# BREATHING DURING SLEEP

## Studies in normal subjects and patients with chronic bronchitis and emphysema

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## ABSTRACT OF THESIS (Regulation 7.9)

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The purpose of the research reported in this thesis was to study the degree, cause and effects of nocturnal hypoxaemia in patients with chronic bronchitis and emphysema. The methods used included the recording of oxygen saturation, airflow, chest movement and electro-encephalogram during sleep in 24 patients with chronic bronchitis and emphysema and 16 age-matched healthy controls. Arterial blood gas tensions were measured in 11 and pulmonary arterial pressure in 3 of the patients during sleep. The results were as follows:

1. Breathing patterns and changes in calculated oxygen tension were similar in patients and controls.
2. Patients who were hypoxic when awake became markedly more hypoxic while asleep. In 11 patients oxygen saturation fell below 50% and directly measured arterial oxygen tension fell as low as 3.5 kPa.
3. Oxygen therapy improved nocturnal oxygenation in these patients.
4. Mean pulmonary arterial pressure rose at least 8 mmHg during each hypoxaemic episode (a desaturation of 10% or more).
5. Of 57 hypoxaemic episodes, 51 occurred during rapid eye movement (REM) sleep. Two thirds of the hypoxaemic episodes in the patients were associated with decreased chest movement and only 2 with apnoea. This reduced chest movement occurred despite a degree of hypoxaemia normally sufficient to stimulate ventilation. It was therefore proposed that, contrary to previous beliefs, both ventilation and the hypoxic ventilatory response are diminished in REM sleep in adult man.
   In order to investigate this hypothesis, ventilation and ventilatory drive were measured in 19 healthy subjects using a face mask with a $CO_2$ sensitive leak detector. The results were as follows:
6. Ventilation was lower in all sleep stages than in wakefulness. There was a further reduction from non-REM to REM sleep when ventilation averaged 84% of the level in the awake subjects.
7. Both the isocapnic hypoxic and the rebreathing hypercapnic ventilatory responses were lower in all sleep stages than in wakefulness. Both responses were lower in REM than non-REM sleep, falling in REM to one third of their level during wakefulness.

The results in the second part of the study reinforce the view that hypoventilation is normal in REM sleep and is permitted by reduced ventilatory drive. In patients with chronic bronchitis and emphysema this REM-related hypoventilation may contribute to the development of pulmonary hypertension, polycythaemia and even death. Oxygen therapy is the current treatment of choice.

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# CHAPTER 1

## INTRODUCTION

The importance of sleep in medicine has been underrated, physicians tending to distance themselves from what has become an area of psychiatric interest. A disproportionate number of deaths occur at night. In a review of 432,892 deaths, Smolensky and colleagues (1972) found that the peak time of death was 6.00 am. Medical problems precipitated by sleep include nocturnal angina (Nowlin et al, 1965), migraine (Kayed et al, 1978), epilepsy (Gibberd & Bateson, 1974), paroxysmal nocturnal haemoglobinuria (Hansen, 1968) and oesophogeal reflux (Orr et al, 1979), but arguably the most important medical conditions aggravated by sleep are disorders of the respiratory system.

Nocturnal wheeze is a common problem for asthmatic patients (Clark & Hetzel, 1977). The majority of asthmatic deaths occur at night, according to some (Cochrane & Clark, 1975; Hetzel et al, 1977) - but not all (MacDonald et al, 1976 a & b) - studies. Sleep apnoeas are probably responsible for some of the tragic deaths in the sudden infant death syndrome (Valdes-Dapena, 1980). In adults the sleep apnoea syndrome (Guilleminault et al, 1976) results from intermittent cessation of breathing during sleep due

either to loss of inspiratory effort or to upper airway collapse (Remmers et al, 1978). Patients with the sleep apnoea syndrome are usually restless sleepers who snore loudly and have marked day-time hypersomnolence, these features leading to employment, driving and marital problems (Guilleminault et al, 1981b). Although apparently more common in North America, the sleep apnoea syndrome is being increasingly recognised in this country.

A much more common condition on both sides of the Atlantic Ocean is chronic bronchitis and emphysema. Approximately 8% of the male and 3% of the female population of Britain between the ages of 40 and 65 years, may have chronic bronchitis and emphysema as defined by the co-existence of dyspnoea on the level, and three weeks of productive cough in two successive winters (College of General Practitioners, 1961). Bronchitis is the commonest cause of work loss in Scotland (Scottish Health Service, 1982) and is largely responsible for respiratory disease being second only to mental illness in terms of the burden of illness on British society (Black & Pole, 1975).

Robin in 1958 first demonstrated that patients with chronic bronchitis and emphysema become hypoxaemic during sleep. I wished to establish whether such hypoxaemia resulted from sleep apnoea. This thesis contains the results of my investigations into the causes,

consequences and treatment of nocturnal hypoxaemia in patients with chronic bronchitis and emphysema.

The studies reported in Part 1 of the thesis were performed from 1977-1979 in the Department of Medicine of the University of Edinburgh under the guidance of Professor D C Flenley. From the results of these investigations, I proposed hypotheses which were tested in the Cardiovascular Pulmonary Research Laboratory of the University of Colorado, Denver, in collaboration with Dr J V Weil in 1980 and 1981, and these studies form Part 11 of the thesis. Thus the research was spread over 5 years and many advances have been reported in this field during that period. Such publications are discussed at the appropriate temporal point in the thesis, that is Part 1 for investigations published between 1977 and 1979 and Part 11 for subsequent relevant studies.

# CHAPTER 2

## THE PHYSIOLOGY OF SLEEP

Sleep is an enigma. Even the purpose of sleep in unclear, although it has been suggested (see Webb, 1979 for review) that sleep:-

a) allows tissue restoration

b) prevents excess wear and tear

c) avoids excess energy expenditure

d) is an adaptive safety response

e) is an instinctive behaviour

While the purpose of sleep may be a combination of the above factors, the single most attractive theory is the tissue restoration hypothesis (Oswald, 1976; Adam & Oswald, 1977). Oswald argues that sleep is associated with increased mitotic activity and increased secretion of anabolic hormones. He observes that the duration of slow wave sleep (see below) correlates with global anabolic requirements and that the duration of rapid eye movement sleep (see below) relates to the intensity of brain synthetic activity.

## Sleep Staging

In this thesis, sleep is staged using the criteria of Rechtschaffen and Kales (1968) who divide sleep into rapid eye movement (REM) and subdivisions of non-rapid eye movement (non-REM) sleep, according to electroencephalographic (EEG), electromyographic (EMG) and electro-oculographic (EOG) features which are outlined below:

| Stage | EEG | EMG Tone | EOG Movements |
|---|---|---|---|
| Awake | alpha ± low voltage mixed frequency | high | occasional, rapid |
| **Non-REM** | | | |
| Stage 1 | loss of alpha | reduced | slow |
| Stage 2 | sleep spindles, K complexes | reduced | absent |
| Stage 3 | > 20% delta waves | reduced | absent |
| Stage 4 | > 50% delta waves | reduced | absent |
| REM | low voltage, saw-toothed waves | markedly reduced | rapid |

Delta waves are high voltage slow (<2 cycles/sec) waves and thus stages 3 and 4 are sometimes termed "slow wave sleep".

These criteria allow sleep staging in adult man, but are not always directly applicable to infants or animals in whom behavioural criteria are often used in addition to EEG features (e.g. Haddad et al, 1980; Rigatto et al, 1980; Phillipson et al, 1976; Jeffrey & Read, 1980; Haddad et al, 1982). This basic difference in sleep staging - and perhaps in underlying neurophysiology - may explain some of the difficulties in extrapolating results from sleeping infants and animals to sleeping adults, a difficulty which becomes a recurrent theme in this thesis.

## NEUROPHYSIOLOGY OF WAKEFULNESS AND SLEEP

This complex field has been extensively reviewed (see Moruzzi, 1972; Pompeiano, 1973; Steriade & Hobson, 1976). Below is a simplified overview.

### Wakefulness

Wakefulness is a state of cortical activation with preserved sensory and motor function. Wakefulness is maintained by tonic activity of the reticular activating system - a network of neurones occupying the paramedian brain stem. The reticular activating system promotes wakefulness by directly stimulating cortical activity (Moruzzi & Magoun, 1949) and by facilitating thalamic

relay neurones thus allowing onward passage of sensory information to the cortex (Purpura et al, 1966).

## Sleep

Sleep is a cyclical process which always starts in normal subjects with non-REM sleep. REM cycles are interspersed throughout non-REM sleep and occur approximately every 90 minutes throughout the night, lasting approximately 15 minutes in the first REM period, the subsequent REM periods tending to be progressively longer (Williams et al, 1974).

There have been significant recent advances in the understanding of factors inducing sleep. A glycopeptide isolated from human urine has recently been shown to promote sleep in rabbits (Krueger et al, 1982). This glycopeptide - Factor S - increases slow wave sleep when infused into the lateral ventricles and is believed to act around the aqueduct, perhaps having a direct effect on the reticular activating system (Pappenheimer, 1982). The identification of this chemical might allow rapid advances in the neurophysiology of sleep and in the manufacture of hypnotics. However, it seems unlikely that this is the only chemical promoting sleep as Factor S does not influence REM duration (Garcia-Arraras, 1981) whereas REM deprivation results in a rebound increase in REM sleep (Dement, 1960).

Non-REM Sleep

Non-REM sleep is characterised by inhibition of the reticular activating system. Inhibition of the reticular activating system may result from Factor S (Pappenheimer, 1982) although previously it was believed that the basal fore-brain activated the nucleus of the tractus solitarius which in turn inhibited the reticular activating system (Moruzzi, 1972).

Inhibition of the reticular activating system deprives the cortex of both direct (Moruzzi & Magoun, 1949) and thalamic-mediated (Purpura et al, 1966) activation. Cortical inhibition in non-REM sleep is also produced by increased firing of cortical inhibitory interneurones in neo-cortical areas (Steriade & Hobson, 1976). Thus non-REM sleep is characterised by cortical suppression and functional deafferentation.

REM Sleep

Although the primary stimulus for REM sleep is not clear, transection studies indicate that the REM sleep generating mechanisms lie in the pons (Steriade & Hobson, 1976). There is some evidence (McCarley et al, 1978) that REM may be generated by activity in cells in the tegmental gigantocellular field of the pons which, passing via vestibular or occulo-motor connections, modulates the firing of ponto-geniculo-occipital (PGO) burst neurones. These PGO burst neurones initiate PGO

waves which pass up the brain stem to the lateral geniculate body and visual cortex. PGO waves are inhibited by both serotoninergic and nor-adrenergic neurones which probably gate the release of the PGO waves. PGO waves are the most basic readily identifiable elements of REM sleep and may be associated with the rapid eye movements themselves (Steriade & Hobson, 1976).

This scheme has been challenged by the finding that the "REM generator" neurones in the tegmental gigantocellular field which are REM specific in restrained animals (McCarley et al, 1978) also fire during body movement in awake animals (Siegel & McGinty, 1977; Vertes, 1977) and thus may be associated with movement, which occurs in both wakefulness and REM sleep, rather than being specific to REM sleep. However, Saito et al (1977), studying unrestrained cats, found REM specific neurones in the dorso-lateral pontine tegmentum which are not related to movement and which were tightly phase locked to PGO waves. Thus it seems probable that there is a pontine REM sleep generator.

During REM sleep the reticular activating system is reactivated producing cerebral stimulation (Steriade & Hobson, 1976) and desynchronised cortical EEG activity. In contrast to wakefulness, sensory and motor functions are impaired during REM sleep. There is both pre- and post-synaptic inhibition of afferent neurones (Pompeiano, 1973) with raised arousal thresholds to a variety of

stimuli (Steriade & Hobson, 1976). Post-synaptic inhibition of motor neurones (Nakamura et al, 1978), probably mediated via the reticulo-spinal tracts, results in the postural atonia which is typical of REM sleep (Pompeiano, 1975). Phasic excitatory influences may overcome this motor neurone inhibition intermittently resulting in myoclonic jerks (Steriade & Hobson, 1976). Thus REM sleep is characterised by cortical reactivation with impaired sensory and motor functions and intermittent myoclonic jerks.

# CHAPTER 3

## REVIEW OF VENTILATION DURING SLEEP

### Ventilation during sleep in normal adults

In 1860, Edward Smith, Fellow of the Royal Society, Assistant Physician to the Hospital for the Consumption, Brompton, reported that ventilation in normal man was lower during sleep than in wakefulness. This observation was confirmed by Mosso (1878), Magnus Levy (1894), Gujer (1928) and by Ostergaard (1944) and was also noted in one of 2 subjects by Loewy (1890) - there being no change in ventilation during sleep in the other subject. The first study of more than two subjects was published by Magnussen (1944) who showed that minute ventilation was lower during sleep than in wakefulness in each of 30 experiments in 11 subjects, the mean decrease being from 7.4 l/min awake to 6.7 l/min when asleep. In 13 subjects, Robin and colleagues (1958) found that average ventilation fell from 7.9 l/min during wakefulness to 5.8 l/min during sleep ($p < 0.001$).

All the above studies defined sleep by behavioural criteria - either by observation alone or by the failure of the subject to respond to external stimuli. Thus there must be some doubt as to whether the subjects were always asleep when measurements were made. Birchfield

and colleagues (1959) published the first study of ventilation during sleep in which sleep was defined by electroencephalographic criteria. They confirmed that ventilation fell during sleep, the decrease in 11 men being from 7.2 l/min awake to 6.6 l/min asleep ($p < 0.05$). Birchfield did not differentiate between the stages of sleep, but Bulow and Ingvar (1961) and Bulow (1963) showed that ventilation decreased in sleep with a mean decrease between wakefulness and what is now termed stage 2 sleep (Rechtschaffen & Kales, 1968) of $0.9 \pm 0.1$ l/min/$m^2$ in 29 subjects. Bulow also found that ventilation decreased in 11 subjects from wakefulness to drowsiness, but that there was no change from drowsiness to stage 2 sleep [Ventilation: Awake 6.1, Drowsy 5.3, stage 2 5.0 l/min - calculated from Bulow (1963) Table 1V]. However, as Bulow did not record the electro-oculogram in the majority of his studies, it is possible that some of the periods of "drowsiness", and perhaps also of stage 2 were actually episodes of rapid eye movement (REM) sleep. Duron (1972) found that minute ventilation was not changed between wakefulness and non-REM sleep but measurements were made in only 4 subjects, and no data are quoted.

All the above measurements were made using either a mouth-piece and noseclip or a facemask and thus have two inherent sources of error. Firstly, both systems may modify the depth and pattern of ventilation (Gilbert et

al, 1972; Askanazi et al, 1980). Secondly, leaks cannot be excluded especially during sleep as facial muscle tone decreases and subjects move. The only pre-1977 study on breathing during sleep in adults performed without facial instrumentation was by Newsom Davis and colleagues (Davis et al, 1976) who, using calibrated magnetometers, found no difference between the level of ventilation in wakefulness and sleep. However, as basal metabolic rate probably falls during sleep (Brebbia & Altshuler, 1965; Webb & Hiestand 1975), considerable doubt is cast on Newsom Davis's findings by the many studies which have demonstrated increased $CO_2$ and decreased $O_2$ levels during sleep.

In 1915, Straub demonstrated that alveolar carbon dioxide tension ($P_ACO_2$) was higher immediately after waking (41.4 mmHg) than prior to sleep (38.2 mmHg) and found similar rises in venous carbon dioxide tension. These results were confirmed by Leathes (1919), Collip (1920) and Endrès (1923). The first measurements of "alveolar" $CO_2$ during sleep were made in 1922 by Bass and Herr who found a small (0.8 mmHg) mean rise in $P_ACO_2$ during sleep using a nasal valve. They almost certainly underestimated the rise, probably because their subjects could mouth breathe during sleep and thus nasal sampling would not provide true alveolar levels. Subsequent studies have shown larger rises in alveolar (Ostergaard, 1944; Magnussen, 1944; Robin et al, 1958; Reed & Kellogg,

1958; Bulow, 1963; Townsend et al, 1973) and arterial (Birchfield et al, 1959) $PCO_2$ and arterial oxygen saturation has also been found to decrease during sleep (Birchfield et al, 1959). All these studies involved facial instrumentation and thus may be criticised, but their findings have been confirmed in the following studies performed without facial instrumentation. In 1940, Hastings and Eisele reported that cutaneous blood carbon dioxide tension rose by 7 mmHg during behavioural "sleep" - although one must assume that the blood sampling aroused the subjects. In 1952 Doust and Schneider used a Millikan ear oximeter to show that arterial oxygen saturation decreased during sleep by an average of 3-9% in 7 normal adults. Subsequently, Birchfield and colleagues (1958) sampled arterial blood via an indwelling Cournand needle during electroencephalographically confirmed sleep and found that in 11 subjects sleep increased arterial carbon dioxide tension ($PaCO_2$) from 43.9 to 49.2 mmHg ($p < 0.01$) and decreased pH from 7.38 to 7.33 ($p < 0.001$). Bristow et al (1969) studied 10 "normal" subjects - 2 of whom were hypoxic whilst awake - and noted that during sleep $PaCO_2$ rose by 4.0 mmHg and pH and $PaO_2$ fell by 0.01 and 5.4 mmHg respectively. Coccagna and colleagues (1976) found that non-REM sleep was associated with a mean increase in $PaCO_2$ of 3 mmHg with a 0.03 drop in pH and a 4 mmHg decrease in $PaO_2$.

Therefore there is considerable evidence that sleep is associated with a rise in carbon dioxide tension and a fall in oxygen tension in adult man. This conclusion was challenged in 1953 by Mills who suggested that there was a diurnal rhythm which caused $CO_2$ levels to rise at night irrespective of sleep. However, Mills's data are open to criticism as they were largely dependent on results on one subject - "M", possibly the author - and the electroencephalograph was not recorded and thus it is impossible to be sure the subjects were awake during their "sleepless" night or sleeping on their "sleep" night. Further, in many studies the $CO_2$ values were not obtained during sleep but soon after awakening. In others, end-tidal values were obtained from a mouthpiece, but inadequate precautions were taken against leaks, which are tacitly admitted. Also some of the sleep periods were induced by hexobarbitone and some followed prolonged periods of sleep deprivation, both of which may modify ventilation (see Appendix 1). While the diurnal pattern of respiration requires further investigation, Mills's study is too insubstantial to challenge the conclusion that ventilation decreases during sleep in normal adult man.

Although the electro-oculogram was not recorded during the majority of these studies, it is reasonable to assume that they were performed in non-REM sleep as most of the measurements were made either soon after sleep

onset, when REM is rare, or during periods of regular breathing, which are unusual in REM. Thus ventilation decreases from wakefulness to non-REM sleep in adult man. Similarly, ventilation has been found to be lower in non-REM sleep than in wakefulness in children (de Bruin, 1936) and also in rats (Pappenheimer, 1977), cats (Orem et al, 1977) and dogs (Phillipson et al, 1976).

Although in their original description of rapid eye movement sleep Aserinsky and Kleitman (1953) observed that breathing was altered in REM, and Aserinsky (1965) later demonstrated decreased chest movement and reduced oxygen saturation in REM sleep, there has hitherto been no adequate study of the level of ventilation in REM sleep in adults. The only previous studies of ventilation during sleep in normal adults in which REM sleep could be identified were those of Bulow (1963) and Duron (1972). Bulow found that ventilation in REM sleep was highly variable and "varied around the same mean as in" drowsiness (12% lower than ventilation in wakefulness), although neither the number of observations nor any data are given. Duron (1972) felt unable to comment on the effect of REM sleep on minute ventilation due to the combination of frequent movement in REM and the long time interval between his pre-sleep control measurements and the onset of REM sleep.

Bristow and colleagues (1969) measured arterial blood gas tensions during REM sleep in 4 normal adults

and found similar values to those in non-REM sleep. Coggagna et al (1976) found no difference in mean arterial blood gas tension or pH between non-REM and REM sleep, although no statistical analysis was performed and it is difficult to evaluate the mean results without knowing whether all 8 subjects were studied in every stage of sleep. Townsend and colleagues (1973) found that end-tidal $PCO_2$ rose towards waking values in REM sleep, but the marked irregularity of breathing in REM sleep makes the interpretation of mean "end-tidal" values difficult and may lead to under-estimation of the true alveolar $PCO_2$ (See Chapter 7).

Thus the level of ventilation in REM sleep has not been well documented in adult man. In contrast several studies in human infants (Bolton & Herman, 1974; Hathorn, 1974; Finer et al, 1976; Purcell, 1976) have shown that ventilation is higher in REM than in non-REM sleep. Similarly, in dogs (Phillipson et al, 1976) ventilation is greater in REM than in non-REM sleep, but in cats (Orem et al, 1977) ventilation is reduced in REM sleep.

## Ventilation During Sleep in Patients with Chronic Bronchitis and Emphysema

Prior to the start of the current study in 1977, ventilation had not been measured during sleep in patients with chronic bronchitis and emphysema. However, several groups had indirectly assessed ventilation by

measuring arterial oxygen and carbon dioxide in such patients during sleep.

Robin and colleagues in 1957 and Robin in 1958 reported that in 7 patients with "emphysema and chronic hypercapnia" "alveolar" $CO_2$ rose by 10 mmHg during sleep and that 4 of the patients exhibited Cheyne-Stokes respiration during sleep. Trask and Cree (1962) used a Waters ear oximeter to measure oxygenation during sleep in 7 "emphysematous" patients with moderate daytime hypoxia but normal or near normal carbon dioxide tensions. Arterial oxygen saturation fell in all the patients during sleep and the authors noted that the lowest saturations during sleep were recorded in those whose saturations were lowest when awake. Neither Robin's group nor Trask and Cree (1962) confirmed sleep electroencephalographically, the first study to do so being that of Pierce and colleagues (1966). These investigators sampled arterial blood via an indwelling Cournand needle in 19 patients with severe chronic airways obstruction and found that during sleep the carbon dioxide tension rose in all 19 and oxygen tension fell in 17. The mean maximal changes observed in both $PaCO_2$ and $PaO_2$ were 7 mmHg. Atlan et al (1968), using a behavioural definition of sleep, found that arterial $PCO_2$ rose in all 9 patients with chronic bronchitis and emphysema studied. In the 5 in whom both oxygen and carbon dioxide tensions were measured during sleep, there

was a mean decrease in $PO_2$ of 4.3 mmHg with an increase in $PCO_2$ of 7.4 mmHg. Conversely, Interiano et al (1972) found that sleep resulted in a larger mean decrease in $PaO_2$ (6 mmHg) than increase in $PaCO_2$ (3 mmHg) in 6 patients with chronic obstructive pulmonary disease.

Koo, Sax and Snider (1975) gave a detailed account of blood gas tension changes during sleep in 15 patients with moderately severe chronic bronchitis and emphysema. In all 15 the arterial $PO_2$ fell and $PCO_2$ rose during sleep, the mean maximal decrease in $PO_2$ being 13.5 mmHg with a mean maximal $PCO_2$ rise of 8.3 mmHg. These changes in $PaO_2$ were significantly ($p < 0.001$) greater than occurred in control patients who failed to sleep, although the difference between the groups for $PCO_2$ change was of borderline significance ($P = 0.08$; unpaired t test on data in Table 11 in Koo et al, 1975). Koo analysed the blood gas changes using the oxygen/carbon dioxide diagram (Rahn & Fenn, 1955) and concluded that in "9 patients more than half of the fall in $PaO_2$ from waking to minimal sleeping value was due to ventilation-perfusion imbalance". This analysis, however, assumes steady state conditions which were not established (see Chapter 5). In the 8 patients in whom sleep was confirmed electroencephalographically, the blood gas changes were more marked in REM than non-REM sleep, although no statistical analysis was performed.

In 1976, Leitch and colleagues in Edinburgh showed that in 10 patients with severe chronic bronchitis and emphysema the mean decrease in oxygen tension was 0.67 kPa ($p < 0.001$) whilst there was no significant change in carbon dioxide tension during sleep (mean increase 0.23 kPa). Although sleep was staged by conventional criteria (Rechtschaffen & Kales, 1968) including the use of the electro-oculogram, no data are quoted for REM sleep except to state that none of the 18 samples obtained during REM showed "marked hypercapnia".

As ventilation has not been measured during sleep in patients with chronic bronchitis and emphysema, comparison is not possible with sleep-induced ventilatory changes in normal subjects. Similarly there had been no direct comparisons of changes in blood gas tensions during sleep between the 2 groups. However, several investigators have compared their own results in patients with earlier studies in normal subjects and have concluded that the increase in $PaCO_2$ during sleep in patients with chronic bronchitis and emphysema is greater than (Robin et al, 1958) or the same as (Pierce et al, 1966; Koo et al, 1975; Leitch et al, 1976) the rise in $PaCO_2$ in normal subjects. Similarly, the decrease in $PaO_2$ during sleep in patients with chronic bronchitis and emphysema has been held to be greater than (Koo et al, 1975) or similar to (Pierce et al, 1966; Leitch et al, 1976) that in normal subjects.

Thus further investigation was required to clarify the cause of nocturnal hypoxaemia in patients with chronic bronchitis and emphysema and specifically to ascertain whether the ventilatory changes are the same as occur in normal subjects, or whether these patients exhibit a sleep apnoea syndrome. The development of a reportedly accurate (Saunders et al, 1976; Scoggin et al, 1977) ear oximeter (Hewlett Packard 47201A) made it possible to measure oxygenation continuously throughout the night and thus allow more precise definition of changes which previously had been recognised only by intermittent arterial blood sampling. It was thought that the ear oximeter might show differences between patients in the extent of nocturnal hypoxaemia, which might help explain some of the variability in the relationship between awake oxygen saturation and either red cell mass (Harrison, 1973) or pulmonary hypertension (Flenley, 1978) that these patients exhibit. A study was therefore designed to define and compare breathing patterns and oxygenation during sleep in normal subjects and in patients with chronic bronchitis and emphysema.

# CHAPTER 4

# METHODS

## EVALUATION OF EQUIPMENT

### Ear Oximeter - Hewlett Packard 47201A

The arterial oxygen saturation measured by the ear oximeter in vivo was compared with that measured in simultaneously sampled arterial blood on 465 occasions. Measurements were made with the oximeter in the "normal" - as opposed to "fast" - operational mode, as described in the manufacturer's handbook, and were only included in this comparison if the oximeter reading did not vary by more than 1% during the period of 10 to 60 seconds in which the arterial blood sample was drawn. Samples were taken by direct puncture of either the brachial or radial artery after infiltration of lignocaine around the vessel. Samples were also taken from indwelling brachial arterial catheters during sleep.

Arterial blood saturation ($SaO_2$) was measured (Instrumentation Laboratory Co-Oximeter 182) in 391 samples, and was calculated in the other 74 from measurements of $PaO_2$ and $H^+$ (Instrumentation Laboratory 313 Blood Gas System) using the patient's directly determined $P_{50}$ - the $PaO_2$ at which the blood is 50%

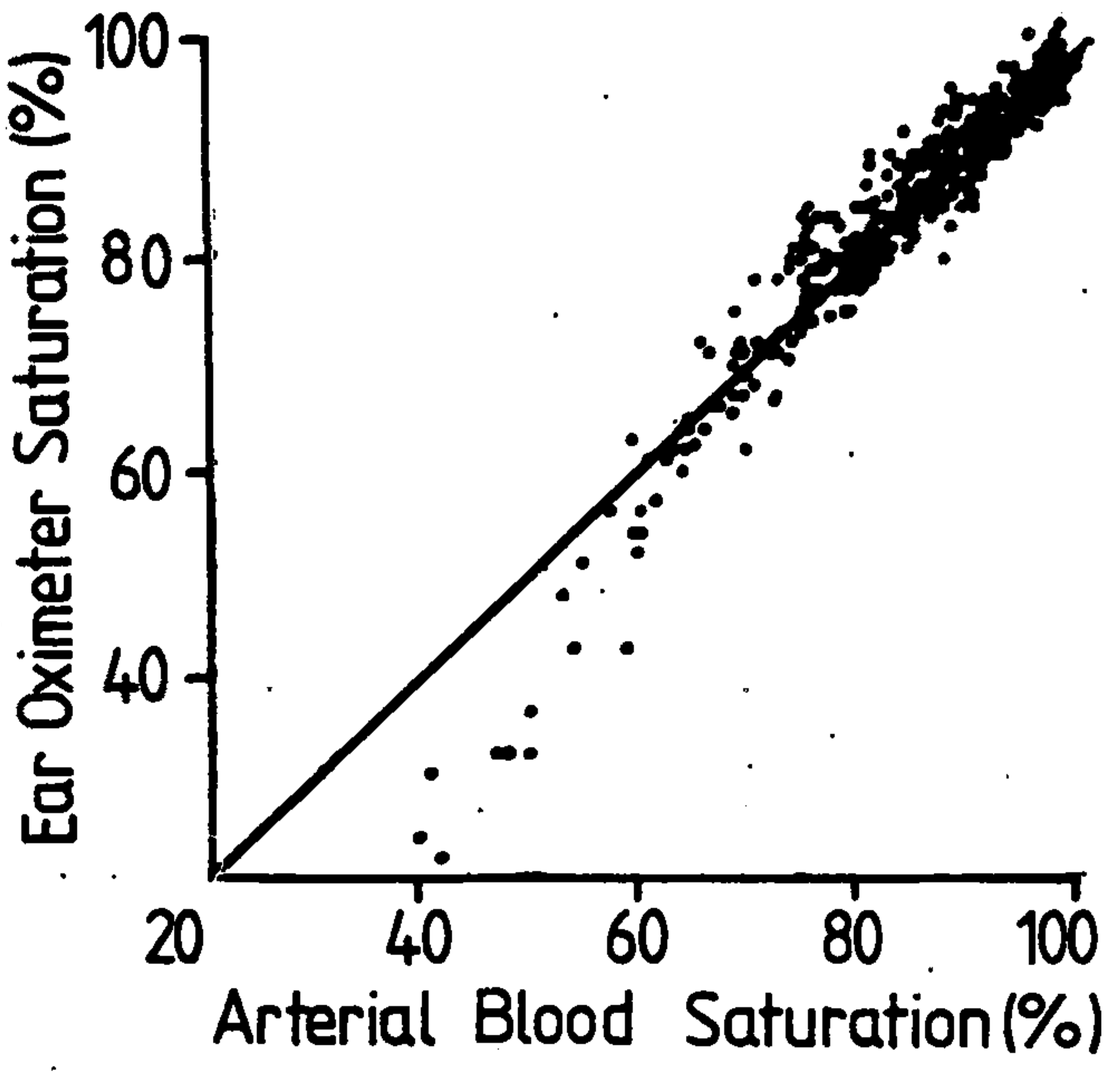



Fig 1 Comparison of haemoglobin saturation measured by the ear oximeter with that obtained from simultaneously sampled arterial blood in 465 samples. The line of identity is shown.

saturated - which was measured within 24 hours of taking the sample. Using this equipment the coefficient of variation (Snedecor & Cochran, 1980) in 21 replicate estimations on the same blood sample was 5.36% for $SaO_2$, 2.95% for $PO_2$ and less than 0.1% for $H^+$.

The oximeter reading was a linear function of $SaO_2$ for values greater than 65%. The linear regression equation (Snedecor & Cochran, 1980)

$$\text{Oximeter reading} = 0.92 \pm 0.02 \text{ (SE) } SaO_2(\%) + 7.44 \pm 1.35$$

$$n = 437 \quad r = 0.94 \quad p < 0.001$$

describes the relationship with 95% confidence limits $\pm$ 5% of $SaO_2$ for values of $SaO_2$ > 65%. When $SaO_2$ was less than 60%, the ear oximeter gave readings which were progressively lower than actual $SaO_2$ (Fig 1) so that when the true $SaO_2$ was 40% the instrument indicated a value of approximately 20%.

These results show that the Hewlett Packard 47201A ear oximeter can measure $SaO_2$ in the range of 65 to 100% with an accuracy of $\pm$ 5%. This accuracy is similar to that derived from 223 observations by Saunders and colleagues (1976) and confirms reports in smaller series (Scoggin et al, 1977; Chaudhary & Burki, 1978) that the Hewlett Packard ear oximeter is relatively accurate. We have shown (Douglas et al, 1979a) that the accuracy can be improved to $\pm$ 4% over the 65 to 100% $SaO_2$ range if

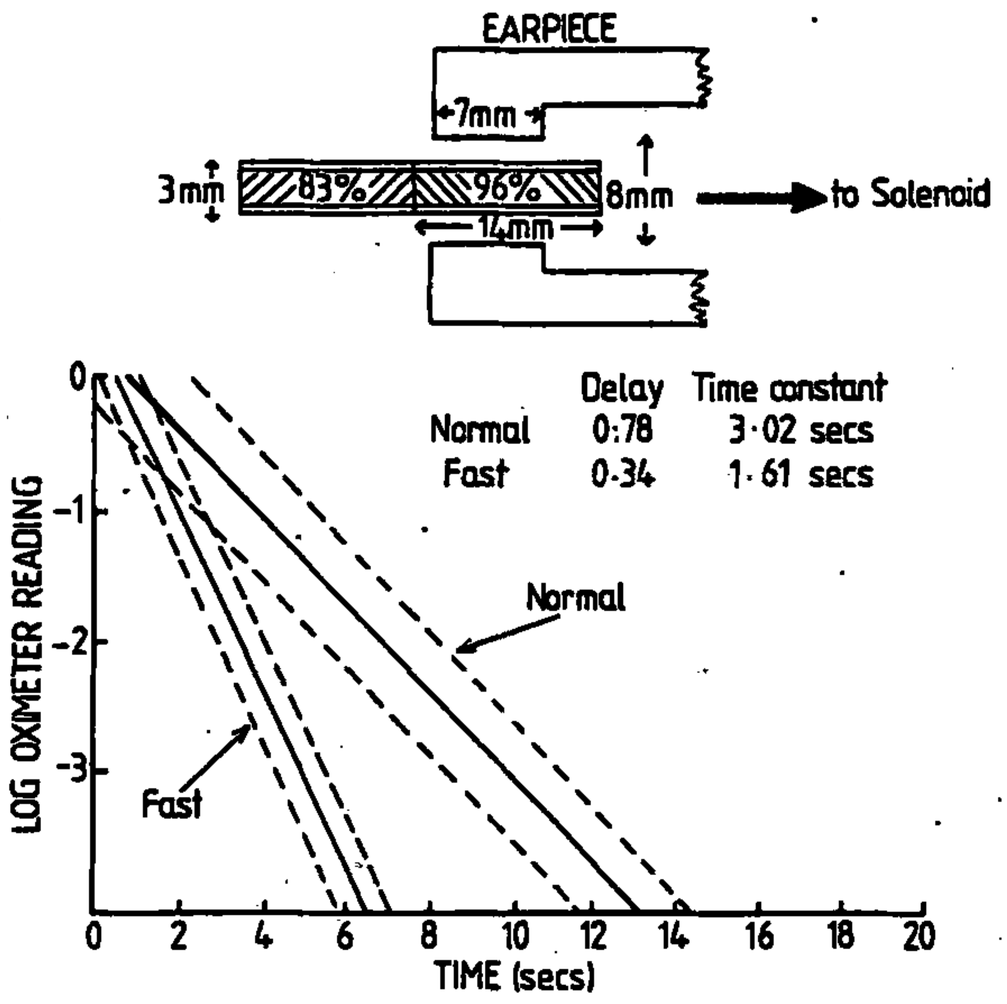



Fig 2 Schematic diagram of the equipment used to assess time response (above). The logarithm of the change in the digital output of the oximeter is plotted against time for the "fast" and "normal" modes of operation showing the means (solid lines) and 95% confidence limits (dashed lines).

only measurements in which the carboxyhaemoglobin is less than 3% are used.

The ear oximeter was found to be progressively more inaccurate as saturation fell below 60%, with a progressive tendency for the oximeter to read too low. Recognition of this error is important when assessing changes in oxygenation during sleep.

The time response of the oximeter was measured in vitro with a solenoid-activated cuvette system, one chamber of which contained blood with $SaO_2$ of 96% and the other blood with $SaO_2$ of 83%. The chamber containing blood with 96% $SaO_2$, lying in the ear position of the cuvette was suddenly moved so that the chamber containing blood with 83% $SaO_2$ lay in this position. Zero time for the movement was recorded by a microswitch at the completion of the movement, the duration of the movement being 26 msec. Measurements were made using both the "fast" and "normal" modes of operation. The results were analysed on-line by a PDP11/34 computer.

The time response to the change in saturation in vitro was exponential (Fig 2) with a time constant of 3.02 seconds after an initial delay of 0.78 seconds in the "normal" operational mode and a time constant of 1.61 seconds with an initial delay of 0.34 seconds in the "fast" mode. Thus the frequency response of this ear oximeter in its "normal" mode of operation is adequate for use in sleep studies, and the instrument was used in this mode for all the investigations reported hereafter.

## Breathing Pattern Analysis

The aim was to identify breathing abnormalities which might contribute to hypoxaemia, particularly apnoea and hypoventilation. Air flow was recorded using thermocouples at the mouth and nostrils, and anteroposterior chest wall movement by an induction stethogram placed in the mid-line at the level of the third intercostal space anteriorly. The time constant of the stethogram circuit was 20 seconds.

An apnoea was defined as cessation of airflow at the mouth and nostrils for 10 seconds or longer (Guilleminault et al, 1976).

Thermocouples merely register the temperature of respired gas and thus would not be expected to be sensitive indicators of expired volume. In practice it was found that respiration could virtually cease before the thermocouple output diminished. Thus the stethogram seemed more likely to give a semi-quantitative indication of ventilation.

The linearity of the stethogram with respect to expired volume was assessed on one normal subject (myself). The stethogram coils were applied in the normal way. The subject wore a noseclip and breathed through a mouthpiece connected by low-resistance respiratory tubing to an Ohio 570 Wedge Spirometer calibrated using a 1 litre gas syringe. Both stethogram

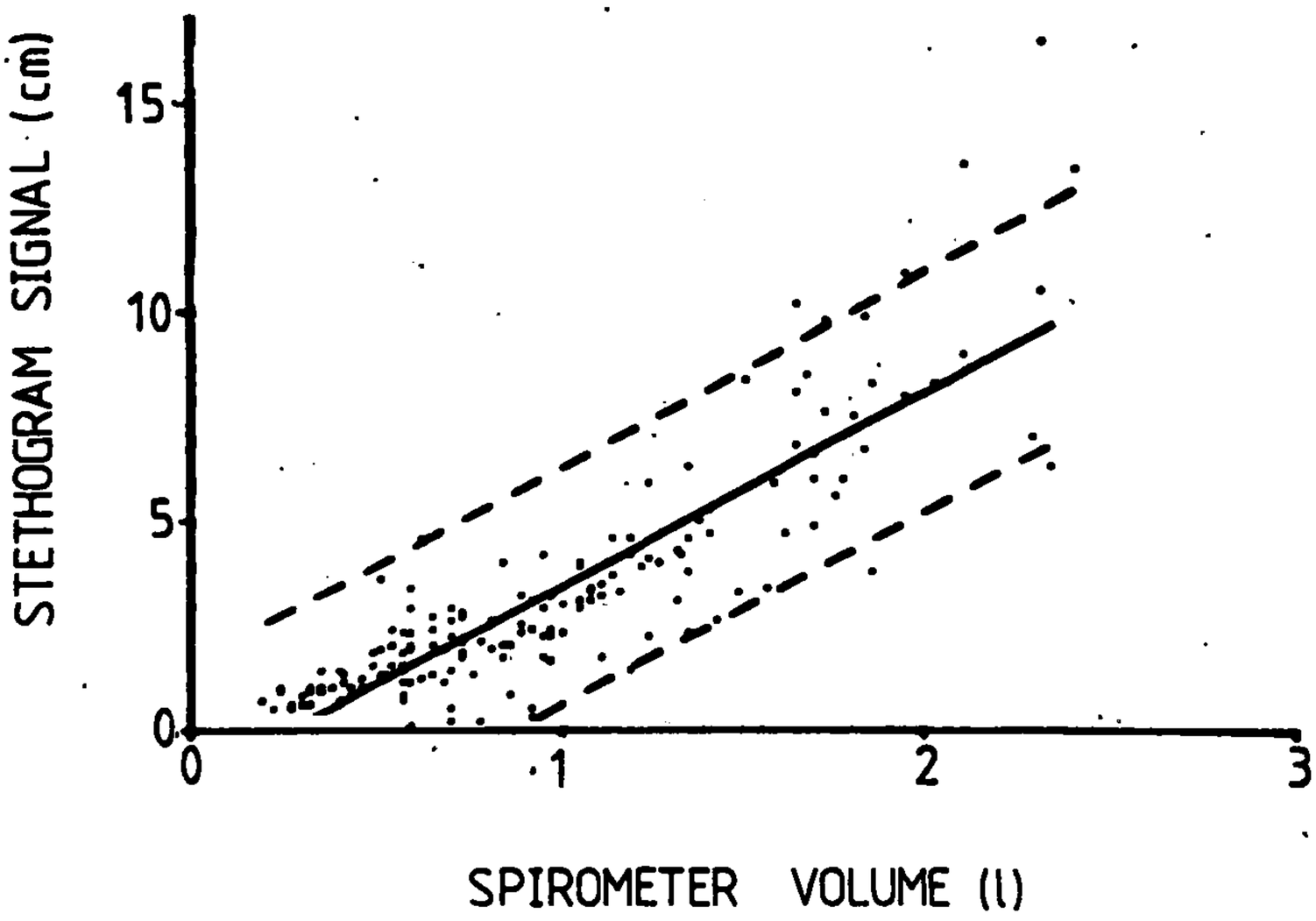



Fig 3 Comparison of stethogram signal with spirometer volume for 165 breaths in one subject. The regression (solid) line and 95% confidence limits for the measurements (dashed) line are indicated.

and spirometer output were recorded on a Bryans 28000 time base recorder.

Recordings were made of 165 breaths in 5 series each of 33 breaths. The first series was with the subject supine, the second in the left lateral position, the third supine, the fourth in the right lateral, and the fifth supine once more. This allowed assessment of posture dependence and whether the calibration returned to its previous level when a given posture was resumed. The majority of measurements were made in the supine posture because most subjects spent most, if not all, of the night in this position.

Analysing all 165 breaths, there was a highly significant linear correlation (Snedecor & Cochran, 1980) ($r = 0.86$; $p << 0.001$) between the stethogram signal and the spirometer measured volume (Fig 3). When only data obtained in the supine posture was used, the correlation was improved ($r = 0.92$; $p << 0.001$).

Thus the stethogram gives a reasonably good index of expired volume in an awake subject, but during sleep the relative contributions of the thorax and abdomen to tidal volume change. In 1878 Mosso first reported that the thoracic contribution increased during sleep, a finding subsequently confirmed by Shepard (1914) but not by Reed and Kleitman (1926) or Magnussen (1944). Studies performed with EEG sleep staging have all shown that the thoracic contribution to tidal volume is increased in

non-REM sleep compared to wakefulness (Goldie & Green, 1961; Timmons et al, 1972; O'Flaherty et al, 1973; Tusiewiczs et al, 1977; Mortola & Anch, 1978). In the largest study in adults (Gothe et al, 1981), the ratio of rib cage to total movement increased significantly from 38±4(SE)% in wakefulness to 49±4% in non-REM sleep.

The relative contribution of the rib cage decreases from non-REM to REM sleep in both adults (O'Flaherty et al, 1973; Tusiewiczs et al, 1977; Mortola & Anch, 1978) and teenagers (Tabachnik et al, 1981a) due to decreased intercostal tone (Tusiewiczs et al, 1977; Tabachnik et al, 1981a). However, it is not clear whether there is a difference between the relative contribution of the rib cage in wakefulness and REM sleep. O'Flaherty and colleagues (1973) and Mortola and Anch (1978) reported no difference in the rib cage contribution between wakefulness and REM sleep, basing their result on 6 and 5 subjects respectively, but in 3 subjects Tusiewiczs reported a decrease in the rib cage contribution in REM sleep [Awake 44±5(SD)%; REM 19±14%]. These discrepancies can perhaps be explained by Mortola and Anch's observation that lateral chest movement increased during REM sleep, as this would have been missed by Tusiewiczs, who only measured antero-posterior chest wall movement but detected by O'Flaherty's circumferential technique. Tabachnik, who like Tusiewiczs worked in Bryans group, reported that in 9 teenagers the Respitrace-measured rib

cage contribution in wakefulness was 40±9(SD)% and in REM 34±5%. Although no statistical comparison was made, both the lack of comment and the results suggest that this difference was not significant. Therefore it seems that the thoracic contribution to tidal volume increases in non-REM sleep compared to wakefulness and probably returns in REM sleep to a level similar to that in wakefulness.

In view of the changing thoracic contribution in different sleep stages, wide limits had to be set to ensure that differences in stethogram output reflected alterations in ventilation. Therefore, an abnormal chest movement was defined as either a halving (hypopnoea) or doubling (hyperpnoea) of the stethogram signal from the previous stable baseline during sleep for each breath during a 10 second period, in the presence of continuing airflow. This definition means that ventilatory changes had to be large before the criteria were met and thus the sensitivity was low but the specificity high.

## METHODS

Arterial oxygen saturation was measured continuously during sleep in 16 healthy subjects and 24 patients with chronic bronchitis (Medical Research Council, 1965) and

TABLE 1 PHYSICAL CHARACTERISTICS OF PATIENTS STUDIED

| Patient Number | Age | Sex | $FEV_1$ | FVC | $PaO_2$ | $PaCO_2$ | $H^+$ | RCM | $\overline{PAP}$ |
|---|---|---|---|---|---|---|---|---|---|
| | yrs | | l | l | kPa | kPa | nmol/l | ml/kg | mmHg |
| "Blue Bloaters" | | | | | | | | | |
| 1 | 55 | M | 0.4 | 1.1 | 6.1 | 7.9 | 46 | 41 | 35 |
| 2 | 57 | M | 1.0 | 2.5 | 5.6 | 6.1 | 42 | 44 | 39 |
| 3 | 52 | M | 0.9 | 1.9 | 6.8 | 6.4 | 50 | 49 | 28 |
| 4 | 61 | M | 0.5 | 3.3 | 4.5 | 7.6 | 45 | 43 | 25 |
| 5 | 51 | M | 0.8 | 2.3 | 6.5 | 5.7 | 39 | 45 | 21 |
| 6 | 52 | F | 0.4 | 1.2 | 5.5 | 6.1 | 46 | 41 | 35 |
| 7 | 66 | F | 0.3 | 1.2 | 5.7 | 7.3 | 37 | 30 | 19 |
| 8 | 57 | F | 0.5 | 1.3 | 5.9 | 8.1 | 39 | 55 | 25 |
| 9 | 58 | F | 0.4 | 1.4 | 5.5 | 8.1 | 42 | 31 | 19 |
| 10 | 62 | F | 0.6 | 1.2 | 5.6 | 7.1 | 45 | 40 | 48 |
| 11 | 62 | F | 0.5 | 1.3 | 6.8 | 7.1 | 45 | 30 | 22 |
| 12 | 58 | F | 0.5 | 1.0 | 6.7 | 7.1 | 43 | 33 | 31 |
| 13 | 68 | M | 0.5 | 1.5 | 7.0 | 7.0 | 42 | 43 | 29 |
| 14 | 58 | F | 0.5 | 1.5 | 7.7 | 6.3 | 35 | 44 | 30 |
| 15 | 46 | M | 0.6 | 1.7 | 6.3 | 7.2 | 41 | 59 | 46 |
| 16 | 61 | M | 0.5 | 1.7 | 5.5 | 7.1 | 44 | 42 | 48 |
| "Pink Puffers" | | | | | | | | | |
| 17 | 59 | M | 0.8 | 3.1 | 9.6 | 4.5 | 39 | | |
| 18 | 70 | M | 0.9 | 2.2 | 10.0 | 5.1 | 41 | | |
| 19 | 66 | M | 0.8 | 1.5 | 8.9 | 5.2 | 40 | | |
| 20 | 53 | M | 0.9 | 2.4 | 9.9 | 5.1 | 40 | | |
| 21 | 60 | M | 0.8 | 1.4 | 8.9 | 3.6 | 44 | | |
| 22 | 71 | M | 0.7 | 1.7 | 9.5 | 5.9 | 38 | | |
| 23 | 66 | F | 0.5 | 1.5 | 10.7 | 4.3 | 36 | | |
| 24 | 62 | F | 0.7 | 1.7 | 9.2 | 4.0 | 36 | | |

Footnote: $FEV_1$, forced expired volume in 1 sec; FVC, forced vital capacity; $PaO_2$, arterial oxygen tension awake; $PaCO_2$, arterial carbon dioxide tension awake; $H^+$, arterial hydrogen ion concentration awake; RCM, red cell mass; $\overline{PAP}$, mean pulmonary arterial pressure.

| Normal Values: | | | |
|---|---|---|---|
| | $PaO_2$ | 12-15 | kPa |
| | $PaCO_2$ | 4.4-6.1 | kPa |
| | $H^+$ | 36-44 | nmol/l |
| | red cell mass | 23-28 | ml/kg |
| | $\overline{PAP}$ | 12-18 | mmHg |

emphysema. Breathing patterns were recorded throughout the night in 11 of the normal subjects and in 16 of the patients. All the patients had severe irreversible airways obstruction ($FEV_1$ < 1 litre) and none had had an exacerbation of their disease for at least 6 weeks prior to being studied. Sixteen of the patients fulfilled our criteria for being "blue and bloated" [type B ( Burrows et al, 1964), non-fighters (Robin & O'Neill 1963)] having daytime arterial hypoxaemia ($PaO_2$ < 8 kPa) and hypercapnia ($PaCO_2$ > 6 kPa), pulmonary hypertension (mean pulmonary arterial pressure > 18 mmHg) and secondary polycythaemia (red cell mass > 28 ml/kg). Eight patients were termed "pink and puffing" (type A, fighters) having relatively mild arterial hypoxaemia ($PaO_2$ > 8 kPa) and a normal $PaCO_2$ (< 6 kPa) when awake. All the healthy subjects had normal chest x-rays, lung volumes and transfer factors (Cotes, 1979) and none smoked nor had a history of respiratory disease. The physical characteristics of the individuals studied are given (Table 1) as are the mean characteristics of the subject groups between which oxygenation (Table 2) and breathing patterns (Table 3) were compared).

TABLE 2 PHYSICAL CHARACTERISTICS OF SUBJECT GROUPS IN WHOM OXYGENATION WAS COMPARED DURING SLEEP

| | Healthy Subjects | "Blue Boaters" | "Pink Puffers" |
|---|---|---|---|
| Number | 16 | 16 | 8 |
| Sex | 7M, 9F | 8M, 8F | 6M, 2F |
| Age (yrs) | 53±2(SE) | 58±1 | 63±2 |

TABLE 3 PHYSICAL CHARACTERISTICS OF SUBJECT GROUPS IN WHOM BREATHING PATTERNS WERE COMPARED DURING SLEEP

| | Healthy Subjects | "Blue Boaters" | "Pink Puffers" |
|---|---|---|---|
| Number | 11 | 11 | 5 |
| Sex | 5M, 6F | 5M, 6F | 5M |
| Age (yrs) | 56±3 | 57±2 | 62±3 |

No subject was receiving hypnotic, sedative or stimulant drugs, and none was more than 20% above his desired weight (Documenta Geigy, 1970). All subjects gave written informed consent to the study which had the approval of the South Lothian Division of Medicine Ethical Advisory Committee.

Fig 4 Illustration of subject under study, showing electroencephalographic, electromyographic and electro-oculographic leads, ear oximeter, thermocouples on nasal prongs and stethogram (white). The black sensor on the left chest is a transcutaneous oxygen electrode which was used in some studies, but proved to be inaccurate.

The subjects slept (Fig 4) in a quiet, darkened room on 2 consecutive nights, the first serving to acclimatise the subject to the surroundings (Agnew et al, 1966), and no data from the first night are reported. Ear oxygen saturation was recorded continuously using a Hewlett Packard 47201A ear oximeter, airflow at the mouth and nostrils by thermocouples mounted on nasal prongs and anteroposterior chest wall movement by an induction stethogram placed in the midline at the level of the third intercostal space anteriorly. Simultaneous recordings were made of electroencephalogram (EEG; by 2 midline fronto-parietal electrodes), electrooculogram (EOG; by 4 electrodes above and lateral to the outer canthi) and electromyogram (EMG; by 2 submental electrodes).

Once this equipment had been attached (c 10.30pm) the subject lay awake for 15 minutes during which data were collected and thereafter the subject was allowed to sleep. Unless assistance was sought from the doctor and/or nurse present, the subjects were not disturbed until 6.30am. After final awakening, at least 15 minutes of data were obtained before the monitoring apparatus was removed.

In 11 of the patients with hypoxic chronic bronchitis and emphysema, brachial artery catheters had already been inserted as part of the Medical Research Council trial of long term oxygen therapy. During study

nights, arterial blood samples were withdrawn before the patient fell asleep (during EEG confirmed wakefulness), at 2 hourly intervals throughout the night, when hypoxaemic episodes were indicated by the ear oximeter, and at least 20 minutes after the final awakening. These samples were analysed within 10 minutes of withdrawal for $PaO_2$, $PaCO_2$ and $H^+$ (Instrumentation Laboratory 313 blood gas system).

In 3 patients a pulmonary arterial catheter had also been inserted as part of the MRC trial and remained in situ during the sleep studies. Pulmonary arterial pressure was measured with an El Cometia 750 pressure transducer.

The effects of oxygen administration on sleep quality and nocturnal oxygenation were assessed in 6 of the "blue and bloated" patients who were studied on 3 consecutive nights. During the acclimatisation night and one study night they received air and on the other night oxygen, both gases being delivered at 2 1/min via nasal prongs. The order of air or oxygen administration during the second and third night was randomised and the patient did not know which gas was being given.

Data were recorded simultaneously on 3 time base recorders synchronised by a computer-generated time code every 15 minutes. EEG, EOG and EMG were recorded on an SLE E8b recorder running at 15 mm/sec and each 20 second epoch was analysed by standard criteria (Rechtschaffen &

Kales, 1968). Oxygen saturation, airflow and chest wall movements were displayed on a Mingograff 81 recorder running at 5 mm/sec. To allow easier identification of long term shifts in oxygenation, saturation was also recorded on a Bryans 28000 recorder running at 30 mm/hour. I analysed all the breathing and oxygenation traces without knowing the diagnosis of the subject under study and the breathing trace was analysed without knowledge of the oxygenation record and vice versa; both were analysed without knowledge of the EEG sleep stage.

The following data were obtained from each oxygen saturation trace;-

1. Awake Saturation, this being the average of the pre and post sleep values, there being no significant difference between these values. This value thus reflected at least 30 minutes of EEG confirmed wakefulness, normally longer depending on sleep onset latency and the time of final awakening, during which the subject was supine.
2. Lowest Oxygen Saturation
3. Number of Hypoxaemic Episodes, defined as a drop in saturation of more than 10% from the immediately preceeding stable saturation during sleep, such a drop lasting at least 1 minute.
4. Arterial Oxygen Tensions were calculated (Severinghaus, 1966) for all subjects from the awake and lowest sleeping oxygen saturations assuming:-

a. A similar oxyhaemoglobin dissociation curve in all subjects.

b. $H^+$ 40 nmol/l

c. Temperature 37°C

This transformation is necessarily an approximation. However, arterial oxygen tension was measured directly in only 11 of the 40 subjects (see below) all of these being "blue and bloated". Consent for arterial catheter insertion was not sought in the remaining subjects as this was not considered ethically justifiable. Further, even in the subjects in whom arterial samples were obtained, samples could only rarely be drawn at exactly the lowest oxygen saturation. Hence to estimate the maximal changes in $PaO_2$ in all groups of subjects it is necessary to calculate oxygen tension from saturation.

Errors due to the first assumption are probably small (Tweeddale et al, 1976 & 1977). However, $H^+$ concentration and temperature do change overnight. The mean lowest hydrogen ion obtained during sleep in the 11 patients in whom arterial blood was sampled was 49 nmol/l. Although temperature was not measured, other workers have shown mean lowest temperatures of 36.2°C during sleep (Kreider et al, 1958). Combining these estimates of $H^+$ 49 nmol/l and 36.2°C introduces a 3% error for the $PaO_2$ calculated from the mean lowest $SaO_2$ for the "blue bloaters" of 52% compared with the oxygen

tension calculated assuming $H^+$ 40 nmol/l and 37°C ($H^+$ 49 nmol/l; 36.2°C - 3.8 kPa; $H^+$ 40 nmol/l, 37°C - 3.7 kPa). The error is relatively small because increasing $H^+$ and decreasing temperature have opposite effects on the dissociation curve. In a worst case situation (temperature 36.2°C, $H^+$ 40 nmol/l or $H^+$ 49 nmol/l, temperature 37°C) - most unlikely events as sleep is associated with falling temperature and rising $H^+$ - the maximal error for the "blue bloaters" lowest $PaO_2$ is still only 0.4 kPa.

For conversions to calculated $PaO_2$ and for comparison of $SaO_2$ changes between groups, ear oximeter readings below 50% were corrected using the graph (Fig 1) illustrated earlier. This is a further source of error, but at oxygen saturations of between 50 and 20%, the dissociation curve is so steep that even an error of 10% $SaO_2$ would result in an error in calculated $PaO_2$ of less than 0.5 kPa.

I feel that the transformation from saturation to $PaO_2$, whilst only an approximation, provides data which allows useful comparison of $PaO_2$ changes between individuals and between groups, changes which could not be measured directly for ethical reasons.

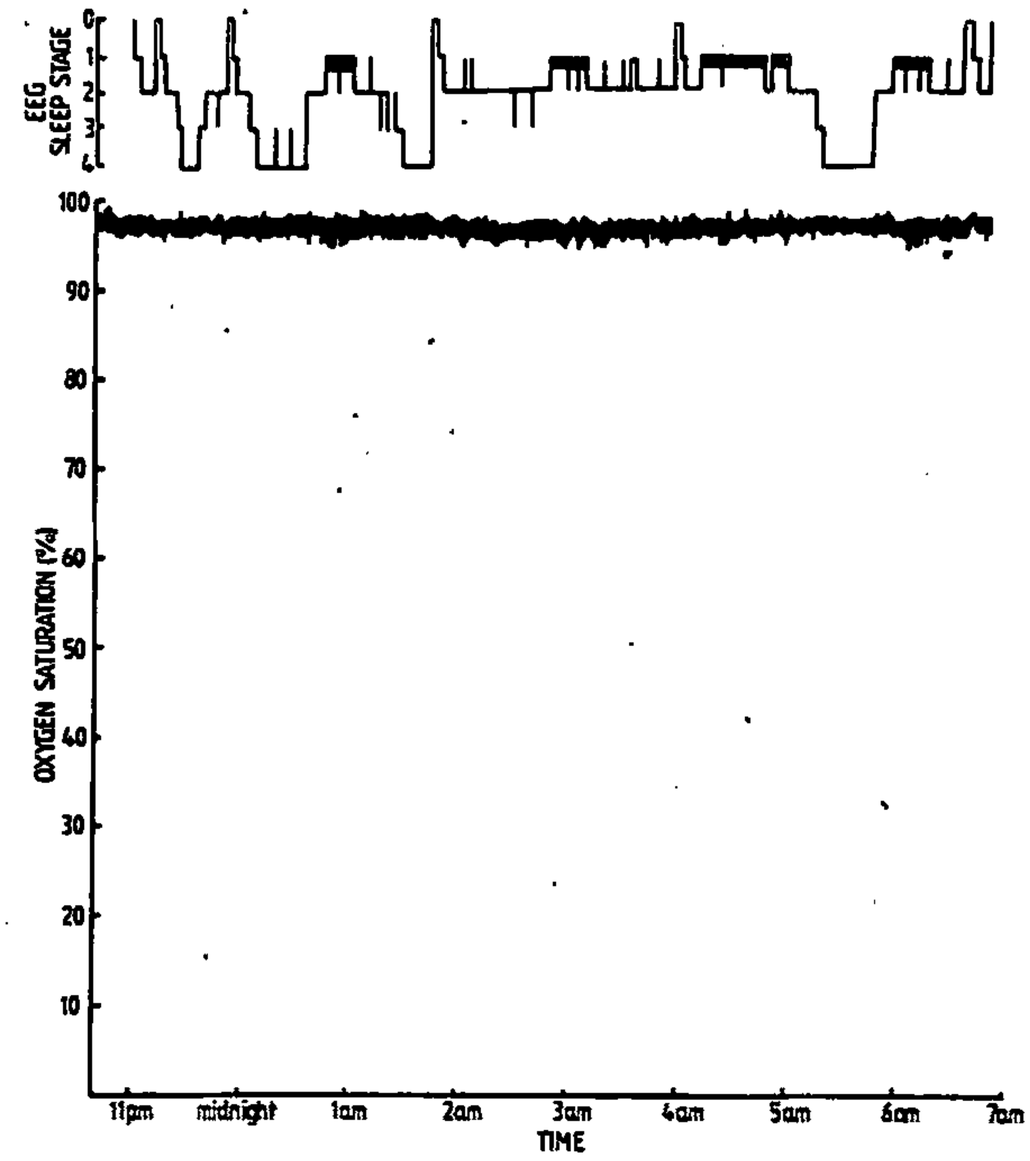
The breathing pattern traces were analysed for:-

1. Apnoea, defined as cessation of airflow at the mouth and nostrils for at least 10 seconds, and classified by conventional criteria (Guilleminault et al, 1976)
2. Hypopnoea, in which, despite continued airflow, the amplitude of the stethogram signal fell to less than 50% of the level during the immediately preceeding regular breathing, for every breath during at least 10 seconds
3. Hyperpnoea, in which the stethogram amplitude doubled for at least 10 seconds with continued airflow

Over 95% of episodes of apnoea, hypopnoea or hyperpnoea occurred repetitively, giving easily recognised "periods of irregular breathing". Such a period was defined as starting with either an apnoea, hypopnoea or hyperpnoea and ending at the beginning of the next 2 minute period in which there was uninterrupted regular breathing. The total duration of irregular breathing was the sum of all these periods. Each period of irregular breathing was classified according to the dominant breathing abnormality. Periods of hyperpnoea were only identified in 3 subjects (2 normal subjects, 1 patient) and lasted a total of 6.5 minutes. They were not associated with any significant EEG or $SaO_2$ change and thus hyperpnoea is not considered further.

The breathing pattern during each hypoxaemic episode was determined from the independent analysis of the breathing trace. If neither apnoea nor hypopnoea had been detected during the hypoxaemic episode, the breathing trace was reanalysed and classified as either regular or cyclical, defining the latter as alternating normal and reduced chest wall movement, reduced movement defined as less than 75% of the preceding stable baseline for at least ten seconds. During 2 hypoxaemic episodes the breathing trace was not analysable due to technical problems.

The significance of observed differences was assessed by paired or unpaired t tests (Snedecor & Cochran, 1980) where appropriate. Data which were not normally distributed were analysed by the Wilcoxon Rank test (Snedecor & Cochran, 1980) or the Kruskal-Wallis test (Siegel, 1956) in conjunction with tests of statistical inference (Miller, 1966). Results are quoted as means $\pm$ standard errors.



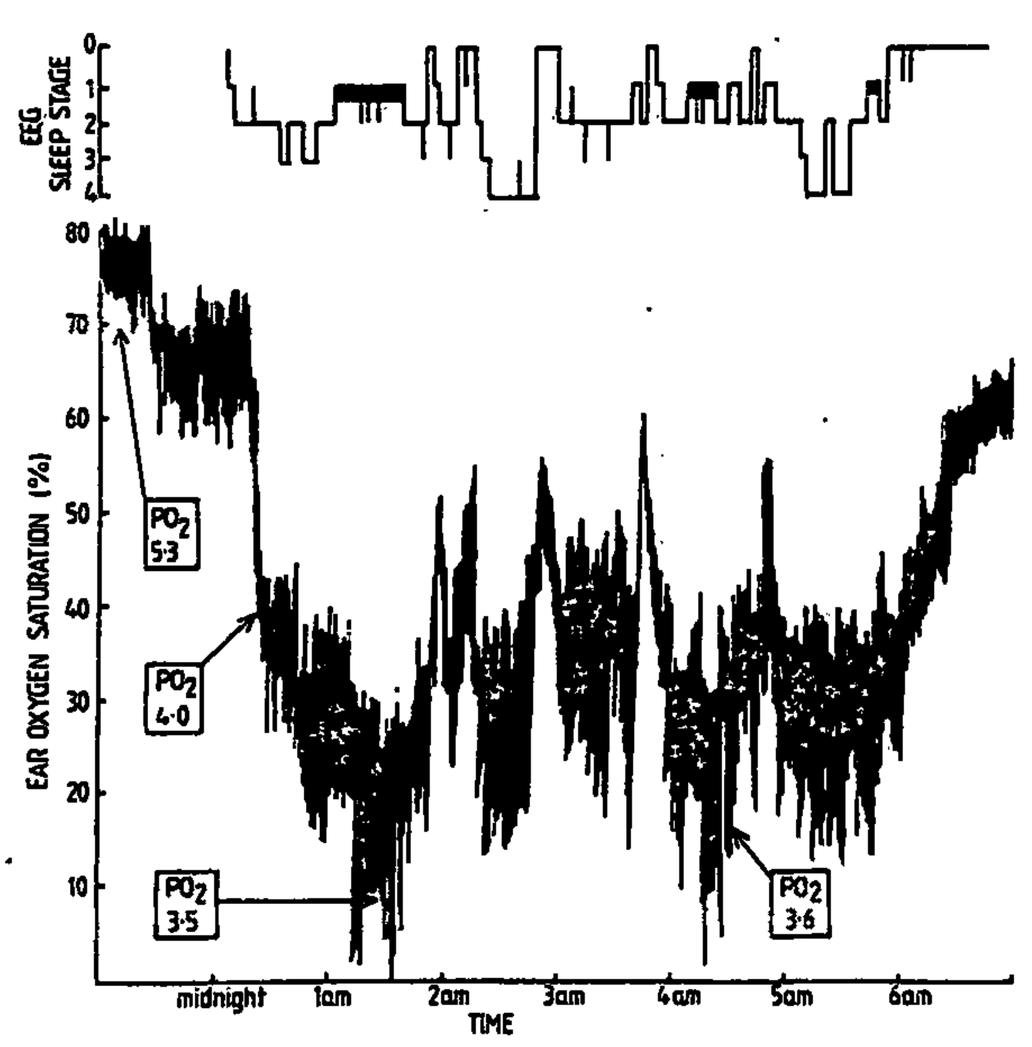




Fig 5 Example of oxygen saturation (ear oximeter) and EEG sleep stage throughout the night in, above, a healthy control (subject 2) and below, a "blue bloater" (patient 10). The shaded areas on the EEG trace represent REM sleep.

# CHAPTER 5

# RESULTS

## Oxygenation

Most normal subjects maintained relatively stable oxygen saturations during sleep (Fig 5) whereas "blue bloaters" had intermittent episodes of severe desaturation during sleep (fig 5). Hypoxaemic episodes occurred in 3 of the 16 normal subjects, and in 3 of the 8 "pink puffers", but in all 16 "blue bloaters" (Table 4). The "blue bloaters" also had significantly more hypoxaemic episodes than either the normal subjects ($p < 0.01$) or "pink puffers" ($p < 0.05$). The mean lowest oxygen saturation during sleep was significantly lower in the "blue bloaters" than in the "pink puffers" ($p < 0.001$) and was also lower in the "pink puffers" than in the normal subjects ($p < 0.05$). Mean maximal falls in arterial oxygen saturation were significantly greater in the "blue bloaters" than in either the normal subjects ($p < 0.01$) or "pink puffers" ($p < 0.05$). However, mean falls in calculated oxygen tension were not different in the 3 groups ($p > 0.1$, Table 5).

When the data for oxygen saturation in normal subjects, "pink puffers" and "blue bloaters" were plotted together, there was a clear and curvilinear relationship

TABLE 4

OXYGEN SATURATION AND BREATHING PATTERNS DURING SLEEP IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

| Subject No. | Age (yrs) | Sex | $SaO_2$% W | $SaO_2$% L | No. of Dips | Dips In Stage 2 | Dips In REM | No. of Apnoeas C | No. of Apnoeas O | Hypop (min) | Total Irreg Breath (min) | Dips In Hypop | Dips In Apnoea | Cycl | Reg | Inadeq Record |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Healthy Subjects** | | | | | | | | | | | | | | | | |
| 1 | 68 | M | 95 | 71 | 2 | - | 1* | - | 14 | - | 4.2 | - | 1 | - | - | 1 |
| 2 | 57 | M | 98 | 94 | 0 | - | - | - | - | 21.4 | 21.4 | - | - | - | - | - |
| 3 | 52 | M | 96 | 92 | 0 | - | - | 4 | - | 30.0 | 31.2 | - | - | - | - | - |
| 4 | 42 | M | 98 | 90 | 0 | - | - | - | 1 | 22.2 | 22.5 | - | - | - | - | - |
| 5 | 37 | M | 97 | 93 | 0 | - | - | - | 2 | 6.1 | 6.5 | - | - | - | - | - |
| 6 | 64 | F | 95 | 93 | 0 | - | - | - | - | - | 0 | - | - | - | - | - |
| 7 | 64 | F | 95 | 92 | 0 | - | - | - | 14 | 2.9 | 16.9 | - | - | - | - | - |
| 8 | 63 | F | 97 | 78 | 1 | - | 1 | - | 4 | 34.0 | 34.0 | - | - | 1 | - | - |
| 9 | 60 | F | 96 | 72 | 2 | - | 2 | - | 62 | 24.1 | 94.3 | - | 2 | - | - | - |
| 10 | 55 | F | 97 | 90 | 0 | - | - | - | - | 24.3 | 24.3 | - | - | - | - | - |
| 11 | 53 | F | 96 | 94 | 0 | - | - | - | - | 8.8 | 8.8 | - | - | - | - | - |
| 12 | 45 | M | 98 | 92 | 0 | - | - | | | | | | | | | |
| 13 | 45 | M | 97 | 90 | 0 | - | - | | | | | | | | | |
| 14 | 50 | F | 97 | 92 | 0 | - | - | | | | | | | | | |
| 15 | 50 | F | 96 | 93 | 0 | - | - | | | | | | | | | |
| 16 | 49 | F | 95 | 93 | 0 | - | - | | | | | | | | | |
| **"Blue Bloaters"** | | | | | | | | | | | | | | | | |
| 1 | 55 | M | 72 | 30 | 5 | - | 5 | - | 1 | 10.0 | 10.0 | 5 | - | - | - | - |
| 2 | 57 | M | 72 | 21 | 3 | - | 3 | - | - | 17.8 | 17.8 | 3 | - | - | - | - |
| 3 | 52 | M | 85 | 48 | 5 | - | 5 | 1 | - | 46.0 | 46.2 | 5 | - | - | - | - |
| 4 | 61 | M | 70 | 37 | 1 | - | 1 | 1 | - | - | 0.2 | - | - | 1 | - | - |
| 5 | 51 | M | 90 | 67 | 2 | - | 2 | 389 | - | 5.0 | 314.3 | - | 2 | - | - | - |
| 6 | 52 | F | 79 | 36 | 3 | - | 3 | 2 | - | 2.8 | 3.2 | 2 | - | 1 | - | - |
| 7 | 66 | F | 91 | 64 | 2 | - | 2 | - | - | 3.5 | 3.5 | 2 | - | - | - | - |
| 8 | 57 | F | 60 | 39 | 3 | 2 | 1 | - | - | 3.3 | 3.3 | 1 | - | 1 | 1 | - |
| 9 | 58 | F | 60 | 22 | 3 | - | 3 | - | - | 38.0 | 38.0 | 2 | - | - | 1 | - |
| 10 | 62 | F | 77 | 0 | 5 | 2 | 3 | - | - | 20.1 | 20.1 | 1 | - | 4 | - | - |
| 11 | 62 | F | 89 | 75 | 2 | - | 2 | - | - | 9.0 | 9.0 | 2 | - | - | - | - |
| 12 | 58 | F | 85 | 15 | 7 | - | 7 | | | | | | | | | |
| 13 | 68 | M | 89 | 74 | 2 | - | 2 | | | | | | | | | |
| 14 | 58 | F | 82 | 39 | 1 | - | 1 | | | | | | | | | |
| 15 | 46 | M | 90 | 79 | 1 | - | 1 | | | | | | | | | |
| 16 | 61 | M | 70 | 9 | 1 | - | 1 | | | | | | | | | |
| **"Pink Puffers"** | | | | | | | | | | | | | | | | |
| 17 | 59 | M | 95 | 70 | 1 | 1 | - | 1 | - | 1.2 | 1.4 | - | - | - | - | 1 |
| 18 | 70 | M | 93 | 83 | 0 | - | - | - | - | 12.0 | 12.0 | - | - | - | - | - |
| 19 | 66 | M | 93 | 88 | 0 | - | - | 2 | 1 | 6.8 | 7.5 | - | - | - | - | - |
| 20 | 53 | M | 96 | 75 | 2 | - | 2 | - | - | 52.0 | 52.0 | 2 | - | - | - | - |
| 21 | 60 | M | 92 | 81 | 2 | - | 2 | - | - | 65.5 | 65.5 | - | - | 1 | 1 | - |
| 22 | 71 | M | 93 | 83 | 0 | - | - | | | | | | | | | |
| 23 | 66 | F | 96 | 89 | 0 | - | - | | | | | | | | | |
| 24 | 62 | F | 95 | 90 | 0 | - | - | | | | | | | | | |

Footnote: $SaO_2$, ear oximeter reading; W, awake; L, lowest oximeter reading during sleep; Dip, hypoxaemic episode, i.e. a drop in $SaO_2$ of more than 10% from the immediately preceding stable $SaO_2$ during sleep, lasting for at least 1 min; C, central apnoea; O, obstructive apnoea; Hypop, hypopnoea; Irreg Breath, irregular breathing; Cycl, cyclical; Reg, regular; Inadeq record, inadequate record; *, inadequate EEG trace; Other definitions, see text.

TABLE 5 OXYGENATION DURING SLEEP

| | Healthy Subjects | "Pink Puffers" | "Blue Bloaters" |
|---|---|---|---|
| Median dips | $0^{+}$ | $0^{+}$ | 3 |
| Mean lowest $SaO_2$ % | $89 \pm 2^{+}$ | $82 \pm 3^{+}$ | $52 \pm 4$ |
| Mean fall $SaO_2$ % | $7.8 \pm 1.9^{+}$ | $11.8 \pm 2.6^{+}$ | $37.9 \pm 4.9$ |
| Mean fall calculated $PO_2$ (kPa) | $3.7 \pm 0.5$ | $3.1 \pm 0.5$ | $2.3 \pm 0.2$ |

Footnote: dip, 10% decrease in saturation from preceding stable saturation during sleep, lasting for at least 1 minute. $SaO_2$, oxygen saturation - corrected oximeter reading.
$^{+}$ $p < 0.05$ versus "blue bloaters".

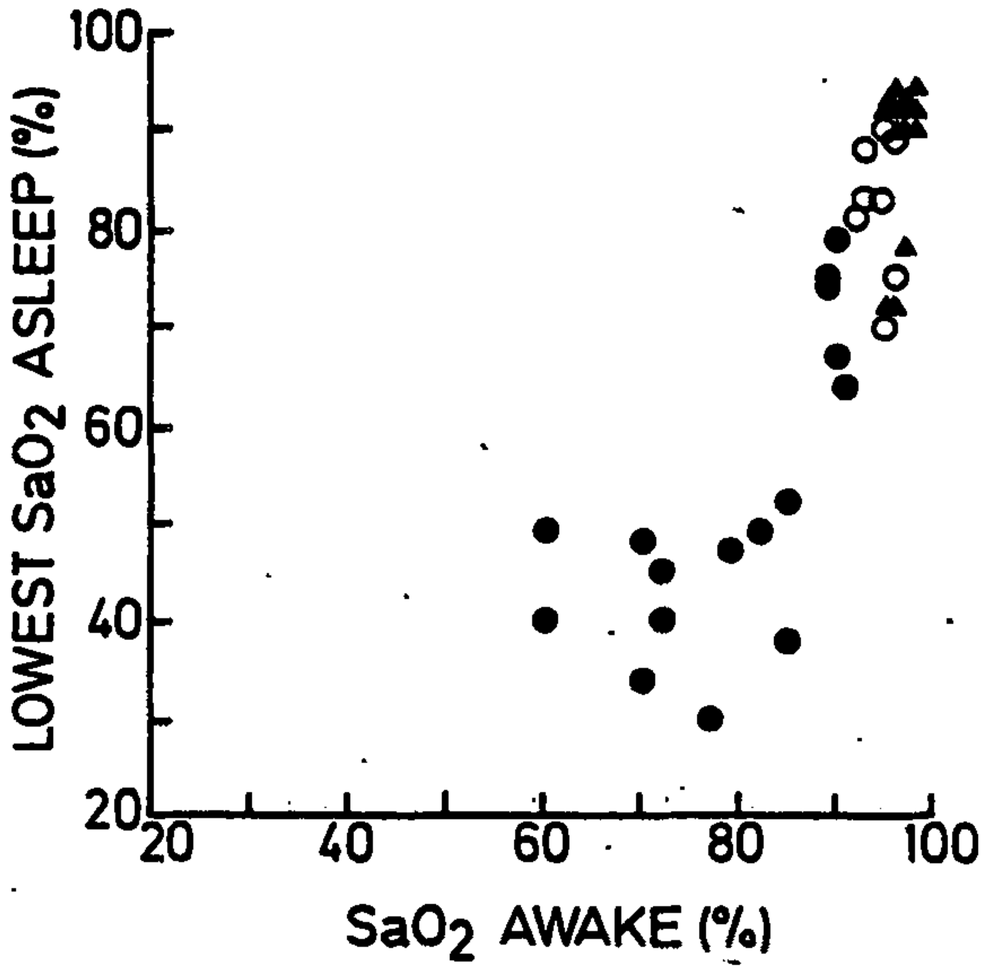



Fig 6 Comparison of lowest oxygen saturation during sleep (corrected ear oximeter reading) and oxygen saturation during wakefulness in normal subjects (triangles), "pink puffers" (open circles) and "blue bloaters" (closed circles).

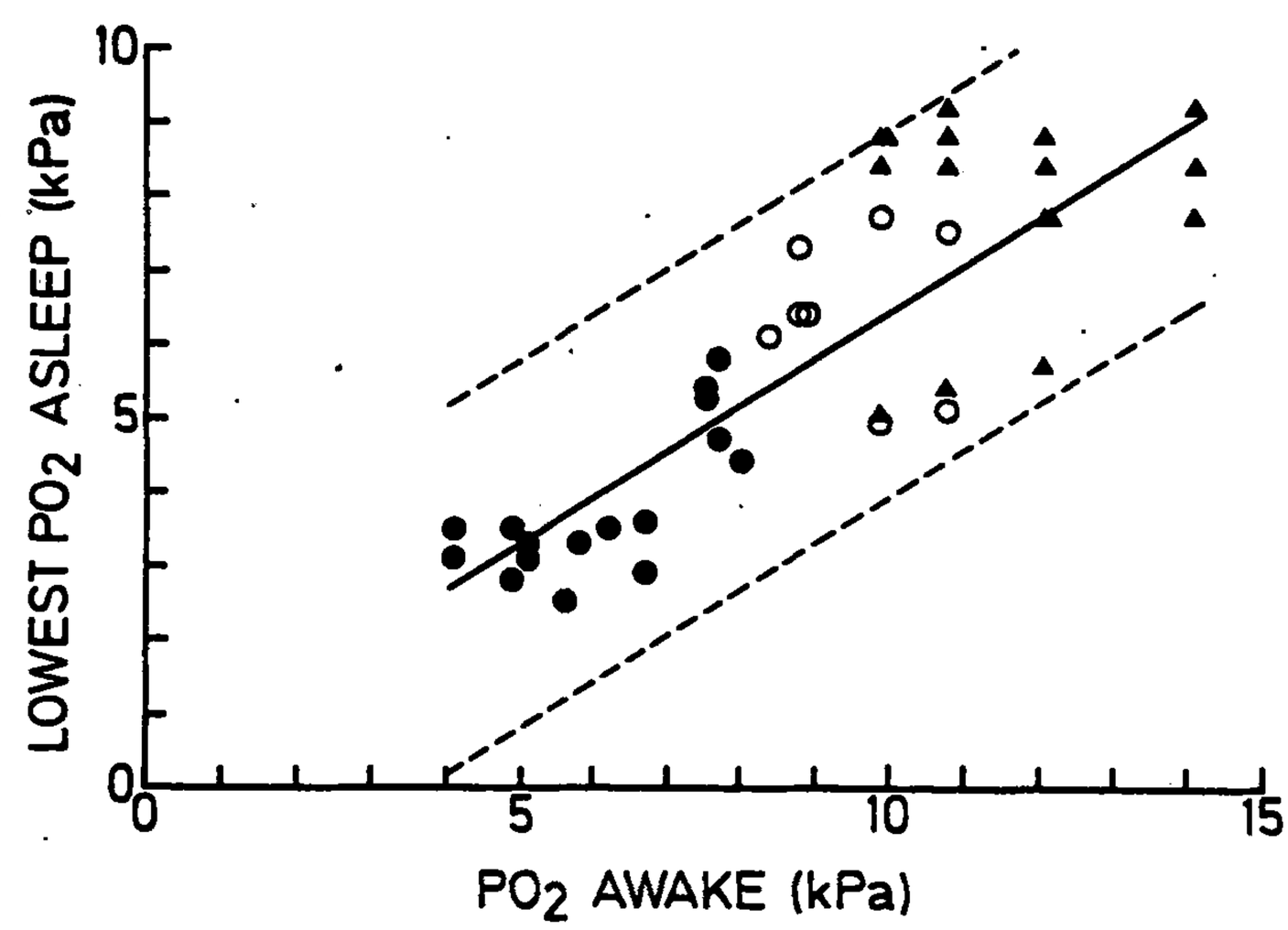



Fig 7 Comparison of lowest calculated oxygen tension during sleep with calculated oxygen tension during wakefulness in healthy subjects (triangles), "pink puffers" (open circles) and "blue bloaters" (closed circles). The regression (solid) line and 95% confidence limits for the data (dashed line) are indicated.

between the oxygen saturation during wakefulness and the lowest oxygen saturation measured during sleep (Fig 6). There was a significant linear correlation ($p < 0.001$; Fig 7) between the calculated $PaO_2$ during wakefulness and the lowest calculated $PaO_2$ during sleep, yielding the equation

$$PaO_2 \text{ asleep (kPa)} = (0.65 \pm 0.07)\ PaO_2 \text{ awake (kPa)} + 0.15 \pm 0.65$$

$$n = 40 \quad r = 0.84$$

## Breathing Patterns

There was no significant difference in the duration of irregular breathing between any of the groups of subjects (Table 4). Similarly, there was no difference between the groups in the duration of either hypopnoea or apnoea during sleep, nor in any sleep stage. In all 3 groups, over 90% of the total duration or irregular breathing was due to hypopnoea.

## Sleep Quality

The sleep quality of the subjects and patients studied is given in Table 6. Comparisons of sleep pattern between the groups do not form part of this thesis as sleep was staged by Drs Brezinova and Shapiro, and the sleep patterns for many of the patients has been reported elsewhere (Brezinova et al, 1982; Calverley et al, 1982b).

TABLE 6 SLEEP QUALITY IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

| Subject No. | TIB (min) | TST (min) | SEI (%) | SOL | % Total sleep time 1 | 2 | 3 | 4 | Stage REM |
|---|---|---|---|---|---|---|---|---|---|
| Healthy Subjects | | | | | | | | | |
| 1 | 435 | 309 | 71 | 7 | 25 | 57 | 12 | 4 | 2 |
| 2 | 363 | 287 | 79 | 29 | 7 | 59 | 13 | 1 | 19 |
| 3 | 473 | 413 | 87 | 8 | 7 | 51 | 16 | 4 | 23 |
| 4 | 452 | 366 | 81 | 28 | 17 | 46 | 9 | 6 | 23 |
| 5 | 374 | 354 | 95 | 6 | 15 | 43 | 8 | 19 | 16 |
| 6 | 436 | 409 | 94 | 16 | 3 | 50 | 11 | 5 | 31 |
| 7 | 386 | 369 | 96 | 2 | 5 | 68 | 6 | 0 | 20 |
| 8 | 398 | 351 | 88 | 6 | 8 | 59 | 6 | 8 | 19 |
| 9 | 441 | 358 | 81 | 27 | 11 | 60 | 9 | 4 | 15 |
| 10 | 450 | 309 | 69 | 54 | 10 | 60 | 18 | 0 | 12 |
| 11 | 400 | 386 | 96 | 11 | 5 | 53 | 7 | 9 | 25 |
| 12 | 410 | 396 | 97 | 12 | 14 | 47 | 5 | 7 | 21 |
| 13 | 455 | 429 | 94 | 14 | 6 | 42 | 10 | 22 | 19 |
| 14 | 370 | 335 | 91 | 3 | 8 | 53 | 12 | 11 | 17 |
| 15 | 457 | 424 | 93 | 7 | 6 | 50 | 5 | 10 | 27 |
| 16 | 445 | 425 | 96 | 2 | 5 | 46 | 7 | 24 | 18 |
| "Blue Bloaters" | | | | | | | | | |
| 1 | 464 | 310 | 67 | 7 | 6 | 45 | 13 | 21 | 15 |
| 2 | 422 | 320 | 76 | 56 | 8 | 80 | 6 | 0 | 6 |
| 3 | 471 | 388 | 82 | 5 | 18 | 56 | 12 | 4 | 11 |
| 4 | 412 | 358 | 87 | 37 | 3 | 66 | 7 | 5 | 18 |
| 5 | 502 | 357 | 71 | 127 | 23 | 65 | 1 | 0 | 11 |
| 6 | 547 | 494 | 90 | 13 | 10 | 48 | 12 | 4 | 26 |
| 7 | 427 | 408 | 96 | 3 | 30 | 67 | 1 | 0 | 2 |
| 8 | 415 | 228 | 55 | 34 | 37 | 52 | 7 | 1 | 3 |
| 9 | 390 | 261 | 67 | 46 | 35 | 51 | 5 | 3 | 5 |
| 10 | 462 | 442 | 96 | 10 | 11 | 42 | 10 | 18 | 19 |
| 11 | 432 | 279 | 65 | 94 | 10 | 51 | 7 | 20 | 13 |
| 12 | 420 | 364 | 87 | 29 | 5 | 23 | 14 | 22 | 33 |
| 13 | 405 | 350 | 86 | 14 | 10 | 53 | 3 | 8 | 20 |
| 14 | 401 | 363 | 90 | 15 | 18 | 59 | 3 | 0 | 21 |
| 15 | 345 | 181 | 53 | 10 | 16 | 64 | 11 | 0 | 9 |
| 16 | 430 | 394 | 92 | 12 | 8 | 58 | 12 | 4 | 18 |
| "Pink Puffers" | | | | | | | | | |
| 17 | 348 | 268 | 77 | 37 | 19 | 52 | 7 | 3 | 19 |
| 18 | 480 | 324 | 68 | 69 | 18 | 48 | 10 | 10 | 15 |
| 19 | 390 | 228 | 59 | 11 | 21 | 42 | 10 | 4 | 22 |
| 20 | 402 | 256 | 64 | 84 | 12 | 49 | 12 | 1 | 28 |
| 21 | 540 | 506 | 94 | 10 | 14 | 60 | 6 | 4 | 16 |
| 22 | 293 | 138 | 47 | 31 | 15 | 60 | 9 | 0 | 16 |
| 23 | 484 | 182 | 38 | 69 | 34 | 56 | 1 | 0 | 9 |
| 24 | 435 | 403 | 93 | 16 | 7 | 54 | 4 | 7 | 21 |
| Mean | | | | | | | | | |
| Healthy Subjects | 422 | 370 | 88 | 15 | 10 | 53 | 10 | 8 | 19 |
| "Blue Bloaters" | 434 | 344 | 78 | 32 | 16 | 55 | 8 | 7 | 14 |
| "Pink Puffers" | 422 | 288 | 68 | 41 | 18 | 53 | 7 | 4 | 18 |
| Normal Sleep* Mean ± SE | 458 40 | 406 50 | 88 8 | 12 10 | 10 4 | 59 9 | 3 4 | 2 2 | 24 4 |

Footnote: TIB, time in bed; TST, total sleep time; SEI, sleep efficiency index; SOL, sleep onset latency; Sleep time defined by criteria of Williams et al, 1974 from which normal values for 60-69 year olds' sleep times are quoted (*).

The patients tended to sleep less well than the healthy subjects, who on average slept normally (Table 6).

## Correlations Between Oxygenation, Sleep Stage and Breathing Pattern

The great majority (51/57) of the hypoxaemic episodes occurred during REM sleep (Fig 8, Table 4) ($p < 0.001$). Of the remaining 6 hypoxaemic episodes, 5 occurred in non-REM sleep and during the sixth the EEG trace was obscured by artefact.

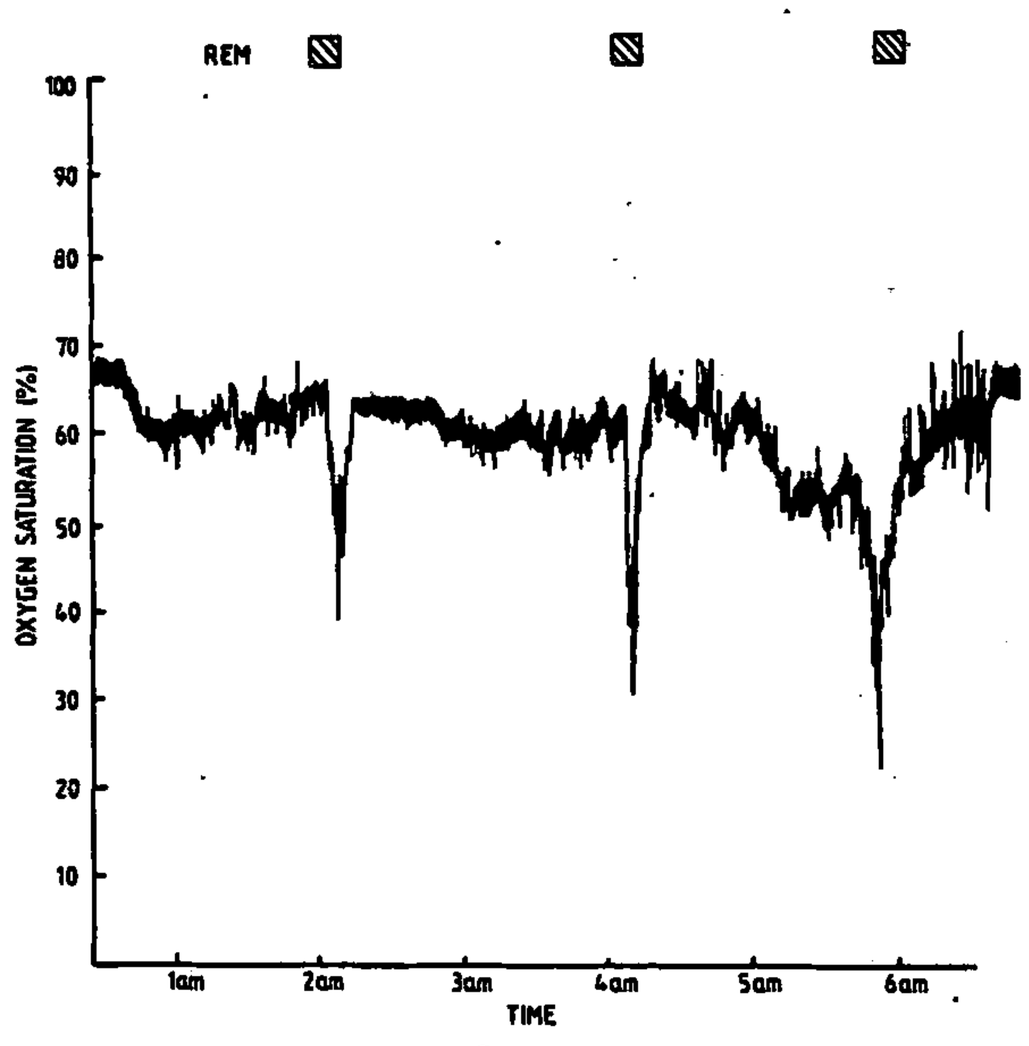



Fig 8 Example of occurrence of hypoxaemic episodes in REM sleep. Oxygen saturation (ear oximeter) throughout the night in a "blue bloater" (patient 2), hatched boxes representing REM sleep.

In the studies in which breathing data were recorded, most (25/38) of the hypoxaemic episodes in the patients with chronic bronchitis and emphysema occurred

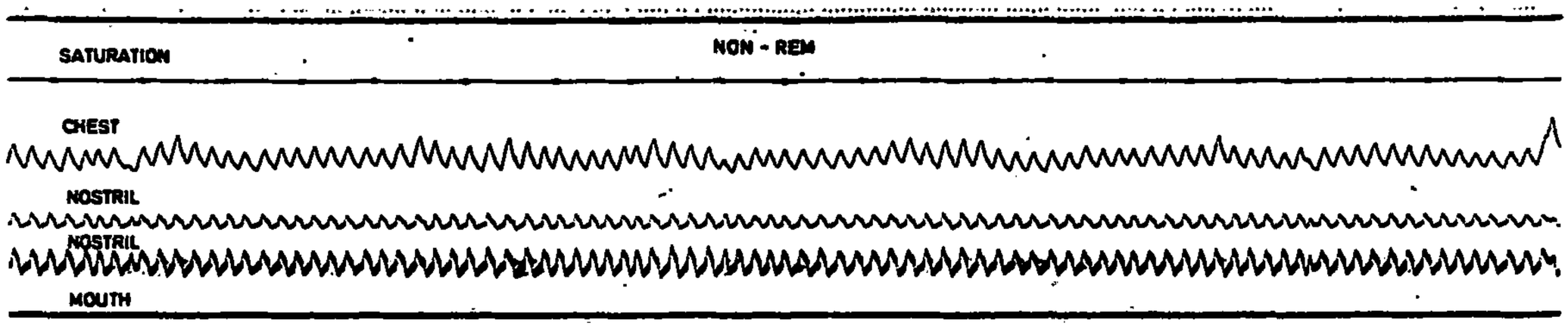



Fig 9 Example of breathing and oxygen saturation traces during non-REM (upper panel) and REM (lower panel) sleep in a "blue bloater" (patient 9). In REM sleep, recurrent hypopnoea is associated with drops in saturation of 5 to 10% in this example.

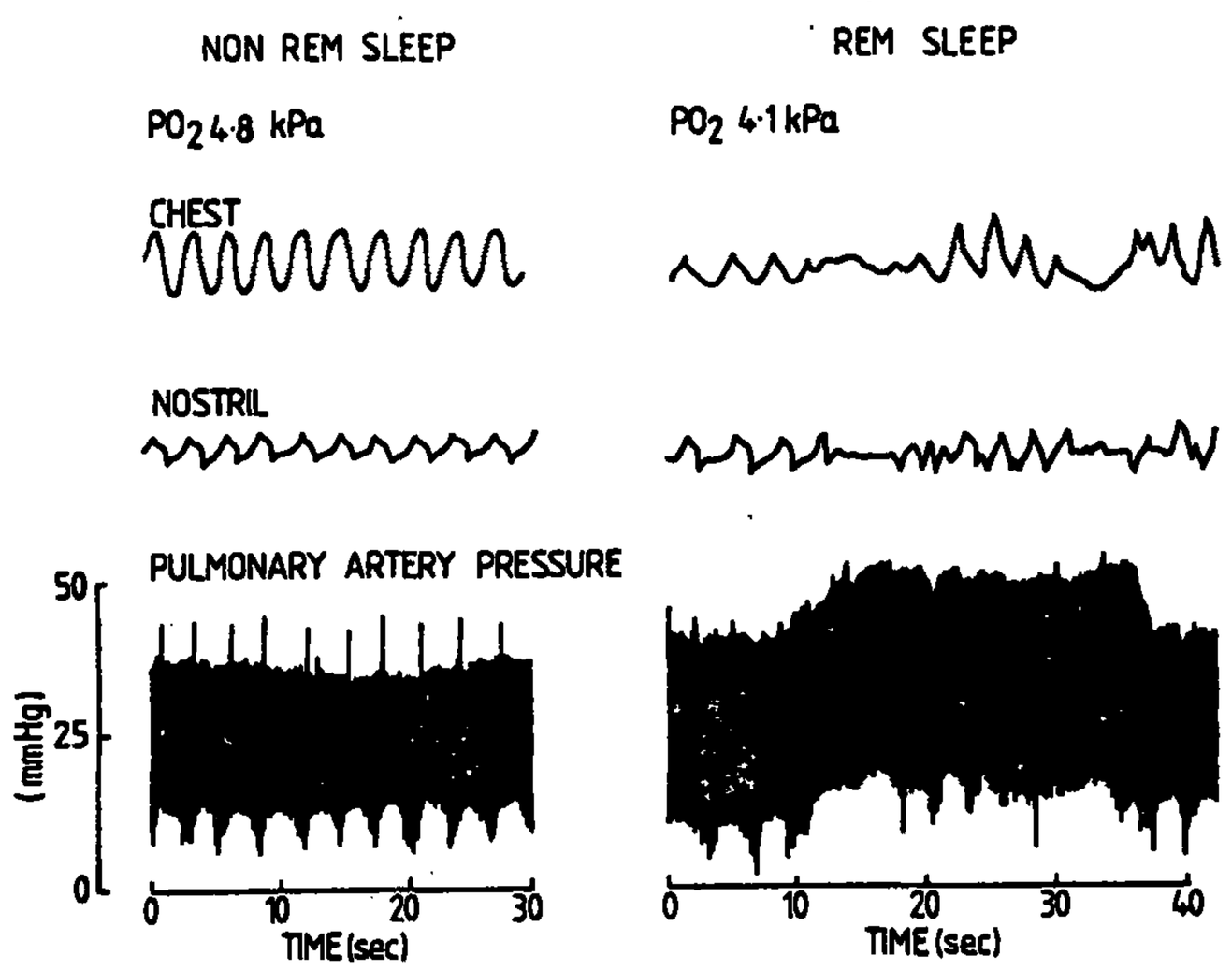



Fig 10 Breathing pattern and pulmonary arterial pressure in patient 9 during: left, non-REM sleep when breathing is regular and oxygenation stable whereas right, in REM sleep, the breathing is irregular, arterial oxygen tension falls and pulmonary arterial pressure rises.

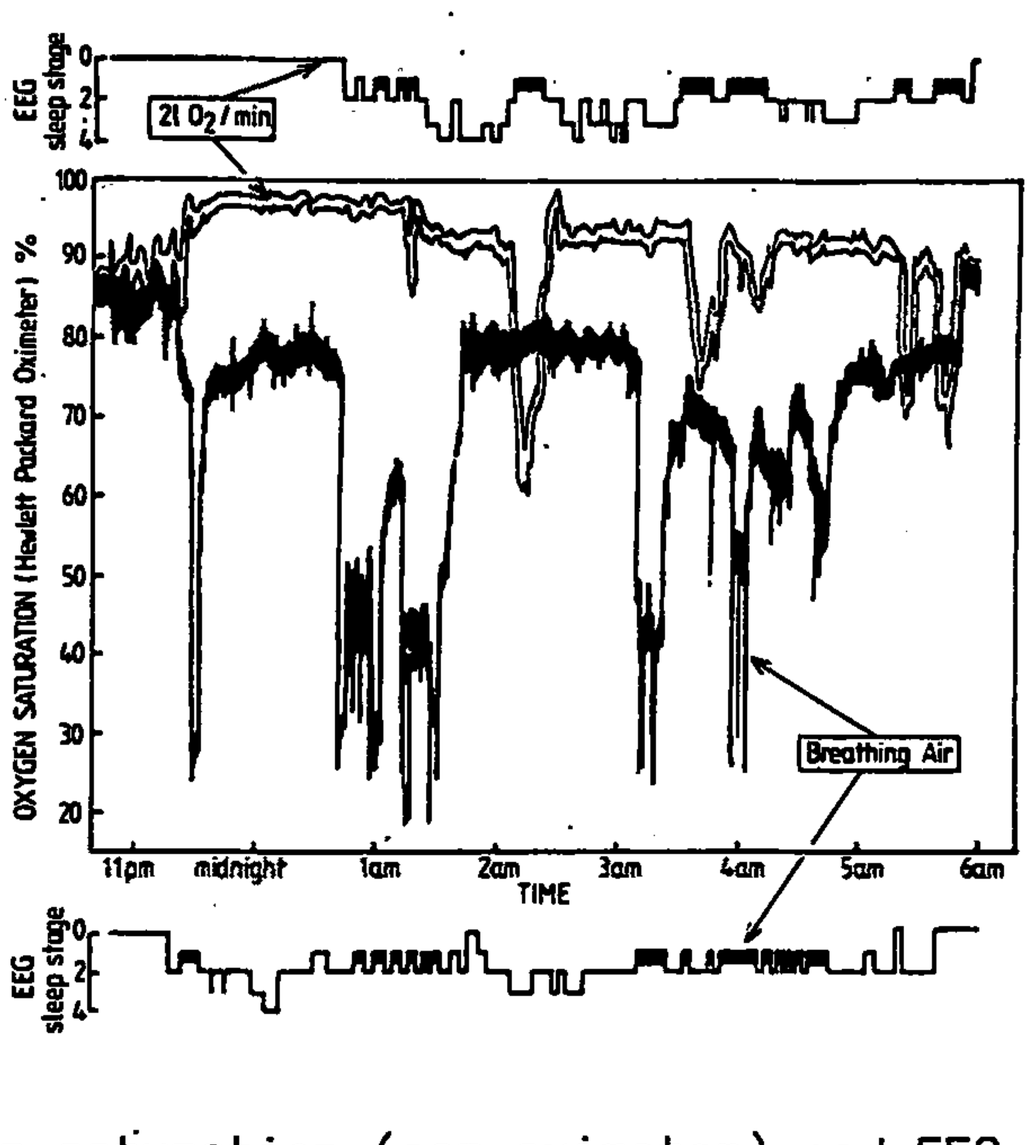



Fig 11 Oxygen saturation (ear oximeter) and EEG sleep stage throughout the night in a "blue bloater" (patient 12) when breathing 2 l/min of oxygen through nasal prongs (above) and on another night when receiving 2 l/min of air (below). Black areas on EEG record are REM sleep.

during periods of hypopnoea (Fig 9), and only 2 were associated with apnoea (Table 4). In contrast, 3 of the 4 hypoxaemic episodes in the normal subjects were associated with obstructive apnoea. Nine of the remaining 12 hypoxaemic episodes occurred during breathing which was classified as cyclical, the stethogram signal being insufficiently reduced to qualify for hypopnoea. The remaining 3 out of the total of 42 hypoxaemic episodes occurred during regular breathing.

Arterial Blood Sampling

In the 11 "blue bloaters" in whom arterial blood was sampled during sleep, the lowest $PaO_2$ ranged from 3.5 to 6.2 kPa (Table 7), the highest $PaCO_2$ from 6.4 to 8.5 kPa and the highest $H^+$ from 40 to 62 nmol/l. The mean decrease in $PaO_2$ was 1.6 kPa, the mean rise in $PaCO_2$ 0.7 kPa and the mean $H^+$ rise 6 nmol/l.

Pulmonary Arterial Pressure

In all 3 patients studied, mean pulmonary arterial pressure rose slightly (range 2-5 mmHg) from wakefulness to non-REM sleep. During hypoxaemic episodes, mean pulmonary arterial pressure always rose to at least 3 mmHg (range 8-16 mmHg) above the level in wakefulness (Fig 10).

Oxygen Therapy

The 6 patients studied had higher levels of oxygenation during sleep (Fig 11) and fewer, briefer and less severe hypoxaemic episodes ($p < 0.05$) breathing

TABLE 7

ARTERIAL BLOOD GAS TENSIONS AND HYDROGEN ION CONCENTRATIONS DURING SLEEP IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

| Patient No. | Pre-sleep | | | At lowest $PO_2$ asleep | | | Highest values asleep | | Post-sleep | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $PO_2$ kPa | $PCO_2$ kPa | $H^+$ nmol/l | $PO_2$ kPa | $PCO_2$ kPa | $H^+$ nmol/l | $PCO_2$ kPa | $H^+$ nmol/l | $PO_2$ kPa | $PCO_2$ kPa | $H^+$ nmol/l |
| "Blue Bloaters" | | | | | | | | | | | |
| 1 | 5.3 | 6.7 | 44 | 3.9 | 7.6 | 47 | 7.6 | 47 | 4.7 | 7.1 | 45 |
| 2 | 5.6 | 6.1 | 42 | 3.9 | 7.9 | 47 | 7.9 | 47 | 5.1 | 6.7 | 43 |
| 3 | 6.7 | 6.4 | 50 | 4.9 | 8.0 | 62 | 8.0 | 62 | 6.9 | 6.3 | 46 |
| 5 | 7.6 | 5.6 | 40 | 6.2 | 6.4 | 45 | 6.4 | 50 | 7.2 | 5.6 | 43 |
| 6 | 5.3 | 7.1 | 40 | 3.8 | 7.3 | 48 | 7.5 | 51 | 4.8 | 6.9 | 44 |
| 8 | 5.6 | 7.2 | 45 | 3.7 | 6.9 | 47 | 7.1 | 54 | 4.8 | 6.5 | 46 |
| 9 | 5.7 | 8.5 | 41 | 4.8 | 8.1 | 40 | 8.1 | 40 | 6.0 | 7.9 | 37 |
| 10 | 5.3 | 6.7 | 42 | 3.5 | 7.2 | 46 | 7.2 | 46 | 5.2 | 6.6 | 43 |
| 12 | 6.5 | 7.1 | 45 | 3.5 | 8.5 | 51 | 8.5 | 51 | 7.0 | 7.5 | 45 |
| 13 | 6.9 | 7.1 | 42 | 5.9 | 7.9 | 45 | 7.9 | 45 | 6.8 | 7.2 | 43 |
| 14 | 6.1 | 7.3 | 46 | 4.9 | 7.9 | 48 | 7.9 | 48 | 6.1 | 7.4 | 44 |
| Mean ± SE | 6.1 ± 0.2 | 6.9 ± 0.3 | 43 ± 1 | 4.5* ± 0.3 | 7.6* ± 0.2 | 48* ± 2 | 7.7* ± 0.2 | 49* ± 2 | 5.9 ± 0.3 | 6.9 ± 0.2 | 44 ± 1 |

* $P < 0.01$ versus pre-sleep value

TABLE 8

EFFECT OF 2 1/MIN OF AIR OR OXYGEN VIA NASAL PRONGS ON OXYGENATION DURING SLEEP IN PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

| Patient No. | No. of Dips | | Ear Oximeter Reading | | | | Arterial Blood Gas Tensions and Hydrogen Ion at Lowest $PO_2$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Awake | | Lowest Asleep | | AIR | | | $O_2$ | | |
| | AIR | $O_2$ | AIR | $O_2$ | AIR | $O_2$ | $PO_2$ kPa | $PCO_2$ kPa | $H^+$ nmol/l | $PO_2$ kPa | $PCO_2$ kPa | $H^+$ nmol/l |
| 2 | 3 | 1 | 72 | 94 | 21 | 82 | 3.9 | 7.9 | 47 | 12.0 | 9.3 | 58 |
| 9 | 3 | 1 | 60 | 92 | 22 | 84 | 4.8 | 8.1 | 40 | 8.7 | 8.4 | 45 |
| 10 | 5 | 1 | 77 | 93 | 0 | 50 | 3.5 | 7.2 | 46 | 5.6 | 8.0 | 53 |
| 12 | 7 | 4 | 85 | 98 | 15 | 61 | 3.5 | 8.5 | 51 | 6.4 | 10.4 | 55 |
| 13 | 2 | 0 | 89 | 97 | 74 | 92 | 5.9 | 7.9 | 45 | 9.5 | 6.5 | 40 |
| 14 | 1 | 1 | 82 | 99 | 39 | 77 | 4.9 | 7.9 | 48 | 6.4 | 7.7 | 53 |
| Mean | 3.5 | 1.3* | 78 | 96* | 29 | 74* | 4.4 | 7.9 | 46 | 8.1* | 8.4 | 51 |

Footnote: Dip, drop in saturation of more than 10% from the immediately preceding stable saturation during sleep, lasting for at least 1 min;
* $P < 0.05$ versus value breathing air

oxygen than when breathing air (Table 8). Sleep quality was also improved by oxygen therapy with a significant reduction in the amount of intervening wakefulness and drowsiness and an increase ($p < 0.05$) in the amount of REM sleep (Table 9). There were also improvements of borderline significance ($0.1 > p > 0.05$) in the total sleep time, sleep onset latency and the mean duration of sleep between arousals.

TABLE 9 EFFECT OF BREATHING AIR OR OXYGEN AT 2 L/MIN VIA NASAL PRONGS ON SLEEP DURATION AND QUALITY

| | | Breathing Air | Breathing Oxygen |
|---|---|---|---|
| Sleep onset latency (min) | | 52±25 | 20±5$^{+}$ |
| Sleep period time (min) | | 336±25 | 395±16 |
| Total sleep time (min) | | 247±33 | 334±12$^{+}$ |
| %SPT | Stage 0+1 | 27±7 | 15±3$^{x}$ |
| | Stage 2 | 51±7 | 49±6 |
| | Stage 3+4 | 11±4 | 20±4 |
| | REM | 11±3 | 17±2$^{x}$ |
| No. of REM periods | | 2.7±0.4 | 4.2±0.4$^{x}$ |
| Duration of uninterrupted sleep | | 6.8±1.4 | 10.3±1.6$^{+}$ |

Footnote: SPT, sleep period time; Sleep times defined by criteria of Williams et al, (1974)

x $p < 0.05$ versus breathing air

+ $0.1 > p > 0.05$ versus breathing air

## DISCUSSION

This study shows that patients with chronic bronchitis and emphysema who are hypoxaemic when awake become profoundly more hypoxaemic during REM sleep with directly measured arterial oxygen tension falling as low as 3.5 kPa. These hypoxaemic episodes are usually associated with hypopnoea. However, there was no difference in either the breathing pattern or the fall in oxygen tension between the normal subjects and these patients with chronic bronchitis and emphysema.

The results confirm previous (see Chapter 2) and concurrent studies which showed that both normal subjects (Block et al, 1979) and patients with chronic bronchitis (Flick & Block, 1977; Coccagna & Lugaresi, 1978; Wynne et al, 1979) become hypoxaemic during sleep. However, this is the first time that breathing patterns and oxygenation have been compared in normal subjects and patients with chronic bronchitis and emphysema studied by the same technique in the same laboratory. The "blue and bloated" patients with chronic bronchitis and emphysema became extremely hypoxaemic during sleep with 10 of the 16 developing oxygen saturations of below 50% and 9 of the 11 in whom arterial blood was sampled dropping their oxygen tensions to below 5 kPa. The degree of hypoxaemia observed was far greater than in these other studies (Koo

et al, 1975; Leitch et al, 1976; Flick & Block, 1977; Coccagna & Lugaresi, 1978; Wynne et al, 1979) reflecting not only the severity of our patients' hypoxic chronic bronchitis, but also the use of the ear oximeter to provide continuous oxygen saturation and to guide arterial blood sampling.

The severe hypoxaemia occurred almost exclusively in REM sleep. When reported (Douglas et al, 1979b), this was the first description of REM related hypoxaemia in patients with chronic bronchitis and emphysema documented by continuous recording of oxygenation and thus demonstrating the tight relationship between REM sleep periods and hypoxaemia. This finding was confirmed later that year (Wynne et al, 1979). Previous (Koo et al, 1975) and concurrent (Coccagna et al, 1978) studies demonstrated REM hypoxaemia in these patients by intermittent arterial blood sampling.

The desaturation found during sleep was greater in the "blue bloaters" than in the "pink puffers" or normal subjects, but the changes in oxygen tension were similar in all 3 groups. Other groups have reported similar changes in $PaCO_2$ in their patients with chronic bronchitis and emphysema when compared to results obtained by other workers in normal subjects (Pierce et al, 1966; Interiano et al, 1972; Koo et al, 1975; Leitch et al, 1976). Robin (1958) reported larger increases in end-tidal $PCO_2$ in patients than in normal subjects but

provided no data. Coccagna and Lugaresi (1973) found larger falls in $PaO_2$ and larger rises in $PaCO_2$ in patients with chronic bronchitis and emphysema than normal subjects. The reason for this discrepancy is not clear but: 1) Coccagna and Lugaresi did not mention prior sleep history and it is possible that their normal subjects, being laboratory staff, might have sleep deprived themselves to ensure adequate sleep, thereby minimising the effect of sleep on ventilation (see Appendix 1). In fact, the changes in both $PaO_2$ and $PaCO_2$ observed by Coccagna & Lugaresi in normal subjects during sleep were smaller than those reported herein or by other groups (Birchfield et al, 1958; Bristow et al, 1969). 2) Their normal subjects slept less well than ours, this difference perhaps relating to the presence of arterial catheters. 3) Coccagna and Lugaresi did not use ear oximetery and thus would have underestimated maximal changes in blood gas tensions. 4) As the authors admit, the patients may have hyperventilated during wakefulness due to their anxiety about the experiments. 5) It is not clear how long the subjects were in a sleep stage before samples were drawn. 6) The patients and normal subjects probably were not age-matched. Thus there is considerable doubt about the validity of Coccagna and Lugaresi's comparisons.

Most previous studies therefore agree with the present conclusion that the changes in blood gas tensions are similar in normal subjects and in patients with chronic bronchitis and emphysema. This is the first time such a conclusion has been reached by comparing the maximal changes which can only be obtained by continuously measuring either oxygen or carbon dioxide levels throughout the night. As the changes in calculated oxygen tension were similar in normal subjects, "pink puffers" and "blue bloaters", the desaturation during sleep in patients with hypoxic chronic bronchitis and emphysema is a function of the position of these patients' arterial blood on the oxyhaemoglobin dissociation curve. "Blue bloaters", who already lie on the steep part of the curve whilst awake, desaturate markedly during sleep, although their change in oxygen tension is similar to that which occurs in normal subjects who only desaturate very slightly.

The study also showed that the breathing patterns in the patients and the normal subjects were similar during sleep. Sleep apnoea was rare in both groups and was associated with only 2 of the 34 hypoxaemic episodes in the "blue bloaters". Thus the nocturnal hypoxaemia in the "blue bloaters" is not due to a sleep apnoea syndrome. What then causes the sleep related hypoxaemia? The majority of hypoxaemic episodes occurred during hypopnoea, and thus hypoventilation must contribute to at least part of this nocturnal hypoxaemia.

The conventional argument against the nocturnal hypoxaemia in patients with chronic bronchitis and emphysema being due to hypoventilation alone is based on the analysis of relative change in $PaO_2$ and $PaCO_2$. As in the present study, the changes in $PaO_2$ observed are usually greater than those in $PaCO_2$, and thus increasing ventilation-perfusion imbalance has been invoked (Koo et al, 1975; Leitch et al, 1976; Flick & Block, 1977; Wynne et al, 1979) as a factor contributing to the hypoxaemic episodes. However, this analysis is dependent on measurements being made in a steady state.

The body stores of oxygen are far smaller than those of carbon dioxide (Fahri & Rahn, 1955). Thus changes in ventilation produce more rapid alterations in $PaO_2$ than in $PaCO_2$ (Fahri & Rahn, 1955; Cherniack et al, 1968). After a stepchange in ventilation, the half time for changes in $PaO_2$ is about 30 seconds (Fahri & Rahn, 1955) whereas that for $PaCO_2$ is longer, perhaps 10-20 minutes (Sullivan et al, 1966; Ivanov & Nunn, 1968). Indeed Sullivan and colleagues (1966) found $PaCO_2$ was still changing 70 minutes after a stepchange in ventilation.

Inspection of a typical trace of either breathing pattern (Figs 9 & 10) or oxygen saturation (Figs 5, 8 & 11) from this study demonstrates that steady state is not achieved during REM related hypoxaemia. Although the hypoxaemic episodes themselves last on average 27 minutes, oxygen saturation is continually changing during

that time. Further, the breath amplitude is continuously waxing and waning with a periodicity of 1 to 2 minutes. Thus the above argument invoking ventilation-perfusion imbalance is invalid, and unsteady state gas dynamics have to be considered.

Thus hypoventilation, such as was suggested by the stethogram pattern during hypoxaemic episodes, would be expected to result in a rapid decrease in $PaO_2$, but the changes in $PaCO_2$ would lag behind the $PaO_2$ drop. As the periodicity of the breathing pattern was only 1-2 minutes (Fig 9), the changes in $PaCO_2$ would never plateau and thus the maximal changes in $PaO_2$ would exceed those in $PaCO_2$. This, therefore, is a possible explanation for the blood gas abnormalities seen during the hypoxaemic episodes. Indeed a study stimulated by my hypothesis has confirmed that transient hypoventilation can reproduce the observed changes in $PaO_2$ and $PaCO_2$ (Catterall et al, 1982b). Thus hypoventilation alone could account for the observed changes in blood gas tension and there is no need to invoke worsening ventilation-perfusion relationships as a major factor. However, hypoventilation per se is bound to alter ventilation-perfusion matching, particularly in patients who already have gross ventilation-perfusion mismatching whilst awake, and thus secondary increases in ventilation-perfusion mismatching may contribute to the observed changes in blood gas tensions.

When breathing patterns and oxygenation in REM sleep were compared between the normal subjects and the patients with chronic bronchitis and emphysema, it was found that both groups exhibited hypopneoa and hypoxaemia in REM sleep. Similarly, in 1965, Aserinsky had demonstrated that 11 normal subjects hypoventilated - as indicated by chest wall movement - and became hypoxaemic during REM sleep. Thus it is postulated that hypoventilation in REM sleep is a normal phenomenon in adult man. This is contrary to results in both infants (Bolton & Herman, 1974; Hathorn, 1974; Finer et al, 1976; Purcell, 1976) and dogs (Phillipson et al, 1976), both of which have been extrapolated to adult man (Phillipson, 1978a & b). It was therefore decided to measure ventilation in adult man during REM sleep, and this is described in Part 11 of this thesis.

## What Are The Clinical Consequences of Such Nocturnal Desaturation?

Four possible sequelae will be considered:- pulmonary hypertension, secondary polycythaemia, cardiac arrhythmias and death. In this study, mean pulmonary arterial pressure was found to rise during the hypoxaemic episodes (Douglas et al, 1979b), a finding confirmed independently and concurrently by both Coccagna and Lugaresi (1978) and by Boysen and colleagues (1979), the latter group elegantly showing that mean pulmonary

arterial pressure rises linearly as oxygen saturation falls during sleep. We suggested "that the recurrent transient hypoxaemia during sleep may in time lead to the sustained pulmonary hypertension and polycythaemia which characterises these blue and bloated patients" (Douglas et al, 1979b). As pulmonary arterial pressure rises during these hypoxaemic events it was felt that the repeated elevation of pulmonary arterial pressure might have a deleterious effect on the pulmonary arterial musculature and perhaps also on the myocardium. Similarly, as red cell mass is normally dependent on oxygen saturation (Weil et al, 1968), it seems reasonable to suggest that episodic severe desaturation during sleep might contribute to the development of polycythaemia. These hypotheses are difficult to prove in man. However, there is a deep freeze full of plasma samples withdrawn before, during and after hypoxaemic episodes which may be analysed for erythropoetin levels once a sufficiently sensitive assay is available to us. So far one attempt to analyse these specimens produced equivocal results, possibly because of assay technique.

Indirect evidence suggesting that the intermittent nocturnal hypoxaemia might contribute to the development of polycythaemia and pulmonary hypertension comes from the observation that patients with the sleep apnoea syndrome, who are relatively normoxic by day ($PaO_2$ > 10 kPa), develop these complications (Coccagna et al, 1972;

Lugaresi et al, 1978). Also, abolition of nocturnal hypoxaemia in these patients - by tracheostomy - reduces their pulmonary arterial pressure both by day (Coccagna et al, 1972) and by night (Coccagna et al, 1972; Motta et al, 1978).

Another possible hazard of REM related hypoxaemia is cardiac arrhythmia. Flick and Block (1979) found that more ventricular extrasystoles occurred during the night than during the day ($p < 0.01$) in a group of 10 patients with chronic obstructive pulmonary disease. Although low concentration oxygen therapy did not significantly reduce arrhythmias ($p = 0.13$) self-terminating ventricular tachycardia and idio-ventricular rhythm only occurred on the air breathing night. Unfortunately, the EEG was not recorded in that study nor is relationship between arrhythmias and oxygen saturation established. Thus further investigation is required to establish whether these cardiac arrhythmias are a consequence of nocturnal hypoxaemia.

I wondered whether the severe nocturnal hypoxaemia in these patients could be fatal. There is no hard evidence on this as yet, but two pointers exist. The peak time of death in patients with pulmonary disease is around 6 am (Smolensky et al, 1972) and REM sleep is maximal late in the night (Williams et al, 1974). This very tenuous evidence receives some slight support from an investigation I carried out into the time of death in

the patients in the Edinburgh limb of the Medical Research Council trial of long term oxygen therapy. Of the 12 deaths occurring in the control patients who were breathing air, 10 occurred between 9 pm and 9 am. In the patients who were receiving nocturnal oxygen, and thus were protected from severe nocturnal hypoxaemia, only 3 of the 7 deaths occurred between 9 pm and 9 am [$Chi^2$ test for small number (Swinscow, 1976), $p = 0.06$]. This was a retrospective analysis and it must be interpreted with caution. Specifically, it should not be assumed that patients dying at night were asleep and those dying by day were awake. These observations, however, merit prospective investigation.

The observation that there is a linear relationship between the lowest oxygen tension during sleep and the oxygen tension during wakefulness is of interest. Firstly, it confirms that sleep hypoxaemia is a continuum from health to disease, and is not singular to "blue bloaters". Secondly, it means that it is not necessary to perform a sleep study on patients with classical chronic bronchitis and emphysema to see whether they desaturate - that can be predicted from their waking $PaO_2$. There may be exceptions to this in that a few such patients may have apnoeas during sleep and further work may be required to try to identify these patients during wakefulness, but in this study the only patient with apnoea related hypoxaemia fell on the regression line of

$PO_2$ awake/$PO_2$ lowest asleep (Fig 7), and thus had no excess hypoxaemia. Thirdly, it implies that differences in nocturnal saturations are unlikely to account for the poor relationships in such patients between oxygen saturation when awake and either red cell mass (Harrison, 1973) or pulmonary hypertension (Flenley, 1978). As nocturnal oxygenation was only assessed in terms of lowest oxygen saturation it is possible that some other function of oxygen level during sleep might help explain this variability. Thus further investigation is required into these relationships, perhaps concentrating on obtaining a less artificial index of oxygenation awake, using a portable oximeter, and a more sophisticated analysis of nocturnal oxygenation. My impression is that other factors, such as carboxyhaemoglobin (Calverley et al, 1982a) are probably more important than sleep oxygenation in producing this variability. Fourthly, any therapy - either oxygen or respiratory stimulant - which increases the waking $PaO_2$ of the patient would be expected to reduce the nocturnal desaturation. Indeed this study shows that such oxygen therapy reduces the severity of nocturnal hypoxaemia and also improves sleep quality.

The improvement in nocturnal oxygenation with oxygen administration confirms the results obtained in 2 patients by Leitch and colleagues (1976). They reported marked hypercapnia during sleep in one of these patients,

with $PaCO_2$ rising as high as 11.1 kPa. While our patients did not become as hypercapnic they tended ($0.2 > p > 0.1$) to become more acidotic breathing oxygen at night. As acidosis increases pulmonary arterial pressure (Bergofsky et al, 1962), investigation of the effect of nocturnal oxygen therapy on the pulmonary arterial pressure is required.

In conclusion, therefore, this study showed that normal subjects and patients with chronic bronchitis and emphysema have similar breathing patterns and falls in oxygen tension during sleep. Patients with chronic bronchitis and emphysema who are sufficiently hypoxic whilst awake to lie near the steep part of the oxyhaemoglobin dissociation curve desaturate markedly during REM sleep. It is suggested that such repetative desaturation may contribute to the development of sustained pulmonary hypertension and secondary polycythaemia, and perhaps to cardiac arrhythmias and even death, in the "blue bloaters".

Analysis of the breathing patterns suggests that hypoxaemic episodes result from hypoventilation during REM sleep. Both the normal subjects and the patients with chronic bronchitis and emphysema exhibited hypopnoea in REM sleep, despite falls in oxygen tension - and in

the "blue bloaters" rises in carbon dioxide tension - which would normally be expected to stimulate respiration. Therefore, it appeared likely that the ventilatory responses to both hypoxia and hypercapnia were lower in REM sleep than in either wakefulness or non-REM sleep. I thus reviewed the published work on ventilatory responses in sleeping adults.

# CHAPTER 6

# REVIEW OF VENTILATORY RESPONSES TO HYPOXIA AND HYPERCAPNIA DURING SLEEP

## Hypoxic Ventilatory Response During Sleep

There had been only one previous investigation of the hypoxic ventilatory response during natural sleep in adult man. Reed and Kellogg (1960a) in their important study, which is discussed more fully in Chapter 9, found that sleep did not change the hypoxic ventilatory response. However, they neither applied an adequate hypoxic stimulus, nor maintained isocapnia, nor recorded the electroencephalogram.

In tracheostomised dogs, Phillipson and colleagues (1978) reported that the isocapnic hypoxic ventilatory response was unchanged from wakefulness to either slow wave or REM sleep. Rats (Pappenheimer, 1977) were thought to have higher ventilatory responses to hypoxia in slow wave sleep than in wakefulness but in that study isocapnia was not maintained, ventilation was related to inspired and not expired oxygen tension and the measurements in slow wave sleep probably included multiple arousals - perhaps accounting for the increase in ventilatory response observed. Further, Pappenheimer's conclusion was not confirmed statistically

and is heavily dependent on an assumed alveolar gas concentration during wakefulness reported in another study. In a recent abstract, it had been reported that the isocapnic hypoxic ventilatory response was similar in slow wave and REM sleep in puppies, but lower in REM than slow wave sleep in lambs (Henderson-Smart and Read, 1978).

Thus there had been no adequate studies of the hypoxic ventilatory response in any sleep stage in adult man, and the conflicting results in different animal species made extrapolation of animal results to man unfruitful.

## Hypercapnic Ventilatory Response During Sleep

It is almost a century since the hypercapnic ventilatory response during sleep was first explored in man. In 1890, Loewy added $CO_2$ to inspired air and examined the relationship between the mean expired $CO_2$ concentration and ventilation in 2 awake subjects, repeating the measurements during sleep. He found no consistent effect of sleep on either the slope or position of the expired $CO_2$/ventilation relationship. In 1915 Straub reported that end tidal $CO_2$ was higher immediately on waking from sleep than during wakefulness and concluded that the ventilatory response to $CO_2$ was reduced during sleep.

The first direct confirmation of this suggestion was in 1944 by both Magnussen and Ostergaard. Magnussen recorded ventilation and end-tidal $CO_2$ tension breathing air and following the addition of 2.5% $CO_2$ to inspired air during both wakefulness and behavioural sleep. The hypercapnic drive fell during sleep in both subjects, the mean values being 1.68 l/min/mmHg $CO_2$ during wakefulness and 0.70 l/min/mmHg $CO_2$ during natural sleep. Ostergaard added 4-6% $CO_2$ to the inspired air and found that in both his subjects the slope of the ventilatory response to $CO_2$ declined during sleep. In one subject, however, the decrease was minimal, but in that subject the response line was markedly displaced to a higher $CO_2$ level during sleep. Three later studies (Robin et al, 1958; Birchfield et al, 1959; Smith et al, 1962) using similar techniques confirmed these results, ventilatory response decreasing during sleep from 1.40 to 0.35 l/min/mmHg in Robin's (1958) 10 subjects and from 1.85 to 0.96 l/min/mmHg in Birchfield's (1959) 4 sleep-deprived subjects.

Amongst the technical faults in all the above studies is the fact that $CO_2$ was added to room air and thus the hypoxic drive might have been contributing to ventilation. This criticism was met by the studies of Reed and Kellogg (1958 & 1960b) and Bellville and colleagues (1959) who added $CO_2$ to oxygen enriched air and reported that sleep produced parallel shifts in the

ventilatory response line to higher $CO_2$ levels with no change in slope. However, analysis of Reed and Kellogg's graphs show that in 6 of the 7 subjects in whom adequate sea level data is available, the slope of the hypercapnic ventilatory response decreased during sleep [Figure 3 in (1958) and Figure 1 in (1960b)] and in all 7 the response line was shifted to higher $CO_2$ levels. Bellville and colleagues (1959) were the first to verify sleep electroencephalographically during studies of hypercapnic ventilatory response. Unfortunately, they do not comment on the slope of the hypercapnic ventilatory response during sleep, merely reporting that the $CO_2$ response lines were displaced to the right by 3.2 to 9.6 mmHg at an alveolar ventilation level of 10 l/min. Fuleihan and co-workers (1963) found no difference in the slope on the $CO_2$ response in wakefulness and sleep, but they induced sleep with sodium pentobarbital and did not record the EEG.

The first measurement of hypercapnic ventilatory response using a rebreathing technique was by Bulow (1963). In his important study, Bulow performed more than 300 experiments in which $CO_2$ was rebreathed in a background of 40% oxygen during different EEG levels of wakefulness. From over 3,000 ventilation/$P_{ET}CO_2$ points, he deduced that the hypercapnic ventilatory response declined progressively with increasing depth of sleep [% decrease from wakefulness; stage 1 12%, stage 2 42%,

stage 3 58%, stage 4 65%; data calculated from Figure 22 in (Bulow, 1963)]. Although Bulow's investigation was a significant contribution to the understanding of respiratory control during sleep, there are several reasons for caution in its interpretation. Firstly, there was no adequate system for detecting leaks around the mouth piece. Secondly, the studies were performed by day mainly on regular or intermittent night shift workers. Shift work affects EEG sleep patterns (Maasen et al, 1980) and its influence on ventilatory response in unknown. Thirdly, Bulow did not perform any statistical analysis and comparisons were made between all the ventilation/$PCO_2$ data points in each sleep stage, and not between the average results in each individual in each sleep stage. Indeed there is no clarification as to whether studies were carried out in every subject in every sleep stage. As he states that "the number of ventilation/$PCO_2$ data points at the highest $PaCO_2$ values is relatively small during sleep" it seems likely that the sleep slopes thus calculated are biased by selection of those subjects with high $CO_2$ arousal thresholds who might perhaps be the subjects with low $CO_2$ responses. The earlier steady state studies may be criticised on similar grounds, as arousal during $CO_2$ inhalation would result in either measurement of ventilation before steady state has been achieved - thus underestimating hypercapnic drive during sleep - or once more in

selection of subjects with high $CO_2$ arousal thresholds and thus perhaps low $CO_2$ responses. Some support for this latter criticism comes from the observation of Birchfield and colleagues (1959) that the 7 subjects unable to sleep during $CO_2$ inhalation had a mean $PaCO_2$ of 44 mmHg when awake as opposed to 49 mmHg in the 4 who slept throughout $CO_2$ responses. Fourthly, Bulow applied local anaesthetic to his subjects' nostrils and it is now known that nasal (Sasaki et al, 1975) or nasopharyngeal (McBride & Whitelaw, 1981; Douglas et al, in press) anaesthesia may alter respiratory timing and ventilatory responses.

Another criticism of Bulow's study (1963) is that an electro-oculogram was only recorded in 14 out of 73 investigations and thus some of the measurements reportedly performed in what are now termed stages 1 and 2 sleep might actually have been made in REM sleep. In none of the studies in which electro-oculography was performed were $CO_2$ responses carried out in uninterrupted REM sleep, but in one subject "the main part of the $CO_2$ test was carried out during REM" and in that study there was marked scatter but it appeared that the $CO_2$ response was similar to that in stage 1 sleep - i.e. 12% lower than in wakefulness.

In rats, Pappenheimer (1977) reported that slow wave sleep increased the hypercapnic ventilatory response. This conclusion, however, was not confirmed

statistically, is heavily dependent on an assumed alveolar gas concentration during wakefulness reported in another study, and is anyway probably invalid as it appears that the sleep was punctuated by arousals. In tracheostomised dogs Phillipson and co-workers (1977) found that the hypercapnic ventilatory response was lower during slow wave sleep than in wakefulness, with a further reduction in REM sleep, but the sleep was staged using a combination of EEG and behavioural changes. Thus the dogs were in slow wave sleep when they were "unresponsive to moderately loud noises and the EEG revealed high voltage slow waves at 2-4 cps" (Phillipson et al, 1976) and in REM sleep when there were EEG changes plus "twitching movements of the ears, whiskers, nose, lips, and limbs" (Phillipson et al, 1977). These criteria are not directly applicable to man and may imply neuro-electrophysiological differences between species. When Phillipson's group divided REM sleep into tonic REM, in which there was loss of EMG tone, and phasic REM during which there were twitching movements of the face and limbs and bursts of rapid eye movements, the hypercapnic ventilatory response was found to be similar in slow wave and tonic REM sleep but to be reduced to one third of this level in phasic REM sleep (Sullivan et al, 1979a). The effect of tracheostomy on ventilatory response awake or during sleep is unknown, but there is some evidence (Gautier et al, 1973; Douglas et al, in

press) that upper airway factors may be important in the control of respiration. Therefore, extrapolation of Phillipson's results in dogs to humans would be hazardous.

Thus it appeared that in non-REM sleep in adult man the ventilatory response to $CO_2$ was probably reduced, but no adequate measurements of the hypercapnic ventilatory response had been made in REM sleep.

## CONCLUSION

Thus my hypotheses that hypoventilation is a normal occurrence in REM sleep in adult man and that this must be accompanied by reductions in both the hypoxic and hypercapnic ventilatory responses, were not answered by the published data. Therefore, in 1979 I applied for, and was fortunate in being awarded, a Medical Research Council Travelling Fellowship to investigate these hypotheses. I chose to perform these studies in the Cardiovascular Pulmonary Research Laboratory, University of Colorado, Denver, because of Dr John Weil's expertise in the investigation of ventilatory control and because that laboratory had the major facilities required for the research project. The remainder of this thesis describes the work I performed in Denver from 1 October 1980 to 30 October 1981 testing these hypotheses.

# PART 11

# INVESTIGATION OF VENTILATION AND HYPOXIC AND HYPERCAPNIC VENTILATORY RESPONSES DURING SLEEP IN NORMAL SUBJECTS

## CHAPTER 7

## METHODS

The major problem in assessing ventilation and ventilatory responses during sleep is how to measure ventilation accurately. Many earlier studies used a mouthpiece and nose clip, but with this technique it is difficult - if not impossible - to prevent leaks during sleep when facial muscle tone drops and movement tends to occur. Mouthpieces alter ventilation, at least in awake subjects (Gilbert et al, 1972). I had hoped to measure ventilation without any such instrumentation to the face. I soon abandoned an "iron lung" which I modified to form a "head out" body plethysmograph because of recurrent leaks and considerable subject discomfort. I next studied techniques based on measurement of chest and abdominal wall movement using either an inductance plethysmograph (Respitrace Inc) or calibrated

magnetometers (Konno & Mead, 1967). However, I abandoned this approach for the following theoretical and practical reasons:

<u>Theoretical</u>

1. Paradoxical movement of part of the chest wall relative either to the remainder of the chest or to the abdomen has been described in both non-REM (Tusiewicz et al, 1977) and REM sleep (Henderson-Smart & Read, 1976; Knill et al, 1976). Although such paradoxical movement has not been reported in normal adults during REM sleep, it is not known whether it might occur during chemostimulated ventilation in REM sleep. Paradoxical movement would make measurement of tidal volume from a limited number of external diameters or circumferences erroneous.

2. Phase differences have been shown to occur between each of the three diameters assessed - antero-posterior chest wall, lateral chest wall and abdomen - in adult man during both non-REM (Tusiewicz et al, 1977; Mortola & Anch, 1978; Gothe et al,

1981) and REM sleep (Tusiewicz et al, 1977; Mortola & Anch, 1978) and these phase differences vary between sleep stages. As both magnetometer and inductance plethysmograph techniques rest on the assumption that a given distance or area change at a specific level on the torso reflects a finite volume change, multiple varying phase differences must increase the error of volume measurement.

3. During non-REM sleep, the relative contribution of the rib-cage to total volume change is greater than in either wakefulness or REM sleep (see Chapter 4). Thus errors in the relative gains of the abdominal and thoracic signals, which might be trivial when the proportional contribution is stable, may assume considerable importance during sleep.

4. It has been reported that functional residual capacity declines during sleep (Henderson-Smart & Read, 1976 & 1979b; Muller et al, 1980). This might

produce gas trapping thus rendering any system based on thoraco-abdominal wall movement inaccurate.

Practical

1. I spent many days evaluating an inductance plethysmograph (Respitrace Inc) against a Steadman Wells water spirometer. The best results obtained yielded a standard error of the estimate of tidal volume of ±8% when used in one posture. This error might have been acceptable but for the other theoretical and practical problems.

2. Alterations of posture into the various lying positions likely to be adopted during sleep altered the calibration of the plethysmograph by ±15%. Further, the resumption of a posture did not result in return to the previous calibration obtained in that posture. Thus it was not possible to make measurements each time the subject adopted a given posture with an accuracy of ±8%. The only way this accuracy could be obtained was if the subject did not move between

calibration and measurement - extremely unlikely in sleeping subjects.

In order to allow delivery of a predictably variable gas concentration during studies of respiratory drive and to permit measurements of exhaled gas concentrations, some instrumentation of the head was necessary. Given the above theoretical and practical problems various gas delivery systems were investigated to see whether they could be adapted to measure expired volumes more accurately.

The use of a perspex box (Sorkin et al, 1980) which totally enclosed the head was explored. This system had 3 major disadvantages:

1) Even minimising dead space and flushing the box at 40 l/min - a flow scarcely compatable with sleep - the inspired $CO_2$ concentration could not be reduced below 0.5% which is unacceptable for studies of baseline ventilation or of hypoxic ventilatory response.
2) For safety reasons it was essential that the inhaled gas concentration could be altered very rapidly. With a head box there would be a delay of at least 15 secs before inhaled gas concentration could be normalised in the event of an emergency, and this was unacceptable.

3) It was not possible to devise a scheme whereby isocapnia could be adequately maintained during hypoxic studies.

4) The technique could not be adapted for rebreathing hypercapnic responses, which are preferable to steady state responses during the irregular breathing of REM sleep (see later in this Chapter).

I acquired from the National Aeronautics and Space Agency an astronaut's helmet, thinking that the minimal dead space might eradicate some of the problems of the head box. Unfortunately, despite the sophistication and comfort of this helmet, a flow-through of 25 l/min only reduced inspired $CO_2$ to 0.5% and at the same time produced an intolerable noise and draught.

Thus I was forced to explore the use of a face mask which at first sight embodied the three features I wished to avoid, namely the risk of leaks and the danger of facial instrumentation modifying both sleep and breathing. The first two risks were minimised by the design of a purpose-built mask, the third is discussed later in this chapter.

With the help of a bio-engineer, I designed a face mask with built-in inspiratory and expiratory valves (Fig 12). The valves, diaphragms and rings were from a Hans Rudolf Inc No. 2600 non-rebreathing valve with a nearly linear flow resistance of 0.7 cm $H_2O$/l/sec on inspiration

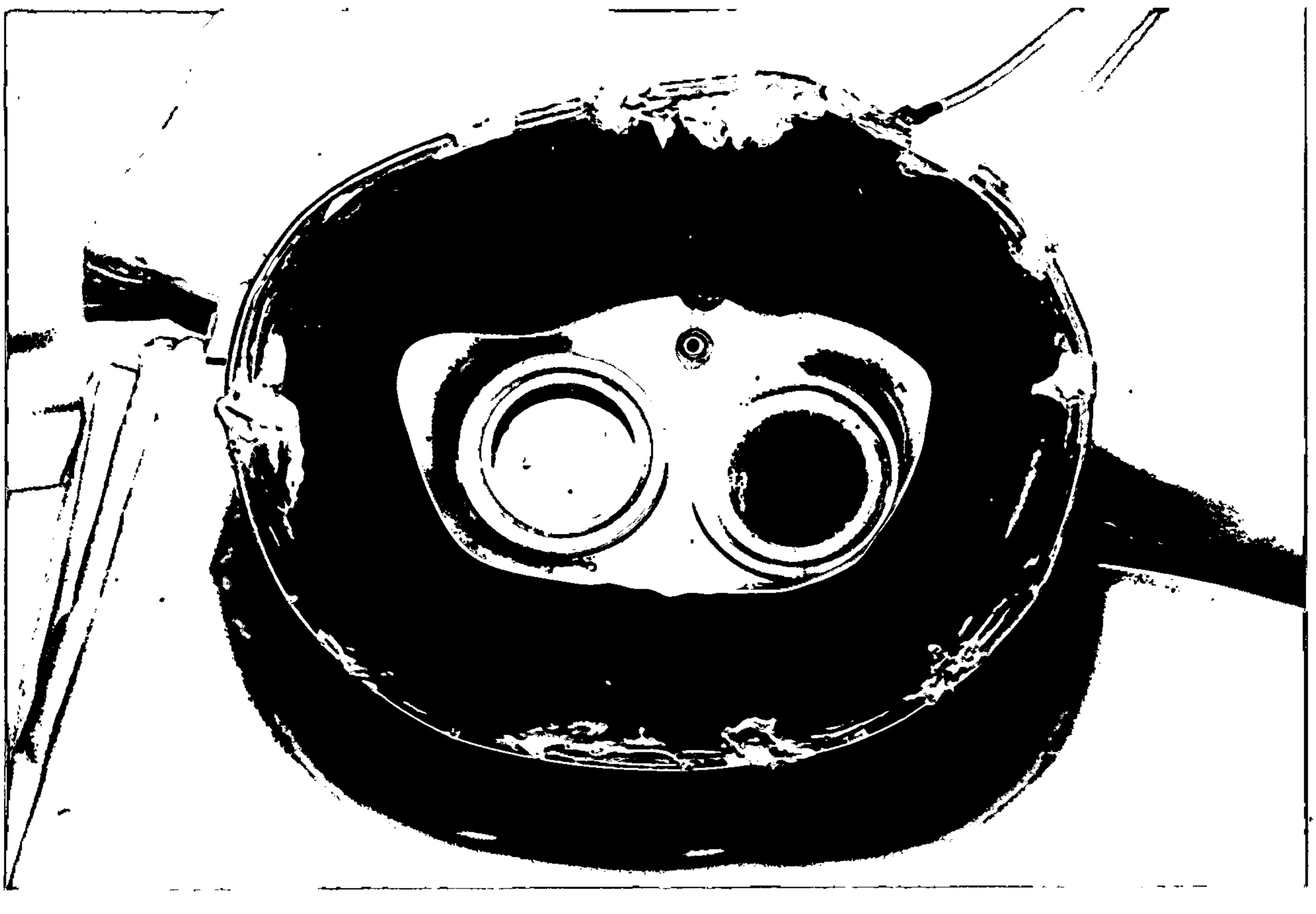


Fig 12 Photograph of facemask illustrating valves, gas sampling ports and circumferential leak detector. The author apologises for his photography and gluing.

and 1 cm $H_2O$/l/sec on expiration. These valves were silent in operation. The mask incorporated a comfortable rubber inflatable face cushion and was applied to the face by elasticated straps. The dead space of the mask was assessed in 4 subjects by measuring the volume of polystyrene beads required to fill the dead space. The values attained ranged from 70-85 ml depending on the subject's facial structure.

Immediately in front of the subject's nose and mouth, sampling ports were constructed to allow measurement of respired gases. Such sampling provided good end tidal plateaux (see below) and confirmed that the inspired $CO_2$ concentration fell to zero on each inhalation.

Leaks from face masks tend to be worse on expiration than inspiration due to the sucking of the mask on to the face during inspiration. Indeed at no point in these studies were we aware of an inspiratory leak without a co-existing expiratory leak. Furthermore, it was desirable to measure expired ventilation. Thus a leak detector was constructed which would sense $CO_2$ escaping from around the mask on expiration. This consisted of a perforated polyethylene catheter attached around the circumference of the mask's face cushion, the catheter being continuously sampled by a Beckman LB2 infra-red $CO_2$ analyser set to maximal gain. The catheter was perforated every centimeter, the size of the perforations

increasing with increasing distance from the connection with the $CO_2$ analyser, in an attempt to equalise resistances and thus sampling flow rates. This was largely successful as leaks at all points around the circumference produced similar signals from the $CO_2$ analyser.

To establish the sensitivity of the leak detector system a closed circuit was devised which incorporated a 200 litre spirometer, to give volume change in the circuit, and a calibrated hot wire anemometer to measure expired volume. Allowance was made for respiratory gas exchange, initial and final mixed gas samples being analysed by the Scholander technique (1947). The mask was adjusted on the face so that there was no inspiratory leak but on each expiration the minimum detectable leak was created, the site of the leak being varied around the circumference. When so tested for 3 separate 5-minute periods, the system was found to be capable of detecting expiratory leaks of 0.9, 1.2 and 1.4%. Thus when an average of 1.2% of the expired volume leaked from the mask a clearly visible signal was recorded on the leak detector.

No studies are hereafter reported if any leak was detected at any stage during that measurement. In all the subjects studied, the application of some lubricant jelly over the bridge of the nose was necessary to produce an adequate seal. However, with the use of such

Fig 13 Illustration of subject under study showing mask connected to the breathing circuit and gas sampling lines.

jelly, it became unnecessary to strap the mask very tightly to the subject's face to avoid a leak. The unanimous opinion of the subjects was that the mask was more comfortable and interfered less with sleep than the Hewlett-Packard 47201A ear oximeter which was used simultaneously in many of the studies.

The mask was connected by 30 inches of 1 inch-diameter light-weight flexible plastic tubing (Inhalation Plastic Inc) to the respiratory circuit (Fig 13). The plastic tubing was suspended above the bed so that the subject could adopt any position in bed - other than face down - with relative comfort and without the mask developing a leak. Occasionally posture changes produced a leak. When this occurred the leak usually disappeared when the subject next moved but rarely it was necessary to adjust the mask.

Expiratory flow was measured using a fixed geometry hot wire anemometer (Thermo Systems Inc). This was calibrated against rotameters traceable to the United States National Bureau of Standards. Before the studies were started and at regular intervals throughout the year, the integrated expiratory flow was compared with the expired volume measured in a Tissot spirometer. These comparisons covered the range of expiratory minute volumes from 4 to 40 litres/min. The resulting error was always less than 8%, mean error 3 $\pm$ 2% (Fig 14).

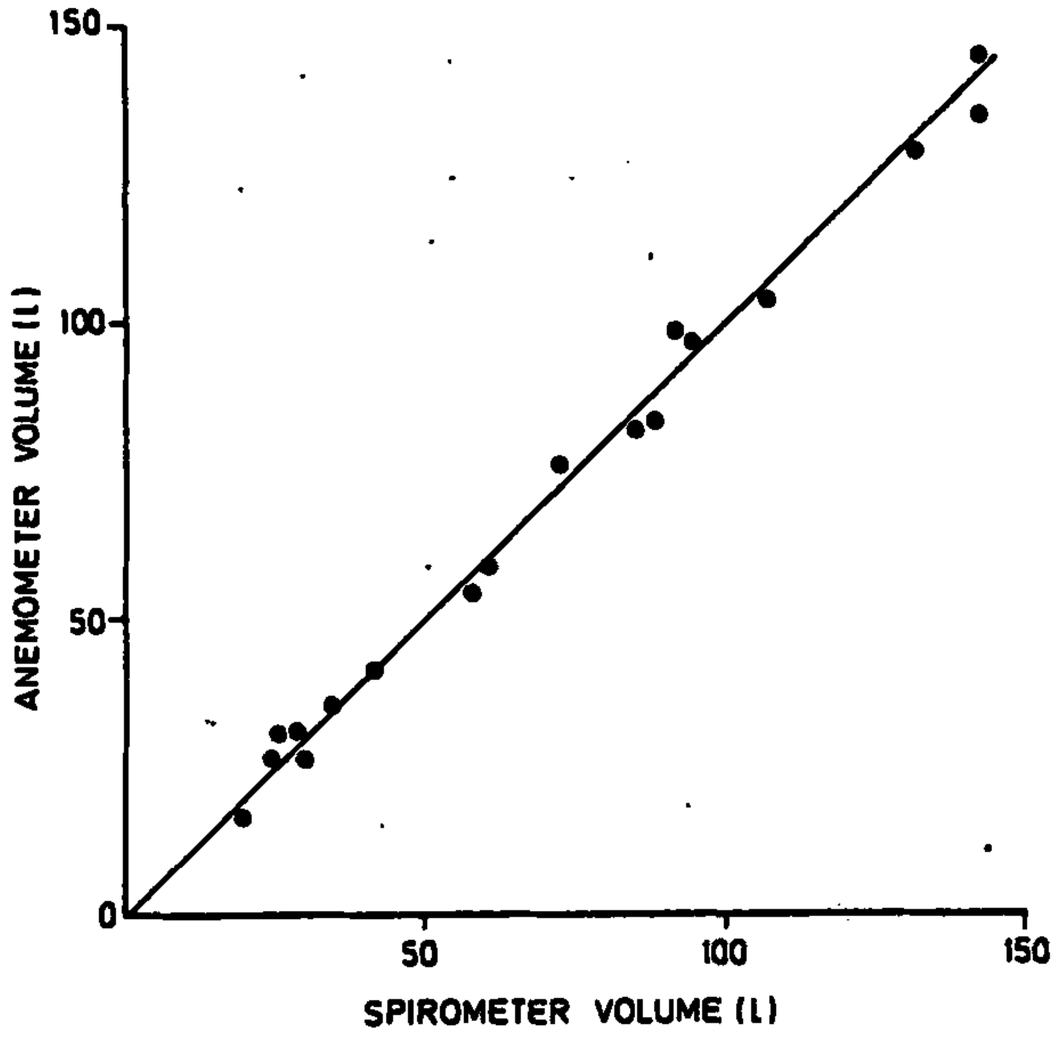



Fig 14 Comparison of expired volume measured from the integrated anenometer output with the volume measured in a Tissot spirometer. The line of identity is shown.

To create an atmosphere conducive to sleep, the subject's bedroom was soundproofed and contained no equipment which generated noise. Thus all gas analysers were in the next room. The respiratory gas concentrations at the mouth and nose were measured via fine bore (internal diameter 1.40 mm) polyethylene catheters (Intramedic Ltd), separate catheters being used for oxygen and carbon dioxide measurement. These catheters were kept as short as possible (<1.9 m) to minimise both initial time delay and possible loss of signal quality.

End-tidal $PO_2$ was analysed using a fuel cell (Sodal et al, 1968) which uses a zirconium oxide tube coated on both the inside and outside with porous platinum. When heated to $80^{o}$-$100^{o}C$ this zirconium oxide acts as a

semi-permeable membrane whilst the platinum layers act as electrodes. Thus the oxygen concentration on the inside of the tube can be determined relative to that of reference gas - usually air. The system was used with a gas sampling rate of 180 ml/min and when tested with the sampling catheter there was initial delay of 0.72±0.04 sec and a subsequent 90% rise time of 0.07±0.01 sec. Both the time response and the linearity and stability of calibration of the fuel cell were regularly checked.

End-tidal $CO_2$ was measured by a second infra-red $CO_2$ analyser. During the studies of hypoxic ventilatory response, a Goddard Capnograph was used but this failed thereafter and a Beckman LB2 was used during the studies of hypercapnic ventilatory response. The time characteristics of the Capnograph in this setting unfortunately were not measured prior to its demise, but it had been working to the manufacturers' specifications. The Beckman LB2 when tested with the sampling catheter had an initial delay of 0.54±0.02 sec and the subsequent 90% response time of 0.26±0.01 sec. The Beckman LB2 sampled at 250 ml/min. Expired volumes were calculated allowing for the sampling volumes of the $CO_2$ and $O_2$ analysers.

The oxygen and carbon dioxide analysers were calibrated against gases whose composition had been accurately determined by the Scholander technique (1947). The composition of these gases spanned the range encountered in the study (25-8% for $O_2$ and 0-10% for $CO_2$). The calibrations of the end tidal gas analysers

were checked before and after each study and at least every 90 minutes throughout the night and were always within 1.5%. During the studies of hypoxic drive, oxygen saturation was measured by the Hewlett Packard 47201A ear oximeter (see Chapter 4). The oximeter was not used during the studies of the hypercapnic ventilatory response as it was felt that it significantly impaired sleep quality.

End-tidal concentrations, oxygen saturation and flows were analysed breath by breath on a NOVA 1200 computer. The computer programme selected the highest stable level of $CO_2$ for each expiration as the $P_{ET}CO_2$ and the lowest stable value of oxygen for $P_{ET}O_2$. This procedure minimised the significance of the initial time delays inherent in sampling gases through catheters from the next room. The computer also calculated the average heart rate every 10 beats from an ECG signal.

Continuous recordings were made on a polygraph recorder (Grass model 78D) of electroencephalogram (by silver disc electrodes in the central and occipital regions), electrooculogram (by one electrode lateral to each outer canthus and one near the nasion) and electromyogram (by 2 sub-mental electrodes). The sleep stage was determined by standard criteria (Rechtschaffen & Kales, 1968). On the same polygraph were also recorded continuous records of respired $CO_2$ concentration, a computer-generated signal for tidal volume, and a computer generated timing code.

Several safety precautions were taken. The ECG was recorded continuously, and each QRS complex produced a quiet sound clearly audible to the operator but not to the subject, and this would have instantly alerted the operator to any arrhythmia. The inspiratory gas was continuously sampled by a separate fuel cell which automatically produced a loud alarm noise if the inspired oxygen concentration fell below 7%. This alarm was designed to detect the accidental filling of the inspiratory bag with the wrong gas mixture. The computer automatically produced an alarm noise if the subject's end-tidal $PO_2$ fell below 5 kPa or oxygen saturation fell below 75%. During all the studies there was always at least one doctor present plus an EEG technician trained in cardio-respiratory resuscitation. Fortunately, none of these safety precautions proved to be necessary.

## EVALUATION OF EQUIPMENT

Because the equipment to be used differed from that conventionally employed, largely due to the use of a mask and the long sampling lines, ventilation and ventilatory responses were compared by the two methods. In the conventional study subjects wore a nose clip and breathed through a mouthpiece attached to a non-rebreathing valve (Hans Rudolph Model No. 1000) with a similar dead space (82ml) and similar low resistance to the mask. The 4cm

sampling probe in the fuel cell was connected directly into the respiratory valve and the $CO_2$ sampling line was kept to 0.5 metres. All other equipment was the same in both sets of studies.

Nine normal men were studied after giving informed consent and having fasted and abstained from caffeine for at least 4 hours. All studies were performed with the subject seated and watching television. Five minutes of resting ventilation, 2 isocapnic hypoxic (Weil et al, 1970) and one rebreathing hypercapnic ventilatory response were measured, as previously described (Hirshman et al, 1975). These studies were performed twice in each subject, once breathing through the mouth and once breathing on the mouthpiece, the order being randomly determined. The data was analysed without knowledge of the breathing route under study. Differences were determined by paired t test (Snedecor & Cochran, 1980) and results are quoted as means $\pm$ standard errors.

Initial breathing frequency was significantly lower ($p < 0.01$) breathing on the mouthpiece (12.3$\pm$0.9) rather than the mask (14.6$\pm$1.0 breaths/minute). This difference was due to prolongation ($p < 0.05$) of both inspired (Ti) and expired (Te) times with mouthpiece breathing (mouthpiece Ti 2.13$\pm$0.06, Te 3.06$\pm$0.05; mask Ti 1.80$\pm$0.19, Te 2.50$\pm$0.27 sec). Resting ventilation was not different ($0.2 > p > 0.1$) between mask (8.66$\pm$0.52 l/min) and mouthpiece (3.24$\pm$0.24 l/min) and thus tidal

volume was significantly greater ($p < 0.02$) on the mouthpiece (0.70±0.06 l) than the mask (0.61±0.05 l). There was no difference ($p > 0.4$) between the ventilatory responses obtained on the mouthpiece and those using the mask either for hypoxia (mouthpiece 1.10±0.19, mask 1.03±0.18 l/min/%$SaO_2$) or for hypercapnia (mouthpiece 14.0±1.0; mask 13.3±1.2 l/min/kPa $CO_2$).

Unfortunately when the study was performed I no longer had access to an inductance plethysmograph, so it was not possible to compare resting ventilatory volumes with and without facial instrumentation. However, breathing frequency was measured over a 5 minute period in the same session in these 9 subjects using a circum-thoracic strain gauge with no mask or mouthpiece attached. This unencumbered frequency (15.1±0.8 breaths/min) was similar to that obtained with the mask but significantly ($p < 0.05$) higher than that with the mouthpiece when tested by two way analysis of variance and the Student-Newman-Keuls multiple comparison test (Steele & Torrie, 1960). Subsequently, Iber and colleagues (1982) have also found that a mask did not alter breathing frequency. These observations suggest, but do not prove, that the respiratory pattern breathing through a mask might be closer to normal breathing than that obtained when breathing through a mouthpiece. Other observations made at the same time, but not included here as they are tangential to this thesis, suggested that the

lower breathing frequency obtained on the mouthpiece was due, at least in part, to differences in respiratory timing between oral and nasal breathing (Douglas et al, in press) possibly due to the presence of upper airway flow receptors (McBride & Whitelaw, 1981).

These results are compatable with Gilbert and colleagues' finding (1972) that breathing frequency is reduced when breathing with a mouthpiece and with Hirsch and Bishop's recent observation (1981) that breathing on a mouthpiece decreased frequency and increased tidal volume compared with breathing through a mask. However, they conflict with Askanazi and colleagues' report (1980) that frequency is unchanged between mask, mouthpiece and free breathing. This discrepancy might be due to a physiological or psychological effect of the head canopy with a 40 l/min blow-through used by Askanazi, or to posture differences as Askanazi's subjects were supine. Askanazi and colleagues found that ventilation was raised during both mouthpiece and mask breathing compared to free breathing, and a similar increase in ventilation when breathing through a mask was found by Iber and colleagues (1982). Although this comparison cannot be made in the current study, it would be expected that the added dead space would result in increased ventilation due to chemostimulation. With the dead space of the mask and at the observed frequencies, the increase in ventilation required to maintain alveolar ventilation would be about 1.2 l/min.

This evaluation shows that the subsequent studies should give comparable results to conventional techniques for ventilatory responses to chemostimulation. It is suggested that the mask might not affect breathing frequency but would probably increase overall ventilation.

## ALTITUDE EFFECTS

The experiments were carried out at 1600 metres above sea level, and the effect of altitude on ventilation, ventilatory drive and breathing during sleep have to be considered. At this height, resting ventilation is raised and thus the absolute values of ventilation obtained are not directly applicable to sea level. There is no evidence that this altitude affects ventilatory drive, the normal values measured in Denver (Hirshman et al, 1975) being similar to those obtained at sea level, both for hypoxic (Kronenberg et al, 1972; Rebuck et al, 1973) and hypercapnic (Read, 1967; Rebuck et al, 1973; Cameron, 1979) ventilatory responses. There is no evidence that either acute or chronic residence at 1600 metres affects breathing during sleep. Acute exposure to high altitude (above 4,000 metres) results in abnormal breathing during sleep with an increase in apnoeas and periodic breathing (Reite et al, 1975), but these abnormalities diminished within 12 days

of arriving at altitude. Thus there is no evidence that respiratory pattern during sleep would be abnormal in healthy subjects who have been in Denver for at least 5 months. Indeed 4 of the male subjects had previously participated in routine sleep studies in Denver, and their breathing traces were similar to those reported from sea level in part 1 of this thesis.

## GENERAL PROTOCOL OF STUDIES OF VENTILATION AND OF VENTILATORY RESPONSE DURING SLEEP

Two separate studies were performed. In the first resting ventilation and hypoxic ventilatory response and in the second resting ventilation and hypercapnic ventilatory response were measured before, during and after sleep in normal adults. The protocols for the two studies were similar and are set out below.

The subjects reported to the laboratory at 9.30 pm having slept normally the night before and having abstained from alcohol, caffeine and food for at least 4 hours. Electrodes were attached for the recording of EEG, EOG, EMG and ECG as previously described. The face mask was then applied and for the studies of hypoxic ventilatory response, the ear oximeter was attached. All ventilatory measurements were made with the subjects lying in bed and none was taken until the subjects had

been resting for at least 30 minutes. During all measurements on awake subjects, the subjects watched television, violent or stimulating programmes being avoided. Television was watched because this had previously been shown in that laboratory (J V Weil, personal communication) to successfully distract the subject from his breathing and to produce the most basal and reproducible measurements of ventilation and ventilatory drives. Initially some measurements were made with the subject's eyes shut as this had been shown (Asmussen, 1977) to reduce ventilation. However, soon after closing their eyes, some subjects showed EEG changes of drowsiness, and thus this was abandoned as we wished to make measurements during EEG verified wakefulness. Indeed as Asmussen (1977) did not record EEG, it is possible that some of the effects he describes are due to the subjects being drowsy when sitting relaxed and blindfolded, as drowsiness has been shown (Bulow, 1963) to decrease minute ventilation.

After the subjects had been resting for at least 30 minutes, resting baseline ventilation breathing room air was measured for 1-3 minutes followed by 2 measurements of the relevant ventilatory response, all these measurements being made during EEG confirmed wakefulness. The subject was then left to sleep in the quiet darkened bedroom and as many measurements of ventilation and ventilatory response as possible were made in the various

sleep stages. After final awakening one measurement of resting ventilation and 2 of ventilatory response were made during EEG confirmed wakefulness with the subject lying in bed watching television.

In order to be included in subsequent analysis, all studies had to meet the following criteria:-

1) No leak was detected at any stage during the study.
2) At least 10 mins had elapsed since the previous episode of chemostimulation prior to the start of the next measurement of either baseline ventilation or ventilatory response.
3) The EEG sleep stage had been stable for at least 2 mins prior to the start of the measurement.
4) There was no EEG sleep stage change, however brief, during the study. The reason for adding the brevity clause was that conventional EEG scoring (Rechtschaffen & Kales, 1968) frequently involves deciding which is the dominant stage during an epoch. Thus a transient but unequivocal arousal which might be expected to have an effect on ventilation might not alter the scoring of an epoch. Therefore the occurrance of any arousal - defined as the occurance of alpha waves plus increased EMG tone - terminated the study. The standard criteria (Rechtschaffen & Kales, 1968) were tightened so that sleep stage was scored every 15 seconds, and so, for

example, any stage 2 study which had more than 20% delta waves in a 15 sec period was terminated. The studies were designed to contrast physiological variables between sleep stages, and thus strict criteria for sleep staging were required. We did not differentiate between stage 3 and stage 4 in this respect as they tended to intermingle and neither resting ventilation nor ventilatory responses were different between these two stages which are hereafter referred to as "stage 3/4".

5) For ventilatory response studies, an adequate stimulus had been administered. These were defined as an ultimate $P_{ET}O_2$ of less than 6.7 kPa for hypoxia studies and for hypercapnic responses an increase in $P_{ET}CO_2$ of at least 0.9 kPa above the stable value in that sleep stage.

Recognition of "tonic" REM sleep (Sullivan et al, 1979a) - identified by the other features of REM sleep (see Chapter 2) in the absence of rapid eye movements - proved extremely difficult in real time. As chemostimulation tended to arouse the subjects, measurements were only made in REM sleep when that stage could be confidently identified, and this usually required the presence of eye movements. Further, pure "tonic" REM, with no eye movements, tends to be short lived. Hence most REM studies were performed in "phasic"

REM sleep. Indeed satisfactory studies were only obtained in both "phasic" and "tonic" REM in 5 subjects for baseline ventilation, 2 for hypoxic response and none for hypercapnic response. There was no consistent difference between the results in "phasic" and "tonic" REM sleep for baseline ventilation or hypoxic response, nor was there any clear relationship between the relative frequency of eye movements and any of the measurements made. Such comparisons, therefore, will not be made in the results sections that follow.

Studies were performed without an acclimatisation night. This was because the nature of the studies precluded the attainment of a normal night's sleep as subjects were repeatedly awoken by chemostimulation. The aim of the study was therefore to obtain reproducible results in stable sleep stages and not to measure ventilation during a normal night's sleep. Furthermore, it was felt that the instrumentation might result in poor sleep quality on the acclimatisation night producing sleep deprivation which might affect ventilatory drive (see Appendix 1).

## HYPOXIC VENTILATORY RESPONSE

### Technique

Isocapnic ventilatory responses were measured (Weil et al, 1970). For the first 30 seconds of these studies the subjects breathed room air and thereafter hypoxia was

induced by addition of nitrogen to a bag of air at a rate designed to reduce end-tidal oxygen tension to 5.3 kPa in 3-4 minutes. The studies ended either at a $P_{ET}O_2$ of 5.3 kPa or when sleep stage change occurred. Isocapnia was maintained at the level measured during resting air breathing in the 2.5 minutes before the induction of hypoxia. This was achieved by the manual addition of $CO_2$ to the inspired line.

Regression lines for ventilation against oxygen saturation were calculated by the least squares method (Snedecor & Cochran, 1980). Hypoxic responses are reported in terms of the slope of the ventilation/oxygen saturation plot rather than in terms of the ventilation/end-tidal $PO_2$ relationship because intermittently during sleep breaths were so small that end-tidal plateaux were not obtained.

This method contains several modifications from the conventional technique (Weil et al, 1970). These modifications and their validations are discussed below.

1. All measurements were made using the mask.
2. All measurements were made with the subject lying in bed. To investigate the effects of posture in each of three subjects, six measurements of hypoxic ventilatory response were obtained with the subjects awake and seated and were compared with six obtained with the subject awake and supine., There were no

posture related differences either in the slope of the ventilation/oxygen saturation plot, the scatter of the data as indicated by the mean square error or in the linearity of the data as determined by visual inspection.

3. The studies were started with the subjects breathing room air, not a hyperoxic mixture, and the rate of decline of oxygen tension was more rapid than usual. These measures allowed hypoxic studies to be performed more rapidly and without any delay whilst hyperoxia was being induced. These steps increased the chances of completing the hypoxic ventilatory response before the sleep stage changed. To validate these alterations, hypoxic ventilatory response was measured in each of three subjects, twice commencing at an end-tidal $PO_2$ of 17 kPa and decreasing $P_{ET}O_2$ at about 1 kPa/min and twice commencing at an end-tidal $PO_2$ of 11 kPa and reducing $P_{ET}O_2$ at about 1.6 kPa/min. There was no significant difference in the results by the two techniques (mean error $1.8 \pm 5.3\%$). In 3 subjects (1-3) the hypoxic ventilatory response was measured using the modified technique on 6 days over a 2-week period, each measurement being made with the subject fasting and rested. The coefficient of variation of the slope of the hypoxic ventilatory response ranged from 11 to 21%.

4. The induced hypoxia sometimes awoke subjects before the end-tidal oxygen tension fell to 5.3 kPa. To determine whether less severe hypoxia would affect the measurement of the ventilation/arterial saturation slope, 17 hypoxic ventilatory drives obtained in three awake subjects over the $P_{ET}O_2$ range of 19-5.3 kPa were reanalysed, comparing hypoxic ventilatory response results over the full range of $P_{ET}O_2$ with those obtained by selecting data over the $P_{ET}O_2$ ranges of 11-5.3, 11-6.0 and 11-6.7 kPa: 11 kPa is the $P_{ET}O_2$ of normal subjects breathing air in Denver. Although scatter increased as the amount of data analysed decreased, there was no systematic error due to decreasing the lowest $P_{ET}O_2$ to 6.7 kPa (% error, 11-5.3 kPa, -0.1$\pm$2.8%; 11-6.0 kPa, -0.3$\pm$5.3%; 11-6.7 kPa, -1.5$\pm$9.8%). Thus as hypoxic ventilatory response studies were considered adequate only if the lowest $P_{ET}O_2$ was 6.7 kPa or less, no inherent bias should have resulted from the use of a less hypoxic stimulus in some studies performed on sleeping subjects.

Hypoxic Ventilatory Response - Subjects Studied

Ten healthy male and six healthy females were studied (see Subject Details below). Four male subjects either did not sleep, or slept so poorly that

measurements could only be made in one stage of sleep, and these four were eliminated from the study. Each man was studied on one night only, but as ventilatory response has been reported to vary during the menstrual cycle (Schoene et al, 1981) each woman was studied in both the follicular (day 6-9) and luteal (day 20-23) phase of the menstrual cycle. Menstrual status was documented by serum progesterone concentrations.

Adequacy of Isocapnia

In non-REM studies, $P_{ET}CO_2$ was always kept within 0.2 kPa of the value during the 2.5 minutes immediately prior to the start of the study. Since tidal volume was variable and often reduced during REM sleep $P_{ET}CO_2$ varied, but isocapnia was attained during REM as judged by the $P_{ET}CO_2$ in the initial ($P_{ET}O_2$ > 8kPa) and latter half of each study, always being within 0.2 kPa (mean $PCO_2$ initial 4.96±0.05, latter 4.91±0.07 kPa). Indeed there was no significant difference between the mean $P_{ET}CO_2$ levels in the two halves of the studies in any sleep stage. The overall mean levels of $P_{ET}CO_2$ in the studies were similar in wakefulness, stage 2 and REM sleep, but were significantly higher in stage 3/4 sleep (awake, 4.91±0.05, stage 2, 4.99±0.07, stage 3/4, 5.13±0.08, REM, 5.01±0.07 kPa).

Adequacy of Hypoxic Studies

Hypoxic ventilatory responses which achieved all five criteria for acceptability were obtained in each sleep stage on each subject with two exceptions. In both

cases several studies were started in the appropriate stage but sleep stage always changed. However, in both cases the deviations from the criteria were minor and thus these studies have been included in our analysis. In the most successful stage 2 study obtained in subject 1, arousal occurred at 6.7 kPa, our limit of adequate hypoxia. This study has been included despite the lowest usable $P_{ET}O_2$ being 6.8 kPa. The best REM study obtained in subject 2 included three short (< 5 sec) arousals, but these were spread over a 3.5 min study in such a way that the standard EEG scoring (Rechtschaffen & Kales, 1968) was uninterrupted REM sleep. It was felt that these arousals, whilst undesirable, would bias the result in the direction of wakefulness and thus diminish rather than exaggerate any REM sleep effect. Subjects 1 and 3 were re-studied on a second night because satisfactory ventilatory responses were not obtained in each sleep stage on the first night. The results for these subjects are the means of all studies obtained on both nights.

## HYPERCAPNIC VENTILATORY RESPONSE

The steady state $CO_2$ response technique is not ideal for studies of hypercapnic ventilatory response during sleep for three major reasons. Firstly, breathing during sleep is often irregular and this is especially true

during REM sleep, the stage that this study was designed to examine. Such irregular breathing precludes the attainment of a steady state and thus the arterial $PCO_2$ would vary continuously and would not reflect the central chemoreceptor $CO_2$ tension. Secondly, the relationship between arterial $PCO_2$ and central $CO_2$ in the steady state technique is highly dependent on cerebral blood flow (Read & Leigh, 1967). There is evidence that cerebral blood flow in man (Townsend et al, 1973) decreases in non-REM sleep compared to wakefulness and increases above the level of wakefulness in REM sleep. This increase in cerebral blood flow in REM has also been found in cats (Reivich et al, 1968) and goats (Santiago et al, 1980). Thus altered cerebral blood flow during REM sleep would make interpretation of "steady state" hypercapnic ventilatory responses extremely difficult. Thirdly, when breathing is regular it takes at least 15 minutes (Reynolds et al, 1972) after the inspired gas concentration is changed before a new steady state is established and measurements can be taken. This delay would reduce the likelihood of completing the study before the sleep stage changed and almost certainly preclude the acquisition of data at more than two levels of $CO_2$ tension.

These problems are reduced using the rebreathing technique. Since the difference between $PaCO_2$ and brain tissue $CO_2$ is minimised (Read & Leigh, 1967) and

irregular breathing has little effect on alveolar or arterial $PCO_2$, this technique is more applicable to REM sleep. Changes in cerebral perfusion occurring before the onset of rebreathing will still affect the relationship of $PaCO_2$ to brain $PCO_2$ resulting in an altered ventilatory response. Any such change occurring after the onset of rebreathing, such as $CO_2$ induced changes, would have only a small influence on the response during rebreathing (Read & Leigh, 1967) compared with the effect that would occur with the steady state technique. Furthermore, rebreathing allows the continuous acquisition of data over a wide range of $CO_2$ levels so maximising the chance of obtaining a usable result before the sleep stage changes.

Hypercapnic ventilatory responses (HCVRs) were performed by rebreathing from a bag containing 40% oxygen and 60% nitrogen. In contrast to the Read technique (1966) there was no $CO_2$ in the initial bag mixture as it was felt the sudden inhalation of $CO_2$ might induce arousal or sleep stage change. Previous work in our own laboratory (Hirshman et al, 1975) has shown that this method results in similar normal values to the Read technique (Read, 1967; Rebuck et al, 1973; Cameron, 1979), although theoretically one might expect slightly lower values for HCVR when there was no $CO_2$ in the bag initially (Read & Leigh, 1967). In the current study, no data was recorded until the inspired $CO_2$ had risen above

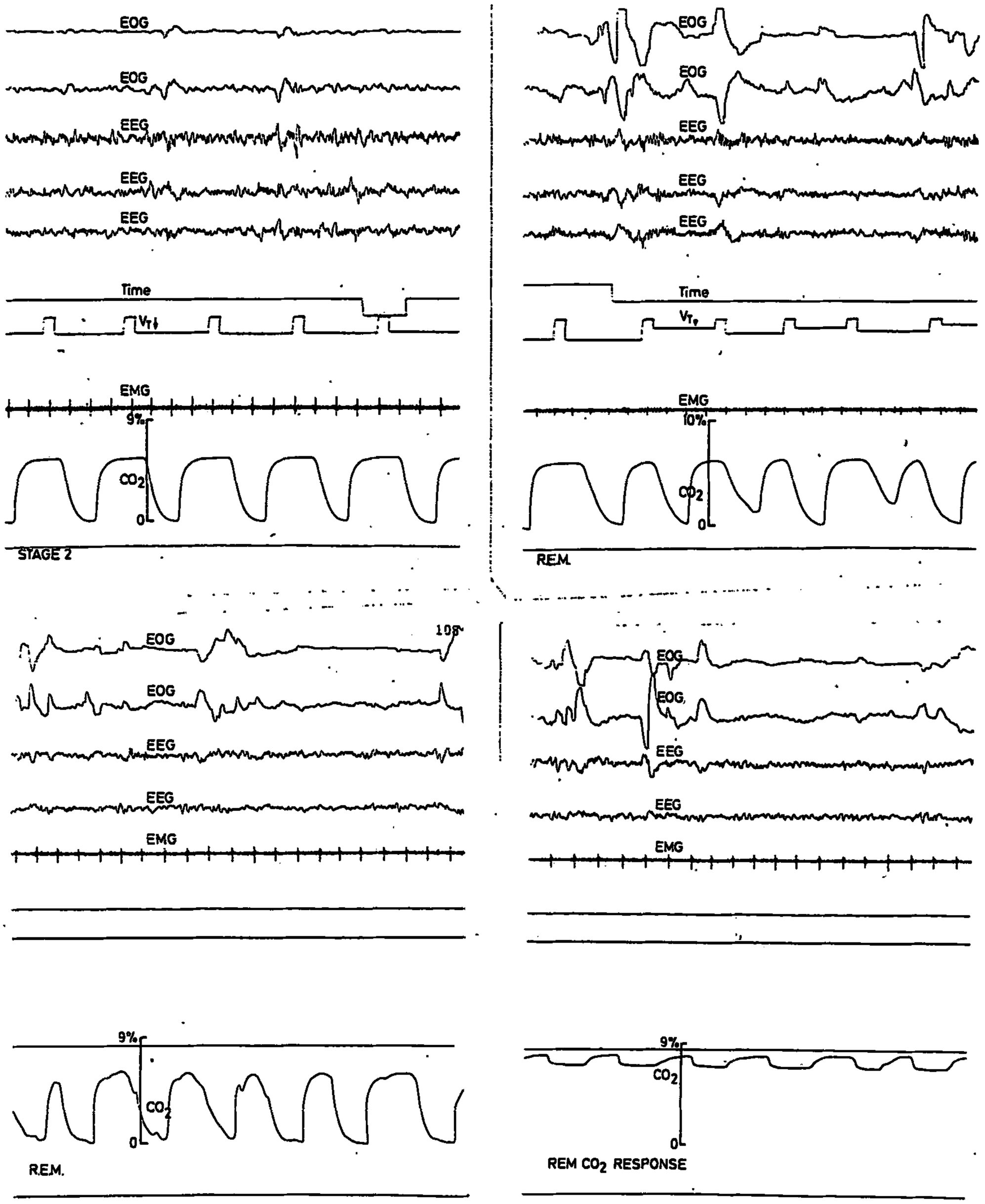



Fig 15 Example of polygraph record illustrating respired $CO_2$ concentrations during baseline ventilation in Stage 2 (top left) and REM sleep and during a $CO_2$ response in REM sleep (bottom right).

4%, after which the rise in $CO_2$ was linear with time. The size of the rebreathing bag was adjusted to give a mean $P_{ET}CO_2$ rise of 0.31±0.01 kPa/min. There was no difference between the rate of $CO_2$ rise in the different stages of sleep and wakefulness.

In order to be considered suitable for analysis, $P_{ET}O_2$ had to be above 17 kPa throughout the study, and the rise in $P_{ET}CO_2$ had to be at least 0.9 kPa above the stable level in that sleep stage. Because of arousal, the rise in $CO_2$ during HCVR studies was significantly smaller ($p < 0.05$) during each stage of sleep than during wakefulness, but there was no difference between the mean rise in the different stages of sleep. (Awake, 1.69±0.04, stage 2, 1.24±0.05, stage 3/4, 1.39±0.05, REM, 1.25±0.08 kPa).

Adequate end-tidal plateaux were not always attained during sleep because of intermittent small breaths (Fig 15). This was a particular problem in REM sleep and presented a greater problem during baseline ventilation than during rebreathing, when ventilation tended to be stimulated and the inspired/expired $CO_2$ difference was small. When true end-tidal plateaux were not obtained in HCVR studies, the end-tidal $CO_2$ level was subsequently edited up to the level deduced from interposing the time of the breath on the ramp of rising true end-tidal $CO_2$. Such $CO_2$ editing was never performed on more than 15% of breaths in any HCVR study. Overall the mean editing

rates were awake, 0.2±0.2%, stage 2, 1.0±0.7%, stage 3/4, 1.3±0.8%, REM, 6.3±1.3%.

The hypercapnic ventilatory response was derived by least squares regression of ventilation against end-tidal $CO_2$.

The hypercapnic ventilatory response was measured by the technique used in this study on 3 subjects (1-3) on 6 days over a 2-week period, each measurement being made at the same time of day with the subject fasted and rested. The coefficient of variation of the slope of the hypercapnic ventilatory response ranged from 12 to 19%.

Hypercapnic Ventilatory Response in Subjects Studied

Twelve normal subjects were studied (6 men, 6 women) each for one night only. This study was performed after the study of hypoxic response and because of the results of that study it was decided only to study women in one stage of the menstrual cycle. Because progesterone is a respiratory stimulant (Zwillich et al, 1978) it was felt that any difference between men and women would be more obvious when progesterone levels were high and thus women were studied during the luteal phase of the menstrual cycle (day 20-23).

Subject Details

During the two investigations 23 normal subjects were studied, but as four failed to sleep all results

refer to the remaining 19. These comprised 8 men (mean age 32±1.8 years) and 11 women (mean age 26.5±1.3 years). Physical characteristics and sleep quality of these 19 subjects are given in Table 10 from which it can be seen that 4 men and 1 woman were subjects in both the studies of hypoxic and hypercapnic drive. None of the subjects smoked, had a history of respiratory disease, was more than 10% above ideal body weight, nor had any sleep complaints. None was taking oral contraceptives nor any other medication. All subjects had resided for at least 5 months in Denver (1600 metres). Each subject was a regular nocturnal sleeper. Each subject gave written informed consent to the studies which had the approval of the University of Colorado Human Subjects Research Committee.

## Data Analysis

No differences were found between the results obtained for any variable before and after sleep and thus these values have been combined to give an "awake" value. For each subject the mean awake values were compared with the mean results in each sleep stage. Significance of differences between sleep stages was determined by two-way analysis of variance, and if significant changes were found the Student-Newman-Keuls multiple comparison test was applied (Steele & Torrie, 1960). Other comparisons were by paired or unpaired 2-tailed Student's t-test (Snedecor & Cochran, 1980). Results are quoted as means ± standard errors.

TABLE 10

PHYSICAL CHARACTERISTICS AND SLEEP QUALITY OF SUBJECTS STUDIED IN PART 11 OF THESIS

| Subject | Age (yr) | Sex | Ht. (cm) | Wt. (Kg) | Response Studied HVR | Response Studied HCVR | Nights Slept | Mean Time in Bed(min) | Mean Total Sleep Time(min) | Mean Sleep Efficiency Index(%) | Mean Sleep Period Time(min) | % Mean Sleep Period Time W | 1 | 2 | 3 | 4 | REM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | M | 178 | 68 | + | + | 3 | 380 | 285 | 75 | 370 | 22 | 9 | 38 | 13 | 1 | 17 |
| 2 | 31 | M | 185 | 73 | + | | 1 | 388 | 197 | 51 | 355 | 44 | 7 | 31 | 9 | 5 | 4 |
| 3 | 32 | M | 179 | 73 | + | + | 3 | 480 | 235 | 50 | 463 | 48 | 2 | 33 | 9 | 2 | 10 |
| 4 | 39 | M | 191 | 73 | + | + | 2 | 446 | 324 | 73 | 410 | 21 | 8 | 48 | 10 | 2 | 11 |
| 5 | 34 | M | 178 | 73 | + | | 1 | 352 | 220 | 62 | 299 | 27 | 4 | 41 | 19 | 4 | 5 |
| 6 | 27 | M | 168 | 72 | + | + | 2 | 347 | 324 | 93 | 343 | 6 | 3 | 51 | 11 | 12 | 17 |
| 7 | 27 | M | 183 | 75 | | + | 1 | 408 | 379 | 93 | 407 | 7 | 5 | 57 | 14 | 4 | 13 |
| 8 | 29 | M | 183 | 66 | | + | 1 | 403 | 326 | 81 | 387 | 16 | 3 | 59 | 11 | 4 | 6 |
| 9 | 20 | F | 173 | 66 | + | | 2 | 285 | 230 | 81 | 278 | 17 | 2 | 43 | 13 | 13 | 10 |
| 10 | 25 | F | 152 | 48 | + | | 2 | 337 | 270 | 80 | 329 | 18 | 5 | 49 | 7 | 15 | 6 |
| 11 | 24 | F | 172 | 58 | + | | 2 | 218 | 143 | 67 | 163 | 12 | 4 | 45 | 20 | 12 | 6 |
| 12 | 26 | F | 165 | 64 | + | | 2 | 431 | 374 | 87 | 426 | 12 | 5 | 54 | 12 | 9 | 8 |
| 13 | 29 | F | 165 | 57 | + | | 2 | 378 | 308 | 81 | 370 | 17 | 6 | 55 | 12 | 2 | 7 |
| 14 | 25 | F | 158 | 52 | + | + | 3 | 315 | 280 | 89 | 306 | 9 | 7 | 50 | 9 | 13 | 12 |
| 15 | 26 | F | 163 | 64 | | + | 1 | 446 | 210 | 47 | 420 | 50 | 0 | 33 | 3 | 8 | 5 |
| 16 | 34 | F | 158 | 48 | | + | 1 | 353 | 206 | 58 | 309 | 33 | 0 | 55 | 2 | 6 | 2 |
| 17 | 29 | F | 165 | 49 | | + | 1 | 379 | 313 | 82 | 366 | 15 | 2 | 42 | 12 | 16 | 14 |
| 18 | 32 | F | 167 | 56 | | + | 1 | 424 | 327 | 77 | 414 | 21 | 10 | 42 | 8 | 13 | 6 |
| 19 | 21 | F | 165 | 55 | | + | 1 | 377 | 296 | 79 | 370 | 20 | 0 | 50 | 9 | 14 | 10 |
| Mean±SE | 29 ±1 | | 171 ± 2 | 63 ±2 | | | 1.7 ±.2 | 376 ±14 | 276 ±14 | 74 ±3 | 357 ±16 | 22 ±3 | 4 ±1 | 46 ±2 | 11 ±1 | 8 ±1 | 9 ±1 |

Footnote: Ht., Height; Wt., Weight; HVR, Hypoxic ventilatory response; HCVR, Hypercapnic ventilatory response; TIB, Time in Bed; TST, Total Sleep Time; SEI, Sleep Efficiency Index; SPT, Sleep Period Time; (Sleep times defined by criteria of Williams et al, 1974)

# CHAPTER 8

# BASELINE VENTILATION

## Data Obtained

Ventilation was measured during wakefulness and each stage of sleep in each subject on each night of study. In the subjects who slept more than one night the values of ventilation quoted are the average of the mean ventilation values obtained on each night. Three subjects were studied on three nights, 7 on two nights and 9 on one night. No significant difference was found either in respired volumes, breathing pattern, or EEG pattern in the first and subsequent nights' sleep in those studied on more than one night. There was no significant difference between the average duration of breathing recorded in wakefulness or in the various stages of sleep (mean duration awake, 5.5±0.7, stage 2, 6.1±0.9, stage 3/4, 5.4±0.8, REM, 4.8±0.8 min/subject).

## Results

Mean minute ventilation was significantly lower in all stages of sleep than in wakefulness (Table 11 & 12, Fig 16). There was no significant difference between the levels of ventilation in non-REM sleep (stages 2 and 3/4) but there was a further fall ($p < 0.05$) in REM sleep when

TABLE 11

MEAN BASELINE VENTILATION IN WAKEFULNESS AND DIFFERENT SLEEP STAGES IN 19 HEALTHY SUBJECTS

| | | Awake | Stage 2 | Stage 3/4 | REM |
|---|---|---|---|---|---|
| $\dot{V}_E$ | l/min | 7.66±0.34 | 7.24±0.39$^{+x}$ | 7.09±0.39$^{+x}$ | 6.46±0.29$^{+}$ |
| $V_T$ | l | 0.56±0.04 | 0.47±0.03$^{+x}$ | 0.45±0.02$^{+}$ | 0.41±0.02$^{+}$ |
| $f$ | b/min | 14.1 ±0.6 | 15.5 ±0.4$^{+}$ | 15.8 ±0.4$^{+}$ | 15.8 ±0.3$^{+}$ |
| $T_i$ | sec | 2.01±0.07 | 1.77±0.04$^{+}$ | 1.78±0.04$^{+}$ | 1.82±0.06$^{+}$ |
| $T_e$ | sec | 2.38±0.15 | 2.13±0.08$^{+}$ | 2.05±0.14$^{+}$ | 2.00±0.08$^{+}$ |
| $Ti/Ttot$ | | 0.46±0.01 | 0.46±0.01 | 0.47±0.01 | 0.48±0.01 |
| $V_T/Ti$ | l/sec | 0.28±0.01 | 0.27±0.02$^{x}$ | 0.26±0.01$^{x}$ | 0.23±0.02$^{+}$ |
| $P_{ET}O_2$ | kPa | 11.1 ±0.1 | 10.7 ±0.1$^{+x}$ | 10.6 ±0.1$^{+}$ | 10.4 ±0.1$^{+}$ |
| $P_{ET}CO_2$ | kPa | 4.7 ±0.1 | 4.9 ±0.1$^{+x}$ | 5.0 ±0.1$^{+o}$ | 5.0 ±0.1$^{+}$ |

Footnote:

$\dot{V}_E$, expired ventilation; $V_T$, tidal volume; f, breathing frequency; $T_i$, inspiratory time; $T_e$, expiratory time; Ttot, breath time; $P_{ET}O2$, end-tidal oxygenation; $P_{ET}CO_2$, end-tidal carbon dioxide tension
Mean ± standard error

\+ P 0.05 versus Awake
x P 0.05 versus REM
o P 0.05 versus Stage 2

TABLE 12 BASELINE VENTILATION DURING SLEEP IN 19 NORMAL SUBJECTS

| | Awake | | | Stage 2 | | | Stage 3/4 | | | REM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $V_E$ | $V_T$ | Ti | $V_E$ | $V_T$ | Ti | $V_E$ | $V_T$ | Ti | $V_E$ | $V_T$ | Ti |
| Subjects | l/min | l | sec | l/min | l | sec | l/min | l | sec | l/min | l | sec |
| 1 | 7.67 | 0.58 | 1.78 | 7.74 | 0.52 | 1.56 | 7.55 | 0.49 | 1.63 | 6.08 | 0.36 | 1.61 |
| 2 | 7.26 | 0.77 | 2.55 | 8.15 | 0.55 | 1.78 | 5.74 | 0.39 | 1.74 | 5.82 | 0.42 | 2.43 |
| 3 | 8.29 | 0.61 | 2.40 | 9.38 | 0.60 | 1.60 | 9.41 | 0.60 | 1.70 | 8.29 | 0.51 | 1.49 |
| 4 | 8.24 | 0.72 | 2.20 | 7.37 | 0.53 | 1.95 | 7.19 | 0.51 | 1.91 | 6.48 | 0.42 | 1.78 |
| 5 | 9.06 | 0.80 | 1.98 | 10.41 | 0.66 | 1.78 | 9.25 | 0.55 | 1.88 | 8.30 | 0.51 | 1.69 |
| 6 | 8.16 | 0.47 | 1.84 | 8.97 | 0.45 | 1.62 | 10.32 | 0.49 | 1.83 | 7.27 | 0.37 | 1.74 |
| 7 | 8.42 | 0.49 | 1.71 | 7.02 | 0.48 | 2.08 | 7.21 | 0.50 | 2.09 | 6.52 | 0.45 | 1.74 |
| 8 | 6.72 | 0.50 | 2.09 | 6.97 | 0.40 | 1.44 | 6.25 | 0.38 | 1.52 | 5.65 | 0.36 | 1.79 |
| 9 | 7.13 | 0.41 | 1.59 | 6.94 | 0.42 | 1.58 | 7.11 | 0.43 | 1.61 | 5.80 | 0.36 | 2.02 |
| 10 | 7.39 | 0.48 | 1.78 | 6.39 | 0.43 | 1.73 | 6.43 | 0.41 | 1.57 | 5.76 | 0.38 | 1.64 |
| 11 | 10.35 | 0.66 | 1.91 | 9.23 | 0.63 | 1.68 | 9.23 | 0.61 | 1.70 | 8.01 | 0.56 | 1.75 |
| 12 | 10.68 | 0.83 | 2.57 | 8.69 | 0.49 | 1.59 | 8.62 | 0.52 | 1.64 | 8.18 | 0.50 | 1.49 |
| 13 | 9.03 | 0.75 | 2.31 | 8.38 | 0.60 | 1.91 | 8.19 | 0.58 | 2.02 | 7.96 | 0.61 | 2.11 |
| 14 | 6.20 | 0.48 | 2.05 | 5.46 | 0.33 | 1.87 | 5.44 | 0.31 | 1.83 | 5.69 | 0.34 | 1.78 |
| 15 | 6.52 | 0.54 | 1.62 | 6.00 | 0.46 | 1.81 | 4.75 | 0.33 | 1.80 | 6.47 | 0.42 | 2.03 |
| 16 | 7.21 | 0.54 | 1.77 | 6.73 | 0.44 | 1.66 | 6.80 | 0.45 | 1.53 | 6.55 | 0.42 | 1.39 |
| 17 | 4.75 | 0.34 | 2.17 | 4.39 | 0.34 | 2.11 | 5.22 | 0.38 | 1.91 | 5.15 | 0.32 | 1.86 |
| 18 | 6.23 | 0.41 | 2.05 | 4.66 | 0.32 | 1.88 | 4.82 | 0.33 | 1.93 | 4.33 | 0.29 | 1.84 |
| 19 | 6.32 | 0.34 | 1.82 | 4.76 | 0.27 | 1.95 | 5.13 | 0.29 | 1.91 | 4.43 | 0.26 | 2.36 |

Footnote: $V_E$, minute ventilation; $V_T$, tidal volume; Ti, inspiratory time. (Other parameters such as f, $\frac{V_T}{Ti}$, or $\frac{Ti}{Ttot}$ can be calculated from the data given)

minute ventilation was reduced to 84% of the level during wakefulness.

Breathing frequency was significantly higher in all stages of sleep than in wakefulness (Table 11, Fig 16). There was no difference in this frequency between the different stages of sleep. Mean tidal volume was lower ($p < 0.05$) in all stages of sleep than during wakefulness with a further significant decrease from stage 2 to REM sleep when tidal volume was only 73% of the value in wakefulness.

Mean inspiratory flow rate ($V_T/Ti$) was significantly lower in REM sleep than in either wakefulness or non-REM sleep (Table 11, Fig 17). There was no difference in the respiratory duty cycle ratio, Ti/Ttot between any stage of wakefulness or sleep, the increased frequency of breathing during sleep being due to parallel reductions in Ti and Te (Table 11).

The subjects were significantly more hypoxic and hypercapnic in all stages of sleep compared to wakefulness (Table 11) with greater changes in REM sleep than in stage 2 ($p < 0.05$). There were no significant differences between the sexes either in ventilation corrected for body surface area (Documenta Geigy, 1970) or in end-tidal concentrations during any stage of sleep.

Breathing patterns tended to be regular in non-REM sleep (Fig 18) with two exceptions. Firstly, in all subjects tidal volume was variable in the first few

minutes after sleep onset and following arousal. Secondly, in 4 male subjects such irregular breathing continued throughout the initial 1-4 hours of non-REM sleep (Fig 18) but regularised in all cases thereafter. In all subjects the breathing pattern in REM was irregular throughout the night.

## Discussion

This study shows that normal human subjects breathe more rapidly and shallowly in all stages of sleep than in wakefulness, the lowest mean tidal volume occurring in REM sleep, when the depth of breathing was highly variable. These changes resulted in decreased expired volumes in non-REM sleep compared to wakefulness with a further marked reduction in ventilation during REM sleep, which was associated with a parallel reduction in inspiratory drive ($V_T$/Ti).

The finding that mean minute ventilation is reduced in adult man in non-REM sleep, compared to wakefulness, confirms many previous studies (e.g. Birchfield et al, 1959; Bulow, 1963) including some (Magnussen, 1944; Robin, 1958) in which measurements were almost certainly made in non-REM although the EEG was not recorded (see Chapter 3). However, Duron (1972) and Newsom Davis (Davis, 1976) both found no difference in the level of ventilation between wakefulness and non-REM sleep. Duron probably failed to find a difference because he only

studied 4 subjects, although he maintained it was because previous studies had attained a spuriously high level of ventilation during wakefulness. Newsom Davis and colleagues published their findings only in abstract and gave neither data nor the number of subjects studied. As they measured ventilation without facial instrumentation, their findings also raised the question as to whether facial instrumentation had previously produced spurious results. However, in 1981 both Gothe and co-workers and Skatrud and colleagues also measured ventilation in normal subjects from chest and abdominal wall movement and both found that ventilation decreased in non-REM sleep compared to wakefulness. Further evidence that there is a genuine decrease in ventilation during non-REM sleep comes from the demonstration that normal subjects without facial instrumentation were relatively hypoxic (Doust & Schneider, 1952; Bristow et al, 1969; Coccagna et al, 1976) and hypercapnic (Hastings & Eisele, 1940; Birchfield et al, 1958; Bristow et al, 1969; Coccagna et al, 1976) during non-REM sleep - a finding also confirmed in studies performed with facial instrumentation (eg Magnussen, 1944; Robin et al, 1958; Bulow, 1963; Townsend et al, 1973). These changes can only result from either hypoventilation or an increase in metabolic rate, but metabolic rate falls in non-REM sleep (Brebbia & Altshuler, 1965). Thus there is unequivocal evidence that ventilation is reduced in non-REM sleep compared to wakefulness in adult man.

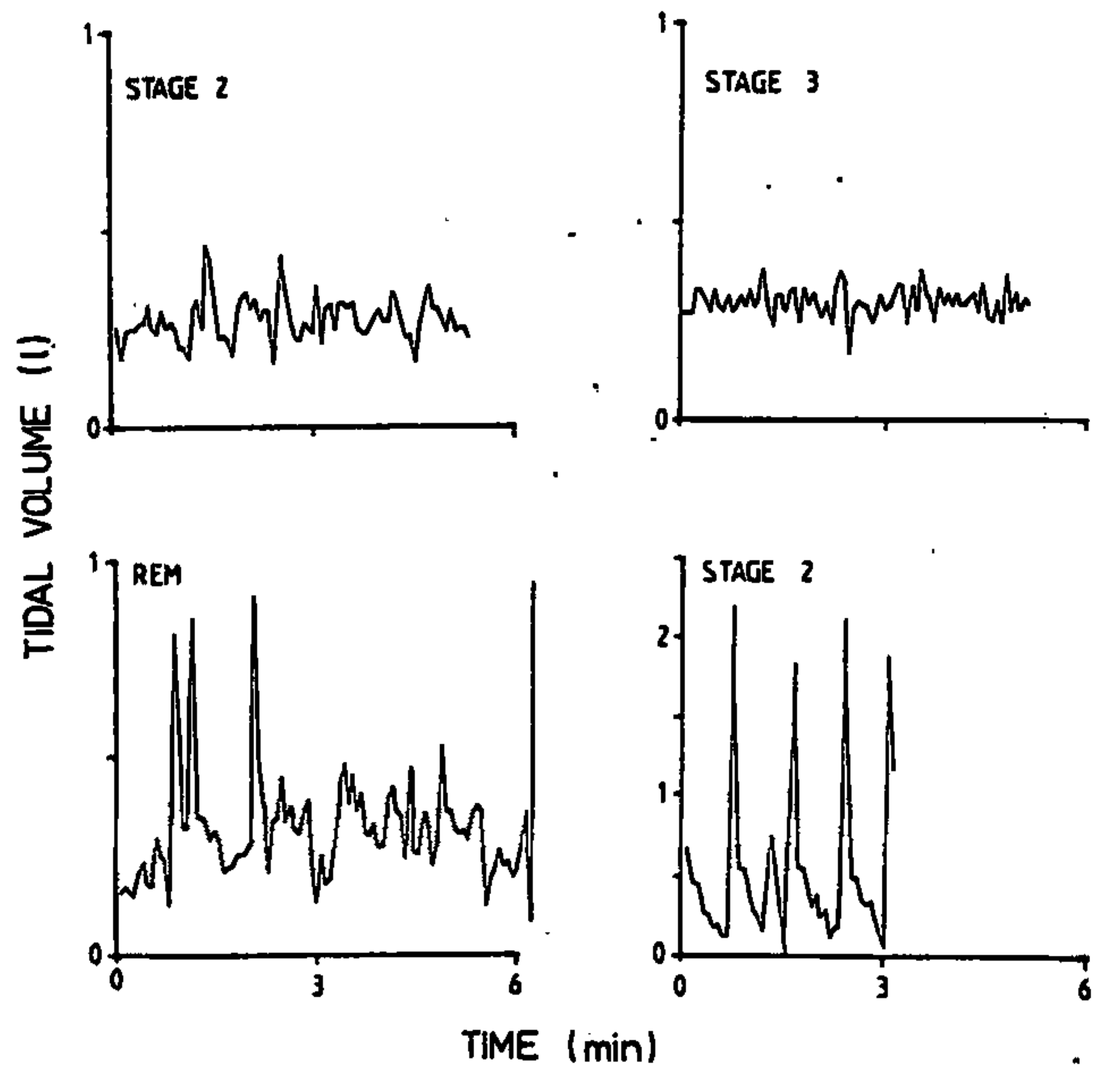



Fig 18 Typical breath-by-breath patterns of tidal volume in Stage 2 (top left), Stage 3 (top right), and REM sleep (bottom left). The bottom right panel illustrates the grossly irregular breathing observed in Stage 2 in 4 male subjects early in the night.

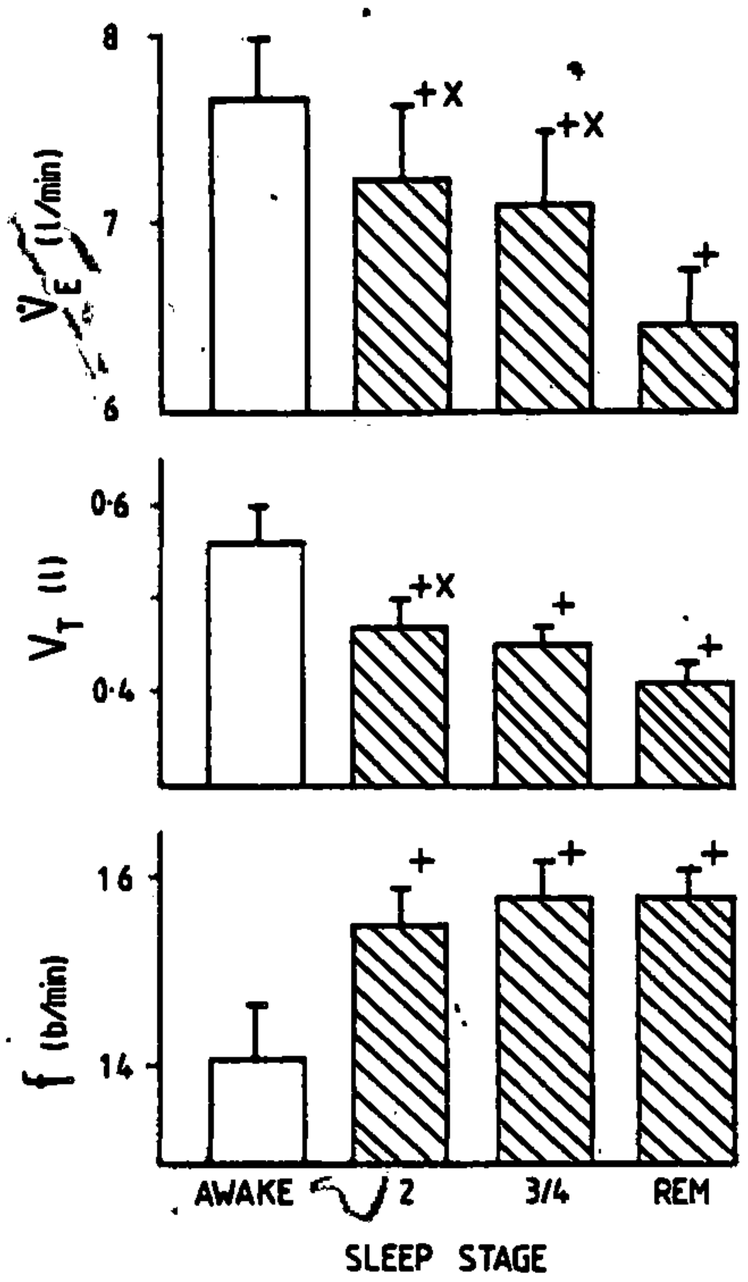



Fig 16 Expired ventilation ($\dot{V}_E$), tidal volume ($V_T$) and breathing frequency (f) in wakefulness and different sleep stages. Mean ± SE in 19 subjects.

\+ p 0.05 versus wakefulness
x p 0.05 versus REM sleep

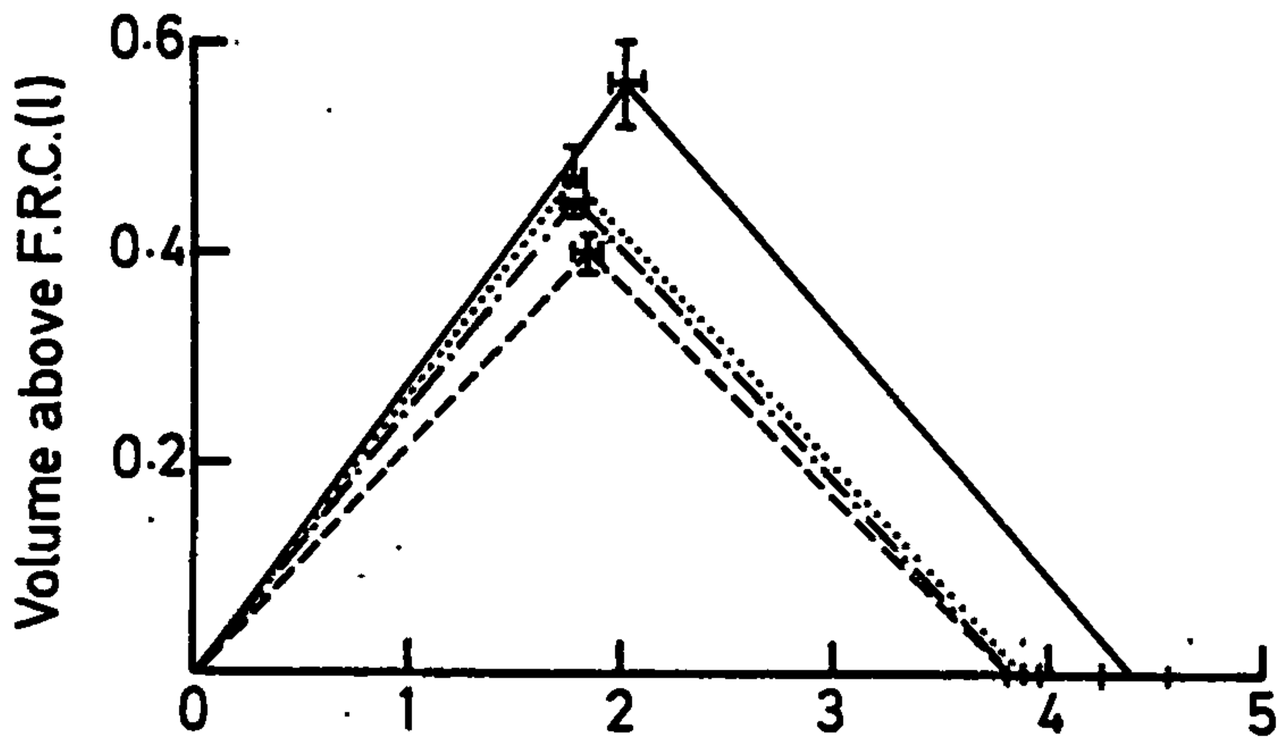



Fig 17 Average spirograms in wakefulness (solid line), Stage 2 (dotted), Stage 3/4 (dashed and dotted) and REM lseep (dashed line). Mean ± SE (in 19 subjects) tidal volumes and respiratory times are indicated.

The reduction in ventilation during non-REM sleep in our study was due to rapid shallow breathing. Smith in 1860 reported that breathing was more rapid during sleep, a finding confirmed by the present and some previous studies (Birchfield et al, 1959; Bulow, 1963; Duron et al, 1968). Other workers have found breathing frequency in non-REM sleep to be similar to (Read & Kleitman, 1926; Magnussen, 1944; Skatrud et al, 1981; Gothe et al, 1981 & 1982) or lower than (Gujer, 1928; Snyder, 1964) that in wakefulness. This discrepancy may partially result from the use of facial instrumentation as most studies performed without mouthpieces or a sealed mask showed no change in frequency from wakefulness to non-REM sleep (Reed & Kleitman, 1926; Skatrud et al, 1981; Gothe et al, 1981 & 1982) despite neither Iber et al (1982) nor ourselves finding any difference in breathing frequency in wakefulness due to breathing on a mask. The varying results of the effect of non-REM sleep on breathing frequency reflect the difficulty in obtaining a truly normal breathing pattern in an observed awake subject. Most (Magnussen, 1944; Birchfield et al, 1959; Bulow, 1963; Duron, 1968; Skatrud et al, 1981; Gothe et al, 1981) - but not all (Gujer, 1928; Gothe et al, 1982) - other studies also found that tidal volume decreased during non-REM sleep in adult man. Thus ventilation decreases in non-REM sleep in adults because the shallower breathing outweighs any slight increase in frequency which may occur.

Ventilation also decreases during non-REM sleep in children (de Bruin, 1936) and teenagers (Tabachnik et al, 1981a) but the pattern of change in frequency and tidal volume is different from that in adults. The reduced ventilation in non-REM sleep results from a decrease in frequency with no change in tidal volume.

This study showed that average minute ventilation was significantly lower in REM than non-REM sleep in adult man. It must be remembered, however, that ventilation is highly variable in REM sleep and the choice of a single mean value is a gross over-simplification. Such variablility means that caution is necessary when interpreting mean ventilations studied over a short duration. However, we recorded an average of 4.8 minutes of ventilation in REM sleep in each subject. Furthermore, the changes were consistent with 15 of the 19 subjects having their lowest ventilation in REM sleep (Table 12). It must also be remembered that the majority of the data was obtained between 3 and 5 minutes into REM periods and thus might not be representative of the entire REM period, although no consistent differences were found in ventilation later in REM periods. Aserinsky (1965) has also reported that the breathing pattern is similar throughout REM periods (1965).

Ventilation had not previously been measured in REM sleep in adults. However, Bulow (1963) noted that "ventilation in REM varies around the same mean" as in drowsiness when ventilation was reduced by 13% compared to wakefulness, but is higher than in stage 2 sleep. No data is shown in support of this statement, nor is the number of subjects who were studied stated. Support for our own observation comes from the recent publication of Skatrud (1981) who showed that ventilation was reduced in "phasic" REM sleep in 3 adult patients with chronic bronchitis and emphysema - a condition in which the breathing pattern in REM sleep is the same as in normal subjects (Chapter 5).

The observed hypoventilation in REM sleep was due to a significant further reduction in mean tidal volume compared to the level in stage 2 sleep. In fact tidal volume was extremely variable in REM with many breaths deeper than in non-REM sleep. We found no significant change in breathing frequency between REM and non-REM sleep. This contrasts with the results of Aserinsky and Kleitman (1953), who in their original description of REM sleep found that breathing frequency was increased ($p < 0.001$) from non-REM (13.4) to REM sleep (16.9 breaths/min) in 14 subjects. Similarly Snyder et al (1964) found in 12 subjects that the respiratory rate in REM sleep (16.1) was greater ($p < 0.001$) than in either stage 2 (15.0) or stage 3/4 sleep (15.7 breaths/min).

Other workers have also found slightly higher frequencies in REM compared to non-REM sleep (Aserinsky, 1965; Spreng et al, 1968; Goodenough et al, 1975). Thus there may be small changes in respiratory frequency during sleep which were undetected in the present study.

The observed changes in ventilation in REM sleep in adult man are at variance with those obtained in children and animals. In infants most studies (Bolton & Herman, 1974; Hathorn, 1974; Finer et al, 1976; Haddad et al, 1979) have shown that breathing is shallower in REM than non-REM sleep, as it is in adults, but in infants, unlike adults, this shallower breathing is more than offset by a marked increase in frequency and thus minute ventilation is higher in REM sleep. Other studies in infants have shown no change in tidal volume (Fagenholz et al, 1976; Purcell, 1976) or frequency (Purcell, 1976) between REM and non-REM sleep. Our results differ from these, probably because of maturity of ventilatory control, the respiratory pattern in infants being very different from adults with breathing frequencies around 45 per minute in non-REM and 60 per minute in REM sleep. Tabachnik and colleagues (1981a) found that in teenagers ventilation increased by 4% from non-REM to REM sleep although the significance of this change is not stated and the raw data is not given. The increased ventilation was due to an increase in breathing frequency, there being no change in tidal volume between REM and non-REM sleep. Again the

difference from our results probably reflects the maturity of ventilatory control but might perhaps also be influenced by Tabachnik's use of an inductance plethysmograph as this apparatus has not been quantitatively validated for the accurate measurement of ventilation during sleep (see Chapter 4).

There are conflicting results on the effect of sleep on ventilation in animals. In both dogs (Phillipson et al, 1976) and cats (Orem et al, 1977) breathing probably becomes slower and deeper in non-REM sleep and more rapid and shallow in REM sleep. However, Neubauer and colleagues (1981) found that breathing frequency was lower in REM sleep than wakefulness in cats, although the resulting changes in ventilation were similar in the studies of Orem et al (1977) and Neubauer and colleagues (1981) with minute ventilation lower in non-REM sleep than wakefulness and a further significant decrease in REM sleep when ventilation was 60-70% of the value in awake cats. These ventilatory changes are supported by Remmers and colleagues'(1976) observation of a progressive rise in end-tidal $PCO_2$ from wakefulness through non-REM to REM sleep in cats, although these differences were not confirmed by other groups (Wurtz & O'Flaherty, 1967; Guazzi & Freis, 1969). Wurtz and O'Flaherty (1967) found that alveolar $PCO_2$ changes "were difficult to evaluate because of the shortened expiratory plateau" during the rapid shallow breathing and this

probably explains why they failed to show an increase in $P_ACO_2$ in REM sleep in cats. Guazzi and Freis (1969) found no difference in $PaO_2$ or $PaCO_2$ tensions between non-REM and REM sleep, but only 5 cats were studied. Thus the pattern of overall ventilation in cats during sleep seems to be similar to that found in man, but the tidal volume increases in non-REM sleep in cats while decreasing in man.

In dogs, Phillipson and co-workers (1976) found overall ventilation to be 14% lower in non-REM sleep than in wakefulness, but despite claims (Phillipson, 1978 a&b) these changes were not significant. In REM sleep the increased frequency more than offset the shallower breathing resulting in a doubling of minute ventilation (Phillipson et al, 1976) but these observations were only made on 10 consecutive breaths in each sleep stage and with the variable breathing in REM will be highly dependent on which breaths were sampled. Further, the possibility that some of these effects are due to bypassing the upper airway with tracheostomy cannot be discounted. Certainly the larynx appears to be important in the control of respiratory timing (Gautier et al, 1973) and there are upper airway receptors senstitive to gas flow which also influence respiratory timing (Boushey et al, 1972; McBride & Whitelaw, 1981). However, Wurtz and O'Flaherty's finding (1967) of a lower $P_ACO_2$ during REM sleep in dogs, in whom they claimed to have obtained

good end-tidal plateaux and in whom tracheostomy had not been performed, suggests that upper airway factors do not explain these differences between dog and man. Thus dogs appear to differ from man in their ventilatory pattern during sleep, indicating the hazards of extrapolating results from animal species to man.

In the present study, the reduction in minute ventilation during sleep resulted in hypoxia and hypercapnia, as has previously been demonstrated on many occasions in normal adults (Magnussen, 1944; Ostergaard, 1944; Robin et al, 1958; Birchfield et al, 1958; Bristow et al, 1969; Coccagna et al, 1976). Although most of these earlier studies were performed either without EEG recordings (Magnussen, 1944; Ostergaard, 1944; Robin et al, 1958) or without differentiation between REM and non-REM sleep (Birchfield et al, 1958) it is likely that the measurements were made in non-REM sleep (see Chapter 3).

Despite ventilation in this study being lowest in REM, no significant difference was found between the end tidal levels in stage 3/4 and REM sleep. This is probably because many of the breaths during REM sleep were very small and thus alveolar plateaux were not obtained (Fig 15) and therefore the "end-tidal" values quoted did not always reflect alveolar gas. Furthermore, the extremely variable tidal volume resulted in marked variability in end-tidal concentrations. These two

problems combine to make the choice of a single end-tidal level for each REM study an error-riddled oversimplification, and this probably explains why neither we nor Townsend et al (1973) found any change in end-tidal levels in REM sleep. Using a Waters ear oximeter, Aserinsky (1965) found that REM sleep was associated with hypoxaemia in 11 normal subjects. Bristow et al (1969) measured arterial blood gas tensions during REM sleep in 4 out of a group of 19 subjects comprising 8 normal subjects and 11 patients with systemic hypertension, 2 of whom had respiratory disease (1 bronchiectasis, 1 chronic bronchitis). Unfortunately, it is not clear how many, if any, of the subjects in whom REM samples were obtained were normal subjects. However, with this proviso and the limitations that the number of samples was not given and no data were provided, these authors reported that there were no differences in arterial $PO_2$ and $PCO_2$ from slow wave to REM sleep but that in 3 of the 4 subjects pH was lower during REM sleep than at any other time. Coccagna et al (1976) measured arterial blood gas tensions in 8 normal subjects, but no comment is made on the number of measurements made, nor even whether all subjects had samples taken at each stage of sleep, nor on the stability of the subjects in each sleep stage when blood was withdrawn, and statistics were not applied. Without this information it is difficult to evaluate the mean data quoted, although superficially it

appears that blood gas tensions and pH were unchanged between non-REM and REM sleep.

An alternative method of assessing the physiological significance of the decrease in minute ventilation would have been to record alveolar ventilation. For methodological reasons this could not be done. However, alveolar ventilation was estimated using the measured frequency and tidal volume, allowing an average of 80 ml for mask dead space, and calculating physiological dead space (Harris et al, 1973) which is thought not to vary significantly between wakefulness and non-REM sleep (Bulow, 1963) although dead space has not been measured during REM sleep. Making these assumptions, alveolar ventilation was found to decrease significantly in all stages of sleep compared with wakefulness, the decrease being 19% in stage 2 and 24% in stage 3/4 with a further significant decrease in REM sleep when alveolar ventilation was 39% lower than in wakefulness (alveolar ventilation awake, 4.27±0.25, stage 2, 3.45±0.27, stage 3/4, 3.23±0.29, REM, 2.61±0.21 l/min). The mean decrements in alveolar ventilation found in non-REM sleep in the current study are similar to those previously reported in either documented (Bulow, 1963) or presumed (Magnussen, 1944; Robin et al, 1958) non-REM sleep, but this is the first estimate of alveolar ventilation in REM sleep in adult man. Magnussen (1944) found that alveolar ventilation decreased more than 15% during sleep in 25

out of 26 experiments in 10 subjects. Robin and colleagues (1958) found a 32% decrease in alveolar ventilation between wakefulness and sleep in 11 normal adults. Bulow (1963) measured alveolar ventilation and analysis of his data [Table 4 in (Bulow, 1963)] shows that in 11 subjects alveolar ventilation fell 12% ($0.1 > p > 0.05$) from wakefulness to stage 1 sleep, and that in 6 subjects alveolar ventilation decreased by 23% ($0.1 > p > 0.05$) from wakefulness to stage 2 sleep.

The present estimates of alveolar ventilation can be used to predict the oxygen tension which would be achieved if the mean level of ventilation observed in REM sleep was continued into steady state. The calculated decrease in $P_AO_2$ due to hypoventilation in REM at sea level would be 2.8 kPa (see Appendix 2). This is close to the difference in calculated $PaO_2$ in normal subjects reported in Part 1 of this thesis ($3.7 \pm 0.5$ kPa). It must remembered that the 2.8 kPa estimate assumes a steady level of ventilation in REM whereas wide fluctuations occur and thus the maximal anticipated $PaO_2$ decrease would be greater than 2.8 kPa. Thus this data is compatable with the hypothesis previously advanced (Chapter 5) that nocturnal hypoxaemia is due to hypoventilation alone.

The decrease in ventilation was accompanied by a significant reduction in mean inspiratory flow rate ($V_T/Ti$) in REM sleep. Remmers et al (1976) reported a

similar trend in cats although the differences mentioned do not appear to approach significance. In the absence of any evidence of increased bronchoconstriction between REM and non-REM sleep in normal adults (Tabachnik et al, 1981b), the decrease in mean $V_T$/Ti is likely to be due to decreased ventilatory drive rather than to mechanical factors.

The increased respiratory frequency during sleep was due to parallel significant decreases in inspiratory (Ti) and expiratory (Te) times during sleep, these changes being similar in all sleep stages. Thus the respiratory duty cycle ratio (Ti/Ttot) (Milic-Emili & Grunstein, 1976) was unchanged by sleep. Such parallel reductions in Ti and Te also occur during $CO_2$ rebreathing (Clark & von Euler, 1972) and may indicate changes in the inspiratory "off switch" sensitivity (von Euler & Trippenbach, 1976) occurring in the brain stem during sleep.

Despite suggestions (Block et al, 1979) that there may be differences between men and pre-menopausal women in breathing during sleep, we could find no difference in the mean level of ventilation or oxygenation between the sexes in any sleep stage. Block's studies are open to criticism. Firstly, his group of "normal" men included 4 subjects who weighed more than 90 kg and these 4 subjects contributed a large proportion of the "sleep disordered breathing". Although the exact numbers are not given, it

appears that these 4 males were responsible for 52-82% of the episodes of desaturation, 65-88% of the episodes of hypopnoea and 37-97% of the episodes of apnoea in the total study group of 30 men and 19 women. Thus it is not possible to determine whether the factor promoting "sleep disordered breathing" is truly the male sex or whether it is obesity, or even whether it is male obesity.

Similarly, in the study of pre-menopausal and post-menopausal women (Block et al, 1980), the post-menopausal women were heavier and shorter than the pre-menopausal women. Secondly, in these studies (Block et al, 1979 & 1980), hypopnoea was defined as decreased signals from mouth and nose thermisters occurring in conjunction with decreased chest wall movement and a 4% drop in saturation. There is no definition of the decrement in thermister and chest movement signals needed to qualify for hypopnoea. Further, temperature sensors cannot be used to quantitate flow (see Chapter 4) and thus this criterion greatly diminishes the sensitivity of the detection of hypopnoea. Also hypopnoea means decreased breathing and should not be defined in terms of a consequence, desaturation. The change in oxygen saturation produced by a given degree of hypoventilation is highly dependent on the starting saturation and on the shape of the oxyhaemoglobin dissociation curve in each individual. Block's pre-menopausal women started with a higher mean saturation in wakefulness (97%) than either

the control men (Block et al, 1979) (95%) or post-menopausal women (Block et al, 1980) (95%). Thus assuming similar standard dissociation curves (Severinghaus, 1966) in the 3 groups, the pre-menopausal women would need to drop their $PaO_2$ by 3.3 kPa to qualify for hypopnoea, whereas the men and post-menopausal women would only need to drop their $PaO_2$ by 1.9 kPa. Furthermore, the shape of the oxyhaemoglobin dissociation curve is probably influenced by both age (Tweeddale et al, 1976) and sex (Humpeler & Amor, 1973), although this latter observation has been challenged (Tweeddale et al, 1976). Thirdly, Block's data refers to the number of episodes of disordered breathing per night, and not per hour of sleep, despite the fact that the average sleep durations were 248 minutes for the pre-menopausal women and 302 minutes ($p < 0.05$) for the post-menopausal women and 310 minutes (no p value given) for the men. Thus although interesting and provocative, Block's data does not conclusively show that breathing or oxygenation changes are different in pre-menopausal women as compared to either men or post-menopausal women of the same body size.

Although we found no differences in the mean levels of ventilation or oxygenation between the men and women, breathing during non-REM sleep was markedly variable in 4 of the men during the first half of the night. It is possible therefore that similar episodes might account

for a sex difference in "sleep disordered breathing" although the mean levels of ventilation were the same in both sexes.

This was not an ideal study of ventilation during sleep. Firstly, a mask was used. While I could find no evidence that the mask altered respiratory timing, the addition of a 70-85 ml dead space would be expected to alter the level of ventilation. Secondly the studies were performed at 1,600 metres above sea level and this would also raise baseline ventilation (see Chapter 7). Thus the absolute levels of ventilation measured in this study are higher than would be obtained at sea level without facial instrumentation, although it seems possible that the relative changes between wakefulness and various stages of sleep might not be affected. Certainly the changes in ventilation between wakefulness and non-REM sleep observed using the mask are compatable with the changes in blood gas tensions recorded by other workers in studies performed at sea level without facial instrumentation (Doust & Schneider, 1952; Birchfield et al, 1958; Bristow et al, 1969; Coccagna et al, 1976). Thirdly, it is not possible to be sure that the data collected were representative of each sleep stage. The studies were primarily designed to assess ventilatory response to chemostimulation during sleep as it was recognised that the mask would alter the absolute level of ventilation. Thus, as it was necessary to record

baseline ventilation when breathing had not been disturbed by chemostimulation for at least 10 minutes, most baseline ventilation was obtained before ventilatory responses were performed. About half of the data were obtained between the third and fifth minute after a sleep stage change. Although the mean ventilation in this period was not different from that obtained later in each sleep stage, this analysis is based on small amounts of data. Fourthly, the repeated chemostimulation and unfamiliar instrumentation and surroundings resulted in disturbed sleep (Table 10). However, the aim was not to record breathing during a normal night's sleep, but rather to obtain comparative data from representative periods of each stage of sleep. With the above provisos it was felt that this was achieved and that the data, whilst not ideal, provide a useful insight into ventilation during sleep in adult man.

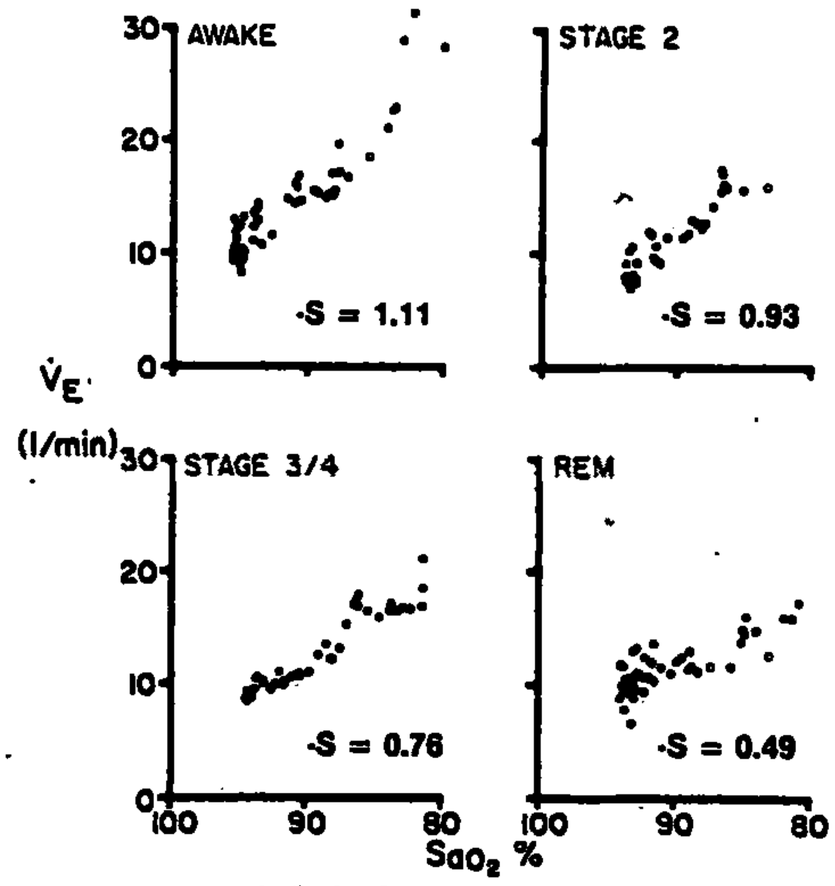



Fig 19a. Representative hypoxic ventilatory response data in Subject 6 indicating the slope of the regression line in each stage. $SaO_2$, haemoglobin saturation; $\dot{V}_E$, expired ventilation.

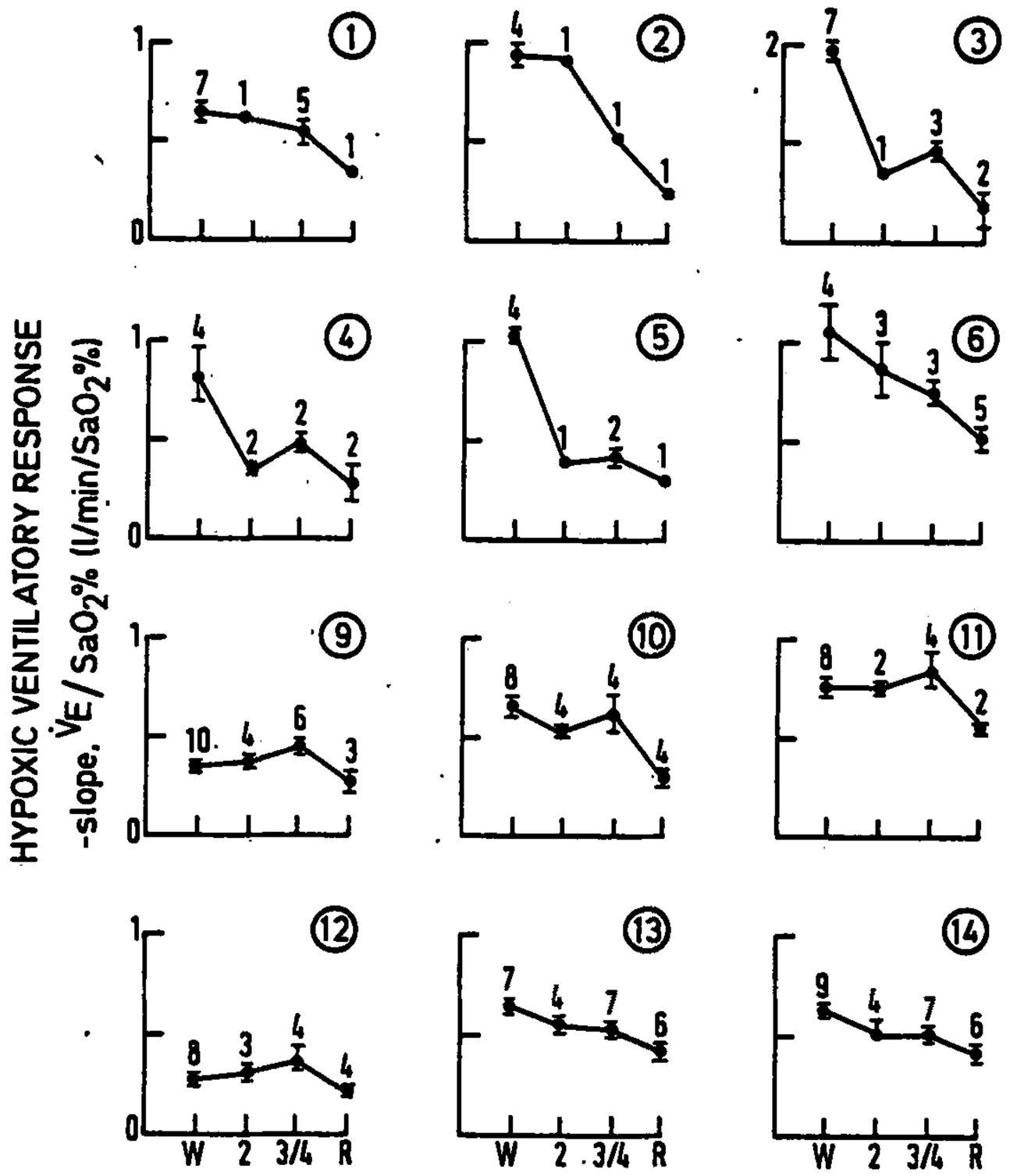



Fig 19b Hypoxic ventilatory response decreases in sleep, the lowest levels being in REM sleep in all 12 subjects. Mean ± SE and number of observations are indicated. Subject numbers are encircled (1-6 male, 9-14 female). $SaO_2$, haemoglobin saturation; $\dot{V}_E$, expired ventilation.

# CHAPTER 9

## HYPOXIC VENTILATORY RESPONSE

The hypoxic ventilatory response (HVR) measured by the slope of ventilation against decreasing oxygen saturation (Fig 19) was significantly reduced in all sleep stages ($p < 0.05$) compared to wakefulness when the data from all 12 subjects (6 men, 6 women) were analysed together (Fig 20). There was no difference between the HVR in stage 2 compared to stage 3/4 sleep, but in all 12 subjects HVR fell to the lowest value in REM sleep when HVR was thus significantly different ($p < 0.05$) from that in any other stage of sleep, and was only 42% of the value in wakefulness.

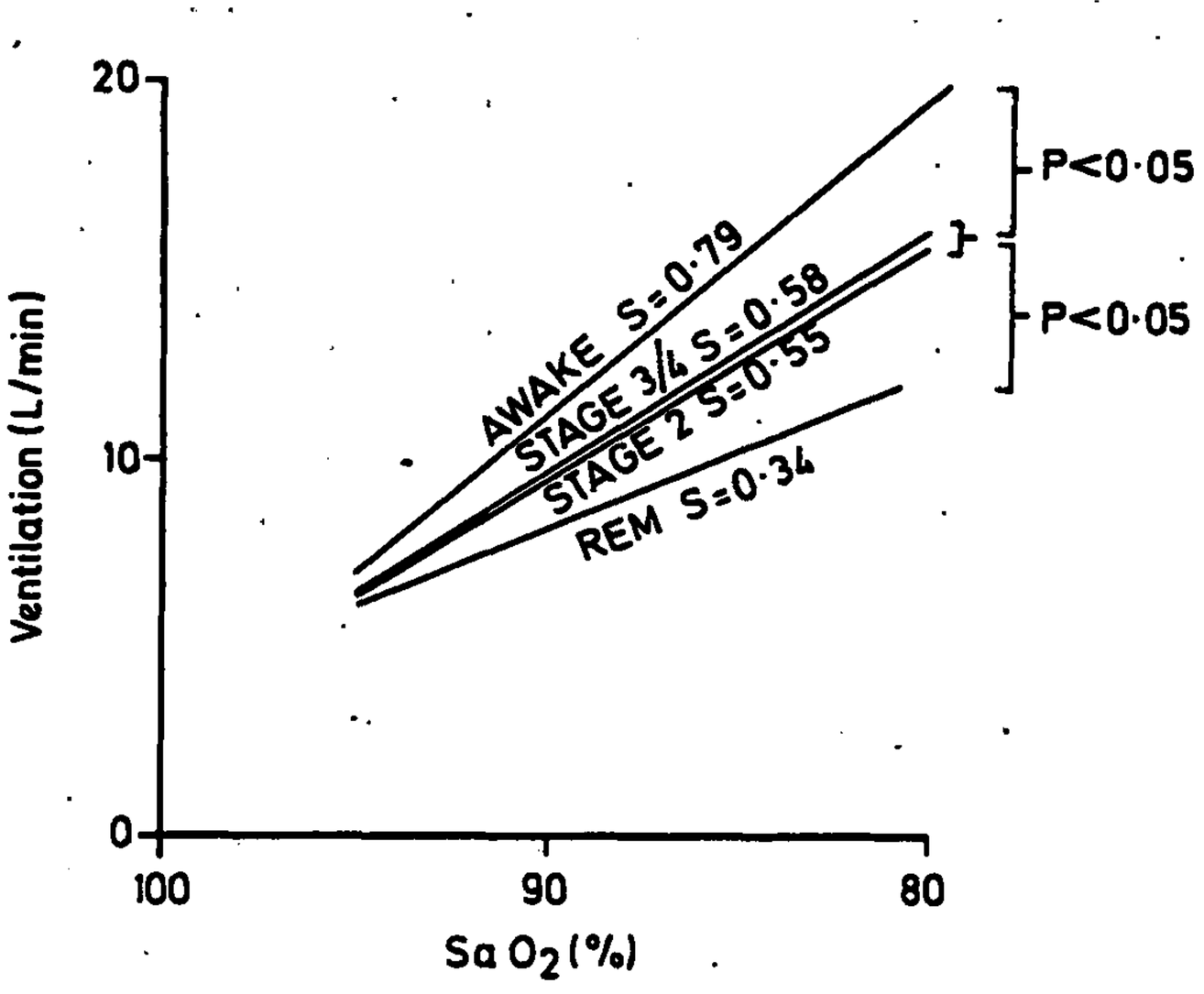



Fig 20 Mean relationships between expired ventilation and decreasing haemoglobin saturation ($SaO_2$%) in all 12 subjects. Mean slopes in each sleep stage and the significance of differences are indicated

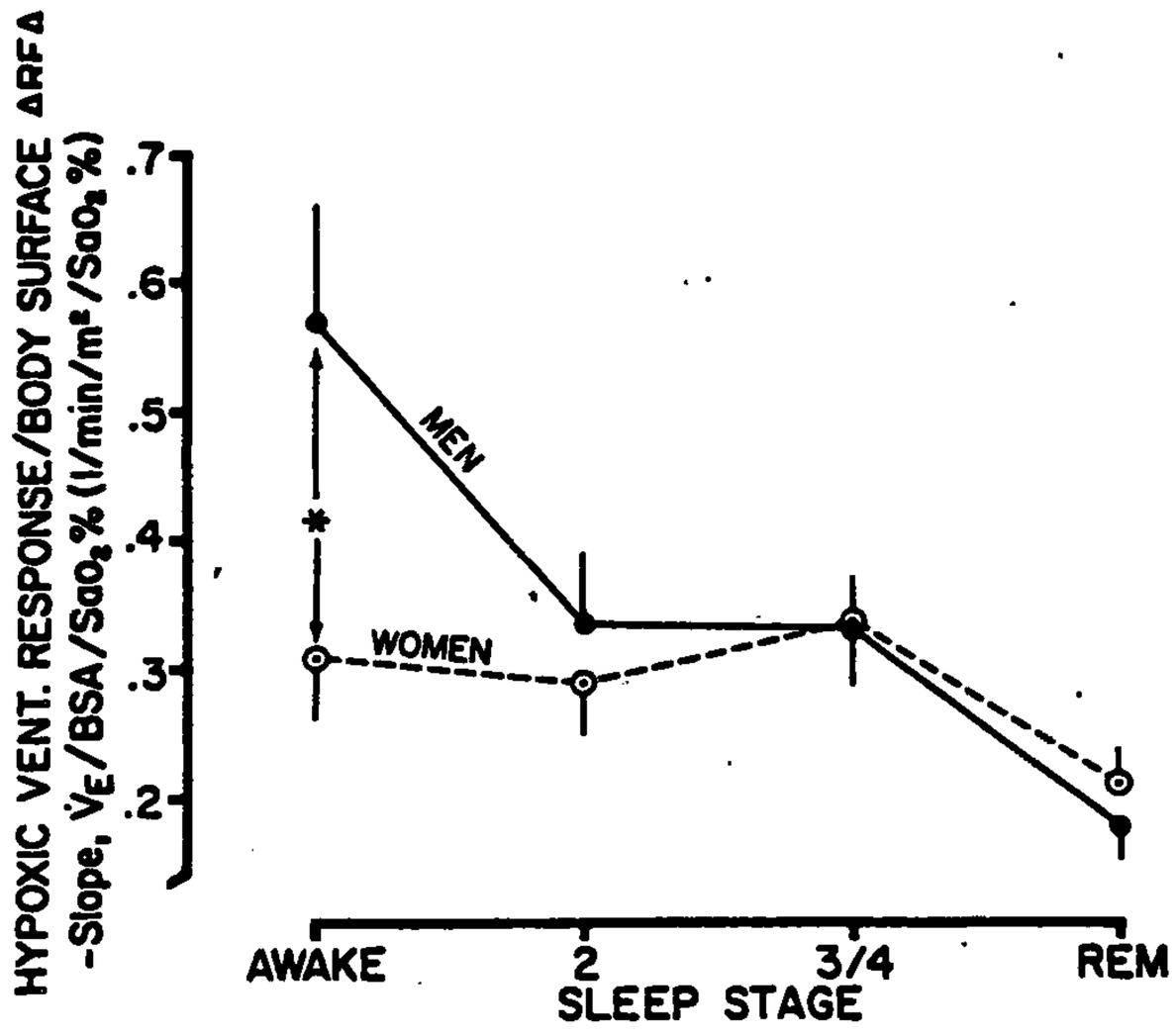



Fig 21 Mean (± SE) hypoxic ventilatory responses, corrected for body surface area, in the 6 men and 6 women during wakefulness and different sleep stages.
* indicates significantly higher responses in men than women during wakefulness.

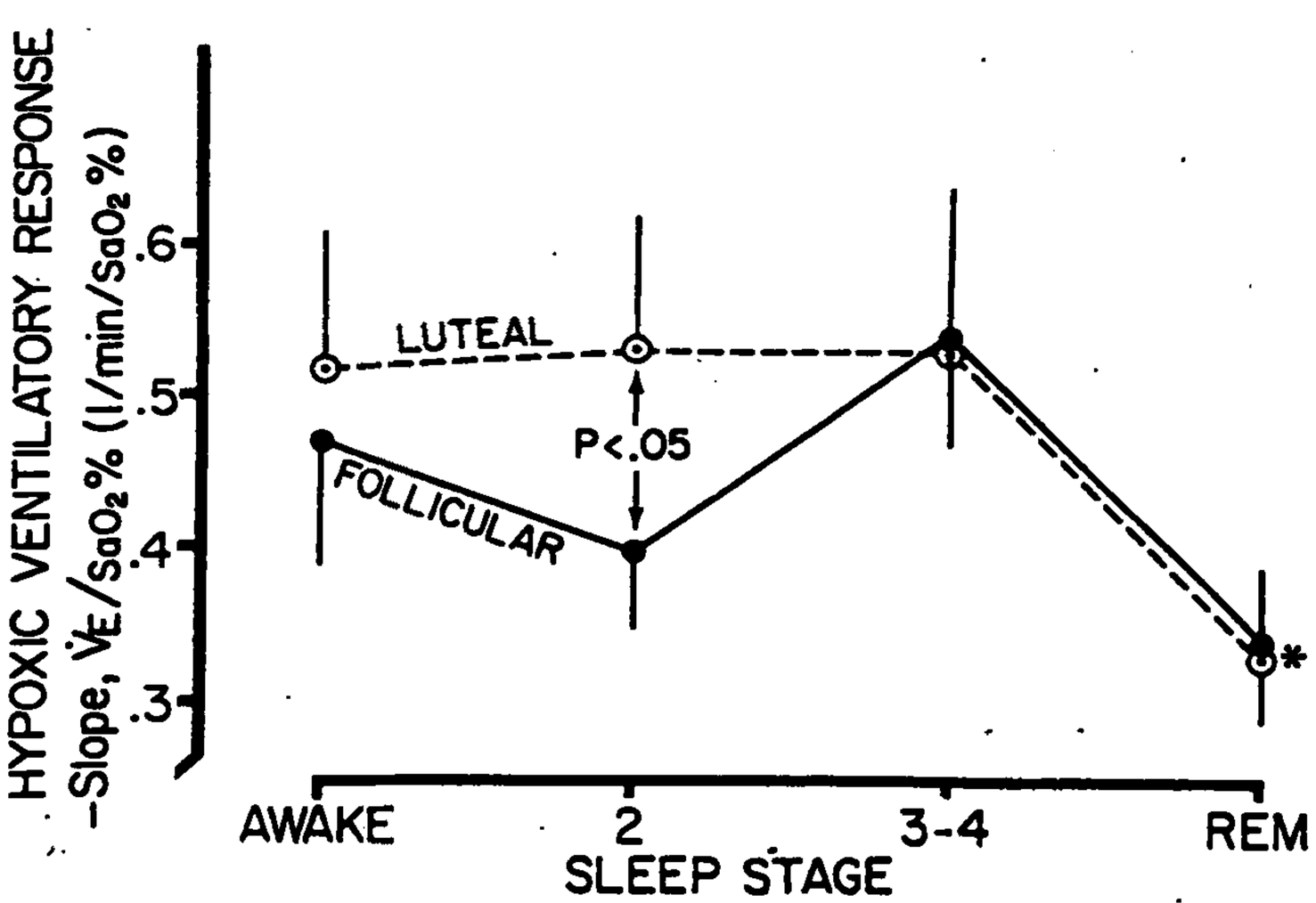



Fig 22 Mean (± SE) hypoxic ventilatory responses in follicular and luteal phases in the 6 women, showing significantly lower responses in Stage 2 in the follicular than luteal phase.
* indicates lower ($p < 0.05$) ventilatory responses in REM than any other sleep stage in both phases of the menstrual cycle.

When the data for the men and women were analysed separately, two differences emerged (Fig 21). Firstly, the men had significantly higher hypoxic ventilatory responses during wakefulness than the women, even when the results were corrected for body size. Secondly, whilst men decreased their HVR in non-REM sleep compared to wakefulness, the women had similar hypoxic responses during wakefulness and non-REM sleep.

Only 4 of the 6 female subjects had the predicted progesterone rise during the luteal phase, the other 2 having no change in progesterone level. In wakefulness, HVR tended to be lower in the "follicular" than "luteal" phase of the menstrual cycle, but the difference was only significant during stage 2 sleep (Fig 22).

The hypoxic heart rate response, measured by the slope of heart rate against decreasing oxygen saturation, behaved in a similar fashion to the hypoxic ventilatory response in all stages of sleep (Table 13). There was no significant difference between any of the stages in the relationship between heart rate and ventilation (Table 13).

## DISCUSSION

The results indicate that the hypoxic ventilatory response (HVR) decreases during sleep in adult humans. Men decrease their hypoxic drive in non-REM sleep when women maintain their HVR at waking levels. In both sexes

TABLE 13

CARDIORESPIRATORY RESPONSES TO HYPOXIA DURING WAKEFULNESS AND SLEEP

| | Awake | Stage 2 | Stage 3/4 | REM sleep |
|---|---|---|---|---|
| Hypoxic ventilatory response, -s, l/min/%sat | 1.07 ± 0.19* | 0.64 ± 0.10†‡ | 0.62 ± 0.09†‡ | 0.33 ± 0.04† |
| Hypoxic heart rate response, -s, b/min/%sat | 1.25 ± 0.19 | 0.77 ± 0.16†‡ | 0.72 ± 0.09†‡ | 0.27 ± 0.20† |
| Heart rate/ventilation, s, b/l | 1.12 ± 0.15 | 1.16 ± 0.28 | 1.18 ± 0.21 | 1.28 ± 0.26 |

Footnote:

s, slope; b, beats, %sat, haemoglobin saturation
*, values are mean ± SE for 6 men
†, $p < 0.05$ versus awake
‡, $p < 0.05$ for other sleep stages versus REM sleep

the hypoxic ventilatory response is lowest in REM sleep.

The only previous study of hypoxic ventilatory response during natural sleep in man is that of Reed and Kellogg (1960a) who found no change in HVR in sleep compared to wakefulness, either at sea level or at altitude. They may have failed to detect any decrease in HVR because end-tidal oxygen tension was not reduced below 60 mmHg - a level barely capable of producing a clear increase in ventilation in normal subjects (Weil et al, 1970). Furthermore, Reed and Kellogg did not maintain isocapnia, which is now known (Weil et al, 1970) to be crucial in order to detect an increase in ventilation in mild hypoxia. In addition, they had no method of detecting leaks around the face mask, nor did they confirm sleep by EEG criteria. Further, the subjects were studied during afternoon or evening naps, not during nocturnal sleep, and it is not known whether this might modify the response. Thus Reed and Kellogg's pioneering studies have many flaws which may account for their failure to detect any alteration in hypoxic ventilatory response during sleep.

The only other previous studies relating to hypoxic ventilatory response in man during sleep were based on the comparison of hypercapnic ventilatory responses in hypoxia and hyperoxia (Bulow, 1963; Honda & Natsui, 1967). In 3 subjects Bulow (1963) found no consistent effect due to "hypoxia" either in wakefulness or sleep,

probably because insufficient hypoxia was used (inspired oxygen tension 100 mmHg). Honda and Natsui (1967) induced sleep using trichlorethylene phosphate, and in the one subject thus studied found that the ratio of hypercapnic ventilatory response in hypoxia ($P_{ET}O_2$ 38 mmHg) to that in hyperoxia ($P_{ET}O_2$ 300 mmHg) was 5.7 in wakefulness and 1.7 during EEG confirmed sleep. This suggests that either sleep or the hypnotic depressed the ventilatory response to hypoxia, and is certainly consistent with the current findings.

Since the first part of the current study was published (Douglas et al, 1982), Berthon-Jones and Sullivan (1982) have confirmed that the hypoxic ventilatory response falls during sleep. Studying 9 subjects (4 women, 5 men) they found a 38% decrease in isocapnic hypoxic response in non-REM compared to wakefulness ($p < 0.005$) and 51% decrease to REM sleep. Although these changes were similar to the mean results for all 12 subjects in the current study (%decrease from wakefulness non-REM 28%, REM sleep 57%) they found no significant difference between hypoxic drives in non-REM and REM sleep. There is no clear reason for this discrepancy between the two studies but perhaps it may be because Berthon-Jones performed fewer studies (26 non-REM and 15 REM versus 78 non-REM and 35 REM in the current study), studied fewer subjects (9 - and only 8 in REM - versus 12) and used conventional EEG scoring criteria

rather than the strict rules which we employed. Berthon-Jones and Sullivan failed to find any sex difference in the hypoxic ventilatory response during sleep, perhaps because fewer studies were performed or because their female subjects were all taking the contraceptive pill, whereas none of ours were. These differences should not be allowed to obscure the wide agreement between the two studies which both showed that the hypoxic ventilatory response decreases during sleep in man, the lowest values tending to be obtained in REM sleep.

Even more recently, Gothe et al (1982) reported no difference between the hypoxic drive in wakefulness and non-REM sleep. This study was performed following sleep deprivation and without isocapnia. Both these factors would decrease the awake hypoxic ventilatory drive, thus making the detection of a subsequent decrease difficult. Also ventilation was measured from chest and abdominal movement to minimise the effect of facial stimulation, yet a "loose-fitting" non-rebreathing mask was used and thus it is likely that this study combines the problems of surface measurement of ventilation and of facial instrumentation. Six of the 17 subjects were female which would further minimise the changes in hypoxic ventilatory response from wakefulness to non-REM sleep. Thus there are methodological reasons for Gothe and colleagues failing to find any change in hypoxic

ventilatory response between wakefulness and non-REM sleep.

In 11-week old human infants, inhalation of 100% oxygen depressed ventilation by 30% in non-REM sleep but had no effect in REM sleep (Fagenholz et al, 1976). This suggests that the hypoxic ventilatory response in infants is also suppressed in REM, but since such oxygen tests are highly dependent on initial level of oxygenation and also may result in alterations in cerebral blood flow and thus brain $CO_2$ tension, this conclusion requires confirmation. In new-born animals, Read's group have found the isocapnic hypoxic ventilatory response to be lower in REM than slow wave sleep in lambs (Henderson-Smart & Read, 1979a) and calves (Jeffrey & Read, 1980) but similar in REM and slow wave sleep in puppies (Henderson-Smart & Read, 1979a). In a recent study performed without isocapnia, Haddad and co-workers (1982) reported that in 14-day old puppies the hypoxic ventilatory response in slow wave sleep was 17% lower ($p < 0.05$) than wakefulness, whereas the HVR in REM was similar to that in wakefulness. With increasing post-natal age, HVR increased in both sleep stages so that by 29 days HVR in both slow wave and REM sleep was 9% higher than in wakefulness ($p < 0.05$). There may be genuine species and age differences in hypoxic sensitivity in neonates, and some of the reported discrepancies may relate to differences in rib cage

rigidity and movement. In infants (Henderson-Smart & Read, 1976; Knill et al, 1976), and lambs (Henderson-Smart & Read, 1979a), in REM sleep, paradoxical rib cage movement occurs and HVR decreases, whereas in puppies (Henderson-Smart & Read, 1979a) there is no paradoxical movement and HVR is similar in REM and non-REM sleep. In adult man marked rib cage paradox does not occur during REM sleep (Tusiewicz et al, 1977; Mortola and Anch, 1978; Tabachnik et al, 1981a) and for this reason and because of maturation of respiratory control, results in neonates should not be extrapolated to adult man.

In mature animals species differences in the effect of sleep on HVR seem also to occur. Phillipson and colleagues (1978) found that in 4 dogs HVR was unchanged from wakefulness to either slow wave or REM sleep. However, in a subsequent investigation by the same group (Bowes et al, 1981) in all 3 dogs studied, the HVR fell from wakefulness to both slow wave and REM sleep, the mean decrease being 24% in both stages. In cats, Neubauer et al (1981) also found no difference between the levels of HVR in slow wave and REM sleep, but no measurements were made during wakefulness. However, in Neubauer's study the cats were sleep deprived (see Appendix 1) and isocapnia was not sought. In rats (Pappenheimer, 1977), also studied without isocapnia, the hypoxic ventilatory drive was greater during slow wave

sleep than in wakefulness, but in this study sleep was probably interrupted by multiple arousals perhaps accounting for the increased ventilatory response.

Thus the original finding in the current study of depressed hypoxic drive during natural sleep in adult man is similar to observations in lambs and calves but contrary reports in puppies, dogs, cats and rats. These discrepancies can probably be accounted for by species differences.

The difference in HVR between men and women was due to differing levels of awake hypoxic ventilatory response whereas there was no statistical difference between the levels of hypoxic ventilatory response, corrected for body surface area, during any stage of sleep (Fig 21). Although there are no previous reports of women having lower awake HVRs than men, there is some evidence in support of this. Hypoxic response, expressed as the parameter A (Weil et al, 1970) averaged 188 in 40 men studied by Hirshman and colleagues (1975) whereas Schoene and co-workers (1981) reported an average A value of 119 in 18 women. Schoene's women included several athletes, but even if they are excluded - on the grounds that athletes may have lower ventilatory responses (Byrne-Quinn et al, 1971) - the resulting average in women is still lower than that for men. The above observations prompted us to perform a direct comparative study of ventilatory response in men and women using

different and larger numbers of subjects, and this study confirmed that hypoxic drive during wakefulness was higher in men than in women (White et al, in press). The reason that men have higher hypoxic ventilatory responses than women while awake is unclear and indeed one might predict that the opposite might occur due to the respiratory stimulant effect (Zwillich et al, 1978) of the higher progesterone level in women.

It is also unclear why men should decrease their hypoxic response in non-REM sleep whereas women do not. I can identify no methodological reason for this discrepancy. Although the studies were performed sequentially, the same protocol and equipment were used in both studies. The men were - if anything - more used to being subjects for respiratory experiments, 3 of the 6 being respiratory physicians, and thus the higher response in the awake men is unlikely to reflect increased anxiety. In both the men and women the post-sleep HVRs were similar ($p > 0.5$) to the pre-sleep values, again arguing against anxiety as a factor elevating the values in wakefulness in either group. The women were significantly younger than the men ($24.8 \pm 1.2$ versus $33.6 \pm 1.6$ years) and while there is no evidence of any change in ventilation during sleep over this age span in either men or women (Webb, 1974; Block et al, 1979) this is a possible, but unlikely, explanation. There is, of course, a 1 in 20 chance that the "difference" between

the sexes in the change in hypoxic drive from wakefulness to non-REM sleep was a chance finding and certainly the changes in one of the men (subject 1) were similar to that in the women. Nevertheless, I think a genuine sex difference exists in the effect of sleep on the hypoxic ventilatory response.

There is some evidence that women have lower basal metabolic rates when awake than men (Boothby et al, 1936) which may contribute (Doekel et al, 1976; Zwillich et al, 1977) to the difference in hypoxic ventilatory response during wakefulness. Preliminary results (White DP, unpublished observation) suggest that the decrease in metabolic rate during non-REM sleep is about 10% greater in men than women and this may help explain the difference in HVR response during non-REM sleep. If these tentative results are confirmed, it only moves the question one stage further back to why there should be a difference in the metabolic response to sleep between the sexes. Thus, as yet, there is no explanation of why sleep produces a greater change in hypoxic ventilatory response in men than in women.

Although one previous study (Schoene et al, 1981) and our own subsequent study (White et al, in press) both showed awake women to have higher ventilatory responses during the luteal than follicular phase of the menstrual cycle, this was not observed in the current study. This was probably due to a combination of the small number of

subjects studied and to the fact that 2 of the 6 women had no progesterone surge in the "luteal" phase. These 2 were considered to have had anovulatory cycles which are not uncommon in normal women (Novak et al, 1975).

This study showed for the first time that the hypoxic ventilatory response is reduced during natural sleep in adult man.

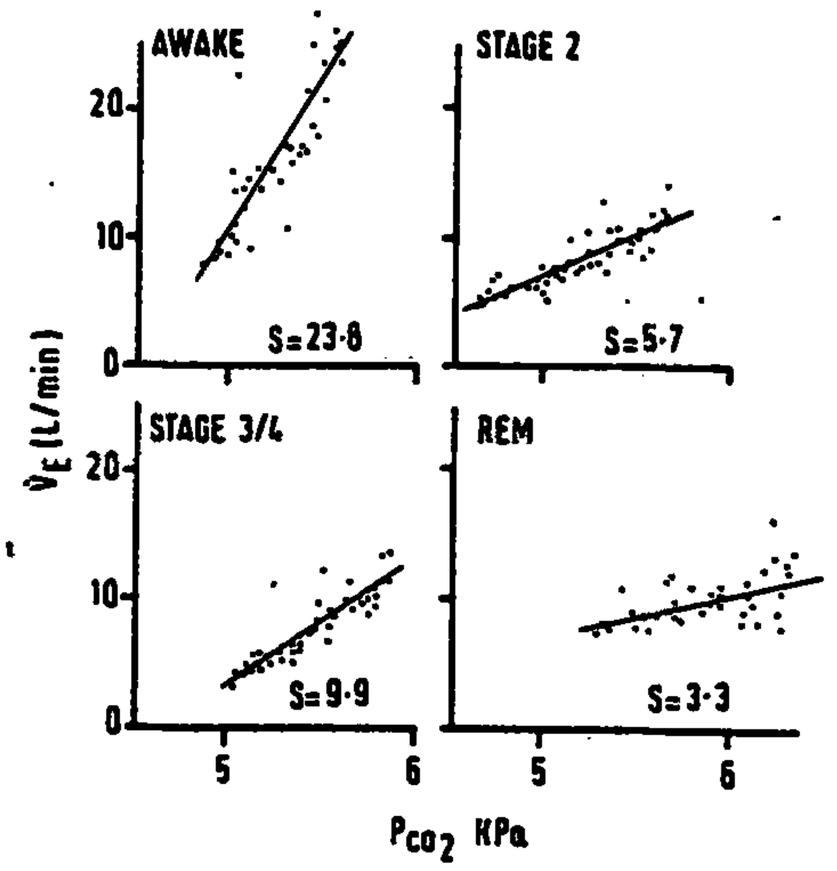



Fig 23 Examples of hypercapnic ventilatory response data in Subject 18, indicating data points, regression lines and slopes in each stage.

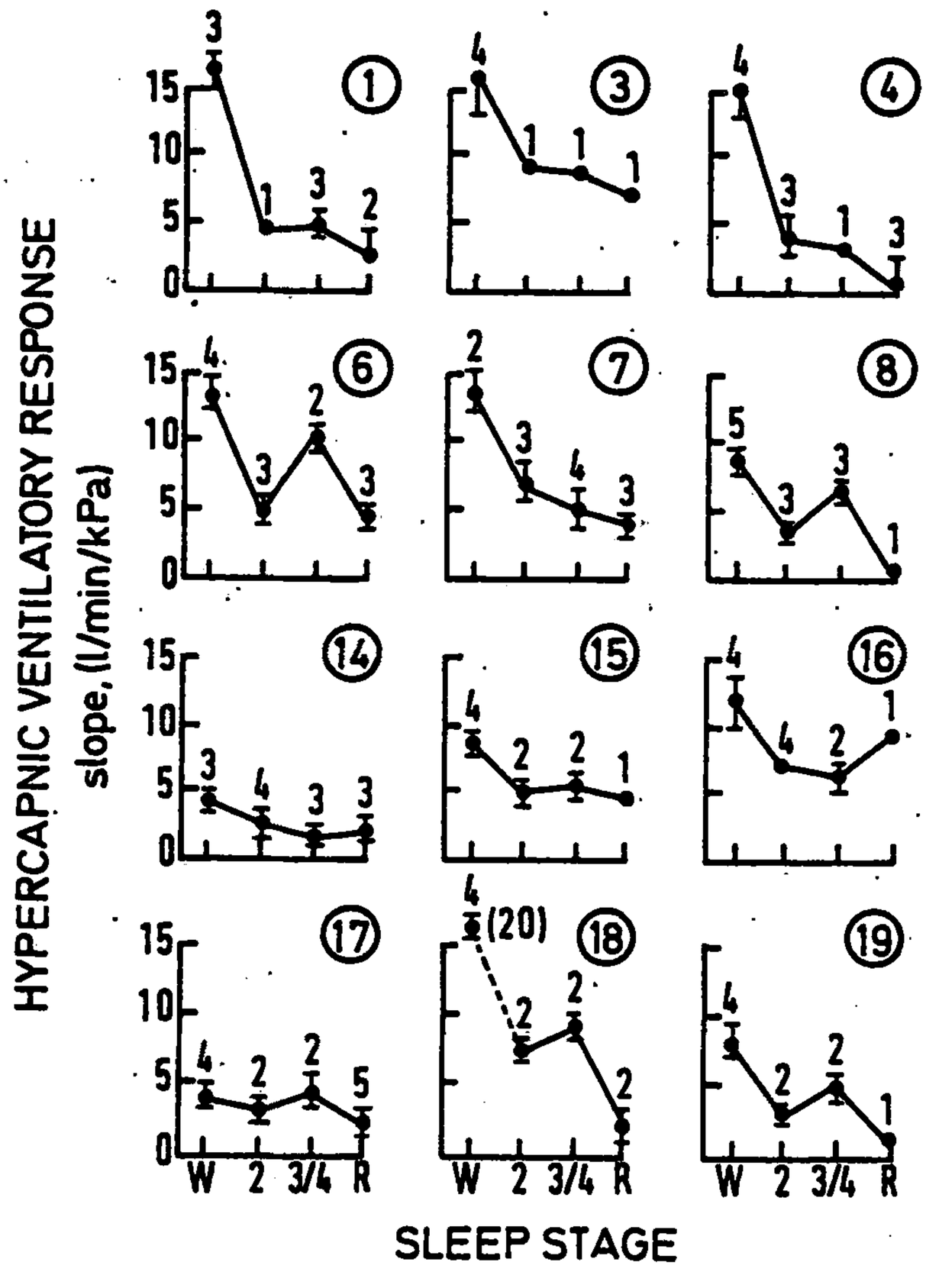



Fig 24 Hypercapnic ventilatory response decreases in sleep, the lowest level being in REM sleep in 10 of 12 subjects. Mean ± SE and number of observations are indicated. Subject numbers are encircled.

# CHAPTER 10

# HYPERCAPNIC VENTILATORY RESPONSE

## RESULTS

In all 12 subjects at least 1 (mean 2.3) satisfactory hypercapnic response (HCVR) was obtained in each stage of sleep and a representative example of the breath by breath relationship between ventilation and $P_{ET}CO_2$ in each sleep stage in 1 subject is shown (Fig 23), as are the mean results for each subject (Fig 24). Overall, the mean HCVR fell significantly ($p < 0.05$) from wakefulness to every stage of sleep (Fig 25), with no significant difference between HCVR in stage 2 and stage 3/4 sleep. There was a further significant reduction ($p < 0.05$) from the HCVR in these non-REM stages to REM sleep in which the HCVR was only 28% of the value in wakefulness (awake, 1.60$\pm$0.19; stage 2, 0.69$\pm$0.08; stage 3/4, 0.81$\pm$0.10; REM, 0.45$\pm$0.10 l/min/mmHg/$CO_2$).

There was no significant difference between wakefulness and the non-REM sleep stages in the position of the HCVR slopes as indicated by their intersection with the $PCO_2$ axis. The position of the REM HCVR slope could not be usefully defined in this way as some responses in REM sleep had negative slopes.

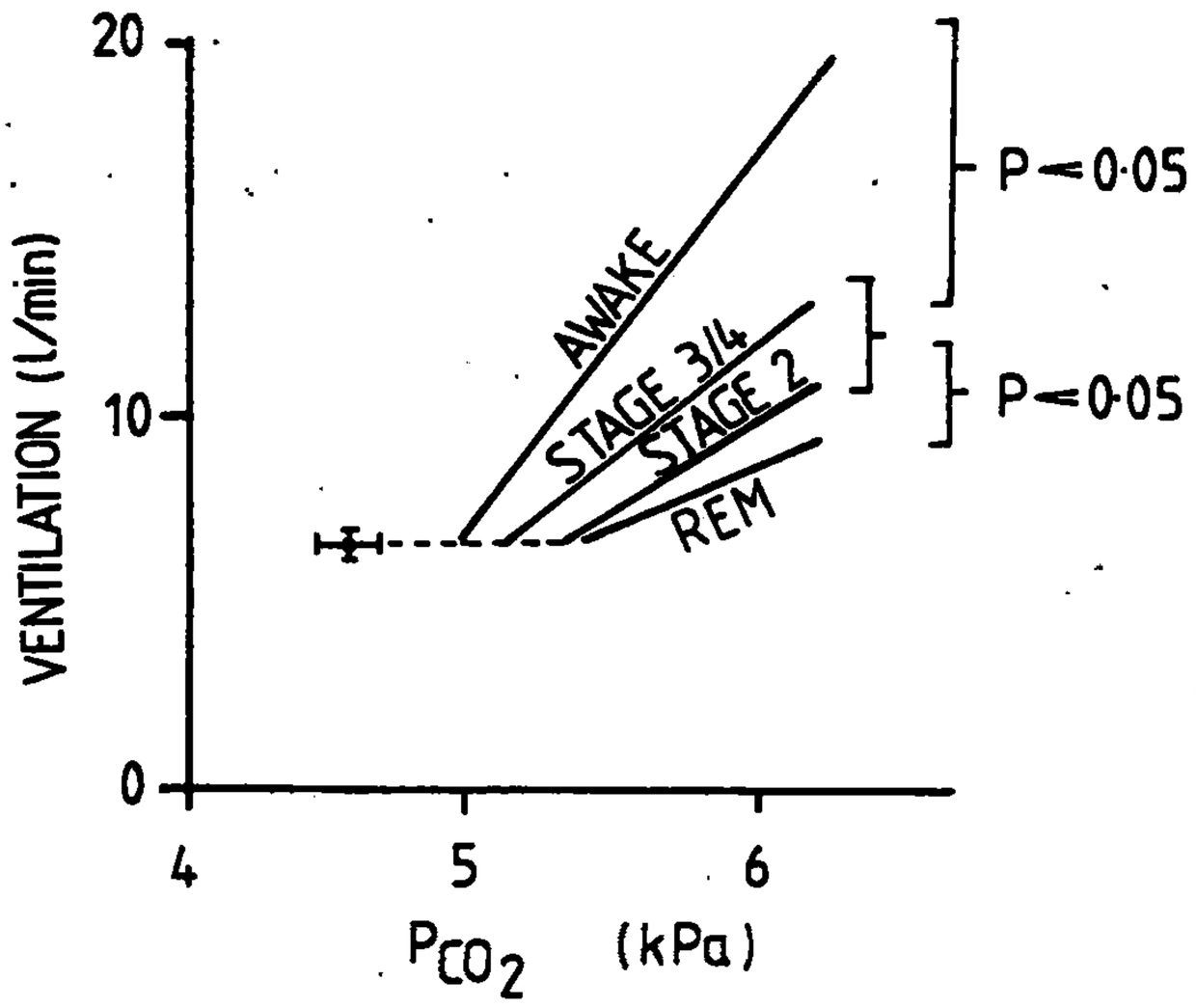



Fig 25 Mean relationships between expired ventilation and end-tidal carbon dioxide tension ($PCO_2$) in each sleep stage in 12 subjects indicating significant differences. The mean (± SE) baseline ventilation and $PCO_2$ point during wakefulness is shown.

There was no significant difference in HCVR between men and women in either wakefulness or any stage of sleep either when analysed using the absolute ventilatory response to $CO_2$ corrected for body surface area (Fig 26) or the % change in HVR from the value in wakefulness. There was no correlation between the changes in $P_{ET}CO_2$ from wakefulness to any sleep stage and either the waking HCVR or the HCVR in that sleep stage, or the absolute or relative change in HVR from wakefulness to that sleep stage.

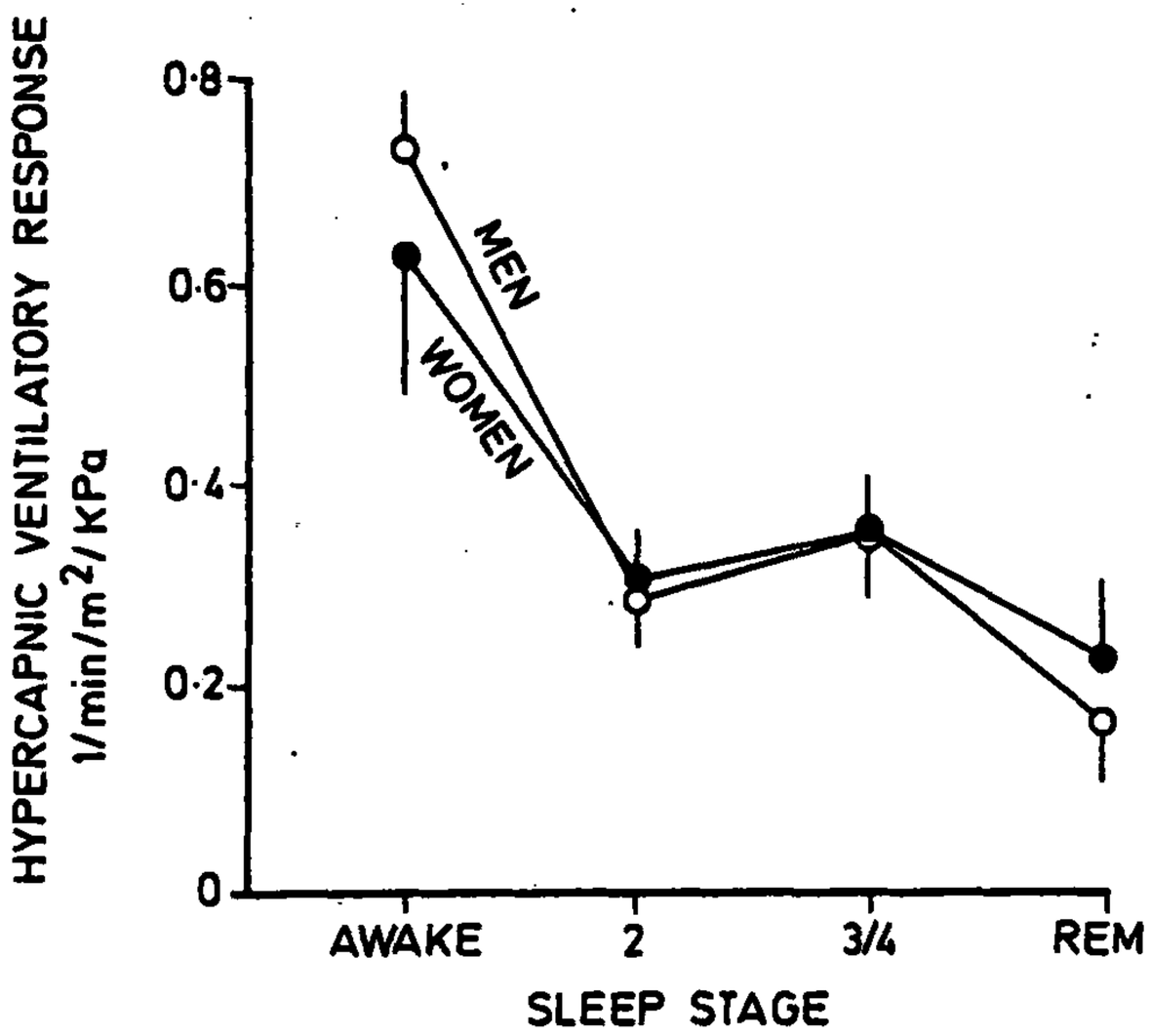



Fig 26 Mean (±SE) hypercapnic ventilatory responses, corrected for body surface area, in the 6 men and 6 women during wakefulness and in each sleep stage.

## DISCUSSION

This study shows that the hypercapnic ventilatory response falls from wakefulness to non-REM sleep in adults with a further reduction in REM sleep when the HCVR is only 28% of the value during wakefulness.

Thus this investigation confirms earlier studies performed either with (Birchfield et al, 1959; Bulow, 1963) or without (Magnussen, 1944; Ostergaard, 1944; Robin et al, 1958) EEG recording that the ventilatory response to $CO_2$ falls during sleep. The results are at variance with the conclusions of Reed and Kellogg (1958 & 1960b) and Bellville et al (1959) who both reported that the ventilatory response line was shifted to higher $CO_2$ levels without any change in slope. As previously mentioned, analysis of Reed and Kellogg's graphs shows that the slope was in fact reduced in 6 of the 7 subjects. In addition, as the EEG was not recorded, it is possible that some of the subjects aroused during the "sleep" studies thus steepening the slopes obtained. Unfortunately, Bellville and colleagues (1959) did not present any data to support their conclusion that the slope of the HCVR was not changed by sleep.

The decrement in HCVR from wakefulness to stage 2 sleep in this study (57%) is greater than that found by either Bulow (1963) (42%) or more recently by Gothe and colleagues (1981) (21%), but the reason for this difference is not clear. The further $CO_2$ rise in the present studies might contribute to this difference, as more rapid $CO_2$ elevation decreases the $CO_2$ response in wakefulness (Read & Leigh, 1967), but the rate of $CO_2$ rise in the present study was similar in wakefulness and all stages of sleep and there is no obvious reason why

this effect should be more marked during sleep than in wakefulness. Certainly the cerebral blood flow response to $CO_2$ is similar in wakefulness and non-REM sleep - at least in goats (Santiago et al, 1980).

Gothe's study (1981) was performed after overnight sleep deprivation which has been shown (Appendix 1) to reduce significantly the hypercapnic ventilatory response in awake subjects, the mean decrease being 32%. This probably explains the small change in hypercapnic response that Gothe observed with sleep. In addition Gothe (1981) used a steady state technique to measure $CO_2$ response which introduces 3 possible sources of further discrepancy. Firstly, although no mention is made of breathing rhythmicity during the studies, breathing irregularity is common in stage 2 sleep (Bulow, 1963) and the steady state technique is of dubious validity during irregular breathing as a steady state is not achieved. Secondly, for reasons that are not fully understood, differences in hypercapnic drive sometimes produce greater changes in the slope of the hypercapnic ventilatory response with the rebreathing technique than with the steady state technique (Linton et al, 1973; Cameron, 1979). Thirdly, Gothe and colleagues admit that they allowed insufficient time (4 mins) for a steady state to develop and this might be a source of error, probably resulting in underestimation of ventilatory responses. As Gothe admits, the use of a non-invasive

technque to measure ventilation during sleep might also lead to errors.

The decrease in the hypercapnic ventilatory response from wakefulness to non-REM sleep in the present study (57%) is similar to that in Bulow's study (42%), this difference being probably within the normal variability of the measurements especially allowing for the flaws in Bulow's investigation (see Chapter 6).

Bulow (1963) indicated that he found lower ventilatory responses in stage 3/4 than in stage 2 sleep whereas there was no such difference in the current study. Bulow, however, did not apply statistics and there appears to be considerable overlap between the different sleep stages. (See Bulow, 1963 Fig 21,26,27). Indeed, there is little separation apparent until $P_{ET}CO_2$ rises above 47 mmHg and Bulow admits that the number of points obtained at high $PCO_2$ levels was small because of arousal. In addition, Bulow's comparison is between all the data points obtained in each sleep stage at each level of $CO_2$ and not between the mean results for each subject in each sleep stage. As it appears unlikely that every subject was studied in each stage of sleep and virtually impossible that a similar number of data points were attained at each $CO_2$ level in each stage of sleep, Bulow's comparisons of hypercapnic ventilatory response between sleep stages are almost certainly invalid.

As previously mentioned, the hypercapnic ventilatory response had not before been measured in REM sleep in adult man, although in one of Bulow's subjects the majority of a $CO_2$ response was carried out in REM sleep. Bulow's impression was that the hypercapnic ventilatory response was similar in REM sleep and drowsiness - i.e. 13% below the level in wakefulness. The marked variability of ventilation in REM plus the occurrence of sleep stage changes, perhaps including arousals, are likely to account for his failure to detect the further decrease in hypercapnic ventilatory response from non-REM to REM sleep. The finding in the current study of a reduction in the hypercapnic ventilatory response from non-REM to REM sleep agrees with previous observations in dogs (Phillipson et al, 1977; Sullivan et al, 1979a). Studies in neonates - both human (Haddad et al, 1980; Rigatto et al, 1980; Kalapesi et al, 1981) and monkey (Guthrie et al, 1980; Guthrie et al, 1981) - have shown no initial differences between hypercapnic ventilatory response in REM and non-REM sleep, but with increasing post-natal age, the hypercapnic ventilatory response becomes lower in REM than non-REM sleep in monkeys (Guthrie et al, 1981). As no hypercapnic ventilatory responses were obtained in pure "tonic" REM sleep (see Chapter 7) it was not possible to determine whether Sullivan and colleagues' observation (1979a) that HCVR is lower in "phasic" than "tonic" REM in dogs is applicable

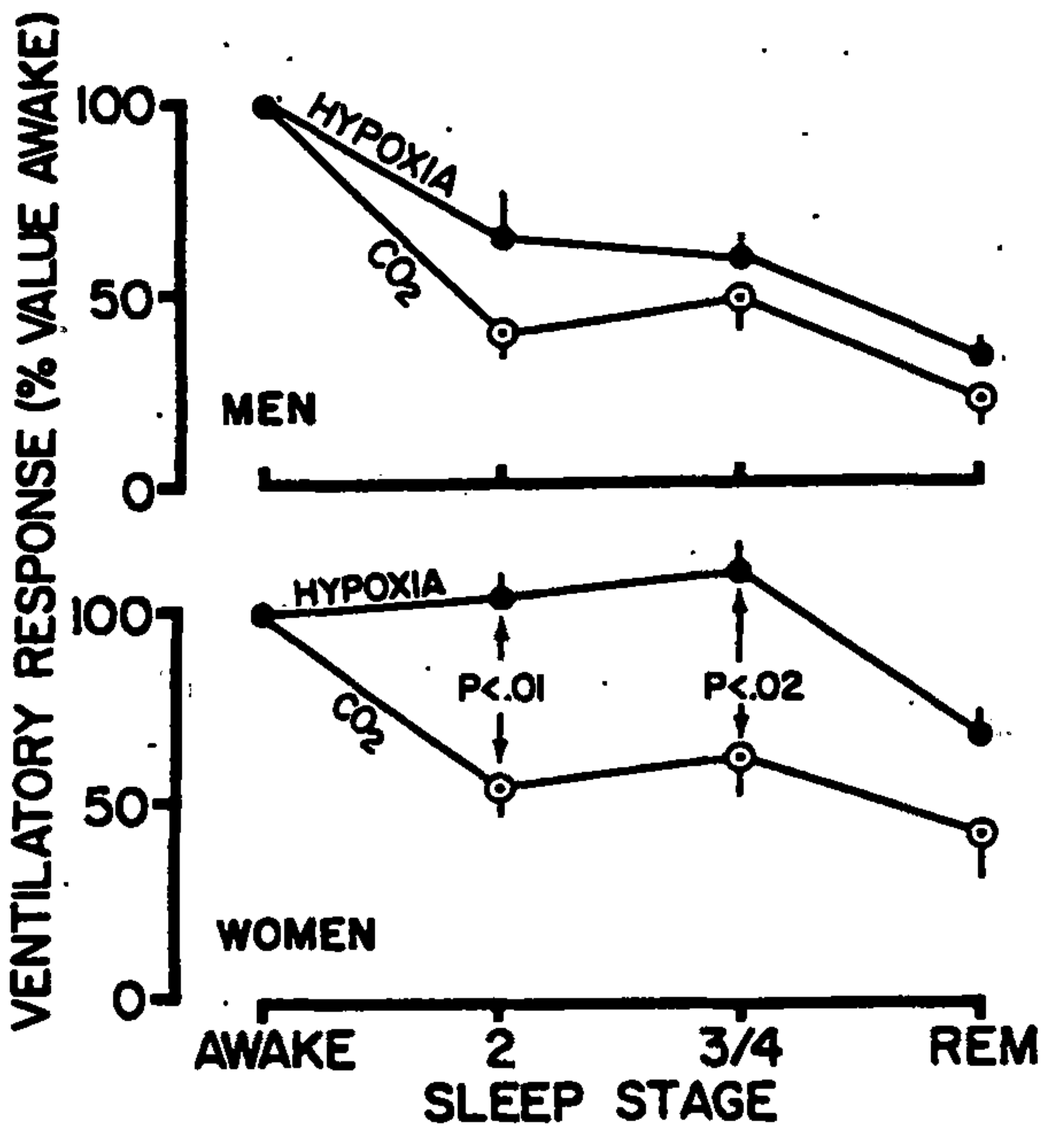



Fig 27 Hypoxic and hypercapnic ($CO_2$) ventilatory responses, as % of the value in wakefulness, in men (above) and women, each point representing the mean (± SE) of 6 subjects. Non-REM sleep had a significantly different effect on the hypercapnic than on the hypoxic ventilatory responses in women.

to man. In 3 subjects, response were obtained both with numerous - "phasic REM - and few eye movements - "mixed" REM - but there was no difference between the hypercapnic ventilatory responses in these two states.

The present study does not confirm the impression of Newsom Davis and co-workers (Davis et al, 1978) that women have higher hypercapnic ventilatory responses than men in non-REM sleep. However, these investigators measured only the inspired and not end-tidal $CO_2$ and thus, as the authors admit, the true hypercapnic ventilatory response was not assessed. Furthermore, the hypercapnic ventilatory response was not measured in their subjects when awake, and thus it is possible that the reported differences existed during wakefulness and were not caused by sleep.

When the results from all 12 subjects (6 men, 6 women) in the study of hypercapnic ventilatory response (HCVR) were compared with those from the 6 men and 6 women in whom hypoxic ventilatory responses (HVR) were measured during sleep (Fig 27) there was no difference in the men between the decrease in HCVR and the decrease in HVR. In contrast, women had a significantly greater reduction in HCVR than HVR in non-REM sleep, and the difference in REM was of borderline significance ($p = 0.07$). Five of the 12 subjects (4 men, 1 woman) had participated in both studies. There was no correlation between the decrements in HVR and HCVR from wakefulness

to any sleep stage in these subjects, either if all 5 were analysed together or if the 4 men were taken separately.

Unlike Gothe and colleagues (1981) we were unable to show a significant correlation between the rise in $P_{ET}CO_2$ from wakefulness to stage 2 sleep with either the waking or the stage 2 hypercapnic ventilatory response, and the same lack of relationship held true for all sleep stage changes. This might be a methodological difference as Gothe used a semi-steady state technique and not a rebreathing technique, but it is not clear why this should affect these correlations.

The current study was designed to measure the slope of the hypercapnic response rather than to define accurately the dog-leg of the hypercapnic response. The length of the dog-leg can be approximately deduced from the rise in $P_{ET}CO_2$ betwen the resting ventilation/$P_{ET}CO_2$ point and the $P_{ET}CO_2$ where the resting level of ventilation intersects the hypercapnic ventilatory response line in each individual in each study. By this method, the mean length of the dog-leg was awake, 0.5$\pm$0.1, stage 2, 0.4$\pm$0.1, stage 3/4, 0.5$\pm$0.1 kPa $CO_2$; these differences were not significant. (As some REM sleep studies had negative slopes, it was not physiologically useful to calculate dog-leg lengths in REM sleep.) Thus the resting ventilation/$P_{ET}CO_2$ point never lay on the linear portion of the ventilatory

response line, suggesting that the hypercapnic ventilatory response does not play a major role in determining normal ventilation during sleep, but rather the role of HCVR is that of a backup defence in the event of disturbance of breathing. Acute exposure to high altitude results in a respiratory alkalosis and so the tolerance in $CO_2$ between the baseline $P_{ET}CO_2$ when awake and the ventilatory response lines during sleep would be transiently even greater. This might help explain the disturbed breathing during sleep which occurs soon after ascent to altitude (Reite et al, 1975; Sutton et al, 1980). However, the true physiological meaning of the dog-leg is open to question, being highly dependent on the technique used (Read & Leigh, 1967; Alison et al, 1982).

Thus this study confirmed that the ventilatory response to hypercapnia was decreased in non-REM sleep compared with wakefulness, and showed for the first time that the ventilatory response in REM sleep is lower than in non-REM sleep in adult man.

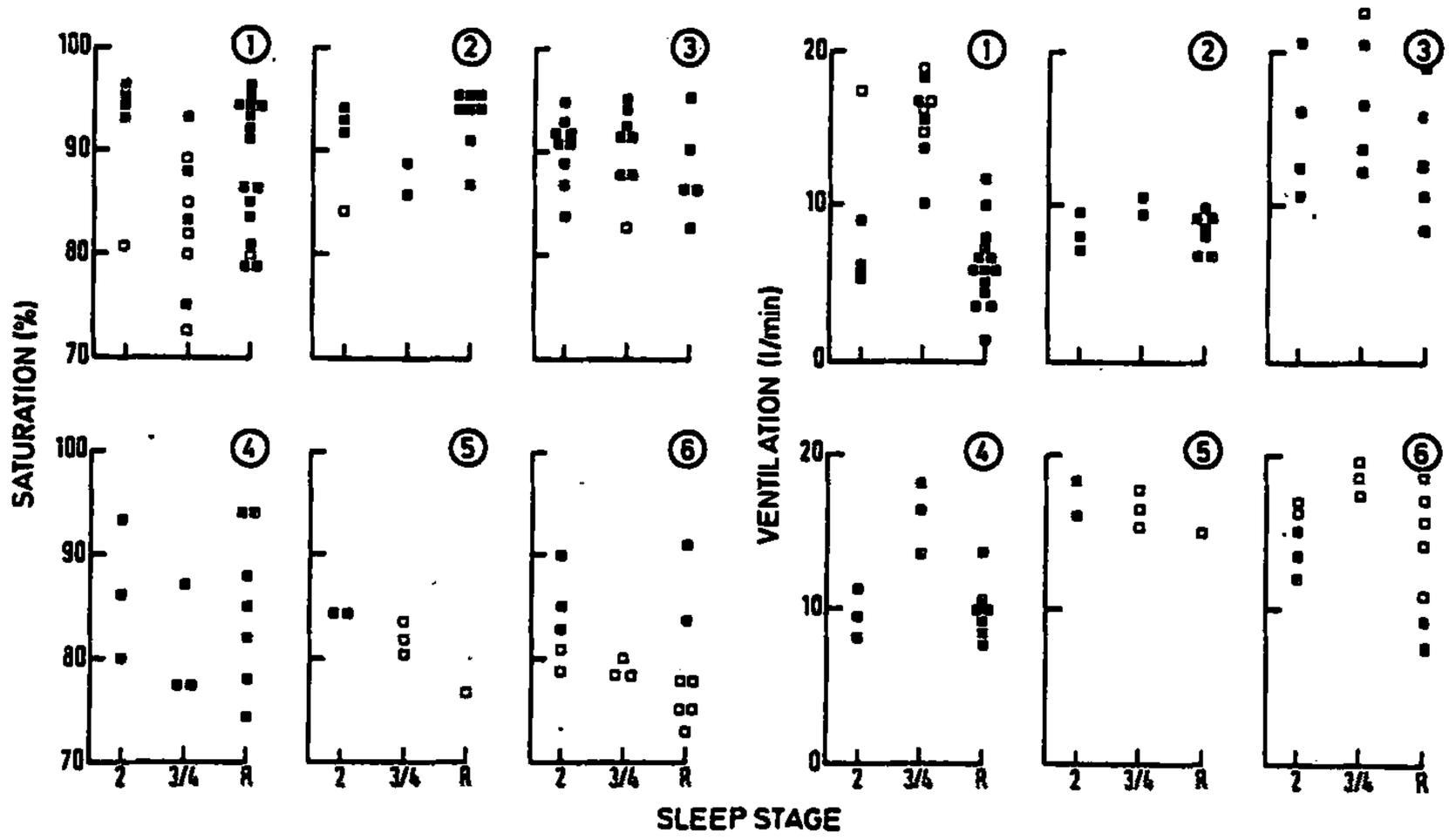



Fig 28 Haemoglobin saturation (left) and minute ventilation at the end of hypoxic responses in each sleep stage indicating whether the subject aroused (solid) or remained asleep (open squares). Subject numbers are encircled.

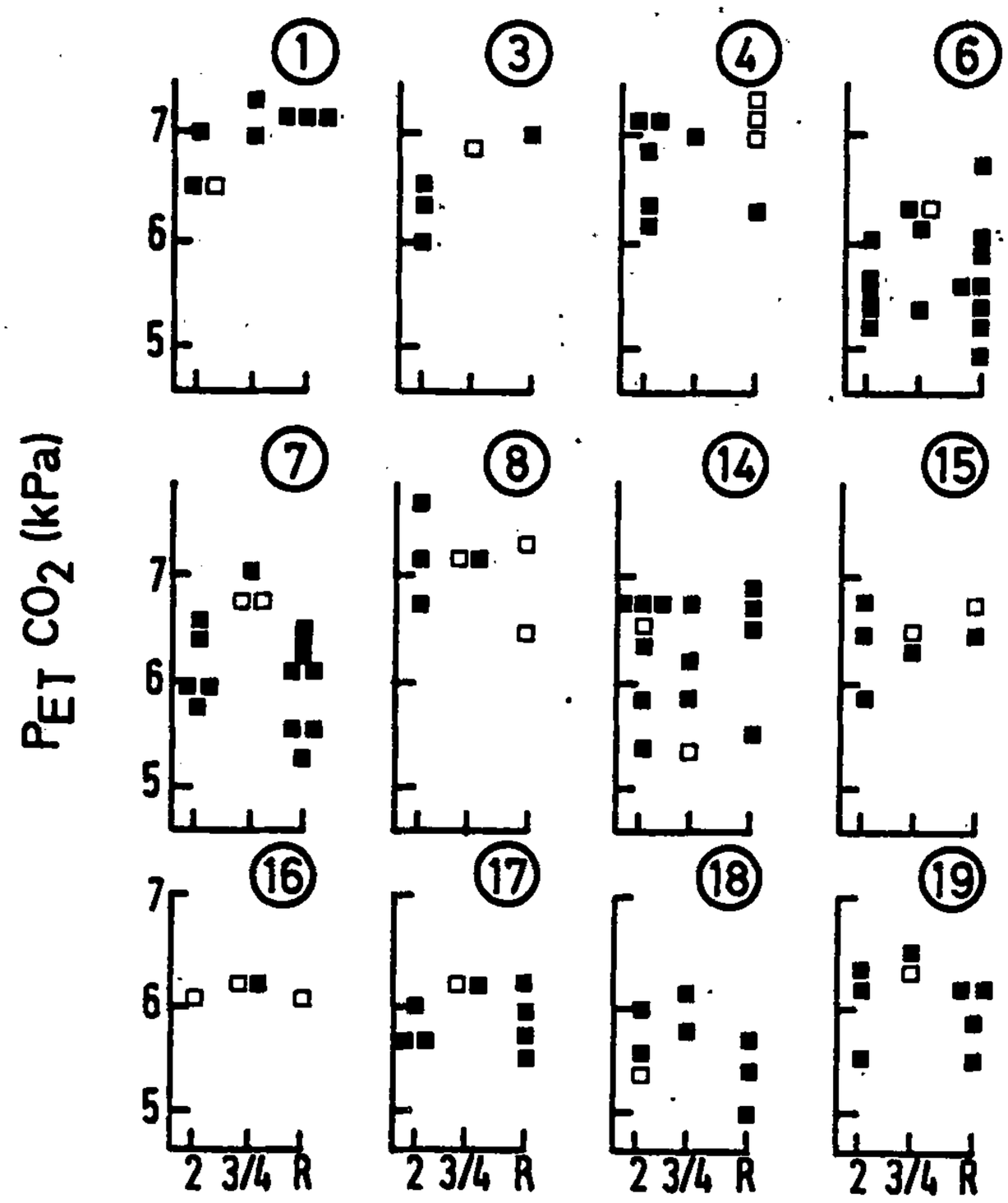



Fig 29 End-tidal carbon dioxide tension ($P_{ET}CO_2$) at the end of hypercapnic responses in each sleep stage indicating whether the subject aroused (solid) or remained asleep (open squares). Subject numbers are encircled.

# CHAPTER 11

## AROUSAL THRESHOLDS

These studies were not specifically designed to investigate arousal thresholds. However, several observations can be made from the results obtained.

Firstly the arousal thresholds both to hypoxia (Fig 28) and hypercapnia (Fig 29) were variable both within and between subjects. Secondly, there was no difference between sleep stages in the arousal thresholds to either stimulus. Thirdly, the level of ventilation at arousal was similarly variable both within and between subjects with no obvious difference between sleep stages (Fig 28). Fourthly, in several studies arousal did not occur despite marked hypoxia ($SaO_2$ < 80%) or hypercapnia ($P_{ET}CO_2$ > 6 kPa, this being 1.5 kPa above the average waking level in the study).

It is difficult to draw physiological conclusions from these studies because some arousals were almost certainly spontaneous and sleep was disturbed due to the strange surroundings, the instrumentation and previous chemostimulation. The sleep disturbance may explain some of the variability found.

Our normal subjects were not more sensitive to arousal from hypoxia or hypercapnia in non-REM sleep than

in REM sleep. Similarly Berthon-Jones and Sullivan (1982) have also reported no difference between sleep stages in the hypoxic arousal threshold in normal man. These results contrast with previous investigations in dogs (Phillipson et al, 1977 & 1978) and cats (Neubauer et al, 1981) and in patients with obstructive sleep apnoea (Sullivan & Issa, 1980). Thus further studies are needed to compare arousal thresholds in non-REM and REM sleep in adult man.

Considerable hypoxia or hypercapnia occurred before some subjects aroused, and these findings for hypoxia have recently been confirmed by other groups (Berthon-Jones & Sullivan, 1982; Gothe et al, 1982). These results are consistent with our observation that "blue bloaters" do not arouse during hypoxaemic episodes as the changes in arterial oxygen and carbon dioxide tension in these patients would have often failed to arouse our normal subjects. It is likely, but unproven, that the absolute levels of oxygen and carbon dioxide arousal threshold is different in the "blue bloaters" than in normal subjects.

However, the direct clinical applicability of these observations on arousal is questionable. During apnoeas and REM-related hypoventilation, hypoxia and hypercapnia both develop. Thus these measurements of single stimuli might over-estimate the tolerance to arousal in clinical situations. Perhaps arousal thresholds should be

investigated using a rebreathing technique - to simulate hypoventilation or central apnoea - or by airway occlusion - to simulate obstructive apnoea.

Arousal appears to be a life-saving response during sleep apnoeas. The mechanism of arousal is very poorly understood and indeed it is not clear from the present study whether hypoxia and hypercapnia are important stimuli to arousal. There is conflicting evidence on the importance of hypoxia as a stimulus to arousal in the sleep apnoea syndrome (Sullivan & Issa, 1980; Martin et al, 1982) and the role of hypercapnia has not been fully investigated. Even in animals in which hypoxic arousal is reproducible, the mechanism of arousal is unclear, for the carotid body appears to be important in hypoxic arousal in dogs (Bowes et al, 1981) but not in cats (Neubauer et al, 1981). This area therefore requires considerable clarification.

# CHAPTER 12

## BREATHING REGULARITY DURING SLEEP

These studies were not primarily designed to investigate breathing rhythm during sleep and the computer was not programmed to analyse breath by breath variability in timing. Breath by breath instantaneous minute ventilation ($V_T \div Ttot$) could be obtained, and the variability in this function is described. Previous studies of breathing rhythm in adult man (Bulow, 1963; Duron, 1972) also refer to variability in expired volume rather than the differences in timing.

### RESULTS

#### Non-REM Sleep

In non-REM sleep, breathing was mainly regular, but became irregular following arousal in all subjects (Fig 18). In most subjects such irregularity lasts between 1-10 minutes after falling asleep, but in 4 men, 1 a snorer, the non-REM irregularity continued for between 1-4 hours, although all 4 breathed regularly during non-REM sleep in the second half of the night. These 4 could not be distinguished from the other subjects in terms of their ventilatory response to hypoxia or hypercapnia either when awake or in non-REM sleep, or by

the change in either ventilatory response between wakefulness and non-REM sleep. The only factor which distinguished them from the other subjects was their male sex [$Chi^2$ for small numbers (Swinscow, 1976), $p < 0.05$].

Carbon dioxide rebreathing did not regularise irregular breathing during non-REM sleep (Fig 30) in any of the 9 studies in which the initial breathing pattern was irregular. Only 4 episodes of irregular breathing were encountered during hypoxic responses in non-REM sleep and in these respiration normalised in 2 but remained irregular in the other 2.

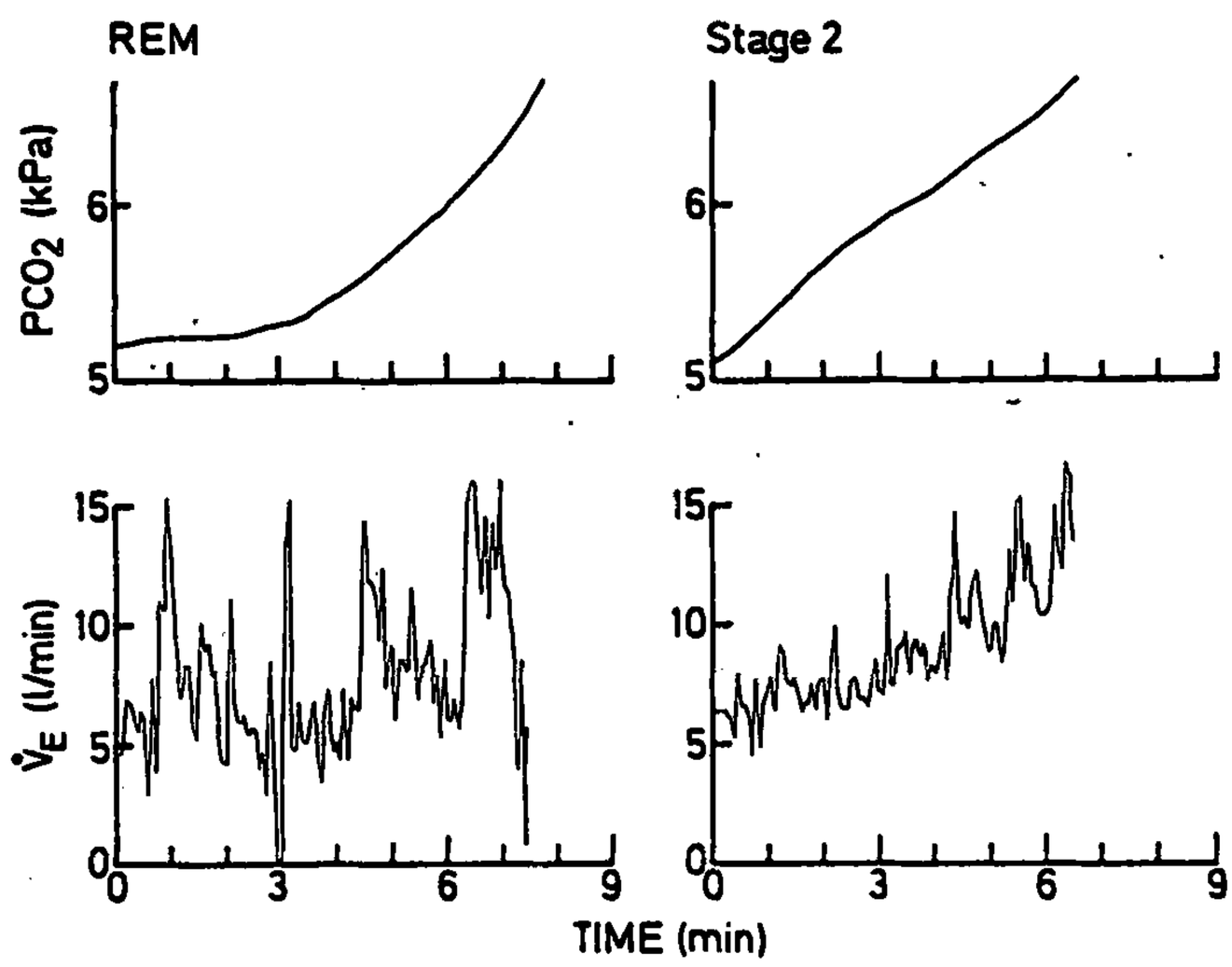



Fig 30 Raising the end-tidal carbon dioxide tension ($P_{ET}CO_2$) did not regularise irregular breathing either in REM (left) or Stage 2 sleep (right). $V_E$, expired ventilation.

REM Sleep

Breathing was irregular in all subjects throughout all REM periods. Neither hypoxia nor hypercapnia regularised breathing in REM (Fig 30). Although no formal attempt was made to correlate the degree of irregularity with the number of eye movements, it was noted that irregular breathing occurred in REM in the absence of eye movement. Indeed the onset of irregular breathing was often the first feature suggestive of the start of a REM sleep period preceding the specific EEG, EMG and EOG changes.

## DISCUSSION

These results confirm that respiration in non-REM sleep is essentially regular but becomes irregular following arousals (Bulow, 1963; Duron, 1972). Contrary to the findings of Bulow in adults and Kalapesi and colleagues (1981) in infants, increasing the inspired $CO_2$ tension did not regularise irregular breathing. The rate of $CO_2$ rise in the current study was greater than in Bulow's study - his subjects rebreathing from a 30 litre bag with the inspired $CO_2$ rising to about 5% in approximately 10 minutes. In both Bulow's and the current study, irregular breathing in non-REM usually lasted for only a few minutes, and thus it is possible that the regularisation which Bulow reported was a purely temporal phenomenon and did not relate to the $CO_2$

inhalation. Although Kalapesi and colleagues (1981) state that increasing inspired $CO_2$ to 0.5-1.5% made breathing "more regular" in non-REM, like Bülow they quote no data to support this contention and the only example given (Fig 1 in Kalapesi et al, 1981) shows that although apnoeic intervals were present before but not after $CO_2$ inhalation, breath frequency and depth still varied during $CO_2$ inhalation.

Contrary to Bulow's report (1963), there was no correlation between the lateral displacement of the ventilation/$CO_2$ response line between wakefulness and stage 2 sleep with the duration of irregular breathing in stage 2 sleep.

All subjects breathed irregularly in REM sleep, as has previously been shown both in man (Aserinsky, 1965; Bulow, 1963; Duron, 1972) and animals (Phillipson et al, 1976; Remmers et al, 1976; Orem et al, 1977; Sullivan et al, 1978). There was no obvious correlation between eye movements and breathing irregularity although more sophisticated investigation of this is required. Chemostimulation did not regularise irregular breathing in REM sleep.

Three factors suggest the control of the depth and timing of respiration is different in non-REM and REM sleep. Firstly, breathing was essentially regular in non-REM sleep but irregular in REM sleep. Secondly, whereas all 19 subjects breathed irregularly throughout

all REM periods, the irregularity in non-REM sleep was a transient phenomenon following arousals in all except 4 men who had prolonged irregular breathing in non-REM sleep. Thirdly, breathing rhythm in REM was independent of chemical stimuli whereas in 2 non-REM studies, breathing regularised during the induction of hypoxia. Whilst this may have been coincidental, it is impossible to exclude hypoxia as a factor. The second observation also suggests that hypoxic responsiveness might be important in non-REM respiratory rhythm, as the only difference in ventilatory control between the sexes was that the women maintained their hypoxic ventilatory response at waking levels in non-REM sleep.

Thus it is possible that the hypoxic ventilatory response preservation might protect women from irregular or "sleep disordered breathing" (Block et al, 1979) during non-REM sleep. However, the evidence that the hypoxic ventilatory response is important in the maintenance of regular breathing in non-REM sleep is inconclusive. Hypoxia did not always regularise breathing in non-REM, and in the 5 subjects in whom both hypoxic and hypercapnic drives were performed there were no correlations between the changes in either ventilatory response and the extent of irregular breathing in non-REM sleep. Thus breathing variability in non-REM may be independent of chemical control. Further investigation into the causes of irregular breathing during non-REM

sleep in normal adults is needed. Perhaps such studies might improve understanding of the sleep apnoea syndrome (Guilleminault et al, 1976) as this too is more common in men and is associated with snoring.

Ventilatory pattern in REM was independent of chemical stimuli and similarly in animals the irregular pattern of breathing in REM sleep continues despite hypoxia (Phillipson et al, 1978), hyperoxia (Sullivan et al, 1978), hypercapnia (Sullivan et al, 1979a), metabolic alkalosis (Sullivan et al, 1978), carotid body resection (Guazzi and Freis, 1969) or vagotomy (Dawes et al, 1972; Phillipson et al, 1976; Remmers et al, 1976). It has been suggested (Phillipson, 1978a) that these irregularities relate to the influence of behavioural factors, perhaps due to the increased dream frequency in REM sleep. However, there is no direct evidence to support this contention. Studying cats, Orem (1980) has found positive correlations between the activity of some medullary respiratory neurones in REM sleep with pontine generated discharges termed ponto-geniculo-occipital (PGO) waves. These waves are one of the most basic electrophysiological phenomena yet recognised in REM sleep (see Chapter 2), and may be associated with the irregular rapid eye movements characteristic of this sleep stage. Thus the dysrrhythmic nature of breathing in REM sleep may relate directly to the dysrrhythmic nature of REM sleep itself.

# CHAPTER 13

## DISCUSSION OF PART 11 OF THE THESIS

These studies show that ventilation and the ventilatory responses to hypoxia and hypercapnia are reduced during sleep, the reductions being maximal in REM sleep. The possible mechanisms for the falls in ventilation and ventilatory drive are discussed below.

### 1) Metabolic Rate

Decreased metabolic rate can result in both hypoventilation and reduced ventilatory drive (Doekel et al, 1976; Zwillich et al, 1977). Unfortunately, it was not possible to measure metabolic rate in the present studies, and so the literature on metabolism during sleep is reviewed. Early studies (Benedict & Carpenter, 1910; Benedict 1915; de Bruin, 1936; Robin et al, 1958; Kreider et al, 1958) found that metabolic rate decreased by 8-20% during sleep, but in none of these studies was sleep confirmed by EEG criteria and in most (de Bruin, 1936; Robin et al, 1958; Kreider et al, 1958) the subjects did not fast and hence it is impossible to separate sleep effects from food effects. Bulow (1963), who fasted his subjects for 3 hours prior to the studies, found no change in oxygen uptake between wakefulness and

either stage 1 or stage 11 sleep. Brebbia and Altshuler (1965) measured oxygen uptake in all sleep stages but the EEG criteria were lax, no mention was made of fasting, and the statistics used were invalid (multiple comparison by t test). They state that oxygen uptake was always higher in wakefulness than in any stage of sleep, yet the only data given shows that the metabolic rate after final arousal was lower than in any stage of sleep (Fig 1 in Brebbia and Altshuler, 1965). Their data does indicate that metabolic rate in REM sleep is higher than in non-REM sleep but this has not been confirmed by Webb and Hiestand (1975) who found no difference in metabolic rate between the different stages of sleep. Recently, Goll and Shapiro (1981) found a mean decrease in oxygen consumption of 9.5% during sleep, the lowest rate being found in stage 4 sleep. No comment is made in this abstract on the metabolic rate in REM sleep.

Thus it is probable that metabolic rate is lower in non-REM sleep compared to wakefulness, but this is currently being further explored. While such a change may contribute to the reduced ventilation and ventilatory drive in non-REM sleep, the further decreases in REM sleep do not reflect further changes in metabolic rate.

2) <u>The Relationship Between Cerebral Metabolism and Blood Flow</u>

In non-REM sleep, cerebral metabolism appears to be unchanged from wakefulness (Mangold et al, 1955), while

the changes in cerebral blood flow are disputed. Mangold and colleagues (1955) reported a 10% increase in global cerebral blood flow whereas Townsend and colleagues (1973) found a 6-14% decrease in grey matter blood flow. This discrepancy could reflect regional differences - Reivich and co-workers (1968) having shown that sub-cortical flow increased markedly in slow wave sleep in cats - or the fact that Mangold's subjects were sleep deprived - which also casts doubt on his observation of unchanged cerebral metabolism in non-REM sleep. In REM sleep, indirect evidence (Oswald 1976; Adam and Oswald, 1977) suggests that cerebral metabolism increases and direct evidence indicates that cerebral blood flow also increases in REM sleep (Reivich et al, 1968; Townsend et al, 1973; Santiago et al, 1980).

Thus in neither REM nor non-REM sleep is there clear evidence of a decreased ratio of cerebral metabolism to blood flow such as might decrease ventilation and ventilatory responsiveness. However, this relationship requires further investigation.

3) Diurnal Variation

The possibility that the results are due to a diurnal rhythm in ventilation and ventilatory control warrants comment. Previous studies in adults, infants and animals have largely ignored this possibility and the current investigation was not specifically designed to

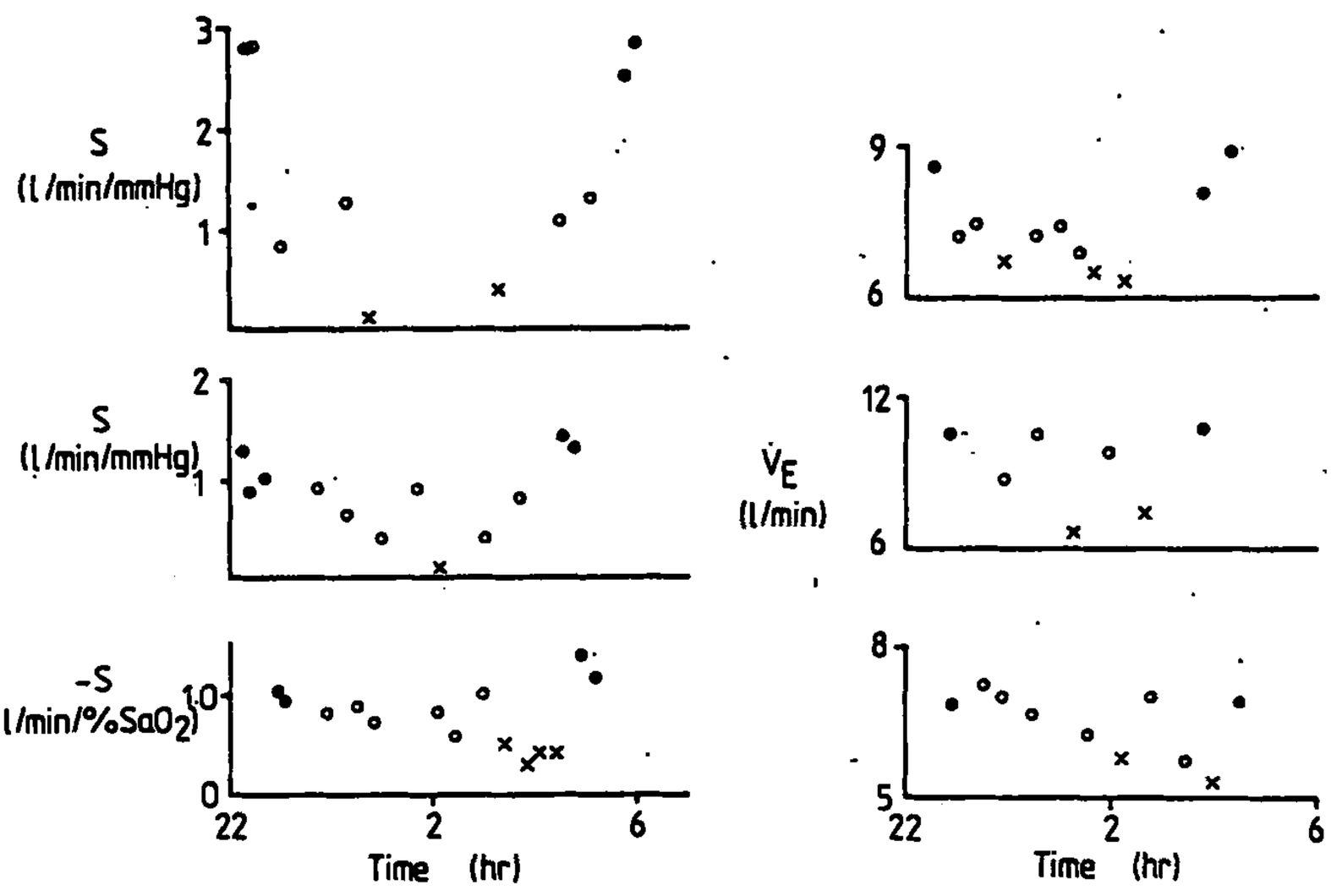



Fig 31 Measurements made in wakefulness (closed circles), non-REM (open circles) and REM sleep (crosses) indicating, by the 24 hour clock, the time measurements were made. Left: upper 2 panels, hypercapnic ventilatory responses; lower panel, hypoxic ventilatory responses. Right: all 3 panels baseline ventilation. s, slope; $\dot{V}_E$, expired ventilation.

answer this question. However, the results (Fig 31) do not support this contention as both ventilation and ventilatory responses tended to be lower in REM than non-REM sleep irrespective of the time when the measurements were made. Further, Berthon-Jones and Sullivan (1982) performed hypoxic ventilatory responses on their subjects during wakefulness intermittently throughout the night and found no significant difference between the pre-sleep control values and those performed later in the night. Similarly in the present study there was no difference between the value obtained before and after sleep, although no measurements were performed during intervening wakefulness. Thus my impression is that there is no major diurnal component to the observed changes in ventilation and ventilatory control. Proof of whether there is a diurnal contribution would require much more data than were obtained in the current studies and probably would involve several nights of study for each subject.

4) Mechanical Factors

a) Bronchomotor Tone

Bronchoconstriction could account for the observed changes in ventilation and ventilatory response, especially as the ventilatory compensation to increased flow resistance is probably impaired during sleep in man

(Iber et al, 1982). Tabachnik and colleagues (1981b) reported that pulmonary resistance trebled in non-REM and almost doubled in REM sleep compared to wakefulness in 4 adults. These results were obtained with a Respitrace and are only published in abstract. Contradictory evidence comes from Robin and colleagues (1958) who found that pulmonary resistance decreased during sleep in all 3 subjects studied with an average reduction of 40%. Although the EEG was not recorded, these measurements were presumably made in non-REM sleep. In dogs, Sullivan and colleagues (1979b) found that bronchomotor tone was reduced in non-REM sleep and was variably decreased in REM sleep. The possibility of bronchoconstriction during sleep requires further clarification, but there is no evidence of increasing bronchoconstriction in REM sleep and thus the observed changes in REM are extremely unlikely to reflect airway narrowing.

b) Functional Residual Capacity

Functional residual capacity has been shown to be lower in REM than non-REM sleep in infants (Henderson-Smart & Read, 1979b) in association with decreased intercostal tone (Henderson-Smart & Reed, 1976). Similar changes have been claimed in adults (Muller et al, 1980) but these results were semi-quantitative and no comparisons were made with the functional residual capacity in wakefulness.

While a decrease in functional residual capacity might not affect minute volume, it will influence ventilatory response (Cherniack et al, 1973), but would result in an increased response, contrary to the changes observed in the present study. Thus any possible reduction in functional residual capacity cannot explain our results.

5) Neurological Affects

a) Sensor

It seems unlikely that chemosensor sensitivity would decrease during sleep. Furthermore, at least in the men, the changes from wakefulness to non-REM and then to REM sleep were similar for the hypoxic and hypercapnic ventilatory responses and the hypoxic heart rate response. These parallel reductions are unlikely to be due to chemosensor effects as different receptors are involved for each of the three responses. The hypoxic ventilatory response reflects the carotid chemoreceptor and the hypercapnic ventilatory response central chemoreceptors whilst I am unclear as to the nature of the hypoxic heart rate response receptor. Certainly this is not the carotid body as this response remains intact despite carotid body resection (Holton and Wood, 1965; Lugliani et al, 1973).

b) Effector

Similarly it is unlikely that parallel changes would occur in end organ sensitivity in the heart and respiratory muscles during REM sleep. Further, cardiac vagal tone remains operative in REM sleep (Baust and Bohnert, 1969).

c) Central Effects

Sleep is a state of altered central nervous system (CNS) function and thus the reduced ventilation and ventilatory responses might reflect changes in CNS function. Virtually all studies of the neural control of respiration during sleep have been performed in animals, which, as has been seen, may not be good models for breathing during sleep in adult man. Thus the majority of the observations below should be interpreted with caution. This complex field has recently been extensively reviewed (Phillipson, 1973a; Orem, 1973; Remmers, 1981).

There is some evidence in man that wakefulness produces a neural drive to breathing as individuals with "Ondine's curse" (Mellins et al, 1970) maintain normal breathing only during wakefulness. Most of these patients have been shown to have neurological disease (Mellins et al, 1970) presumably interrupting the "automatic" drive to breathing during sleep and thus they require the continued respiratory drive of wakefulness to stimulate ventilation.

In cats, perhaps the nearest animal model of human breathing during sleep, excitation of the reticular activating system increases ventilation (Hugelin & Cohen, 1963). This suggests that the decreased reticular activating system activity during non-REM sleep might be associated with decreased central ventilatory drive.

Orem and colleagues (1974) demonstrated that sleep produced derecruitment of respiratory neurones in the ventro-lateral brain stem of cats, but the precise function of these neurones is unclear. It has been suggested (Orem, 1978) that these neurones probably control upper airway tone, and as both the upper airways and the diaphragm are believed to be controlled by the same neural oscillating system (Cohen, 1975), Orem's observation may indicate a generalised decrease in respiratory neurone output with the transition from wakefulness to sleep. Such decreased respiratory neurone activity might contribute to the reduced ventilation and decreased ventilatory responses found in non-REM sleep.

One of the characteristic features of REM sleep is a generalised insensitivity to external stimuli resulting from both afferent and efferent inhibition (Pompeiano, 1973). In cats there is presynaptic inhibition of afferent information arising from muscles, skin (Pompeino, 1973) and retina (Steriade & Hobson, 1976). Efferent inhibition is modulated by ventral reticulo-spinal pathways (Pompeiano, 1975) resulting in

tonic post-synaptic inhibitory potentials in alpha motor neurones (Pompeiano, 1973; Nakamura, 1978). The most likely explanation for the decreased ventilatory responses in REM sleep observed in the present study is that this insensitivity in REM sleep extends to chemostimuli which are thus blocked both at the afferent and efferent level.

Orem's observation that REM sleep is associated with decreased activity in some respiratory associated neurones in the ventro-lateral medulla (Orem et al, 1974; Orem, 1980) are difficult to evaluate as the precise function of these neurones is unclear. Should they prove to be related to respiratory muscles, then these findings could either reflect a decrease in central respiratory drive in REM sleep or, perhaps more likely, be a reflection of inhibited afferent information.

Phillipson (1978a) has suggested that impaired ventilatory responses in REM sleep are related to the activation of a behavioural inhibitory pathway. There is no direct evidence to support this.

It is unclear whether the efferent inhibition during REM sleep affects the intercostals and diaphragm equally. The postural hypotonia of REM sleep is partially mediated via the gamma loop system (Pompeiano, 1973). Muscle-spindles have been reported to be scarce in the diaphragm (Corda et al, 1965) - a finding disputed by Muller et al (1979) - and thus it has been suggested that

the REM related hypotonia might involve the intercostals but spare the diaphragm (Remmers, 1981). There is considerable evidence that intercostal EMG activity is decreased in REM as opposted to non-REM sleep in animals (Parmeggiani, 1978; Duron et al, 1973) and man (Duron, 1972; Tusiewicz et al, 1977; Tabachnik et al, 1981a) but there is no convincing evidence that the intercostal activity in REM sleep is different from that in wakefulness in adult man. This, however, is clearly the conclusion of Tusiewicz and colleagues (1977) but they only studied 3 subjects, noted variable inhibition of intercostal EMG tone, and reported no objective data. In a later study of 9 adolescents by the same group (Tabachnik et al, 1981a) the mean increase in intercostal EMG ($EMG_{ic}$) in non-REM compared to wakefulness was 34±6 (SD)% and $EMG_{ic}$ decreased by 49±24% from non-REM to REM sleep. Measurements were made in wakefulness, non-REM and REM sleep in only 3 of the subjects in whom the mean increase in $EMG_{ic}$ from wakefulness to non-REM sleep was 32% with a mean decrease of 38% from non-REM to REM sleep. This suggests that any change in intercostal activity between wakefulness and REM is very small. The mean level of diaphragmatic activity in REM sleep is unclear as the same group has reported both increased phasic (Tabachnik et al, 1981a) and decreased tonic (Muller et al, 1979) diaphragmatic EMG activity in REM sleep in comparison to wakefulness. Thus the relative activity of the intercostal muscles and diaphragm during REM sleep in adult man has not been established and requires further investigation.

## CONCLUSION

This review of factors which might contribute to the decrease in ventilation and ventilatory drive observed during sleep, has produced almost as many questions as answers, and my conclusions are necessarily speculative. I suggest that the decreases observed during non-REM sleep are due to a combination of decreased metabolic rate plus the loss of the cortical drive to ventilation. The further decrease in ventilation and ventilatory drive during REM sleep is probably due to the neuronal basis of REM sleep itself, reflecting inhibition of both sensory and motor impulses during REM sleep, but a REM specific decrease in central ventilatory drive is an intriguing possibility.

## CLINICAL CONSEQUENCES

Hypoventilation in REM sleep, permitted by decreased ventilatory drive, would explain the REM related hypoxaemia seen not only in patients with chronic bronchitis and emphysema (discussed in detail in the next chapter) but also in patients with chronic mountain sickness (Kryger et al, 1978), cystic fibrosis (Muller et al, 1980), kyphoscoliosis (Mezon et al, 1980; Guilleminault et al, 1981a), myotonic dystrophy (Guilleminault et al, 1978), and diaphragmatic paralysis (Skatrud et al, 1980). The relationship between the

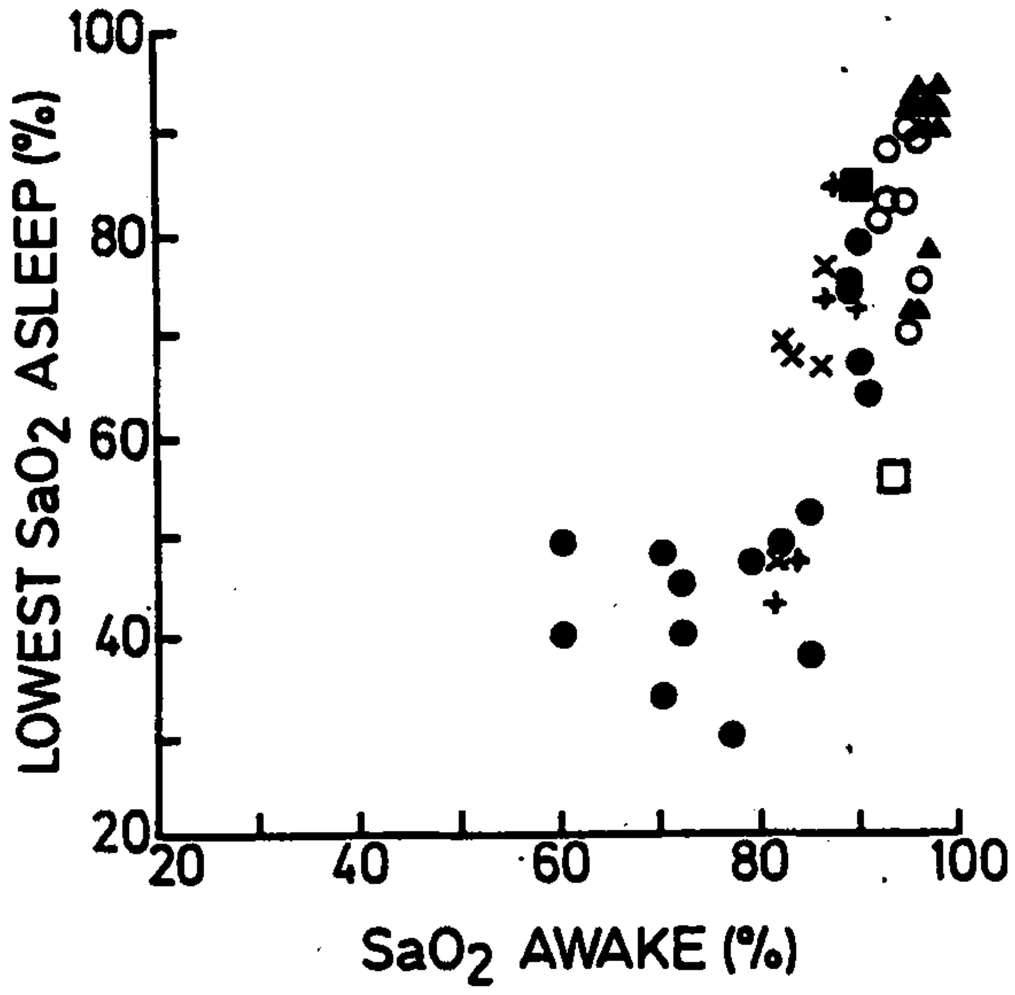



Fig 32 Relationship between lowest corrected oxygen saturation ($SaO_2$) asleep and oxygen saturation during wakefulness in: current healthy subjects (triangles), "pink puffers" (open circles) and "blue bloaters" (closed circles); patient from other studies with chronic mountain sickness (x, Kryger et al, 1978), cystic fibrosis (solid square, mean data of Muller et al, 1980), kyphoscoliosis (+, Mezon et al, 1980) and diaphragmatic paralysis (open square, Skatrud et al, 1980).

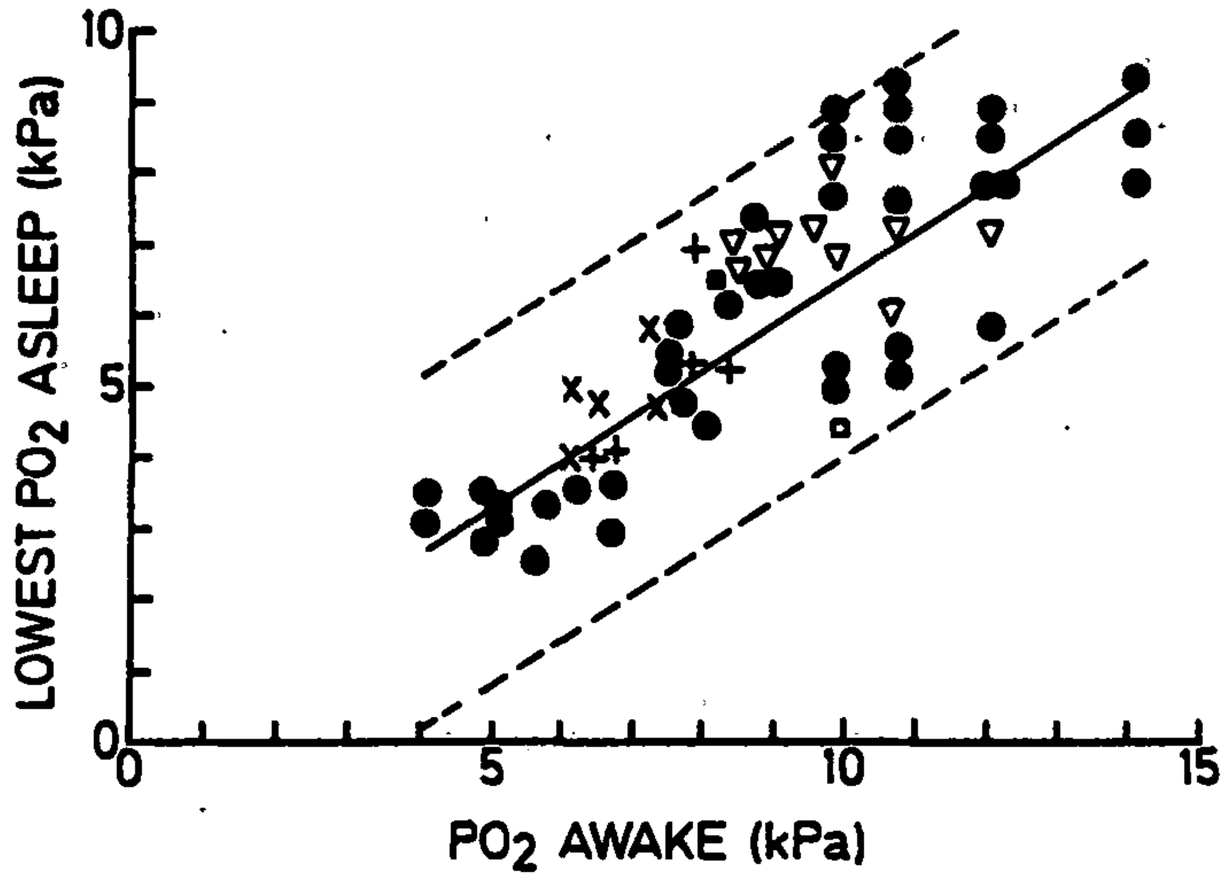



Fig 33 Relationship between calculated arterial oxygen tensions ($PO_2$) at lowest oxygenation asleep and during wakefulness. The data for healthy subjects and patients with chronic bronchitis and emphysema in the current study are indicated (all closed circles) with regression line and 95% confidence limits for the data. Patients from other studies are indicated as in Fig 32 with the addition of triangles for asthmatics showing mean data for Tabachnik et al (1981c) and each subject from Catterall et al (1982a).

oxygenation during wakefulness and the lowest oxygenation when asleep is similar in the above patients to that in our own subjects (Fig 32 & 33). In each of these conditions, the REM related hypoxia may be clinically important, accelerating the development of polycythaemia and cor pulmonale.

It is of interest that the one patient with diaphragmatic paralysis reported by Skatrud et al (1980) lies just within the 95% confidence limits of the data from our own subjects. It must be repeated that this was a study on one subject only but this finding would suggest the diaphragm, although probably important, is not as critical to ventilation in REM sleep as Tusiewicz and colleagues (1977) suggest.

Similarly the physiological hypoventilation in REM sleep probably explains some of Block's "sleep disordered breathing" as 30% of the desaturations in "normal subjects" occurred in REM sleep (Block et al, 1979). Also much of the irregular breathing and hypoxia reported in asthmatic patients (Tabachnik et al, 1981c; Catterall et al, 1982a; Montplaisir et al, 1982) may be due to physiological hypoventilation in REM sleep as in all 3 series the lowest oxygen saturations were obtained during REM sleep. Indeed the relationship between the saturation during wakefulness and the lowest saturation during sleep in these patients was similar to that observed in our normal subjects and "pink puffers", but

was not displayed in Fig 32 for reasons of clarity. I have transformed the available saturation data (Tabachnik et al, 1981c; Catterall et al, 1982) into calculated $PO_2$ and the results (Fig 33) indicate that there is no evidence of excess hypoxaemia due to overnight bronchoconstriction in these patients. It remains to be seen whether asthmatics have more irregular breathing during sleep than normal subjects, for this was found in our own series (Catterall et al, 1982a) but not by Montplaisir et al (1982). There may be methodological reasons for this as our patients were older and we included hypopnoea as well as apnoea in our analysis. Interestingly, both studies showed that the asthmatics had more intervening wakefulness and drowsiness than the controls, but the cause of this is unclear and requires further investigation. This abnormality would predispose to irregular breathing.

The decreased hypoxic and hypercapnic ventilatory drives during sleep may have a permissive role in the sleep apnoea syndrome, but other, as yet unidentified, neurological abnormalities probably initiate apnoeas in these patients. Patients with a sleep apnoea syndrome have longer apnoeas and become more hypoxaemic in REM than non-REM sleep (Sullivan & Issa, 1980). This may reflect impaired ventilatory drive during REM sleep. The increased hypoxaemia in REM may partially be due to REM related hypoventilation prior to the onset of apnoeas.

The weak arousal responses to both hypoxia and hypercapnia may be important in understanding why patients with this syndrome do not arouse more rapidly from apnoeas. This failure of arousal permits the development of hypoxaemia and the resulting polycythaemia and cor pulmonale (Coccagna et al, 1972; Lugaresi et al, 1978), which may be life threatening in these patients (Guilleminault et al, 1981b).

The recognition that hypoventilation and decreased ventilatory drive during REM sleep are normal in adult man helps explain the REM related desaturation seen in a wide variety of conditions.

# CHAPTER 14

## CONCLUSIONS

The studies reported in part 11 of this thesis confirm the hypotheses which they were constructed to test. Thus both ventilation and the ventilatory responses to hypoxia and hypercapnia have been found to be reduced in REM sleep in adult man. These observations are compatable with the earlier suggestion that the desaturation observed in hypoxic patients with chronic bronchitis and emphysema resulted from hypoventilation, which is a normal physiological response in REM sleep, and that this hypoventilation is permitted by reduced ventilatory responses in REM sleep.

There have been many publications on breathing and oxygenation during sleep in patients with chronic bronchitis and emphysema since the studies reported in part 1 of this thesis were completed in 1979. These reports are reviewed below.

Block's group have performed many studies on similar lines to those reported in part 1 of this thesis and our results are largely in agreement. There are two main methodological differences between the Edinburgh and Florida groups. Firstly Block's group defines a desaturation as a drop of oxygen saturation of more than

4% from the sleeping baseline. I chose a 10% drop to represent a desaturation because with our severely hypoxic patients it was not possible to define a sleeping baseline saturation more accurately than ±5% saturation. Secondly, Block's group defines "hypopnoea" as "a distinct episode of reduced airflow at nose and mouth causing thermister deflection of less than one third baseline levels for at least 10 seconds" (Wynne et al, 1979). As the temperature of the respired air is largely independent of tidal volume, this is not a good method of quantitating ventilation and indeed it is really able to detect only very marked decreases in ventilation. Thus with the less sensitive system for detecting hypopnoea during episodes of lesser desaturation, one might expect Block's group to find a poorer correlation between hypopnoea and desaturation than in the present study. Whereas Wynne and colleagues (1979) found 42% of the desaturations in 7 patients with chronic bronchitis and emphysema (plus several other co-existing diseases) occurred during apnoea and hypopnoea, in the present study, of 3 times as many patients, the equivalent figure is 71%.

Block's group also found that oxygen therapy improved both oxygenation during sleep and sleep quality in patients with chronic bronchitis and emphysema (Kearley et al, 1980) although 4 of the 11 patients were grossly overweight (> 198lbs and < 5'10") and these 4

patients contributed over 90% of the desaturation events and thus it is difficult to decide whether this was a study of the effects of oxygen therapy on obesity or on chronic bronchitis and emphysema. Also the difference in sleep quality was only significant for the percentage of study time in which the patients slept, and the study time averaged only 140 minutes with sleep times as low as 15 minutes. Further, the order of air or oxygen studies was not randomised, 7 of the 11 patients receiving air in the first half of the night which would predispose to improved sleep quality on oxygen. In another study (DeMarco et al, 1981) the same group confirmed our observation (Douglas et al, 1979) that "blue boaters" desaturate more than "pink puffers" during sleep. Their data also shows that breathing patterns during sleep were similar in the 4 "blue bloaters" and the 6 "pink puffers", although this observation was not considered worthy of comment. In this study another difference in definition emerges as their "blue bloaters" had to have a body weight of > 110% predicted and a total lung capacity (TLC) of <120% predicted, whereas the "pink puffers" were of normal or low body weight with a TLC > 120% predicted and a transfer factor for carbon monoxide of < 50% predicted. All our bronchitic patients were of normal body weight and neither TLC nor transfer factor were used in sub-classification. The weight criteria might be expected to increase "sleep disordered breathing" in the

"blue bloaters" (Harman et al, 1981) but probably had little effect on the overall results. More concerning is the fact that sleep quality was again poor and results are quoted for subjects who only slept for 41 minutes and had no REM sleep. Thus true comparison of either breathing or oxygenation during sleep cannot be made from this data.

Many workers other than our own and Block's group, have recently investigated breathing and oxygenation during sleep in patients with chronic bronchitis and emphsyema. Most reports agree with the conclusion of part 1 of this thesis that major desaturations in sleeping patients with chronic bronchitis and emphysema occur predominantly during REM sleep. (Coccagna and Lugaresi, 1978; Wynne et al, 1979; Fleetham et al, 1980; Littner et al, 1980; Guilleminault et al, 1980; Arand et al, 1981; Skatrud et al, 1981) and are associated with hypopnoea (Littner et al, 1980; Arand et al, 1981; Skatrud et al, 1981; Fletcher et al, 1982) and not with apnoea. Indeed both Skatrud and colleagues (1981) and Fletcher and colleagues (1982) have recently shown that ventilation is lower in REM than in non-REM sleep in patients with chronic bronchitis and emphysema, although these measurements were made in small numbers of patients using the Respitrace and thus require confirmation. Guilleminault and colleagues (1980) however found that obstructive apnoeas were common in his

patients with "chronic obstructive airflow disease", but, as the authors point out, the patients had been selected in a sleep disorders clinic and 23 of the 26 patients complained of day-time hypersomnolence. Further, 11 of the patients were grossly overweight ( >100kg) and many did not have significant airways obstruction. Thus the results of this study are not typical of patients with chronic bronchitis and emphysema who present to physicians.

There is some agreement (Arand et al, 1981; Skatrud et al, 1981) with the current finding that hypoventilation in REM sleep is the major cause of desaturation, but many other factors have also been invoked. Worsening of ventilation-perfusion matching has often been suggested (Koo et al, 1975; Leitch et al, 1976; Flick and Block, 1977). As discussed in Chapter 5, the data previously quoted to support ventilation-perfusion imbalance may be explained by unsteady state gas exchange, however it seems likely that REM related hypoventilation per se would have some deleterious effect on ventilation-perfusion matching in these patients who already have gross ventilation-perfusion mis-matching when awake. In a recent abstract, Fletcher and colleagues (1982) claim that ventilation perfusion mis-matching is more important than alveolar hypoventilation in REM-related desaturation. However, there are three major problems

with this study. Firstly the data is highly dependent on steady state as the calculations demand that the arterial and mixed venous blood samples are taken at the same level of alveolar ventilation. This stipulation is not proved and is extremely unlikely to be true as ventilation is continuously varying in REM sleep. Secondly their results are critically dependent on measuring respiratory quotients in blood to a degree of accuracy that has defeated previous workers who have been dealing with steady state situations. Thirdly, if one calculates expected arterial oxygen tension from the ventilation data quoted in the abstract (see Appendix 2) the decrease in ventilation in REM is more than sufficient to account for the decrease in arterial oxygen tension observed ($PaO_2$ expected 35, observed 42 mmHg). Thus I disagree with Fletcher and colleagues' conclusions. Further investigation into the role of ventilation-perfusion mis-matching in REM related hypoxaemia is required. The unsteady state precludes multiple inert gas techniques (Wagner et al, 1974), but I am currently preparing to measure intrapulmonary shunting during sleep in patients with chronic bronchitis and emphysema by infusing a solution of the highly insoluble gas sulphur hexafluoride into a peripheral vein and measuring the quantity reaching the systemic circulation.

Decreased intercostal tone in REM sleep has been blamed for REM related desaturation by causing either

inefficient chest wall expansion (Wynne et al, 1979; Arand et al, 1981) or reduced functional residual capacity (Fleetham et al, 1980). There is no good evidence (see Chapter 13) that intercostal tone is significantly lower in REM sleep than wakefulness in normal adults and EMG studiees have not been performed in sleeping patients with chronic bronchitis and emphysema. Similarly there is conflicting evidence (reviewed in Chapter 4) about the relative contributions of the thorax and abdomen to tidal volume in REM sleep. In adults, most data suggests that the thoracic contribution to tidal volume increases in non-REM sleep compared to wakefulness and decreases once more in REM sleep to a level similar to that in wakefulness. Thus results in normal adults cannot be extrapolated (Wynne et al, 1979; Arand et al, 1981) to explain hypoventilation in patients with chronic bronchitis and emphysema on the grounds of selective impairment of chest wall expansion in REM sleep. Skatrud et al, (1981), however, found that the rib cage contribution to tidal volume fell from 48±12(SE)% whilst awake to 19±10% in phasic REM in patients with chronic bronchitis and emphysema. However, the rib cage contribution in REM was higher than that in wakefulness in 1 of the 3 subjects studied and the data quoted represents only 1-2 minutes of phasic REM sleep in each subject and thus it might have been difficult to avoid sampling bias during the variable breathing of REM sleep.

The suggestion that functional residual capacity (FRC) might be reduced in REM sleep in patients with chronic bronchitis and emphysema is again unproven. In adolescent and young adult normal subjects and patients with cystic fibrosis Muller et al (1980) found that FRC decreased from non-REM to REM sleep, confirming previous findings in neonates (Henderson-Smart & Read, 1979b), but once more comparisons were not made with the awake state and it remains to be seen whether it is REM or non-REM that differs from wakefulness. Further, with increasing age the chest wall becomes less compliant and it is unlikely that a similar FRC reduction would occur in our patients even if intercostal tone decreased. In the current study no drift downwards in stethogram signal was observed in REM sleep, but the short time constant (20 seconds) of the stethogram circuit may have prevented this. In chronic bronchitis and emphysema FRC reduction would result in airway closure and thus greater decreases in oxygen tension would be expected in these patients than in normal subjects, but this did not occur. Thus it seems unlikely that decreasing FRC is a major factor in REM related hypoxaemia.

Littner and colleagues (Littner et al, 1980; Arand et al, 1981) have suggested that upper airways obstruction might be important in episodes of minor desaturation during sleep in patients with chronic bronchitis and emphysema, but in both studies the

patients who had partial upper airways obstruction were overweight and thus this abnormality may have resulted from their obesity (Harman et al, 1981). I analysed all the respiratory traces reported in part 1 of this thesis looking for airways obstruction (defining this as a 50% decrease in the thermocouple signal without a parallel reduction in chest wall movement) and found no episodes of partial airways obstruction in either the normal subjects or in the patients with chronic bronchitis and emphysema, all of whom were of normal body weight. Thus, I do not think that upper airways obstruction is a major factor in sleep desaturation in non-obese patients with chronic bronchitis and emphysema.

Impaired mucociliary clearance (Bateman et al, 1977) and suppressed cough reflexes during sleep (Sullivan et al, 1979b) may play a role in impaired oxygenation during sleep in patients with chronic bronchitis and emphysema. However, the rapid desaturation at REM sleep onset excludes these factors as causes of the major hypoxaemic episodes.

Several papers have been published since 1979 on the consequences of nocturnal desaturation. In an important abstract, Moore-Gillon and Cameron (1982) have shown that short term hypoxia, such as occurs in sleep in "blue bloaters" increased both right ventricular weight and packed cell volume in rats, and in presentation it was shown that red cell mass was also raised. These effects

could be produced by as little as 2 hours of 12% oxygen breathing per 24 hours or by 30 minute episodes of 12% oxygen breathing every hour for 8 hours per day. Although it is hazardous to translate these results to man, they are at least compatable with the earlier hypothesis that REM related desaturation may contribute to the development of secondary polycythaemia and cor pulmonale in "blue and bloated" patients.

Aubert-Tulkens and colleagues (1980) have confirmed the finding of Coccagna et al (1972) - reported in Chapter 5 - that correction of nocturnal hypoxaemia reduces the day-time pulmonary arterial pressure in patients with the sleep apnoea syndrome. Tracheostomy also resulted in improved day-time arterial blood gas tensions and an increase in the hypercapnic ventilatory response. This was a case report and thus requires confirmation, but it raises the possibility that intermittent nocturnal hypoxaemia and hypercapnia may blunt respiratory drive, and perhaps therefore accelerate the development of day-time hypoxia and hypercapnia. Similar acquired attentuation of ventilatory drive has been documented with both prolonged exposure to hypoxia at altitude (Weil et al, 1971) and intermittent hypoxia and hypercapnia in divers (Schaefer, 1965). This therefore is a further mechanism by which nocturnal hypoxaemia might contribute to the clinical deterioration of patients with chronic bronchitis and emphysema.

Tirlapur and Mir (1982) recently confirmed the observation of Flick and Block (1979) that "blue bloaters" have a high rate of ventricular ectopics during the night. However, 2 of Tirlapur and Mir's "blue bloaters" appear to have had the sleep apnoea syndrome, being hypersomnolent with multiple apnoeas and being non-smokers with no evidence of airways obstruction. Although in their summary they claim that oxygen therapy decreased ventricular ectopics, the only reference to this in the results section refers to the decrease in one of two patients, and interestingly there appeared to be no correlation between oxygen saturation and ectopic frequency. I also reserve judgement on the validity of their PR and QT interval findings because the changes they report are very small (0.01 sec) and the quality of the traces appears to have been poor. Further, these intervals were measured manually from 12 complexes recorded at 3.00 am, without EEG monitoring to ensure that the patients were asleep, far less that the "differences" were not sleep stage rather than oxygen related. These workers also claim that ST depression occurred during sleep in 3 patients and was corrected by oxygen therapy. Despite all these claims, I feel that further work is need to clarify whether REM related hypoxaemia produces deleterious effects on the electrocardiographs in hypoxic patients with chronic bronchitis and emphysema.

Several groups have tried to predict which patients will desaturate during sleep. Before clinically useful correlations can be made between desaturation and any other parameter, it is necessary to prove sleep quality was good and certainly to document that REM periods occurred in all patients. Unfortunately, no previous study fulfills these criteria. Fleetham and colleagues (1980) only performed EEGs in 17 of 41 patients, and in these mean sleep time was 250±15(SE) minutes with only 12 patients having any REM sleep. They found a significant correlation between the fall in saturation from awake to lowest saturation when asleep with the awake saturation ($p < 0.05$, r value not given). They also showed that the degree of nocturnal desaturation was significantly correlated ($p < 0.05$, $r = 0.37$) with the hypercapnic drive assessed in terms of mouth occlusion pressure. Although Fleetham states that "awake $SaO_2$ was independent of hypercapnic drive" no p value was quoted and there is some evidence from other studies that waking saturation may be correlated with hypercapnic drive (Flenley et al, 1970; Matthews, 1977). Thus the weak correlation between hypercapnic drive and desaturation might merely reflect the relationship between awake oxygenation and hypercapnic drive. Littner and colleagues (1980) also found an association between hypercapnic drive and desaturation, but sleep quality is not quoted and 3 of the 9 subjects were obese, weighing 200-320lbs and all

being 5'10" or shorter. I do not feel that the poor correlation between $CO_2$ drive and desaturation provides any useful aetiological insight. Further, the relationship described herein between awake oxygen tension and lowest sleeping oxygen tension ($r = 0.81$, $p < 0.001$) is a more clinically useful predictor and also rests on data with confirmed reasonable sleep quality. This relationship which I first described at a meeting of the Thoracic Society in 1980, has the advantage of giving a linear fit, but merely confirms the observations by Trask and Cree (1962) and Koo et al (1975) that patients with the lowest saturations during wakefulness became most hypoxic during sleep. This observation has been subsequently confirmed by other groups (Fleetham et al, 1980; Stradling et al, 1981).

From the relationship betwen awake oxygen tension and the lowest sleeping oxygen tension one would predict that any therapy which improves the awake $Po_2$ would decrease the amount of nocturnal desaturation. This presumably is the mechanism by which progesterone improves oxygenation during sleep in "blue bloaters" (Skatrud et al, 1981). As almitrine is a more potent respiratory stimulant than progesterone, it might be even more effective, and thus we are currently studying the effect of almitrine on nocturnal desaturation in "blue bloaters". Preliminary results indicate that the drug improves nocturnal oxygenation, but at the expense of

increasing the patient's sensation of breathlessness when awake. The value of oxygen therapy in preventing nocturnal desaturation (Douglas et al, 1979) has been confirmed by several other studies (Kearley et al, 1980; Goldstein et al, 1982; Calverley et al, 1982b). The current study illustrates that nocturnal oxygen therapy also improves sleep quality and is thus in my opinion the current treatment of choice for nocturnal hypoxaemia in patients with chronic bronchitis and emphysema. Indeed the publications of the report of the Nocturnal Oxygen Therapy Trial (1980) and the Medical Research Council Working Party Report on long term oxygen therapy (1981) both make the administration of oxygen during the night almost mandatory in non-smoking "blue bloaters".

Lindsay et al (1982) have recently reported that the application of continuous positive airway pressure (CPAP) throughout the night in patients with chronic bronchitis and emphysema prevents nocturnal hypoxaemia. These results are only in abstract, and it is not possible to check the body weight of the patients or whether the patients slept adequately during CPAP. If these results are confirmed they are of patho-physiological as well as therapeutic interest. It is possible that CPAP prevents upper airways collapse, but this appears to account for little of the nocturnal hypoxaemia (see above). CPAP could either increase functional residual capacity, thus improving oxygenation either directly or via increased

body oxygen stores, or alternatively perhaps CPAP influences upper airway receptors (Boushey et al, 1972; Sasaki et al, 1975) promoting ventilation. Either way I feel oxygen therapy is likely to be more generally acceptable to patients during sleep.

An alternative method of reducing nocturnal hypoxaemia would be to reduce the amount of REM sleep, which can be done by drugs including barbiturates, monoamine oxidase inhibitors and amphetamines (Oswald, 1974). The disadvantages of such an approach seem to outweight any advantages as not only do these drugs have significant side effects - including respiratory depression in some cases - but also the body appears to need REM sleep, REM deprivation being followed by a rebound increase in REM sleep (Dement, 1960).

Thus I conclude that the currently available data are consistent with the hypothesis that REM related hypoxaemia found in patients with chronic bronchitis and emphysema is due to hypoventilation. Such REM related hypoventilation is a normal physiological response in adult man and is permitted by a decrease in ventilatory drive. Hypoventilation would be expected to have a minor effect on ventilation-perfusion matching in these patients, but there is no evidence that major changed in ventilation-perfusion matching occur. Impaired chest wall mechanics and FRC reduction may play a role, but this is unproven, and upper airways obstruction might

contribute to minor hypoxaemic episodes, especially in obese patients.

As the drop in oxygen tension in patients with chronic bronchitis and emphysema is similar to that in normal subjects, the patients who are hypoxic when awake develop very low oxygen tensions during sleep. This REM related hypoxaemia probably contributes to the development of pulmonary hypertension and secondary polycythaemia and may perhaps result in cardiac arrhythmias and death. Nocturnal oxygen therapy is the current treatment of choice.

# APPENDIX 1

## Sleep Deprivation

Having found that ventilatory drive decreased during sleep I wondered whether ventilatory drive might also be reduced in the "half asleep" state which follows sleep deprivation. Some support for this hypothesis came from the observation by Guilleminault (1980) that overnight sleep deprivation increased both the frequency and duration of apnoeas in patients with the sleep apnoea syndrome.

## Methods

Nine healthy male subjects aged 28-40 years were studied. Before and after 24 hours of sleep deprivation 2 measurements were made of isocapnic hypoxic ventilatory response and 1 of the rebreathing $CO_2$ response. All measurements were made breathing on a mouthpiece, and the techniques used have been described earlier in this thesis. Measurements before and after sleep deprivation were made at the same time of day. All subjects fasted and abstained from caffeine for at least 6 hours prior to the study and all measurements were made with the subjects seated and watching television and having rested for at least 30 minutes prior to the studies.

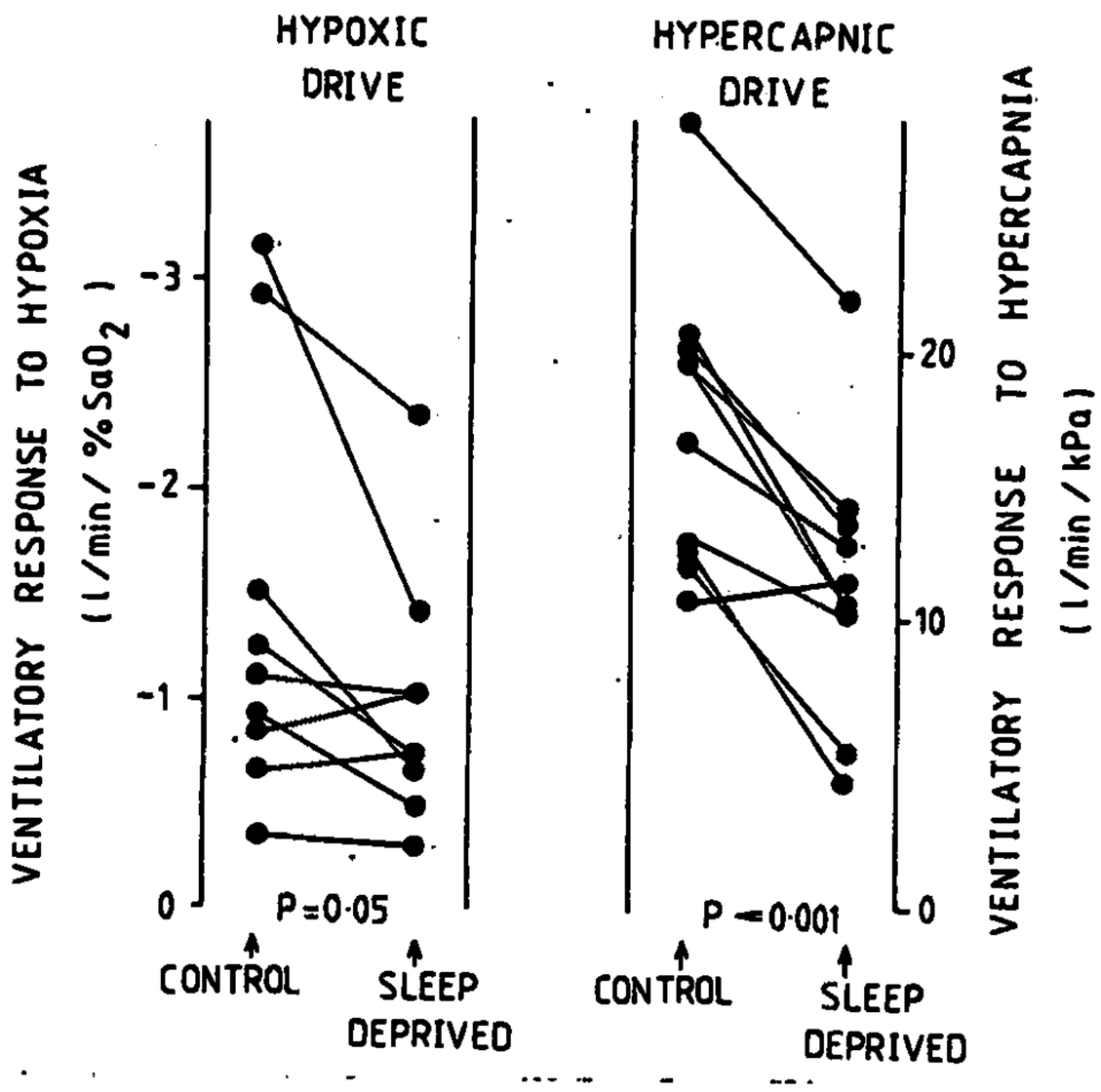



Fig 34 Hypoxic (left panel) and hypercapnic (right). ventilatory responses before and after overnight sleep deprivation in 9 subjects, indicating the significance of the changes observed.

The subjects were deprived of sleep for 24 hours by being kept mentally active throughout the night under the direct supervision of either myself or one of my colleagues. If the subject showed any signs of becoming drowsy, they were alerted. EEGs were not recorded during sleep deprivation but I am sure that none of the subjects had any true sleep. Because I was concerned that the subjects might fall asleep during the ventilatory responses performed after sleep deprivation, these measurements were made during EEG confirmed wakefulness.

## RESULTS

The ventilatory response to hypoxia fell after sleep deprivation in 7 of the 9 subjects, the mean decrease being from 1.42±0.32 to 0.96±0.20 l/min/%$SaO_2$ ($p = 0.05$, Fig 34). The hypercapnic ventilatory response was lower after sleep deprivation in 8 of the 9 subjects, the mean decrease being from 17.6±1.9 to 12.0±1.5 l/min/kPa ($p < 0.001$).

## DISCUSSION

Both the hypoxic and the hypercapnic ventilatory responses decrease by one third following overnight sleep deprivation in normal man. Since this study was completed, Cooper et al (1981) have reported in an abstract that the hypercapnic drive falls after sleep deprivation both in normal subjects and in patients with chronic bronchitis and emphysema.

The mechanism for the decreased drive following sleep deprivation is unclear. I started these studies only 3 weeks before leaving Denver and report above the studies I performed in that time. Since my departure these studies have been confirmed and extended. My colleagues have been unable to increase the post-sleep deprivation ventilatory response with naloxone (2mg i.v.) and thus endorphins appear unlikely to be involved. Also no reduction in basal metabolic rate could be found to account for the changes in drive. Thus no clear cause has been found.

The EEG following 24 hours of sleep deprivation is abnormal with intermittent slow waves and decreased alpha activity (Rodin et al, 1962; Horne, 1978) despite satisfying Rechtschaffen and Kales' criteria (1968) for wakefulness. Thus, I think that the same central factors which decrease ventilatory drive during sleep probably cause the decreased ventilatory responses following sleep deprivation. It is probable that this results from impaired function of the reticular activating system, perhaps as a direct results of factor S, the sleep promoting substance which accumulates in cerebro-spinal fluid during sleep deprivation - at least in goats (Pappenheimer, 1982).

As sleep is believed to allow tissue restoration (Oswald, 1976; Adam & Oswald, 1977), sleep deprivation might impair respiratory muscle function. Vondra and

colleagues (1981) found decreased enzymatic activity in skeletal muscle after 120 hours of sleep deprivation, but the changes were small and are unlikely to account for a significant decrease in ventilatory response after only 24 hours' sleep deprivation. Further, our subjects reported being less breathless during ventilatory responses when sleep deprived. Hence I feel it is unlikely that the decreased ventilatory response was due to impaired respiratory muscle function.

Whatever the cause, the decrease in ventilatory response after sleep deprivation is important. Firstly, many studies comparing respiration during wakefulness and sleep were performed following sleep deprivation and their results (Ostergaard, 1944; Mills, 1953; Mangold, 1955; Birchfield et al, 1959; Gothe et al, 1981 & 1982) must be interpreted with caution. Secondly, patients with asthma or chronic bronchitis and emphysema are often kept awake during exacerbations of their disease. This is especially a problem in asthma which is often worse at night (Clark & Hetzel, 1977). Thus this sleeplessness may, along with intrapulmonary factors and muscle fatigue, contribute to the deterioration of such patients during prolonged exacerbations of their disease. Thirdly, the study suggests that attention should be given to ensuring adequate sleep quality for patients in intensive care, who tend to be disturbed frequently while observations are made. This perhaps should be especially

true prior to weaning patients from mechanical ventilators. Fourthly, the impaired ventilatory response might be related to the increase in frequency and duration of apnoeas in patients with the sleep apnoea syndrome after sleep deprivation (Guilleminault, 1980).

# APPENDIX 2

## CALCULATION OF HYPOXAEMIA RESULTING FROM HYPOVENTILATION

The alveolar oxygen tension resulting from a given alveolar ventilation under steady state conditions can be calculated from the formula quoted by Otis (1964):

$$P_AO_2 = P_IO_2 - (P_B - 47)\ \frac{\dot{V}O_2}{\dot{V}_A} + P_IO_2\ (1 - R)\ \frac{\dot{V}O_2}{\dot{V}_A}$$

where $P_AO_2$ = Alveolar oxygen tension
$P_IO_2$ = Inspired oxygen tension
$P_B$ = Barometric pressure
$\dot{V}O_2$ = Oxygen uptake
$\dot{V}_A$ = Alveolar ventilation
R = Respiratory quotient

As breathing air $P_IO_2 = \frac{P_B - 47}{5}$

Thus $\frac{P_AO_2}{P_IO_2} = 1 - 5\ \frac{(\dot{V}O_2)}{(\dot{V}_A)} + (1 - R)\ \frac{\dot{V}O_2}{\dot{V}_A}$

Thus $\frac{P_IO_2 - P_AO_2}{P_IO_2} = (4 + R)\ \frac{\dot{V}O_2}{\dot{V}_A}$ equation (1)

As a first order approximation 4 + R is a constant. Bulow (1963) showed that R was not changed in non-REM sleep. R is not directly applicable to the unsteady state of REM, but if one extrapolates to the steady state which would occur if the mean level of ventilation found in REM was invariable, then 4 + R is likely be little changed in REM from wakefulness. Thus using $_S$ to denote sleep and $_W$ to denote wakefulness, equation (1) becomes:

$$\frac{P_IO_2 - P_AO_{2S}}{P_IO_2} = \frac{\dot{V}O_{2S}}{\dot{V}_{AS}} \quad (4 + R) \qquad \text{equation (2)}$$

and

$$\frac{P_IO_2 - P_AO_{2W}}{P_IO_2} = \frac{\dot{V}O_{2W}}{\dot{V}_{AW}} \quad (4 + R) \qquad \text{equation (3)}$$

Dividing equation (2) by equation (3) and inspiring the same gas in wakefulness and sleep, then:

$$\frac{P_IO_2 - P_AO_{2S}}{P_IO_2} = \frac{r_1}{r_2} \left(\frac{P_IO_2 - P_AO_{2W}}{P_IO_2}\right)$$

where $r_1 = \frac{\dot{V}O_{2S}}{\dot{V}O_{2W}}$

and $r_2 = \frac{\dot{V}_{AS}}{\dot{V}_{AW}}$

Thus $P_AO_{2S} = \frac{r_1}{r_2} P_AO_{2W} - P_IO_2 \left(\frac{r_1}{r_2} - 1\right)$ equation (4)

During sleep $r_1 \simeq 0.9$ (Benedict & Carpenter, 1910; Brebbia & Altshuler, 1965; Goll & Shapiro, 1981)

NORMAL SUBJECTS

Applying this equation to normal subjects at sea level with a $P_AO_2$ awake of 13 kPa, and assuming the 39% mean decrease in $\dot{V}_A$ during REM sleep found in Chapter 8, then

$$P_AO_2 \text{ REM} = \frac{0.9}{0.61} (13) - 18.9 \left(\frac{0.9}{0.61} - 1\right) \text{ kPa}$$

$$= 10.2 \text{ kPa}$$

Thus the mean drop in $P_AO_2$ from wakefulness to REM sleep

$$= 13 - 10.2 \text{ kPa} = 2.8 \text{ kPa}$$

## PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

If equation (4) is applied to the data of Fletcher et al (1982) and one assumes:

1) that the $P_AO_2$ Fletcher derived is correct and thus

$$\text{mean } P_AO_2 \text{ awake} = \frac{(9 \times 87) + (5 \times 73)}{14} \text{ mmHg}$$

$$= 82 \text{ mmHg}$$

2) that $V_A$ decreases by 27%, in parallel with $\dot{V}_E$

$$\text{Then } P_AO_2 \text{ anticipated asleep} = \frac{0.9}{0.73}\left(82 - 142\left(\frac{0.9}{0.73} - 1\right)\right) \text{mmHg}$$

$$= 67 \text{ mmHg}$$

Mean awake alveolar arterial oxygen gradient

$$(A\text{-}adO_2) = 82 - 50$$

$$= 32 \text{ mmHg}$$

Thus if $A\text{-}adO_2$ is unchanged in sleep, the predicted lowest $P_aO_2$ asleep

$$= 67 - 32 \text{ mmHg}$$

$$= 35 \text{ mmHg}$$

The observed $P_aO_2$ was 42 mmHg. Thus it is not necessary to postulate an increase in alveolar-arterial oxygen gradient and the observed hypoxaemia can be accounted for by hypoventilation.

# PUBLICATIONS

The following publications include work described in this thesis.

1. Douglas NJ, Brash HM, Wraith PK, Calverley PMA, Leggett RJE, Flenley DC.
Accuracy, sensitivity to carboxyhemoglobin and speed of response of the Hewlett Packard 47201A ear oximeter.
Am Rev Respir Dis .1979;119:311-313

2. Douglas NJ, Calverley PMA, Leggett RJE, Brash HM, Flenley DC, Brezinova V.
Transient hypoxaemia during sleep in chronic bronchitis and emphysema.
Lancet 1979;i:1-4

3. Douglas NJ, White DP, Weil JV, Pickett CK, Martin RJ, Hudgel DW, Zwillich CW.
Hypoxic ventilatory response decreases during sleep in normal man.
Am Rev Respir Dis 1982;125:286-289

4. Calverley PMA, Brezinova V, Douglas NJ, Catterall JR, Flenley DC.
The effect of oxygenation on sleep quality in chronic brochitis and emphysema.
Am Rev Respir Dis 1982;126:206-210

5. White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW.
Hypoxic ventilatory response during sleep in normal women.
Am Rev Respir Dis (in press)

6. Douglas NJ, White DP, Weil JV, Pickett CK, Zwillich CW.
Hypercapnic ventilatory response in sleeping adults.
Am Rev Respir Dis (in press)

7. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW.
Respiration during sleep in normal man.
Thorax (in press)

8. Douglas NJ, White DP, Weil JV, Zwillich CW.
Effects of breathing route on ventilation and ventilatory drive.
Respir Physiol (in press)

9. Douglas NJ, White DP, Weil JV, Pickett CK, Zwillich CW.
Overnight sleep deprivation decreases ventilatory drive.
Thorax (Abstract in press)

## FORMAL DECLARATION

I declare that I have written this dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine. All the studies reported in this thesis were performed by research groups of which I was a member. My own contributions included analysing and interpreting all the data in this thesis, with the exception of the EEG sleep staging. I performed the majority of the studies reported in each Chapter of the thesis. I initiated all of the studies reported in Part 11 of the thesis and many of those reported in Part 1. Those I did not initiate on my own were:-

a) The evaluation of the Hewlett Packard ear oximeter (Publication 1. above) which was jointly initiated by myself and Professor D C Flenley.

b) The study of oxygenation during sleep in patients with chronic bronchitis and emphysema (Publication 2.) which was initiated by Professor Flenley. I designed the study of age-matched patients and controls reported herein and developed and applied the analytical techniques used.

c) In conjunction with Dr Brezinova, I initiated the trial of oxygen therapy on sleep quality in "blue bloaters". This is the only part of Publication 4 used in this thesis.

W. S. Douglas

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I am gratèful to all the physicians, nurses, physicists, technicians, statisticians, volunteers and patients who have helped in the research reported in this thesis: the names of the major collaborators are included on the list of publications. I particularly thank: Professor D C Flenley for stimulating my interest in this field of research and for guiding the studies in the first part of the thesis, Dr J V Weil for supervising the investigations in part two of the thesis, and Drs V Brezinova and C M Shapiro and Ms C K Pickett for staging the electro-encephalograms.

I also thank medical artists in both Edinburgh and Denver for drawing the figures and Ms M Newlands for cheerfully typing the thesis.

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# Notes

## ACCURACY, SENSITIVITY TO CARBOXYHEMOGLOBIN, AND SPEED OF RESPONSE OF THE HEWLETT-PACKARD 47201A EAR OXIMETER[1]


**Summary**

We have shown that the Hewlett-Packard 47201A ear oximeter measures arterial $O_2$ saturation within 95 per cent confidence limits of ±4 per cent when arterial blood saturation is more than 65 per cent, but at lower saturations the oximeter consistently provides a reading that is too low. The oximeter is sensitive to carboxyhemoglobin, progressively overestimating arterial saturation as carboxyhemoglobin concentration increases from 0 to 18 per cent. The time response is exponential, with a normal time constant of 3 sec, but this is halved in the fast mode of operation.


Ear oximetry offers an attractive noninvasive method for monitoring arterial oxygenation, and the recent descriptions of the Hewlett-Packard 47201A ear oximeter have suggested that previous problems of instability and insensitivity in such instruments have now been overcome (1–4). We describe the time response, sensitivity to carboxyhemoglobin (COHb), and accuracy of this instrument over a wider range of saturation values than has previously been reported.

We compared the saturation measured by the ear oximeter *in vivo* with that measured in simultaneously sampled arterial blood on 465 occasions. Measurements were made with the oximeter in the "normal" operational mode, and were only included in this comparison if the oximeter readings did not change by more than 1 per cent during the period of 30 sec to one min in which the arterial blood sample was drawn. Samples were taken by direct brachial or radial arterial puncture, after infiltration of lidocaine hydrochloride (Lignocaine®) around the vessel. Samples were also taken as part of studies of arterial oxygenation during sleep, and these samples were taken from an indwelling brachial arterial catheter during 30 sec.

Samples were taken from both normal subjects and patients with chronic bronchitis and emphysema with varying degrees of hypoxemia, both when awake and during sleep. Arterial blood saturation ($Sa_{O_2}$) and concentrations of COHb were measured in an Instrumentation Laboratory co-oximeter 182 in 391 samples, and in the other 74, $Sa_{O_2}$ was calculated from measurements of $Po_2$ and pH (Instrumentation Laboratory 313 blood gas system) using the patient's directly determined $Po_2$ at which the blood is 50 per cent saturated ($P_{50}$), which was measured within 24 hours of taking the sample (5). Using this equipment, the coefficient of variation (6) in 21 replicate estimates on the same blood sample was 2.95 per cent for $Po_2$, 0.98 per cent for $Pco_2$, 5.36 per cent for $Sa_{O_2}$ (co-oximeter), and 7.39 per cent for COHb (co-oximeter).

The time response of the oximeter was measured *in vitro* with a solenoid-activated cuvette system, one chamber of which contained blood with $Sa_{O_2}$ of 96 per cent, and the other, blood with $Sa_{O_2}$ of 83 per cent. The chamber containing blood with 96 per cent $Sa_{O_2}$, lying in the "ear" position of the cuvette, was suddenly moved so that the chamber containing blood with 83 per cent $Sa_{O_2}$ lay in this position, zero time for this movement being recorded by a microswitch at the completion of the movement. The duration of the movement was 26 msec. Measurements were made using both the "fast" and "normal" modes of operation, after change of the internal jumper lead of the instrument, as described in the manufacturer's handbook. The results were analyzed on-line by a PDP 11/40 computer.

The oximeter reading was a linear function of $Sa_{O_2}$ for values greater than 65 per cent. The linear regression equation (6): oximeter reading $= 0.92 \pm 0.02$ (±SE) $Sa_{O_2} + 7.44 \pm 1.35$ (±SE), $n = 437$, $r = 0.94$, $P \ll 0.001$, describes the relationship, with 95 per cent confidence limits ± 5 per cent of $Sa_{O_2}$ for values of $Sa_{O_2} > 65$ per cent (figure 1). In these samples, COHb varied between 0.3 and 18.1 per cent. When $Sa_{O_2}$ was less than 65 per cent, the instrument gave readings that were progressively lower than the $Sa_{O_2}$ (figure 1), so that when the true $Sa_{O_2}$ was 40 per cent, the instrument indicated a value of approximately 20 per cent. These samples of low $Sa_{O_2}$ values were obtained from patients during hypoxemic episodes in sleep, these episodes lasting for more than 5 minutes (7). If the relationship between the oximeter reading and measured $Sa_{O_2}$ was considered only for blood samples with COHb values of less than 3 per cent (figure 2a), the equation was: oxi-


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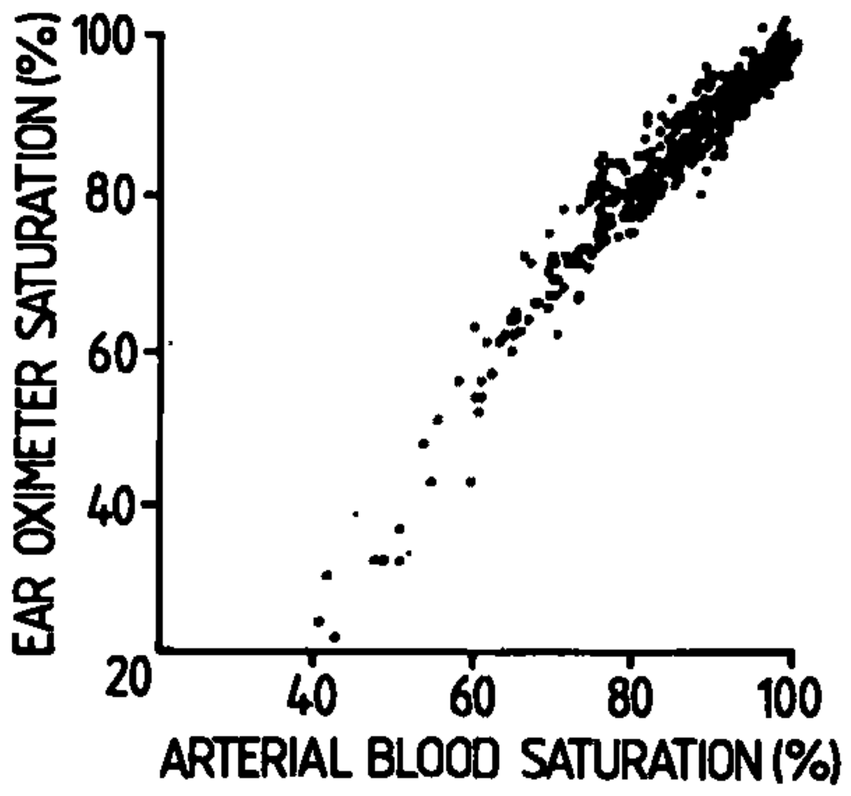


Fig. 1. Comparison of hemoglobin saturation measured by the ear oximeter with that obtained from simultaneously sampled arterial blood in 465 samples.

meter reading $= 0.999 \pm 0.016$ $Sa_{O_2} - 0.814 \pm 1.397$ with 95 per cent confidence limits of $\pm$ 4 per cent, $n = 201$, $r = 0.977$, $P \ll 0.001$.

Direct comparison of the readings in 201 samples with COHb values of less than 3 per cent with the results in 42 samples with COHb values of more than 9 per cent (figure 2b) showed that the oximeter had an average reading approximately 7 per cent higher when COHb was more than 9 per cent, but this response was again linear for $Sa_{O_2}$ values of 65 to 100 per cent. Multiple regression analysis of the 375 points with known COHb and $Sa_{O_2}$ values greater than 65 per cent gives the equation: oximeter reading $= 0.987 \pm 0.005$ $Sa_{O_2} + 0.628 \pm 0.038$ COHb $-$ 1.465. This equation accounts for 93 per cent of the variance in $y$ (the ear oximeter reading), which is significantly more than the value of 83 per cent ($F = 2.42$, $P < 0.05$), with the equation relating the ear oximeter reading with $Sa_{O_2}$ alone, in the same samples.

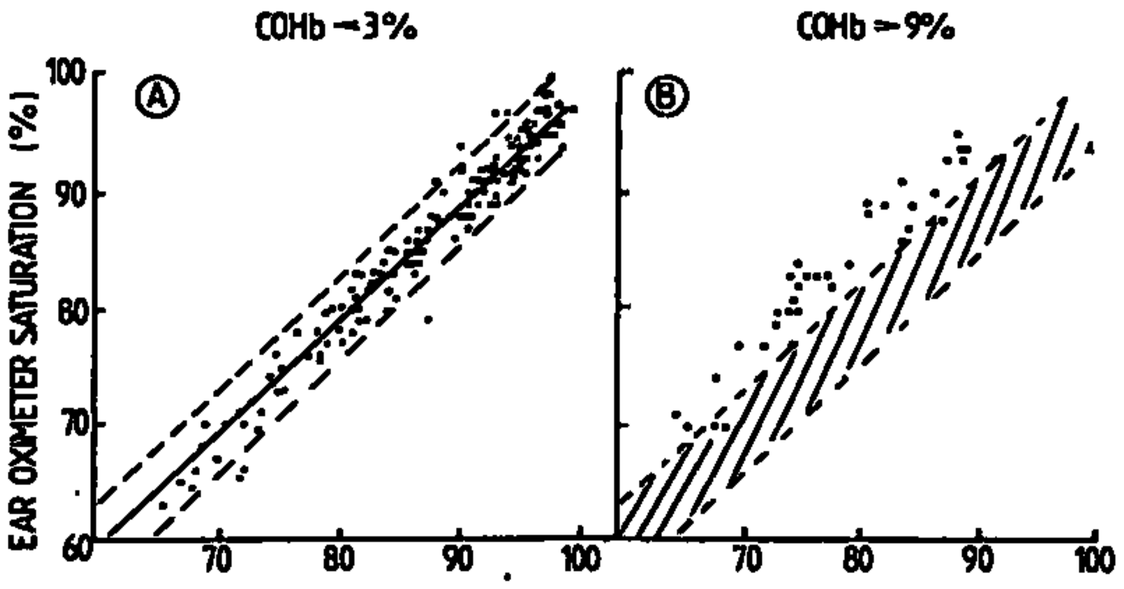


Fig. 2. Comparison of ear oximeter with measured arterial saturation for (*A*) 201 samples with carboxyhemoglobin (COHb) values of less than 3 per cent where oximeter reading $= 0.999 \pm 0.016$ $Sa_{O_2} - 0.814$ ($\pm$ 1.397); $r = 0.977$, $P << 0.001$. (*B*) 42 samples with carboxyhemoglobin (COHb) values of more than 9 per cent where oximeter reading $= 0.961 \pm 0.043$ $Sa_{O_2} + 8.450$ $\pm$ 3.422, $r = 0.962$, $P << 0.001$. The shaded area represents the 95 per cent confidence limits for COHb values of less than 3 per cent.

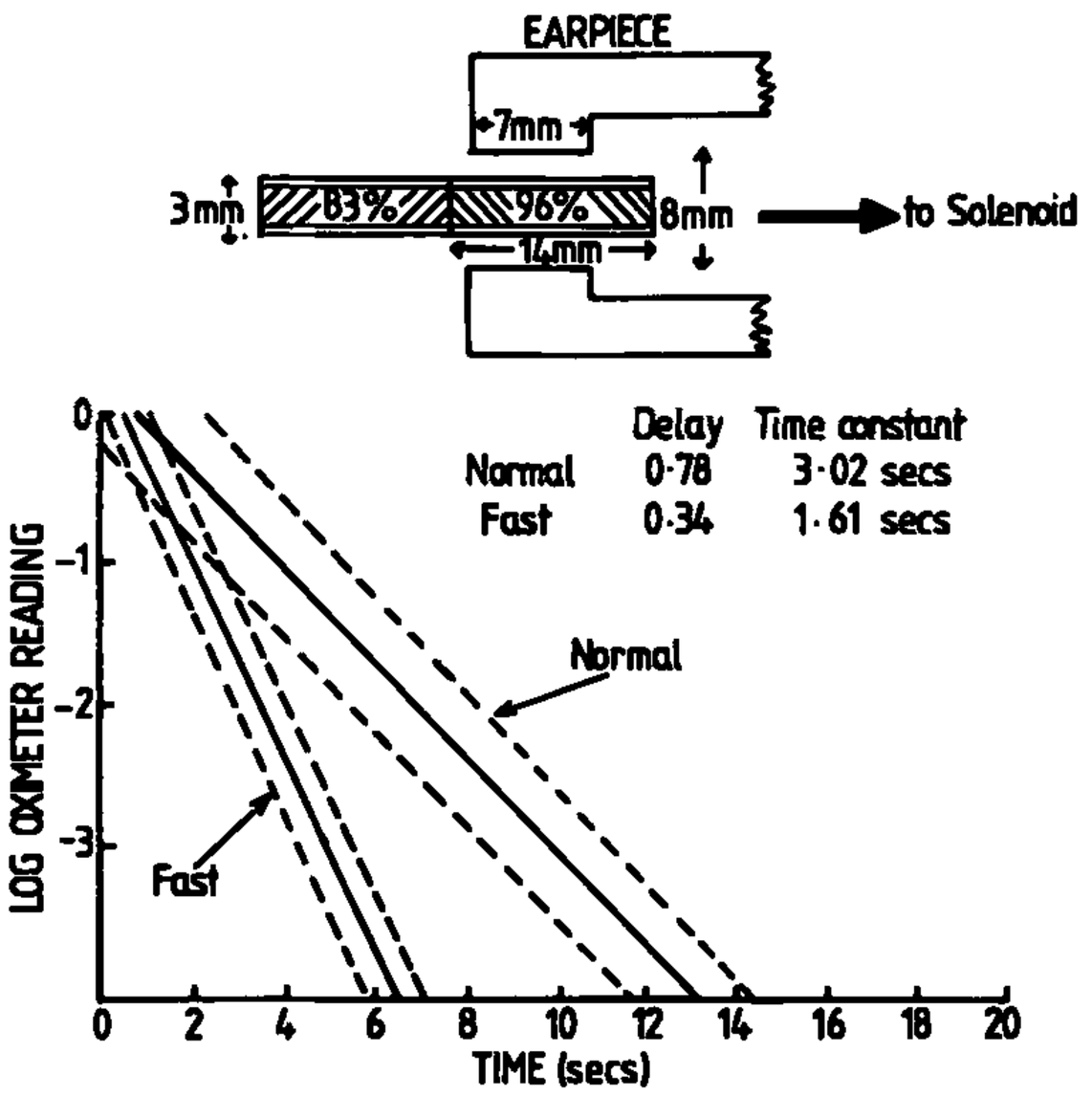


Fig. 3. Schematic diagram of the equipment used to assess time response (*above*). Comparison of the logarithm of the digital output of the oximeter plotted against time for the "fast" and "normal" modes of operation, showing the mean (_____) and 95 per cent confidence limits ( - - - - ).

The time response to the change in saturation *in vitro* was exponential (figure 3), with a time constant of 3.02 sec after an initial delay of 0.78 seconds in the "normal" operation mode, but this was decreased to a time constant of 1.61 sec in the "fast" mode with a decrease in the initial delay to 0.34 sec.

* * *

Our results show that the Hewlett-Packard 47201A ear oximeter can measure $Sa_{O_2}$ in the range of 65 to 100 per cent with an accuracy of $\pm$ 4 per cent (95 per cent confidence limits), if the concentration of COHb is less than 3 per cent. This accuracy is slightly better than that which we have derived from comparable measurements by other investigators (1), which did not take the COHb concentration into account. However, the response was not linear for saturation of less than 65 per cent, with a progressive tendency for the oximeter readings to be lower than the true reading as $Sa_{O_2}$ decreased. Although $Sa_{O_2}$ values less than this are unlikely to be encountered often in clinical practice, such small values have recently been found during transient hypoxemia in sleep, particularly in patients with chronic bronchitis and emphysema (3, 7, 8). This progressive error in readings at these low saturations is therefore important.

COHb must now be added to bilirubin and indocyanine green dye as a coloring substance in the blood that may affect the reading (2). Again, this is important when studying patients with chronic bronchitis and emphysema, many of whom are heavy cigarette smokers. In our experience, COHb concentrations greater than 9 per cent are not un-

common, although on first inquiry such patients may deny that they are smokers.

The noninstantaneous response of the oximeter appears to occur with the use of a microprocessor to solve a series of simultaneous equations describing absorbance at 8 separate wave bands, which are measured repetitively in sequence. The digital and analog outputs are also processed further, resulting in the over-all response shown in figure 3. The smoothed output signal obtained in the "normal" mode of operation appears adequate for most clinical use. However, for studies involving rapid changes in $Sa_{O_2}$, the "fast" mode of operation may be preferable, but it is then important to know the initial delay and time constant of the instrument, which we describe. Because the response is exponential, it may be possible to deconvolute a monophasic response to transient changes in $Sa_{O_2}$ to estimate the true time course of such changes.

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# TRANSIENT HYPOXÆMIA DURING SLEEP IN CHRONIC BRONCHITIS AND EMPHYSEMA

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***Summary*** **Arterial oxygenation, breathing pattern, and electroencephalogram were studied during sleep in patients with chronic bronchitis and emphysema and in healthy subjects. All of the 10 "blue and bloated" patients had episodes of transient hypoxæmia lasting 1–100 min, when their oxygen saturation fell by more than 10%, whereas such desaturation did not occur in 2 "pink and puffing" patients or in 4 healthy subjects. Hypoxæmic episodes usually occurred during the rapid-eye-movement stage of sleep. It is suggested that these hypoxæmic episodes result from a combination of hypoventilation and impaired ventilation/perfusion relationships and that these episodes may contribute to the development of the pulmonary hypertension and secondary polycythæmia which characterises "blue and bloated" patients.**

## Introduction

IN 1955, Dornhorst[1] distinguished two clinical patterns in patients with chronic bronchitis and emphysema. The "blue and bloated" (type B,[2] non-fighters[3]) have hypoxæmia, $CO_2$ retention, secondary polycythæmia and pulmonary hypertension, along with cor pulmonale; whereas the "pink and puffing" (type A, fighters) have relatively normal blood-gas tensions, despite severe breathlessness, and they have neither pulmonary hypertension nor polycythæmia. Many patients have some features of both, but the reasons for these two clinical presentations remain unknown, since earlier suggestions that "pink puffers" had mainly emphysema

and "blue bloaters" only bronchitis have not been substantiated.[4]

Acute hypoxæmia causes pulmonary vasoconstriction,[5] and when the hypoxæmia persists, secondary polycythæmia often also develops. Evidence is accumulating that both these adaptations to hypoxia can be reversed in "blue and bloated" patients by long-term oxygen therapy.[6 7] Nonetheless, the relationship between the arterial oxygen saturation and either the mean pulmonary arterial pressure or the red-cell mass in such patients is not very close,[8–10] suggesting that some factor other than daytime hypoxæmia may contribute to these physiological responses.

We have therefore put forward the hypothesis[8] that the recurrent transient hypoxæmia during sleep which has been found in the majority of a heterogeneous group of bronchitic patients[11] may in time lead to the sustained pulmonary hypertension and polycythæmia which characterises these "blue and bloated" patients. We also suggest that such transient sleep hypoxæmia may not occur as often, if at all, in those who develop the "pink and puffing" pattern. This idea stems from the rapidly expanding interest in breathing during sleep, with recognition of the clinical syndromes associated with sleep apnœa,[12] when breathing temporarily stops for a few seconds during sleep. Intermittent sampling of arterial blood during sleep has shown that minor falls in $P_{O_2}$ with a rise in $P_{CO_2}$ can occur in normal subjects[13 14] and also that pre-existing hypoxæmia can become more severe during sleep in patients with chronic bronchitis and emphysema.[15–17] To test our hypothesis, we have continuously monitored the arterial oxygen saturation and other related variables, as well as the electroencephalogram (E.E.G.), during sleep in healthy subjects and in "pink and puffing" and "blue and bloated" patients with chronic bronchitis and emphysema.

## Methods

Respiration and arterial oxygenation were monitored during sleep in 4 healthy subjects and in 12 patients with chronic bronchitis and emphysema (see table).

In 6 patients with pulmonary hypertension and polycythæmia (patients 1–6), studies were carried out on three consecutive nights, while the patients slept in a quiet darkened room. Ear-oxygen saturation was recorded continuously (Hewlett Packard 47201A ear oximeter). In patients 1–3, gas-flow at the mouth and nostrils was recorded by thermocouples mounted on nasal prongs and anteroposterior thoracic movements were recorded by induction stethogram. In all 6 patients simul-

taneous recordings were made of E.E.G. (by two mid-line frontoparietal electrodes), electro-oculogram (by four electrodes outside and above the outer canthi), and electromyogram (by two sub-mental electrodes). The first night familiarised the patient with sleeping with the equipment attached. On the second and third nights the patients slept breathing either air or oxygen at 2 litres/min through the nasal prongs, in a randomised single-blind study. A catheter had previously been inserted into the brachial artery as part of an assessment for the Medical Research Council trial of long-term oxygen therapy, and on the second and third nights arterial-blood samples were withdrawn before the patients fell asleep, at 2-hourly intervals during sleep, when hypoxæmic episodes were indicated by the ear oximeter, and finally 30 min after waking. In patients 2 and 3 a pulmonary-arterial catheter had also been previously inserted as part of the M.R.C. trial, and this remained in situ during the second and third nights of the study, pulmonary-arterial pressure being measured with a Statham pressure transducer.

On one night only, ear-oxygen saturation, respiratory movements, and E.E.G. were monitored in 4 healthy subjects (subjects 13–16), 2 "pink and puffing" patients with chronic bronchitis and emphysema (patients 11 and 12), and 4 "blue and bloated" patients with chronic bronchitis and emphysema (patients 7–10).

All physiological variables were recorded on tape (Bell and Howell VR 3360) for subsequent off-line analysis. The E.E.G. was analysed with standard criteria.[18] Each patient gave informed consent to the study, which was approved by the hospital ethical committee. No patient had had an exacerbation of chronic bronchitis for 6 weeks before the studies, none was receiving hypnotic, sedative, or stimulant drugs, and none was more than 20% above his desired weight.[19]

## Results

All 4 healthy subjects and the 2 "pink and puffing" chronic bronchitic patients had constant high levels of oxygenation and regular breathing patterns throughout the night (fig. 1). In contrast, transient hypoxæmic episodes occurred in all 10 "blue and bloated" patients during sleep, one example being shown in fig. 1. We have defined a transient hypoxæmic episode—or dip—as a drop in the oximeter reading of more than 10% from the immediately preceding stable base-line recorded during sleep, such a drop lasting more than 1 min. During the 15 nights when "blue and bloated" patients were studied, we observed 36 such hypoxæmic episodes lasting on average 30 min (range 2–100 min) with a mean drop in oximeter reading of 35% (range 10–77%). On average, 3 episodes occurred during the night in each patient

when they breathed air, the maximum drop in oxygen saturation on average then being from 81 to 38% (see table), with the oximeter reading dropping to below 50% in 7, to below 30% in 3, and to below 10% in 2 patients. We find from simultaneous measurements on arterial blood that this oximeter reads too low below 65% saturation.[20] The lowest arterial $Po_2$ measured directly in these patients varied from 3·5 to 5·9 kPa (26–44 mm Hg) (see table), but these samples were not always drawn exactly at the time of the lowest oximeter reading. 5 of these patients also slept while breathing 2 litres/min of oxygen, with the expected increase in arterial oxygen saturation: transient falls in saturation still occurred, although to a less profound level (fig. 2, table).

In the 6 "blue and bloated" patients in whom the E.E.G. was recorded, a total of 29 hypoxæmic episodes occurred in the 11 nights. 1 such episode being when the patient was awake and micturating (patient 5, oxygen

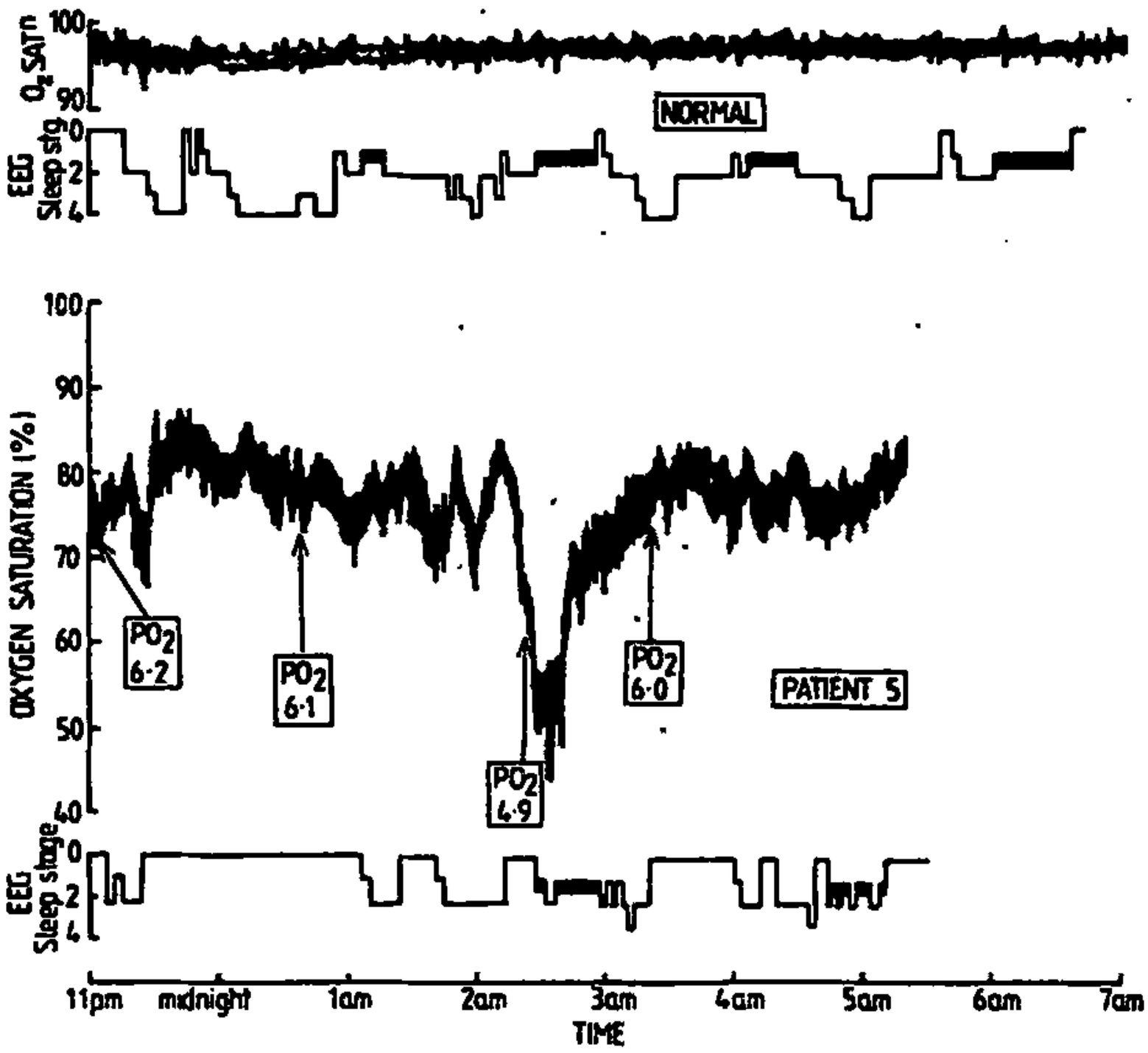


**Fig. 1—Oxygen saturation (ear oximeter) and E.E.G. sleep stage (1–4) throughout the night in a healthy subject (subject 14 above) and in a "blue bloater" (patient 5, below).**

Arrows indicate directly measured arterial $Po_2$ values (1 kPa=7·5 mm Hg). Black areas on the E.E.G. record of sleep stage are R.E.M. periods.

LUNG FUNCTION, BLOOD-GAS TENSIONS, AND OCCURRENCE OF HYPOXAEMIC EPISODES IN PATIENTS WITH BRONCHITIS AND EMPHYSEMA AND IN HEALTHY CONTROLS

| Subject no. | Age (yr) | Sex | F.E.V.$_1$ (l) | F.V.C. (l) | Red cell mass (ml/kg) | $\overline{P.A.P}$ (mm Hg) | When awake | | | | | At lowest $Po_2$ when asleep | | | | | | | | No of dips | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Air | | | | $O_2$ | Air | | | | $O_2$ | | | | | |
| | | | | | | | $Po_2$ (kPa) | $Pco_2$ (kPa) | $H^+$ (nmol/l) | $SaO_2$ (%) | $SaO_2$ (%) | $Po_2$ (kPa) | $Pco_2$ (kPa) | $H^+$ (nmol/l) | Lowest $SaO_2$ (%) | $Po_2$ (kPa) | $Pco_2$ (kPa) | $H^+$ (nmol/l) | Lowest $SaO_2$ (%) | Air | $O_2$ |
| ***Blue and bloated patients*** | | | | | | | | | | | | | | | | | | | | | |
| 1 | 58 | F | 0·5 | 1·0 | 33 | 31 | 6·7 | 7·1 | 43 | 85 | 98 | 3·5 | 8·5 | 52 | 15 | 6·4 | 10·4 | 55 | 61 | 7 | 4 |
| 2 | 68 | M | 0·5 | 1·5 | 43 | 29 | 7·0 | 7·0 | 42 | 89 | 97 | 5·9 | 7·9 | 45 | 74 | 9·5 | 6·5 | 36 | 92 | 2 | 0 |
| 3 | 62 | F | 0·6 | 1·2 | 57 | 35 | 5·6 | 7·1 | 45 | 77 | 93 | 3·5 | 7·1 | 46 | 0 | 5·6 | 8·0 | 53 | 50 | 5 | 3 |
| 4 | 58 | F | 0·4 | 1·2 | 40 | 46 | 5·6 | 8·4 | 39 | 80 | 97 | 4·8 | 8·1 | 39 | 48 | 8·7 | 8·3 | 45 | 84 | 4 | 1 |
| 5 | 58 | F | 0·5 | 1·5 | 44 | 30 | 7·7 | 6·3 | 35 | 82 | 99 | 4·9 | 7·9 | 48 | 39 | 6·4 | 7·7 | 47 | 77 | 1 | 1 |
| 6 | 61 | M | 0·5 | 3·3 | 43 | 25 | 4·5 | 7·6 | 45 | 70 | .. | 3·6 | 8·0 | 47 | 37 | .. | .. | .. | .. | 1 | .. |
| 7 | 50 | F | 0·3 | 0·9 | 42 | 50 | 4·7 | 10·5 | 39 | .. | 93 | .. | .. | .. | .. | .. | .. | .. | 36 | .. | 2 |
| 8 | 46 | M | 0·6 | 1·7 | 59 | 46 | 6·3 | 7·2 | 41 | 90 | .. | .. | .. | .. | 79 | .. | .. | .. | .. | 1 | .. |
| 9 | 61 | M | 0·5 | 1·7 | 42 | 48 | 5·5 | 7·1 | 44 | 70 | .. | .. | .. | .. | 9 | .. | .. | .. | .. | 1 | .. |
| 10 | 52 | M | 0·9 | 1·8 | 55 | .. | 6·5 | 6·1 | 44 | 87 | .. | .. | .. | .. | 36 | .. | .. | .. | .. | 3 | .. |
| ***Pink and puffing patients*** | | | | | | | | | | | | | | | | | | | | | |
| 11 | 62 | F | 0·7 | 1·7 | .. | .. | 9·2 | 4·0 | 36 | 95 | .. | .. | .. | .. | 91 | .. | .. | .. | .. | 0 | .. |
| 12 | 71 | M | 0·7 | 1·7 | .. | .. | 9·5 | 5·9 | 38 | 93 | .. | .. | .. | .. | 85 | .. | .. | .. | .. | 0 | .. |
| ***Healthy subjects*** | | | | | | | | | | | | | | | | | | | | | |
| 13 | 28 | M | 5·4 | 5·9 | .. | .. | .. | .. | .. | 99 | .. | .. | .. | .. | 97 | .. | .. | .. | .. | 0 | .. |
| 14 | 28 | M | 4·9 | 5·9 | .. | .. | .. | .. | .. | 95 | .. | .. | .. | .. | 94 | .. | .. | .. | .. | 0 | .. |
| 15 | 32 | M | 3·9 | 6·0 | .. | .. | .. | .. | .. | 98 | .. | .. | .. | .. | 95 | .. | .. | .. | .. | 0 | .. |
| 16 | 45 | M | 4·8 | 5·4 | .. | .. | .. | .. | .. | 99 | .. | .. | .. | .. | 96 | .. | .. | .. | .. | 0 | .. |

F.E.V.$_1$, forced expiratory volume in one second. F.V.C., forced vital capacity. $\overline{P.A.P.}$, mean pulmonary arterial pressure. $Po_2$, arterial oxygen tension. $Pco_2$, arterial carbon-dioxide tension. $H^+$, hydrogen-ion concentration $SaO_2$, ear-oximeter reading. When asleep, the blood-gas tensions given were those measured in the arterial blood sample taken within 10 min of the lowest recorded $SaO_2$. A "dip" was a drop in $SaO_2$ of more than 10% from the immediately preceding stable $SaO_2$ during sleep, lasting for at least 1 min.

Normal values: red-cell mass 22–28 ml/kg; $\overline{P.A.P.}$ 12–18 mm Hg; $Po_2$ 12–15 kPa; $Pco_2$ 4·4–6·1 kPa; $H^+$ 36–44 nmol/l.

night). Of the remaining 28 episodes, 23 occurred during the rapid-eye-movement (R.E.M.) phase of sleep[18] (figs. 1 and 2). R.E.M. sleep occupied on average 16% of the night's sleep in these patients (whereas in health R.E.M. normally occupies 20–25% of sleep). However, as 2 of the 6 patients had hypoxæmic episodes during both R.E.M. and non-R.E.M. sleep, the association between hypoxæmic episodes and R.E.M. sleep was not statistically significant. Those hypoxæmic episodes which occurred during R.E.M. sleep persisted throughout the R.E.M. period (overall duration of hypoxæmic episodes

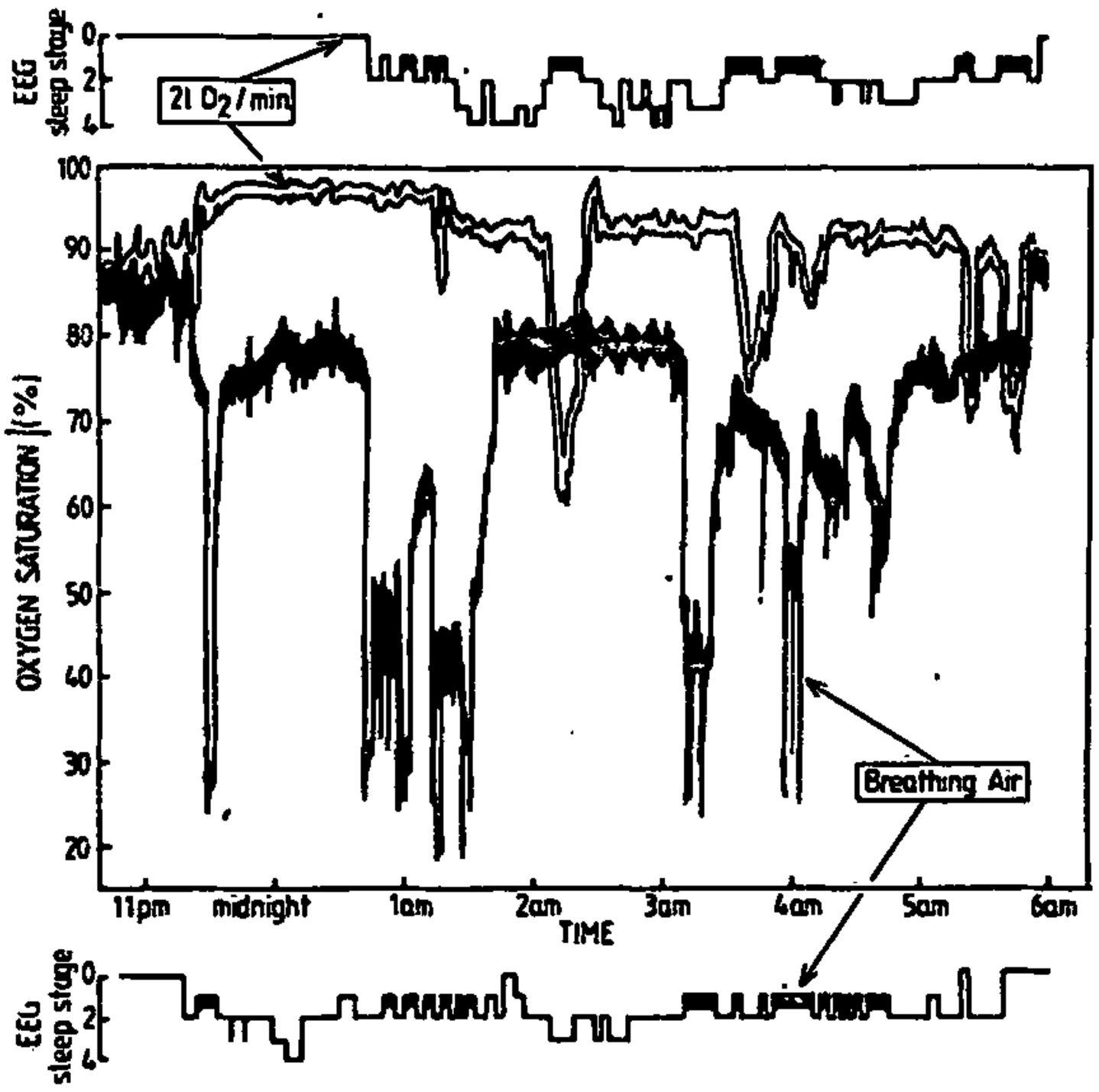


**Fig. 2—Oxygen saturation (ear oximeter) and E.E.G. sleep stage throughout the night in a "blue bloater" (patient 1) when breathing 2 litres of oxygen/min through nasal prongs (above) and on another night when breathing air (below).**
Black areas on E.E.G. record are R.E.M. periods.

32 [S.D. 13] min; R.E.M. periods 28 [S.D. 9] min). R.E.M. sleep was more interrupted during air breathing (when hypoxæmic episodes were more frequent) than during oxygen breathing.

Of the 3 patients in whom nasal and oral gas flow and chest movements were studied, 2 (patients 1 and 2) had continued respiratory movement throughout these hypoxæmic episodes, but with a diminished amplitude of both gas flow and chest movements, suggesting that ventilation was reduced. Patient 3 had 84 apnœic episodes

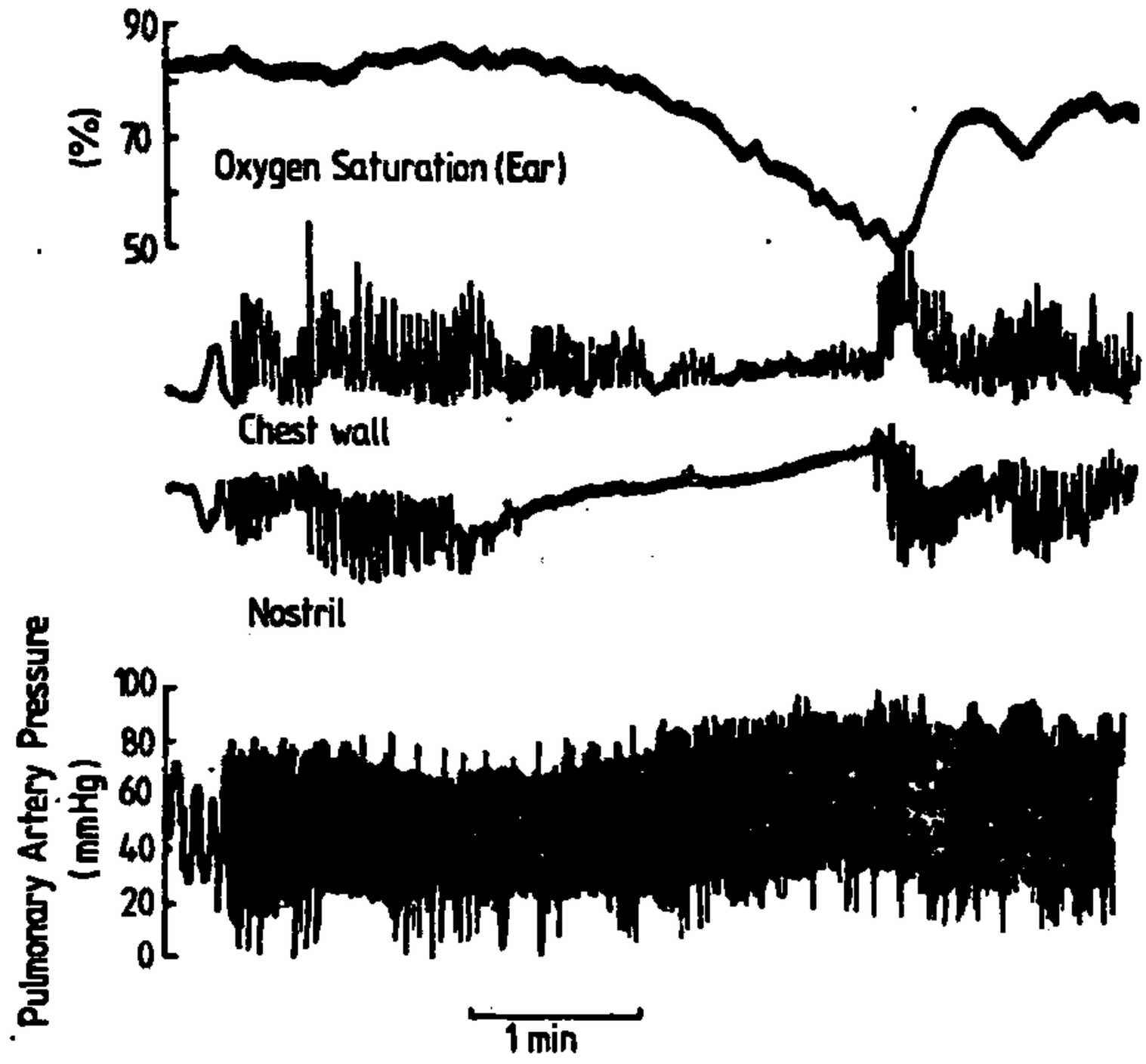


**Fig. 3—Oxygen saturation (ear oximeter), chest-wall movement, nostril gas flow, and pulmonary-arterial pressure in a "blue bloater" (patient 3) over a 5 min period during R.E.M. sleep, showing the longest apnœic episode, with associated hypoxæmia and rise in pulmonary arterial pressure.**

(respiration stopping for more than 10 s) during an 8-hour sleep: the most prolonged apnœa lasted for 140 s (fig. 3), when airflow stopped but chest-wall movement continued, indicating obstructive apnœa, and there was an associated fall in oxygen saturation from 84 to 48% with a rise in mean pulmonary arterial pressure from 40 to 50 mm Hg (fig. 3). In the other patient in whom pulmonary arterial pressure was measured, it also rose during the hypoxæmic episodes.

## Discussion

These studies confirm that patients with chronic bronchitis and emphysema can develop transient hypoxæmia during sleep, but we have found more profound and prolonged hypoxæmic episodes during sleep than have previously been described.[16 21–23] Our direct measurements of arterial $Po_2$ have shown lower values than in previous studies of oxygenation in sleeping patients with chronic bronchitis and emphysema.[11 15–17 21–23] This results in part from our selection of patients who were already notably hypoxic when breathing air when awake but also from the continuous recording with the ear oximeter[11] which was used to

guide arterial-blood sampling. We did not observe episodes of transient hypoxæmia in either the 2 "pink and puffing" patients or the 4 healthy subjects.

What is the cause of these hypoxæmic episodes in the "blue and bloated" patients? In patients 1 and 2 hypoxæmic episodes were associated with a reduction in chest movements and gas flow, with hypoxæmic episodes occurring only during R.E.M. sleep. The ventilatory response to $CO_2$ is reduced during sleep in dogs, and it may be that the central drive to breathing is then reduced. Patient 3 showed apnœic episodes, mainly of the obstructive type. Obstructive apnœa has been related to upper airways collapse during inspiration, possibly due to reduction in tone of either the genioglossus or the pharangeal abductors.[24] In this patient the majority of hypoxæmic episodes were in R.E.M. sleep, but episodes of apnœa with associated hypoxæmia occurred throughout all stages of sleep. In 5 of the 6 patients in whom arterial samples were taken, the rise in $P_{CO_2}$ during these episodes could not by itself account for the fall in $P_{O_2}$ if the gas-exchange ratio were unchanged, so that ventilation perfusion relationships in the lung appeared to be further impaired in sleep, as has been suggested previously.[16 17]

The lower arterial $P_{O_2}$ in "blue and bloated" patients than in "pink and puffing" patients and healthy subjects cannot itself account for these hypoxæmic episodes, for correction of the hypoxæmia in the "blue and bloated" patients did not abolish these episodes.

We have thus shown that "blue and bloated" patients with chronic bronchitis and emphysema can have periods of profound transient hypoxæmia during sleep and that these episodes usually occur in R.E.M. sleep. However, further studies will be needed to confirm this association with R.E.M. sleep and also that such episodes do not occur in "pink puffers". However, the drive to breathing from hypoxia is already known to be reduced in some "blue bloaters" but normal in "pink puffers",[25] when measured with the patient awake: and this diminished drive may contribute to the transient sleep hypoxæmia. We have also shown that transient sleep hypoxæmia can be associated with a further rise in pulmonary arterial pressure, which lends some support to the hypothesis that we have proposed to explain these two different clinical patterns in patients with chronic bronchitis and emphysema.

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# Hypoxic Ventilatory Response Decreases During Sleep in Normal Men[1-3]

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**SUMMARY** Ventilatory drives are presumed to be important in the maintenance of ventilation during sleep. Although the hypercapnic ventilatory response has been shown to decrease during sleep, the hypoxic ventilatory response (HVR) has not been well studied in humans. We therefore measured the ventilatory response to isocapnic hypoxia in 6 sleeping men. The HVR, measured as the slope of the relation between ventilation and decreasing hemoglobin saturation, was significantly lower in all sleep stages than in wakefulness (1.07 ± 0.19 SEM L/min/%saturation). The HVR decreased to two thirds of this waking value in non-REM sleep (0.63 ± 0.09 L/min/%saturation) with a further significant decrease in REM sleep when HVR was less than one third of the waking value (0.33 ± 0.04 L/min/%saturation). The decreased HVR may help to explain the REM-sleep-related hypoxemia found in normal persons and patients with various cardiorespiratory diseases.

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## Introduction

The level of ventilation during sleep is believed to depend largely on the sum of the hypoxic and hypercapnic drives. Although the hypercapnic ventilatory response decreases during sleep (1, 2), previous studies have indicated that the hypoxic ventilatory response (HVR) is maintained at the awake level (3, 4), thus implying a more prominent role for HVR in the maintenance of ventilation during sleep.

Hypoxemic episodes during sleep, however, are common both in normal persons (5, 6) and in those with a variety of diseases (6–13). Such hypoxemia is often most frequent and most severe during REM sleep (6, 8, 10, 11, 13). Although the hypercapnic ventilatory response is markedly diminished during REM sleep in dogs (2, 14), in human adults (1) and infants (15–17), the hypercapnic ventilatory response during REM sleep has not been found to be reduced below the level observed in non-REM sleep. The hypoxemic episodes are usually associated with decreased ventilation (7, 10, 18) despite degrees of hypoxia that would stimulate breathing in awake subjects, thus suggesting that HVR might be decreased during sleep and particularly during REM sleep. Because of the paucity of information concerning HVR in humans during sleep and no studies at all during REM sleep, we measured the ventilatory response to isocapnic hypoxia in 10 men during wakefulness and during REM and non-REM sleep.

## Methods

Ten healthy nonsmoking men 29 to 39 yr of age were studied. All were born at low altitude but had been living in Denver (1,600 m), where the studies were performed, for at least 5 months. None of the subjects was obese, taking any medication, nor had they any sleep complaints. Each subject was a regular nocturnal sleeper and all studies were performed between 10 P.M. and 7 A.M. Four subjects were eliminated from the study because they either did not sleep or because adequate studies were obtained in only one sleep stage. Results are given only for the remaining six.

Isocapnic hypoxic ventilatory responses were measured with the subject breathing through a light face mask with built-in inspiratory and expiratory valves, the system having a dead space of 70 to 85 ml depending on the subject's facial structure. A leak detector was attached around the circumference of the face cushion of the mask and consisted of a perforated polyethylene catheter attached to an infrared $CO_2$ analyzer (Beckman LB2; Beckman Instruments, Schiller Park, IL) set at maximal gain. When tested in a closed circuit this system was found to be capable of detecting an expired leak of 1.2%. Studies were reported only if there was no detectable leak throughout. For the first 30 s of each study the subjects breathed room air and then they were made hypoxic by the addition of nitrogen to a bag of air at a rate designed to reduce end tidal oxygen tension to 40 mmHg in 3 to 4 min. Isocapnia was maintained, at the degree measured while breathing air during the 2.5 min before the induction of hypoxia, by the addition of carbon dioxide to the inspired line. Arterial oxygen saturation was measured by an ear oximeter (Model 47201 A; Hewlett-Packard, Waltham, MA), flow by a hot wire anemometer (Thermo-Systems, Inc., St. Paul, MN), end-tidal $P_{O_2}$ by a fuel cell (19), and end tidal $P_{CO_2}$ by another infrared $CO_2$ analyzer (Godart capnograph, DeBilt, Holland). Regression lines for ventilation against saturation were calculated by the least squares method. Hypoxic ventilatory responses were reported in terms of the slope of the ventilation/oxygen saturation plot and not in terms of the ventilation/end-tidal $P_{O_2}$ relationship. This was done because intermittently during REM sleep, breaths were so small that an accurate end-tidal oxygen tension could not be obtained.

To validate these methods, in each of 3 awake, seated subjects (Subjects 1 to 3) hypoxic ventilatory responses were determined 6 times, alternating the mask or a mouthpiece in random sequence. There was no difference in the HVR obtained using the 2 systems. To investigate the effects of posture on the relation between ventilation and saturation, 6 measurements of HVR obtained in each of these 3 subjects, awake and seated, were compared with 6 obtained when supine and awake. There was no posture-related difference either in the

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slope of the ventilation/oxygen saturation plot, in the scatter of the data as indicated by the mean square error, or in the linearity of the data as determined by visual inspection. Similarly, there was no difference between the responses obtained when the studies were performed over 3 to 4 min starting with room air as opposed to 8 to 10 min studies starting with 40% oxygen.

The induced hypoxemia sometimes waked subjects before their end-tidal oxygen tension ($ETPo_2$) decreased to 40 mmHg. To determine whether less severe hypoxia would affect the measurement of the ventilation/arterial saturation slope, 17 hypoxic ventilatory drives obtained in 3 awake subjects over the $ETPo_2$ range of 140 to 40 mmHg were reanalyzed comparing drive results over the full range of $ETPo_2$ with those obtained by selecting data over the $ETPo_2$ ranges of 80 to 40, 80 to 45, and 80 to 50 mmHg; 80 to 85 mmHg is the $ETPo_2$ in normal subjects breathing Denver air. Although scatter increased as the amount of data analyzed decreased, there was no systematic error caused by increasing the lowest $ETPo_2$ to 50 mmHg. (Mean error compared with $ETPo_2$, 140 to 40 mmHg; 80 to 40 mmHg, 0.08 ± 2.50% (SEM); 80 to 45 mmHg, 0.34 ± 5.36%; 80 to 50 mmHg, 1.55 ± 9.86%). As we considered HVR studies adequate only if the lowest $ETPo_2$ was 50 mmHg or lower, no inherent bias is likely to result from the use of a less hypoxic stimulus during some of the studies performed on the sleeping subjects.

Continuous recordings were made on a polygraph recorder (Model 78D; Grass Instruments, Quincy, MA) of electroencephalogram (by silver disk electrodes in the central and occipital regions), electro-oculogram (by one electrode lateral to each outer canthus and one near the nasion), and electromyogram (by two submental electrodes). Sleep stage was determined by standard criteria (20). As stages 3 and 4 tend to intermingle and no difference in breathing pattern or hypoxemic response was found between these stages, their results were merged as "Stage 3/4". Otherwise, hypoxic responses were considered satisfactory only if there was no sleep stage change, however brief, during the response test.

With the subject lying in bed, 2 measurements of hypoxic ventilatory response were made immediately before sleep and 2 after final awakening during EEG-confirmed wakefulness. As the presleep and postsleep results were similar, the mean results from these studies were compared with the means during each sleep stage. Subjects 1 and 3 were restudied on a second night and the results for these subjects were the means of all studies obtained on both nights.

Hypoxic ventilatory responses that achieved the 3 criteria for acceptability (no detectable leak throughout, lowest $ETPo_2$ less than 50 mmHg, and no sleep stage change however brief) were obtained in each sleep stage in each subject with two exceptions. In both subjects, several studies were started in the appropriate stage but sleep stage changes always occurred. However, in both subjects, studies were obtained in which two criteria were met and there was only a minor deviation from the third criterion, and these studies have been included in our analysis. In the best Stage 2 study obtained in Subject 1, arousal occurred at a $Po_2$ of 50 mmHg and this study has been included as Stage 2 despite the lowest usable $ETPo_2$ being 51 mmHg. The REM sleep study for Subject 2 included three short (< 5 s) arousals, but these were spread over a 3.5-min study in such a way that the standard EEG scoring (20) was uninterrupted REM sleep.

The significance of the changes observed was determined by two-way analysis of variance and the Newman-Keuls multiple comparison test (21). Results are quoted as means ± standard errors.

The HVR studies were only started after an observation period of at least 2 min to ascertain stability of sleep stage and in non-REM sleep studies of $ETPco_2$ also. Thereafter, each HVR included 30 s of data obtained with the subject breathing air. In non-REM sleep studies, $ETPco_2$ was kept within 2 mmHg of the value obtained during air breathing. Because in REM sleep ventilation was variable and reduced, $ETPco_2$ varied, and the computer program, which yielded mean results only, gave an $ETPco_2$ in REM sleep that was always lower than the true alveolar value. However, isocapnia was maintained in REM sleep studies as mean $ETPco_2$ in the initial half of each study (when $Po_2 > 60$ mmHg) was always within 2 mmHg of that in the latter half (mean initial $Pco_2$, 37.3 ± 0.8; latter, 36.8 ± 0.9 mmHg). Indeed there were no significant differences between $Pco_2$ in the two halves of the studies in any sleep stage. The overall mean values of $ETPco_2$ in the studies were similar in wakefulness, Stage 2, and REM sleep, but were significantly higher ($p < 0.05$) in Stage 3/4 (awake, 36.7 ± 0.8; Stage 2, 37.4 ± 0.9; Stage 3/4, 38.7 ± 1.0; REM sleep, 37.2 ± 0.8 mmHg).

## Results

The HVR measured by the slope of the plot of ventilation/saturation was significantly reduced in all sleep stages ($p < 0.05$) compared with wakefulness (figure 1, table 1). There was no difference between HVR in Stage 2 compared with Stage 3/4, but in all 6 subjects, HVR decreased to the lowest value during REM sleep (figure 2) when HVR was significantly different ($p < 0.05$) from that in any other stage of sleep, and was only 31% of the value during wakefulness ($p < 0.05$).

The hypoxic heart-rate response, measured by the slope of heart rate/saturation, behaved in a similar fashion to the HVR, and was lower during Stages 2 and 3/4 than during wakefulness with a further reduction during REM sleep (Table 1). There was no significant difference between any of the stages in the slope of the plot of heart rate/ventilation.

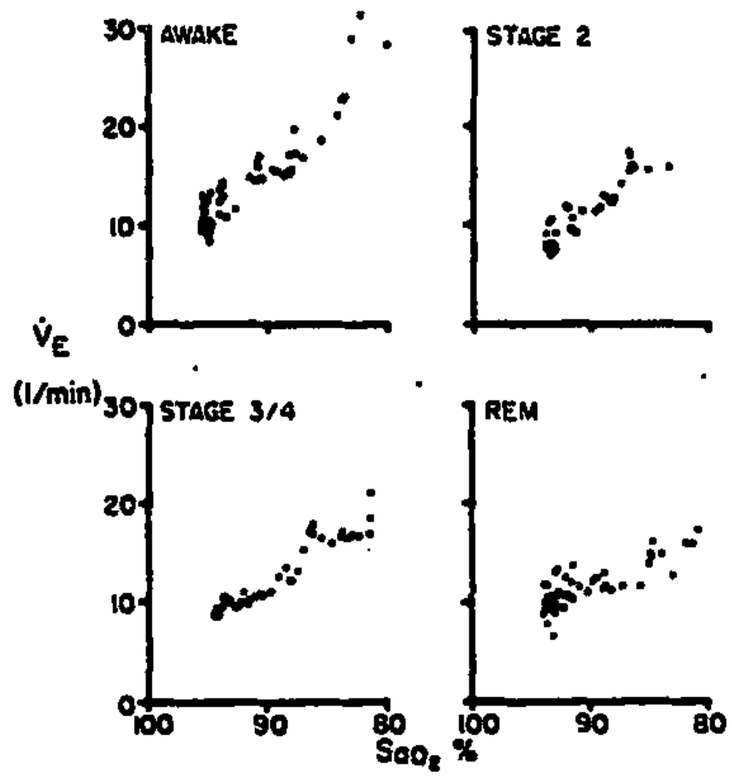


Fig. 1. Representative hypoxic ventilatory response data in Subject 6 showing decreased HVR during sleep, most marked during REM sleep ($SaO_2$ = hemoglobin saturation; $\dot{V}E$ = expired ventilation).

There was no clear relation between sleep stage and the degree of oxygenation at arousal. In many studies, arousal did not occur even when arterial saturation decreased to 80% or less.

Baseline ventilation was measured in the first 30 s of those HVR studies prior to which the subjects had been breathing air for at least 10 min. Baseline expired minute ventilation was significantly lower during REM sleep than during wakefulness or non-REM sleep, ($p < 0.05$: awake, 8.79 ± 0.40; Stage 2, 9.00 ± 0.57; Stage 3/4, 8.35 ± 0.65; REM sleep, 7.00 ± 0.50 L/min), this decrease being due to shallow breathing during sleep, which was most marked during REM sleep (tidal volume: awake, 0.71 ± .06; Stage 2, 0.58 ± 0.02*†; Stage 3/4, 0.52 ± 0.03*; REM sleep, 0.43 ± 0.03* liters. (*$p < 0.05$ versus awake; †$p < 0.05$ versus REM sleep).

## Discussion

The present study indicates that HVR is decreased during sleep in adult men. The degree of depression is related to sleep stage, being most marked during REM sleep when the response is reduced to less than one third of the value when awake.

TABLE 1

CARDIORESPIRATORY RESPONSES TO HYPOXIA DURING WAKEFULNESS AND SLEEP

| | Awake | Stage 2 | Stage 3/4 | REM Sleep |
|---|---|---|---|---|
| Hypoxic ventilatory response, -s, L/min/%sat | 1.07 ± 0.19* | 0.64 ± 0.10†‡ | 0.62 ± 0.09†‡ | 0.33 ± 0.04† |
| Hypoxic heart rate response, -s, b/min/%sat | 1.25 ± 0.19 | 0.77 ± 0.16†‡ | 0.72 ± 0.09†‡ | 0.27 ± 0.20† |
| Heart rate/ventilation, s, b/L | 1.12 ± 0.15 | 1.16 ± 0.28 | 1.18 ± 0.21 | 1.28 ± 0.26 |

*Definition of abbreviations*: s = slope; b = beats; %sat = % hemoglobin saturation.
* Values are mean ± SEM.
† $p < 0.05$ versus awake.
‡ $p < 0.05$ for other sleep stages versus REM sleep.

The only previous study of HVR in sleeping humans is that of Reed and Kellogg (3), who found no change in HVR in sleep compared with wakefulness either at sea level or at altitude. They may have failed to detect any decrease in HVR because end tidal oxygen tension was not reduced below 60 mmHg—a value barely capable of producing a clear increase in ventilation in normal subjects. Furthermore, Reed and Kellogg did not maintain isocapnia, which is now known (22) to be crucial in order to detect an increase in ventilation during mild hypoxia, nor did they use an EEG to document sleep. In dogs, Phillipson and coworkers (4) found no change in hypoxic ventilatory drive during sleep. This may have resulted from a species difference between dogs and humans in the effect of sleep on HVR. Our results agree with a recent study showing that the HVR decreases during REM sleep in calves (23).

The changes in the heart rate response to hypoxia with sleep were very similar to the alterations in HVR. As the relation between heart rate and ventilation did not change in any sleep stage, the reduction of both the ventilatory and heart rate responses to hypoxia during sleep probably involve a similar mechanism. In awake humans, both heart rate and HVR parallel metabolic rate. However, changing metabolic rate is probably not the explanation for alterations in HVR and hypoxic heart rate during sleep, as metabolic rate has been reported to be highest during REM sleep (24) with only an 8% change between sleep stages, whereas HVR and hypoxic heart rate decreased by about 50% from Stages 2 and 3/4 to REM sleep. Hypoxic responses rely on a receptor mechanism (carotid body), the brain stem, and an effector mechanism. It is not clear why hypoxic responses decrease during sleep, but as sleep is primarily a state of altered central nervous system function, altered modulation of the hypoxic response in the central nervous system seems more likely than either receptor or effector failure. Phillipson (25) has suggested that during REM sleep ventilatory control is "behavioral" rather than metabolic. Our data suggest that the hypoxic metabolic component is still present during REM sleep, although markedly reduced, but we cannot comment on whether this attenuation is due to behavioral influences. Because Sullivan and associates (14) found that hypercapnic drive was much lower during phasic than during tonic REM sleep in dogs, we subdivided REM sleep according to the dominance of eye movements into phasic, tonic, or mixed. Adequate studies were obtained in both phasic and tonic REM sleep in only 2 subjects, but there was no obvious difference between the hypoxic ventilatory responses obtained. Further studies are needed to confirm this.

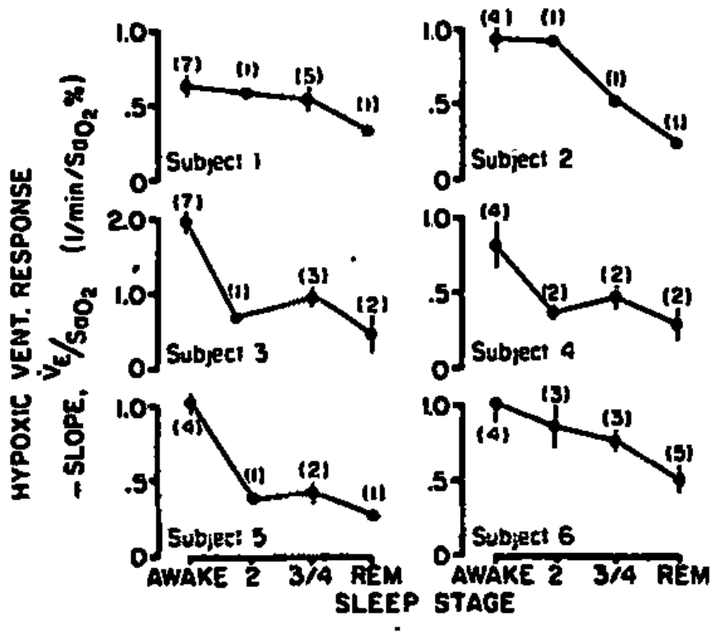


Fig. 2. Hypoxic ventilatory responses decrease during sleep in all subjects, and was constantly lowest during REM sleep. Mean data ± SEM, with number of observations in each stage in parentheses ($V_E$ = expired ventilation; $SaO_2$ = hemoglobin saturation).

The observed decrease in HVR during sleep may contribute to the occurrence of hypoxemia during sleep in normal persons (5) and in patients with a variety of diseases (6–13) including chronic obstructive pulmonary disease. These hypoxemic episodes are most common and most severe during REM sleep (6, 8, 10, 11, 13) when the lowest degrees of HVR were found and the lowest degree of ventilation noted. However, our observation of reduced minute ventilation during REM sleep needs to be confirmed by studies in which sleep is not perturbed by induced hypoxia and obtrusive instrumentation, and in which the sampling period for baseline ventilation is greater than the 1.1% of sleep time in this study. Even allowing for the small number of observations of HVR in each sleep stage, there seemed to be a difference between the subjects in the extent of HVR reduction, particularly during Stages 2 and 3/4 sleep (Figure 2), and this may contribute to the variability in the amount of "sleep-disordered breathing" and desaturation found in normal men (5). (As breathing during sleep may be different in men from what it is in women (5), our results should not be extrapolated to women.)

The reduction in HVR during sleep may help to explain why respiratory efforts are not resumed promptly after apnea onset in central sleep apnea. Decreased HVR during sleep might also be important in relation to airway patency during sleep, as it has recently been shown that the genioglossus electromyograph activity is stimulated by chemoreceptor activity (26). Thus, the decreased HVR during sleep could be accompanied by decreased genioglossus activity that might contribute to the development and perpetuation of obstructive apneas in susceptible persons. In support of this, it has been suggested that sedative drugs, many of which depress HVR, prolong obstructive apneas (27). Also, obstructive apneas have been found (28) to be longer and associated with more severe hypoxemia during REM sleep, when we find HVR to be most reduced.

It is not possible to achieve an HVR without altering sleep pattern to some extent and thus normal sleep was not sought in this study. The aim was to obtain reproducible hypoxic ventilatory responses in stable sleep stages and this was achieved. These results clearly show a diminution in HVR dur-

ing sleep, particularly marked during REM sleep, in normal men.

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# The Effect of Oxygenation on Sleep Quality in Chronic Bronchitis and Emphysema[1,2]

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**SUMMARY** We recorded the electroencephalogram, electrooculogram, electromyogram, and ear oxygen saturation ($Sa_{O_2}$) during sleep in 20 patients with chronic bronchitis and emphysema, 13 of whom had a low arterial $P_{O_2}$ and elevated $P_{CO_2}$ ("blue and bloated") and 7 of whom had a relatively normal arterial $P_{O_2}$ and $P_{CO_2}$ ("pink and puffing"), and compared the findings in these patients with 9 healthy subjects of similar age. All subjects slept for 2 nights and there was no difference between the groups in the total sleep period. The patients had a lower stable $Sa_{O_2}$ than the normal subjects, the "blue and bloated" patients having significantly more hypoxemic episodes during sleep ($p < 0.01$). Transient nocturnal hypoxemia was commonest during REM sleep in both patients and healthy subjects and its duration was not related to any sleep variable examined. The patients had significantly shorter periods of sleep between the episodes of brief arousal occurring during the night ($p < 0.02$). Six representative "blue and bloated" patients (mean $FEV_1$, 0.6 ± 0.2 L; mean $Pa_{O_2}$, 48 ± 7 mmHg; mean $Pa_{CO_2}$, 50 ± 6 mmHg) were studied for a further night receiving either air or oxygen on successive study nights. When breathing oxygen there were fewer hypoxemic episodes per night (mean, 3.7 breathing air; mean, 1.5 breathing oxygen) and the amount of sleep proper (Stages 2, 3, and 4) increased in 5 of 6 patients. Intervening wakefulness and drowsiness was reduced by oxygen, and the amount of time spent in REM sleep increased to 17% of total sleep. The total sleep period and distribution of sleep stages in the "blue and bloated" patients breathing oxygen resembled that seen in normal subjects rather than in the "pink and puffing" patients with a similar degree of airway obstruction, suggesting that differences in the ability to arouse from sleep may be related to the frequency and severity of nocturnal hypoxia.

AM REV RESPIR DIS 1982; 126:206-210

## Introduction

Impairment of cerebral function can be induced by chronic hypoxia both experimentally and clinically (1, 2). Recurrent transient hypoxemia has been shown to be particularly frequent and profound during sleep in patients with chronic bronchitis and emphysema (3–5) but the frequency and duration of such nocturnal hypoxemic episodes vary considerably from patient to patient. We have previously shown that administration of oxygen improves cerebral function in chronic bronchitis and emphysema as assessed by the daytime electroencephalogram (EEG) (6). We have now studied a similar group of patients to see if their sleep is more disturbed than that of healthy subjects of similar age sleeping under the same conditions. We have also examined the relationship between the EEG pattern and the severity of nocturnal hypoxemia, and the effects on the EEG of improving oxygen saturation during the night by nocturnal oxygen therapy.

## Methods

We studied 20 patients with chronic bronchitis and emphysema, 13 of whom were participants in the Medical Research Council's trial of domiciliary oxygen therapy (7). These 13 were of the "blue and bloated" type (7 men, 6 women); the remaining 7 were of the "pink and puffing" type (6 men, 1 woman). All the patients had severe irreversible airflow obstruction. The "blue and bloated" patients showed significant daytime hypoxemia and hypercapnia, whereas the "pink and puffing" patients were less hypoxemic and did not retain carbon dioxide (table 1). No patient had had an exacerbation of chronic bronchitis for 6 wk prior to study, none was receiving hypnotics, sedatives, or stimulant drugs, and none was more than 20% above his or her desired weight. All were treated with $beta_2$-sympathomimetic agents given by aerosol. Our control group was comprised of 9 subjects (5 men and 4 women), all of whom were free from respiratory disease and had normal spirometric tests and a normal waking ear oxygen saturation. These subjects were drawn from hospital staff and a group of healthy volunteers.

The subjects slept in a quiet darkened room for 2 consecutive nights, the first night serving to accustom them to the monitoring equipment, and data were not collected until the second night of study. The whole night's sleep was recorded on an 8-channel Galileo EEG apparatus with the usual electrophysiologic technique including EEG (from 2 midline frontoparietal electrodes), electro-oculogram (from 4 frontal electrodes outside and above the outer canthi), and electromyogram (from 2 submental electrodes). Ear oxygen saturation was continuously recorded using a Hewlett-Packard 47201A ear oximeter, airflow at the mouth and nostrils was monitored by thermocouples mounted on nasal prongs, and anteroposterior thoracic movements were measured using an induction stethogram. These respiratory variables were recorded on paper and analyzed off-line. We considered arterial oxygen saturation ($Sa_{O_2}$) to be stable when it did not vary by more than 5% over a 15-min period and transient nocturnal hypoxemia to occur when the $Sa_{O_2}$ fell from its previously stable level by more than 10% for longer than 1 min.

A computer-generated signal was recorded on the EEG trace every 15 min to provide a frame of synchronization for the oxygen saturation, respiration, and EEG sleep data. The sleep pattern was scored visually according to the standard criteria (8), except for the amplitude criteria of the slow wave Stages 3 and 4, which were decreased to 50 microvolts. The maximal amplitude of the slow waves of Stages 3 and 4 was also measured. All the EEGs were scored without knowledge of the type of subjects studied or the severity of nocturnal hypoxemia during that study.

Six of the "blue and bloated" patients (2 men and 4 women with a mean age of 60 ±

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TABLE 1

CLINICAL DETAILS OF 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND 9 NORMAL CONTROL SUBJECTS*

| | "Blue bloated" (n = 13) | "Pink puffing" (n = 7) | Normal Subjects |
|---|---|---|---|
| Age, yr | 57.4 ± 5.0 | 62.1 ± 7.0 | 53.0 ± 9.0 |
| $FEV_1$, L | 0.58 ± 0.18 | 0.75 ± 0.20 | 2.70 ± 1.0† |
| FVC, L | 1.76 ± 0.67 | 1.95 ± 0.64 | 3.31 ± 1.1† |
| Ear oxygen saturation awake, % | 80.0 ± 9.2† | 94.1 ± 1.6† | 97 ± 1.0† |
| $Pa_{O_2}$, mmHg | 47.0 ± 6.8† | 72.3 ± 4.8 | — |
| $Pa_{CO_2}$, mmHg | 51.4 ± 6.7† | 36.0 ± 5.6 | — |

*Definition of abbreviations*: $FEV_1$ = forced expiratory volume in one second; FVC = forced vital capacity; $Pa_{O_2}$ = arterial oxygen tension; $Pa_{CO_2}$ = arterial carbon dioxide tension.
* Values are expressed as mean ± SD.
† Significantly different ($p < 0.001$) from results in the other patients.

4 yr) who did not differ significantly from the rest of the "blue and bloated" group in the severity of their hypoxemia or airway obstruction (mean $FEV_1$, 0.6 ± 0.2 L; mean FVC, 1.5 ± 0.5 L; mean $Pa_{O_2}$, 48 ± 7 mmHg; mean $Pa_{CO_2}$, 50 ± 6 mmHg) were studied on 3 nights using similar techniques. On one of the nights after adaptation they breathed 2 L of air, whereas on the other 2 nights they breathed 2 L of oxygen given through nasal prongs on both occasions. The order of the air or oxygen nights was randomized and the subjects did not know which gas mixture they were receiving. All patients gave informed consent to the studies, which were approved by the Hospital Ethical Committee.

Statistical analysis was made using nonparametric tests, differences between subjects being compared with the Mann-Whitney U test and differences within subjects using Wilcoxon's signed rank test, as previously described (9). The degree of significance is given as for the two-tailed *t* test and all values are expressed as mean ± SD throughout.

## Results

*Comparison of the 2 patients groups and control subjects.* The characteristics of nocturnal oxygenation in the 2 groups of patients with chronic obstructive airway disease and in the groups of normal subjects are summarized in table 2. Both groups of patients differed significantly from the normal control subjects in that they had a lower stable level of oxygen saturation during sleep, a greater number of transient hypoxemic episodes, and a greater fall in $Sa_{O_2}$ during these episodes (all differences significant at $p < 0.002$). When the 2 groups of patients were compared with each other the "blue and bloated" patients showed a significantly lower stable $Sa_{O_2}$ during sleep, more hypoxemic episodes, and a more profound fall in $Sa_{O_2}$ during the hypoxemic episodes, than did the "pink and puffing" patients (all differences significant at $p < 0.01$). Transient hypoxemic episodes occurred predominantly during periods of hypoventilation and there was no significant difference in the incidence of hypoventilation in the 3 groups. No subject showed evidence of a sleep apnea syndrome when breathing air.

*The sleep EEG.* The time from the onset of sleep to the final awakening (total sleep period), the percentage of this time the subjects spent in the various sleep stages or awake, the amount of sleep proper (summed amount of Stages 2, 3, and 4 and REM), and some derived variables are shown in table 3.

The sleeping EEG of the patients compared with that of the normal control subjects was more disturbed, with a tendency to a longer sleep onset latency, more intervening wakefulness and drowsiness, less Stage 3 and 4 sleep, and less REM sleep. These differences, however, did not reach statistical significance because of the wide

TABLE 2

OXYGEN SATURATION DURING SLEEP IN 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND 9 NORMAL CONTROL SUBJECTS*

| | BB (n = 13) | PP (n = 7) | Normal Subjects | Significance of Differences Between BB/N | PP/N | BB/PP |
|---|---|---|---|---|---|---|
| Stable $Sa_{O_2}$ asleep, % | 71 ± 14 | 92 ± 2 | 96 ± 1 | $p < 0.002$ | $p < 0.002$ | $p < 0.002$ |
| Lowest $Sa_{O_2}$ asleep, % | 39 ± 22 | 78 ± 14 | 86 ± 8 | $p < 0.002$ | ns‡ | $p < 0.002$ |
| Hypoxemic episodes† per night | | | | | | |
| Total | 3.3 ± 2.0 | 0.9 ± 1.1 | 0.3 ± 0.7 | $p < 0.005$ | ns | $p < 0.01$ |
| In non-REM sleep | 0.6 ± 1.0 | 0 | 0 | | | |
| In REM sleep | 2.7 ± 1.9 | 0.9 ± 1.1 | 0.3 ± 0.7 | | | |
| Total duration of hypoxemic episodes per night, min | 79 ± 58 | 13 ± 18 | 6 ± 15 | $p < 0.01$ | | |

*Definition of abbreviations*: BB = "blue and bloated" patients; PP = "pink and puffing" patients; $Sa_{O_2}$ = arterial oxygen saturation measured by ear oximeter.
* Values are expressed as mean ± SD.
† A fall in $Sa_{O_2}$ greater than 10% lasting longer than 1 min.
‡ Insufficient data points for comparison.

TABLE 3

SLEEP PATTERN IN 20 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA AND 9 NORMAL CONTROL SUBJECTS*

| | BB (n = 13) | PP (n = 7) | Normal Subjects | Significance of Differences Between BB/N | PP/N | BB/PP |
|---|---|---|---|---|---|---|
| Sleep onset latency, min | 35 ± 44 | 62 ± 46 | 20 ± 16 | ns | $p < 0.02$ | $p < 0.0$ |
| Total sleep period, min† | 361 ± 66 | 343 ± 94 | 399 ± 43 | ns | ns | ns |
| Sleep proper, min‡ | 265 ± 89 | 219 ± 106 | 307 ± 54 | ns | $p < 0.05$ | ns |
| Total sleep period, % | | | | | | |
| awake (stage 0) | 17 ± 16 | 25 ± 19 | 14 ± 7 | | | |
| stage 1 | 10 ± 4 | 12 ± 2 | 9 ± 5 | | | |
| stage 2 | 51 ± 15 | 40 ± 11 | 49 ± 5 | | | |
| stage 3 | 7 ± 5 | 6 ± 3 | 7 ± 2 | ns | ns | ns |
| stage 4 | 4 ± 5 | 2 ± 3 | 5 ± 4 | | | |
| stage REM | 11 ± 7 | 15 ± 7 | 16 ± 6 | | | |
| Mean duration of uninterrupted sleep episodes, min | 6 ± 3 | 5 ± 2 | 10 ± 4 | $p < 0.02$ | $p < 0.05$ | ns |

For definition of abbreviations, see table 2.
* Values are mean ± SD.
† Time from sleep onset to final awakening.
‡ Summed duration of Stages 2, 3, 4, and REM sleep.

intersubject variability. Both groups of patients differed significantly ($p < 0.05$) from the control subjects in showing shorter duration periods of sleep between the brief episodes of arousal occurring during the night. The group of "blue and bloated" patients had less REM sleep than the normal subjects, whereas the "pink and puffing" patients showed a significantly longer sleep onset latency ($p < 0.02$) and a shorter duration of sleep proper ($p < 0.05$) than the healthy control subjects.

*Comparison between the level of oxygenation and the characteristics of sleep.* The transient falls in $Sa_{O_2}$ were commoner during periods of REM sleep than during non-REM sleep in all groups of subjects (table 2). In the "blue and bloated" group the number of hypoxemic episodes per night occurring during REM sleep averaged 2.7 ± 1.9 compared with 0.6 ± 1.0 hypoxemic episodes occurring during non-REM sleep. The number of hypoxemic episodes was significantly higher in the "blue and bloated" patients with a greater amount of Stages 3 and 4 sleep ($p < 0.05$), and a nonspecific trend in the same direction was also seen in the "pink and puffing" group ($0.05 < p < 0.1$). In the "pink and puffing" patients the hypoxemic episodes were more frequent in those with a greater amount of REM sleep ($p < 0.05$); this relationship was not significant in the "blue and bloated" group. In both groups of patients the number of hypoxemic episodes was greater in those subjects showing less intervening wakefulness and drowsiness and this relationship was significant at 2% in both groups combined (figure 1).

The duration of hypoxemic episodes was not significantly related to any of the sleep characteristics examined. However, the stable level of oxygen saturation during sleep was positively correlated with the amount of REM sleep; patients with the lowest stable level of nocturnal oxygen saturation had the fewest periods of REM sleep ($p < 0.05$).

*The effect of correcting nocturnal hypoxemia.* The 6 hypoxic "blue and bloated" patients studied breathing air or oxygen at 2 L/min via nasal prongs showed a similar sleep disturbance to the group as a whole when breathing air, the only significant difference was a longer sleep onset latency in this subgroup (table 4). During the night's sleep

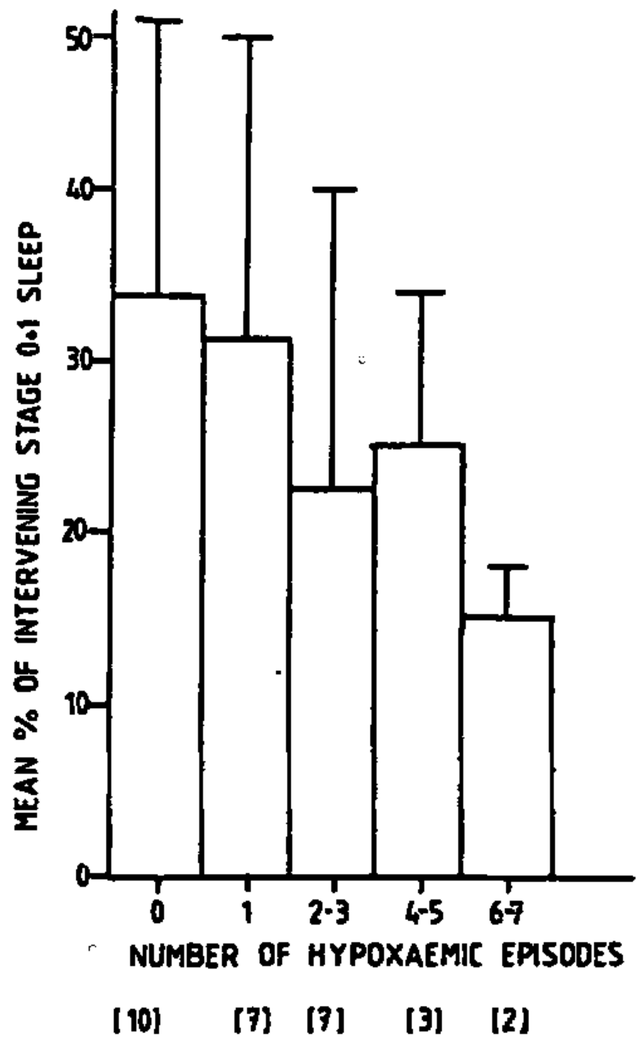


Fig. 1. Relationship between sleep disturbance and number of hypoxemic episodes. The greater number of hypoxemic episodes, the less disturbed the patient's sleep. Figures in parentheses refer to number of subjects with that frequency of hypoxemic episodes. Results given as mean ± SD.

breathing air, an average of 3.7 hypoxemic episodes were observed with a mean duration of 31 min, the lowest $Sa_{O_2}$ reached varying from 74 to 10%. When breathing oxygen all patients showed an improvement in their level of nocturnal oxygen saturation and sleep pattern. The mean number of hypoxemic episodes was reduced and their duration consistently decreased from 31 to 20 min. In 2 patients no hypoxemic episodes occurred duri the oxygen treatment night.

Sleep onset latency fell during t night breathing oxygen, whereas t amount of sleep proper (Stages 2, 3, and REM) increased in 5 of the 6 p tients ($0.05 < p < 0.1$). The amount intervening wakefulness and drowsin decreased ($p < 0.05$) in all 6 patien and averaged 15% of the total slee The number of periods of REM sle increased significantly as did t amount of REM sleep. The duration Stages 3 and 4 reached an unusual high level of 20% but this change w not significant because of the wide v riability within the subjects. The me duration of uninterrupted episodes sleep (Stages 2, 3, 4, and REM) i creased in 5 of the 6 patients from group mean of 6.7 to 10.3 min whi breathing oxygen. The majority of t hypoxemic episodes occurred duri the period of REM sleep wheth breathing air or oxygen.

## Discussion

Severe airway obstruction is known be associated with frequent and pr found episodes of nocturnal oxyge desaturation especially if the patient already hypoxic during the day (4, 5 These episodes of additional hypo emia are usually associated with pe ods of relative hypoventilation (10), was the case in these studies, and c increase the resting pulmonary arte pressure (5).

Significant disturbances in the slee ing EEG have been reported in patien with a similar degree of airway o

TABLE 4

THE EFFECTS OF IMPROVING OXYGENATION ON SLEEP IN 6 SUBJECTS WITH HYPOXIC CHRONIC BRONCHITIS AND EMPHYSEMA*

| | Breathing Air | Breathing Oxygen | |
|---|---|---|---|
| Stable $Sa_{O_2}$ awake, % | 81 ± 6 | 97 ± 2 | ($p < 0.05$) |
| Mean stable $Sa_{O_2}$ asleep, % | 53 ± 23 | 90 ± 9 | ($p < 0.05$) |
| Lowest $Sa_{O_2}$ asleep, % | 33 ± 27 | 76 ± 17 | ($p < 0.05$) |
| Hypoxemic episodes† per night, n | 3.7 ± 2.2 | 1.5 ± 1.6 | ($p < 0.05$) |
| Sleep onset latency, min | 52 ± 60 | 20 ± 13 | ($0.05 < p <$ |
| Total sleep period, min‡ | 336 ± 60 | 395 ± 40 | ns |
| Sleep proper, min§ | 247 ± 82 | 334 ± 29 | ($0.05 < p <$ |
| Total sleep period, % | | | |
| Stage 0 + 1 | 27 ± 18 | 15 ± 8 | ($p < 0.05$) |
| Stage 2 | 51 ± 17 | 49 ± 14 | ns |
| Stage 3 + 4 | 11 ± 9 | 20 ± 11 | ns |
| Stage REM | 11 ± 7 | 17 ± 6 | ($p < 0.05$) |
| Duration of uninterrupted sleep, min | 6.8 ± 3.4 | 10.3 ± 3.9 | ($0.05 < p <$ |
| REM periods, n | 2.7 ± 1.0 | 4.2 ± 1.0 | ($p < 0.05$) |

For definition of abbreviations, see table 2.
* Values are expressed as mean ± SD.
† A fall in $Sa_{O_2}$ greater than 10% lasting longer than 1 min.
‡ Time from sleep onset to final awakening.
§ Summed duration of Stages 2, 3, 4, and REM sleep.

struction, the sleep period time and amount of sleep proper (summed Stages 2, 3, 4, and REM) being reduced when compared with control subjects of similar age (4). However, in the above studies the patients slept for only one night study in unfamiliar surroundings, wearing a variable amount of monitoring equipment. Furthermore, the results of these single night studies have been compared with retrospective studies carried out with better acclimatization and without the same amount of monitoring apparatus. The disturbance in sleep pattern that we now report still had a nonspecific component to incomplete adaptation, as shown by the lower percentage of REM sleep in our control group (16%), when contrasted with a normal value of approximately 22% for similar age groups (11, 12). Nevertheless, the total sleep duration for our more severely disabled "blue and bloated" patients was 361 ± 66 min, considerably longer than the 266 ± 136 min in the one night study of similar patients reported by Wynne and colleagues (4). Because we were interested in the amount of disturbed sleep shown by our groups of patients and control subjects we concentrated on the total sleep period rather than on the total sleep time in our analysis because the latter term excludes the stages awake during the night's sleep.

Although the total duration of sleep was not significantly reduced when compared with that of similarly aged and acclimatized normal control subjects, there was evidence of more sleep disturbance in the patients with airway obstruction. They took longer to fall asleep, had more intervening wakefulness, and less Stages 3 and 4 and REM sleep. However, other differences between the groups emerged that could not be attributed to the irreversible airway obstruction that was of similar severity in both "blue and bloated" and "pink and puffing" patients. Although the "blue and bloated" had a significantly greater fall in $Sa_{O_2}$ than the "pink and puffing" patients, to our surprise it was the "pink and puffing" patients who had the most disturbed sleep as shown by the EEG recordings. Similarly, even within any group, the patients with more frequent episodes of hypoxemia had EEG characteristics usually associated with "good sleep," e.g., less intervening wakefulness and drowsiness, and more Stages 3 and 4 sleep. These results are supported by the findings of Demarco and coworkers (13) who studied 6 "pink and puffing" and 4 "blue and bloated" patients for one night only. The "pink and puffing" patients spent 43.4% of the total sleep period in Stages 0 and 1 sleep compared with 36.7% in the 4 "blue and bloated" patients who also spent more of the night in Stages 3 and 4 sleep. These results suggest that the disturbance of sleep might have a protective effect in preventing the development of profound hypoxemia.

The 6 "blue and bloated" patients who were studied without and during nocturnal oxygen administration had fewer episodes of transient nocturnal hypoxemia when breathing oxygen, probably reflecting their different starting point on the oxygen dissociation curve (10). When breathing oxygen there was a significant reduction in the amount of Stages 0 and 1 sleep, and an increase in REM sleep. The total sleep period and the distribution of sleep stages in this group of "blue and bloated" patients when breathing oxygen resembles that seen in the control subjects rather than that seen in the normally better oxygenated "pink and puffing" patients with an equivalent degree of airflow obstruction. This objective evidence of more normal sleep supports the frequent subjective observations made by patients who start nocturnal oxygen therapy that they get a better night's sleep as a result of this treatment and waken less frequently. It may also account for the improved neuropsychologic function observed in patients receiving long-term domiciliary oxygen therapy (14).

It has been suggested that the variation in the ventilatory response to hypoxia and hypercapnia may account for the variation in prevalence of arousal from sleep in humans (15). Patients with hypoxic chronic bronchitis and emphysema have a reduced hypoxic drive to breathing when studied awake (16), and it is possible that this reduction in the ventilatory response to hypoxia contributes to the relatively "good" sleep quality of these patients. Animal studies suggest that a reduced $CO_2$ response occurs during REM sleep (17) but the significance of this in humans is not clear because only small changes in the directly measured arterial $CO_2$ tension are seen during the hypoxemic episode (10). Animal experiments also suggest that the hypoxic drive is preserved during REM sleep but recent measurements in normal human subjects have found it to be diminished (18). It is possible that some of the differences in the clinical course of patients with chronic obstructive airway disease may depend upon the interplay of factors such as the hypoxic and hypercapnic ventilatory drives and the sleep arousal threshold, which determine whether sleep is disturbed, while the arterial $Po_2$ is maintained relatively normal as in the "pink and puffing" patients or whether the quality of sleep is good but profound hypoxia develops as in the "blue and bloated" patients.

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