SLEEP APNOEA: PREVALENCE IN ESSENTIAL HYPERTENSION AND EFFECTS ON RENAL FUNCTION

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by

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ABSTRACT

It has been suggested by several recent publications that nocturnal hypoxia, as a result of disordered nighttime breathing or sleep apnoea syndromes, may be an important, hitherto unrecognised, cause of hypertension. Part 1 of this thesis describes an outpatient survey of nocturnal hypoxia in two age, weight and height matched groups (n=32 in each group) with and without hypertension. Sustained hypertension was confirmed in the study group by 24 hr ambulatory monitoring. Using a portable oximeter incorporating solid-state memory, continuous recordings of overnight oxygen saturation were made in all subjects. There was no difference in the saturation records of the two groups, thus providing no support for the contention that sleep-related breathing disorders might be associated with hypertension. Because the oximeter had only recently become available, and as a preliminary to the study, validation of the oximeter against other oximeters and direct arterial samples was undertaken.

Part 2 describes the overnight natriuresis and diuresis which occurs in a severe example of sleep disordered breathing (obstructive sleep apnoea), and its prompt disappearance with treatment. This is an original observation, and the remaining chapters describe three further studies into the potential mechanisms responsible for this effect. Measurements of plasma levels of atrial natriuretic peptide were made in patients with obstructive sleep apnoea, and normal subjects in whom the effect of obstructive apnoea on inspiratory intrathoracic pressure was simulated by an inspiratory resistance. No evidence that abnormally large negative intrathoracic pressures were associated with excessive release of atrial natriuretic peptide, or indeed any important effect on renal function, was found in either study. In the final study measurements of inulin and lithium clearance were made in patients with obstructive sleep apnoea before and during treatment with continuous positive pressure applied via the nose. The results suggest that obstructive sleep apnoea affects proximal renal tubular function. The final chapter discusses these results and presents a review of the literature concerning interactions between lung and kidney.

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LIST OF ABBREVIATIONS

SAS: Sleep apnoea syndrome

OSA: Obstructive sleep apnoea

CSA: Central sleep apnoea

CPAP: Continuous positive airway pressure

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

MBP: Mean blood pressure

S_aO_2: Haemoglobin saturation

P_aO_2: Arterial partial pressure of oxygen

P_aCO_2: Arterial partial pressure of carbon dioxide

FRC: Functional residual capacity

SVC: Superior vena cava

C_{in}: Inulin clearance

GFR: Glomerular filtration rate

RBF: Renal blood flow

C_{Li}: Lithium clearance

C_{Na}: Sodium clearance

BMI: Body mass index (Wt Height^{-2})

ANP: Atrial natriuretic peptide

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PART 1

SLEEP APNOEA: PREVALENCE IN SYSTEMIC HYPERTENSION

1: INTRODUCTION and HISTORICAL BACKGROUND

1:The sleep apnoea syndromes

Literature from many historical cultures contains descriptions of illnesses that have been rediscovered in modern times, and reference to extreme obesity, somnolence and breathing difficulties have been found in Ancient Greek literature (Gulick 1863). The most celebrated literary description of someone who almost certainly had a specific breathing disorder associated with sleep and causing hypersomnolence is that of the fat boy, Joe, in Dickens' Pickwick Papers.

..`and on the box sat a fat, red-faced boy in a state of somnolency'..

..`Joe- damn that boy, he's gone to sleep again'..

..`slumbering over the stones, as if it had been a down bed with watchsprings'..

..`everybody was excited except the fat boy, and he slept as soundly as if the cannon were his ordinary lullaby. Be good enough to pinch him, Sir; in the leg if you please-nothing else wakes him'..

Although this represents a remarkably accurate description of a patient almost certainly suffering from what we now know as the syndrome of obstructive sleep apnoea (OSA) neither Dickens nor any medical practitioners of the time had appreciated the factors which conspired to produce this collection of symptoms (predominantly obesity, extreme hypersomnolence and a ruddy complexion), indeed it is unlikely that it occurred to anyone that they would have a distinct and readily identifiable cause.

As had Lamacq (Lamacq 1897) two years previously, Dr R Caton of Liverpool came tantalisingly close to making the connection between excessive sleepiness and sleep-related breathing difficulty. In a presentation to the Clinical Society of London on Feb 8 1889, he

reported the case of an apparently healthy 30 year-old man:

...'(who) unless in exercise, found it impossible to keep awake'...

...'During sound sleep a convulsive closure of the glottis occured, during which entrance or exit of air was entirely suspended, and violent inspiratory efforts were made. Respiration was suspended for a minute, or a minute and a half, or even longer, and the most marked cyanosis occured. At length the spasm yielded, respiration was re-established and the cyanosis disappeared. Attacks of this kind occurred at short intervals, all night and in the day during sleep'...

The symptoms were ascribed to an excess of poisonous extractives, leucomaines or ptomaines in the blood, and treated, apparently with some success, by the administration of napthalin, iodoform and charcoal. In the ensuing discussion reference was made to Dickens' classic description, and a number of other similar cases known to the physicians present (Caton 1889).

The American ENT surgeon Walter Wells reported a strong association between a number of nervous and mental symptoms and nasal obstruction, many of which could be reversed by nasal surgery. He noted that sleep was often greatly disturbed in these patients but felt that this could not explain the association, which he thought were due to a malfunction of the cerebral lymphatics, which lie in close proximity to the nose (Wells 1898). His British counterpart William Hill reported that nasal obstruction in children was frequently associated with mental backwardness and stupidity, and that this could be rectified by nasal scarification and removal of the tonsils. He concluded somewhat sombrely:

...'(that) the stupid-looking lazy child who frequently suffers from headache at school, breathes through his mouth instead of his nose, snores and is restless at night, and wakes with a dry mouth in the morning, is well worth the solicitous attention of the school medical officer...' (Hill 1889).

These observations did not receive widespread prominence,

Figure 1

MR PICKWICK IN CHASE OF HIS HAT.

Hypersomnolence

although in the first edition of The Principles and Practice of Medicine (Osler 1892) Osler did draw attention to the fact that the sufferer from chronic tonsillitis is often backward, and in a subsequent edition (1916) mentioned Pickwick in connection with the association between obesity and somnolence, which he thought was a manifestation of disturbed internal secretions. In a detailed and lengthy treatise Ker and Lagen described the effects of obesity, and although concentrating mainly on orthopaedic aspects of the condition, mention was made of oedema, a ruddy complexion and cyanosis as common symptoms (Ker and Lagen 1936).

In the 1950s, sporadic case reports of patients with various combinations of obesity, sleepiness, cyanosis, polycythaemia and ankle oedema began to appear. (Sieker et al 1955, Auchinloss et al 1955, Burwell et al 1956). Burwell and colleagues described a patient who liked to play poker, and who was moved to seek medical help when he fell asleep during a game when holding a hand of three aces and two queens. The patient was obese and hypercapnic, and the authors thought that the hypersomnolence was due to hypercapnia, which they in turn thought was a consequence of the increased ventilatory load imposed by obesity.

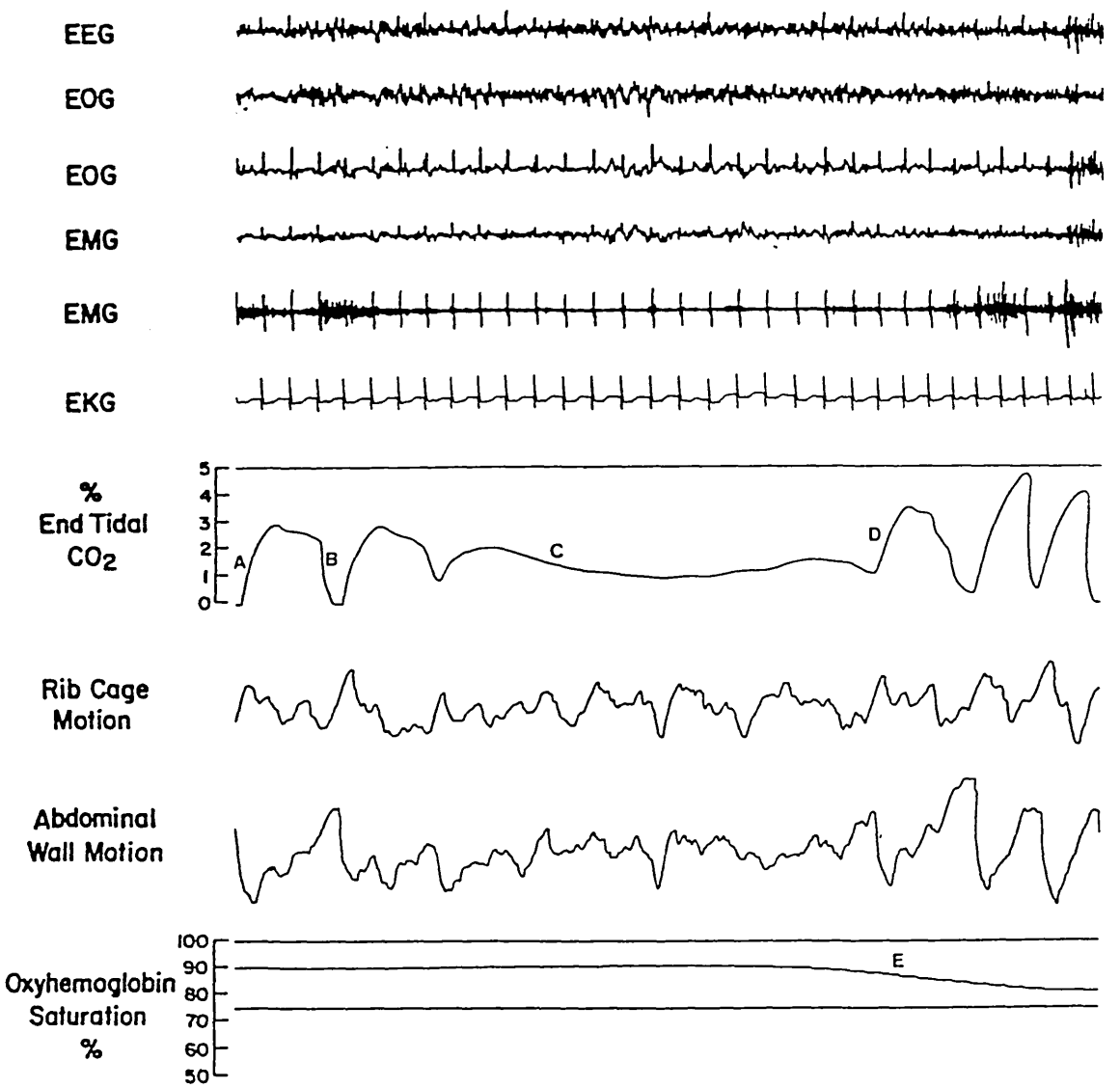
In the mid 60's the technique of polysomnography became more widespread. This initally involved monitoring and recording electroencephalographic (EEG), electrooculographic (EOG) and electromyographic (EMG) signals and was later extended to include transcutaneous oximetry and respiration, usually by change in intra-abdominal and intra-thoracic volume (figure 2). In 1965 two articles were published one in English and one in French, describing for the first time recurrent apnoeas during sleep. This lead to the

recognition of what are now known as the sleep apnoea syndromes (SAS) (Gastaut et al 1965, 1966).

These reports initiated an explosion of interest in sleep and breathing and large numbers of articles appeared on the subject, mainly in American publications. Many different eponyms were advanced leading to enormous confusion over the exact pathophysiology of the various syndromes that had been identified, especially those apparently characterised by recurrent central apnoeas (see below). Kryger and colleagues described a patient with profound hypersomnolence and recurrent upper airway obstruction when asleep, and amongst other things emphasised that bypassing the obstruction by tracheostomy resulted in complete resolution of the symptoms (Kryger et al 1974). Fourteen years later, neither the aetiology, nor the precise location of the upper airway obstruction are completely understood.

Obstructive sleep apnoea (OSA) occurs as a result of passive collapse of the pharyngeal walls (Remmers et al 1978). This will occur when the dilating forces in the pharyngeal muscles are insufficient to overcome the negative pressures generated by the inspiratory muscles. Although an increase in upstream resistance (eg in the nose) may lead to much larger than normal negative pressures being generated, thereby rendering the pharynx more susceptible to collapse (Zwillich et al 1981), the fact that it is precipitated by sleep suggests that sleep itself is in some way responsible (Stradling 1986). The dilator muscles of the upper airway are known to receive neural input from the medulla corresponding to that received by the diaphragm and rib cage musculature. During sleep the respiratory centre output is diminshed, and it has been suggested that loss of tone in the pharyngeal dilator

Figure 2



Polysomnographic recording: Ten channels are recorded. The first five allow sleep staging, and the bottom four show respiration. In this example end-tidal CO_2 is measured to identify whether respiration is occurring, although thermistors placed over mouth and nose are used more commonly. An obstructive apnoea is shown with persisting ribcage and abdominal movements, but zero end-tidal CO_2 (indicating an absence of airflow) and a falling S_aO_2. Upon arousal, seen as an increase in frequency in all EEG leads, deflections in end-tidal CO_2 restart.

muscles occurs as a result of exaggerated diminution in the normal respiratory centre output that occurs during sleep (Brouillette and Thach 1979, Sauerland and Harper 1976).

Alternatively, the superimpositon of a normal reduction in pharyngeal dilator tone upon diminished pharyngeal size may be all that is necessary for pharyngeal collapse to occur (Lopes et al 1983). Many physical abnormalities have been reported to cause OSA; these include mucopolysaccaridoses (Perks et al 1980a), acromegaly (Perks et al 1980b), myxoedema (Orr et al 1981), tonsillar enlargement (Stradling 1982) and vena caval obstruction (Stradling et al 1981). Although the majority of patients with OSA do not have a gross anatomical abnormality, recent evidence using an ac oustic reflectance technique has shown that patients with OSA do have smaller pharyngeal sizes than normal, and that the smaller the size of the pharynx the more severe the OSA (Rivlin et al 1984).

It has been suggested that an instability or abnormal reduction in respiratory centre output during sleep may allow upper airway collapse during sleep (Onal et al 1984). This could only occur if there was differential output to the upper airway and inspiratory muscles. There is experimental evidence supporting this (Brouillette and Thach 1979, Weiner et al 1982). Furthermore alcohol, which has a greater depressant effect on the upper airway muscles than the diaphragm (Bonora et al 1984) is known to both convert heavy snoring to OSA, and worsen established OSA (Issa and Sullivan 1982). Current evidence supports the theory both pharyngeal size and compliance (affected by neural input) determine its susceptibility to collapse during sleep (Brown et al 1985). The exact site of the obstruction probably varies between individuals, but there is some radiological

evidence that the uvula and soft palate can be pulled down to impact like a cork in an oropharynx already narrowed by close apposition of the back of the tongue and posterior pharyngeal wall (Guilleminault et al 1978).

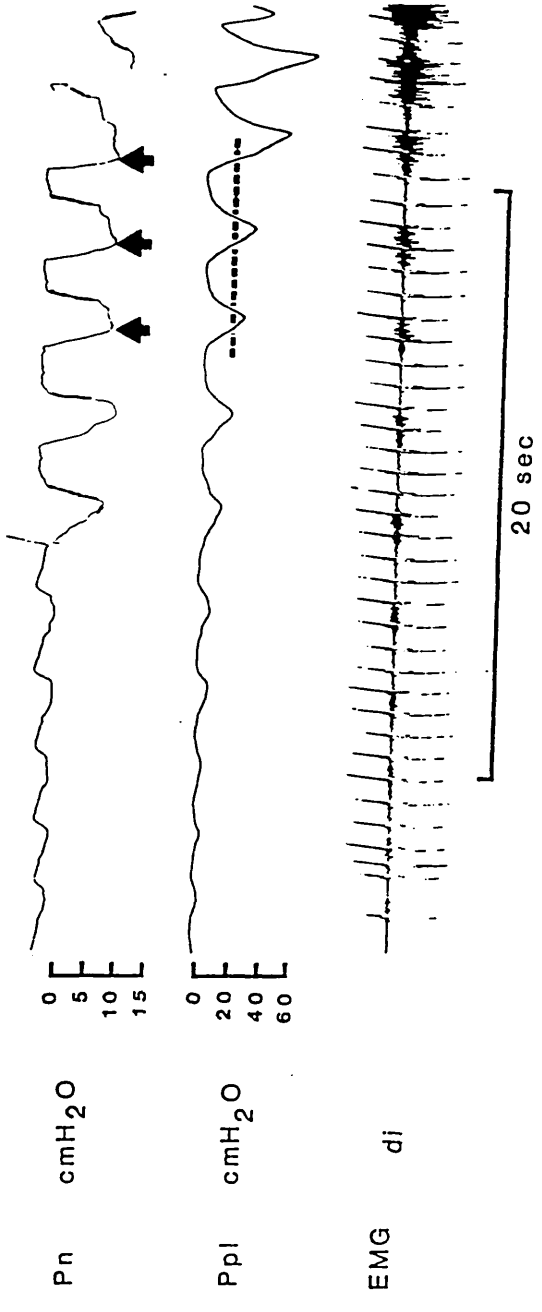
Intra-oesophageal pressure measurements during an obstructive apnoea have shown that as respiratory movements persist, progressively greater efforts are made throughout the apnoea (fig 3). As it continues blood gas tensions become progressively more deranged, with the haemoglobin saturation of arterial blood (S_aO_2) falling sometimes to as low as 40%. Whether as a result of hypoxia, hypercapnia, or the sensation of increasing respiratory effort arousal eventually occurs, whereupon upper airway patency is restored, allowing respiration to restart (Sullivan et al 1984).

In severe cases sleep and upper airway patency are mutually incompatible, and patients can only sleep for brief periods (30-90s) between periods of unobstructed respiration before the blood gas derangement wakes them once more. In such cases this means a short (5-10s) microarousal every minute or so. As the syndrome becomes established these micro-arousals, although clear on EEG, do not result in complete return of consciousness. Nevertheless they have a profoundly fragmentary effect on normal sleep architecture, and the sufferer wakes in the morning having had a very unsatisfactory night but not having been aware of either his recurrent apnoea or the necessity to awake so frequently.

The cardinal pathophysiological consequences of this condition are therefore:

1. Profound sleep disruption, sufferers spend the greater part of the night in fragmented stage 1 and 2 sleep, and almost never achieve

Figure 3



Successive decrease in pleural pressure during obstructive sleep apnoea. In this example, nasal CPAP (see chapter 5) of 4.5 cm H_2O was applied during the first (left-hand) half of the tracing. When it was removed the subject immediately experienced obstructive apnoea, and it can be seen that with each breath, a progressively greater (negative) pressure is generated, until the apnoea is terminated by arousal (seen by the sudden increase in the amplitude of the EMG tracing)

stage 3 or 4 (slow wave) sleep, because of the necessity to arouse in order to breathe. Although they do experience REM sleep, the hypoxaemia tends to be even worse during this stage of sleep, either because of a higher arousal threshold or due to the loss of tone in all skeletal muscle (including the pharyngeal dilators) in this stage of sleep. This sleep disruption is thought to be responsible for the most common and disabling symptom of this condition, excessive daytime somnolence. Characteristically, the sufferer, or more commonly his or her spouse will complain of gradually progressive sleepiness, intellectual deterioration, irritability and sometimes impotence. The sleepiness can often be overcome when there are sufficient external stimuli, but sufferers frequently cannot stay awake to perform everyday activities such as reading, watching television, driving and even eating. A general practitioner who presented to the Oxford Sleep Unit had found himself falling asleep not only during consultations with patients, but also whilst flying his aeroplane! Although a history of heavy snoring is almost universal, the snoring sometimes becomes less noticeable once patients begin to suffer long periods of (quiet) obstructive apnoea (Guilleminault et al 1976).

2. Repetitive hypoxaemia and hypercapnia. Although daytime blood gas tensions are usually normal in these patients, the long term effects of the reccurrent and often severe desaturation that occurs is not known, but in the absence of lung disease there is evidence that daytime respiratory failure does not occur, whereas if there is even mild airway obstruction, daytime hypoxaemia, hypercapnia and cor pulmonale may occur (Bradley et al 1985, Bradley et al 1986, Weitzenblum et al 1987).

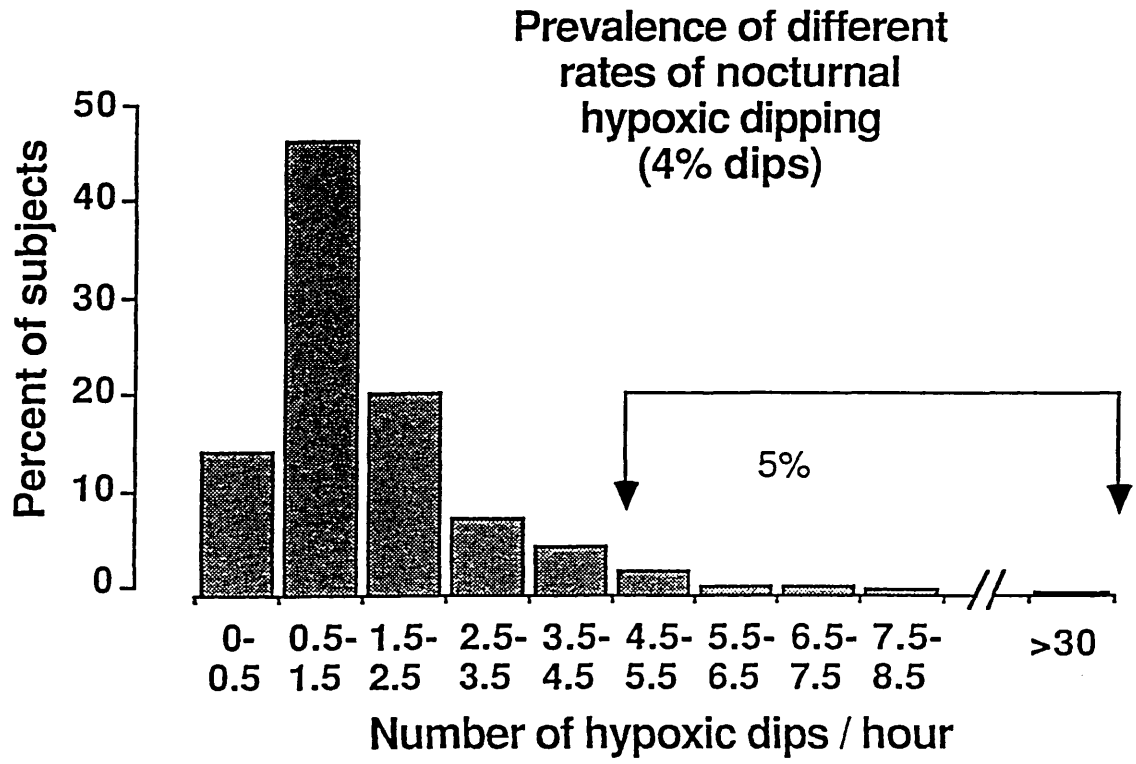
With the development of increasingly sensitive monitoring

equipment, it was also recognised that apnoeas were not always obstructive in origin, some being associated with an apparent cessation of respiratory effort. This was termed central because it was felt that they were caused by a temporary failure of medullary breathing centre output. A number of apnoeas appeared to have both central and obstructive components, and were termed mixed. Whilst central apnoeas undoubtedly occur, their recognition has contributed substantially to the confusion and multiple eponymous descriptions put forward for what should be called sleep disordered breathing or sleep apnoea syndromes (SAS). Current thinking suggests that whilst of interest to respiratory physiologists, central sleep apnoea is extremely rare in comparison to obstructive sleep apnoea, and probably represents a heterogenous group of disorders, of which some are in fact variants of obstructive sleep apnoea (Stradling 1986).

If a set of pathological features does not consistently produce a recognisable clinical entity, it can only be labelled a syndrome using arbitrary criteria. Any cessation of airflow at the mouth and nose is technically an apnoea, yet an apnoea of one or two seconds is unlikely to have any particularly serious consequences. Whilst there are clearly a group of patients who have apnoeas that are severe enough, in both length and frequency, to produce very severe symptoms, and in whom prevention of the apnoeas is associated with disappearance of these symptoms, a normal range for length and frequency of sleep associated apnoeas has yet to be established. Guilleminault defined a sleep apnoea syndrome as being present if either more than five apnoeas of 10 or more seconds occured per hour of sleep, or more than 30 occured during a night of sleep (Guilleminault et al 1975). This definition therefore did not contain any requirement for a fall in

arterial oxygen level or that it be terminated by arousal. A 10s apnoea will have different implications for gas exchange in different people and indeed for the same person at different lung volumes. It has been shown that the rate of decline of S_aO_2 during a breathold is intimately related to both the lung volume and the starting S_aO_2, and that continuing respiratory effort as would occur during an obstructive apnoea, was not associated with a more rapid decline in S_aO_2 (Strohl and Altose 1984). In common with many physiological variables, it is likely that numbers of nocturnal apnoeas are continuously distributed throughout the population, and this has been born out by the early results from the Oxford community survey into the prevalence of OSA in a normal, unselected population (Stradling and Mitchell, unpublished observations, see fig 4). Such a definition is therefore unsatisfactory, because many apnoeas of ten seconds, unattended by substantial hypoxia or arousal, are probably of no consequence. If this is so, making a diagnosis of a sleep apnoea syndrome (SAS) on these criteria would overstate the importance of SAS as a problem rather than a natural phenomenon occurring in excess. Because of this most workers now do not diagnose a SAS unless there are ten apnoeas per hour of sleep (Fletcher et al 1985). Nevertheless, it is unlikely (although not proven) that an apnoea is important unless it leads to hypoxaemia, arousal or both. As interest has grown in the possible role of SAS in daytime respiratory disorders, it has been appreciated that hypoventilation as well as apnoea can cause substantial desaturation during sleep. This is often prolonged and not repeatedly terminated by microarousal (Gould et al 1988) and therefore making a diagnosis on the basis of apnoea alone may result in important `breathing events' being overlooked.

Figure 4



Distribution of frequency of different rates of hypoxic dipping (numbers of 4% drops in S_aO_2 per hour) in an unselected group (N=482) of men aged 35-65 from a village near Oxford.

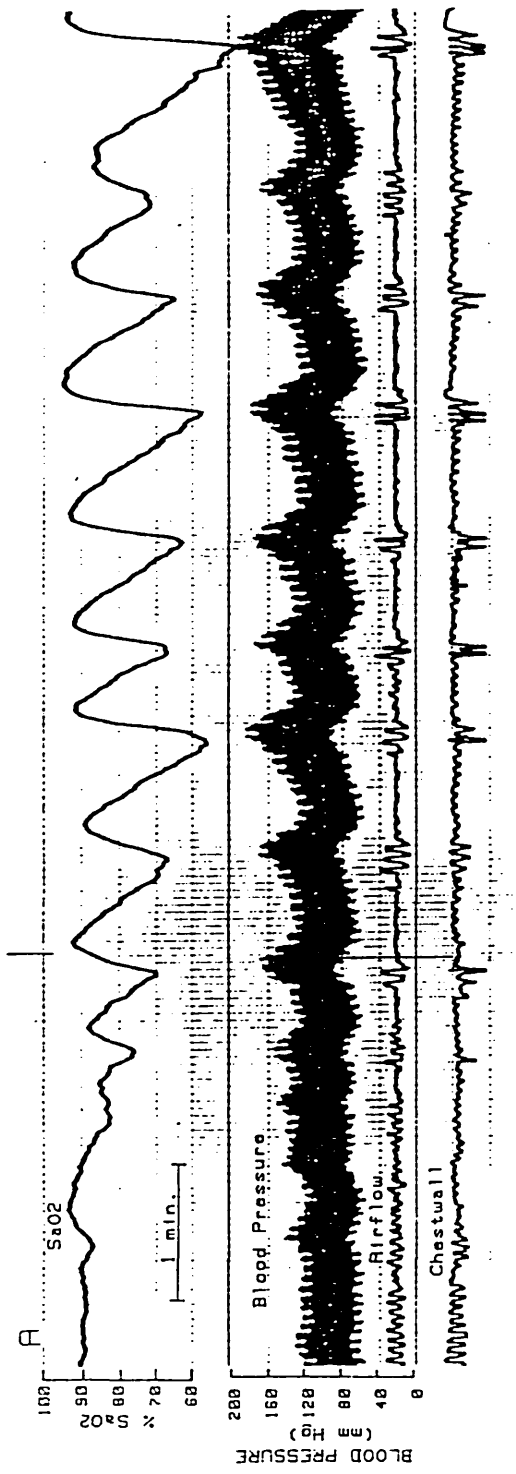
2:Hypertension in sleep apnoea:

The acute haemodynamic effects of sleep-related apnoeas have been extensively studied. Although the degree is variable an apnoea severe enough to cause desaturation is associated with a rise in both pulmonary and systemic arterial pressures. In ten patients with OSA both systolic and diastolic blood pressures rose by 25% in response to obstructive apnoeas producing a mean fall in S_aO_2 of 18% (from 93% to 75%). Between apnoeas, the pressures return to baseline levels (figure 5). Although the negative intrathoracic pressures render the situation more complicated for the pulmonary artery pressure, the situation is broadly the same in that expiratory pulmonary artery pressures have been shown to rise with the highest levels corresponding to the nadirs in S_aO_2. (Shepard et al 1985).

Tilkian and colleagues performed invasive haemodynamic monitoring in a group of twelve patients with OSA. Seven of these had originally been thought to have hypertension, but at cardiac catheterisation only one had severe hypertension (200/110) and three more had mild to moderate hypertension (150/90, 155/80, and 150/90) whilst awake and at rest. During sleep, however, nine of the twelve sustained appreciable rises in BP. These were always transient and occurred in association with apnoeic episodes. Of the remaining three, one had an autonomic neuropathy, and the other two had no appreciable change in BP during their apnoeic episodes. The length of apnoea or degree of fall in S_aO_2 was not reported (Tilkian et al 1976).

Any rise in BP during sleep is probably abnormal, Snyder and colleagues observed twelve healthy subjects during 30 nights of uninterrupted sleep. Using a sphygmomanometer, they found that BP fell

Figure 5



Acute effects of OSA on systemic arterial pressure. With each apnoea (dip in S_aO_2) systemic blood pressure rises transiently (from Shepard JW. Medical Clinics of North America 69:1243-1263, 1985).

slightly after the onset of sleep, and this was then followed by a gradual rise to awake levels throughout the night. Although this general trend was fairly consistent, they also observed considerable fluctuations in BP that appeared unrelated to sleep stage. None of the fluctuations took the BP to above 140 systolic (Snyder et al 1964). Khatri and Freis were able to measure BP continuously with an indwelling cannula during sleep in 15 healthy subjects (aged 16-34) and confirmed these findings, although the BP appeared to be most labile in REM sleep (Khatri and Freis 1967). Littler and colleagues monitored BP continuously in a group of eighteen subjects 12 of whom had hypertension. Falls in BP were observed in all patients during sleep (Littler et al 1975).

Whether or not transient episodes of hypertension can lead to sustained daytime hypertension is not known, but mild hypertension has been reported in 48-96% of patients with OSA (Guilleminault et al 1976, Guilleminault et al 1978b, Burack et al 1977), and reversal of hypertension has been reported following successful treatment of OSA with tracheostomy (Guilleminault et al 1981). Two teenage members of the group with severe hypertension had normal BP immediately afterwards, and 10/25 adults experienced a mean decrease of 18/25 mmHg.

The prevalence of OSA in the general population is not known, but four recent studies have suggested that a sleep apnoea syndrome (SAS) may occur in up to 30% of patients with essential hypertension, leading to the speculation that previously unrecognised sleep apnoea may be an important cause of the hypertension (Fletcher et al 1985, Kales et al 1984, Lavie et al 1984, Williams et al 1985). Although firm evidence as to the nature of a putative aetiological association

between SAS and hypertension is lacking at present, it has been proposed that recurrent hypoxaemia causes bursts of sympathetic discharge with accompanying surges in arterial pressure (Fletcher et al 1985, Fletcher et al 1987). If allowed to continue, these may lead to either resetting of arterial baroceptors or permanent structural changes in vessel walls (or both), and sustained hypertension (Folkow et al 1970).

Although these studies contain important flaws (see chapter 3), their implication is that SAS should be sought in all patients with essential hypertension. This in turn has enormous financial implications not least because of the necessity, if the studies are correct, to increase (possibly by a factor of tenfold) the existing facilities for the diagnosis and treatment of sleep disorderd breathing. A fully confident diagnosis of SAS requires polysomnography (see above) and/or observation of sleep. This is very costly, time-consuming, and necessarily requires admission to a hospital bed to sleep in unfamiliar surroundings. However, the development of a portable oximeter with solid-state memory allows a simple screening test for the main pathophysiological consequence of apnoea, arterial oxygen desaturation (Farney et al 1986, Gould et al 1987, Kripke et al 1988, Rosenthal et al 1988). An outpatient survey of overnight arterial oxygen saturation (S_aO_2) was therefore carried out in a group of untreated male subjects with mild hypertension and the results compared with a group of age, height and weight-matched control subjects without hypertension. A further group of more severely hypertensive individuals who had not been matched with the study group were also included in the analysis.

2: PATIENTS AND METHODS

Study Group (Group A)

Thirty-two patients (age 35-65) with essential hypertension referred to the Hypertension Unit at the John Radcliffe Hospital for 24 hour ambulatory monitoring of blood pressure, were invited to partake in the study. The only criteria for selection were that the mean 24hr diastolic (see below) blood pressure was >90 mmHg, and that they were not currently on anti-hypertensive medication. In addition, two patients under 40 were included who had mean 24 hr BP of 150/85 and 151/89. To prevent selection bias, patients were approached without any knowledge of their history, and the request to visit their homes did not refer to sleep or snoring. No patient refused to participate.

Control Groups (Groups B & C)

A survey of nocturnal hypoxaemia in 1000 randomly selected men aged between 35-65 is currently in progress in a village near Oxford. The survey includes measurement of blood pressure, and 32 normotensive subjects (BP< 140/90) from the 481 subjects studied up to the time of writing were individually matched for age, height and weight with the 32 hypertensive subjects in group A. These therefore constituted the controls (Group B). In addition, the 32 most hypertensive patients from the community survey provide a third group (Group C) for further comparison.

Protocol

All subjects were approached by telephone, and visited at home during the early evening. The study group (Group A) was collected and

the subjects visited by the author. Subjects in the control group (Groups B and C) were collected and visited by the nurse, Miss J Mitchell, carrying out the survey. An identical questionaire was administered to both groups (see over).

Blood Pressure

In order to confirm sustained hypertension in the study group, ambulatory recordings were made using the modified Copal system, which is in widespread use in the Hypertension Department, and which has been validated previously against a random-zero sphygmomanometer (Conway et al 1988). Readings are obtained half-hourly during the day and the value obtained is a mean of 20-30 values. In the control group blood pressure was measured using an electronic sphygmomanometer (Omron Tatsei Electronics Co, Japan), which had been validated against sphygmomanometer recordings in a group of 30 subjects, and found to give almost identical results (Mitchell JH, unpublished observations). Thereafter it was checked weekly against a mercury sphygmomanometer. Although not of random-zero type these devices are free from observer bias, and both incorporate a microphone which registers the Korotkov sounds simultaneously with an electronic measurement of cuff pressure. Readings of BP in the control group were made in duplicate by JHM performing the study, after administering the questionaire (about 15 mins) during which time the subject was seated.

Overnight Oximetry

The Ohmeda 3700 (see chapter 4) is a portable pulse-oximeter which provides a continuous transcutaneous measurement of arterial S_aO_2 and pulse. The probe was applied to the finger just before the subjects went to sleep and removed upon waking. The memory was

Questionaire

1. **Do you get chronic sleepiness, fatigue or weariness that you cannot explain?**
2. **Do you fall asleep during the day when you are not busy?**
3. **Do you fall asleep watching television?**
4. **Do you ever fall asleep against you will?**

Answers to these questions were scored either 1,2,3 or 4; corresponding to a frequency of Never, Rarely, Sometimes or Often respectively.

An arbitrary sleepiness score was calculated from the answers as follows:

$$0.25xQ1+0.25xQ2+0.125xQ3+0.375xQ4.$$

(Because falling asleep watching television was found to be so common it was weighted less important than frequently falling asleep against ones will)

5. **Do you snore or have you been told that you do so ?**
6. **When did your snoring start?**
   <1 y:score 1; 1-3 y:score 2; 4-9 y:score 3; >10 years:score 4

7. **How much alcohol do you drink in a day?**
   <10g:score 1; 10-30g:score 2; 30-70g:score 3: >70g:score 4

8. **How much do you smoke?**
   none:score 1; 1-5:score 2; 6-15:score 3; >15:score 4

9. **Are you being treated for any other medical conditions?**
   Yes:score 1; No:score 2

10 **Are you receiving any drug therapy at present?**
   Yes:score 1; No:score 2

Measurements of height and weight were made and the body mass index (BMI) calculated from the formula weight/ height^2. The use of the oximeter was demonstrated, an awake value recorded, and all subjects then subsequently slept with it on a finger throughout the night. The following morning, all were asked to confirm that the study night was representative of a normal night, with particular regard to alcohol consumption and sleep quality.

The following morning subjects were asked:

11. **How well did you sleep last night?**

much less than normal:score 1; slightly less than normal: score 2; normally: score 3; more than normal:score 4.

unloaded using a BBC 'B' computer via an RS232 interface. The following characteristics of the full overnight S_aO_2 record were then computed. Median and lowest S_aO_2, frequency of transient 4% and 3% dips in S_aO_2, and the total time spent with S_aO_2 below 90% and 80%.

Data analysis

All data was entered on to an IBM VAX computer, and analysed using SAS software (SAS institute Inc, Cary, NC 27511-8000, USA). Students t test was used to compare the means of all data presented in groups A and B, and all three groups were further compared using one-way analysis of variance.

RESULTS

Table 1 shows the results from groups A and B. Those from group C are shown in table 2. Groups A and B are well matched for age, weight, height, and cigarette and alcohol consumption. Systolic, diastolic and mean blood pressure ($p<0.001$) and median overnight pulse rate ($p<0.05$) were significantly different in the two groups. All subjects reported a night of satisfacory sleep. There were no overall differences in symptoms (snoring or sleepiness scores) between groups A and B, nor in any of the parameters of overnight oxygenation. The similarities in overnight oxygenation extend to those in group C. The median overnight pulse rate in group C was higher than that in both groups A and B, although significantly higher only than group A ($p<0.02$). Figure 6 shows a plot of median overnight pulse rate (abscissa) against mean blood pressure for all 96 patients. Examples of overnight saturation recordings are shown in Figure 7. Six original tracings are shown, the most normal and the two most abnormal from groups A and B, along with the derived saturation parameters. The full set of saturation recordings for groups A and B are included in the appendix. It can be seen that the range of overnight saturation patterns is quite wide, and that both groups contain patients in whom there is obvious and quite marked desaturation at various times throught the night. However there is no suggestion from these results that there are any overall differences in terms of overnight oxygen saturation between the groups.

TABLE 1

MEAN (SD, RANGE)

CONTROL			HYPERTENSIVE		p
49.03	(9.1, 35-64)	AGE	49.03	(8.9, 35-63)	NS
3.30	(1.56,1-5)	SOCIAL CLASS	2.94	(1.34,1-5)	NS
1.57	(0.50,1-3.25)	SLEEPINESS	1.48	(0.47,1-3.3)	NS
2.72	(0.92,1-4)	SNORING	2.89	(1.09.1-4)	NS
3.59	(1.05,1-4)	DURATION of SNORING	3.40	(0.95,1-4)	NS
1.56	(0.67,1-3)	ALCOHOL	1.56	(0.95,1-4)	NS
1.4	(0.84,1-4)	SMOKING	1.66	(1.10,1-4)	NS
1.6	(0.50,1-2)	OTHER ILLNESS	1.94	(0.25,1-2)	NS
1.6	(0.50,1-2)	DRUG THERAPY	1.91	(0.30,1-2)	NS
176.5	(5.57,159-187)	HEIGHT/cm	177.06	(6.02,168-193)	NS
79.0	(8.89,53-97)	WEIGHT/kg	80.09	(9.58,60-108)	NS
25.3	(2.38,20.8-30.8)	OBESITY INDEX/ kg m^{-2}	25.6	(3.17,18.1-32.8)	NS
125.7	(8.4,109-140)	SYSTOLIC BP /mmHg	152.4	(17.2,123-207)	<.001
78.4	(7.69,63-90)	DIASTOLIC BP/mmHg	100.03	(7.15,84-116)	<.001
93.99	(5.84,82.5-104.5)	MEAN BP/mmHg	117.3	(8.48,104.9-137.3)	<.001
96.3	(1.15,94-98)	AWAKE SAT /%	96.25	(1.14,94-99)	NS
94.7	(1.06,92-97)	MED NOCTURNAL SAT /%	94.56	(1.34,91-97)	NS
87.72	(4.4,73-93)	MIN NOCTURNAL SAT /%	88.00	(4.62,72-93)	NS
11.9	(10.44,1-44)	NUMBER of 4% DIPS	9.56	(10.40,0-37)	NS
19.8	(14.74,2-55)	NUMBER of 3% DIPS	16.28	(15.03,1-58)	NS
1.7	(1.49,0.19-5.9)	4% DIPRATE h^{-1}	1.5	(1.61,0.0-5.9)	NS
2.8	(2.09,0.37-7.6)	3% DIPRATE h^{-1}	2.5	(2.34,0.2-9.04)	NS
1.87	(3.58,0-16)	TIME < 90% SAT /min	1.84	(3.49,0.-16)	NS
0.06	(0.35,0-2)	TIME < 80% SAT /min	0.00	(0)	NS
2.7	(0.53,1-3)	SLEEP QUALITY	2.59	(0.61,1-3)	NS
58.9	(7.65,45-76)	MED NOCTURNAL PULSE min^{-1}	63.8	(10.49,50-85)	<.05
66.9	(26.65,33-149)	SD NOCTURNAL PULSE min^{-1}	59.3	(13.10,40-92)	NS

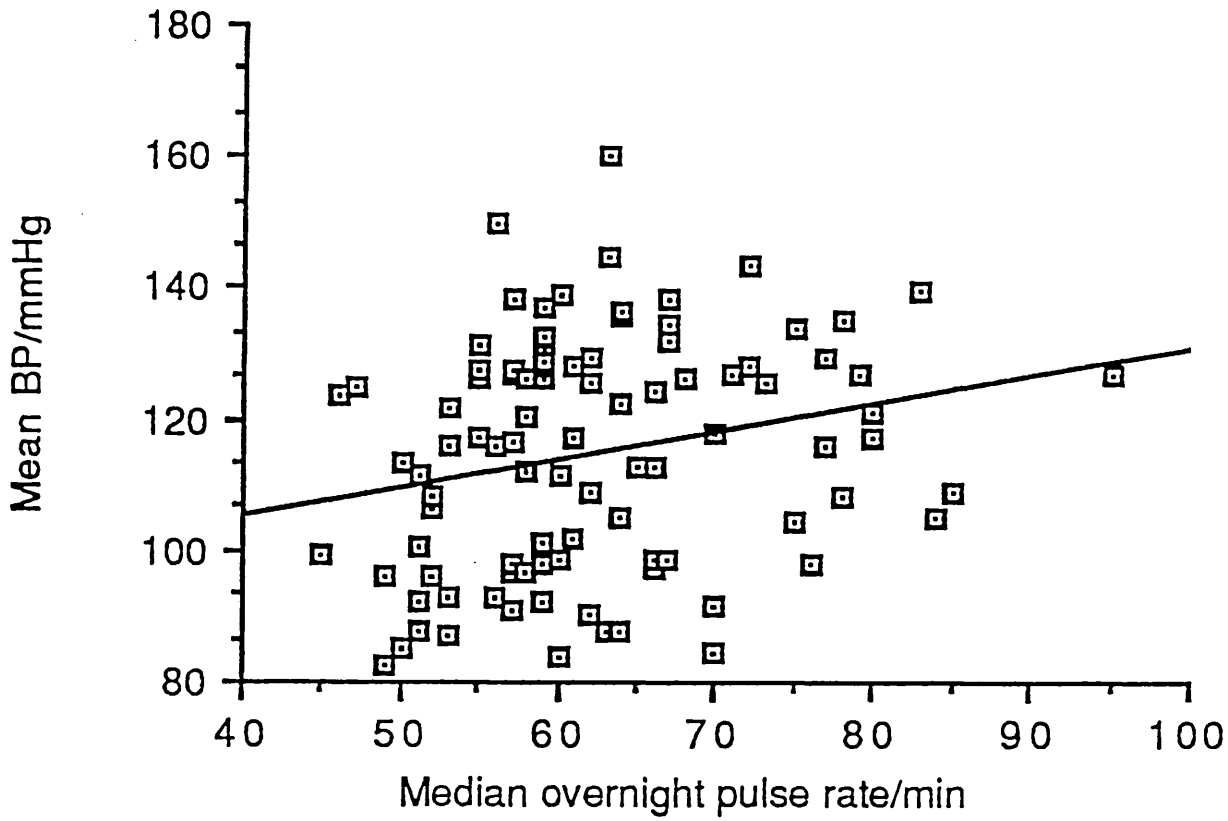
TABLE 2

MEAN (SD, RANGE)

MOST HYPERTENSIVE 32 PATIENTS FROM COMMUNITY SURVEY

AGE	51.5	(7.34,37-62)
SOCIAL CLASS	2.89	(1.35,1-5)
SLEEPINESS	1.52	(0.46,1-2.75)
SNORING	2.63	(1.13,1-4)
DURATION of SNORING	3.82	(0.53,2-4)
ALCOHOL	1.8	(0.89,1-4)
SMOKING	1.53	(0.95,1-4)
ILLNESS	1.46	(0.51,1-2)
DRUG THERAPY	1.56	(0.50,1-2)
HEIGHT/cm	175.09	(7.03,157-188)
WEIGHT/kg	81.84	(13.7,55-111)
OBESITY INDEX	26.61	(3.61,20-34.64)
SYSTOLIC BP/mmHg	174.12	(16.86,146-221)
DIASTOLIC BP/mmHg	112.06	(8.48,97-130)
MEAN BP/mmHg	132.54	(8.33,123.2-160.03)
AWAKE SAT/%	96.06	(0.98,94-98)
MED NOCTURNAL SAT/%	94.18	(1.38,91-97)
MIN NOCTURNAL SAT/%	88.78	(2.77,83-93)
NUMBER of 4% DIPS	10.78	(8.85,1-39)
NUMBER of 3% DIPS	18.65	(13.87,3-64)
4% DIPRAT h^{-1}	1.58	(1.29,0.13-5.9)
3% DIPRAT h^{-1}	2.73	(2.04,0.51-9.69)
TIME < 90% SAT/min	4.19	(8.15,0-36)
TIME < 80% SAT/min	0.0	
SLEEP QUALITY	2.53	(0.57,1-3)
MED NOCTURNAL PULSE	64.44	(9.76,47-95)
SD NOCTURNAL PULSE	61.43	(15.75,38-102)

Figure 6

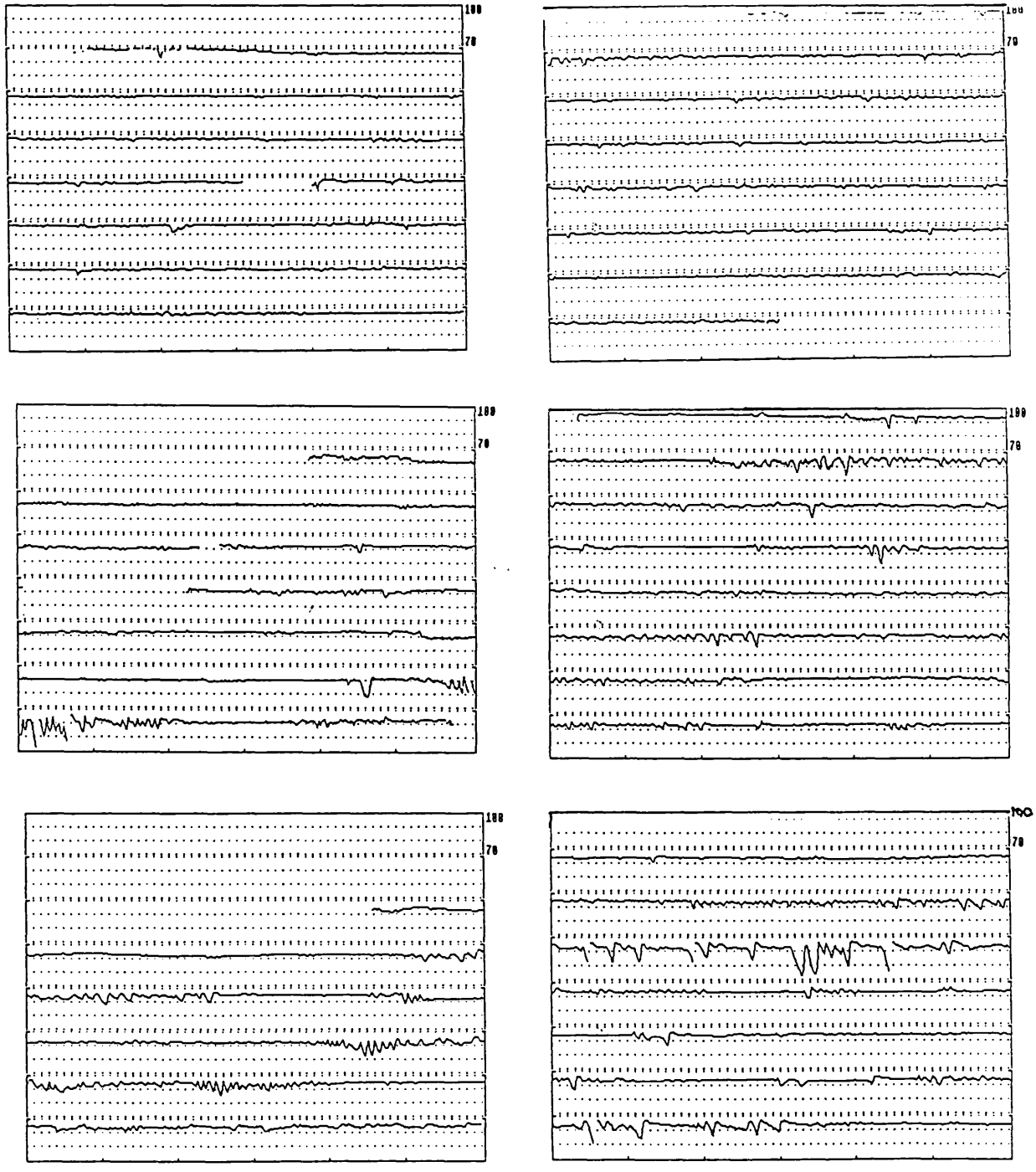


$y = 87.851 + 0.42958x \quad R^2 = 0.056$

Relationship of median overnight pulse rate and daytime blood pressure in all the groups (n=96)

Figure 7

GROUP A (Hypertensive) GROUP B (Normal)



Examples of overnight oximeter tracings from the two groups (see text). Each box represents an eight hour (overnight) record of saturation. Each row (3 lines) is one hour long and each dot one minute. The scale is 70-100% S_aO_2.

3: DISCUSSION

This study did not include sleep staging, and therefore there is no objective measure of the quality or length of sleep experienced by the participants. The possibility that the relatively minor amount of hypoxaemia found in either group could be due to that group having spent a greater part of the study period awake, cannot be absolutely discounted. However, all subjects reported a night of satisfactory sleep, and it is unlikely that the failure to detect any differences in overnight oxygenation could be explained on this basis. Separate studies have documented adequate sleep during home studies by both wrist actigraphy and 'ambulatory' EEG, EMG and eye movement recordings (Stradling et al 1987, Sharpley et al 1987, Sharpley et al 1988).

Although blood pressure was measured differently in the two groups, the two devices used employ a similar mechanism, and both were shown to be accurate. When casual measurements of blood pressure are made, those made by a nurse after 10 mins sitting quietly appear to be most representative of the mean 24hr value (Mancia 1983). In the hypertensive patients (group A) the mean 24hr value was lower than the mean of the General Practitioners recordings made prior to their referral to the Hypertension Unit. Although it would have been desirable, it was in practice impossible to obtain 24hr recordings in every member of group B, but 24hr recordings were obtained in a sample (n=18) from the survey population (none of whom were included in group B), and in no case was the 24hr value higher than that measured by JHM in their own home. It would therefore seem likely that the two groups did have significantly different blood pressures. The slightly, but significantly, greater median overnight pulse rate in the hypertensive

groups is of some interest. This observation and the fact that median overnight pulse rate correlates with mean daytime blood pressure has not been reported before, and provides further evidence of a cardiovascular difference between the groups.

Although not strictly comparable to this study, a number of previous studies have examined the relationship between SAS and hypertension. All have used the criteria of 5 or 10 apnoeas per hour of sleep to diagnose SAS. Lavie and colleagues administered a questionaire to 50 hypertensive patients (BP>160/95, mean age 48.4), all of whom were on treatment. This was designed to detect symptoms that might be due to SAS, and as a result 16 (12 male) patients underwent polysomnography, but without oximetry. Thirteen of these (26% of the original 50) were found to have SAS (more than 5 apnoeas per hour). The number of apnoeas that caused arousal was not reported, and the study did not contain a control group (Lavie et al 1984). Kales and colleagues compared polysomnographic records from 50 patients with hypertension and 50 age and sex, but not weight, matched normotensive controls. Forty-eight of the patients were on antihypertensive therapy. Fifteen of the 50 (30%) in the hypertensive group met the criteria for a SAS, compared with none from the control group. No measurements of arterial oxygenation were made in the control group, so a direct comparison could not be made, but it is likely that this group had less nocturnal desaturation. Nearly one third of the hypertensive patients approached declined to take part in the study, and the hypertensive group may thus have been biased in favour of people with symptoms that might have been due to SAS (Kales et al 1984). Using more stringent criteria (10 apnoeas per hour), Fletcher et al found SAS in 30% of 46 hypertensive patients

(BP>140/90) compared to 8.8% of 34 controls. Over half of the patients were on antihypertensive therapy at the time of the study. Whether the apnoeas were all associated with arterial desaturation and/or arousal from sleep was not reported, although the mean fall per apnoea was greater in the hypertensive group. A surprising finding was a high incidence SAS in the control group. In the hypertensive patients with SAS, treatment of the SAS in 8 patients resulted in a significant improvement in apnoea rate, and systolic (10mmHg), but not diastolic blood pressure (Fletcher et al 1985).

Respiratory movements and transcutaneous oximetry were measured alone in 23 hypertensive patients (all on treatment) and 8 age and weight-matched controls, during short (3hr) morning nap studies after a night of as much sleep deprivation as possible. Although 35% of the hypertensives had SAS, in such abnormal circumstances (ie, a short daytime nap) it is possible that subjects only experienced stage 1,2 sleep when ventilatory irregularities are common (Williams et al 1985).

All the above studies contained substantial numbers of subjects on treatment (mostly diuretics, but also beta-blockers, alpha methyldopa and vasodilators). In two, the possibility that antihypertensive treatment might affect nocturnal breathing was examined. Kales and colleagues reported 3 patients who were not on diuretic therapy, and none had SAS; conversely, all patients with SAS were on diuretic therapy. In Fletcher`s patients there appeared to be no suggestion that any particular form of treatment was associated with SAS. In the face of inadequate potassium replacement, diuretics can cause a mild metabolic alkalosis. Such an alkalosis has been shown to decrease ventilation in sleeping dogs, presumably as a consequence

of diminished medullary chemoreceptor output (Sullivan et al 1985). Whether this occurs in humans is not known, but it is possible that a mild diuretic-induced alkalosis superimposed upon the ventilatory instability that occurs in sleep could have provoked many of the central apnoeas seen in the above studies. Furthermore alpha methyldopa, a widely used antihypertensive agent in North America, has been recently shown to selectively reduce ala nasae activity (Lahive et al 1988). This might be expected to reduce upper airway patency, thereby increasing susceptibility to the development of obstructive apnoea. The effects of other medications on both respiratory control and upper airway patency are not known. Many have either central depressant effects or cause smooth muscle relaxation and it would be surprising if either the chemoreceptors or the tone in the upper airway dilator muscles were not affected by these powerful agents. Although not seen by Fletcher, an effect of medication on nocturnal breathing cannot be discounted as an explanation for the high incidence of SAS seen in the above studies.

There are two main consequences of an apnoea during sleep, arterial desaturation and sleep disruption. A few apnoeas are not attended by either important desaturation and/or arousal from sleep. Similarly, some desaturations may not be attended by arousal. Oximetry alone may therefore slightly underestimate the number of apnoeas, depending on the S_aO_2 criteria used. However recent studies comparing oximetry alone with full polysomnography have suggested that the error is small (Gould et al 1987, Kripke et al 1988, Rosenthal et al 1988). If SAS were implicated in the aetiology of hypertension, it is likely that either sleep disruption or hypoxaemia would be responsible.

The hypothesis that SAS may be an important cause of arterial

hypertension is an attractive one. In normal subjects, blood pressure falls slightly during the early part of the night, and gradually rises to awake levels by the morning (Khatri and Freis 1967, Littler et al 1975, Snyder et al 1964). If this is prevented by lack of sleep the daytime pressure may tend to rise. The acute haemodynamic effects of an apnoea leading to serious desaturation are variable but most investigators have found a rise in pulmonary and systemic arterial blood pressure during the apnoea which then returns to normal when respiration restarts (Motta et al 1978, Podszus et al 1986, Tilkian et al,1976). Such changes could be mediated by sympathetic discharge, and it is possible that repetitive surges of blood pressure could in the long term lead to resetting of arterial baroreceptors, and sustained hypertension. A recent study has documented increased levels of urinary catecholamines in patients with obstructive sleep apnoea which returned to normal after treatment (Fletcher et al 1987).

First described by Lugaresi (Lugaresi 1980), there is now a strong body of epidemiological data suggesting a relationship between arterial blood pressure and snoring. Koskovenuo and colleagues examined the snoring history of 3847 men and 3664 women in Finland between the ages of 40-69. Although only 9% of men and 3.6% women were habitual snorers, there was a highly significant association between snoring and hypertension in both sexes. This persisted after adjustment for both age and body mass index (BMI, weight/height^2). A similar relationship was observed for angina pectoris in men only, and this was strongest for the 40-49 age group (Koskovenuo et al 1985). Jennum and colleagues studied 544 men and women aged 70. Sixty-five percent of men and 54% of women were hypertensive, and heavy snoring was associated with significantly higher blood pressures and use of

antihypertensive medication (Jennum et al 1985). In a study of 50 men admitted to hospital with cerebral infarction, Partinen and Palomaki found that snorers were 2.8 times as likely to have a stroke compared to non-snorers (Partinen and Palomaki 1985). These relationships persisted when age and BMI were taken into account. In a prospective study, a questionaire was sent to 4388 men aged 40-69, asking them if they were habitual or frequent snorers (29%), occasional snorers (60%) or non-snorers (11%). During three years of follow-up, 187 episodes of cardiac ischaemia or stroke were recorded. The relative risk ratio for habitual snorers versus non-snorers was 2.38, and the relationship could not be explained by excessive smoking, hypertension or weight in the snorers, although alcohol use could not be discounted (Koskovenuo et al 1987). All these authors suggest that the substantial morbidity associated with snoring could be explained by there being a high incidence of sleep apnoea in those who snore.

Although all the above studies have found a relationship between cardiovascular disease and snoring which persists after allowing for overall obesity, the distribution of obesity has been ignored. It has been suggested that individuals with a predominantly lower body distribution of fat are less susceptible to coronary and cerebral vascular disease, hypertension and diabetes, than those with an upper body distribution (Vague 1956). Some studies have shown a relationship between hypertension or stroke and upper-body obesity, but not overall obesity (Larson et al 1984, Lapidus et al 1984, Weinsier et al 1985). Preliminary analysis of the data obtained from the community survey (see methods section), suggests that there is a highly significant association between snoring and neck circumference. Furthermore over the whole group of 500 or so subjects studied so far, there is no

relationship between blood pressure and overnight rates of 4% or 3% S_aO_2 dipping. There is a relationship between weight and hypoxic dipping, which can be accounted for by the effect of weight on neck size (Stradling and Mitchell unpublished observations). If, as therefore seems likely, snoring is associated with an upper body distribution of fat, it may be this, rather than SAS which provides the explanation for the apparent relationship between snoring and cardiovascular disease.

This study was not designed to establish, by the conventional criteria of cessation of airflow at the nose and mouth, the prevalence of SAS in mild to moderate hypertension. However, the results provide no support for the hypothesis that nocturnal hypoxaemia as a result of SAS is associated with, or causative of, mild to moderate hypertension, and therefore no support for the contention that a sleep study is indicated in the investigation of hypertensive patients. If further controlled studies are able to eliminate drug therapy as an reason for the increased frequency of apnoeas (lasting 10s or more) in patients with hypertension observed in earlier studies, the hypothesis proposed by Przybylski and colleagues may provide an explanation. They propose that the two conditions are simultaneous manifestations of arterial chemo- and baro-receptor hyper-responsiveness (Przybylski et al 1986). They have shown that young men with mild hypertension have an augmented ventilatory and circulatory drive from the arterial chemoreceptors (Trzebski et al 1982). This may by responsible for the hypertension, possibly mediated via increased sympathetic tone. In the case of the chemoreceptors, increased excitability may result in respiratory cycling at sleep onset when variations in sleep state cause fluctuations in respiratory controller gain. A brief period of

hyperventilation drives down the P_aCO_2 which causes apnoea, by inhibiting medullary chemoreceptor output. This in turn allows the P_aO_2 to fall which eventually results in arousal, and a resetting of ventilatory controller gain. As a result, a new (higher) level of ventilation is demanded, and a compensatory period of hyperventilation occurs, thereby re-establishing the cycle.

4: EVALUATION OF THE OHMEDA 3700 PULSE-OXIMETER

The Ohmeda 3700 is a portable pulse oximeter incorporating a memory (figure 8). It uses a small probe attached to the finger which transmits and receives red and infra-red light. Up to eight hours of S_aO_2 and pulse rate data can be stored in solid-state memory. Because the device requires a pulsatile signal it is able to discard readings obtained when perfusion is low and therefore likely to be inaccurate. As a prelude to the hypertension survey described in chapters 1-3, validation of the device against previous oximeters and arterial blood samples was undertaken.

Study 1: comparison with direct arterial sampling.

Methods: Oxygen and carbon dioxide tension was measured and S_aO_2 calculated on 65 direct arterial samples. These were compared with the simultaneous values given by three different oximeters attached by three different probes (see figure 8). Two normal subjects breathed nitrogen through a Venturi mask, and eight hypoxic, non-smoking inpatients breathed various fractions of inspired oxygen during determination of the most appropriate concentration of long term oxygen therapy, thereby providing a range of S_aO_2 values between 60%-90%. When steady-state conditions had been achieved at a particular F_IO_2, blood was withdrawn through an indwelling arterial cannula inserted at the beginning of each experiment. P_aO_2 and P_aCO_2 were measured on a blood gas machine (ABL-2, Radiometer, Copenhagen). If any of the three displayed S_aO_2 values changed by more than 2% during the period of blood withdrawal or the previous 30s the sample was discarded. Haemoglobin saturation was estimated from a blood gas

calculator (Severinghaus 1966).

Results: These are shown as scatter plots in figure 9. There is excellent agreement, particularly at higher S_aO_2 levels, the flex probe proving overall to give values closest to arterial values. Estimated S_aO_2 values in one chronically hypoxic patient were consistently greater than the S_aO_2 values displayed on the oximeter, but this discrepancy was corrected when allowance was made for her abnormal p_{50} (29 mmHg measured by whole blood tonometry). The mean and standard deviation of the percentage S_aO_2 differences between individual oximeter and arterial readings (representing bias and precision) were -0.1(3.4), -0.4(1.8) and -0.5(2.9) for ear, flex and finger probes respectively.

Study 2: speed of response

Methods: The three probes from the Ohmeda, and the ear probes from the Hewlett-Packard and Biox 2A oximeters were connected to ear finger or toe as appropriate with the outputs displayed on a chart recorder. After a steady-state had been reached with low F_IO_2, a mask delivering 100% O_2 was substituted. The response time was recorded from the first deep breath of 100% O_2 to the start of a rise in S_aO_2.

Results: With ear probes, the times taken for the Hewlett Packard, Biox 2A and 3700 oximeters to detect a rise following sudden onset of oxygen breathing were 9.3(SD3.2), 11.1(2.8) and 9.8(2.6) seconds. These differences are not significant, but the finger and toe probe times (23.6(4.1), 56.8(15.8) seconds respectively) were proportionately longer because of greater lung to probe circulation times.

Study 3: Assessment of ability to detect artifact.

The functioning of the 3700 requires pulsatile blood within the light path to differentiate arterial blood from non-pulsatile venous blood or capillary blood. An inadequate pulse could lead to falsely low values being recorded, and therefore the warning `low quality signal' is displayed.

Methods: a. In three normal subjects an arterial cuff was applied to the limb proximal to the flex probe, and repeatedly inflated to above systolic blood pressure. As soon as low quality signal was displayed, any fall in S_aO_2 was noted and the finger moved in an attempt to simulate pulsatile blood flow and thereby deceive the instrument.
b. Two flex probes attached to different oximeters were worn on opposite hands by five healthy subjects overnight. The paired overnight tracings were then inspected visually for differnces, particularly S_aO_2 dips appearing on one tracing only, which would be likely to be artifact.

Results: a. With the cuff inflated, it proved impossible to cause the machine to record a saturation fall of more than 2% without registering `low quality signal'. If inflation of the arterial cuff was combined with repeated movement of the finger, so simulating a pulse, the instrument sometimes recorded a false saturation fall without registering `low quality signal'. Unless the movement was similar to the previous heart rate, however, this was readily detectable by inspection of the simultaneous pulse rate signal.
b. The five pairs of overnight tracings from opposite hands were very similar (fig 10). There were never more than three S_aO_2 dips appearing

on one of the paired tracings alone. The greatest difference in the whole night mean value of S_aO_2 between a pair of records was 0.9%.

Study 4. Effect of the 12s sampling algorithm on signal shape.

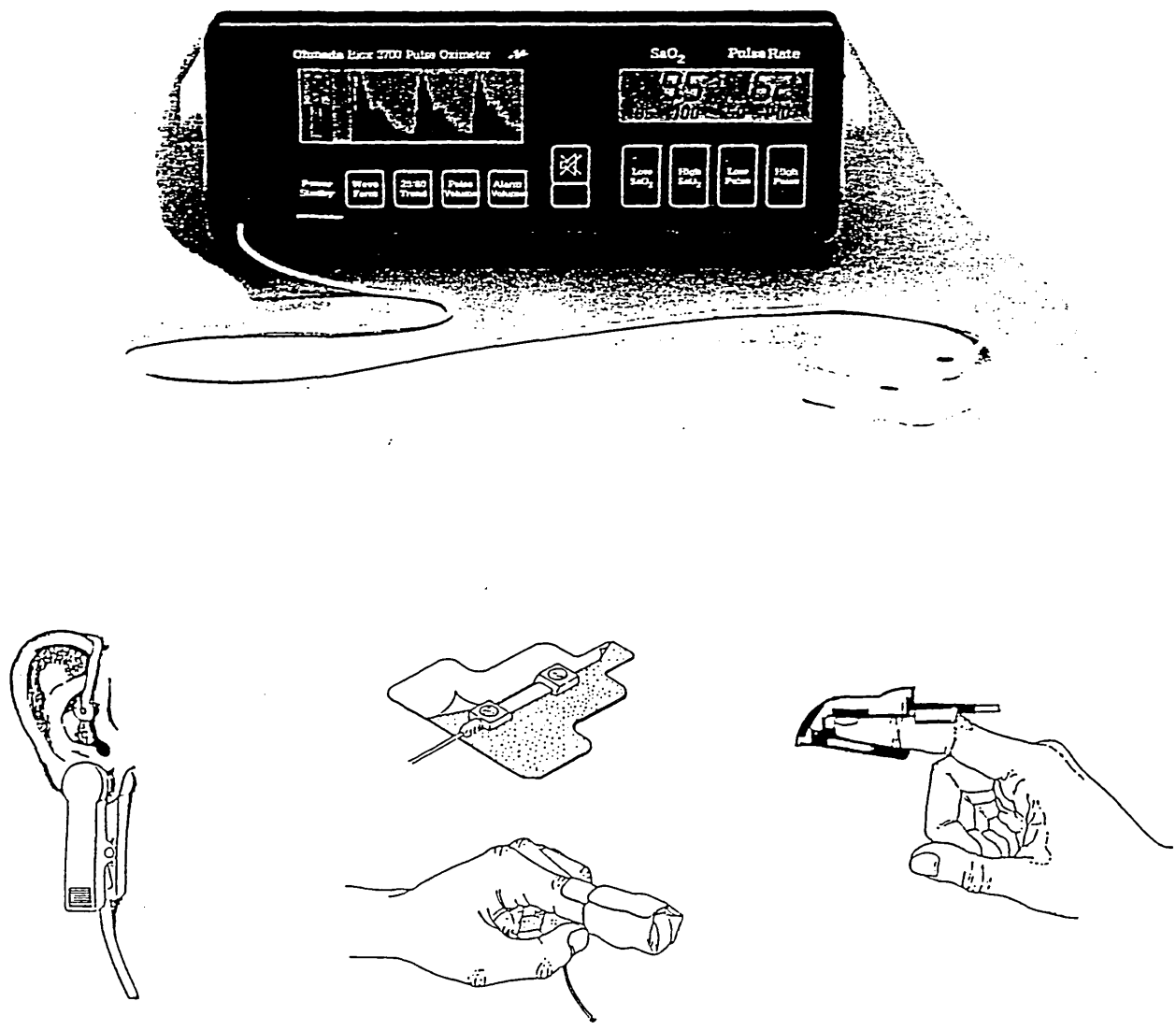
The 3700 memory saves values every 12s. The actual value of S_aO_2 stored is the lowest seen in that previous 12s and the pulse value stored is that which occurred simultaneously with the S_aO_2 value. In the detection and measurement of 4% and 3% dips in S_aO_2, any drop in S_aO_2 of more than 4% (or 3%) is registered as a dip provided that the oximeter has detected rise of at least 3%, since the nadir at which a 4% dip had been deemed to have occurred. This ensured for example that a fall in S_aO_2 from 96% to 92% and then 88% before returning to 96% was only counted as one dip in S_aO_2, and thereby prevented the overestimation of numbers of apnoeas.

Methods: The ability of the algorithm to reproduce the original signal accurately was assessed by simulating an oscillating S_aO_2 signal on a BBC B computer and sampling this signal with the algorithm used by the 3700. Simulated cycle lengths between 30 and 70s were used (similar to those seen in sleep apnoea), and a visual comparison of the tracings made.

Results: The sampling algorithm used by the oximeter allowed adequate resolution of the signal with some deterioration when the wavelength was less than 35s. Fig 11 shows phasic dipping in S_aO_2 at two different frequencies with the pattern recreated by the 3700 sampling algorithm. Because the lowest S_aO_2 observed in the previous 12s is stored, the trough values are identical. As the wavelength shortens, the maximum recovery S_aO_2 is under-estimated.

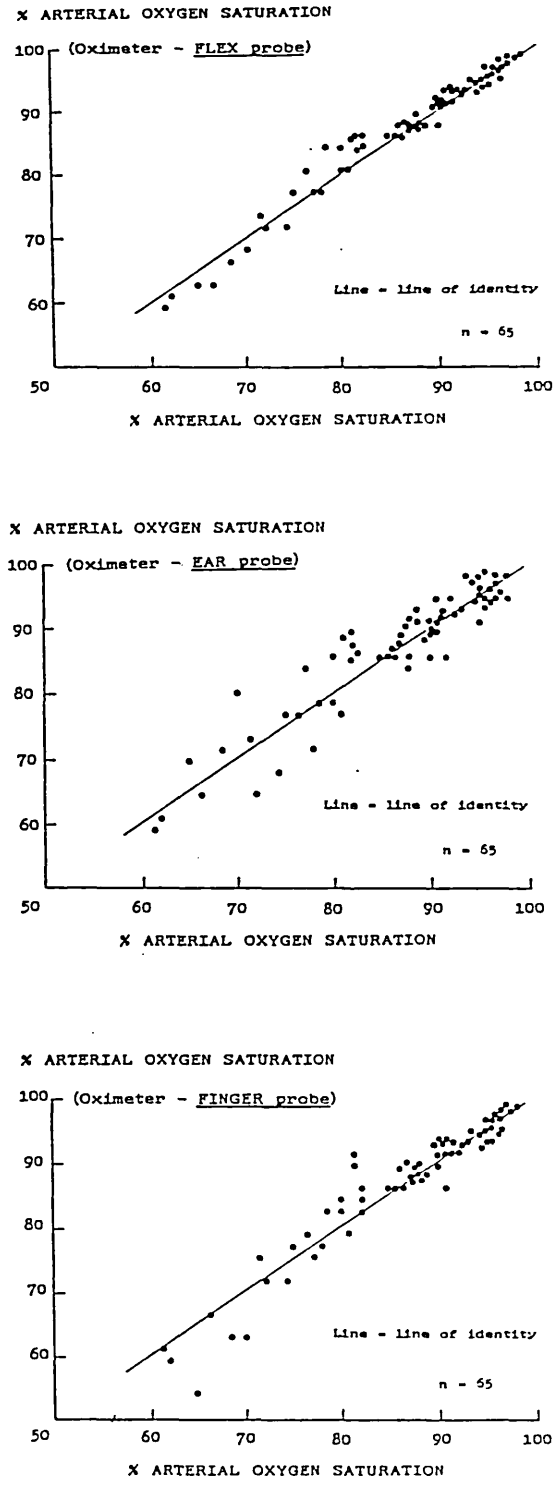
Comment: The memory will not store a low quality signal (for example, one due to lying on the probe site) and a blank appears in the data. This ability to reject low quality data makes the device particularly suitable for unattended monitoring of overnight oxygenation, and therefore use in the survey described above. If an inaccurate signal caused by simultaneous arterial compression and probe site movement is read into the memory, this should be detectable by inspection of the pulse rate tracing, which would show considerably more variation than would be usual. The eight hours of memory can be unloaded in eight minutes, and the data analysed with the help of a microcomputer. Thus mean, median and minimum overnight S_aO_2; numbers of 3% or 4% dips in S_aO_2; and median and standard deviation pulse rate can all be readily computed.

Figure 8



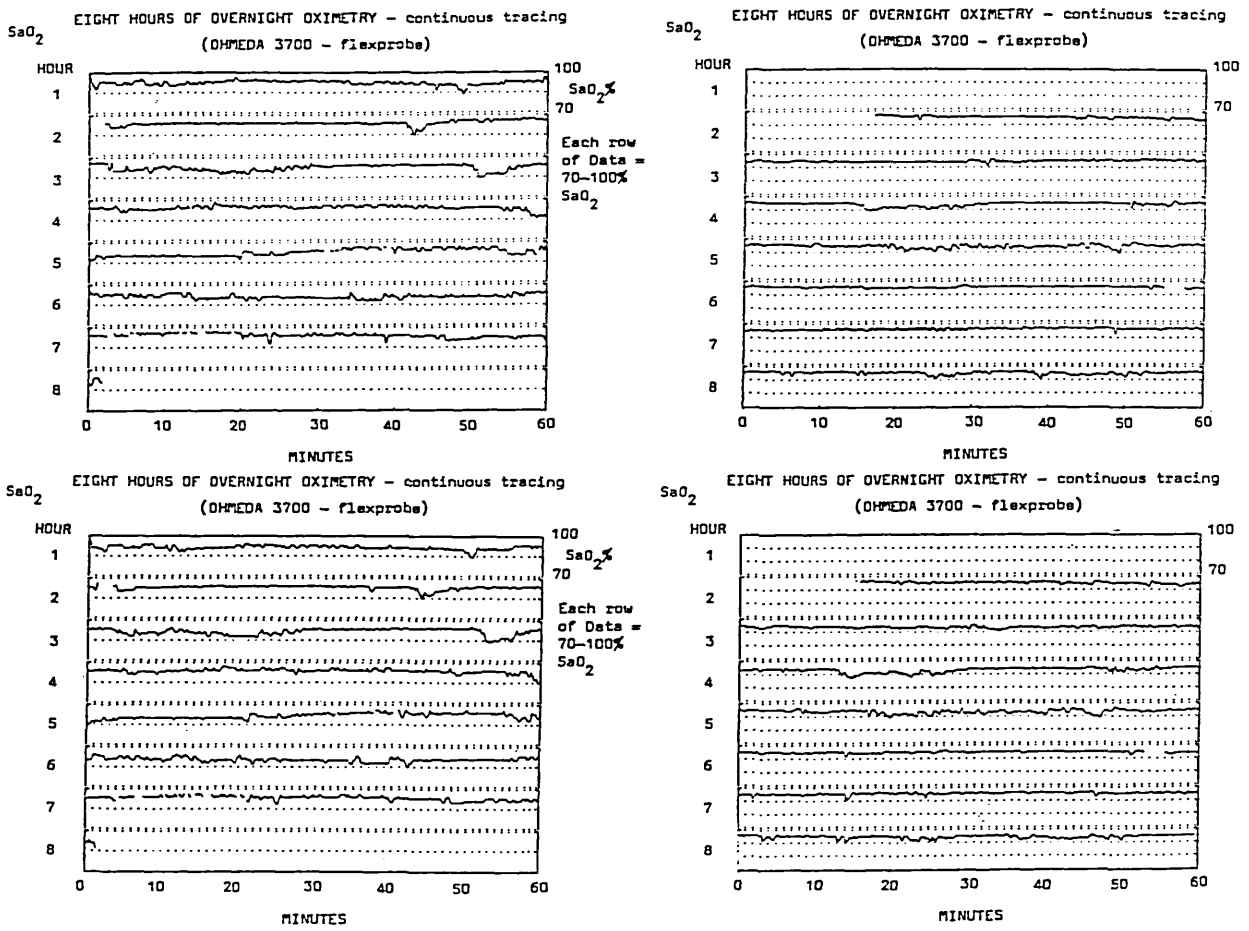
The Ohmeda 3700 oximeter and its three probes. Flex , Ear and Finger

Figure 9



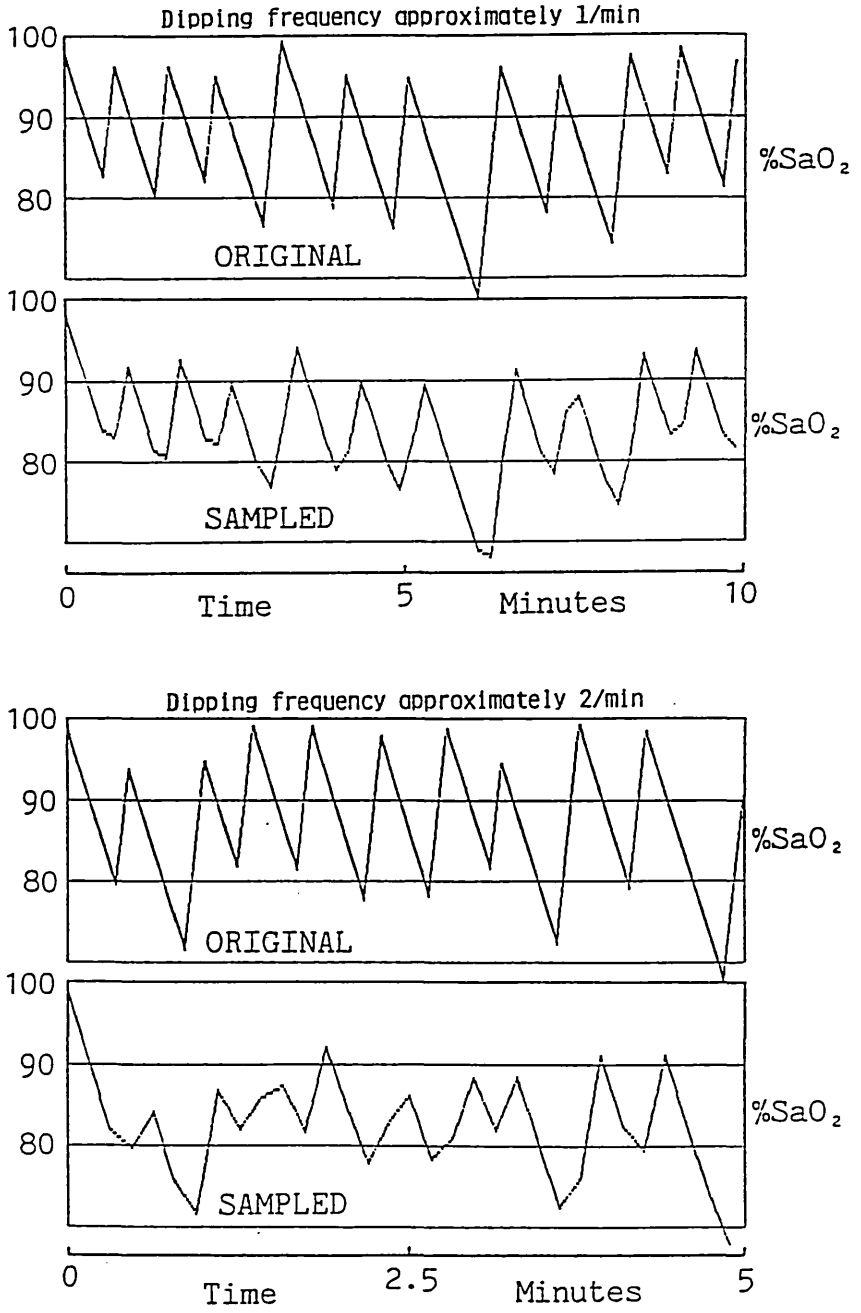
Scatter plots showing oximeter readings (each individual probe) against S_aO_2 calculated from direct arterial samples

Figure 10



Comparison of simultaneous overnight oximeter tracings obtained from opposite hands in two individuals. Visual inspection of both pairs of tracings confirms their similarity.

Figure 11



Ability of the oximeter algorithm to reproduce signal shapes of different cycle lengths. Varying S_aO_2 signals of two different wavelengths have been simulated by the computer (original) and analysed using the algorithm employed by the oximeter (sampled). Both are faithfully reproduced, although at the shorter wavelength (which would represent much more rapid fluctuations in S_aO_2 than are normally seen in OSA) the recovery S_aO_2 is underestimated.

PART 2

SLEEP APNOEA: EFFECTS ON RENAL FUNCTION

5: INTRODUCTION

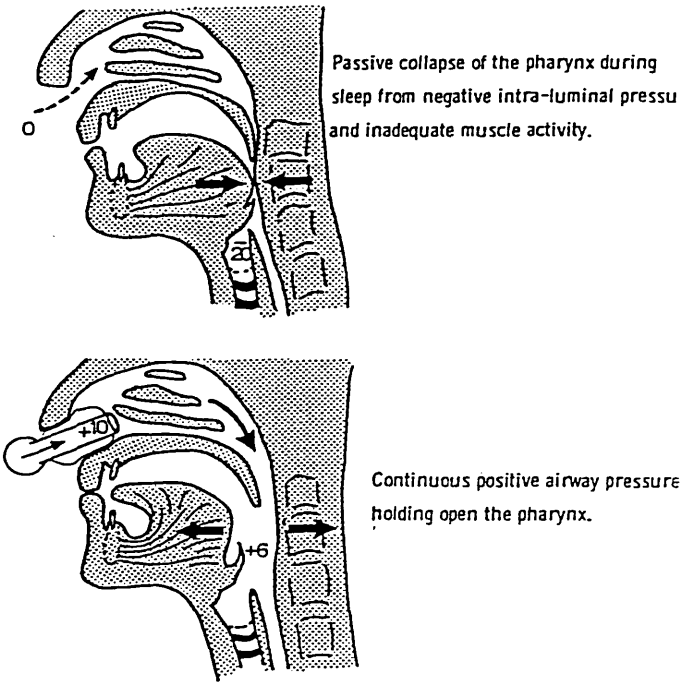
The second part of this thesis describes three studies on patients with severe obstructive sleep apnoea, and one in which the obstructed inspiration of obstructive sleep apnoea was simulated in normal subjects.

Obstructive sleep apnoea can be readily prevented by the application of continuous positive pressure to the upper airway (CPAP) via the nose (Sullivan et al 1981). This provides a pneumatic splint, preventing pharyngeal collapse when inspiratory efforts generate what would normally be subatmospheric pressures in the pharynx (fig 12). Although the patient is required to sleep with a tight fitting mask over the nose, so great is the relief of symptoms afforded by the device that it has proved highly acceptable, and the patients treated in our department seldom wish to sleep without it. Figure 13 shows the effect of CPAP on overnight oxygen saturation.

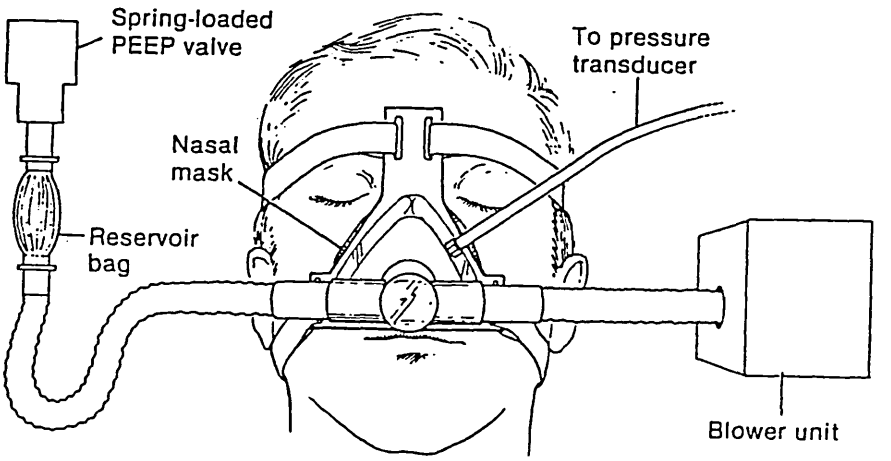
As well as being a very effective form of treatment, CPAP also provides a unique opportunity to study a pathological condition that can be readily reversed, since patients with OSA can be allowed normal sleep by applying the device on one night and severely disturbed sleep the following night by simply removing the mask.

As part of the investigation into the possible link between SAS and daytime hypertension, day and night urinary collections were made for estimation of urinary catecholamine (adrenaline and noradrenaline) levels on and off CPAP. It was immediately clear that OSA was associated with a substantial nocturnal diuresis and natriuresis which was promptly reversed by CPAP therapy. This original observation and the results of the urinary catecholamine estimations are reported in chapter 6.

Figure 12

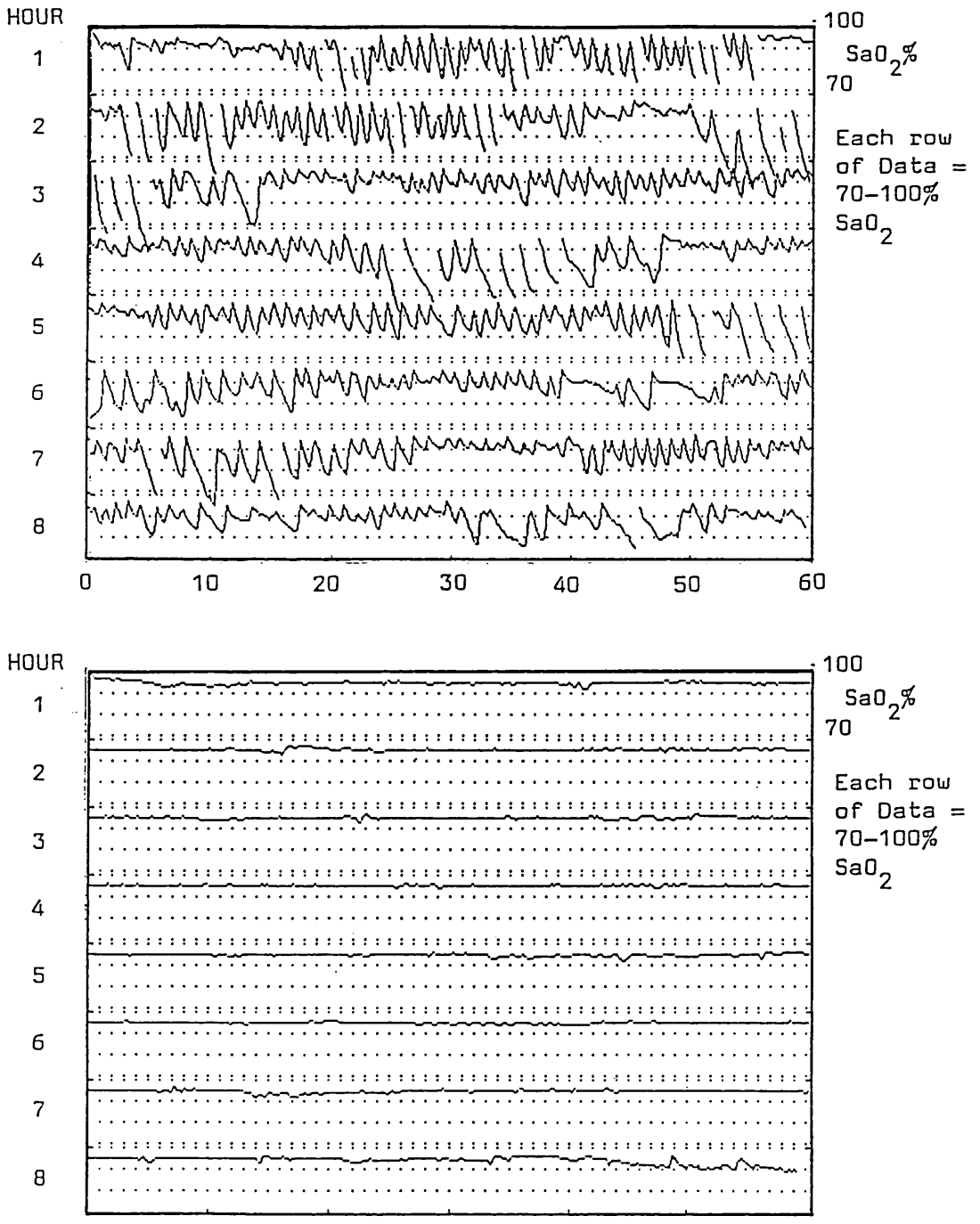


Intra-pharyngeal pressures



Nasal CPAP

Figure 13



Effect of treatment with nasal CPAP on overnight S_aO_2 in severe OSA

Previous workers have reported an increase in heart size (Lugaresi et al 1979) during obstructive apnoeas. The recently discovered atrial natriuretic peptide (ANP) (de Bold et al 1981) is known to be released in circumstances in which right atrial pressure increases (Raine et al 1986). A diuresis and natriuresis would be consistent with excessive release of ANP. In order to establish whether OSA is associated with excessive release of ANP, plasma levels were measured in six patients during and after OSA and CPAP sleep. The experiments are described in chapter 7.

Because the results suggested that ANP is not released in excess during OSA, and because of the implications for other obstructive lung diseases in which abnormally large negative intrathoracic pressures are generated during inspiration, a pilot study was carried out in a normal volunteer in which the pressure in the right atrium was measured during resistive breathing (thereby simulating the intrathoracic pressure changes of OSA). This showed that abnormally large negative intrathoracic pressures generated during inspiration were associated with the development of dilating pressure across the right atrium (fig 16). In order to eliminate the possibility that an effect of ANP in OSA had been missed, a controlled study was carried out in six normal male volunteers. In order to simulate OSA, subjects breathed through an inspiratory resistance for ninety minutes. The experiments are decribed in chapter 8.

Measurements of lithium and inulin clearance allow the relative contribution of proximal and distal renal tubular function to be examined (Thomsen 1984). In order to investigate the renal mechanism underlying the effects that OSA and its treatment have on sodium and water handling, inulin and lithium clearance measurements were made in

six OSA patients on and off treatment with nasal CPAP. These experiments are described in chapter 9.

In chapter 10 the results of the preceeding four studies are discussed in the light of the general body of literature that exists on the various interactions between lung and kidney.

6: INTRODUCTION

Urine flow and sodium excretion are subject to a diurnal variation which results in a fall in both during the hours of sleep (Stanbury and Thomson 1951). This allows uninterrupted sleep, and loss of this diurnal variation, resulting in nocturnal polyuria, is a feature of cardiac failure and hepatic cirrhosis (Goldman 1951). In contrast, assumption of the supine posture whilst awake causes a diuresis and a natriuresis (Thomas 1957, Thomas 1959). The mechanisms responsible for the apparent inhibition of sodium and water excretion by sleep have not been fully elucidated.

This chapter describes eight patients with severe OSA syndrome, but without systemic hypertension (see chapter 1). Each exhibited reversal of the normal diurnal variation with an increase in urine and sodium output at night. This was promptly restored by successful abolition of the apnoeas with continuous positive airway pressure (CPAP) via the nose. Nocturia is not commonly quoted as a symptom of OSA, but seven patients who had been established on CPAP prior to the study had all noticed marked reductions in nocturnal urinary production since the introduction of the treatment.

The repetitive episodes of hypoxia and arousal which characterise OSA might be expected to be associated with overactivity of the sympathetic nervous system. Previous studies have all suggested that this might be so, although the effects are small (Clark et al 1980, Vitiello et al 1982, Fletcher et al 1987a). In five patients, day and nighttime urine collections were analysed for adrenaline and nor adrenaline levels, to establish whether OSA was indeed associated with excessive catecholamine production and if this might be reversed by nasal CPAP.

METHODS

Patients

Eight men (aged 39-62, mean 54) with more than 300 obstructive apnoeas per night (see fig 12). All were overweight (body mass index 26-48, mean 32.3 kg m^{-2}). With the exception of one patient with maturity onset diabetes controlled on glibenclamide, all were otherwise in good health and none had had peripheral oedema at any time. All were normotensive both at the time of the study and before CPAP had been instituted (BP <150/90 mean of at least six readings). Seven had been established on nasal CPAP previously. The one remaining was successfully established on treatment in hospital during the course of the study.

Techniques

Urine was collected into a plastic bottle containing 0.5 gm glutathione (in one patient, sodium metabisulphate was used and consequently sodium could not be measured) as a preservative to stabilise catecholamines. Each morning and evening the volume was recorded and an aliquot saved at -20·C for later analysis. Urinary sodium concentration was estimated by flame photometry. Urinary adrenaline and noradrenaline was estimated by radioenzymatic assay (Brown and Jenner 1981).

Protocol

The study took place over four nights and days in hospital. Each patient was admitted to hospital in the evening and the bladder emptied before retiring. Thereafter all urine was collected and separated into day and night. Thus any urine passed during the night and the first specimen on rising constituted the night samples and all

urine passed during the day, including the last before retiring, the day samples. In order to simulate normal circumstances as far as possible, patients were allowed to retire and rise at their own preferred times, samples being timed, so that rates of excretion could be calculated. An estimate of normal sodium intake was made for each subject at the beginning of each study and as far as possible this was held constant throughout the four days of study by provision of a constant amount of sodium in the diet. Although subjects were allowed a degree of dietary freedom, a dietary assessment was made at the end of each day to estimate sodium and potassium intake and ensure that there had not been any substantial deviation. Each subject recorded his own fluid intake.

During the first two nights, patients slept without CPAP, and arterial oxygenation was monitored continuously to confirm obstructive sleep apnoea. For the subsequent two nights CPAP was administered and its efficacy confirmed by oximetry and the patients' own assessment of the quality of sleep.

Statistical analysis

The means of each of the paired values of urine flow and sodium excretion during nights 1 and 2 were compared with the means of the values from days 1 and 2, and nights 3 and 4 using a t test for paired data. For the catecholamines, the means of the paired values of data from nights 1 and 2 were compared with means of the paired values form nights 3 and 4, and with the means of the paired values from days 1 and 2 and days 3 and 4 using a t test for paired data.

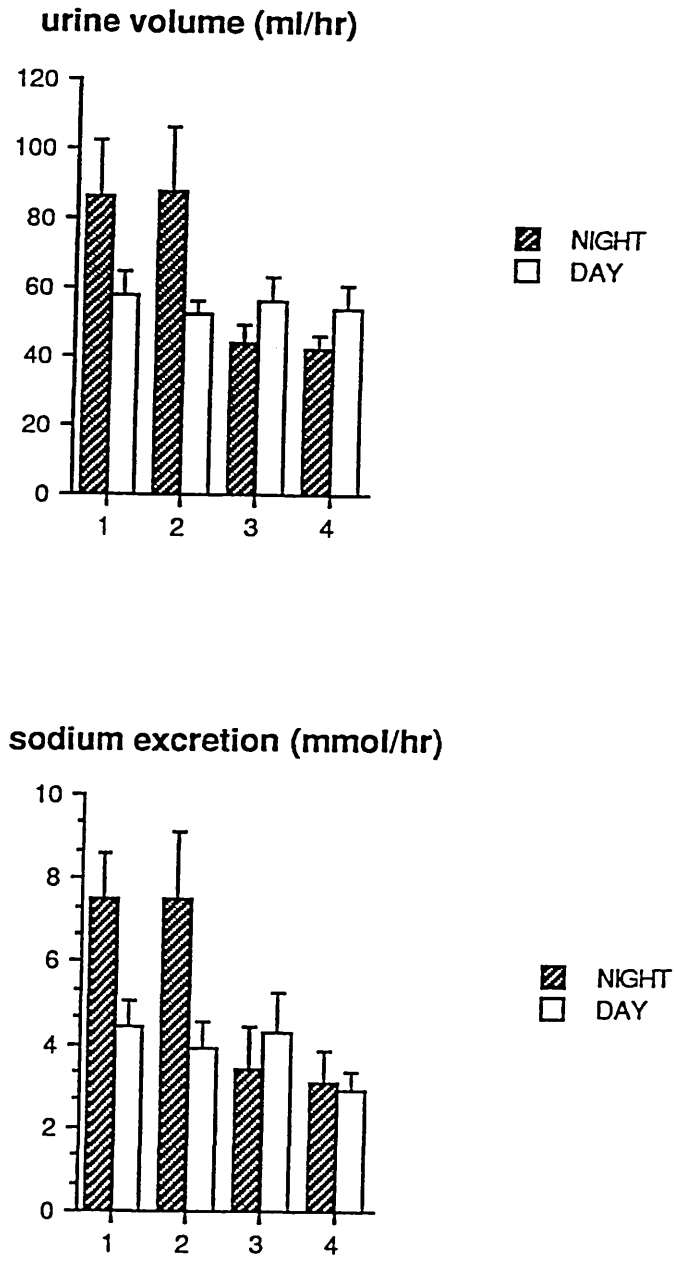
RESULTS

Individual results are given in the appendix. The fluid, sodium and potassium intakes were similar throughout the four days. The values are lower on day 4 because the times of collections were much shorter.

In all cases oximetry confirmed severe OSA during nights 1 and 2. In seven cases CPAP was successful on night 3 and in one patient (SA), a leak prevented the total abolition of apnoea. In all cases apnoea was completely abolished on night 4, as evidenced by a normal oximetry trace and self-reported excellent sleep quality. Urine production rates are available for all eight patients, sodium excretion could only be calculated in seven, because the catecholamine preservative contained sodium. Although there is considerable variation all subjects exhibited the same pattern. Compared to nights 1 and 2, both sodium and urine output were significantly lower on days 1 and 2 ($p<0.05$), and nights 3 and 4 ($p<0.02$). Sodium output was less on night 3 than day 3 and urine output was less on nights 3 and 4 than on days 3 and 4, but the differences do not reach statistical significance. One patient (TK) made an incomplete collection on night four and could not stay for day four. The day four sample from RK was lost during transport to the laboratory. Individual results are given in contained in the appendix, and the combined results presented in graphic form in figures 14 and 15.

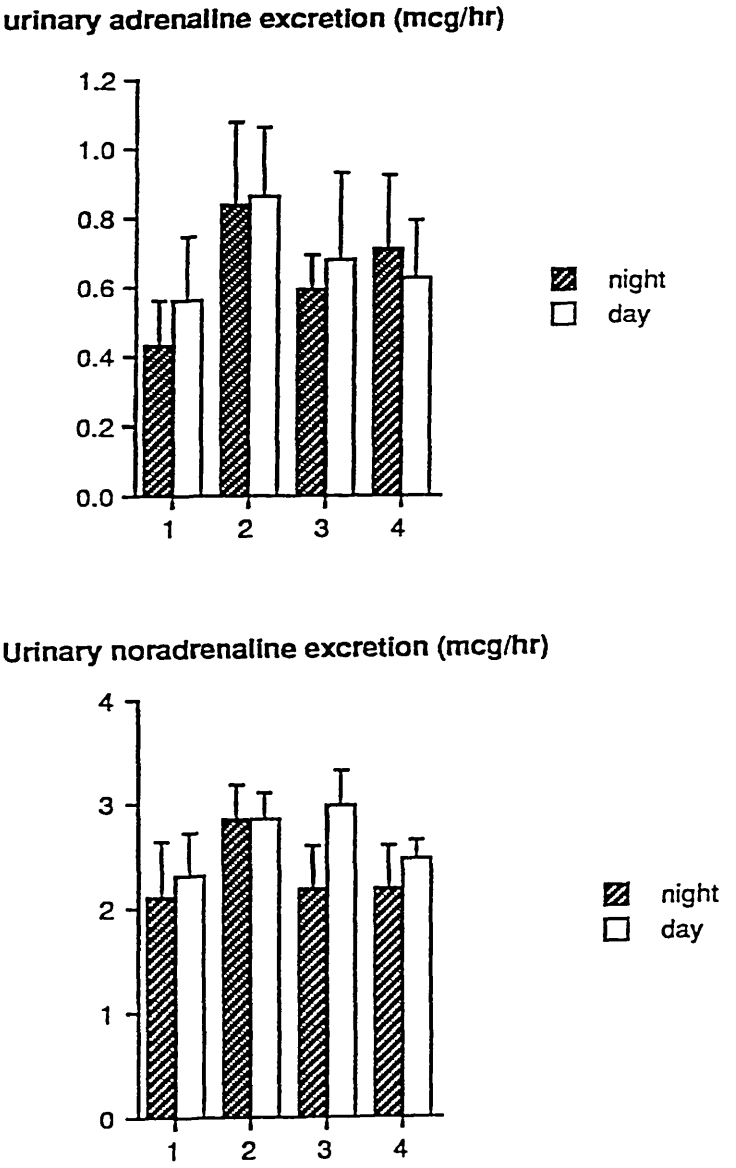
There is no difference between the day and night rates of catecholamine excretion, and there is therefore no suggestion from these results that CPAP in anyway modifies catecholamine excretion in patients with severe OSA.

Figure 14



Day and night time rates of urine and sodium output in patients (n=8 for urine and n=7 for sodium) with severe OSA. During nights 1 and 2 patients slept without CPAP and experienced OSA, the mask was then applied on nights 3 and 4. Values are mean +/- SE. The fall in urine production and sodium excretion on nights 3 and 4 is significant ($P < 0.02$ for urine and $P < 0.05$ for sodium, see text for details)

Figure 15



Day and night rates of urinary catecholamine output on and off CPAP. During nights 1 and 2 subjects (n = 5) experienced OSA and during nights 3 and 4 nasal CPAP was applied. Values are mean +/- SE

DISCUSSION

Stanbury and Thomson observed as much as a fourfold fall in both urine production and electrolyte excretion during the hours of sleep in normal subjects (Stanbury and Thomson 1951). In contrast, the patients in this study exhibited a significant rise in urine and sodium output when experiencing obstructive sleep apnoea. Although a fourfold fall in overnight urine production was not observed when treatment was instigated, every patient conformed to the same pattern in that a highly abnormal situation, in which urine production and sodium excretion was extremely high at night, tended to reverse toward normal on the treatment nights. It is not possible to draw accurate conclusions as to the precise magnitude of these effects from this study. It would clearly have been desirable to perform a longer study with sodium and fluid intake much more rigidly controlled, however this was not possible with these patients all of whom were in full-time employment and voluntarily gave of their time for the study. Since these results were published (Warley and Stradling 1987, 1988), Krieger and colleagues have reported identical findings in a larger group of OSA patients (Krieger et al 1988b).

Stimulation of renal sympathetic nerves causes renin release and inhibits sodium and water excretion (Katholi 1983). The diuresis and natriuresis is therefore consistent with OSA not having an important effect on the sympathetic nervous system. A recent publication (Fletcher et al 1987), has demonstrated high urinary levels of noradrenaline in OSA patients when compared to non-apnoeic hypertensive controls. The levels returned toward normal following tracheostomy, although all values were within or almost within the normal range for their laboratory. There was no difference in

adrenaline levels. The present study has not confirmed these results with respect to overnight noradrenaline excretion. The number of patients in both studies is small (five in each), but the results are not consistent with there being major differences in overnight sympathetic function before and after treatment (either permanent or temporary) for obstructive sleep apnoea.

As well as profound sleep disruption, OSA has two other major pathophysiological characteristics: Recurrent (and often severe) arterial hypoxaemia, and the repetitive generation of abnormally large negative intrathoracic pressure during attempted inspiration through an obstructed pharynx (Sullivan et al 1984). Hypoxaemia is a potent stimulus to chemoreceptor discharge and has been shown to promote sodium and water excretion in the cat (Schmidt et al 1985a). This was seen in both intact and denervated kidneys, and appeared not to be mediated through suppression of aldosterone secretion alone (Schmidt et al 1985b). This is discussed further in chapter 10.

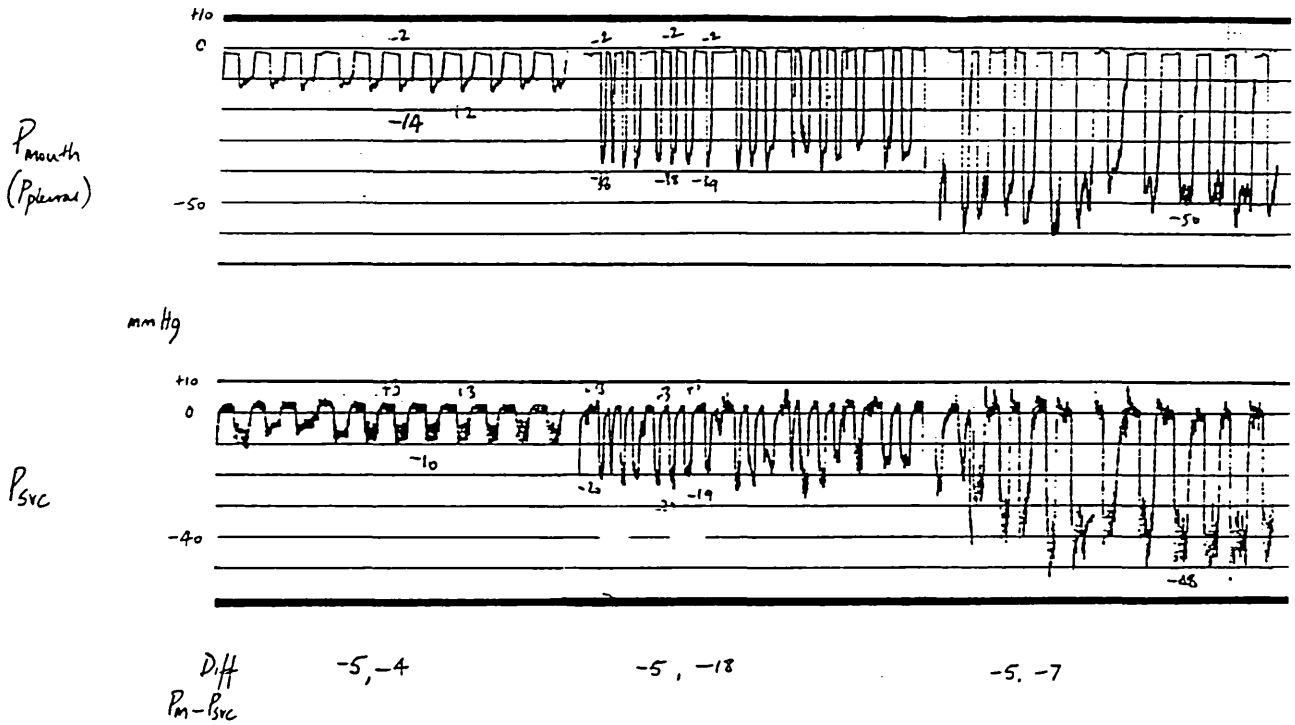
7: INTRODUCTION

In the 1960's Gauer and Henry showed that distension of the cardiac atria caused an increase in urine flow and demonstrated the existence of a neural reflex with specific atrial stretch receptors as the afferent sensor (Gauer and Henry 1963). Although granules in the right atrium had been observed by several workers, it was not until 1981 that de Bold and colleagues provided evidence of hormonal secretion by the atria, when they were able to demonstrate a diuresis in a rat into which concentrated atrial extract had been injected (de Bold et al 1981).

Atrial natriuretic peptide (ANP) was isolated, and using recombinant DNA technology, found to be a 28-aminoacid peptide. The gene responsible codes for a 152-aminoacid prehormone, which is then stored as a 126-aminoacid prohormone (Kangawa and Matsuo 1984, Oikawa et al 1984). Since then many studies have established that ANP has natriuretic (Atlas et al 1984), vasorelaxant (Currie et al 1983), anti-aldosterone (Atarashi et al 1984) and anti-angiotensin 2 properties (Harris et al 1987). The mechanism responsible for release of ANP has not been fully elucidated. Increased levels have been demonstrated in situations in which an increase in central blood volume and atrial distension occur (Tikkanen et al 1985, Lang et al 1985, Sugawara et al 1985, Yamaji et al 1985), and Raine and colleagues were able to demonstrate a significant correlation between atrial pressure and plasma ANP levels in patients with congestive cardiac failure (Raine et al 1986).

Figure 16 shows the mouth and superior vena caval pressure tracings obtained from a healthy male breathing through an inspiratory resistance. In the absence of airway obstruction, mouth pressure

Figure 16



Simultaneous recording of SVC and mouth pressure when breathing through a variable inspiratory resistance. Three different resistances are shown. When a low resistance is appplied, such that -14 cm H_2O intrathoracic pressure is necessary to inspire, the difference between P_{mouth} and P_{SVC} is the same during inspiration and expiration (ie +5 cm H_2O in the SVC). When greater resistance is applied (P_{mouth} = -38 cm H_2O) the difference between P_{mouth} and P_{SVC} is the same (5 cm H_2O during expiration), but during inspiration blood is aspirated into the thorax, thereby attenuating the fall in P_{SVC} and increasing the pressure difference across the wall of the SVC (to 18 cm H_2O). When the resistance is increased further (P_{mouth} -50 cm H_2O) the P_{SVC} falls to a similar levels as the P_{mouth}, and there is no appreciable difference between inspiration and expiration. This is likely to be due to collapse of the great veins entering the thorax

reflects pleural pressure. When inspiration requires the generation of an abnormally large negative (with respect to atmospheric) pleural pressure, the pressure in the superior vena cava (SVC) also falls. Presumably as a consequence of aspiration of blood into the thorax, the fall in pressure in the SVC is attenuated. The result of this is a pressure difference across the wall of the SVC and right atrium which will tend to dilate the atrium. Obstructive lung diseases are associated with large negative intrathoracic pressures during inspiration, and cardiac distension has been demonstrated radiologically in patients with obstructive sleep apnoea (OSA) in which very large negative pressures are generated as a result of inspiratory effort against a closed pharynx (Lugaresi et al 1979). Obstructive lung diseases differ from OSA with regards to expiration in that in OSA there is no increase (positive) in intrathoracic pressure during expiration, whereas in obstructive lung diseases, the substantial airway resistance means that large positive pressures have to be generated during expiration.

It is conceivable that OSA may therefore be associated with abnormal release of ANP, and indeed from our knowledge of the actions of ANP, the effects of OSA on salt and water excretion (described in chapter 6) could be mediated by ANP. A study was therefore carried out to determine whether OSA was associated with abnormal circulating levels of ANP.

METHODS

Patients

Six men with severe OSA (>300 apnoeas per night, see fig 14). All were overweight (mean 95.8 kg, range 79-120). All were in good health with the exception of one patient with maturity-onset diabetes, well controlled on glibenclamide.

Protocol

Patients were studied on two separate nights. Blood was withdrawn from a peripheral vein into an EDTA tube at approx 0030 (after 1-2 hrs sleep), 0730 (immediately on waking) and at 1600 hrs. Plasma was immediately separated in a refrigerated centrifuge (3000 rpm for 7 min), and then stored until analysis at -70°C. All patients were fully accustomed to CPAP and on one of the nights slept without the pump and therefore experienced OSA. On the other night, CPAP was applied thereby abolishing the OSA (random order). Arterial oxygenation was monitored continuously to confirm OSA on the first night, and to confirm successful CPAP on the second night. Sleep staging was not performed, sleep being confirmed by direct observation and also by the subjects themselves on awakening.

ANP assay

ANP levels were measured using a radioimmunoasssay technique (Morice et al 1988) modified by the use of sheep anti-human polyclonal antibody- 95% confidence limits 2.5 fmol (Morice A, personal communication 1988).

Stastical analysis

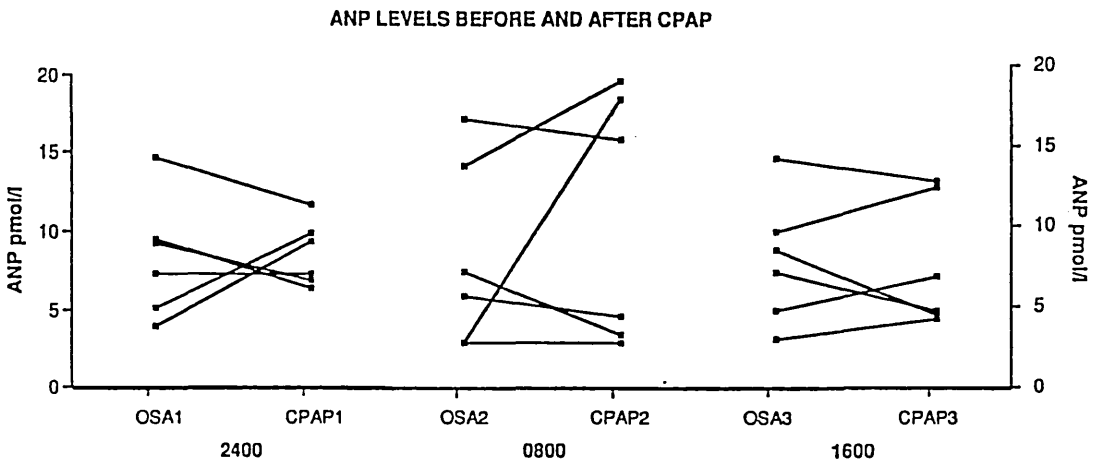
Values for the different times of each day (OSA and CPAP) were

compared by analysis of variance, and those for the equivalent times of each day were compared using a students' t test for paired data.

RESULTS

Oximetry confirmed OSA on the non CPAP nights, and its successful abolition on the nights on which it was applied. The full results are given in the appendix, and are shown in graphic form in figure 17 overleaf. There is no difference between the ANP values obtained at similar times on the two days, nor is there any significant diurnal variation in ANP levels.

Figure 17



Plasma ANP levels in six subjects with severe OSA. Samples were drawn at three different times (2400 after 90 mins sleep, 0730 immediately om waking and 1600 in mid-afternoon) on two nights on and off treatment with nasal CPAP.

There is no difference in the means of any of these values. There is also no suggestion from figure 17 that any consistent pattern of ANP release has emerged in these six subjects, all of whom had been demonstrated previously to have a profound diuresis when experiencing OSA which was promptly and completely reversed by treatment (see chapter 6).

Since this study was completed, Krieger et al have reported similar findings in OSA patients at the most recent meeting of the American Thoracic Society (Las Vegas, 1988). In their patients, there was a tendency for the peripheral venous ANP levels to fall on CPAP treatment, but the difference was not statistically significant. They were, however, able to demonstrate a significant lowering of pulmonary arterial ANP levels when CPAP was applied (Krieger et al 1988). There was, however, no consistent pattern in their patients and the significance may have been achieved by a very sizeable change in two of their patients. Their criticism of these results rests on the fact that only two samples were taken, and only one in the middle of the night. However, in all cases the patients had been witnessed both visually and by continuous oximetry to be experiencing severe OSA immediately prior to the midnight sample (in some cases they were awoken by the needle entering their arms). Similarly, the morning samples were drawn immediately upon waking. Whilst there is disagreement, the issue must remain not proven, although these results are in agreement with those from the experiments described in the following chapter in which ANP was measured in a different laboratory, thereby minimising, the other main possibility - an unreliable assay for ANP.

8: INTRODUCTION

Although extensively studied in the 1950s and 60s, the relationships between extra and intravascular pressures within the thorax have assumed considerable importance following the discovery of ANP which is thought to be released from the atria in response to distending pressure (see chapter 7).

In normally compliant lungs, unobstructed inspiration is achieved by generating a pleural pressure of -4 to -8 cm H_2O (relative to atmospheric). If obstruction of either upper or lower airways is present, or if lung compliance is increased, greater negative pleural pressures are required to effect inspiration. Thus in acute asthma (lower airway), and OSA (upper airway), pressures as low as -60 cm H_2O occur during inspiration (see figure 3).

Gauer and colleagues showed that in spontaneously breathing, anaesthetised dogs the application of -8 cm H_2O pressure at the mouth throughout the respiratory cycle resulted in increased urine output (Gauer et al 1954). Murdaugh and colleagues confirmed this observation in healthy volunteers using pressures of -18 to -22 cm H_2O, although they were unable to demonstrate an effect on electrolyte excretion (Murdagh et al 1959). The converse effect was observed in four healthy men, in whom continuous positive pressure (20 mmHg) reduced urea clearance, and the effect was progressive as the airway pressure was increased up to 40 mmHg (Drury et al 1947).

Figure 16 (see chapter 7) illustrates mouth pressure (which reflects pleural pressure in the absence of lower airway obstruction) and right atrial pressure in a subject breathing through a variable resistance, such that differing degrees of negative intrathoracic pressure was necessary to achieve inspiration. Whilst the pressure in

the right atrium falls in line with the pleural pressure surrounding it, the fall is attenuated by the aspiration of blood into the superior vena cava during inspiration. The net effect of these pressure changes is to create a distending pressure across the wall of the right atrium during an obstructed inspiration.

Increased urine flow has been reported in association with an acute asthmatic attack, and also in association with untreated obstructive sleep apnoea (see chapter 6). Atrial natriuretic peptide (ANP) is known to promote sodium and water excretion, and is thought to be released from cardiocytes in response to distension of the right atrium (chapter 7). This study was carried out to determine whether breathing through an inspiratory resistance and thereby generating excessive negative intrathoracic pressure is associated with increased release of ANP which might therefore mediate the previously reported effects of negative pressure on renal function.

METHODS

Subjects

Six healthy men (aged 22-35) mean weight 85kg (range 72-102). All were aware of the purpose of the experiment.

Techniques

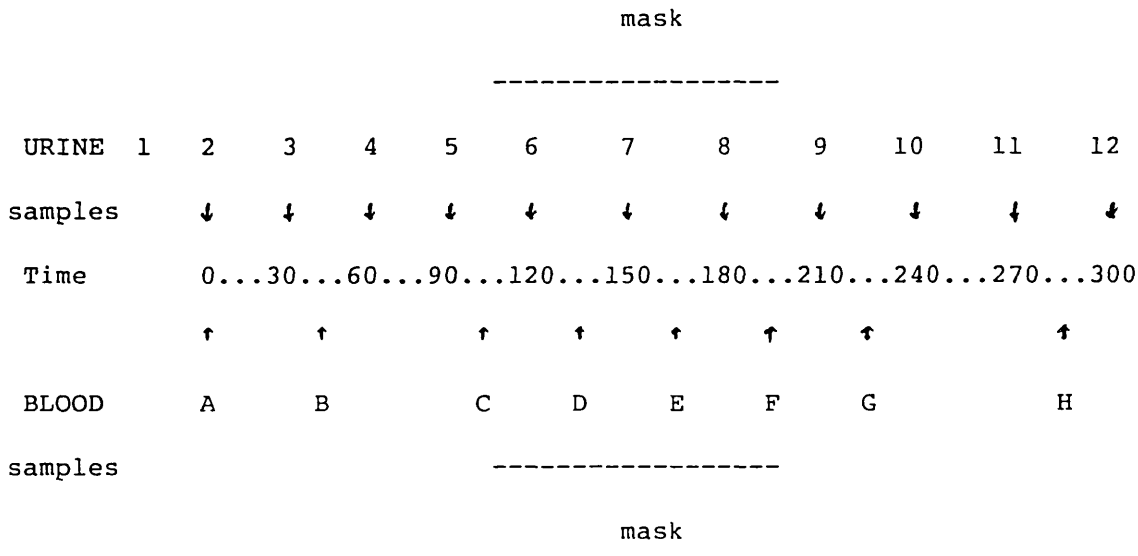
The negative pressure valve was incorporated into the mask on the experimental day. It contained a variable inspiratory resistance which could not be overcome unless a certain threshold pressure was generated by the inspiratory muscles. Before each experiment this was set to -30cm H_2O.

Blood was withdrawn from an anticubital vein into commercially prepared bottles containing potassium EDTA to which aprotinin (10,000 inactivator units) had been added. Plasma was separated in a refrigerated centrifuge (4°C) at 2200 rpm for 7 min and stored for later analysis (-70°C) within 15 minutes. Plasma ANP levels were determined by radioreceptor assay as described elsewhere (Burgisser et al 1985). Urine and plasma sodium concentrations were determined by flame photometry.

Protocol

All subjects were studied on two separate days, one week apart. Identical meals were consumed during the 24 hours prior to each experiment, and urine was collected during that period to confirm similar water, sodium and potassium intake and output. No food was consumed during the study. On the morning of each study day subjects drank 5 ml/kg tap water. At approx 0900 blood was withdrawn for ANP (sample A) and the subjects were recumbent for the duration of the experiment thereafter, rising only briefly to empty the bladder. Urine

was collected every thirty min, and the fluid replaced with an equal volume of tap water. Further blood samples (B to H) were drawn at the times shown. After a 105 min run-in period the subjects breathed through a mask for 90 min. On the negative pressure day, the mask incorporated an inspiratory resistance which necessitated the generation of -30 cm H_2O at the mouth for inspiration to proceed. The expiratory valve offered no appreciable resistance. The control day, when the inspiratory resistance was removed from the mask, was included to correct for the effect of prolonged recumbency. The protocol is summarised in the following diagram. Urine sample 1 was the 24hr collection prior to the experimental day. The results are expressed in ml h^{-1} and mmol h^{-1} for urine production and sodium excretion respectively.



Statistical analysis

The mean of the values for the two 30min urine collections immediately prior to the application of the mask (samples 4 and 5) was compared with each of the values of the 30min collections during the mask period (samples 6, 7 and 8) and the mean of the values of the two

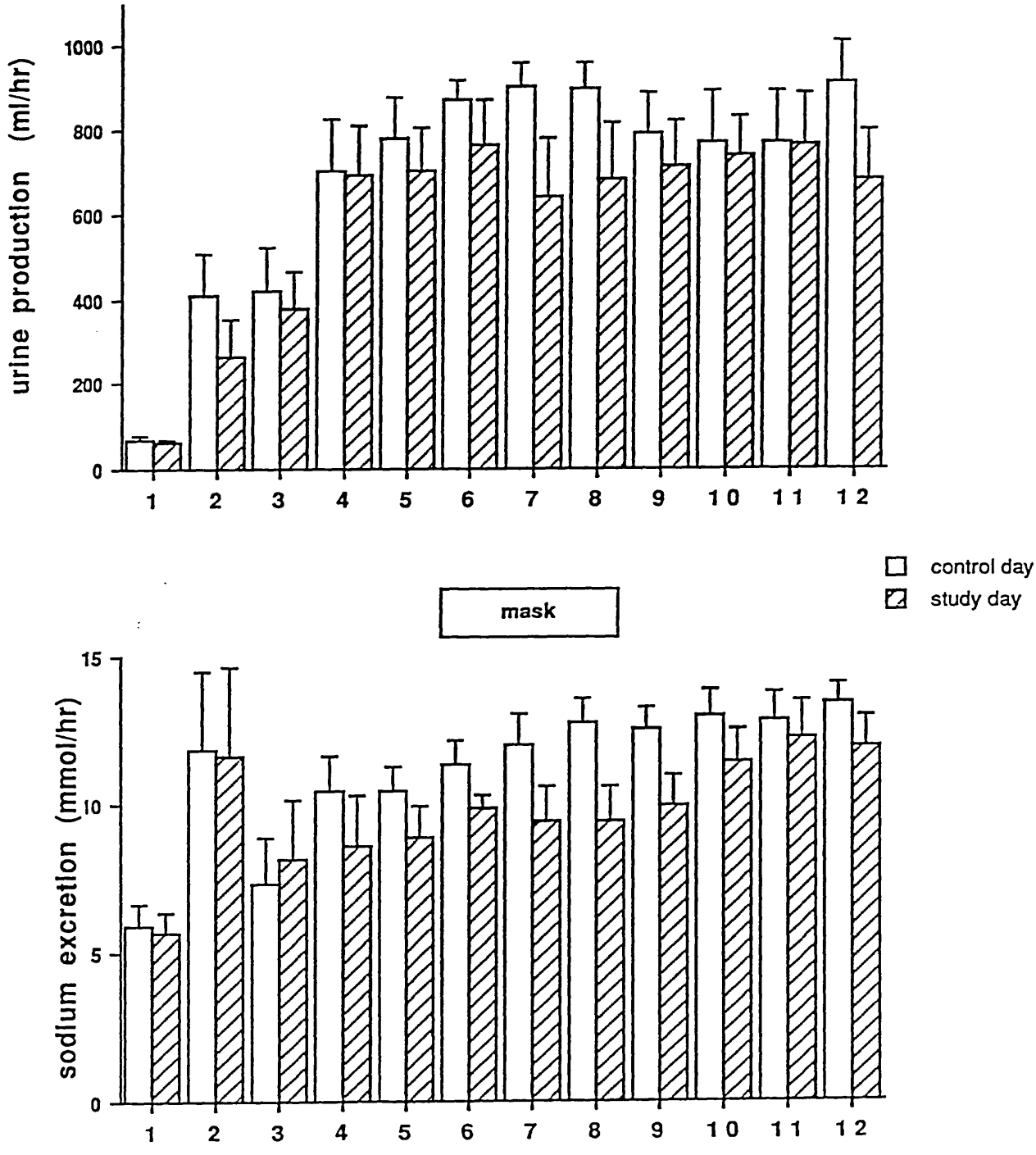
30min collections after the mask was removed (samples 9 and 10) using a students' t test for paired data. The mean of the two ANP determinations immediately prior to the application of the mask (samples B and C) were compared individually with each of the values (samples D,E and F) obtained during the study period on each day.

RESULTS

All subjects completed the study without difficulty. Although there was some intra-individual variability, the previous days urine and sodium output was very similar for the whole group. Full individual values are given in the appendix. Figure 18 shows the mean urine production and sodium excretion over the course of the study on the two days. Values tended to be slightly higher on the control day, and the inspiratory resistance appears to have attenuated the progressive rise in urine and sodium output seen in collections 6,7 and 8 on the control day. However, the differences do not reach statistical significance, and the results may have been influenced by one subject who produced much less urine on the study day resulting in a larger standard error. There is no suggestion from analysis of individual results that an effect of resistive breathing of this magnitude was masked by the intra-individual variation in previous 24 hr sodium and urine output seen in some subjects.

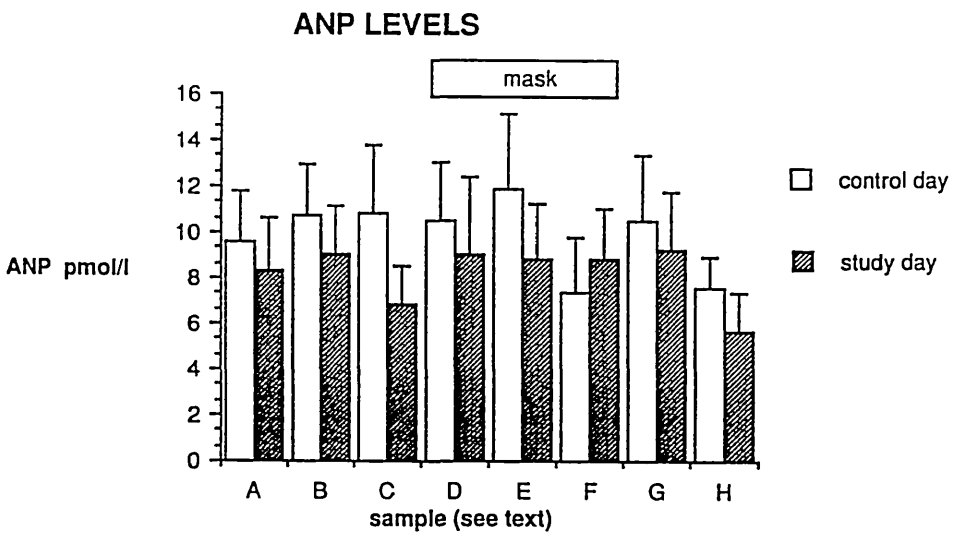
The ANP results are given in the appendix and in diagramatic form in figure 19. The large drop seen in sample C and onwards for subject 1 on the study day is unexplained. Although no technical error has been identified, this cannot be ruled out, and highlights the inherent difficulties in studies which require measurement of plasma ANP levels. No effect, either of prolonged recumbency or resistive breathing on ANP levels is seen.

Figure 18



Urine and sodium output during resistive breathing. Consecutive 30 min urine collections in recumbent subjects (n = 6). During collection periods 6,7 and 8 (ie a total of 90 min) subjects breathed through a mask. On the study day (hatched bars) an inspiratory resistance was applied, such that -30 cm H_2O intrathoracic pressure was required to achieve inspiration. On the control day there was no resistance to inspiration. Values are mean +/- SE

Figure 19



ANP levels during resistive breathing. Samples were drawn from a peripheral vein (n = 6). Samples D,E and F were drawn whilst breathing through the mask. On the study day (hatched bars), an inspiratory resistance was applied. On the control day there was no resistance to inspiration. Values are mean +/- SE

DISCUSSION

This study has not demonstrated any significant effect of abnormally large negative intrathoracic pressures on ANP release or renal function in healthy, water-loaded subjects in the recumbent position.

It has been known for over thirty years that the great veins of the thorax collapse when subjected to very large negative aspiration pressures (Brecher 1952). It is possible that the intrathoracic pressures generated during the periods of resisted breathing caused this phenomenon to occur, thereby preventing aspiration of blood into the thorax and the generation of a distending pressure across the right atrial wall. In the pilot study described earlier on one of the subjects this effect was not seen until pressures of -50 cm H_2O were generated (figure 16), and it is therefore unlikely that the substantially lower level of -30cm H_2O was associated with collapse of the great veins.

When substantial airflow obstruction is present, pulsus paradoxus occurs. In three subjects in whom it was measured, inspiratory systolic blood pressure fell by 22,25 and 30 mmHg during negative pressure breathing. Unless total peripheral resistance falls, the fall in systolic blood pressure would be accompanied by a fall in cardiac output. Falls in cardiac output have been reported during the frustrated inspiratory efforts of simulated OSA in baboons (Fletcher et al 1987b). Although we did not make measurements of glomerular filtration rate, renal plasma flow or tubular function during this study, these substantial falls in blood pressure might be have been expected to alter renal haemodynami cs, although no effect on urine and sodium output was seen.

Raine and colleagues have reported a close relationship between atrial (both right and left) pressure and plasma levels of ANP in patients with congestive cardiac failure, and suggested that atrial distension is responsible for ANP release (Raine et al 1986). Fluoroscopy has demonstrated generalised cardiac enlargement during the obstructive apnoeas of OSA (Lugaresi et al 1979), and although the possibility was not specifically examined, right atrial enlargement could have occurred in our subjects in response to the pressure changes depicted in figure 16. We cannot exclude the possibility that ANP is released in reponse to less negative intrathoracic pressures, but as the transmural pressure across the right atrium increases with increasing inspiratory resistance (and therefore more negative intrathoracic pressure), this would seem unlikely. A further possibility is that ANP stores were depleted in the first few minutes by the large stimulus of negative pressure breathing, but this is not supported by the results which show consistent ANP levels throughout the 90 min period.

If atrial distension is an important stimulus to ANP release, it would appear that it is necessary for this to be provoked by increased (positive) intravascular pressure as opposed to decreased (negative) extravascular pressure. These results suggest that lung diseases associated with abnormal negative intrathoracic pressures are unlikely to be associated with excessive production of ANP, and are consistent with the previous results in which obstructive sleep apnoea was not associated with increased ANP levels (Chapter 7).

9: INTRODUCTION

The experiments described in chapter 6 indicate that OSA has a substantial effect on urine and sodium output. This can be reversed by treatment with nasal CPAP. It would seem likely that the effects of OSA on renal function are abnormal in that OSA is itself a highly abnormal situation, and the effects (ie an increase in overnight urine and sodium output) are also abnormal and unphysiological. There are several mechanisms which could be responsible for the phenomenon, and the results presented in chapters 7 and 8 suggest that neither abnormally large negative intrathoracic pressures during inspiration nor excessive circulating levels of ANP are responsible.

The measurement of renal clearance of lithium is a relatively new technique for determining the relative contributions of proximal and distal tubular function to the excretion of sodium and water (Thomsen 1984). The validity of the measurement depends on the assumption that lithium is reabsorbed isotonically in the proximal convoluted tubule (as is sodium), and that it is neither absorbed nor excreted in the loop of Henle, distal convoluted tubule or collecting ducts. Evidence for the first assumption comes from both human and animal studies. Using micropuncture techniques in rats, measurements of tubular lithium concentration have demonstrated that lithium is reabsorbed in the proximal tubule to the same extent as sodium and water (Hayslett and Kashgarian 1979). Similarly, direct comparisons of the delivery of fluid from the proximal tubule with lithium clearance have yielded very close concordance (Shirley et al 1983). In humans, the fraction of filtered lithium which is excreted in the urine is similar to the fraction of filtered sodium which is delivered from the proximal tubules (Thomsen et al 1969). The delivery of sodium from the proximal

tubule has been shown to fall in parallel with glomerular filtration rate (GFR) when the number of functioning nephrons has been reduced (Hayslett et al 1969). Lithium clearance has also been shown to fall in parallel with GFR in such circumstances, whereas the clearance of sodium does not change (Thomsen et al 1969, Steele et al 1975). In healthy subjects on normal salt intakes, neither frusemide nor amiloride had a significant effect on the fractional excretion of lithium, suggesting strongly that lithium clearance provides a reliable measure of outflow from the proximal tubule. This was not so in sodium depletion because of distal reabsorption of lithium (Atherton et al 1987).

Inulin is a polymer of fructose derived from dahlias. It is freely filtered by the glomerulus and neither absorbed nor excreted by the tubules. Measurements of inulin clearance therefore provide an accurate measurement of GFR and are still the yardstick by which other measurements of GFR are judged (Shannon et al 1935, Jones 1985). Simultaneous determination of GFR by C_{in} and proximal tubular function by C_{Li} therefore allows the relative contributions of proximal and distal tubules to overall sodium and water excretion to be assessed, and enables corrections to be made for incomplete collections of urine.

In order to elaborate the intra renal mechanism whereby OSA and its treatment alter renal function, inulin and lithium clearance measurements were made in patients with OSA on and off treatment with nasal CPAP.

METHODS

Subjects

Six men (aged 40-58, mean 47) with severe obstructive sleep apnoea, previously documented by full polysomnography were studied. Some were overweight, and all had been successfully established on nasal CPAP therapy (see chapter 5 and 6) previously. No attempt was made to control dietary intake of either sodium or fluids prior to either study period. Two subjects were on medication at the time of the study. One was on prednisolone 15 mg daily for asthma, and another with well-controlled maturity onset diabetes mellitus was on glibenclamide 10 mg daily. Both subjects took identical medication during the day prior to each study.

Protocol

All subjects were studied on two separate nights. During one clearance period, the subjects slept without the CPAP (therefore experiencing OSA), and during the other period CPAP was applied. Transcutaneous S_aO_2 was measured to confirm OSA and its abolition by the CPAP. The order of studies was randomised. In three subjects the studies took place on successive nights and in the other three there was a gap of at least 7 days (maximum 26) between studies.

Clearance measurements were made over approximately two hours at similar times on the two nights. Lithium carbonate (600 mg) was administered at 1400 in the afternoon prior to the study. At 2130 4g inulin was injected intravenously, and thereafter an infusion at a rate of 2g h^{-1} established. At 2230 blood was withdrawn and the bladder emptied. Thereafter subjects went to sleep for approximately two hours, whereupon they were awoken. The bladder was emptied, the

volume recorded and an aliquot saved for analysis. A further sample of blood was also withdrawn to ensure stable plasma levels of inulin and lithium during the experiment.

Techniques

Plasma was separated by centrifugation at 2200 rpm for seven minutes. Inulin was measured by standard techniques (Schreiner 1950). Lithium, sodium and potassium were measured by flame photometry. In order to take account of the matrix effect, experimental samples were compared against standards containing known quantities of sodium and potassium (Brown and Corr 1987).

The study was carried out without the use of indwelling bladder catheters. In order to avoid errors due to incomplete bladder voiding inherent in any such study, the results are expressed as ratios as follows rather than absolute values of individual clearances:

Calculations

Clearances of inulin, lithium and sodium were calcualted using the standard formula:

$$C=[U]V/[P]$$

where [U]= urinary concentration, [P] = plasma concentration and V rate of urine production.

Fraction of GFR leaving the proximal tubule (FC_{Li}) = C_{Li}/C_{in}

Fraction of filtered sodium excreted = C_{Na}/C_{in}

Sodium excretion (Na_{ex}) = $[U_{Na}] \times V$

Potassium excretion (K_{ex}) = $[U_K] \times V$

Ratio of potassium to sodium excretion = K_{ex}/Na_{ex}

Statistical analysis

The clearance values obtained on OSA and CPAP nights were compared using a Wilcoxon matched rank sum test. $P < 0.05$ was considered to be significant.

RESULTS

The individual results for all six subjects are given in the appendix. The tables below summarise the derived values (***CPAP values in bold italic***).

SUB	V	C_{in}	C_{Li}	C_{Na}	FC_{Li}	Na_{ex}	K_{ex}	C_{Na}/C_{in}	K_{ex}/Na_{ex}
RT	2.56	118	33.2	2.03	0.280	0.284	0.037	0.0170	0.13
	2.83	***113***	***27.3***	***1.43***	***0.240***	***0.200***	***0.043***	***0.0130***	***0.22***
FR	2.70	122	30.7	1.69	0.252	0.235	0.052	0.0139	0.23
	0.93	***118***	***22.8***	***0.82***	***0.193***	***0.115***	***0.056***	***0.0069***	***0.49***
RK	1.12	79	19.5	0.84	0.248	0.116	0.038	0.0106	0.33
	0.57	***129***	***12.3***	***0.45***	***0.095***	***0.062***	***0.039***	***0.0035***	***0.63***
WW	3.0	109	64.5	1.32	0.590	0.185	0.052	0.0121	0.28
	0.44	***55***	***9.5***	***0.32***	***0.170***	***0.045***	***0.014***	***0.0058***	***0.33***
KN	2.67	113	28.4	1.72	0.251	0.240	0.034	0.0150	0.14
	1.04	***111***	***21.4***	***0.87***	***0.193***	***0.120***	***0.054***	***0.0078***	***0.45***
RG	2.82	182	53.5	2.12	0.294	0.298	0.025	0.0116	0.08
	1.16	***133***	***29.5***	***0.70***	***0.220***	***0.099***	***0.019***	***0.0053***	***0.19***

Means (SE)

FC_{Li} = 0.318 (0.055)
0.185 (0.021)

C_{Na}/C_{in} = 0.0133 (0.0009)
0.0071 (0.001)

K_{ex}/Na_{ex} = 0.198 (0.039)
0.385 (0.069)

Units
V = urine production/ml min^{-1}; C_{in} = inulin clearance/ml min^{-1}; C_{Li} = lithium clearance/ml min^{-1}; C_{Na} = sodium clearance/ml min^{-1}; Na_{ex} = sodium excretion/mmol min^{-1}; K_{ex} = potassium excretion/mmol min^{-1}; The remainder are fractions.

The results are shown graphically in figures 20, 21 and 22. For reasons already stated, no accurate inferences can be drawn from the individual clearance values. Subjects RT, FR, and KN all had similar inulin clearances over the two study periods. In the other three subjects the inulin clearances varied randomly suggesting incomplete bladder emptying. This might suggest relative constancy of the GFR. Conversly, the lithium clearance fell on the CPAP nights in all subjects. CPAP resulted in a significant ($P<0.05$) fall in fracti onal lithium clearance and amount of filtered sodium excreted, and a significant increase in the proportion of potassium to sodium excreted. Because of the possibilty of incomplete collections, only the fractional values have been subjected to statistical analysis.

Figure 20

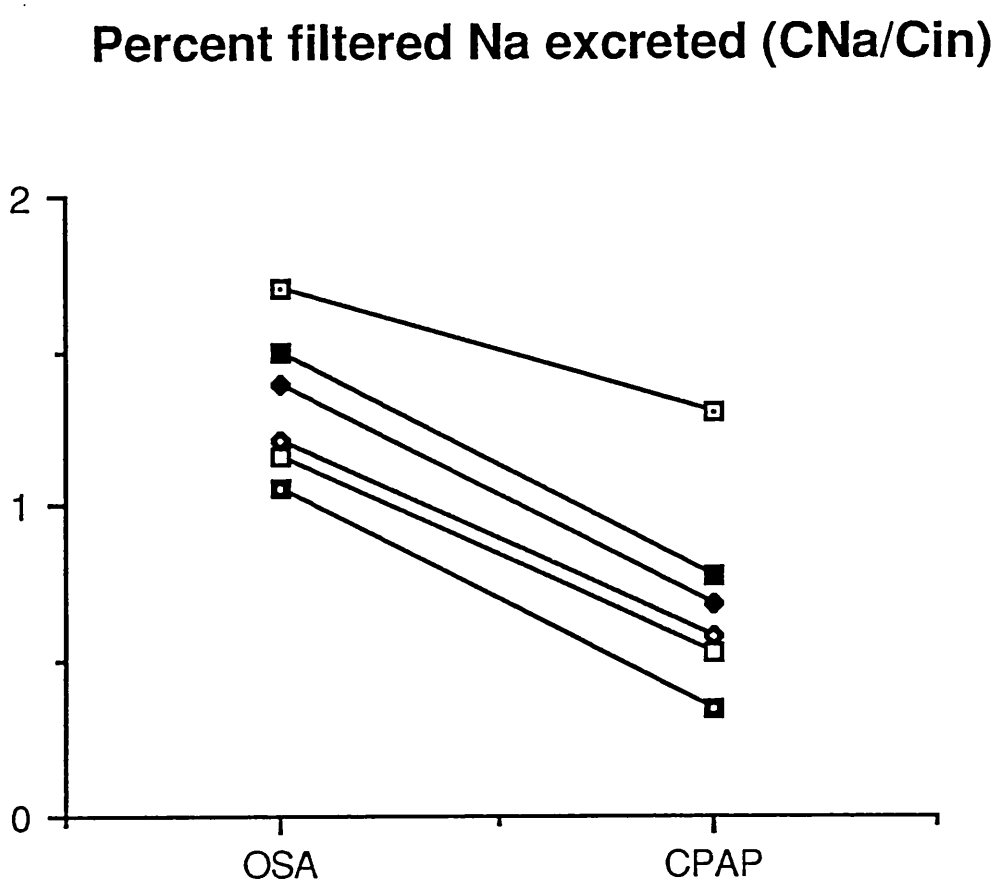


Figure 21

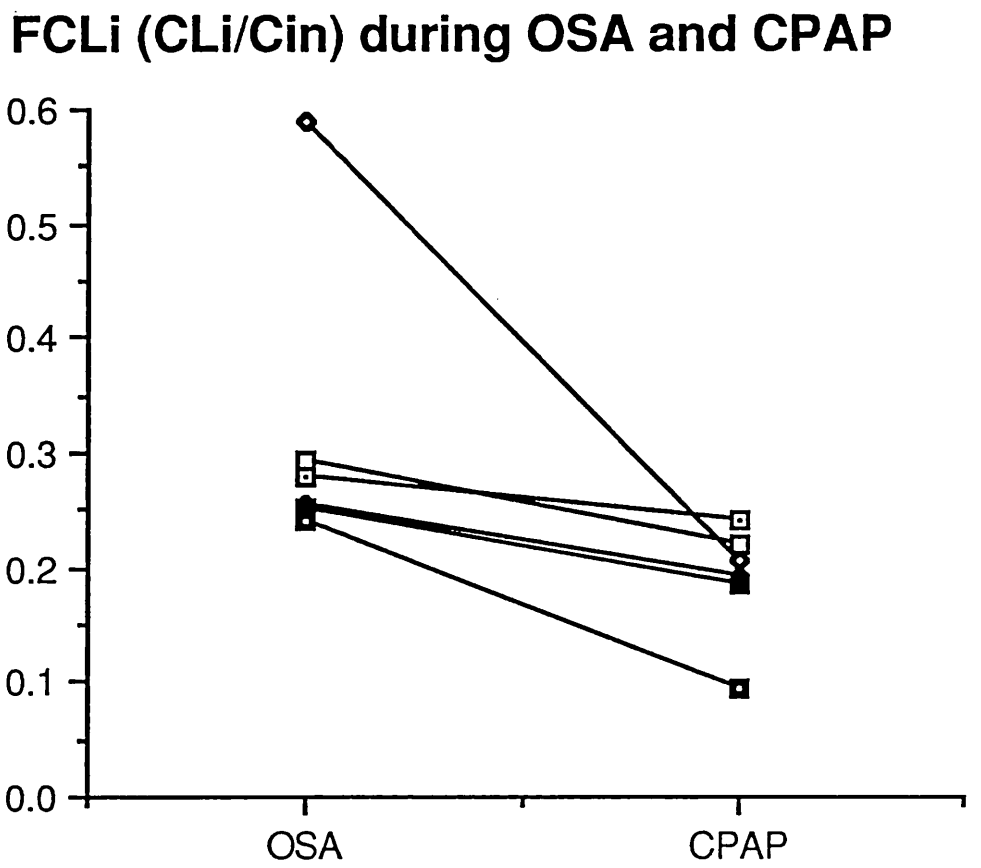
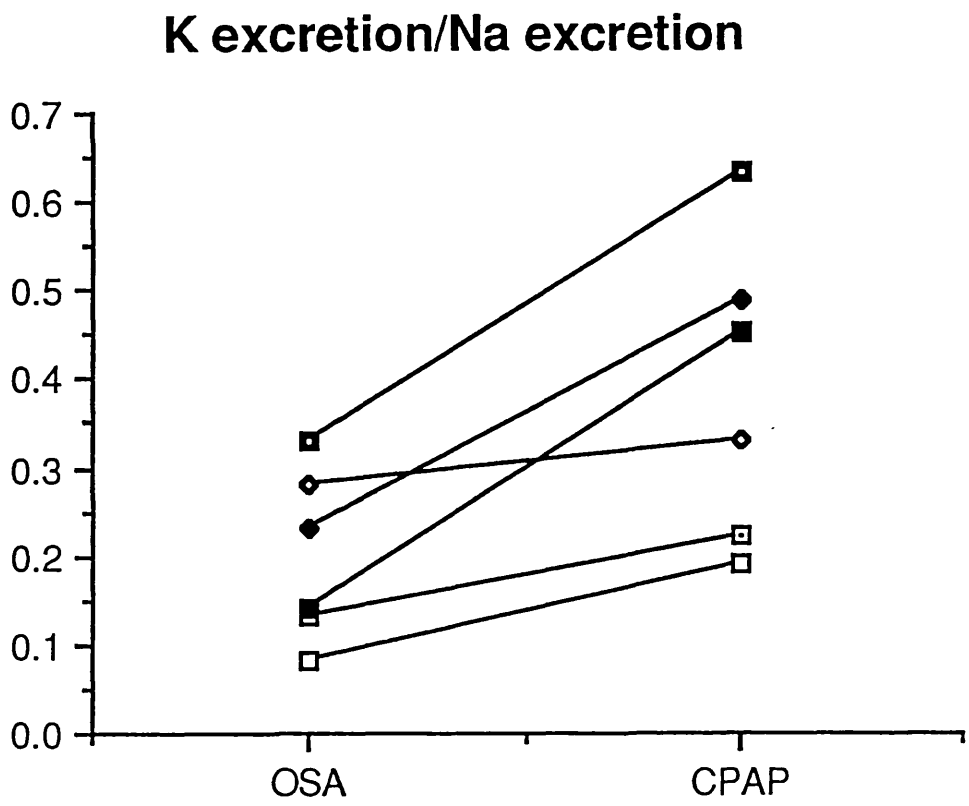


Figure 22



DISCUSSION

These results confirm and extend those of the experiments described in chapter 6. Although dietary sodium intake was not controlled, the fraction of the total amount of sodium in the glomerular filtrate which was actually excreted was significantly higher whilst the patients were experiencing OSA than when they were allowed normal sleep by the application of nasal CPAP. In addition every subject experienced a fall in FC_{Li} when on CPAP which was significant ($P<0.05$), and the results therefore suggest that OSA exerts its effect on sodium and water excretion by reducing proximal tubular reabsorption of sodium. In three of the six subjects there was no change in GFR as measured by inulin clearance. The differences seen in the other three would be consistent with incomplete urinary collections. Use of the fractional lithium clearance ($FC_{Li} = C_{Li}/C_{in}$) corrects for an incomplete collection, and allows comparison of all the results obtained on and off CPAP.

The variability of FC_{Li} within individuals has been studied in eleven healthy subjects on three different occasions at a similar time of day. Providing the dietary salt intake is not extremely low (Atherton et al 1987), the overall SD of the intra individual differences was 8.5% (Strazzullo et al 1988). This is similar to the variation seen in the subjects in this study either when studied on or off CPAP, and considerably less than the variation in FC_{Li} that was observed within each individual when values on and off CPAP are compared. It is not known whether FC_{Li} is subject to a diurnal variation, but the fact that the studies were carried out at similar times of the day would mitigate against this as an explanation for the changes observed.

There are a number of possible explanations for the present results. As previously discussed, OSA is characterised by 1, repeated apnoea throughout the night with associated with hypoxaemia and hypercapnia. 2, progressive decrease in intrathoracic pressure with each inspiratory effort. 3, severe disruption of normal sleep. 4, transient surges in arterial pressure. Any of these could therefore be responsible for the observed effects of OSA on renal function. An effect of sleep disruption cannot be ruled out, as it is possible that normal sleep is associated with a fall in FC_{Li}, and that this is prevented by OSA.

Small fracti onal changes in GFR could produce large absolute differences in sodium (and lithium) excretion, because such small changes in GFR represent very large changes in the filtered load of sodium. The present results do not completely exclude this possibility, although the consistency of the effect on lithium as opposed to inulin clearance makes it unlikely.

The rise in the ratio of potassium to sodium excretion during CPAP raises the possibility of an effect of aldosterone. The only plausible hypothesis is that OSA in some way reduces aldosterone production. The fracti onal distal reabsorption of sodium (C_{Na}/C_{Li}), however, was not significantly different in the two study periods, which is not consistent with an alteration in aldosterone secretion. Furthermore, the clearance measurments were made over 90-120 minutes at the beginning of the sleep period, and it is unlikely that plasma aldosterone levels could be significantly altered in that time (Ganong and Mulrow 1958).

The experiments described in chapters 7 and 8 are not consistent with the hypothesis that the abnormal intrathoracic pressures either

via the release of ANP or another unspecified mechanism are responsible. However, ANP may exert some of its effects via the proximal tubule, and ANP has been shown to inhibit reabsorption of sodium and water in the proximal tubule (Brown and Corr 1987) by antagonising the effect of angiotensin 2 (Harris et al 1987). Studies using angiotensin converting enzyme inhibitors have suggested that angiotensin 2 has a direct effect on the proximal tubule to increase the reabsorption of sodium (Brown 1987).

A parallel increase in FC_{Li} and plasma ANP levels has been observed upon assumption of the supine posture, although the two may not have been related (Solomon et al 1986). Could therefore an effect of ANP have been missed in chapter 7? ANP has been demonstrated to increase GFR possibly by a differential effect on afferent and efferent glomerular arterioles (Atlas et al 1984, Marin-Grez et al 1986), although in other studies in which plasma ANP levels have been altered within the physiological range, no effect of ANP on GFR has been found (Brown and Corr 1987). Whether or not an alteration of plasma ANP within the (so-called) physiological range could be responsible for changes of the magnitude seen in this study is not known. It is conceivable that such changes in sodium excretion would require alterations in the plasma ANP level that would also affect GFR. This however is speculative, and further studies will be necessary to determine if the GFR is indeed unaffected by the application of nasal CPAP. Although ANP has been shown to inhibit the aldosterone response to angiotensin 2 (Anderson et al 1986), Brown and Corr found that infused ANP had no effect on potassium excretion (Brown and Corr 1987). Thus the known effects of ANP could theoretically be responsible for some of the changes seen in the

present study. However, whilst no evidence of increased ANP secretion was found in chapter 7, until further data are available the question must remain open.

It has been known for many years (Ludwig 1843, Cushny 1917) that the rate of urine production is related to the arterial pressure. Previous workers have observed transient surges in systemic blood pressure which accompany the arterial desaturation of OSA, and several have reported a high incidence of sustained hypertension in patients with OSA (see chapter 1 and figure 5). Blood pressure was not measured in this study, but the effects of OSA on sodium and water excretion may therefore be a manifestation of this so-called pressure diuresis. The intrarenal mechanisms responsible for this pressure diuresis remain the subject of controversy (Roman 1986). Several groups of investigators have shown that a rise in blood pressure is associated with inhibition of tubular reabsorption of sodium and water, independent of changes in RBF and GFR (Forster and Maes 1947, Selkurt et al 1949), and studies in isolated perfused kidneys have shown this to be independent of changes in sympathetic nerve activity and changes in circulating renal hormones (Selkurt et al 1966). It has been variously thought to be due to changes in proximal tubular, loop of Henle and collecting duct function (Roman 1986). Whether or not the pressure diuresis is accompanied by changes in lithium clearance is not known.

Stimulation of the renal sympathetic nerves has been shown to cause sodium and water retention (Katholi 1983). Fletcher and colleagues have demonstrated increased overnight urinary adrenaline levels in patients with OSA which return to normal after treatment with CPAP (Fletcher et al 1987a). If OSA is associated with excessive

catecholamine output, the opposite effect on sodium excretion to that seen might be expected, and in chapter 6 no evidence of a major effect of OSA on urinary catecholamines was found. If there are adrenergic nerves supplying the kidney which, when stimulated, cause sodium and water retention, there may be others which have the opposite effects when stimulated.

Hypoxia and hypercapnia would be expected to stimulate the output from both medullary and peripheral chemoreceptors. During an apnoea, hypoxia and hypercapnia are progressive, and the stepwise *increase* in (negative) intrathoracic pressure with each frustrated inspiration suggests that chemoreceptor output does indeed increase as the apnoea progresses (see fig 3).

Hypoxia has been known to affect sodium excretion and urine output for many years, but the mechanism has not been elucidated (see chapter 10). Honig and colleagues have demonstrated an increase in sodium excretion when the carotid body is perfused with venous blood. The effect persisted when all visible renal nerves had been sectioned although denervation may not have been complete because the the renal vasculature was left intact. No consistent pattern of hormone release was observed, aldosterone levels were not suppressed until sometime after the effect had begun, and it was suggested that an as yet unidentified hormone might be responsible (Schmidt et al 1985 a&b). Bardsley has shown that stimulation of the carotid body in the rat with almitrine causes increased sodium and water excretion (Bardsley 1987), and a similar effect has been seen in humans (Ledderhos et al 1987). It may therefore be via repetitive chemoreceptor stimulation that OSA exerts its effect on renal function.

In summary OSA appears to have a major inhibitory effect on

proximal reabsorption of sodium leading to a diuresis and natriuresis. This effect can be promptly reversed by the application of CPAP. Whether or not GFR changes cannot be stated with certainty, but the present results suggest that this is unlikely. The renal mechanisms responsible for these effects are not known.

10: DISCUSSION

LUNG-KIDNEY INTERACTIONS

It is unclear who first coined the phrase cor pulmonale, but the symptom complex of oedema, raised jugular venous pressure, hepatic congestion, right ventricular enlargement and functional tricuspid incompetence occurring in association with severe pulmonary disease has been recognised for many years. Because the signs are identical to those occuring in right ventricular failure secondary to left-sided cardiac failure, it was inevitable that they should be attributed to "failure" of the right side of the heart (White 1947). However, it soon became apparent that the function ie output of the right side of the heart was normal or even raised in patients with cor pulmonale and that this term was therefore a misnomer (Richards 1945, Howarth et al 1947, Harvey et al 1951, Wade and Bishop 1962). Attention therefore focussed on the kidney and the possibility that cor pulmonale represented an inability to handle salt and water appropriately. There have been a large number of published studies on the various perturbations of renal function that occur in chronic lung disease. They can broadly be divided up into those in which various physiological parameters of renal function have been measured, and those in which the plasma levels of the various hormones that affect renal function have been estimated. This chapter reviews some of the available literature, and proposes a hypothesis to accomodate the results obtained from the studies on a very specific type of lung disease (OSA) described in chapters 6-8.

RENAL PHYSIOLOGY

Renal function and its various parameters can be measured in a

number of ways. Renal blood flow can be measured using any substance that is completely eliminated by the kidney, and the most widely used has been para-amino hippurate (PAH). Early workers coined the term effective renal plasma flow (ERPF) because not all the PAH is excreted and it was assumed that this implied that some of the renal blood flow went to non-functioning areas of the kidney although it is now known that PAH is not completely excreted by all parts of the renal cortex (Jones 1984). Glomerular filtration rate (GFR) can be measured using inulin, radiolabelled EDTA, or endogenous creatinine. The usual technique is to measure the clearance of the substance in question. The clearance in a given time of a substance which passes freely through the glomerulus and is neither reabsorbed nor excreted by the renal tubules will be equal to the amount of plasma filtered by the glomerulus in that time. Similarly the clearance of a substance that is filtered and reabsorbed only in the proximal tubule will provide a measure of the amount of filtrate leaving the tubule (see chapter 9). The kidney contains a complex autoregulatory mechanism that maintains both RBF and GFR remarkably constant under normal circumstances despite variations in arterial pressure, and in addition the GFR can be defended within tight limits when renal blood flow changes (Pitts 1972).

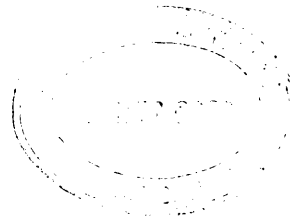
Caldwell and colleagues measured PAH and inulin clearances in 2 healthy male subjects under conditions of normoxia and hypoxia induced by breathing a low oxygen (9-12%)/nitrogen mixture. The study was essentially negative, although one of the subjects did show a reduction in both clearance values which they attributed to renal vasoconstriction of psychic origin (Caldwell et al 1949). Similar results were obtained in a larger study of seven healthy subjects and

two with emphysema, although they did observe a pronounced natriuresis, leading the authors to speculate that hypoxia was unimportant in the genesis of cor pulmonale (Berger et al 1949).

Fishman and colleagues made similar measurements in patients with, and patients who had recovered from cor pulmonale. They concluded that both renal blood flow (RBF) and glomerular filtration rate (GFR) were reduced in patients with cor pulmonale when compared to those without, and that this difference was still apparent when those with cor pulmonale had recovered. They also concluded that neither RPF or GFR was influenced by the changing levels of arterial oxygenation in individual patients, they did however, notice a striking increase in urinary sodium excretion when the arterial PO_2 was lowered and this occurred in both groups of patients. On the basis that cardiac failure was usually associated with sodium retention, they concluded that hypoxia was not an important factor in the development of the clinical syndrome of cor pulmonale (Fishman et al 1951). In 55 patients with cor pulmonale inulin and PAH clearances were lower than in a group without cor pulmonale. However in contrast to the results published by Fishman and colleagues, recovery in these patients was associated with a return of the clearance levels to similar values to those seen in the control subjects (Stuart-Harris et al 1956, Platts et al 1959). Aber and colleagues measured PAH and inulin clearances in two groups of patients with chronic airways disease. One group contained patients without, and the other with, cor pulmonale. The patients had all been on a fixed sodium intake for three days prior to the study. They confirmed the earlier observations of a highly significant reduction in RPF and GFR in the patients with cor pulmonale. Whilst renal blood flow and cardiac output were

positively correlated, the two groups had similar cardiac indexes (cardiac output/surface area) implying that the group with cor pulmonale were smaller, analysis of the individual surface areas confirms this, and this may account for some of the differences in renal clearances observed. Patients with cor pulmonale exhibited a diminished excretion of sodium, despite similar intakes over the previous three days, and the authors surmised that this may have been due to an effect on tubular absorption of sodium as the reductions in GFR were not thought to be adequate to account for the sodium retention that was observed (Aber et al 1963). The same workers were able to demonstrate a fall in RPF and GFR in excess of that which could be accounted for by a fall in cardiac output when breathing high concentrations of oxygen. As had Fishman and colleagues, they speculated that hypoxia was not the important cause of the renal perturbations seen in cor pulmonale (Aber et al 1964). In a study in which serial measurements of blood gases, RPF and GFR were made in a group of patients with CAWO and cor pulmonale Aber and Bishop (1965) were able to show a rise in RPF during recovery although the GFR did not exhibit a consistent parallel rise. The rise in RPF was not temporally related to the disappearance of oedema, or changes in blood gas tensions, and all subjects excreted a substantial amount of sodium during their recovery.

In healthy subjects, exposure to hypoxic gas mixtures resulted in an increased excretion of water, sodium, potassium, bicarbonate and chloride. In order to prevent the development of a respiratory alkalosis, carbon dioxide was added to the gas mixture in subsequent experiments and this appeared to abolish the increase in solute, but not water excretion caused by hypoxia. No measurements of the levels



of arterial blood gases were made and it is not possible to know if similarly low levels of arterial PO_2 were achieved in the two experiments (Ullman 1961). The question however was important as it had been reported that hyperventilation increased the rate of urine production and sodium excretion in normal subjects (McCance and Widdowson 1936). Hyperventilation is the usual result of measures designed to disturb arterial blood gas tensions, and it is therefore possible that it is the hyperventialtion per se that is responsible for the renal effects of induced hypoxaemia reported in the studies described above. A subsequent study demonstrated that the respiratory alkalosis resulting from the hyperventilation rather than hyperventilation per se was responsible for the natriuresis and diuresis (Gordon and Robbins 1981).

Kilburn and Dowell (1971) found that in patients with CAWO who were already hypoxaemic (mean pO_2 54 mmHg) further hypoxia (pO_2 30 mmHg) induced by breathing a low oxygen mixture was associated with a fall in urine volume, RPF, GFR and sodium excretion. Hyperoxia (pO_2 162 mmHg) was associated with similar changes in renal function, and hypercapnia had similar effects. However from their analyses of subjects exposed to two or more levels of oxygenation, they were able to conclude that hypoxia, down to an arterial pO_2 of approximately 40 mmHg was associated with an increase in urine production and sodium excretion, whereas levels below this resulted in a progressive reduction in both. A similar threshold effect was observed when the pCO_2 was elevated progressively in that elevations of the pCO_2 to levels below 65mmHg were not associated with any demonstrable effect on renal function, whereas above this level, urine production, sodium excretion and RPF all fell, although GFR was by and large maintained.

In a comparison of non-oedematous patients with CAWO and normal subjects, patients with CAWO were shown to have an impaired ability to excrete a water load. All CAWO patients had blood gas derangements of varying degrees of severity, and there was a significant difference in GFR and sodium excretion rate, confirming the earlier studies. There was a suggestion that the impairment of water excretion was correlated with the arterial PCO_2 (White and Woodings 1971).

Chronic lung disease is usually associated with arterial hypoxia and sometimes with additional hypercapnia. Either or both could therefore be responsible for the decrease in RBF, GFR sodium and water excretion seen in such patients. Campbell and Short suggested that hypercapnia was the important determinant of fluid retention. They hypothesised that the necesity to excrete hydrogen ions led to retention of sodium and fluid, with the consequent pulmonary oedema further exacerbating the blood gas derangements (Campbell and Short 1960). Respiratory acidosis is the usual accompaniment of hypercapnia and it not would be surprising if this had the opposite effect on renal function to a respiratory alkalosis (ie caused fluid and sodium retention, see above). However, early experiments (Davies et al 1920, Barbour et al 1953) suggested that when CO_2 was added to the inspirate a diuresis occured. Subsequent experiments in anaesthetised dogs suggested that very high levels of CO_2 were associated with a reduction in renal plasma flow, and that this effect could be reversed by sympathetic blockade (Stone et al 1958). Increasing CO_2 tension increases tubular reabsorption of bicarbonate, and this will tend to lessen the excretion of sodium, as pointed out by Campbell, and alterations in P_aCO_2 and pH have been shown to have large effects on RPF (Bersentes and Simmons 1967). Powerful indirect

evidence for the role of hypercapnia in the genesis of fluid retention comes from the ancient observation that patients with pure hypoxia, do not get oedema (Campbell and Short 1960). At levels of arterial CO_2 seen in CAWO, it is difficult to refute the fact that the hypercapnia is more important than hypoxia (White and Woodings 1971, Daggett 1977).

RENAL HORMONES

Several workers have suggested that hypoxia might be associated with inhibition of ADH secretion (Ullman 1961, White and Woodings 1971). ADH levels were normal in two groups of CAWO patients with a comparable degree of hypoxaemia (pO_2 61&57 mmHg) one with hypercapnia (pCO_2 62 mmHg) and one without (pCO_2 39 mmHg). As in White and Woodings patients, the hypercapnic group were unable to excrete a water load normally, and this was associated with and possibly caused by an inability to excrete sodium. Whether this was a result of the observed diminution on RPF or to the increased reabsorption of bicarbonate is not known (Farber et al 1975). In a subsequent study, the same group (Farber et al 1977) confirmed that CAWO was not associated with abnormal production or metabolism of ADH, and found increased circulating levels of aldosterone and renin, in patients with hypercapnia, which in turn were not suppressed by the administration of a water load.

Campbell and colleagues measured total body weight, body water, exchangeable sodium and potassium in 17 patients with CAWO with hypercapnia at various times of illness and convalescence and found increases in total body water at the time of acute exacerbations of cor pulmonale, exchangeable sodium levels were high at the time of acute illness in 2 of 3 patients in whom these measurements were made.

They also observed that recovery was associated with a loss of weight which frequently returned during convalescence, without return of oedema, implying either that acute exacerbations of cor pulmonale are associated with loss of body tissue, or redistribution of body fluid. The treated and convalescent exchangeable sodiums were normal (Campbell et al 1975). This is in contrast to the situation in patients with oedema from primary cardiac disease in whom even when free of oedema, exchangeable Na has been shown to be raised. (Farber and Soberman 1956).

Anderson and colleagues studied the effects of isocapnic hypoxia on anaesthetised dogs. They observed that profound hypoxia (pO_2 32.7 mmHg) caused an anti-diuresis in the absence of any demonstrable effect on cardiac output, mean arterial pressure or GFR. The anti-diuresis persisted after renal denervation. They observed a substantial rise in plasma ADH levels and were able to show that the anti-diuretic effects of this profound hypoxia could be abolished by hypopysectomy. They then went on to show that ADH release could blocked by barorceptor, but not chemoreceptor denervaton. They also showed that the kidney responded similarly to exogenous ADH in hypoxia and normoxia (Anderson et al 1978), confirming earlier studies (Forsling and Ullman 1974). Evidence in humans for an effect of hypoxia on ADH has been conflicting. No rise in ADH was found in six of eight healthy male subjects acutely exposed to hypoxia, in two subjects there was a rise in ADH, but this was associated with a rise in the serum cortisol (Bayliss et al 1977). Heyes and colleagues found an anti-diuresis and an increase in ADH levels in four of eight healthy water-loaded subjects acutely exposed to hypobaric hypoxia. In the remaining four no such effect was observed and they concluded that

the ADH release was mediated by nausea and/or hypotension (Heyes et al 1982), an observation which was confirmed in a subsequent publication, in which plasma renin, angiotensin, and angiotensin converting enzyme, were shown not to change in healthy, waterloaded men exposed to acute hypoxic hypoxia (Ashack et al 1985). Similar observations were made in four men exposed acutely to a simulated altitude of 4760 m, although plasma aldosterone level was somewhat depressed (Sutton et al 1977).

Farber and colleagues showed that hypoxic, normocapnic patients with CAWO had normal GFR, ERPF, ADH and were able to excrete a water and load normally. In contrast, these were impaired in those with hypercapnia, but a similar degree of hypoxia. This effect appeared not to be mediated by ADH which was similar in both groups and appropriately suppressed by water loading (Farber et al 1975). These findings were confirmed in a subsequent study which included measurements of renin and aldosterone (Farber et al 1977). They proposed the following sequence. Hypoxic normocapniic patients with CAWO have normal endocrine function. Hypercapnia causes renal retention of Na (to balance the necessary excretion of H+). RPF falls, FF rises, raising the peritubular oncotic pressure and further increasing the reabsorption of Na. The renin angiotensin is stimulated, and in parallel ADH is as well, hence sodium and water retention (Farber 1982).

Angiotensin converting enzyme inhibition with captopril has been shown to improve the ability of hypercapnic CAWO patients to excrete a sodium load. Although aldosterone levels fell, this fall was no greater than that observed after sodium loading following placebo. An impaired ADH response to the increase in osmolarity provoked by sodium loading was also seen, and it was concluded that captopril was

exerting its diuretic effect via an effect on RPF rather than aldosterone, and that angiotensin 2 is implicated in ADH secretion (Farber et al 1987).

In summary the renal effects of acute and chronic perturbations in blood gases have been extensively studied in healthy subjects, patients with lung disease and animals. In healthy subjects, no clear consensus exists as to the effects of hypoxia and hypercapnia on the simpler aspects of renal function such as sodium and water handling. Some have found hypoxia to be associated with a diuresis and natriuresis (Ullman 1961) others have found the opposite effect (Granberg 1962). It is fairly well established that the oedema and salt retention of CAWO is associated with a reduced GFR and RBF, and increased activity of the renin angiotensin system, which may or may not be the cause of the sodium and water retention. Whether the hypercapnia or hypoxia is the initiating factor is also not known, but if one single factor is responsible, available evidence points to the hypercapnia.

OBSTRUCTIVE SLEEP APNOEA

The model of obstructive sleep apnoea provides a unique opportunity to examine the effects of acute blood gas derangements on renal function. Subjects with the condition usually have normal lung function and daytime blood gases. At night they are subjected to repetetive and often severe derangements of blood gas levels. The P_aO_2 falls and this is of course an analogous situation to the ascent to altitude, or studies in which normal subjects are rendered hypoxic by breathing a low F_iO_2. In contrast to this situation, though, OSA patients experience an acute rise in P_aCO_2 during the apnoeas. In

contrast to the CAWO patients who have a chronic elevation of P_aCO_2, no renal adaptation to the chronic acidosis therefore occurs.

The experiments in chapter 6 have demonstrated that OSA is associated with marked alterations in renal function. The possible reasons for this effect have already been discussed. The experiments described in chapters 7 and 8 suggest that the pressure changes within the thorax are not reponsible and neither is excessive release of ANP. The experiments described in Chapter 9 suggest that OSA and its treatment in some way affects proximal tubular function.

Although not seen in early experiments in which the carotid body was stimulated directly in anaesthetised dogs (Michaelis and Gilmore 1969), evidence for an effect of carotid body stimulation on renal excretion of water and sodium has been accumulating steadily over the last few years. Animal studies, in which the carotid body is perfused with venous blood have shown a clear increase in sodium and water excretion, and this effect can be abolished by section of the carotid sinus nerve (Schmidt et al 1985a&b). Almitrine bismesylate is a specific peripheral chemoreceptor stimulant, and it has been shown to have very powerful stimulatory effects on ventilation (Stradling et al 1982). Administration of almitrine to rats (Bardlsey et al 1987) and humans (Ledderhos et al 1987) has also been shown to cause an increase in sodium excretion without change in GFR.

The mediators of these effects are not known. They were not abolished by renal nerve section in cats (Schmidt et al 1985), but the denervation may not have been complete. No major hormonal effects have been identified, although the aldosterone to renin ratio has been found to be suppressed some time after the natriuresis has started (Schmidt et al 1985b, Honig et al 1987b). ADH levels tended to be

suppressed by almitrine (Honig et al 1987a). The majority of renal hormones exert their major effects on distal tubular function. Whether or not proximal tubular function is altered by chemoreceptor stimulation is not known.

HYPOTHESIS

Obstructive sleep apnoea would be expected to be a powerful chemoreceptor stimulant since it causes simultaneous hypoxia and hypercapnia. Indirect evidence for this fact comes from the intraoesophageal pressure measurements shown in figure 3. With each frustrated inspiration the intraoesophageal pressure falls further, implying progressive stimulation of ventilatory drive. This repetitive and intense chemoreceptor stimulation may therefore provide the explanation for the overnight diuresis and natriuresis reported in chapter 6. Further studies will be necessary to clarify these effects and determine whether the effects of chemoreceptor stimulation on sodium and water excretion are neurally or humorally mediated.

Loss of chemoreceptor sensitivity may be responsible in part for the respiratory failure seen in patients with CAWO. In addition to the deleterious effects on ventilation, such loss of sensitivity may have important implications for the kidneys ability to handle salt and water. It is a common observation, for example, that oxygen therapy alone will frequently result in the disappearance of peripheral oedema, and this may be acting by restoring chemoreceptor function.

APPENDIX

The results from all the experiments described in this thesis are contained in the following pages

Pages 110-125: Individual oximeter tracings from the all the subjects in groups A and B are shown, together with the computed parameters of the overnight saturation record (chapter 2).

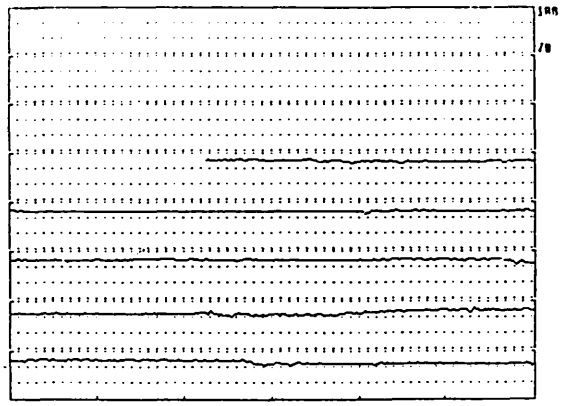
Pages 126-130: Individual results from urine, catecholamine and sodium excretion study (Chapter 6).

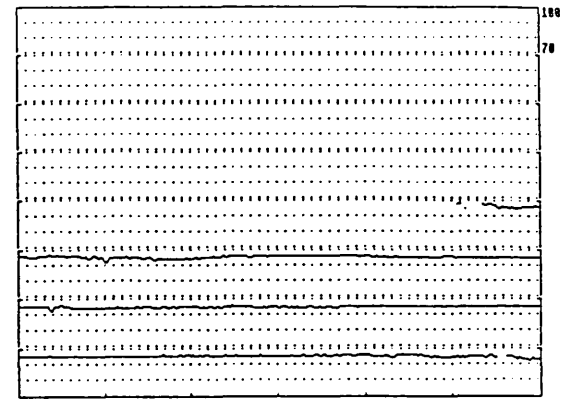
Page 131: ANP levels in OSA (Chapter 7).

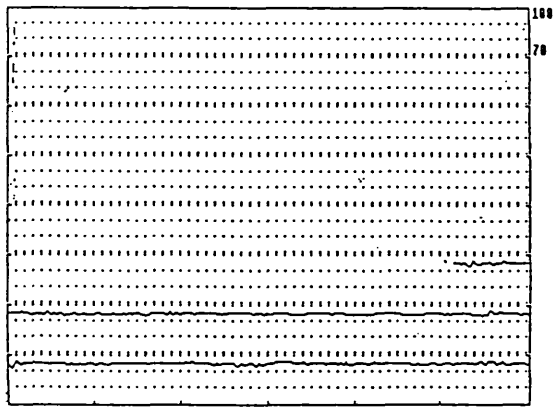
Pages 132-134: Urine and sodium output and ANP levels during resistive breathing (Chapter 8).

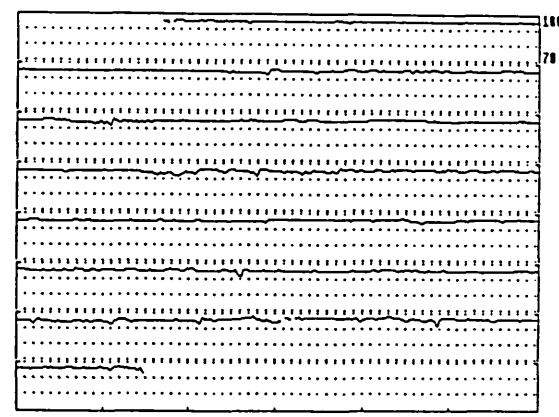
Pages 135-137: Individual results from inulin and lithium clearance studies in OSA (Chapter 9).

Appendix (Gp A (hypertensive) oximeter tracings (ch 2)

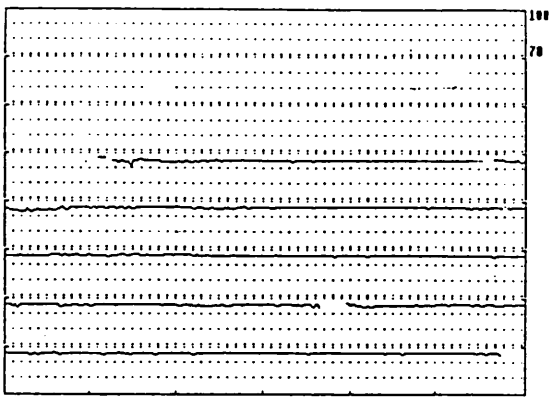


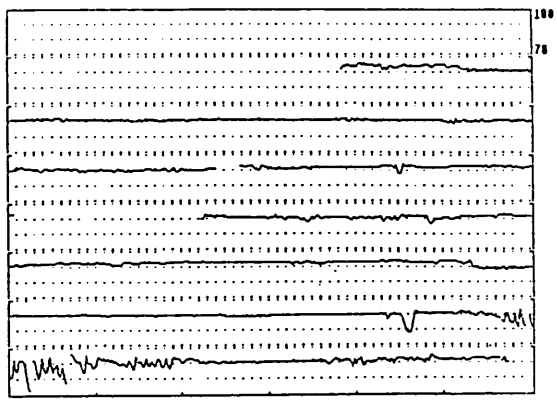


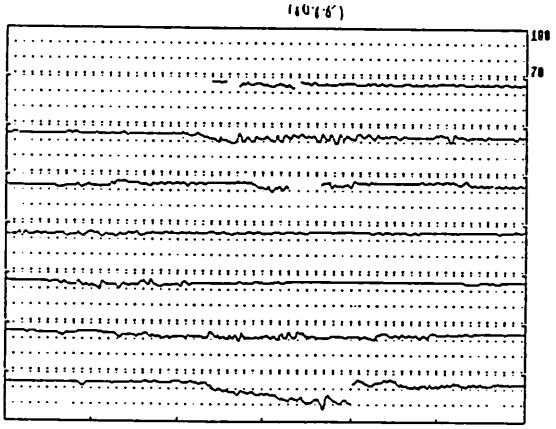


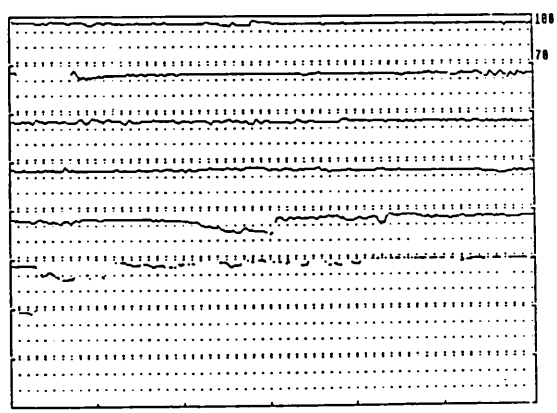


Appendix (Gp A (hypertensive) oximeter tracings (ch 2)

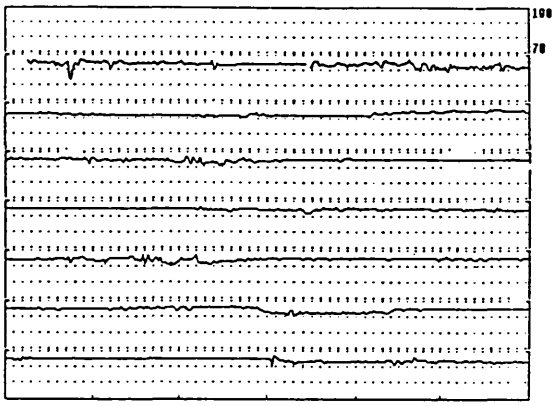


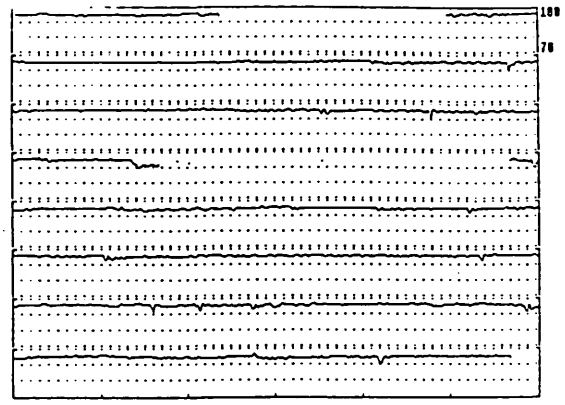


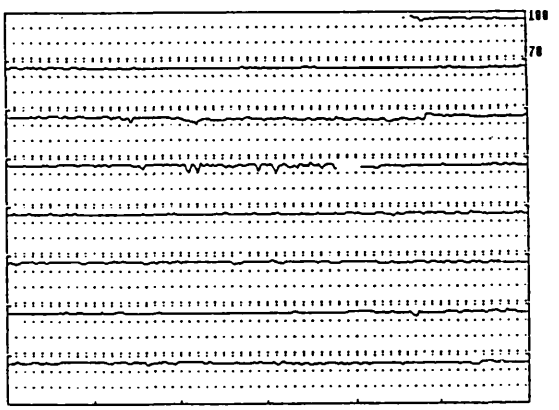


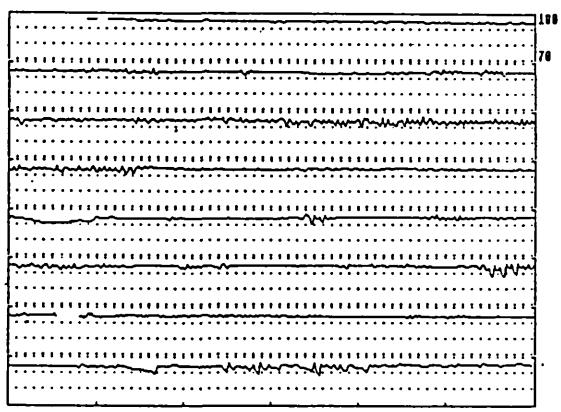


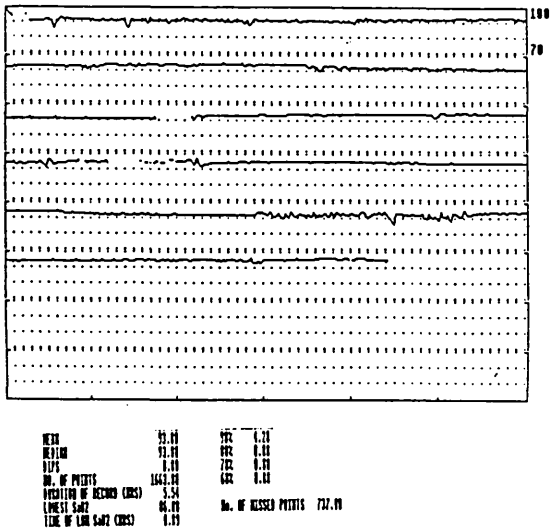
Appendix (Gp A (hypertensive) oximeter tracings (ch 2)







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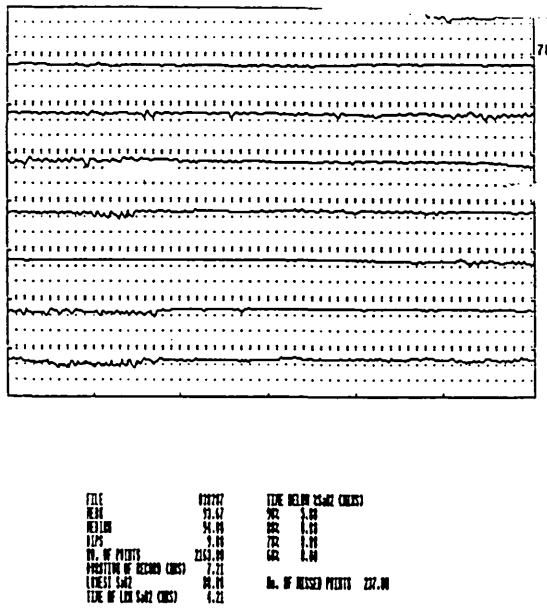
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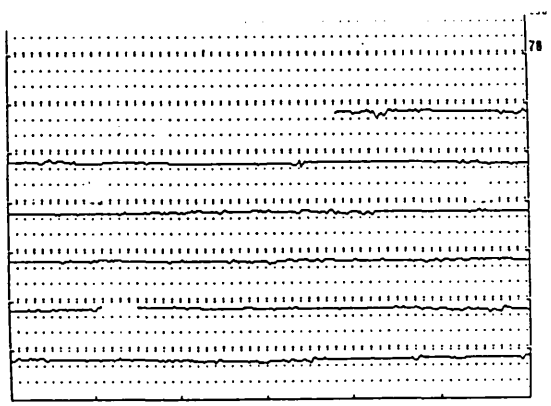
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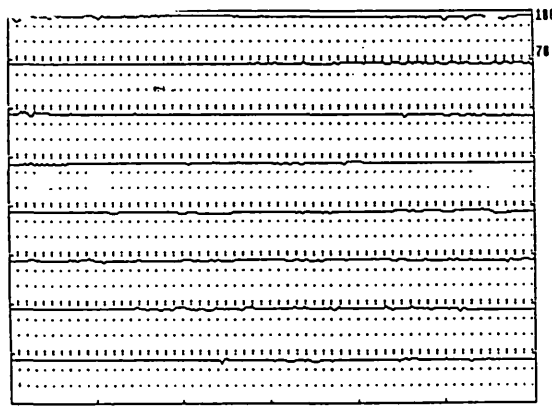
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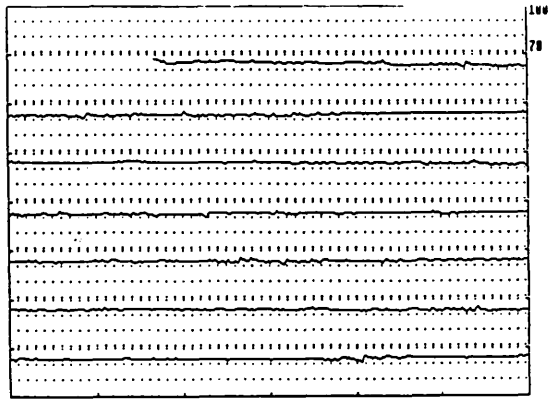
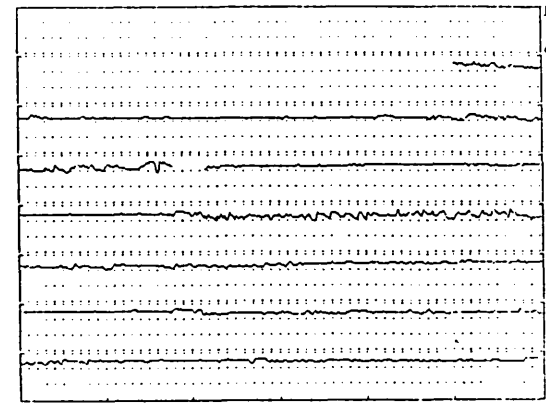
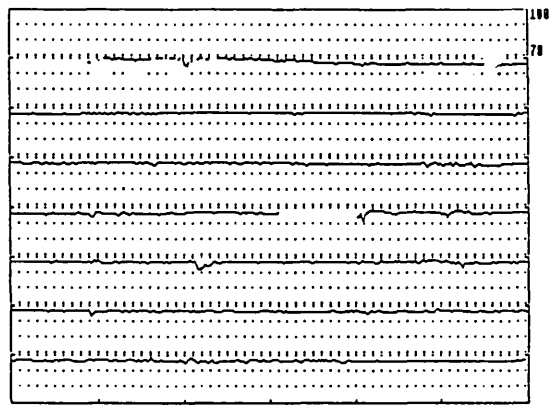
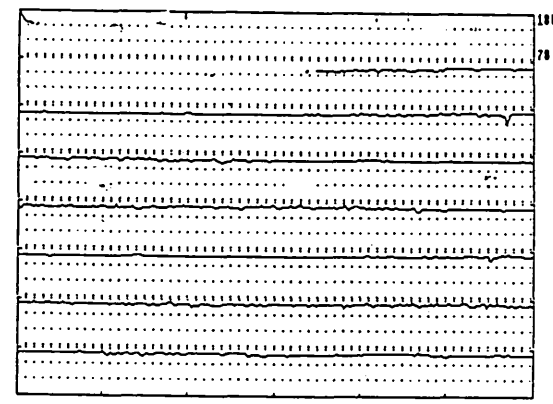
Appendix (Gp A (hypertensive) oximeter tracings (ch 2)









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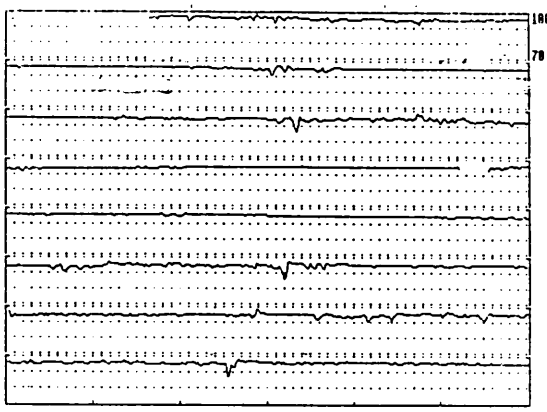

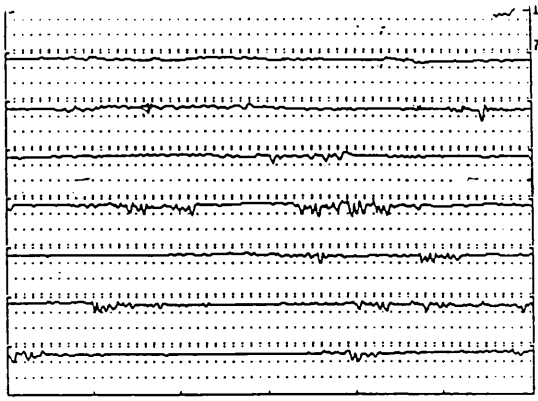

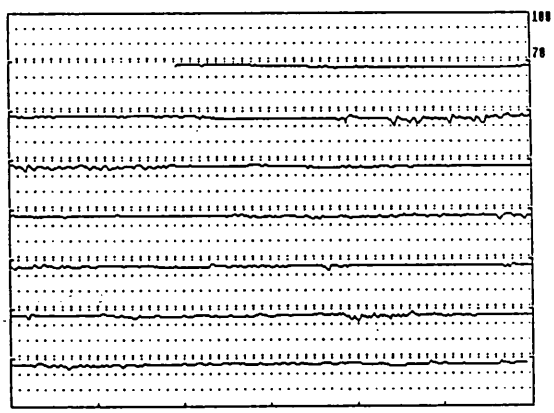

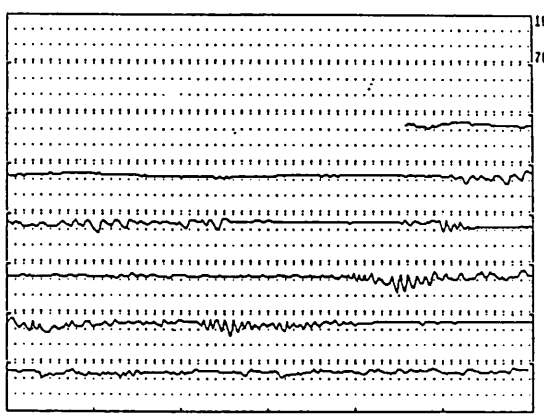

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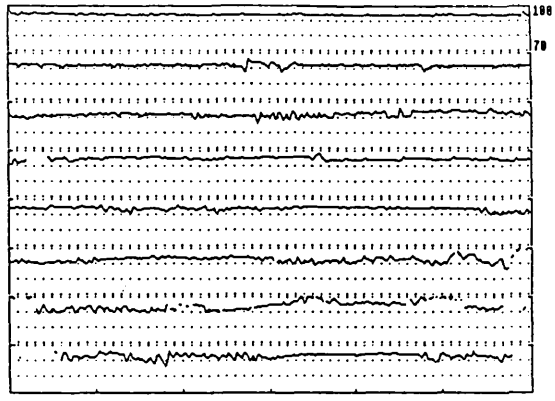

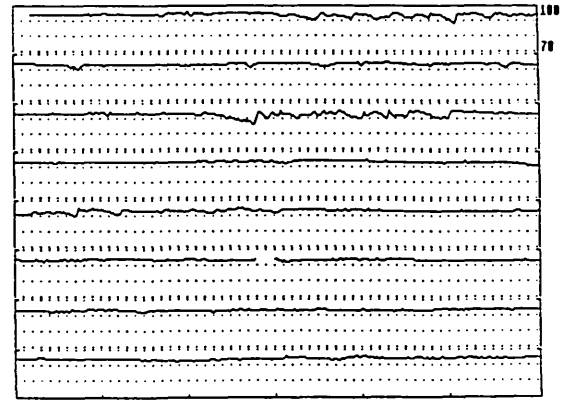

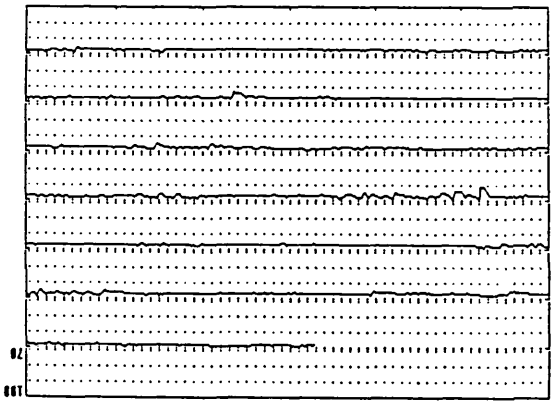

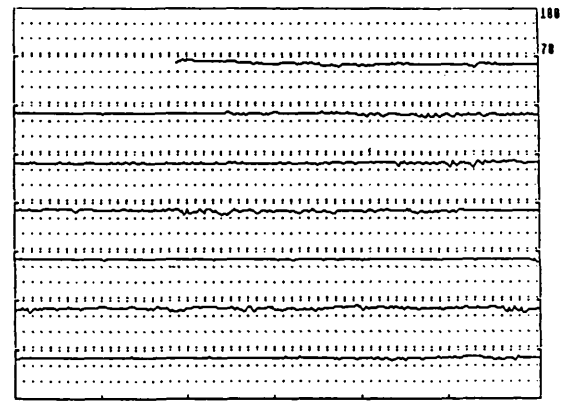

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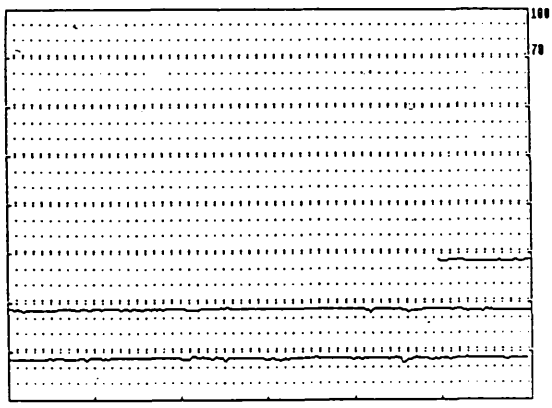

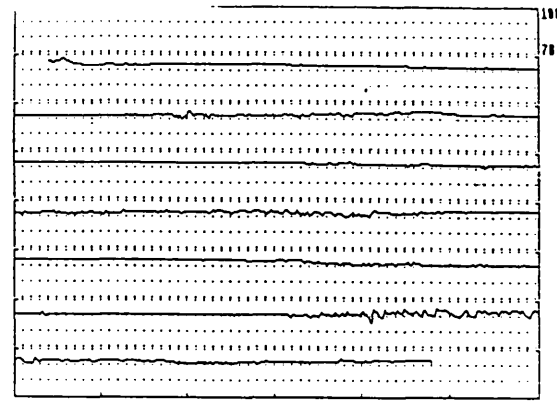

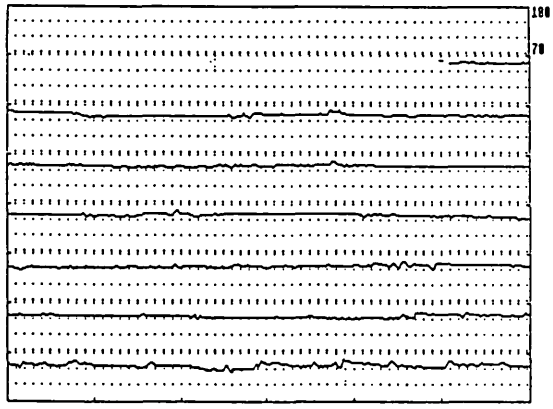

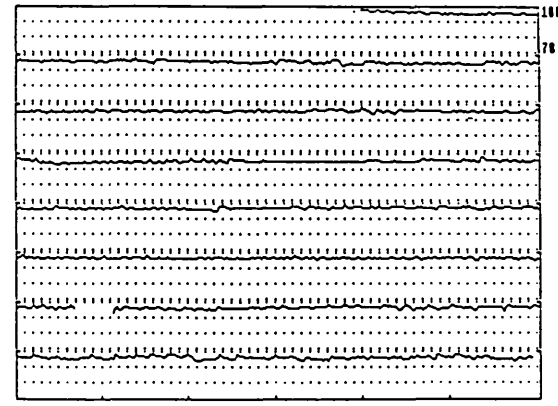

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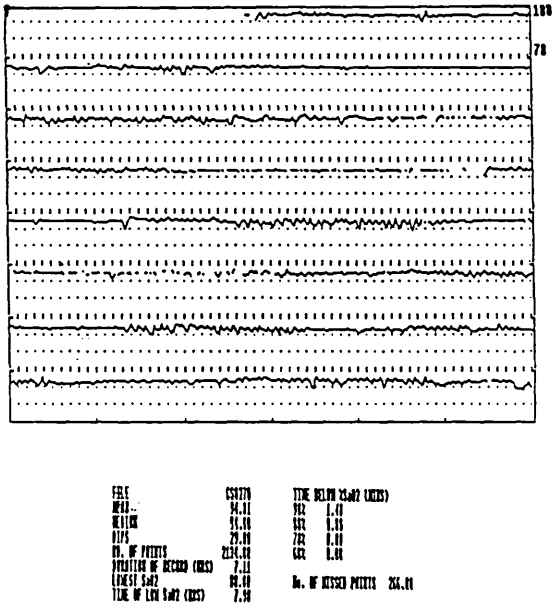

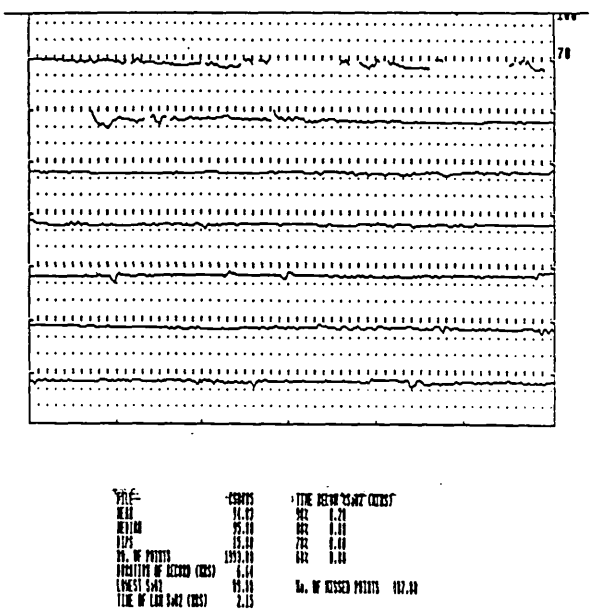

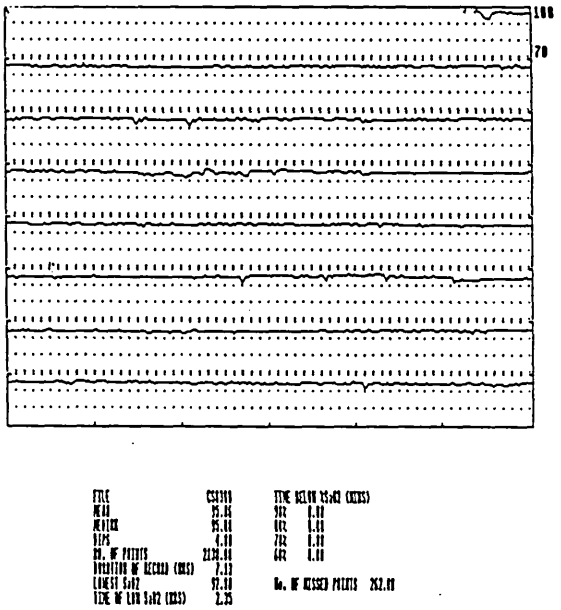

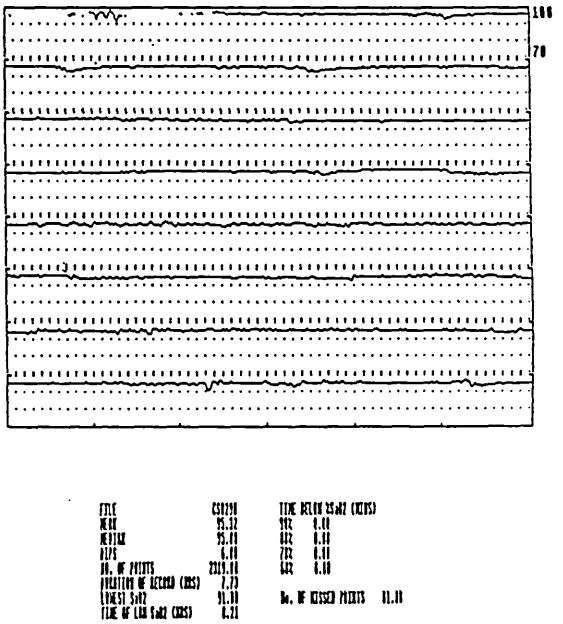

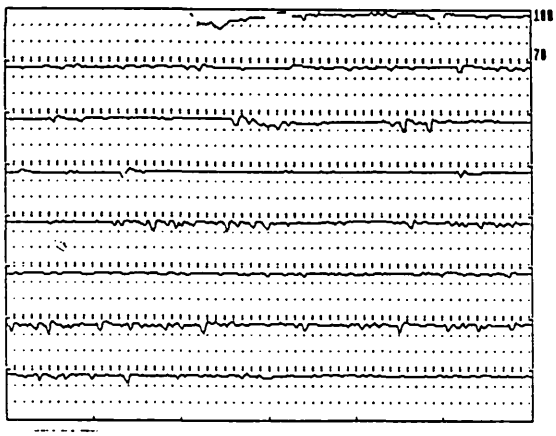
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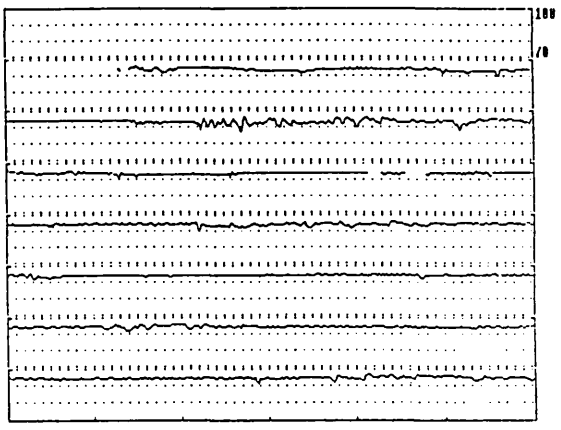
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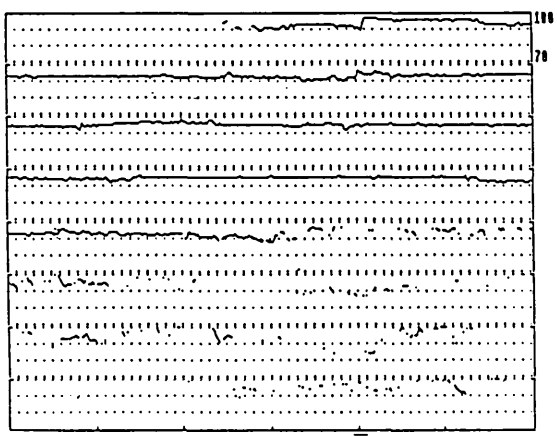
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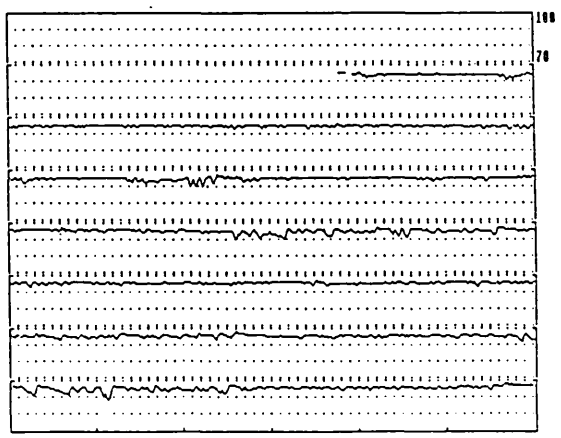
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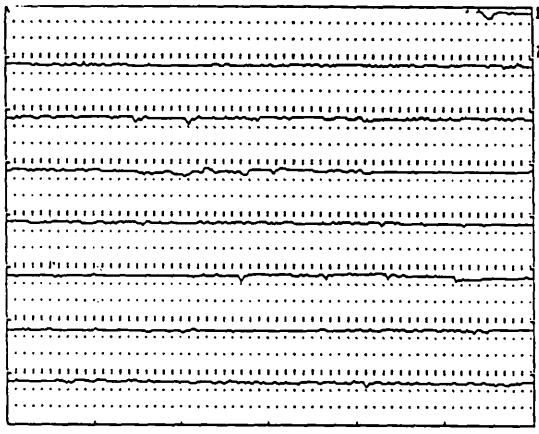

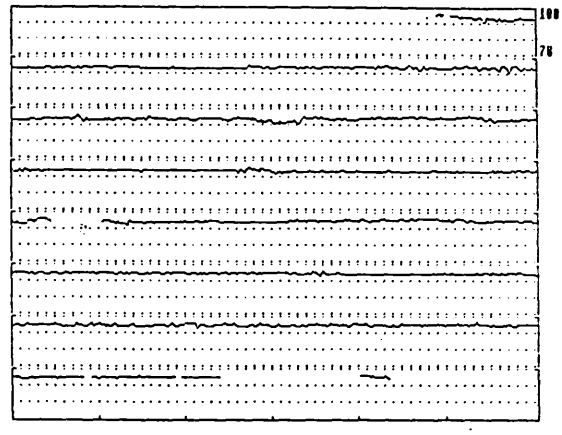

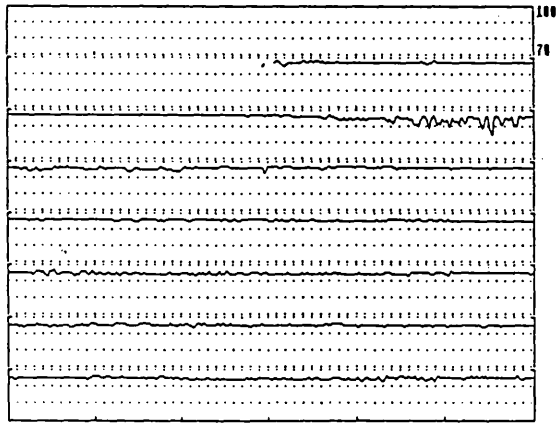

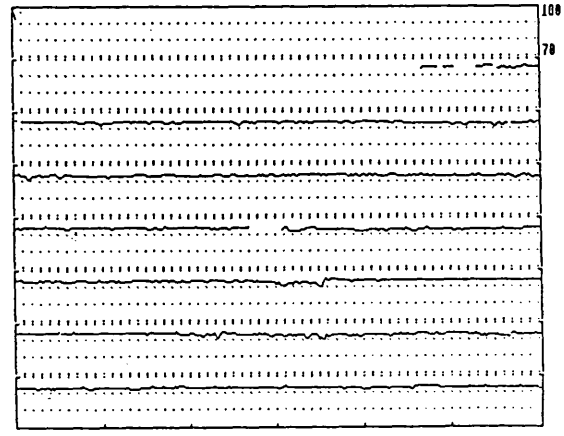

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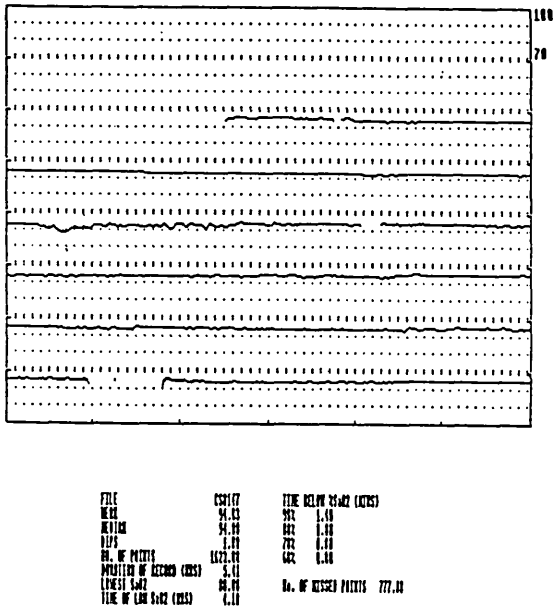

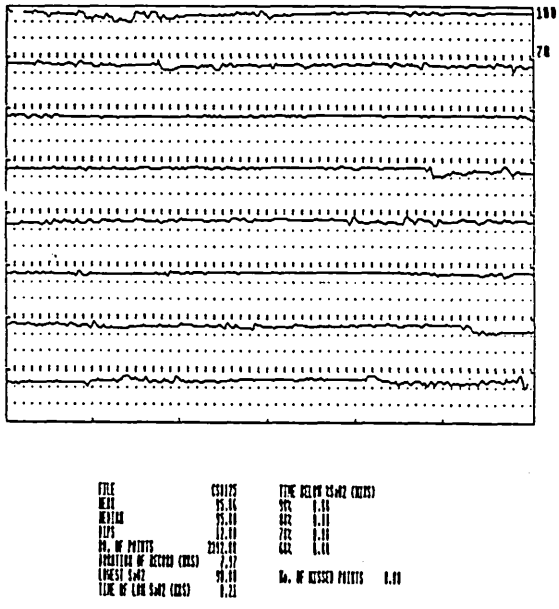

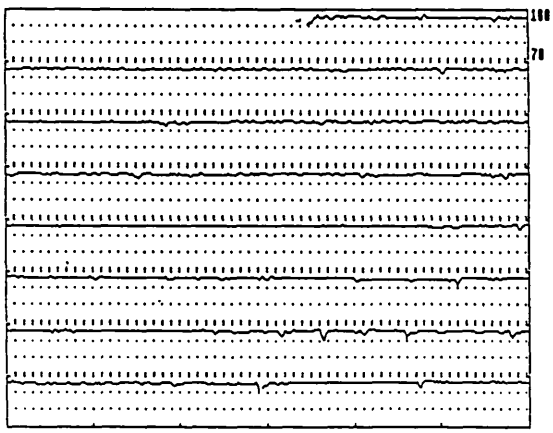

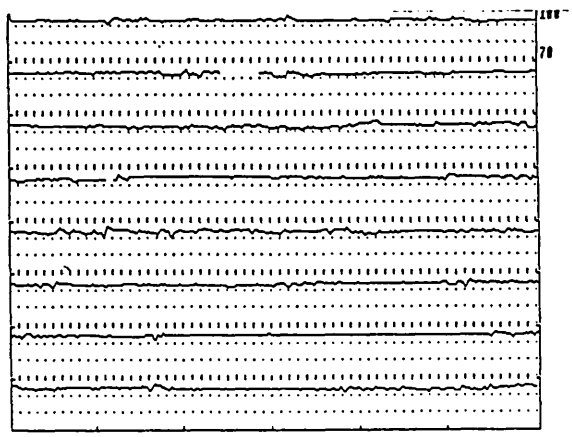

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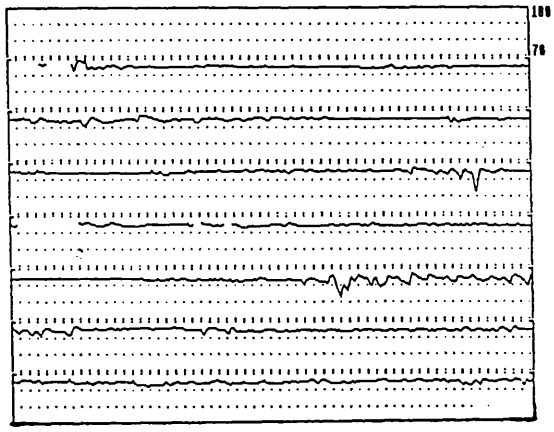
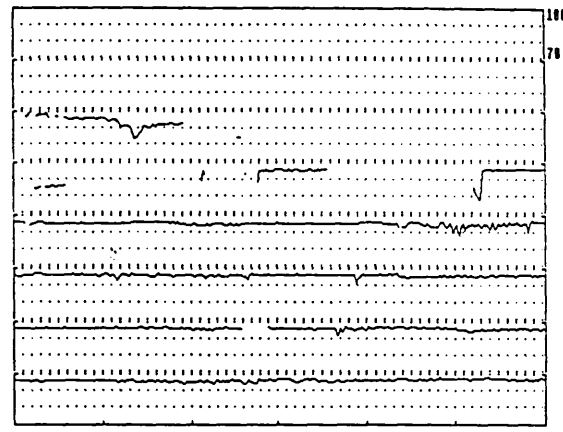
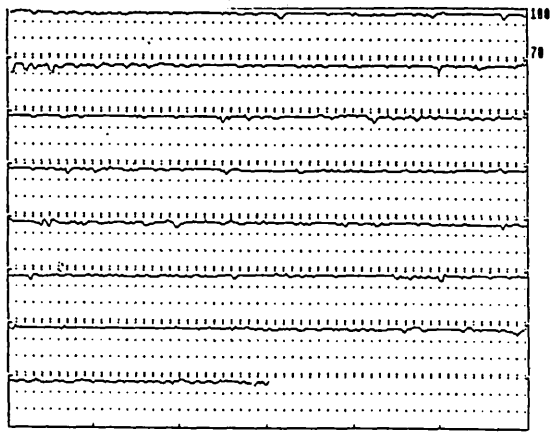
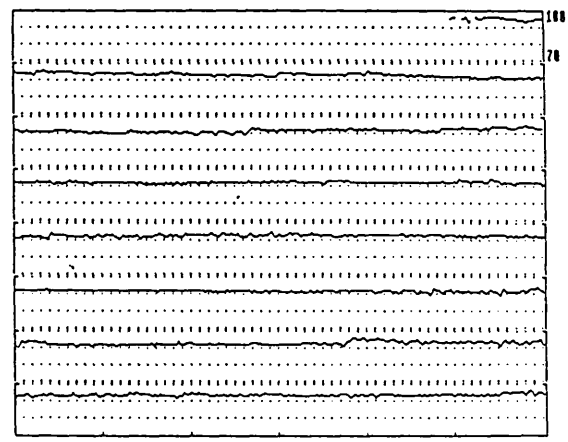
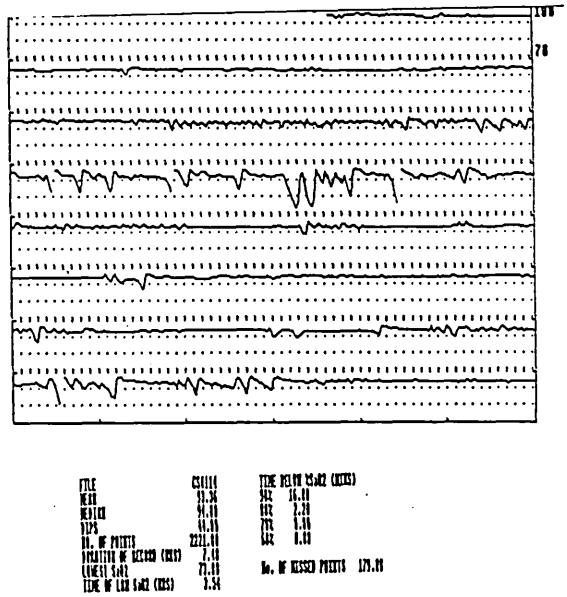
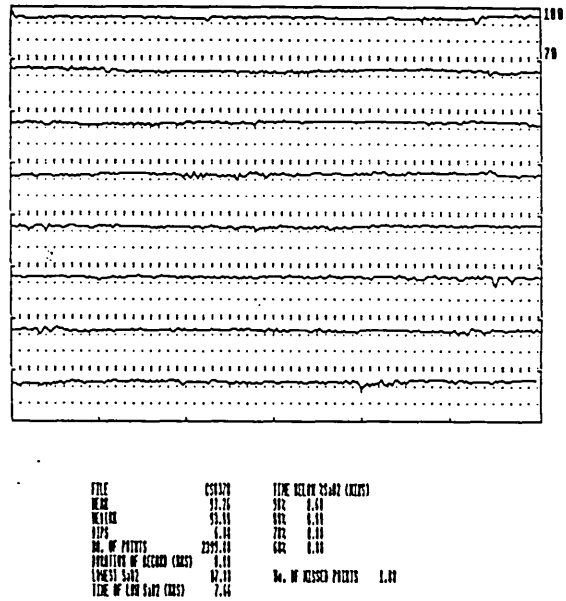


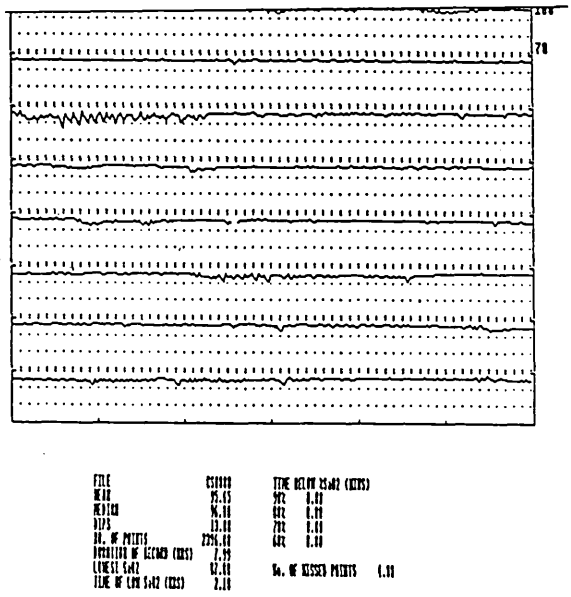


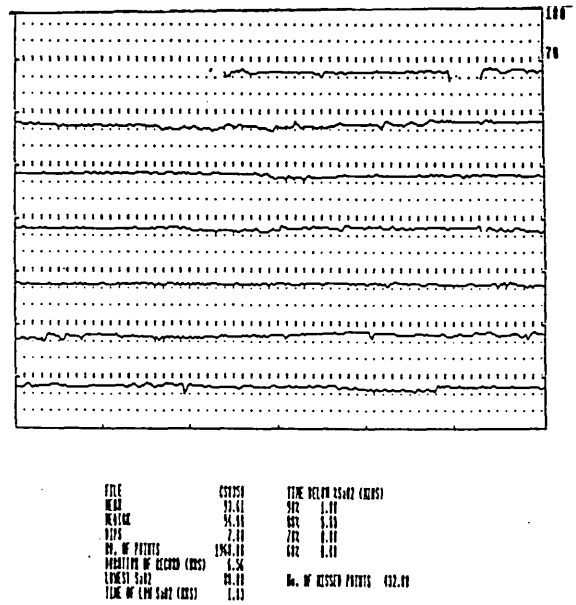




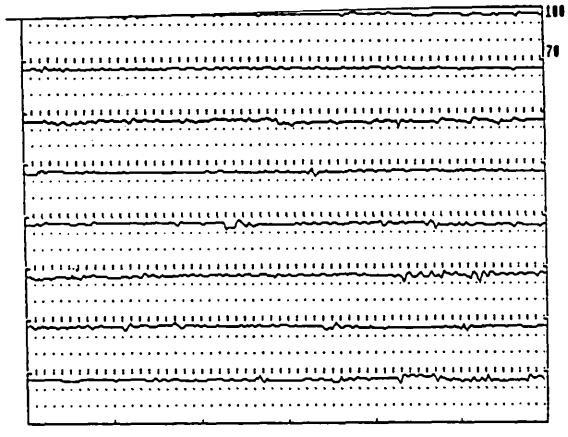


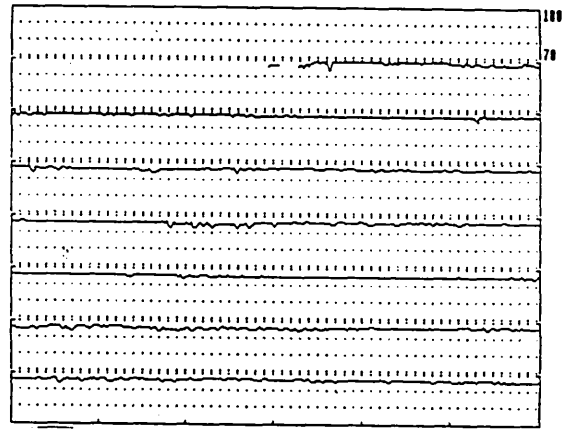


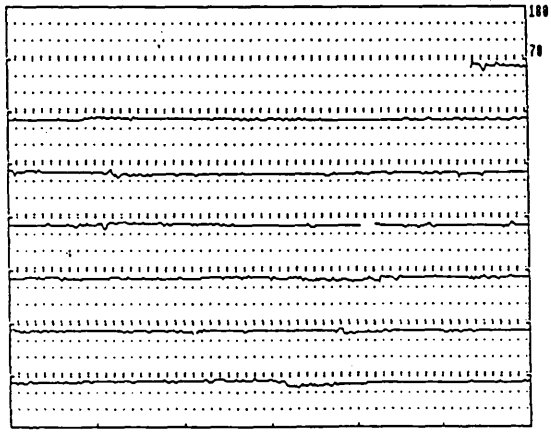


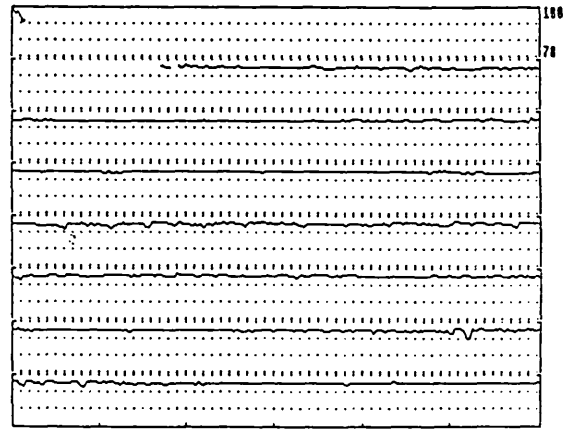


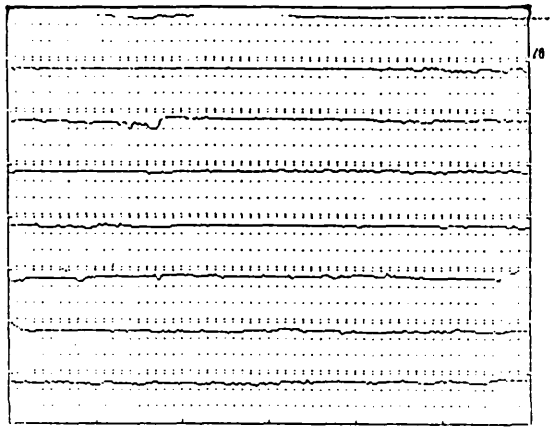
Gp B (control) oximeter tracings (Ch 2)

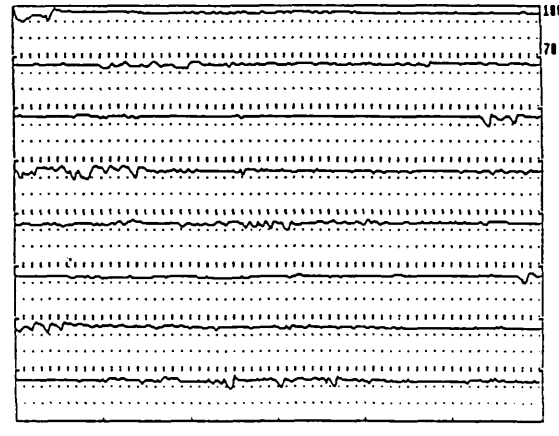


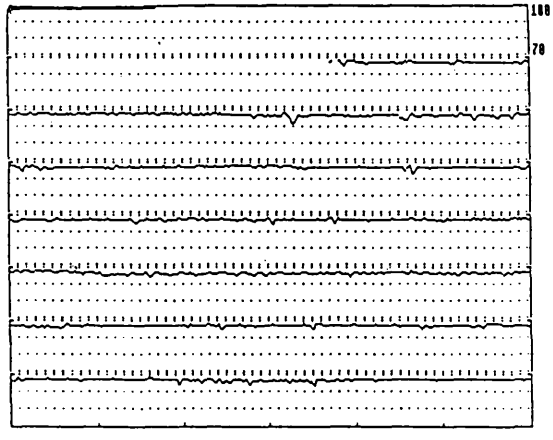


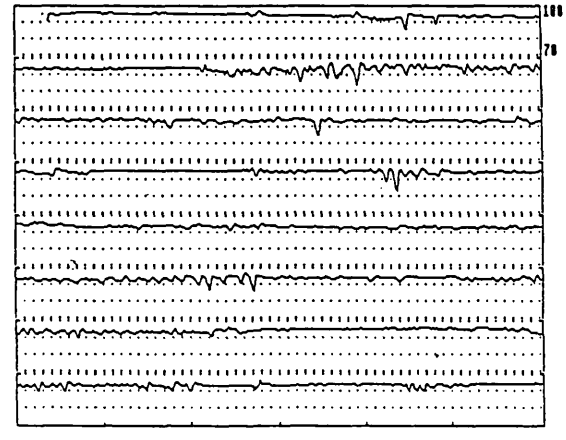












Appendix

The following tables contain individual results from each of the experiments described in chapters 6,7,8 and 9. Tables 1 and 2 give the results from chapter 6. The columns are labelled as follows. N or D for night or day, followed by the number (1-4), UR for urinary concentration, followed by NA (for sodium), K (for potassium), UR (for urea) or CR (for creatinine). Columns showing daily intakes of fluid, sodium and potassium are labelled D (for daytime, nothing being consumed during the night time collection periods) followed by the number (1-4), followed by FL (for fluid), NA (for sodium) and K (for potassium), followed by INT. In table 3 urinary production rates (URRAT), sodium excretion rates (NAEX), potassium excretion rates (KEX), creatinine excretion rates (CREX), and urea excretion rates (UREX) are shown.

Weights are in kg, all volumes in ml, Time in hours, Na, K, Urea and creatinine estimations in mmol l^{-1}.

Table 4 shows the individual catecholamine excretion rates. Columns are numbered in the same way. D1-D4, NOR: noradrenaline, ADR: adrenaline. Table 5 gives the results of the ANP estimations in the OSA patients.

Tables 6,7 and 8 give the data from the resistive breathing study (chapter 8).

Table 1: OSA urine and sodium results (Ch 6)

NAME	WT	N1 URVOL	N1 TIME	N1 URNA	N1 URK	N1 URECR	D1 FLINT	D1 NAINT	D1 KINT	D1 URVOL	D1 TIME	D1 URNA	D1 URK	D1 URECR	D1 URCR	N2 URVOL	N2 TIME	N2 URNA	N2 URK	N2 URECR	N2 URCR	D2 FLINT	D2 NAINT	D2 KINT	D2 URVOL	D2 TIME	D2 URNA	D2 URK	D2 URECR	D2 URCR
MS	112	850	12.0	87	34	25	960	118	79	860	15.5	81	43	25	8	320	7.8	135	41	30	11	600	79	53	600	14.3	80	56	29	10
SA	79	620	10.3	76	30	20	1100	57	52	700	14.5	31	43	22	10	500	9.0	57	15	18	8	1100	72	37	600	13.0	19	24	13	5
VK	120	550	12.3	180	49	29	1480	87	54	850	13.5	137	35	21	10	380	9.8	163	58	39	18	1720	87	54	670	15.0	129	60	41	17
WW	84	380	8.8	73	48	40	1040	190	56	860	14.3	57	30	23	7	600	9.5	102	39	35	9	1440	234	76	730	14.5	103	48	32	8
TK	81	860	6.5	77	22	19	6	1680	.	.	750	17.0	84	67	28	8	760	7.0	78	29	17	6	1200	.	.	800	17.0	101	62	29	12
RK	89	450	8.6	162	47	39	14	1200	130	56	720	15.3	131	82	36	11	780	9.6	201	56	25	8	1700	160	85	410	9.3	103	99	36	15
FR	92	1330	7.8	68	19	12	4	1960	92	45	1650	16.2	29	18	11	4	900	7.4	49	14	18	6	2100	92	45	1340	16.8	33	21	17	5
KN	99	910	8.0	.	.	.	.	1250	.	.	700	15.5	.	.	.	.	1600	8.5	.	.	.	.	1650	.	.	910	15.5	.	.	.	.
mean								1330	112	57												1440	121	58						
SD								346	45	12												463	64	18						

Table 2: OSA urine and sodium results (Ch 6)

NAME	WT	N3URVOL	N3TIME	N3URNA	N3URUREA	N3URCR	D3FLINT	D3NAINT	D3KIINT	D3URVOL	D3TIME	D3URNA	D3URUREA	D3URCR	N4URVOL	N4TIME	N4URNA	N4URUREA	N4URCR	D4FLINT	D4NAINT	D4KIINT	D4URVOL	D4TIME	D4URNA	D4URUREA	D4URCR
MS	112	340	10.5	53	56	50	17	600	79	53	600	15.5	45	47	38	12	220	7.0	35	56	50	17	240	.	.	70	4.0	38	69	49	19
SA	79	.	.	.	.	.	.	1200	57	52	800	15.0	29	29	17	7	340	8.0	25	18	21	8	1080	85	50	850	14.0	25	43	29	12
VK	120	260	9.0	59	63	40	22	2400	120	80	730	15.5	129	68	39	12	400	9.5	84	69	49	19	350	25	12	260	4.3	73	43	23	9
WW	84	260	7.8	76	32	39	12	1920	234	76	720	15.3	59	32	31	9	270	9.0	96	35	41	15	840	.	.	350	5.3	83	51	26	7
TK	81	680	9.6	68	21	15	6	1040	.	.	130	3.3	74	55	27	13	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
RK	89	720	14.3	162	44	43	13	1700	120	70	750	15.0	169	59	36	11	260	8.0	184	87	42	15	400	25	10	200	3.7	.	.	.	.
FR	92	450	9.9	26	26	21	8	1450	92	45	1390	14.8	46	37	21	7	500	8.8	69	31	28	9	.	20	15	200	3.0	47	24	17	5
KN	99	430	9.0	.	.	.	.	1600	.	.	1130	15.0	.	.	.	.	500	9.0	.	.	.	.	500	.	.	350	5.5	.	.	.	.
mean								1700	117	63													568	36	24						
SD								420	63	15													323	27	23						

Table 3: OSA urine and sodium results (Ch 6)

	N1 URINE	N2 URINE	N3 URINE	N4 URINE	D1 URINE	D2 URINE	D3 URINE	D4 URINE	N1 NEXT	N2 NEXT	N3 NEXT	N4 NEXT	D1 NEXT	D2 NEXT	D3 NEXT	D4 NEXT
MS	71	41	32	31	55	42	39	18	6.2	5.5	1.7	1.1	4.5	3.4	1.7	0.7
SA	60	56	.	43	48	46	53	61	4.6	3.2	.	1.1	1.5	0.9	1.5	1.5
VK	45	39	28	42	63	45	47	60	8.0	6.3	1.7	3.5	8.6	5.8	6.1	4.4
WW	43	63	33	30	60	50	47	66	3.2	6.4	2.5	2.9	3.4	5.2	5.2	2.8
TK	132	109	71	.	44	47	39	.	10.2	8.5	4.8	.	3.7	4.8	2.9	.
RK	52	81	50	33	47	44	50	54	8.5	16.3	8.2	6.0	6.2	4.5	8.5	.
FR	171	122	45	57	101	80	94	67	11.6	6.0	1.2	3.9	3.0	2.6	4.3	3.1
KN	114	188	48	56	45	59	75	.	.	.	.	.	.	.	.	.
mean	86	88	44	42	58	52	56	54	7.5	7.5	3.4	3.1	4.4	3.9	4.3	2.9
SD	47	51	15	11	19	12	19	18	2.9	4.2	2.7	1.9	2.3	1.7	2.5	1.2

	N1 KREX	N2 KREX	N3 KREX	N4 KREX	N1 CREX	N2 CREX	N3 CREX	N4 CREX	N1 UREX	N2 UREX	N3 UREX	N4 UREX
	2.4	1.7	1.8	1.8	0.57	0.45	0.55	0.53	1.8	1.2	1.6	1.6
	1.8	0.8	.	0.8	0.54	0.44	.	0.34	1.2	1.0	.	0.9
	2.2	2.2	1.8	2.9	0.58	0.70	0.63	0.80	1.3	1.5	1.2	2.1
	2.1	2.4	1.1	1.1	0.56	0.57	0.40	0.45	1.7	2.2	1.3	1.2
	2.9	3.1	1.5	.	0.79	0.65	0.43	.	2.5	1.8	1.1	.
	2.5	4.6	2.2	2.8	0.73	0.65	0.65	0.49	2.0	2.0	2.2	1.4
	3.2	1.7	1.1	1.8	0.68	0.73	0.36	0.51	2.0	2.2	1.0	1.6
mean	2.3	2.4	1.6	1.9	0.63	0.60	0.50	0.52	1.8	1.7	1.4	1.5
SD	0.5	1.2	0.4	0.9	0.10	0.12	0.12	0.15	0.4	0.5	0.2	0.2

The sodium excretion and urine production rates are shown graphically in figure 14. Missing values are shown by a dot. These occurred either as a result of specimen tubes being broken, or samples being lost or known to be incomplete. (Subjects were asked to record if they accidently failed to empty their bladders into the bottle, and if this were so the sample was not analysed). In the case of subject KN, the catecholamine preservative used was sodium metabisulphate, thereafter glutathione was used.

Table 4: OSA catecholamine results (Ch 6)

URINARY CATECHOLAMINE EXCRETION/mcg h^{-1}

	N	D	N	D	N	D	N	D
N	1	1	2	2	3	3	4	4
A	N	N	N	N	N	N	N	N
M	O	O	O	0	O	O	O	O
E	R	R	R	R	R	R	R	R
MS	3.05	3.33	3.17	3.80	3.49	4.20	2.69	2.02
KN	1.51	1.83	2.62	2.34	1.86	2.24	1.04	2.24
WW	1.76	2.72	1.93	3.03	2.30	2.60	1.79	2.95
TK	3.18	0.81	2.59	2.11	1.01	3.30	.	.
FR	.	2.80	3.90	2.90	2.30	2.55	3.20	2.65
mean	2.10	2.30	2.84	2.84	2.19	2.98	2.18	2.47
SD	1.20	0.99	0.74	0.60	0.90	0.79	0.96	0.42

Noradrenaline

	N	D	N	D	N	D	N	D
N	1	1	2	2	3	3	4	4
A	A	A	A	A	A	A	A	A
M	D	D	D	D	D	D	D	D
E	R	R	R	R	R	R	R	R
MS	0.15	0.31	0.95	1.50	0.43	1.20	0.98	0.49
KN	0.80	0.84	1.40	0.89	0.56	0.16	0.07	0.16
WW	0.20	0.33	0.47	0.43	0.33	0.47	0.59	0.73
TK	0.57	0.10	0.33	0.67	0.69	0.23	.	.
FR	.	1.20	1.50	0.86	0.93	1.36	1.20	1.10
mean	0.43	0.56	0.84	0.86	0.59	0.68	0.71	0.62
SD	0.31	0.45	0.56	0.46	0.23	0.59	0.50	0.40

Adrenaline

Individual catecholamine excretion rates over the four days and nights. Three samples were lost due to the specimen tubes breaking. Results shown graphically in figure 15.

	OSA			CPAP		
SUBJECT	0030	0730	1600	0030	0730	1600
MS	8.7	2.5	8.0	6.3	18.0	4.0
SA	3.4	7.0	6.7	8.8	3.0	4.2
VK	9.0	5.5	4.3	5.8	4.1	6.4
WW	6.7	6.2	2.5	6.7	5.6	3.8
TK	5.1	15.0	9.2	9.3	19.2	12.0
KN	14.2	16.7	13.7	11.2	15.5	12.3
MEAN	7.9	8.8	7.3	7.4	9.7	9.1
SD	3.8	5.7	4.1	1.6	5.3	5.1

Individual plasma ANP levels in six patients with severe OSA at different times of the day. The 0030 sample was taken after 90-120 mins sleep. The 0730 sample was taken immediately on arousal from sleep, and the 1600 sample during mid-afternoon.

Appendix Table 6 Urine excretion (Ch 8)

	Sample											
	1	2	3	4	5	6	7	8	9	10	11	12
Subject 1												
Control	57	540	828	780	804	772	962	926	790	864	990	884
Neg pres	*43*	*80*	*340*	*704*	*680*	*876*	*944*	*1024*	*796*	*818*	*852*	*814*
Subject 2												
Control	69	610	494	880	920	980	884	844	870	854	868	954
Neg pres	*73*	*494*	*726*	*948*	*990*	*840*	*830*	*672*	*724*	*768*	*916*	*944*
Subject 3												
Control	96	436	270	588	880	920	980	1040	900	1000	1010	900
Neg pres	*52*	*166*	*254*	*714*	*720*	*890*	*170*	*170*	*882*	*754*	*1014*	*570*
Subject 4												
Control	64	108	290	914	830	990	1016	1034	984	932	780	910
Neg pres	*57*	*90*	*282*	*820*	*770*	*944*	*1000*	*1070*	*970*	*930*	*860*	*840*
Subject 5												
Control	55	700	600	980	980	910	956	954	920	870	860	850
Neg pres	*59*	*610*	*580*	*884*	*862*	*854*	*700*	*780*	*800*	*900*	*840*	*840*
Subject 6												
Control	72	46	36	80	278	680	620	594	262	92	122	.
Neg pres	*87*	*148*	*70*	*90*	*174*	*190*	*196*	*368*	*144*	*260*	*92*	*90*
Mean	67	407	420	703	782	875	905	899	788	767	771	912
sd	15	247	255	305	233	113	133	151	242	307	301	26
Mean	*62*	*265*	*375*	*693*	*700*	*766*	*640*	*681*	*719*	*738*	*762*	*683*
sd	*14*	*208*	*217*	*283*	*256*	*260*	*337*	*326*	*264*	*223*	*305*	*288*

Individual values of urine excretion (ml hr^{-1}) during each 30 min sample period for all six subjects. Shown graphically in figure 18. Sample 1 is the previous 24 hr urinary production rate. Negative pressure applied during samples 6, 7 and 8.

Appendix Table 7 Sodium excretion (Ch 8)

	Sample											
	1	2	3	4	5	6	7	8	9	10	11	12
Subject 1												
Control	7.0	22.0	10.6	10.8	12.0	11.6	15.4	16.6	15.0	16.4	16.8	15.0
Neg pres	*5.6*	*7.1*	*6.5*	*4.9*	*7.5*	*9.6*	*13.2*	*11.3*	*6.4*	*6.5*	*7.7*	*9.8*
Subject 2												
Control	7.4	18.4	12.8	15.8	12.0	13.8	11.5	11.8	14.0	13.6	11.2	13.4
Neg pres	*7.3*	*21.8*	*18.8*	*17.0*	*13.8*	*11.0*	*10.0*	*8.0*	*9.4*	*11.6*	*13.8*	*15.0*
Subject 3												
Control	2.8	7.8	4.8	6.4	7.0	7.4	8.8	11.4	10.8	14.0	12.2	10.8
Neg pres	*3.8*	*3.4*	*2.8*	*5.0*	*5.0*	*9.8*	*6.1*	*6.1*	*8.8*	*11.4*	*15.2*	*10.2*
Subject 4												
Control	6.8	5.4	2.8	8.2	8.2	10.0	9.2	10.4	10.8	11.2	10.2	12.8
Neg pres	*4.3*	*5.8*	*6.2*	*6.6*	*9.2*	*11.4*	*13.0*	*15.0*	*14.6*	*16.0*	*16.4*	*16.0*
Subject 5												
Control	4.7	14.0	9.6	12.8	12.8	12.0	12.4	13.4	13.8	13.0	14.6	15.2
Neg pres	*5.0*	*22.6*	*11.8*	*11.5*	*9.5*	*9.4*	*7.0*	*8.6*	*8.8*	*11.7*	*10.1*	*10.9*
Subject 6												
Control	6.7	2.9	2.7	8.7	10.6	13.0	14.8	12.5	10.5	8.9	11.5	.
Neg pres	*8.0*	*8.8*	*4.2*	*6.6*	*8.6*	*7.6*	*7.2*	*7.4*	*11.4*	*11.0*	*10.0*	*9.2*
Mean	5.9	11.8	7.3	10.4	10.4	11.3	12.0	12.7	12.5	12.9	12.8	13.4
sd	0.7	6.9	4.0	3.1	2.1	2.1	2.5	2.0	1.8	2.3	2.3	1.6
Mean	*5.7*	*11.6*	*8.1*	*8.6*	*8.9*	*9.8*	*9.4*	*9.4*	*9.9*	*11.4*	*12.2*	*11.9*
sd	*0.7*	*7.7*	*5.1*	*4.4*	*2.6*	*1.2*	*2.9*	*3.0*	*2.6*	*2.8*	*3.2*	*2.6*

Sodium excretion rate (mmol hr^{-1}) in all six subjects. Sample 1 is the previous 24 hr rate. Negative pressure applied during samples 6,7 and 8.

Appendix Table 8: ANP results/resistive breathing (Ch 8)

Control day

Sample Subject	A	B	C	D	E	F	G	H
FF	7.8	11.3	12.1	9.4	10.9	8.1	8.1	7.3
YB	12.6	10.1	7.4	14.3	5.7	4.2	7.9	6.0
AW	12.8	16.8	18.8	13.7	17.3	17.6	12.0	10.7
JS	16.4	16.2	19.6	16.9	22.4	9.7	20.5	10.6
MW	5.1	7.1	4.1	5.2	-	3.2	3.9	3.6
MR	2.6	2.6	2.6	1.8	3.0	1.4	-	-
mean	9.6	10.7	10.8	10.5	11.9	7.4	10.5	7.6
SD	5.3	5.4	7.3	6.3	8.1	5.9	6.3	3.1

Study day

Sample Subject	A	B	C	D	E	F	G	H
FF	9.6	11.2	1.5	2.8	3.4	2.9	5.2	1.4
YB	5.1	7.9	8.9	7.4	9.6	6.6	6.6	6.3
AW	9.5	7.8	10.6	7.6	16.2	14.5	16.7	11.7
JS	17.8	18.0	12.7	26.0	16.0	16.6	14.7	6.3
MW	5.9	7.0	4.5	5.5	3.4	5.8	3.1	2.8
MC	1.9	1.9	2.3	5.4	4.1	6.5	-	-
mean	8.3	9.0	6.8	9.1	8.8	8.8	9.3	5.7
SD	5.5	5.3	4.6	8.5	6.1	5.4	6.1	4.0

Technical difficulties resulted in 5 samples being unobtainable and these are shown as blanks in the table. Samples D,E and F were drawn during the period of inspiratory resistance. These results are summarised in figure 19.

Appendix Individual C_{Li} and C_{in} results

Individual results of inulin and lithium levels in patients with OSA. The results are summarised in the table in chapter 9, and in graphical form in figures 20,21 and 22.

The units are as follows: Urine production (V): ml . Plasma and urinary concentrations of sodium, potassium and lithium ($[P_{Na}]$, $[U_{Li}]$ etc): mmol L^{-1}. Plasma and urinary concentrations of inulin ($[P_{in}]$): mg L^{-1}. Time: mins.

Subject 1 (RT)

OSA night:

blood sample 1: $[P_{Li}]$ = 0.30, $[P_{in}]$ = 291, $[P_{Na}]$ = 140, $[P_K]$ = 4.6

blood sample 2: $[P_{Li}]$ = 0.27, $[P_{in}]$ = 282, $[P_{Na}]$ = 140, $[P_K]$ = 4.3

Urine sample:
Time = 107; Vol = 274; $[U_{Li}]$ = 3.7; $[U_{in}]$ = 12,400; $[U_{Na}]$ = 111; $[U_K]$ = 15

CPAP night

blood sample 1: $[P_{Li}]$ = 0.30, $[P_{in}]$ = 302, $[P_{Na}]$ = 140, $[P_K]$ =4.2

blood sample 2: $[P_{Li}]$ = 0.30, $[P_{in}]$ = 280, $[P_{Na}]$ = 141, $[P_K]$ = 4.4

Urine sample:
Time = 110; Vol = 311; $[U_{Li}]$ = 2.9; $[U_{in}]$ = 11,600; $[U_{Na}]$ = 71; $[U_K]$ = 15

Subject 2 (FR)

OSA night:

blood sample 1: $[P_{Li}]$ = 0.19, $[P_{in}]$ = 247, $[P_{Na}]$ = 139, $[P_K]$ = 4.0

blood sample 2: $[P_{Li}]$ = 0.18, $[P_{in}]$ = 246, $[P_{Na}]$ = 139, $[P_K]$ = 3.9

Urine sample:
Time = 107; Vol = 289; $[U_{Li}]$ = 2.1; $[U_{in}]$ = 11,100; $[U_{Na}]$ = 87; $[U_K]$ = 19

CPAP night

blood sample 1: $[P_{Li}]$ = 0.24, $[P_{in}]$ = 258, $[P_{Na}]$ = 140, $[P_K]$ = 4.7

blood sample 2: $[P_{Li}]$ = 0.24, $[P_{in}]$ = 243, $[P_{Na}]$ = 140, $[P_K]$ = 4.2

Urine sample:
Time = 111; Vol = 103; $[U_{Li}]$ = 5.9; $[U_{in}]$ = 31,850; $[U_{Na}]$ = 124; $[U_K]$ = 60

Subject 3 (RK)

OSA night:

blood sample 1: $[P_{Li}] = 0.34$; $[P_{in}] = 191$; $[P_{Na}] = 138$; $[P_K] = 4.1$

blood sample 2: $[P_{Li}] = 0.32$; $[P_{in}] = 193$; $[P_{Na}] = 137$; $[P_K] = 3.8$

Urine sample:
Time = 121; Vol = 135; $[U_{Li}] = 5.74$; $[U_{in}] = 23,200$; $[U_{Na}] = 104$; $[U_K] = 34$

CPAP night

blood sample 1: $[P_{Li}] = 0.32$; $[P_{in}] = 225$; $[P_{Na}] = 138$; $[P_K] = 3.9$

blood sample 2: $[P_{Li}] = 0.30$; $[P_{in}] = 217$; $[P_{Na}] = 138$; $[P_K] = 4.4$

Urine sample:
Time = 125; Vol = 71.5; $[U_{Li}] = 6.68$; $[U_{in}] = 50,090$; $[U_{Na}] = 109$; $[U_K] = 69$

Subject 4 (WW)

OSA night:

blood sample 1: $[P_{Li}] = 0.31$; $[P_{in}] = 232$; $[P_{Na}] = 142$; $[P_K] = 4.4$

blood sample 2: $[P_{Li}] = 0.30$; $[P_{in}] = 243$; $[P_{Na}] = 140$; $[P_K] = 4.0$

Urine sample:
Time = 111; Vol = 333; $[U_{Li}] = 6.56$; $[U_{in}] = 8,530$; $[U_{Na}] = 62$; $[U_K] = 17$

CPAP night

blood sample 1: $[P_{Li}] = 0.30$; $[P_{in}] = 243$; $[P_{Na}] = 143$; $[P_K] = 3.9$

blood sample 2: $[P_{Li}] = 0.30$; $[P_{in}] = 239$; $[P_{Na}] = 143$; $[P_K] = 3.9$

Urine sample:
Time = 112; Vol = 49; $[U_{Li}] = 6.46$; $[U_{in}] = 30,100$; $[U_{Na}] = 104$; $[U_K] = 33.5$

Appendix Individual C_{Li} and C_{in} results

Subject 5 (KN)

OSA night:

blood sample 1: $[P_{Li}] = 0.23$, $[P_{in}] = 277$, $[P_{Na}] = 140$, $[P_K] = 4.5$

blood sample 2: $[P_{Li}] = 0.22$, $[P_{in}] = 269$, $[P_{Na}] = 139$, $[P_K] = 4.3$

Urine sample:
Time = 105; Vol = 280; $[U_{Li}] = 2.39$; $[U_{in}] = 11,600$; $[U_{Na}] = 90$; $[U_K] = 9.0$

CPAP night

blood sample 1: $[P_{Li}] = 0.31$, $[P_{in}] = 252$, $[P_{Na}] = 139$, $[P_K] = 4.2$

blood sample 2: $[P_{Li}] = 0.29$, $[P_{in}] = 252$, $[P_{Na}] = 140$, $[P_K] = 4.3$

Urine sample:
Time = 113; Vol = 118; $[U_{Li}] = 6.17$; $[U_{in}] = 26,960$; $[U_{Na}] = 117$; $[U_K] = 53$

Subject 6 (RG)

OSA night:

blood sample 1: $[P_{Li}] = 0.24$, $[P_{in}] = 240$, $[P_{Na}] = 141$, $[P_K] = 4.0$

blood sample 2: $[P_{Li}] = 0.22$, $[P_{in}] = 231$, $[P_{Na}] = 141$, $[P_K] = 4.7$

Urine sample:
Time = 100; Vol = 284; $[U_{Li}] = 4.36$; $[U_{in}] = 15,200$; $[U_{Na}] = 106$; $[U_K] = 8.9$

CPAP night

blood sample 1: $[P_{Li}] = 0.34$, $[P_{in}] = 274$, $[P_{Na}] = 142$, $[P_K] = 4.3$

blood sample 2: $[P_{Li}] = 0.32$, $[P_{in}] = 259$, $[P_{Na}] = 142$, $[P_K] = 4.3$

Urine sample:
Time = 129; Vol = 149; $[U_{Li}] = 8.39$; $[U_{in}] = 30,660$; $[U_{Na}] = 86$; $[U_K] = 17$

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Abnormal diurnal variation in salt and water excretion in patients with obstructive sleep apnoea

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SUMMARY

1. In healthy individuals, sleep is associated with a fall in urine and sodium output.

2. Seven male patients with obstructive sleep apnoea exhibited a paradoxical rise in both urine and sodium output during the hours of sleep.

3. Continuous positive airway pressure applied via the nose abolished both the apnoea and the nocturnal rise in urine and sodium output, thereby restoring the diurnal pattern towards normal.

Key words: obstructive sleep apnoea, sodium output, urine output.

Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea.

INTRODUCTION

Urine flow and sodium excretion are subject to a diurnal variation which results in a fall in both during the hours of sleep [1]. This allows uninterrupted sleep, and loss of this diurnal variation, resulting in nocturia, is a feature of cardiac failure and hepatic cirrhosis [2]. In contrast, assumption of the supine posture while awake causes a diuresis and a natriuresis [3, 4]. The mechanisms responsible for the inhibition of sodium and water excretion by sleep have not been fully elucidated.

The syndrome of obstructive sleep apnoea (OSA) is characterized by repetitive upper airway collapse and apnoea throughout the night. Each apnoea leads to arterial hypoxaemia, and arousal is necessary to break the apnoea and enable respiration to restart. Patients are seldom aware that arousals are occurring. Definition of the syndrome is necessarily arbitrary, but it is usually said to be present if the patient has more than five apnoeas per hour of sleep, an apnoea being defined as cessation of airflow for 10 s or more [5]. In its most severe form, when 300 or more apnoeas may occur during the course of a night, the syndrome causes profound sleep disruption, and sufferers usually never achieve stage 3–4 slow wave sleep or consolidated periods of rapid eye movement sleep. The syndrome is thought to have long-term haemodynamic consequences, chief among which is systemic hypertension [5].

We report seven patients with a severe form of the syndrome, but without systemic hypertension. Each exhibited reversal of the normal diurnal variation with an increase in urine and sodium output at night. This was promptly restored by successful abolition of the apnoeas with continuous positive airway pressure (CPAP) via the nose. Although nocturia is not commonly quoted as a symptom of OSA, six patients who had been established on CPAP before the study had all noticed marked reductions in nocturnal urinary production.

PATIENTS AND METHODS

Seven male patients (aged 39–62, mean 54, years) with severe (more than 300 apnoeas per night) OSA documented by full polysomnography were studied over 4 days in hospital. All were overweight (body mass index 26–48, mean 32.3, kg/m^2). With the exception of one patient with maturity onset diabetes controlled on glibenclamide, all were otherwise in good health and none had had peripheral oedema at any time. All were normotensive both at the time of the study and before CPAP had been instituted (blood pressure < 150/90 mmHg, mean of at least six readings). Six had been established on nasal CPAP previously. The one remaining was successfully established on treatment in hospital during the course of the study. Each was admitted to hospital in the evening and the bladder emptied before retiring. Thereafter all urine was collected and separated into day and night samples. Thus any urine passed during the night and the first specimen on rising constituted the night samples, and all urine passed during the day, including the last before retiring, the day samples. In order to simulate normal

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circumstances as far as possible, patients were allowed to retire and rise at their own preferred times, samples being timed so that rates of excretion could be calculated. An estimate of normal sodium intake was made for each subject at the beginning of each study and as far as possible this was held constant throughout the 4 days of study by provision of a constant amount of sodium in the diet. Although subjects were allowed a degree of dietary freedom, a dietary assessment was made at the end of each day to estimate sodium and potassium intake and ensure that there had not been any substantial deviation. Each subject recorded his own fluid intake.

During the first 2 nights, patients slept without CPAP, and arterial oxygenation was monitored continuously to confirm obstructive sleep apnoea. For the subsequent 2 nights CPAP was administered, and its efficacy confirmed by oximetry and the patients' own assessment of the quality of sleep. The means of each of the paired values of urine flow and sodium excretion during nights 1 and 2 were compared with the means of the values from days 1 and 2, and nights 3 and 4, using a *t*-test for paired data.

RESULTS

Fluid and sodium intake remained constant throughout the 4 days of study (Table 1). In all cases oximetry confirmed severe OSA during nights 1 and 2. In six cases CPAP was successful on night 3 and in one patient a leak prevented the total abolition of apnoea. In all cases apnoea was completely abolished on night 4, as evidenced by a normal oximetry trace and self-reported excellent sleep quality. Urine production and sodium excretion rates are shown in Fig. 1. Sodium excretion is only available for five subjects. Although there was considerable variation, all subjects exhibited the same pattern. Compared with nights 1 and 2, both sodium and urine output were significantly lower on days 1 and 2 ($P<0.05$), and nights 3 and 4 ($P<0.02$). Although both urine and sodium output were less on nights 3 and 4 than on days 3 and 4, the difference did not reach statistical significance.

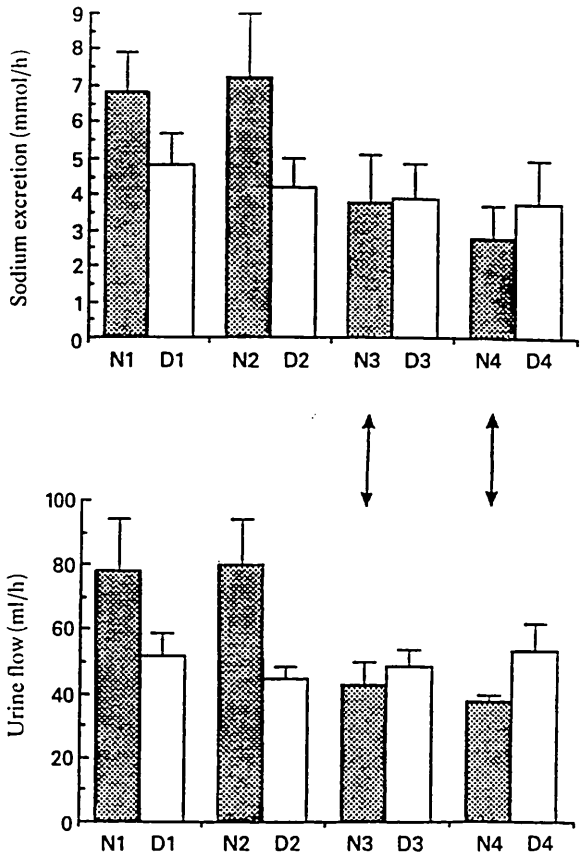

Fig. 1. Urine production ($n=7$) and sodium excretion ($n=5$) rates for all patients over 4 continuous days and nights of study. Shaded columns represent nights. Values are means and SEM. CPAP was administered on nights 3 and 4 (N3 and N4, arrowed). Compared with nights 1 and 2 (N1 and N2), values of both urine flow and sodium excretion are significantly lower on day 1 and day 2 (D1 and D2) ($P<0.05$), and on N3 and N4 ($P<0.02$). The daytime rates are not significantly different from each other. Values for N3 and N4 are less than those on day 3 and day 4 (D3 and D4), but the difference is not significant.

DISCUSSION

Stanbury & Thomson [1] observed as much as a fourfold fall in both urine production and electrolyte excretion during the hours of sleep in normal subjects. In contrast, the patients in this study exhibited a significant rise in nocturnal urine and sodium output when experiencing obstructive sleep apnoea. Although we did not observe such profound falls in relation to daytime levels during the nights on treatment, every patient conformed to the same pattern in that a highly abnormal situation, in which urine production and sodium excretion was high at night, tended to reverse toward normal on the treatment nights. It would be necessary to repeat the study with more rigidly controlled sodium and fluid intake to quantify the changes more accurately.

As well as profound sleep disruption, OSA has two other major pathophysiological characteristics: recurrent (and often severe) arterial hypoxaemia, and the repetitive generation of abnormally large negative intrathoracic pressure during attempted inspiration through an obstructed pharynx [6]. Hypoxaemia is a potent stimulus to chemoreceptor discharge and has been shown to promote sodium and water excretion in the cat [7]. This was

Table 1. Fluid and sodium intakes over the 4 days of study

Results are shown as means ± SEM.

	Day 1	Day 2	Day 3	Day 4
Fluid intake (ml)	1100 ± 21	1293 ± 18	1476 ± 27	1280 ± 38
Sodium intake (mmol)	117 ± 30	113 ± 31	116 ± 31	102 ± 33

seen in both intact and denervated kidneys, and appeared not to be mediated through suppression of aldosterone secretion alone [8]. Conversely, stimulation of renal sympathetic nerves causes renin release and inhibits sodium and water excretion [9]. A recent publication [10] has demonstrated high urinary levels of noradrenaline in OSA which returned towards normal after tracheostomy.

The persistent and repetitive generation of large negative intrathoracic pressures during OSA may cause sufficient cardiac distension to stimulate the release of atrial natriuretic peptide. A preliminary experiment in our laboratory suggests that breathing through an inspiratory resistance, generating pleural pressures of up to -40 cmH_2O (similar to values seen in severe obstructive apnoea [6]) causes a small rise in distending pressure across the wall of the superior vena cava and therefore presumably the right atrium.

Further studies are necessary to elucidate the mechanisms responsible for these results. It is of some interest that none of the patients studied had significant arterial hypertension. We do not know what long-term implications OSA and its treatment may have for sodium and water balance, and it remains to be determined whether our patients differ in some way from those in whom hypertension and obstructive sleep apnoea coexist.

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Evaluation of the Ohmeda 3700 pulse oximeter

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ABSTRACT Arterial oxygen saturation values (Sa_{O_2}) from 60% to 98% were measured by the Ohmeda 3700 pulse oximeter with the three types of probe available and compared with values of oxygen saturation estimated from direct arterial sampling (arterial oxygen and carbon dioxide tensions and pH) on 65 occasions. The response time of the oximeter was measured after a sudden rise in inspired oxygen concentration. Artefact rejection was assessed by arterial compression proximal to the probe site, and by simultaneous recordings of overnight Sa_{O_2} on opposite hands. The ability to recreate patterns of oscillating Sa_{O_2} from the data stored in the oximeter was also investigated. With the best probe system the oximeter measured Sa_{O_2}, relative to arterial values estimated from Pa_{O_2}, with a mean (SD) difference of −0·4% (1·8%). The response time was comparable with those of previous oximeters. It was not possible to generate artefactual dips in excess of 2% Sa_{O_2}, and the dual overnight recordings rarely showed even small dips on one tracing alone. The stored data can recreate oscillating Sa_{O_2} signals with wavelengths down to about 35 seconds, but not below. The Ohmeda 3700 pulse oximeter appears to be suitable for unattended overnight recordings of Sa_{O_2}.

The Ohmeda Biox 3700 pulse oximeter is a new continuous monitor of arterial oxygen saturation and pulse rate. Its easy portability, the availability of finger as well as ear probes, eight hours of internal memory, and apparently better ability to reject low quality signals should constitute important advantages over previous oximeters, particularly for unattended overnight recordings of arterial oxygen saturation (Sa_{O_2}).

We have tested aspects of the machine's performance with particular attention to inaccuracies that might occur during unattended overnight recordings. These include comparison of the oximeter Sa_{O_2} with values obtained from arterial sampling, speed of response, artefact rejection, and the ability of the stored data to recreate the original pattern of Sa_{O_2} oscillations.

Methods

STUDY 1: COMPARISON WITH DIRECT ARTERIAL SAMPLING

Sixty five simultaneous comparisons between direct arterial samples taken for Sa_{O_2} estimation and all three probes (finger, flex, and ear) connected to three oximeters were obtained. Two normal subjects breathed nitrogen at varying concentrations through a Venturi mask and eight hypoxic, non-smoking inpatients breathed various fractional inspired concentrations of oxygen (F_{IO_2}) to determine the most appropriate concentration of long term supplemental oxygen, providing a range of Sa_{O_2} values from 60% to 98%. The flex probe was held in place over the tip of a finger by purpose made sticky tape supplied by the company. The finger probe is a more bulky, thimble like device, which slips over the end of the finger, and the ear probe is like a clothes peg, similar to that from the Biox 2A oximeter. When steady state conditions had been achieved at a particular F_{IO_2}, blood was withdrawn from an indwelling radial artery cannula inserted at the beginning of the experiment. Arterial oxygen tension (Pa_{O_2}) and carbon dioxide tension (Pa_{CO_2}) and pH were measured on a blood gas machine (ABL–2, Radiometer; Copenhagen). If any of the three displayed Sa_{O_2} values changed by more than 2% during the period of blood withdrawal or the previous 30 seconds, the sample was not analysed. Haemoglobin saturation was estimated from blood gas values with a Severinghaus blood gas calculator.[5]

STUDY 2: SPEED OF RESPONSE

The three different probes from the Ohmeda 3700 and ear probes from the Hewlett-Packard 47201A or Biox

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2A were connected to either ear, finger, or toe as appropriate with the outputs displayed on a chart recorder. After steady state conditions had been achieved with low FIO_2, a mask delivering 100% oxygen was rapidly substituted. The response time was recorded from the first deep breath of 100% oxygen to the start of the rise in SaO_2.

STUDY 3: ASSESSMENT OF ABILITY TO DETECT ARTEFACT

The functioning of the oximeter requires pulsatile blood within the light path to differentiate arterial blood from non-pulsatile capillary or venous blood. An inadequate pulse could lead to falsely low SaO_2 values, and therefore the warning "low quality signal" is displayed.

(*a*) In three normal subjects an arterial cuff was applied to the limb proximal to the flex probe, and repeatedly inflated to above systolic blood pressure. As soon as "low quality signal" was indicated on the display panel the fall in SaO_2 (if any) was noted; the limb was then moved in an attempt to simulate pulsatile blood flow and thus deceive the instrument.

(*b*) Two flex probes attached to different oximeters were worn on opposite hands by five healthy subjects overnight. The paired eight hour SaO_2 tracings were then inspected visually for differences, particularly SaO_2 dips appearing on only one of the tracings, which would be likely to be artefact.

STUDY 4: EFFECT OF THE 12 SECOND SAMPLING ALGORITHM ON SIGNAL SHAPE

The Ohmeda 3700 memory saves SaO_2 and pulse rate values every 12 seconds. The actual value of SaO_2 stored is the lowest that occurred in the previous 12 seconds, and the pulse rate stored is the value which was synchronous with the SaO_2.

The ability of the algorithm to reproduce the original SaO_2 signal accurately was assessed by simulating an oscillating SaO_2 signal on a BBC "B" computer and sampling this signal with the algorithm used by the Ohmeda 3700. Simulated cycle lengths of SaO_2 from 30 to 70 seconds were used (similar to that seen in sleep apnoea) and a visual comparison was made between the original and the sampled tracings.

Results

The Ohmeda 3700 proved simple to use. It was usually easy to find a suitable finger on which the flex probe could be sited to give a strong signal, relatively immune from movement artefact. As the signal becomes weaker it becomes more sensitive to artefact because increased amplification is necessary. The measurement of pulse rate is more susceptible to movement artefact than SaO_2, although it is accurate when the probe site is not moving. The purpose made tapes to attach the flex probe to a finger are white and sometimes allowed enough light through in bright conditions to cause "probe off patient" to appear incorrectly on the display, and extra shielding was required in these circumstances. The instrument has an alarm that can be programmed to sound in response to preset SaO_2 and pulse limits as well as to a low quality signal. It can be silenced permanently by minor internal modification. The internal battery can power the instrument only for up to two hours, but stored data are retained when the battery becomes exhausted.

STUDY 1: COMPARISON WITH DIRECT ARTERIAL SAMPLING

The comparisons of arterial values and those simultaneously recorded by the three different probes are shown as scatter plots in figure 1. There is excellent agreement, particularly at higher SaO_2 levels, the flex probe proving overall to give values nearest to arterial values. Estimated SaO_2 in one chronically hypoxic patient was consistently greater than SaO_2 with the oximeter but this discrepancy was corrected when allowance was made for her abnormal P_{50} (29 mm Hg (3·9 kPa) measured by tonometry) in the calculation of SaO_2. The mean and standard deviation of the percentage SaO_2 differences between individual oximeter and arterial readings (representing bias and precision respectively) were −0·1 (3·4), −0·4 (1·8), and −0·5 (2·9) for ear, flex, and finger probes respectively.

STUDY 2: SPEED OF RESPONSE

With ear probes, the times taken for the Hewlett Packard, Biox 2A, and Ohmeda 3700 oximeters to detect a rise following sudden onset of oxygen breathing were 9·3 (SD 3·2), 11·1 (2·8), and 9·8 (2·6) seconds. These differences are not significant, but the finger and toe probe times (23·6 (4·1), 56·8 (15·8) s respectively) were proportionately longer because of the greater lung to probe site circulation times.

STUDY 3: ASSESSMENT OF ARTEFACT DETECTION

Using an arterial cuff above the probe site we were able to show that it was impossible to cause the machine to record a saturation fall of more than 2% without it registering "low quality signal." If inflation of the arterial cuff is combined with repeated movement of the finger, so simulating a pulse, the instrument may then record a false saturation fall without registering "low quality signal." Unless the movement was similar to the previous heart rate, however, this could usually be detected by inspection of the simultaneous pulse rate signal.

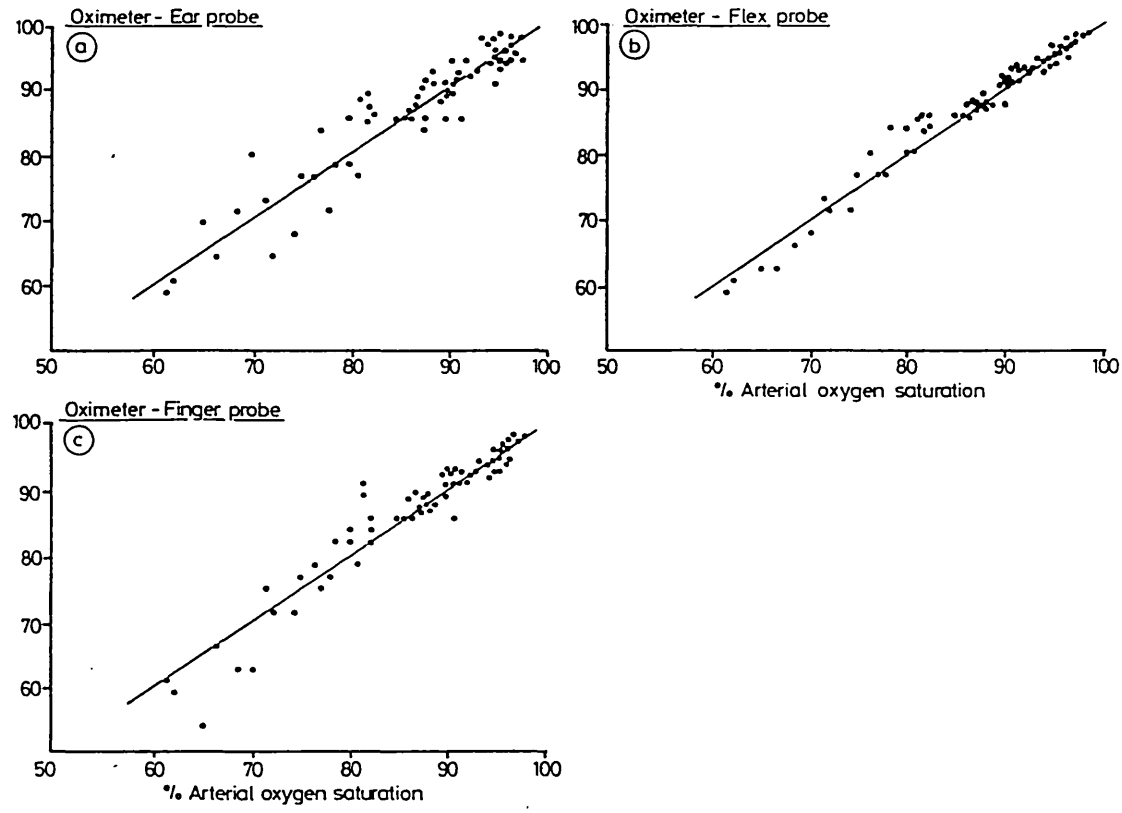

Fig 1 *Relationship between the estimated percentage arterial oxygen saturation (%Sa_{O_2}) value from arterial blood gas tensions (x axis) and the %Sa_{O_2} from the Ohmeda 3700 oximeter (y axis). a—ear probe; b—flex probe; c—finger probe. The line is the line of identity.*

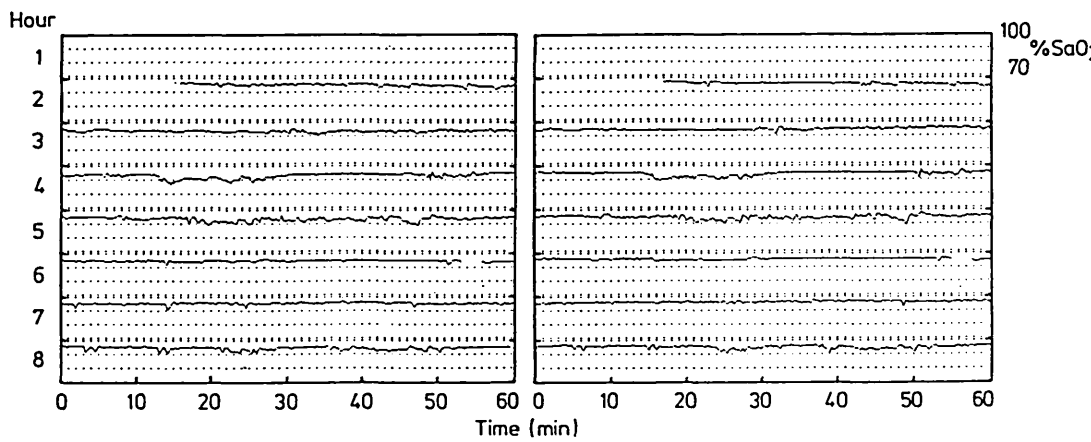

Fig 2 *Two overnight oximeter tracings, each from a flexprobe on a finger from opposite hands. Note that any dips usually occur on both tracings.*

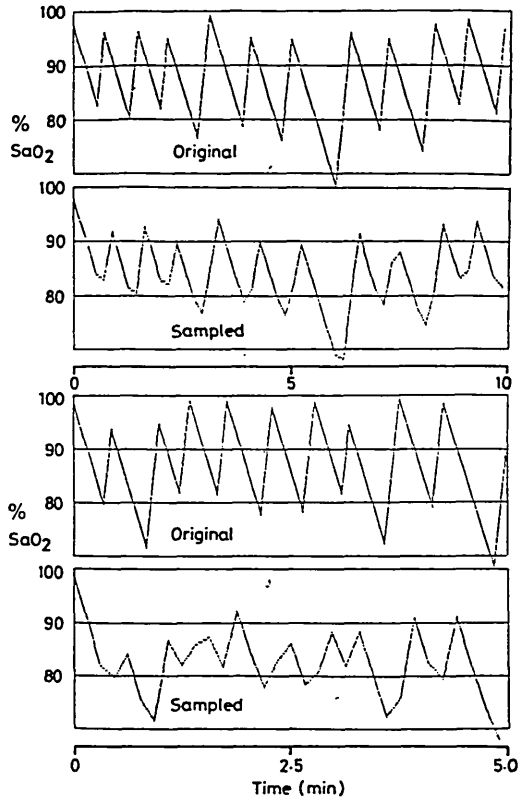

Fig 3 *Two computer simulations of fluctuating saturation (top line) and the recreated signal from the memory (bottom line) using the 12 second sampling algorithm (points joined) for two approximate cycle lengths, 60 seconds and 30 seconds.*

The five pairs of overnight tracings from opposite hands were very similar (fig 2). There were never more than three Sao_2 dips of more than 2% appearing on one of the paired tracings alone over the eight hour record. The greatest difference in the whole night mean value of Sao_2 between a pair of records was 0·9%.

STUDY 4: EFFECT OF SAMPLING ALGORITHM ON SIGNAL SHAPE

A 12 second sampling frequency on the basis of spot samples should in theory allow reasonable resolution of oscillations with a wavelength down to 30 seconds. This proved to be true for the sampling algorithm used by the oximeter when storing data to memory, with some deterioration when the wavelength was less than 35 seconds. Figure 3 shows phasic dipping in Sao_2 at two different approximate frequencies and the recreated pattern from the 12 second sampling algorithm. Because the lowest Sao_2 observed in the previous 12 seconds was stored rather than a regular point sample, the lowest values are of course the same value as the original; but the maximum recovery Sao_2 is underestimated.

Discussion

The Ohmeda 3700 pulse oximeter (using the flex probe) measured steady state arterial oxygen saturation, with an agreement of +3·2% and −4·0% Sao_2 (95% confidence limits) when compared with values derived from direct arterial sampling. Its mode of action ensures that it can issue a warning when the signal is inadequate for an accurate estimation of Sao_2. We have shown its accuracy compared with arterial samples to be at least as good as the previous Biox 2A,[1 4] and with the flex probe possibly a little better. Tweeddale and Douglas[3] found a mean difference of 1·5% (SD 3·0%) using the ear probe and Biox 2A, similar to our figures (−0·1% (3·4%) with the ear probe. The response characteristics to changes in Sao_2 were similar to the Biox 2A and Hewlett-Packard 47201A oximeters, and use of the ear probe would allow comparable measurements of hypoxic ventilatory drive by the method of Rebuck and Campbell.[6]

The memory will not store a low quality signal (for example, one due to lying on the probe site) and a blank appears in the data. This ability to reject low quality signals and the eight hours of memory make the Ohmeda 3700 particularly useful for unsupervised screening of oxygen saturation. The 12 second sampling algorithm, saving the lowest Sao_2 in that period, allows adequate reproduction of an oscillating signal down to a wavelength of 30 seconds and ensures that the lowest arterial oxygen saturation is not missed. If an inaccurate signal caused by simultaneous arterial compression and probe site movement is read into the memory, this should be detectable by simultaneous inspection of the pulse rate tracing, which will usually display considerably more variation than is usual in the pulse rate, owing to the irregular movement of the probe site that simulated a pulse. The eight hours of memory can be unloaded in eight minutes, and the data subsequently analysed with the help of a microcomputer.

The Ohmeda 3700 pulse oximeter is at present under evaluation in our department as a screening tool for the detection and diagnosis of hypoxaemia during sleep. We have found that patients with obstructive sleep apnoea commonly have a cyclical dipping wavelength in arterial oxygen saturation of 45 to 60 seconds, and the Ohmeda 3700 therefore appears to be technically satisfactory for unattended use in screening for nocturnal hypoxia.

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