Sleep and breathing problems in general medicine

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The previous reviews in this series have focused on the pathophysiology and treatment of obstructive sleep apnoea which is much the commonest sleep and breathing disorder. However, there is an increasing awareness that normal sleep physiology interacts with co-existing medical diseases to promote sleep disruption and daytime sleepiness. Sleep fragmentation induces more daytime tiredness than does simple sleep deprivation and can produce depression of the hypoxic and hypercapnic ventilatory responses, depression of upper airway dilatory muscle activity, and a reduction in the critical closing pressure within the pharynx. These changes become important when the upper airway is already compromised by disease - for example, a large tongue in Down's syndrome or when unrelated pathology coexists with the medical problem as in chronic obstructive pulmonary disease (see below). In this case the additional problems are largely those associated with obstructive sleep apnoea and they can act to accelerate patient decline.

Two further mechanisms operate singly or together with the unstable upper airway to produce sleep and breathing problems in medical illness. It is now accepted that both the hypercapnic and hypoxic ventilatory responses decline with the onset of sleep and become flatter still in stages 3/4 sleep. These adjustments probably represent a change in respiratory controller gain and are associated with a change in the carbon dioxide set point such that apnoea occurs during sleep at a higher carbon dioxide tension than during wakefulness. In normal subjects the PaCO₂ during sleep is still well above the apnoeic threshold. However, if the PaCO₂ is reduced, as happens at altitude or in some medical conditions such as congestive cardiac failure, then controller instability produces periodic breathing during sleep. These apnoeic events are entirely central, associated with an open glottis, and are not accompanied by increased respiratory efforts. They differ from the reflex central apnoea described by Bradley et al where apnoeas are promoted by contact of the walls of the upper airway during a period of previous increased inspiratory effort. Sometimes obstructive and central events can coexist in the same disease category as has recently been described in acromegaly. Whilst most patients with acromegaly are predisposed to obstructive events by changes in the dimensions of their upper airways, some are relatively hypocapnic, particularly if they have high circulating levels of IgF and increased hypercapnic ventilatory drives. These subjects develop prolonged central apnoea. Studies of this kind are likely to be extended to other conditions as the wider relevance of sleep disordered breathing is recognised.

A final, less well understood problem is that of hypoventilation during sleep. Normal subjects show state-related falls in minute ventilation which are probably central in origin. In addition, as sleep deepens the response to ventilatory loading is impaired, as is load detection, at least in stage 2 sleep. The effects of mass loading, whether due to obesity or thoracic cage restriction, are to reduce ventilation further - probably by an increase in thoracic impedance - although detailed studies directly measuring ventilation in the latter condition are lacking. Nonetheless, assisted ventilation during the night by nasal intermittent positive pressure ventilation (NIPPV) does appear to produce significant changes in blood gas tensions and exercise performance over time, implying that such hypoventilation is clinically important.

Cardiovascular disease

The interactions between cardiovascular function, sleep, and obstructive sleep apnoea have already been reviewed by Ferguson and Fleetham in the September issue of Thorax (pp 998–1004). There is increasing evidence that sleep-related respiratory problems either accelerate or even act as primary causes for certain cardiovascular illnesses.

Although disturbances of cardiac rhythms have been suspected of being related to the sleep state, the evidence for this is relatively weak. Thus, in a recent prospective study of consecutive referrals to an Alberta sleep clinic there was no excess of either atrial, ventricular, or conduction disturbances in 97 patients with established sleep apnoea compared with 76 controls. Previous studies have suggested that ventricular rhythm problems are worse in the most hypoxaemic patients who are underestimated in the above report. Data on rhythm disturbances during sleep in hypoxaemic COPD are lacking and, in any case, it would be hard to exclude the effects of
other risk factors. If there is a primary effect of sleep-disturbed breathing it is likely to be a small one.

The situation in hypertension is more controversial. Snoring – a marker of partial upper airway obstruction – has been associated with hypertension epidemiologically as has sleep apnoea itself. However, there are many confounding risk factors associated with snoring, particularly obesity and smoking, which may mean that snoring is simply a marker for these factors. Thus, Hoffstein found no relationship between snoring and blood pressure when awake in 1415 patients studied prospectively in his laboratory. There was an independent relationship between the apnoea/hypopnoea index and hypertension, and this is in agreement with data from the Madison group. Unfortunately, there was no detailed analysis of the snoring data in this large epidemiological study.

Whatever the underlying mechanisms, snoring is associated with considerable cardiovascular and cerebral vascular morbidity and mortality. The risk of ischaemic heart disease and stroke are doubled among men who snore, and in one case-control study the relative risk of cerebral infarction was 2.8 times greater, and that of any cerebral vascular event 10.3 times greater, in regular snorers than in those who never snored. Patients with sleep apnoea which had been successfully treated showed substantial reduction in cardiovascular events compared with equally severe patients who rejected treatment. Other circumstantial data are that ischaemic stroke occurs most frequently in the early morning and patients admitted with a stroke are more likely to have a large stroke and more persistent neurological deficits if they are regular snorers (fig 1).

A possible mechanism linking these vascular events and sleep-related breathing problems is the rise in blood pressure which consistently accompanies arousal from partial or complete upper airways obstruction. Although related to the change in oxygen saturation during the event, such a correlation may well be spurious as correction of hypoxaemia or comparison of events with and without large changes in PaO₂ does not change the extent of the arousal response. Moreover, it has been estimated that about 75% of the rise in blood pressure at apnoea termination can be explained purely by the arousal itself. Such short term but frequent increases in blood pressure may lead to resetting of the baroreceptors and contribute to sustained hypertension by day or, alternatively, simply add to the overall stress on the vessel wall and resultant atheroma formation. Studies in normal subjects have shown graded increases in the size of the systolic and diastolic blood pressure rise during auditory-induced arousals, suggesting that other disorders such as COPD or even asthma that are associated with a poor sleep quality may also contribute to cardiovascular morbidity by this sleep-related mechanism.

Cheyne-Stokes respiration, in which periods of central apnoea alternate cyclically with hypoventilation, has been recognised for many years and is now known to be common during sleep in patients with chronic heart failure. Such patients are often hypersonnomlent by day and have frequent arousals from sleep. The traditional explanation for their apnoeas is prolongation of the circulation time such that changes in alveolar gas tensions are no longer synchronous with the breathing pattern and ventilatory stimuli from the peripheral chemoreceptors promote an inappropriate and phase lagged hyperventilation. This lowers the carbon dioxide tension below the apnoea threshold and the cycle begins again. This form of control system oscillation may explain the more severe cases where such breathing is seen during wakefulness, but these are infrequent. Prolongation of the circulation time is related to the duration of the Cheyne-Stokes respiration cycle, but other mechanisms appear to be more important. Of particular relevance are the sleep-related shifts in apnoeic thresholds already referred to. Such changes are known to be important in people who develop mountain sickness and may explain why mild hypocapnia by day is sufficient to induce central apnoea when asleep.

Recent data have suggested that cyclical fluctuations in the EEG track those in ventilation, while others have found that the intensity of EEG arousal at the end of apnoea parallels the degree of post-apnoeic hyperventilation (fig 2). Thus, both a change in the carbon dioxide threshold during sleep and the arousal response from the apnoea are needed to produce Cheyne-Stokes respiration. The best way to treat this problem is controversial. Previous reports have suggested that nasal continuous positive airway pressure (CPAP) can reverse Cheyne-Stokes respiration and improve left ventricular function,
possibly by reducing arousal-related rises in blood pressure. However, these results have not been easy to replicate and, although some patients benefit, others may deteriorate. A simpler and equally effective approach is to administer oxygen which may ameliorate both the hypoxaemia and, by diminishing minute ventilation, promotes a small change in PaO₂ which abolishes the central apnoea.

### Respiratory disease

Disturbed sleep is an important clinical and diagnostic feature of many respiratory disorders, asthma and COPD being the most intensively studied. In each case normal changes in sleep physiology, coupled with circadian rhythms in airway calibre, interact with abnormal respiratory function to disrupt sleep and exacerbate the respiratory disease. Thus, asthmatic attacks occur most frequently at night but are not associated with specific sleep stages. The mechanisms underlying nocturnal asthma have been reviewed with changes in vagal tone and possibly a loss of non-adrenergic non-cholinergic function being important. However, there is a circadian variation in airway calibre in asthma irrespective of sleep which is associated with a fall in peak expiratory flow in the morning. Whether this reflects fluctuations in endogenous hormones and/or related inflammatory changes occurring within the airways is unclear. Studies of the larger airways accessible to bronchoscopy have produced conflicting results, although all seem agreed that eosinophilia is an important feature. However, it is important to remember that airway calibre shows similar circadian variation in normal subjects which parallels those occurring in asthma in their timing but not in their amplitude.

Small changes in functional residual capacity occur during sleep which would tend to exacerbate this effect. Recent theoretical observations on the effect of airway calibre on airway reactivity have demonstrated that a small increase in submucosal or smooth muscle thickness can produce dramatic changes in airways resistance. Undoubtedly some patients show substantial falls in peak flow overnight which are out of keeping with their daytime airway calibre, and these subjects may be those most likely to benefit from long acting β agonist therapy. However, until more acceptable means are developed of measuring airways resistance during sleep, the mechanisms and the degree of variability between subjects of these phenomena will remain difficult to understand.

The normal fall in ventilation during sleep is insufficient to compromise gas exchange in normal subjects or, indeed, in those with bronchial asthma, but it does produce dramatic falls in oxygen saturation in people who already exhibit waking hypoxaemia (PaO₂ <80 kPa). Such falls are associated with transient increases in pulmonary artery pressure and relatively modest rises in PaCO₂. Although changes in cardiac output occur during sleep, most of the change in gas tensions can be accounted for by these physiological levels of hypoventilation on a background of unsteady state gas exchange. Whilst some marginally less hypoxaemic patients do show transient falls in oxygen saturation during sleep, the clinical impact of these effects appears to be modest.

In general, measurement of daytime PaO₂ remains the simplest (and cheapest) means of predicting nocturnal oxygenation in patients with COPD.

Whatever the nature of the sleeping breathing disorder, the presence of fixed or variable air flow limitation disrupts sleep quality. Patients with asthma exhibit poorer concentration and perform worse on neuropsychological testing than do controls. All studies agree that sleep quality – whether measured by the relative amounts of different sleep stages or the number of sleep state changes or arousals – is poor in all forms of COPD, especially those who are "pink puffers". Whether domiciliary oxygen improves this is less clear, and present data suggest that any significant benefit in EEG-defined sleep is only seen in the most hypoxaemic patients. Nocturnal oxygen does improve subjective sleep quality and daytime performance in an approximately dose-related fashion.

Upper airways dysfunction can coexist with both asthma and COPD simply by chance as all three conditions are relatively common. Some patients who snore loudly and are asthmatic can have their asthma control improved by nasal CPAP, whilst patients with obstructive sleep apnoea are more likely to develop fluid retention at an earlier stage in their natural history than are similar
neurological diseases and their implications. Figure 3 (A) Polysomnographic recording from a boy with advanced Duchenne muscular dystrophy during REM sleep. Note that there is cessation of detectable rib cage and abdominal movement but phasic respiratory bursts are present in the subsequent EMG recording, confirming the persistence of central respiratory activity. (B) Similar recording from a man aged 25 years with myotonic dystrophy and daytime sleepiness. A central apnoea occurs with no respiratory activity after an EEG arousal. The subsequent EMG trace shows no respiratory bursts and cardiogenic oscillations can be seen on the airflow channel indicating an open glottis without continuing respiratory effort.

Non-apnoeic patients who form most of the cases of COPD. The Sydney group has suggested that hypercapnia in COPD is related to impaired upper airways function, particularly in people who drink alcohol, but this has not been confirmed in the UK.

Neurological disease

Although a range of disordered breathing during sleep is seen in different neurological diseases, the most intensively studied patients have been those where ventilatory failure and/ or breathlessness are prominent features – the so-called neuromuscular diseases. All of these are associated with a reduction in maximum inspiratory and usually expiratory mouth pressures, but the associated sleep-related breathing disorders are relatively varied, reflecting the impact of subtle differences in the distribution of respiratory muscle weakness.

Boys suffering from Duchenne muscular dystrophy provide the best example of relatively pure respiratory muscle weakness with relative preservation of diaphragm function, although patients with severe respiratory muscle weakness after polio appear to behave identically. Boys with Duchenne muscular dystrophy show progressive falls in ventilatory capacity and maximum inspiratory pressures with age and commonly die from inspiratory failure in their late teens or early twenties. They do not complain of daytime tiredness or dyspnoea but are prone to obesity as they become more sedentary. Those who do not undergo spinal surgery at puberty often have marked kyphoscoliosis. In the more advanced cases, especially if the patients are relatively heavy, the onset of REM sleep is accompanied by recurrent apnoeas which are apparently central in nature (fig 3A). They are associated with episodes of oxygen desaturation, falling to 74% from a normal baseline in one series. These apnoeas are unlikely to be truly central as there is evidence of continuous phasic respiratory activity in the submental EMG. This can be abolished by nasal CPAP, and other workers using different respiratory sensors have seen frank obstructive events. It seems likely that the fall in muscle tone associated with REM sleep produces a physiological increase in airways resistance and this is accompanied by a further reduction in ventilatory drive to the diaphragm. In boys who have weak diaphragms, when supine at rest, this may be sufficient to produce apparent central events. As the disease progresses similar apnoeas may occur in other sleep stages. Simple predictors of the likelihood of sleep-disordered breathing are lacking at present, although one small study has found a good relationship between the PaO2 and the apnoea/hypopnoea index. Significant disturbances in cardiac rhythm occur during sleep in these patients, and these are likely to be more dangerous during hypoxaemic periods so their abolition would seem desirable. Suppression of REM sleep by protriptyline abolishes most events but the side effects, especially constipation, make it unacceptable.

Low flow oxygen by nasal cannulae controls the hypoxaemia but at the cost of lessening the apnoeas. Whether this promotes clinically significant carbon dioxide retention is not known. Nocturnal ventilation by face mask is well tolerated and, coincidentally, prevents the desaturations, but a decision to use it in all patients must be questioned following a randomised clinical trial which showed excess mortality in those treated with ventilation. This does not agree with our clinical experience, but we have always selected patients for this treatment who already show high normal day-time carbon dioxide tensions and who have oxygen desaturations at night. Bilateral diaphragm paralysis or diaphragm weakness due to acid malate deficiency or occasionally in patients with limited motor neuron disease can also produce REM-related falls in oxygen saturation due to central sleep apnoea. The motor weakness is usually associated with day-time symptoms, especially tachypnoea and breathlessness, which can be reduced by non-invasive ventilatory support. An elegant dog model using cooling of the phrenic nerves has shown that it is possible to induce central apnoeas in REM sleep when phrenic nerve function is impaired, although not all subjects with bilateral diaphragm paralysis show this.

The other major neuromuscular disease as-
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