Sleep

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Sleep Physiology

The function of sleep is still largely unknown, but it should be considered a homeostatic drive just like thirst and hunger, and can be divided into phases defined by muscle activity and eye movement. Sleep usually consists of four or five cycles of quiet non-rapid eye movement (NREM) sleep, alternating with periods of rapid eye movement (REM), the latter usually beginning after about 90 min and increasing in length throughout the night. Stage 1 is brief and transitional, then briskly followed by stage 2 sleep when electroencephalography (EEG) shows evidence of sleep spindles, the appearance of delta and theta rhythms, and reduced muscular activity, with a slight decrease in heart rate and respiratory frequency. Stage 2 sleep occupies approximately half of total sleep time, and increases in old age. Stages 3 and 4 are known as slow-wave sleep (SWS) because of the increasing predominance of high-amplitude slow delta waves, and it is during this phase that body restoration occurs. SWS is most prevalent in the early part of the night, but with age, the amount of SWS progressively diminishes as stage 2 sleep lengthens. Eye movement is absent and muscle tone reduced in stages 2–4 sleep. REM occupies about 20% of adult sleep (although it predominates in neonates) and is associated with EEG evidence of cortical activity, but accompanied by muscular paralysis apart from the extraocular muscles, the diaphragm, and the posterior crico-arytenoid muscles which abduct the vocal cords. REM is when most dreaming takes place, and this loss of muscle activity is an important mechanism which prevents individuals from acting out dreams. Following sleep deprivation there is a rebound catch-up of SWS and then REM.

Sleep and Respiration

During wakefulness, activation of the upper airway and intercostal muscles ensure that the subatmospheric intrapleural pressure of inspiration does not narrow the upper airway or reduce the outward motion of the ribcage when the diaphragm descends. NREM sleep inhibits neural activity in the medulla, with a resultant reduction in output to the hypoglossal and phrenic nerves. Minute ventilation decreases by 10–15% during both NREM and REM sleep, and there are small decreases in arterial oxygen saturation and increases in alveolar and arterial CO_2 [1]. This is partly due to a blunted ventilatory response of the peripheral and central chemoreceptors, but also there is reduced upper airway calibre and an

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increase in upper airway resistance (UAR). Imaging confirms that the airway lumen is narrowed, opens at transition to expiration, and then narrows again during mid and late expiration. The increase in resistance may be minor in the young and thin but sizeable in obese snorers. With the rise in UAR there is increased EMG input to the diaphragm and accessory muscles, which persists until the airway narrowing resolves. In REM sleep diaphragmatic activity predominates over intercostal activity and inhibition of the upper airway dilator muscles predisposes to airway closure.

Obstructive Sleep Apnoea

The human upper airway is crucial for respiration, swallowing, and speech, and the latter requires pharyngeal mobility so that the hyoid bone, an important anchoring site for pharyngeal muscles, is not firmly attached to the skeleton, as it is in other species. The nasal and laryngeal segments of the upper airway are rigid, but the pharynx is a collapsible tube subject to surrounding pressure and muscular activation. A key physiological abnormality in the airway of obstructive sleep apnoea (OSA) patients is the presence of a higher critical closing pressure (Pcrit), so when muscular activation is negated (for instance by general anaesthesia) the upper airway may collapse at atmospheric pressure, whereas normal individuals require a negative pressure. This increased tendency of the airway to collapse is due to a combination of anatomical crowding and abnormalities of neuromuscular control, although in an individual patient one or other may predominate.

Numerous imaging studies in OSA patients confirm lumen size is compromised compared to non-apnoeic subjects. Luminal anatomy may be influenced by a number of factors including obesity, jaw position, tongue size, and craniofacial anatomy. Mandibular and hyoid position and maxillary height are factors which can increase the risk of OSA, and are a plausible explanation for familial aggregation. During wakefulness, OSA patients show increased pharyngeal dilator muscle activity compared to non-apnoeic controls, that is they offset their airway's tendency to collapse. However, they have less activation when asleep, and this has been attributed to subtle muscle denervation and neuropathy in the upper airway.

The strong association between OSA and obesity is multifactorial: firstly the tongue may contain relatively more fat, and secondly, increased thickness of the lateral pharyngeal wall may explain the reduced lateral diameter of the airway over and beyond fat pad thickness. In health, negative intrathoracic pressure and diaphragm descent on inspiration increases traction on the trachea and reduces upper airway resistance. However, if end-expiratory lung volume is reduced by recumbency and obesity, then upper airway calibre is also likely to be reduced, making it more prone to collapse. The reestablishment of tone in the upper airway musculature which leads to the termination of the apnoea is often associated with EEG evidence of electrophysiological arousal (defined as an abrupt shift in EEG frequency of 3s preceded by a minimum of 10s sleep). At sleep onset and during REM, reflex upper airway muscle activation is reduced, as is the response to arousal. This explains the observation that apnoeas are more common in light sleep (stages 1 and 2) and REM, but relatively uncommon in SWS. Blunted responsiveness in a compromised airway may be sufficient to result in an apnoea or hypopnoea, following which hypoxia and minor hypercapnia develops, respiration is stimulated, and arousal occurs, with activation of the upper airway dilators to restore airway patency. These muscles can respond to resistive loading and rising CO_2 without necessarily eliciting an arousal, which explains why despite their compromised anatomy, most OSA patients maintain normal ventilation for at least part of the night, and why not all sleep-disordered breathing is accompanied by sleep fragmentation. Hypoxia, hypercapnia, and increased airflow resistance *per se* do not seem to be the cause of the arousal, and the signal to the brain may be the increasingly negative pleural pressure, although whether the sensor is in the lungs or the chest wall is still unclear.

The Epidemiology of OSA

The obstructive sleep apnoea syndrome (OSAS) is defined as an abnormal number of events in sleep caused by repetitive upper airway obstruction, and associated with symptoms of sleep fragmentation. A landmark epidemiological study in North America [2] showed that sleep-disordered breathing (defined here as an apnoeic-hypopnoeic index (AHI) >5 events per hour) was present in 24% of middle-aged men and 9% of women, but when combined with symptoms of excessive daytime somnolence (EDS) the prevalence was 4% and 2% respectively. Similar figures have been obtained in Hong Kong, Korea, and India [3]. Most studies show a male: female ratio of 2:1, and follow-up studies show a tendency of the condition to deteriorate with time. Even moderately severe OSAS (AHI >15 plus frequent sleepiness) is underdiagnosed, with only 18% of men and 7% of women in the Wisconsin Sleep Cohort Study known to have the condition. Snoring, a strong predictor of OSA, is less likely to be reported by women, but does not fully explain the gender bias. A variant of OSA is the upper airway resistance syndrome (UARS), although its existence has been disputed. Patients present with snoring and EDS, but tend to be female, not overtly overweight, and may have a high, narrow hard palate with an abnormal overjet. They do not fulfil the usual AHI criteria for OSA, but sleep studies show multiple respiratory effort-related arousals (RERAs) which cause sleep fragmentation. Identification of RERAs requires measurement of oesophageal pressure or pulse transit time to demonstrate increasing respiratory effort with evidence of inspiratory flow limitation [4].

The Physiology of an Apnoea

Intermittent obstruction of the upper airway has profound effects on a number of organs, but particularly the cardiovascular system. Increasing respiratory effort against an obstructed airway produces abnormally large swings in pleural pressure, and affects the heart. Feedback from respiratory muscles, reduced lung inflation, and chemoreceptor stimulation due to blood gas derangement lead to an increase in respiratory effort. The fall in intrathoracic pressure lowers intracardiac pressure in relation to extrathoracic structures with reduced perfusion pressure, reduced stroke volume, and a fall in cardiac output. Sympathetic tone increases and muscle bed vasoconstriction occurs. Blood pressure (BP) and heart rate fall, but when the apnoea terminates, blood pressure, heart rate, and cardiac output all rise. The rise in BP, which may be of the order of 15–50 mmHg, is due to arousal and increased sympathetic tone rather than hypoxia *per se*.

It is assumed that excessive daytime somnolence (EDS) in OSAS is due to sleep fragmentation as a result of multiple arousals. This results in a greater time spent in light sleep, reduced SWS, hypoxaemia, and autonomic activation, all of which *might* contribute to EDS. However, many individuals have markedly abnormal sleep studies without EDS, whereas others remain somnolent despite treatment effecting a dramatic reduction in the number of apnoeas. There is surprisingly little correlation between the severity of OSA (as judged by either AHI or the number of arousals) and more objective tests of daytime sleepiness such as MSLT (multiple sleep latency test).

Symptoms of OSA

- Excessive daytime somnolence or unrefreshing sleep
- Snoring
- Witnessed apnoeas, choking, waking with gasping
- Nocturia
- Erectile dysfunction, low libido
- Irritability, impaired concentration, depression, cognitive blunting

EDS has a number of different causes, of which inadequate sleep time is probably the commonest:

Differential diagnosis of excessive daytime somnolence

- Inadequate sleep time
- Sleep apnoea
- Chronic ventilatory failure caused by restrictive or obstructive lung disease
- Circadian rhythm disorder including shift work
- Medical condition (diabetes, pituitary or thyroid disease, renal failure)
- Chronic fatigue syndrome and fibromyalgia
- Drugs (prescribed or recreational)
- Alcohol
- Depression
- Chronic pain syndromes
- Neurological (narcolepsy, idiopathic hypersomnia, Parkinson's Disease, tumour, post stroke, epilepsy)
- Chronic insomnia

Chronic fatigue ("tired all the time") is a common presentation in both primary and secondary care, but if it occurs without daytime naps is unlikely to be due to OSAS. Somewhat counter-intuitively, insomnia (often of the sleep maintenance type) may co-exist with OSAS, and complicates both diagnosis and management. It is more common in women, and may be indicative of recurrent arousals with brief awakenings secondary to obstructive events. The Epworth Sleepiness Score (ESS) is a subjective quantification of an individual's propensity to fall asleep in eight different situations (Fig. 8.1) and has a maximum possible score of 24. The ESS has high test-retest reliability, but the cut-off is poorly defined. Although a score of 10 or less is considered normal, scores of 11 are seen in 10% of the population, and scores of 12 or greater are probably abnormal.

The STOP-Bang questionnaire (Fig. 8.2) concentrates less on EDS, but identifies associated features of OSAS such as snoring, witnessed apnoeas, hypertension, and obesity. The probability of OSA is low with scores of 2 or less, whereas scores of 6 or more have high sensitivity and specificity. It has been validated in the preoperative setting as a useful screening tool (albeit with high sensitivity and low specificity) for those who may require further investigation. Local factors may determine the threshold for performing respiratory polysomnography, and common indications are listed in the Table 8.1 below. Isolated snoring or occasional witnessed apnoeas do not require investigation with a sleep study unless upper airway surgery is being considered, there are other features to suggest sleep fragmentation, or reassurance is needed.

Sleep Studies

Overnight oximetry is widely available, but not sufficiently sensitive for the diagnosis of all cases of OSA [5]. The ODI (oxygen desaturation index) measures the number of episodes per hour where saturation falls by 4%, with diagnostic cut-offs of greater than 10 or 15 per hour being suggestive of OSA. Some services use oximetry as a screening test, referring on for more detailed studies if the clinical picture requires it, or directly for treatment if repetitive desaturation is shown. Arrhythmias can lead to imprecise estimation of oxygen saturation, and comorbidities such as COPD with low baseline saturations confound the interpretation of desaturation events. Conversely, individuals with a large lung capacity can have prolonged apnoeas but with little desaturation, as they are on the upper flat portion of the oxygen dissociation curve.

More accurate systems are now widely available and monitor saturation, heart rate, airflow, and respiratory effort (Fig. 8.3). Airflow is measured at the nose with a thermistor or nasal pressure transducer and can detect apnoeas and flow limitation. The reliability of the signal is compromised by mouth breathing and nasal obstruction. Movement sensors detect changes in the volume of chest and abdomen by inductance plethysmography and can distinguish between obstructive and central events by recording either paradoxical or absent movement of chest

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 situations, 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. 8.1 The Epworth Sleepiness Scale. The patient is asked to rate their likelihood of falling asleep in eight different situations. The maximum possible score is 24. From ESS © MW Johns 1990-1997. Used under License. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14(6):540–5.Mapi Research Trust, Lyon, France https://eprovide.mapi-trust.org. Reproduced with permission

STOP-BANG Questionnaire

S – Snoring: Do you snore loudly?

T – Tired: Do you feel tired, sleepy during daytime?

O – Observed: Has anyone observed you stop breathing during sleep?

P – Blood Pressure: Are you being treated or have you been treated for hypertension?

B – BMI: Body mass index > 35

A – Age: Age over 50 years

N – Neck: Neck circumference greater than 40 cm

G – Gender: Male gender

Fig. 8.2 The STOP-Bang Questionnaire: a pre-operative screening tool for identifying individuals requiring a sleep study for exclusion or confirmation of OSA. Reproduced with permission

Table 8.1 Possible indications for respiratory sleep study

- Excessive daytime somnolence
- Recurrent witnessed apnoeas
- Nocturnal choking, gasping or "dyspnoea"
- Restless sleep, excessive limb movements, parasomnia
- Drug resistant hypertension or refractory atrial fibrillation
- Unrefreshing sleep despite adequate sleep time and continuity
- Near-miss events or accidents caused by reduced vigilance
- Screening prior to bariatric surgery or upper airway surgery for snoring
- Otherwise unexplained polycythaemia, pulmonary hypertension or ventilatory failure

Fig. 8.3 Patient set up for outpatient multichannel respiratory polysomnography. The nasal cannulae are connected to a pressure transducer to measure changes in nasal airflow and snoring, while the two belts measure thoracic and abdominal movement respectively and detect body position. Pulse oximetry provides continuous monitoring of oxygen saturation and pulse rate

and abdomen respectively (Figs. 8.4 and 8.5). Changes in tidal volume are used to detect hypopnoeas, although there is controversy about the optimal definition and whether or not such an event requires an element of desaturation. These studies can be performed in patients' homes and are widely used. More sophisticated polysomnography—so-called level 1 or, if performed unsupervised, level 2 studies—are expensive, technically demanding, and rarely used in the UK except in equivocal cases or where parasomnias are suspected. In addition to respiratory monitoring, recording of EEG (for sleep staging), chin EMG (for REM detection), limb movements, and perhaps oesophageal manometry (for detection of RERAs) are recorded. Level 3 studies monitor at least three different parameters (e.g. oximetry, snoring, airflow, respiratory effort, position) using portable monitors in the patient's home and are more than adequate for patients with a moderate probability of OSA. Position-dependent OSA (Fig. 8.6), defined as a difference of 50% or more in apnoea index between supine and non-supine positions, is surprisingly common, with a prevalence of >50% reported in several studies.

NICE stratifies OSAS by AHI as follows: mild (5–14 events/h), moderate (15–30), severe (greater than 30), but this classification makes no allowance for the severity of symptoms, which may be severe in patients with "mild" disease.

Sleep Apnoea and Vascular Risk

OSA has been associated with a number of adverse cardiovascular consequences, including hypertension, stroke, coronary artery disease, heart failure, and arrhythmias, but causality has been hard to prove, except for systemic hypertension.

Most, but not all, studies confirm the association of hypertension with OSA. The Wisconsin Sleep Cohort Study prospectively demonstrated a dose-response relationship between the severity of sleep apnoea and the development of hypertension over a 4-year follow-up period [6]. During a longer period of follow-up, a Spanish cohort also found the incidence of hypertension increased with disease severity, and that those adherent to CPAP treatment had the lowest risk of developing hypertension [7]. Patients with resistant hypertension seem more likely to have

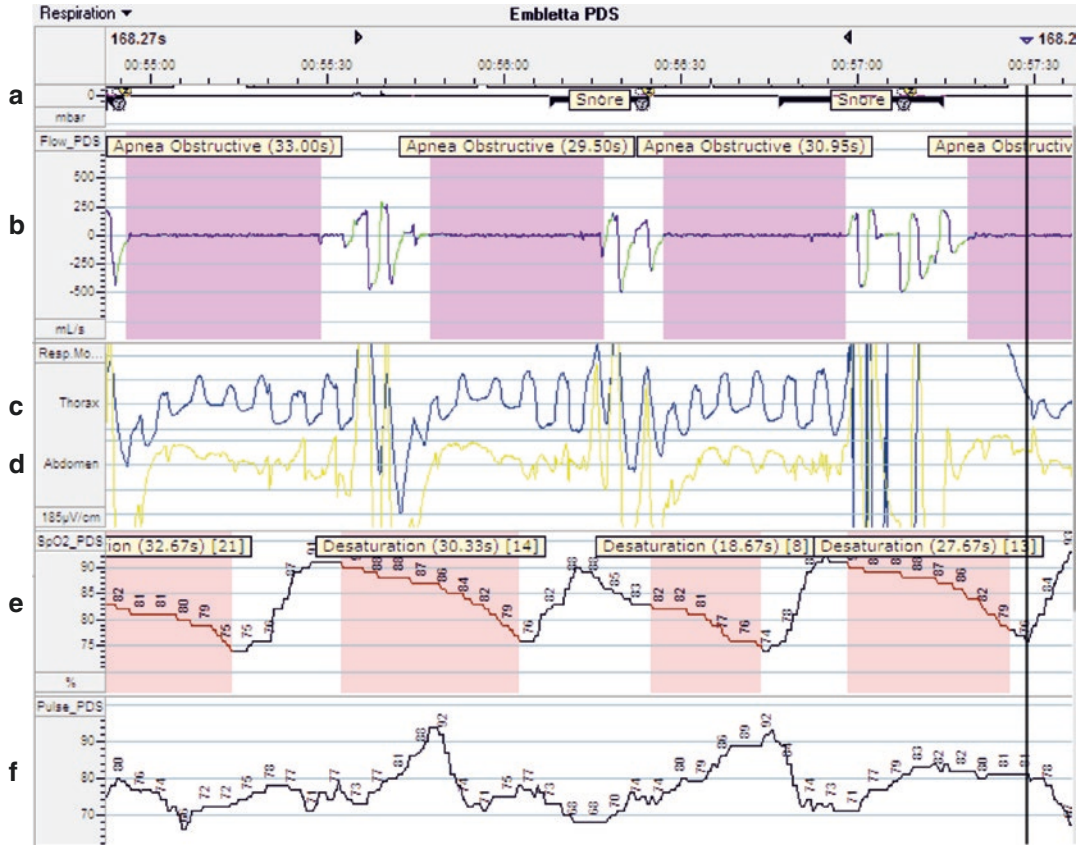

Fig. 8.4 Obstructive sleep apnoea. Apnoeas are registered as periods of absent air flow detected by nasal cannulae (channel B) and are followed by normal breaths as the apnoea is terminated. Channels C and D allow categorisation of these apnoeas as obstructive events. During normal breaths there is synchronisation of thoracic (C) and abdominal (D) movements, which are of similar amplitude and direction. During the obstructive apnoea there is uncoupling of the movements which are out of phase and in different directions. This multichannel recording also shows that the apnoea is associated with snoring (channel A), desaturation (channel E), and pulse rate change (F)

OSA than their well-controlled counterparts, and screening for OSA is often recommended. The mechanism of the association between OSA and hypertension is complex and incompletely understood. Intermittent hypoxia leads to increased oxidative stress, systemic inflammation, and sympathetic activity. Changes in intrathoracic pressure lead to mechanical pressures on the heart, and arousals cause sympathetic activation. Chemoreflex activation with increased sympathetic neural outflow in response to hypoxia seems to be exaggerated during wakefulness in subjects with OSA [8], but resetting of baroreflexes and endothelial activation are also likely to be important. Meta-analysis suggests the overall hypotensive effect of treating OSA is modest, perhaps in the order of 2 mm Hg, but there may be greater benefits to be had in patients with difficult hypertension or more severe OSA [9]. In patients with minimal symptoms of sleep fragmentation, the effects on BP are trivial, and only present if treatment is used >4 h/night. Pulmonary hypertension is present in about 20% of patients with OSA, but is usually mild and improves with treatment. The mechanism is unclear, but the contribution of recurrent nocturnal hypoxia and left ventricular dysfunction will vary from patient to patient.

Sleep-disordered breathing is common in heart failure patients, and both heart failure and incident coronary disease were increased in populations with severe sleep apnoea [10, 11]. Severe OSA appears to be an independent risk factor for stroke, [12] even allowing for confounders such as hyper-

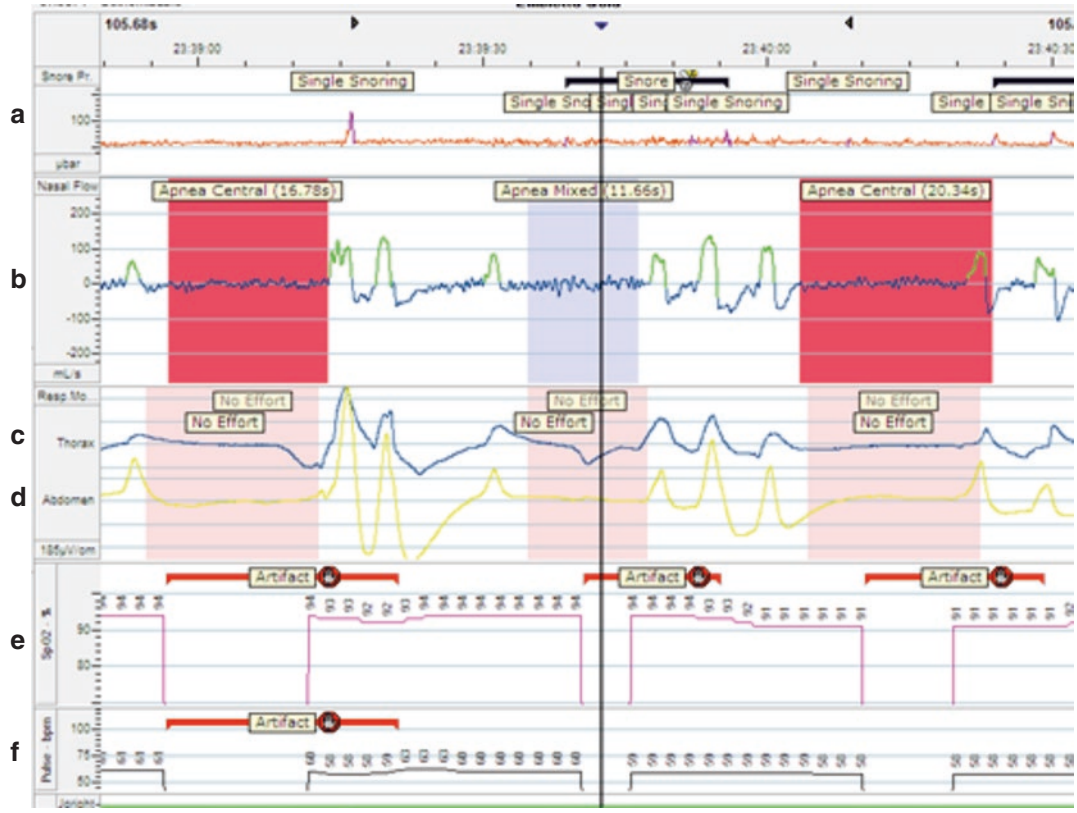

Fig. 8.5 Central sleep apnoea. Multichannel recording shows absence of nasal flow (channel B) accompanied by no movement recorded by either the thoracic (C) or abdominal (D) sensors. The termination of the apnoea is indicated by resumption of nasal flow as synchronised chest and abdominal movements return

tension, atrial fibrillation, and obesity. The risk of atrial fibrillation is much increased in OSA patients, and emerging data suggests that treatment of the latter may be associated with more successful treatment of the arrhythmia. Following stroke, obstructive sleep apnoea is common, but it is unclear if treatment improves outcomes from the acute event. The association of heart disease with OSA is complex, and it is likely that there are common mechanisms which also lead to the development of hypertension. The hypoxia-reoxygenation cycle which accompanies obstructive apnoeas generates reactive oxygen species, and this oxidative stress is thought to result in endothelial dysfunction and atherosclerosis mediated through nuclear transcription factor-kappa B and the expression of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8).

The prevalence of OSA (ODI >10/h) in type 2 diabetics was high (23%) in a community-based UK study, [13] and was even higher (86%) in a more obese North American population using a cut-off AHI of >5/h [14]. Such is the strength of the association that it has recently been suggested that OSA should be regarded as part of the metabolic syndrome, and it is recognised that OSA has an adverse impact on glucose homeostasis and lipid metabolism, perhaps mediated through oxidative stress, inflammation, and intermittent hypoxia. Animal models challenged with the latter develop decreased insulin sensitivity, increased sympathetic activation, and hypertension. Poor diabetic control is associated with more severe OSA, and it was hoped that treatment of the latter might improve insulin sensitivity and glycaemic control. Most studies are short-term, with highly variable adherence, and while some show

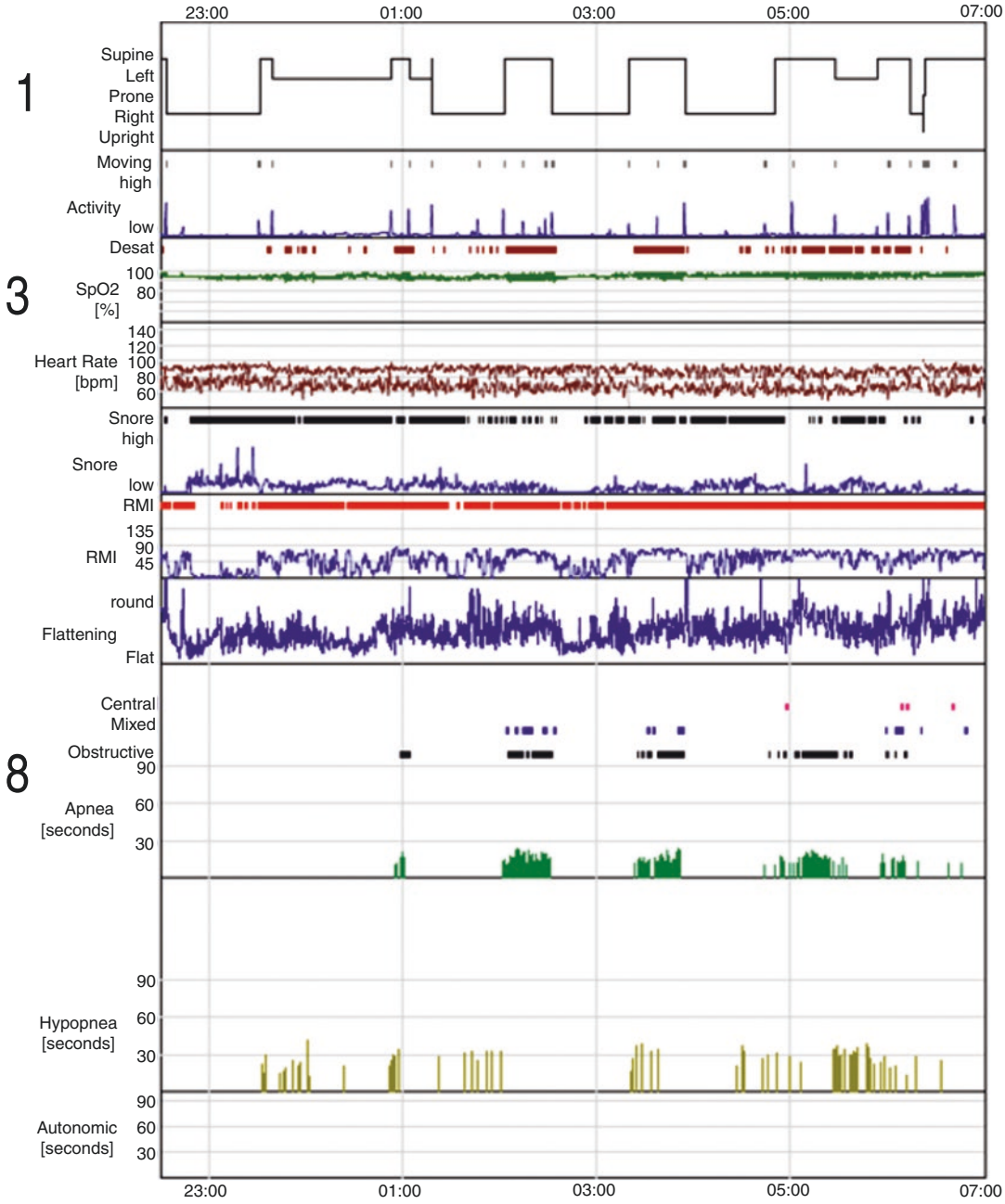

Fig. 8.6 Positional sleep apnoea. Desaturation (channel 3) and clusters of apnoeas (channel 8) occur when subject is in supine position (topmost horizontal "supine" signal in channel 1)

improvement in insulin sensitivity, there is an inconsistent effect on HbA1c, so CPAP remains unproven as adjunctive therapy [15].

A non-randomised observational study [16] indicated that the risk of fatal and non-fatal cardiovascular events was three times higher in patients with untreated severe OSA, and that this risk was attenuated in a control group of severe patients who were compliant with treatment and whose risk was similar to healthy individuals

and snorers. More recently, the SAVE study [17] randomised 2700 non-somnolent patients with moderate or severe OSA and previous coronary disease or stroke to CPAP or usual care. Over a 3.7-year follow-up period, the incidence of further vascular events did not differ between the groups. Thus there is no prospective data to show that treating OSA reduces mortality, although the studies that show less hypertension [7] or markers of endothelial activation suggest that some of the underlying risk factors might change for the better. In patients with OSA and symptoms of sleep fragmentation, the decision to treat is uncontroversial; when an abnormal sleep study is found in an individual with minimal symptoms, then the benefits of treatment are unclear, and currently it is not known if vascular risk is attenuated.

Treatment

General measures include advice about weight, alcohol, and sleep position. Obesity is prevalent in the OSA population but, realistically, sustained weight loss sufficient to cure the condition is rarely achieved. Bariatric surgery is remarkably effective in this respect, but invasive and resource-intensive. Weight loss might be an option for patients who are not very symptomatic and only mildly overweight. However, for patients with significant sleep fragmentation, there is no justification for withholding treatment in the hope that they might eventually lose sufficient weight to cure their condition. Alcohol undoubtedly worsens OSA, but there are no long-term studies of the effects of abstention or moderation. Given the prevalence of positional sleep apnoea, treatments to encourage avoidance of the supine position therapy have received surprisingly little attention. Positional therapy usually consists of a device such as a modified vest or backpack which makes the supine position uncomfortable, and appears moderately effective in short-term case series. Recent developments include signal-emitting position sensors that provide feedback for the sleeping patient, but long-term compliance is untested.

Continuous Positive Airway Pressure (CPAP)

CPAP is the most commonly prescribed treatment for OSA, and is the treatment of choice for severe OSA. As discussed, flow in the upper airway depends on minimal upstream intraluminal airway pressure (Pcrit) of the collapsible segment exceeding the pressure around it—namely the negative intraluminal pressure resulting from inspiration. CPAP pneumatically opens the upper airway by constant pressure throughout the respiratory cycle. CPAP machines generate large flows passing via tube and mask into the oropharynx (Fig. 8.7). The mask incorporates a leakage that induces resistance, and thus positive pressure, in the mask that splints open the upper airway. An additional stabilising effect on the upper airway by a CPAP-induced increase in lung volume is unlikely, as upper airway muscular activity has been shown to be reduced by CPAP. In the heart failure population, there are likely to be additional benefits because positive intrathoracic pressure reduces venous return (preload) and left ventricular transmural pressure (afterload). CPAP should be distinguished from non-invasive ventilation (NIV), where cyclical positive pressure applied to the airway increases tidal volume, thereby augmenting lung inflation and improving gas exchange in patients with ventilatory failure.

Treatment usually results in a dramatic improvement in symptoms of sleep fragmentation (namely EDS, poor concentration, loss of energy), snoring, and sometimes nocturia. A Cochrane review comparing CPAP with placebo or an oral appliance showed large improvements in Epworth sleepiness score (mean 3.8) and various quality-of-life indicators [18]. Individuals with very abnormal sleep studies who agree to a trial of CPAP may volunteer improvement in hitherto underappreciated symptoms. Early problems are common, and a good sleep service should be responsive to patients struggling to acclimatise themselves to treatment, with often minor modifications (mask fit, humidification) making an important contribution to long-term adherence (Table 8.2). The minimum effective usage time is unknown, but 4 h use per night is

Fig. 8.7 CPAP treatment. On the left is an early individually moulded nasal mask and, below, the bulky flow generator. On the right is a modern CPAP machine with a full face mask

Table 8.2 Troubleshooting CPAP

Symptom	Possible solution
Rhinitis	Humidification; topical steroids
Dry nose or mouth	Humidification; if leak, full face mask
Mask removal in sleep	Review mask fitting; pressure adjustment
Intolerant to pressure	Gradual pressure increment during sleep onset (ramp function); consider auto-adjusting CPAP or bilevel ventilation
Difficulty initiating sleep	Ramp function; sleep hygiene; short course of non-benzodiazepine hypnotic
Swallowing air (aerophagy)	Reduce pressure transiently; sleep propped up
Skin irritation	Mask hygiene; liners; change interface
Claustrophobia	Nasal cushions; acclimatisation; address anxiety

generally considered a minimum for symptom control, and may be higher to achieve any putative cardiovascular benefit. At least 20% of patients are unable to tolerate treatment, and if adherence is defined as >4 h use per night, then 46–83% of patients fail to achieve this.

All modern CPAP machines can measure hours of usage, and diagnostic devices can detect persistent apnoeic events, the CPAP pressure required to abolish them, and quantify the presence of mask leak. Most patients will be treated in the first instance with a fixed-pressure CPAP machine set at about 10 cm H_2O, perhaps determined by an auto-titrating CPAP study which can determine the pressure required to abolish the majority of apnoeic events. Auto-CPAP machines can respond flexibly to the state of the upper airway, where the pressure required to eliminate the apnoeas may vary with position, sleep stage, or alcohol consumption. Direct comparison of auto-CPAP and fixed-pressure CPAP suggests that while the former allows a reduction in mean pressure, there is only a trivial improvement in compliance, and no major difference in AHI or

Table 8.3 Persisting EDS in CPAP patient

Cause	Possible solution
Inadequate use	Aim for >4 h/night; small increase may be worthwhile
Failure to control apnoeas	Identify mask leak, pressure titration; consider missed central apnoeas
Wrong or additional sleep diagnosis	Repeat equivocal sleep study, other sleep investigation (MSLT, full polysomnography, sleep diary)
Inadequate sleep time	Education
Medication	Alternative drug where possible
Comorbidities	Address, but often chronic and intractable
Depression	Treat, if indicated
Unrealistic expectation	Education

sleepiness scores [19]. Autotitrating CPAP is more expensive, but is often preferred by patients, and should be considered when patient intolerance is preventing effective treatment. Failure to improve should prompt consideration of an alternative explanation (Table 8.3). Drug therapy is generally ineffective in OSAS, but wake-promoting agents such as modafanil have been used as adjunctive off-license treatment in CPAP patients complaining of residual EDS.

Oral Appliances (OAs)

These work by enlarging the upper airway, either by protruding the mandible (mandibular advancement devices or MADs, Fig. 8.8) or advancing the position of the tongue (tongue retaining devices, Fig. 8.9). Mandibular advancement devices move the tongue anteriorly as well as enlarging the lateral dimensions of the velopharynx, the area between the margin of the hard palate and the soft palate. The further the mandible can be advanced, the greater the efficacy. Customised devices made with dental casts and supervised by dental practitioners are probably the ideal, but semi-personalised devices are cheaper (yet broadly as efficacious) and tend to be preferred to thermoplastic ("boil and bite") appliances. The development of materials that improve intraoral retention,

Fig. 8.8 A semi-bespoke commercially available mandibular advancement device. Courtesy of Meditas/SleepPro Ltd.

Fig. 8.9 A commercially available tongue-retaining device

and adjustable appliances that allow progressive advancement of the mandible, have made devices more acceptable and effective. Unfortunately, the acclimatisation and advancement process takes many months. Common side effects include

excess salivation, xerostomia, dental and temporomandibular joint pain, and gum irritation. Partially or totally edentulous patients are unsuitable for MADs. Compared to CPAP, OAs are not as effective at reducing AHI, but are probably as effective in improving daytime somnolence and health status [20]. A complete response is achieved in approximately half the population of users. Perhaps surprisingly, patient preference outcomes tend to favour OAs over CPAP, and this may be the result in greater hours of use per night, but most commercially available devices do not have any way of measuring compliance. Currently the provision of these devices in the UK is patchy, whereas they have become part of the standard treatment armamentarium in Europe and North America. In patients with severe OSA, CPAP remains first-line treatment, but in mild and moderate disease, OAs can be considered as a potentially effective treatment that may be preferred by the patient, or as second-line if CPAP is not tolerated. Uncomplicated non-apnoeic snoring can also be treated with OAs if nasal obstruction is not the cause.

Hypoglossal Stimulation

Recently it has been shown that implantable hypoglossal nerve stimulators can dramatically improve OSA by dilating the muscles of the upper airway [21]. No randomised data is available, but trials suggest at least a 50% fall in AHI, with greater likelihood of success if patients with concentric upper airway collapse are excluded by nasendoscopy. The equipment is expensive, but might be an option in the future for patients who are CPAP intolerant.

Surgery for OSA

Although superficially an attractive option for what might be seen as an anatomical problem, the results of surgery have been disappointing, perhaps because obstruction often occurs at multiple levels. There is a dearth of rigorously controlled trials, and the reported outcomes often lack detail on sleep parameters or measures of daytime somnolence.

Palatoplasty may help non-apnoeic snoring, but produces inconsistent and rather small improvements in OSA. The previously popular radical uvulopalatopharyngoplasty (UVPPP) is painful, and may cause palatal incompetence and stenosis. The benefit on OSA is unclear, but may make subsequent CPAP harder to tolerate because of problems creating an effective palatal seal. In adults with a particular palatal phenotype and without severe obesity, UVPPP can be effective [22]. Laser-assisted palatoplasty is less invasive, but has not been rigorously evaluated, and reported benefits deteriorate with time. Radiofrequency thermoplasty aims to produce scarring and stiffening of the soft palate and tongue base, but the improvements in sleep parameters are disappointing, long term data are lacking, and multiple treatments may be required. Hyoid suspension aims to prevent hypopharyngeal tongue base collapse and is ineffective in isolation, although it may have a role when it is a component of multilevel surgery [23].

Maxillo-mandibular advancement (MMA) enlarges the velo-orohypopharynx by advancing the structures (soft palate, tongue base, and suprahyoid musculature) attached to the maxilla, mandible, and hyoid bone and, apart from tracheostomy, is probably the most successful surgical option in adults. It is achieved by bilateral osteotomies that are stabilised with plates or bone grafts. Meta-analysis showed mean reductions in AHI from 64 to10 events/h and a cure rate of 67% in those with AHI < 30/h [24]. These results are impressive, but the surgery is invasive, technically challenging, and carries an attendant risk. It seems to be particularly suited to individuals with hypopharyngeal narrowing, which is often found with co-existent skeletal hypoplasia such as retrognathia.

Surgical correction of an obstructed nasal airway hardly ever cures sleep apnoea, but the identification and correction of obstructive pathology may improve CPAP compliance by reducing nasal symptoms and allowing lower treatment pressures.

OSA in Childhood

Childhood OSA is said to have a prevalence of 1–5%, and is associated with tonsillar hypertrophy, obesity, and various craniofacial syndromes. Snoring, restless sleep, sweating, and enuresis are common features, but EDS is rarer than hyperactivity. Adenoidal enlargement is not visible in clinic, but can be inferred by the presence of tonsillar hypertrophy. In the UK, ENT surgeons rarely carry out sleep studies in children because adenotonsillectomy is almost invariably effective treatment in the non-obese child. In less clear-cut cases there may be spontaneous improvement if surgery is deferred. If mild disease is present, weight loss (where appropriate) and topical steroids and/or oral montelukast may reduce adenoidal size sufficiently to effect an improvement, but this is not widely practised. CPAP may be indicated for children with persistent OSA post-surgery, obesity, craniofacial abnormalities, or neuromuscular disorders.

OSA and the Surgical Patient

The risks of desaturation, respiratory failure, reintubation, ICU transfer, and cardiac events are doubled in the OSA population undergoing surgery [25]. General anaesthesia and post-operative analgesia pose a particular risk for the patient with OSA. Anaesthetic agents reduce ventilatory drive, increase the tendency to upper airway collapse, and impair normal arousal mechanisms, all of which will increase the pre-existing tendency to obstructive apnoeas. Not only may the upper airway anatomy of the OSA patient contribute to a difficult intubation, but the timing and monitoring of extubation is critical. If the patient is known to have treated OSA, they should bring their CPAP machine with them to hospital, and post-extubation CPAP is tolerated and safe. If the OSA only becomes apparent post-extubation, then urgent management with an oropharyngeal or nasal airway can be followed by CPAP, although if the patient is not familiar with this treatment it may be poorly tolerated. The risk of adverse outcomes is highest in the first 24 h, and reversal of anaesthesia and narcotics may be necessary. Increasingly, patients scheduled for elective surgery undergo questionnaire screening for OSA and are referred for diagnostic studies. Surgery may then be delayed until patients with abnormal studies are established on CPAP regardless of symptoms, yet the evidence for the necessity of this strategy is far from convincing [26]. In the bariatric population (where there is a particularly high prevalence of OSA), acclimatising affected patients to treatment means that perioperative CPAP is less likely to cause aerophagy and threaten the integrity of the surgical anastomosis.

Central Sleep Apnoea (CSA)

Central apnoeas and hypopnoeas arise from complete or partial cessation of neural output to the respiratory muscles, and are much rarer then obstructive apnoeas. In the latter there are continuing efforts to overcome an obstructed airway, and this is detected by out-of-phase thoracic–abdominal movement detected by respiratory impedance plethysmography or flow limitation on a nasal pressure signal. Distinguishing central from obstructive hypopnoeas is more difficult, as in both cases diminished respiratory efforts continue. There are no consistent diagnostic criteria to define a clinically significant degree of CSA, but arbitrarily CSA is considered the primary diagnosis if >50% apnoeas are central. Obstructive and central events frequently coexist in the same patient, and central apnoeas can lead to obstructive events and vice versa.

Central sleep apnoea is less well understood than OSA, and has varying aetiologies. One classification of CSA is based on the presence or absence of hypercapnia.

Hypercapnia CSA

Neurological Disease

Any brainstem pathology (trauma, infarcts, tumours) can adversely affect ventilatory output. The cause is usually obvious, and the other neu-

rological consequences of the brainstem injury tend to dominate the clinical picture. Congenital central hypoventilation syndrome (previously known as Ondine's curse) usually presents in infancy or childhood, and is due to inherited mutation in the PHOX2B gene. There are impaired responses to hypoxia and hypercapnia and daytime ventilatory failure due to low tidal volume and marked alveolar hypoventilation, which is worse in NREM sleep.

Opiate-Induced CSA

Opioids are potent respiratory depressants, particularly in overdose, but it is increasingly recognised that chronic opiate use is associated with CSA, with a quoted prevalence of 24%. This ill-understood phenomena is dose-related and is particularly likely with a morphine equivalent daily dose >200 mg. The central depressant effect is probably due to their effect on brainstem and carotid bodies. Mild hypoxia is common in chronic opiate use, and if further central respiratory depression occurs, worsening hypoxaemia will result. The peripheral chemoreceptor response corrects hypoxaemia and blows off CO_2, but blunting of central chemoreceptors prevents a brisk response to CO_2 tension changes, and continuing exposure to the opiate propagates the cycle.

Obesity Hypoventilation Syndrome (OHS)

This is the combination of obesity (BMI > 30 kg/m^2) and hypercapnia during wakefulness that is unexplained by neuromuscular, metabolic, or ventilatory defects (FEV1/FVC ratio >60%) and is an increasingly prevalent condition, albeit prone to diagnostic delay. Patients normally present with oedema, and this is often misdiagnosed as cardiac failure. Morning headache, somnolence, and neurocognitive impairment are usually present. Obesity impairs respiratory mechanics and there may be an element of respiratory muscle weakness. Obstructive sleep apnoea is present in up to 90% of individuals, and the condition is present in 10% of OSA patients. Why some individuals develop OHS is incompletely understood, but differences in fat distribution and blunted chemosensitivity have been invoked, and perhaps permit tolerance to the hypercapnia that develops during sleep. Leptin is an adipose tissue-derived protein that controls appetite and acts on central respiratory pathways to increase respiration. In OHS patients leptin levels are higher than weight-matched controls, and this has led to the theory that OHS represents a state of reduced drive and hypercapnic response caused by leptin resistance. OHS patients frequently present in extremis with acidotic exacerbations of chronic ventilatory failure and temporary mild left ventricular impairment. Treatment usually involves long-term, non-invasive bilevel ventilation with high expiratory pressures to treat the associated OSA.

Mixed CSA and OSA

This is encountered in the early stages of CPAP treatment of patients with OSA, and is known variously as "complex sleep apnoea" or "treatment-emergent central apnoeas." It may become apparent during the initial CPAP titration if the pressure is increased too rapidly. Why this develops is unclear: pressure-activated lung stretch receptors may inhibit central motor output via the Hering-Breuer reflex, or mask leak might increase CO_2 excretion and lead to readier crossing of the apnoeic threshold. These central events almost invariably resolve with continued CPAP over the ensuing month, and although quite common, are of uncertain significance.

Non-hypercapnic CSA

Cardiac Failure

Approximately 50% of all patients with cardiac failure have some form of sleep apnoea, either central, obstructive, or both. Although initially thought to be a marker of severe cardiac dysfunction, it is now clear that central apnoeas may be present with mild disease. Some, but not all, stud-

ies have associated CSA with increased mortality, but when adequately controlled for heart failure severity, the association is not strong. Cheyne-Stokes (CS) breathing is the waking manifestation of the central apnoeas, and both are characterised by 20–30 s of hyperventilation followed by 10–40 s of hypopnoeas or apnoeas. The waxing and waning in tidal volume distinguishes CSA-CS from other causes of CSA. Unlike OSA, these events occur in wakefulness or stages 1 and 2 non-REM rather than REM sleep.

Pathophysiology of CSA-CS

Raised left atrial pressure and pulmonary venous congestion are consequences of heart failure and stimulate pulmonary receptors, causing hyperventilation and lowering the $PaCO_2$ nearer to the apnoeic threshold. With sleep onset, the waking drive to breath is removed and as the $PaCO_2$ falls below this threshold, the patient remains apnoeic until the CO_2 rises again and ventilation is re-established. Shortly after the arousal occurs, sleep is resumed and the cycle begins again. This oscillation of the feedback loop around the apnoeic threshold is critical to the perpetuation of CSA, but there is no single unifying explanation as to why the system is inherently more unstable than in health, and with a tendency to both overshoot and undershoot. The length of the ventilatory phase is proportional to cardiac output, suggesting (oversimplistically) that the low cardiac output results in a prolonged transit time between lungs and chemoreceptors, and that there is a delay before the $PaCO_2$ in the lungs is sensed in the brainstem and carotid bodies. Supine low-volume lungs, fluctuations in alveolar ventilation, and changes in sleep stage destabilise ventilatory control and predispose to CSA.

Increased central and peripheral chemoreceptor responses to CO_2 have been described in heart failure patients with CSA, and may predispose to instability, indeed central apnoeas can be abolished by small increments in inspired CO_2. While cardiac-induced central apnoeas can cause sleep fragmentation and swings in intrathoracic pressure, the effects on daytime sleepiness and left ventricular afterload appear less than in the OSA population. Bronchoscopic measurements show that during a central apnoea, upper airway closure on expiration may occur, blurring the distinction between the two forms of apnoea.

Patients with CSA may complain of EDS and choking, but are more likely than OSA patients to be elderly and complain of difficulty initiating and maintaining sleep. Treatment for heart failure, including cardiac resynchronisation therapy, improves CSA, but if it persists and is accompanied by symptoms of sleep fragment, targeted treatment should be considered. The CANPAP study [27] randomised patients with heart failure and predominant CSA (mean AHI 40 events/h) to medical treatment or non-titrated CPAP. Although the primary endpoint of transplant-free survival was no different between the groups, the CPAP group had significant falls in AHI, nocturnal desaturation, and noradrenaline levels. A post-hoc analysis suggested that in those patients where CPAP suppressed AHI <15 events/h, survival was improved [28]. Adaptive Servo-Ventilation (ASV) is a pressure preset form of non-invasive ventilation which can be volume- or flow-cycled, and can have variable inspiratory and expiratory pressure to ensure upper airway patency. ASV attenuates hyperventilation and hypocapnoea by delivering preset minute ventilation and providing CPAP to reverse any upper airway obstruction. Early studies suggested ASV was very effective at reducing AHI and improving left ventricular ejection fraction, and it was widely anticipated that in patients with heart failure and CSA this form of ventilatory support would improve sleep quality, left ventricular function, and survival. SERVE-HF was a large multicentre trial examining use of ASV in patients with systolic heart failure and predominant CSA [29]. Although ASV was effective in reducing AHI (from a mean of 25 to 3 central events/h) and improving Epworth scores, there were no improvements in functional outcomes or quality-of-life measurements, and an unexpected increase in all cause and cardiovascular mortality (28% and 34% respectively), with the risk of death greatest in

the patients with more severe heart failure. ASV is now contraindicated in patients with chronic heart failure (NYHA 2–4) and left ventricular ejection fraction (LVEF) <45%, but may still be useful in patients with CSA and other forms of heart failure, including those with a preserved ejection fraction. Oxygen treatment suppresses chemoreceptor drive and dampens the oscillations of the respiratory control system. Meta-analyses from a limited number of trials confirm considerable improvement in AHI, arterial desaturation and, to a lesser extent, left ventricular ejection fraction.

Idiopathic CSA

Idiopathic CSA is rare and poorly understood. The key seems to be an unexplained tendency to hyperventilate during wakefulness and sleep, and increased peripheral and central responsiveness to CO_2. When the waking drive to breathe is withdrawn at sleep onset, the low CO_2 from previous hyperventilation is below the apnoeic threshold, which results in an apnoea, then an arousal. Once sleep is firmly established, the apnoeas become less frequent. Only small changes in CO_2 seem to be necessary to perpetuate the cycle of apnoea and hyperventilation, and the degree of oxygen desaturation is typically small. Generally this seems to be a benign condition, but can be symptomatic with either insomnia or excessive daytime somnolence Because of the rarity of the condition, treatment is not clearly established. Acetazolamide and sedatives such as zolpidem and triazolam appear to have some efficacy, [30] by either providing a constant non-fluctuating respiratory stimulus or deliberately blunting the arousal threshold. CPAP seems to be effective, but there is no long-term data, and the mechanism of action is probably different from in OSA.

Non-apnoeic Sleep Disorders

A number of non-apnoeic sleep disorders may present to respiratory physicians because of their expertise in the diagnosis of somnolent patients with sleep-disordered breathing. Although traditionally these patients may be regarded as having a neurological disorder, familiarity with these conditions is useful.

Myotonic Dystrophy

This autosomal dominant disorder is not uncommon, but sporadic cases occur or the classical facial features or muscle weakness may be absent. Obstructive sleep apnoea is common, but if respiratory muscle weakness is present, then nocturnal hypoventilation and diurnal ventilatory failure may develop. Adherence to the recommended form of respiratory support (be it CPAP or bilevel ventilation) may be patchy, as a degree of apathy is often part of the condition. Somnolence may be present without any evidence of sleep-disordered breathing, and REM sleep dysregulation has been identified. Trials of stimulants such as modafanil are sometimes helpful.

Narcolepsy

This condition is now known to be caused by a deficiency of the neurotransmitter hypocretin in the lateral hypothalamus. It can be regarded as a disorder where the demarcation between wakefulness, NREM, and REM sleep is disorganised. It has a bimodal age of onset, with peaks at 16 and 36, and diagnostic delay is usual. Sleep may be irresistible, with a need to take frequent short naps (which are characteristically refreshing), but often occurring in highly inappropriate circumstances. Microsleeps and semi-automatic behaviours are common, but nighttime sleep is often fragmented, and other parasomnias can occur. Cataplexy develops in 60–70% of cases and, if recognised, confirms the diagnosis. Attacks of transient muscular weakness of neck (head nod), leg, arm or facial sagging, or slurred speech with preserved consciousness, usually precipitated by laughter or anger, should be specifically enquired about. Vivid dreams at sleep onset or termination which are hard to distinguish from wakefulness,

and routinely dreaming during short naps, is suggestive. Sleep paralysis completes the tetrad, but is sometimes seen in normal individuals as an isolated phenomenon. Although essentially a clinical diagnosis, investigation may be helpful. The Multiple Sleep Latency Test (MSLT) offers up to five nap opportunities at two hourly intervals with EEG monitoring, and can provide useful confirmation if rigorously performed. Narcoleptics have a short sleep latency and may show episodes of REM within 15 min of falling asleep (so-called sleep onset REM). The DQB1*0602 haplotype is found in over 95% of patients with narcolepsy and cataplexy, but is also found in about 30% of the normal population, so has little diagnostic utility. Recently, cases of narcolepsy were associated with vaccination with H1N1 influenza vaccine and the development of antibodies to the hypocretin receptor, suggesting an autoimmune basis to the condition. Management of the EDS requires stimulant medication (modafanil, dexamphetamine) and cataplexy may respond to tricyclics or SSRIs, which suppress REM sleep. Sodium oxybate improves both symptoms, but has an inconvenient dosing schedule and is very expensive.

Another primary sleep disorder that is sometimes hard to distinguish from narcolepsy is idiopathic hypersomnolence. The aetiology is unknown, but subjects need more sleep than normal people and have prolonged nighttime sleep, difficulty waking, unrefreshing daytime naps, and confusional arousals (sleep drunkenness) on waking. There are no other features of the narcolepsy tetrad, and the response to modafanil is often disappointing.

Parkinson's Disease (PD) and Other Neurodegenerative Disorders

Sleep disturbance is common, particularly daytime sleepiness, which may occur with little warning and which may be due to initiation of treatment with dopamine agonists. A surprisingly common parasomnia in this group of patients is REM sleep behaviour disorder (REMBD), where there is a failure of the normal muscle atonia during REM sleep. Subjects act out dreams with often violent limb movements and injuries to themselves or bed partner. If woken, confusion is unusual, and dreams may be recalled. Polysomnography, if performed, shows muscle tone to be preserved during REM sleep. REMBD may develop in otherwise healthy individuals, but at least half of these patients will eventually develop PD or some other neurodegenerative disease. Treatment with clonazepam is usually effective, and failing that, melatonin. The syndrome may be caused by antidepressants, which should be stopped on a trial basis.

Restless Legs Syndrome

This is a common movement disorder that often presents with daytime somnolence due to sleep initiation insomnia or more subtle sleep fragmentation. Uncomfortable legs, worse in the evening and at rest and relieved by movement, are essential to diagnosis. A useful screening question is: "When you try and relax in the evening or sleep at night, do you ever have unpleasant restless feelings in your legs that can be relieved by walking or movement?". The diagnosis is a clinical one and sleep studies are rarely required, although repetitive clusters of periodic limb movements (PLM) may be detected with actigraphy, and are a frequent association. Milder cases may respond to non-pharmacological interventions such as warm baths or avoidance of caffeine and alcohol. Drugs prescribed for comorbid conditions, particularly dopamine antagonists and antidepressants, may exacerbate RLS and can be temporarily withdrawn. Drug therapy is often considered necessary for moderate/severe disease, and transdermal (rotigotine) and oral dopamine agonists (ropinirole and pramipexole) are usually effective. However, there is growing concern about their role in the eventual development of augmentation (earlier timing of symptom onset, reduced response to medication, extension to other body parts) and gabapentin or low-dose opiates may be preferred as initial treatment. Iron deficiency if present, requires replacement therapy.

Circadian Rhythm Disorders

Identification of these conditions is usually clear from the history. Jet lag is transient, but shift work disorder is commoner with age, and a cause of daytime somnolence which is rarely amenable to treatment other than job change. Delayed sleep phase syndrome is common in adolescents and young adults, and is an inability to initiate sleep until the early hours of the morning, and a need to wake later than traditional employment usually demands. Increasingly, abnormalities of the intrinsic clock mechanism are recognised.

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