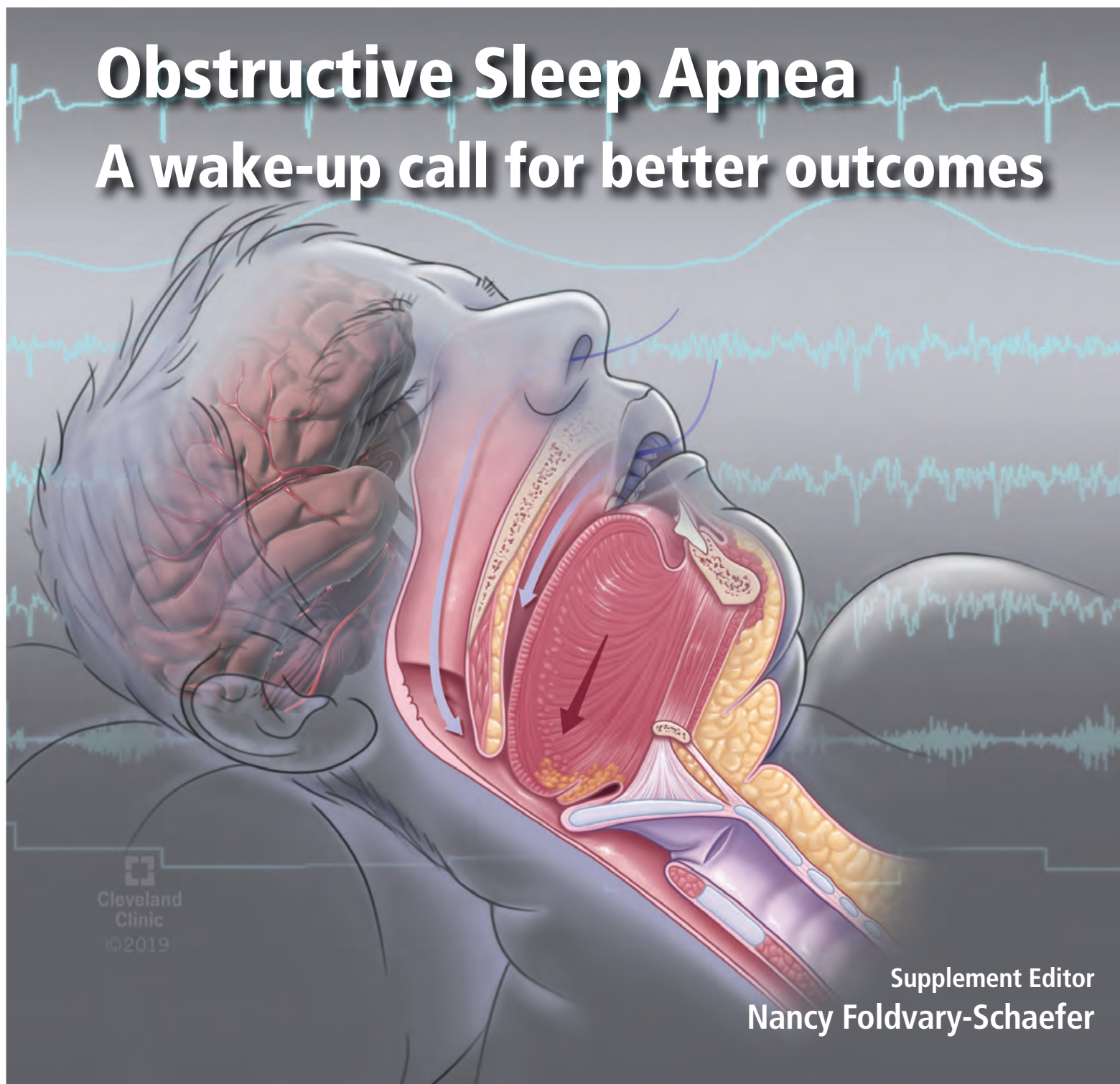


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Obstructive Sleep Apnea A wake-up call for better outcomes



Obstructive sleep apnea: A wake-up call for better outcomes

Supplement Editor

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Obstructive sleep apnea: A wake-up call for better outcomes

For too many of us, a good night's sleep is a rare occurrence. Lack of quality sleep has profound negative effects on our health, safety, and well-being. An estimated 50 to 70 million Americans have sleep disturbances, including 10% to 17% of men and 3% to 9% of women with moderate to severe obstructive sleep apnea (OSA).¹ Not only is OSA highly prevalent, 82% to 93% of individuals with moderate to severe OSA are unaware they have it, and it remains undiagnosed.²

OSA is a potentially serious medical disorder affecting the heart, brain, and metabolism. These physiological changes negatively impact public safety, occupational and academic achievement, and even mortality.

This *Cleveland Clinic Journal of Medicine* supplement presents a state-of-the-art review of OSA, including the health and societal consequences of OSA and current treatment options. The goal of this publication is to inform and educate healthcare providers from all backgrounds and levels of care who are interested in improving patient outcomes through attention to sleep medicine.

Because OSA is prevalent and underdiagnosed, Jessica Vensel Rundo, MD, MS, reviews the symptoms of OSA, clinical presentation, and the readily available, effective screening tools for detecting sleep apnea. Greater awareness and screening for sleep disturbances informs the need for further diagnostic tests such as laboratory polysomnography and home sleep apnea testing.

The link between OSA and the heart is presented by Reena Mehra, MD, MS, with an overview of the physiology of sleep-heart interactions and the association of OSA and cardiovascular health. Dr. Mehra also reviews central sleep apnea and discusses 2 newer therapies for it: adaptive servoventilation and phrenic nerve stimulation.

Beyond heart health, OSA also adversely affects quality of life, safety, and other important health factors. Harneet Walia, MD, discusses consequences of sleep apnea such as daytime sleepiness, fatigue, drowsy driving, depression, metabolic diseases, and cognitive impairment.

Several treatment options exist for patients diagnosed with OSA. Positive airway pressure (PAP) therapy is the gold standard for treatment of OSA. Colleen G. Lance, MD, reviews and presents case scenarios about the efficacy of PAP therapy, features of continuous PAP therapy, and innovative strategies to improve adherence to therapy.

In addition to PAP therapy, there are alternative treatments for OSA that may benefit some patients. Tina Waters, MD, considers alternatives to PAP therapy, such as lifestyle changes, expiratory PAP therapy, oral appliances, upper airway surgery, and hypoglossal nerve stimulation.

I hope you enjoy this supplement and find it useful to improving the health and quality-of-life outcomes of patients in your care.



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Obstructive sleep apnea basics

■ ABSTRACT

Obstructive sleep apnea (OSA) is a condition caused by repeated episodes of upper airway collapse and obstruction during sleep associated with arousal from sleep with or without oxygen desaturation. OSA is a highly prevalent condition, particularly in individuals with established risk factors and comorbid conditions. Screening for OSA includes a sleep history, review of symptoms, and physical examination, the results of which can identify patients that need testing for OSA. The polysomnogram or home sleep apnea test results aid in the diagnosis of OSA and its severity.

■ KEY POINTS

OSA is characterized by repeated episodes of complete or partial obstruction of the airway during sleep.

The prevalence of OSA is underestimated and underdiagnosed.

A sleep history, simple upper airway examination, and quick validated screening tool like the STOP-BANG or Epworth Sleepiness Scale aid in identifying the need for testing for OSA.

Polysomnogram is the gold standard for evaluation of OSA. Home sleep apnea tests can be used to confirm a diagnosis of OSA in patients at high risk for moderate to severe OSA.

Dr. Vensel Rundo reported no financial interests or relationships that pose a potential conflict of interest with this article.

This article is based on Dr. Vensel Rundo's "Obstructive Sleep Apnea Basics" webcast released January 30, 2019, part of the "Obstructive Sleep Apnea: A Cleveland Clinic State-of-the-Art Review" online series (available at www.clevelandclinicmeded.com/online/sleep-apnea/default.asp). The article was drafted by Cleveland Clinic Journal of Medicine staff and was then reviewed, revised, and approved by Dr. Vensel Rundo.

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■ DEFINITION

Obstructive sleep apnea (OSA) occurs when there are recurrent episodes of upper airway collapse and obstruction during sleep associated with arousals with or without oxygen desaturations. The oropharynx in the back of the throat collapses during OSA events to cause arousal or oxygen desaturation or both resulting in fragmented sleep.

■ PREVALENCE

Studies reveal OSA is prevalent. A 2015 study in Switzerland reported 50% of men and 23% of women had at least moderate OSA.¹ In 2002, the Sleep Heart Health study found that 24% of men and 9% of women have at least mild OSA.² In the Wisconsin Sleep Study Cohort, it was reported that 10% of men and 3% of women age 30 to 49 have at least moderate OSA, while 17% of men and 9% of women age 50 to 70 have at least moderate OSA.³ OSA is highly underrecognized and it is estimated that 82% of men and 93% of women in the United States with OSA are undiagnosed.⁴

■ SYMPTOMS

There are several common sleep and daytime symptoms associated with OSA though patients vary in the number and combination of symptoms reported (Table 1).⁵ During sleep, snoring is one of the most common symptoms. Common daytime symptoms of OSA include excessive daytime sleepiness or fatigue. Excessive daytime sleepiness is feeling very drowsy or very sleepy at times whereas fatigue is feeling tired, low on energy, and unmotivated. Feeling unrefreshed despite getting the recommended 7 to 9 hours of sleep is also a symptom.

■ RISK FACTORS

The risk of OSA is influenced by unmodifiable and modifiable factors. Unmodifiable risk factors include male sex, age, and race. Genetic predisposition or a family history of OSA as well as cranial facial anatomy resulting in narrow airways may impart higher

risk of OSA. Modifiable risk factors include obesity, medications that cause muscle relaxation and narrowing of the airway (opiates, benzodiazepines, alcohol), endocrine disorders (hypothyroidism, polycystic ovarian syndrome), smoking, and nasal congestion or obstruction.⁶

Sex

Men are at higher risk for OSA than women although once women reach menopause they have a risk similar to men. Postmenopausal women on hormone replacement therapy were found to have lower rates of OSA, suggesting that loss of hormones results in greater risk of OSA.^{7,8} Women also have more OSA during rapid eye movement (REM) sleep and less OSA when sleeping supine, whereas most men have OSA when sleeping supine.^{9,10} OSA is less severe in women compared with men of similar body mass index (BMI).¹¹ Symptoms vary in men and women: snoring and witnessed apneas are more common in men whereas insomnia and excessive daytime sleepiness are more common in women.¹¹ This may account for delayed diagnosis and the higher mortality in women compared with men.

Age

The risk of OSA increases with age. In a study of men 65 or older, the prevalence of moderate OSA was 23% in men younger than 72 and 30% in men older than 80.¹² By comparison, the prevalence of moderate OSA in men 30 to 40 years was 10%.³ Increased risk of OSA with age may be due to age-related reduction in slow wave sleep (ie, deep sleep), which is protective against sleep-disordered breathing and airway collapse.¹³ Older adults are also less symptomatic, reporting less daytime sleepiness and fatigue.¹⁴

Race

The Sleep Heart Health Study found a slightly increased risk of moderate to severe OSA in blacks (20%) and American Indians (23%) compared with whites (17%).² Another study showed the prevalence of OSA was 30% in whites, 32% in blacks, 38% in Hispanics, and 39% in Chinese individuals.¹⁵ A higher prevalence of OSA in young blacks (≤ 25 years) compared with whites was reported,¹⁶ although another study found no differences based on race in older patients.¹⁷ These differences among racial groups may be due to variations in craniofacial anatomy.

Obesity

There is a correlation between increased risk of OSA and obesity (BMI > 30 kg/m²) and its correlates of greater waist-to-hip ratio and neck circumference.²

TABLE 1
Obstructive sleep apnea symptoms

Sleep	Daytime
Snoring	Excessive sleepiness
Gasping	Fatigue
Snorting	Morning headaches
Not breathing	Memory or concentration issues
Fragmented sleep	Mood disturbances or irritability
Sleep maintenance insomnia (inability to stay asleep or waking and not returning to sleep)	Decreased libido
Nocturia	
Bedwetting	
Night sweats	

Data from reference 5.

A 10% increase in body weight results in a sixfold increase in moderate to severe OSA and increases the apnea-hypopnea index (AHI; number of breath pauses or respiratory events per hour) by 32% whereas a 10% decrease in weight decreases the AHI by 26%.¹⁸

COMORBIDITIES

OSA is associated with a number of comorbid conditions including stroke, myocardial infarction, hypertension, hyperlipidemia, glucose intolerance, diabetes, arrhythmias including atrial fibrillation, pulmonary hypertension, congestive heart failure, and depression. Patients with moderate or severe OSA are at higher risk of these comorbid conditions.¹⁹

Patients with cardiovascular disease have a very high prevalence of OSA: hypertension (83% mild to 30% moderate to severe OSA), heart failure (55% to 12%), arrhythmias (50% to 20%), stroke (75% to 57%), and coronary heart disease (65% to 38%).²⁰ Increased awareness and early diagnosis of OSA is critical to reducing cardiovascular disease burden.

SCREENING

Screening patients for OSA starts with a good sleep history to identify symptoms, risk factors, and comorbid conditions, as well as a physical examination for OSA-related features (Table 2). The Epworth Sleepiness Scale and STOP-BANG questionnaire are brief, effective screening tools that can inform the need for further testing.

TABLE 2
Screening for asymptomatic populations

- Sleep history
- Epworth Sleepiness Scale
- Upper airway examination
- STOP-BANG

Sleep history

A sleep history starts with determining the patient's total sleep time, based on time to bed, time to fall asleep, and time of wake up, including any difficulty falling asleep, staying asleep, or daytime naps.

Symptoms. Daytime naps generally indicate a sleep deficit or sleep that is not refreshing. A review of sleep and daytime symptoms associated with OSA (Table 1) helps determine if excessive daytime sleepiness or unrefreshing sleep is out of proportion with the amount of sleep the patient is getting at night.

Some patients with OSA may have memory or concentration issues or feel like they have attention deficit disorder. In fact some patients are diagnosed with attention deficit disorder because of their insufficient sleep or unrefreshing sleep.

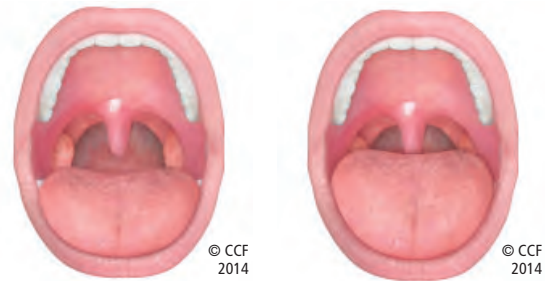
Drowsy driving is a special concern in patients with untreated OSA and sleep deprivation. Many patients have drowsy driving episodes or difficulty staying awake during long-distance driving. Caffeine use is also important information as excessive caffeine may be used to combat sleepiness during the day.

The Epworth Sleepiness Scale is a clinical screening tool that presents 8 situations for patients to consider and indicate their level of sleepiness and likelihood of falling asleep (never = 0; slight = 1; moderate = 2, high = 3).^{21,22} A total score ≥ 10 is considered abnormal in that the patient is excessively sleepy compared with most people.

Risk factors and comorbid conditions. OSA risk factors and comorbidities, including a BMI obesity assessment, should be reviewed with patients. Nasal congestion or mouth breathing especially at night could be due to airway obstruction increasing the risk of OSA. Family history of OSA, tobacco, alcohol use, other medical conditions, and medications should also be discussed.

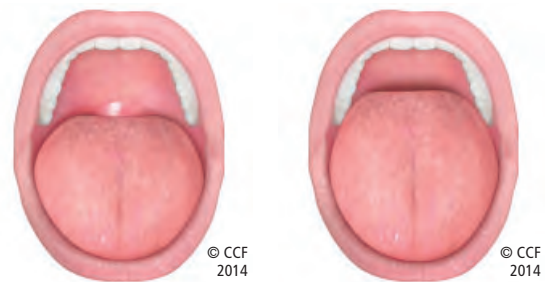
Physical examination

Certain findings on physical examination could suggest the presence of OSA:



Class 1: soft palate, fauces, uvula, anterior and posterior pillars visible

Class 2: soft palate, fauces and uvula visible



Class 3: soft palate and base of uvula visible

Class 4: soft palate not visible

Figure 1. Friedman palate positions (classes 1, 2, 3, and 4).

- Neck circumference greater than 17 inches for men or greater than 16 inches for women
- BMI greater than 30
- Friedman class tongue position class 3 or greater (Figure 1)
- Mouth features (present/enlarged tonsils, macroglossia, jaw misalignment)
- Nasal abnormalities (turbinate hypertrophy, deviated septum).⁵

Patients with Friedman palate positions class 3 and 4 have a higher risk of OSA due to airway crowding during sleep when the airway naturally collapses a little and is even more restricted.

Narrow airways or oropharyngeal crowding can also be due to a swollen, enlarged, or elongated uvula; present or enlarged tonsils; or lateral wall narrowing. Alone or in combination, these features can contribute to airway obstruction.

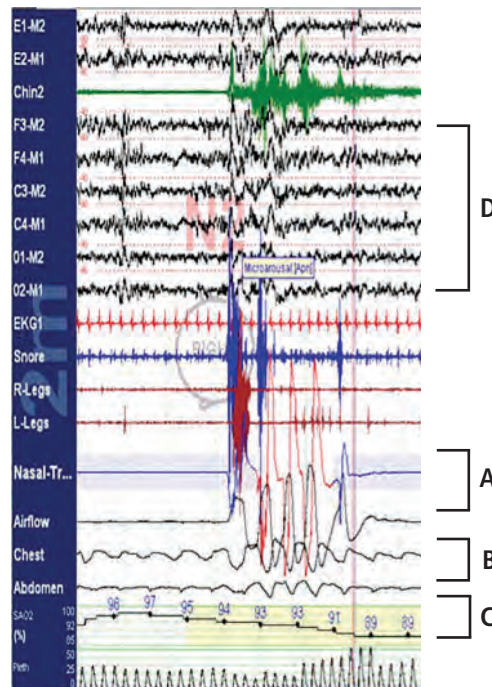
Other signs in the mouth suggestive of obstruction are macroglossia (enlarged tongue) and tongue ridging. Tongue ridging or scalloping impressions typically occur during sleep and are caused by the tongue moving forward to open the airway and pressing against the teeth.

Normal sleep



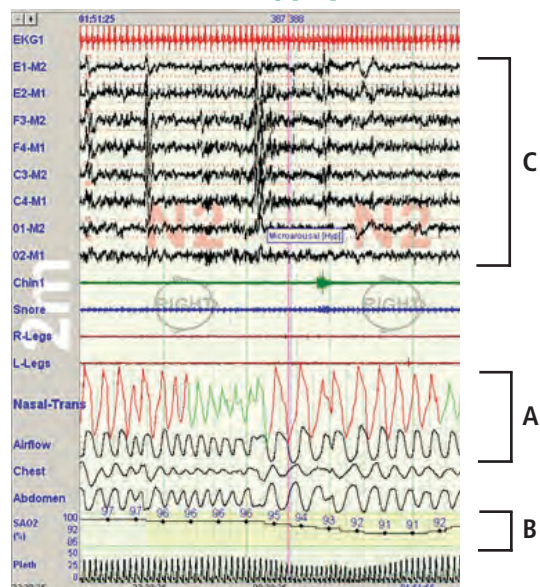
Waveform patterns typical of sleep.

Obstructive apnea



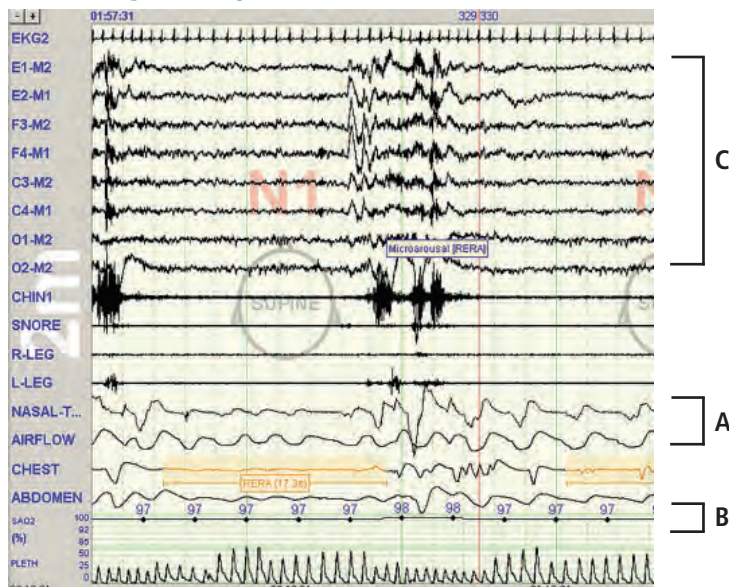
Airflow in the nasal transducer and the airflow leads (A) show no airflow but there is persistent effort in the chest and abdomen leads (B). Oxygen desaturation (C) and arousal in the electroencephalogram leads (D) also occurs in association with this respiratory event.

Obstructive hypopnea



Reduced flow in the nasal transducer and airflow leads (A) with increased oxygen desaturation (B) and arousal (C).

Respiratory event-related arousal



Reduction in airflow in the nasal transducer and airflow leads (A) and slight oxygen desaturation (B) and arousal from sleep in the electroencephalogram leads (C).

Figure 2. Polysomnogram excerpts with normal sleep, obstructive apnea, obstructive hypopnea, and respiratory event-related arousal waveform findings.

TABLE 3
Polysomnogram parameters and associated leads

Parameter	Lead(s)
Heart rate and rhythm (EKG/ECG)	EKG2
Brain waves (EEG)	F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M2
Eye movement (EOG)	E1-M2 and E2-M1
Awake/asleep, REM sleep, chin and leg movement (EMG)	CHIN1, R-LEG, L-LEG
Nasal-oral airflow	NASAL-TRANS, AIRFLOW
Thoraco-abdominal effort	CHEST, ABDOMEN
Oxygen saturation	SAO ₂
Snore	SNORE
Body position	SUPINE (watermark)

EEG = electroencephalogram; EKG/ECG = electrocardiogram; EMG = electromyogram; EOG = electrooculography; REM = rapid eye movement

■ SLEEP STUDIES

Polysomnography (PSG) is the gold standard of evaluation for OSA. The more recently available home sleep apnea test (HSAT) is convenient for select patients as a confirmatory test but results may underestimate the severity of sleep-related breathing disorders.

Polysomnography

PSG is a monitored, 8-hour sleep study conducted in a laboratory with an established scoring criteria for OSA-related respiratory events.²⁴ The test can be tailored to a patient’s clinical history to determine the need for supplemental oxygen and positive airway pressure titration, detect elevated carbon dioxide (hypercapnia or hypoventilation) due to shallow breathing, and monitor for seizures or parasomnias. The PSG also records REM and nonREM sleep for REM-related sleep disorders, body position (supine and off supine), and variability in muscle tone that corresponds to the different stages of sleep (**Figure 2, Table 3**).

Hypnogram. A hypnogram is a type of polysomnography that illustrates the different stages of sleep over time: wake, stage 1, stage 2, and stage 3, and REM sleep (**Figure 3**). In a typical night’s sleep of 7 to 9 hours, patients cycle through the sleep stages 4 to 5 times. A hypnogram can also include waveforms for other parameters such as body position, respiratory events (apnea and hypopneas), microarousals, continuous positive airway pressure therapy, and oxygen saturation.

Home sleep apnea test

HSATs record 4 to 7 parameters including airflow (thermal and nasal pressure), effort (inductive plethysmography), and oximetry. No electroencephalogram is used, so sleep is not recorded; it is assumed the patient is sleeping for the duration of the test. As such, respiratory events are based on oxygen desaturations and reduced airflow and pressure as well as chest and abdomen effort. The raw data are edited and manually scored and reviewed by a sleep specialist.²⁵

Although the HSAT is convenient for many

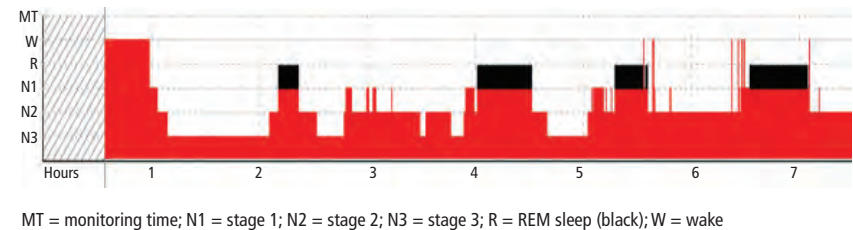


Figure 3. A hypnogram depicts the recorded levels of sleep over time.

Retrognathia (lower jaw offset behind upper jaw) can narrow the airway and increase the risk of OSA as can a high arch palate, overbite (upper teeth forward), or overjet (upper teeth over the top of lower teeth). A nasal examination for nasal valve collapse (ie, nostril collapses with inhalation), deviated septum, and inferior turbinate hypertrophy impart an increased risk of OSA.

Screening tools

In addition to the Epworth Sleepiness Scale, the STOP-BANG questionnaire can help determine if a patient should be tested further for OSA. The STOP-BANG questionnaire consists of 8 yes-no questions where more than 2 yes responses indicate the patient is at higher risk for moderate to severe OSA (93% sensitivity): Snore, Tired, Observed stopped breathing, high blood Pressure, BMI > 35 kg/m², Age > 50, Neck > 15.75 inches, Gender = male).²³

patients, it underestimates the severity of sleep-related breathing disorders. HSAT is intended to confirm OSA in patients with a high likelihood of OSA based on their sleep history.²⁶ It is ideally employed for adult patients with no major medical problems or other sleep problems who are at high risk for moderate to severe OSA based on the STOP-BANG questionnaire or those with daytime sleepiness and 2 of the 3 symptoms of snoring, witnessed apnea, or hypertension.²⁷

A negative or inconclusive HSAT warrants a PSG to ensure the patient does not have OSA. Use of HSAT is contraindicated in patients with

- Significant cardiopulmonary disease
- Potential weakness due to a neuromuscular condition
- Awake hypoventilation or high risk for sleep-related hypoventilation (severe obesity)
- History of stroke
- Chronic opioid use
- Severe insomnia
- Symptoms of other significant sleep disorders
- Environmental/personal factors that would preclude adequate acquisition and interpretation of data (disruptions from children, pets, other factors).²⁷

■ DIAGNOSTIC CRITERIA

Results from a PSG or HSAT inform the diagnosis of OSA and the need for treatment. The current diagnostic criteria for OSA were established in 2014 by the American Academy of Sleep Medicine (Table 4).²⁸

Respiratory events captured on a PSG or HSAT

The OSA diagnostic criteria are based on the occurrence of obstructive respiratory events recorded during sleep such as apneas, hypopneas, and respiratory event-related arousals.

Apneas. An apnea is a respiratory event resulting in a complete lack of airflow as measured by a greater than 90% reduction in thermal sensor for 10 or more seconds. Apneas can be obstructive, central, or mixed (Figure 4). Obstructive apneas occur when the airway is closed and respiratory effort is present in the chest

TABLE 4
Obstructive sleep apnea diagnostic criteria

Polysomnogram or home sleep apnea test reveals

- ≥ 15 predominantly obstructive respiratory events per hour of sleep OR
- ≥ 5 predominantly obstructive respiratory events per hour of sleep and at least 1 of following:
 - Daytime sleepiness, nonrestorative sleep, fatigue, or insomnia
 - Waking with breath holding, gasping, or choking
 - Observed loud snoring, breathing interruption, or both
 - Hypertension, mood disorder, cognitive dysfunction, ischemic heart disease, stroke, congestive heart failure, atrial fibrillation, or diabetes type 2

Data from reference 28.

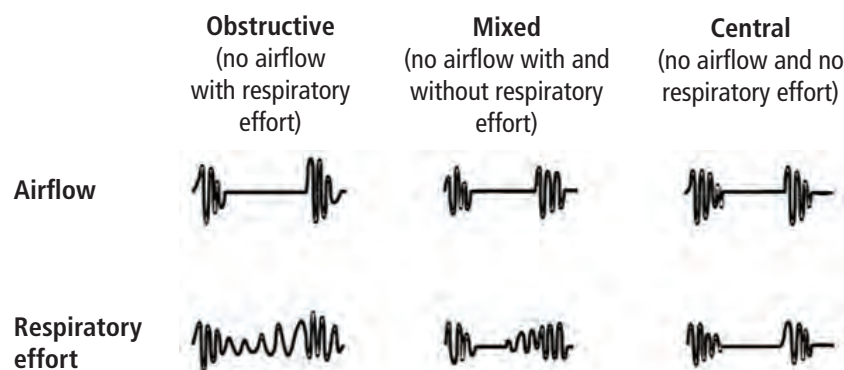


Figure 4. Apneas can be obstructive, mixed, or central.

and abdomen (Figure 2). In central apnea, there is no airflow and no respiratory effort, meaning the brain is not directing the body to breathe. Mixed apneas cause a lack of airflow with and without respiratory effort.

Hypopneas. A hypopnea is a respiratory event resulting in reduced airflow. The American Association of Sleep Medicine's preferred definition is a reduction in nasal pressure of at least 30% for 10 seconds or longer with 3% or greater oxygen desaturation or an electroencephalogram arousal. Another acceptable definition is at least 30% reduction in thoracoabdominal movement or airflow with 4% or greater oxygen desaturation, which is used by the Centers for Medicare and Medicaid Services and other insurers.^{29,30} Hypopnea requires greater oxygen desaturation and is not dependent on arousals, which can sometimes make it more challenging to identify OSA (Figure 2).

Respiratory event-related arousals. Respiratory event-related arousals are respiratory events not meeting apnea or hypopnea criteria. They are measured

TABLE 5
Obstructive sleep apnea severity

Index	Calculation
Apnea–hypopnea index (AHI)	$\frac{\text{Apneas} + \text{Hypopneas}}{\text{Total sleep time, hours}}$
Respiratory disturbance index	$\frac{\text{AHI} + \text{Respiratory event-related arousals}}{\text{Total sleep time, hours}}$
Respiratory event index	$\frac{\text{Apneas} + \text{Hypopneas}}{\text{Total monitoring time, hours}}$

Respiratory event index is typically used for home sleep apnea testing as it is based on monitoring time as distinct from actual sleep time.

as a sequence of breaths of 10 or more seconds with increasing respiratory effort or flattening of the nasal pressure waveform leading to arousal (Figure 2).²⁹ Respiratory event-related arousals are disruptive to sleep and have many of the same consequences as apneas and hypopneas.

Severity

A diagnosis of OSA should include a measure of severity (mild, moderate, or severe) as the severity may determine if a patient with OSA is treated or not. Severity is determined by AHI, respiratory disturbance index, or respiratory event index (Table 5).²⁹ For any of the 3 indexes, a value 5 to 14.9 is considered mild, 15 to 29.9 is considered moderate, and 30 or greater is considered severe.

SUMMARY

OSA results from airway collapse and obstruction during sleep, often causing arousal from sleep with or without oxygen desaturation. The prevalence of OSA is underestimated and it is underdiagnosed despite known risk factors and comorbid conditions. Screening for OSA with a sleep history, simple upper airway examination, and quick validated screening tool like the STOP-BANG or Epworth Sleepiness Scale aid in identifying the need for testing for OSA. A laboratory sleep study with a PSG can confirm the diagnosis and severity of OSA. HSATs are available to confirm the diagnosis of OSA in patients at high risk for moderate to severe OSA.

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Sleep apnea and the heart

■ ABSTRACT

The normal sleep-wake cycle is characterized by diurnal variations in blood pressure, heart rate, and cardiac events. Sleep apnea disrupts the normal sleep-heart interaction, and the pathophysiology varies for obstructive sleep apnea (OSA) and central sleep apnea (CSA). Associations exist between sleep-disordered breathing (which encompasses both OSA and CSA) and heart failure, atrial fibrillation, stroke, coronary artery disease, and cardiovascular mortality. Treatment options include positive airway pressure as well as adaptive servo-ventilation and phrenic nerve stimulation for CSA. Treatment improves blood pressure, quality of life, and sleepiness, the last particularly in those at risk for cardiovascular disease. Results from clinical trials are not definitive in terms of hard cardiovascular outcomes.

■ KEY POINTS

Diurnal variations in blood pressure, heart rate, and cardiac events occur during normal sleep.

While normal sleep may be cardioprotective, sleep apnea disrupts the normal sleep-heart interaction.

Untreated severe sleep apnea increases the risk for cardiovascular events.

Treatment with continuous positive airway pressure (CPAP) may reduce the risk of cardiac events based on some data, though randomized studies suggest no improvement in cardiovascular mortality.

Poor patient adherence to CPAP makes it difficult to evaluate the efficacy of CPAP treatment in clinical trials.

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■ SLEEP AND CARDIOVASCULAR PHYSIOLOGY

Wakefulness and sleep, the latter comprised of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, comprise our primary states of being. Sleep states oscillate between NREM and REM sleep. The first and shortest period of REM sleep typically occurs 90 to 120 minutes into the sleep cycle. Most REM sleep, including the longest period of REM sleep, occurs during the latter part of the sleep cycle.

With these sleep state changes, physiologic changes also occur, such as reduced heart rate and blood pressure because of enhanced parasympathetic tone. During REM sleep, there are also intermittent sympathetic nervous system surges. Other physiologic changes include a regular respiratory rate during NREM sleep and an irregular respiratory rate during REM sleep. Body temperature is normal during NREM sleep and poikilothermic (ie, tends to fluctuate) during REM sleep. Blood pressure is reduced 10% to 15% during sleep¹ and then rises, so that the highest blood pressure occurs in the morning. Data from 10 million users of activity-monitoring devices show that the heart rate changes during sleep.² The heart rate is decreased in those who get less than 7 hours of sleep, then increases with longer sleep duration in a U-shaped distribution.

Cardiovascular events are more likely to occur at certain times of day. Myocardial infarction is more likely in the morning, with a threefold increased risk within the first 3 hours of awakening that peaks around 9 AM.^{3,4} Similar diurnal patterns have been observed with other cardiovascular conditions such as sudden cardiac death and ischemic episodes, with the highest risk during morning hours (6 to 9 AM).⁴

The reason for this morning predisposition for cardiovascular events is unclear, but it is thought that perhaps the autonomic fluctuations that occur during REM sleep and the predominance of REM sleep in early morning may be a factor. Diurnal changes in blood pressure and cortisol levels may also contribute, as well as levels of systemic inflammatory and thrombotic markers such as plasminogen activator inhibitor 1.

Arrhythmias are also more likely to occur in a diurnal pattern. Atrial fibrillation (AF), particularly paroxysmal AF, is believed to be vagally mediated in 10% to 25% of patients.⁵ Therefore, for those who are predisposed, sleep may represent a period of increased risk for AF. In a study of individuals 60 years and older, the maximum duration and peak frequency of AF occurred from midnight to 2 AM.⁵

Recent studies have found that REM-related obstructive sleep apnea (OSA) is associated with increased cardiovascular risk. Experimental models show that REM sleep may increase the risk for compromised coronary blood flow.⁶ Increased heart rate corresponds to reduced coronary blood flow and thus, to decreased coronary perfusion time and less time for relaxation of the heart, increasing the risk for coronary artery disease, thrombosis, and ischemia.

■ SLEEP APNEA PATHOPHYSIOLOGY

The normal physiology of the sleep-heart interaction is disrupted by sleep apnea. OSA is defined as episodes of complete or partial airway obstruction that occur during sleep with thoracoabdominal effort. Central sleep apnea (CSA) is the cessation of breathing with no thoracoabdominal effort. The pathophysiology of the sleep-heart interaction varies for OSA and CSA.

Diurnal variations in blood pressure, heart rate, and cardiac events occur during normal sleep.

Obstructive sleep apnea

OSA is a nocturnal physiologic stressor that is highly prevalent and underrecognized. It affects approximately 17% of the adult population, and the prevalence is increasing with the obesity epidemic. Nearly 1 in 15 individuals is estimated to be affected by at least moderate OSA.^{7,8} OSA is underdiagnosed particularly in minority populations.⁹ Data from the 2015 Multi-Ethnic Study of Atherosclerosis (MESA) showed undiagnosed moderate to severe sleep apnea in 84% to 93% of individuals,⁹ similar to an estimated 85% of undiagnosed cases in 2002.¹⁰

OSA is highly prevalent in individuals with underlying coronary disease^{11–13} and in those with cardiovascular risk factors such as diabetes, hypertension, and heart failure. The prevalence of OSA in patients with cardiovascular disease ranges from 30% (hypertension) to 60% (stroke or transient ischemic attack, arrhythmia, end-stage renal disease).¹⁴

Pathophysiology of OSA

The pathophysiology of OSA can be observed during polysomnography, characterized by autonomic nervous system disturbances, intermittent hypoxia, and intra-

thoracic pressure alterations, (Figure 1). Intermittent bouts of hypoxia or oxygen-lowering occur because airflow is obstructed despite persistent thoracic and abdominal effort. Systemic inflammation and oxidative stress occur due to these intrathoracic pressure alterations, increased CO₂ and reduced oxygen levels, and autonomic nervous system disturbances.

The alterations in sympathetic activation that occur during sleep in patients with OSA persist during wakefulness. Microneurographic recording of sympathetic nerve activity in the peroneal nerve reveal that the rate of sympathetic bursts doubles and the amplitude is greater in individuals with OSA compared with a control group.¹⁵

Sympathetic nerve activity, blood pressure, and heart rate were shown to increase during REM sleep in individuals with OSA on continuous positive airway pressure (CPAP) during an induced apneic event (pressure reduction from 8 cm to 6 cm of water).¹⁵

During OSA episodes, there is an increased cardiac load. Impaired diastolic function and atrial and aortic enlargement, and in particular, the thin-walled atria are very susceptible to the intrathoracic pressure swings caused by OSA. Physiologic changes with OSA from pressure changes in the chest result in shift of the intraventricular septum, causing a reduction in cardiac output.¹⁶ With the lowering of oxygen during episodes of apnea, constriction of the pulmonary vasculature leads to elevation of pressure in the pulmonary vasculature reflected by the increase in mean pulmonary arterial pressures.¹⁷

Other studies have shown that OSA increases upregulation of markers of systemic inflammation and prothrombotic markers, the very markers that can increase cardiovascular or atherogenic risk.^{18–22} One example is the soluble interleukin 6 receptor, shown to be elevated in the morning relative to sleep apnea compared with the evening.²⁰ Other biomarkers observed to be associated with sleep apnea include markers of prothrombotic potentials such as plasminogen activator inhibitor 1.¹⁹ Oxidative stress occurs because intermittent bouts of lower oxygen can lead to oxidation of serum proteins and lipids. Endothelial dysfunction has been observed as well as insulin resistance and dyslipidemia.²³ Taken together, these are pathways that lead to atherogenesis and increased cardiovascular risk.

Central sleep apnea

CSA episodes are the cessation of breathing without thoracoabdominal effort, in contrast to the persis-

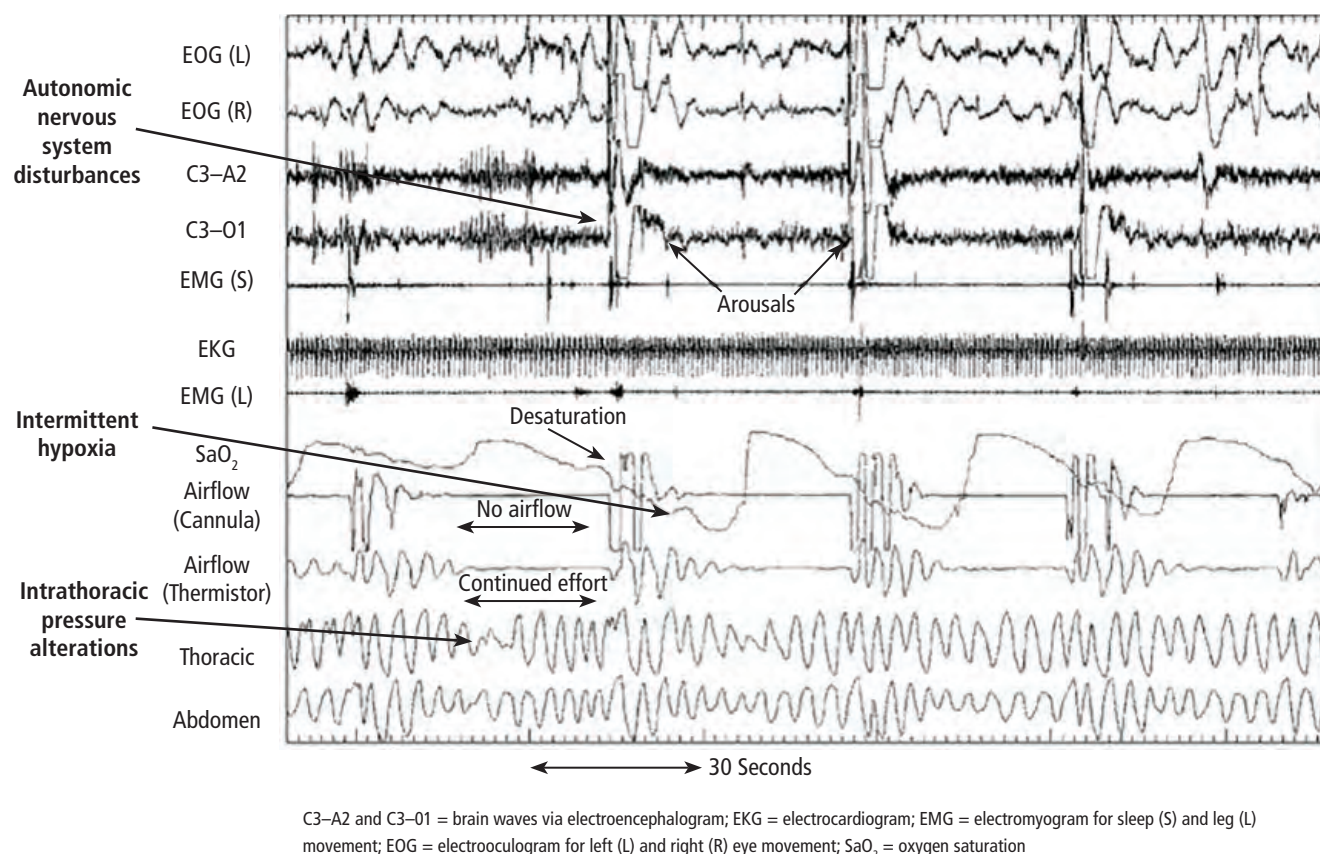


Figure 1. A polysomnogram showing autonomic nervous system disturbances, intermittent hypoxia, and intrathoracic pressure alterations.

tence of thoracoabdominal effort in OSA. CSA is characterized by breathing instability with highly sensitive chemoresponses and prolonged circulation time.²⁴ This can be physiologic in some cases, as when it occurs after a very large breath or sigh and then a central apnea event occurs after the sigh. The alterations in oxygen and CO₂ and the stretch of the receptors in the alveoli of the lungs initiate the Hering-Breuer inhalation reflex.

Pathophysiology of CSA

Complex pathways of medullary and aortic receptor chemosensitivity are at the root of the pathophysiology of CSA.²⁴ With CSA there is often a relative state of hypocapnia at baseline. During sleep, there is reduction in drive, thus chemosensitivity can be activated so that central apnea episodes can ensue as a result of alterations in CO₂ (ie, hypocapnia). Another factor that can contribute to the pathophysiology of CSA is arousal from sleep that can reduce CO₂ levels and therefore perpetuate central events.

The concept of loop gain is used to understand

the pathophysiology of CSA. Loop gain is a measure of the relative stability of a ventilation system and indicates the likelihood of an individual to have periodic breathing. It is calculated by the response to a disturbance divided by the disturbance itself.²⁵ With a high loop gain, there is a more pronounced or exuberant response to the disturbance, indicating more instability in the system and increasing the tendency for irregular breathing and CSA episodes.

Hunter-Cheyne-Stokes respiration occurs with CSA and is characterized by cyclical crescendo-decrescendo respiratory effort that occurs during wakefulness and sleep without upper-airway obstruction.^{26,27} Unlike OSA, which is worse during REM sleep, Hunter-Cheyne-Stokes breathing in CSA is typically worse in NREM sleep, during N1 and N2 in particular.

SLEEP APNEA AND HEART FAILURE

Both OSA and CSA are prevalent in patients with heart failure and may be associated with the progression of heart failure. CSA often occurs in patients with heart failure. The pathophysiology is multi-

factorial, including pulmonary congestion that results in stretch of the J receptors in the alveoli, prolonged circulation time, and increased chemosensitivity.

Complex pathways in the neuroaxis or somnogenic biomarkers of inflammation or both may be implicated in the paradoxical lack of subjective sleepiness in the presence of increased objective measures of sleepiness in systolic heart failure. One study found a relationship with one biomarker of inflammation and oxidative stress as it relates to objective symptoms of sleepiness but not subjective symptoms of sleepiness.²⁸

Another contributing factor in the relationship between OSA and CSA in heart failure has also been described related to rostral shifts in fluid to the neck and to the pulmonary receptors in the alveoli of the lungs.²⁹ These rostral shifts in fluids may contribute to sleep apnea with parapharyngeal edema leading to OSA and pulmonary congestion leading to CSA.

Sleep apnea is associated with increased post-discharge mortality and hospitalization readmissions in the setting of acute heart failure.³⁰ Mortality analysis of 1,096 patients admitted for decompensated heart failure found CSA and OSA were independently associated with mortality in patients compared with patients with no or minimal sleep-disordered breathing.³⁰

CSA has also been shown to be a predictor of readmission in patients admitted for heart failure exacerbations.³¹ Targeting underlying CSA may reduce readmissions in those admitted with acute decompensated heart failure. While men were identified to be at increased risk of death relative to sleep-disordered breathing based on the initial results of the Sleep Heart Health Study, a subsequent epidemiologic substudy reflective of an older age group showed that OSA was more strongly associated with left ventricular mass index, risk of heart failure, or death in women compared with men.³²

Treatment

Standard therapy for treatment of OSA is CPAP. Adaptive servo-ventilation (ASV) and transvenous phrenic nerve stimulation are also available as treatment options in certain cases of CSA.

One of the first randomized controlled trials designed to assess the impact of CSA treatment on survival in patients with heart failure initially favored the control group then later the CPAP group and was terminated early based on stopping rules.^{33,34} While adherence to therapy was suboptimal at an average of 3.6 hours, post hoc analysis showed that patients with CSA using CPAP with effective suppression of

CSA had improved survival compared with patients who did not have effective suppression using CPAP.³⁴

ASV is mainly used for treatment of CSA. In ASV, positive airway pressure for ventilation support is provided and adjusts as apneic episodes are detected during sleep. The support provided adapts to the physiology of the patient and can deliver breaths and utilize anticyclic modes of ventilation to address crescendo-decrescendo breathing patterns observed in Hunter-Cheyne-Stokes respiration.

In the Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) trial, 1,300 patients with systolic heart failure and predominantly CSA were randomized to receive ASV vs solely standard medical management.³⁵ The primary composite end point included all-cause mortality or unplanned admission or hospitalization for heart failure. No difference was found in the primary end point between the ASV and the control group; however, there was an unanticipated negative impact of ASV on cardiovascular outcomes in some secondary end points. Based on the secondary outcome of cardiovascular-specific mortality, clinicians were advised that ASV was contraindicated for the treatment of CSA in patients with symptomatic heart failure with a left ventricular ejection fraction less than 45%. The interpretation of this study was complicated by several methodologic limitations.³⁶

The Cardiovascular Improvements With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure (CAT-HF) randomized controlled trial also evaluated ASV compared with standard medical management in 126 patients with heart failure.³⁷ This trial was terminated early because of the results of the SERVE-HF trial. Compliance with therapy was suboptimal at an average of 2.7 hours per day. The composite end point did not differ between the 2 groups; however, this was likely because the study was underpowered and was terminated early. Subgroup analysis revealed that patients with heart failure with preserved ejection fraction may benefit from ASV; however, additional studies are needed to confirm these findings.

Therefore, although ASV is not indicated when there is predominantly CSA in patients with systolic heart failure, preliminary results support potential benefit in patients with OSA and preserved ejection fraction.

Another novel treatment for CSA is transvenous phrenic nerve stimulation. A device is implanted that stimulates the phrenic nerve to initiate breaths.

The initial study of transvenous phrenic nerve stimulation reported a significant reduction in the number of episodes of central apnea per hour of sleep.^{38,39} The apnea-hypopnea index improved overall and some types of obstructive apneic events were reduced with transvenous phrenic nerve stimulation.

A multicenter randomized control trial of transvenous phrenic nerve stimulation found improvement in several sleep apnea indices, including central apnea, hypoxia, reduced arousals from sleep, and patient reported well-being.⁴⁰ Transvenous phrenic nerve stimulation holds promise as a novel therapy for central predominant sleep apnea not only in terms of improving the degree of central apnea and sleep-disordered breathing, but also in improving functional outcomes. Longitudinal and interventional trial data are needed to clarify the impact of transvenous phrenic nerve stimulation on long-term cardiac outcomes.

■ SLEEP APNEA AND ATRIAL FIBRILLATION AND STROKE

Atrial fibrillation

AF is the most common sustained cardiac arrhythmia. The number of Americans with AF is projected to increase from 2.3 million to more than 10 million by the year 2050.⁴¹ The increasing incidence and prevalence of AF is not fully explained by the aging population and established risk factors.⁴² Unrecognized sleep apnea, estimated to exist in 85% or more of the population, may partially account for the increasing incidence of AF.⁴³

There are 3 types of AF, which are thought to follow a continuum: paroxysmal AF is characterized by episodes that occur intermittently; persistent AF is characterized by episodes that last longer than 7 days; chronic or permanent AF is typically characterized by AF that is ongoing over many years.⁴⁴ As with sleep apnea, AF is often asymptomatic and is likely underdiagnosed.

Sleep apnea and AF share several risk factors. Obesity is a risk factor for both OSA and AF; however, a meta-analysis supported a stronger association of OSA and AF vs obesity and AF.⁴⁵ Increasing age is a risk factor for both OSA and AF.^{46,47} Although white populations are at higher risk for AF, OSA is associated with a 58% increased risk of AF in African Americans.⁴⁸ Nocturnal hypoxia has been associated with increased risk of AF in Asians.⁴⁹

In terms of pathophysiology of sleep apnea and cardiac arrhythmia, OSA increases inflammation,

intrathoracic pressures, and CO₂ levels. The increase in inflammation and oxidative stress is thought to alter the cardiac electrophysiology of the heart and contribute to structural remodeling of the heart that increases the risk of cardiac arrhythmia (**Figure 2**).⁵⁰

Experimental data continue to accrue providing biologic plausibility of the relationship between sleep apnea and AF. OSA contributes to structural and electrical remodeling of the heart with evidence supporting increased fibrosis and electrical remodeling in patients with OSA compared with a control group.⁵¹ Markers of structural remodeling, such as atrial size, electrical silence, and atrial voltage conduction velocity, are altered in OSA.⁵⁰

Data from the Sleep Heart Health Study show very strong associations between atrial and ventricular cardiac arrhythmias and sleep apnea with two- to fivefold higher odds of arrhythmias in patients with severe OSA compared with controls even after accounting for confounding factors such as obesity.⁵²

A multicenter, epidemiological study of older men showed that increasing severity of sleep apnea corresponds with an increased prevalence of AF and ventricular ectopy.⁵³ This graded dose-response relationship suggests a causal relationship between sleep apnea and AF and ventricular ectopy. There also appears to be an immediate influence of apneic events and hypopneic events as it relates to arrhythmia. A case-crossover study showed an associated 18-fold increased risk of nocturnal arrhythmia within 90 seconds of an apneic or hypopneic event.⁵⁴ This association was found with paroxysms of AF and with episodes of nonsustained ventricular tachycardia.

Data from a clinic-based cohort study show an association between AF and OSA.⁵⁵ Specifically, increased severity of sleep apnea was associated with an increased prevalence of AF. Increasing degree of hypoxia or oxygen-lowering was also associated with increased incidence of AF or newly identified AF identified over time.

Longitudinal examination of 2 epidemiologic studies, the Sleep Heart Health Study and Outcomes of Sleep Disorders Study in Older Men, found CSA to be predictive of AF with a two- to threefold higher odds of developing incident AF as it related to baseline CSA.⁵⁶ According to these data, CSA may pose a greater risk for development of AF than OSA.

With respect to AF after cardiac surgery, patients with sleep apnea and obesity appear to be at higher risk for developing AF as measured by the apnea-hypopnea index and oxygen desaturation index.⁵⁷

Treatment of sleep apnea may improve arrhythm-

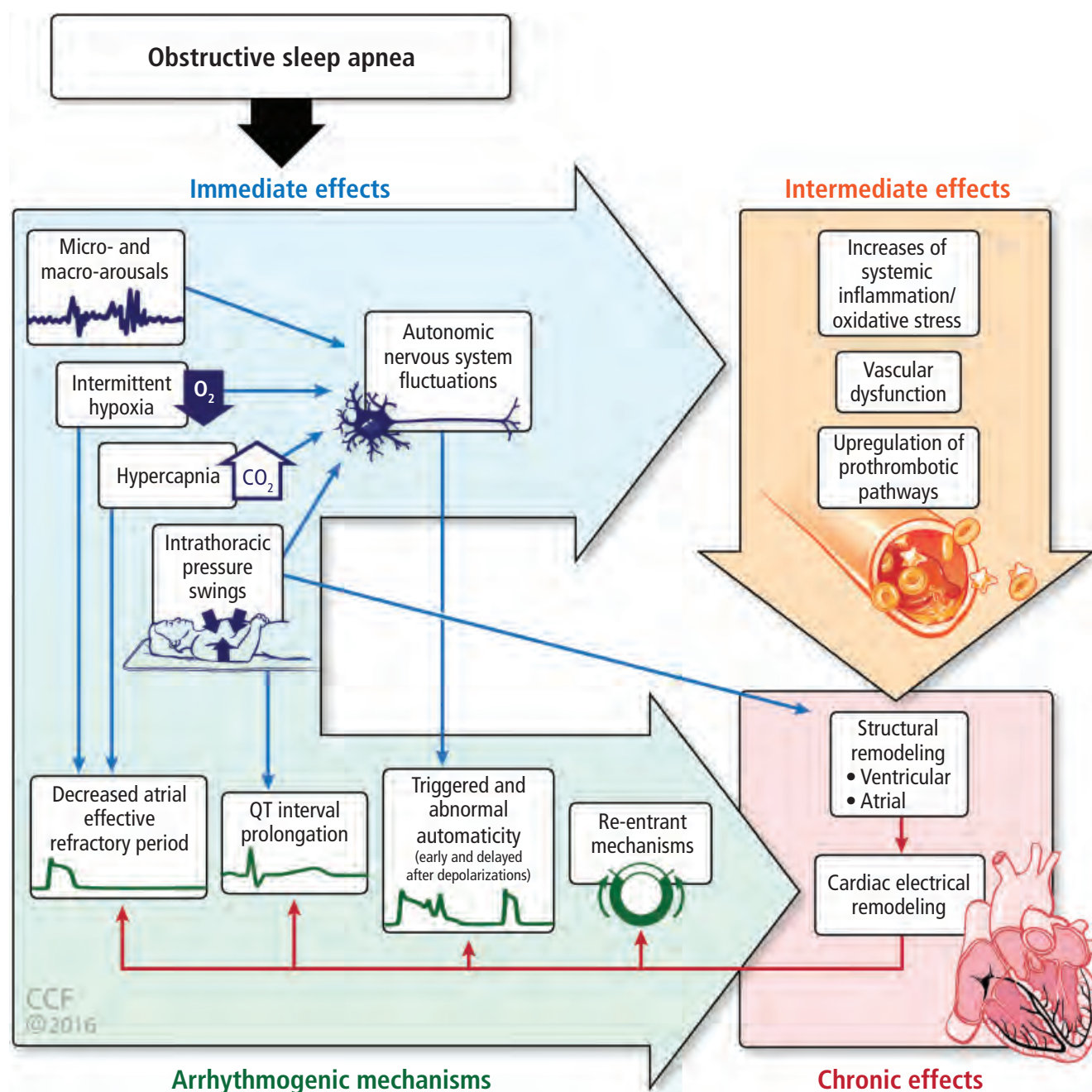


Figure 2. Pathophysiologic pathways of obstructive sleep apnea and cardiac arrhythmia.

mic burden. Case-based studies have shown reduced burden and resolution of baseline arrhythmia with CPAP treatment for OSA as therapeutic pressure was achieved.⁵⁸ Another case-based study involved an individual with snoring and OSA and AF at baseline.⁵⁹ Several retrospective studies have shown that treatment of OSA after ablation and after cardio-

version results in reduced recurrence of AF; however, large definitive clinical trials are lacking.

Stroke

Sleep apnea is a risk factor for stroke due to intermittent hypoxia-mediated elevation of oxidative stress and systemic inflammation, hypercoagulability, and

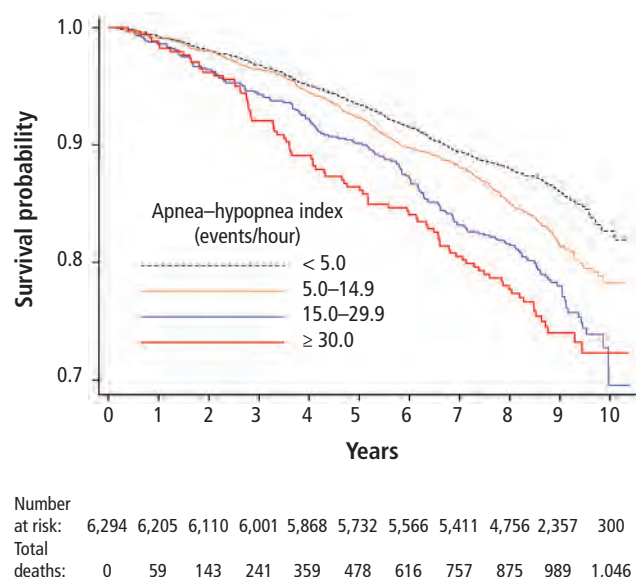


Figure 3. Survival of patients with obstructive sleep apnea by apnea-hypopnea index.

Punjabi NM, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; 6(8):e1000132.

impairment of cerebral autoregulation.⁶⁰ However, the relationship may be bidirectional in that stroke may be a risk factor for sleep apnea in the post-stroke period. The prevalence of sleep apnea post-stroke has been reported to be up to 70%. CSA can occur in up to 26% during the post-stroke phase.⁶¹ Data are inconsistent in terms of the location and size of stroke and the risk of sleep apnea, though cerebrovascular neuronal damage to the brainstem and cortical areas are evident.⁶² In one study, the incidence of stroke appeared to increase with the severity of sleep apnea.⁶³ These findings were more pronounced in men than in women; however, this study may not have captured the increased cardiovascular risk in postmenopausal women. The Outcomes of Sleep Disorders in Older Men study found that severe hypoxia increased the incidence of stroke, and that hypoxia may be a predictor of newly diagnosed stroke in older men.⁶⁴ Although definitive clinical trials are underway, post-hoc propensity-score matched analysis from the Sleep Apnea Cardiovascular Endpoints (SAVE) study showed a lower stroke risk in those adherent to CPAP compared with the control group (HR=0.56, 95% CI: 0.30-0.90).⁶⁵

■ SLEEP APNEA, CORONARY ARTERY DISEASE, AND CARDIOVASCULAR MORTALITY

The association between sleep apnea and coronary artery disease and cardiovascular mortality was considered in a Spanish study of 1,500 patients followed for

TABLE 1

Sudden death from cardiac causes by time of day

	Proportion of patients with cardiac sudden death		
	With OSA (n = 78)	Without OSA (n = 34)	General population
Midnight to 5:59 AM	46	21	16
6 AM to 11:59 AM	20	41	30
Noon to 5:59 PM	9	26	29
6 PM to 11:59 PM	24	12	25

Data from reference 69.

10 years, which reported that CPAP therapy reduced cardiac events in patients with OSA.⁶⁶ Patients with sleep apnea had an increased risk of fatal myocardial infarction or stroke. Survival of patients treated for sleep apnea approached that of patients without OSA.

In a study of a racially diverse cohort, an association of physician diagnosed sleep apnea with cardiovascular events and survival was identified.⁶⁷ Diagnosed sleep apnea was estimated to confer a two- to three-fold increase in various cardiovascular outcomes and all-cause mortality.

All-cause mortality data from the Sleep Heart Health Study of more than 6,000 participants showed that progressive worsening of OSA as defined by the apnea-hypopnea index resulted in poorer survival even after accounting for confounding factors (Figure 3).⁶⁸ Decreased survival appeared to mostly affect men or patients under age 70.

The diurnal pattern of cardiovascular physiology as it relates to sleep is thought to be cardioprotective because of reductions in blood pressure and heart rate. However, in the case of OSA, there appears to be a nocturnal vulnerability or predilection for sudden cardiac death. Patients with OSA were shown to have a higher risk of sudden nocturnal cardiac death occurring from midnight to 6 AM compared with individuals without OSA and the general population (Table 1).⁶⁹

The effect of treatment for sleep apnea on cardiovascular outcomes was the focus of a recent randomized controlled trial of nearly 3,000 participants with a mean follow-up of 4 years.⁶⁵ Use of CPAP compared with usual care found no difference in cardiovascular outcomes. However, secondary analysis revealed a possible benefit of a lower risk of stroke with use of CPAP therapy. Several factors should be considered in interpreting these findings: ie, low adherence

with CPAP therapy (3 hours), whether the study was sufficiently powered to detect a change in cardiovascular outcomes, and if the duration of follow-up was adequate. In terms of patient demographics and study generalizability, the study did not include patients with severe sleep apnea and hypoxia, and most participants were men, of Asian descent, with a mean body mass index of 28 kg/m², and low levels of sleepiness at baseline.

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Beyond heart health: Consequences of obstructive sleep apnea

■ ABSTRACT

Obstructive sleep apnea (OSA) is a serious condition associated with impaired quality of life, depression, drowsy driving and motor vehicle accidents, metabolic disease, and cognitive decline. The mechanisms accounting for OSA and metabolic disease include hypoxia, sleep fragmentation, and systemic inflammation. OSA appears to advance cognitive decline, and the relationship between the 2 conditions may be bidirectional. Treatment of patients with continuous positive air pressure therapy improves many of the impaired outcomes associated with OSA. Greater awareness, screening, and treatment of patients with OSA can reduce the negative consequences associated with OSA.

■ KEY POINTS

OSA is associated with negative health consequences such as depression, drowsy driving, metabolic disease, and cognitive decline.

Several possible mechanisms to explain the health consequences of OSA have been explored.

Treatment of patients with OSA may improve outcomes for many of the health consequences associated with OSA.

Screening for OSA is important to identify and treat patients to reduce the associated health risks.

Obstructive sleep apnea (OSA) is a serious condition that impacts quality of life and causes drowsy driving and depression. Research also reveals an interrelationship between OSA and metabolic disease and an association between OSA and cognitive impairment.

The diagnostic criteria of OSA are based on the number of apneic or hypopneic episodes per hour of sleep, called the apnea-hypopnea index (AHI) as recorded during sleep testing. Diagnosis of OSA is warranted if the AHI is 15 or more per hour or if the AHI is 5 or more per hour with 1 or more of the following features: sleepiness; nonrestorative sleep; fatigue or insomnia; waking up with breath-holding spells, gasping, or choking; snoring or breathing interruptions; or a coexisting diagnosis of hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type II diabetes.¹

Many patients with an AHI less than 15 may also have OSA, given the number of coexisting medical conditions included in the OSA diagnostic criteria. Heart conditions such as coronary artery disease, atrial fibrillation, and congestive heart failure encompassed in the OSA diagnostic criteria have increased awareness of the link between OSA and heart health. Less well-known, and the subject of this review, are the negative consequences of OSA, particularly poor quality of life, drowsy driving, depression, metabolic disease, and cognitive impairment.

■ QUALITY OF LIFE

Reduced quality of life is the most fundamental patient-reported outcome of OSA. OSA is associated with excessive daytime sleepiness, inattention, and fatigue, which increase the risk of accidents and medical disability. These quality-of-life impairments are often the main reason patients seek medical care for sleep disorders.² Improved quality of life is a central goal of OSA treatment and is the best indicator of the effectiveness of treatment.³ Sleep health

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TABLE 1**Symptoms of depression and obstructive sleep apnea (OSA)**

Depression	Depression or OSA	OSA
Sadness, anhedonia, agitation, guilt, weight loss	Daytime sleepiness, fatigue, loss of energy, poor concentration, irritability, psychomotor retardation, weight gain	Snoring, witnessed apneic episodes, snorting

Data from reference 13.

and its effect on quality of life is an area of focus of Healthy People 2020 (healthypeople.gov).

The American Academy of Sleep Medicine identified quality of life, along with detection of disease and cardiovascular consequences, as an outcome measure for assessing the quality of care for adults with OSA.² The assessment of quality of life for patients with OSA is a 4-part process: use evidence-based therapy, monitor the therapy, assess symptoms with a validated tool such as Epworth Sleepiness Scale, and assess the incidence of motor vehicle accidents. Information from these 4 processes can inform changes in a patient's quality of life.

Treatment for OSA has been shown to improve quality of life. A study of 2,027 patients with OSA evaluated therapy adherence relative to mean Functional Outcomes of Sleep Questionnaire and European Quality of Life-5D scores.⁴ In patients with the most impaired quality of life, those adherent to positive airway pressure (PAP) therapy had improved quality of life as measured by these scores.

With respect to sleepiness, a systematic review of continuous PAP (CPAP) in patients with OSA found a 2.7-point reduction (mean difference; 95% confidence interval 3.45–1.96) in the Epworth Sleepiness Scale in patients using CPAP compared with the control group.⁵ Treatment of OSA improves patient quality of life and symptoms such as sleepiness.

■ DROWSY DRIVING

Drowsy driving by people with OSA can lead to motor vehicle accidents, which result in economic and health burdens.^{6,7} National Center for Statistics and Analysis data reveal that of 6 million motor vehicle accidents (5-year average, 2005–2009), 1.4% involve drowsy driving and 2.5% of fatal crashes involve drowsy driving.⁸ Among noncommercial drivers, untreated OSA increases the risk of motor vehicle accidents 3- to 13-fold.⁹ The odds ratio of traffic acci-

dents in drivers with untreated OSA is 6 times greater than in the general population.⁷

In a study of men and women in the general population (N = 913), individuals with moderate to severe OSA (AHI > 15) were more likely to have multiple motor vehicle accidents in the course of 5 years (odds ratio = 7.3) compared with those with no sleep-disordered breathing.¹⁰ The association between OSA and motor vehicle accidents is independent of

sleepiness, and drivers with OSA may not perceive performance impairment.

There are 2 main reasons OSA increases the risk and incidence of motor vehicle accidents. OSA causes changes in attention and vigilance resulting from sleep deprivation and fragmentation. OSA also affects global cognition function, which may be due to intermittent hypoxia attributable to OSA.²

Treatment for OSA is effective in reducing the incidence of motor vehicle accidents. One study found the risk of motor vehicle accidents was eliminated with the use of CPAP treatment in patients with OSA.¹¹ A recent study of nearly 2,000 patients with OSA found a reduction in self-reported near-accidents from 14% before PAP therapy to 5.3% after starting PAP therapy.¹²

■ DEPRESSION

Depression can occur as a consequence of OSA. Depression and OSA have several symptoms in common (Table 1).¹³

Estimates of the prevalence of depression in patients with OSA range from 5% to 63%.^{13,14} One year after patients were diagnosed with OSA, the incidence of depression per 1,000 person-years was 18% compared with 8% in a group without OSA.¹⁴ Women with OSA reportedly have a higher risk of depression (adjusted hazard ratio [HR] 2.7) than men (HR 1.81) at 1-year follow-up.¹⁴ In the same study, with respect to age, there was no significant relationship noted between OSA and patients over age 64.

A one-level increase in the severity of OSA (ie, from minimal to mild) is associated with a nearly twofold increase in the adjusted odds for depression.¹⁵ On the other hand, studies have also found that patients on antidepressants may have an increased risk of OSA.¹⁶

Several potential mechanisms have been proposed to explain the link between depression and OSA.¹³ Poor-quality sleep, frequent arousal, and fragmentation

of sleep in OSA may lead to frontal lobe emotional modulation changes. Intermittent hypoxia in OSA may result in neuronal injury and disruption of noradrenergic and dopaminergic pathways. Pro-inflammatory substances such as interleukin 6 and interleukin 1 are increased in OSA and depression and are mediators between both conditions. Neurotransmitters may be affected by a disrupted sleep-wake cycle. And serotonin, which may be impeded in depression, could influence the upper-airway dilator motor neurons.

Treatment of OSA improves symptoms of depression as measured by the Patient Health Questionnaire (PHQ-9). After 3 months of compliance with CPAP therapy, mean PHQ-9 scores decreased from 11.3 to 2.7 in a study of 228 patients with OSA.¹⁷ A study of 1,981 patients with sleep-disordered breathing found improved PHQ-9 scores in patients compliant with CPAP therapy and a greater improvement in patients with a baseline PHQ-9 higher than 10 (moderate severity).¹⁸

METABOLIC SYNDROME

OSA is associated with metabolic disorders, including metabolic syndrome, though the causality between these 2 conditions is yet to be illuminated. Metabolic syndrome is a term used when an individual has 3 or more of the following features or conditions:

- Waist circumference greater than 40 inches (men), greater than 35 inches (women)
- Triglycerides 150 mg/dL or greater or treatment for hypertriglyceridemia
- High-density lipoprotein cholesterol less than 40 mg/dL (men), less than 50 mg/dL (women), or treatment for cholesterol
- Blood pressure 130/85 mm Hg or greater, or treatment for hypertension
- Fasting blood glucose 100 mg/dL or greater, or treatment for hyperglycemia.¹⁹

Metabolic syndrome increases an individual's risk of diabetes and cardiovascular disease and overall mortality. Like OSA, the prevalence of metabolic syndrome increases with age in both men and women.^{20,21} The risk of metabolic syndrome is greater with more severe OSA. The Wisconsin Sleep Cohort (N = 546) reported an odds ratio for having metabolic syndrome of 2.5 for patients with mild OSA and 2.2 for patients with moderate or severe OSA.²² A meta-analysis also found a 2.4 times higher odds of metabolic syndrome in patients with mild OSA, but a 3.5 times higher odds of metabolic syndrome in patients with moderate to severe OSA compared with the control group.²³

Patients with both OSA and metabolic syndrome

are said to have syndrome Z²⁴ and are at increased risk of cardiovascular morbidity and mortality.²⁵ Syndrome Z imparts a higher risk of atherogenic burden and prevalence of atheroma compared with patients with either condition alone.²⁶ In comparing patients with metabolic syndrome with and without OSA, those with OSA had increased atherosclerotic burden as measured by intima-media thickness and carotid femoral pulse-wave velocity.²⁷ Syndrome Z is also linked to intracoronary stenosis related to changes in cardiac morphology²⁸ and is associated with left ventricular hypertrophy and diastolic dysfunction.²⁹

OSA and hypertension

Hypertension is one of the conditions encompassed in metabolic syndrome. Several studies report increased risk and incidence of hypertension in patients with OSA. In a community-based study of 6,123 individuals age 40 and older, sleep-disordered breathing was associated with hypertension, and the odds ratio of hypertension was greater in individuals with more severe sleep apnea.³⁰ Similarly, a landmark prospective, population-based study of 709 individuals over 4 years reported a dose-response relationship between patients with OSA and newly diagnosed hypertension independent of confounding factors.³¹ Patients with moderate to severe OSA had an odds ratio of 2.89 of developing hypertension after adjusting for confounding variables.

A study of 1,889 individuals followed for 12 years found a dose-response relationship based on OSA severity for developing hypertension.³² This study also assessed the incidence of hypertension based on CPAP use. Patients with poor adherence to CPAP use had an 80% increased incidence of hypertension, whereas patients adhering to CPAP use had a 30% decrease in the incidence of hypertension.

Resistant hypertension (ie, uncontrolled hypertension despite use of 3 or more antihypertensive and diuretic medications) has been shown to be highly prevalent (85%) in patients with severe OSA.³³ An analysis of patients at increased risk of cardiovascular disease and untreated severe OSA was associated with a 4 times higher risk of elevated blood pressure despite intensive medical therapy.³⁴

Mechanisms of altered metabolic regulation in OSA

Mechanisms implicated in altering metabolic regulation in OSA include intermittent hypoxia, sleep fragmentation and glucose homeostasis, and obesity. Intermittent hypoxia from OSA results in sympathetic nervous system activation that affects the pancreas, skeletal muscle, liver, and fat cells resulting in

TABLE 2**PAP vs control conditions (change in mean 24-hour blood pressure, all patient types)**

Study or subgroup	PAP			Control conditions			Weight	Mean difference IV, Random, 95% CI	Mean difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Becker	-9.8	13.4	16	0.6	11	16	2.1%	-10.40 [-18.89, -1.91]	
Campos-Rodriguez	-1.2	10.1	34	-0.3	10.4	34	6.4%	-0.90 [-5.77, 3.97]	
Duran-Cantolla	-2	8.5	169	0	9	171	44.0%	-2.00 [-3.86, -0.14]	
Gottlieb	-1.7	8.4	90	1.3	10.3	97	21.1%	-3.00 [-5.69, -0.31]	
Hui	-2.4	9.8	23	1.3	10.1	23	4.6%	-3.70 [-9.45, 2.05]	
Martinez-Garcia	-4.1	12.4	98	-0.8	14.5	96	10.6%	-3.30 [-7.10, 0.50]	
Pepperell	-2.5	9.6	48	0.8	10.8	47	9.0%	-3.30 [-7.41, 0.81]	
Robinson	-2	12	16	-1.2	12.4	16	2.1%	-0.80 [-9.26, 7.66]	
Total (95% CI)			494			500	100.0%	-2.63 [-3.86, -1.39]	
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.75$; $df = 7$ ($P = 0.69$); $I^2 = 0\%$									
Test for overall effect: $Z = 4.17$ ($P < 0.0001$)									

CI = confidence interval; PAP = positive airway pressure; SD = standard deviation

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altered insulin secretion, lipid-bile synthesis, glucose metabolism, and lipoprotein metabolism.³⁵

Sleep fragmentation is a cardinal feature of OSA and the resulting suppression of sleep may alter insulin sensitivity. Studies have implicated disruptions to slow-wave sleep specifically, as well as disruption of any stage of sleep in reduced insulin sensitivity.^{35,36} In addition to decreased insulin sensitivity, sleep fragmentation also increases morning cortisol levels and increases sympathetic nervous system activation.³⁷

Obesity and OSA share a pathway imparting increased cardiometabolic risk.³⁸ Fat tissue causes higher systemic inflammation and inflammatory markers. A recent report describes a bidirectional relationship between metabolic syndrome and OSA.³⁹ While OSA increases the risk for metabolic syndrome, metabolic syndrome by virtue of body mass index with changes in mechanical load and narrow airway and physiology can predispose for OSA.

Effect of treatment for OSA on metabolic syndrome

Several studies have evaluated the effect of CPAP treatment for OSA on metabolic syndrome overall, as well as the specific conditions that comprise metabolic syndrome. In evaluating CPAP use and metabolic syndrome overall, studies have found a reduced prevalence of metabolic syndrome,^{40,41} CPAP benefit only in complying patients,⁴² and a reduction in oxidative stress with a single-night use of CPAP.⁴³

With respect to insulin sensitivity, a study of 40 men with moderate OSA using CPAP therapy (mean use 5 hours) reported an increase in the insulin sensitivity index after 2 days, and a further increase after 3 months.⁴⁴ Another study found no improvement in insulin resistance in severe OSA.⁴⁵ A meta-analysis reported improved insulin resistance with CPAP,⁴⁶ although a recent meta-analysis assessing hemoglobin A_{1c} level, fasting insulin level, and fasting glucose did not show improvement in these parameters. Large-scale clinical trials with longer treatment duration and better CPAP compliance are warranted.⁴⁷

CPAP use in patients with OSA has been found to affect hypertension in a number of studies (Table 2).^{48–55} In a comparison of therapeutic CPAP with suboptimal CPAP for 9 weeks, ambulatory blood pressure was reduced in the therapeutic group, and no change was seen in the subtherapeutic group, illustrating the importance of optimal pressure settings in treating OSA.⁴⁸

A randomized controlled trial of nearly 300 individuals found improvement in 6 blood pressure parameters in a group using CPAP compared with a group using sham CPAP after 12 weeks.⁵⁰ A large clinic-based cohort of 894 individuals with hypertension and resistant hypertension (15%) found that after 1 year, CPAP use was associated with 2 to 3 mm Hg of reduction in blood pressure (Figure 1).⁵⁶ Meta-analysis of randomized controlled trials on the effectiveness of CPAP on hypertension found reductions of 2 mm Hg to 3 mm Hg in blood pressure.⁵⁷ Another

meta-analyses showed a reduction of 2.6 mm Hg in 24-hour mean blood pressure with CPAP therapy (Table 2).^{48–55} This reduction may appear modest in nature; however, any reduction in blood pressure can result in decreased cardiovascular morbidity and mortality. A meta-analysis of randomized controlled trials indicated reductions in mean systolic blood pressure of 5.4 mm Hg and diastolic blood pressure of 3.86 mm Hg after CPAP in those with resistant hypertension and OSA.⁵⁸

Weight loss has been shown to reduce the AHI and other parameters related to sleep apnea such as oxygen desaturation index in patients with obesity and diabetes.⁵⁹ Weight loss combined with CPAP compared with CPAP or weight loss alone showed an incremental benefit in improving glucose parameters, triglycerides, and possibly systolic blood pressure and triglycerides.⁶⁰

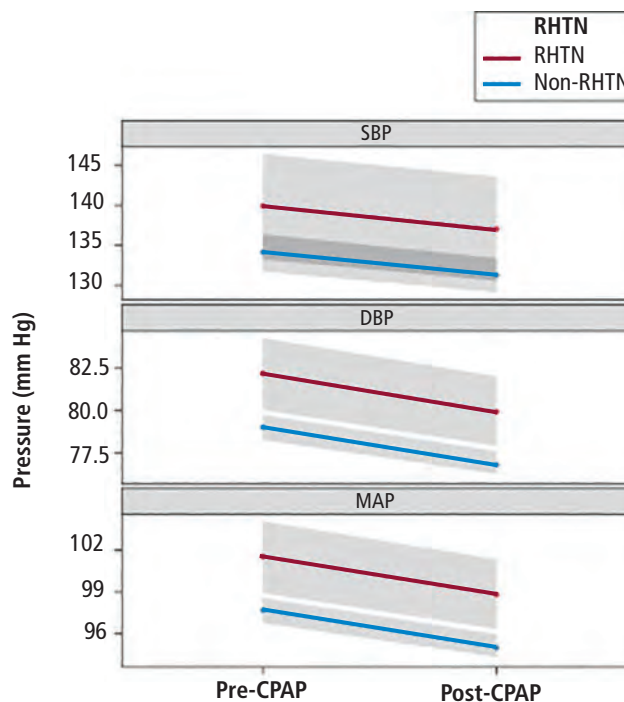
COGNITIVE IMPAIRMENT

Data suggest that OSA is linked with cognitive impairment, may advance cognitive decline, and is a bidirectional relationship. Women with OSA were reportedly more likely to develop mild cognitive impairment compared with women without OSA.⁶¹ An elevated oxygen desaturation index and a high percentage of time spent with hypoxia was associated with increased risk of developing mild cognitive impairment and dementia.

OSA was found to be an independent risk factor for cerebral white matter changes in middle-age and older individuals. Moderate to severe OSA imparted a 2 times higher risk of cerebral white matter changes compared with individuals without OSA.⁶² Another study of 20 patients with severe OSA compared with 40 healthy volunteers found diffusion imaging consistent with impaired fibrin integrity in those with OSA, indicative of white matter microstructure damage, and the impairment was associated with increased disease severity and higher systemic inflammation.⁶³

Individuals with hypoxia for a high percentage of time during sleep had a 4 times higher odds of cerebral microinfarcts.⁶⁴ Cognitive scores decreased less in men. Men typically have more time in slow-wave sleep, suggesting that slow-wave sleep may be protective against cognitive decline. Mild cognitive impairment and Alzheimer disease were found more likely to develop and occur at an earlier age in individuals with sleep-disordered breathing compared with individuals without sleep-disordered breathing.⁶⁵

OSA was also associated with increased serum amyloid beta levels in a study of 45 cognitively nor-



DBP = diastolic blood pressure; MAP = mean arterial pressure; RHTN = resistant hypertension; SBP = systolic blood pressure

Figure 1. Blood pressure trends in patients before and after continuous positive airway pressure (CPAP) use.

Reprinted from Walia HK, et al. Longitudinal effect of CPAP on BP in resistant and nonresistant hypertension in a large clinic-based cohort. *Chest* 2016; 149(3):747–755. Copyright © 2016 with permission from the American College of Chest Physicians. <http://www.sciencedirect.com/journal/chest>

mal patients with OSA compared with 49 age- and sex-matched control patients. Increased amyloid beta levels correlated with increasing severity of sleep apnea as measured by the AHI.⁶⁶

Mechanism linking OSA and cognition

One possible mechanism linking sleep quality and cognitive impairment or Alzheimer disease is the role of unfragmented sleep in attenuating the apolipoprotein E e4 allele on the incidence of Alzheimer disease.⁶⁷ Beta amyloid is released during synaptic activity. Neuronal and synaptic activity decreases during sleep, and disrupted sleep could increase beta amyloid release.⁶⁸ Sleep has been found to enhance the clearance of beta amyloid peptide from the brain interstitial fluid in a mice model.⁶⁹

Recent data point toward the bidirectional relationship between the sleep and Alzheimer disease in that excessive and prolonged neuronal activity in the absence of appropriately structured sleep may be the reason for both Alzheimer disease and OSA.^{70,71}

Effect of treatment for OSA on cognition

White matter integrity in 15 patients with OSA before and after treatment with CPAP was compared with 15 matched controls. Over 12 months, there was a nearly complete reversal of white matter abnormalities in patients on CPAP therapy.⁷² Improvement in memory, attention, and executive function paralleled the changes in white matter after the treatment.

CONCLUSION

OSA is a serious condition with far-reaching consequences associated with impaired quality of life, depressive symptoms, drowsy driving, metabolic disease, and cognitive decline. Treatment of OSA improves many of these health consequences, emphasizing the need for OSA screening. Large randomized studies are needed to assess the efficacy of CPAP on metabolic outcomes, including insulin sensitivity and glucose tolerance, in reducing disease burden. Study of the endophenotypes of patients with OSA is needed to define and target the mechanisms of OSA-induced adverse health outcomes and perhaps lead to personalized care for patients with OSA.

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Positive airway pressure: Making an impact on sleep apnea

■ ABSTRACT

Positive airway pressure (PAP) devices deliver a pressurized column of air to open the airway in patients with sleep apnea. For patients with moderate to severe sleep apnea, PAP therapy is the gold standard for treatment, with demonstrated improvements in daytime sleepiness and cardiovascular measures that are superior to conservative treatments. For a variety of reasons, adherence to PAP therapy is a challenge for many patients, resulting in deficits in the frequency and duration of use. To improve use and compliance to therapy, several advanced features are available to enhance comfort, pressure, and humidification factors associated with PAP devices. Patient motivation strategies such as motivational interviews, desensitization protocols, and PAP “NAPs” are also being employed to improve adherence to therapy.

■ KEY POINTS

PAP therapy is the gold standard treatment for moderate to severe sleep apnea.

Adherence to PAP therapy remains a challenge due to the PAP device itself and various patient comfort factors.

Features of PAP devices that may improve adherence are advanced pressure control, including ramp, auto and bilevel, heated humidification, and compliance data reporting.

Strategies to motivate patients to use PAP therapy include motivational interviewing, desensitization, and PAP “NAPs.”

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Positive airway pressure (PAP) therapy is used to open an obstructed upper airway (**Figure 1**). PAP therapy consists of a small bedside unit that creates a pressurized column of air that is delivered through tubing to a facial interface, which can be nasal, oral, or both. Collin Sullivan, MD, created the nasal continuous PAP (CPAP) in 1982 using parts of a vacuum cleaner to create positive pressure that successfully resolved hypoxemia in a patient.¹ Today, the various forms of PAP therapy include CPAP, the most common, auto-PAP (APAP), and bilevel PAP (BiPAP).

■ EFFICACY OF PAP THERAPY

The American Academy of Sleep Medicine practice guidelines for PAP are based on 342 articles, most rated as evidence levels I and II, concluding that CPAP is superior to conservative treatment to:

- Eliminate respiratory disturbances
- Reduce the apnea–hypopnea index
- Decrease the arousal index on electroencephalogram
- Increase in the total amount of slow-wave or N3 sleep
- Reduce daytime sleepiness.²

These practice parameters are based on evidence of improved daytime sleepiness and reduced incidence of cardiovascular events in patients with moderate to severe obstructive sleep apnea (OSA) treated with PAP. The evidence is less clear for neurocognitive markers and cardiovascular events in the treatment of patients with mild sleep apnea.

Sleepiness

A study evaluated sleepiness outcomes in 149 patients with severe sleep apnea with an average apnea–hypopnea index of 69 relative to the duration of nightly CPAP use. Sleepiness was measured using the Functional Outcomes of Sleep Questionnaire, Epworth Sleepiness Scale, and Multiple Sleep Latency Test. Results suggest that a greater percent-

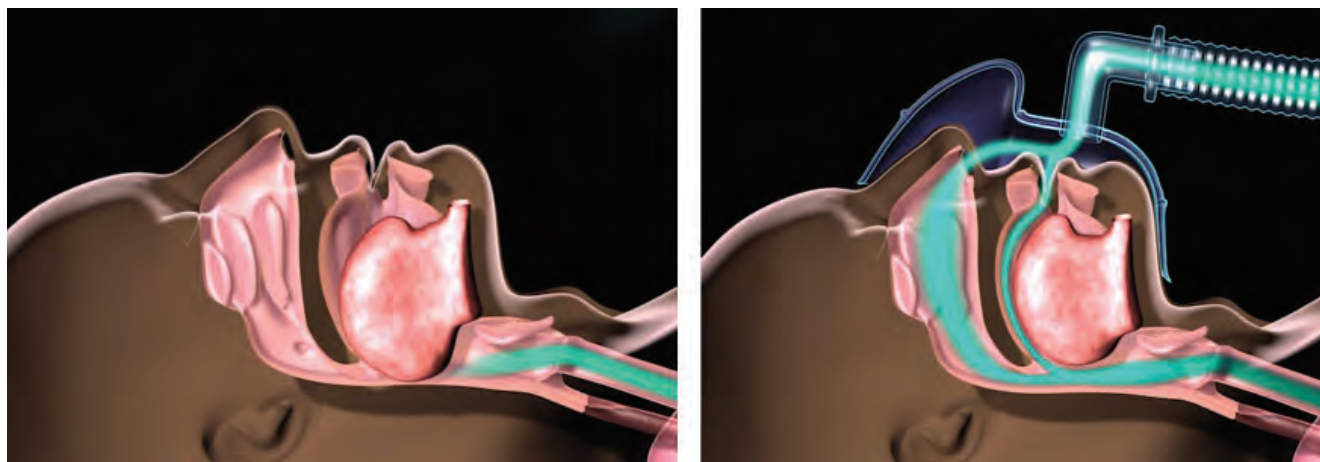


Figure 1. Obstructed airway (left) is opened with a column of air delivered using positive airway pressure therapy (right).

Cleveland Clinic. PAP therapy. <https://my.clevelandclinic.org/health/treatments/17320-pap-therapy>. Accessed July 19, 2019.

age of patients had improved daytime sleepiness as the total hours of sleep using CPAP increased.³

The Apnea Positive Pressure Long-term Efficacy Study (APPLES) was a 6-month, multicenter, randomized study of neurocognitive function in patients with OSA (N = 1,098).⁴ Subjective sleepiness as measured by the Epworth Sleepiness Scale showed statistically significant improvement at 2 and 6 months for patients with moderate to severe OSA using CPAP. Objective sleepiness as measured by the Maintenance of Wakefulness Test showed statistically significant improvement (ie, improved daytime alertness) at 2 and 6 months for patients with severe OSA using CPAP.

Neurocognitive function

APPLES also tested for attention and psychomotor function as well as verbal learning and memory, though no statistically significant improvements were found in these parameters.⁴ Executive function and frontal lobe function showed transient improvement at 2 months in patients with severe sleep apnea using CPAP, but the improvement was not statistically significant at 6 months.

Cardiovascular outcomes

Hypertension and cardiovascular disease. Use of CPAP therapy reduces blood pressure in individuals with hypertension. A study of 32 patients who had a baseline polysomnography with 19 hours of continuous mean arterial blood pressure monitoring were treated with therapeutic CPAP (n = 16) or subtherapeutic CPAP (n = 16).⁵ Therapeutic treatment with CPAP for patients with moderate to severe OSA resulted in statistically significant reductions in

mean arterial pressure for both systolic and diastolic pressures. The blood pressure reductions achieved are estimated to reduce coronary artery diseases by 37% and stroke by 56%.⁵

The risk of cardiovascular events in men with severe sleep apnea is high but mitigated by the use of CPAP. In a cohort of 1,651 men, untreated severe sleep apnea resulted in a threefold increase in the rate of cardiovascular events per 1,000 patient-years compared with 4 other groups: a control group, men who snore, men with untreated mild to moderate sleep apnea, and men with OSA using CPAP.⁶ However, when men with severe sleep apnea use CPAP, the risk of cardiovascular events is reduced to the rate in men who snore.

Atrial fibrillation. In patients with atrial fibrillation treated with direct-current cardioversion-defibrillation, the recurrence of atrial fibrillation at 12 months was greater in patients with untreated OSA (82%) compared with a control group (53%) and patients treated for OSA (42%).⁷

Heart failure. In a study of 24 patients with heart failure, an ejection fraction less than 45%, and OSA, patients were randomized to a control group for medical treatment or medical treatment and nasal CPAP for 1 month.⁸ In the CPAP group, mean systolic blood pressure and heart rate were reduced, resulting in an improved ejection fraction compared with baseline, as well as compared with patients in the control group.

In patients with heart failure (N = 66) with and without Cheyne-Stokes respirations in central sleep apnea, patients treated with CPAP were found to have a 60% relative risk reduction in mortality-cardiac transplant rate compared with the control group not using CPAP.⁹ Further stratification in this



Figure 2. Download of positive airway pressure use data for a month (A) and leak data for a night (B).

study showed that patients with significant Cheyne-Stokes respirations and central sleep apnea had an improved ejection fraction at 3 months and an 81% reduced mortality-cardiac transplant rate.⁹

ADHERENCE

Adherence to PAP therapy is a problem in terms of both frequency of use and duration of use per night. A review of randomized control trials of CPAP compliance between 2011 and 2015 found adherence varied widely from 35% to 87%.¹⁰ The average hours of PAP use per night was found to be 5 hours in APPLES.⁴ Patients adherent to PAP therapy at 1 month remained adherent at 1 year, suggesting patients using CPAP for 1 month were more likely to continue use at 1 year.¹⁰ Impediments to PAP use typically involve the facial interface discomfort, lack of humidity, and pressure intolerance.

FEATURES OF PAP DEVICES

Today's PAP devices have features designed to make them easier to use and more comfortable to improve adherence to therapy. Facial interface options, heated

humidifiers, tubing accessories, cleaning devices, reporting of compliance data via telecommunication, and pressure adjustment features of PAP devices may improve patient adherence and comfort, as highlighted in the case scenarios presented below.

Interfaces

Case scenario #1

A 32-year-old woman with moderate sleep apnea complains that her PAP nasal mask is making very loud noises and is disturbing her bed partner. She is a side sleeper and also reports that she wakes with an extremely dry mouth.

Management of the leak could include which of the following?

1. Chin strap
2. Avoidance of facial creams before bedtime
3. CPAP pillow
4. Clean the mask daily
5. All of the above

Answer: All of the above.

Figure 2 shows an overview of data from the patient's machine for the past month and 1 night of leak data.

Both the month-use data and single-night leak data show mask leakage.

There are many types of PAP interfaces such as nasal masks, nasal pillows, nasal cushions, full-face masks, and less frequently used oral and total face masks. The mask interface is a common impediment to use of PAP therapy often due to poor mask fit or leakage.

Nasal masks cover only the nose and require that the mouth remains closed, which can be achieved with the addition of a chin strap. Nasal masks are available in a variety of materials including cloth. Nasal pillows actually go into the nostrils whereas the nasal mask is positioned under the nose. A nasal cushion mask sits under the nose but does not go into the nostrils.

A study by Lanza and colleagues¹¹ evaluated patient comfort with PAP therapy based on the type of nasal interface mask. Patients using nasal pillows had improvement with respect to swollen eyes, discomfort, skin breakdown, and marks on the face compared with patients using nasal masks; however, nasal pillows can cause nostril pain.

Several types of full-face masks are available, some that fit over the bridge of the nose and some that fit just under the nose. A variety of head straps are available to secure full-face masks. One benefit of full-face masks is that air pressure is delivered to both the nose and the mouth, so the mouth can be open or closed. However, the larger surface area of the full-face mask increases the potential for leaks. A study of adherence in 20 patients using CPAP with nasal masks or full-face masks evaluated hours per use, adherence at 12 months, and comfort.¹² Patients using full-face masks had more hours per use, better adherence at 12 months, and more comfort than patients using nasal masks.

Interface skin irritation and leak management.

To help combat skin irritation, particularly for patients with rosacea, cloth products are available for use beneath the mask and headgear. Silicone pads for masks that cause pressure on the bridge of the nose can help protect against skin breakdown. Sleeping positions other than the supine position can contribute to mask leak. CPAP pillows are designed to allow patients to sleep in their desired position while maintaining an adequate mask seal. The pillows are shaped or have cutouts that prevent the mask from pushing on the pillow and creating a leak.

Humidification

Case scenario #2

A 54-year-old man with severe sleep apnea recently initiated CPAP therapy. He quickly discontinued use due to nasal congestion.

Which of the following is NOT recommended?

1. Assure adequate heated humidification
2. Assure that the apnea is adequately treated
3. Use of a full-face mask
4. Use of short-acting nasal decongestants
5. Use of a topical nasal steroid

Answer: Use of short-acting nasal decongestants.

Nasal congestion is a common reason for nonadherence to CPAP therapy.¹³ Pressurized air is very drying and can be very uncomfortable. Residual apneic events can even precipitate further congestion. The use of humidification with CPAP can improve patient comfort and compliance. The vast majority of patients use CPAP devices with heated humidifiers. Heated humidification has been found to increase CPAP use and improve daytime sleepiness and feelings of satisfaction and being refreshed compared with cold humidity or no humidity.¹⁴ Cold humidification improved daytime sleepiness and satisfaction, but not to the degree found with heated humidification.

Heated humidifiers are incorporated in the CPAP machine or attach to it. Heated in-line tubing helps with “rain out,” which refers to water condensation inside the tubing and mask associated with CPAP humidification.

Topical decongestants can actually worsen congestion and cause a reflex vasodilation. Topical nasal steroids can be used for nasal congestion and may be beneficial.

Tubing

The tubing from the PAP device to the facial interface can be a source of irritation to patients due to rubbing against the skin or entanglement. Products to cover the tubing to reduce irritation and avoid entanglement are available. Extra-long tubing is also available.

Cleaning

Some people find cleaning CPAP equipment daunting. Cleaning devices are available and recommended to patients looking for reassurance about how to keep their CPAP equipment clean. There are also CPAP wipes to clean the mask of oils and creams from the skin to improve the mask seal and reduce leaks.

Pressure control

Advanced modalities are available to adjust how pressure is delivered by PAP devices, including ramp, APAP, pressure relief, and BiPAP. Ramp is a feature that delivers a lower pressure at the beginning of the sleep cycle and slowly increases pressure to therapeutic

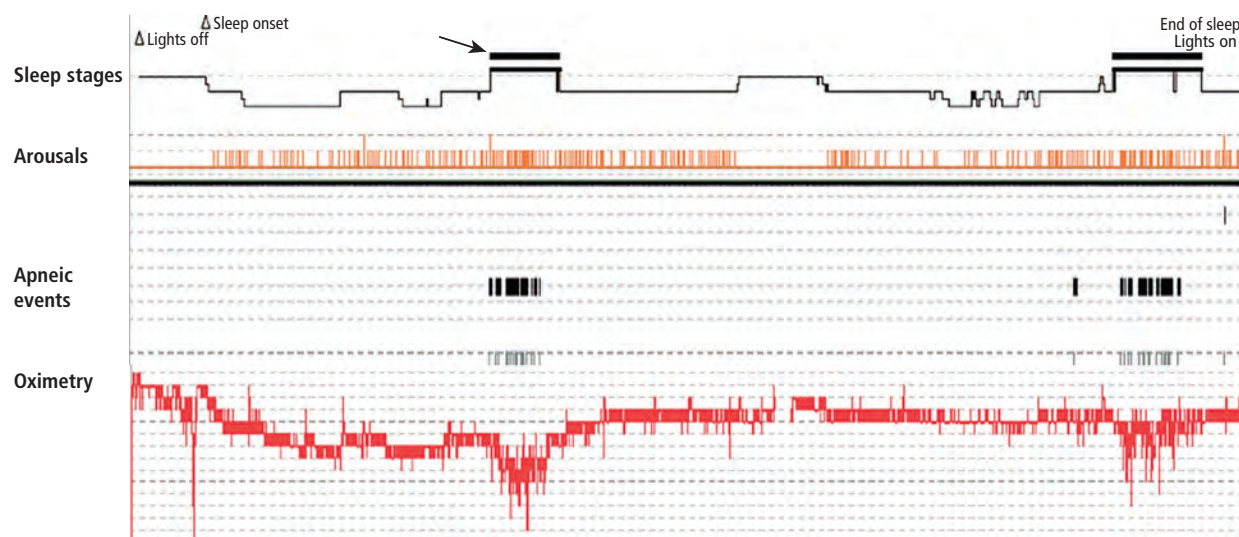


Figure 3. Sleep study overview showing rapid eye movement sleep (arrow/black bar) associated with increased arousals and apneic events and decreased oxygen levels.

tic levels. The lower pressure makes it easier for the user to fall asleep and builds to therapeutic pressure once asleep. APAP adjusts the pressure automatically when needed and reduces the pressure when not needed. Pressure relief is a feature that allows the PAP pressure to decrease at the point of expiration. BiPAP gives a distinct pressure on inspiration and a distinctively different and lower pressure at the point of expiration.

Auto-PAP

Case scenario #3

A 52-year-old woman with hypertension and mild sleep apnea has a polysomnogram with an apnea-hypopnea index of 7 events per hour that increase to 32 events per hour in rapid eye movement (REM) sleep. She is on CPAP at 5 cm of water, but complains of waking every 2 hours with a sense of panic and hot flashes.

Which of the following is the most likely cause of her symptoms?

1. An underlying anxiety disorder
2. An underlying heart condition
3. Perimenopausal symptoms
4. Undertreated REM-related apnea
5. None of the above

Answer: While all of these choices can occur, the most likely cause is undertreated REM-related apnea.

The sleep study overview for this patient is shown in **Figure 3**. During REM sleep, arousals and apneas are clustered and associated with a severe drop in oxygen

levels. While doing well on CPAP at 5 cm of water, when the patient dreams, the apnea may become worse and more pressure may be needed.

What would be the best next step in treatment for this patient?

1. Hormonal replacement therapy
2. Positional therapy in addition to CPAP
3. APAP
4. Anxiolytic medication
5. All of the above

Answer: APAP.

APAP incorporates an algorithm that detects and adjusts to airflow, pressure fluctuations, and airway resistance. The consensus from the American Academy of Sleep Medicine is that APAP is useful in the case of:

- Pressure intolerance
- REM apnea or positional apnea
- Inadequate in lab PAP titration
- Planned weight loss (bariatric surgery)
- Recurrent symptoms after long-term CPAP use.¹⁵

Pressure relief

Case scenario #4

A 45-year-old man with severe sleep apnea uses CPAP at 10 cm of water. He complains of the inability to exhale against the pressure from the device.

What would be the best next step?

1. Set the pressure relief to a maximum of 3

2. Lower the pressure of CPAP and check a download use at a lower pressure
3. BiPAP titration study in the laboratory
4. Switch to BiPAP if insurance allows
5. Change to a different mask

Answer: Set the pressure relief to a maximum of 3.

The CPAP device delivers pressure in conjunction with the patient's inspiration and expiration. At the point of expiration, there is a decrease in the pressure delivered by the device to make it easier for the user to exhale. Three selectable settings provide flow-based pressure relief with a setting of 1 for the least degree of pressure reduction and a setting of 3 for the greatest degree of pressure reduction.¹⁶

In a study of the effect of PAP with pressure relief, 93 patients were assigned to use APAP without pressure relief, CPAP with pressure relief (C-Flex), or APAP with pressure relief (A-Flex).¹⁶ At 3 and 6 months, patients using A-Flex had the best adherence to therapy.

Quality of life was also examined in this same study.¹⁶ For patients using APAP alone, there was no statistically significant difference in the Epworth Sleepiness Scale measuring daytime sleepiness or the Pittsburgh Sleep Quality Index. However, in patients using A-Flex, daytime sleepiness improved, as did sleep quality, with statistically significant improvement at 3 months.

Bilevel PAP

Case scenario #5

A 62-year-old man with severe sleep apnea uses CPAP set at 17 cm of water and pressure relief set at 3. He stopped using CPAP due to abdominal pain, extreme belching, and pressure intolerance.

What would be the appropriate next step?

1. Use of simethicone
2. Elevate the head while using PAP therapy
3. BiPAP titration study in the laboratory
4. Switching directly to BiPAP if insurance allows
5. All of the above

Answer: All of the above.

BiPAP devices provide 2 distinct pressures, one for inhalation and one for exhalation. BiPAP also has the ability to deliver a higher overall pressure. A CPAP device typically has a maximum pressure of 20 cm of water, but BiPAP has a maximum pressure of 25 cm of water on inspiration. BiPAP may be helpful in patients with air aphasia and extreme belching. If

a patient cannot tolerate CPAP because of the pressure, and if C-Flex has not alleviated the problem, BiPAP would be the next step.

The effectiveness and level of comfort of BiPAP compared with CPAP for the treatment of OSA was evaluated by the American Academy of Sleep Medicine.² The analysis of 7 randomized control trials reporting level I and II evidence found that BiPAP was as effective as CPAP in the treatment of OSA in patients with no comorbidities. For patients with OSA and comorbidities, a level III evidence study reported an increased level of comfort in patients using BiPAP.

PATIENT-CENTERED STRATEGIES TO IMPROVE ADHERENCE

Innovative strategies and approaches focusing on patient factors affecting PAP adherence include motivational interviewing, motivational enhancement, telemedicine, and desensitization techniques.

Motivational interviews and enhancement

Motivational interviewing and motivational enhancement were first used to help with alcohol abuse.¹⁷ Motivational interviewing is goal-oriented, patient-centered counseling to elicit a particular behavioral change. The goal is to explore and resolve ambivalence, increase engagement, and evoke a positive response and perspective that builds momentum and results in action.

Motivational enhancement and motivational engagement in the use of PAP therapy were evaluated in the Patient Engagement Study.¹⁸ Patients were assigned to usual care (n = 85,358) or active patient engagement (APE) (n = 42,679). Usual care involved diagnosis of apnea, initiation of CPAP, and follow-up, whereas APE included daily feedback (ie, daily scores of apnea-hypopnea index, mask leaks, hours used), positive praise messages, and personal coaching assistance. Overall adherence for patients assigned to APE was 87% compared with 70% in the usual-care group. The hours of use per night also increased for patients in the APE group.

The Best Apnea Interventions for Research trial randomized patients with or at risk of cardiovascular disease (N = 169) to CPAP alone or CPAP with motivational enhancements for 6 months.¹⁹ Motivational enhancements and interventions included brief in-person and phone interventions. An overall average difference of 99 minutes per night improvement in CPAP use was reported in the motivational enhancement group compared with CPAP alone.

TABLE 1

Home-base continuous positive airway pressure (CPAP) desensitization protocol

- | | |
|---------|---|
| Step 1: | Turn on the CPAP device, hold the mask in front of the face, and breathe calmly for a few minutes. Repeat this several times a day until comfortable, then proceed to step 2. |
| Step 2: | With the mask unattached from the CPAP device, place the mask on the face for 15 minutes at a time while doing normal daily activities. Repeat several times until comfortable, then proceed to step 3. |
| Step 3: | Use the mask attached to the CPAP device for short daytime naps. Repeat several times until comfortable, then proceed to step 4. |
| Step 4: | Use CPAP at night. |

The Motivational Interviewing Nurse Therapy study trained nurses in motivational interviewing and randomized 106 patients with newly diagnosed OSA to CPAP alone or CPAP plus motivational interviews.²⁰ Motivational interviews involved 3 sessions: 1 to build motivation prior to the CPAP titration, 1 to strengthen the commitment to achieve the prescribed time, and a booster session 1 month after CPAP setup. Adherence was found to improve at 1, 2, and 3 months in the motivational interview group; however, no difference between the 2 groups in adherence was noted at 12 months.

Telemedicine

The role of telemedicine in improving adherence with CPAP therapy was evaluated in 75 patients with moderate to severe apnea randomized to APAP alone or with phone call support from a research coordinator.²¹ Phone calls occurred 2 days after device setup, and daily monitoring of several factors was done via modem. Patients were contacted if the mask was leaking more than 30% of the night, use was less than 4 hours per night on 2 consecutive nights, the apnea-hypopnea index was greater than 10, or the average pressure needed was higher than 16 cm of water. Statistically significant improvement was found in the telemedicine group in mean adherence, minutes used per day, and mean amount of time spent with the patients.

Desensitization to PAP therapy

Case scenario #6

A 33-year-old woman with a history of anxiety and depression and a remote history of abuse as a child was

diagnosed with severe apnea. When she tries to use her CPAP, she has a sense of panic and cannot proceed.

Which of the following has NOT been shown to be beneficial in this situation?

1. Psychologist for behavioral therapy
2. Desensitization protocol
3. PAP "NAP"
4. Short-acting hypnotics
5. None of the above

Answer: Short-acting hypnotics.

The short-acting hypnotic zaleplon (Sonata) was evaluated in a 1-month study of 88 patients compared with placebo control, and no difference was found between the 2 groups in measures of adherence to therapy or symptoms.²²

A protocol for desensitization to CPAP use is helpful to assist patients in acclimating to therapy. An example of the steps in a desensitization protocol that patients can do at home is provided in **Table 1**.

PAP NAP. For some people, at-home desensitization is not enough, and a sleep lab session may be needed. A PAP NAP is a daytime study conducted in the sleep lab. Patients do not necessarily sleep, but work with a technologist with a minimal hookup to polysomnography equipment on mask desensitization, as well as biofeedback techniques. PAP NAPs are indicated for patients with claustrophobia, anxiety surrounding PAP therapy, or pressure intolerance.

A study of 99 patients with moderate to severe apnea and insomnia and concomitant psychiatric disorders resistant to CPAP evaluated adherence in a group receiving a PAP NAP (n = 39) compared with a control group (n = 60).²³ The PAP NAP group had marked improvement in completion of CPAP titration in the lab, filling the CPAP prescription, and using CPAP more than 5 days a week and more than 4 hours a night.

A new innovative concept called the Sleep Apnea Patient-Centered Outcomes Network is a collaborative group that includes patients, researchers, and clinicians.²⁴ The group addresses issues such as cost, outcomes, and value in the diagnosis and treatment of sleep apnea. A patient-centered website provides forums, education, and data collection capability for researchers (myapnea.org).

SUMMARY

PAP therapy is the gold standard for treatment of patients with moderate to severe OSA, though poor adherence to PAP therapy is a persistent problem.

Advanced features in PAP devices such as APAP and other innovative strategies like motivational enhancement and desensitization protocols and PAP NAP are being used to address poor adherence. More randomized controlled trials are needed to evaluate PAP for sleep apnea.

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Alternative interventions for obstructive sleep apnea

■ ABSTRACT

Positive airway pressure (PAP) therapy is the gold standard treatment for patients with obstructive sleep apnea (OSA) and has been shown to positively impact quality of life and cardiovascular outcomes. However, not all patients with OSA can use or tolerate PAP therapy. Alternative interventions to PAP include lifestyle measures, surgical interventions, hypoglossal nerve stimulation, oral appliance therapy, and expiratory PAP devices for OSA. While these alternative interventions may benefit patients and have demonstrated improvements in OSA and quality-of-life measures, the cardiovascular impact of these interventions is uncertain as data are limited.

■ KEY POINTS

Alternative interventions for OSA are available for patients who cannot use PAP therapy.

Lifestyle interventions that may benefit patients with OSA are weight loss, exercise, change in sleep position, alcohol avoidance, and a review of concomitant medications.

Surgical interventions for OSA target the airway obstruction and include uvulopalatopharyngoplasty, maxillomandibular advancement, and bariatric surgery. Drug-induced sleep endoscopy is increasingly used to locate airway obstruction in patients with OSA.

Alternative device therapies for OSA are the implanted hypoglossal nerve stimulation system, oral appliances, and nasal expiratory PAP therapy valves.

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The most widely used treatment for patients with obstructive sleep apnea (OSA) is positive airway pressure (PAP) therapy. Improved quality of life and cardiovascular outcomes for patients with OSA using PAP have been demonstrated. However, for some patients with OSA, PAP therapy is difficult to use or tolerate. Fortunately, there are other available treatment interventions for patients with OSA such as lifestyle interventions, surgical interventions, hypoglossal nerve stimulation (HNS), oral appliance therapy (OAT), and expiratory PAP (EPAP) devices. These alternative treatments can also improve symptoms of OSA though data regarding cardiovascular outcomes are lacking.

■ LIFESTYLE INTERVENTIONS

Weight loss

Because a higher body mass index (BMI) increases the risk for OSA, weight loss should be recommended for patients with OSA who are overweight. Much of the research evaluating the effect of weight loss on OSA has methodologic limitations such as lack of randomization or controls, potential confounding variables, and limited follow-up. A randomized controlled trial of 72 overweight patients with mild OSA (apnea-hypopnea index [AHI] of 5 to 15) compared a group assigned to a very low calorie diet and lifestyle counseling with a control group.¹ At 1 year, weight loss of 15 kg or more resulted in a statistically significant reduction in their AHI to normal, resolving their OSA. A 15 kg weight loss in this study was associated with an overall reduction in the AHI of at least 2 units.

Exercise

Exercise is also recommended for patients with OSA, and it can lessen the severity of symptoms even without weight loss. A meta-analysis of 5 randomized trials of 129 patients reported a reduction in the AHI of as much as 6 events per hour in individuals assigned to a strict exercise regimen.² The reduction in the AHI occurred despite a slight reduction in BMI (1.37 kg/m²).

Sleep position

For some patients, sleeping in the supine position may worsen their OSA, in which case avoiding the supine sleep position is recommended. A sleep study such as polysomnography should be performed to confirm the resolution of OSA in the nonsupine position.³ Products such as pillows or vibratory feedback devices can help the patient avoid sleeping on the back. The ability to monitor patient adherence to sleep position therapy alone is very limited.

Alcohol avoidance

Alcohol consumption depresses the central nervous system, promotes waking, and increases daytime sleepiness, thus exacerbating OSA. Patients with untreated OSA should avoid alcohol because it worsens the duration and frequency of obstructive respiratory events during sleep, and it can worsen the degree of oxygen desaturation that occurs during abnormal respiratory events.⁴

Concomitant medications

A review of medications in patients with OSA is warranted. Use of benzodiazepines, benzodiazepine-receptor agonists, barbiturates, and opiates in patients with OSA should be avoided especially if OSA is untreated. If these medications are necessary, careful monitoring is recommended. Medications that can cause weight gain such as some antidepressants should also be avoided.

SURGICAL INTERVENTIONS

Surgical interventions for OSA target the location of the obstruction in the upper airway. The upper airway consists of 3 regions: the palate, oropharynx, and larynx.⁵ More than 30 surgical soft-tissue and skeletal interventions for OSA are reported in the literature.⁶

Evaluating the outcomes of various surgical interventions for OSA is hindered by differences in the definition of surgical success or cure. As such, surgical interventions for OSA remain controversial. The practice parameters from 2010 reviewed surgical modifications of the upper airway for adults with OSA.^{7,8} Success is defined as a greater than 50% reduction in the AHI to fewer than 20 events per hour, whereas surgical cure is defined as a reduction in the AHI to fewer than 5 events per hour.⁷

Table 1 lists commonly used surgical procedures for OSA and reported outcomes, though the quality of evidence to evaluate these procedures is low.⁸

Uvulopalatopharyngoplasty

Uvulopalatopharyngoplasty (UPPP) is a surgical procedure that remodels the throat via removal of the

TABLE 1
OSA surgical procedures and reported outcomes

Procedure	Outcome
Nasal surgery alone	Limited efficacy; 15.8% success rate in patients with OSA with snoring and nasal congestion
Tracheostomy	100% success rate; 83% cure; morbid procedure; last resort
Laser-assisted uvulopalatoplasty	18% reduction in AHI
Radiofrequency ablation	34% reduction in AHI
Implants	25% reduction in AHI
Uvulopalatopharyngoplasty	33% reduction in AHI
Maxillomandibular advancement	87% reduction in AHI
Bariatric surgery	75% improvement in AHI

Data from references 8 and 16.

AHI = apnea-hypopnea index; OSA = obstructive sleep apnea

tonsils and the posterior surface of the soft palate and uvula and closure of the tonsillar pillars, and thus addresses retropalatal collapse. UPPP rarely achieves a surgical cure (ie, AHI < 5) and has been shown to have a 33% reduction in the AHI, with a post-operative average AHI remaining elevated at 29.8 (ie, moderate to severe OSA).⁸ In general, 50% of patients have a 50% reduction in AHI.⁹ The 4-year responder rate for UPPP is 44% to 50%.¹⁰ Factors limiting the long-term success of this procedure include weight gain, assessment of surgical candidates,¹¹ and decreased adherence to PAP therapy after the procedure.

The use of UPPP in combination with other surgical procedures has also been evaluated.⁸ The AHI in patients with OSA improved postoperatively when UPPP was done simultaneously or in a multiphase approach with radiofrequency ablation, midline glossectomy, tongue advancement, hyoid suspension, or maxillomandibular advancement, though greater improvement was noted with the multiphase approach.

Maxillomandibular advancement

Maxillomandibular advancement is a surgical procedure that moves the maxilla and mandible forward and expands the facial skeletal framework via LeFort I maxillary and sagittal split mandibular osteotomies. Maxillomandibular advancement achieves enlarge-

Drug-induced sleep endoscopy (DISE)

The success of surgical interventions for obstructive sleep apnea (OSA) depends on correctly identifying the area of airway obstruction. Use of DISE to locate the area of obstruction in patients with OSA is becoming more common. Intravenous propofol or midazolam or both is used to sedate the patient, with a sedation target of snoring onset, lack of response to verbal stimuli, and decreased response to eyelash stimulation. A flexible fiber-optic nasopharyngoscope is then used to assess the pattern of pharyngeal collapse in the airway, noting the level of obstruction (palate, oropharynx, base of tongue, hypopharynx/epiglottis), direction of collapse (anteroposterior, lateral, concentric), and degree of collapse (none, partial, complete).¹²

Research on DISE for patients with sleep-disordered breathing (N = 1,249) found the level of collapse at the palate in 81% of patients, base of tongue in 46% of patients, hypopharyngeal in 39% of patients, and multilevel in 68% of patients, most commonly of the palate and base of tongue (25%).¹³ The prevalence of complete collapse, multilevel collapse, and hypopharyngeal collapse increased with increased severity of OSA. Multilevel and complete collapse patterns were more prevalent in patients with obesity and more severe OSA.

ment of the nasopharyngeal, retropalatal, and hypopharyngeal airway. This increases tension on the pharyngeal soft tissue, which enlarges the medial-lateral and anteroposterior dimensions of the upper airway.¹⁴

A meta-analysis of 45 studies evaluated the change in the AHI after maxillomandibular advancement in 518 patients.¹⁵ Secondary outcomes were surgical success (> 50% reduction in AHI to < 20 events per hour) and surgical cure (AHI < 5). Patients with a higher preoperative AHI achieved the greatest magnitude reduction in AHI but were less likely to achieve surgical success or cure. Patients with a lower preoperative AHI had a greater likelihood of surgical success and cure.

Bariatric surgery

Bariatric surgery is increasingly used for treatment of OSA in individuals with morbid obesity. A systematic review of bariatric surgery including the roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, and biliopancreatic diversion evaluated 69 studies with 13,900 patients with OSA.¹⁶ OSA was found to be improved or eliminated in 75% of patients for all bariatric surgery procedures.

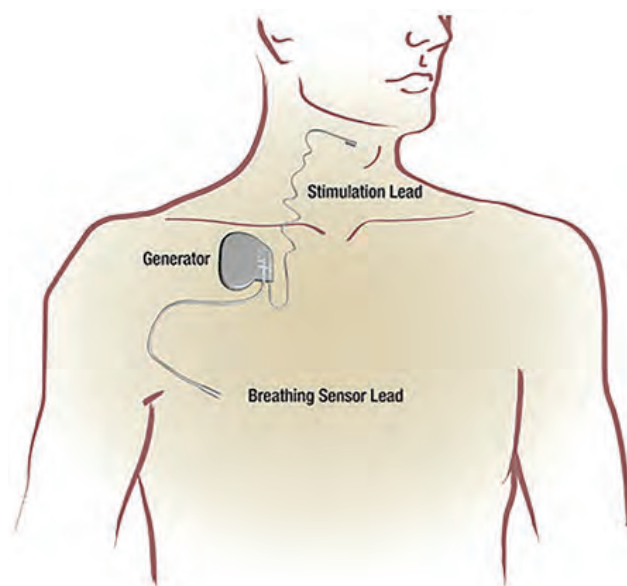


Figure 1. Hypoglossal nerve stimulation consists of an implanted pulse generator, sensing lead, and stimulation lead.

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HYPOGLOSSAL NERVE STIMULATION

HNS, or upper airway stimulation, is a new, fully implantable treatment for patients with OSA. The system consists of an implanted pulse generator (IPG), sensing lead, and stimulation lead.¹⁷ The device is implanted unilaterally via incisions under the clavicle for the IPG, on the chest for the sensing lead, and on the neck for the stimulation lead (Figure 1).

The IPG contains a battery, computer, and lead connector block. It receives information from the sensing lead, operates timing and output algorithms, conveys energy to the stimulation lead, and also serves as a return electrode for advanced stimulation configurations. The sensing lead monitors breathing during sleep and detects pressure changes in the respiratory cycle and conveys this information to the IPG. The stimulation lead encircles the medial branch of the hypoglossal nerve (cranial nerve XII) with an electrode cuff. Stimulation as generated from the IPG is delivered to key airway muscles, which are controlled by the hypoglossal nerve, primarily the genioglossus muscle responsible for tongue protrusion. The device can be turned on and off with a handheld sleep remote.

Indications and contraindications

The indications and contraindications for HNS are shown in Table 2.

TABLE 2
Hypoglossal nerve stimulation indications and contraindications

Indications	Contraindications
<ul style="list-style-type: none"> • Age greater than 22 • Apnea–hypopnea index of 15–65 events per hour (< 25% central or mixed apneic events on polysomnography) • Body mass index < 32 kg/m² • Failure of or intolerant to positive airway pressure therapy • Airway anatomy appropriate on drug-induced sleep endoscopy (no concentric collapse at retropalatal level) 	<ul style="list-style-type: none"> • > 25% central or mixed apneic events on polysomnography • Anatomic findings that compromise performance (ie, complete concentric collapse) • Pre-existing condition that compromises neurologic control of the upper airway • Inability to operate the system • Pregnancy or planning to become pregnant • Require magnetic resonance imaging (in some cases)

Airway collapse and hypoglossal nerve stimulation (HNS)

Patients with obstructive sleep apnea (OSA) due to an anteroposterior airway collapse pattern are most likely to benefit from HNS therapy; a complete concentric collapse at the retropalatal airway is an exclusion criteria for HNS therapy.^{12,17,18}

Efficacy and outcomes

Stimulation of the hypoglossal nerve results in a multilevel mechanism of action: activation and protrusion of the tongue opens the oropharyngeal airway directly but also affects the retropalatal airway by a palatoglossal coupling action.¹⁹ Sleep lab testing with polysomnography is used to titrate the voltage of HNS to achieve an open airway that resolves apneic events and normalizes airflow, breathing patterns, and oxygen saturation levels.

Approval of HNS for OSA by the US Food and Drug Administration was based on findings in the Stimulation Therapy for Apnea Reduction (STAR) trial,¹⁷ a prospective trial of 126 patients at 22 centers in the United States and Europe with the primary outcomes of AHI and oxygen desaturation index. Secondary outcomes included quality of life as measured by the Functional Outcomes of Sleep Questionnaire and Epworth Sleepiness Scale (ESS). Patient demographics included mean age 54.5, 83% men, mean BMI of 28 kg/m², and mean baseline AHI of 34 (ie, severe OSA).

Data at 5 years for 97 of the 126 patients on HNS in the STAR trial is available.²⁰ The AHI was reduced

an average of 70% to levels in the mild OSA range.^{20,21} Overall, 85% of the patients had improved quality-of-life measures after HNS implantation, with increased Functional Outcomes of Sleep Questionnaire scores and ESS scores in the normal range over time. Consistent HNS therapy demonstrated sustained benefits at 5 years. The AHI improved by 50% or to less than 20 in 75% of patients, with 44% having resolved OSA and 78% improved to mild OSA (AHI < 15). Device-related adverse events occurred in 6% (9 of 126) of patients requiring replacement or repositioning of the stimulator or leads.²⁰

Moderate to severe snoring was prevalent at baseline in the STAR trial, but over the course of 5 years, 85% of bed partners of patients on HNS reported no or soft snoring.^{17,21} Nightly use averaged 80% over 60 months based on patient reporting, with 87% reporting use at least 5 nights per week at 36 weeks.²⁰

In terms of predictors of response to HNS therapy, the oxygen desaturation index is the only characteristic that reached a level of statistical significance; patients with higher levels of oxygen desaturation tended to improve and tolerate therapy better long-term.²⁰ A randomized controlled trial of withdrawal of HNS therapy demonstrated increased AHI and oxygen desaturation index when therapy was withdrawn, followed by improvement when therapy resumed.²²

A clinical trial of 20 patients implanted with HNS after its approval in 2014 reported that the mean AHI decreased from 33 before implant to 5.1 after implant.²³ The ESS also improved from 10.3 before implant to 6 after implant. Mean adherence to device use was 7 (± 2) hours per night. The average stimulation amplitude was 1.89 (± 0.5) volts after the titration sleep study was completed. Similar

reductions in AHI were reported by Huntley et al²⁴ for patients receiving HNS implant at 2 academic centers, with no differences between the 2 cohorts in postoperative AHI.

Adverse events

The adverse events reported with HNS are related to the implant procedure or the device.²¹ Procedure-related adverse events are incision discomfort, temporary tongue weakness, headache, and mild infection of incisions. The most common device-related adverse event is discomfort from the electrical stimulation. Tongue abrasion can also occur if the tongue protrudes and rubs against a sharp tooth. Dry mouth is also commonly reported.

HNS compared with UPPP

Outcomes in patients with moderate to severe OSA matched for BMI, demographics, and preoperative AHI were evaluated comparing patients undergoing HNS (n = 20) with patients receiving UPPP (n = 20).²⁵ The AHI decreased 29% postoperatively in patients with UPPP compared with 88% in patients with HNS, 65% of which had normalization of their AHI. Surgical success was achieved in 40% of patients in the UPPP group compared with 100% in the HNS group. Greater improvement in daytime sleepiness was noted in patients in the HNS group compared with the UPPP group.

ORAL APPLIANCE THERAPY

OAT devices help protrude the mandible forward and stabilize it to maintain a more patent airway during sleep. Oral appliances can be custom-made or prefabricated. Oral appliances can be titratable or non-titratable; titration provides a mechanism to adjust mandibular protrusion analogous to PAP titration, whereas the absence of titration holds the mandible in a single position. The most effective oral appliances are custom-made and titratable.

Types of OAT devices

Custom oral appliances. Custom oral appliances are fabricated using digital or physical impressions of the patient's oral structures. Custom oral appliances are made of biocompatible materials and engage both the maxillary and mandibular arches.

Custom oral appliances are made by a qualified dentist who takes maxillary and mandibular impressions with a bite registration using the George Gauge with 40% to 50% of maximum protrusion. The appliance is fabricated in a laboratory and then fitted to the patient, who is instructed to titrate the device 0.5

Use of oral appliance therapy (OAT)

For patients with moderate to severe obstructive sleep apnea (OSA), the odds of achieving a target apnea–hypopnea index are greater with continuous positive airway pressure (PAP) or bilevel PAP compared with OAT. OAT should be reserved for patients with severe OSA who do not benefit from or are intolerant to PAP.²⁶

mm to 1 mm per week and follow-up with the dentist at 2-week intervals. Once the patient has titrated the device to the point of comfort or improved sleep quality or snoring, polysomnography should be done with the device in place and titrated to improve the AHI as much as possible. Follow-up is recommended at 6 months and annually thereafter.

Prefabricated oral appliances. Prefabricated oral appliances are of the boil-and-bite type, only partially modified to the patient's oral structures.

Tongue-retaining devices. Another type of oral appliance is a tongue-retaining device, which is designed to hold the tongue forward and can be custom-made or prefabricated.

Patient considerations for OAT

OAT is not appropriate for all patients with OSA, and the indications and contraindications for use of OAT are presented in Table 3. If OAT is indicated, several considerations may influence the type of device that is most appropriate for the patient (Table 4).

Practice recommendations

The American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine established clinical practice guidelines and recommendations for OAT in patients with OSA:

- Prescribed OAT should be done by a qualified dentist, and a custom, titratable appliance is preferred
- OAT is preferred over no therapy for adults with OSA who are intolerant to PAP or prefer alternative therapies
- A qualified dentist should provide oversight for dental-related side effects or occlusal changes
- Follow-up sleep testing should be conducted to confirm efficacy or titrate treatment
- Periodic office visits with the sleep physician and qualified dentist are recommended.²⁶

The quality of evidence for these recommendations is low, with the exception of use of OAT rather than no therapy, which is considered of moderate quality.

Effects of OAT

Anatomic and physiologic effects. With OAT in place in the mouth, the airway caliber in the lateral dimension are increased, and the airway size at the retropalatal level is increased.^{27–30} With respect to the tongue, increased genioglossus muscle activity has been reported with OAT.

Side effects. Side effects of OAT include excess salivation, dry mouth, tooth tenderness, soft-tissue changes, jaw discomfort, tooth movement, and occlusal changes such as difficulty chewing in the morning. Feelings of suffocation, vivid dreams, and anxiety have also been reported with OAT.^{31–33}

Efficacy and outcomes

Review of the data on the efficacy of OAT did not illuminate factors that predict treatment success.²⁶ Data indicate that in patients with mild OSA using OAT or PAP therapy, there was no significant difference in the percentage achieving their target AHI; however, patients with moderate to severe OSA had a statistically significant greater odds of achieving their target AHI using PAP therapy compared with OAT. Therefore, OAT should be reserved for patients with severe OSA who cannot use or are intolerant to PAP.

Moderate-grade quality of evidence was reviewed for the established OAT practice recommendations for OSA outcomes before and after use of custom, titratable OAT devices.²⁶ Use of a custom OAT device reduced the mean AHI, increased mean oxygen saturation, decreased the mean oxygen desaturation, decreased the arousal index, decreased the ESS, and increased quality of life compared with values prior to use of OAT.

With respect to adherence and discontinuation, patients using OAT had higher mean adherence and lower discontinuation because of side effects compared with patients using continuous PAP.²⁶

NASAL EPAP THERAPY

Nasal EPAP is a new treatment for OSA that consists of a mechanical valve worn in each naris at night. The valves have a low inspiratory resistance and a high expiratory resistance thus increased pressure occurs at exhalation.

Pressure at exhalation may counter the airway collapse in OSA. With the mouth closed and use

TABLE 3

Oral appliance therapy indications and contraindications

Indications	Contraindications
<ul style="list-style-type: none"> • Younger age • Lower body mass index • Smaller neck size • Lower apnea–hypopnea index • Positional obstructive sleep apnea • Retrognathia • Good ability to advance mandible 	<ul style="list-style-type: none"> • Recent or active orthodontics • Periodontally compromised dentition • Acute temporomandibular joint dysfunction • Unrealistic expectations • Uncontrolled seizure disorder • Growth potential (orthodontist supervision) • Limited ability to advance mandible

TABLE 4

Patient characteristics that influence the type of oral appliance used

Number of teeth
Bruxism
Nasal or oral breather
Occlusal scheme
Overbite and overjet
Angulation of teeth
Periodontal health status
Size of mouth
Gag reflex
Mental and physical capabilities and dexterity
Material allergy
Sleep position

of the nasal valves, the positive pressure during the normal respiratory cycle is utilized to maintain an open airway.³⁴ At the onset and throughout inspiration, the activity of the airway dilator muscles increases. At maximum expiration, right before the end of the expiratory pause, the dilator muscle stops abruptly and the airway is of its smallest caliber. The presence of the nasal valve at this point is thought to act as a pneumatic splint to the airway, and the nasal EPAP helps keep the airway patent during the next inspiratory phase.

Nasal EPAP valves are available in a 30-day starter kit. Intended for single-night use, the kit includes

valves of increasing levels of expiration resistance: low (nights 1 and 2), medium (nights 3 and 4), and normal (nights 5–30).

Outcomes of nasal EPAP therapy

A multicenter 30-day in-home trial evaluated efficacy and compliance of nasal EPAP therapy.³⁵ The AHI was reduced by 50% or more in 14 of 34 (41%) patients using nasal EPAP compared with the control group at the 30-day follow-up. The patient-reported compliance with nasal EPAP was 94%. Patients in this study had mild to moderate OSA and did not have obesity or other comorbidities such as pulmonary hypertension or cardiovascular disease.

A randomized controlled trial compared nasal EPAP with a sham device in patients with newly diagnosed or untreated OSA (N = 250) for 3 months.³⁶ A median reduction of 52% in the AHI was noted in the intention-to-treat group (N = 229) during rapid eye movement (REM) and non-REM sleep, though it was statistically significant only during REM sleep and supine sleep. At 3 months, improved OSA was maintained in 42% of the patients using nasal EPAP compared with 10% of patients using a sham device. Improvements in daytime sleepiness and adherence with 88% using EPAP the entire night were also noted.

In a 12-month study of nasal EPAP, 67% of patients (34 of 51) used nasal EPAP for the full trial duration.³⁷ Of patients using nasal EPAP for 12 months, the median AHI was reduced by 71%, the ESS improved, and adherence to full-night use was 89%.

Patient considerations for nasal EPAP

In clinical practice, nasal EPAP therapy requires nasal patency and use of a chin strap in patients with mouth leakage. Nasal EPAP may be recommended for patients who travel frequently and can go without continuous PAP or bilevel PAP for short periods of time, and for patients who do not have significant medical comorbidities.

Side effects and limitations of nasal EPAP

Reported side effects of nasal EPAP include difficulty with exhalation, nasal discomfort, dry mouth, and headache. Nasal EPAP therapy is of limited use in patients with severe OSA and severe oxygen desaturation. The efficacy of nasal EPAP beyond 12 months is unknown. Use of nasal EPAP in patients with prior upper-airway surgery and in combination with other therapies is yet to be evaluated.

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