Disorders of Sleep and Breathing

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Objectives:

1. Describe the changes in respiratory function that accompany sleep.
2. Illustrate how sleep-related changes in respiratory function lead to clinical syndromes in patients with underlying lung disease.
3. Review the mechanisms and treatment of nocturnal asthma.
4. Define the terms used to assess sleep-disordered breathing.
5. Review the mechanisms of obstructive and central sleep-disordered breathing.
6. Describe treatment strategies for sleep-disordered breathing.

Key words: central sleep apnea; obstructive sleep apnea; sleep and breathing disorders; sleep apnea; sleep-disordered breathing; sleep in asthma; sleep in COPD

Sleep is a distinct behavioral state that is characterized by the disassociation of the CNS and external environmental stimuli. The rapidly reversible nature of this behavioral state serves to separate sleep and similar behavioral states such as coma. All living mammals known to man sleep. However, the restorative functions of sleep are not clearly understood.

Sleep and its disorders have gained broad appeal as a medical issue in recent years. This is exemplified by a report of the National Commission on Sleep Disorders Research that was submitted to the US Congress and to the Secretary of the US Department of Health and Human Services in 1993. The document serves to highlight the prevalence, health, and economic impact of sleep disorders in our population. In this study, it was concluded that 40 million Americans are chronically ill with various sleep disorders and an additional 20 to 30 million experience intermittent sleep-related problems. Sleep apnea alone is the cause of excessive daytime sleepiness experienced by almost 20 million Americans. It is estimated that a little over 3 million Americans experience sleep apnea at a moderate to severe level. In one study, 87% of 156 commercial truck drivers were found to have sleep apnea and 46% of these suffered from the disorder at a moderate to severe level. In the adult population, sleep apnea is more common than asthma. The commission proposed that the 1990 direct cost of sleep disorders and sleep deprivation approached $16 billion and one estimate of the cost of sleep-related, reduced workplace productivity was $150 billion.

Disorders of sleep and breathing are not limited to sleep apnea. Asthma, COPD, and restrictive disorders of the lungs and thoracic cage are all significantly affected by the changes in respiratory physiology that accompany normal sleep. The purpose of this article is to review the normal sleep and its impact on cardiopulmonary physiology in normal humans as well as in those afflicted with illnesses of the respiratory system. Additionally, I will review the salient literature pertaining to obstructive and central sleep-disordered breathing.

Sleep in Normal Humans

General

Sleep is determined by homeostatic factors, circadian rhythms, behavior, and age. Like most biological processes, physiologic control systems can be overridden by behavior. However, it is clear that the response to nocturnal sleep loss is an increase in excessive daytime sleepiness. It is generally believed that the amount of sleep necessary is that which permits us to be wide awake, alert, and energetic throughout the day. Usually this requires about 8 h of sleep in a 24-h period and the minimum amount of sleep necessary is postulated to be about 4 h.

Circadian rhythms play a major role in the timing of sleep. Normal humans are sleepiest at two times in the 24-h cycle and these periods of somnolence are predictable (typically the post lunch dip and the nocturnal sleep episode). Some other physiologic parameters seem to follow a similar 24-h rhythm. Core body temperature is commonly used to measure one's circadian rhythm and it

oscillates in a parallel manner with sleep timing such that sleep onset often coincides with rapidly declining core body temperature. The pacemaker of the circadian rhythm for sleep is the super chiasmatic nucleus, which is located just above the optic chiasm. Melatonin appears to be an important hormonal neurotransmitter element governing circadian rhythms relating to sleep.

Sleep efficiency and continuity are both worsened with advancing age. However, the need to sleep does not diminish. Hence, in the elderly, the ability to sleep decreases but not the need for sleep, a feature that explains why many elderly Americans use napping as a means to combat the effects of a poor night's sleep.

The nocturnal pattern of sleep in a normal healthy young adult is quite predictable. One enters sleep through light nonrapid eye movement (NREM) stage 1 or 2 sleep and rapidly progresses into deep sleep (stage 3 and 4). Approximately 90 to 120 min after sleep onset, the first REM episode appears. The duration of the first REM episode is generally the shortest across the night and subsequent REM episodes tend to be progressively longer. As the night progresses, REM sleep alternates with NREM sleep in cycles of 90 to 120 min. Deep sleep (stage 3 and 4) rarely occurs after the first half of the night. The greatest proportion of REM sleep usually occurs in the early morning hours. A typical sleep hypnogram of a normal young adult can be seen in Figure 1.

Normal Respiration During Sleep

Ventilation is routinely decreased during sleep and the majority of the declines in ventilation can be explained by a reduction in tidal volume. Supraglottic resistance increases between threefold and sevenfold in sleeping humans. Further, the ventilatory set point of arterial carbon dioxide tension and the ventilatory response to hypercarbia are suppressed during sleep, particularly REM sleep, as compared with wakefulness. Similar observations hold for the effects of hypoxia. It appears as though respiration is down regulated when a normal human falls asleep. In those with normal lungs, this is of little consequence. However, in patients with diseased lungs in whom the resting oxyhemoglobin saturation is close to the steep portion of the oxygen-hemoglobin dissociation curve, normal sleep-related declines in ventilation have profound implications on nocturnal hypoxemia (Fig 2).

There is evidence to support the notion that respiratory stimuli induce arousal from sleep in relation to level of inspiratory effort that contributes to ventilatory drive. A portion of the arousal stimulus proportional to inspiratory effort may originate in the mechanoreceptors of the upper airways and respiratory pump. The level of inspiratory effort triggering arousal is an index of the sensitivity of the brain to respiratory stimuli (arousal threshold). Arousal from upper airway narrowing or occlusion involves more than chemoreceptor stimuli as predicted by arterial blood gas composition, as apneas and hypopneas too brief to produce significant alterations in the composition of arterial blood gases can lead to arousal. In upper airway occlusion during sleep, arousal occurs at apnea termination, whereas in central apnea during sleep the arousal, when it occurs, coincides with the hyperpnic phase of the respiratory cycle, a time in which inspiratory effort is greatest.

Normal Cardiac Function in Normal Sleep

As sleep progresses from light NREM 1 to 2 to NREM stage 3 to 4 and to REM sleep, parasympathetic activity seems to increase. Hence, heart rate tends to slow down by approximately 5 to 10% and there is a similar decline in cardiac output. In most, BP declines slightly during NREM sleep and is variable during REM sleep. To my knowledge, studies on changes in coronary artery flow or pulmonary artery pressures during sleep have not been reported in normal subjects.

The most frequently observed changes in the heart rhythm of normal sleeping humans are sinus bradycardia and sinus arrhythmia. A minimum heart rate of < 40 beats/min was observed during sleep in 24% of male subjects but only 8% of female subjects, suggesting that men have slower heart rates during sleep than women. Sinus pauses have been well documented to occur in up to 30% of healthy sleeping subjects. In general, the longest pauses observed were 2s. Marked sinus bradycardia and sinus pauses can be seen during the sleep of highly trained athletes with heart rates < 40 beats/min occurring in about 67% of such patients and with sinus pauses of 2 to 3 s in duration in 19 to 37% of the athletes. First degree and Wenckebach atrioventricular block may occur in normal subjects during sleep. The influence of sleep on ventricular arrhythmias and sudden cardiac deaths remains poorly defined.

Normal Gastric Function in Sleep

Basal gastric acid secretion has its daily peak between 10 PM and 2 AM and is minimal during the waking period. Twenty-four–hour gastric pH measurements subsequent to vagotomy do not exhibit this circadian fluctuation, suggesting that autonomic control of gastric acid secretion plays a critical role in the circadian oscillation of gastric pH. The observation that serum levels of the hormone gastrin remain relatively constant over a 24-h period also lends credence to this notion. Gastric acid secretion does not appear to be dependent on sleep stages.

Sleep is relatively free of episodes of gastroesophageal reflux. If reflux occurs during sleep, it is associated with prolongation of the acid clearance time. Since acid clearance from the distal esophagus requires swallowing, a conscious act, an arousal response is necessary before acid clearance from the distal esophagus can proceed. Although swallowing frequency substantially diminishes during sleep, peristalsis of the esophagus appears to be normal.

Colonic activity declines during sleep, as does the external anal sphincter response to rectal distention. Conversely, the internal anal sphincter response to transient distention remains unaltered, suggesting that the internal anal sphincter acts via a reflex to rectal distention whereas the external anal sphincter response is learned.

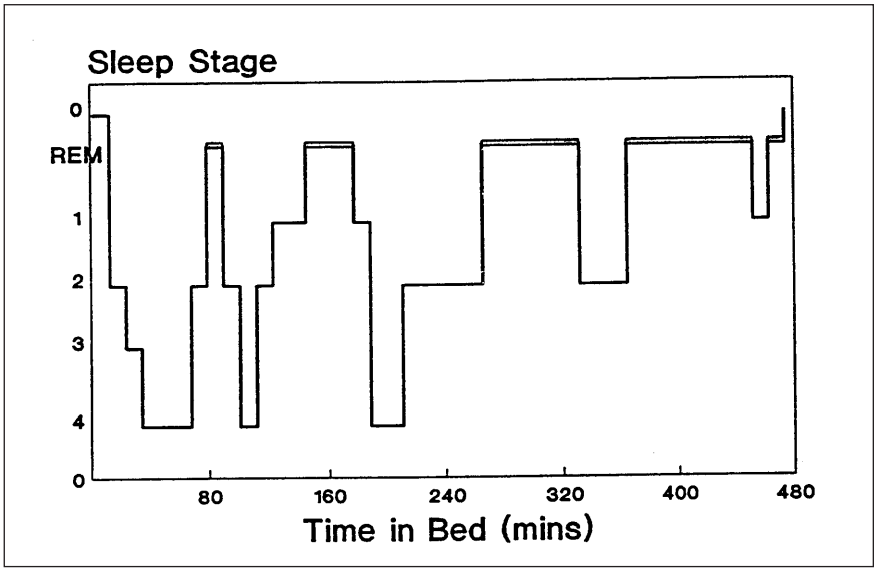


Figure 1. Typical sleep of a healthy young adult. Note that NREM stage 3 to 4 sleep (also termed Delta sleep) is limited to the first half of the time in bed and that REM sleep occurs in increasing amounts during the second half of the night.

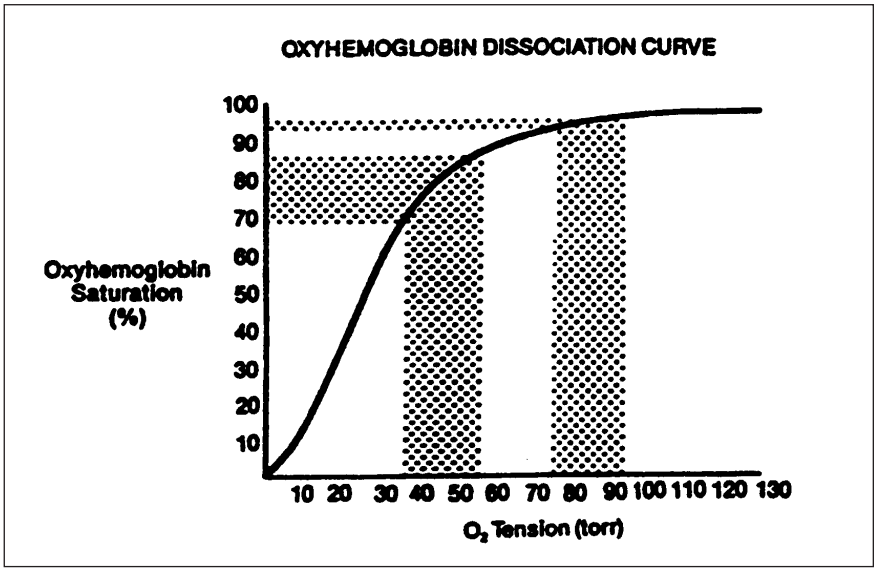


Figure 2. The oxyhemoglobin dissociation curve indicates that a 20 mm Hg decrease in Pa_{O_2} from a value above 90 mm Hg would result in a decline in arterial oxygen saturation (Sa_{O_2}) of only several percentage points. In contrast, a 20 mm Hg decrease in Pa_{O_2} from an initial value of 55 mm Hg would produce an almost identical percentage reduction in Sa_{O_2}. (Modified from Shepard JW. Cardiorespiratory changes in obstructive sleep apnea. In: Kryger M, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: WB Saunders, 1994; 657-666.)

Thermal Regulation in Sleep

Thermal regulatory responses in humans are markedly inhibited during REM sleep. For example, shivering in cool environments during sleep is confined to NREM sleep stages 1 and 2. Sweating is similarly reduced during REM sleep. Ambient temperature is an important determinant of both the quantity and quality of sleep with total sleep time being greatest in thermal neutrality. REM sleep appears to be more sensitive than NREM sleep to deviations of air temperature outside of thermal neutrality.

Sleep and Breathing in Obstructive Lung Diseases

Obstructive lung diseases are a heterogeneous group of disorders that affect the respiratory tract. Among the most common of these disorders is asthma, with cigarette related obstructive lung disease, bronchiectasis, and occupational airway diseases included in the category of obstructive lung disorders. Many patients suffering with obstructive lung disorders will have complaints about their sleep. Sleep complaints in patients with obstructive lung diseases can occur as a result of the respiratory disease itself or as a result of pharmaceutical aids used to control the airway disorder. In this section, I will outline how the alterations of breathing during sleep that occur in patients with respiratory tract illnesses can translate into poor sleep.

Consequences of Sleep-Related Alterations in Breathing for Patients With Obstructive Lung Disease

Naturally occurring sleep-related hypoventilation leads to an increase in arterial carbon dioxide tension and a decline in arterial oxygen tension. One expects a 4- to 7-mm Hg increase in arterial carbon dioxide tension and a 6- to 10-mm Hg decline in oxygen tension when a normal human transitions from wakefulness to sleep and particularly into REM sleep. In humans with resting diurnal hypoxemia and hypoventilation, sleep may induce a potentially deleterious respiratory acidemia and / or hypoxemia. Considering the combined effect of sleep-related declines in minute ventilation and functional residual capacity (FRC) on gas exchange, one appreciates that patients with advanced lung disease can develop hypoxemia during sleep in the absence of sleep-disordered breathing.

The hallmark physiologic alteration of breathing in patients with obstructive lung diseases is elevated airways resistance. In sleep, supraglottic resistance increases and this contributes to the work of breathing. In some humans with advanced obstructive lung diseases, the added work of breathing may contribute to nocturnal hypoventilation and subsequently diurnal hypoventilation. Hence, while sleep may be a period of rest for certain skeletal muscles and biological tissues, it may well be a period of stress to the inspiratory muscles of respiration. A rise in supraglottic resistance during sleep may facilitate gastroesophageal reflux, a known trigger of airway narrowing for patients with asthma and other forms of respiratory disorders.

Sleep and Breathing in Asthma

Sleep Architecture in Asthma

Forty percent of patients with asthma wake up each night with wheezing. Seventy-five percent of patients have asthma during sleep at least once weekly. As compared with normal control subjects, asthmatics have an increased time awake, decreased mean sleep time, and an increased number of awakenings. Sleep latencies and number of REM episodes are similar in asthmatics when compared with matched control subjects. Asthmatics seem to have less stage 4 sleep, which is compensated for by an increase in the amount of stage 2 and stage 1 sleep. Daytime cognitive performance and objective overnight sleep quality are worse in patients with nocturnal asthma when compared with a normal control population.

Airway Resistance During Sleep in Asthma

Several studies have demonstrated circadian changes in flow rates and airway resistance during sleep (Fig 3). Using the peak expiratory flow rate (PEFR) as a measure of airway caliber, several investigators have demonstrated nocturnal reductions in PEFR in both normal and asthmatic subjects. The lowest values for PEFR occurred in the early morning hours. Asthmatic subjects have a much lower morning PEFR, indicating more severe bronchial narrowing. The early morning decline in PEFR can be attributed to increases in lower airway resistance.

The effect of sleep stages on airway resistance in asthmatic subjects is inconsistent. In an analysis relating sleep stages and sleep time with changes in airways resistance, the latter part of sleep was a more important determinant of increased airway resistance than the sleep stage. Hence, sleep *per se* plays an important role in the alterations of airway dynamics that occur during the night.

Bronchial Hyperresponsiveness During Sleep in Asthma

The variation in airflow rates across a 24-h period observed in asthmatic subjects is related to changes in bronchial hyperresponsiveness. Potential mechanisms for enhanced bronchial hyperresponsiveness include elevated parasympathetic tone, hormonal variations, and inflammation of the airways.

In asthmatic subjects, nocturnal reductions in airway caliber can be blocked by the administration of atropine. The dose of atropine that was required to block vagally mediated bronchial narrowing was higher at 4 AM than at 4 PM.

Circadian variations in plasma cortisol and histamine concentrations such that the lowest values for cortisol occur at midnight and highest value for histamine at 4 AM have been described in normal subjects. However, normalizing nocturnal plasma histamine and cortisol concentrations does not prevent the nocturnal decline in PEFR seen in asthmatics. Mononuclear and polymorphonuclear leukocytes obtained at 4 AM from asthmatics subjects had a 33% lower β-adrenergic receptor density and an impaired response to β_2-agonist stimulation when compared with a 4 PM sample. These observations indicate that variations in hormones and mediators likely play a minor role in the worsening of airway narrowing at night seen in asthma.

Airway inflammation is the main mechanism of airway hyperresponsiveness in asthma. BAL studies of patients with nocturnal asthma show more intense nocturnal inflammatory responses in the airways. Patients with asthma but without nocturnal symptoms do not demonstrate increased inflammatory responses at night compared with patients who have nocturnal asthma. In asthmatics, the nocturnal decline in PEFR can correlate with changes in BAL counts of neutrophils and eosinophils.

Lung Volume Changes During Sleep in Asthma

A 20% and 40% decline respectively, in the FRC in normal humans and asthmatics accompanies sleep. Asthmatics with nocturnal symptoms have a

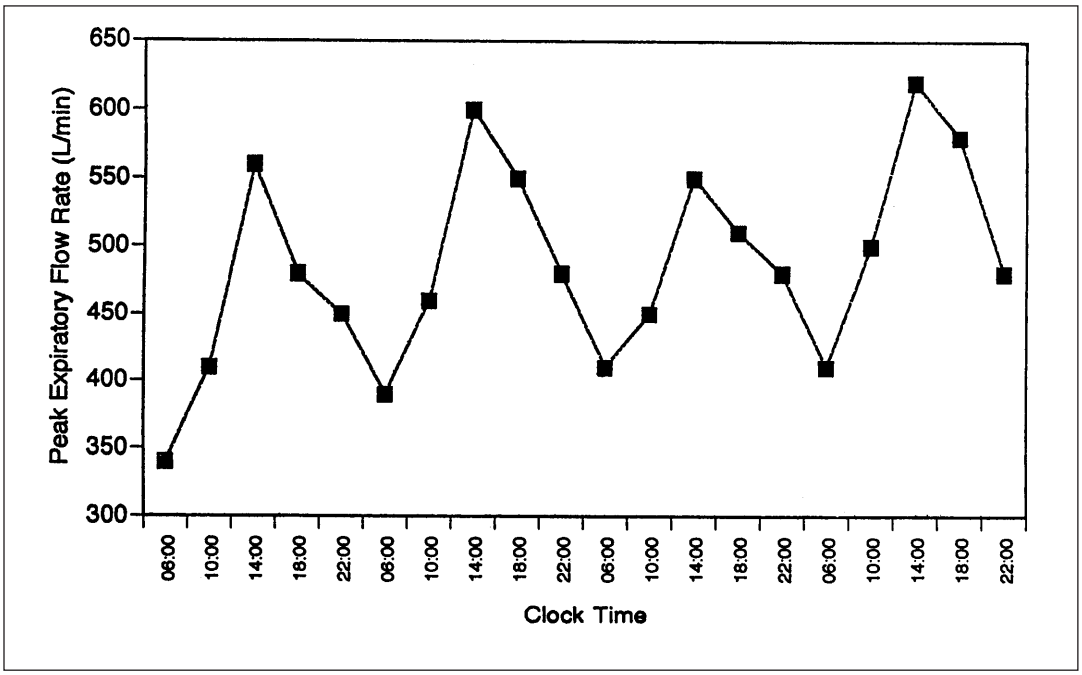


Figure 3. Diurnal variation in peak expiratory flow rate in an asthmatic patient over 4 days. (Adapted from D'Ambrosio CM, Mohsenin V. Sleep in asthma. In: Strollo PJ, Sanders MH, eds. Clinics in chest medicine. Philadelphia: WB Saunders, 1998; 19:127-137.)

relatively greater decline in the FRC. Sleep-related inhibition of inspiratory muscle tone and an increase in pulmonary capillary blood volume have been implicated as mechanisms involved in sleep-related declines of the FRC. The decline in lung volume during sleep may be important in the development of nocturnal bronchial narrowing in asthma.

Management Strategies for Nocturnal Asthma

The strategies used to control nocturnal asthma symptoms are similar to those used for diurnal symptoms. Minimizing the exposure to allergens in the sleeping environment by encasing the pillow and mattress in special covers in combination with high-efficiency filtration systems can be used to decrease allergen exposure. Long-acting β-adrenergic agonists can be used to minimize nocturnal bronchial narrowing. Although likely less effective, long-acting theophyllines, leukotriene antagonists, and inhaled anticholinergic medications may be of benefit in selected asthmatics with nocturnal symptoms. However, most patients with asthma should be treated with inhaled glucocorticosteroids and with proper dosing, inhaled glucocorticosteroids often provide sufficient protection against nocturnal asthma.

Summary: Sleep and Breathing in Asthma

The precise mechanism to explain nocturnal worsening of asthma is not fully understood. Sleep rather than clock time or circadian time may have the most important effect on nocturnal airway function. An elevation in bronchial inflammation and bronchial hyperreactivity associated with an increase in airway resistance and diminished airflow rates and FRC occur during nocturnal asthma. Nocturnal and diurnal asthma can be managed using similar strategies.

Sleep and Breathing in Patients With COPD

Humans afflicted with COPD become more hypoxemic during sleep than during wakefulness. The decline in oxygen saturation occurring during sleep is approximately double that observed during maximal exercise. Sleep-related hypoxemia in COPD is greatest during REM sleep. There is a relationship between oxygenation during wakefulness and during sleep such that patients who are hypoxemic prior to sleep exhibit the greatest amount of nocturnal hypoxia. Equations attempting to relate oxygenation during wakefulness and sleep have derived regression lines that are statistically significant, but their clinical importance is limited due to considerable variability (Fig 4).

Nocturnal Oxygen Desaturation in COPD

Some patients with COPD exhibit nocturnal declines in oxyhemoglobin saturation in the absence of diurnal hypoxia. One definition used to characterize such patients included oxyhemoglobin desaturation to $< 90\%$ for at least 5 min with a trough of $\leq 85\%$. These nocturnal oxygen desaturators (NOD) have survival rates that are worse than COPD patients with similar lobe functioned and diurnal arterial blood gas composition but without nocturnal oxyhemoglobin desaturation. Finally, NOD could not be predicted from lung function or symptoms.

Causes of Hypoxemia During Sleep in COPD

There are several factors that can be used to explain nocturnal hypoxemia in COPD. Table 1 lists some of these factors.

Hypoventilation is often implicated as a cause of nocturnal hypoxemia in COPD. Usually, nocturnal hypoxemia is associated with continued ventilation and not with apnea. Nocturnal hypoventilation is most severe during periods of REM sleep, particularly in association with frequent eye movements (phasic REM sleep). Considering that patients with COPD have larger physiologic dead space, sleep-related alterations in breathing pattern would be expected to produce a relatively greater decline in alveolar ventilation than that observed in normal humans. Sleep-related hypoventilation is considered the most important contributing factor to nocturnal hypoxemia in COPD (Fig 5).

Sleep-related declines in FRC might also contribute to nocturnal hypoxemia in COPD. However,

Table 1—*Potential Causes of Nocturnal Hypoxemia in COPD*

Sleep-related hypoventilation
Decreased lung volume
Ventilation perfusion mismatch
Sleep apnea

Figure 4. The relationship between mean Sa_{O_2} during wakefulness and nadir Sa_{O_2} during sleep in 97 patients with chronic obstructive pulmonary disease. (From Douglas NJ. Sleep in patients with chronic obstructive pulmonary disease. In: Strollo PJ, Sanders MH, eds. Clinics in chest medicine. Philadelphia: WB Saunders, 1998; 19:115-125.)

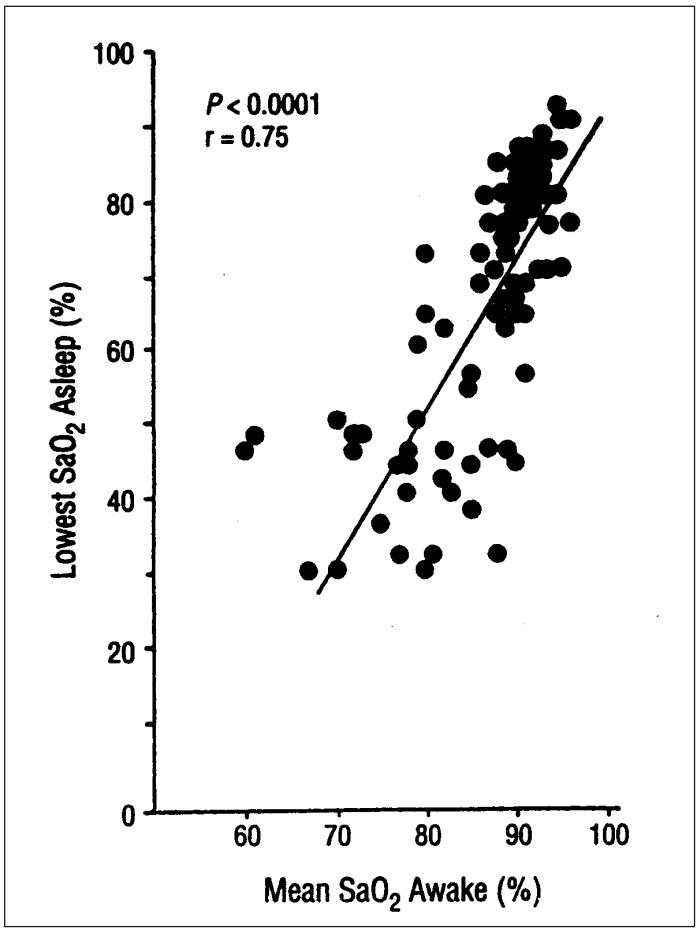
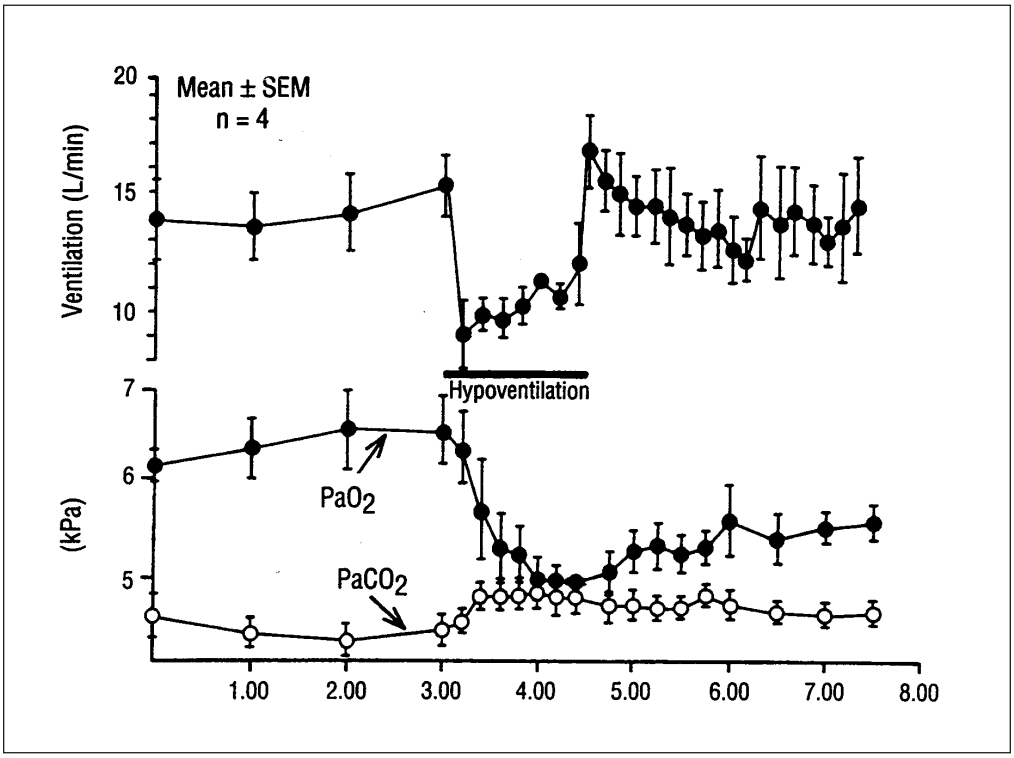


Figure 5. Effect of transient hypoventilation on arterial Pa_{O_2} and Pa_{CO_2} in normal subjects mimicking the ventilatory changes that accompany REM sleep. Note how transient hypoventilation reduces Pa_{O_2} and raises Pa_{CO_2}. (From Douglas NJ. Sleep in patients with chronic obstructive pulmonary disease. In: Strollo PJ, Sanders MH, eds. Clinics in chest medicine. Philadelphia: WB Saunders, 1998; 19:115-125.)



not all studies have shown a decline in FRC during sleep in individuals with COPD.

Current technology does not allow assessment of ventilation perfusion mismatching during sleep. However, ventilation perfusion matching during sleep-related hypoventilation is likely to worsen and may contribute to nocturnal hypoxemia.

COPD can coexist with obstructive sleep apnea (OSA). In patients with combined OSA and COPD, the pattern of nocturnal hypoxemia is characterized by cyclical brief declines in the oxyhemoglobin saturation tracing. Nocturnal hypoxemia in COPD sufferers without OSA is characterized by profound "spike-like" decline in the oxyhemoglobin saturation tracing that typically occurs during REM sleep (Fig 6).

Consequences of Sleep-Related Hypoxemia in COPD

Patients with COPD have sleep that is fragmented relative to normal control subjects. This is true when assessed by the ECG and by questionnaire. Sleep fragmentation in COPD may not translate into excessive daytime sleepiness as measured by the multiple sleep latency test (MSLT), an objective test used to determine physiologic sleepiness.

Ventricular ectopic beats are more common in the sleep of patients with COPD than in normal humans. In contrast to patients with OSA, there is no clear, direct relationship between oxygen saturation and frequency of ventricular ectopic beats during sleep in patients with COPD. In one study, supplemental oxygen during sleep failed to produce a statistically significant reduction in the frequency of cardiac ectopy. The clinical relevance

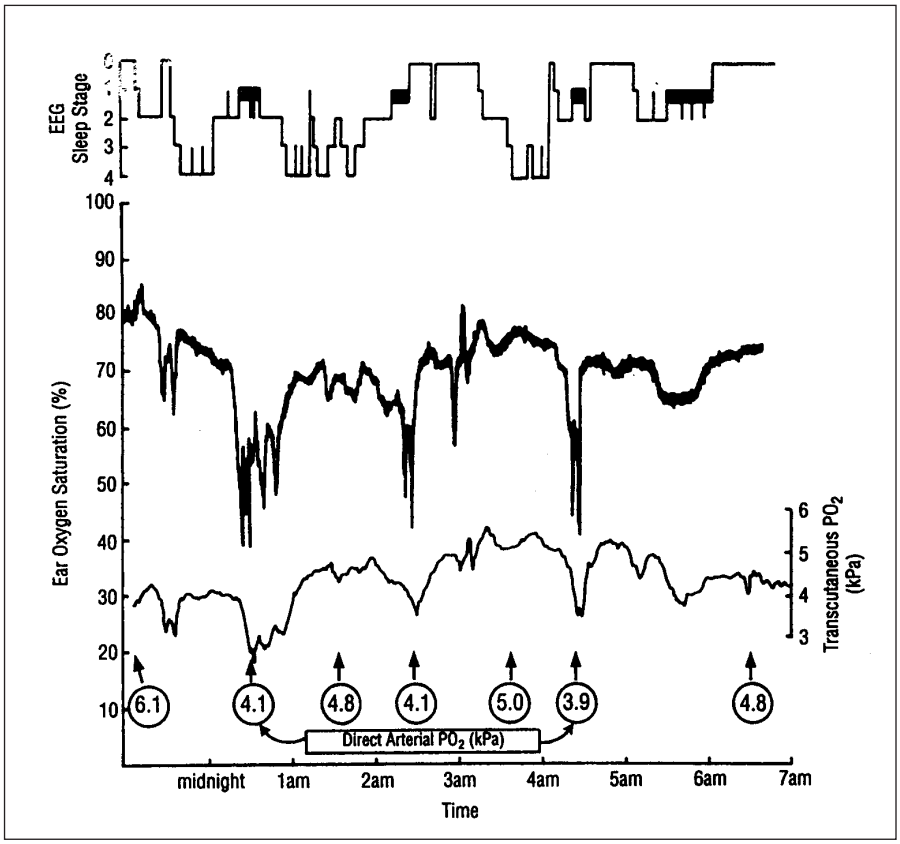


Figure 6. Overnight recordings of sleep, oximetry, and transcutaneous Pao_2. Note how marked dips in Sao_2 accompany REM sleep (the dark shaded areas in the sleep hypnogram to the right of EEG sleep stage). REM sleep related hypoventilation in this 55-year-old hypoxemic patient COPD explains the nocturnal oxygen desaturation pattern. (From Douglas NJ. Sleep in Patients with chronic obstructive pulmonary disease. In: Strollo PJ, Sanders MH, eds. Clinics in chest medicine Philadelphia: WB Saunders, 1998; 19:115-125.)

of ventricular ectopic beats in the sleep of patients with COPD has yet to be established.

COPD patients with diurnal hypercapnia and hypoxemia have greater mortality during the night than daylight. Supplemental oxygen reduces the frequency of nocturnal deaths in COPD sufferers with diurnal hypercapnia and hypoxia.

Pulmonary arterial pressure increases during sleep in COPD patients with nocturnal hypoxemia. In rats, hypoxemia for 2 h/d over a 4-week period significantly increased right ventricular mass. In COPD, REM sleep-related oxyhemoglobin desaturation might have a similar long-term effect. However, the clinical data to support this notion are currently lacking.

Indirect evidence suggests that nocturnal hypoxemia in COPD increases RBC mass. For example, nocturnal erythropoietin levels are elevated in COPD patients in whom oxygen saturation declines below 60% during sleep. COPD patients with NOD have significantly higher diurnal pulmonary arterial pressures and RBC mass than COPD patients without NOD. Supplemental oxygen used during sleep improves diurnal pulmonary artery pressure in COPD patients with NOD.

Consequences of OSA Combined With COPD

OSA patients with lung disease are more likely to develop pulmonary hypertension, right heart failure, and diurnal hypercapnia. This may be explained in part by having dual causes for nocturnal hypoventilation, accentuated elevation in total respiratory resistance, and hypoxemia.

The presence of COPD does not mask the symptoms commonly ascribed to OSA. If patients with COPD have experienced symptoms suggestive of OSA, polysomnography should be performed. Polysomnography may also be useful for patients with COPD in whom the degree of lung dysfunction does not explain the presence of polycythemia and cor pulmonale. Routine polysomnography in all patients with COPD is discouraged.

Treatment of Nocturnal Hypoxemia in COPD

Long-term, home oxygen therapy remains the only treatment shown by controlled clinical trials to prolong life in patients with diurnal hypoxemia and COPD. Several studies have shown that the use of supplemental oxygen during sleep in hypoxemic COPD patients improves sleep architecture. The role of supplemental oxygen during sleep in COPD patients with NOD remains controversial. COPD patients who develop sleep offset headaches after using supplemental oxygen during sleep should have polysomnography to exclude coexisting OSA.

Nocturnal positive pressure ventilation (NPPV) can be used to support nocturnal hypoventilation, and ameliorate sleep-related hypoxemia and hypercapnia. NPPV can improve arterial blood gas tensions in hypercapnic, hypoxemic patients with COPD. Further, sleep architecture and quality of life may be improved substantially after NPPV treatment.

Respiratory stimulants such as, almitrine, protriptyline, medroxyprogesterone, acetazolamide, and theophyllines have all been used in COPD patients for control of nocturnal hypoxemia. The data to support the use of respiratory stimulants for sleep-related hypoxemia in COPD are controversial. Nevertheless, most of these agents will improve either nocturnal or diurnal hypoxia and some may improve hypercapnia. Side effects often limit the utilization of respiratory stimulants for patients with COPD.

Negative pressure ventilation can reduce arterial carbon dioxide tension in COPD patients with hypercapnia. However, negative pressure can produce upper airway occlusion and lead to apneas. At the present time, NPPV is preferred over negative pressure ventilation.

Certain pharmaceutical agents and alcohol can worsen hypoxemia and sleep in COPD. Opiates and benzodiazepines can exacerbate hypoventilation and hypoxemia.

Summary: Sleep and Breathing in COPD

COPD may be accompanied by nocturnal hypoxemia. Sleep-related hypoxemia is best explained by normal sleep-related alveolar hypoventilation in a human with lung disease. Other factors may also play a role in this phenomenon (Table 1). Therapy is aimed at ameliorating nocturnal hypoxia usually by using supplemental oxygen during sleep. Polysomnography is not indicated in the routine management of COPD. If cor pulmonale, polycythemia, sleep offset headaches, and diurnal hypoventilation are present and out of proportion to the degree of lung dysfunction, polysomnography may be useful to exclude concomitant sleep apnea.

Sleep in Restrictive Chest Bellows Disorders

Chest Wall Deformities

Kyphoscoliosis, fibrothorax, and thoracoplasty are associated with thoracic cage deformities that can lead to chronic hypercapnic respiratory failure. Considering that kyphoscoliosis is the one chest wall deformity most frequently associated with diurnal and nocturnal respiratory complications, the section will focus attention on patients with kyphoscoliotic respiratory failure.

The restrictive physiology that accompanies kyphoscoliosis is primarily the result of a reduction in chest wall compliance. A Cobb angle (a measure of spinal curvature) in excess of 120º heralds dyspnea and impending respiratory failure. The decrease in chest wall compliance reduces tidal volume and raises dead space despite significant alteration in alveolar dead space. The resulting hypoventilation explains most of the hypoxemia that accompanies kyphoscoliotic respiratory failure. The down regulation of ventilation that accompanies normal sleep (particularly REM sleep) can lead to profound nocturnal hypercapnia and hypoxia in patients with kyphoscoliosis and diurnal respiratory failure. Patients with kyphoscoliotic respiratory failure predominantly hypoventilate during sleep and may have some central apneas during REM sleep but do not have a greater than expected frequency of upper airway obstructive apneas.

Neuromuscular Disorders

Central respiratory drive is usually well preserved in patients with neuromuscular disease. Diurnal hypoventilation is best explained by inspiratory muscle weakness. The prognosis and degree of respiratory impairment attributable to a neuromuscular disorder are dependent on the underlying disease.

Sleep in neuromuscular disorders is characterized by numerous episodes of nocturnal oxyhemoglobin desaturation, particularly during REM sleep. Sleep-related oxyhemoglobin desaturation is explained by hypoventilation and correlates with the severity of the inspiratory muscle dysfunction. During normal REM sleep, there is relative thoracic cage muscular atonia and the diaphragm provides the greatest muscular support to ventilation. Hence, in diaphragmatic dysfunction disorders, profound hypoventilation and hypoxia accompany REM sleep.

Treatment of Respiratory Dysfunction During Sleep in Restrictive Chest Bellows

The hypoxemia that develops during sleep in these patients is often a consequence of alveolar hypoventilation. Therefore, the administration of supplemental oxygen may not correct the underlying cause of nocturnal hypoxemia. Further, the use of supplemental oxygen during sleep may worsen existing hypercapnia. Many patients with thoracic cage and neuromuscular disorders have normal central respiratory drive, and respiratory stimulants such as medroxyprogesterone, theophylline, acetazolamide, and almitrine are of limited value. Nocturnal mechanical ventilation is indicated for symptoms of nocturnal hypoventilation, for hypoventilation that induces cor pulmonale, and for persistent nocturnal hypoxemia arterial oxygen saturation < 88%) despite supplemental oxygen. Invasive ventilation by tracheostomy, NPPV, and negative pressure noninvasive ventilation can be used to support breathing in patients with restrictive chest bellows disorders and nocturnal respiratory failure. In appropriately selected patients with restrictive chest bellows disorders, assisted ventilation during sleep has been shown to have a favorable effect on the need for hospitalization to treat respiratory failure, daytime well-being, objective measurements of sleep continuity, subjective ratings of sleep quality, survival, and diurnal hypoventilation and hypoxia.

Sleep-Disordered Breathing

We now have a superior understanding regarding the nature of normal breathing during sleep. The muscles of the upper airway and the thoracic muscles play a major role in maintaining adequate ventilation and oxygenation during sleep. Clinical studies have defined a group of obese and nonobese patients in whom elevated airway resistance and/or apnea/hypopnea occurred during sleep and led to cyclical hypoxemia and hypercarbia with profound disruption of sleep architecture. These individuals frequently complain of excessive daytime sleepiness and may suffer severe, adverse

physiologic consequences. Humans afflicted with sleep fragmentation due to upper airway narrowing and/or closure are termed to have OSA or obstructive sleep-disordered breathing (OSDB). Individuals with OSDB usually have a combination of obstructive apnea, hypopnea, and respiratory effort related arousals (RERA). The notion that upper airway narrowing can lead to sleep fragmentation without frank apnea, hypopnea, and hypoxia is consistent with our understanding of respiratory arousal mechanisms (Fig 7).

Individuals with upper airway narrowing leading to sleep fragmentation and excessive daytime sleepiness in the absence of detectable apnea and hypopnea (RERA) are sometimes labeled as having the upper airways resistance syndrome. For the purposes of this article, the term OSDB will be used to encompass OSA and the upper airways resistance syndrome.

Clinical investigations of sleeping humans have identified individuals in whom apnea and hypopnea occurring during sleep are not a consequence of upper airway narrowing and/or occlusion. The clinical syndrome in which symptomatic, pathologic apnea, and hypopnea occur as a consequence of alterations in central respiratory control rather than upper airway narrowing is usually termed central sleep apnea (CSA) syndrome.

Definition of Apnea/Hypopnea and RERA

Apnea in adults is defined as absence of airflow at the nose or mouth for ≥ 10 s. Hypopnea can be defined as a reduction in airflow of > 50% from the previous stable baseline lasting > 10 s. Apnea during sleep may be classified as one of three types: central, mixed, and obstructive. On respiratory tracings, central apnea is characterized by the absence of airflow and respiratory effort while obstructive apnea is characterized by persistent respiratory effort during the apneic period (Figs 8 and 9). Apneas that commence with a central component and are followed by an obstructive portion are termed mixed apnea. In the same night, a patient may experience all the patterns of apnea; most often there is a preponderance of obstructive. Mixed and obstructive apnea/hypopnea often have a common pathogenesis and treatment so that they are usually discussed collectively.

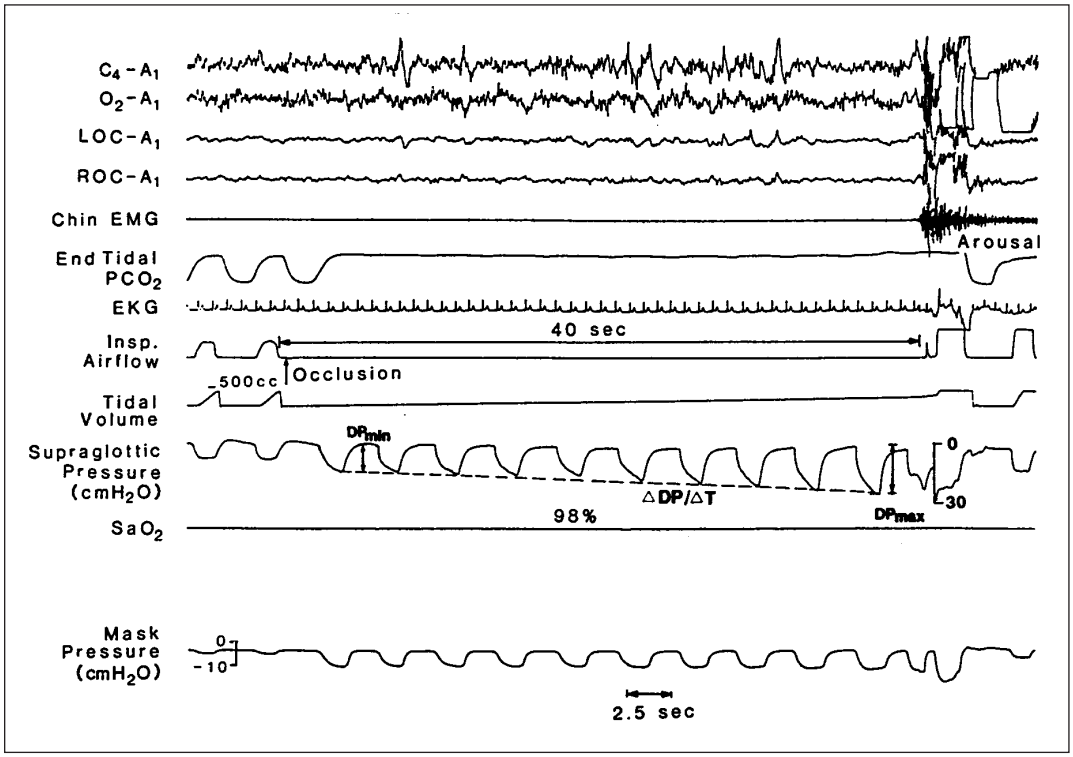


Figure 7. Mask occlusion in normal subjects during NREM sleep under hyperoxia conditions. The supraglottic pressure deflections (DP) increased until arousal. The initial (minimum) pressure deflections (DPmin), the maximum deflection prior to arousal (DPmax), and a mean rate of increase in the pressure deflection with time (ΔDP/ΔT) reflect initial respiratory center output, arousal threshold, and respiratory center sensitivity, respectively. (From Sleep 1997; 20:654-675.)

Another form of abnormal breathing during sleep occurs when upper airway narrowing raises respiratory resistance sufficiently to trigger arousal from sleep (RERA). On respiratory tracings, RERA is characterized by increasing respiratory effort with sustained breath volume and oxyhemoglobin saturation terminating in arousal with subsequent normalization of respiratory effort. A respiratory pattern characterized by inspiratory flow limitation without apnea and hypopnea and terminating with simultaneous arousal and relief of inspiratory flow limitation has sometimes been used to herald RERA (Fig 10).

The presence of apnea during sleep may not be pathologic. In normal young adults, up to five apneas per hour of sleep is considered physiologic. However, an apnea frequency > 20 / h of sleep is associated with increased mortality. The number of physiologic apneas increases with age and it is not uncommon to see 8 to 12 apneas per hour of sleep in asymptomatic elderly men. In general, physiologic apneas are brief and not associated with significant oxyhemoglobin desaturation (<85%).

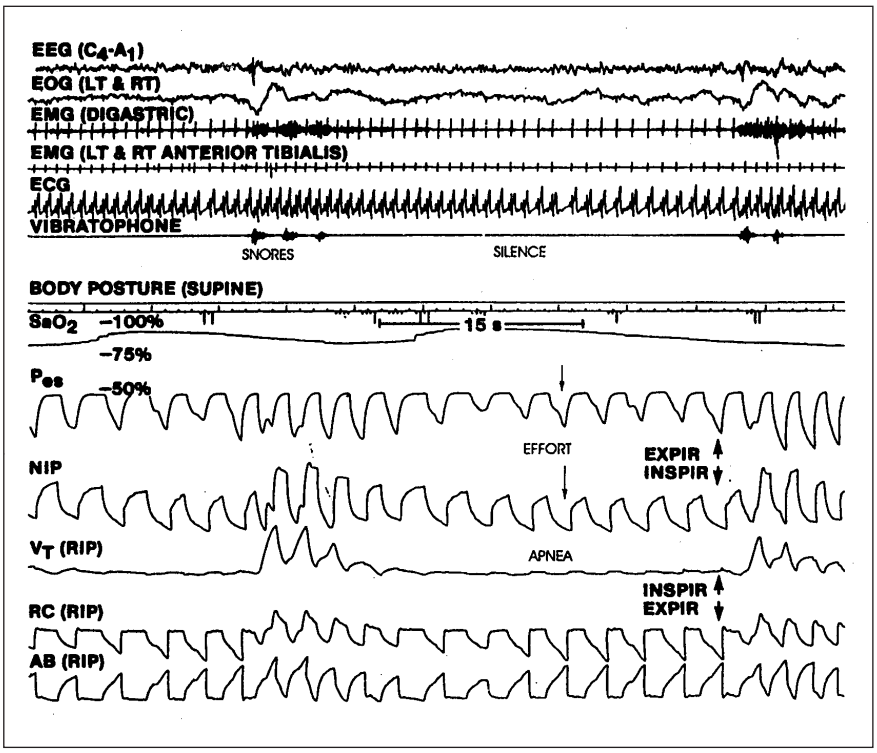
The Pathophysiology of OSDB

Upper Airway Anatomy in OSDB: The upper airways begin at the nasal and oral orifices and terminate at the glottic aperture. The site of airway occlusion in OSA can occur at single and / or multiple sites between the soft palate and the epiglottis. Narrowing of the upper airway most commonly occurs at the soft palate, but there may be considerable variability. In some patients with OSA, upper airway occlusion occurs at more than one site and the site of airway collapse can move caudally when one transitions from NREM to REM sleep.

The Upper Airway as a Collapsible Tube: The "balance of pressure" theory considers the upper airway as a collapsible tube where upper airway transmural pressure (Ptm) is defined as the difference between luminal (Pl) and tissue pressure (Pti) and where Pti may not always equal atmospheric pressure (Fig 11). Accordingly, increases in Ptm serve to augment the cross-sectional area of the passive upper airway as predicted by a Ptm-area relationship. In the absence of airflow, Pl is equal to atmospheric pressure. Inspiration is accompanied by a reduction in Pl owing to dissipation of energy used to overcome upstream resistance and because of acceleration of gas flowing through a narrowed airway. Pti is influenced by forces acting on the outside surface of the pharyngeal walls such as neck compression, excessive submandibular fat, and macroglossia, all of which may potentially augment Pti. The relationship between Ptm and upper airway cross-sectional area is curvilinear and as such its slope (dA / dPtm) or compliance varies with luminal aperture (Fig 11). A similar relationship between pressure and area was demonstrated in the hypotonic pharynx of humans with OSA. Activation of upper airway dilating muscles increases luminal area for a fixed Pl and Pti thereby shifting the Ptm- cross-sectional area curve to the left with the maximal effect seen near the upper airway closing pressure (Fig 11). Sleep-induced alterations of upper airway muscular forces and declines in lung volume serve to enhance upper airway collapsibility and facilitate inspiratory flow limitation and periodic obstructive apnea and hypopnea.

Neuromuscular Influences on Upper Airway Function: We now recognize that pharyngeal patency is attributable in part to behavioral influences. Flow of air into the lungs requires coordinated activation of upper airway, thoracic, and diaphragmatic muscles. Analysis of upper airway and diaphragmatic electromyogram (EMG) activity during inspiration demonstrates upper airway activation that precedes diaphragmatic activity by 0.2 s. Contraction of upper airway dilating muscles before inspiratory airflow serves to stiffen and increase the aperture of the upper airway and prepare it for the suction forces that accompany inspiration. Submental electrical stimulation of upper airway muscles has been shown to abbreviate and reduce in number obstructive apneas and hypopneas in humans with OSA, but the effect appeared to be mediated through arousal from sleep. The precise contribution to upper airway patency afforded by the contraction or relaxation of an isolated upper airway muscle is currently not known. Contraction of upper airway dilating muscles shifts the relationship of Ptm and cross-sectional area to the left (Fig 11); however, it is not possible to estimate the magnitude of change in dA / dPtm. During sleep, tonic and phasic respiratory activity of the upper airway muscles is somewhat reduced and dA / dPtm increases, in contrast to diaphragmatic activity that appears to be preserved in normal sleeping humans and in those with OSA. The net result favors pharyngeal narrowing during sleep. As upper airway aperture declines, there is a further loss in Pl owing

Figure 8. Typical obstructive apnea showing abdominal paradox and persistent respiratory effort throughout the apnea as measured by esophageal balloon (Pes) and similar oscillations from neck inductive plethysmography (NIP). VT, RC, and AB denote tidal volume, rib cage, and abdominal contributions to breathing recorded by respiratory inductive plethysmography (RIP), respectively. EOG = electro-oculogram; EMG = electromyogram; Expir = expiration; Inspir = inspiration. (From Chediak AD, Krieger BP. Obstructive sleep apnea syndrome. In: Bone RC, ed. Pulmonary and critical care medicine. Chicago: Mosby, 1994; Q2:1-28.)



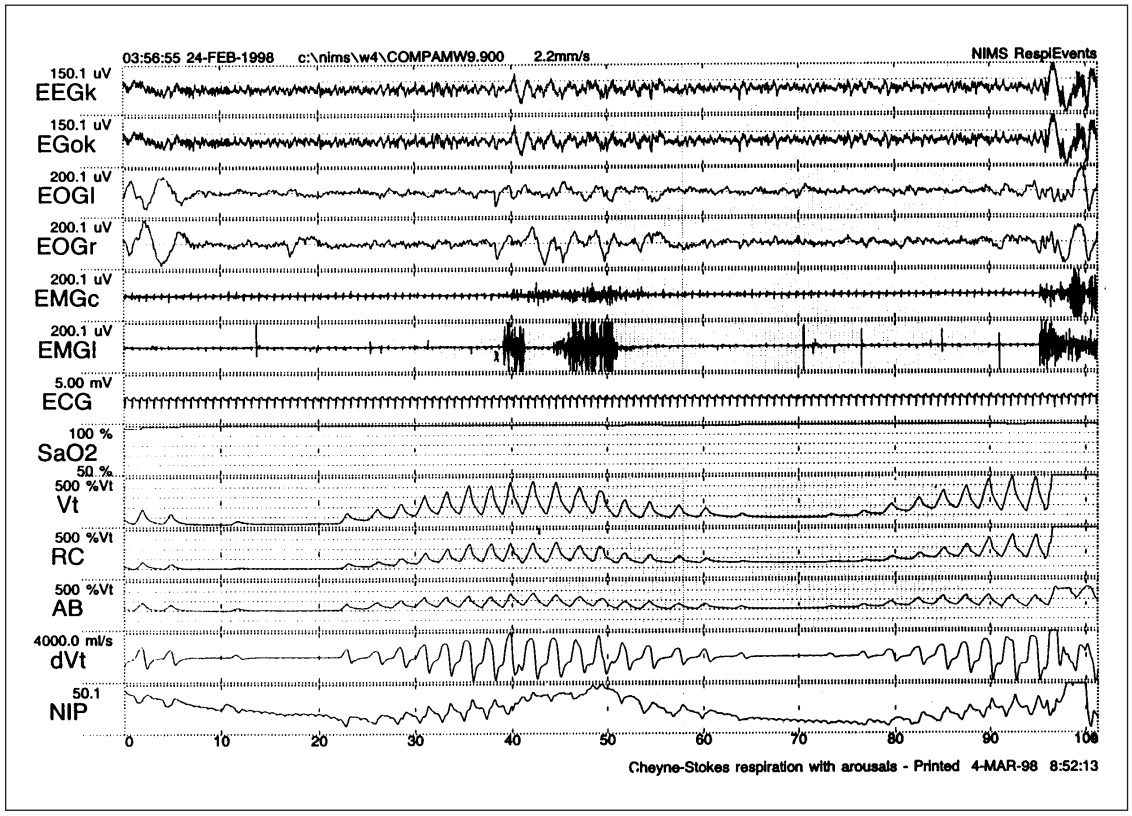


Figure 9. Typical Cheyne-Stokes respiration-central sleep apnea demonstrating the absence of respiratory effort during apnea. Also notice that arousals, as depicted by increased activity in the EMGl lead, occur during the hyperpnic phase of the Cheyne-Stokes respiratory cycle. EEGK, EGok = central and occipital electroencephalogram, respectively; EOGl and EOGr = left and right electro-oculogram, respectively; EMGc = digastric electromyogram, EMGl = combined right and left anterior tibialis electromyogram; Sa_{O_2} = oxyhemoglobin saturation; V_T, RC, and AB denote tidal volume, rib cage, and abdominal contributions to breathing as detected by respiratory inductive plethysmography, respectively; dVt = flow derived from the mathematical derivative of the volume-time tracing; NIP = neck inductive plethysmograph a measure of respiratory effort. The tracing is provided from the Mount Sinai Medical Center sleep laboratory courtesy of A.D. Chediak and M.H. Keil.

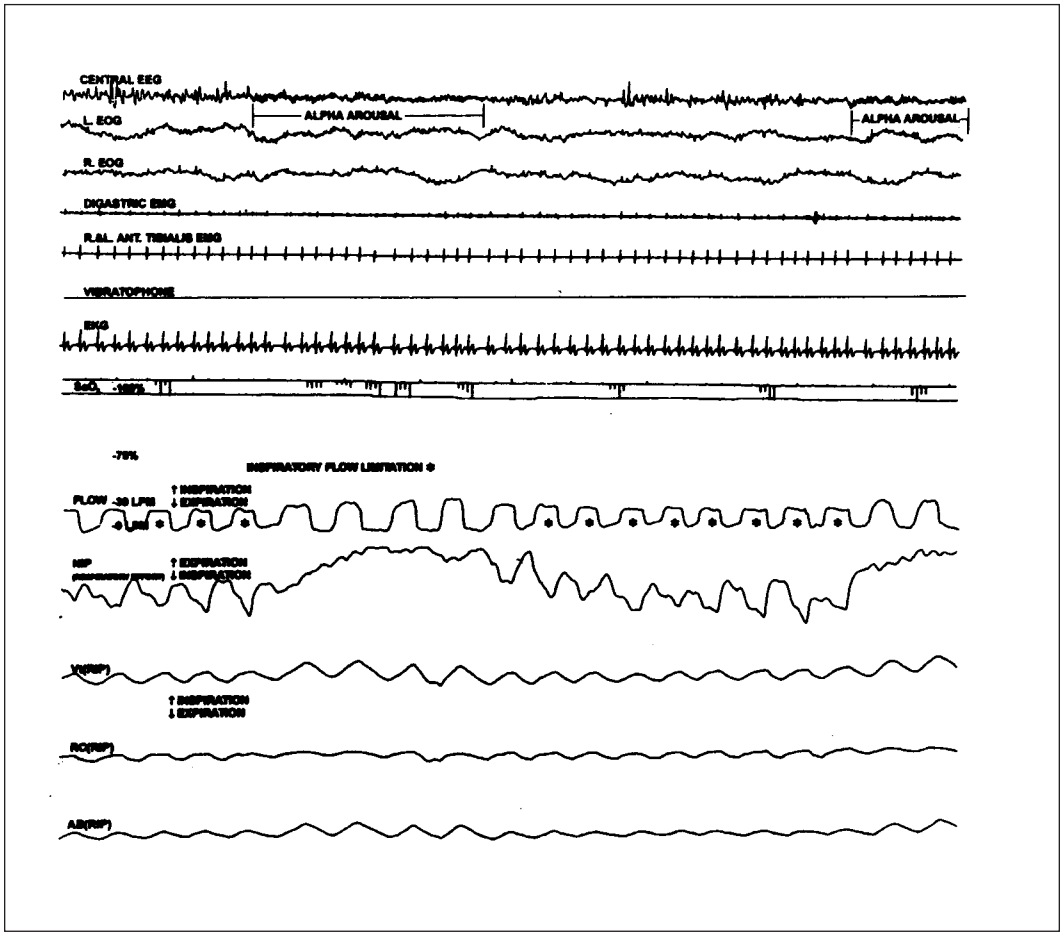


Figure 10. Typical appearance of a respiratory effort related arousal on polysomnography. Note inspiratory flow limitation on the breaths denoted by the asterisk. Inspiratory flow limitation is accompanied by increasing respiratory effort as depicted in the neck inductive plethysmograph (NIP) and is terminated by alpha EEG arousal. Note the relative stability in tidal volume (V_T) and Sa_{O_2} throughout flow-limited breathing and subsequent arousal. In this example, flow-limited breathing was not associated with upper airway vibration as measured in the vibratophone. The tracing is provided from the Mount Sinai Medical Center sleep laboratory courtesy of A.D. Chediak and M.H. Keil.

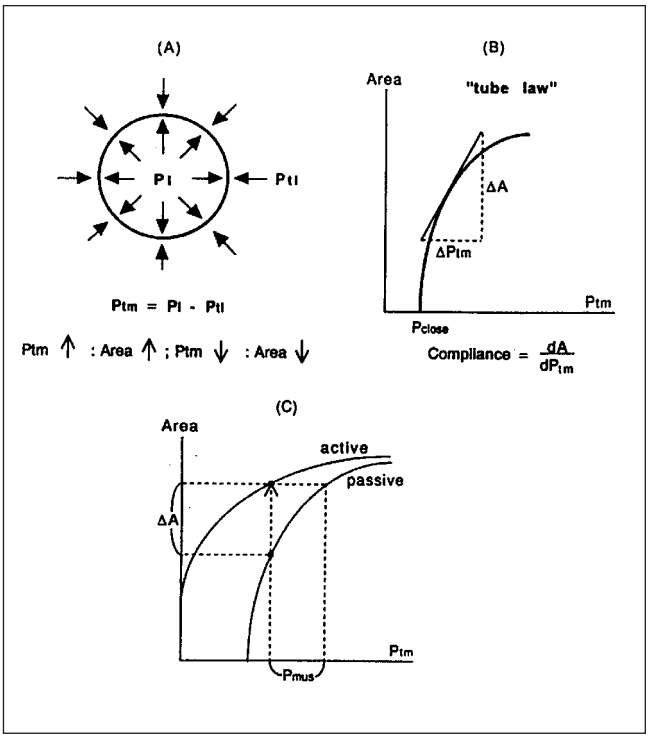


Figure 11. The concept of transmural pressure (Ptm) of the pharynx is illustrated. In panel A, Ptm is defined as intraluminal pressure (Pl) minus surrounding tissue pressure (Pti). Panel B shows how an increase in Ptm results in an increase in the cross-sectional area of the pharynx. The slope of the area-Ptm relationship represents the compliance of the pharynx. Panel C depicts the changes in pharyngeal compliance that accompany transition into sleep (from active to passive). (From Isono S, Remmers JE. In: Kryger M, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: WB Saunders, 1994; 642-656.)

to the conversion of potential energy to kinetic energy as the velocity of gas increases when it passes through the narrow airway segment. The resultant loss in muscular forces and Pl eventually leads to inspiratory flow limitation and / or complete upper airway occlusion. Snoring or other injury to the upper airway associated with repetitive airway closure may lead to a local neuropathy and facilitate the development of OSDB. Additionally, sleep deprivation *per se* can suppress upper airway motor function during sleep. In general, pharmacologic agents that inhibit CNS activity tend to depress motor output to upper airway muscles such as the genioglossus. Topical anesthetics applied to the upper airway can increase the frequency of sleep-related obstructive apneas and hypopneas perhaps by a reflex mechanism. A list of commonly used pharmacologic agents that are known to facilitate upper airway occlusion during sleep can be seen in Table 2. The notion that behaviorally dependent neuromuscular mechanisms play an important role in OSDB is exemplified by the observation that upper airway occlusion in OSDB occurs solely during sleep. Patients with OSDB exhibit greater than normal sleep-related depression of upper airway neuromuscular activity. The observation that exaggerated depression of upper airway function during sleep in OSDB normalizes after treatment mitigate against a primary neural disorder.

Anatomic Factors: The notion that anatomic factors influence upper airway patency in OSDB is supported by the observation that gains and losses of body weight tend to worsen and improve the frequency of obstructive apneas and hypopneas during sleep, respectively. Weight gain may further compromise upper airway patency by increasing the weight and bulk of the tissues surrounding the pharyngeal lumen and elevating Pti. The upper airway area enclosed by the mandible ramus as well as the volume of adipose and muscular tissue surrounding the upper airway of patients with OSDB correlates with the frequency of apneas / hypopneas. The cumulative effects of increasing body weight on upper airway function would serve to facilitate closure of the passive airway either by elevating Pti or altering dA / dPtm.

Upper airway collapsing pressure during sleep in normal subjects can be up to -15 cm H_2O. In OSDB, closing pressures during sleep are usually < -3 cm H_2O pressure and often positive. Investigators have explained the differences in upper airway collapsing pressure during sleep in OSDB on alterations of upper airway structure. The pressure / area relationship of the pharynx (specific pharyngeal compliance) measured during wakefulness is greater in OSDB subjects when compared with control subjects.

Abnormalities of upper airway structures are commonly found in OSDB subjects. Such abnormalities can be functionally demonstrated by standard and tidal breath flow volume curves that may show rapid flow oscillations, variable extrathoracic obstruction, and in the case of tidal breath curves, a posture related change in the terminal portion of the expiratory flow volume curve in patients with OSDB. Cine CT of the upper airway used to record the effect of respiration on upper airway caliber in normal humans, mild snorers and in OSDB subjects demonstrated smaller upper airway size and a greater tendency to airway closure at the end of expiration in OSDB. These observations implicate structural abnormalities as the primary defect in OSDB. Patients with OSDB have supranormal activation of upper airway dilating muscles while awake and one would predict even greater differences in waking upper airway size after controlling for muscular factors.

Cephalometric studies have demonstrated cranial facial abnormalities in most patients with OSDB. The length of the soft palate and the position of the hyoid bone, together with the size of the posterior airway space are of particular interest in OSDB. Using magnetic resonance imaging, Shelton and coworkers demonstrated a significant correlation between the frequency of apneas and hypopneas during sleep and the area enclosed by the mandible ramus and the distance between the teeth and the posterior mandible ramus. Additionally, subjects with OSDB had a collection of adipose tissue adjacent to the upper airway. The volume of pharyngeal adipose tissue correlated with the frequency of apneas and hypopneas and weight loss related improvement in OSDB was accompanied by a reduction in the volume of adipose

Table 2—*Commonly Prescribed Agents That Can Worsen OSDB*

Opiates
Benzodiazepines
Alcohol
Oxygen

tissue adjacent to the upper airway. Several other techniques have demonstrated smaller pharyngeal areas in patients with OSDB than in non-weight matched control subjects.

Superglottic resistance during wakefulness is greater in patients with OSDB than in normal control subjects. Advanced age has a significant correlation with increasing pharyngeal resistance in men but not in women. Sleep-disordered breathing is more common in groups in which pharyngeal resistance is reportedly elevated such as the obese, the elderly, and in men.

In summary, the existing evidence supports the notion that structural abnormalities of the upper airways are present in patients with OSDB and that alterations of upper airway anatomy play a major role in the pathogenesis of upper airway occlusion during sleep.

Effect of Gender: While OSDB is more prevalent in men, healthy women have smaller pharyngeal areas than healthy men during wakefulness. However, men were shown to have a larger change in pharyngeal area relative to lung volume, a factor consistent with the greater incidence of OSDB in men. A comparison of clinical features of women and men with OSDB who had been matched for the frequency of sleep apneas and hypopneas and craniofacial structure by cephalograms found that the women with OSDB were much more obese than their male counterparts suggesting superior protection of upper airway patency during sleep by women. In awake healthy women, there is elevated genioglossal activity with quiet breathing and in response to inspiratory loading as compared with healthy awake men. It appears that the female upper airway may be more stable and better suited to withstand collapsing forces that accompany sleep.

Posture and Gravitational Influences: Patients with OSDB often have more apneas and hypopneas when recumbent than while in other postures. Using a diaphragmatic EMG, Takasaki and colleagues estimated the effect of gravity on upper airway resistance in subjects aboard a short-term space mission and concluded that gravity played a greater role than upper airway muscle atonia in sleep-related elevation of upper airway resistance.

Surface Adhesive Forces: Upper airway closure is accompanied by surface adhesive forces between the opposed upper airway walls. Surface adhesive forces must be overcome to reopen the collapsed upper airway. The observation that the pressure required to reestablish airway patency exceeds closing pressure may be partially explained by surface adhesive forces.

Vascular Factors: Pharyngeal vasomotion may modify in upper airway mechanics and thereby influence obstructive breathing during sleep. Measurement of upper airway perfusion in sleeping humans is technically difficult and has not been reported to my knowledge. However, in awake normal humans, pharmacologic agents shown to act as upper airway vasodilators and vasoconstrictors failed to alter the static pressure volume relationship of the upper airway. Nevertheless, dynamic upper airway properties can be influenced by topically applied vasoconstrictors.

Circadian Rhythms of Hormones and Cytokines: Investigations into circadian cytokine release in OSDB patients demonstrate significant disturbance in the secretion of tumor necrosis factor-α (TNF). Circadian variations in interleukin-1, interleukin-6, α-interferon, and the hormones cortisol and melatonin did not differ between control subjects and subjects with OSDB. Three months of therapy with nasal continuous positive airway pressure failed to normalize TNF rhythms suggesting that the cytokine TNF may be involved in the pathophysiology of OSDB.

Nasal Influences on Upper Airway Patency: Nasal airflow may have a stimulant effect on respiration during sleep and nasal resistance increases while flow decreases progressively during NREM sleep. Nasal abnormalities such as septal deviation are known to induce or exacerbate sleep-disordered breathing. Surgical correction of nasal obstruction has been demonstrated to improve sleep-disordered breathing in selected cases. To overcome upstream nasal obstruction, energy is dissipated resulting in a decline of Pl that serves to promote pharyngeal closure. Nasal airway resistance is higher than oral airway resistance in normal awake humans. Observations in sleeping humans suggest that oral airway resistance may exceed nasal airway resistance, possibly because the nasal airway is rigid and hence its caliber is not dependent on neuromuscular factors.

Pathophysiology of OSDB Summary: The cycle of events detailed in Figure 12 illustrates the potential relationship between behavioral state and the collapsible human upper airway. The currently available data support the notion that the periodic

airway occlusion occurring in the sleep of patients with OSDB can be explained by alterations in upper airway anatomy that facilitate upper airway occlusion during sleep and that perturbations of upper airway neuromuscular control may participate in sleep-mediated closure of the upper airway. The combined effect of abnormal structure and function in the upper airway of subjects with OSDB serves to alter the balance of forces affecting the compliant upper airway such that collapsing forces exceed distending forces.

Epidemiology of OSDB

Almost every report describing large numbers of patients with OSDB have demonstrated a strong male predominance. The male to female ratio has been reported between 4 and 20 to 1. OSDB in premenopausal women, even when obese, is uncommon. In a study of 602 randomly selected men and women between the ages of 30 to 60 years, 2% of the women and 4% of men met a minimal criteria for OSDB (more than five apneas/hypopneas per hour of sleep and daytime sleepiness). OSDB does not appear to occur as a consequence of normal pregnancy. Some investigators have demonstrated an increased number of "physiologic" apneas in normal men vs women, a finding that has not been universally reproduced. However, the prevalence of subjective hypersomnia seems to be higher in women even though they underreport snoring, snorting, and gasping during sleep. The administration of androgens to hypogonadal men leads to an increase in the number of apneas during sleep and may lead to frank OSDB. Progesterone, a known ventilatory stimulant, has been of little benefit to men with OSDB. Therefore, hormonal influence on breathing during sleep cannot fully account for the male predominance observed in OSDB.

OSDB is commonly seen in the younger population. In several large studies of patients with OSDB, the mean age of the individuals was between 40 and 50 years. OSDB has also been described in children and adolescents. Nevertheless, healthy older subjects are commonly noted to have a higher frequency of sleep-disordered breathing events, with one publication reporting an incidence of 62% and 60% in older male and female patients, respectively. Longitudinal worsening in the frequency of sleep-disordered breathing events has been demonstrated by a doubling in sleep-disordered breathing (10 vs 21 events per hour of sleep) after an average follow-up of 16 months and without a significant alteration in body weight. Although most patients with OSDB are overweight, not all are obese.

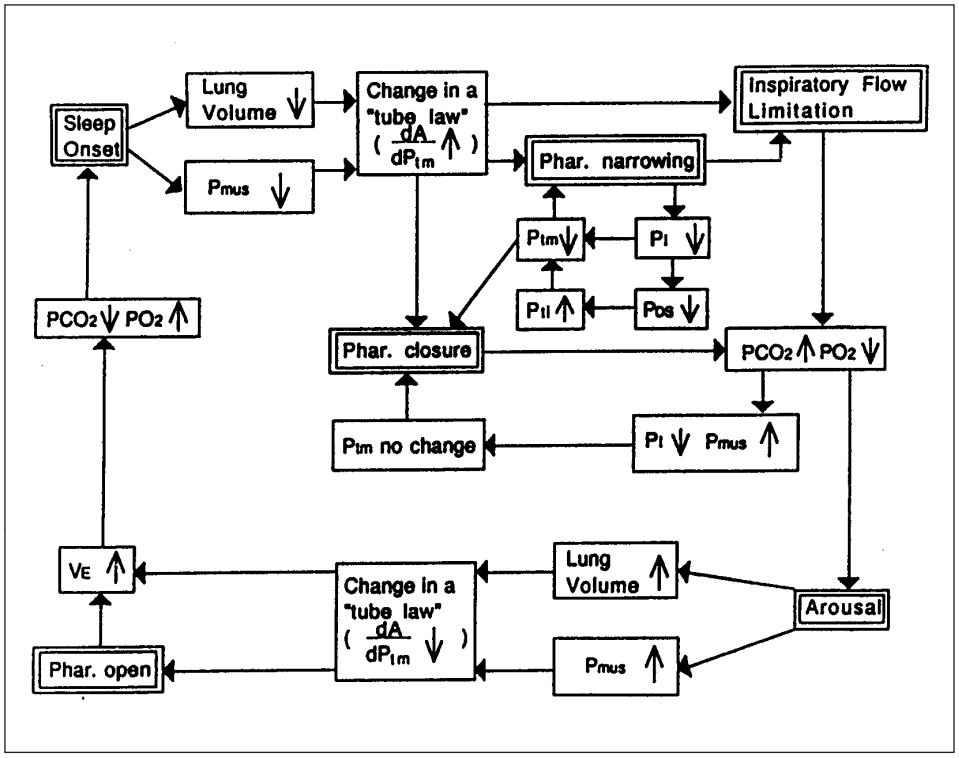


Figure 12. Schematic diagram indicating the sequential events leading to the periodic ventilation-apnea cycle in OSA in terms of changing collapsibility and transmural pressure of the pharynx. Pmus = muscle pressure; dA/dPtm = compliance of the pharynx; Pi = intraluminal pressure; Pti = surrounding tissue pressure; PDS = downstream pressure; VE = minute ventilation. (From Isono S, Remmers JE. In: Kryger M, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: WB Saunders, 1994; 642-656.)

The true incidence of the OSDB in the general population is open to speculation, partly because of controversies concerning appropriate monitoring techniques and the definition of significant OSDB. If one includes only individuals with obvious and pathologic hypersomnolence and cardiopulmonary sequelae of OSDB, then the incidence in the adult population approaches 1to 4%. It is generally believed that approximately 5% of adult men suffer from OSDB with physiologic sequelae or hypersomnolence.

Clinical Features

Symptoms: The symptoms most often used to characterize OSDB can be grouped into breathing disturbances occurring during sleep, sleep difficulties, daytime sleepiness, mood effects, and cardiopulmonary sequela. Table 3 lists the distribution of some symptoms obtained by sleep questionnaire in subjects with diagnosed OSDB. Reported snoring has a relatively high sensitivity and reported apnea has a high specificity in OSDB.

Risk Factors: Male gender and obesity (particularly central obesity) are the strongest risk factors for the development of OSDB. Additional risk factors include arterial hypertension, advancing age, craniofacial anatomic abnormalities that reduce upper airway size, familial factors, cigarette smoking, alcohol consumption, the use of sedatives, snoring, and sleep deprivation.

Effects on Daytime Alertness: The severe fragmentation of sleep that accompanies repetitive obstructive apneas during sleep and the associated declines in arterial oxygen saturation have both been implicated as causes of excessive daytime sleepiness in OSDB patients. Using a multiple linear regression technique, excessive sleepiness, as measured objectively by the MSLT, correlates best with apnea frequency and less so with apnea duration and the nadir in apnea-related arterial oxygen saturation. Sleep fragmentation that accompanies apnea termination is believed to be the major determinant of excessive daytime sleepiness in OSDB. The observation that cyclical hypoxia during sleep did not alter the MSLT values in a group of OSDB patients being treated with nasal continuous positive airway pressure (NCPAP) is consistent with the notion that fragmented sleep best explains sleepiness in OSDB. Loss of alertness may be quantified using the maintenance of wakefulness test (MWT). In OSDB the MWT is reduced and correlates with the respiratory arousal index ($r = -0.35$) and mean oxygen saturation ($r = 0.30$). Some investigators promote the notion that the MWT is better suited to assess daytime performance, such as the ability to drive a motor vehicle, than the MSLT. Daytime hypersomnolence in subjects with OSDB has been shown to decrease productivity, impair work performance, and is reported to account for the sevenfold increase in motor vehicle accidents observed in patients with this disorder.

Daytime hypersomnolence is the most common daytime complaint and is noted by 78 to 92% of patients (Table 4). Some OSDB patients may not perceive themselves as being excessively sleepy; however, they acknowledge falling asleep during most monotonous situations such as watching television or reading newspapers and books. Excessive daytime sleepiness is present throughout the day and, in contrast to narcolepsy, only partially relieved by naps. Automatic behavior and hypnagogic hallucinations are manifestations of excessive daytime sleepiness. Automatic behavior refers to episodes of purposeful but inappropriate behavior occur-

Table 3—*Prevalence of Self Reported Symptoms in OSDB Patients*

Symptom	% With Symptom
Snoring ever disruptive to others	95
Loud snoring	
Rarely	4
Sometimes	10
Frequently	12
Always	68
Snoring quality	
Slightly lower than breathing	9
As loud as mumbling	15
Louder than talking	17
Extremely loud	49
Snorting or gasping	
Rarely	5
Sometimes	10
Frequently	14
Always	72
Stopped breathing	
Rarely	10
Sometimes	16
Frequently	11
Always	48
Daytime sleepiness	
Rarely	5
Sometimes	10
Frequently	14
Always	72

ring in a sleepy person. It is often associated with impaired attention and vigilance with amnesia for the event, such as missing freeway exits or driving through stop signs. Polygraph recordings suggest that micro sleeps may be partly responsible for automatic behavior. Hypnagogic (sleep onset) and hypnopopnic (sleep offset) hallucinations may be auditory, tactile, or visual and usually occur in the interface between wakefulness and sleep. Feelings of weightlessness and loss of balance or support are common and the hallucinations may terminate with a brisk body movement termed the hypnic jerk. Sleep-related hallucinations are not unique OSA and in fact are more commonly observed in narcoleptics.

Arterial Hypertension and OSDB: Experimental evidence obtained in dogs indicates that periodic upper airway occlusion during sleep can lead to the induction of chronic arterial hypertension. Epidemiologic studies have shown associations between snoring and/or OSDB and arterial hypertension. The relationship between OSDB and arterial hypertension is stronger in individuals under age 50 years. Resolution of sleep-related upper airway occlusion in hypertensive patients with OSDB leads to a modest improvement in systolic (10 mm Hg) and diastolic (5 mm Hg) BP. The association between arterial hypertension and OSDB persists even after adjustment for confounding factors such as obesity, male gender, and age. Additionally, there appears to be a dose response relationship between the frequency of upper airway occlusion during sleep and diurnal BP. The relative risk of hypertension in OSDB is estimated to be between 1.5 and 2.5.

Ischemic Heart Disease and OSDB: One study of snoring in postmyocardial infarction patients that was matched for age and gender suggests that habitual snoring increases the odds for a myocardial infarction approximately fourfold. A self-reported history of myocardial infarction is reported more frequently in snorers than nonsnorers. In one study of > 400 male twins, a history of snoring increased the risk of ischemic heart disease twofold. Clinical studies have demonstrated a high prevalence of OSDB after myocardial infarction.

Cerebrovascular Disease and OSDB: A history of snoring increases the risk of combined ischemic heart disease and stroke twofold. A similar increase in stroke incidence is seen in individuals with a history of excessive daytime sleepiness and a total sleep time that exceeds 8 h.

Pulmonary Hypertension and Right Heart Failure in OSDB: Pulmonary hypertension has been observed in 10 to 30% of patients with OSDB without lung disease and in as much as 70% in OSDB patients with underlying lung disease. OSDB rarely leads to a mean pulmonary arterial pressure in excess of 40 mm Hg. In OSDB and right heart failure, the severity of OSDB, as determined by the frequency of apnea and hypopnea during sleep, does not correlate with the presence or absence of right ventricular failure. Right heart failure and resting pulmonary arterial pressure correlate best with diurnal hypoxemia and hypercarbia, lower vital capacity, and FEV_1. The available data suggest that in some cases, OSDB alone may produce substantial pulmonary hypertension. Concomitant obstructive lung disease or morbid obesity with hypoventilation and diurnal hypoxemia contributes to the development of diurnal pulmonary arterial hypertension in others. Correction of OSDB often leads to improvement or resolution of pulmonary hypertension.

Diurnal Hypoventilation in OSDB: Most patients with OSDB do not have daytime hypercapnia. Obesity *per se* can be associated with the development of diurnal hypoventilation and has been termed the obesity hypoventilation syndrome (OHS). As compared to patients with simple obesity, OHS patients have a total lung capacity and maximum breathing capacity that is 20% and 40% lower, respectively. Inspiratory muscle strength and chest wall and lung compliance are decreased in OHS patients. However, a defect in the central respiratory controller responsiveness to appropriate chemical and mechanical stimuli associated with obesity appears to be the most important cause of the hypoventilation. The pickwickian syndrome has been used to determine the clinical scenario

Table 4—*The Incidence of Selected Symptoms Suggestive of OSDB*

Symptom	Incidence (%)
Loud snoring	94
Excessive daytime sleepiness	78
Restless sleep	100
Abnormal mentation	58
Personality changes	48
Impotence	42
Morning headaches	36
Nocturia	30
Insomnia	10

characterized by excessive daytime sleepiness, diurnal pulmonary hypertension, OHS, and OSDB. Alleviating sleep-related upper airway obstruction often leads to correction of the pickwickian syndrome's clinical manifestations.

Mortality and OSDB: Vascular diseases, fatal vehicular accidents and work-related accidents can increase mortality in OSDB. Retrospective studies have demonstrated increased mortality in untreated patients with severe OSDB compared with patients treated with tracheostomy or NCPAP. One often-quoted study described an apnea index above 20 as the threshold for increased risk of mortality. Increased mortality was more apparent in subjects under age 50 years. Mortality-focused studies in elderly (> 65 years) community-based populations have failed to demonstrate a relationship between OSDB and mortality. A history of sleepiness and sleeping in excess of 8 h, features suggestive of OSDB, were associated with a 30% increase in mortality in one prospective community-based study. Our current state of knowledge with regards to the overall impact of OSDB on mortality is limited. However, increased mortality rates are likely in severe OSDB, particularly in younger individuals.

Miscellaneous Clinical Features in OSDB: Enuresis may be seen in up to 5% of patients with OSDB. Morning headaches and excessive nighttime perspiration have been reported, the latter being more common in adolescents and children with OSDB. Altered neuropsychological function (depression and memory loss) and sexual dysfunction in men are reversible consequences. Polycythemia is seen in only 7% of OSDB patients without coexisting chronic lung disease.

Laboratory Evaluation

Polysomnography and Respiratory Monitoring: OSDB is graded based on its frequency and on the degree of associated oxyhemoglobin desaturation. The number of respiratory events divided by the total sleep time (hours) termed the apnea/hypopnea index (AHI) or respiratory disturbance index (RDI), is routinely used to establish the diagnosis of sleep apnea and as a measure of severity. The AHI and RDI are also used to characterize CSA.

Polysomnography is a multiple physiologic recording performed while the subject is asleep. Other techniques used to detect abnormal respiration during sleep and diagnose OSDB are less efficient and polysomnography is considered the "gold standard." A single night in the sleep laboratory is usually sufficient to establish the diagnosis and severity of OSDB. Further, the relationship with apnea, sleep stages, and body posture may be established by polysomnography. Split-night polysomnography has been used to reduce the number of sleep recordings necessary to diagnose and treat OSDB. In this modification of conventional full-night polysomnography, the first portion of the night is used to establish the presence of OSDB and then followed by a therapeutic portion with adjustment of NCPAP. In moderate-to-severe OSDB, split-night polysomnography has demonstrated accuracy in characterizing the AHI when compared with a full-night baseline polysomnogram. NCPAP adjustments obtained using the split-night strategy approximate those derived from a full night of NCPAP titration in approximately 55% of cases.

Oximetry is highly sensitive but it lacks sufficient specificity to be used as a clinical tool in establishing a diagnosis of OSDB. However, a "normal" overnight oximetry study can reliably exclude the presence of OSA. Considering that some hypopneas and RERA occur without declines in oxyhemoglobin saturation, overnight oximetry will miss such cases. Respiratory monitoring alone or in conjunction with oximetry may be helpful in cases in which polysomnography may not be performed such as in the critically ill patient. Unattended polysomnography and respiratory monitoring performed in the home are not considered reliable for routine clinical use.

Multiple Sleep Latency Test: There are many causes of hypersomnolence, not all of which are characterized by repetitive disturbances in nighttime sleep as is OSDB. Narcolepsy and idiopathic hypersomnia are characterized by pathologic sleepiness in the absence of significant repetitive nighttime sleep fragmentation. Affective disorders may produce insomnia or, less frequently, hypersomnia. In selected patients being evaluated for excessive daytime sleepiness, the MSLT is useful to quantify the degree of sleepiness and to exclude narcolepsy from the differential diagnosis. For example, a hypersomnolent patient who was mildly overweight and snored was referred for an evaluation of possible sleep apnea and was found to have normal sleep architecture and AHI. In such cases, the MSLT is warranted to determine the cause of the hypersomnia. The presence of pathologic sleepi-

ness, as manifested by a mean sleep latency of < 8 min, in conjunction with two or more REM onset sleep periods, is used to diagnose narcolepsy.

Maintenance of Wakefulness Test: This test is a variation of the MSLT in which one monitors for sleep while a patient is asked to remain awake while sitting in a quiet room. In the evaluation of OSDB, the MWT has been performed in sequence with the MSLT such that there is little additional burden on the sleep laboratory and patient. In contrast to the MSLT, which measures one's propensity to fall asleep on command, the MWT is designed to evaluate the capacity to remain awake. Normal mean latency to sleep onset in the MWT generally exceeds 30 min and in a study of 322 patients with OSA, this value was 26.0 ± 11.8 (SD) min. The MWT appears to be useful in measuring disability from excessive daytime somnolence in OSDB.

Miscellaneous Tests: Several imaging techniques of the upper airway have been used to identify anatomic abnormalities that predispose to OSDB but they cannot diagnose or exclude sleep apnea. Imaging studies are helpful to select appropriate patients for surgery of OSDB.

Flow-volume loops show a characteristic "saw toothing" pattern in approximately 40 to 60% of patients with OSDB. Similar "saw toothing" may be seen in subjects with Parkinson's disease and many other upper airway disorders; therefore, this test is neither sufficiently specific nor sensitive enough to be used routinely in sleep apnea syndromes.

Management of OSA

General Measures: Weight reduction may substantially improve or even cure overweight OSDB patients, hence all such patients should be encouraged to maintain their body weight near ideal. However, in my experience, even well-motivated patients with OSDB rarely achieve substantial weight reduction, possibly because they remain somnolent and do not exercise.

Benzodiazepines, opiates, and alcohol worsen obstructed breathing during sleep. These pharmaceuticals selectively depress upper airway motor tone during sleep and increase apnea threshold, thereby prolonging the duration of apnea. Further, apnea may be produced by pharmacologic doses of these agents. Therefore, these drugs should be avoided in known or suspected OSDB.

Positive Airway Pressure: At the present time, NCPAP is the most effective nonsurgical therapy for OSDB. Beneficial effects are felt almost immediately after a single night of sleep with this device. NCPAP acts as a pneumatic splint by elevating the pressure in the oropharyngeal airway and thereby maintaining a positive airway pressure throughout the entire respiratory cycle. A list of common NCPAP complications can be found in Table 5.

NCPAP requires adjustment so that the optimal amount of pressure may be prescribed. Automatic NCPAP systems offer the opportunity to adjust NCPAP in the home setting and often yield prescription pressures comparable to those obtained in the sleep laboratory. However, unattended automatic NCPAP adjustment may not be safe without prior polysomnogram to exclude patients who have OSDB overlapping with other nocturnal breathing disorders and with arrhythmia. The effect of automatic NCPAP adjustment on compliance with subsequent treatment is unknown.

Although OSDB can be easily treated with NCPAP, acceptance and adherence to long-term NCPAP use is poor. In general, patients overestimate their use of NCPAP. When compliance is assessed by covertly monitoring the NCPAP device, only 46% of patients use the device for ≥ 4 h on 70% of nights. Compliance at 1 month of treatment predicts compliance at 3 months.

Bilevel positive airway pressure (ventilatory support system [BiPAP]) can effectively treat OSDB. The ventilatory support system (BiPAP) allows independent adjustment of inspiratory and expiratory pressure. The device is adjusted to deliver an expiratory pressure sufficient to prevent upper airway closure during expiration and, after inspiratory flow triggering, a predetermined level of inspiratory pressure aimed at supporting the upper airway during inspiration. Theoretically, the expiratory pressure would be less than that required during inspiration. The resultant decrease in expiratory pressure might improve comfort and compliance with positive pressure treatment. Complications of treatment with this venilatory support system are similar to those of NCPAP and, unfortunately, the use of this ventilatory support system has not provided a compliance advantage over NCPAP.

The AHI may improve after prolonged use of NCPAP, an observation that cannot be accounted for by decreasing body weight or increases of pharyngeal size during wakefulness. Bilateral,

complete nasal obstruction is the only absolute contraindication to NCPAP therapy. The major limitations of positive airway pressure treatment are related to patient tolerance and compliance. Newer mask designs,

Surgical Techniques: Several surgical procedures have been proposed for treating OSDB (Table 6). Although tracheostomy is universally effective, uvulopalatopharyngoplasty (UPPP) has received the greatest attention in medical and surgical investigations. If one uses a 50% reduction in the AHI as the criterion for UPPP success, then UPPP provides a beneficial response in approximately 50% of unselected patients with OSDB. However, normalization of breathing during sleep in OSDB patients after UPPP rarely occurs. Failure of this type of surgery has been attributed to the presence of obstruction other than in the oropharynx, areas not addressed by UPPP. Imaging and direct fiberoptic techniques aimed at identifying the site of obstruction can substantially improve the success of UPPP. However, beneficial responses are seen in only 60 to 70% of cases selected in this manner. Laser-assisted UPPP is less successful than surgery performed in the conventional manner. A relatively new technique, somnoplasty, uses radiofrequency energy to reduce the size of the soft palate, uvula, and base of the tongue. Somnoplasty appears to be safe and as effective as conventional UPPP. Somnoplasty applied to reduce tissue volume at the uvula, soft palate, and at the base of the tongue may prove to be of greater efficacy, but the data are currently lacking. Maxillomandibular advancement cures OSA in > 80% of cases, but this surgical technique is much more aggressive. Tracheostomy is usually reserved for severe cases of OSDB in which other therapeutic modalities fail or are not acceptable to the patient.

Pharmacologic Agents: Medroxyprogesterone may be of benefit to sleep apnea patients with daytime hypercarbia (OHS). In other patients with OSDB, medroxyprogesterone may worsen upper airway collapse during sleep. Methylxanthines and acetazolamide have no proven role in managing OSDB. Protriptyline, a tricyclic antidepressant, enhances upper airway tone and reduces hypoxemia without decreasing the frequency of obstructive apnea during sleep. Fluoxetine and sertraline, serotonin reuptake inhibitors, increase upper airway motor tone during sleep and may be helpful in the mildest cases of OSDB.

Table 5—*Common Problems Associated With Positive Pressure Treatment*

Symptom or Complaint
Rhinorrhea
Nasal congestion
Nasal and oral dryness
Epistaxis
Skin abrasion (pressure sore and allergy)
Conjunctivitis (air leaks)
Sinus pressure
Aerophagia
Chest pain
Smothering sensation
Pneumothorax and pneumomediastinum
Pneumocephalus
Excessive noise
Cumbersome and inconvenient
Loss of intimacy

Table 6—*A Guide to Therapy for OSDB*

Treatment Approach	Favorable Clinical Characteristics
NCPAP	Preserved nasal functioning No claustrophobia Overweight Sleepier patients Hypercapnia Pulmonary hypertension
Oral appliances	Mild-to-moderate AHI AHI reduced > 50% when not in supine position Preserved nasal functioning
Antidepressants	Relatively asymptomatic Lower AHI Minimal hypoxia REM associated OSDB Concomitant depression
UPPP	Not overweight Younger patients Isolated retropalatal obstruction Other methods not tolerated
Hyoid advancement surgery	Younger patients Isolated retrolingual obstruction Moderate to severe OSDB Ineffectiveness of NCPAP Intolerance of NCPAP
Maxillomandibular surgery	Younger patients Retropalatal and retrolingual Obstruction Moderate to severe OSDB Ineffectiveness of NCPAP Intolerance to NCPAP
Tracheostomy	Life-threatening OSDB Ineffectiveness of NCPAP Intolerance to NCPAP

Oxygen: Supplemental oxygen may diminish the degree of hypoxemia that accompanies obstructive breathing during sleep. Unfortunately, apnea duration is often lengthened by the administration of supplemental oxygen and thus hypercarbia may be worsened. NCPAP is more effective than oxygen at alleviating hypersomnia in OSDB. Further, oxygen alone will not normalize waking donor artery pressure when administered to patients with OSDB and diurnal pulmonary hypertension.

Sleep Position Training: Some patients will have OSA only in the supine posture. Instructing these individuals on techniques to maintain the lateral decubitus position during sleep is sufficient to treat their sleep apnea. This may be true even in the morbidly obese OSDB patient. In most cases, sleeping in the lateral decubitus posture lessens the frequency and severity of obstructive apneas.

Oral Devices: Several different orthodontic appliances have been tested in patients with OSDB. The devices that have received the greatest attention are those that advance the mandible (mandibular advancement appliances). The nadir in apnea related oxyhemoglobin saturation and REM sleep-related apnea hypopnea frequency are relatively unaffected by mandibular advancement appliances. Posture-dependent OSDB and nonobese OSDB patients reap the greatest improvement in AHI when using oral appliances. Mandibular advancement oral appliances exert their beneficial effects by increasing the resting size of the pharyngeal airspace. Tolerance to the use of oral appliances is similar to that of NCPAP. Oral appliances should not be used in patients with temporomandibular joint disease. The use of a mandibular advancement oral appliance limits oral airflow. Hence, individuals with high-grade bilateral nasal obstruction may find it difficult to breathe with these devices.

OSDB During Pregnancy: Despite the associated weight gain and impaired pulmonary mechanisms that accompany pregnancy, obstructive apnea only rarely presents during pregnancy. The precise explanation for this observation remains speculative but hormonal factors have been implicated. Although OSDB during pregnancy may have deleterious effects on the fetus, NCPAP and tracheostomy appear safe. In a recent publication, the presence of self-reported nightly snoring and diurnal arterial hypertension was associated with fetal developmental delay. However, controlled data are lacking to support broad conclusions regarding the effect of maternal OSDB on fetal development.

Approach to Patients With OSDB: Not all patients who complain of excessive daytime somnolence have OSDB. If OSDB is documented by a polysomnogram, then a trial of NCPAP is warranted. If daytime somnolence is unaffected, then it is unlikely that the OSDB is the sole cause of the patient's sleepiness. Alternate diagnoses (*eg*, narcolepsy or atypical depression) should then be considered. UPPP surgery, orthodontic devices and pharmacotherapy for OSDB are generally less effective than NCPAP and are usually reserved for patients who cannot tolerate NCPAP. Surgical techniques may be best suited for OSDB patients who have clearly defined craniofacial abnormalities and in those who cannot use NCPAP. Weight reduction to a body weight near ideal and avoidance of benzodiazepines, opiates, and alcohol should be emphasized in all patients with OSDB. A guide to therapy of OSDB is presented in Table 6. With proper treatment of OSDB, its symptoms and physiologic sequela can usually be reversed.

Central Sleep-Disordered Breathing

In contrast to OSDB, CSA can occur in a variety of distinct clinical situations. The group of pulmonary disorders that are associated with diurnal hypoventilation will commonly have central apnea during sleep. CSA in these patients is usually a consequence of the underlying disorder of the respiratory system rather than a primary sleep disorder. Similarly, a variety of rhythmic and dysrhythmic respiratory patterns have been described after CNS injury. Ataxic breathing usually heralds brain stem injury. Cheyne-Stokes respiration (CSR) a crescendo-decrescendo form of breathing associated with hyperpnea and apnea/hypopnea (Fig 9), has been associated with CNS lesions and, more commonly, with congestive heart failure (CHF). CSA may also occur without recognized underlying etiology in which case it is termed idiopathic CSA. The diverse etiologies of CSA make it difficult to advocate specific treatment strategies. In clinical practice, most cases of CSA are seen in association with CHF and CSR. Hence, in this review, I will focus the attention on the clinical syndrome of CSR-CSA in CHF.

Pathophysiology of CSR-CSA: In contrast to OSDB, CSR-CSA is a consequence rather than a

contributor to CHF. The key pathophysiologic feature of CSR-CSA is hyperventilation causing arterial $Paco_2$ to fall below apnea threshold. Patients with CHF and CSR-CSA usually have low $Paco_2$ during wakefulness. Hyperventilation is thought to arise from effects of pulmonary vagal stimulation due to venous congestion. This is consistent with the observation that CSR-CSA occurs in association with diastolic cardiac dysfunction syndromes. Transitions from wakefulness to non-REM sleep participate in central apneas by raising apnea threshold. Apnea is terminated when $Paco_2$ reaches ventilatory threshold with further hyperventilation lowering $Paco_2$ below the apnea threshold secondary to sighs and arousals from sleep. Daytime hypoxia is uncommon in these patients but the dips in oxyhemoglobin saturation that accompany apnea/hypopnea in CSR potentiate ventilatory responses and serve to perpetuate CSR-CSA. Patients with idiopathic CSA share the tendency to hyperventilate described in CHF patients with CSR-CSA. Central apneas and CSR-CSA are observed predominantly during stages 1 to 2 non-REM sleep and are infrequent in non-REM stage 3 to 4 and REM sleep. Relatively greater down-regulation of the respiratory center explains the paucity of central apneas in REM and stage 3-4 non-REM sleep.

Clinical Consequences of CSR-CSA in CHF: CSR-CSA probably has adverse effects similar to OSDB in CHF. Apnea-related arousals and sleep fragmentation but not the effect of negative intrathoracic pressure generation occur with CSR-CSA. Individuals with CHF and CSR-CSA have higher overnight urinary norepinephrine and daytime plasma norepinephrine concentrations than those without CSR-CSA. Norepinephrine levels are related to the degree of apnea-related hypoxia and frequency of arousals from sleep rather than the left ventricular ejection fraction. Sleep fragmentation leads to fatigue, excessive daytime sleepiness, and insomnia. CSR-CSA patients more often complain of insomnia than sleepiness.

CSR-CSA in CHF is a marker of increased mortality. The most likely cause of elevated mortality is sympathetic nervous system activation. Studies have not directly addressed the potential mechanisms of increased mortality in relation to CSR-CSA. However, elevated sympathetic nervous system activity and high circulating catecholamine considerations have direct cardiotoxic effects, predispose to cardiac arrhythmias, increase systemic BP and heart rate, raise myocardial oxygen consumption, and when combined with apnea-related hypoxia can participate in myocardial ischemia.

Management of CSR-CSA in CHF: The presence of CSR-CSA is not by itself an indication for treatment. In CSR-CSA, the presence of sleep complaints, excessive daytime sleepiness, significant hypoxia, paroxysmal nocturnal dyspnea, and nocturnal cardiac arrhythmias are indications for treatment. Considering that CSR-CSA in CHF arises primarily from pulmonary venous congestion, a logical therapeutic approach is to optimize medical therapy of CHF. Respiratory stimulants (theophylline and inhaled carbon dioxide), supplemental oxygen, CNS depressants (benzodiazepines), and NCPAP have been used with success to treat symptomatic CSR-CSA. The most excessively tested treatment and the only therapy shown to have beneficial acute and chronic cardiovascular effects is NCPAP. When NCPAP is used for CHF related CSR-CSA, patients can experience a significant reduction frequency of CSA, improvement in symptoms of heart failure and sleep fragmentation, increase in left ventricular ejection fraction, decrease in heart rate, decline in plasma atrial natriuretic peptide, lowered overnight and daytime norepinephrine concentrations, and an increase in inspiratory muscle strength. NCPAP does not require laboratory adjustment when used for CSR-CSA. The target prescription pressure is 10 to 12.5 cm H_2O. In order to avoid acute hemodynamic compromise from positive airway pressure related declines in cardiac preload, a lower pressure is initially selected with subsequent increases in NCPAP over several weeks as tolerated by the patient. Treatment of idiopathic CSA is similar to that described for CSR-CSA in CHF albeit without the proven cardiovascular benefits that NCPAP affords when it is used to treat CSR-CSA in CHF.

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Notes