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Breathing Disorders During Sleep

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INTRODUCTION

During the past decade there has developed a widespread realization that sleep exerts a profound impact on individuals with underlying disturbances of respiratory structure or function. In some instances, such as chronic obstructive pulmonary disease, the underlying disorder may be clinically apparent, whereas in other cases, such as obstructive sleep apnea, the underlying problem may be subtle and unsuspected clinically. In both instances the nocturnal events can produce important manifestations during wakefulness, and may be either entirely responsible for the patient's clinical syndrome, or may aggravate the clinical condition and contribute to its natural progression. The purpose of this article is to review recent advances in the field of breathing disorders during sleep and to highlight these advances by discussing in detail the more common problems encountered in clinical practice.

IMPACT OF SLEEP ON BREATHING

Sleep states

Sleep is not a homogeneous phenomenon but rather consists of two distinct states that are referred to as non-rapid-eye movement (NREM) and rapid-eye movement (REM) sleep (1). The two states can be distinguished by a combination of behavioural, electroencephalographic (EEG), electrooculographic (EOG) and electromyographic (EMG) criteria (2). NREM sleep consists of four stages representing progressively deeper stages of sleep. Stages 3 and 4 are referred to as slow-wave sleep because the EEG is dominated by high voltage waves ($>100\,\mu V$) of low frequency (1–2 Hz). REM sleep, often referred to as dreaming sleep, is characterized by a desynchronized EEG resembling that of wakefulness, abolition of skeletal muscle tone, and bursts of rapid-eye-movements as well as other phasic muscular events. In the normal adult NREM and REM sleep alternate cyclically throughout the night with a cycle length of 90 to 120 min.

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Respiratory stability

The two states of NREM and REM sleep exert several influences on breathing (3), the most important of which from the clinical standpoint are reductions in respiratory stability and changes in respiratory drive and mechanics. However these effects are not necessarily consistent throughout all sleep; hence clinical abnormalities of breathing during sleep may be limited to one or other sleep stage. For example, during the light stages of NREM sleep, as the central nervous system state fluctuates between being more awake and more asleep, there is a waxing and waning of neural stimuli to the medullary respiratory neurons. This fluctuation in neural inputs related to the state of wakefulness interacts with classical chemical respiratory stimuli to produce an instability in respiratory drive (3). The instability may manifest clinically as a waxing and waning of ventilation (periodic breathing), which often includes a short period of apnea (Cheyne–Stoke's respiration). Typically such periodic breathing disappears during slow-wave sleep, when non-chemical respiratory inputs are minimized and breathing is regulated solely by the brainstem metabolic control system (3). In contrast during REM sleep, which is characterized by phasic autonomic and neuromuscular discharges, breathing is characteristically irregular and short periods of central apnea of 10 to 20 s duration are common (3).

Respiratory drive and mechanics

In addition to changes in respiratory stability during light NREM and REM sleep, overall respiratory drive is less during sleep than during wakefulness, resulting in changes in respiratory mechanics and ventilation that may become of clinical importance in patients with underlying respiratory system abnormalities. During NREM sleep these is a decrease in diaphragmatic drive, resulting in a small reduction in ventilation of 1–2 l/min, an increase in $Paco_2$ of 0.3 to 1.0 kPa (2–8 mmHg), and a decrease in Pao_2 of 0.6 to 1.3 kPa (5–10 mmHg) (4). During REM sleep intercostal and accessory muscle activity is reduced as part of the generalized inhibition of skeletal muscle tone characteristic of this state. As a result thoracoabdominal coupling may be diminished, resulting in further reductions in ventilation (4). In addition functional residual capacity may be reduced (5).

These effects of NREM and REM sleep are also exerted on the upper airway dilator and abductor muscles whose activity is normally modulated phasically with breathing (4, 6). Thus during NREM sleep there is an increase in upper airway resistance compared with wakefulness which may contribute to the reduction in ventilation (7). During REM sleep both the resting tone and phasic respiratory discharges of the upper airway dilator muscles may be abolished completely, further increasing upper airway resistance and predisposing to upper airway occlusion in susceptible individuals (6, 7).

Clinical importance

The physiological impact of sleep on breathing is of little consequence in healthy individuals. However, in patients with abnormalities of the respiratory system, the superimposition of these sleep-related respiratory changes on the underlying disturbance may have major clinical consequences. For example, in a patient with a primary alveolar hypoventilation syndrome who lacks the normal chemical respiratory drives, withdrawal of the stimulatory effect of wakefulness on breathing at sleep onset may result in a complete cessation of respiratory drive and the development of central apnea (8). Similarly the patient with diaphragm weakness or paralysis, who is dependent upon intercostal and accessory muscle activity for maintenance of adequate ventilation, is particularly vulnerable to the development of profound hypoventilation during

REM sleep when the activity of the intercostal and accessory muscles is physiologically inhibited (9). However the best described and most important clinical disorders of breathing during sleep occur in patients with chronic obstructive pulmonary disease and in patients with obstructive sleep apnea. Therefore the remainder of this review will focus in detail on these two clinical entities.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Observations

Decreases in arterial oxygen saturation (Sao_2) during sleep in patients with chronic obstructive pulmonary disease were first described over 20 years ago (10). However only during the past few years, with the advent of newer and more widely applicable ear oximeters, has the magnitude of the problem become appreciated. Several studies have now confirmed that arterial blood gas pressures and Sao_2 deteriorate during sleep in patients with chronic bronchitis and emphysema, with the most marked changes occurring during REM sleep (11). Transient falls in Pao_2 to as low as 2.5 kPa (20 mmHg) and in saturation to as low as 30 per cent have been recorded during REM sleep, levels that would be incompatible with life if sustained. Typically the most severe episodes of desaturation occur during the longest period of REM sleep between 5 and 7 a.m., a time which corresponds to the period of highest mortality for patients with respiratory disease (12).

Arterial desaturation during sleep in patients with chronic obstructive pulmonary disease is not limited to REM sleep (Fig. 1). The transition from wakefulness to NREM sleep is generally accompanied by a decrease in Pao_2 of 1 to 1.5 kPa (7–10 mmHg) (11). During REM sleep Pao_2 decreases on average another 0.5–1.0 KPa (4–8 mmHg), superimposed on which are recurrent transient dips of up to 3 kPa (25 mmHg). Although some studies have found these sleep induced changes in Pao_2 to be greater in patients with chronic obstructive pulmonary disease than in normal subjects (13, 14), in most studies the magnitude of changes has been comparable with

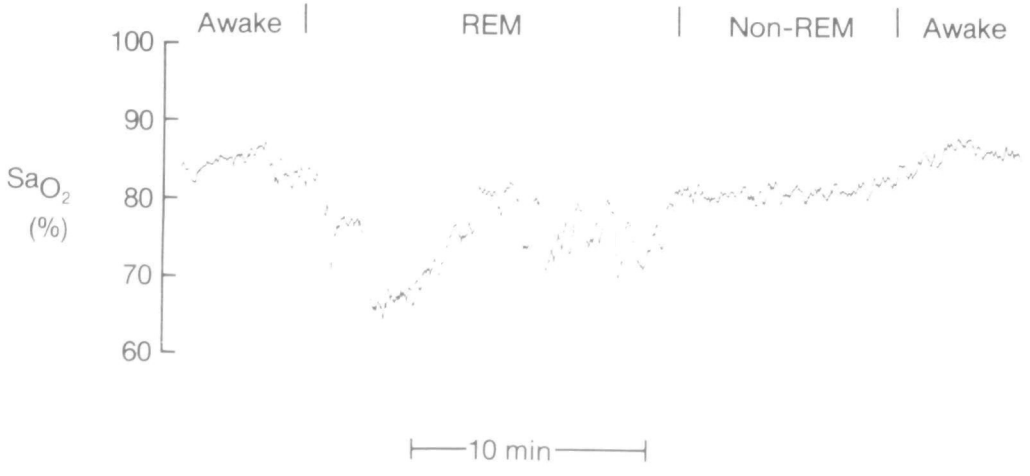

FIG. 1. Recorder tracing of arterial oxygen saturation (Sao_2) measured by ear oximetry in a patient with chronic obstructive pulmonary disease. Record moves from right to left. Note the decrease in baseline Sao_2 during non-rapid-eye movement (non-REM) sleep, and the transient periods of further desaturation during REM sleep. Sleep stages were identified from more detailed recordings (see Fig. 2).

that in healthy subjects (15–18). However because most patients with chronic obstructive pulmonary disease are hypoxic while awake, falls in Pao_2 during sleep tend to occur on the steep portion of the oxyhemoglobin dissociation curve. As a result the magnitude of arterial oxygen desaturation for a given change in Pao_2 is generally much greater in patients with chronic obstructive pulmonary disease than in healthy subjects (18). For example a decrease in Pao_2 of 1.3 kPa (10 mmHg) reduces Sao_2 by 1 per cent when baseline Sao_2 is 97 per cent, and by 15 per cent when baseline Sao_2 is 80 per cent. As a result transient episodes of desaturation of 10 to 50 per cent are not uncommon during REM sleep in patients with chronic obstructive pulmonary disease who are hypoxemic while awake (Fig. 1). Furthermore such episodes tend to either recur frequently or to persist for long periods of time. Thus in terms of oxygen delivery to the tissues, the changes in arterial oxygenation induced by sleep impose a considerably greater burden on these hypoxic patients than on normoxic individuals.

Pathogenesis

The mechanisms responsible for episodic arterial oxygen desaturation during REM sleep in patients with chronic obstructive pulmonary disease have been the subject of considerable interest in recent years (11). In general terms desaturation results from the impact of the normal respiratory changes induced by sleep superimposed on the underlying physiological disturbances characteristic of the disorder. The major cause of arterial desaturation during REM sleep appears to be a decrease in alveolar ventilation (19), which can be attributed to two causes. First, patients with chronic obstructive pulmonary disease are more dependent upon the intercostal and accessory muscles than are healthy subjects, since the diaphragm is often at a mechanical disadvantage because of hyperinflation or fatigue. The normal inhibition of inter-

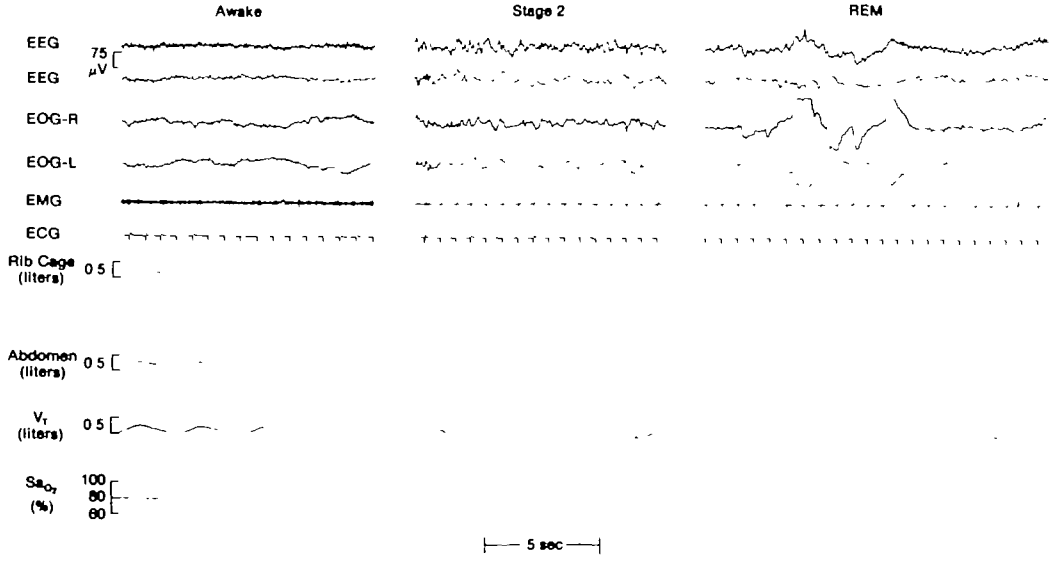

FIG. 2. Recorder tracings in a patient with chronic obstructive pulmonary disease during wakefulness, stage 2 NREM sleep, and REM sleep. Channels from above down show electroencephalogram (EEG); right and left electrooculogram (EOG); submental electromyogram (EMG); electrocardiogram (ECG); movements of the ribcage and abdomen; tidal volume (V_T); and arterial O_2 saturation (Sao_2). Note marked decrease in ribcage excursions during REM sleep, resulting in decreased tidal volume and Sao_2. (Reproduced from *Chest* 1984; 85S: 24S–30S, with permission.)

costal and accessory muscles in REM sleep thus impairs tidal volume generation and reduces the overall level of ventilation in these patients (Fig. 2). Second, the pattern of breathing during REM sleep may normally be more rapid and shallow than during NREM sleep (3, 4). Because the fraction of wasted ventilation is generally greater than normal in these patients, the change to more shallow breathing in REM sleep reduces alveolar ventilation, proportionally more than in healthy subjects. In addition to these causes of alveolar hypoventilation, the reduction in upper airway muscle tone that occurs in REM sleep results in an increase in upper airway resistance which may further impair ventilation and contribute to hypoxemia (20). However outright upper airway occlusion (i.e. obstructive sleep apnea) is not particularly common in these patients (17, 20).

In addition to changes in alveolar ventilation, ventilation–perfusion ($\dot{V}/Q$) matching may also deteriorate during REM sleep in patients with chronic obstructive pulmonary disease, thereby contributing to the transient episodes of arterial desaturation (21). This deterioration in gas exchange might result from a decrease in functional residual capacity secondary to the coincident reduction in intercostal and accessory muscle tone, as occurs in healthy subjects and in patients with cystic fibrosis (5). Any reduction in functional residual capacity in patients with diffuse airways obstruction would tend to further reduce airway caliber, thereby decreasing $\dot{V}/Q$ ratios in dependent lung zones. To what extent this mechanism contributes to the hypoxemia of REM sleep is not clear, since the transient nature of the events precludes a simple analysis of $\dot{V}/Q$ matching from calculation of the alveolar-arterial P_{O_2} difference (17, 18, 21). Changes in cardiac output during REM sleep could also alter $\dot{V}/Q$ matching and contribute to hypoxemia, although the available data suggest that this mechanism is not of major importance (22).

Pathophysiology

Because Sa_{O_2} during sleep is lower in 'blue and bloated' chronic obstructive pulmonary disease patients than in 'pink-puffers' (17, 23), it has been suggested that pulmonary hypertension, cor pulmonale, and right heart failure in chronic obstructive pulmonary disease is induced by nocturnal episodes of arterial oxygen desaturation (24, 25). This is an attractive hypothesis and is supported by the fact that the hypoxemic episodes during sleep in 'blue-bloaters' are accompanied by substantial increases in pulmonary arterial pressure (14, 22, 26). Furthermore, supplemental oxygen, sufficient to attenuate the degree of nocturnal desaturation, also blunts the acute increases in pulmonary arterial pressure (22, 26), and over the long term may halt the progression of cor pulmonale and polycythemia, and prolong survival (27–29).

Despite these intriguing observations, the long-term consequences of the sleep-induced falls in Sa_{O_2} in patients with chronic obstructive pulmonary disease are not clear. On a theoretical basis the changes should add to the overall hypoxic load and thus increase target organ damage. However the patients who experience the most severe nocturnal desaturation also demonstrate the most severe daytime hypoxemia (18). Hence the relative contribution of the nocturnal events has been difficult to establish, particularly with regards to the development of polycythemia and chronic pulmonary hypertension. Neither is there clear evidence that nocturnal oxygen treatment is more effective in the long term than would be an equivalent day-time exposure (29). However it is known that in patients with mild to moderate disease, who develop severe nocturnal desaturation because of obstructive sleep apnea, cor pulmonale and chronic hypercapnia develop with less impaired lung function than in patients without sleep apnea (30, 31). These data suggest that nocturnal hypoxemia does accelerate the rate of progression of the complications of chronic obstructive pulmonary disease.

Apart from the possible long-term consequences of nocturnal hypoxemia, the recurrent

episodes of severe arterial desaturation during REM sleep appear to be associated with the development of cardiac arrhythmias that could predispose to sudden death (32, 33). In addition because each episode of desaturation is usually terminated by a partial or complete arousal, the sleep of patients with chronic obstructive pulmonary disease is often disrupted, with the amounts of slow-wave and REM sleep tending to be reduced (17, 34, 35). The abolition of episodic desaturation by supplemental oxygen appears to alleviate the tendency to cardiac arrhythmias (32, 33) and to improve sleep quality in such patients (34, 35).

Treatment

Nocturnal oxygen treatment in patients with hypoxemic chronic obstructive pulmonary disease has been shown to reduce long-term mortality (27, 29). Furthermore in stable patients such treatment is associated with only small and clinically unimportant increases in $Paco_2$ of 0.75 kPa (5 mmHg) on average (35). In addition to reduced mortality, nocturnal oxygen treatment has also been associated with other more immediate benefits, as noted above. Thus there would appear to be little question that supplemental nocturnal oxygen can be of benefit in certain patients. What is less clear is whether decisions regarding oxygen treatment should include an analysis of nocturnal oxygenation. This uncertainty arises from the fact that there is a close relationship between daytime and night-time oxygenation in patients with chronic obstructive pulmonary disease (18). Hence it can be argued that little useful extra information about hypoxic load is obtainable from an overnight sleep study. Indeed the long-term oxygen trials that demonstrated the benefits of supplemental nocturnal oxygen used only daytime Pao_2 values to define suitability for such treatment (27–29). On the other hand, the failure to study patients during sleep may result in oxygen being prescribed for the 10 to 15 per cent of patients with chronic obstructive pulmonary disease who also have unsuspected episodes of obstructive sleep apnea (35). Supplemental oxygen in such patients may be detrimental or at least inappropriate. Thus pending further studies, the question remains unresolved as to the role of overnight polysomnography in the management of hypoxemic patients with chronic obstructive pulmonary disease.

In addition to nocturnal oxygen two alternative treatments to prevent nocturnal desaturation in these patients have been investigated recently. The first is almitrine (36), a medication that increases ventilation by stimulating the peripheral chemoreceptors, thereby increasing daytime (and thus nocturnal) Pao_2 with attenuation of nocturnal arterial oxygen desaturation. Compared with supplemental oxygen, this medication is not only more convenient but also achieves a reduction of $Paco_2$ levels. The other alternative to supplemental oxygen is assisted nocturnal ventilation by means of a negative pressure ventilator. Such treatment over a period of weeks has been shown to reverse chronic hypercapnic respiratory failure (37). It is not clear whether the mechanism involved in this improvement is one of respiratory muscle rest and relief of muscle fatigue, or a resetting of the chemical respiratory drives.

OBSTRUCTIVE SLEEP APNEA (OSA)

The clinical importance of sleep apnea arises from the fact that it is a leading cause of excessive daytime sleepiness (38). In addition sleep apnea may contribute to the development of pulmonary hypertension and right heart failure, nocturnal cardiac arrhythmias, and possibly sudden unexplained death during sleep (39, 40). During the past decade it has evolved from a disorder that was rarely recognized clinically to one of major medical proportions.

Sleep apnea is defined as a cessation of airflow at the nose and mouth during sleep. For practical clinical purposes sleep apneas are classified into three types, central, obstructive and

mixed (39, 40), although the mechanisms underlying the three types are closely related (41). In central apnea drive to all the respiratory muscles is abolished, whereas in obstructive apnea there is continued activation of the diaphragm but an absence of airflow because of complete occlusion of the upper airway at the oropharyngeal level. Mixed apneas, which begin as central events followed by an obstructive component, are generally considered a variant of obstructive apneas. Although central sleep apnea is by no means a rare disorder, obstructive sleep apnea appears to be a more frequent cause of clinical manifestations, and hence will be the focus of this review. The exact incidence of sleep apnea disorders is unknown, but may approach 1 per cent in adult males (42).

Pathogenesis (Fig. 3)

The definitive event in obstructive sleep apnea is posterior movement of the tongue and soft palate into apposition with the posterior pharyngeal wall, resulting in occlusion of both the nasopharynx and oropharynx (43, 44). As a result of the obstruction to airflow the patient becomes progressively asphyxiated until the apnea is terminated by a brief arousal from sleep, coincident with which the patency of the upper airway is restored and airflow resumes. With the resumption of breathing and relief of asphyxia, the patient returns to sleep, only to have the sequence of events repeated over and over again.

The critical event leading to upper airway occlusion during sleep is the generation of a subatmospheric airway pressure during inspiration as a result of diaphragmatic and intercostal

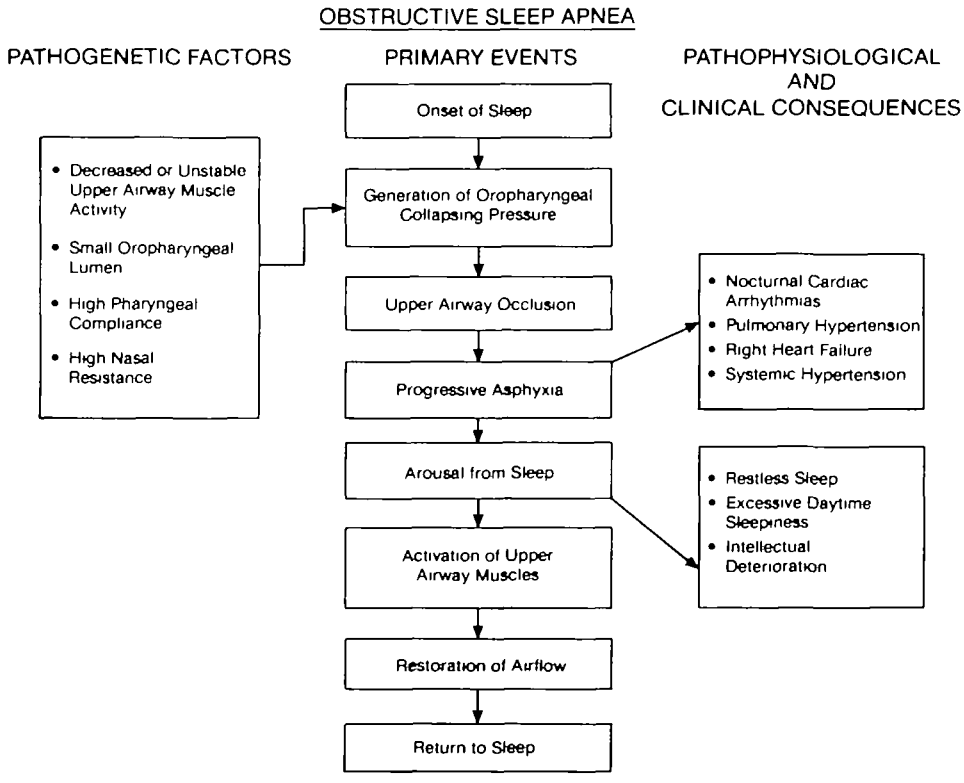

FIG 3. Schematic diagram of the primary sequence of events in obstructive sleep apnea, the underlying pathogenetic factors, and the pathophysiological and clinical consequences.

muscle contraction (45). When this pressure exceeds the stabilizing forces generated by contraction of the dilator and abductor muscles of the oropharynx, passive collapse of the upper airway results. Several pathogenetic mechanisms, both anatomical and functional, contribute to the development of this critical collapsing pressure (46). The most important of these mechanisms are the reduction and instability of drive to the dilator and abductor muscles of the upper airway, characteristic of light NREM sleep and of REM sleep; and a geometrically small upper airway lumen. It is not clear whether the sleep-induced changes in upper airway muscle activity in patients with obstructive sleep apnea are greater than in healthy subjects (45, 47). It is clear however that agents such as alcohol (48, 49), or other sedatives (50) which selectively decrease upper airway muscle activity in doses that have no effect on diaphragmatic drive (51), can induce the disorder in susceptible individuals, and play a role in the pathogenesis of the disorder in many patients. It has also become clear in recent years that the majority of patients with obstructive sleep apnea have a structurally small oropharyngeal lumen (52, 53) even in the absence of obvious anatomical abnormalities such as micrognathia and retrognathia, adenotonsillar hypertrophy, macroglossia, or obesity. In addition to a reduction in oropharyngeal size, there is an increase in pharyngeal compliance (54, 55), indicating that the pharynx is floppy and easily collapsible In many patients varying degrees of nasal obstruction are also present. Such obstruction is thought to predispose to oropharyngeal collapse by increasing the degree of subatmospheric pharyneal pressure generated during inspiration, as the strength of diaphragmatic contraction is increased to overcome airflow resistance in the nose. Thus, based on these concepts obstructive sleep apnea can be considered to result from the impact of normal or possibly exaggerated sleep-induced changes in upper airway function, superimposed on obvious or subtle abnormalities in upper airway structure.

Pathophysiology (Fig. 3)

The immediate consequence of upper airway occlusion during sleep is the interruption of alveolar ventilation and development of progressive asphyxia. After a variable period of time, ranging from 20 to 120 s, the asphyxia and other related stimuli result in arousal to a lighter stage of sleep or in a brief outright awakening. Coincident with arousal there is activation of the upper airway muscles and a resumption of airflow, followed by a return to sleep. Thus there develops a periodic cycle of sleep and apnea alternating with arousal and breathing, such that in the fully developed case sleep and breathing become mutually exclusive events (56). As a result the patient is subjected to recurrent episodes of nocturnal asphyxia, and sleep fragmentation by recurrent arousals. These two events, asphyxia and arousal, are the key physiological events leading to the clinical manifestations of obstructive sleep apnea.

The degree of arterial oxyhemoglobin desaturation that develops during obstructive sleep apnea is not simply a function of the duration of apnea (57). Equally important are the baseline awake Pa_{O_2}, which determines the position of the patient on the oxyhemoglobin dissociation curve at the beginning of the apnea; and the lung volume (functional residual capacity) at which the apnea begins, which determines the size of oxygen reservoir in the lungs during the apnea. Thus baseline hypoxemia as a result of diffuse airways obstruction (chronic bronchitis or asthma), or a reduced functional residual capacity as a result of obesity accelerate the rate of arterial oxygen desaturation during each obstructive event. Similarly the termination of each apnea by a momentary arousal response is not dependent solely on the degree of coincident asphyxia, but also on the arousability of the central nervous system. Because arousal thresholds to respiratory stimuli are elevated during REM sleep (58), obstructive apneas are typically longer in this state of sleep and associated with more severe degrees of asphyxia (59). Alcohol and medications that impair central nervous system arousability also prolong obstructive

apneas (48, 49), as do the chronic sleep fragmentation and loss of slow-wave sleep that are associated with recurrent obstructive sleep apnea (60, 61).

Clinical features (Table 1)

In most patients with clinically important obstructive sleep apnea, the disorder can be suspected on clinical grounds, with the two most important features being snoring and excessive daytime sleepiness (39, 40, 62). However the patient is commonly unaware of these symptoms, and it is therefore important that a history be obtained from the spouse or other family members. Snoring, indicative of incomplete upper airway obstruction during sleep, typically precedes other symptoms by many years. When obstructive apneas develop, often following a period of weight gain, the snoring acquires an intermittent pattern, being interrupted by periods of silence during which the patient is seen to be making vigorous breathing efforts. The termination of each apnea by an arousal response is usually accompanied by abrupt, loud snoring or gurgling sounds, and by flailing of the limbs or thrashing about in bed. Occasionally the patient is aware of the recurrent awakenings from sleep and complains of insomnia, often with a sensation of choking or dyspnea. More commonly the patient claims to sleep soundly throughout the night Nevertheless most patients complain of awakening unrefreshed in the morning, often with disorientation and mental fogginess, and occasionally with a headache.

TABLE 1. *Clinical features of obstructive sleep apnea*

Nocturnal	Daytime
Snoring	Unrefreshing sleep
Excessive motor activity	Morning headache
Recurrent awakenings	Excessive daytime sleepiness
Witnessed apneas	Intellectual deterioration
Cardiac arrhythmias	Pulmonary hypertension
Sudden death (?)	Right heart failure
	Systemic hypertension
	Obesity
	Small oropharynx

The most frequent daytime symptom of obstructive sleep apnea is excessive sleepiness. Initially drowsiness and napping occur in situations conducive to sleep, but as the disorder progresses, daytime sleepiness encroaches more and more into all daily activities. Furthermore it is frequently associated with intellectual deterioration, memory loss, and poor judgement, and with a history of industrial or automobile accidents and marital disharmony. Although the degree of excessive daytime sleepiness is related to the severity of nocturnal sleep fragmentation (63), other unknown factors are probably also involved, since patients with an equal degree of nocturnal sleep disruption may have widely differing degrees of daytime impairment.

Ten to 15 per cent of patients with obstructive sleep apnea develop sustained pulmonary hypertension leading to right heart failure (39, 62, 64). These complications arise secondary to the recurrent episodes of nocturnal asphyxia which induce acute pulmonary vasoconstriction (65, 66). In the majority of patients pulmonary arterial pressures probably revert to normal during wakefulness. However in those with sustained daytime hypoxemia (usually due to diffuse obstructive airways disease), the nocturnal events may accelerate the development of chronic pulmonary hypertension and eventually cardiac failure (64). Over 60 per cent of patients with the disorder also have systemic hypertension (39, 40, 62), the mechanism of which is not clear. While obesity is a contributing factor, snoring and obstructive sleep apnea *per se*

appear to be associated with the development of hypertension (67, 68). Conversely among patients with systemic hypertension there is evidence of an increased prevalence of obstructive sleep apnea (69, 70).

The suggestion that the disorder may result in sudden unexplained death during sleep arises from the observation that cardiac arrhythmias are common during the obstructive events (71–73). In most patients the only arrhythmia is a moderate bradycardia of 30 to 50 per min during the apneas, alternating with a tachycardia of 90 to 120 per min following the resumption of breathing (72, 73). However in a small percentage of patients profound bradycardia develops during the apneas, with periods of sinus arrest lasting 10 to 12 s and dangerous ventricular premature beats or runs of ventricular tachycardia (72, 73) The last events may result in sudden death, although for obvious reasons the association has been difficult to establish. Alternatively profound bradycardia or episodes of ventricular tachycardia may be associated with diminished cardiac output, predisposing to cerebrovascular accidents or myocardial infarction in patients with underlying vascular disease. However firm data to support these ideas are lacking.

Diagnosis

The typical patient with obstructive sleep apnea is a middle-aged or elderly male, mildly to severely overweight and hypertensive, who presents with a history of snoring and excessive daytime sleepiness (39, 40, 62). Many of the patients also give a history of chronic nasal stuffiness, and have been told that they thrash about considerably during their sleep. Physical examination is typically normal apart from obesity, mild to moderate hypertension, and a somewhat small oropharyngeal lumen. However it should be noted that this stereotypic clinical description does not apply to all patients with the disorder, since it also occurs in children and young adults, women, and non-obese individuals, and not all patients complain of excessive daytime sleepiness.

In the patient with a clinical picture typical of obstructive sleep apnea, the diagnosis can often be confirmed by observation of the patient during sleep together with relatively simple screening tests. The most useful tests are overnight Holter cardiac monitoring demonstrating cyclical fluctuations in heart rate (74); and overnight ear oximetry demonstrating recurrent episodes of arterial oxygen desaturation (Fig. 4). However the exact role of these screening tests in the diagnosis of the disorder has not been established because their sensitivity, specificity, and diagnostic accuracy has yet to be determined. Therefore the definitive diagnosis of the disorder

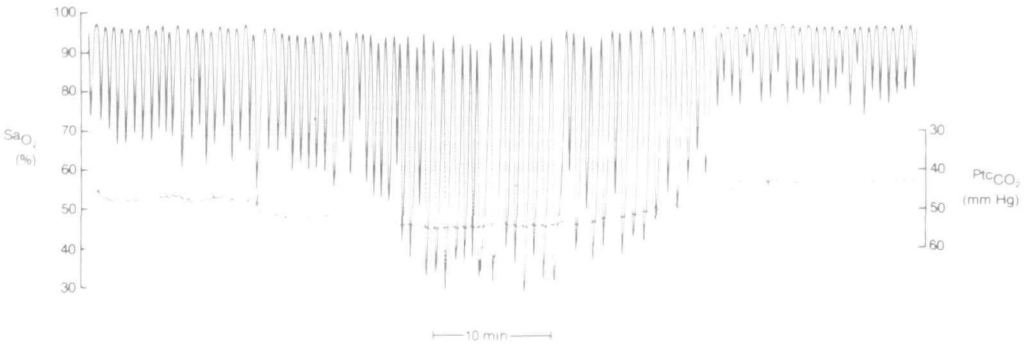

FIG. 4. Recorder tracings of arterial oxygen saturation (Sao_2) measured by ear oximetry, and of transcutaneous Pco_2 ($Ptcco_2$) in a patient with obstructive sleep apnea. Note typical recurrent episodes of desaturation, with the more severe episodes occurring during REM sleep.

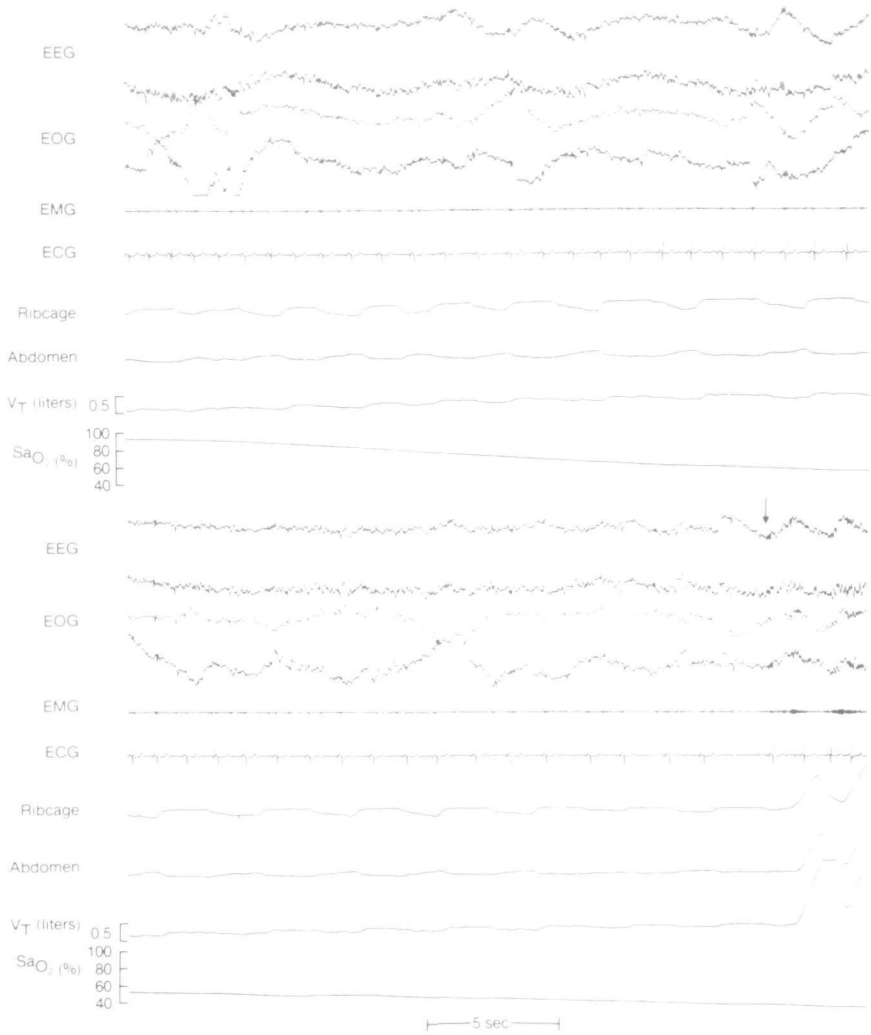

FIG. 5. Recorder tracings in a patient with obstructive sleep apnea (same patient as in Fig. 4). Abbreviations as in Fig. 2. Upper and lower panels form a continuous record. Patient is in REM sleep, and is apneic throughout the record until arousal and a resumption of airflow (at the arrow). Note that during the apnea Sao_2 falls progressively and heart rate slows. During the apnea, the ribcage moves in (downwards) when the abdomen moves out (upwards), indicating that the apnea is obstructive in type and that breathing efforts continued.

often requires a detailed polysomnographic study (Fig. 5), although there is considerable controversy as to the number of physiological variables that should be recorded in a patient with suspected obstructive sleep apnea. Conventionally such studies include recording of the EEG, EOG, and submental EMG, which permits an analysis of the amount of sleep and its distribution among the various stages, and an assessment of the degree of sleep fragmentation by brief arousals (2). In addition some index of airflow is recorded to identify apneas, as well as measurement of thoracoabdominal motion which usually permits distinction of central and obstructive apneas (56). Finally heart rate and arterial oxygen saturation (by ear oximetry) are measured in order to assess the severity of the consequences of apnea.

Although overnight polysomnography can identify the occurrence of apneas during sleep, determination of the clinical importance of these events depends upon several considerations. Until recently a sleep apnea disorder was said to exist if a patient experienced five or more apneas per hour of sleep (30 or more per night) (39). However a number of recent studies have shown that healthy asymptomatic individuals may demonstrate five to 10 apneas per hour of sleep (75, 76). In our experience patients with symptoms related to obstructive sleep apnea usually experience 20 or more obstructive events and brief arousals per hour of sleep. Therefore in symptomatic individuals with fewer than 20 such events per hour, it is important to exclude other disorders that may in fact be the cause of the patient's excessive daytime sleepiness, including drug effects, narcolepsy, nocturnal myoclonus, non-restorative sleep syndromes, neurologic disorders, psychiatric disturbances, and simply insufficient sleep (38).

Treatment

A multitude of different treatments has been proposed for patients with obstructive sleep apnea but most of these approaches have not been subjected to rigorous trials (77). However there is broad agreement that several general measures are indicated, including the avoidance of alcohol or other central nervous system depressants, and weight reduction in obese individuals. In patients with obvious nasal narrowing, or pharyngeal pathology such as adenotonsillar hypertrophy, medical or surgical correction is indicated and is often very beneficial (78–82). However for the majority of symptomatic patients with moderate to severe obstructive sleep apnea, for whom the above measures are either not indicated or are not sufficient, there is considerable controversy regarding management. Three different approaches have been recommended: pharmacological, surgical, and mechanical. The most effective medications are the tricyclic antidepressants such as protriptyline (83), which appear to function by increasing the tone of the upper airway muscles (84). Whether such medications provide long-term improvement in patients with severe obstructive sleep apnea has not been established. The most popular surgical approach is uvulopalatopharyngoplasty which is designed to increase the size of the oropharyngeal lumen by removing redundant soft tissues (85). Although this procedure provides short-term improvement in about 50 per cent of cases, its long-term efficacy has not been established. Thus the most effective current treatment for the disorder is the application of a continuous positive pressure to the airway through the nose (nasal CPAP) (86). This positive pressure serves as a pneumatic splint that prevents the development of a critical subatmospheric collapsing pressure. Nasal continuous positive airway pressure appears to be well tolerated by most patients and is highly effective (87) Therefore in many centres it is currently the treatment of choice, even in patients with dangerous cardiac arrhythmias, severe arterial oxygen desaturation, or profound daytime somnolence. If the technique cannot be used in such patients or is not effective, tracheostomy is indicated and usually provides immediate relief by bypassing the site of oropharyngeal obstruction during sleep (88, 89). However in many centres tracheostomy is now performed rarely, if at all, having been replaced by nasal continuous positive airway pressure.

REFERENCES

1. Parmeggiani PL, Morrison A, Drucker-Colin RR, McGinty D. Brain mechanisms of sleep: an overview of methodological issues. *In*: McGinty DJ, Drucker-Colin R, Morrison A, Parmeggiani PL, eds. Brain Mechanisms of Sleep. New York: Raven Press, 1985; 1–33.
2. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: National Institutes of Health, Publication no. 204, 1968.

3. Phillipson EA. Control of breathing during sleep. Am Rev Respir Dis 1978; 118: 909–939.
4. Phillipson EA, Bowes G. Control of breathing during sleep. *In*: Cherniack NS, Widdicombe JG, eds. Handbook of Physiology, The Respiratory System II, Control of Breathing. Bethesda MD: Am Physiol Soc, 1985. In press.
5. Muller NL, Francis PW, Gurwitz D, *et al.* Mechanism of hemoglobin desaturation during rapid-eye-movement sleep in normal subjects and patients with cystic fibrosis. Am Rev Respir Dis 1980; 121: 463–469.
6. Mathew OP, Remmers JE. Respiratory functions of the upper airway. *In*: Saunders NA, Sullivan CE, eds. Sleep and Breathing. Lung Biology in Health and Disease, New York: Marcel Dekker, 1984; 21: 163–200.
7. Orem J. Control of the upper airways during sleep and the hypersomnia-sleep apnea syndrome. *In*: Orem J, Barnes CD, eds. Physiology in Sleep. New York: Academic Press, 1980; 273–313.
8. Farmer WC, Glenn WWL, Gee JBL. Alveolar hypoventilation syndrome: studies of ventilatory control in patients selected for diaphragm pacing. Am J Med 1978; 64: 39–49.
9. Skatrud J, Iber C. McHugh W, *et al.* Determinants of hypoventilation during wakefulness and sleep in diaphragmatic paralysis. Am Rev Respir Dis 1980; 121: 587–593.
10. Trask CH, Cree EM. Oximeter studies on patients with chronic obstructive emphysema, awake and during sleep. N Engl J Med 1962; 266: 639–642.
11. Phillipson EA, Goldstein RS. Breathing during sleep in chronic obstructive pulmonary disease. Chest 1984; 85S: 24S–30S.
12. Smolensky M, Halberg F, Sargent F. Chronobiology of the life sequence. *In*: Itoh S, Ogata K, Yoshimura H, eds. Advances in Climatic Physiology. New York: Springer-Verlag, 1972; 281–318.
13. Koo KW, Sax DS, Snider GL. Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. Am J Med 1975; 58: 633–670.
14. Coccagna G, Lugaresi E. Arterial blood gases and pulmonary and systemic arterial pressure during sleep in chronic obstructive pulmonary disease. Sleep 1978; 1: 117–124.
15. Pierce AK, Jarrett CE, Werkle G Jr, *et al.* Respiratory function during sleep in patients with chronic obstructive lung disease. J Clin Invest 1966; 45: 631–636.
16. Leitch AG, Clancy LJ, Leggett RJE, *et al.* Arterial blood gas tensions, hydrogen ion, and electroencephalogram during sleep in patients with chronic ventilatory failure. Thorax 1976; 31: 730–735.
17. Catterall JR, Douglas NJ, Calverly PMA, *et al.* Transient hypoxemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. Am Rev Respir Dis 1983; 128: 24–29.
18. Stradling JR, Lane DJ. Nocturnal hypoxemia in chronic obstructive pulmonary disease. Clin Sci 1983; 64: 213–222.
19. Hudgel DW, Martin RJ, Capehart M, *et al.* Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. J. Appl Physiol 1983; 55: 669–677.
20. Littner MR, McGinty DJ, Arand DL. Determinants of oxygen desaturation in the course of ventilation during sleep in chronic obstructive pulmonary disease. Am Rev Respir Dis 1980; 122: 849–857.
21. Fletcher EC, Gray BA, Levin DC. Nonapneic mechanisms of arterial oxygen desaturation during rapid-eye-movement sleep. J Appl Physiol 1983; 54: 632–639.
22 Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. Chest 1984; 85: 1–14.
23. Demarco FJ Jr, Wynne JW, Block AJ, *et al.* Oxygen desaturation during sleep as a determinant of the "blue and bloated" syndrome. Chest 1981; 79: 621–625.
24. Flenley DC. Clinical hypoxia: causes, consequences, and correction. Lancet 1978; 1: 542–546.
25. Block AJ, Boysen PG, Wynne JW. The origins of cor pulmonale: a hypothesis. Chest 1979; 75: 109–110.
26. Boysen PG, Block AJ, Wynne JW, *et al.* Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. 1979; 76: 536–542.
27. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Int Med 1980; 93: 391–398.
28. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981; 1: 681–686.

29. Timms RM, Khaja FU, Williams GW, *et al.* Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Ann Int Med 1985; 102: 29–36.
30. Guilleminault C, Cummiskey J, Motta J. Chronic obstructive airflow disease and sleep studies. Am Rev Respir Dis 1980; 122: 397–406.
31. Bradley TD, Rutherford R, Grossman RF, *et al.* Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. Am Rev Respir Dis 1985; 131: 835–839.
32. Flick MR, Block AJ. Nocturnal *vs.* diurnal cardiac arrhythmias in patients with chronic obstructive pulmonary disease. Chest 1979; 75: 8–11.
33. Shepard JW, Garrison MW, Grither DA, *et al.* Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. Am J Med 1985; 78: 28–34.
34. Calverly PMA, Brezinova V, Douglas NJ, *et al.* The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis 1982; 126: 206–210.
35. Goldstein RS, Ramcharan V, Bowes G, *et al.* Effect of supplemental nocturnal oxygen on gas exchange in patients with severe obstructive lung disease. N Engl J Med 1984; 310: 425–429.
36. Connaughton JJ, Morgan AD, Douglas NJ, *et al.* Almitrine reduces the frequency and severity of recurrent transient nocturnal hypoxaemia in chronic bronchitis and emphysema. Thorax 1983; 38: 717 (Abstract).
37. Braun NMT. Effect of daily intermittent rest of respiratory muscles in patients with severe chronic airflow limitation. Chest 1984; 85S: 59S–60S.
38. Coleman RM, Roffwarg HP, Kennedy SJ, *et al.* Sleep–wake disorders based on a polysomnographic diagnosis. JAMA 1982; 247: 997–1003.
39. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Annu Rev Med 1976; 27: 465–484.
40. Lugaresi E, Coccagna G, Mantovani M. Hypersomnia With Periodic Apneas. New York: Spectrum Publications, 1978.
41. Cherniack NS. Sleep apnea and its causes. J Clin Invest 1984; 73: 1501–1506.
42. Lavie P. Incidence of sleep apnea in a presumably healthy working population: a significant relationship with excessive daytime sleepiness. Sleep 1983; 6: 312–318.
43. Weitzman ED, Pollack CP, Borowiecki B, *et al.* The hypersomnia–sleep apnea syndrome: site and mechanism of upper airway obstruction. *In*: Guilleminault C, Dement WC, eds. Sleep Apnea Syndromes. New York: Alan R. Liss, 1978; 235–248.
44. Suratt PM, Dee P, Atkinson RL, *et al.* Fluoroscopic and computed tomographic features of the pharyngeal airway in obstructive sleep apnea. Am Rev Respir Dis 1983; 127: 487–492.
45. Remmers JE, De Groot WJ, Sauerland EK, *et al.* Pathogenesis of upper airway occlusion during sleep. J. Appl Physiol 1978; 44: 931–938.
46. Bradley TD, Phillipson EA. Pathogenesis and pathophysiology of the obstructive sleep apnea syndrome. Med Clin N Am 1985. In press.
47. Onal E, Lopata M, O'Connor T. Pathogenesis of apneas in hypersomnia-sleep apnea syndrome. Am Rev Respir Dis 1982; 125: 167–174.
48. Issa FG, Sullivan CE. Alcohol, snoring and sleep apnea. J Neurol Neurosurg Psych 1982; 45: 353–359.
49. Taasan VC, Block AJ, Boysen PG, *et al.* Alcohol increases sleep apnea and oxygen desaturation in asymptomatic man. Am J Med 1981; 71: 240–245.
50. Dolly FR, Block AJ. Effect of flurazepam on sleep-disordered breathing and nocturnal oxygen desaturation in asymptomatic subjects. Am J Med 1982; 73: 239–243.
51. Krol RC, Knuth SL, Bartlett D Jr. Selective reduction of genioglossal muscle activity by alcohol in normal human subjects. Am Rev Respir Dis 1984; 129: 247–250.
52. Haponik EF, Smith PL, Bohlman ME, *et al.* Computerized tomography in obstructive sleep apnea. Am Rev Respir Dis 1983; 127: 221–226.
53. Rivlin J, Hoffstein V, Kalbfleisch J, *et al.* Upper airway morphology in patients with idiopathic obstructive sleep apnea. Am Rev Respir Dis 1984; 129: 355–360.
54. Issa FG, Sullivan CE. Upper airway closing pressures in obstructive sleep apnea. J Appl Physiol 1984; 57: 520–527.
55. Brown IG, Bradley TD, Phillipson EA, *et al.* Pharyngeal compliance in snoring subjects with and without obstructive sleep apnea. Am Rev Respir Dis 1985; 132: 211–215.

56. Phillipson EA, Bowes G. Sleep disorders. *In*: Fishman AP, ed. Update of Pulmonary Diseases and Disorders. New York: McGraw-Hill 1982; 256–273.
57. Bradley TD, Rutherford R, Martinez D, *et al.* Physiological determinants of nocturnal arterial oxygenation in patients with obstructive sleep apnea. J Appl Physiol 1985; 59: 1364–1368.
58. Bowes G, Phillipson EA. Arousal responses to respiratory stimuli during sleep. *In*: Saunders NA, Sullivan CE, eds. Sleep and Breathing. Lung Biology in Health and Disease. New York: Marcel Dekker, 1974; 21: 137–161.
59. Sullivan CE, Issa FG. Pathophysiological mechanisms in obstructive sleep apnea. Sleep 1980; 3: 235–246.
60. Bowes G, Woolf GM, Sullivan CE, *et al.* Effect of sleep fragmentation on ventilatory and arousal responses of sleeping dogs to respiratory stimuli. Am Rev Respir Dis 1980; 122: 899–908.
61. Guilleminault C, Rosekind M. The arousal threshold: sleep deprivation, sleep fragmentation, and obstructive sleep apnea syndrome. Bull Physiopathol Respir 1981; 17: 341–349.
62. Strohl KP, Saunders NA, Sullivan CE. Sleep apnea syndromes. *In*: Saunders NA, Sullivan CE, eds. Sleep and Breathing. Lung Biology in Health and Disease. New York: Marcel Dekker, 1984; 21: 365–402.
63. Stepanski E, Lamphere J, Bachia P, *et al.* Sleep fragmentation and daytime sleepiness. Sleep 1984; 7: 18–26.
64. Bradley TD, Rutherford R, Grossman RF, *et al.*, Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. Am Rev Respir Dis 1985; 131: 835–839.
65. Coccagna G, Montovani M, Brignani F, *et al.* Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. Bull Physiopathol Resp 1972; 8: 1159–1172.
66. Tilkian AG, Guilleminault C, Schroeder JS. Hemodynamics in sleep-induced apnea: Studies during wakefulness and sleep. Ann Int Med 1976; 85: 714–719.
67. Lugaresi E, Cirignotta F, Coccagna G, *et al.* Some epidemiological data on snoring and cardiocirculatory disturbances. Sleep 1980; 3: 221–224.
68. Koskenvuo M, Kaprio J, Partinen M, *et al.* Snoring as a risk factor for hypertension and angina pectoris. Lancet 1985; 1: 893–896.
69. Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension. Am Heart J 1984; 108: 373–376.
70. Kales A, Bixler EO, Cadieux RJ, *et al.* Sleep apnea in a hypertensive population. Lancet 1984; 2: 1005–1008.
71. Tilkian AG, Guilleminault C, Schroeder JS, *et al.* Sleep-induced apnea syndrome: prevalence of cardiac arrhythmias and their reversal after tracheostomy. Am J Med 1977; 63: 348–358.
72. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Am J Med 1982; 73: 317–321.
73. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 1983; 52: 490–494.
74. Motta J, Guilleminault C, Schroeder JS, *et al.* Tracheostomy and hemodynamic changes in sleep-induced apnea. Ann Int Med 1978; 89: 454–458.
75. Carskadon MA,, Dement WC. Respiration during sleep in the aged human. J. Gerontol 1981; 36: 420–423.
76. McGinty D, Littner M, Beahm E, *et al.* Sleep related breathing disorders in older men: a search for underlying mechanisms. Neurobiol Aging 1982; 3: 337–350.
77. Bradley D, Phillipson EA. The treatment of obstructive sleep apnea: separating the wheat from the chaff. Am Rev Respir Dis 1983; 128: 583–586.
78. Eliaschar I, Lavie P, Halperin E, *et al.* Sleep apneic episodes as indications for adenotonsillectomy. Arch Otolaryngol 1980; 106: 492–496.
79. Orr WC, Martin RJ. Obstructive sleep apnea associated with tonsillar hypertrophy in adults. Arch Int Med 1981; 141: 990–992.
80. Kuo PC, West RA, Bloomquist DS, *et al.* The effect of mandibular osteotomy in three patients with hypersomnia sleep apnea. Oral Surg 1979; 48: 385–392.
81. Heimer D, Scharf SM, Lieberman A, *et al.* Sleep apnea syndrome treated by repair of deviated nasal symptom. Chest 1983; 84: 184–185.

82. Irvine BWH, Dayal VS, Phillipson EA. Sleep apnea due to nasal valve obstruction. J Otolaryngol 1984; 13: 37–38
83. Brownell LG, West P, Sweatman P, *et al* Protriptyline in obstructive sleep apnea. N Engl J Med 1982; 307: 1037–1042.
84. Bonora M, St John WM, Bledsoe TA. Differential elevation by protriptyline and depression by diazepam of upper airway respiratory motor activity. Am Rev Respir Dis 1985; 131: 41–45.
85. Fujita S, Conway W, Zorick F, *et al.* Surgical correction of anatomic abnormalities in obstructive sleep apnea syndrome: uvulopalatopharyngoplasty. Otolaryngol Head Neck Surg 1981; 89: 923–934.
86. Sullivan CE, Issa FG, Berthon-Jones M, *et al.* Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981; 1: 862–865.
87. Sullivan CE, Issa FG, Berthon-Jones M, *et al.* Home treatment of obstructive sleep apnoea with continuous positive airway pressure applied through a nose-mask. Bull Eur Physiopathol Respir 1984; 20: 49–54.
88. Weitzman ED, Kahn E, Pollack CP. Quantitative analysis of sleep and sleep apnea before and after tracheostomy in patients with the hypersomnia-sleep apnea syndrome. Sleep 1980; 3: 407–423.
89. Guilleminault C, Simmons FB, Motta J, *et al.* Obstructive sleep apnea syndrome and tracheostomy: long-term follow-up experience. Arch Int Med 1981; 141: 985–988.