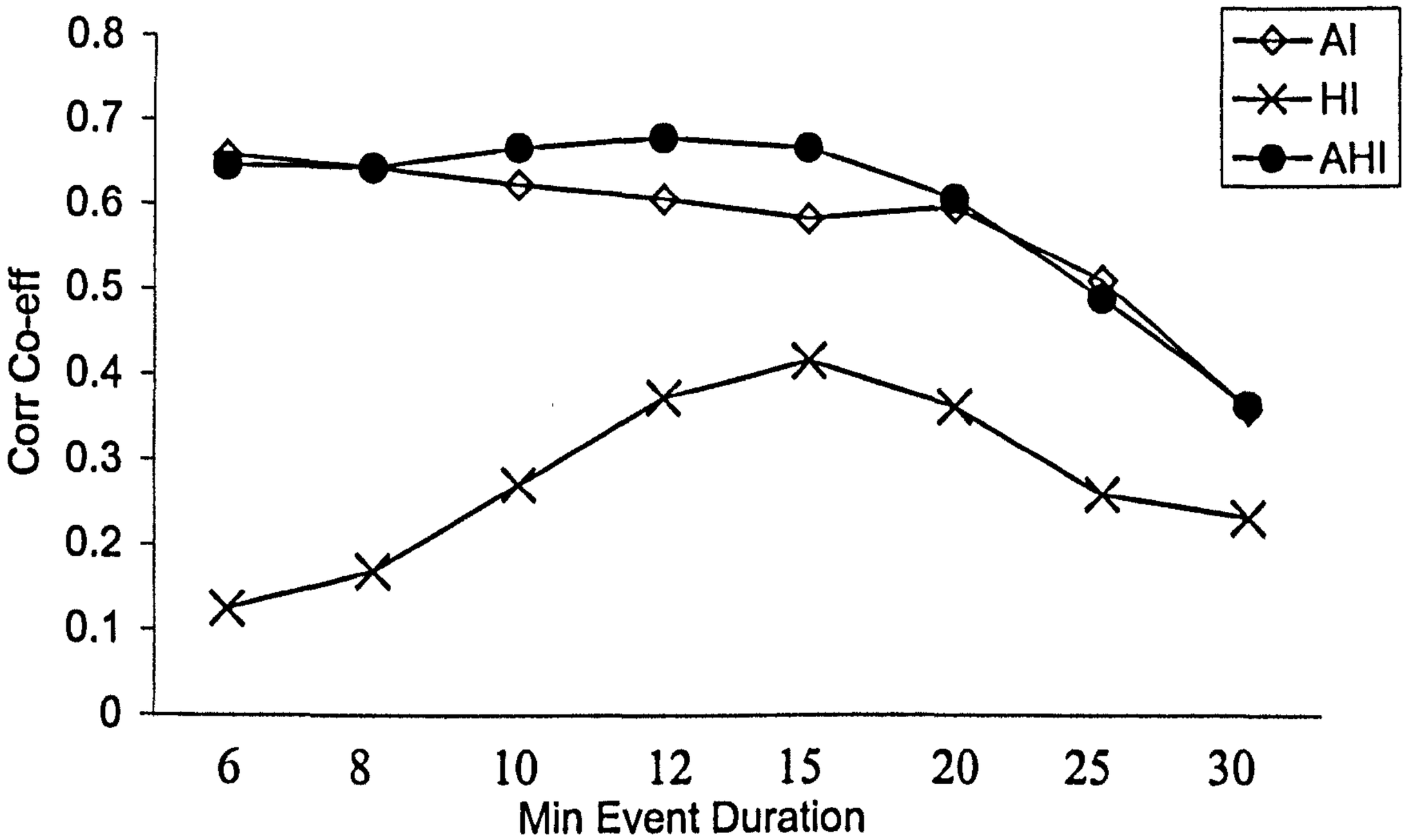

8 Sec
R^2 = 0.4124
AHI
ESS
0
20
40
60
80
100
120
0
10
20


6 Sec
R^2 = 0.4167
AHI
ESS
0
20
40
60
80
100
120
0
10
20

The relationships between the ESS and the Apnoea Index, Hypopnoea Index and Apnoea-Hypopnoea Index

In figure 3.13 the relationships between the ESS and the apnoea index, hypopnoea index and apnoea-hypopnoea index are shown. The figure also demonstrates the influence of the apnoea index and hypopnoea index on the relationship between AHI and ESS. The apnoea index and AHI correlated strongly with ESS. The hypopnoea index correlated less well, but it still contributes to the overall AHIs relationship with ESS for events with a minimum duration between 10 and 15 seconds.

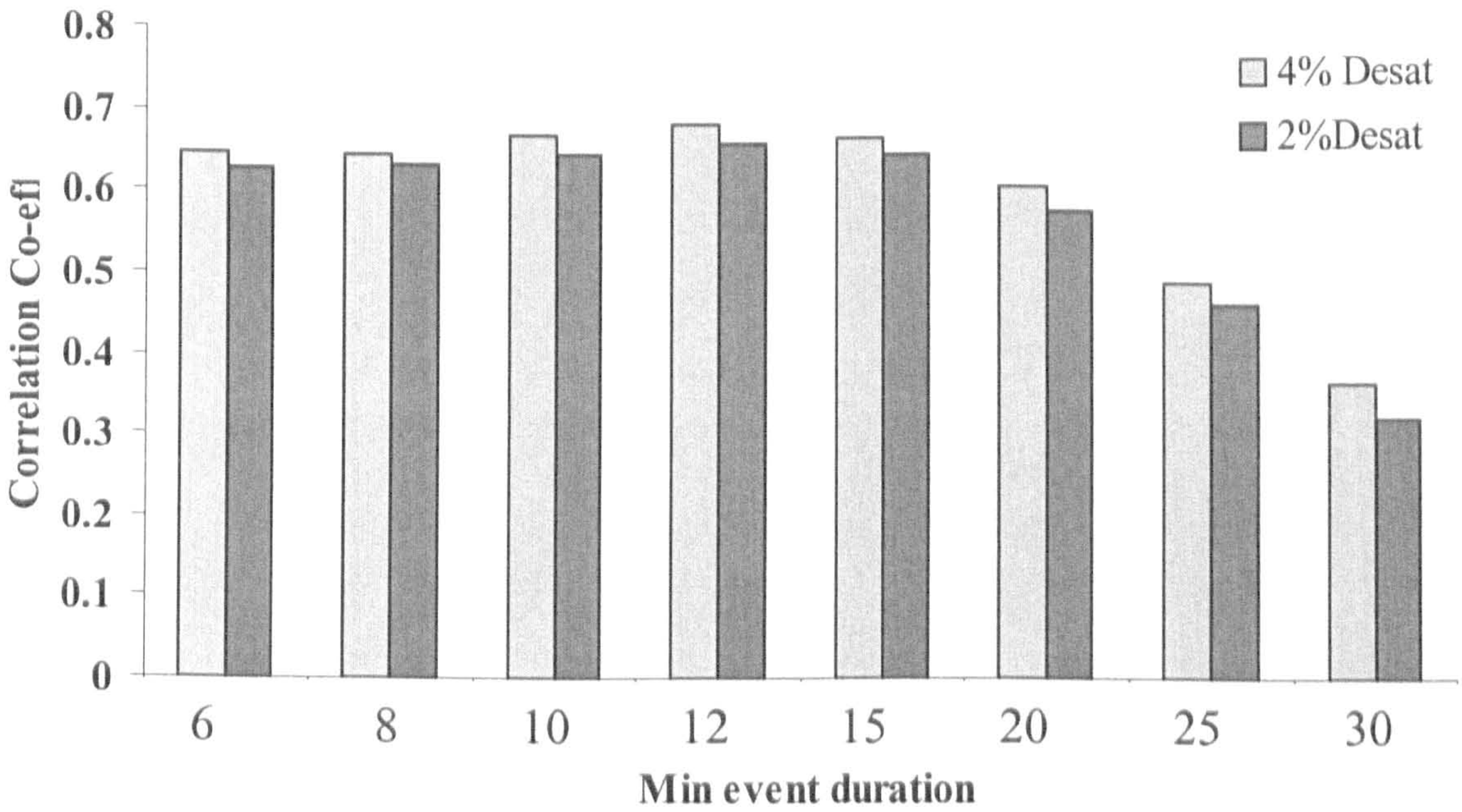
Fig 3.13 - Correlations of respiratory event indices and ESS



3.5.8 The Effect of Altering the Desaturation Criteria on the Relationship Between AHI and ESS

There was a strong relationship between the AHI and the ESS. Figue 3.14 shows the peak correlation coefficient was seen when events lasing a minimum of twelve seconds with a 4% desaturation were scored. Although more events were scored using the 2% desaturation requirement, there was a slight reduction in the relationship between the AHI and daytime sleepiness measured using the ESS.

Fig 3.14 - The correlations between the modified AHI and ESS

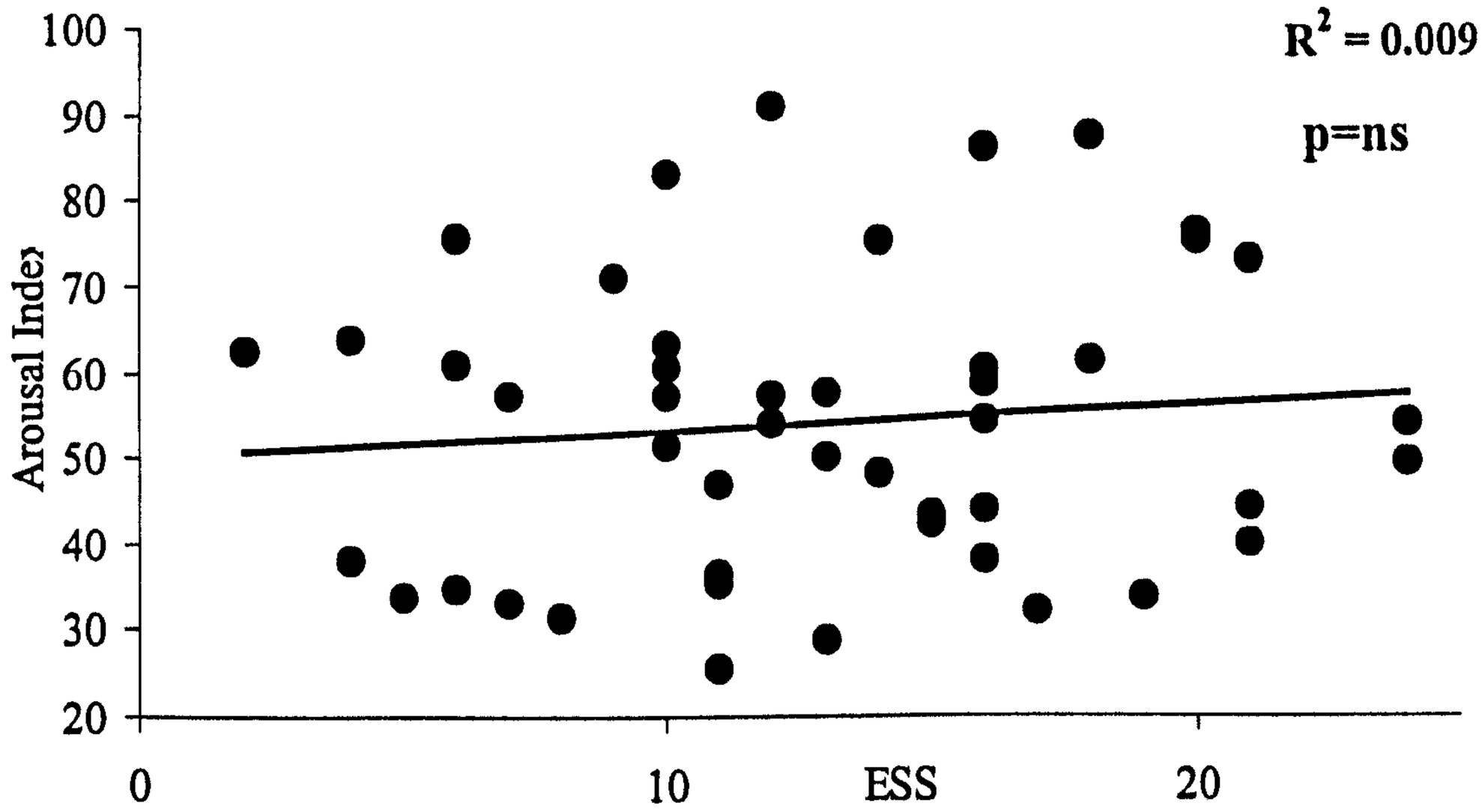


3.5.9 Relationships with the Arousal Index

Relationship between the ESS and Arousal Index

In this population there was no relationship between daytime sleepiness reported by an individual, using the ESS, and the arousal index..

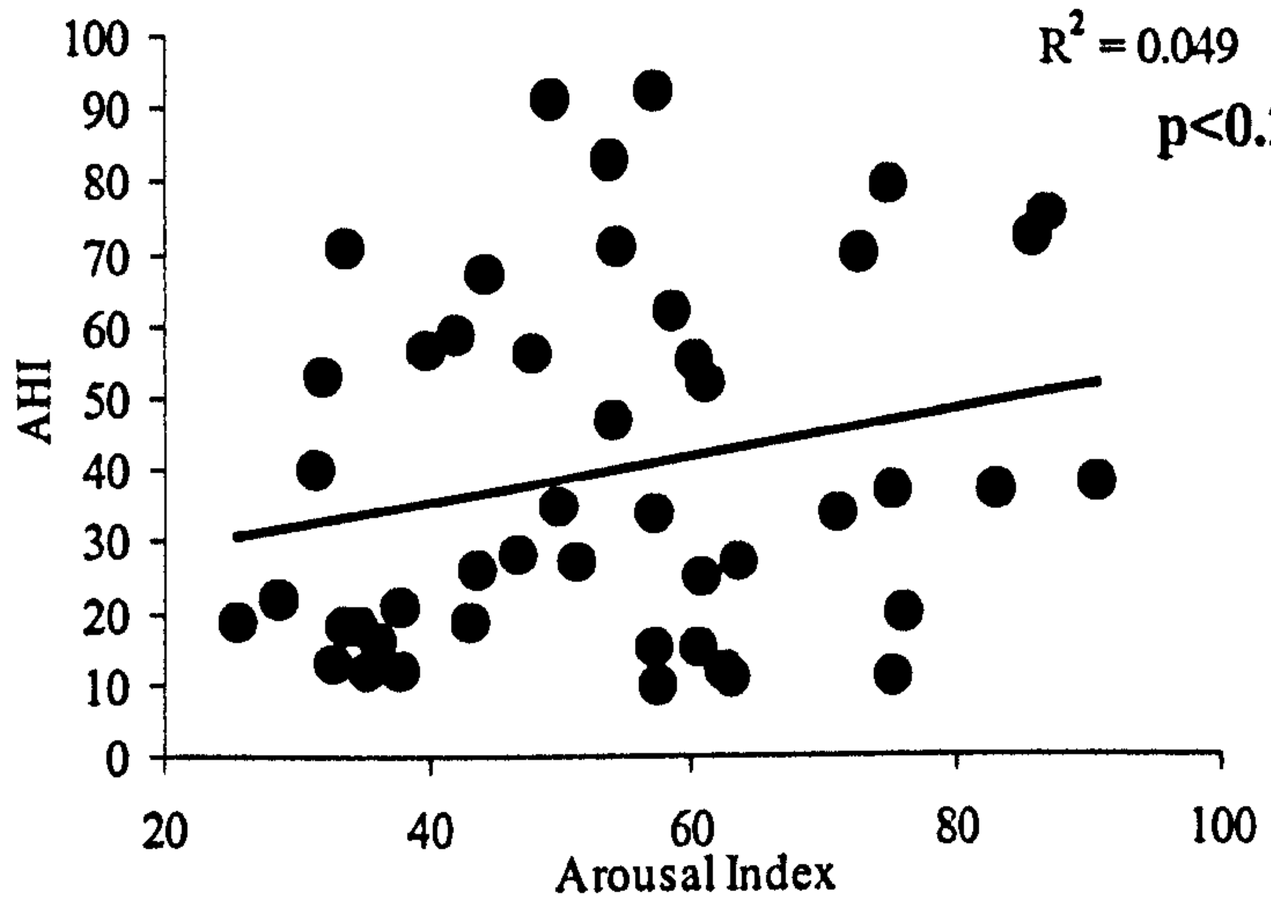
Fig 3.15 - The Correlation between ESS and Arousal Index



The relationship between the AHI and arousal index

There was a poor correlation between the number of arousals and the number of respiratory events experienced by the group during each hour of sleep.

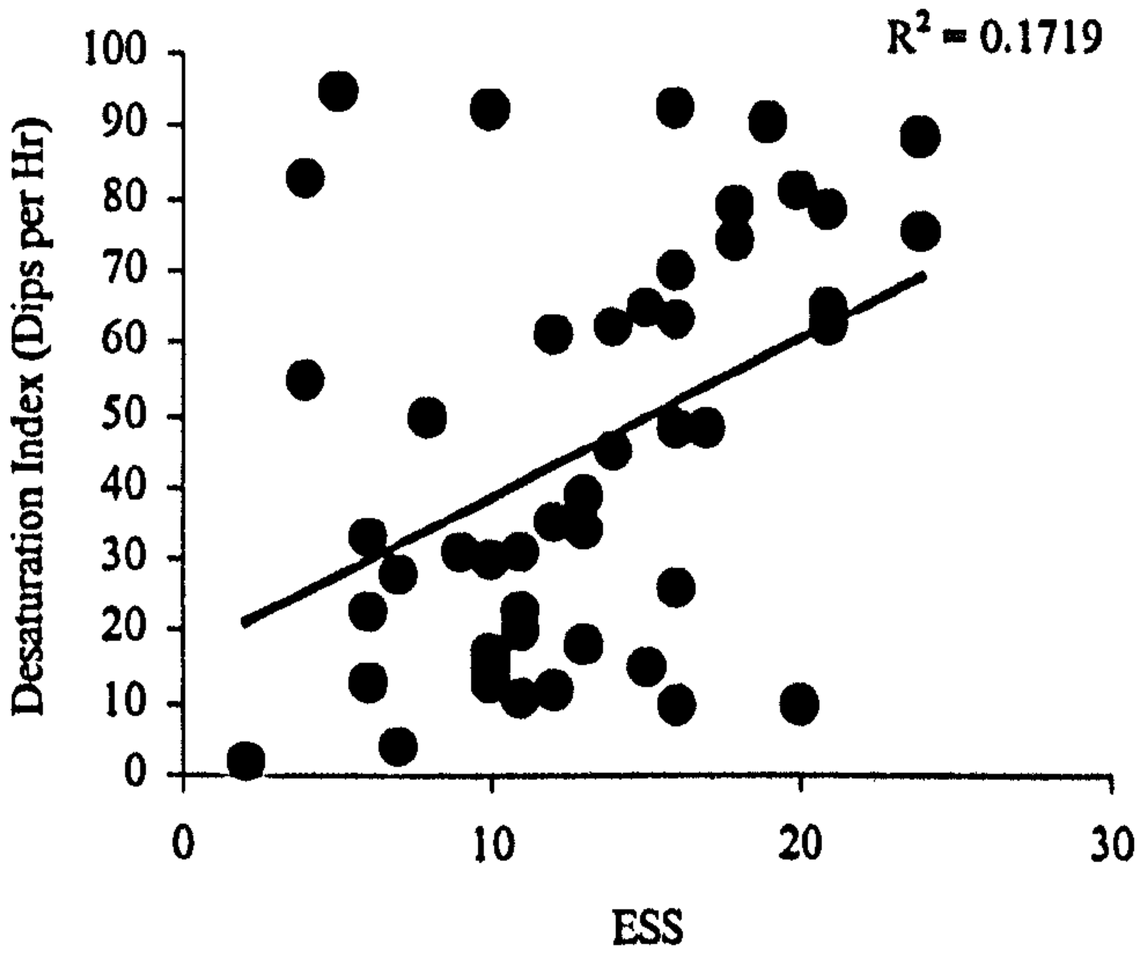
Fig 3.16 - The correlation between AHI and the arousal index



The relationship between the 4% desaturation index and ESS

A significant relationship was seen between the 4% desaturation index, which was not affected when the respiratory event criteria were altered, and the ESS ($p<0.01$) (Fig 3.17). The positive relationship indicates that patients with a high desaturation index were more likely to have excessive daytime sleepiness, the variance was high.

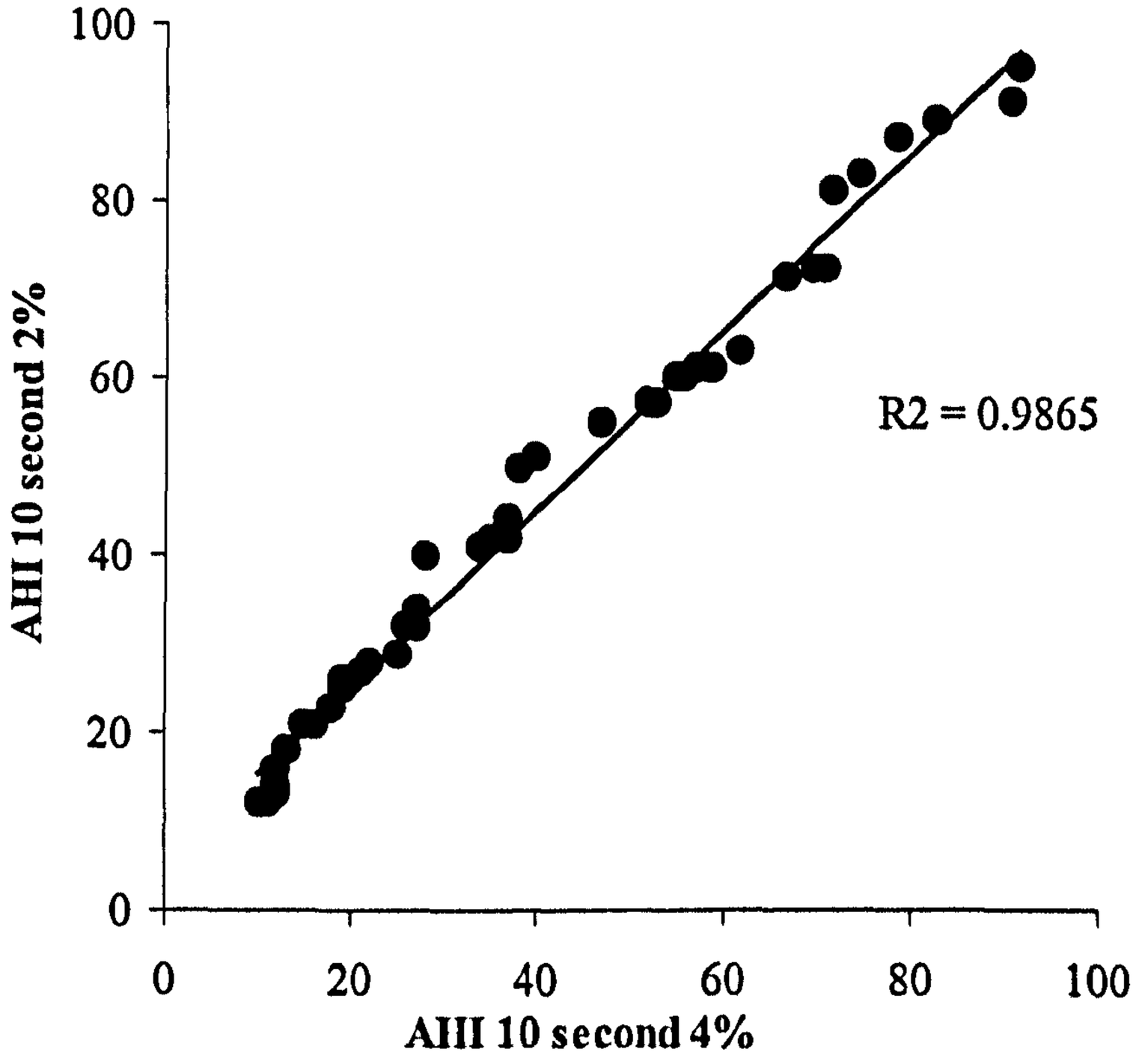
Fig 3.17 - The correlation between the 4% desaturation index and ESS



The relationship between AHIs scored with 2% and 4% desaturations

Fig 3.18 demonstrates that, when observing events lasting a minimum of 10 seconds, there was an exceptionally strong relationship between the AHI scored with 2% and the AHI scored with 4% desaturations. Figure 3.18 indicates that more events are scored with 2% desaturations. However, reducing the desaturation criteria affects all individual AHIs to a similar extent; demonstrated by the correlation coefficient (r) of 0.993.

Fig 3.18 - The correlation between the events scored with 2% and 4% desaturations



The relationships between the AHI scored ASDA criteria and the AHI scored with a minimum event criteria of 6, 20 and 30 seconds.

The three subsequent Figs demonstrate there is a strong correlation between the AHI scored using the conventional ASDA criteria, and those scored using different minimum event durations. Lowering the desaturation requirement and minimum event duration had little effect on the number of events scored, suggesting that, in this group of patients, most apnoeas exceeded the 10 second duration, and had an associated desaturation of 4% or greater. Different numbers of events are were scored when the minimum event criteria were extended, but, the individual AHIs were affected to a similar degree. These data suggest that changing the desaturation requirment or the minimum event duration may score different numbers of events but this will effect will not be bias toward any subgroups of the OSAHS patient population.

Fig 3.19 - The correlation between AHIs derived using 10 second and 6 second minimum event criteria

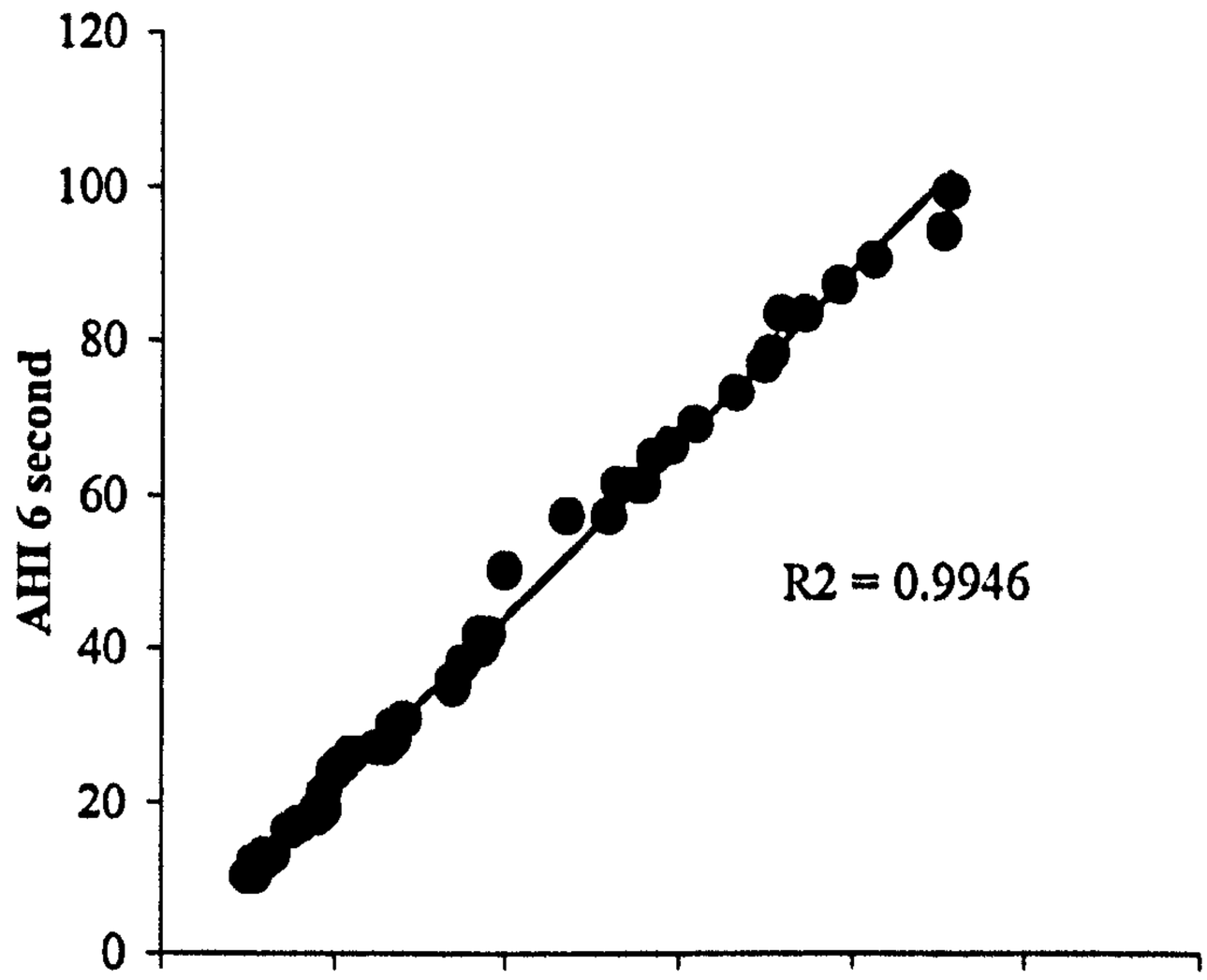


Fig 3.20 - The correlation between AHIs derived using 10 second and 20 second minimum event criteria

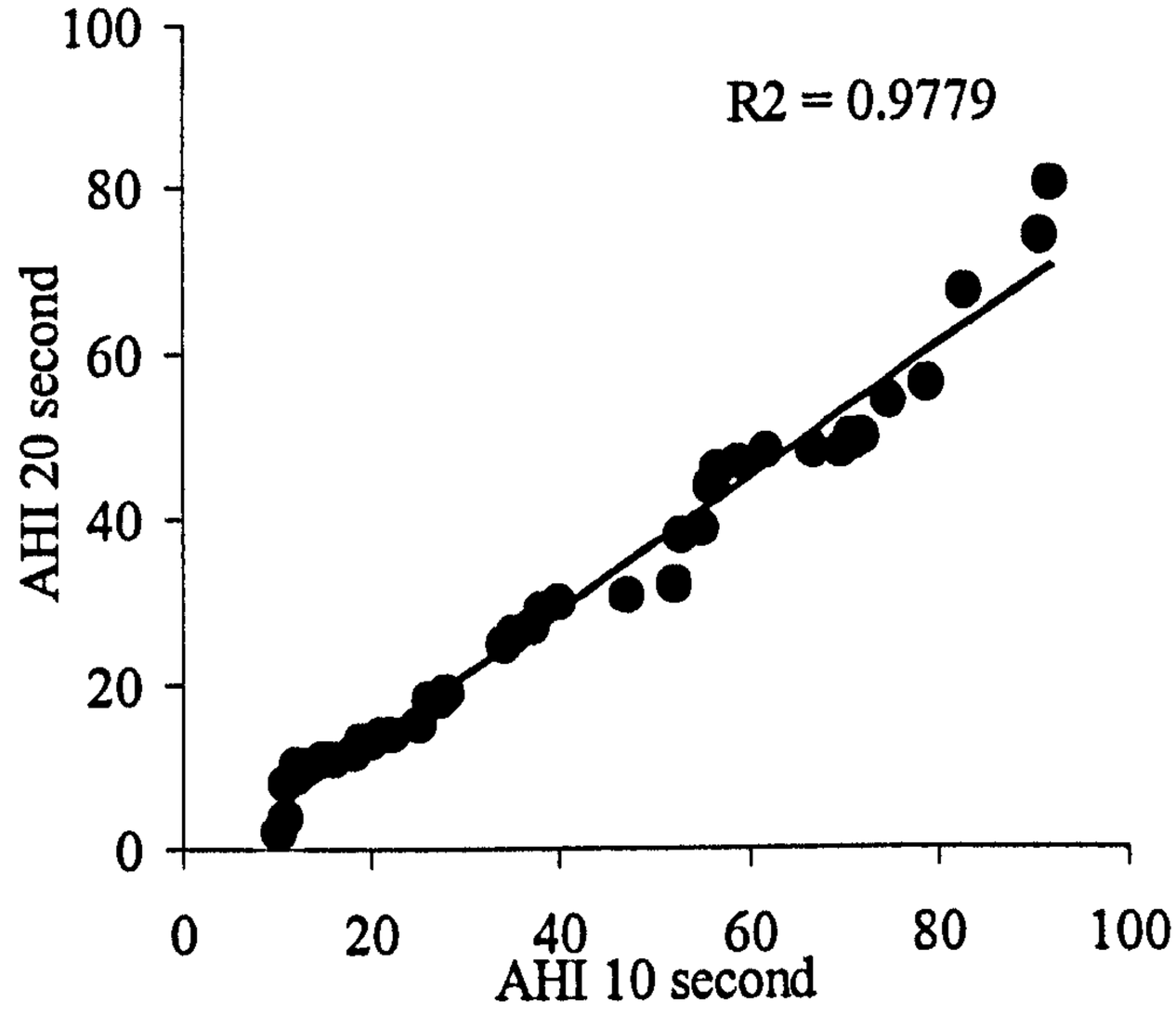
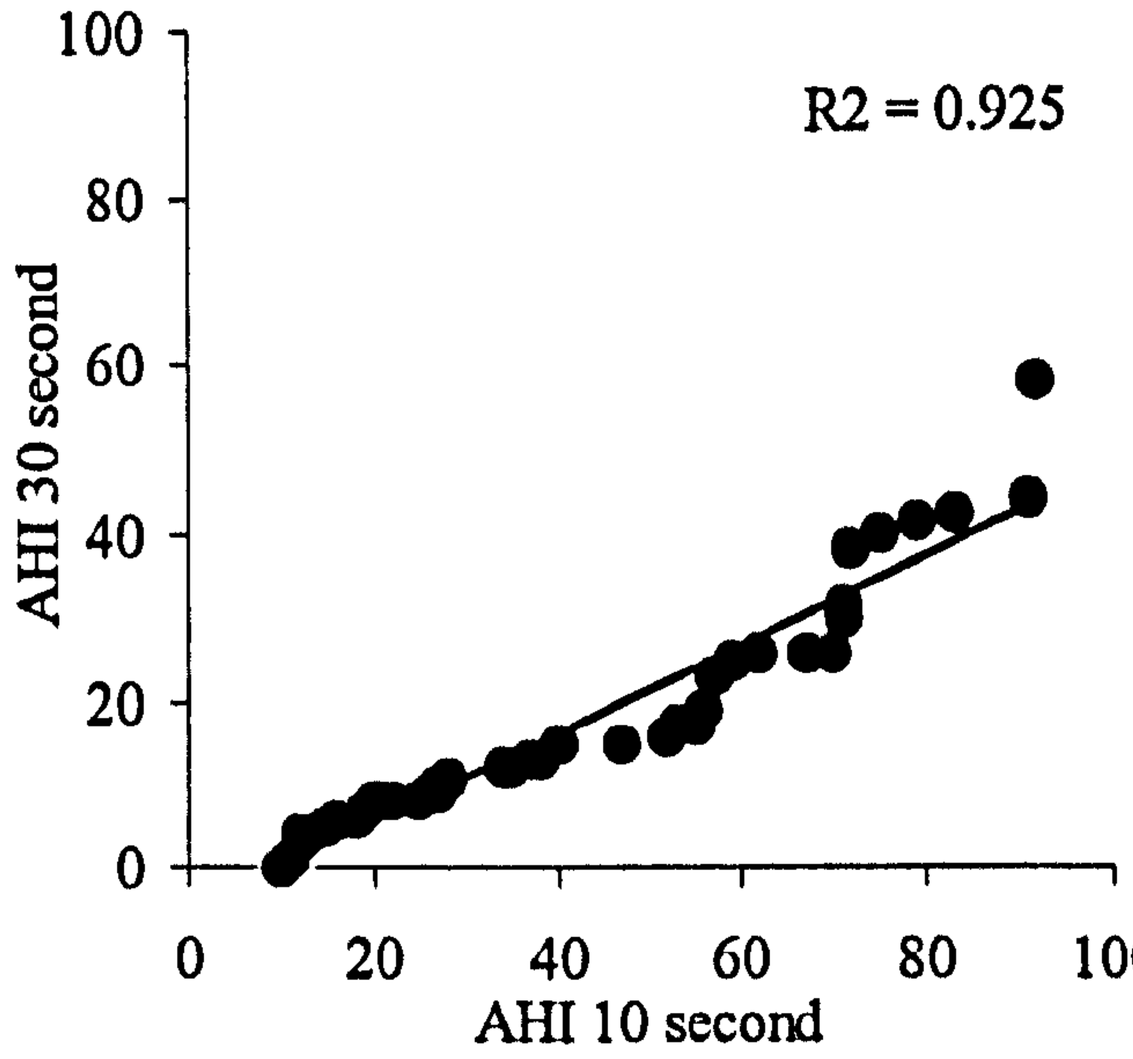


Fig 3.21 - The correlation between AHIs derived using 10 second and 30 second minimum event criteria



3.6 DISCUSSION

As noted previously (pages 63-65) the criteria adopted to define OSAHS were arbitrarily chosen to define easily detectable deviances from the random variation in oximetey and breathing pattern. Remarkably it is only recently that the metric properties of these measurements and their sensitivity to change have been reported. Redline *et al* 2000 investigated the effects of varying approaches to measuring the RDI. They performed 11 analyses with different criteria for defining respiratory events. The 10 second flow reduction criteria remained unchanged throughout their analyses, but the associated desaturation and/or arousal requirement were altered. The magnitude of the median RDI varied 10-fold (from 29.3 when the RDI was based on flow or volume changes alone, to 2.0 for an RDI that required an associated 5% desaturation with events). The RDIs with desaturations correlated well, weaker correlations were seen between RDIs defined on the basis of flow or volume changes and RDIs scored with a desaturation requirement. This has strong implications on the validity of the RDI as a measure of disease severity.

Without a 'gold standard' standardized approach to identifying respiratory events, there is a wide variability in diagnosis and epidemiogoical data from the many sleep centers around the world. Our study took a complimentary approach to these investigations. We wished to determine whether the results of the reported AHI would differ substantially if events of different duration were excluded or included, whether the individual components, namely apnoea and hypopnoea contributed equally to the diagnosis and whether lessening the criteria for an accompanying event eg 2% rather than 4% desaturation influenced the outcome.

This retrospective study used a semi-automated polysomnographic system to stage sleep and score respiratory events. Apnoeas and hypopnoeas were automatically scored after the various flow and desaturation parameters were set, but after each analysis the data were manually screened for artifact and anomalous results. This system used a thermistor as the flow detection device and the signal for apnoea and hypopnoea detection. The thermistor has been demonstrated to be poor measure of flow (Rapoport 1994), but remains the most commonly used device in polysomnographic systems as it easy to use and comfortable for patients to wear for long periods of time. We report thermistor data in this study as it was a retrospective

study conducted at a time when we routinely employed a thermistor as the flow detection device.

Patients PSG data were analyzed if they had been diagnosed with having 10 or more respiratory events per hour. Most patients presenting to a sleep clinic suffer with excessive daytime sleepiness, so therefore most had OSAHS and a high ESS (mean 13.0 (SD 5.5)). This will influence the results as the study was performed to investigate the relationship between various measures of disease severity and ESS. Unlike a population based study, where patients with EDS and without OSAHS, and vice-versa, would be recruited (Young 1997), most patients in this study had significant sleep related breathing disturbances and experienced excessive daytime sleepiness. There are many ways of assessing EDS. It can be assessed objectively using the Multiple Sleep Latency Test (MSLT)(Sangal *et al* 1992), which assesses how long it takes a person to fall asleep, or the Osler, which assesses how long a person can resist sleep. These are time consuming and costly investigations. A quick and inexpensive alternative is to assess subjective sleepiness using the ESS. This is a simple validated questionnaire in which a person reports how likely they are to doze in 8 everyday situations, such as 'sitting and talking to someone' (Appendix 1). ESS scores have been shown to correlate significantly with sleep latency measured during the MSLT and during overnight polysomnography (Johns 1993). The validation study also demonstrated that the respiratory disturbance index in OSAHS patients correlated with the ESS. However, the ESS is subjective, and when used as a diagnostic aid, can be misleading; ESS is not exclusively associated with OSAHS. In the chosen population for this study the AHI determined using the ASDA respiratory event criteria was significantly correlated with the ESS ($p<0.001$), this is likely to reflect the deliberate selection of a wide range of AHI values and the frequency of sleepiness in our OSAHS population.

In this study there was no significant relationship between the hypopnoea index and the apnoea index. This is in keeping with the data of Gould *et al* (Gould *et al* 1988), where a population comprised of some patients who experienced many apnoeas and few hypopnoeas and others vice versa.

The apnoea index, hypopnoea index and AHI were affected in different ways when the respiratory event criteria where altered.

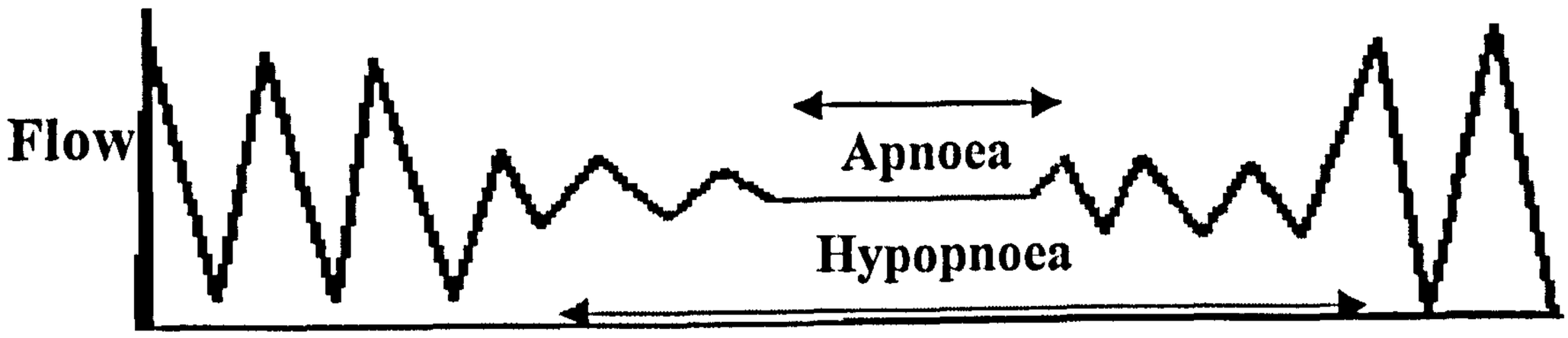
The Apnoea Index.

As the minimum event duration was increased from 6 to 30 seconds, the number of apnoeas scored linearly decreased due to the exclusion of briefer events from the analysis. Reducing the desaturation requirement from 4% to 2% saw more short events being scored, the group mean apnoea index, for events lasting a minimum of 6 seconds, increased by 20.5 % (6.5 apnoeas per hour). However, this effect linearly diminished as the longer apnoeas were scored; reducing the desaturation requirement resulted in an 3.6% increase (0.2 apnoeas per hour) in the apnoea index when events lasting for a minimum of 30 seconds were considered. This demonstrates that longer apnoeas are more likely to have an associated desaturation, whereas the short apnoeas have lesser gas exchange effects. In our population, reducing the desaturation requirement, while maintaining the standard ten second criteria, would see the inclusion of an additional 3.5 apnoeas per hour, which would increase the apnoea index by 15%.

The Hypopnoea Index

Altering the minimum event criteria had different and subtler effects on the hypopnoea index. The number of hypopnoeas scored peaked at 16.6 per hour when events longer than 15 seconds were scored. However, as the duration criteria was extended or reduced, the number of hypopnoeas scored fell. The fall in the hypopnoea index, when the minimum event duration is reduced, is not because fewer respiratory events are occurring, but because of different classification of the events. Figure 3.22 demonstrates that during a hypopnoeic episode there may be a period of absent ventilation, respiratory event analysis scores apnoeas before scoring hypopnoeas, thus reducing the minimum event duration allows some short periods of absent ventilation to be scored as apnoeas, and hence the previously scored hypopnoea will be unrecognized.

Fig 3.22 - Digramatic example of short apnoeas occurring within hypopnoeic episodes.



Increasing the duration requirement beyond 15 seconds resulted in a reduction in the number of events scored by excluding the shorter events.

Reducing the desaturation requirement from 4% to 2% had little effect on the hypopnoea index and appeared to be unaffected by the minimum duration of the hypopnoeas. The maximum effect was seen in hypopnoeas lasting for a minimum of twelve seconds; the mean hypopnoea index increased by 1.7 events per hour (10.4%). The smallest effect was seen for events lasting a minimum of 30 seconds; the mean hypopnoea index increased by 0.9 events per hour (9%). This is likely to reflect the fact that the majority of the hypopnoeas scored are severe enough to create a 4% fall in arterial oxygen saturation, or have an associated EEG arousal.

Reducing the desaturation requirement for events hypopnoeas scored with the standard minimum duration of ten seconds, would result in an additional 1.5 hypopnoeas per hour being scored.

The Apnoea-Hypopnoea Index

When these data were combined and considered as the apnoea hypopnoea index they demonstrated a linear fall as the minimum event duration was increased from 6 to 30 seconds demonstrated. Figure 3.9 (page 114) demonstrates that in this population, increasing the minimum event duration by 1 second will see a mean reduction in the AHI of 1.14 events per hour. Reducing the desaturation requirement when events with a minimum duration of ten seconds are scored, will see an increase in the AHI of 5 events per hour.

Figures 3.9a and 3.9b (pages 115 and 116) demonstrate that increasing the minimum event duration results in a decrease in AHI whether scored with a 2% or a 4% desaturation. There were no subgroups in this population who experienced different degrees of changes in AHI when the respiratory event criteria were altered, all AHIs were similarly proportionally affected.

The Relationships between AHI and Sleepiness

A potentially important consequence of modifying the event criteria would be to improve the relationship with daytime symptom intensity or with sleep disruption as assessed by arousal index.

ESS and Apnoea Index

The ESS was strongly correlated to the apnoea index. The relationship was strongest when all apnoeas with a minimum duration of 6 seconds were scored. The relationship was slightly but not significantly weakened as the minimum event duration criteria were increased to exclude the shorter events. The weakest, but still significant relationship, was between the ESS and the apnoea index derived from scoring only the events lasting over 30 seconds ($p<0.02$).

ESS and Hypopnoea Index

The ESS had markedly weaker relationships with the hypopnoea indices. Statistically significant correlations were only seen when the minimum event duration was set between 10 and 20 seconds. These minimum event criteria were the only ones that resulted a hypopnoea index greater than 15 events per hour.

ESS and AHI

The relationship between the ESS and AHI appears to be influenced primarily by the apnoea index. Figure 3.13 (page 126) demonstrates that the relationships between the ESS and apnoea index, and the ESS and apnoea-hypopnoea index are very closely matched. However, when the minimum event duration is set between 10 and 15 seconds the relationship with the ESS is weaker with the apnoea index than the AHI. The relationship between the ESS and hypopnoea index is at its greatest with these minimum event criteria, thus the scoring of hypopnoeas strengthens the relationship between respiratory events and daytime sleepiness when the standard ten second events are considered. The best relationship was seen between the ESS and AHI was when events longer than 12 seconds are scored.

The Effect of Desaturation Criteria on the Correlations with Sleepiness

Reducing the desaturation requirement resulted in more respiratory events being scored, but this worsened the AHI-ESS relationship. Hypopnoeas are only scored if they have an associated desaturation or an EEG arousal, and so the additional hypopnoeas scored when the desaturation criteria was relaxed, consisted of hypopnoeas that had not been scored with an EEG arousal and therefore may not have been severe enough to significantly disrupt sleep and influence the daytime sleepiness. The additional apnoeas scored when the desaturation requirement was reduced, consisted mainly of short apnoeas, which were excluded from the AHI when the event duration criteria were increased. However, reducing the desaturation requirement affected the AHI-ESS relationship to a similar extent regardless if the minimum event duration, this also suggests that the large numbers of short events scored when the desaturation requirement was reduced, are also unlikely to exert any significant influence on subjective daytime sleepiness. The short apnoeas scored with 2% desaturations may or may not have an associated arousal, however it appears that events which cause a 2% fall in SaO2 have little effect on daytime sleepiness.

In this structured population, the arousal index was not correlated with the ESS. This further emphasizes the poor relationship between sleep disruption measured using standard EEG techniques and daytime sleepiness, and is not surprising given the number of events where significant changes in EEG frequency occur at apnoea termination without the ASDA criteria being met (Rees *et al* 1995). Observations of the disruptive effects of brief arousal from sleep on reduced mental functioning (Martin *et al* 1997) support the need for developing alternative approaches to assessing sleep disruption.

We were disappointed not to see better relationships of the AHI with the 2% desaturation threshold and ESS. Even though this identified more events, including these briefer episodes did not improve the relationship with ESS or arousal frequency. One important reason for the similarity of our data was the strong correlation of the AHI defined at seconds and most of the other derivatives. This study suggests that most of the 'signal' is being captured using the conventional form of data expression, and relatively little is to be gained by modifying it. The suggestion that 'larger' events might provoke a greater arousal which would relate

better to symptoms (Collard *et al* 1996) is not supported by this data. A greater sleep disruptive effect of large events cannot be excluded but it is possible that that the disruptive properties of larger apnoeas are lost by excluding the arousals with briefer episodes.

In summary, the conventional method of reporting 10 second events is surprisingly robust and explains a significant amount of the variance of daytime sleepiness in a structured population of patients attending for the assessment of possible OSAHS. However, this data also suggests that scoring hypopnoeas, while quantifying more abnormal respiratory events and increasing the AHI, does not improve the relationship between the apnoea index and ESS. The strongest relationship between polysomnographic measures and measures of daytime sleepiness, and one that has been consistently shown in this work and by several other authors, is that between the desaturation index and ESS. Davies et al (2000) also demonstrated that the desaturation index (4% desaturations as opposed to 2% and 3%) was the measure from overnight oximetry that best predicted a symptomatic response to nasal continuous positive when using the ESS. Arousal index and other EEG related indices contribute little to the relationship, possibly because respiratory events are a better marker of sleep disruption than visible EEG events. Thus, although the ASDA criteria for defining OSAHS is robust, it appears is may be too elaborate and that measuring 4% desaturations may be sufficient. Polysonography may be used in cases where a diagnosis is unclear.

Chapter Four

The ventilatory and cardiovascular responses to progressive hypoxia during wakefulness in normal subjects and patients with obstructive sleep apnoea hypopnoea syndrome.

4.1 INTRODUCTION

As discussed earlier (pages 2-15), the importance of CO_2 and O_2 in controlling ventilation has been established for many years, yet their exact actions and mechanisms are still not fully understood. Small perturbations in inhaled CO_2 tensions produce large changes in minute ventilation (Haldane and Priestly 1905). and the increase in ventilation in response to hypoxia is significantly increased by hypercapnia, the increase was greater than the arithmetic sum of the two combined responses (Weil et al 1970).

Much less is understood about the cardiovascular responses to hypoxia and hypercapnia in man. Hedner *et al* (Hedner *et al* 1992) demonstrated the potent pressor effects of hypoxia in normal subjects and OSAHS patients under eucapnic conditions, but other authors have demonstrated OSAHS patients have an augmented response (Narkiewicz *et al* 1998). There is a need to investigate the cardiovascular responses to transient acute hypoxia under both eucapnic and hypercapnic conditions in man to assess whether hypercapnia augments the heart rate and blood pressure responses to hypoxia, as seen with the ventilatory response, or whether the separate groups of caudal hypothalamic neurons, which separately regulate the cardiovascular responses to hypoxia and hypercapnia, produce independently modulated responses without the interaction of the combined stimuli.

Several recent studies have demonstrated that there is a complex neural feedback mechanism between lung inflation and blood pressure. The mechanical effects of ventilation on heart rate and blood pressure have been established for many years. During expiration the positive intrathoracic pressure results in a small rise in arterial pressure, the baroreceptors response to this results in a fall in heart rate. During inspiration the opposite occurs. However, recent studies have demonstrated lung stretch limits blood pressure changes. Work with dogs has shown that lung inflation causes a reflex induced increase in systemic vascular capacitance as well as a decrease in both peripheral resistance and cardiac sympathetic nerve efferent activity. This lung inflation reflex is mediated primarily through vagal afferent nerve fibers with a small contribution from other afferent nerve pathways, and has the potential to attenuate the pressor effects of hypoxia (Vatner et al 1981 and Cheng et al 1989).

It has been suggested that elevated wakeful sympathetic nerve activity seen in OSAHS patients occurs as a result of the recurrent hypoxaemia, and may contribute to chronically elevated blood pressure (Leuenberger *et al* 1995, Somers 1995). Animal models for sleep disordered breathing demonstrate that recurrent intermittent hypoxia, without airway obstruction or repetitive arousals from sleep, leads to the development of hypertension (Fletcher *et al* 1996). Not all patients with OSAHS develop hypertension and studies investigating peripheral chemoreceptor function in these patients have been contradictory, as discussed earlier, Narkiewicz *et al* (Narkiewicz *et al* 1998) suggested there is a potentiation of peripheral chemoreflex sensitivity in OSAHS patients, whereas Osanai (Osanai *et al* 1999) reported a depression of peripheral chemosensitivity.

The accurate functioning of the peripheral chemoreceptor response in OSAHS patients, and the role of the hypoxic stimulus in the development of hypertension remain unclear. Rebuck and Campbell (Rebuck and Campbell 1974) used a closed circuit rebreathing technique, modified from the circuit used by Read et al (Read 1967), to assess the ventilatory responses to progressive hypoxia. Their work demonstrated that variation in the ventilatory response to hypoxia was significant between subjects but was reproducible for an individual over time. This simple and validated technique can be applied to assess the ventilatory and cardiovascular responses to hypoxia in hypercapnia in OSAHS patients and healthy subjects, without the need for making repeated measures.

4.2 STUDY AIMS

In this study we wished to test the hypothesis that augmenting chemoreceptor function by CO_2 will increase the cardiovascular response, assessed using the slope of the BP/SaO_2 and HR/SaO_2 relationships, to determine:

- if similar or different relationships apply to OSAHS patients
- whether they relate to disease severity, assessed by AHI and desaturation index.

4.3 STUDY POPULATION

Volunteers from the University Hospital Aintree were recruited as healthy subjects, the majority being nurses or student nurses. Subjects were aged over 18 years and free from cardiovascular and respiratory disease, disorders that would affect cardiac or respiratory function, diabetes, and be free of symptoms indicative of OSAHS, such as self reported snoring and excessive daytime sleepiness (EDS). A range of ages was recruited with a non-intentional bias towards a younger group reflecting the higher availability of the student and newly qualified nursing population. Patients who had been referred from the University Hospital Aintree outpatients sleep clinic for a diagnostic PSG were recruited. Patients who were aged over 18 years and diagnosed with having moderate or severe OSAHS indicated with an ASDA scored AHI over 30 events per hour, and no other cardio-respiratory or endocrine disorder, were eligible and undertook the study the morning after their diagnostic PSG. Patients were not yet receiving CPAP treatment. They were normotensive, not taking any cardiovascular medication, and were not suffering with any cardiac or respiratory disorders other than OSAHS.

4.3 Methods

4.3.1 Measurements

The measurement of the principal outcome variables is detailed in chapter two (pages 47-64). We recoreded:

- **Beat by beat systolic and diastolic arterial blood pressure** using the non-invasive 'Finapres 2300' digital plethysmograph. The cuff was placed around the middle finger of the subjects' left hand and the hand rested on the arm of the chair to ensure it remained in a fixed position relative to the mid-sternum for the duration of the test.
- **Heart Rate and SaO_2** using a Datex-Ohmeda 3700 pulse Oximeter with an ear probe. This was set for a fast response time which gives an averaged signal over 3 seconds.
- **Breath-by-Breath respiratory cycle and gas analysis** using a Medgraphics CPX CardioRespiratory system. During the hypoxic challenges we monitored breath-by-breath FiO2, FiCO2, FeO2, FeCO2, EtCO2, EtO_2, V_E, Vt, Ti and Te.

4.3.2 Procedures

Ethical approval was given by the South Sefton ethics board and written consent was obtained from all participants. Subjects abstained from alcohol, caffeine and exercise during the morning prior to the testing. All tests were performed between 10.00 and 12.00 am. Subjects were studied while seated in a comfortable chair, facing away from the recording and rebreathing apparatus, and wearing the ear oximeter probe, finger BP monitor and nose clips. They breathed through a mouthpiece attached to a circuit which could be used to induce progressive hypoxia under isocapnic conditions. Resting data was acquired for 4 to 6 minutes or until a steady baseline ventilation was observed. The circuit was then closed and the hypoxic challenge commenced as described earlier. Subjects had progressive hypoxia induced under both isocapnic normocapnic and isocapnic hypercapnic conditions administered in a random order, with a 40-minute break between tests.

Data are expressed as the group mean absolute change in ventilation, blood pressure and heart rate from rest to hypoxic under both CO_2 conditions. The relationships between the responses of the two groups of subjects and the two CO_2 tensions were assessed using the Pearsons correlation coefficient.

4.5 RESULTS

4.5.1 Study Population

Table 4.1 shows the group mean and standard deviations for the two groups of subjects in this study. They comprised of 12 healthy subjects and 13 OSAHS patients. There was a significantly greater ratio of males in the OSAHS group, they were also significantly older and heavier then the healthy subjects. The OSAHS patients had a group mean AHI of 62.5 events per hour whilst the healthy subjects did not have any symptoms indicative of sleep disordered breathing, including snoring and excessive daytime sleepiness.

Table 4.1 – Study Population

	HEALTHY	OSAHS
n	12	13
SEX	6 MALE	12 Male
AGE	34.2 (10.0)	55.5 (8.2)
HEIGHT (m)	1.74 (10.3)	1.75 (5.1)
WEIGHT (Kg)	77.7 (7.24)	107 (20.1)
BMI (Kg/m2)	26.2 (5.07)	34.9 (6.9)
AHI	-	62.5 (18.4)

group mean (standard deviation)

4.5.2 End-Tidal CO_2 Tensions

Table 4.2 shows the group mean data for the $EtCO_2$ during the hypoxic challenges. Normocapnia was maintained at the individuals resting level, which, in both the normals and OSAHS group, was 38mmHg. The standard deviations demonstrate some variance around this mean. The group mean hypercapnic $EtCO_2$ was significantly higher than the resting CO_2 levels ($p<0.001$), but not different between the two groups. The individual variation was the mean standard deviation of the $EtCO_2$ during the hypoxic period and demonstrated isocapnia was well maintained in each individual during the progressive hypoxic periods.

Table 4.2 - End-tidal CO_2 tensions.

	Group Mean EtCO2 mmHg (SD)	Group Mean Individual Variation during the challenge (SD)
Normocapnic Healthy	38.0 (2.2)	1.58 (0.52)
Normocapnic OSAHS	38.3 (2.8)	1.53 (0.48)
Hypercapnic Healthy	45.3 (1.9)	1.49 (0.49)
Hypercapnic OSAHS	46.4 (2.2)	1.57 (0.56)

4.5.3 Oxygen Saturation Data

All subjects started the hypoxic challenges with a similar resting SaO_2. Table 4.3 demonstrates that the group mean resting SaO_2 under normocapnic and hypercapnic conditions lay between 97 and 98%. There was no significant difference between the resting SaO_2 of the 2 groups ($p>0.1$), and the small standard deviation shows the limited inter-subject variability.

Table 4.3 - The Oxygen Saturation at rest and when hypoxic

	Group Mean Resting SaO_2 (SD)	Group Mean Lowest SaO_2 (SD)	Mean % change
Normocapnic Healthy	98.0 (1.1)	85.3 (5.2)	12.8 (5.4)
Normocapnic OSAHS	97.2 (1.0)	85.6 (4.3)	11.6 (4.8)
Hypercapnic Healthy	97.8 (1.4)	85.3 (5.2)	12.5 (5.3)
Hypercapnic OSAHS	97.1 (0.8)	85.6 (4.3)	11.8 (4.8)

Each individual's data sets were adjusted so that under both CO_2 tensions they received the same hypoxic stimulus, with a mean minimum SaO_2 of 85%.

4.5.4 Changes in ventilation with Progressive Hypoxia

The minute ventilation at rest, at the minimum level of SaO_2, and the percentage change for the normal and OSAHS groups are presented in table 4.4.

Table 4.4 - Group mean minute ventilation at rest and

	Resting Ventilation Group Mean L/min (SD)	Hypoxic Ventilation Group Mean L/min (SD)	Percentage Change Group Mean (SD)
Normocap Healthy	12.1 (4.1)	29.7 (13.8)	188.2 (207.1)
Normocap OSAHS	14.1 (4.7)	21.2 (8.8)	55.0 (55.8)
Hypercap Healthy	11.6 (4.4)	44.8 (18.1)	299.7 (164.8)
Hypercap OSAHS	13.7 (7.4)	41.7 (12.5)	296.6 (183.7)

There was no significant difference between the resting ventilation of the groups or after 4 –5 mins of acclimatization to the higher CO_2 tension or in the peak ventilation at the end of the tests. Minute ventilation increased during the progressive hypoxic challenge in all but one of the normal subjects and was consistently higher during the hypercapnic study.

4.5.5 The Acute Hypoxic Ventilatory Response

The acute hypoxic ventilatory response (AHVR), calculated from the slope of the VE/SaO_2 response is demonstrated in table 4.5 and figure 4.1. Normal subjects and OSAHS patients have similar responses under normocapnic ($p>0.1$) and hypercapnic conditions ($p>0.05$). The large standard deviation and range indicate that, in these small groups, there was significant inter-subject variability within the groups

Table 4.5 - The Acute Hypoxic Ventilatory Responses

	Hypoxic Ventilatory Response ($L/min/\%SaO_2$)		
	Group Mean	SD	Range
Normocapnic Healthy	-1.40	1.30	-0.13 to -4.58
Normocapnic OSAHS	-0.81	0.73	-0.27 to -2.86
Hypercapnic Healthy	-3.98	2.41	-0.91 to -8.22
Hypercapnic OSAHS	-2.76	1.64	-0.64 to 6.38

Fig 4.1 - The effect of hypercapnia on the AHVR in normal subjects and OSAHS patients.

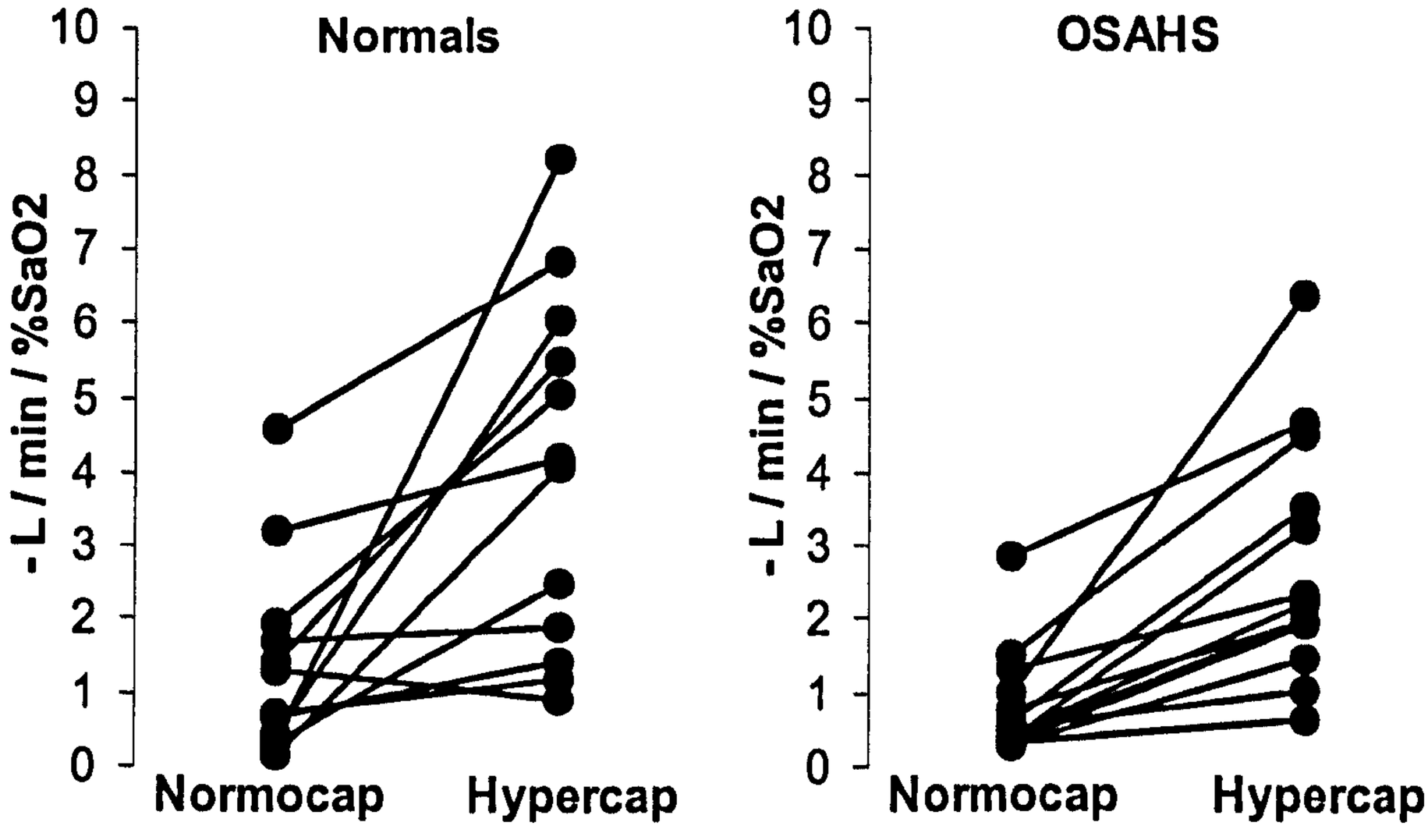


Figure 4.2 demonstrates increasing the CO_2 tension significantly increased ($p<0.005$) the ventilatory response for the same degree of hypoxia in both groups of subjects. There was no significant difference in the degree of increase between the two groups ($p>0.1$).

4.5.6 The Absolute Heart Rate Response to Hypoxia

The heart rate responses to progressive hypoxia have been expressed in a similar fashion to the ventilatory response data. The group mean absolute heart rates at rest and the peak in response to hypoxia are presented in table 4.6.

Table 4.6 - The resting heart rate with normocapnic and hypercapnic conditions in healthy subjects and OSAHS patients.

	Resting Heart Rate Group Mean Beats/min (SD)	Hypoxic Heart Rate Group Mean Beats/min (SD)	Precentage Change Group Mean (SD)
Normocap Healthy	77.8 (14.7)	90.4 (13.9)	17.1 (10.1)
Normocap OSAHS	83.2 (10.4)	89.8 (9.9)	8.2 (6.4)
Hypercap Healthy	79.7 (10.7)	93.1 (11.1)	18.1 (17.1)
Hypercap OSAHS	84.1 (11.1)	89.2 (9.4)	6.6 (4.6)

There was no significant difference between the resting heart rates of the groups with either CO_2 tension ($p>0.1$). There was also no significant difference between the resting heart rates under normocapnic or hypercapnic conditions ($p>0.1$).

Both healthy subjects and OSAHS patients demonstrated a significant increase in heart rate when exposed to hypoxia. The healthy subjects had a slightly, but not significantly, greater increase in heart rate in response to the hypoxic conditions.

4.5.7 The Acute Hypoxic Heart Rate Response

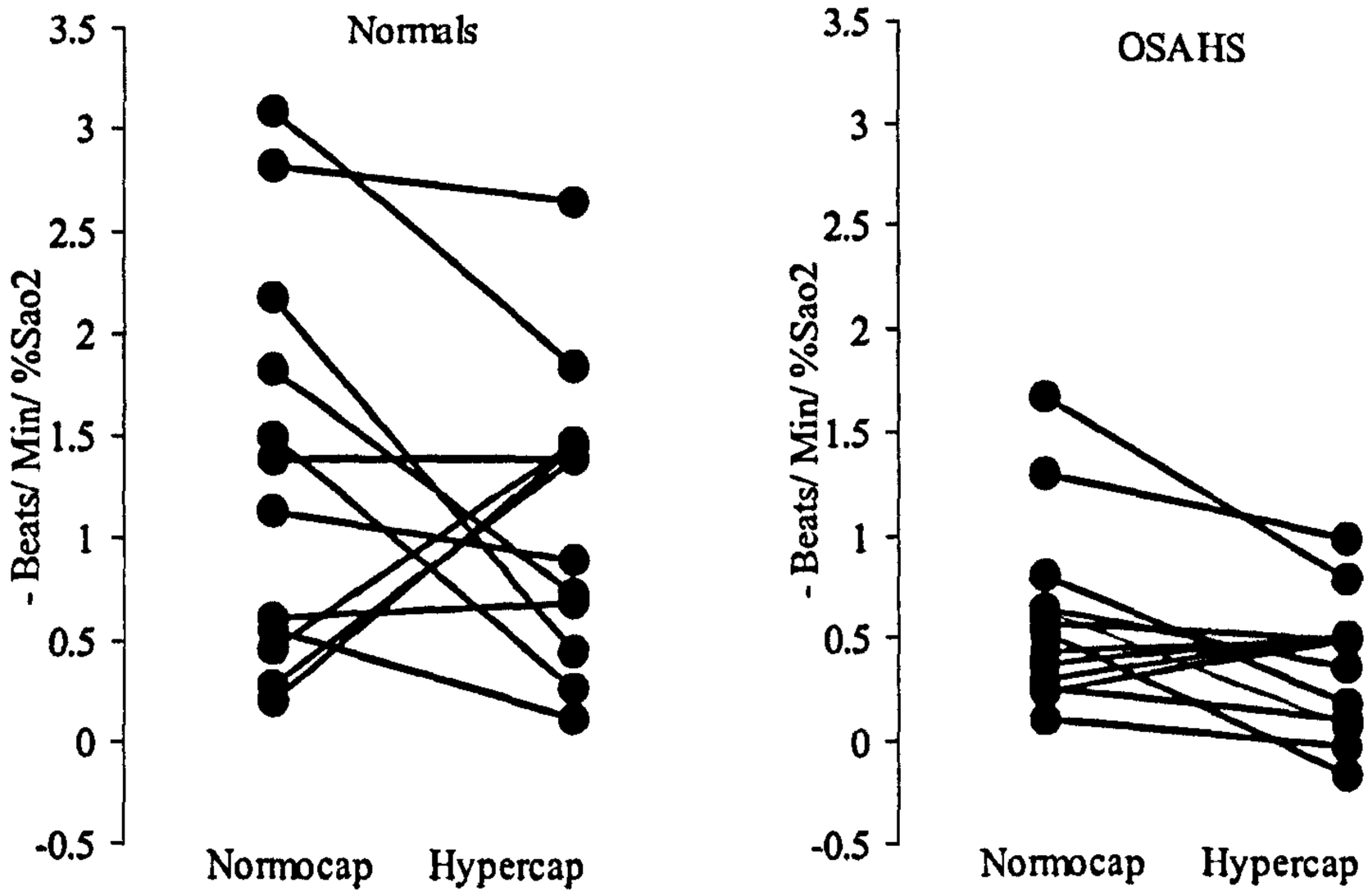
Tables 4.7 and figure 4.2 demonstrate the group mean acute hypoxic heart rate responses under normocapnic and hypercapnic conditions

Table 4.7 - The acute hypoxic heart rate response

	Hypoxic Heart Rate Response (Beats/Min/%SaO_2)		
	Group Mean	SD	Range
Normocapnic Healthy	1.34	0.94	0.20 – 3.10
Normocapnic OSAHS	0.59	0.44	0.09 – 1.66
Hypercapnic Healthy	1.11	0.73	0.12 – 2.64
Hypercapnic OSAHS	0.36	0.33	-0.17 – 0.98

The data demonstrates that an average healthy subject had an increase in heart rate of 1.3 beats per minute for each 1% fall in SaO_2 under normocapnic conditions and 1.1 beats per minute under hypercapnic conditions. The large standard deviations show a large inter-subject variability in the heart rate response to hypoxia within these small populations.

Fig 4.2 - The Effects of Hypercapnia on the Acute Hypoxic Heart Rate Responses.



Both groups of subjects demonstrated an increase in heart rate in response to the progressive hypoxia under both CO_2 tensions. These graphs demonstrate a wide range of responses in the healthy subjects, and less variation in the OSAHS group. OSAHS patients had a reduced response compared to the normals under normocapnic conditions ($p<0.05$), this difference was more marked with hypercapnia ($p<0.005$).

Hypercapnia did not increase the heart rate response to hypoxia in the healthy subjects, but a significant attenuation of the heart rate response to hypoxia was seen in the OSAHS patients when the CO_2 tension was increased ($p<0.05$).

4.5.8 The Absolute Blood Pressure Response to Hypoxia

Mean Blood Pressure

Table 4.8 shows the mean blood pressure at rest and the peak mean blood pressure seen in response to the hypoxic stimulus for the healthy subjects and OSAHS patients.

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Tables 4.8 - The mean blood pressure at rest in healthy subjects and OSAHS patients.

	Resting BP Group Mean mmHg (SD)	Hypoxic BP Group Mean mmHg (SD)	Precentage Change Group Mean (SD)
Normocap Healthy	103 (13.3)	116 (12.2)	14.5 (18.6)
Normocap OSAHS	119 (23.3)	126 (23.3)	6.7 (4.2)
Hypercap Healthy	111 (18.3)	140 (20.2)	27.1 (19.8)
Hypercap OSAHS	127 (23.3)	142 (23.5)	14.7 (8.7)

Table 4.8 demonstrates that OSAHS patients had a higher resting blood pressure than the healthy subjects ($p<0.05$). Both groups showed significant increases in mean blood pressure in response to progressive hypoxia. This hypoxic pressor response was augmented with the higher CO_2 tension.

4.5.9 The Acute Hypoxic Mean Blood Pressure Response

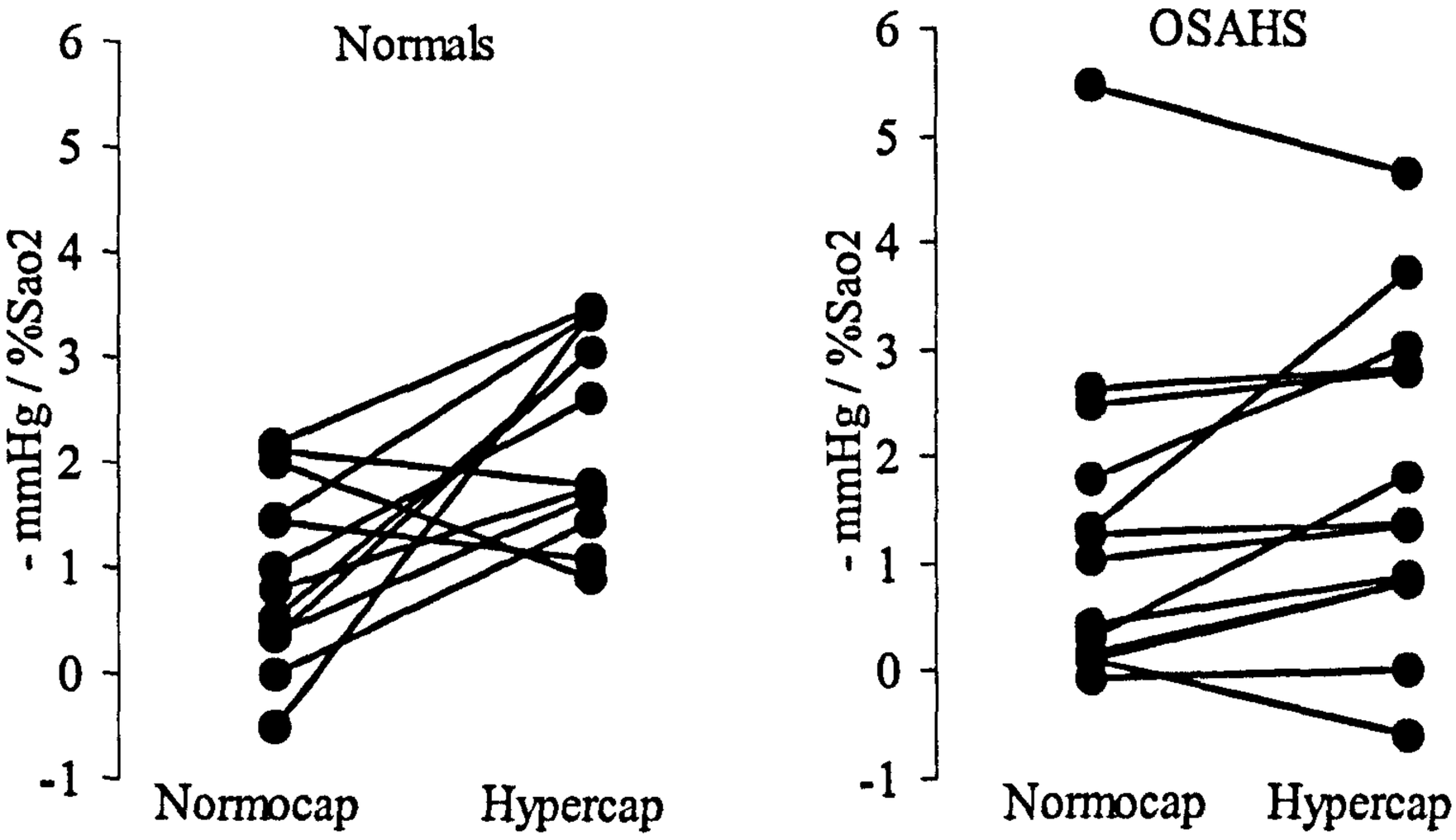
Table 4.9 and figure 4.3 demonstrate the group mean acute hypoxic pressor responses. This response was not significantly different between the two groups under normocapnic or hypercapnic conditions (p=0.26 and 0.17 respectively).

Table 4.9 - The acute hypoxic pressor response.

	Hypoxic Mean Blood Pressure Response (mmHg / %SaO_2)		
	Group Mean	SD	Range
Normocapnic Healthy	- 0.98	0.87	+0.49 to -2.178
Normocapnic OSAHS	- 1.23	1.54	+0.07 to -5.44
Hypercapnic Healthy	- 2.31	0.96	-0.92 to -3.47
Hypercapnic OSAHS	- 1.81	1.51	+0.06 to -4.65

Both groups did however demonstrate a significant augmentation of the response when the higher CO_2 tension was maintained (Healthy $p<0.005$, OSAHS $p<0.05$).

Fig 4.3 - The Effect of Hypercapnia on the Acute Hypoxic Mean Blood Pressure Response.



These data demonstrate that the increase in the acute hypoxic mean blood pressure response with the increased CO_2 tension, was less consistent in the OSAHS group compared to the normal subjects and when compared to the change in the ventilatory responses.

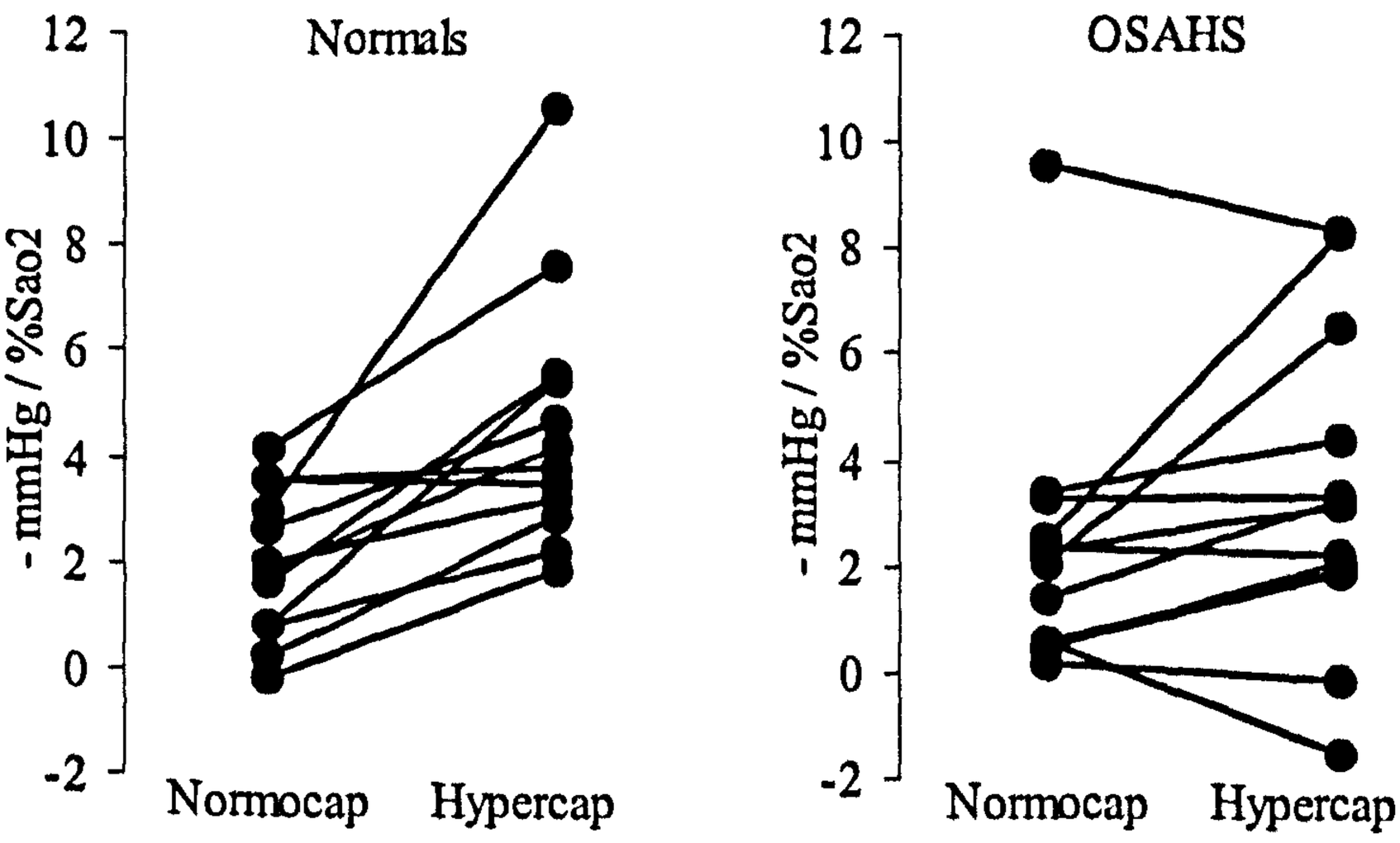
4.5.10 The Acute Hypoxic Systolic Blood Pressure Response

Table 4.10 and fig 4.4 demonstrate no significant difference between the systolic blood pressure responses of the two groups under either CO_2 tension (p=0.45 with normocapnia, p=0.12 with hypercapnia). Both groups showed a significant augmentation of the response when the higher $EtCO_2$ was maintained (normals p=0.0006, OSAHS p=0.02).

Table 4.10 - The acute hypoxic systolic blood pressure response

	Hypoxic Systolic Blood Pressure Response (mmHg / $\%SaO_2$)		
	Group Mean	SD	Range
Normocapnic Healthy	-2.06	1.41	+0.12 to -4.20
Normocapnic OSAHS	-2.24	2.46	-0.15 to –9.53
Hypercapnic Healthy	-4.68	2.46	-1.93 to -10.67
Hypercapnic OSAHS	-3.36	2.92	+1.53 to -8.28

Fig 4.4 - The Effects of Hypercapnia on the Acute Hypoxic Systolic Blood Pressure Response



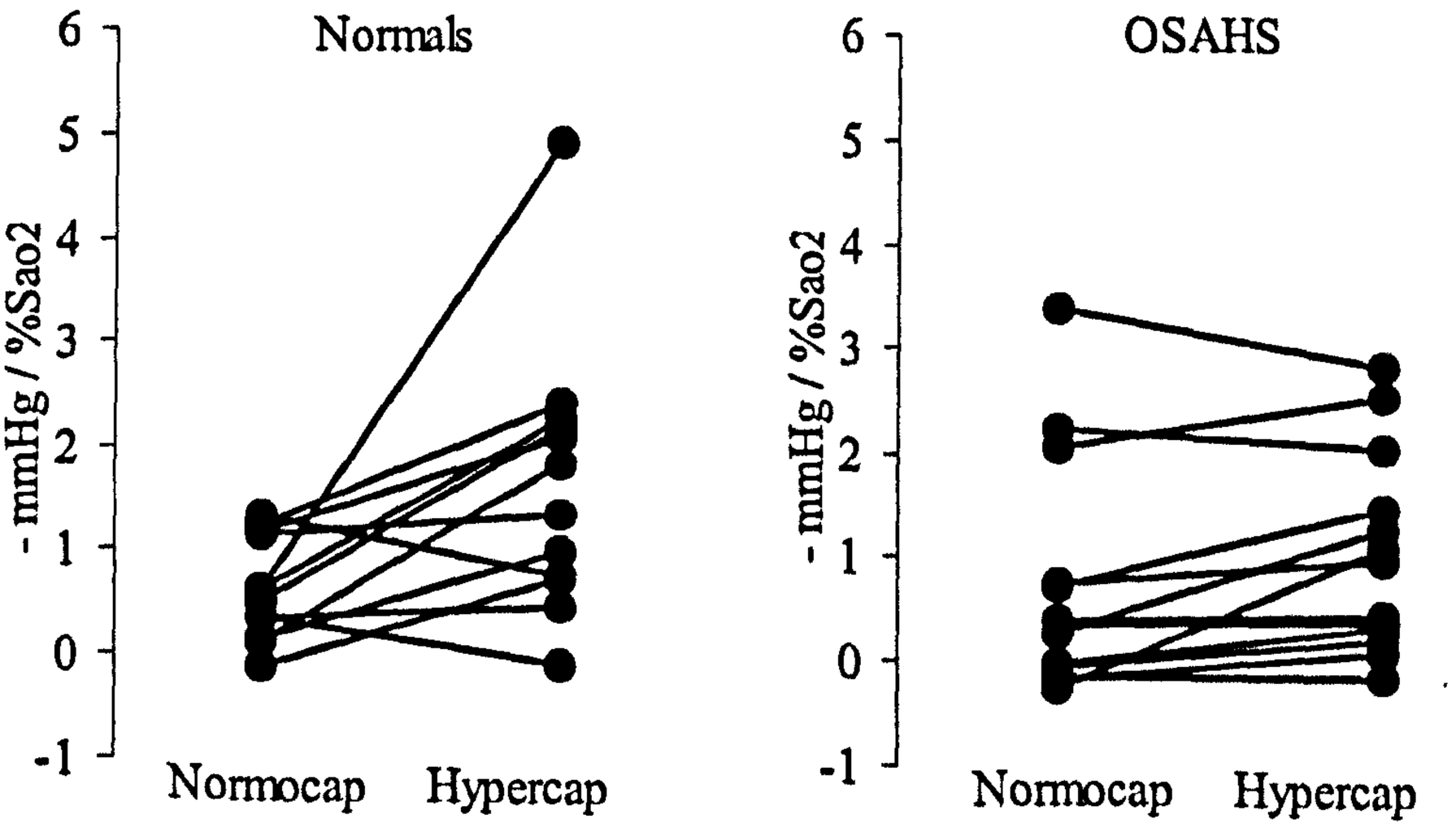
4.5.11 The Acute Hypoxic Diastolic Blood Pressure Response

Table 4.11 and figure 4.5 show the acute hypoxic diastolic blood pressure responses followed the same trend as the systolic blood pressure responses. There was no significant difference between the responses of the two groups under either CO_2 tension (p=0.39 with normocapnia, p=0.08 with hypercapnia), and both groups showed a significant augmentation of the response under the higher CO_2 tension (nomals p=0.002, OSAHS p=0.016).

Table 4.11 - The acute hypoxic diastolic blood pressure response.

	Hypoxic Diastolic Blood Pressure Response (mmHg / $\%SaO_2$)		
	Group Mean	SD	Range
Normocapnic Healthy	-0.65	0.49	+0.09 to -1.36
Normocapnic OSAHS	-0.72	1.13	+0.27 to -3.39
Hypercapnic Healthy	-1.69	1.32	+0.06 to -4.97
Hypercapnic OSAHS	-1.03	0.96	+0.14 to -2.83

Fig 4.5 - The Effects of Hypercapnia on the Acute Hypoxic Diastolic Blood Pressure Responses



4.5.12 The interaction of Minute Ventilation and Blood Pressure

The increases in mean blood pressure and ventilation in response to hypoxia were positively correlated for both normal subjects and OSAHS patients. Table 4.12 presents the group mean correlation coefficients for the relationships between the changing mean blood pressure and minute ventilation during the hypoxic challenges, and demonstrates that the increase in CO_2 tension significantly improved the relationship between the blood pressure and ventilation ($p<0.05$ normals, $p<0.01$ OSAHS). The relationships were not significantly different between the two groups ($p>0.05$)

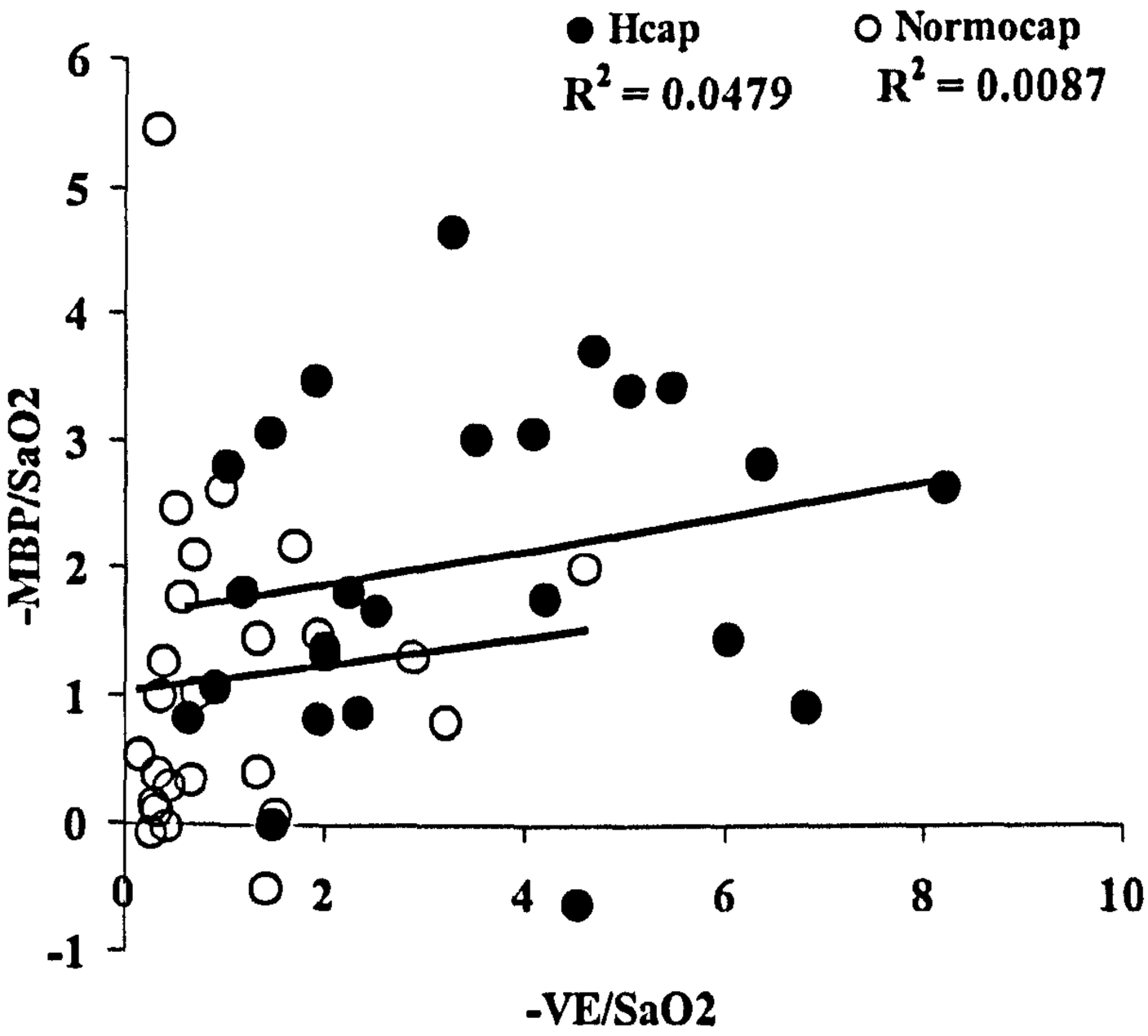
Table 4.12 – The relationship between the increase in ventilation and mean blood pressure with hypoxia.

	ΔBP/ ΔVE Normocapnic Hypoxia	ΔBP/ ΔVE Hypercapnic Hypoxia
Healthy	0.443 (0.331)	0.598 (0.441)
OSAHS	0.189 (0.312)	0.531 (0.499)

Group mean correlation coefficients (SD)

There was no significant difference between the blood pressure/ventilation interaction of the two groups. Their data were then pooled and analysed collectively. Figure 4.6 demonstrates the relationship between the pressor response and the ventilatory response to hypoxia, with normocapnia and hypercapnia. The wide scatter shows there was no direct interaction between the two responses. There was no improvement in these relationships when looking at the collective data compared to analyzing the separate OSAHS and healthy groups data.

Fig 4.6 The interaction of the pressor responses and ventilatory responses to hypoxia for the OSAHS and Healthy combined data.



The Interaction of Tidal Volume and Blood Pressure

The increases in mean blood pressure and tidal volume in response to hypoxia were also positively correlated for both groups of subjects. Table 4.13 presents the group mean correlation coefficients for the relationships between the changing mean blood pressure and tidal volume during the hypoxic challenges. As with the relationship between minute ventilation and mean blood pressure, the increase in CO_2 tension significantly improved the relationship between the blood pressure and tidal volume for both groups (normals $p<0.05$, OSHAS $p=0.02$).

Table 4.13 – The relationship between the increase in tidal volume and mean blood pressure with hypoxia.

	BP/Vt Normocapnic Hypoxia	BP/Vt Hypercapnic Hypoxia
Healthy	0.417 (0.312)	0.528 (0.390)
OSAHS	0.141 (0.401)	0.485 (0.355)

Group mean correlation coefficients (SD)

4.5.13 The effects of age on the ventilatory and cardiovascular hypoxic responses.

The OSAHS patients were significantly older than the healthy group ($p<0.001$). Table 4.14 demonstrates that there are variable and generally weak correlations between age and the cardiovascular responses to hypoxia.

Table 4.14 - The correlation coefficients between age with the acute hypoxic responses in healthy subjects and patients with OSAHS

		Acute Hypoxic Ventilatory Response	Acute Hypoxic Heart Rate Response	Acute Hypoxic Mean BP Response
Healthy	Normocapnic	-0.322	-0.686	-0.485
OSAHS	Normocapnic	0.164	-0.261	-0.673
Healthy	Hypercapnic	0.362	-0.347	0.044
OSAHS	Hypercapnic	-0.247	-0.253	-0.748*

Values reported are Pearson correlation coefficients (r). (* $p<0.05$)

The only significant correlation with age was the mean blood pressure response seen in OSAHS patients under hypercapnic conditions. This suggests as the age of the patients increases their acute hypoxic blood pressure response under hypercapnic conditions becomes more negative i.e a greater response.

4.5.13 The effects of BMI on acute hypoxic responses.

The OSAHS group were significantly heavier than the healthy group ($P<0.005$). There were variable and generally weak correlations between the hypoxic responses and BMI, none of which were statistically significant.

Table 4.15 The correlation coefficients for the relationships between BMI and hypoxic responses .

		Acute Hypoxic Ventilatory Response	Acute Hypoxic Heart Rate Response	Acute Hypoxic Mean BP Response
Healthy	Normocapnic	0.504	0.406	0.495
OSAHS	Normocapnic	-0.05	-0.211	-0.364
Healthy	Hypercapnic	-0.043	0.164	-0.177
OSAHS	Hypercapnic	-0.134	0.014	-0.446

Values reported are Pearson correlation coefficients (r).

4.5.14 The effects of AHI on the acute hypoxic responses.

Table 4.16 shows there was no significant correlation between the disease severity and any of the responses to acute progressive hypoxia.

Table 4.16 - The correlation coefficients between AHI and the acute hypoxic responses in healthy subjects and patients with OSAHS

		Acute Hypoxic Ventilatory Response	Acute Hypoxic Heart Rate Response	Acute Hypoxic Mean BP Response
OSAHS	Normocapnic	-0.181	-0.276	-0.5
	Hypercapnic	-0.281	0.058	-0.493

Values reported are Pearson correlation coefficients (r).

Mulitiple Regression Analyses

The data for both the healthy subjects and OSAHS patients were pooled and analysed as a single group using multiple regression analysis. This showed that with normocapnia, the heart rate response to hypoxia was strongly influenced by age ($p=0.001$) and was also associated with the size of the ventilatory response ($p<0.05$). With hypercapnia these relationships remain significant ($p=0.02$).

The ventilatory response, with normocapnia or hypercapnia is only associated with the heart rate responses ($p<0.05$).

The mean blood pressure response to hypoxia for the pooled data was influenced by age and BMI, with normocapnia ($p<0.05$). This relationship is strengthened under hypercapnic conditions ($p<0.01$ with age, $p=0.01$ with BMI).

4.6 Discussion

The work in this chapter has demonstrated that OSAHS patients have normal ventilatory responses and blood pressure responses to progressive hypoxia. It has shown that small increases in the $EtCO_2$ significantly augment these responses to a similar degree in healthy subjects and patients with OSAHS. This suggests that peripheral chemoreceptor sensitivity in OSAHS patients, when measured awake, remains normal.

Obstructive sleep apnoea hypopnoea syndrome is known to be associated with changes in arterial blood pressure; small increases during the apnoea (Rees PhD 1995), large surges at arousal (Horner 1996) and the development of chronic hypertension (Lavie *et al* 2000). The development of chronically elevated blood pressure in OSAHS has recently been the subject of much debate. Much of the work undertaken in an attempt to establish a causal association between OSAHS and hypertension has been unsuccessful due to confounding factors such as obesity and age. However, recent data from Young *et al* (Young *et al* 1997) and Lavie *et al* (Lavie *et al* 2000) have added strong support to the argument that OSAHS causes hypertension. The mechanisms underlying these processes remain unknown.

Small rises in blood pressure during the latter part of an apnoea are associated with changes in gas tensions during the apnoea. The $EtCO_2$ of a post-apnoeic breath is associated with the blood pressure rise seen during the event (Rees 1995) and surges in muscle sympathetic nerve activity during an obstructive respiratory event are linked to the degree of hypoxaemia (Leuenberger *et al* 1995). It has been proposed that this recurrent stimulation of peripheral chemoreceptors during apnoeic events may lead to some long-term modification of blood pressure control in OSAHS.

Increasing ventilatory efforts in response to chemoreceptor stimulation and/or airway obstruction during an apnoea can contribute to the arousal and termination of an obstructive event. Gleeson et el demonstrated, in healthy subjects tested with inspiratory loads, hypoxia and hypercapnia, that arousal occurred at different levels of ventilation and arterial chemistry but at similar levels of peak negative oesophageal pressure suggesting that chemoreceptor stimulation and the resulting respiratory drive are important factors in apnoea termination (Gleeson *et al* 1990). The transient acute blood pressure increases at arousal from sleep are a normal phenomenon and occur in the absence of sleep-disordered breathing (Baust *et al*

1968). However, repetitive arousals in OSAHS may contribute to the development of chronically elevated sympathetic activity and blood pressure. Arousals and the associated autonomic surges following respiratory events are not significantly different from those associated with other forms of spontaneous or induced arousal data. Ringler *et al* (Ringler *et al* 1990) demonstrated that auditory arousal from sleep resulted in similar increases in blood pressure to those observed after an apnoeic episode, and oxygen supplementation before spontaneous apnoeas did not significantly reduce the blood pressure increase at apnoea termination. Thus the increased cardiovascular activity at arousal can not fully be explained by individual factors such as hypoxaemia, and may be a result of a number of influences including the increase in CO_2 during the apnoea and the onset of wakefulness. However stimuli that are too small to evoke an EEG visible arousals have also been demonstrated to produce significant blood pressure increases (Davies *et al* 1993). This finding has prompted the investigation of autonomic arousals, specifically reductions in pulse transit time, as a more precise detector of respiratory events and sleep disturbance (Pitson 1995 and 1998)

Other data has suggest that baroreceptor and chemoreceptor sensitivities may be altered in OSAHS patients and this may influence daytime blood pressure (Carlson *et al* 1996, Okabe 1995). Venodilatory responsiveness in OSAHS patients is blunted (Duchna *et al* 2000 and Hedner 1996) and vasoconstrictor activity is increased (Kraiczi 2000). It has also been demonstrated there is an increase in wakeful sympathetic nerve activity (Narkiewicz 1998 and Somers 1995). However, the state of peripheral chemoreceptor function is unclear (Bonsignore et al 1994). Narkiewicz *et al* demonstrated an augmented hypoxic ventilatory response in OSAHS patients compared to normal subjects, whereas Osanai (Osanai *et al* 1999) reported a depression of patients peripheral chemosensitivity.

This study demonstrated that the acute hypoxic ventilatory responses displayed by both healthy subjects and OSAHS patients, when using the Rebuck and Campbell method, were remarkably similar to the previously published data on healthy subjects. Our measured responses (0.13 – 4.58 l/min/%SaO_2 in healthy subjects and 0.27 – 2.86 l/min/%SaO_2 in OSAHS patients) compare well with Rebuck and Campbell's documented normal range (0.26 – 4.12 L/min/% fall in SaO_2). The acute hypoxic ventilatory response was significantly augmented by mild hypercapnia, in

both normal subjects and OSAHS patients. The hypercapnic-hypoxic ventilatory responses were almost three-fold greater than those under normocapnic conditions. The magnitude of this potentiated response was also very comparable to the data of Weil et al (Weil *et al* 1970).

This hypercapnic and hypoxic stimulation of the carotid body increases respiratory efforts which may contribute to the cortical arousal response at the termination of the obstructive event. The blood pressure rise seen during the apnoea may also be a result of the hypoxia-hypercapnia interaction; separate investigators have found associations of this blood pressure rise with hypoxaemia and CO_2 tension (Lueneberger 1995, Rees 1995). Rees also demonstrated that the level of respiratory effort at the end of an apnoea and the change in inspiratory duration account for 80% of the total variability in apnoea duration.

Work by Narkiewicz *et al* (1999) demonstrated an augmented peripheral chemoreceptor response in OSAHS patients compared to normal subjects; they showed there was an absence of a pressor response to hypoxia under normocapnic conditions in normal subjects and a significant mean blood pressure increase (mean 9mmHg) with the 13% fall in SaO_2. The OSAHS patients also had significantly higher ventilatory and heart rate responses to the hypoxic stimulus. The OSAHS patients did however have their $EtCO_2$ maintained at a higher tension compared to normal subjects (38 (SD 1) versus 34 (SD 2) mmHg); although this difference is small our data has suggested that perturbations in CO_2 tensions as small those seen in this study, may result in large augmentations of the acute hypoxic responses.

The findings from Narkiewicz study are contradictory to those published by Osanai *et al* (1999) who reported a depression of peripheral chemosensitivity by a dopaminergic mechanism in OSAHS patients. Using the rebreathe technique they demonstrated significantly reduced ventilatory and heart rate responses in their OSAHS group, and like the OSAHS patients in Narkiewicz group, they also had significantly higher $EtCO_2$ compared to their healthy subjects. Hypoxic withdrawal tests confirmed the reduced peripheral chemoreceptor response. They then used the administration of domperidone, a known stimulant of the AHVR, to show an enhanced responses in the normal group and no significant change in the OSAHS patients. This suggests that the reduced responses were mediated via a dopaminergic mechanism. Hedner *et al* (1992) and Wilcox (1994) have both demonstrated similar

mean blood pressure responses to eucapnic hypoxia in OSAHS patients to those seen in our two groups. Observing the responses to progressive normocapnic hypoxia, Wilcox reported a pressor response was present in all patients (mean 1.4 +/- 1.1 mmHg/%SaO2, range 0.1 - 4.5) and, although there was no significant difference between these responses and those observed in their control group, they found a correlation between the blood pressure response and AHI. Hedner had similar results, using a hypoxic ramp test and maintaining the $EtCO_2$ at 'approximately 40mmHg' and found the same association with AHI. We demonstrated mean blood pressure responses, with normocapnia, of the same magnitude, (0.98 (SD 0.87) mmHg/%SaO_2 in healthy subjects and 1.23 (SD 1.54) mmHg/%SaO_2 in OSAHS) but with no correlation to disease severity. We also demonstrated the important augmenting effects of CO_2 on the acute hypoxic blood pressure responses, and recognize the significance of small changes in CO_2 affecting both blood pressure responses seen during daytime experimental procedures and those during spontaneous apnoeic episodes. The interaction of these two stimuli should not be overlooked when performing standard hypoxic challenges or investigations into the responses to apnoea associated desaturations, as small changes in CO_2 can result in large physiological changes, and so when the effect of hypoxia is being assessed it is crucial that the CO_2 tension is well controlled.

The heart rate responses, which have been shown in other studies to be variable, were unexpected in our data. The lack of augmentation with hypercapnia in healthy individuals and the significant fall in response seen with the higher CO_2 tension in OSAHS patients, suggest that mechanisms other than peripheral chemoreceptor stimulation are involved. The baroreceptor response may be implicated in this observation. As the peripheral chemoreceptors increase the blood pressure in response to hypercapnic hypoxia, the baroreflex will have an increasing function in maintaining homeostatic conditions. Hence the resultant maintenance of, or fall in heart rate with hypercapnic hypoxia may occur as the baroreceptor attempts to maintain blood pressure. However, as we did not assess baroreceptor function in these patients at rest or during the hypoxic challenges its implication in the observed heart rate responses remains speculative.

There was no indication of the lung inflation feedback mechanism limiting or reducing blood pressure. During the progressive hypoxia, tidal volume increased as

expected from the effects of chemoreceptor stimulation. while during hypercapnic hypoxia the increases were more profound. It could be anticipated that the larger increases in tidal volume resulting from both hypercapnic and hypoxic stimuli, would limit or reduce blood pressure and result in a worsening of the correlation, between the ventilatory and pressor responses. This did not occur. The higher CO_2 tension resulted in a stronger positive correlation.

Age, BMI and AHI, did not consistently influence the responses to hypoxia when analysed as two separate groups but when the data were combined stronger associations were seen. Age appeared to influence both heart rate and blood pressure responses to hypoxia. This suggests that repetitive stimulation of the peripheral chemoreceptors does not result in tachyphylaxis and a blunting of their sensitivity, but the responses become blunted with age. However the healthy group, who had greater responses were significantly younger than the OSAHS group. There may be some implication of long-term exposure to repetitive peripheral chemoreceptor stimulation in the dysfunctional control of the cardiovascular system, age matched populations are needed to be able to exclude age as confounding factor.

While the experiments performed in this chapter are satisfactory for assessing the responses to transient falls in SaO_2, small increases in CO_2, and provide a good tool for assessing responses to conditions similar to those met during an obstructive event, the results must not be over interpreted. The recurrent changes in gas tensions and chemoreceptor stimulation may see some adaptation to CO_2. Shifts in the slopes of the responses rather than a change in the slope may occur. There is a need for long-term studies to observe the interaction of: CO_2 tensions, sympathetic activity and blood pressure. 'state effect' on these responses must also be investigated.

Douglas *et al* (1982 a 1982c) and Berthon-Jones *et al* (1982 and 1984) have demonstrated a reduction in the acute ventilatory response to hypoxia and the acute ventilatory response to hypercapnia during stable NREM sleep. The next chapter of this thesis will assess the complex state dependant effects of wake and NREM on the

cardiovascular response to progressive hypoxia and the augmenting effects of hypercapnia.

In summary:

Augmenting chemoreceptor function by CO_2 did increase the cardiovascular responses to hypoxia in theses patients, to a similar extent to that seen in healthy individuals. The size of these responses was not associated with disease AHI or desaturation index.

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Chapter Five

The ventilatory and cardiovascular responses to normocapnic and hypercapnic progressive hypoxia in normal subjects awake and asleep.

5.1 INTRODUCTION

5.1.1 The Effect of Sleep on Ventilation

The onset of sleep and the loss of α-activity in the EEG is associated with significant, rapid and reproducible reductions in minute ventilation (Colrain *et al* 1987). The reduction in metabolic drive and the loss of the waking drive to breathe reduce tidal volume. Douglas *et al* demonstrated that, in 19 healthy adults, this rapid shallow breathing pattern persists in all stages of sleep, and showed that minute ventilation during REM sleep is significantly lower than that during NREM (awake 7.66 ± 0.39, REM 6.46 ± 0.29 NREM 7.18 ± 0.39 l/min) (Douglas 1985).

Peripheral chemoreceptor responses to hypoxia are reduced during sleep. Douglas el al (1982a and 1982c) was one of several authors who investigated the changes in ventilation associated with altered gas tensions during sleep. He demonstrated, in two separate studies, that the hypoxic ventilatory response and the hypercapnic ventilatory response in normal subjects were significantly reduced during sleep compared to wakefulness. Using a modified rebreathing method he showed that the hypoxic response was reduced by one third during NREM and by two thirds during REM. The hypercapnic responses were reduced by 50% during REM and two thirds during REM. The data from the other authors are in general agreement with these results (White *et al* 1982, Sullivan *et al* 1979), most demonstrate a significant amount of variation in the wakeful responsiveness to hypoxia and hypercapnia, but most show similar attenuated responses during sleep, especially during REM. The main differences between the studies, are the wakeful responses, and so the size of the reduction attributed to sleep varies. Sex hormones are known to reduce the ventilatory responses to hypoxia and hypercapnia. The investigations studying large proportions of female subjects or all female groups (White *et al* 1982, Gothe *et al* 1981 and 1982), showed lower wakeful responsiveness and with a smaller effect of sleep than seen in the mixed or all male groups (Sullivan *et al* 1982, Douglas *et al* 1982).

Although the responses to hypoxia and hypercapnia have been individually assessed, little is known about the responses to these combined stimuli during sleep. It has been well established that hypercapnia has an augmenting effect on the hypoxic ventilatory response during wakefulness (Weil *et al* 1971). However,

hypercapnic hypoxia, which is an environment created during a spontaneous apnoea has not been studied during sleep.

5.1.2 Effect of Sleep on Blood Pressure

Healthy adults demonstrate a small but significant fall in mean arterial blood pressure during sleep. This 'nocturnal dip' in mean blood pressure of approximately 10% during the night reaches the nadir at around 3 am, and contrasts strongly with the peak blood pressure associated with awakening from sleep (Millar Craig 1978). The mechanisms controlling this 'nocturnal dip' are unknown but are likely to include the effects of the loss of wakefulness and a reduction in the peripheral chemoreceptor sensitivity. In the previous chapter, we demonstrated that hypercapnia significantly augments the hypoxic pressor response as well as the hypoxic ventilatory response. Blood pressure responses to hypoxia and hypercapnia have not been studied during sleep. As ventilation and blood pressure are affected similarly by hypoxia during wakefulness, it is possible there may be a reduction in the hypoxic pressor response as well as the hypoxic ventilatory response during sleep. The situation is complicated by changes in baroreceptor sensitivity, which has been shown to increase during sleep (Conway *et al* 1983), therefore the increases in blood pressure associated with hypoxia may be reduced during sleep through a reflex reduction in heart rate. Hypoxia reduces the baroreflex (Ziegler *et al* 1995) during wakefulness, and so the hypoxia associated with obstructive apnoeas may, via modulation of the baroreceptor response, further confound the changes in blood pressure and heart rate.

Muscle sympathetic activity is inhibited during the second half of phasic lung inflation associated with normal breathing, via a neural reflex as well as in response to the changing intra thoracic pressure. The negative feedback effect of lung inflation on blood pressure has not be investigated during sleep. The influence of increasing tidal volume in response to chemoreceptor stimulation, on the hypoxic pressor response during NREM remains unknown. During an obstructive apnoea there may be larger increases in blood pressure resulting from the chemoreceptor stimulation, as there is an absence of the vagal lung inflation reflex. The resultant blood pressure change in response to hypercapnic and hypoxic peripheral chemoreceptor stimulation during spontaneous apnoeas and during the challenges

performed in this chapter, will potentially be influenced by an interaction of lung inflation, peripheral chemoreceptor sensitivity, baroreceptor sensitivity, and the effects of sleep and hypoxia on them. This study will investigate the total resultant change in blood pressure in response to chemoreceptor stimulation during sleep.

5.2 STUDY AIMS

We aim to assess the ventilatory, heart rate and arterial blood pressure responses to peripheral chemoreceptor stimulation in normal subjects during wakefulness and stable NREM sleep to test the hypothesis that-

- The cardiovascular responses to hypoxia will be significantly reduced during stable NREM sleep.
- The augmenting effects of hypercapnia on the hypoxic pressor response and hypoxic ventilatory response seen during wakefulness will persist during NREM sleep

5.3 STUDY POPULATION

Seven healthy subjects (4 male) were recruited for this study, all were members of staff at the University Hospital Aintree; two were undergraduate students, one a medical technician and four were nurses. Inclusion required subjects to be aged over 18 years and free from: cardiovascular and respiratory disease, disorders which would affect cardiac or respiratory function, diabetes, and symptoms indicative of OSAHS, such as snoring and EDS.

5.4 METHODS

5.4.1 Measurements

All of the apparatus and the procedures used in this chapter are detailed in chapter 2 (pages 47-64) The variables monitored were:

- Beat by beat systolic and diastolic arterial blood pressure using the non-invasive 'Finapres' digital plethysmograph.
- Heart Rate and SaO_2 using a Datex-Ohmeda 3700 pulse Oximeter.
- Breath by Breath respiratory cycle and gas tension analysis using a Medgraphics CPX CardioRespiratory system.
- Sleep State using the Jaeger Sleeplab 1000p polysomnographic montage.

5.4.2 Procedures

Written consent was obtained from all subjects prior to the study. Subjects abstained from alcohol, caffeine and exercise for a minimum of 4 hours prior to the tests. Subjects were connected to the PSG, pulse oximeter, Finapres the forced end-tidal hypoxic challenge apparatus. They were then allowed to rest in the supine position. Monitoring was done from an adjacent room. The hypoxic challenge commenced after 4 minutes of steady baseline ventilation was observed. The inspired gas tensions were then adjusted to reduce the arterial oxygen saturation by 20% over a 5-6 minute period.

The challenge was terminated,

- when the SaO_2 fell below 80%.
- when conditions could no longer be tolerated by the subject.
- when a cortical arousal was observed.
- when any movement of the hand or arm fitted with the Finapres system was observed.

The hypoxic challenges were performed randomly under both eucapnic and hypercapnic conditions during EEG confirmed wakefulness and EEG confirmed stable stage 2 NREM sleep. If an EEG visible arousal was observed at anytime during the challenges, the challenge was terminated and the data discarded.

5.4.3 Data Analysis

The absolute changes in minute ventilation, heart rate and mean blood pressure were calculated. The acute hypoxic ventilatory, heart rate and blood pressure responses were calculated by observing slope of the linear regression between these variables and the fall in SaO_2. Paired t-tests were performed to assess the significance of any changes associated with altered CO_2 tension and/or sleep state.

5.5 RESULTS

5.5.1 Study Population

Seven subjects (4 male) were recruited for this study. Table 5.1 demonstrates the group mean characteristics of the subjects.

Table 5.1 – Study Population

	Mean	SD	Lowest	Highest
Age (years)	29.6	18.1	19	69
Height (cm)	174.4	19.1	155	211
Weight (Kg)	70.4	18.6	50	98
BMI (Kg/m2)	23	3.81	17.4	29.7

5.5.2 End-tidal CO_2 Tensions

The group mean data shown in table 5.2 demonstrates that isocapnia was maintained at the individual's resting level, which, during both EEG confirmed wakefulness and NREM sleep, was 35mmHg. The standard deviation of 3.2 shows there was some variance around this mean; the normal subjects had a range of resting $EtCO_2$ levels from 29.8 to 38.6mmHg

Table 5.2 - Group mean end-tidal CO_2 results.

	Group Mean $EtCO_2$ mmHg (SD)	Group Mean Individual Variance SD (SD)
Normocapnic Wakeful	35.3 (3.2)	0.72 (0.14)
Normocapnic NREM	35.2 (3.1)	0.67 (0.12)
Hypercapnic Wakeful	40.2 (1.7)	0.54 (0.10)
Hypercapnic NREM	39.9 (2.6)	0.59 (0.12)

Hypercapnic conditions were also well maintained when awake and asleep, the mean $EtCO_2$ was maintained at 5 mmHg above resting for 4 minutes before hypoxaemia was progressively induced over 4-5 minutes. The individual variance is the standard deviation of $EtCO_2$ during a hypoxic challenge and demonstrates there was little variability during the challenge.

5.5.3 Oxygen Saturation Data

The group mean SaO_2 at rest was 98% under normocapnic and hypercapnic conditions when awake and asleep. Hypoxia was progressively induced over a 4-5 minute period. The data sets for each individual were truncated to ensure the same degree of hypoxia was assessed under both CO_2 tensions and both sleep states, thus the group mean SaO_2 at challenge termination and the standard deviation were identical under both CO_2 tensions and both sleep states, to ensure different hypoxic stimuli could not be a confounding factor when interpreting the results.

Table 5.3 – Oxygen Desaturation Data

	Group Mean Resting SaO_2 % (SD)	Group Mean Hypoxic SaO_2 % (SD)
Normocapnic Wakeful	98.1 (1.1)	86.1 (2.2)
Normocapnic NREM	98.0 (1.2)	86.1 (2.2)
Hypercapnic Wakeful	97.9 (0.9)	86.1 (2.2)
Hypercapnic NREM	97.6 (1.2)	86.1 (2.2)

5.5.4 The Change in Ventilation

Table 5.4 demonstrates the group mean minute ventilation, averaged from the three breaths prior to the hypoxic challenge, the three breaths at the end of the hypoxic challenge and the mean change in ventilation.
Under all circumstances, hypoxia increased ventilation.

Table 5.4 - Group mean minute ventilation at rest and at termination of the hypoxic challenges.

	Minute Ventilation (l/min)		
	Rest	Hypoxic	Percent change
Normocapnic Wakeful	7.8 (3.2)	9.8 (3.0)	25.6
Normocapnic NREM	5.7 (7.4)	7.4 (2.2)	29.8
Hypercapnic Wakeful	7.7 (2.5)	16.9 (4.5)	119.5
Hypercapnic NREM	6.8 (2.3)	10.1 (3.9)	48.5

5.5.5 The Acute Hypoxic Ventilatory Response

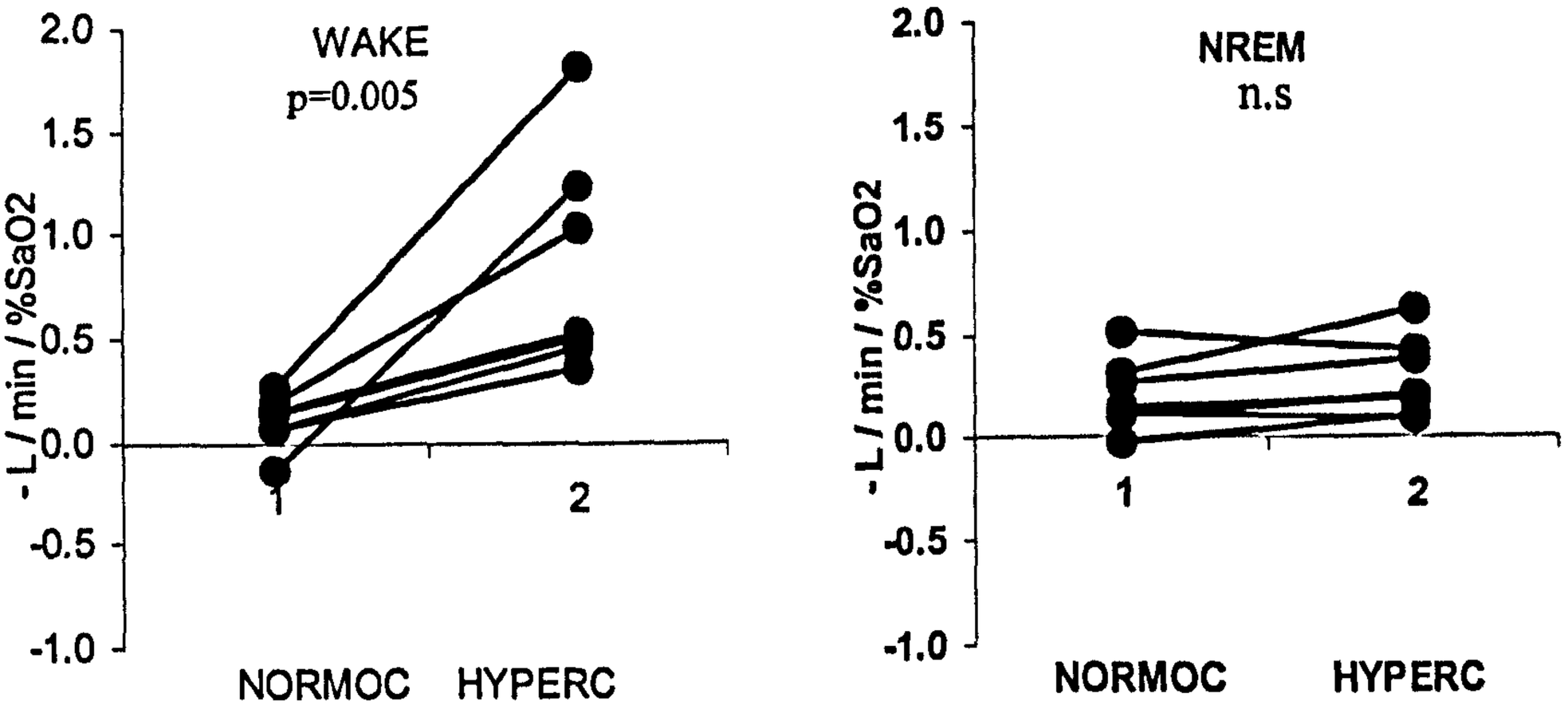
Table 5.5 demonstrates the group mean AHVR, i.e the mean increase in ventilation per 1% fall in SaO_2.

Table 5.5 Group Mean AHVR

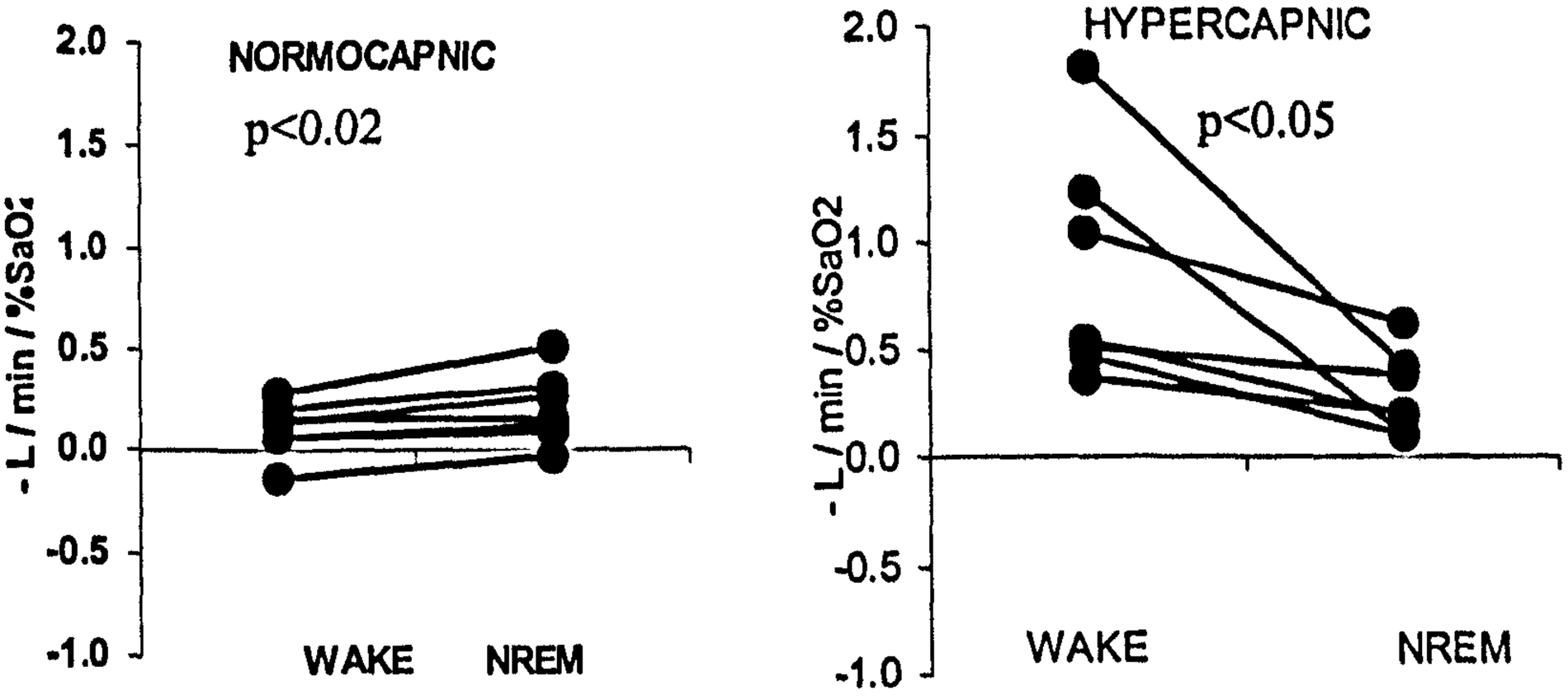
	AHVR (L/min/%SaO2)	SD
Normocapnic Wakeful	-0.11	0.129
Normocapnic NREM	-0.2	0.17
Hypercapnic Wakeful	-0.85	0.538
Hypercapnic NREM	-0.29	0.195

Table 5.5 and figure 5.1 demonstrate the effects of CO_2 on the AHVR. A strong augmentation was observed with the higher CO_2 tension during wakefulness, however no significant effect was seen during NREM sleep.

Figure 5.1 - The effects of hypercapnia on the acute hypoxic ventilatory responses during wake and NREM sleep



Figures 5.2 - The effects of sleep state on the acute hypoxic ventilatory responses



Figures 5.2 are plotted using the same data but are arranged to demonstrate the effects of sleep state on the AHVR. A significant increase in AHVR was seen under normocapnic conditions when subjects were asleep, however, under hypercapnic conditions there was a significant attenuation of the ventilatory response during NREM.

5.5.6 Changes in Heart Rate

Table 5.6 demonstrates the group mean heart rate, averaged from time encompassing the three breaths prior to the hypoxic challenge, and the last three breaths of the hypoxic challenge. There was a lower resting heart rate during NREM sleep compared to wakefulness, and all hypoxic challenges resulted in an increase in heart rate. Hypercapnia had variable effects on the heart rate response to hypoxia, increasing it during wakefulness and reducing it during NREM sleep.

Table 5.6 Group mean minute heart rate at rest and at termination of the hypoxic challenges.

	Heart Rate (beats/min)		
	Rest	Hypoxic	Percent change
Normocapnic Wakeful	72.7 (13.9)	80.3 (4.5)	10.5
Normocapnic NREM	66.4 (16.8)	79.9 (14.5)	20.3
Hypercapnic Wakeful	71.4 (10.4)	83.9 (7.0)	17.5
Hypercapnic NREM	65.7 (15.1)	75.9 (16.5)	15.5

5.5.7 The acute hypoxic heart rate response

Table 5.7 demonstrates that the heart rate response to progressive hypoxia, during both sleep states and both CO_2 tensions. Subjects demonstrated highly variable responses that were unaffected by NREM sleep. Figure 5.3 demonstrate the effects of CO_2 on the acute hypoxic heart rate response. No significant augmentation was observed with the higher CO_2 tension during wakefulness although the higher CO_2 did have an augmenting effect on the heart rate response during NREM sleep.

Table 5.7 The acute hypoxic heart rate response group mean data

	Acute Hypoxic Heart Rate Response (Beats/min/%SaO2)	SD
Normocapnic Wakeful	-0.51	0.21
Normocapnic NREM	-0.36	0.21
Hypercapnic Wakeful	-0.81	0.53
Hypercapnic NREM	-0.72	0.48

Figure 5.3 - The effects of hypercapnia on the acute hypoxic heart rate responses during wake and NREM sleep

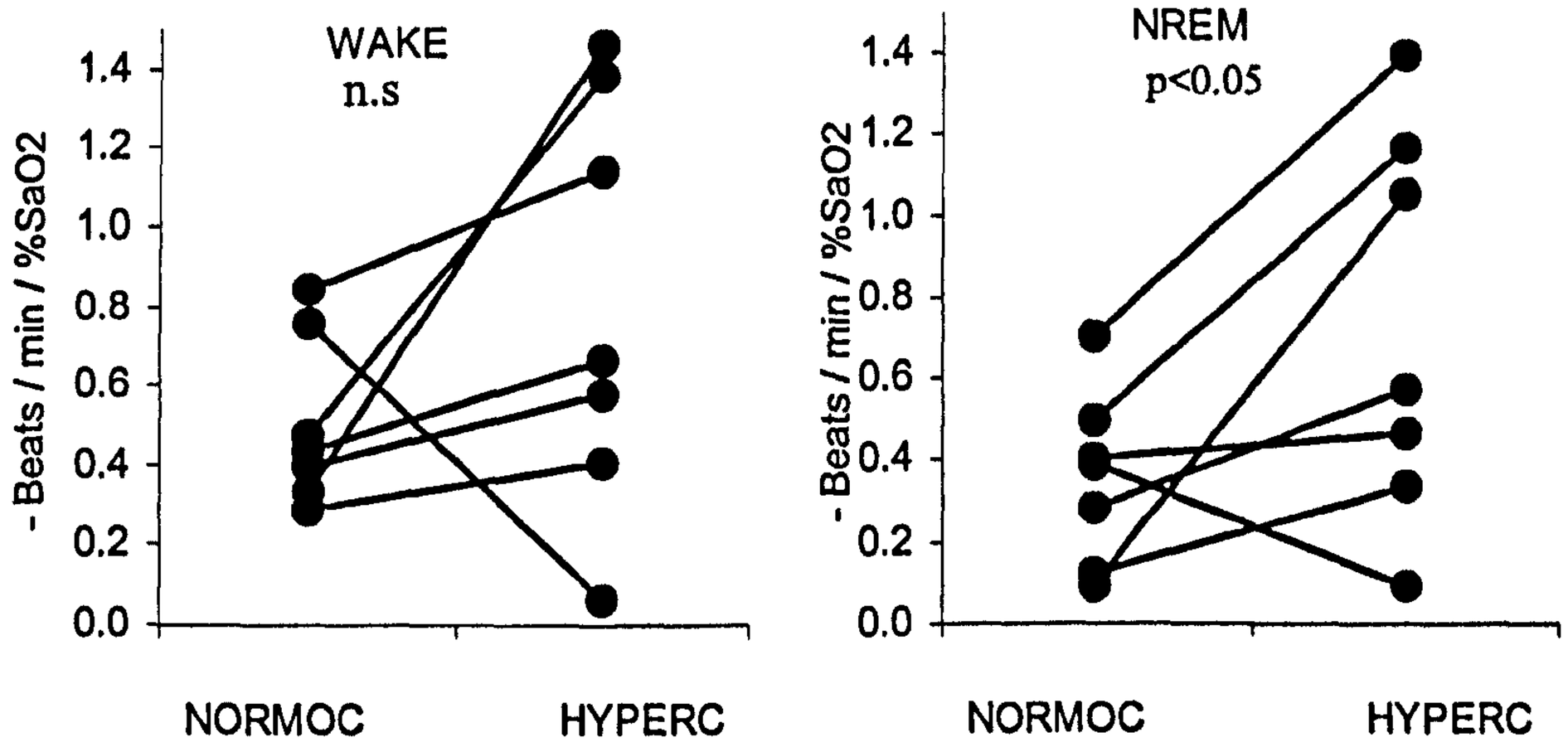
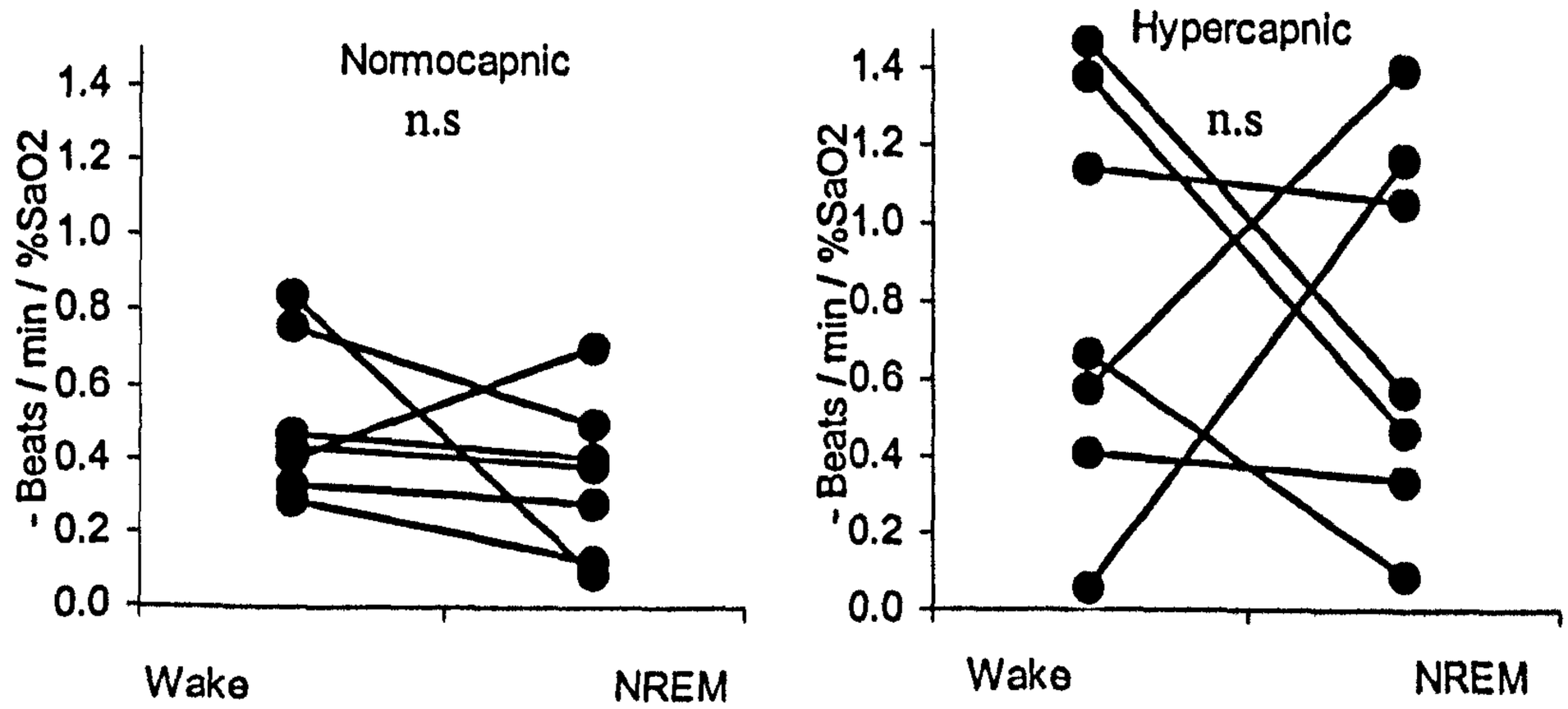


Figure 5.4 show the same data but are arranged to demonstrate the effects of sleep state on the heart rate response. There was no significant difference between the wakeful and NREM responses to progressive hypoxia with either CO_2 tension.

Figure 5.4 - The effects of sleep state on the acute hypoxic heart rate responses.



5.5.8 The Change in Mean Blood Pressure

Table 5.8 demonstrates the group mean mean-blood pressure, averaged from the periods encompassing the three breaths prior to the hypoxic challenge and the three breaths prior to terminating the challenge. Similar resting blood pressures were seen regardless of sleep state or CO_2 tension.

Table 5.8 Group mean minute ventilation at rest and at termination of the hypoxic challenges.

	Mean Blood Pressure (mmHg)		
	Rest	Hypoxic	Percent change
Normocapnic Wakeful	104 (26.4)	111 (27.1)	6.7
Normocapnic NREM	101 (16.6)	99.0 (15.3)	-2.0
Hypercapnic Wakeful	109 (19.5)	119 (25.3)	9.2
Hypercapnic NREM	99.4 (17.9)	104 (17.9)	4.6

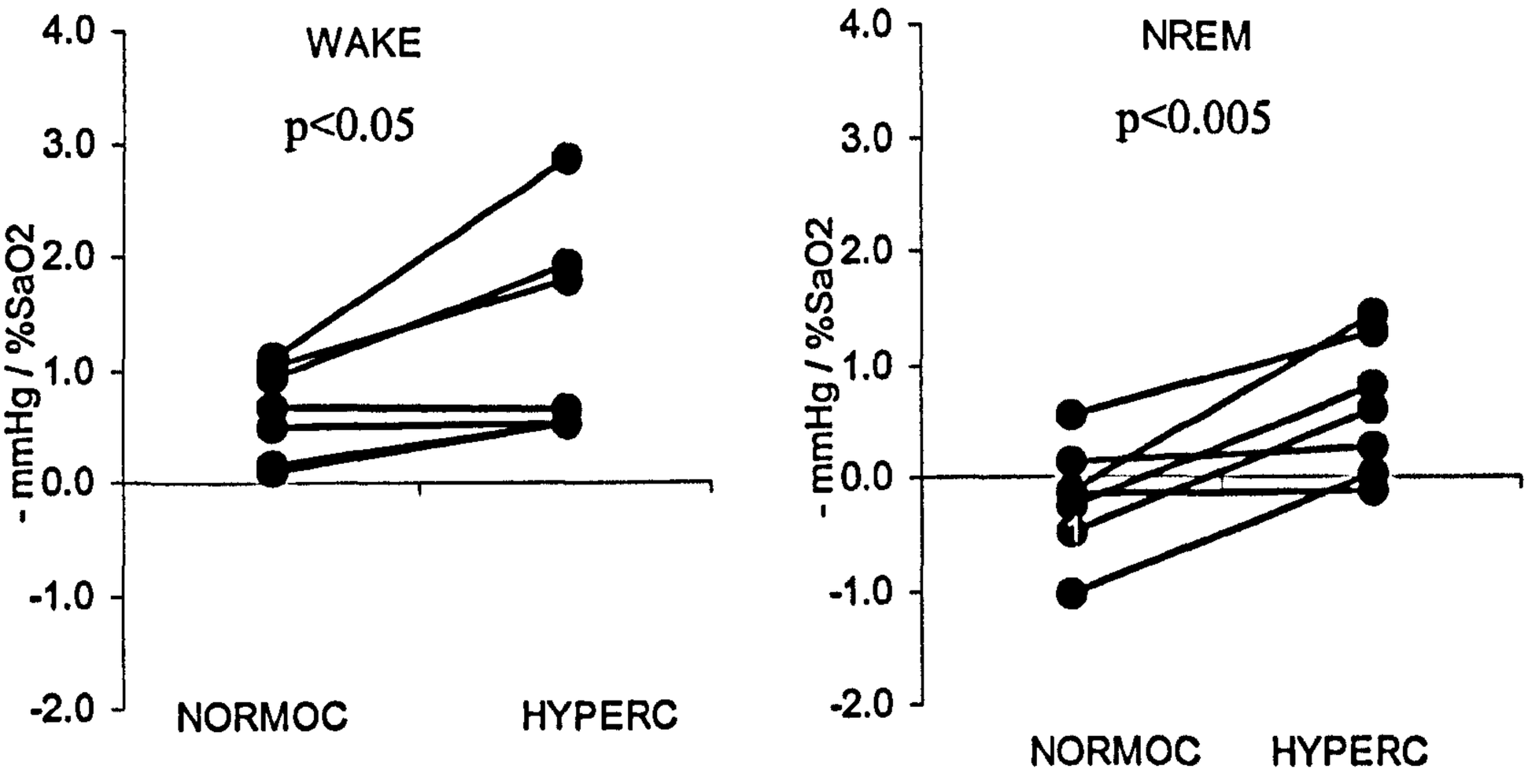
5.5.9 The Acute Hypoxic Mean Blood Pressure Response

Table 5.9 demonstrates the group mean pressor responses to hypoxia. An increase in mean blood pressure with a fall in oxygen saturation was observed in all circumstances except during sleep under normocapnic conditions. Figure 5.5 demonstrates the effects of CO_2 on the acute hypoxic pressor response. There was a significant augmentation of the response when the higher CO_2 tension was maintained during wakefulness and during NREM sleep.

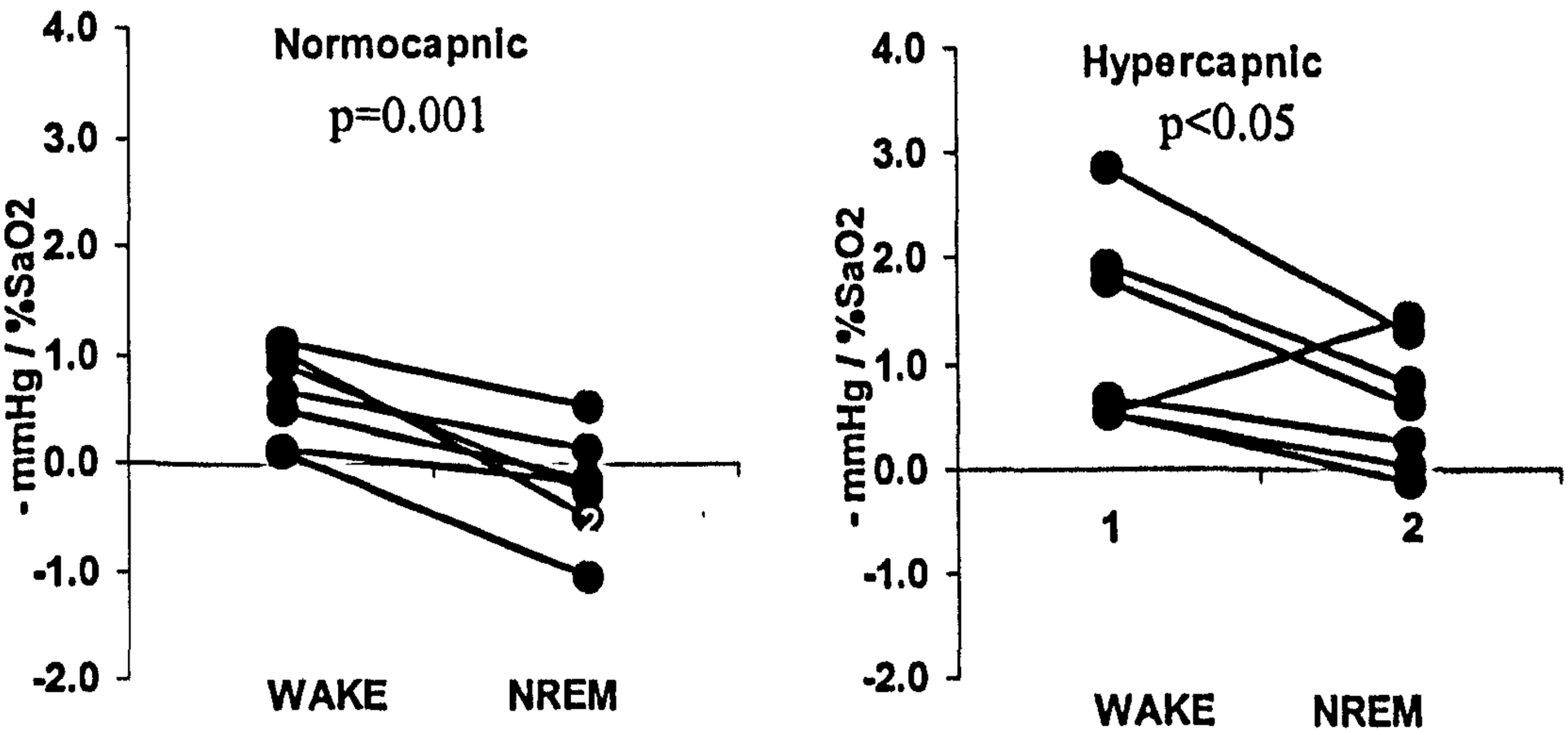
Table 5.9 - The group mean acute hypoxic mean blood pressure responses.

	Acute Hypoxic Pressor Response (mmHg/%SaO2)	SD
Normocapnic Wakeful	-0.647	0.41
Normocapnic NREM	0.199	0.49
Hypercapnic Wakeful	-1.258	0.94
Hypercapnic NREM	-0.612	0.60

Figure 5.5 - The effects of hypercapnia on the acute hypoxic pressor responses during wake and NREM sleep



Figures 5.6 - The effects of sleep state on the acute hypoxic pressor responses



These graphs show the same data but are arranged to demonstrate the effects of sleep state on the mean blood pressure response. NREM sleep demonstrated a significant attenuation in the responsiveness to hypoxia under both normocapnic and hypercapnic conditions.

Summary

		Normocapnic	Hypercapnic
Ve/SaO2 (l/min/SaO2)	**Wake**	-0.11 (0.13)	-0.85 (0.54)
	NREM	-0.2 (0.17)	-0.29 (0.20)
HR/SaO2 (beat/min/SaO2)	**Wake**	-0.51 (0.21)	-0.81 (0.53)
	NREM	-0.36 (0.21)	-0.72 (0.48)
BP/SaO2 (mmHg/SaO2)	**Wake**	-0.647 (0.41)	-1.258 (0.94)
	NREM	0.199 (0.49)	-0.612 (0.60)

5.5.8 The Relationships Between Age, BMI And The Hypoxic Responses

There were no consistent relationships between the age or BMI of the subjects and the responses to hypoxia. The only relationship was between the ventilatory response to normocapnic hypoxia and BMI.

5.6 DISCUSSION

Previous work investigating state dependant effects on peripheral chemoreceptor responses in healthy subjects have demonstrated, using eucapnic hypoxia, or euoxic hypercapnia, that the ventilatory response is diminished during stable NREM sleep, compared to wakefulness (Douglas *et al* 1982a and 1982c, Berthon-Jones *et al* 1982 and 1984). This study set out to investigate whether this reduction in peripheral chemoreceptor mediated response was exclusive to ventilation, or whether a reduction in the magnitude of the cardiovascular responses would also be observed during stable NREM sleep. This study also aimed to investigate the effects of sleep state on the interaction of hypoxic and hypercapnic stimuli by assessing the resultant ventilatory and cardiovascular responses.

Ventilatory Responses

This study used a tight fitting full-face mask instead of the mouthpiece and nose clip. A mouth piece is a known respiratory stimulant and was the apparatus we used in the previous chapter. The subjects studied in this chapter were different individuals to those previously studied. Subjects were also studied in the supine position, whereas in our previous work they were studied while prone. These differences may account for some of the dissimilarity in the data from the two studies.

The resting minute ventilation with both normocapnia and hypercapnia was lower in this study compared to the data presented in chapter 4 (Normocapnic: 7.8 l/min (SD 3.2) vs 12.1 l/min (SD 4.1). Hypercapnic 7.7 l/min (SD 2.5) vs 11.6 l/min (SD 4.4) respectively).

The resting end-tidal CO_2 in this group of subjects was also significantly lower than that seen in the previous chapter (35.3 vs 38.0 mmHg). This would suggest their ventilation is greater although measuring it using the facemask suggests it is not. This may explain why the mean AHVR with normocapnia was more than ten fold greater in the previous work compared with this study (Normocapnic 1.4l/min/%SaO_2 (SD 1.3) vs. 0.11 (0.129). Hypercapnic 3.98l/min/%SaO_2 (SD 2.41) vs. 0.85 (0.54)). This would also imply that, in this chapter, the 'hypercapnic' environment was nearer normocapnia than hypercapnia, and would explain why there was such a small response to 'hypercapnic hypoxia'. As can be seen from the figues on page 163, every individual in this group had a small response to hypoxia. The large proportion of female subjects may also have influenced this. As discussed earlier, females have been shown to have a much smaller reponse to hypoxia than seen in males.

Heart Rate Responses

Hypoxia increased the heart rate in all subjects, but as demonstrated in other studies this response is highly variable (Bonsignore *et al* 1997, Sato *et al* 1997). With the higher CO_2 tension, all but one of the subjects demonstrated an augmentation of their heart rate response to hypoxia during wakefulness and sleep, but sleep state did not significantly influence the heart rate response. Douglas et demonstrated that the

heart rate response to hypoxia fell from 1.25 (SEM 0.19) b/min/%SaO_2 to 0.77 (SEM 0.16). Our subjects demonstrated a smaller wakeful response and a small but nonsignificant fall from 0.51 (SD 0.21) to 0.36 (SD 0.21) with the transition into stage 2 sleep.

Blood Pressure Responses

All subjects demonstrated a significant pressor response to hypoxia. In all but one of the subjects, the mean blood pressure response to hypoxia was significantly augmented by hypercapnia during both wakefulness and sleep. The wakeful response increased two fold with hypercapnia (0.65 and 1.26mmHg/%SaO_2 respectively); a similar magnitude increase to that demonstrated in chapter 4. During NREM sleep, the eucapnic response to hypoxia was abolished, but increasing the end-tidal CO_2 tension by 5mmHg increased the response to a level similar to that seen with normocapnic wakefulness (0.65 mmHg/%SaO_2 and 0.61 mmHg/%SaO_2 respectively). Hedner *et al* investigated the pressor effects of hypoxia in healthy subjects and OSHAS patients. They demonstrated no significant change in blood pressure in healthy subjects when their SaO_2 was reduced to 75% during wakefulness. However, OSAHS patients did have a significant pressor response during eucapnic wakefulness. Although the authors present the correlations between these blood pressure responses and polysomnographic variables, they failed to present the data for the hypoxic pressor responses. From the figures of correlations they present in their publication, it appears the mean blood pressure response to hypoxia is 0.6mmHg/%SaO_2 , which is very similar to that demonstrated by our healthy subjects.

Neither age nor BMI had any significant influence on the ventilatory or cardiovascular responses to hypoxia, with either CO_2 tension or sleep state, and were not significantly different from the groups of subjects studied by the other authors assessing the hypoxic ventilatory responses.

Conclusion

The ventilatory response data in this study was surprising. Other studies have shown a larger responses to hypoxic challenge during sleep, and an attenuation of these response during NREM sleep. Our data may represent the lower end of the normal response range or the consequences of using a different method of inducing

this response with relatively less instruementation. Nonetheless, the aims of this study were to assess the effects of stage 2 sleep on the hypoxic pressor response and its augmentation by hypercapnia. We demonstrated that sleep does attenuate the hypoxic pressor response, and that the augmenting effects of CO_2 persist during NREM sleep. This could potentially have implications in the development of hypertension seen in OSAHS patients. The mechanism of this development is unknown, but possible factors contributing to it include the repetitive increases in blood pressure associated with arousal responses, and the blood pressure rises during the apnoea. During an apnoea increases in CO_2 occur as well as the fall in SaO_2. Our data suggests that the combination of these two stimuli will result in significant increase in blood pressure. Animal models have demonstrated that recurrent episodic hypoxia can lead to sustained hypertension in rats (Fletcher *et al* 1996). Under hypocapnic conditions there was no sustained increase in blood pressure (Bao *et al* 1997). Clearly no direct comparisons can be made between OSAHS patients and rats. Nonetheless our data imply that if this mechanism is present in humans, then hypercapnic hypoxic stimulation of the peripheral chemoreceptors during sleep, which has similar pressor effect to eucapnic hypoxia during wakefulness, may have produce sustained changes in waking arterial blood pressure. The next chapter of this thesis will investigate whether OSAHS patients demonstrate the same blood pressure responses during sleep as healthy subjects, and investigate the blood pressure changes associated with chemoreceptor stimulation and arousal from sleep

Chapter Six

The ventilatory and cardiovascular responses to normocapnic and hypercapnic hypoxia in OSAHS patients while awake, asleep and during spontaneous apnoeas.

6.1 INTRODUCTION

In chapter four we demonstrated that normal subjects and OSAHS patients have similar ventilatory and cardiovascular responses to progressive hypoxia when awake. Work by Douglas *et al* (??) showed that normal subjects have reduced ventilatory responses to hypoxia when in stable NREM sleep compared to wakefulness. In chapter five we demonstrated that our normal subjects had a similar reduction in the ventilatory response to hypoxia to the values documented by Douglas, and also demonstrated that CO_2 augments this response during NREM sleep. We also found that, in this small group of subjects, there was a significant attenuation of the hypoxic pressor response during stable NREM sleep, and hypercapnia augmented the pressor response regardless of sleep state. This chapter investigates the ventilatory and cardiovascular responses in patients with OSAHS when awake and asleep, and in response to arousal from spontaneous apnoeas

6.1.1 Blood Pressure in OSAHS Patients

OSAHS patients have been shown to exhibit various blood pressure profiles during sleep. A study by Suzuki *et al* demonstrated 50% of normotensive OSAHS patients and 57% of hypertensive patients did not have a normal nocturnal dip in BP (Suzuki *et al* 1996). Pankow *et al* (Pankow *et al* 1997) concluded that 'nondipping' is related to apnoea severity. Davies *et al* demonstrated the average mean blood pressure during sleep is elevated compared to wakefulness in OSAHS patients as it encompassed the acute surges in BP associated with apnoea termination and arousal from sleep. The blood pressure profile can thus be useful in identifying OSAHS and other sleep disruption syndromes (Davies *et al* 1994).

6.1.2 Peripheral Chemoreceptor Sensitivity

There are a number of factors that may influence the peripheral chemoreceptor mediated responses during wakefulness and sleep:

Sleep deprivation reduces chemoreceptor responses; White *et al* demonstrated a 29% reduction in the mean AHVR in healthy subjects after just 24 hours of sleeplessness (White *et al* 1993). It is plausible that disrupted sleep, as seen in OSAHS may reduce the ventilatory and cardiovascular responses to hypoxia.

However, it may be possible there is long-term adaptation to sleep deprivation and the responses may normalize after some time.

OSAHS patients experience repetitive chemoreceptor stimulation throughout the night. The work investigating the effects of this, and the sensitivity of these receptors in OSAHS patients have been contradictory. The work in chapter 4 of this thesis suggested there was no significant difference between the responses of healthy subjects or OSAHS patients when awake.

6.1.3 Baroreceptor sensitivity is increased during sleep in normal subjects (Conway *et al* 1983), this has the potential to suppress the blood pressure increase in response to hypoxia during sleep. Conway and co-workers also demonstrated that, in healthy subjects, there is a blood pressure rise and a decrease in baroreceptor sensitivity with increasing mental arousal from sleep. Thus the acute blood pressure rise in response to an arousal from an apnoeic event may be potentiated by an associated fall in baroreceptor sensitivity with arousal. Carlson *et al* demonstrated that, in OSAHS patients, baroreceptor sensitivity is only 60% of that demonstrated by healthy subjects during wakefulness (Carlson *et al* 1996), this may persist during sleep and therefore these patients would have greater increases in blood pressure when exposed to hypoxia compared to healthy subjects.

6.1.4 The Effect of Arousals on Blood Pressure and Ventilation

A study by Carley et al demonstrated that acoustic stimuli increased ventilation for at least 4 breaths prior to EEG arousal in healthy subjects, and also occurred in the absence of a cortical arousal (Carley *et al* 1996). Similarly, Davies *et al* demonstrated that blood pressure increases in response to an external stimulus, even with the absence of an EEG arousal. Stimuli that evoked an EEG arousal lasting longer than 10 seconds produced a blood pressure rise approximately 75% of that seen with arousal from an apnoeic event (Davies *et al* 1993).

Hypoxia is a poor at stimulating a ventilatory response during sleep and is a weak arousal stimulus; 12 of their 26 healthy subjects failed to arouse when the SaO_2 was reduced to 70% during NREM sleep (Berthon-Jones *et al* 1982). Berthon-Jones *et al* also demonstrated that the hypercapnic ventilatory response, in healthy subjects fell by 49% in NREM, but was a strong arousal stimulus (Berthon Jones *et al* 1984).

However, in OSAHS patients, the administration of oxygen prolongs apnoeas by decreasing the rate of increase in the magnitude of inspiratory efforts (Berry *et al* 1992). The fall in SaO_2 has been correlated with the change in mean BP during an apnoea, and that the blood pressure response to desaturation whilst awake was about one third of that in response to apnoeic episodes (Okabe 1995). Ringler *et al* also used oxygen supplementation to conclude that in NREM sleep post apnoeic BP elevations are not primarily attributable to hypoxaemia. Other factors such as the onset of wakefulness and lung inflation may contribute to these elevations. Berry *et al* also used CO_2 administration before airway occlusion to demonstrate that apnoea termination occurs more rapidly due to the increasing inspiratory efforts reach the arousal threshold sooner (Berry *et al* 1993), and Rees (Rees 1995) demonstrated the blood pressure change during the latter part of an apnoea was associated with the CO_2 increase during the apnoea.

6.2 STUDY AIMS

This chapter will assess the cardiovascular responses to peripheral chemoreceptor stimulation in OSAHS patients, during wakefulness, stable stage 2 sleep and in response to spontaneous apnoeic episodes with and without CO_2 administration, to test the hypothesis that:

- The cardiovascular responses to hypoxia will be reduced during NREM sleep in OSAHS patients

- Hypercapnia will augment the cardiovascular responses to hypoxia when awake and asleep.

- Hypercapnia will reduce the duration of spontaneous obstructive apnoeas.

- The interaction of the hypoxic and hypercapnic stimuli, resulting from CO_2 administration before an apnoea, will result in greater increases in blood pressure associated with arousal from apnoeic events, demonstrating the influence of the peripheral chemoreceptors on the arousal responses.

6.3 STUDY POPULATION

Six patients (5 male) who had been diagnosed with OSAHS at the University Hospital Aintree, were recruited for this study. Inclusion criteria required subjects to be aged over 18 years, normotensive, have an AHI greater than 15 events per hour, and have no co-existing cardiovascular or respiratory disorders. All subjects had been newly diagnosed with OSAHS and were waiting for a trail of CPAP to assess its suitability as a treatment for their condition.

6.4 METHODS

This chapter employed two different types of apparatus to create hypoxic environments.

- The standard forced end-tidal technique was used, as in the previous chapter with healthy subjects, to create eucapnic and hypercapnic hypoxia during wakefulness,
- The CPAP forced end-tidal technique was used to assess the cardiovascular responses to hypoxic and hypercapnic stimulation in OSAHS patients during sleep. This technique used CPAP to abolish the spontaneous apnoeas and thus allowed us to assess these responses without the interuption of altered gas exchange, large swings in pleural pressure, and surges in autonomic activity associated with the arousals accompanying the termination of most apnoeas. The constant flow used to create CPAP made it impossible to measure ventilation using this technique.

6.4.1 Measurements

Using the forced end-tidal technique, for assessing the wakeful responses the responses to apnoeic events, we monitored:

- **Breath by Breath respiratory cycle and gas analysis** using a Medgraphics CPX CardioRespiratory system for wakeful data.

- **Beat by beat mean arterial blood pressure** using the non-invasive 'Finapres' digital plethysmography.
- **Heart Rate and SaO_2** using a Datex-Ohmeda 3700 pulse oximeter.
- **Sleep State** using the Jaeger Sleeplab 1000p polysomnogram

Using the CPAP technique to assess the cardiovascular responses to hypoxia and hypercapnia, we monitored the same variables as detailed above, with the exception of the breath by breath respiratory cycle and gas analysis, instead we monitored:

- **Breath by Breath FiO_2 and $FiCO_2$ analysis** using a Datex capnograph, attached to the CPAP mask, used when patients are sleeping and receiving CPAP therapy, rendering the Medgraphics system unsuitable due to the constant flow.

6.4.2 Procedures

Responses During Wakefulness

The procedures for wakeful assessment of the hypoxic responses are the same as described in the previous chapter. Written consent was obtained from all subject. Subjects abstained from alcohol, caffeine and exercise for a minimum of 4 hours prior to the testing. They were connected to the PSG, pulse oximeter, Finapres systems and were fitted with the tight fighting face mask/forced end-tidal system. Subjects we studied in the supine position and monitoring was done from an adjacent room. The hypoxic challenge was performed during EEG confirmed wakefulness and commenced after 4 minutes of steady baseline ventilation was observed. Progressive hypoxia was induced over a 4 to 5 minute period.

The challenge was terminated,

- when the SaO_2 fell below 80%.
- when conditions could no longer be tolerated by the subject.
- when any movement of the hand or arm fitted with the Finapres system was observed.

The hypoxic challenges were performed randomly under both eucapnic and hypercapnic conditions with a thirty-minute break between challenges.

Responses Associated with Spontaneous Apnoeas

While subjects were wearing this apparatus during EEG confirmed stage 2 sleep, we were able to assess the ventilation, heart rate and blood pressure before, during and after spontaneous apnoeas. These were assessed under eucapnic and hypercapnic conditions when $FiCO_2$ was increased by 2.5%. Data were acquired during ten minutes of eucapnic and ten minutes of hypercapnia, and later analysed to assess the changes in ventilation, heart rate and mean blood pressure associated with the apnoeas occurring during this time.

Responses During Stable Stage 2 Sleep

Patients were then fitted with a ResMed Autoset CPAP titration system and allowed to sleep for two to three hours until a level of CPAP sufficient to abolish snoring and desaturations was established. The CPAP unit was then set at this pressure. Hypoxic conditions could be created by progressively titrating nitrogen into the air inlet port of the CPAP unit over a 5-minute period. Hypercapnic conditions were maintained by titrating CO_2 into the air inlet of the CPAP unit. The mean inspired gas tensions need to create the desired changes in arterial oxygen saturation (80% SaO_2) and end-tidal CO_2 (5mmHg above resting) were estimated from those observed when using the forced end-tidal system during wakefulness, and the data from the healthy subjects (detailed in chapter 5).

During EEG confirmed stable stage 2 sleep, progressive hypoxia was induced with eucapnia and hypercapnia in a random order, with a twenty minute break between subsequent challenges.

6.5 RESULTS

The results in this chapter have been separated into two sections.

The first section describes and compares the data obtained when patients were awake (using the forced end-tidal system), and when they were in stable stage 2 sleep without spontaneous apnoeas (using the CPAP system). As discussed in chapter two, the combined stimuli of: sleep study apparatus, CPAP, hypercapnia and hypoxia was so great that few patients who were recruited for the study were able sleep for long enough to enable us to generate sufficient data. Patients who were recruited, but were not included in the analysis either: failed to sleep, would not tolerate CPAP, or arouse before the hypercapnic or hypoxic stimuli were applied. This may have created an unintentional bias toward a group of people who have a low chemoreceptor response and/or a high arousal threshold.

The second section, starting on page 180, details the data recorded during the spontaneous apnoeas and their associated arousals, these were recorded from the same individuals that had were studied in section one.

Section One – Responses to Hypoxia When Awake and Asleep

6.5.1 Study Population

Six subjects (5 male) were recruited for this study. Table 6.1 demonstrates there was a wide range of ages, body mass indices and disease severity.

Table 6.1 – Study Population

Subject	Age	Height (cm)	Weight (Kg)	BMI (Kg/m2)	AHI (events/hour)
1	72	165	98	36.0	70
2	28	190	140	38.8	42.8
3	50	182	95	28.7	19.8
4	44	180	91	28.1	27.1
5	38	173	130	43.4	56.7
6	52	183	80	23.9	16.8
Mean	**47.33**	**178.83**	**105.67**	**33.14**	**38.87**
SD	**14.90**	**8.70**	**23.74**	**7.44**	**21.40**

End-tidal CO_2 Data

Table 6.2 demonstrates the normal data from the previous chapter, as well as the data obtained from the OSAHS patients. The OSAHS patients, when awake, had a group mean end-tidal CO_2 of 39.4 mmHg during the normocapnic hypoxic challenge and 44.3 mmHg during the hypercapnic hypoxic challenge. The hypercapnia during wakefulness was maintained by delivering 2.59% CO_2 to the patient via the forced end-tidal apparatus

Table 6.2 - CO_2 Tensions when Awake and When Asleep with CPAP

	Normal		OSAIIS	
	FiCO2	EtCO2	FiCO2	EtCO2
Normocapnic Wake	0.06 (0.03)	35.3 (3.2)	0.06 (0.03)	39.4 (4.0)
Normocapnic Sleep	0.06 (0.03)	35.2 (3.1)	0.06 (0.03)	-
Hypercapnic Wake	2.39 (0.24)	40.3 (1.7)	2.59 (0.31)	44.3 (3.0)
Hypercapnic Sleep	2.48 (0.22)	39.9 (2.6)	2.52 (0.38)	-

It was not possible to monitor the $EtCO_2$ when patients were asleep and receiving CPAP, therefore similar amounts of CO_2 were supplied via the CPAP unit during NREM sleep, with the intention of maintaining the $EtCO_2$ at a similar tension to that observed during wakefulness. The previous work demonstrated that, in healthy subjects, the same inspired CO_2 tensions are needed to increase the $EtCO_2$ by 5 mmHg whether awake or asleep. Therefore, although we did not directly measure the $EtCO_2$, we can be confident that when 2.52% CO_2 was given to the patients via their CPAP this will result in an increase in $EtCO_2$ of a similar magnitude to that seen with the forced end-tidal system.

6.5.3 Oxygen Desaturation Data

The group mean SaO_2 at rest did not vary significantly with different CO_2 tensions or sleep states. The data sets for each individual were truncated to ensure the same degree of hypoxia was experienced under both CO_2 tensions and both sleep states, however only 4 of the 6 patients could tolerate hypercapnic hypoxia during sleep. Therefore, the group mean SaO_2 and standard deviation at termination of the hypoxic challenges are identical except for those performed during NREM with hypercapnia, which is a mean of the 4 patients who could tolerate it.

Table 6.3 - SaO_2 at the start and end of the hypoxic challenges

	Start SaO2	**End SaO2**
Normocapnic Wake	**96.5** (1.6)	**85.3** (1.0)
Hypercapnic Wake	**96.2** (1.5)	**85.3** (1.0)
Normocapnic Sleep	**94.3** (1.7)	**85.3** (1.0)
Hypercapnic Sleep	**95.5** (0.6)	**84.8** (1.3)*

(* note only 4 of the 6 patients data)

6.5.4 The Change in Heart Rate

Table 6.4 demonstrates the group mean heart rate at the start and end of the hypoxic challenges. There were no significant differences in the resting heart rates except between hypercapnic wakefulness and hypercapnic sleep, when there was a significantly higher resting heart rate during wakefulness. There was a significant increase in heart rate ($p<0.05$) in response to hypoxia under all conditions except when hypercapnic hypoxia and sleep were combined and tolerated by only four of the patients.

Table 6.4 - Group mean heart rate at rest and at termination of the hypoxic challenges.

	Heart Rate (beats/min)		
	Rest	Hypoxic	Percent change
Normocapnic Wakeful	76.7 (10.9)	84.5 (11.7)	10.2
Normocapnic NREM	73.2 (9.1)	80.0 (8.6)	9.3
Hypercapnic Wakeful	78.0 (6.8)	87.5 (10.7)	12.2
Hypercapnic NREM	65.8 (4.9)*	69.5 (9.1)*	5.7

(* note only 4 of the 6 patients data)

6.5.5 The acute hypoxic heart rate response

Table 6.5 demonstrates the acute hypoxic heart rate response, expressed as the mean change in heart rate per change in SaO_2, during both sleep states and with both CO_2 tensions. Patients demonstrated highly variable responses that were unaffected by sleep state or CO_2 tension.

Table 6.5 - The acute hypoxic heart rate response group mean data

	Acute Hypoxic Heart Rate Response (Beats/min/%SaO2)	SD
Normocapnic Wakeful	-0.74	0.51
Normocapnic NREM	-0.76	0.38
Hypercapnic Wakeful	-0.70	0.26
Hypercapnic NREM	-0.42*	0.64*

(* note only 4 of the 6 patients data)

Figure 6.1 demonstrates the effects of CO_2 on the acute hypoxic heart rate response. No significant augmentation was observed with the higher CO_2 tension during wakefulness or during NREM sleep.

FIgure 6.1 - The effects of hypercapnia on the acute hypoxic heart rate responses during wake and NREM sleep

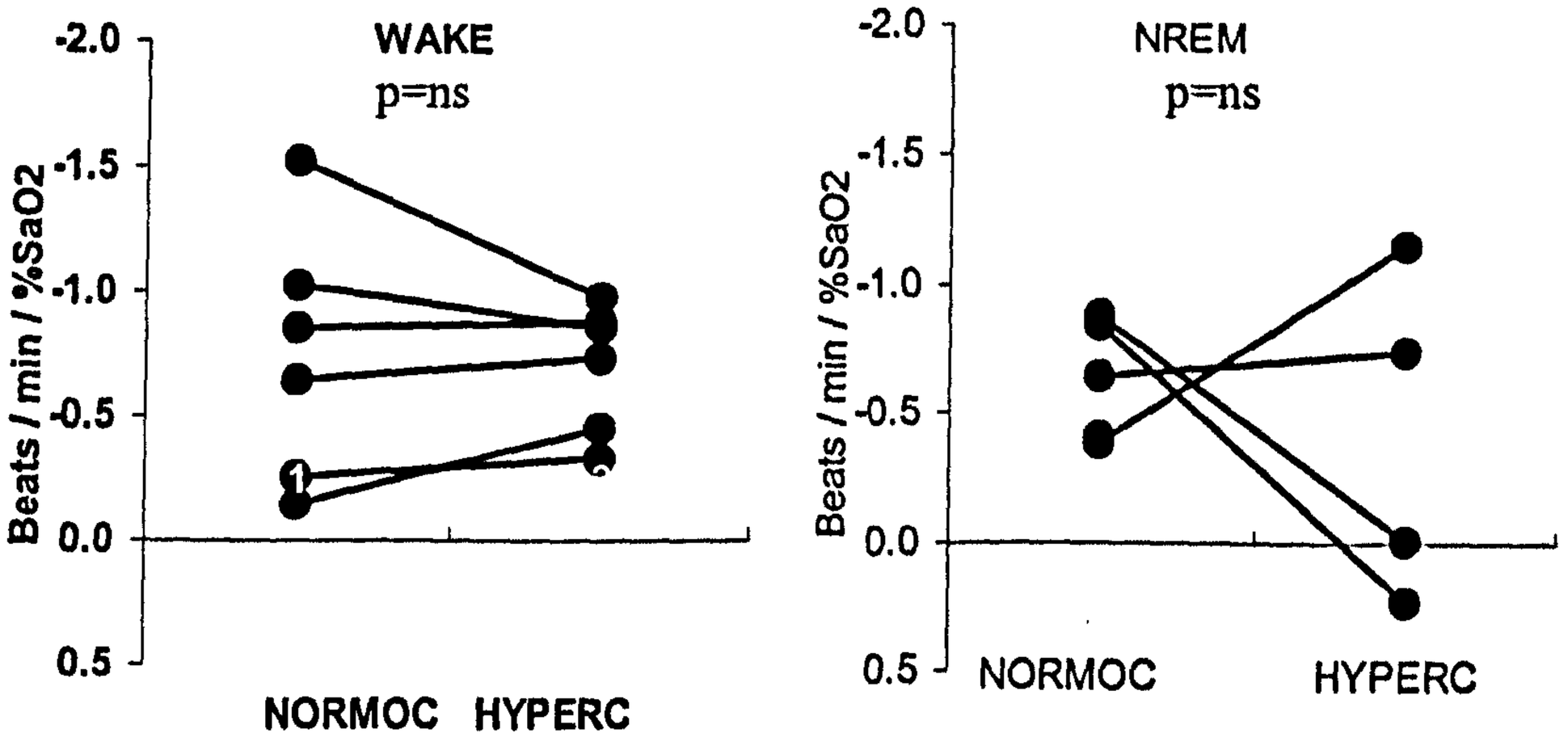
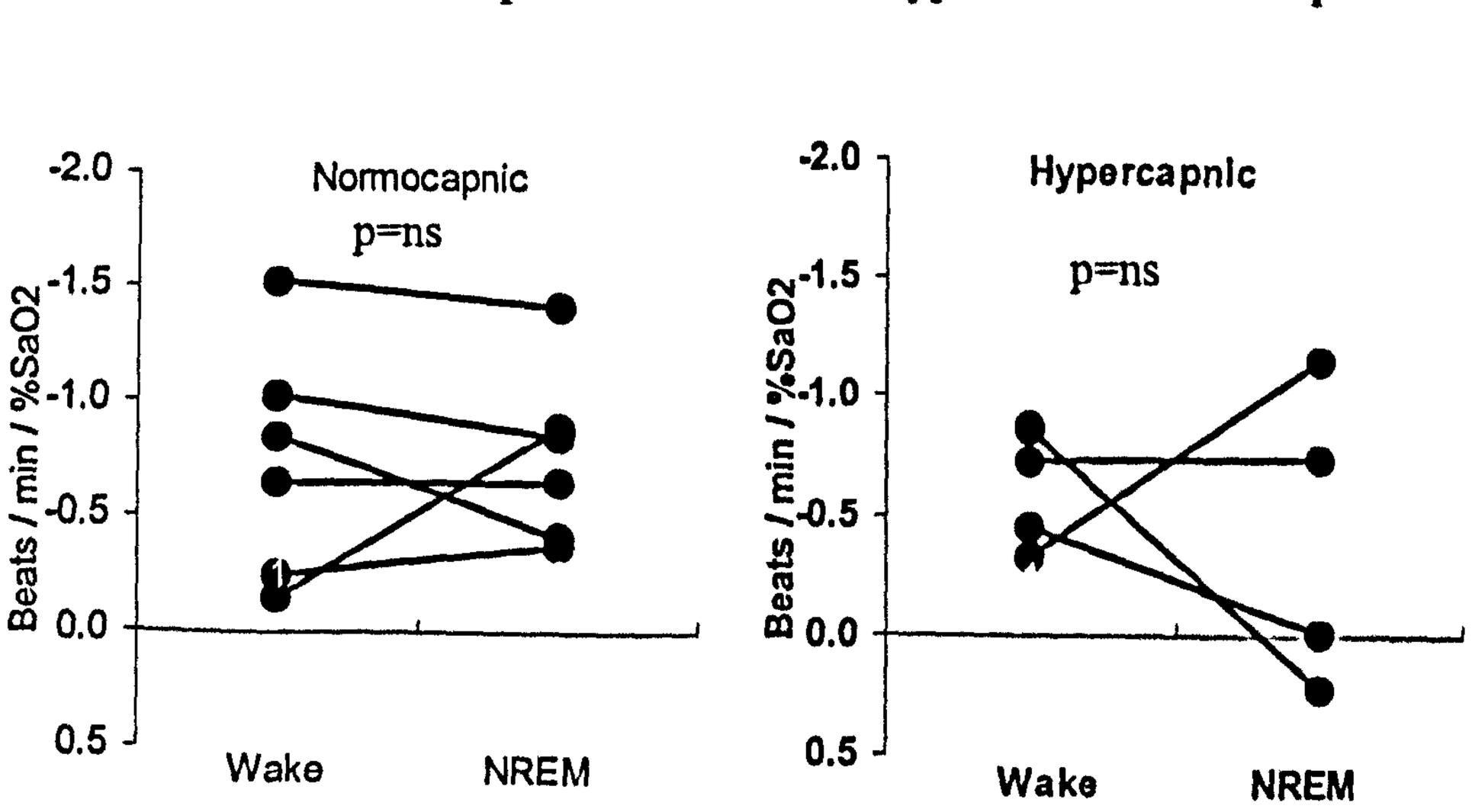


Figure 6.2 shows the same data but are arranged to demonstrate the effects of sleep state on the heart rate response. There was no significant difference between the wakeful and NREM responses to progressive hypoxia with either CO_2 tension.

Fig 6.2 - The effects of sleep state on the acute hypoxic heart rate responses



6.5.6 Changes in Mean Blood Pressure

Table 6.6 demonstrates the group mean mean-blood pressure, averaged from the periods encompassing the three breaths at the start of the challenge and the three breaths at the end of the challenge. Similar resting blood pressures were seen under all conditions. There was a significant increase in mean blood pressure during the hypoxic challenge when awake ($p>0.05$) but not during sleep.

Table 6.6 - Group mean blood pressure at rest and at termination of the hypoxic challenges.

	Mean Blood Pressure (mmHg)		
	Rest	Hypoxic	Percent change
Normocapnic Wakeful	89.4 (15.7)	100.0 (19.7)	11.9
Normocapnic NREM	97.0 (7.1)	97.2 (9.6)	0.20
Hypercapnic Wakeful	95.1 (18.5)	109.0 (22.1)	14.6
Hypercapnic NREM	105.5 (15.8)	108.3 (22.9)	2.6

6.5.6 The Acute Hypoxic Mean Blood Pressure Response

Table 6.7 demonstrates the group mean pressor responses to hypoxia expressed as the mean change in blood pressure per % change in SaO_2. There was a large degree of variability within the group, demonstrated by the large standard deviations, and no statistically significant differences were demonstrated in the responses with either sleep state or CO_2 tension.

Table 6.7 - The group mean acute hypoxic mean blood pressure responses.

	Acute Hypoxic Pressor Response (mmHg/%SaO2)	SD
Normocapnic Wakeful	-1.00	1.19
Normocapnic NREM	-0.07	0.25
Hypercapnic Wakeful	-0.88	0.86
Hypercapnic NREM	-0.87	1.29

Figure 6.3 demonstrates the effects of CO_2 on the acute hypoxic pressor response. There was no significant augmentation of the response when the higher CO_2 tension was maintained during wakefulness or during NREM sleep.

Fig 6.3 - The effects of hypercapnia on the acute hypoxic pressor responses during wake and NREM sleep

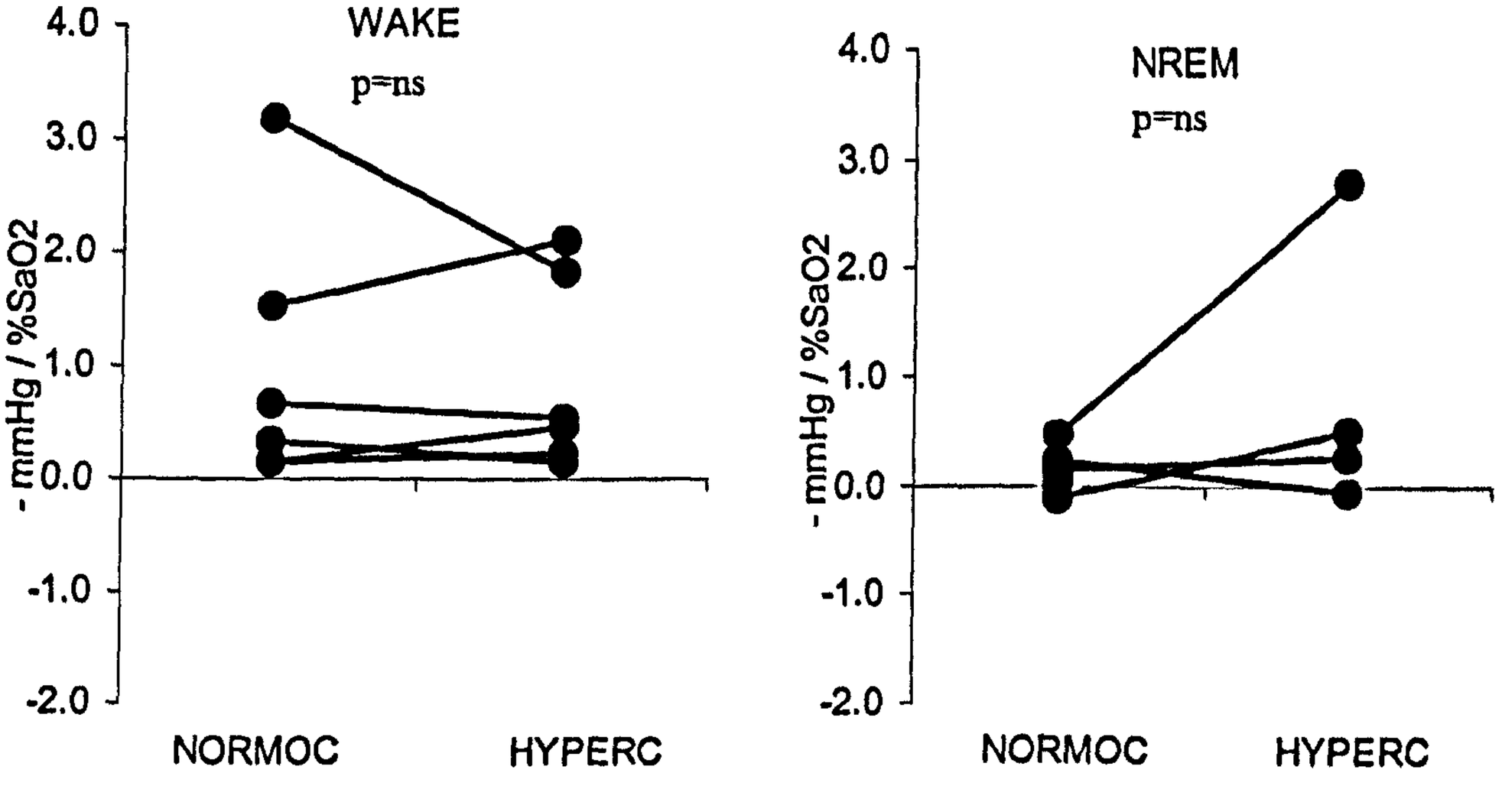


Figure 6.4 - The effects of sleep state on the acute hypoxic pressor responses

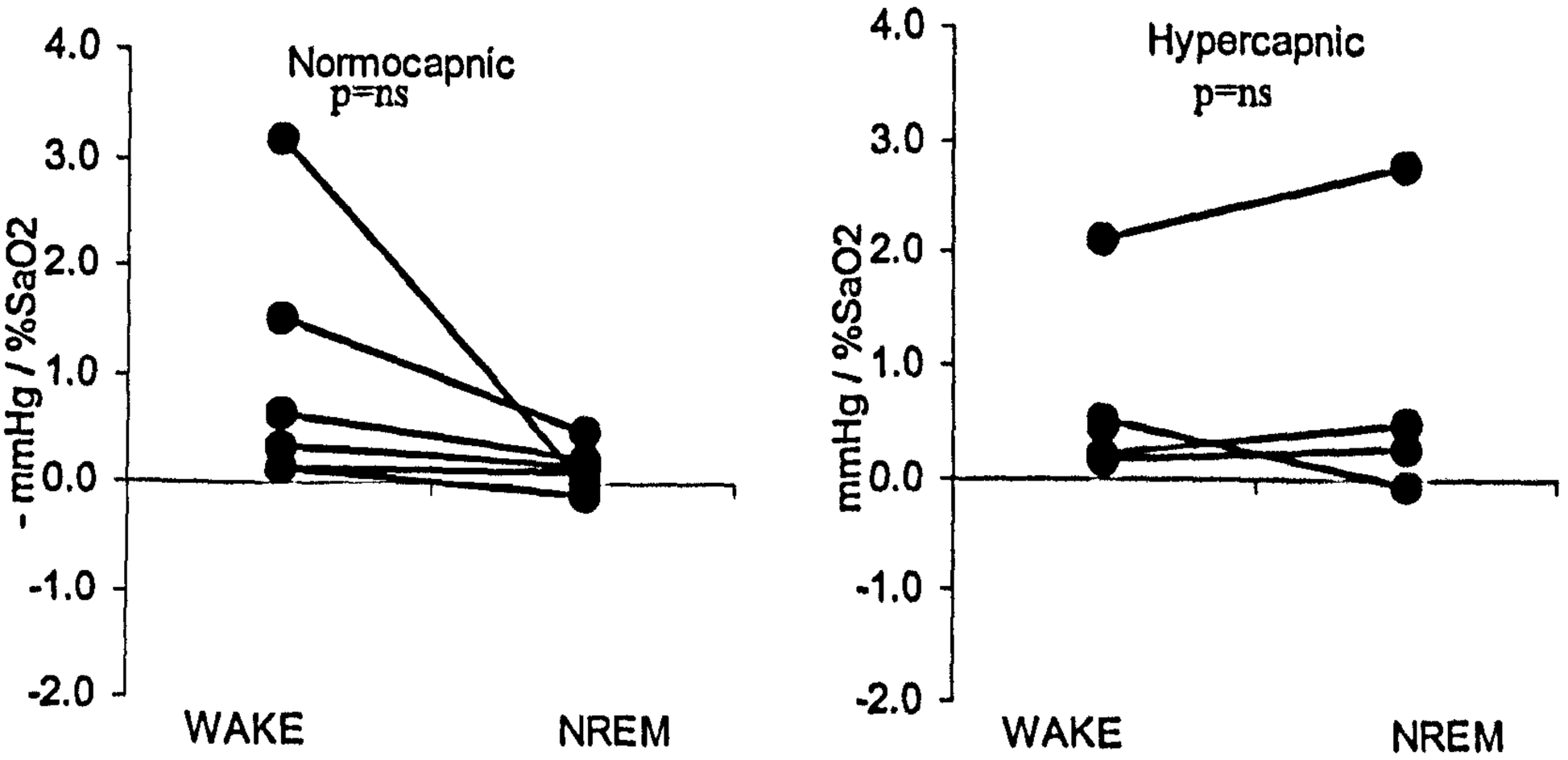


Figure 6.4 demonstrates that, although there is a trend for the mean blood pressure response to fall with NREM sleep under normocapnic conditions, sleep state does not significantly alter the hypoxic pressor response in these patients

6.5.8 The Acute Hypoxic Systolic Blood Pressure Response

Table 6.8 demonstrates the group mean systolic blood pressure response to hypoxia. Again, there was a large degree of variability with in the group, however with normocapnia, the systolic blood pressure response to hypoxia was significantly attenuated during NREM sleep

Table 6.8 - The group mean acute hypoxic systolic blood pressure responses.

	Acute Hypoxic Systolic Response (mmHg/%SaO2)	SD
Normocapnic Wakeful	-1.04	0.70
Normocapnic NREM	-0.27	0.44
Hypercapnic Wakeful	-1.97	1.88
Hypercapnic NREM	-0.96	1.06

Figure 6.5 demonstrates that CO_2 had no effect on the systolic blood pressure responses to hypoxia during wakefulness or NREM sleep

Figure 6.5 The effects of hypercapnia on the acute hypoxic systolic blood pressure responses during wake and NREM sleep

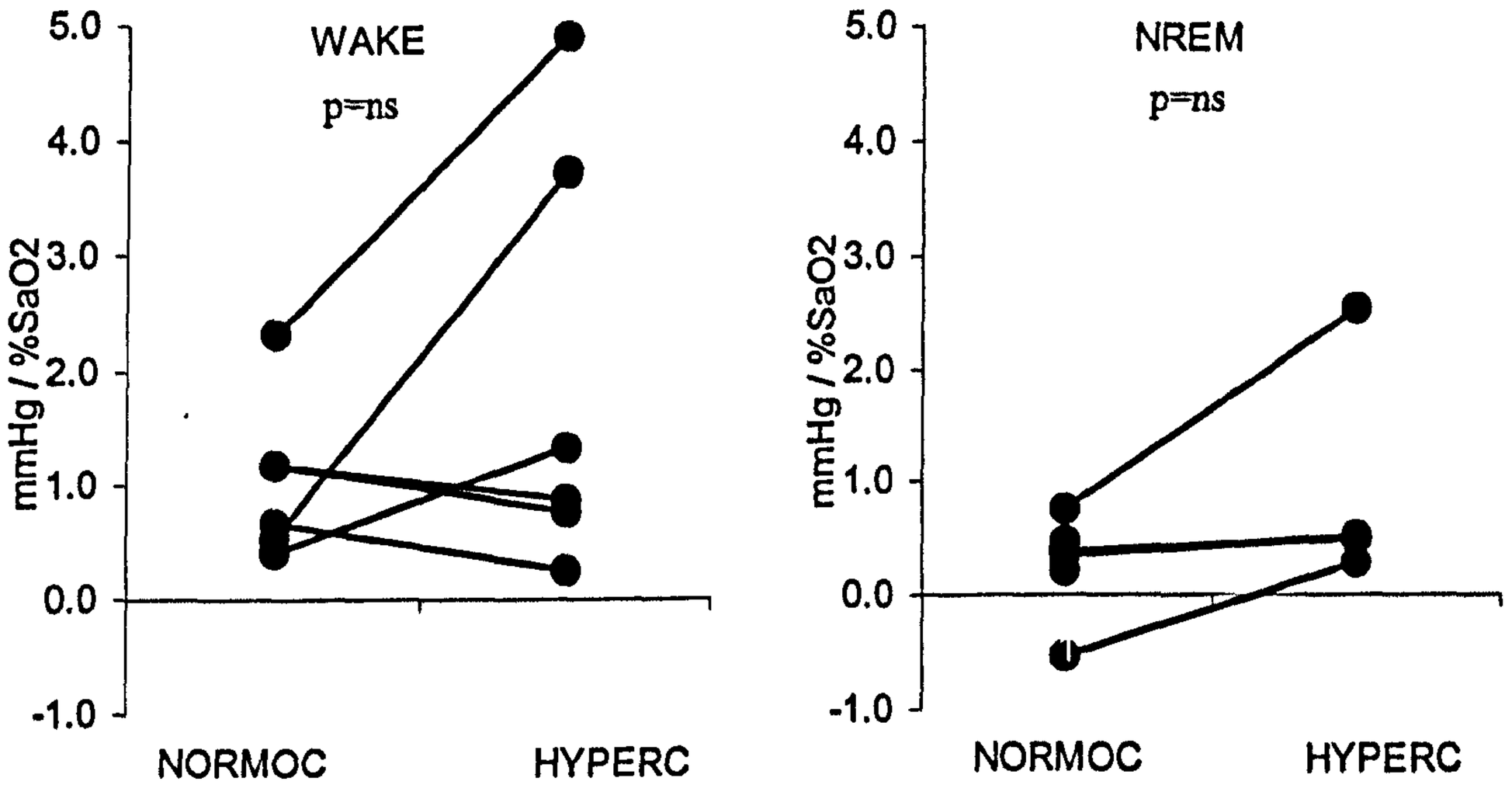


Figure 6.6 - The effects of NREM sleep on the acute hypoxic systolic blood pressure responses

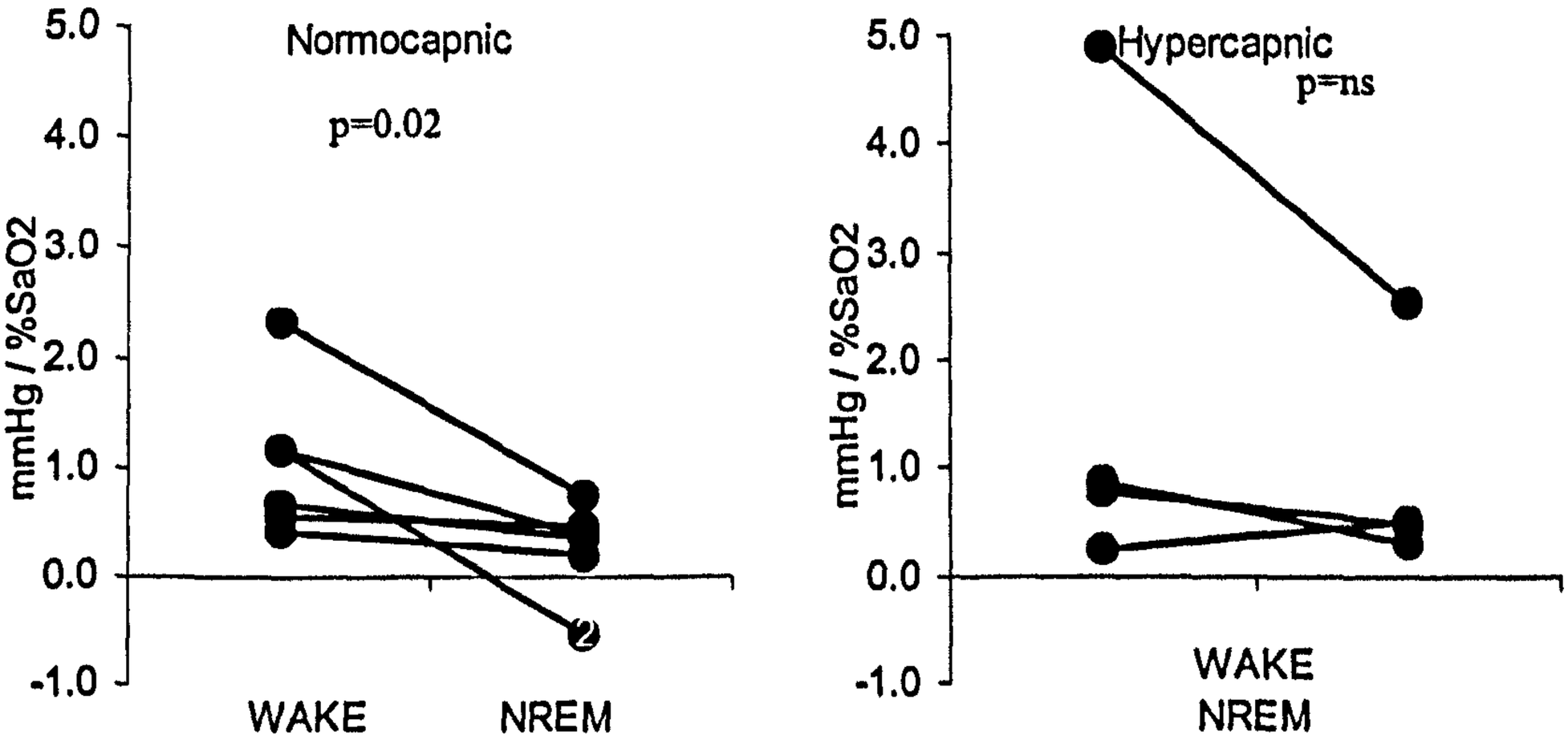


Figure 6.6 shows the same systolic blood pressure response data but are arranged to demonstrate the effects of sleep state on the hypoxic pressor response. A significant attenuation in the responsiveness to hypoxia was seen during NREM sleep with normocapnia, but no significant effect with hypercapnia.

6.5.9 The Acute Hypoxic Diastolic Blood Pressure Response

Table 6.9 demonstrates the group mean diastolic blood pressure response to hypoxia. CO_2 and sleep state had no significantly influence on the diastolic blood pressure responsiveness. This is also demonstrated in figures 6.7 and 6.8.

Table 6.9 - The group mean acute hypoxic diastolic blood pressure responses.

	Acute Hypoxic Diastolic Response (mmHg/%SaO2)	SD
Normocapnic Wakeful	-0.57	0.89
Normocapnic NREM	0.32	0.39
Hypercapnic Wakeful	-0.34	0.25
Hypercapnic NREM	-0.82	1.42

Figure 6.7 - The Effects Of Hypercapnia On The Acute Hypoxic Diastolic Blood Pressure Responses During Wake And NREM Sleep

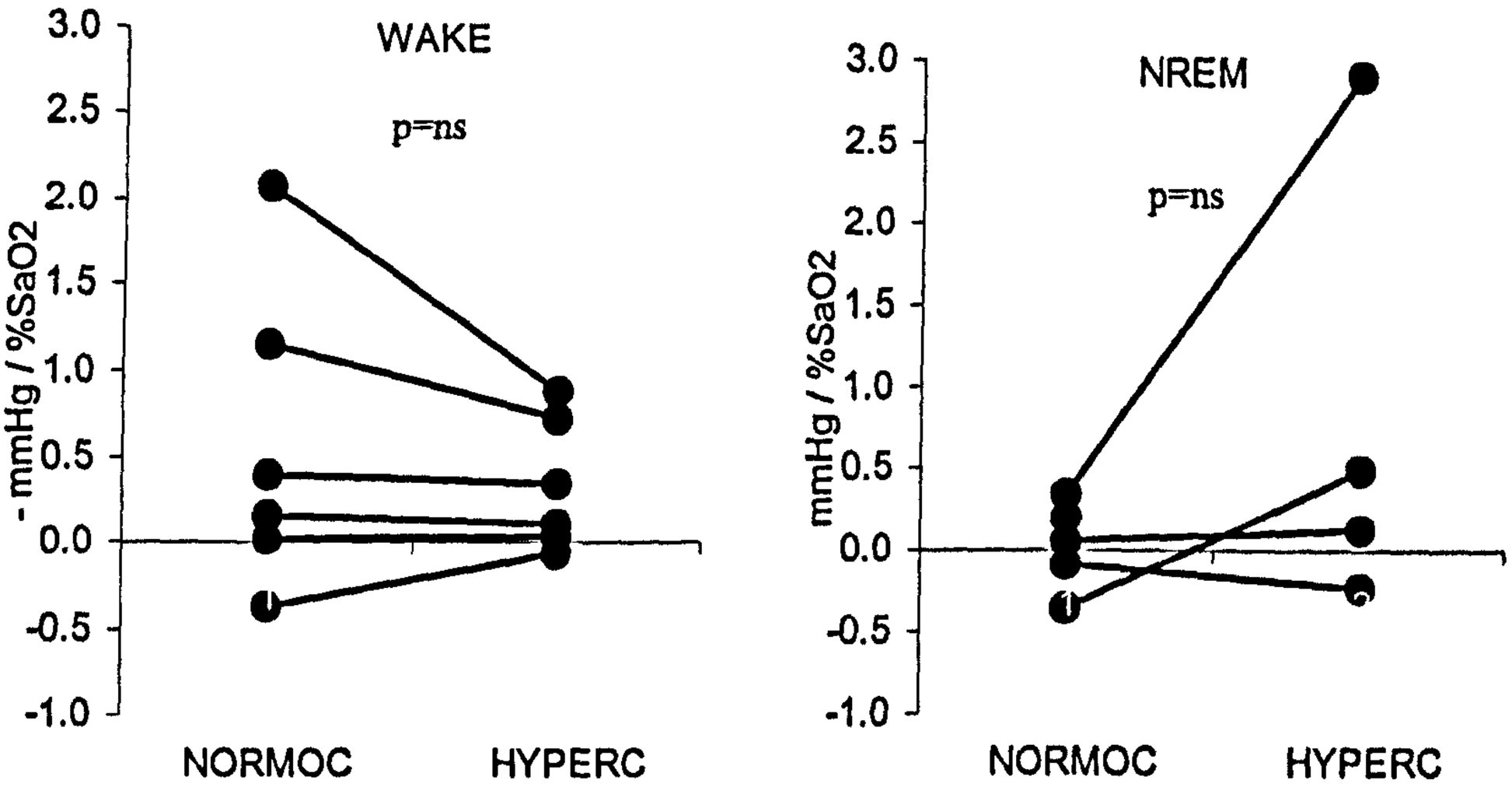
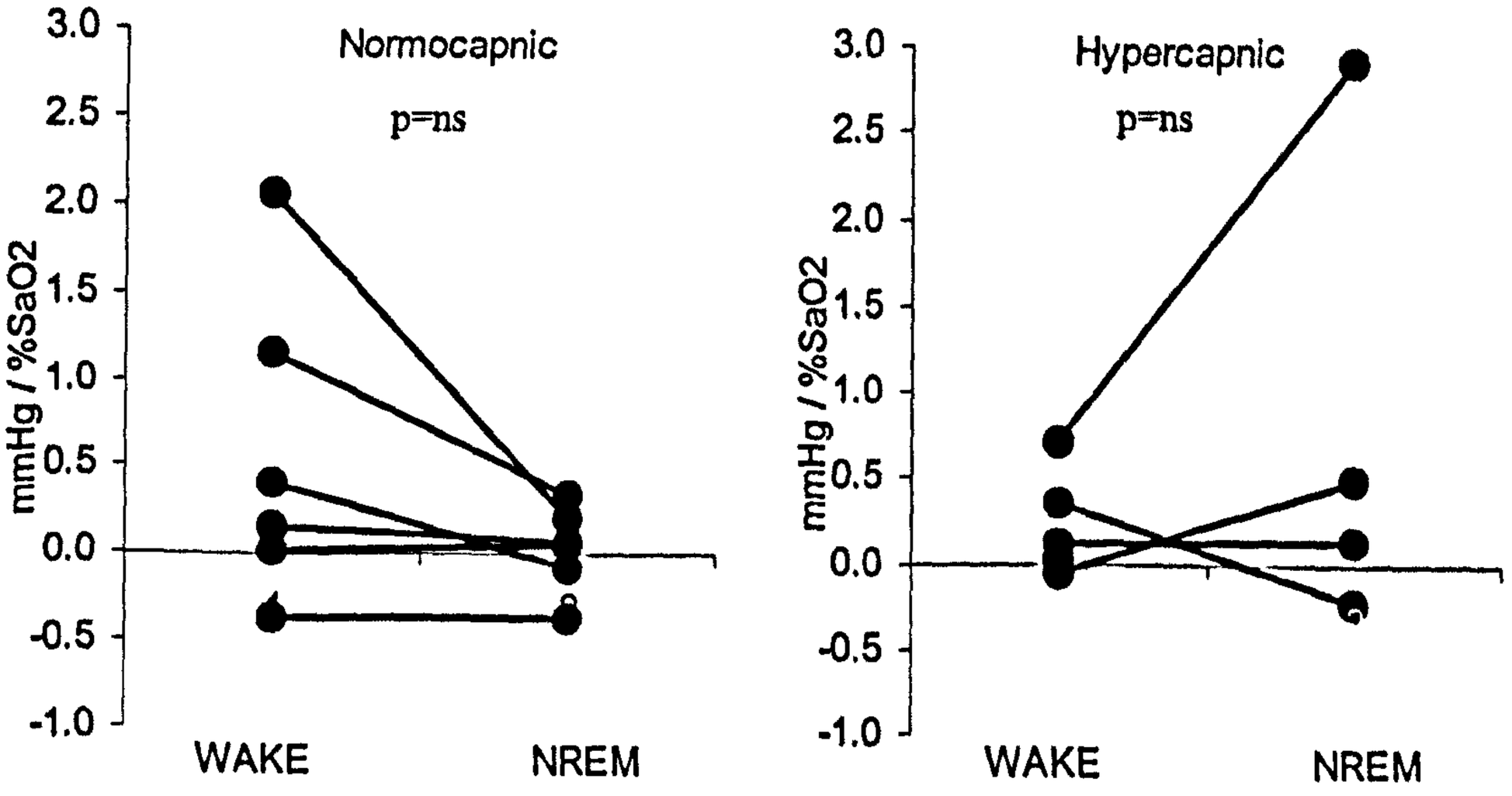


Figure 6.8 The Effects Of NREM Sleep On The Acute Hypoxic Diastolic Blood Pressure Responses



6.5.10 The relationships between Age, BMI and AHI and the cardiovascular responses to hypoxia.

There were no significant correlations between age, BMI, AHI and the cardiovascular responses to hypoxia with normocapnia (NC), hypercapnia (HC), wakefulness and NREM sleep. The AHI range was from 16.8 to 70.0 events per hour. It is possible that choosing a more select population of moderate to sever OSAHS patients may have highlighted any associations between the disease severity and hypoxic responses. In the selected population, there were patients that had very mild OSAHS and thus the influence of episodic hypercapnic hypoxia may be masked in the small group that was studied. BMI appeared to influence the blood pressure responses to hypoxia. However, under these conditions, data were only obtained from 4 patients and hence the relationship should be interpreted with caution.

SECTION 2 : ANALYSIS OF SPONTANEOUS APNOEAS WITH NORMOCAPNIA AND HYPERCAPNIA

From the 10 minute recordings during the first hour of sleep, a total of 65 spontaneous obstructive apnoeas, that terminated with an arousal were obtained from the 6 patients. They had a mean duration of 20.7 (7.8) sec, and reached a mean low SaO_2 of 89.2%. 48 spontaneous obstructive apnoeas, that terminated with an arousal, while breathing the hypercapnic gas mixture were also analysed. These had a significantly shorter duration (17.3 sec, SD 6.2) than the apnoeas with normocapnia (p=0.01), and reached a mean low SaO_2 of 90.7%.

6.5.11 End-tidal CO_2 Tensions

The $EtCO_2$ of the breath prior to and proceeding the hypercapnic apnoeas were significantly greater than the breaths before and after the normocapnic apnoeas (Table 6.14). However there was no significant difference in the rate of rise in CO_2 during the two groups of apnoeas.

Table 6.14 - CO_2 tensions pre and post apnoea

	EtCO2 Pre	EtCO2 Post	Abs Change	%change
Normocapnic	38.0 (3.0)	42.5 (4.9)	4.5 (3.7)	11.9 (9.9)
Hypercapnic	43.3 (2.6)	48.7 (5.3)	5.4 (4.3)	12.4 (10.0)
p=	**0.001**	**0.001**	0.253	0.766

6.5.12 Oxygen Desaturation Data

Table 6.15 - demonstrates that the SaO_2 immediately prior to the apnoeic events were not different with hypercapnia or normocapnia. However, the hypercapnic apnoeas, which were shorter in duration, demonstrated a smaller fall in SaO_2 and significantly different nadir SaO_2.

Table 6.15 - SaO_2 pre and post apnoea

	Sao2 Pre	Sao2 Post	Abs Change	%change
Normocapnic	96.8 (1.5)	89.2 (3.5)	7.6 (3.4)	7.8 (3.4)
Hypercapnic	96.43 (2.04)	90.71 (3.66)	5.72 (2.48)	5.95 (2.62)
P=	0.126	**0.016**	**0.001**	**0.001**

6.5.13 Changes in Heart Rate.

The heart rates immediately prior to apnoeas were not affected by hypercapnia. Although there was no significant difference between the absolute increase or the percentage change in heart rates of the two groups, the peak heart rates, associated with arousal from the hypercapnic apnoeas were significantly lower than those associated with normocapnic apnoeas..

Table 6.16 - Mean heart rate pre and post apnoea.

	HR pre	HR post	Abs Change	%change
Normocapnic	75.6 (9.3)	81.6 (8.9)	6.0 (5.6)	8.4 (7.8)
Hypercapnic	72.3 (8.7)	76.9 (9.6)	4.5 (5.4)	6.5 (8.1)
P=	0.060	**0.009**	0.159	0.225

6.5.14 Changes in Blood Pressures.

The three subsequent tables demonstrate that the systolic, diastolic and mean blood pressure immediately before an apnoea, and the peak pressure observed with the arousal response. The pressures all significantly increased after an obstructive apnoea ($p<0.005$), however, hypercapnia had no effect on the blood pressure pre or post apnoea, or the blood pressure change.

Table 6.17 - Blood pressures pre and post apnoea

	Systolic Pre	Systolic Post	%Change
Normocapnic	140.2 (18.8)	169.0 (22.3)	21.1 (10.5)
Hypercapnic	137.2 (29.9)	165.5 (37.7)	20.8 (7.8)
P=	0.272	0.283	0.445

	Diastolic Pre	Diastolic Post	%change
Normocapnic	65.7 (9.3)	80.9 (8.8)	24.2 (13.2)
Hypercapnic	65.6 (15.9)	83.1 (20.1)	27.4 (14.8)
P=	0.481	0.245	0.120

	MeanBP Pre	Mean BP Post	%change
Normocapnic	90.6 (10.8)	110.3 (11.5)	22.4 (10.4)
Hypercapnic	89.5 (19.6)	110.5 (25.3)	23.8 (9.7)
P=	0.366	0.473	0.235

6.5.15 The Relationship Between the Duration of the Apnoea and the Physiological Changes.

Table 6.18 shows the correlation coefficients for the relationships between the changes associated with the termination of apnoeas (65 normocapnic and 48 hypercapnic), and the duration of the apnoea. The $EtCO_2$ of the post apnoeic breath and the nadir SaO_2 were significantly associated with the duration of events, whereas only the peak post apnoeic blood pressures with hypercapnia were associated with the duration.

Table 6.1 Correlations of apnoea duration and physiolocial changes.

	Normocapnic	Hypercapnic
Post $EtCO_2$	**-0.446**	**-0.462**
% Change in $EtCO_2$	**-0.465**	**-0.671**
Post SaO_2	**0.343**	**0.66**
% Change in SaO_2	**-0.426**	**-0.800**
Post HR	**0.343**	**0.542**
% Change in HR	-0.218	-0.031
Post Systolic BP	-0.013	**-0.646**
% Change in Systolic BP	0.209	-0.225
Post Diastolic BP	0.201	**-0.510**
% Change in Diastolic BP	0.015	-0.207
Post Mean BP	0.094	**-0.592**
% Change in Mean BP	0.123	-0.228

Bold = $p<0.05$ **underlined = $p<0.001$**

6.5.16 The Relationship Between the Nadir SaO_2 and the Physiological Changes.

Table 6.19 shows the correlation coefficients for the relationships between the changes associated with the termination of apnoeas, and the lowest SaO_2 . The systolic and mean blood pressures were significantly associated to the nadir SaO_2.

Table 6.19 - Correlations of post apnoeic SaO_2 and physiological changes

	Normocapnic	Hypercapnic
Post $EtCO_2$	-0.159	**-0.300**
% Change in $EtCO_2$	-0.068	-0.270
Post HR	-0.133	0.167
% Change in HR	-0.101	**-0.419**
Post Systolic BP	**-0.306**	**<u>-0.667</u>**
% Change in Systolic BP	**-0.329**	**-0.323**
Post Diastolic BP	-0.241	**<u>-0.708</u>**
% Change in Diastolic BP	**-0.277**	0.270
Post Mean BP	**-0.320**	**<u>-0.708</u>**
% Change in Mean BP	**-0.342**	**-0.335**

Bold = p<0.05 **<u>underlined = p<0.001</u>**

6.5.17 The Relationship Between the Change in SaO_2 and the Physiological Changes.

Table 6.20 shows the correlation coefficients for the relationships between the changes associated with the termination of apnoeas, and the percentage change in SaO_2. Thses relationships are all weaker than those demonstrated when observing the nadir SaO_2.

Table 6.20 - Correlations of percentage change in SaO_2 and physiological changes.

	Normocapnic	Hypercapnic
Post $EtCO_2$	-0.034	-0.268
% Change in $EtCO_2$	-0.118	**-0.383**
Post HR	0.141	**0.314**
% Change in HR	-0.035	-0.230
Post Systolic BP	-0.148	**<u>-0.609</u>**
% Change in Systolic BP	**-0.354**	**-0.311**
Post Diastolic BP	0.014	**<u>-0.587</u>**
% Change in Diastolic BP	**-0.329**	-0.242
Post Mean BP	-0.087	**<u>-0.615</u>**
% Change in Mean BP	**-0.384**	**-0.306**

Bold = $p<0.05$ **<u>underlined = $p<0.001$</u>**

6.5.18 The Relationship Between the Post Apnoeic $EtCO_2$ and the Physiological Changes.

Table 6.21 shows the correlation coefficients for there were few significant relationships between the changes in heart rate and blood pressure associated with the termination of apnoeas, and the post apnoeic $EtCO_2$.

Table 6.21 - Correlations of post apnoeic $EtCO_2$ with physiological changes.

	Normocapnic	Hypercapnic
Post HR	0.039	**-0.364**
% Change in HR	**0.535**	0.137
Post Systolic BP	**0.437**	0.233
% Change in Systolic BP	-0.036	0.049
Post Diastolic BP	0.200	0.094
% Change in Diastolic BP	-0.104	0.247
Post Mean BP	**0.381**	0.166
% Change in Mean BP	-0.094	0.175

Bold = $p<0.05$ **underlined = $p<0.001$**

6.19 The Relationship Between the Change in $EtCO_2$ and the Physiological Changes.

Table 6.22 demonstrates that there were also no consistent relationships with changes in heart rate and blood pressure associated the termination of apnoeas, and the change in $EtCO_2$.

Table 6.22 - Correlations of percentage change in $EtCO_2$ and physiological changes.

	Normocapnic	Hypercapnic
Post HR	-0.244	**<u>-0.472</u>**
% Change in HR	0.209	-0.116
Post Systolic BP	0.142	0.283
% Change in Systolic BP	0.021	-0.042
Post Diastolic BP	-0.058	0.080
% Change in Diastolic BP	0.091	0.191
Post Mean BP	0.061	0.183
% Change in Mean BP	0.054	0.091

Bold = $p<0.05$ **<u>underlined = $p<0.001$</u>**

6.20 Acute Hypoxic Responses

The acute hypoxic cardiovascular responses were calculated from the change in heart rate or blood pressure and the change in SaO_2, and expressed as the mean change per 1% fall in SaO_2. These responses are not exclusively in response to hypoxia, as the hypoxia was induced by an obstructive apnoea which terminated in a cortical arousal. Both airway obstruction and cortical arousals result in changes in heart rate and blood pressure.

Table 6.23 demonstrates that significant increases in heart rate were seen in all patients when the SaO_2 fell, there was a group mean increase in 0.85 beats per minute per 1% fall in SaO_2 with normocapnia. Hypercapnia had no significant influence on these responses.

Table 6.23 - Acute Hypoxic Heart Rate Response

Patient	Normocapnic Beats/min/%SaO_2	Hypercapnic Beats/min/%SaO_2
1	1.76	1.98
2	0.70	0.78
3	1.37	0.04
4	0.77	0.28
5	0.23	1.20
6	0.27	0.30
Mean	**0.85**	**0.76**
SD	0.61	0.73

Table 6.24 - Acute Hypoxic Systolic blood pressure responses

Patient	Normocapnic mmHg/%SaO_2	Hypercapnic mmHg/%SaO_2
1	4.83	4.78
2	4.69	5.59
3	5.57	5.43
4	2.74	5.87
5	4.23	5.86
6	2.21	3.44
Mean	**4.04**	**5.16**
SD	1.30	0.93

Table 6.25 - Acute Hypoxic diastolic blood pressure responses

Patient	Normocapnic mmHg/%SaO_2	Hypercapnic mmHg/%SaO_2
1	2.14	3.84
2	2.13	3.02
3	3.01	4.48
4	1.80	3.02
5	3.04	4.33
6	1.17	1.44
Mean	**2.22**	**3.35**
SD	0.72	1.12

Table 6.26 Acute Hypoxic mean blood pressure responses

Patient	Normocapnic mmHg/%SaO_2	Hypercapnic MmHg/%SaO_2
1	3.04	4.15
2	2.99	3.88
3	3.86	4.80
4	2.11	3.97
5	3.44	4.84
6	1.52	2.11
Mean	**2.83**	**3.96**
SD	0.86	1.00

These tables show that there were large oncreases in blood pressure in response to hypoxia. These responses were significantly augmented by hypercapnia (systolic $p<0.05$, diastolic and mean $p<0.001$).

6.5.21 The correlation between apnoeic hypoxic responses and the responses to induced hypoxia.

The responses to hypoxia induced by apnoea do not significantly correlate with the responses to hypoxia induced experimentally during wakefulness or sleep. Increasing the CO_2 tension does not improve these poor relationships with the exception of the heart rate responses. The heart rate response to hypercapnic hypoxia during wake and sleep are correlated to the hypercapnic apnoeic heart rate response.

6.6 DISCUSSION

This study assessed the cardiovascular responses to peripheral chemoreceptor stimulation during wakefulness and sleep, and the response to arousal from spontaneous apnoeic events after breathing different CO_2 tensions. CPAP was used to abolish airway obstruction during sleep and thus a measure of ventilation and end-tidal gases could not be obtained. Wakeful and NREM arterial oxygen saturations were not significantly different from each other, demonstrating the CPAP was efficient at preventing airway obstruction and maintaining undisturbed gas exchange during NREM sleep. However, CPAP appears to act as an arousal stimulus. When CPAP and hypercapnia were combined, only 4 of the 6 OSAHS patients could tolerate hypoxia to an extent resulted in a significant fall in SaO_2. The other patients were repeatedly aroused from sleep before hypoxaemia was induced. Therefore, the hypercapnic-hypoxic responses during sleep were only calculated for 4 patients and the statistical significance of these responses should be interpreted with caution. The effects of the combined stimuli, in promoting arousals and so excluding some patients from our analyses may have created a select group of patients with low responses to hypoxia and hypercapnia. Subjects who have a normal or high response to these stimuli may, as seen with two of our patients, arouse before significant levels of hypoxaemia are attained.

Several assumptions were made when using the CPAP system to maintain hypercapnia. One particular problem was our inability to monitor the end-tidal CO_2. In the previous chapter, when healthy subjects were studied while awake and asleep, similar levels of inspired CO_2 were needed to increase the end-tidal CO_2 by 5 mmHg during both sleep states (Wake 2.39% (SD 0.24), NREM 2.48% (0.22)). During the OSAHS patients wakeful challenges the fraction of inspired CO_2 needed to maintain eucapnia and to increase the end-tidal CO_2 by 5mmHg was monitored. These fractions were assumed to provide levels of CO_2 for necessary to maintain eucapnia and increase the $EtCO_2$ by approximately 5mmHg during NREM sleep (Eucapnic 0.06% (SD 0.03), Hypercapnic 2.59 (SD 0.31)). Thus when presenting the responses to hypoxia during sleep, it was assumed the end-tidal CO_2 tensions were maintained at the individuals eucapnic tension and at 5mmHg above this.

Heart Rate Responses

As demonstrated in the previous two chapters, and by several other authors (Okabe et al 1995), the heart rate response to hypoxia is highly variable. All subjects increased their heart rate with hypoxia during wakefulness, but this was not significantly affected by CO_2 or sleep state. This was not unexpected, as there are many sympatho-vagal reflexes that exert chronotropic effects on the heart. Chemoreceptor stimulation is one of these effectors, but as well as directly stimulating the heart, it can also have indirect effects via changes in blood pressure and the baroreflex response.

Blood Pressure Responses

Effects Of Sleep. The blood pressure response in our group of patients was also variable. Although there was a trend for the mean blood pressure response to fall during NREM sleep with normocapnia a statistically significant difference was not attained. The data from our wakeful normocapnic challenges did not differ from the data of Hedner *et al.* We demonstrated a range of mean blood pressure responses from 0.14 to 3.18 mmHg/%SaO_2, while the group of patients studied by Hedner had a range of responses from –0.4 to 2.3mmHg/%SaO_2. Hedner also found a relationship between apnoea index and the pressor response, but we did not see any relationships between the pressor response and either AHI, BMI or age. There was a strong correlation between BMI and the pressor response to hypercapnic hypoxia during sleep. However with only four subjects completing these challenges, the statistical significance is dubious.

Effects Of Added Carbon Dioxide. Increasing the CO_2 tension did not affect the blood pressure response during wakefulness or sleep. This differed from the responses of our healthy subjects as described in chapter five. The healthy subjects had normocapnic and hypercapnic hypoxic responses that encompassed those found in OSAHS patients (Healthy normocapnic 0.65, hypercapnic 1.26 vs OSAHS normocapnic1.00, hypercapnic 0.88 mmHg/%SaO_2). The OSAHS wakeful response was greater than that of the normal subjects, which could add further support to the work by Narkiwicz *et al.* This work suggests that OSAHS patients have a potentiated chemoreflex sensitivity and a higher tonic chemoreflex activation

(Narkiewicz *et al* 1998 and 1999). We saw no significant increase in mean blood pressure at the higher CO_2 tension would suggest these patients do not have increased peripheral chemoreceptor sensitivity.

Spontaneous Apnoeas

Spontaneous apnoeas and the arousal responses associated with their termination were studied while the subjects were breathing room air or a hypercapnic gas mixture (2.5% CO_2, 97.5% Air). This allowed us to investigate the responses to hypoxia and hypercapnia with out the cardiovascular suppressing effects of the lung inflation reflex.

Breathing the hypercapnic gas increases the pre and post-apnoeic $EtCO_2$ but does not affect the percentage change in CO_2 that occurred during the apnoea. However CO_2 does affect the duration of the apnoea, the fall in SaO_2, and the post apnoeic SaO_2. Increasing the CO_2 tension reduced the duration of the apnoea, and thus smaller falls in SaO_2 and lower post apnoeic SaO_2 values were observed. Hypercapnia also improved the strength of the relationship between the duration of the apnoea and the changes in arterial saturation. The effect of CO_2 on apnoea duration was investigated by Berry *et al* (1993). They demonstrated, in healthy subjects, that increasing the $EtCO_2$ tension by 3.5mmHg, before occluding a mask covering the nose and mask, resulted in shorter apnoeas. They suggested the CO_2 influenced arousal by increasing the peak negative supraglottic airway pressure, which reflects the intrathoracic pleural pressure. The pressure measured during the first obstructed respiratory effort, was greater with hypercapnia. The rate of change in airway pressure was also greater with hypercapnia. Thus the peak pressure during the breath preceding arousal, which was *the same at both levels of peripheral* chemoreceptor stimulation, was reached more rapidly with hypercapnia. This mechanism is probably involved in evoking the arousals associated with apnoea termination in patients with OSAHS. In our study, the higher CO_2 tension may have prompted an EEG arousal and apnoea termination sooner than during the 'normocapnic' apnoea, by increasing the respiratory efforts in response to airway occlusion.

Heart rate was generally unaffected by CO_2 tension, the pre apneoic heart rates and changes in heart rate were not significantly different with normocapnia or

hypercapnia. However the post apnoeic heart rate was significantly less following a hypercapnic apnoea, compared to one with eucapnia. CO_2 tension, and apnoea duration were negatively and positively correlated with heart rate respectively, suggesting the higher CO_2 tensions and shorter apnoeas, have a smaller heart rate associated with their arousal. Hypercapnia strengthens this relationship.

Blood pressure significantly increased during an apnoea-terminating arousal. CO_2 tension did not affect the pre apnoeic, post apnoeic or change in blood pressure. However the blood pressure rise in result of arousing from a hypercapnic apnoea was consistently significantly associated with the apnoea duration, change in SaO_2, post apnoeic SaO_2. The shortest apnoeas, with the smallest changes in SaO_2, had the greatest increase in blood pressure. Some of these relationships are also seen with normocapnic apnoeas, but the correlation coefficients demonstrate they are strongest with hypercapnia. Blood pressure responses on arousal have been investigated by Davies *et al* (1993) and Rees *et al* (1995). They both demonstrated significant increases in mean blood pressure with arousal from sleep. Davies *et al* demonstrated a mean increase of 26.5mmHg when arousal was induced by auditory and vibratory stimuli, Rees *et al* demonstrated a 19mmHg increase during arousal from a spontaneous apnoea. Our work showed subjects had a 19.7mmHg increase in mean blood pressure when arousing from spontaneous normocapnic apnoeas. Both of Davies and Rees also demonstrated that significant blood pressure increases occur in the absence of an EEG arousal, suggesting arousals are continuous and not discrete, and that autonomic brain stem arousals occur before, and sometimes without, EEG visible changes are seen. The work in this chapter only assessed apnoeic events that terminated with an EEG arousal. Increasing the arousal stimuli, ie adding CO_2 to the stimulation from spontaneous airway occlusion and hypoxaemia, resulted in the arousal threshold being reached sooner, but no greater blood pressure changes were seen.

The acute pressor responses to hypoxia were determined by calculating the slope of the blood pressure change with the fall in SaO_2. This slope was drawn from just 2 points, the values immediately prior to the apnoea, and the peak BP/low SaO_2 associated with arousal. This is inherently likely to have more error than when using multiple points, as used in the previous chapters, and also incorporates the effects of arousal from sleep. However, a significant number of apnoeas were assessed to

reduce the errors that may occur when using a 2 point regression. The blood pressure rise after the apnoea was strongly associated with the fall in SaO_2. The pressor effects of hypoxia are enhanced with CO_2 and thus these data demonstrate that the blood pressure response to hypoxia and hypercapnia, and arousals . The blood pressure increases associated with arousal are much larger than, and not statistically associated with, the wakeful or NREM responses. However, the onset of wakefulness does not appear to be the only influence on blood pressure. CO_2 tension, although not shown to be directly associated with the absolute blood pressure or change in blood pressure, it significantly improved the relationships between these variables and both apnoea duration and SaO_2. The elevated CO_2 tension also increased the hypoxic pressor response.

Chapter Seven

Conclusions and Directions for Future Work

7.1 CONCLUSIONS

The work in this thesis has added further support what is known about OSAHS, and has also presented some fresh data on the subject of hypoxic pressor responses in man.

In chapter three, we demonstrated that desaturations are a crucial measure when defining OSAHS. Our work backs up the findings from Redline et al (2000) and Davies et al (2000), who both showed that desaturations correlate well with ESS and hence are a good marker of disease severity that can be associated with symptoms. Redline et al demonstrated that the apnoea index, scored with desaturations, was the best correlate with ESS compared with other measures of flow limitation with or without desaturations and cortical arousals. Davies at al demonstrated that the difference in the 4% desaturation indices, before and during CPAP best correlated with the improvement in ESS in patients treated with CPAP. Our work also shows that the 4% desaturation index is the best correlate with ESS, and that hypopnoeas have little influence on both the AHI and its effect on daytime sleepiness.

This group of works would suggest that, for routine diagnosis of sleep disordered breathing, polysomnography is excessive. To obtain a measure of disease severity that correlates well with daytime sleepiness, overnight oximetry is suffice.

In the latter chapters, we demonstrated that the hypoxic pressor response in man is augmented by hypercapnia, and that in our small groups of healthy individuals and OSAHS patients, there were no significant differences in these chemoreceptor mediated responses. Narkeiwicz et al (1999) and Osanai (1999) have conflicting results, suggesting that OSAHS patients have potentiated and depressed ventilatory responses respectively, compared to healthy subjects, and our work has demonstrated they have normal responses. This implies that the range of responses is large and that larger groups of healthy subjects and OSAHS patients need to be studied. Different methodological techniques may also contribute to these differences. An important variable that needs to be very tightly controlled during these investigations is the CO_2 tension. It is well established that very modest increases in CO_2 can significantly augment the ventilatory responses to hypoxia. Our work has shown this is also true for

the pressor responses. The increase in CO_2 during apnoeic events is something that has been largely overlooked by investigators studying the physiological changes that occur during and after an apnoea. The work in this thesis stresses the importance of CO_2 in OSAHS and proposes that the interaction of the hypoxic and hypercapnic stimuli is important in influencing the blood pressure increase during the apnoea, the apnoea duration, the burst of sympathetic activity and surge in blood pressure seen with arousals, and potentially may be involved in the development of hypertension. This work would imply that most animal experiements investigating the role of episodic hypoxia in the mechanism underlying the development of hypertension may see greater or more rapid responses if a hypercapnic hypoxic stimulus was applied. The influence of hypercania should not be ignored.

7.2 FUTURE WORK

Although the present studies indicate that peripheral chemoreceptor stimulation has important cardiovascular effects their magnitude as compared to the sympathetic activation that accompanies arousal is hard to estimate. One approach would be to stimulate the chemoreceptor independently of additional hypoxia or hypercapnia.

Almitrine, a peripheral chemoreceptor agonist has been used to increase ventilation in COPD patients during wakefulness and sleep and shows a significant interaction with the prevailing CO_2 tension. However its effect on blood pressure has not been assessed. Our data would suggest there would be no difference in the responses of the healthy subjects and normotensive patients. In healthy subjects we would expect to see a pressor response to the adminsitration of almitrine, and, as we have demonstrated the chemoreceptor mediated responses are reduced during sleep, we would predict that the effects of this drug would be supressed during sleep.

In OSAHS, almitrine may contribute to increasing ventilatory efforts and the more rapid termination of apnoeas, but this would not improve daytime functioning. In fact,

reducing the duration of respiratory events would have the potential for a greater number of events during the same period of sleep, and thus greater sleep disruption.we would anticipate that the blood pressure response , graded for apnoea duration, would be increased with this drug.

There is a further need to assess whether episodic rather than sustained stimuli have similar effects on blood pressure as suggested by experiments on rats have demonstrated that episodic exposure to hypoxia does indeed lead to the development of sustained hypertension. The baroreceptor response and lung inflation response also merit investigation. These responses mask the outflow of neural stimuli from the chemoreceptors by suppressing the pressor response to hypoxia and hypercapnia and may prevent sustained hypertension. Current investigations have not assessed the ventilation, baroreceptor and chemoreceptor function simletaneously. It is possible that, as a population, these independent responses in OSAHS patients have appeared normal, but there may be a correlation between the intensity and interaction of these responses and the likelihood of becoming hypertensive.

Many of these studies will require patient investigation and fortunately the availability of effect therapy with CPAP which reverses the physiological abnormality permits a 'before and after' type of protocol which greatly increases the power of these studies. Assuming that resolution of the reflex changes can be demonstrated as work from the Mayo clinic group suggests is possible, then more detailed examination of the time course of these changes is needed.

Finally the interaction of these chemoreceptor-mediated responses and the other regulatory mechanisms especially indices of sympathetic activation derived from heart rate variability may give more insight into the long term cardiovascular consequences of recurrent upper airway obstruction during sleep.

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Appendix One: Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired. This refers to your usual way of life in recent times, even if you have not done some of these things recently, try to work out how they would have affected you.

0= would never doze
1= slight chance of dozing
2= moderate chance of dozing
3= high chance of dozing

Situation	Chance of Dozing
Sitting and reading	____
Watching TV	____
Sitting inactive in a public place	____
As a passenger in a car for an hour	____
Lying down in the afternoon	____
Sitting and talking to someone	____
Sitting quietly after lunch without alcohol	____
In a car while stopped for a few mins in traffic	____

Appendix Two: Subject Details in Chapter Three

Subject Number	Age	BMI	ESS	AHI	Desat Index
1	51	38.7	2	12	2
2	37	30.3	5	18	25
3	71	28.8	10	27	17
4	51	37.5	10	37	30
5	64	29.2	12	38	35
6	61	29.1	24	91	88
7	37	32.8	11	16	11
8	66	32.4	4	27	33
9	50	28.9	13	10	18
10	40	44.2	11	19	31
11	40	31.1	10	15	15
12	72	45	20	20	10
13	67	30.7	21	57	62
14	67	29	19	71	90
15	53	42.3	13	22	39
16	49	34.4	6	18	33
17	64	34.4	21	67	65
18	52	29.6	4	21	55
19	52	42	20	79	81
20	52	44.5	16	62	63
21	46	31.6	16	72	70
22	52	32.2	14	37	45
23	52	36.5	14	56	62
24	62	30.9	15	19	15
25	65	33.8	11	28	23
26	46	35.4	11	12	20
27	52	27	16	12	10
28	50	28.7	18	52	74
29	70	28.3	7	13	4
30	51	26.5	15	59	65
31	45	26.3	18	75	79
32	52	25.5	13	35	34

33	29	38.3	6	11	13
34	66	39.7	12	47	61
35	62	39.8	12	15	12
36	63	32.6	6	25	23
37	50	45	10	92	92
38	61	30.7	9	34	31
39	43	29	8	40	50
40	60	42.3	10	11	13
41	53	34.4	17	53	48
42	49	34.4	16	71	92
43	64	29.6	16	55	48
44	52	42	24	83	75
45	52	44.5	16	26	26
46	52	31.6	7	34	28
47	46	32.2	21	70	78

Appendix Three: Subjects Details From Chapter Four

Healthy				
Subject	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (Kg/m2)
1	24	186	76	22.0
2	44	159	84	33.2
3	43	168	82	29.1
4	25	183	76	22.7
5	34	156	88	36.2
6	34	166	82	29.8
7	21	186	72	20.8
8	26	184	78	23.0
9	32	171	62	21.2
10	28	177	69	22.0
11	49	170	80	27.7
12	50	178	83	26.2

OSA				
Subject	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (Kg/m2)
1	56	180	114.0	35.2
2	60	178	98.0	30.9
3	64	178	89.0	28.2
4	58	180	76.0	23.4
5	51	173	114.5	38.4
6	52	183	108.2	32.3
7	54	173	89.1	29.9
8	38	168	102.0	36.3
9	44	180	150.0	46.3
10	61	168	125.0	44.3
11	55	170	86.0	29.8
12	62	171	127.0	43.9
13	67	176	108.0	34.9

Appendix Four: Subject Details in Chapter Five

Age	Height	Weight	BMI	Resting PEtCO2		Hypercapnic PEtCO2	
(Yrs)	(cm)	(Kg)	(Kg/m2)	(mmHg)		(mmHg)	
				Wake	REM	Wake	REM
20	211	98	22.01	38.6	38.5	42.6	42.9
20	180	75	23.15	38.6	38.6	40.9	42.1
19	160	57	22.27	35.8	37	41.6	41.8
34	155	50	20.81	33.7	34.2	40.9	39.1
24	179	56	17.48	36.6	33.4	39.4	38.4
69	176	92	29.7	29.3	29.8	38.3	35.6
21	160	65	25.39	34.4	34.6	38	39.3

Appendix Five: Subject Details in Chapter Six

Subject	Age	Height	Weight	BMI	AHI
	(Yrs)	(cm)	(Kg)	(Kg/m2)	(Events/Hour)
1	72	165	98	36	70
2	28	190	140	38.7	42.8
3	50	182	95	28.7	19.8
4	44	180	91	28.1	27.1
5	38	173	130	43.4	56.7
6	52	183	80	23.9	16.8

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