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Sleep-Disordered Breathing

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ABSTRACT

Purpose of Review: This article introduces readers to the clinical presentation, diagnosis, and treatment of sleep-disordered breathing and reviews the associated risk factors and health consequences.

Recent Findings: Sleep-disordered breathing is associated with significant impairments in daytime alertness and cognitive function as well as adverse health outcomes. The initial treatment of choice is positive airway pressure. Improvements in technology and mask delivery systems have helped to make this treatment more comfortable and convenient for many patients.

Summary: Sleep-disordered breathing, particularly in the form of obstructive sleep apnea, is highly prevalent in the general population and has important implications for neurology patients. Sleep-disordered breathing is characterized by repetitive periods of cessation in breathing, termed *apneas*, or reductions in the amplitude of a breath, known as *hypopneas*, that occur during sleep. These events are frequently associated with fragmentation of sleep, declines in oxygen saturation, and sympathetic nervous system activation with heart rate and blood pressure elevation. Obstructive sleep apnea, which represents cessation of airflow, develops because of factors such as anatomic obstruction of the upper airway related to obesity, excess tissue bulk in the pharynx, and changes in muscle tone and nerve activity during sleep. Central sleep apnea represents cessation of airflow along with absence or significant reduction in respiratory effort during sleep and is more commonly found in the setting of congestive heart failure, neurologic disorders, or cardiopulmonary disease.

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INTRODUCTION

Sleep-disordered breathing is an overarching term used to describe various distinct or occasionally overlapping syndromes, including obstructive sleep apnea (OSA), central sleep apnea, and hypoventilation. Sleep-disordered breathing is characterized by intermittent periods of apnea, hypopnea, or respiratory effort–related arousals (RERAs). Obstructive apnea events consist of transient cessations in airflow (90% or greater airflow reduction for at least 10 seconds, as defined by the American Academy of Sleep Medicine [AASM]), whereas hypopneas are char-

acterized by diminished amplitude of the inspiratory breath (30% to 90% airflow reduction for at least 10 seconds with at least 4% reduction in baseline oxygen saturation), as depicted in **Figure 5-1**.¹ Although the AASM recommends the former definition of a hypopnea, the alternative AASM definition may be appropriate to use for selected patients: a hypopnea is scored when airflow drops by at least 50% for at least 10 seconds with either an associated 3% or greater reduction in oxygen saturation, or an associated arousal from sleep.¹ RERAs are periods of increased respiratory effort with

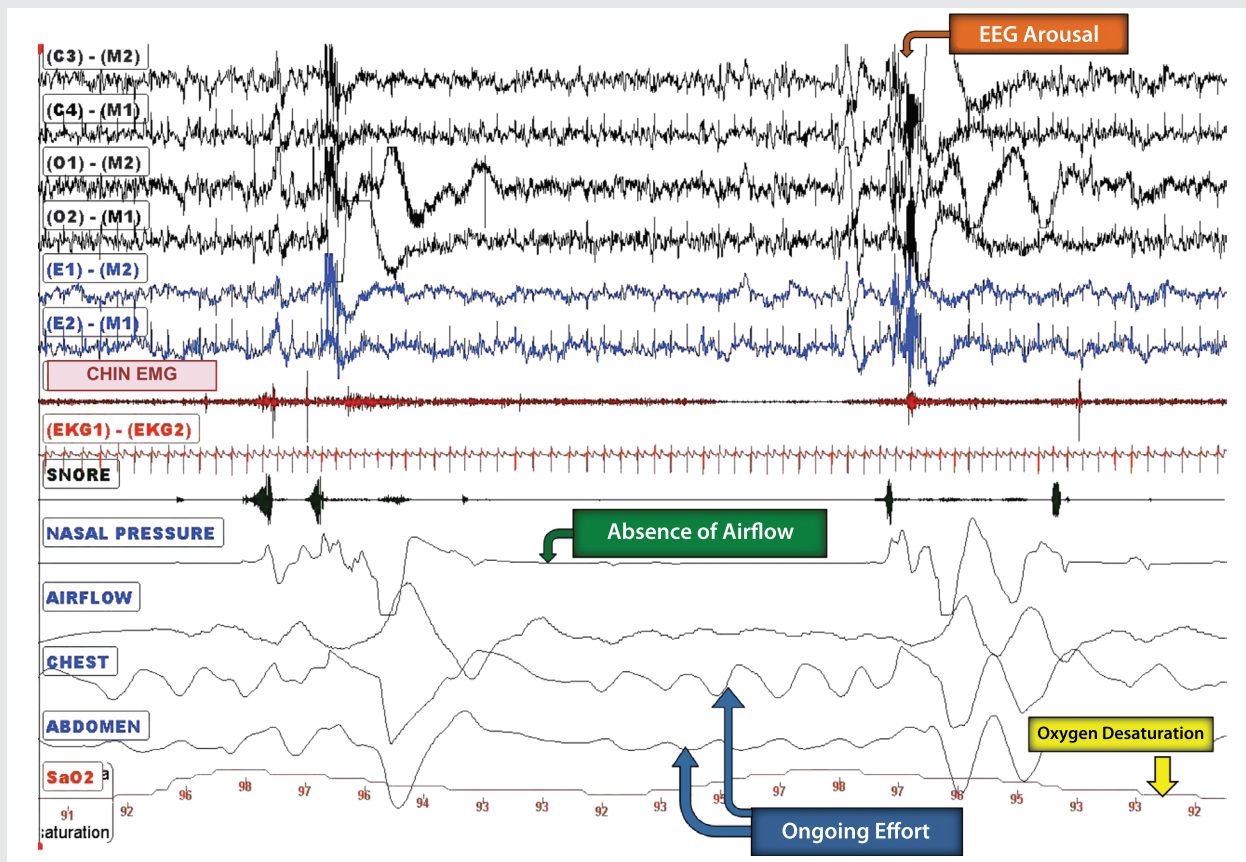


FIGURE 5-1 Polysomnographic example of obstructive apnea. A 60-second epoch of polysomnography during non-REM stage N2 sleep demonstrating an obstructive apnea, defined as a 90% or greater loss of airflow for at least 10 seconds with preserved respiratory effort. Note the absence of airflow through the nose and mouth despite ongoing respiratory effort (as seen by the tracings of thoracic and abdominal movement), signifying obstruction of the upper airway with consequences including oxygen desaturation and an EEG arousal from sleep. Channels from top to bottom represent EEG (left and right central, left and right occipital), electrooculogram (left and right eyes), chin EMG, EKG, snoring, nasal pressure transducer, oral thermistor, respiratory effort (thoracic and abdominal movement), and arterial oxygen saturation.

EEG = electroencephalograph; EMG = electromyogram; EKG = electrocardiogram; SaO2 = arterial oxygen saturation.

decreased airflow, crescendo snoring, and transient EEG arousals from sleep that do not meet AASM criteria for apneas or hypopneas.²

The respiratory events that occur in sleep-disordered breathing are typically transitory and self-limited. They often induce brief arousals or microarousals from sleep, which in turn restore a normal breathing pattern.³ Apneas and hypopneas frequently cause transient oxygen desaturation, but this may not always occur, especially among patients with normal baseline pulmonary func-

tion. A subtype of sleep-disordered breathing termed *upper airway resistance syndrome* occurs among some patients with primarily RERAs, without associated significant oxygen desaturation or frank apneas and hypopneas. Upper airway resistance syndrome is thought to have similar pathophysiology and presents with similar symptoms as OSA.²

OSA occurs as a result of apneas and hypopneas that are primarily caused by physical obstruction of the extrathoracic upper airway. Typically during these

KEY POINTS

- An obstructive apnea is defined as cessation of airflow with continued respiratory effort due to complete upper airway occlusion.
- A hypopnea is a partial decrement in airflow with an associated physiologic consequence, either an arousal or oxygen desaturation, due to partial upper airway collapse.

events, complete or partial collapse of soft tissue and pharyngeal musculature occurs during sleep. This pattern can vary by stage of sleep and by body or head position and tends to be particularly severe when in the supine position or during REM sleep. The normal skeletal muscle atonia associated with REM sleep can exacerbate airway collapse in susceptible people.^{4,5}

On the other hand, central sleep apnea (CSA) is unrelated to physical obstruction but instead is caused by

cessation or significant reduction in respiratory effort or drive (Figure 5-2). Respiratory effort, mediated by CNS brainstem respiratory control centers in the pons and medulla, can be assessed during polysomnography (PSG) by the use of thoracic and abdominal respiratory inductance plethysmography belts. The belts detect movements of the chest and abdomen during inspiration and expiration, which are surrogates for respiratory effort. In central apnea, transient

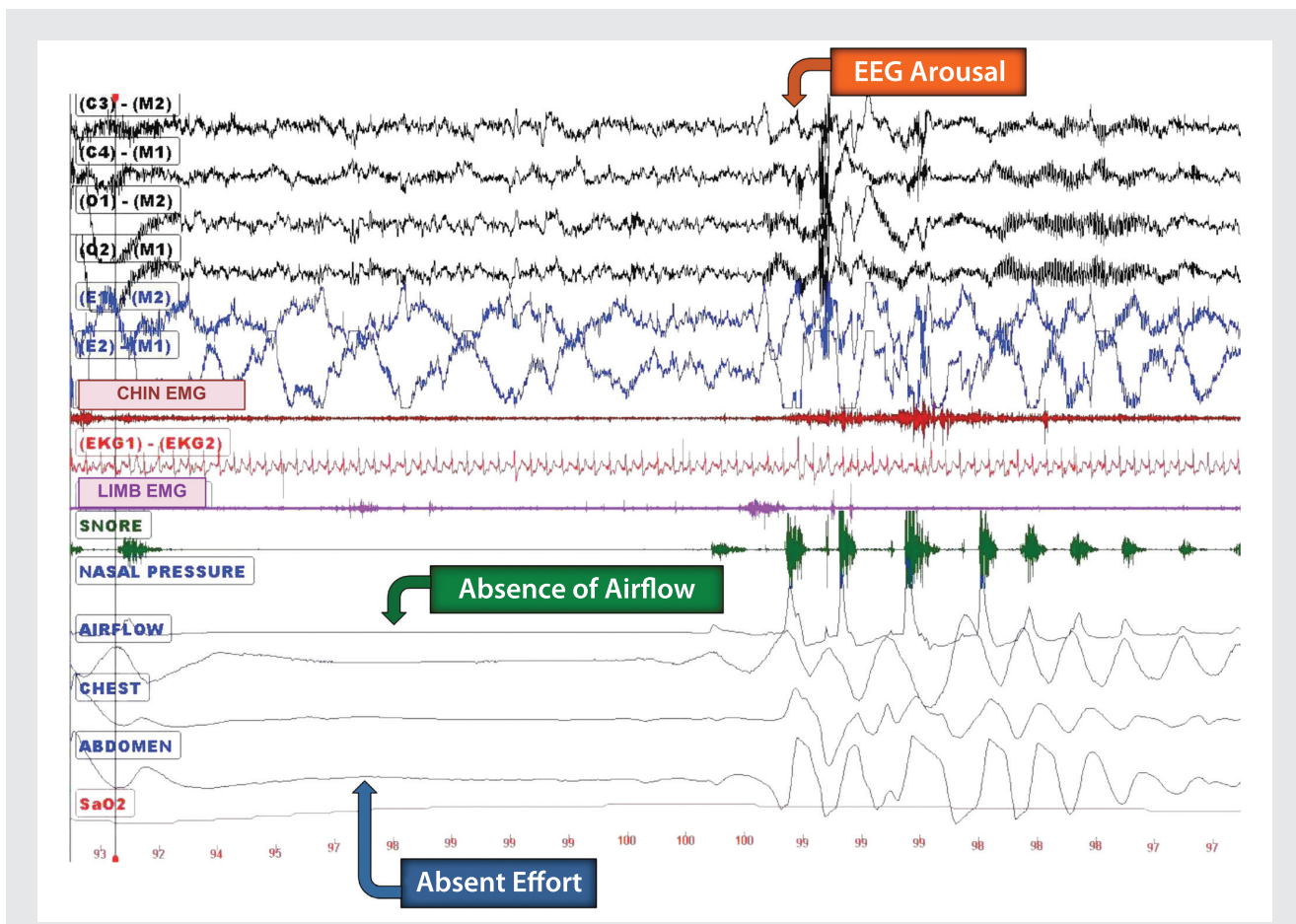


FIGURE 5-2 Polysomnographic example of central apnea. A 60-second epoch of polysomnography during non-REM stage N1 sleep demonstrating a central apnea, defined as a minimum of 10 seconds of airflow loss with associated absence of respiratory effort. Note the absence of airflow through the nose and mouth and the loss of respiratory effort in the chest and abdomen. The event is terminated by an EEG arousal from sleep. Channels from top to bottom represent EEG (left and right central, left and right occipital), electrooculogram (left and right eyes), chin EMG, EKG, snoring, nasal pressure transducer, oral thermistor, respiratory effort (thoracic and abdominal movement), and arterial oxygen saturation.

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pauses in respiratory effort result in cessation of airflow, often followed by oxygen desaturation or an arousal from sleep. Combinations of central and obstructive apneas can occur in the same individual, a condition termed *complex sleep apnea syndrome* when the events occur with sufficient frequency. When a combination of central and obstructive components occurs within the same breath, it is termed a *mixed apnea*. During mixed apneas, no respiratory effort occurs during the initial portion of the breath, followed by resumption of effort but persistently diminished or absent airflow.

OBSTRUCTIVE SLEEP APNEA Epidemiology and Risk Factors

OSA is highly prevalent in the general population. Population-based studies estimate the prevalence of OSA among working people aged 30 to 60 to be approximately 2% of women and 4% of

men.^{6,7} When not including sleepiness symptoms in the criteria, the prevalence of OSA characterized solely by apnea or hypopnea events is 9% among middle-aged women and 24% in men. This number may actually be an underestimate of the true prevalence. Most epidemiologic studies for OSA were performed during the previous 2 decades; in the interim, advances have occurred in the sensitivity of polysomnographic equipment (thereby increasing the likelihood of detection of OSA), and rates of obesity, which is a major risk factor for OSA, have significantly increased.⁸ OSA is 1.5 to 4.0 times more common in men, and prevalence also increases with age.^{7,9} After menopause, women's risk approximates that of men (**Case 5-1**).⁷ Craniofacial bony dimensions are a significant contributor even in the absence of obesity, especially among Asian populations and some whites.¹⁰

KEY POINTS

- A mixed apnea is defined as a period of airflow cessation without respiratory effort followed by a period of resumed effort with continued decrements in airflow.
- Obstructive sleep apnea is a highly prevalent condition that occurs predominantly in middle-aged or older men and postmenopausal women.

Case 5-1

A 63-year-old woman reported unrefreshing sleep and frequent awakenings during which she felt sweaty and hot with nocturia twice nightly. She snored softly and often awoke with a dull bitemporal headache that resolved spontaneously within hours. She was postmenopausal, and her daytime hot flashes had stopped at age 56. She requested a prescription for sleeping pills to prevent awakenings.

During the day, she felt tired and had difficulty concentrating and remembering tasks. She slept for 8 hours nightly and had a regular bedtime. She had no cataplexy, sleep paralysis, hypnagogic hallucinations, or dream enactment behavior.

Examination findings were blood pressure, 123/78 mm Hg; body mass index, 27 kg/m²; and neck circumference, 38.6 cm (15.2 in). Nasal turbinates and septum were normal, uvula and tonsils were not enlarged, and no macroglossia or retrognathia was present. The hard palate was high-arched and narrow. The peritonsillar lateral walls had redundant tissue.

Polysomnography (PSG) demonstrated moderate obstructive sleep apnea (OSA) with an overall apnea-hypopnea index (AHI) of 16 events/h, supine AHI of 19 events/h, and REM-sleep AHI of 43 events/h (**Figure 5-3**). The oxygen saturation nadir was 83%. The periodic limb movement index was 8 per hour. The PSG was repeated for continuous positive airway pressure (CPAP) titration. The patient was fitted with a variety of masks and liked a nasal mask best. At a CPAP pressure of 9-cm water, the AHI improved to 2 events/h, supine AHI to 3 events/h, and REM-sleep AHI to 0 events/h. The oxygen saturation nadir was 94%. The periodic limb movement index was 0 events/h.

After 6 weeks of using CPAP, she reported significantly improved symptoms. She initially had difficulty falling asleep with CPAP but was now using it for 8 hours nightly with refreshing sleep

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Continued from page 89

and improved subjective memory and concentration. Awakenings were now rare, and her nocturia and morning headaches had resolved.

Comment. Women may have atypical OSA presenting symptoms, with older age; lower body mass index; and lower incidence of snoring,

witnessed apneas, or choking arousals. Symptoms often develop when the woman is perimenopausal. Sleep-maintenance insomnia may present similarly, but patients with OSA-suggestive features (eg, snoring, morning headaches, oropharyngeal crowding) should first undergo evaluation for sleep-disordered breathing. Sedative-hypnotic drugs can worsen OSA severity and are contraindicated in untreated OSA. The PSG also demonstrated mild periodic limb movements, which can be secondary to untreated OSA and frequently resolve with CPAP. OSA was moderate overall but severe during REM sleep (**Figure 5-3**). Isolated REM-related OSA can also occur but has an unknown impact on long-term health.

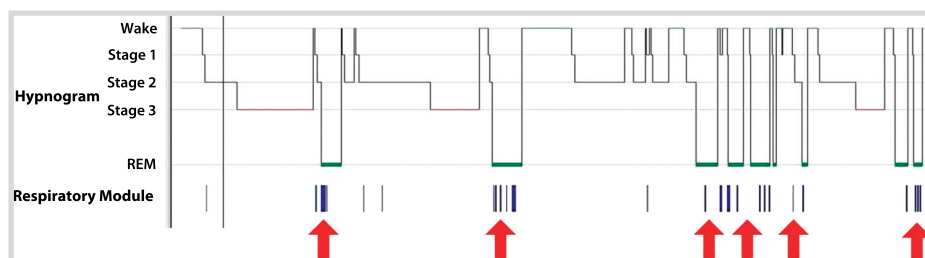


FIGURE 5-3

Hypnogram of REM-related apnea. This hypnogram summarizes stages of sleep over the course of the night and temporally correlates them with respiratory events. As shown by the red arrows, this patient exhibits apneas and hypopneas (vertical dashes) that occur primarily during periods of REM sleep (horizontal green bars).

A family history of snoring or sleep-disordered breathing can increase one's risk of OSA, possibly because of similar craniofacial anatomic features as well as similar incidences of obesity among relatives. Behavioral risk factors for OSA include use of sedatives or alcohol and sleeping in the supine position. OSA incidence is especially high in people with certain medical comorbidities, including type 1 and type 2 diabetes mellitus, polycystic ovarian syndrome, congestive heart failure, stroke, or Down syndrome.^{7,11–13} Hypothyroidism can also exacerbate OSA.¹⁴ While frequently associated with snoring, chronic nasal obstruction plays a relatively minor role in the pathogenesis of OSA, although use of intranasal steroid medications can help to improve the efficacy of OSA treatment.¹⁵ Neurologic disorders associated with an increased risk of sleep-disordered breathing include stroke, epilepsy, Parkinson dis-

ease, multiple system atrophy, and neuromuscular disorders that weaken the diaphragm (causing hypoventilation) or pharynx (contributing to OSA), such as myasthenia gravis or ALS (Table 5-1).^{16–25}

Pathophysiology

Most people with OSA have normal respiratory patterns during wakefulness with appropriate feedback control systems. However, changes occur during sleep that predispose them to a sleep-disordered breathing pattern. A normal sleep-related decrease, which occurs in neuronal excitatory input to pharyngeal dilator muscles, is excessively reduced among many individuals with OSA, resulting in hypotonic pharyngeal muscles and increased risk of airway collapse.²⁶ This abnormality may be due to impaired sensory, cortical, or motor components of the upper airway reflex that serves to resist upper airway collapse in response to negative pressure

TABLE 5-1 Mechanisms of Sleep-Disordered Breathing Induction in Key Neurologic Diseases

Neurologic Disease	Type and Presumed Mechanism of Sleep-Disordered Breathing
Acute stroke	Obstructive sleep apnea (OSA): dysphagia and upper airway muscle weakness, supine positioning. ¹⁹ Central sleep apnea: injury to brainstem respiratory control centers, cerebral edema, impaired consciousness. ²⁰
Neuromuscular disease	OSA: upper airway muscle weakness. Central sleep apnea: weakness of chest wall muscles and diaphragm, exacerbated by sleep-related physiologic muscle relaxation. ²¹
Parkinson disease	No clear association. OSA (when present) possibly caused by motor symptoms affecting upper airway patency at the level of the glottis. ²²
Multiple system atrophy	OSA: respiratory stridor during sleep. Cheyne-Stokes respirations: caused by vocal cord abductor paralysis, bulbar weakness, injury to brainstem respiratory control neurons. ^{23,24}
Epilepsy	OSA: Antiepileptic drugs can exacerbate OSA risk factors such as obesity, increased neck circumference, and upper airway collapsibility. Vagus nerve stimulators can affect respiration during sleep. ²⁵

KEY POINT

■ Obstructive sleep apnea is viewed as a primarily mechanical problem of the upper airway, with both neuronal and anatomic factors contributing to increased collapsibility.

during inspiration.²⁷ Sensory deficits may include impaired functioning of mechanoreceptors that sense airflow, pressure, and muscle tone.²⁸ Cortical arousability may be blunted during apneas, hypoxia, or hypercapnia. Motor nerve dysfunction may reduce activation of important pharyngeal dilator muscles such as the genioglossus, resulting in pharyngeal muscle hypotonia and increased susceptibility to airway collapse.^{27,29} Snoring-induced vibratory trauma and mechanical strain from repeated upper airway collapse may contribute to the development of irreversible peripheral nerve injury in OSA.^{28,30}

Anatomic factors also play a prominent role. People with OSA can have differences in upper airway soft tissue volume and craniofacial anatomy that result in a narrowed pharyngeal lumen, causing abnormal increases in upper

airway pressure even while awake. When coupled with even a normal degree of reduced pharyngeal muscle tone during sleep, airway obstruction occurs.³¹ Craniofacial factors can include a high-arched palate and insufficient protrusion or width of the maxilla and mandible.¹⁰ Common soft tissue features include adenotonsillar hypertrophy, an elongated and edematous uvula, and an enlarged tongue relative to the size of the oropharyngeal cavity (macroglossia). Obesity can significantly contribute to soft tissue hypertrophy and narrowing of the pharyngeal space. Each of these predisposing factors may be present to differing degrees in different people.

Symptoms

The diagnosis of OSA is based on a combination of clinical and PSG criteria.

KEY POINT

■ Symptoms suggestive of obstructive sleep apnea include snoring; witnessed apneas; arousals associated with choking, gasping, and diaphoretic awakenings from sleep; and excessive daytime sleepiness.

The clinical presentation of OSA may include symptoms such as snoring, apneas in sleep that are witnessed by observers, a history of awakenings associated with a sensation of choking or gasping for air, nocturia, morning headaches, heavy diaphoresis during sleep (especially in the upper chest and neck area), and excessive daytime sleepiness. The degree of subjective daytime sleepiness can be gauged using the Epworth Sleepiness Scale (see the article “Approach to and Evaluation of Sleep Disorders”), an eight-question measure of the subjective likelihood of the patient dozing unintentionally in various common daytime situations.³² An Epworth Sleepiness Scale score greater than 10 of 24 is consistent with subjective excessive daytime sleepiness. Screening tools such as the STOP-BANG questionnaire or Berlin Questionnaire can also aid practitioners in assessing their patients’ OSA risks.^{33,34} Patients may report memory problems, irritable mood, and reduced alertness and concentration.³⁵ People with OSA have a significantly higher risk of motor vehicle accidents because of impaired alertness or falling asleep while driving, and this risk does not necessarily correlate with the severity of the OSA.³⁶ This issue can be of particular concern for commercial drivers.³⁷ OSA is also associated with nocturnal gastroesophageal reflux because obstructive events can increase intra-abdominal pressure, which may eventually weaken lower esophageal sphincter tone.^{38,39} Less common symptoms include periodic limb movements in sleep, dream enactment behavior, and sleepwalking caused by incomplete arousals triggered by obstructive events.^{40,41}

Physical Examination

Suggestive physical examination findings for OSA include an enlarged neck circumference (greater than or equal to

43.2 cm [17 in] in men or greater than or equal to 40.6 cm [16 in] in women) and obese body habitus as determined by a BMI of greater than 30 kg/m². The anatomy of the face and oral cavity is also helpful in gauging the likelihood of developing a mechanical obstruction during sleep. One prospective study of 420 subjects found an up to 2.6-fold increase in the adjusted odds ratio for OSA if subjects had abnormal morphometric measures of the upper airway. These included narrowing of the posterior pharyngeal space due to impingement by peritonsillar tissues, tonsillar hypertrophy, macroglossia (tongue enlarged above the level of the mandibular occlusion plane), retrognathia (recessed chin), and enlarged uvula (greater than 1.5 cm [0.6 in] in length or greater than 1.0 cm [0.4 in] in width).⁴² Such physical measures of oral cavity parameters, BMI, neck circumference, and pharyngeal adiposity are strongly associated with OSA.^{43,44} Thus, facial morphology and oropharyngeal examination are important parts of the OSA evaluation. The Mallampati classification, originally developed to assess for ease of endotracheal intubation, has also been adapted to help predict likelihood of OSA (see the article “Approach to and Evaluation of Sleep Disorders”).⁴⁵

Polysomnography

Patients who have history and examination findings suggestive of OSA should undergo confirmatory testing with PSG. Full PSG combines EEG for determination of sleep stages, surface EMG to measure neck muscle tone and limb movements, electrooculogram for assessing eye movements, respiratory inductance plethysmography belts for measurement of thoracic and abdominal respiratory effort, pulse oximetry, ECG, and monitors to detect snoring and airflow movement through the

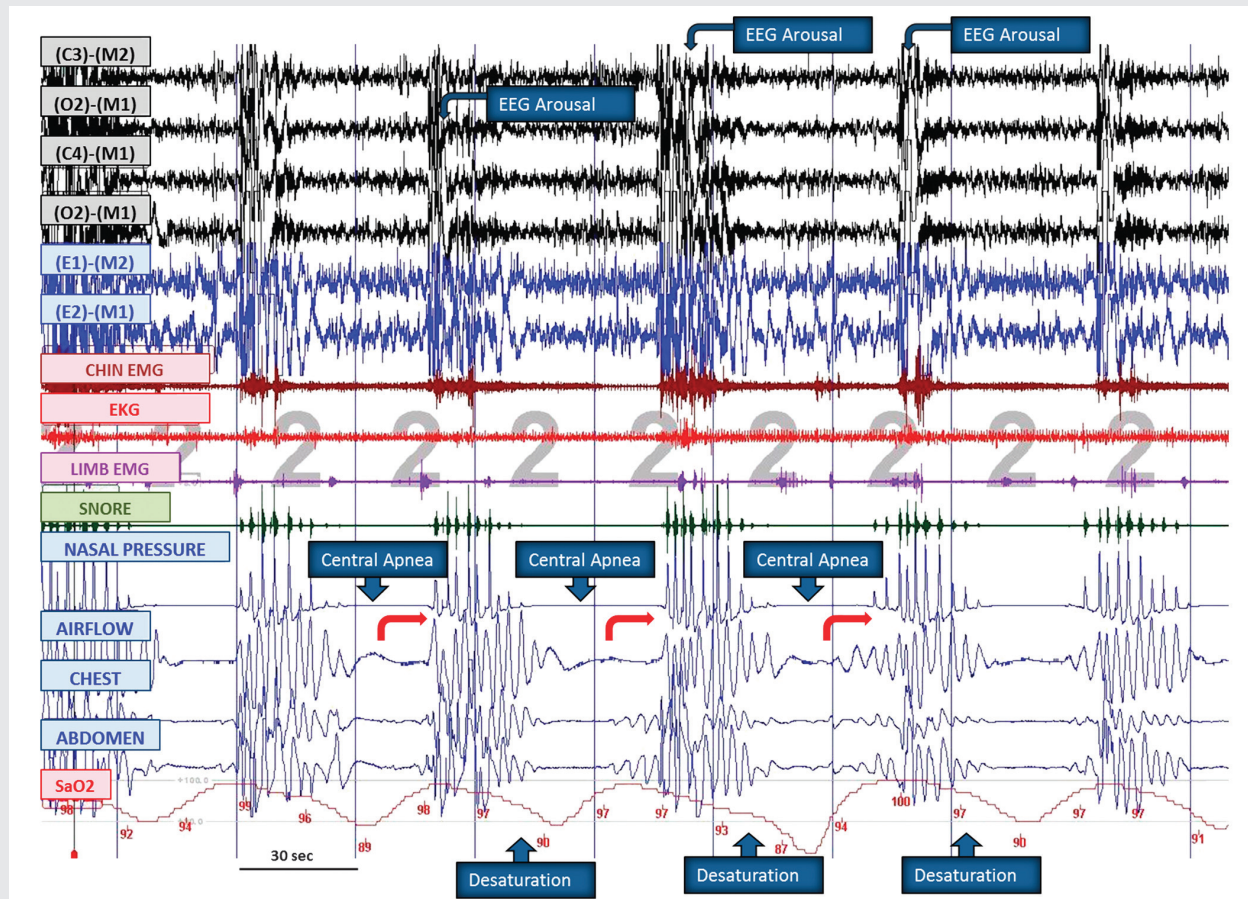


FIGURE 5-4 Polysomnographic depiction of Cheyne-Stokes respirations. A 5-minute epoch from a polysomnogram depicting Cheyne-Stokes respirations, defined as three or more cycles of crescendo-decrescendo respiratory amplitude alternating with central apneas. Red curved arrows denote resumption of crescendo-decrescendo breathing pattern. Channels from top to bottom represent EEG (left and right central, left and right occipital), electrooculogram (left and right eyes), chin EMG, EKG, snoring, nasal pressure transducer, oral thermistor, respiratory effort (thoracic and abdominal movement), and arterial oxygen saturation.

EEG = electroencephalograph; EMG = electromyogram; EKG = electrocardiogram; SaO2 = arterial oxygen saturation.

nose and mouth (Figure 5-1, Figure 5-2, Figure 5-4). While PSG is typically performed in the sleep laboratory, this test has also been adapted and simplified for home diagnostic use, with measures of airflow and oxygenation but without use of EEG in some circumstances. In the appropriate clinical context, home portable monitor testing can result in satisfactory treatment outcomes that are comparable to using in-laboratory PSG.⁴⁶ However, because most home monitors cannot distinguish between sleep and wake states,

they tend to underestimate the severity of OSA, particularly when apneas or hypopneas are associated with arousals without significant oxygen desaturation. AASM guidelines recommend using portable monitors for diagnosis only in patients with a high pretest probability of OSA and no significant medical comorbidities.⁴⁷ Further discussion of home sleep testing is provided in the article “In-Home Testing for Obstructive Sleep Apnea.”

The severity of OSA is determined by the AHI, which is a measure of the

KEY POINT

- Polysomnography is the diagnostic modality of choice for obstructive sleep apnea and other sleep disorders, although monitors with fewer channels have been validated in certain populations for obstructive sleep apnea detection.

KEY POINTS

- The apnea-hypopnea index is the measure used to define the severity of sleep apnea; 5 or greater is considered to be abnormal.
- Continuous positive airway pressure uses forced air to stent the airway open and reduce obstructive events.

number of apneas and hypopneas per hour. In adults, an AHI of 5 events/h or greater is consistent with a diagnosis of OSA. The AHI is further gradated to quantify the degrees of severity of OSA, with an AHI between 5 events/h and 14 events/h considered mild OSA, 15 to 29 events/h considered moderate OSA, and 30 events/h or greater considered severe OSA.

Long-Term Consequences

Many patients are motivated to initiate treatment for OSA due to symptoms such as excessive daytime sleepiness, fragmented sleep, and bed partner reports of snoring and periods of breathing cessation. However, some patients experience no overt daytime symptoms and may be reluctant to treat an “asymptomatic” disorder. In all instances, it is the clinician’s responsibility to counsel patients about the serious potential consequences of OSA and the importance of adequate treatment. Educating patients about the pathophysiology and consequences of OSA, including the risks of drowsy driving, can significantly affect treatment adherence.⁴⁸

Untreated, OSA can cause or exacerbate a substantial number of medical comorbidities. Most of the sequelae stem from physiologic changes that occur in response to chronic apneas or hypopneas. Fragmentation of sleep due to repeated respiratory arousals can adversely affect wake behavior, including mood, concentration, vigilance, and attention (Case 5-1).⁴⁹ Intermittent hypoxia and hypercapnia over time can increase cardiovascular risk and cause neuronal injury.^{50,51} OSA is also associated with altered sympathetic and catecholaminergic neuronal activity, with overcompensatory elevations in autonomic tone that increase risk of hypertension, cor pulmonale, congestive heart failure, arrhythmias, and sudden death. Physiologic changes

associated with OSA also include platelet aggregation, vascular endothelial cell dysfunction, and metabolic dysregulation, which can increase the overall incidence of coronary artery disease and stroke and worsen glycemic control in patients with diabetes mellitus.^{50,52,53} Among patients with epilepsy, OSA can worsen seizure frequency if left untreated.⁵⁴ It can also increase the risk of developing dementia and exacerbate the degree of cognitive dysfunction in people with mild cognitive impairment.^{55,56}

Treatment Options

The mainstay of treatment for OSA consists of the delivery of positive airway pressure (PAP) through a tightly fitted facial mask. The pressurized air acts as a pneumatic stent to maintain patency of the upper airway during sleep. PAP treatment typically uses room air, although supplemental oxygen may also be used if a concurrent pulmonary problem is present. Different PAP modalities include CPAP, wherein a set air pressure is delivered throughout sleep; auto-CPAP, which detects variations in the degree of obstruction and automatically adjusts the amount of air pressure to compensate; and bilevel PAP, which delivers two different air pressures with each breath (a higher pressure during inspiration and a lower pressure during expiration), noninvasively ventilating the patient (Table 5-2). The appropriate pressure settings are typically determined during a PAP titration PSG. PAP is a highly effective treatment for OSA, successfully normalizing AHI and improving waking symptoms in most patients. It is therefore considered the current treatment of choice for OSA.

Limitations of PAP treatment are primarily related to patient discomfort or difficulty acclimating to the device. Technologic advances in delivery systems have helped with some of these

TABLE 5-2 Summary of Treatment Options for Sleep-Disordered Breathing

Treatment Modality	Specific Treatment	Indication
Positive airway pressure (PAP)	Continuous positive airway pressure (CPAP)	Obstructive sleep apnea (OSA) Central/complex sleep apnea in some cases
	Bilevel PAP	OSA with intolerance of CPAP pressure or aerophagia (unintentional passage of air through the lower esophageal sphincter into the stomach during PAP treatment) Central/complex sleep apnea, Cheyne-Stokes respirations Obesity hypoventilation syndrome Neuromuscular disease or diaphragmatic weakness
	Adaptive servo-ventilation	Central/complex sleep apnea, Cheyne-Stokes respirations
Oral appliances	Tongue retaining device	Mild to moderate OSA
	Mandibular repositioning device	Severe OSA with PAP intolerance
	Soft palate lifting device	Mild to moderate OSA
Positional therapy	Avoidance of supine sleep	Primarily positional OSA
Surgical treatments	Septoplasty	Nasopharyngeal obstruction
	Turbinate reduction	
	Adenoidectomy	
	Tonsillectomy	Oropharyngeal obstruction
	Uvulopalatopharyngoplasty	Hypopharyngeal obstruction
	Midline glossectomy	
	Base-of-tongue reduction	
	Genioglossus advancement	
	Hyoid suspension	
	Mandibular advancement	
Tracheostomy	Tracheal obstruction	
Maxillomandibular advancement	Obstruction at multiple sites	
Bariatric surgery	Morbid obesity	
Expiratory positive airway pressure (EPAP)	Single-use nasal EPAP	Mild OSA

issues. Some newer mask styles such as the “nasal pillows” interface are smaller with less obtrusive headgear. The use of heated humidification has helped reduce nasal congestion and mouth dryness that can occur with PAP treatment. Treatment of chronic nasal congestion with intranasal saline or steroid sprays can also improve PAP tolerance. For patients with claustrophobia, gradual desensitization programs have been used with some success.⁵⁷ Bilevel PAP may be better tolerated by patients requiring higher PAP pressures and is also an effective treatment for CSA.

For some patients, OSA is primarily present when sleeping in the supine position because of mechanical changes associated with neck positioning and gravity. The severity of their OSA improves dramatically when sleeping in the lateral or prone positions. For such patients, an effective treatment may exclusively consist of using special pillows or other positioning devices to help them avoid supine sleep. This strategy is termed *positional therapy*. It is associated with modest reductions in the AHI but is less effective for severe OSA. A concern is that treatment may not be completely effective throughout the night or that patient adherence to therapy may wane with time. However, a recent study demonstrated a reasonable compliance of 74% and persistent efficacy in lowering AHI after 3 months of use at home.³²

Surgical treatment options for OSA consist of a variety of procedures intended to reduce pharyngeal soft tissue bulk and correct nasal obstruction (Table 5-2). These range from more aggressive surgeries, such as maxillo-mandibular advancement and uvulopalatopharyngoplasty, to somewhat less complex procedures, such as radiofrequency ablation and soft palatal implants.⁴⁷ Tracheostomy is also used but is typically reserved for very severe

OSA with significant medical comorbidities when all other treatment options have been exhausted. A recent update of AASM practice parameters reviewing studies of surgical treatment options for OSA found varying degrees of success for these procedures, and no one procedure was consistently effective.⁵⁸ One of the most commonly performed procedures, uvulopalatopharyngoplasty, appears to be more effective in mild OSA and has an approximately 40% to 50% success rate.⁵⁹ However, surgical success is defined by most studies as a 50% reduction in baseline AHI; therefore, the postoperative AHI may remain in the abnormal range and patients may still have significant residual OSA.^{60,61} The surgical cure rate (AHI less than 5 events/h) of uvulopalatopharyngoplasty is estimated at 16%.⁵⁹

Other alternatives to PAP therapy include oral appliances, typically fashioned by dentists or oral surgeons specializing in OSA, which can be used in some patients with mild to moderate disease (Table 5-2).⁶² A variety of styles of oral appliances are available, and most work by repositioning the mandible to increase forward and downward protrusion, thereby widening the upper airway space in the posterior pharynx.⁶³ A recently developed treatment for OSA is nasal expiratory positive airway pressure (EPAP), which is a single-use device sealed into each nostril with adhesive. Its mechanical valves provide high expiratory resistance, creating positive airway pressure during expiratory breaths and acting as a pneumatic splint to maintain upper airway patency.⁶⁴ A multicenter, double-blind, randomized, controlled trial found that 3 months of nasal EPAP reduced AHI by at least 50% from a baseline in the mild to low-moderate OSA range (median baseline AHI 13.8 events/h to 16.7 events/h) in 51% of patients.⁶⁴ Therefore, nasal EPAP may

be a useful new treatment option for mild OSA, but insufficient data exist for its role in moderate to severe OSA with significant oxygen desaturation events. No effective pharmacologic treatment for OSA is available, and oxygen treatment in the absence of PAP is also ineffective.⁶⁵ Weight loss (by either surgical means or dietary and lifestyle modifications) should be recommended for all obese patients with OSA and can significantly improve sleep-disordered breathing.^{66,67} The various treatment options for sleep-disordered breathing are summarized in **Table 5-2**.

CENTRAL SLEEP APNEA

Central apnea is defined as at least a 10-second period of loss of airflow with the absence of respiratory effort indicative of a brief loss of ventilatory drive.¹ During sleep, respiration is primarily dictated by partial pressure of arterial carbon dioxide (PaCO₂). There is a level of PaCO₂ below which a pause in breathing will occur, termed the apneic threshold.⁶⁸ The apneic threshold is higher during wake than sleep; thus, a brief central apnea may normally be observed during the transition from wake to sleep at sleep initiation and following brief arousals, as the PaCO₂ levels rise again to the level that will stimulate respiration.

The respiratory control system is regulated by pulmonary vagal receptors and central and peripheral chemoreceptors. Central sensors in the medulla are stimulated by hypercapnia, while peripheral sensors in the carotid body are driven by both hypercapnia and hypoxia. Voluntary mechanisms compensate for any disruptions in this automated control during wakefulness and are absent during sleep, which may facilitate the emergence of abnormal breathing patterns (**Case 5-2**).

For instance, in heart failure, CSA can develop because of chronic hypocapnia

related to changes in hemodynamics in the left heart, and consequent augmentation of peripheral and central chemosensitivity. This hypersensitivity can lead to an exaggerated response to the fall in partial pressure of arterial oxygen (PaO₂) and rise in PaCO₂ seen during a single apnea, overstimulating ventilation and again reducing PaCO₂ below the apneic threshold.⁶⁹ This can lead to a cyclic pattern of hyperventilation and hypoventilation, known as Cheyne-Stokes respirations (**Figure 5-4**).⁴ Central apneas can also be seen in other hypocapnic states, such as the periodic breathing of high altitudes. Central apneas may also occur in the setting of hypercapnia. Medications such as opiates can lead to CSA by suppressing neuronal activity in respiratory brain centers.⁷⁰ Diseases of brainstem or autonomic dysfunction, such as multiple system atrophy or lesions of the cervical spinal cord, may be associated with central apneas.

SLEEP-RELATED HYPOVENTILATION

Sleep-disordered breathing also encompasses hypoventilation, which can be exacerbated during sleep or may precede the onset of hypoventilation during wakefulness. These conditions include obesity hypoventilation syndrome (OHS), hypoventilation due to neuromuscular disorders, medication-related hypoventilation, hypoventilation with brainstem dysfunction, and central alveolar hypoventilation.

OHS is defined as a triad of obesity (BMI of 30 kg/m² or greater): (1) waking hypercapnia (PaCO₂ of 45 mm Hg or greater), (2) hypoxemia (PaO₂ of 70 mm Hg or less), and (3) sleep-disordered breathing in the absence of any other cause of hypoventilation such as pulmonary disease, metabolic conditions, or neuromuscular disorders.⁷¹ The type of sleep-disordered breathing seen in OHS is most commonly OSA, but

KEY POINT

- A central apnea is defined by cessation of airflow without evidence of respiratory effort.

Case 5-2

A 57-year-old man presented with a long history of snoring and disrupted sleep. He went to bed regularly between 10:00 PM and 11:00 PM, and would fall asleep quickly. He aroused briefly twice a night for nocturia and awakened at 7:30 AM. He often fell asleep unintentionally when inactive. His Epworth Sleepiness Scale score was 15 of 24, consistent with hypersomnolence.

His medical history was notable for nonischemic cardiomyopathy, congestive heart failure with an ejection fraction of 15% to 20%, hypertension, and type 2 diabetes mellitus. His medications included carvedilol, hydralazine, lisinopril, and furosemide.

Examination findings were blood pressure, 146/70 mm Hg; heart rate, 68; height, 1.8 m (5 ft 11 in); weight, 82 kg (181 lbs); body mass index, 25.31 kg/m². Notable findings included a crowded oropharynx and a modified Mallampati class IV airway. No peripheral edema was present.

A diagnostic polysomnogram (PSG) demonstrated severe obstructive sleep apnea (OSA) with an apnea-hypopnea index of 40 events/h and oxyhemoglobin saturation nadir of 73%. During the continuous positive airway pressure (CPAP) titration PSG at CPAP levels that alleviated his obstructive events, significant central sleep apnea (CSA) emerged, with several prolonged episodes of crescendo-decrescendo breathing consistent with Cheyne-Stokes respirations (**Figure 5-4**).

Adaptive servo-ventilation titration PSG found that at settings of an end-expiratory pressure of 7 cm of water with variable-pressure inspiratory support, both the obstructive and central apneas improved (residual apnea-hypopnea index of 4.6 events/h) and oxyhemoglobin saturation nadir improved to 86%. At follow-up after 1 month of therapy, the patient reported a great alleviation of his hypersomnolence.

Comment. The most common condition associated with CSA is congestive heart failure. Often, the Cheyne-Stokes respiratory pattern is observed. First-line therapy for this condition in the setting of heart failure is medical optimization, as this may dramatically improve sleep-disordered breathing. However, CSA and Cheyne-Stokes respirations may persist even when the patient's heart failure is well controlled. Severe OSA may prevent the manifestation of central apnea on PSG, and this breathing pattern may only emerge once CPAP therapy is initiated. The clinical significance of CPAP-emergent central apnea, also termed complex sleep apnea, remains controversial as it self-resolves over time in most cases. Given this patient's underlying heart failure, an alternate mode of pressure support was justified. Adaptive servo-ventilation and other modes of variable pressure support use a constant end-expiratory pressure to reduce or eliminate obstructive events. On a breath-by-breath basis, they deliver varying levels of inspiratory pressure support to maintain the tidal volume and overall minute ventilation.

10% of patients also have sleep hypoventilation (PaCO₂ that is at least 10 mm Hg greater in sleep than in waking, or significant oxygen desaturations unrelated to apneas or hypopneas).⁷¹ This syndrome is distinct from simple obesity with OSA, in that OHS patients have increased risk of pulmonary hypertension, more severe upper airway obstruction, abnormally high mechanical load on respiratory muscles due to adiposity, and blunted compensatory respiratory drive in response to hypercapnia and hypoxia.⁷¹ Patients often present with typical OSA symptoms of snoring, nocturnal apneas, and excessive daytime sleepiness, but in contrast to uncompl-

cated OSA they also have concurrent dyspnea, peripheral edema, and other physical examination findings of cor pulmonale.⁷² OHS is a diagnosis of exclusion; once other causes of hypoventilation have been ruled out, the diagnosis is based on physical examination, PSG findings, and hypercapnia on an arterial blood gas. The preferred treatment is nocturnal CPAP, or bilevel PAP for patients with predominantly central hypoventilation.⁷³

Hypoventilation is frequently seen in the setting of neuromuscular disease associated with decreased vital capacity and respiratory muscle weakness. Hypoventilation is further exacerbated during

sleep, especially during REM sleep when ventilation is driven primarily by the diaphragm because of normal REM-related skeletal muscle atonia. Patients who are dependent on skeletal accessory muscles of respiration may experience profound hypoventilation during REM sleep, especially if there is concurrent diaphragmatic weakness such as in ALS.⁷⁴ Symptoms can include excessive daytime sleepiness, headaches, and poor sleep quality with nightmares and enuresis.⁷⁵ Treatment with noninvasive mechanical ventilation modalities such as bilevel PAP can alleviate symptoms in the short term and may prolong survival in patients with motor neuron diseases.⁷⁵

Chronic opioid medication use can also result in sleep hypoventilation. Opioids binding to CNS receptors impair central respiratory control centers, with ensuing central apnea, hypoventilation, or ataxic breathing pattern.^{70,76} Patients on long-term opioid treatment have a greater risk of hypoxemia in sleep that is independent of apneas or hypopneas. Treatment consists of PAP, particularly bilevel PAP with a backup rate in patients with significant central apneas or hypoventilation.⁷⁷ CPAP can be effective but may exacerbate central apneas; use of adaptive servo-ventilation (ASV) is controversial in this setting and requires further study.

Hypoventilation may ensue after brainstem or spinal cord injury because of lesions to neural pathways controlling diaphragm, chest, and abdominal muscles.⁷⁸ Hypotonia of respiratory muscles can result in a restrictive ventilatory defect with hypercapnia and hypoxia and increased work of breathing. This can lead to alveolar hypoventilation that is exacerbated during sleep, especially REM sleep. Diagnostic tests include arterial blood gas analysis and PSG. Optimal treatment consists of noninvasive positive pressure ventila-

tion, particularly bilevel PAP with or without a backup rate.^{78,79}

Another condition characterized by central events is central alveolar hypoventilation, which comes in two forms, acquired and congenital. Acquired central alveolar hypoventilation may be seen following injury to the respiratory centers in the medulla, for instance from trauma, encephalitis, neoplasms, or stroke. A much rarer, congenital, central hypoventilation syndrome typically presents in the first year of life with hypoxia, hypercapnia, and prolonged central apneas during sleep, although a late-onset form has been described in adults.^{80,81} This condition is caused by trinucleotide expansion mutations in the *PHOX2B* gene, a transcription factor regulating development of the autonomic nervous system.⁸²

Several options are available for treatment of central sleep apnea.⁸³ CPAP, bilevel PAP, and other ventilator support modalities, such as ASV, have been extensively studied (Table 5-2). CPAP may improve left ventricular ejection fraction and, if titrated to adequately treat the sleep-disordered breathing, improves survival. One caveat to this is that most studies were done before the widespread use of spironolactone or beta-blockers for treatment of heart failure; patients on these more effective medications may therefore show a smaller magnitude of cardiac improvement with CPAP. ASV or bilevel PAP (in spontaneous mode with patient-triggered breaths, or with an automated backup respiratory rate) have similarly beneficial effects on cardiac function and may be used to improve comfort if higher levels of CPAP pressure are needed, or to improve ventilation in hypercarbia. The use of supplemental oxygen is typically limited to patients with CSA who are unable to comply with PAP therapy. Also, the use of acetazolamide, a carbonic anhydrase inhibitor, induces

KEY POINT

- Central sleep apnea can be seen in a variety of conditions, including congestive heart failure, medullary lesions, and autonomic dysregulation.

KEY POINT

- Successful treatment of central sleep apnea associated with heart failure is associated with improved cardiac function and survival.

a metabolic acidosis that may lead to a decrease in central apnea frequency, although the evidence is much weaker for its effectiveness when compared to either oxygen or PAP.⁵⁵

CONCLUSION

Sleep-disordered breathing is a highly prevalent disorder and can occur comorbid to many medical and neurologic conditions. Untreated, it may significantly affect daytime alertness and concentration; increase risk of cardiovascular events, such as stroke, arrhythmia, or myocardial infarction; worsen hypertension; exacerbate mood disorders; and interfere with optimal seizure control. PAP, the first-line treatment option, is safe and effective in normalizing breathing during sleep. Other treatment options include craniofacial or upper airway surgery, oral appliances, and weight loss. Effective treatment of sleep-disordered breathing can reduce symptoms of excessive daytime sleepiness, snoring, and fragmented sleep and may improve health outcomes.

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