British Journal of Anaesthesia **86 (2)**: 254–66 (2001)

BJA

REVIEW ARTICLE

Anaesthesia and sleep apnoea

J. A. Loadsman[1]* and D. R. Hillman[2]

[1]Department of Anaesthetics, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia. [2]Departments of Pulmonary Physiology and Anaesthesia, Sir Charles Gairdner Hospital, Nedlands WA 6009, Australia

**Corresponding author*

Br J Anaesth 2001; **86:** 254–66

Keywords: sleep, sleep apnoea; ventilation, anaesthesia; surgery

*Falstaff:*Now, Hal, what time of day is it, lad?
*Prince Henry:*Thou art so fat-witted, with drinking of old sack, and unbuttoning thee after supper, and sleeping upon benches after noon . . .
Act I, Scene II
*Poins:*Falstaff!—fast asleep behind the arras, and snorting like a horse.
*Prince Henry:*Hark, how hard he fetches breath . . .
Act II, Scene IV
King Henry IV Part I
William Shakespeare

While the first detailed description of *obstructive sleep apnoea* (OSA) only appeared in 1966,[31] many had noted its characteristics prior to this. The best known of these descriptions is Dickens' portrayal of Joe the Fat Boy in *The Posthumous Papers of the Pickwick Club*, although it would seem that Shakespeare had observed the symptoms at least three centuries earlier. Considering Shakespeare's comic intent, it is clear that the audience would have been aware of them also. This suggests the problem to be a common one as several large studies now confirm.[11 120 139] These studies demonstrate that between 2 and 4% of middle aged adults have clinically significant sleep apnoea with a male:female ratio of 2:1.

Sleep apnoea is of particular concern to anaesthetists. The patient with disordered breathing during sleep is likely to also have disturbed breathing when sedated. This effect is compounded by sedation-related compromise of arousal, the mechanism that protects the sleeping patient from life threatening consequences of a breathing disturbance. Furthermore, the upper airway abnormalities that predispose to breathing obstruction during sleep may also make tracheal intubation difficult.

This review is presented in three sections. In the first, sleep-related breathing disorders are defined and the pathophysiology, clinical features, and management discussed. In the second, the nature of sleep and anaesthesia and their effects on ventilation are considered and in the third, the anaesthetic management of patients with sleep apnoea examined.

Sleep-related breathing disorders

Definitions

Disappointingly, there is as yet no broad consensus regarding standard definitions, including thresholds of significance, for many of the terms used to describe sleep-related breathing disturbances, although a recent report has addressed these issues.[4] It is generally agreed that an *apnoea,* defined as a cessation of airflow, has to exceed 10 s duration to be considered significant. No standard definition of an *hypopnoea* exists. It is usually defined as a reduction in airflow or respiratory effort for more than 10 s accompanied by a desaturation of 3% or more and/or electroencephalographic evidence of arousal.[4 126] The *apnoea hypopnoea index* (AHI) is the number of apnoeas and hypopnoeas per hour of sleep and is used more or less interchangeably with the term *respiratory disturbance index.*

The apnoeas may be obstructive, central or mixed. Obstructive apnoeas are characterized by persistent effort without airflow, while with central apnoea, effort is absent. OSA, where the apnoeas are predominantly obstructive or mixed, is much more common than *central sleep apnoea*. *Sleep disordered breathing* is a term commonly used to encompass both these and other related conditions, some of which are mentioned below. The term *obstructive sleep*

apnoea syndrome is applied when OSA is accompanied by daytime sequelae such as excessive daytime sleepiness.

As there is a continuum of possible AHIs from trivial to severe, defining the presence of clinically significant sleep apnoea is somewhat arbitrary. It is generally agreed that the AHI should exceed five to be considered significant, with some advocating an AHI of 10 or more. It has been suggested that an AHI of five to 15 represents mild sleep apnoea, 15–30 moderate and greater than 30, severe.[4] However, the magnitude of associated symptoms and hypoxaemia also need to be considered when severity is determined.[77]

Hoffstein and Szalai[51] found that even with the inclusion of a 'clinical impression' by the examining sleep physician, clinical features could not reliably predict the presence or otherwise of OSA. Many patients, brought along to clinics by concerned bed partners who have witnessed apnoeas, deny symptoms. Conversely, some patients exhibiting all the daytime features of OSA have few apnoeas or hypopnoeas. Some of these habitual snorers have been found to have recurrent arousals from sleep resulting from increases in upper airway resistance not sufficient to cause apnoeas or hypopnoeas as usually defined, a condition now known as *upper airway resistance syndrome*.[45] Complicating matters still further is the variation in daytime sequelae, a few patients, and women in particular, presenting not with excessive daytime sleepiness but with other symptoms such as anxiety.[5] Nor do the above criteria always apply satisfactorily to children.[97]

Pathophysiology

OSA

A narrow, floppy upper airway provides the pathophysiological basis for OSA. This may have a congenital or acquired origin (Table 1). Usually such an airway does not cause problems during wakefulness. However, with sleep the associated loss of skeletal muscle tone makes the upper airway still narrower and floppier, particularly during rapid eye movement (REM) sleep when muscle relaxation is profound. This has two important consequences as gas is accelerated through it. First, the structures will tend to vibrate as turbulent flow patterns are produced, with snoring the result. Second, the pharynx will tend to collapse due to the Bernoulli effect, with resultant partial or complete obstruction. Obstruction will persist until sleep is interrupted and muscle tone is restored. Usually these interruptions are momentary arousals lasting less than 15 s and the sufferer is unaware of them. Occasionally, the obstructive event will result in an awakening, and the sufferer may complain of waking suddenly or with a snort or a snore. With arousal, breathing is restored and after a few breaths deeper sleep will resume with recurrence of the problem as the muscles again relax. In the more severe cases of OSA, this cycle of apnoeas and arousals may occur hundreds of times a night. In the more subtle cases, it may only occur in certain sleep stages (particularly REM sleep) and postures (particularly supine) or after alcohol consumption. The result of this constant sleep disruption is lethargy and somnolence during wakefulness.

Central sleep apnoea

Inadequate breathing during sleep due to diminished or absent respiratory effort (central sleep apnoea) may occur in association with disorders of ventilatory control or neuromuscular function or where the respiratory musculature is excessively loaded (Table 2). Patients with such conditions have diminished ventilatory capacity that may be sufficient for their needs during wakefulness but results in hypoventilation during sleep when the drive to ventilation is reduced and the compensatory mechanisms fail. Consequences

Table 1 Known and suspected predisposing conditions for obstructive sleep apnoea

Condition	Examples	Contribution
Obesity, body fat distribution[41 46]	Adult obesity, Prader-Willi syndrome	Complex and ill-defined
Race/genetics[6 92]		?Anatomical similarity
Age[13]		?Tissue laxity
Male gender[139]		Unclear
Alcohol,[123] sedatives, analgesics, anaesthetics		Muscle relaxation, depressed arousal
Smoking		?Chronic nasal congestion, pharyngeal oedema
Nasal obstruction[82]	Septal deviation, chronic nasal congestion	Increased pharyngeal negative pressure
Pharyngeal obstruction[47]	Tonsillar and adenoidal hypertrophy	Increased pharyngeal negative pressure
Cranio-facial abnormality[20 39 78 95 118 125]	Down's, Pierre-Robin, Treacher-Collins, Apert's, Crouzon's, Beckwith-Wiedemann, achondroplasia, acromegaly, fragile-X	Mid-face hypoplasia, macroglossia or micrognathia
Laryngeal obstruction	Laryngomalacia, tracheomalacia	Laryngeal collapse
Endocrine/Metabolic[40]	Hypothyroidism, androgen therapy, Cushing's	Upper airway infiltration or myopathy, obesity
Neuromuscular disorders[29 42 44 52 83]	Stroke, cerebral palsy, head injury, Shy-Drager, poliomyelitis, myotonic dystrophy, dysautonomia, tetraplegia	Disordered pharyngeal neuromuscular function
Connective tissue disorders[19]	Marfan's	Abnormal upper airway connective tissue
Storage diseases[109]	Mucopolysaccharidoses	Macroglossia
Chronic renal failure[63 73]		Unclear

Table 2 Known and suspected predisposing conditions for central sleep apnoea

Condition	Examples	Contribution
Neuromuscular disorders[32 52]	Poliomyelitis, amyotrophic lateral sclerosis, muscular dystrophy	Respiratory muscle weakness
Excessive respiratory load[41]	Obesity, airways disease, kyphoscoliosis	Excessive elastic, resistive or threshold loading of muscles
Disordered peripheral chemosensitivity[22 115]	Cardiac failure, bilateral carotid body excision	Delay or failure of ventilatory feedback from peripheral chemoreceptors
Disordered central ventilatory control	Stroke, head injury	Impaired ventilatory drive
Endocrine/metabolic[39]	Acromegaly	?Increased growth hormone and insulin like growth factor 1

Table 3 Symptoms associated with sleep apnoea

Adults	Children[47]
Heavy snoring	Snoring
Excessive daytime sleepiness	Restless sleeping
Witnessed apnoeas	Somnolence
Sudden awakenings with 'choking'	Aggression/behavioural problems
Accidents related to sleepiness	Hyperactivity
Poor memory/concentration	Odd sleeping postures
Delirium	Frequent coughs/colds
Gastro-oesophageal reflux	
Mood/personality changes	
Nocturnal sweating	
Restlessness during sleep	
Nocturia	
Enuresis (uncommon)	
Dry mouth on awakening	
Nocturnal or morning headache	
Impotence	
Nocturnal epilepsy	

Table 4 Signs associated with sleep apnoea

Oedematous soft palate or uvula
Long soft palate and uvula
Decreased oropharyngeal dimensions
Nasal obstruction
Maxillary hypoplasia
Retrognathia
Central adiposity/increased neck circumference
Hypertension and other cardiovascular consequences
Conditions/syndromes (listed in Tables 1 and 2) associated with sleep apnoea

include hypoxaemia, hypercarbia, sleep disruption and daytime somnolence. Unrecognized and untreated, polycythaemia and/or respiratory and right heart failure may supervene if sleep related hypoventilation is sufficiently severe. Similar consequences can accompany hypoventilation due to severe OSA.

Symptoms and signs

The key symptoms present in most cases of sleep apnoea are heavy snoring, occasional sudden awakenings that may be associated with momentary choking, apnoeas witnessed by a bed partner and excessive daytime sleepiness. Obtaining a history from the bed partner can be vital in eliciting several of these symptoms. Apart from these cardinal features, other recognized symptoms are listed in Table 3 and the signs in Table 4. While the symptoms lack specificity, in many cases a reasonably confident diagnosis may be made on history alone.

Investigation

The gold standard investigation for sleep apnoea is full overnight *polysomnography* (PSG) from which the type and severity of any apnoea may be determined. Electroencephalogram (EEG), electro-oculogram and submental electromyogram (EMG) are recorded for the purpose of staging sleep. Respiration is assessed by monitoring oronasal airflow (pressure transducer or thermistor), respiratory effort (inductance or impedance pneumography to monitor thoracoabdominal motion and/or diaphragmatic EMG) and pulse oximetry. Additionally, it is usual to monitor body position, sound and electrocardiogram. Videotape to record body movements and transcutaneous carbon dioxide are also used in selected cases. Subsets of these may be used for screening purposes, an example being the MESAM 4 system using oximetry, heart rate, snoring and position.[119]

Originally, the PSG data were printed out in real time using a polygraph. This method has now largely been replaced by digital storage techniques using a variety of commercially available software packages. Either way, the records are examined in 30 s 'epochs' and the sleep stage for each epoch is determined using the criteria of Rechtschaffen and Kales.[91] Respiratory events are scored using the definitions listed above and the total number of events, their duration and the degree of desaturation summarized for the whole night and for specific sleep stages.

Nasopharyngoscopy or upper airway imaging (lateral cephalometry or computed tomography) may be performed to guide treatment; for example, whether or not surgery will be of any benefit.

The results of these investigations are relevant for anaesthetists as they give some indication of the likelihood of difficulty with intubation or airway maintenance.

Sequelae

There are many sequelae of sleep apnoea which have limited relevance to anaesthesia. A variety of confounding

Table 5 Potential sequelae of sleep apnoea

Neuropsychological[58 59 71]	Sleepiness, impaired memory and cognition, decreased vigilance, increased accident risk, anxiety and depression, chronic headache, intracranial hypertension
Cardiovascular[17 53 56 68 74 135]	Hypertension, ischaemic heart disease, cerebrovascular disease, right heart failure
Pulmonary[72 106]	Hypoxaemia, hypercapnia, pulmonary hypertension
Endocrine[15 38]	Decreased growth hormone and testosterone levels, diabetic instability
GIT[62]	Gastro-oesophageal reflux

factors exists which make this issue a complex one.[69] The symptomatic accompaniments have already been listed (Table 3) and other sequelae are summarized in Table 5.

While yet unproven, several of the acute changes associated with apnoeic episodes have the potential to influence perioperative progress. Possible complications include arythmias, myocardial ischaemia, cerebrovascular insufficiency, intracranial hypertension, mental dysfunction and poor wound healing.[30 34 35 58 93 98 99 101]

Chronically, if the sleep apnoea is severe enough, respiratory and right heart failure may develop as the result of persistent, severe nocturnal hypoxaemia and hypercapnia, further increasing the risk of anaesthesia and surgery.

Treatment

OSA

In mild cases, conservative measures alone may lead to a satisfactory improvement. These measures include weight loss, reduction of alcohol or sedative consumption, sleeping laterally, and cessation of smoking. In most cases, however, these form an adjunct to more aggressive therapy, either because they are insufficient by themselves or because they prove difficult to achieve.[37] Trials of drugs that alter sleep architecture or upper airway muscle tone and electrical stimulation of the upper airway muscles during sleep have so far proved disappointing.

Introduced by Sullivan in 1981,[121] nasal continuous positive airway pressure (nCPAP) remains the treatment of choice for OSA of at least moderate severity.[36] This treatment is highly effective and prevents obstructive events by pneumatically splinting the upper airway.[90] Compliance, however, is variable and in milder forms of sleep apnoea, where daytime symptoms are mild, it is often not well accepted by patients, being moderately intrusive.[36]

In severe OSA, particularly when associated with morbid obesity or other coexisting disease such as chronic airflow limitation, the patient may present in respiratory and right heart failure. In addition to the obstructive apnoeas, central sleep hypoventilation can be present in such cases, particularly during REM sleep. If so, initial control is often best achieved with non-invasive bi-level ventilatory assistance. This involves the delivery of intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure via a nasal or face mask using BiPAP (*Bilevel positive airway pressure*) or similar device. Once control of sleep hypoventilation and respiratory failure have been achieved it is often possible to convert to CPAP, a cheaper therapy, if the predominant problem has been OSA.[89]

The use of oral appliances that reposition the mandible (forwards), increasing the pharyngeal dimensions, is becoming more common for the treatment of snoring and milder forms of OSA.[2 86] Potential complications of these devices such as temporomandibular joint dysfunction have not yet been widely investigated,[36] but there is now evidence that they are associated with dental side-effects which, while generally mild and temporary in nature, may necessitate treatment cessation in some individuals.[88]

Palatal surgery is a reasonable treatment alternative for habitual snoring but a less certain treatment for OSA.[1 3 37 110] Surgical correction of nasal obstruction is important but, of itself, does not usually result in resolution of sleep apnoea. Surgical removal of obstructing lesions in the pharynx can be definitive and tonsillectomy/adenoidectomy is a front-line treatment of obstructive sleep apnoea in childhood.[47] Maxillofacial surgery may be necessary where craniofacial abnormalities exist that are associated with OSA,[23] but its use is limited.[18] Tracheostomy, the main method of treating sleep apnoea prior to the development of CPAP, is now only indicated in life-threatening OSA when non-invasive forms of respiratory support are not tolerated.

Central sleep apnoea

Patients with sleep-related hypoventilation due to neuromuscular disease or one of the other causes listed in Table 2 may respond to treatment with CPAP or respiratory stimulants. More usually, if sufficiently severe, non-invasive ventilatory assistance is required and IPPV via nasal or face mask is the method of choice.[37] In those patients requiring IPPV for greater than 12 h a day and in patients with inadequate airway patency or protection, a tracheostomy may be necessary. External negative pressure ventilation, such as with a cuirass, may exacerbate or induce upper airway obstruction[49] and the cumbersome nature of this treatment has rendered it largely obsolete.

Sleep and anaesthesia–their nature and effects on ventilation

Sleep

Unlike anaesthesia, sleep is a state of *rousable* unconsciousness. While much is known about the electrochemical

factors influencing sleep onset and the sleep–wakefulness cycle, the exact function of sleep remains unclear, apart from the fact that it is essential for wellbeing.

Electrophysiology of sleep

The EEG was first used to investigate and characterize sleep by Loomis and colleagues in the 1930s.[76] It was not until 20 yr later that Aserinsky and Kleitman recognized the association between eye movement and the phases of sleep[7] but this soon led to the definition of sleep stages based on EEG, eye movements and muscle tone, more or less as we now know them (non rapid eye movement (NREM) stages 1 through 4 and REM), by Dement and Kleitman in 1957.[24] Rechtschaffen and Kales subsequently refined these definitions into guidelines that remain the international standard after 30 yr of use.[91]

A single pair of EEG leads may be used to stage sleep. Typically, one electrode is placed adjacent to the vertex (C3 or C4) and another over the contralateral mastoid (A2 or A1). The differential input from these is referred to a third, often the other mastoid. An occipital electrode may also be used. For the eye movements, another pair of electrodes is used, one *above* the outer canthus of one eye, the other *below* the outer canthus of the other eye. Both are referred to one of the mastoids. This results in out-of-phase deflections for both horizontal and vertical eye movements, allowing differentiation from artefacts, which are usually in-phase. A third pair of electrodes is placed under the chin to monitor the EMG.

Relaxed wakefulness is characterized by sinusoidal alpha (8–12 Hz) and low voltage, mixed frequency activity on the EEG, accompanied by eye movements, blinking, and high submental EMG tone. With sleep onset (stage 1) there is muscle relaxation, slow horizontal rolling of the eyes and a marked reduction in the amount of alpha activity, leaving mainly the low voltage, mixed frequency component.

Stage 2 may be associated with a further reduction in the EMG, but it is particularly defined by the appearance, superimposed upon the stage one type EEG background, of sleep spindles (short bursts of 12–14 Hz activity similar to waking alpha) and K-complexes (a sharp negative wave immediately followed by a broader, high voltage positive component). K-complexes may be either spontaneous or a response to an external stimulus, and are frequently closely associated temporally with spindles.

Stages 3 and 4, together referred to as *slow wave sleep* (SWS), are characterized by high voltage delta (1–4 Hz) activity (hence its other less common name, *delta sleep*). If the epoch has between 20 and 50% of its record consisting of slow waves then it is scored as stage 3. Epochs containing more than 50% SWS are classified as stage 4.

Stage REM has an EEG pattern similar to stage 1. It is, however, clearly defined by the presence of episodic rapid eye movements, very low EMG amplitude and a variety of other physiological changes as described below.

The typical sleep pattern

Of the few previous depictions in the anaesthetic or surgical literature of the normal human sleep pattern,[61 103 104] at least one is somewhat inaccurate[104] and none mention the changes in this pattern with age. Knowledge of the typical pattern is necessary before assessment of perioperative changes can be made and as a number of assumptions and speculations have been drawn from relatively few observations of perioperative sleep this is all the more important.

In *young adults*[24 60 136] a brief initial period of stage 1 is usually followed by stages 2, 3 and 4 in that order. The SWS component normally predominates this first NREM period and after about 70 min of sleep the first REM stage occurs, preceded by a period of stage 2. This cycle is repeated, depending upon the total sleep time, up to six times but the later cycles usually lack stage 4. The REM periods tend to lengthen as sleep progresses while the cycle length, averaging 70–90 min, shortens as the NREM component decreases more than the increase in REM. Stage 2 is the predominant stage for the total period of sleep, usually making up about 50%. Stage 1 totals about 5%, SWS about 20% and REM about 25%. The graphical depiction of sleep in stages is known as the hypnogram and an example from a young adult male is shown in Fig. 1.

Influence of age

The changes in sleep pattern with age are profound[28] and have the potential to heavily influence interpretation of studies into perioperative sleep. Total sleep time shows a precipitous decline during adolescence from an average of 10 h day^{-1} or more at age 6 yr to about 7.5 h in early adulthood. There is then a plateau until old age when a further but less dramatic decline occurs. The proportion of time spent in bed but awake remains at a few per cent until mid-life whereafter it rapidly increases to about 20% or more in old age. The number of arousals per night increases more linearly. As a result of these changes ageing is associated with more frequent and prolonged interruptions to sleep.

REM sleep decreases from more than 50% of total sleep time in neonates[117] to about 30% in later childhood before a plateau of about 25% for most of adulthood and a further decline to about 20% late in life. Stage 4 sleep, on the other hand, displays no plateau, its total amount declining sharply during adolescence, then halving again between the ages of 20 and 60 yr. This decline in stage 4, about half of which normally occurs in the first sleep cycle on any given night, results in a shorter first cycle and hence a reduction in REM latency, the time to first REM onset. This first REM period also becomes longer in old age, leading to a more even distribution of REM throughout the sleep cycles, the number of which is about the only sleep variable to remain constant with age.

Other physiological variables in sleep

A complete account of the gamut of physiological changes during sleep is outside the scope of this work. Each stage of

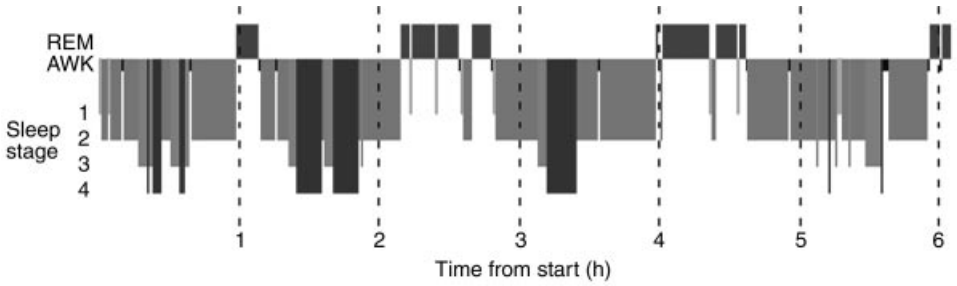

Fig 1 Actual hypnogram of a young adult male medical student—a graphical depiction of the sleep stages during one night's sleep (recorded and manually scored with a commercial sleep monitoring system; Compumedics, Melbourne, Australia). REM=rapid eye movement sleep; AWK=awake or movement time. The final REM period ended prematurely as a consequence of study termination.

sleep has a fairly distinct pattern of physiological phenomena [26 43] and the complexity is such that any attempt at classifying sleep stages according to some arbitrary measure of 'depth' amounts to gross oversimplification. Nevertheless, in order to examine the impact of sleep in the perioperative period knowledge of some of these changes is required.

Skeletal muscle function. All skeletal musculature, be it postural, chest or abdominal wall, diaphragm or upper airway, is subject to state-related activity changes. There are, however, marked differences between the groups. The tone of postural muscles, compared with wakefulness, is reduced somewhat in NREM and almost completely abolished in REM. This is a consequence of hyperpolarization of alpha motor neurones[108] which is most marked during the transition from NREM to REM sleep and during bursts of eye movement activity, commonly referred to as *phasic REM sleep*.[81] Despite this, phasic REM is characterized by rapid, random fluctuations in motor neurone membrane potential, hence varying levels of excitation and inhibition resulting in the eye movements and twitches of limbs and facial muscles. This occurs against the background active inhibition of *tonic REM sleep.* In contrast to non-respiratory muscles, the inspiratory activity of the chest wall, accessory and diaphragm muscles is preserved in NREM, as is the expiratory activity of the abdominal wall.[48 112 113 124] During REM, the tonic and phasic activity of all of these muscles except the diaphragm is greatly reduced. The diaphragm's phasic activity is preserved, albeit on a background of reduced tone.[128] This explains the profound hypoventilation seen when patients with diaphragmatic weakness enter REM sleep.[111] The upper airway musculature follows the same pattern as the postural muscles,[107] increasing the tendency to collapse,[55] especially during REM, but as some muscles are constrictors rather than dilators, and as the state-related changes differ from muscle to muscle and from individual to individual, this tendency may not be universal.

Ventilation-perfusion relationship. Functional residual capacity (FRC) is reduced during sleep, presumably as a consequence of sleep related changes in respiratory muscle tone together with gravitational effects of the supine position on the lung and abdominal contents.[54] This results in atelectasis in the dependent regions of the lung with shunt, particularly in the case of patients with obesity and chronic lung disease.[10]

Load compensation. The application of resistive or elastic respiratory loads during wakefulness leads to a rapid increase in the motor output to the respiratory musculature as well as an increase in the duration of inspiration.[57 134 137] In addition, increased negative pharyngeal pressure resulting, for example, from increased upper airway resistance leads to an increase in the neural output to upper airway dilator muscles.[79 132] Sleep not only imposes both resistive and elastic loads on the respiratory muscles, via upper airway narrowing and decreasing FRC, respectively, but it also compromises the compensatory mechanisms that cope with these changes. During NREM sleep, load compensation occurs but is slow and incomplete[7 134 137] with increased reliance on chemical drive which itself may be depressed (see below), the end result being a degree of hypoxaemia and carbon dioxide retention. The situation in REM is worse still, with a further increase in loading and a simultaneous failure of intercostal, accessory, upper airway dilator and expiratory muscles to assist in the necessary compensation. The coexistence of either neurological or mechanical respiratory disease, already challenging the compensatory mechanisms, further increases the tendency to hypoventilation.

Ventilatory control. Wakefulness has an important stimulatory effect on ventilation. While it appears that chemosensitivity is important for maintaining ventilation during sleep, as indicated by the increased sleep-related hypoventilation seen in patients with carotid body denervation,[22] the effects of sleep on chemoreception are far more complex and difficult to define. Standard tests of acute ventilatory responses have demonstrated varying degrees of inhibition, particularly of the response to combined hypoxia and hypercapnia, but these may overestimate the reduction in chemosensitivity as other factors such as increased upper airway resistance, impaired load compensation and changes in cerebral blood flow need to be considered.[26] On the other hand, sleep does unmask the 'apnoeic threshold', not normally seen in wakefulness.[25] Thus, in sleep, apnoeas or hypopnoeas can be produced by lowering the P_{CO_2}, as may occur during hypoxic hyperventilation.[12] This reduction in

ventilation may then result in an overshoot into hypoxic hypercapnia again, leading itself to hyperventilation and consequently a cycle of hypoxia-induced periodic breathing with large swings in oxygen saturation—a variant of *central sleep apnoea*. Ironically, sufficiently large increases in upper airway resistance may be one factor preventing periodic breathing in some subjects by limiting the hyperventilation.[26] Despite the lack of clarity with respect to sleep effects on chemosensation, it appears that there is a reduction in output from medullary respiratory neurones, particularly during NREM, whereas in REM the output from these neurones tends to be related to the variability in breathing pattern.[26] REM, however, is associated with a depression of the arousal responses to hypoxia and hypercapnia, leading to a tendency for apnoeas to be longer and desaturations more severe in that sleep stage.

Anaesthesia

In contrast to sleep, anaesthesia is a state of *unrousable* unconsciousness.

The electrophysiological nature of anaesthesia is an area of intense ongoing investigation, particularly now with devices allegedly able to monitor 'depth' of anaesthesia becoming available. It is, however, a very complex issue as different anaesthetic agents have different effects on the EEG[14] so that no unitary pattern indicating anaesthetic 'depth' exists. It is, therefore, very difficult to make any electrophysiologic comparisons between sleep and anaesthesia, although attempts are being made,[114] and such comparisons are probably irrelevant in any case, as the two states are quite distinct. With few exceptions, anaesthetic and sedative drugs produce a dose dependent depression not only of consciousness, but also of most other vital functions, including all those related to respiration. Apart from abolition of the stimulatory effects of wakefulness these include depression of hypoxic and hypercapnic responses,[116] load compensation reflexes[85]and the arousal responses that normally protect against asphyxia. As with sleep there is depression of skeletal muscle tone with reduction in FRC, predisposing to atelectasis, and upper airway muscle relaxation predisposing to obstruction. These effects are compounded by reduction in the phasic activity of intercostal and accessory respiratory muscles, increasing dependence on the diaphragm, and of the upper airway muscles during inspiration, further predisposing to obstruction as this activity acts to stiffen the airway as intraluminal pressure falls.[127]

The presence of a vigilant anaesthetist to monitor and maintain vital functions during anaesthesia protects the patient from these effects. However, drug induced sedation and post-anaesthesia drowsiness, where the borders between wakefulness, sleep and anaesthesia are less distinct and monitoring perhaps less rigorous, present great potential danger to the patient with a sleep-related breathing disorder because of the depression of these responses.

Sleep in the post–operative period

There has only been one study examining the effects of general anaesthesia alone (with isoflurane) on subsequent sleep and it would appear that this effect is negligible.[84] Other studies imply that the type of anaesthesia is also not important.[61 75] The addition of a surgical insult changes things considerably.[102] Sleep architecture is disrupted to a degree which is generally proportional to the 'magnitude' of the surgery as is the duration of the disruption, but it is important to note that there is considerable inter-individual variation and specific situations where the generalization may not hold. The disturbance takes the form of reduced total sleep time with a disproportionate reduction in REM and SWS.[8 61] At some point during the first postoperative week there is a rebound, firstly of total sleep time with mainly stage 2 usually, then a resurgence of REM ('REM rebound') and to a lesser extent SWS.[65 87]

The precise mechanism by which the surgical insult produces the sleep disruption is not completely clear but it is likely that pain plays a major role. Other factors, which may be independent of the surgery and thus account for some of the variability, are neuroendocrine, metabolic and psychological responses, opioid analgesia, and environmental factors such as noise, light and nursing activity.[75 102 105]

The extent to which these changes in sleep architecture after surgery influence morbidity and mortality is currently unknown but there has been considerable speculation based on indirect evidence.[102 104] Patients with REM predominant apnoea, for example, might be expected to have an increase in the number and degree of desaturations over a night where REM rebound is occurring[103] but this possibility has been inadequately investigated. Similarly, the occurrence of REM rebound has led to the suggestion that an associated late postoperative increase in nocturnal hypoxaemia could be contributing to mental confusion, wound breakdown, myocardial ischaemia and infarction, stroke and death.[34 35 93 98–101] While some relevant associations have been demonstrated direct evidence of causation is lacking.

While anaesthesia, of itself, may not effect subsequent sleep once the anaesthetic agents are eliminated, a considerable amount of research over the last 20 yr has considered the effects of subanaesthetic concentrations on sleep and ventilatory control. Commencing with the work of Knill's group in the 1970s,[64] conflicting results have emerged regarding the effects on ventilatory responses to hypoxia and hypercapnia of subanaesthetic concentrations of potent inhalational agents, such as might be present in the minutes to hours after emergence,[33] as well as some other drugs commonly used perioperatively. One reason for these conflicts appears to be the effect of sleep as van den Elsen, Dahan and colleagues have shown that subjects stimulated and kept awake exhibited more or less normal ventilatory responses despite the presence of the potent inhalational agent whereas those allowed to sleep exhibited ventilatory depression.[130 131] The mechanism by which

sleep might contribute to the depression of ventilatory responses by sedative agents has not yet been investigated.

Anaesthesia and sleep disordered breathing

Perioperative risks for sleep apnoea

Notwithstanding the relative paucity of specific information, knowledge of their physiological effects strongly suggests that anaesthetic, sedative and analgesic agents will aggravate or precipitate OSA by decreasing pharyngeal tone, depressing ventilatory responses to hypoxia and hypercapnia and inhibiting arousal responses to obstruction, hypoxia and hypercapnia. These latter effects frequently result in varying degrees of central respiratory depression.

A variety of surgical factors are also contributory. Surgery of the thorax and upper abdomen compromises ventilatory function,[27 66] potentially compounding the effects of any OSA or centrally mediated hypoventilation that might occur postoperatively. Surgery involving the upper airway carries the risk of postoperative swelling that can worsen or precipitate obstruction.[16 70 80 18] The same applies to situations where the nose is packed or a nasogastric tube is required, as the reduced lumen calibre will necessitate the generation of more negative pharyngeal pressures during inspiration thus promoting collapse.[122] They may also compromise therapy by making nasal CPAP difficult or unusable, and a full-face mask may be required in such circumstances. Patients are frequently nursed supine, sometimes for good reason, and as OSA is often position-dependent this, too, may contribute to increased risk of upper airway obstruction.

To whom might these risks be important?

OSA is common and anaesthetists will often deal with sufferers. There are those who present having already been diagnosed with the disorder. The majority of this group will be on some sort of treatment, usually CPAP, but with a variable degree of compliance.[36] Some will bring their CPAP machines with them to hospital while others will arrive without their equipment, seemingly quite prepared to forego treatment for the duration of their hospital stay. It can reasonably be assumed that many in this latter group are poorly compliant at home. Another group will have been diagnosed with sleep apnoea but either declined treatment from the start or failed a trial of therapy.

There are still a large number of people who present for surgery with features suggestive of sleep apnoea but who have either never even heard of the condition and/or have not sought diagnosis or treatment. There is also a final group of patients who have apnoea but either lack the overt features or have features that are missed perioperatively. Given the high prevalence of OSA in the community, there appears to be little doubt that the number of patients in these last two groups far outweighs the number having already been diagnosed.

Suspected or undiagnosed apnoea

Enquiry about snoring and sleep should be a routine component of the preoperative visit. Patients should be asked about common symptoms: heavy snoring with, perhaps, sudden awakenings associated with a choking sensation or similar; witnessed apnoea by a bed partner; waking unrefreshed in the morning perhaps even with a headache; excessive daytime sleepiness. These symptoms should particularly be sought in obese patients, middle aged and older patients and in patients with conditions leading to narrowing of the upper airway such as nasal obstruction, tonsillar hypertrophy, or retrognathia. Where difficult intubation is anticipated the possibility of sleep apnoea should also be entertained.[50] The presence of otherwise unexplained respiratory or right heart failure or polycythaemia might also point to undiagnosed (and severe) sleep apnoea.

In cases of suspected sleep apnoea, especially if thought to be severe, deferral of the surgery should be considered to enable investigation and, where indicated, institution of treatment preoperatively. In many instances, the delay this entails would be inconvenient or, in the case of emergency surgery, impossible. Where available and practicable, preoperative consultation with a sleep physician may allow a sleep study to be performed and the problem defined and treated at short notice. If not, perioperative management should be planned on the basis that the patient has the condition, according to the principles outlined in the following section with an intention to refer the patient for definitive investigation at the earliest opportunity.

Anaesthetists are in an excellent position to screen patients for sleep apnoea and as it can be associated with substantial morbidity it is a responsibility they should not ignore. A clinical suspicion of sleep apnoea may first develop at the preoperative consultation, intraoperatively (if the patient proves difficult to intubate or it is difficult to maintain the airway[50]) or postoperatively with snoring and obstruction observed in the recovery room and/or beyond. These considerations are as important to children as they are to adults, with growth and development potentially compromised by untreated sleep apnoea.[96]

Diagnosed apnoea

The preoperative assessment of patients where the diagnosis of sleep apnoea has been made should be used to establish the severity of the sleep apnoea, mode of treatment, compliance with and complications of treatment, complications of the apnoea itself and conditions the patient might have which are the cause of or otherwise associated with the apnoea.

OSA is, by definition, an airway problem and its presence may indicate a predisposition to difficulty with intubation or airway maintenance under anaesthesia. Severity of sleep apnoea may be an important predictor of these difficulties. While there are good theoretical grounds on which to suspect these associations, it is important to note that, at the

current state of knowledge, they remain speculative. Prudent anaesthetic management is guided by awareness of these possibilities.

The anaesthetic management plan is determined by the severity of sleep apnoea, how it has been managed prior to anaesthesia, the planned surgical procedure and the likely postoperative analgesic requirements. In the case of mild OSA, managed conservatively (without CPAP) presenting for a simple procedure with little anticipated postoperative discomfort, an anaesthetic technique which either avoids unconsciousness or ensures its early recovery together with close observation and nursing in the lateral posture during the early recovery process may be the only specific measures necessary. In contrast, the patient with severe OSA who has substantial analgesic requirements will need close supervision in a high dependency area postoperatively and use of nasal CPAP whenever sedated or otherwise asleep. Such patients particularly may benefit from regional anaesthetic and analgesic techniques, the potential benefit increasing with OSA severity, although complications of such techniques have occurred in this setting.[67]

Provision for 'the worst case scenario' of persistent upper airway obstruction should be made even with patients with mild OSA and a breathing circuit capable of delivering CPAP should always be available when the presence of OSA is known or suspected.

Preoperative preparation. Patients with diagnosed apnoea who are being treated with CPAP should take their equipment to the operating theatre with them for use postoperatively. These arrangements should be discussed with the patient. There are psychological as well as physiological aspects to consider. While less compliant patients may care little, there are many that are very concerned at the idea that they may stop breathing. The knowledge that their CPAP machine is available is likely to be important to them.

Attending staff must understand the use of the CPAP machine so that they are able to apply it to the patient while he/she is unable to apply it him/herself. While this knowledge may be commonplace amongst the nursing staff of some hospitals it should not be assumed. Staff should be instructed in its use prior to surgery, the patient demonstrating its function if necessary. Hospitals with their own sleep units will have nurses and/or technologists who are familiar with CPAP therapy and able to render assistance where required. This should be established beforehand and the hospital's sleep unit may have CPAP machines available to loan where needed.

It has been argued that sedative premedicants should be avoided in OSA patients.[21 133] Certainly it is sensible to exercise some care with premedication but in those patients on CPAP there is no real contraindication to even quite heavy premedication as their CPAP may be applied if they get sleepy and oxygen can be added if necessary.[94] It is appropriate to monitor oxygen saturation and for the patient to be observed. An unsupervised holding area is inappropriate for a premedicated sleep apnoea patient. If more than light premedication is prescribed then an i.v. cannula should be placed in case antagonists are required urgently. Appropriate antagonists should be immediately available. Some authors have suggested aspiration prophylaxis[21] and the possibility of airway difficulty may justify the use of antisialogogues in these patients.[133]

Intraoperative care. Choice of anaesthetic technique is important. The problems of airway maintenance intra- and postoperatively and suppression of arousal responses can be circumvented by use of regional techniques. If the surgical procedure lends itself to them and the patient is otherwise suitable they should be considered, bearing in mind the necessity for airway management should the regional technique result in unconsciousness or respiratory paralysis. If general anaesthesia is necessary then the following considerations apply.

Preparation for a possible difficult intubation should be made along with strategies to manage what may be a difficult airway intraoperatively if the patient is not to be intubated. The choice of induction and maintenance agents is probably not important although it would seem sensible to avoid large doses of longer acting drugs, especially neuromuscular blocking agents. Opioids should be used judiciously although the availability of CPAP will obviate potential difficulty postoperatively, particularly if the patient is already familiar with it. The issue of familiarity is important, as the early postoperative period is not the ideal environment for introduction of CPAP therapy, particularly if the patient is restless, in pain or hypoxaemic.

Postoperative care. In the recovery room and the postoperative ward the patient should be nursed in the lateral posture because of the particular tendency to upper airway obstruction when supine. A nasopharyngeal airway can be a useful aid during emergence.[138] Nasal CPAP should be applied where obstruction persists despite these simple measures.

Oxygen therapy alone is not an adequate treatment of OSA as the issues of recurrent arousals and of carbon dioxide retention remain. The absence of recurrent desaturation may also act to mask the presence of obstructive episodes, particularly in the presence of an inexperienced observer. Oxygen can be added to CPAP treatment. The most economical place to add it is via a side port on the CPAP mask where relatively low flows (2–4 litre min^{-1}) can produce a high $F_{I_{O_2}}$. This addition does not change the CPAP pressure supplied by most modern machines.

The potential problems associated with the use of postoperative sedatives may be circumvented by the use of regional analgesia and/or non-steroidal analgesics or, if opiates are needed, effective use of CPAP.

It is important that the patient with OSA is nursed in the appropriate postoperative environment. This issue is closely related to the patient's analgesic requirements. For the patient who requires CPAP therapy direct supervision is needed while sedated or otherwise asleep until they are

capable, unaided, of applying their therapy correctly. This may require admission to a high dependency unit for one or more days postoperatively, particularly for those patients not already familiar with CPAP therapy. On the other hand, patients who recover quickly from general anaesthesia and have little narcotic or sedative requirement, or who have good regional analgesia, may be in a position to manage their own CPAP therapy immediately following discharge from the recovery room with no need for special nursing. Where upper airway surgery has been performed, especially in the case of children, high dependency care is warranted. Postoperative swelling has been known to exacerbate apnoea after adenotonsillectomy or uvulopalatopharyngoplasty[16 80] and death due to obstruction has occurred after velopharyngeal repair of cleft palate.[70 129] If serious compromise of upper airway patency is anticipated after upper airway surgery then undue reliance on CPAP is inappropriate. The patient may require prolonged tracheal intubation or, where several days or more of airway compromise is anticipated, tracheotomy.

Patients with nasogastric tubes and those having nasal surgery present a special difficulty. The presence of a nasogastric tube does not preclude the application of CPAP as the nasal mask can be applied over the tube, which runs under the mask cushion, but leakage and comfort may be a problem. Patients who have had nasal surgery performed are problematic, particularly if their noses have been packed. A nasopharyngeal airway may be tolerated and it may also be possible to have the surgeon pack the nose around it, although it may have limited calibre. CPAP may need to be applied via a full face rather than nasal mask in such cases.

Summary

Sleep disordered breathing is a common problem affecting all age groups, particularly in association with certain other medical conditions and syndromes. The pathological consequences of the disorder may be severe, with significant implications for the perioperative management of sufferers.

Research into the effects of surgery and anaesthesia on sleep is very much in its infancy. Understanding of the implications of sleep disturbance and sleep disordered breathing for perioperative morbidity and mortality is limited. While several observations have led to considerable speculation in the literature, evidence of a causal relationship is still largely lacking.

Anaesthetists are ideally placed to screen large numbers of people for sleep disordered breathing, a source of considerable community morbidity. Recognizing the symptoms, signs and associations of the condition during the preoperative visit is important in planning management, as is recognition of the likelihood of OSA in patients who present difficulty with tracheal intubation or airway maintenance. Particular care is required in the perioperative management of patients with diagnosed or suspected sleep apnoea.

Acknowledgements

John Loadsman is the recipient of grants from the Australian and New Zealand College of Anaesthetists and the Australian Society of Anaesthetists, as well as departmental research donations from Roche Pharmaceuticals, Novartis Pharmaceuticals and Hewlett-Packard. We are grateful for this assistance.

References

1 Practice parameters for the use of laser-assisted uvulopalatoplasty. Standards of Practice Committee of the American Sleep Disorders Association. *Sleep* 1994; **17**: 744–8

2 Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. American Sleep Disorders Association. *Sleep* 1995; **18**: 511–3

3 Practice parameters for the treatment of obstructive sleep apnea in adults: the efficacy of surgical modifications of the upper airway. Report of the American Sleep Disorders Association. *Sleep* 1996; **19**: 152–5

4 AASM taskforce report: sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; **22**: 667–89

5 Ambrogetti A, Olson LG, Saunders NA. Differences in the symptoms of men and women with obstructive sleep apnoea. *Aust N Z J Med* 1991; **21**: 863–6

6 Ancoli-Israel S, Klauber MR, Stepnowsky C, *et al.* Sleep-disordered breathing in African-American elderly. *Am J Respir Crit Care Med* 1995; **152**: 1946–9

7 Aserinsky E, Kleitman N. Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 1953; **118**: 273

8 Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *BMJ Clin Res Ed* 1985; **290**: 1029–32

9 Badr MS, Skatrud JB, Dempsey JA, Begle RL. Effect of mechanical loading on expiratory and inspiratory muscle activity during NREM sleep. *J Appl Physiol* 1990; **68**: 1195–202

10 Ballard RD, Saathoff MC, Patel DK, Kelly PL, Martin RJ. Effect of sleep on nocturnal bronchoconstriction and ventilatory patterns in asthmatics. *J Appl Physiol* 1989; **67**: 243–9

11 Bearpark H, Elliott L, Grunstein R, *et al.* Snoring and sleep apnea. A population study in Australian men. *Am J Respir Crit Care Med* 1995; **151**: 1459–65

12 Berssenbrugge A, Dempsey J, Iber C, Skatrud J, Wilson P. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. *J Physiol* 1983; **343**: 507–26

13 Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med* 1998; **157**: 144–8

14 Black S, Mahla ME, Cucchiara RF. Neurologic Monitoring. In: Miller RD, eds. *Anesthesia*. Vol 1, 4 Edn. New York: Churchill Livingstone, Inc., 1994; 1322–1325

15 Brooks B, Cistulli PA, Borkman M, *et al.* Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *J Clin Endocrinol Metab* 1994; **79**: 1681–5

16 Burgess LP, Derderian SS, Morin GV, Gonzalez C, Zajtchuk JT. Postoperative risk following uvulopalatopharyngoplasty for obstructive sleep apnea. *Otolaryngol Head Neck Surg* 1992; **106**: 81–6

17 Carlson JT, Hedner JA, Ejnell H, Peterson LE. High prevalence of

hypertension in sleep apnea patients independent of obesity. *Am J Respir Crit Care Med* 1994; **150**: 72–7

18 Cistulli PA. Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment. *Respirology* 1996; **1**: 167–74

19 Cistulli PA, Sullivan CE. Sleep-disordered breathing in Marfan's syndrome. *Am Rev Resp Dis* 1993; **147**: 645–8

20 Colmenero C, Esteban R, Albarino AR, Colmenero B. Sleep apnoea syndrome associated with maxillofacial abnormalities. *J Laryngol Otol* 1991; **105**: 94–100

21 Connolly LA. Anesthetic management of obstructive sleep apnea patients. *J Clin Anesth* 1991; **3**: 461–9

22 Connolly RA, Baker AB. Excision of bilateral carotid body tumours. *Anaesth Intens Care* 1995; **23**: 342–5

23 Conradt R, Hochban W, Heitmann J, *et al.* Sleep fragmentation and daytime vigilance in patients with OSA treated by surgical maxillomandibular advancement compared to CPAP therapy. *J Sleep Res* 1998; **7**: 217–23

24 Dement WC, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalogr Clin Neurophysiol* 1957; **9**: 673

25 Dempsey JA, Skatrud JB. A sleep-induced apneic threshold and its consequences. *Am Rev Resp Dis* 1986; **133**: 1163–70

26 Dempsey JA, Skatrud JB, Badr MS, Henke KG. Effects of Sleep on the Regulation of Breathing and Respiratory Muscle Function. In: Crystal RG, West JB, *et al.*, eds. *The Lung: Scientific Foundations*. New York: Raven Press, Ltd., 1991; 1615–1629

27 Entwistle MD, Roe PG, Sapsford DJ, Berrisford RG, Jones JG. Patterns of oxygenation after thoracotomy. *Br J Anaesth* 1991; **67**: 704–11

28 Feinberg I. Changes in sleep cycle patterns with age. *J Psychiatr Res* 1974; **10**: 283–306

29 Flavell H, Marshall R, Thornton AT, *et al.* Hypoxia episodes during sleep in high tetraplegia. *Arch Phys Med Rehabil* 1992; **73**: 623–7

30 Galatius-Jensen S, Hansen J, Rasmussen V, *et al.* Nocturnal hypoxaemia after myocardial infarction: association with nocturnal myocardial ischaemia and arrhythmias. *Br Heart J* 1994; **72**: 23–30

31 Gastaut H, Tassinari CA, Duron B. Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick syndrome. *Brain Res* 1966; **1**: 167–86

32 Gay PC, Westbrook PR, Daube JR, *et al.* Effects of alterations in pulmonary function and sleep variables on survival in patients with amyotrophic lateral sclerosis. *Mayo Clin Proc* 1991; **66**: 686–94

33 Gelb AW, Knill RL. Subanaesthetic halothane: its effect on regulation of ventilation and relevance to the recovery room. *Can Anaesth Soc J* 1978; **25**: 488–94

34 Gill NP, Wright B, Reilly CS. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. *Br J Anaesth* 1992; **68**: 471–3

35 Goldman MD, Reeder MK, Muir AD, *et al.* Repetitive nocturnal arterial oxygen desaturation and silent myocardial ischemia in patients presenting for vascular surgery. *J Am Geriatr Soc* 1993; **41**: 703–9

36 Grunstein RR. Sleep-related breathing disorders. 5. Nasal continuous positive airway pressure treatment for obstructive sleep apnoea. *Thorax* 1995; **50**: 1106–13

37 Grunstein RR, Ellis E, Hillman D, *et al.* Treatment of sleep disordered breathing. Thoracic Society of Australia and New Zealand. *Med J Aust* 1991; **154**: 355–9

38 Grunstein RR, Handelsman DJ, Lawrence SJ, *et al.* Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. *J Clin Endocrinol Metab* 1989; **68**: 352–8

39 Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. *Ann Intern Med* 1991; **115**: 527–32

40 Grunstein RR, Sullivan CE. Sleep apnea and hypothyroidism: mechanisms and management. *Am J Med* 1988; **85**: 775–9

41 Grunstein RR, Wilcox I. Sleep-disordered breathing and obesity. *Baillieres Clin Endocrinol Metab* 1994; **8**: 601–28

42 Guilleminault C, Cummiskey J, Motta J, Lynne-Davies P. Respiratory and hemodynamic study during wakefulness and sleep in myotonic dystrophy. *Sleep* 1978; **1**: 19–31

43 Guilleminault C, Dement WC. General Physiology of Sleep. In: Crystal RG, West JB, *et al.*, eds. *The Lung: Scientific Foundations*. New York: Raven Press, Ltd., 1991; 1609–1614

44 Guilleminault C, Lehrman AT, Forno L, Dement WC. Sleep apnoea syndrome: states of sleep and autonomic dysfunction. *J Neurol Neurosurg Psychiatry* 1977; **40**: 718–25

45 Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest* 1993; **104**: 781–7

46 Harris JC, Allen RP. Is excessive daytime sleepiness characteristic of Prader-Willi syndrome? The effects of weight change. *Arch Pediatr Adolesc Med* 1996; **150**: 1288–93

47 Helfaer MA, Wilson MD. Obstructive sleep apnea, control of ventilation, and anesthesia in children. *Pediatr Clin North Am* 1994; **41**: 131–51

48 Henke KG, Dempsey JA, Badr MS, Kowitz JM, Skatrud JB. Effect of sleep-induced increases in upper airway resistance on respiratory muscle activity. *J Appl Physiol* 1991; **70**: 158–68

49 Hill NS, Redline S, Carskadon MA, Curran FJ, Millman RP. Sleep-disordered breathing in patients with Duchenne muscular dystrophy using negative pressure ventilators. *Chest* 1992; **102**: 1656–62

50 Hiremath AS, Hillman DR, James AL, *et al.* Relationship between difficult tracheal intubation and obstructive sleep apnoea. *Br J Anaesth* 1998; **80**: 606–11

51 Hoffstein V, Szalai JP. Predictive value of clinical features in diagnosing obstructive sleep apnea. *Sleep* 1993; **16**: 118–22

52 Hsu AA, Staats BA. 'Postpolio' sequelae and sleep-related disordered breathing. *Mayo Clin Proc* 1998; **73**: 216–24

53 Hu FB, Willett WC, Colditz GA, *et al.* Prospective study of snoring and risk of hypertension in women. *Am J Epidemiol* 1999; **150**: 806–16

54 Hudgel DW, Devadatta P. Decrease in functional residual capacity during sleep in normal humans. *J Appl Physiol Resp Environ Exercise Physiol* 1984; **57**: 1319–22

55 Hudgel DW, Martin RJ, Johnson B, Hill P. Mechanics of the respiratory system and breathing pattern during sleep in normal humans. *J Appl Physiol Resp Environ Exercise Physiol* 1984; **56**: 133–7

56 Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990; **336**: 261–4

57 Iber C, Berssenbrugge A, Skatrud JB, Dempsey JA. Ventilatory adaptations to resistive loading during wakefulness and non-REM sleep. *J Appl Physiol Resp Environ Exercise Physiol* 1982; **52**: 607–14

58 Jennum P, Borgesen SE. Intracranial pressure and obstructive sleep apnea. *Chest* 1989; **95**: 279–83

59 Kales A, Caldwell AB, Cadieux RJ, *et al.* Severe obstructive sleep apnea-II: Associated psychopathology and psychosocial consequences. *J Chronic Dis* 1985; **38**: 427–34

60 Kales A, Jacobson A, Kales JD, Kun T, Weissbuch R. All-night EEG sleep measurements in young adults. *Psychonomic Sci* 1967; **7**: 67

61 Kavey NB, Ahshuler KZ. Sleep in herniorrhaphy patients. *Am J Surg* 1979; **138**: 683–7

62 Kerr P, Shoenut JP, Millar T, Buckle P, Kryger MH. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. *Chest* 1992; **101**: 1539–44

63 Kimmel PL, Miller G, Mendelson WB. Sleep apnea syndrome in chronic renal disease. *Am J Med* 1989; **86**: 308–14

64 Knill RL, Gelb AW. Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. *Anesthesiology* 1978; **49**: 244–51

65 Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; **73**: 52–61

66 Knudsen J. Duration of hypoxaemia after uncomplicated upper abdominal and thoraco-abdominal operations. *Anaesthesia* 1970; **25**: 372–7

67 Kontrobarsky Y, Love J. Gluteal compartment syndrome following epidural analgesic infusion with motor blockage. *Anaesth Intens Care* 1997; **25**: 696–8

68 Koskenvuo M, Kaprio J, Telakivi T, *et al.* Snoring as a risk factor for ischaemic heart disease and stroke in men. *BMJ Clin Res Ed* 1987; **294**: 16–9

69 Koskenvuo M, Partinen M, Kaprio J, *et al.* Snoring and cardiovascular risk factors. *Ann Med* 1994; **26**: 371–6

70 Kravath RE, Pollak CP, Borowiecki B, Weitzman ED. Obstructive sleep apnea and death associated with surgical correction of velopharyngeal incompetence. *J Pediatr* 1980; **96**: 645–8

71 Kudrow L, McGinty DJ, Phillips ER, Stevenson M. Sleep apnea in cluster headache. *Cephalalgia* 1984; **4**: 33–8

72 Laks L, Lehrhaft B, Grunstein RR, Sullivan CE. Pulmonary artery pressure response to hypoxia in sleep apnea. *Am J Respir Crit Care Med* 1997; **155**: 193–8

73 Langevin B, Fouque D, Leger P, Robert D. Sleep apnea syndrome and end-stage renal disease. Cure after renal transplantation. *Chest* 1993; **103**: 1330–5

74 Lavie P, Herer P, Peled R, *et al.* Mortality in sleep apnea patients: a multivariate analysis of risk factors. *Sleep* 1995; **18**: 149–57

75 Lehmkuhl P, Prass D, Pichlmayr I. General anesthesia and postnarcotic sleep disorders. *Neuropsychobiology* 1987; **18**: 37–42

76 Loomis AL, Harvey EN, Hobart GA. Cerebral states during sleep as studied by human brain potentials. *J Exp Psychol* 1937; **21**: 127

77 Lugaresi E, Mondini S, Zucconi M, Montagna P, Cirignotta F. Staging of heavy snorers' disease. A proposal. *Bull Eur Physiopathol Resp* 1983; **19**: 590–4

78 Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SL. Obstructive sleep apnea in children with Down syndrome. *Pediatrics* 1991; **88**: 132–9

79 Mathew OP, Abu-Osba YK, Thach BT. Influence of upper airway pressure changes on genioglossus muscle respiratory activity. *J Appl Physiol Resp Environ Exercise Physiol* 1982; **52**: 438–44

80 McColley SA, April MM, Carroll JL, Naclerio RM, Loughlin GM. Respiratory compromise after adenotonsillectomy in children with obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 1992; **118**: 940–3

81 McGinty DJ, Drucker-Colin R, Morrison A, Parmeggiani PL. *Brain Mechanisms of Sleep*. New York: Raven Press, 1985

82 Miljeteig H, Hoffstein V, Cole P. The effect of unilateral and bilateral nasal obstruction on snoring and sleep apnea. *Laryngoscope* 1992; **102**: 1150–2

83 Mohsenin V, Valor R. Sleep apnea in patients with hemispheric stroke. *Arch Phys Med Rehabil* 1995; **76**: 71–6

84 Moote CA, Knill RL. Isoflurane anesthesia causes a transient alteration in nocturnal sleep. *Anesthesiology* 1988; **69**: 327–31

85 Moote CA, Knill RL, Clement J. Ventilatory compensation for continuous inspiratory resistive and elastic loads during halothane anesthesia in humans. *Anesthesiology* 1986; **64**: 582–9

86 O'Sullivan RA, Hillman DR, Mateljan R, Pantin C, Finucane KE. Mandibular advancement splint: an appliance to treat snoring and obstructive sleep apnea. *Am J Respir Crit Care Med* 1995; **151**: 194–8

87 Orr WC, Stahl ML. Sleep disturbances after open heart surgery. *Am J Cardiol* 1977; **39**: 196–201

88 Pantin CC, Hillman DR, Tennant M. Dental side effects of an oral device to treat snoring and obstructive sleep apnea. *Sleep* 1999; **22**: 237–40

89 Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. *Chest* 1994; **105**: 434–40

90 Popper RA, Leidinger MJ, Williams AJ. Endoscopic observations of the pharyngeal airway during treatment of obstructive sleep apnea with nasal continuous positive airway pressure – a pneumatic splint. *West J Med* 1986; **144**: 83–5

91 Rechtschaffen A, Kales A. *A Manual of Standardised Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects.* Bethesda, Maryland: US Department of Health, Education and Welfare, 1968

92 Redline S, Tosteson T, Tishler PV, *et al.* Studies in the genetics of obstructive sleep apnea. Familial aggregation of symptoms associated with sleep-related breathing disturbances. *Am Rev Resp Dis* 1992; **145**: 440–4

93 Reeder MK, Muir AD, Foex P, *et al.* Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia. *Br J Anaesth* 1991; **67**: 626–31

94 Rennotte MT, Baele P, Aubert G, Rodenstein DO. Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. *Chest* 1995; **107**: 367–74

95 Roa NL, Moss KS. Treacher-Collins syndrome with sleep apnea: anesthetic considerations. *Anesthesiology* 1984; **60**: 71–3

96 Rosen CL. Obstructive sleep apnea syndrome (OSAS) in children: diagnostic challenges. *Sleep* 1996; **19**: S274–7

97 Rosen CL, D'Andrea L, Haddad GG. Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. *Am Rev Resp Dis* 1992; **146**: 1231–4

98 Rosenberg J, Dirkes WE, Kehlet H. Episodic arterial oxygen desaturation and heart rate variations following major abdominal surgery. *Br J Anaesth* 1989; **63**: 651–4

99 Rosenberg J, Kehlet H. Postoperative mental confusion—association with postoperative hypoxemia. *Surgery* 1993; **114**: 76–81

100 Rosenberg J, Pedersen MH, Ramsing T, Kehlet H. Circadian variation in unexpected postoperative death. *Br J Surg* 1992; **79**: 1300–2

101 Rosenberg J, Rasmussen V, von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG abnormalities. *Br J Anaesth* 1990; **65**: 684–91

102 Rosenberg J, Rosenberg-Adamsen S, Kehlet H. Post-operative sleep disturbance: causes, factors and effects on outcome. *Eur J Anaesthesiol* 1995; **10** (Suppl): 28–30

103 Rosenberg J, Wildschiodtz G, Pedersen MH, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *Br J Anaesth* 1994; **72**: 145–50

104 Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth* 1996; **76**: 552–9

105 Rosenberg-Adamsen S, Skarbye M, Wildschiodtz G, Kehlet H, Rosenberg J. Sleep after laparoscopic cholecystectomy. *Br J Anaesth* 1996; **77**: 572–5

106 Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 1994; **149**: 416–22

107 Sauerland EK, Harper RM. The human tongue during sleep: electromyographic activity of the genioglossus muscle. *Exp Neurol* 1976; **51**: 160–70

108 Seigel JM. Brain stem mechanisms generating REM sleep. In: Kryger M, Roth R, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia: WB Saunders, 1989; 104–120

109 Semenza GL, Pyeritz RE. Respiratory complications of mucopolysaccharide storage disorders. *Medicine* 1988; **67**: 209–19

110 Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996; **19**: 156–77

111 Skatrud J, Iber C, McHugh W, Rasmussen H, Nichols D. Determinants of hypoventilation during wakefulness and sleep in diaphragmatic paralysis. *Am Rev Resp Dis* 1980; **121**: 587–93

112 Skatrud JB, Dempsey JA. Airway resistance and respiratory muscle function in snorers during NREM sleep. *J Appl Physiol* 1985; **59**: 328–35

113 Skatrud JB, Dempsey JA, Badr S, Begle RL. Effect of airway impedance on CO_2 retention and respiratory muscle activity during NREM sleep. *J Appl Physiol* 1988; **65**: 1676–85

114 Sleigh JW, Andrzejowski J, Steyn-Ross A, Steyn-Ross M. The bispectral index: a measure of depth of sleep? *Anesth Analg* 1999; **88**: 659–61

115 Solin P, Roebuck T, Swieca J, Walters EH, Naughton MT. Effects of cardiac dysfunction on non-hypercapnic central sleep apnea. *Chest* 1998; **113**: 104–10

116 Sollevi A, Lindahl SG. Hypoxic and hypercapnic ventilatory responses during isoflurane sedation and anaesthesia in women. *Acta Anaesthesiol Scand* 1995; **39**: 931–8

117 Stern E, Parmelee AH, Akiyama Y, Schultz MA, Wenner WH. Sleep cycle characteristics in infants. *Pediatrics* 1969; **43**: 65–70

118 Stokes DC, Phillips JA, Leonard CO, *et al.* Respiratory complications of achondroplasia. *J Pediatr* 1983; **102**: 534–41

119 Stoohs R, Guilleminault C. MESAM 4: an ambulatory device for the detection of patients at risk for obstructive sleep apnea syndrome (OSAS). *Chest* 1992; **101**: 1221–7

120 Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991; **46**: 85–90

121 Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981; **1**: 862–5

122 Taasan V, Wynne JW, Cassisi N, Block AJ. The effect of nasal packing on sleep-disordered breathing and nocturnal oxygen desaturation. *Laryngoscope* 1981; **91**: 1163–72

123 Taasan VC, Block AJ, Boysen PG, Wynne JW. Alcohol increases sleep apnea and oxygen desaturation in asymptomatic men. *Am J Med* 1981; **71**: 240–5

124 Tabachnik E, Muller NL, Bryan AC, Levison H. Changes in ventilation and chest wall mechanics during sleep in normal adolescents. *J Appl Physiol Resp Environ Exercise Physiol* 1981; **51**: 557–64

125 Tirosh E, Borochowitz Z. Sleep apnea in fragile X syndrome. *Am J Med Genet* 1992; **43**: 124–7

126 Tsai WH, Flemons WW, Whitelaw WA, Remmers JE. A comparison of apnea-hypopnea indices derived from different definitions of hypopnea. *Am J Respir Crit Care Med* 1999; **159**: 43–8

127 Tusiewicz K, Bryan AC, Froese AB. Contributions of changing rib cage—diaphragm interactions to the ventilatory depression of halothane anesthesia. *Anesthesiology* 1977; **47**: 327–37

128 Tusiewicz K, Moldofsky H, Bryan AC, Bryan MH. Mechanics of the rib cage and diaphragm during sleep. *J Appl Physiol Resp Environ Exercise Physiol* 1977; **43**: 600–2

129 Valnicek SM, Zuker RM, Halpern LM, Roy WL. Perioperative complications of superior pharyngeal flap surgery in children. *Plast Reconstr Surg* 1994; **93**: 954–8

130 van den Elsen M, Sarton E, Teppema L, Berkenbosch A, Dahan A. Influence of 0.1 minimum alveolar concentration of sevoflurane, desflurane and isoflurane on dynamic ventilatory response to hypercapnia in humans. *Br J Anaesth* 1998; **80**: 174–82

131 van den Elsen MJ, Dahan A, Berkenbosch A, *et al.* Does subanesthetic isoflurane affect the ventilatory response to acute isocapnic hypoxia in healthy volunteers? *Anesthesiology* 1994; **81**: 860–7; discussion 26A

132 van Lunteren E, Van de Graaff WB, Parker DM, *et al.* Nasal and laryngeal reflex responses to negative upper airway pressure. *J Appl Physiol Resp Environ Exercise Physiol* 1984; **56**: 746–52

133 Warwick JP, Mason DG. Obstructive sleep apnoea syndrome in children. *Anaesthesia* 1998; **53**: 571–9

134 Wiegand L, Zwillich CW, White DP. Sleep and the ventilatory response to resistive loading in normal men. *J Appl Physiol* 1988; **64**: 1186–95

135 Wilcox I, Grunstein RR, Hedner JA, *et al.* Effect of nasal continuous positive airway pressure during sleep on 24-hour blood pressure in obstructive sleep apnea. *Sleep* 1993; **16**: 539–44

136 Williams RL, Agnew HW Jr, Webb WB. Sleep patterns in young adults: An EEG study. *Electroencephalogr Clin Neurophysiol* 1964; **17**: 376

137 Wilson PA, Skatrud JB, Dempsey JA. Effects of slow wave sleep on ventilatory compensation to inspiratory elastic loading. *Resp Physiol* 1984; **55**: 103–20

138 Young ML, Hanson CW. An alternative to tracheostomy following transsphenoidal hypophysectomy in a patient with acromegaly and sleep apnea. *Anesth Analg* 1993; **76**: 446–9

139 Young T, Palta M, Dempsey J, *et al.* The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; **328**: 1230–5