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Table 18.5.1.2 Features distinguishing periodic occurrence of laryngeal obstruction from asthma

	Inducible laryngeal obstruction	Asthma
Onset	Rapid (within seconds)	Variable (within minutes)
Pattern	Can resolve rapidly	Variable but typically symptoms but persistent during exacerbation
Inhaled drug therapy	Largely ineffective	B_2 agonist usually effective
Breathing characteristics	Monophonic inspiratory wheeze, prolonged inspiratory phase	Polyphonic expiratory wheeze, prolonged expiratory phase
Regional limitation	Upper airways, neck	Lower airways, chest
Symptoms	Dyspnoea, wheeze, stridor, cough, throat/chest tightness, dysphonia	Dyspnoea, wheeze, cough, chest tightness
Precipitating factors	Exercise, emotional stress, cold air, strong odours/scents	Exercise, infections, cold air, allergies, stress

Laryngeal dysfunction

The anatomical position of the larynx dictates its role as the true 'gateway' to the airways, and complex reflex mechanisms have evolved to prime the larynx in a state of 'readiness for closure' (i.e. in order to protect the lower airways). Despite this, on a day-to-day basis, and in most individuals, the larynx functions autonomously many thousands of times daily, and without higher cortical response. However, in some situations the larynx may adopt a physiological state that could be considered maladaptive or 'dysfunctional' and close acutely (e.g. in the state of laryngospasm).

There is a spectrum of 'laryngeal dysfunction' disorders, which may be viewed as overlapping conditions with shared manifestations. Many patients with chronic nonproductive cough can describe features of a general 'laryngeal hypersensitivity', and at times this may extend to a clinical situation characterized by laryngeal narrowing with symptoms arising from the voice box (e.g. dysphonia or globus). However, it is important that clinicians consider and exclude structural or neurological causes of laryngeal disease before they consider the diagnosis of dysfunction or hypersensitivity.

The term *vocal cord dysfunction* has been used for over 40 years to describe the phenomenon of inappropriate vocal cord adduction, which results in distressing symptoms such as dyspnoea, wheeze, and laryngeal discomfort. Several terms have subsequently been used to describe a variety of laryngeal closure syndromes, and most recently the term *periodic occurrence of laryngeal obstruction (POLO)* has been advocated. This term is preferred because it aptly describes the temporal nature of the condition, but also acknowledges the fact that, in many cases, the obstruction may involve structures within the larynx that are distinct from the vocal cords (i.e. supraglottic adduction classically seen in exercise-induced laryngeal obstruction). The term laryngospasm is best reserved for the condition of acute, catastrophic laryngeal closure, which can result in a loss of consciousness. This typically occurs following laryngeal instrumentation.

A diagnosis of POLO may be suggested by features in the history (Table 18.5.1.2) and intermittent abnormalities on lung function testing, but ultimately a secure diagnosis is often dependent on nasendoscopy being performed when symptoms are present.

Treatment is targeted at minimizing any aggravating factors (e.g. reflux or sino-nasal disease) and use of speech and language therapy. Low doses of amitriptyline have been used to treat vocal cord dysfunction, and local botulinum toxin injection has been used successfully to treat laryngospasm.

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18.5.2 Sleep-related breathing disorders

Mary J. Morrell, Julia Kelly, Alison McMillan, and Matthew Hind

ESSENTIALS

Obstructive sleep apnoea and other sleep-related breathing problems significantly impair the functioning of about 0.5–1% of the population.

Obstructive sleep apnoea

Obstructive sleep apnoea in adults is usually caused by obesity and fat deposits in the neck area (typically collar size of 17 inches (43 cm) or more), when the withdrawal of postural muscle tone during sleep allows the pharyngeal dilators to be overwhelmed, leading to

excessive narrowing or collapse of the airway, with consequent apnoea and sleep fragmentation.

Clinical features—there is a continuum from light intermittent snoring through to severe obstructive sleep apnoea, the main symptom of which is daytime hypersomnolence. Other common symptoms are loud snoring, restless or unrefreshing sleep, observed apnoeas, nocturia, and changes in mood.

Diagnosis—the Epworth Sleepiness Scale, in which the patient is asked to state how likely they are to doze off or fall asleep in several ordinary situations (e.g. sitting and reading), is well validated. Patients with high scores generally merit a sleep study to (1) assess sleep fragmentation, (2) establish if a respiratory problem is responsible, and (3) decide if upper airway obstruction is the primary cause. Classical obstructive sleep apnoea causes a snoring–silence–snoring pattern of sleep, together with body movements and oscillations in the pulse and Sao_2.

Management—mild symptoms may resolve with lifestyle changes such as: (1) losing weight, the most important recommendation; (2) learning to sleep on the side and avoiding sleeping on the back; (3) no alcohol after 18.00 h; (4) no sedatives; (5) stopping smoking; (6) keeping the nose as clear as possible. There is only one fully effective therapy for moderate to severe obstructive sleep apnoea—continuous positive airway pressure.

Prognosis—vascular mortality is higher than average, although some studies have questioned this link.

Sleep-induced hypoventilation and central sleep apnoea

Aetiology—breathing during sleep may decrease because of a reduction in Central neural output to the respiratory muscles, which can be caused by (1) absent ventilatory drive—Ondine's curse; (2) unstable ventilatory drive; (3) REM-related oscillations.

Clinical features—some central apnoeas present with daytime sleepiness (similar to obstructive sleep apnoea), whereas others present with symptoms of respiratory failure such as morning headaches with confusion, cyanosis, and ankle oedema.

Management—without treatment, the chronic ventilatory failure associated with some neurological disorders usually progresses rapidly to death, or more slowly in lung disease or chest wall disease. Supporting breathing overnight can reverse both nocturnal and daytime ventilatory failure in the short term, and can also prolong life.

Introduction

Establishing and maintaining sleep involves complex neural processes. The deregulation of these processes can result in sleep disorders, including those caused by breathing-related complaints. Sleep is a fundamental requirement for life and as such the symptoms associated with breathing disorders that occur during sleep are common (e.g. hypersomnolence) and changes in mood. All physicians from all specialties are likely to encounter them and need to understand their aetiology and treatment. This chapter focuses on the diagnosis and clinical management of sleep-related breathing disorders, the most common of which is obstructive sleep apnoea (OSA). It will also include brief descriptions of the differential diagnosis for respiratory and nonrespiratory sleep disorders.

Breathing during sleep

Healthy sleep

Sleep onset occurs through a process of reciprocal inhibition between wake and sleep promoting neurons located in the ventrolateral preoptic nucleus, and other areas of the hypothalamus and reticular activating system; an 'all-or-nothing' neural switching mechanism prevents occurrence of intermediate conscious states. Sleep is most often initiated (in adults) as nonrapid eye movement (NREM) sleep, defined by the synchronization of electro-encephalogram (EEG) producing characteristic waveforms. NREM predominates early in sleep and is split into light sleep (stages 1 and 2) and deep or slow wave sleep (stage 3; see Fig. 18.5.2.1a).

Episodes of rapid eye movement (REM) sleep occur approximately every 90 minutes, and the duration of REM sleep increases as the night progresses. REM sleep is also called desynchronized sleep, because it is defined by EEG desynchronization, postural muscle atonia, and rapid eye movements; in patients with sleep-related breathing disorders, muscle atonia during REM can exacerbate disease severity.

Each night, the 90 minute NREM–REM cycles are repeated approximately 3–6 times. The occurrence of NREM sleep early

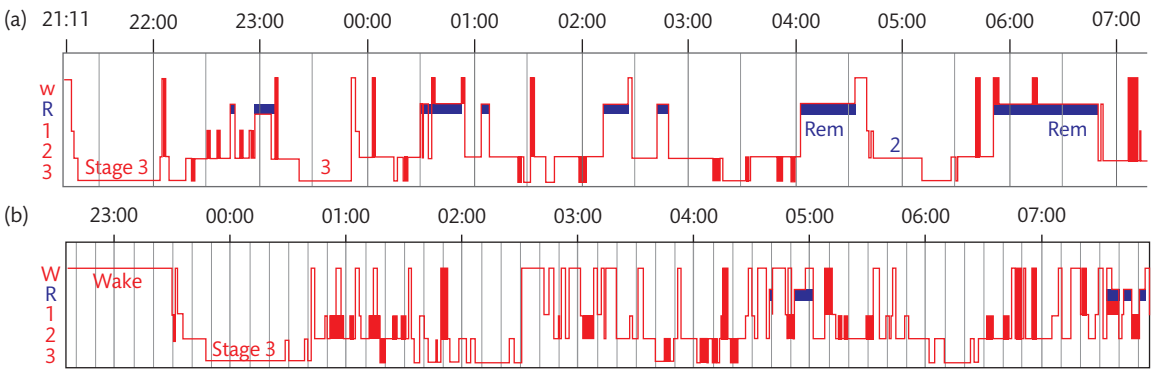

Fig. 18.5.2.1 (a) Overnight sleep patterns (hypnogram), obtained from electroencephalography, illustrating sleep cycles in a young healthy person. Note that NREM is the first sleep, and the first REM sleep occurs after approximately 90 minutes; throughout the night there are occasional brief arousals from sleep. (b) Sleep cycles in a patient with OSA. Note, throughout the night there are frequent, brief arousal from sleep with a reduction in both NREM stage 3 and REM sleep. W: wake; R: REM sleep (marked in blue); 1, 2, 3: NREM stage 1, 2, and 3 sleep.

in the night is regulated by the need to sleep (sleep homeostasis). The predominance of REM sleep later in the night is controlled by circadian rhythm. Sleep cycles can be disturbed by sleep-related breathing disorders that typically cause a reduction in the amount of NREM stage 3 sleep, delayed or reduced REM sleep, and frequent arousal from sleep (Fig. 18.5.2.1b). Nonrespiratory sleep disorders, such as narcolepsy and parasomnias, can also disrupt overnight sleep and their recognition is essential when making a differential diagnosis.

Regulation of breathing during sleep

Minute ventilation is reduced by approximately 10% at sleep onset, mainly due to a reduction in tidal volume. The sleep-related changes in breathing result from a loss of the 'wakefulness drive to breathe', a reduction in chemosensitivity and metabolism (with an associated decrease in both CO_2 production and oxygen consumption) plus changes in respiratory mechanics. The ability to establish stable breathing during sleep depends on the respiratory control system responding appropriately to these changes. If it does not, breathing disorders occur, such as OSA, central sleep apnoea, and Cheyne–Stokes respiration (Fig. 18.5.2.2).

The term 'wakefulness drive to breathe' describes the influence of wake-related cerebral activity on the regulation of breathing. The specific neural origin of the drive to breathe remains uncertain, though it includes suprabrainstem structures. The wakefulness drive is by definition absent during sleep, which means that breathing is primarily controlled by the central and peripheral chemoreceptors. In the case of the central chemoreceptors (located in the brainstem), changes in the pH of the cerebral spinal fluid elicit a central chemoreceptor response resulting in an appropriate change in ventilation. Cerebral blood flow is exquisitely sensitive to CO_2, which effectively modulates the stimulation of the central chemoreceptors. The cerebral blood flow response to CO_2 is reduced in NREM sleep, as are the ventilatory responses, contributing to a relative hypercapnia. In healthy people at sea level, the sleep-related increase in $PaCO_2$ is approximately 0.2–1 KPa, with a decrease in arterial oxygen saturation of approximately 1–2%.

Waking from sleep triggers hyperventilation (due to sleep-related hypercapnia), with a resulting fall in $PaCO_2$ to presleep (wake) levels. Upon resumption of sleep, the wake-related $PaCO_2$ is detected as a relative hypocapnia that causes a subsequent hypoventilation (hypopnoea), or apnoea if the $PaCO_2$ is below the level required to maintain stable breathing (the apnoeic threshold). This feedback and feed-forward mechanism explains how one respiratory event begets another to perpetuate (central) respiratory instability (Fig. 18.5.2.2).

Failure of the regulation of breathing during sleep in heart failure

Close proximity of the sleeping PaCO2 to the apnoeic threshold increases the propensity to develop central sleep apnoea. In chronic heart failure, stimulation of juxtacapillary receptors, due to pulmonary oedema exacerbated by a supine posture (increased venous return), produces hyperventilation and a lowering of the PaCO2 towards the apnoeic threshold.

There is a high prevalence of central sleep apnoea in patients with chronic heart failure, independent of the severity of heart failure, as measured by left ventricular ejection fraction. Additional mechanisms which may contribute to central sleep apnoea in heart failure include: (1) poor sleep with increased spontaneous arousal, due to increased sympathetic activity or related to medication (e.g. diuretics, β-blockers, ACE inhibitors, and ARBs); (2) increased central and peripheral chemosensitivity; (3) prolonged circulation time; (4) development of OSA due to upper airway oedema.

Respiratory muscle activity during sleep

Sleep is associated with a reduction in efferent activity to the thoracic and pharyngeal muscles. In young, nonobese people who do not snore, the sleep-related reduction in neural drive results in a relatively small reduction in pharyngeal airway lumen calibre, whereas in people who snore the reduction in the size of the airway lumen is greater, with a subsequent increase in resistance and turbulent airflow passing over the vocal cords causing snoring. Further reduction in airway calibre and flow can lead to mild sleep apnoea and upper airway resistance syndrome (Fig. 18.5.2.2). The mechanical load on the respiratory system during sleep must be overcome if stable breathing is to be maintained. The ability to elicit a compensation to the added load is protective, and occurs as a result of stimulation of the chemo and mechanoreceptors, plus upper airway reflex mechanisms. When compensation is incomplete, obstructive apnoeas and hypopnoeas develop (Fig. 18.5.2.2).

Breathing during REM sleep

The respiratory control system is particularly vulnerable in REM sleep due to both inhibition of respiratory muscles and reduced chemosensitivity. REM sleep is associated with a 5–15% reduction in ventilation, and respiratory rate is more variable, notably during phasic REM, which is associated with bursts of rapid eye movements; tonic REM sleep is REM sleep with the absence of the eye movements. The REM-related muscle atonia, reduces upper airway reflexes and increases airway compliance, contributing to the REM-related increased prevalence of snoring, airway obstruction, and OSA. In patients with pre-existing respiratory conditions (such as obstructive (COPD) and restrictive (neuromuscular disease, obesity, or chest wall disease) pathophysiologies), REM-related hypoventilation is often the first sign of nocturnal hypoventilation (discussed further in Chapter 18.15). Untreated, this can lead to daytime hypercapnia and chronic respiratory failure. Conversely, central sleep apnoea is uncommon in REM sleep the ventilatory responses to both hypercapnia and hypoxia are reduced.

Obstructive sleep apnoea

Classification

Obstructive sleep apnoea is caused by occlusion of the upper airway during sleep. The closure can be complete with no airflow (apnoea), or partial narrowing with reduced airflow (hypopnoea), as shown in Fig. 18.5.2.2. Both events are associated with hypoxia and hypercapnia. Respiratory effort continues during the occlusion, producing increasing inspiratory effort that leads to a brief cortical arousal from sleep, which in turn restores airway patency. The resumption of breathing is accompanied with an acute surge in blood pressure and heart rate. Many hundreds of apnoeas and hypopnoeas can occur throughout the night, leading to sleep fragmentation (Fig. 18.5.2.1b), symptoms of daytime sleepiness and arterial hypertension, plus other consequences.

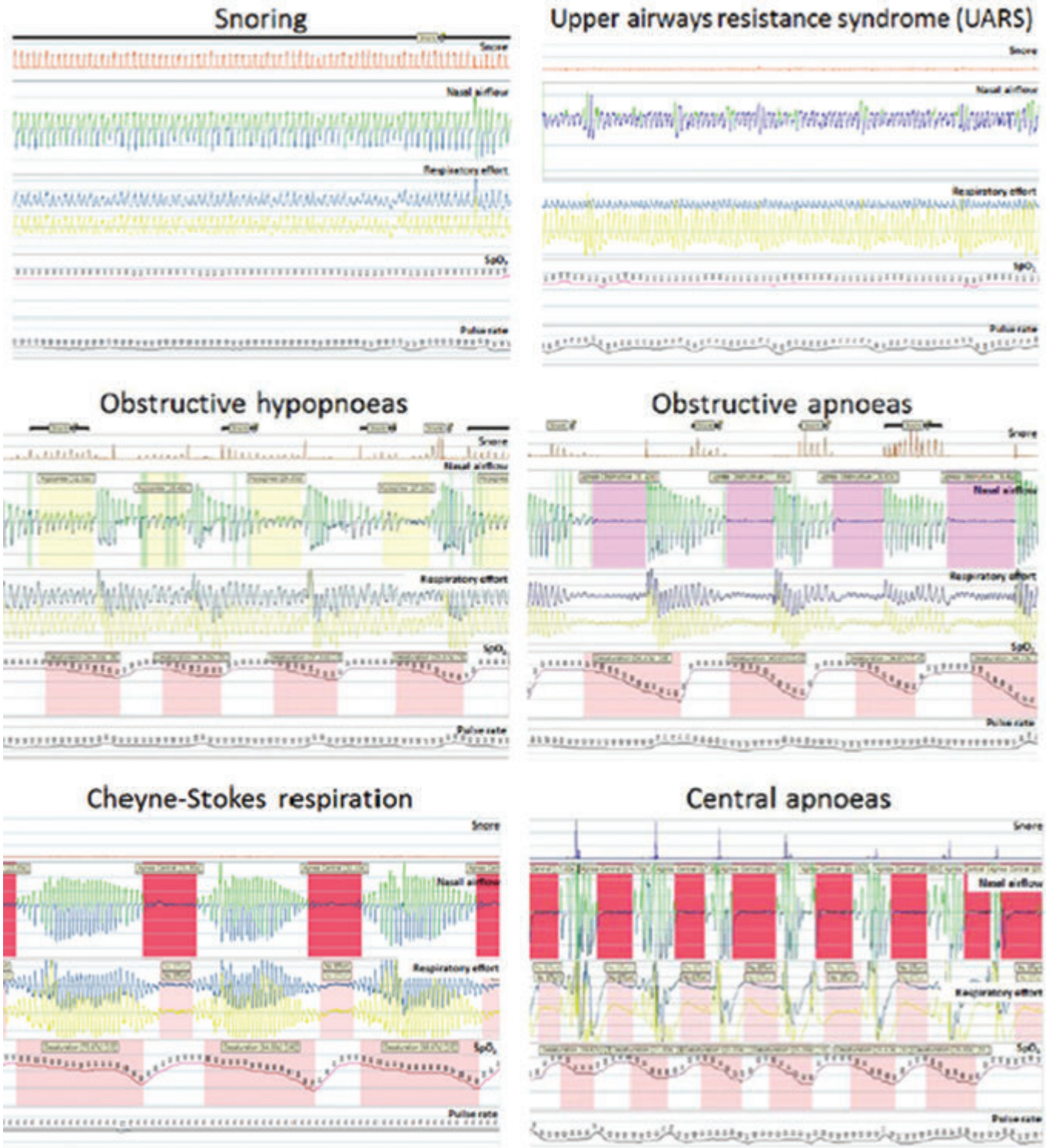

Fig. 18.5.2.2 Types of sleep-disordered breathing measured using a microphone (snore) and cardiorespiratory signals (nasal flow, respiratory effort, oxygen saturations, and pulse) recorded during 5-minute epochs of breathing asleep. Hypopneas are highlighted in yellow, obstructive apnoea in pink, and central apnoea in red.

OSA falls into the broad category of a dyssomnia when classified using the International Classification of Sleep Disorders (American Academy of Sleep Medicine). Dyssomnias are disorders characterized by either difficulty initiating or maintaining sleep, or excessive sleepiness. They are divided into three groups: intrinsic sleep disorders, extrinsic sleep disorders, and circadian rhythm sleep disorders. OSA is an intrinsic sleep disorder which is commonly associated with the term 'sleep-disordered breathing'. This is an umbrella term used to describe a group of disorders characterized by abnormalities of respiratory pattern, or quantity of ventilation,

that occur periodically during sleep (e.g. primary or secondary central sleep apnoea), Cheyne–Stokes respiration, high-altitude periodic breathing, nonobstructive hypoventilation, or hypoxemia disorders secondary to pulmonary parenchymal, vascular, neuromuscular, or chest wall disorders, as well as upper airway resistance syndrome. Some of these disorders are illustrated in Fig. 18.5.2.2.

Aetiology

During wakefulness, patency of the pharyngeal airway is maintained by upper airway dilator muscles. The tone of the dilator muscles decreases at sleep onset, which results in airway narrowing. In patients with neuromuscular weakness (e.g. Bulbar weakness), neurological degenerative disorders (e.g. motor neurone disease), and myopathies (e.g. Duchenne muscular dystrophy), the sleep-related reduction in pharyngeal dilator muscle activity is exacerbated, increasing the risk of OSA. Drugs that reduce muscle tone (e.g. alcohol, sedatives, and antidepressants) also increase the risk of upper airway occlusion and OSA.

The transmural pressure across the airway lumen, which in turn is influenced by the extraluminal pressure, is also a key factor regulating pharyngeal airway patency. Therefore, increased soft tissue surrounding the upper airway, such as neck obesity, macroglossia, and oedema due to heart failure or endocrine disorders (e.g. hypothyroidism) plus normal physiological changes that occur in pregnancy or menopause are also risk factors for OSA.

Other factors that predispose to OSA are those that reduce the size of the airway lumen including an enlarged uvula, tonsillar hypertrophy, and acromegaly. Anatomical risk factors include retrognathia and mandibular hypoplasia. If narrowing occurs at multiple sites along the pharynx, this can accelerate precipitating pharyngeal collapse. The role of nasal blockage as a risk factor for OSA is debated, and that increased inspiratory effort could in theory increase pharyngeal collapse. Overall, obesity is by far the most common, and potentially modifiable, established risk factor for the development of OSA (Table 18.5.2.1).

Community-based observational cohort studies have shown that excess body weight is uniformly associated with a graded increase in OSA prevalence. Additionally, longitudinal studies have shown that weight gain, and loss, influenced the severity of OSA. Increased weight gain is a contributory factor for progression of disease severity from snoring, though upper airway resistance syndrome, to OSA, which occurs in some people. Other interrelated markers of obesity such as neck or waist circumference are independently associated with OSA severity.

Table 18.5.2.1 Mechanisms linked to obesity that contribute to the pathogenesis of Obstructive Sleep Apnoea

Increased pharyngeal fat deposits and subsequent narrowing of the pharyngeal airway
Reduced lung volumes by a combination of increased abdominal fat and recumbent posture
Impairment of the Leptin signalling pathway and other endocrine signals
The possibility of pro-inflammatory cytokines derived from visceral adipose impacting on sleep or inflammatory response in upper airway tissues

In the early 1990s, the seminal Wisconsin Sleep Cohort reported 4% of men and 2% of women met the diagnostic criteria for OSA with symptoms of sleepiness. Around the same time in the United Kingdom, a similar study of middle-aged men suggested a more conservative figure of 0.3%. More recent estimates from the Wisconsin Cohort have predicted that up to 14% of males and 5% of females have OSA with symptoms of sleepiness. This represents a substantial increase in the last two decades, in part due to the increasing prevalence of obesity.

There is also a high prevalence of OSA with increasing age. The mechanisms proposed for the age-related increase in prevalence include: (1) a reduction in pharyngeal muscle function; (2) age-related differences in pharyngeal morphology; (3) changes in the central control of breathing; (4) the increased prevalence of comorbidities associated with sleep apnoea such as heart failure.

Symptoms

The most common symptom of OSA is excessive sleepiness that occurs in most, but not all patients. When OSA is associated with symptoms, it is referred to as obstructive sleep apnoea syndrome (OSAS) or obstructive sleep apnoea/hypopnoea syndrome.

OSA also causes loud snoring, reported by bed partners in over 60% of patients, witnessed episodes of gasping or choking, dyspnoea during sleep, and frequent movements that disrupt sleep are also seen. Patients awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. Quality of life is adversely affected by the unrefreshing sleep, and by the disruption of the bed partner's sleep and resultant irritability. Less common symptoms (10–60%) include morning headaches, enuresis, reduced libido, nocturnal sweating, and a partner worried by apnoeic episodes. Less common symptoms such as insomnia, nocturnal cough, and oesophageal reflux are also reported.

A useful observation for identifying patients with OSA is nocturnal choking or gasping. Snoring, although common in OSA patients, is not useful for establishing a diagnosis as it lacks specificity. The presence of loud intermittent snoring can be of value when combined with daytime symptoms.

Several clinical prediction formulae have been used in the diagnosis of OSAS, most are based on body mass index (BMI) and male gender. None have been shown to be sufficiently accurate to discriminate between patients with or without OSAS, hence a diagnostic test is required to confirm the diagnosis and inform treatment choices.

Diagnosis

OSA is diagnosed using a combination of history, clinical examination, and a diagnostic study that measures physiological variables before and during sleep. The history should include the presence of the symptoms discussed earlier. Excessive sleepiness is commonly assessed using the Epworth Sleepiness Scale (ESS). This subjective questionnaire is used to determine how likely the patient is to doze in eight frequently encountered situations (Fig. 18.5.2.3). An Epworth score of 10 is usually considered abnormal. The ESS, while not a perfect measure of sleepiness, is very useful in monitoring efficacy of treatment.

The clinical examination is frequently normal in patients with OSA but silent features may include obesity, BMI more than 30 kg/m^2, and neck circumference (>43 cm in men and 37 cm in women). Examination of the pharynx with a tongue depressor and light

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situation, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0–3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Fig. 18.5.2.3 The Epworth Sleepiness Scale (ESS) is commonly used to assess excessive sleepiness. The likelihood of dozing in eight frequently encountered situations is measured on a four point scale (0 to 3) with a maximum score of 24. A score of 0–7 is considered normal, 8–9 is considered as average sleepiness, 10–15 is considered excessively sleepy, while 16–24 is considered excessive, with a need for medical treatment.

From Johns MW (1991). A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*, 14(6), 540–5, by permission of Oxford University Press.

source is essential; an increased Mallampati score, narrowing of lateral upper airway walls, enlarged tonsils, a high arched palate, retrognathia, or micrognathia should be noted.

Systemic arterial hypertension is found in 50% of patients with OSA, and coexistent congestive cardiac failure, pulmonary hypertension, stroke, and type II diabetes may be evident. Measurement of blood pressure, fasting blood sugar, lipid status, and thyroid function should be considered. Arterial, blood gas sampling, either from the radial artery or preferably an arterialized blood gas from the ear lobe, can be requested together with lung function if nocturnal hypoventilation suspected. A raised $Paco_2$ should suggest the possibility of lower airways obstruction (so-called 'overlap syndrome') because patients with 'simple' OSA rarely have hypercapnia when awake: an additional factor(s) such as plus chronic obstructive pulmonary disease (COPD) or morbid obesity usually needs to be present.

The most comprehensive test for the diagnosis of OSA is a nocturnal polysomnogram (NPSG) which simultaneously records the electroencephalogram, electrooculogram, electromyogram, oronasal airflow, and oxygen saturations. This test is used in some UK tertiary referral centres, however, it is not required for diagnosis in the majority of cases. The most common test used in UK sleep centres is a cardiorespiratory study (e.g. respiratory polygraphy) or

continuous single or dual bioparameter recording (e.g. overnight pulse oximetry). A comprehensive overview of the tests used to diagnose OSA, including, nocturnal polysomnogram, cardiorespiratory studies (respiratory polygraphy) and overnight pulse oximetry is shown in Video 18.5.2.1.

The diagnostic tests for sleep-related breathing disorders allow the measurement of apnoeas and hypopnoeas. An apnoea is defined as a complete cessation of airflow lasting for at least 10 seconds. Apnoeas are further classified as obstructive, central, or mixed based on whether there is respiratory effort during the event. A hypopnoea is defined as a reduction in airflow. Different cut-off criteria are used for the required reduction in airflow; usually a 30% reduction for more than 10 seconds with a 4% reduction in oxygen saturation, or a 3% reduction in oxygen saturation with an arousal from sleep. The average number of apnoeas and hypopnoea per hour of sleep is defined as the apnoea-hypopnoea index (AHI). The amount of nocturnal hypoxia can be expressed as the oxygen desaturation index (ODI), mean oxygen saturation, the time spent with an oxygen desaturation of less than 90%, or the nadir saturation overnight. Overnight oximetry traces in a healthy person, and a patient with severe OSA are shown in Fig. 18.5.2.4.

Complications and their mitigation

Cardiovascular disease

Physiological studies in animals and humans have identified biologically plausible mechanisms whereby OSA can cause cardiovascular injury, including increased sympathetic nervous system activity, hypoxic and oxidative stress, systemic inflammation, and mechanical factors secondary to intrathoracic pressure oscillations such as reduced left ventricular stroke volume, systemic arterial pressure, cardiac output, and heart rate.

Early studies in people with severe OSA showed a threefold increased likelihood of developing hypertension over 4 years, independent of other risk factors. Additionally, randomized treatment trials in patients with severe OSAS produced a 2–3 mm Hg reduction in blood pressure sufficient to reduce vascular risk by about 20%. Subsequently the cardiovascular impact of OSAS has been established using community based epidemiological studies to show that people with untreated severe OSAS have an increased incidence of coronary heart disease, myocardial infarction, heart failure, stroke, and mortality after adjusting for established cardiovascular disease risk factors. Observational studies comparing OSAS patients treated with continuous positive airway pressure (CPAP) versus those not treated with CPAP have also found elevated cardiovascular risk in those with untreated OSAS.

Whether or not to recommend OSA treatment in patients who do not report excessive daytime sleepiness is controversial, with some arguing that OSA should be treated even in subjects without daytime symptoms due to elevated cardiovascular risks. In a long-term observational cohort study, OSA with and without sleepiness was equally predictive of cardiovascular mortality. A multicentre randomized controlled trial of CPAP found no reduction in cardiovascular risk in minimally symptomatic OSA despite improvements in sleepiness. Furthermore, a meta-analysis of randomized controlled treatment trials of CPAP on blood pressure in mildly symptomatic patients suggested CPAP treatment elevated blood pressure.

Cerebrovascular disease

Observational cohort studies within the general population have shown an increased risk of stroke in patients with moderate to severe OSA. However, it has been difficult to determine whether OSA preceded the stroke or was independent of the confounding risk factors of age, sex, smoking, BMI, diabetes mellitus, and cardiovascular disease. Longitudinal analysis of OSA and stroke risk found moderate to severe OSA (AHI ≥20) was associated with increased risk of stroke, whereas no increased risk was observed in patients with mild OSA. Others have also reported an increased incidence of stroke, including transient ischaemic attacks, or death from any cause in patients with pre-existing OSA, and demonstrated a relationship between OSA severity and risk, independent of confounding factors. Taken together, these data suggest that a trial of CPAP treatment may be advised where the risk of stroke is high.

Metabolic disease

OSA is associated with obesity (Table 18.5.2.1). Observational cohort studies have found that OSA is also associated with insulin resistance, which is correlated with the severity of OSA but independent of general obesity. It is postulated insulin resistance in OSA is due to visceral obesity and increased sympathetic drive from frequent arousals, intermittent hypoxia, and sleep fragmentation. The metabolic response to CPAP treatment has been variable and at this time randomized controlled trials do not support the use of CPAP

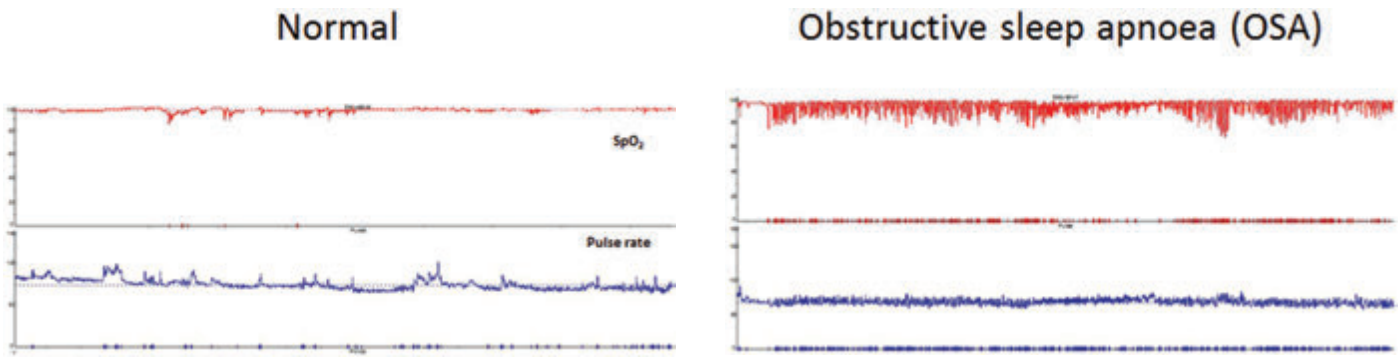

Fig. 18.5.2.4 An example of overnight oxygen saturation, recorded by oximetry in a healthy person (left) and a patient with OSA (right). Note the hundreds of dips in oxygen saturation overnight in the patient with OSA.

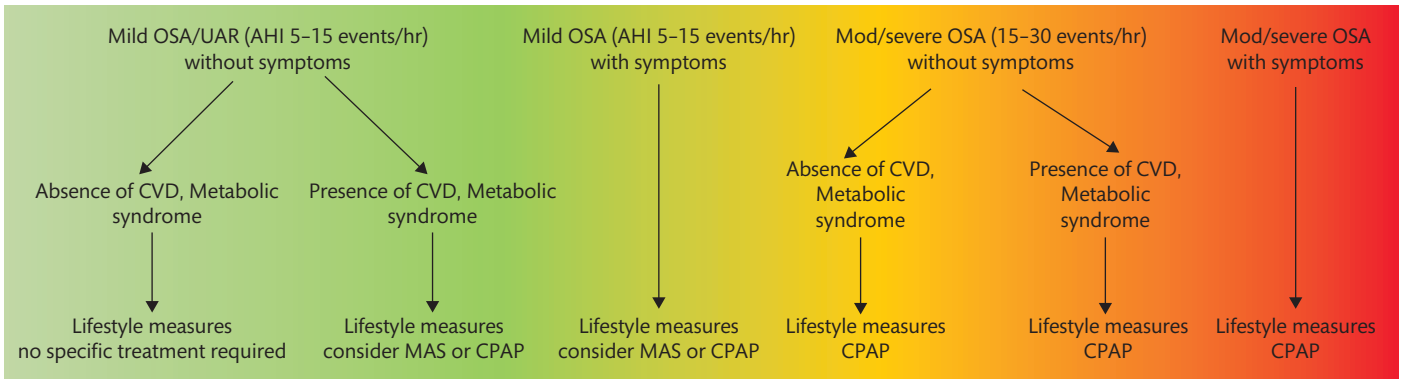

Fig. 18.5.2.5 An algorithm for the treatment of mild, moderate, and severe obstructive sleep apnoea (OSA). CPAP, continuous positive airway pressure; CVD, cardiovascular disease; MAS, mandibular advancement splints; UAR, upper airway resistance.

treatment solely for treatment of metabolic syndrome in OSA in the absence of sleepiness symptoms.

Social/lifestyle impact

OSAS patients experience mood changes, depression, and reduced quality of life that is attributed to reduced social functioning and vitality.

Cognitive function

OSAS is characterized by chronically fragmented sleep and daytime sleepiness both of which are thought to contribute to cognitive dysfunction, although the relative contributions of each remains poorly understood. More recently, chronic intermittent hypoxia has been proposed as a third factor contributing to neural inflammation. Research is now concentrated on the role of OSA on accelerated cognitive decline. It should be noted that in a subset of OSA patients who do not report daytime sleepiness, CPAP treatment has been proven to successfully improve memory and cognitive function.

OSA and driving

Daytime sleepiness impairs function and importantly increases accident risk. OSAS patients are 2–4 times more likely than healthy people to have road traffic accidents as a result of reduced alertness while driving.

United Kingdom law (2015) stated that drivers are must tell the Driver and Vehicle Licensing Agency (DVLA) if they have OSAS, or OSA with symptoms that affects their ability to drive safely, who then send a questionnaire to the patient. In January 2016 new guidelines were adopted to comply with the conclusions of a European Union OSA Working Group published in 2013 (see Ghosh et al., 2016). In an attempt to guide decision making here is now a requirement to submit information about sleep test measurements, notably the AHI. Patients are advised to stop driving until their condition has been successfully treated. Licences are only revoked if sleepiness continues following treatment.

Guidance for UK patients is given by the Sleep Apnoea Trust (see 'Further reading' and for healthcare professionals up-to-date information can be found in the British Thoracic Society Driving and Obstructive Sleep Apnoea (OSA)/Obstructive Sleep Apnoea Syndrome (OSAS) Position Statement (see 'Further reading').

Management

Treatments for OSA depend on the disease severity, patient symptoms and the presence of cardiovascular or metabolic disease (Fig. 18.5.2.5). Treatments include advice on modifying lifestyle, including weight loss, stopping smoking, and increasing cardiovascular exercise, improving sleep opportunity and environment, optimizing medical management of comorbidities, and reducing the use of stimulants such as caffeine, and substances such as alcohol, sedatives, and recreational drugs.

Positional measures and oral mandibular advancement splints are recommended in mild to moderate OSAS, with upper airway and bariatric surgery also being considered by some patients. However, positive airway therapy is the mainstay treatment for patients with moderate to severe OSA and as such will be the focus of this chapter.

Positive airway therapy

There are several variants of positive airway therapy including CPAP (see Video 18.5.2.2), auto-titrating CPAP (autoCPAP), compensated pressure waveform, bilevel and adaptive servoventilation. Each of these modes may be used in the treatment of OSAS, although the last two are considered forms of ventilation and there is little evidence in the nonhypercapnic patients for their use however in selected cases these modes of respiratory support may be very useful. The use of overnight ventilation in overlap syndromes is covered in Chapter 18.15.

Most evidence for the treatment of OSAS is based on CPAP and autoCPAP treatment. Multiple systematic reviews and meta-analyses of randomized controlled trials have assessed the efficacy of CPAP in OSAS. These data are summarized in National Institute of Clinical Excellence (NICE) systematic review and economic analysis which supports the use of CPAP as the evidence-based treatment of choice for moderate to severe OSAS in middle-aged patients and more recent evidence has extended the evidence base for older people with OSAS.

The therapeutic benefit of CPAP is typically defined as an improvement in sleepiness, using the ESS (Fig. 18.5.2.3) as a measure of subjective sleepiness. The mean difference between patients treated with CPAP versus conservative (or placebo) treatment is a reduction of 2.7 points (95% CI interval −3.45 to −1.96) and the magnitude of change is greater in patients with severe symptoms (mean difference in ESS −5.0, 95% CI −3.0 to −1.6). Not only is CPAP efficacious,

it was also deemed to be cost-effective treatment for moderate to severe OSA in well-defined middle-aged populations. The cost of CPAP therapy is approximately £4000 per quality-adjusted life year gained; allowing for changes in sleepiness, quality of life, vascular risk, driving performance, and CPAP equipment costs.

Adherence to CPAP

The adherence to CPAP is estimated to range from 46% to 83%, with an average nightly usage of 2.39 hours per night in minimally symptomatic middle-aged OSA patients and 2 hours 22 mins in older OSA patients at 12 months. This is somewhat lower than the 4 hours per night on 70% of nights which is commonly used as the benchmark for CPAP adherence, and less than the optimal outcomes archived with at a usage of least 5 hours per night. Factors that impact CPAP compliance are shown in **Table 18.5.2.2**.

The percentage of patients who continue using their CPAP device falls over time, (e.g. 84% at the end of the first year to 68% after 4 years), remaining at this level for a further 3 years. This equates to a discontinuation rate of 5% per annum over 4 years. The weighted average for studies that report discontinuation rates over more than 3 years was estimated to be 3.8% per annum.

Telemedicine is increasingly being used in the management of chronic diseases and in the management of OSA patients it has been used to enable remote CPAP titration and follow-up. It has also been used to provide additional feedback aimed at promoting and reinforcing CPAP adherence, with improved CPAP adherence and reduced associated symptoms observed in some, but not all, studies. The mechanisms for the improved CPAP adherence include early detection of issues such as air leak around the mask and nasal drying, with prompt intervention to improve mask fit and initiate humidification. Since adherence to CPAP in the first week of treatment has been shown to be a good marker of long-term compliance, and intensive support has been shown to increase CPAP usage it is proposed that the use of telemonitoring in the early management of OSAS could improve CPAP compliance.

Other treatment approaches

Upper airway surgery

Procedures vary depending on the amount of soft tissue and palate that is removed. Uvulopalatopharyngoplasty typically removes the tonsils and adenoids, plus tissue from the uvula, soft palate, and pharyngeal walls, to enlarge the airway lumen. Before upper airway surgery is recommended, it is important to establish the site of airway collapse. Unsuccessful surgery can cause complications (typically air leaks and nasal problems) if subsequent CPAP treatment is required.

The use of laser or radiofrequency to scar and stiffen the uvula is a less radical surgical technique that is carried out to reduce snoring and mild sleep hypopneas. More radical maxillofacial surgical techniques are performed in a small number of patients to advance the maxilla and increase the size of the oropharyngeal airway lumen. Typically, these patients have specific craniofacial abnormalities, are young and nonobese. In these patients, high success rates are reported.

Table 18.5.2.2 Predictors of poor CPAP adherence include

Patient characteristics—increased nasal resistance, depression
Disease characteristics—either severe or mild minimally symptomatic disease
Psychological or social—less self-efficacy, poor social support, limited disease and/or treatment knowledge
Technical—lack of heated humidification and flexible pressure

Bariatric surgery

Bariatric surgery has been shown to successfully treat OSAS as well as associated metabolic abnormalities. It is important to note these patients are particularly vulnerable during the perioperative period because of a predisposition towards airway collapse. Full multidisciplinary assessment prior to bariatric intervention is recommended.

Oral mandibular advancement splints

Evidence shows they are clinically effective in mild to moderate OSAS, reducing subjective sleepiness. Mandibular advancement splints are worn intraorally during sleep to bring the mandible and tongue forward, which reduces airway narrowing. There are many splints commercially available, ranging from simple self-moulded, fixed devices, to bespoke splints that allow adjustment to gradually advance the jaw. A UK-based study has shown that nonadjustable devices can produce clinically important improvements in mild to moderate OSAS and are cost-effective. A microchip has been developed that allows adherence or splint used to be monitored. However, tolerance can be an issue, with mouth problems, discomfort, and excess salivation being the most common side effects. Patients with significant periodontal disease or tooth decay, partial or complete edentulism, fixed orthodontic devices, or temporomandibular joint pain may find it difficult to use these devices.

Positional therapy

When patients with OSA are supine, the pharyngeal lumen is reduced in size as the tongue and soft palate are pushed back due to gravitational force. Positional therapy should be considered in mild to moderate OSAS, when the disease severity is increased twofold during supine sleep. Moving to the lateral position can increase the size of the airway lumen and prevent collapse. Newer targeted vibrotactile feedback to deter patients from the supine position is also now available.

Central sleep apnoea

Central sleep apnoea is much less common that OSA and caused by factors that disrupt the neural regulation of breathing, as in the example of heart failure described previously. Central sleep apnoea may also occur following stroke, or be induced by centrally acting drugs, with opioids being the most common respiratory depressant.

Complex sleep apnoea is a term recently used in cases where patients with OSA develop central sleep apnoea following CPAP treatment. The term 'complex' therefore refers to combination of obstructive and central sleep apnoea.

The symptoms of central sleep apnoea are similar to those of OSA. Apnoeas lead to awakenings and are sometimes associated with shortness of breath, especially in heart failure. However, daytime sleepiness appears to be less common in central sleep apnoea, compared to OSA; perhaps due to arousals from sleep being less intense. Symptoms of insomnia, mood changes, poor cognitive function, and difficulty in concentrating are all reported by patients with central sleep apnoea.

The diagnosis of central sleep apnoea depends on documenting an absence of respiratory efforts during the apnoea; or reduced efforts during the hypopnoea. This can be very difficult to distinguish, especially as some patients have one or two obstructed breaths at the end of the apnoea due to passive collapse of the upper airway lumen, which is secondary to the central apnoea. The presence of snoring indicates obstruction to airflow, and can be used as a marker of OSA in most cases; however, snoring often occurs in complex sleep apnoea.

Treatment of central sleep apnoea should be based on optimizing care of the underlying cause (e.g. heart failure). Specialized positive pressure support (e.g. adaptive servoventilation) may be considered in patients with both obstructive and central hypopnoea, and an ejection fraction of more than 45%. For patients who cannot tolerate CPAP, nocturnal oxygen may be considered. For patients with ejection faction less than 45% and with mainly central sleep apnoea, adaptive servoventilation is not recommended. In these cases noninvasive ventilation may be helpful as the first-line therapy with a backup respiratory rate. Future pharmacological approaches may be useful in this patient group. Acetazolamide, a carbonic anhydrase inhibitor and diuretic, increases urinary bicarbonate excretion lowering blood pH resulting in compensatory hyperventilation which modulates the apnoeic threshold, has been used in a research setting.

Congenital central hypoventilation syndrome

CCHS is a rare autosomal dominant inherited disease; approximately 1000 individuals worldwide have been identified to date. Patients with CCHS hypoventilate or stop breathing during sleep. In these patients, chemosensitivity is reduced or absent and breathing during wakefulness is controlled via the motor cortex. The disease is usually diagnosed after birth in children and associated with mutations in the *PHOX2B* gene. These mutations inhibit the PHOX2B protein's role in neuronal development of the autonomic nervous system, causing other co-morbidities such as Hirschsprung's disease. The patients have an increased risk of tumours, and learning may also be impaired, either due to sleep deprivation, or hypoxia-related neural damage. Eye abnormalities are also common. Patients also report a decreased pain threshold and difficulty in regulating body temperature (low body temperature). It is treated with long term nocturnal ventilation.

Overlap syndromes

Obstructive sleep apnoea plus chronic obstructive pulmonary disease

Where OSA and COPD coexist there is a combined effect to worsen lung function with a greater risk of morbidity and mortality and reduced quality of life. Nocturnal oxygenation is adversely affected, with nocturnal desaturation being more profound in overlap patients due to the lover waking saturations exacerbating the sleep-related hypoventilation.

Treatment may require oxygen therapy in addition to CPAP. The systemic consequence of OSA combined with COPD is cardiovascular disease, via shared pathways of inflammation and oxidative stress. Investigation of spirometry and lung volume measurements, as well as arterial blood gas analysis should be undertaken in patients with OSA and a history of smoking.

Obstructive sleep apnoea plus obesity hypoventilation syndrome

Obesity hypoventilation syndrome is defined as the combination of obesity (BMI >30 kg/m^2), sleep-disordered breathing, and daytime hypercapnia. OSA is present in approximately 90% of patients with obesity hypoventilation syndrome. Nocturnal hypoventilation in these patients is due to an interaction of obesity-related respiratory impairment and OSA, and has several proposed mechanisms. A high AHI is an independent risk factor for the development of hypercapnia. The duration of the disordered breathing events and the interim period of relative hyperventilation are also thought to influence the loading/unloading balance of CO_2. Long-term buffering and reductions in chemosensitivity, plus reduced respiratory drive lead to the presence of daytime hypercapnia. This is associated with significant morbidity and a greater risk of pulmonary hypertension and mortality.

Bilevel positive pressure (NIV) may be necessary in symptomatic patients with daytime hypercapnia (Pco_2 >7.3 kPa (>50 mm Hg)) primarily induced by nocturnal hypoventilation. However in patients where OSA predominates, CPAP is the first-line treatment. CPAP has also been shown to be effective in 50–80% of patients with mild nocturnal hypoventilation and is assessed by the control of overnight AHI, SaO_2, and $PtcCO_2$ on CPAP therapy.

Differential diagnosis for nonrespiratory sleep disorders

There are several nonrespiratory sleep disorders that can produce excessive daytime sleepiness that should be considered in the differential diagnosis of sleep-related breathing disorders.

Periodic limb movements during sleep

Periodic limb movements occur during NREM sleep, and frequently present in association with restless leg syndrome, which manifests during wakefulness usually in evening when tired.

The periodic limb movements are simple, repetitive movements that cannot be controlled; often tightening of the lower leg muscles (e.g. flexing the foot). The movements tend to be of short duration (0.5 to 5 seconds) and occur every 20–40 seconds for up to an hour (movements occurring after 90 seconds are not counted as periodic), usually just one leg is affected at a time.

The movements do not delay sleep onset, but they can produce brief arousals from sleep that disrupt nocturnal sleep and can lead to daytime sleepiness. However, the limb movements do not always cause cortical arousals from sleep, and not all patients in whom arousals occur complain of daytime sleepiness. The bed partner can be disturbed by restlessness.

Periodic limb movements are common in older people, and patients with renal impairment (especially if on dialysis), those with low ferritin level, peripheral neuropathy, and previous sciatica. The limb movements are diagnosed on a nocturnal recording of limb electromyography, and/or video. If symptomatic they may be treated with iron replacement, aiming for stores at the high end of the normal

range, or with dopaminergic agonists (e.g. ropinirole, pramipexole, L-dopa, and rotigotine), benzodiazepines (e.g. clonazepam), opioids (e.g. codeine), or anticonvulsants (e.g. pregabalin and gabapentin).

Restless legs syndrome

This is typically described as an unpleasant sensation (burning and/or itching) in the legs, causing an overwhelming urge to move the legs. The syndrome is often worse when tired, making falling asleep, or laying still difficult. Women are more likely than men to develop the condition, sometimes triggered by the hormonal changes of pregnancy, and there may be a family history. It can cause patients to have reduced nocturnal sleep with an associated irritability and difficulty in concentration. Treatment is similar to that for periodic limb movement disorder.

Narcolepsy

Narcolepsy is produced by a reduction in the orexin (also known as hypocretin) neurons in the hypothalamus, which play a key role in maintaining the conscious state. The loss of neurones is thought to be immunological, and there is a very strong association with human leukocyte antigen (HLA) DQB1 0602 subtype (>95% compared to 30% in the general population). There is also thought to be a genetic predisposition that can produce a family history of narcolepsy.

Narcolepsy is associated with a tetrad of symptoms: (1) excessive uncontrollable sleepiness 'sleep attacks'; (2) cataplexy, loss of muscle tone/falling in response to strong emotion or laughter); (3) hypnagogic hallucinations, vivid disturbing dreams—particularly at sleep onset; (4) plus sleep paralysis, persistence of REM atonia into wakefulness.

Diagnosis is based on history, rather than a sleep study. Early-onset REM sleep, disrupted night time sleep patterns, and multiple daytime (refreshing) naps are helpful disease markers. A multiple sleep latency test (consisting of five opportunities of nap during the day spaced by 2 hour intervals) that results in a mean sleep latency of less than 8 minutes and two or more naps (20 minutes) that contain REM sleep strongly suggests narcolepsy. When available, measurement of orexin in cerebrospinal fluid can be used to aid diagnosis, and the patient can be HLA typed, with absence of the relevant HLA type strongly refuting the diagnosis

Narcolepsy is a lifelong condition with multiple implications for lifestyle, employment, and driving. Specialist referral is required for diagnosis and management. See Chapter 24.5.2 for further discussion.

Parasomnia

Parasomnias are nonrespiratory disorders that manifest as unwanted behaviour and events that occur during sleep. The behaviours may be complex, but the patient remains asleep during the event, and importantly has no memory that it has occurred on waking, although patients often find their sleep is not refreshing. Parasomnias include behaviours that occur during NREM sleep, typically during the first half of the night, such as sleep walking, sleep talking, sleep eating, and bedwetting. Additionally arousal disorders such as confusion arousals, sleep terrors, and exploding head syndrome, and finally REM behaviour disorder, which occurs during REM sleep typically towards the end of the night.

REM behaviour disorder is produced by damage to neurons in the pons (around the locus coeruleus) that cause a loss of the atonia normally present during REM sleep. It is often described as acting out vivid (and sometimes violent, action-packed) dreams. The episodes can result in injury to the patient or the bed partner and are likely to get worse with ageing.

The diagnosis of parasomnia is based on history, and patients do not typically complain of excessive daytime sleepiness, although they may have fatigue. REM behaviour disorder typically occurs in older men, sometimes with neurologic comorbidity. More recent data suggests that approximately one-third of patients with the condition go on to develop Parkinson's disease, and up to 90% will develop multiple system atrophy. It can be treated with clonazepam, which generally reduces muscular tone. Patients should also be advised on keeping the environment safe (e.g. removing furniture close to the bedside, and moving the bed away from any windows) and avoiding alcohol. See Chapter 24.5.3 for further discussion.

Multisystem atrophy

Patients with multisystem atrophy can present to respiratory sleep clinics with apparent snoring and sleep fragmentation. However, the 'snoring' can be caused by laryngeal abductor weakness and laryngeal closure during sleep, with inspiratory stridulous obstruction. These patients can suddenly die from nocturnal respiratory arrest, but may be successfully treated with standard CPAP therapy.

FURTHER READING

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