VI VENTILATORY CONTROL DURING WAKEFULNESS AND SLEEP

Kingman P. Strohl, m.d.

Overview

Ventilation is a critical function for eliminating carbon dioxide and acquiring oxygen. At or near sea level, ventilation maintains arterial carbon dioxide tension (P\textsubscript{CO\textsubscript{2}}) values in the range of 38 to 42 mm Hg and arterial oxygen tension (P\textsubscript{O\textsubscript{2}}) values in the range of 85 to 100 mm Hg. What is remarkable is that P\textsubscript{CO\textsubscript{2}} values vary relatively little over the human life span despite substantial alterations in the mechanical properties of the chest wall and lungs that accompany birth, maturation, and aging. The control system for ventilation not only optimizes gas exchange but also serves a role in acid-base balance, speech, defecation, and posture.

The components of ventilatory behavior (i.e., breathing rate and depth) are the result of a feedback control system in which the brain (controller) organizes neuromuscular output to the respiratory muscles of the upper airway, chest wall, and lungs (controlled system). The controlled system alters arterial pH, CO\textsubscript{2}, and O\textsubscript{2} in response to impulses from the brain. Specialized sensors located in the respiratory system monitor the rate of gas exchange and send impulses to sensors located in the brain to prompt adjustments in system regulation. A feedback control model of the respiratory system provides insights into the effects of sleep on ventilation and gas exchange [see Figure 1].

Genetic factors influence disorders of ventilatory control (e.g., sleep apnea); however, there are adaptive components. One example is the periodic breathing during sleep that occurs with adaptation to high altitude. Such functional flexibility, or plasticity, is an essential feature of development, maintenance, and expression of effective ventilation and is not merely the result of mechanical operation of the lungs and chest wall. Consequently, genes, maturation, and experience all influence the adult phenotype for breathing and sleep and the clinical disorders resulting from this physiology.

This chapter focuses on the respiratory control system and how its elements contribute to sleep apnea and other state-related disorders of ventilation.

Physiology of Ventilatory Control

Inhalation begins with the discharge of inspiratory neural impulses from respiratory centers located in the medulla.\(^1\) This neural network is embedded in a system of adjacent medullary neurons, pontine neurons, and regions such as the nucleus tractus solitarius (NTS) that receive neural impulses resulting from lung inflation, blood pressure, and other afferent systems. Inhalation continues until the respiratory centers receive negative feedback from the adjacent medullary neurons and from peripheral receptors, some of which are activated by lung inflation. The intensity of the activity of medullary neurons is affected by input from chemoreceptors [see Figure 1]. Influences from higher centers also adjust inspiratory and expiratory activity for speech and swallowing. With inhibition, inspiration ceases and expiration continues until inhibitory influences wane sufficiently to allow initiation of the next inspiration. Simply put, the rate of inspiratory ventilation is determined by the intensity of medullary discharge; duration and depth of inspiraton are determined by the timing and intensity of inhibitory influences.

Chemoreceptors are specialized cells that sense O\textsubscript{2} and CO\textsubscript{2} through changes in pH. The peripheral chemoreceptors (i.e., the carotid and aortic bodies) are highly vascular collections of specialized sensory cells.\(^2\) The carotid bodies are located bilaterally at the bifurcations of the common carotid arteries; the aortic bodies are situated anterior and posterior to the arch of the aorta and the left main pulmonary artery. The peripheral chemoreceptors are stimulated primarily by a low P\textsubscript{O\textsubscript{2}}, although hypcapnia, acidemia, and possibly hyperthermia may influence an increased response to hypoxemia. Impulses travel from the carotid and aortic bodies to the NTS in the brain stem via sensory ganglia and the afferent nerves that follow along the ninth and 10th cranial nerves, respectively. Increases in P\textsubscript{CO\textsubscript{2}} stimulate cells on the ventral medullary surface (VMS), primarily by lowering the pH of the medullary extracellular fluid.\(^3\) In the steady state, the pH of cerebrospinal fluid reflects the pH of the medullary microenvironment and may differ significantly from blood pH. This discordance is thought to result in transient stimulation of ventilation, even in the presence of a respiratory alkalosis (e.g., in persons who return to sea level after spending several weeks at high altitude).

Specialized sensory cells (i.e., mechanoreceptors) located in the upper airway, chest wall, and lung detect mechanical deformation and temperature changes resulting from inhalation and exhalation.\(^4\) Afferent nerve signals from mechanoreceptors are directed to the medulla (NTS), where information is integrated with chemoreceptor information to influence the medullary timing and volume of ventilation; integrated information is relayed through thalamic connections to the cortex. In the presence of parenchymal lung disease, the information received by the cortex may contribute to perceptions of breathlessness (dyspnea). Thus, lung inflammation and bronchoconstriction will activate unmyelinated pulmonary C fibers, thereby resulting in hyperventilation, tachypnea, and dyspnea. Myelinated fibers from stretch receptors carry impulses that influence the duration of inspiration and expiration. Impulses from stretch receptors and C fibers travel through the pulmonary branch of the 10th cranial nerve. Segmental intercostal nerves carry impulses to the brain stem from the chest wall, muscle spindles, and joint proprioceptors.\(^5\) Mechanoreceptors in these areas are influenced by the position of the rib cage and by the muscular tension required to inflate the lungs, and the rate of change in the afferent neurogram resembles flow rate. This receptor system acts in concert with chemoreceptors to control the timing of exhalation and control ventilation.

Other brain centers (e.g., the hypothalamus and cortex) provide input to pontomedullary respiratory centers.\(^6\) These pathways coordinate neuromuscular outputs with voluntary respiratory acts, such as talking or expulsive maneuvers, and coordinate ventilation with metabolism, posture, and swallowing. Hypothalamic influences are in part responsible for the so-called wakefulness stimulus—the increased activity of medullary neurons in the cortex that occurs during wakefulness, as opposed to the activity that occurs during sleep. Some cortical cerebral path-
ways circumvent the medulla and pass directly to respiratory muscles via pyramidal tracts. The cerebellum plays a role in both coordinating and adjusting respiratory neural output to the upper airway and chest wall muscles.

Putative set points for the ventilatory control system help ensure homeostatic control of acid-base balance (pH) and O₂ delivery. One example of a set point is the apneic threshold, which is defined as that level of arterial (or central) CO₂ below which there is little or no inspiratory activation. This set point is higher in sleep. Central chemoreceptors—for example, those located in the medulla near the ventral medullary surface (VMS)—are stimulated by increases in PCO₂. Information received from the chemoreceptors is integrated in the medulla, and neural impulses from the medullary system (red arrows) travel to the muscles of the upper airway and chest wall to influence timing and volume of ventilation. Peripheral mechanoreceptors in the upper airway, chest wall, and lung detect mechanical deformation and temperature changes resulting from inhalation and exhalation; neural signals from these mechanoreceptors are sent to the central and peripheral chemoreceptors. This scheme of respiratory feedback control is a basic concept for understanding how sleep affects ventilation and gas exchange.

Integration and coordination of neuromuscular activity are most apparent during inhalation. In health, exhalation occurs as a result of the passive recoil of the lungs and chest wall; however, the duration of expiration and the start of a new inspiration are actively controlled events. In a healthy person, breathing is a sequence of inhalations and exhalations that serve to maintain alveolar ventilation at a level that is appropriate for meeting metabolic demands during wakefulness, exercise, and sleep. The increased metabolic requirements of exercise are met by increases in respiratory frequency and tidal volume (and therefore in minute and alveolar ventilations). During exercise, activation of abdominal and intercostal muscles during expiration allows more rapid emptying of the lungs at higher tidal volumes. Environmental stresses, metabolic disturbances, hormonal changes, drugs, sleep-wake activity, and exercise may influence the output of a normal control system. Excessive respira-
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Disorders with Increased Ventilatory Drive

Interstitial lung diseases (e.g., pulmonary fibrosis) increase resting ventilation and lower $P_{ACO_2}$ as a result of increased activity of lung receptors (probably C fibers). The hyperventilation that accompanies pulmonary edema, pneumonia, interstitial disease, and the acute respiratory distress syndrome is a rapid, shallow breathing pattern that results from activation of these lung receptors. Hypocapnia with dyspnea may occur in the absence of hypoxemia in this setting. Unilateral vagal interruption in patients with parenchymal lung disease has been shown to reduce ventilation, as well as dyspnea, and may contribute to the improvement in breathlessness after unilateral lung transplantation.

Hyperventilation is regularly produced by exposure to high altitude or other hypoxic environments, metabolic acidosis, pregnancy and other conditions associated with elevated progestational hormones, anxiety states, and mildly toxic doses of salicylates, amphetamines, or other CNS-stimulating drugs. Unlike the hyperventilation associated with parenchymal lung disease, the hyperventilation that occurs during progesterone stimulation (e.g., that which occurs during pregnancy) or metabolic acidosis is associated with an increased tidal volume and little increase in respiratory rate. The hyperventilation characterized by high tidal volume and relatively low frequency that accompanies diabetic ketoacidosis (Kussmaul respiration) is pH mediated and may not be as apparent to an observer as the breathlessness that occurs in interstitial lung disease.

Disorders with Decreased Ventilatory Drive

Hypoventilation occurs when alveolar ventilation is insufficient to eliminate metabolically produced $CO_2$. Hypoventilation may be caused by metabolic or mechanical factors. Metabolic causes of hypoventilation may include metabolic alkalosis, deficiency of thyroid hormone, and excess doses of sedative and narcotic agents. In each of these conditions, there is a relatively steady breathing pattern accompanied by a lowered respiratory rate, a lowered tidal volume, or both. Dyspnea is often absent despite an elevation of resting $P_{ACO_2}$.

In diseases that mechanically restrain ventilation (e.g., ankylosing spondylitis and chronic obstructive pulmonary disease [COPD]), hypoventilation may occur despite preserved activity of the medullary inspiratory neurons. A perception of dyspnea occurs because of the increased work of breathing and the incongruity between central inspiratory activity and activation patterns detected by mechanoreceptors of the chest wall and lungs. In some persons, ventilation may be reduced to a degree that is out of proportion to the mechanical properties of the lungs or chest wall (possibly because of a genetic predisposition), and dyspnea may be a less prominent feature. As hypoventilation becomes chronic, adaptation of receptors, of central inspiratory neurons, of metabolic alkalosis, or of all three may occur. Adaptation to chronic hypoventilation in sleep apnea, COPD, neuromuscular disease, and chest wall disease may eventually depress responsiveness to $CO_2$ and depress ventilation during rest.

Both resting $CO_2$ and ventilatory responsiveness to $CO_2$ may be increased by treatment of sleep apnea or by lowering $CO_2$ with ventilatory support. Hypoventilation can also be caused by hemodialysis, during which $CO_2$ removal lowers the $P_{ACO_2}$ sufficiently to depress the rhythmic activity of medullary respiratory neurons and produce apneas.

An uncommon condition called primary alveolar hypoventilation can be present at birth (congenital hypoventilation syndrome) or can be acquired as a result of morbid obesity, cerebrovascular accidents, meningitis, encephalitis, bulbar poliomyelitis, or damage to afferent pathways in the cervical spinal cord. In all these conditions, however, no structural abnormality is found at autopsy. Presenting symptoms, which

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**Figure 2**  (a) The existence of an apnea threshold (broken line) for arterial carbon dioxide tension ($P_{ACO_2}$) during sleep provides an explanation for the changes in breathing that occur at the onset of sleep. A transient increase in ventilation from brief arousal results in a lowering of $P_{ACO_2}$ below the apnea threshold. Breathing effort ceases until $P_{ACO_2}$ rises above the $CO_2$ threshold. The effect of lowering $P_{ACO_2}$ on ventilation is trivial in awake individuals. Sleep is associated with expression of this apnea threshold and may even raise the threshold, causing hypoventilation and apnea to occur more readily. Conditions that produce frequent arousals and large breaths may result in apneas or hypopneas as sleep resumes after the arousal. (b) The graph shows the cycles that occur when the set-point (white circle) is moved from wakefulness to sleep. With snoring, a new set point (blue circle) is established. A small increase in ventilation may lower the $P_{ACO_2}$, resulting in reductions in or cessation of breathing. $P_{ACO_2}$ will then rise and increase ventilation abruptly as the arousal threshold is reached. The length of an apneic episode depends in large part on the arousal threshold, the recovery mechanisms, and the tendency for sleep to persist without an arousal.
are a result of blood gas derangement, often include lethargy, somnolence, headaches, and dependent edema. Such patients may not complain of shortness of breath. Physical findings may include cyanosis and evidence of right-sided heart failure. Secondary erythrocytosis is common. In congenital hypoventilation syndrome, alveolar ventilation is improved by exercise, indicating that the disturbance in ventilatory control is functionally determined.

The diagnosis of hypoventilation syndrome is one of exclusion and is considered when hypercapnia cannot be accounted for by disorders of the lungs, chest wall, respiratory muscles, or breathing during sleep. All hypoventilation syndromes worsen during sleep. In extreme cases, breathing occurs only with voluntary efforts and ceases entirely with inattention or during sleep. Management of hypoventilation related to CNS defects includes ventilatory assistance at night without or with respiratory stimulants such as medroxypregosterone.

Abnormal Breathing Patterns and Sleep Reports

Brain injury and certain drugs and toxins affect breathing patterns during both wakefulness and sleep; however, there is a growing awareness of how abnormal breathing only during sleep may affect health. Periods of cessation of airflow into and out of the lungs (apnea) regularly occur at sleep onset, and episodes of partial upper airway obstruction during inspiration (snoring) are very common. Some irregularity of breathing is considered normal during sleep, including mild CO₂ retention and a reduction in PₐCO₂, as well as irregular breathing at sleep onset or with dreaming. As with many biologic phenomena, breathing irregularities that occur during sleep are designated as abnormalities only if they are sufficient in magnitude and frequency to disrupt sleep continuity or impair oxygenation enough to affect a person during wakefulness.

ATAxic AND APNEustic BREATHING

Ataxic (Biot) breathing is a random pattern of shallow and deep breaths interspersed with irregular pauses [see Figure 3]. Ataxic breathing results from disruption of medullary neural pathways by trauma, hemorrhage, or extrinsic compression caused by cerebellar or pontine hemorrhage; it can be seen in terminally ill patients because respiratory control systems are affected by multisystem failure. Complete apnea may ensue, especially in patients given sedative or narcotic drugs. Another disturbance, apneustic breathing, is characterized by an end-inspiratory pause of 2 to 3 seconds before exhalation is begun [see Figure 3]. Apneustic breathing is associated with caudal pontine lesions and is sometimes intermixed with ataxic breathing patterns.

Three patterns of apnea, or cessation of breathing, can be observed during sleep. These apneas are defined as episodes of a reduction in airflow of more than 80% occurring for more than 10 seconds. Apneas may be classified as central (or nonobstructive), obstructive, or mixed [see Figure 4]. In central apnea, which implies a cessation of respiratory activity at a brain stem level, both airflow and respiratory efforts are absent. During obstructive apnea, respiratory efforts persist, although airflow is absent at the nose and mouth. Obstructive and central apneas are related clinically and pathophysiologically. Many adult patients exhibit mixed apneas in which both central and obstructive patterns occur. In a single apneic episode, there may be a period in which no efforts occur, followed by the appearance of respiratory efforts, also without airflow. In addition, in the same night, patients may have all three types of apneas in varying proportion. If more than 80% of apneas are of a central type, the patient is classified as having central sleep apnea. If apneas are predominantly mixed and obstructive apneas, the patient is classified as having obstructive apnea.

Hypopneas or hypoventilation during sleep may arise by mechanisms similar to those producing apnea. Hypopneas are defined as episodes of a reduction in airflow of 30% to 80% occurring for more than 10 seconds. Hypoventilation (hypopnea) leads to increased CO₂ and decreased O₂ levels in arterial blood and causes arousals from sleep; as with apneas, hypopnea may result from reduction in respiratory efforts or partial upper airway obstruction. Snoring is a form of partial airway obstruction and is called obstructive hypopnea. Snoring is common, but some patients who snore have symptoms similar to those of sleep apnea syndrome even if complete cessation of airflow (apnea) never occurs during sleep. Moreover, such patients may exhibit abnormal sleep and cardiorespiratory changes.

VENTILATORY BEHAVIOR IN SLEEP

The transition from wakefulness to non–rapid eye movement (NREM) sleep is accompanied by a reduction in metabolic rate and therefore a reduced need to breathe. Consequences of sleep onset include reduced tidal volume, changes in lung mechanics, reduced activity and upper airway dilators, reduced upper airway caliber, and loss of load compensation [see Load Compensation, below].

Sleep is accompanied by reduced postural muscle tone. In NREM sleep, the ratio of rib cage displacement to abdominal displacement is greater than it is during wakefulness, whereas in REM sleep it is less. These changes in displacement may affect the distribution of ventilation in the lungs, increasing ventilation-perfusion mismatching and contributing to hypoxia; the development of hypoxia, in turn, may necessitate changes in respiratory output, which may initiate an unstable breathing pattern.

Figure 3 Irregular breathing patterns may reflect central nervous system disease or an inherent alteration in the apneic threshold. Three examples of irregular breathing are illustrated: (a) Ataxic breathing is characterized by an unpredictable sequence of breaths varying in rate and depth and is associated with medullary disease. (b) Apneustic breathing involves repetitive gasps, with pauses at full inspiration lasting a few seconds, and is associated with pontine disease. (c) Cheyne-Stokes respiration is cyclic, with a crescendo-decrescendo pattern interrupted by apneas.
Upper Airway Function

Upper airway caliber is reduced during sleep, and air passage is further impaired by decreased activity of upper airway muscles,16,17 especially the muscles involved with tonic activity (independent of the phase of respiration), such as the tensor veli palatini muscle.18 The mechanical consequence of reduced airway caliber is increased upper airway resistance.19 Because pharyngeal compliance increases during NREM sleep, negative intrathoracic pressures normally produced in the upper airway during inspiration will result in airway collapse. Even in healthy persons, negative intrathoracic pressure during NREM sleep limits inspiratory flow, resulting in an inspiratory plateau that persists in the presence of increasing negative pressure.19

Curiously, the retropalatal airway is less compliant during REM sleep, when muscle activity is much reduced, than during NREM sleep.20 This finding points to the significance of nonneuromuscular factors (e.g., bony and cartilaginous support) in the maintenance of upper airway patency during sleep.

Load Compensation

When the ratio of load to inhalation is increased (whether because of resistive factors or obstructive factors), a concomitant increase in breathing effort is required to restore tidal volume (i.e., load compensation). During sleep, however, immediate and subsequent load compensation is compromised and results in decreased tidal volume and minute ventilation, which thereby results in alveolar hypoventilation. The ensuing elevation of arterial $P_{aco_2}$ restores CO$_2$ elimination toward normal levels.7 The inability to perceive and immediately respond to increased loads allows for sleep to continue undisturbed. Thus, the main consequence of sleep is an increase in PaCO$_2$ of 4 to 5 mm Hg. Such elevations in PaCO$_2$ result in mild acidosis in both healthy persons and in persons with cardiopulmonary disorders but without sleep-disordered breathing (SDB).

Heavy snorers may not arouse from sleep despite continuous generation of subatmospheric intraluminal pressure that is several times higher than that which occurs during wakefulness [see Figure 5]. If increased resistance and inspiratory flow limitation are prolonged, the increased work of breathing or hypoventilation, or both, leads to respiratory-related arousals (RERA) from sleep. Partial obstruction of the upper airway (with RERAs) and daytime sleepiness are the features associated with upper airway resistance syndrome (UARS).21

The Hypocapnic-Apneic Threshold

In NREM sleep, a highly reproducible hypocapnic-apneic threshold is unmasked, and a central apnea will occur if the $P_{aco_2}$ is lowered, even by a small amount.22 As a result, hypocapnia is the most important inhibitory factor to breathing during NREM sleep. This threshold level of $P_{aco_2}$ is decreased by hypoxia, possibly by excitation caused by miscellaneous nonchemical stimuli. One major cause of SDB is breathing instability produced by this threshold effect and by arousals, hypoxia, and other factors that alter this threshold over time.

Sleep Effects on Cardiovascular Physiology

The cardiovascular system adjusts to the changes in gas exchange that accompany sleep and to the apneas and hypopneas that may interrupt sleep. Normally, during NREM sleep there is a withdrawal of sympathetic tone, both neural and humoral, and an increase in parasympathetic tone—changes that result in a reduction in heart rate, blood pressure, and cardiac output.23 The decreased cardiac workload and O$_2$ demand are accompanied by a diminished ability to provoke an arrhythmia.

Gradual awakening is accompanied by a modest increase in sympathetic outflow without much evidence of parasympathetic withdrawal. In contrast, with an abrupt arousal caused by noise or sleep apnea, there occurs an abrupt increase in sympathetic drive manifested by increases in blood pressure and heart rate and by marked parasympathetic withdrawal.24

In REM sleep, cardiovascular and breathing systems are relatively independent of metabolic drive and inhibition of muscle activity. Sympathetic activation increases to levels seen during wakefulness but is often episodic, leading to transient changes in heart rate, blood pressure, and breathing. Such surges in blood pressure may play a part in triggering ischemic events in patients with heart disease or diabetes.25

In general, however, sleep is cardioprotective in healthy persons. Sleep apnea disrupts cardiovascular regulation during sleep because of repetitive arousals, hypoxemia, and increased

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<tr>
<th>Type of Apnea</th>
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<th>OBSTRICTIVE</th>
<th>MIXED</th>
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<td>Arterial Oxygen Saturation ($S_pO_2$)</td>
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**Figure 4** This schematic representation of the ventilatory signals recorded during a sleep study (polysomnogram) illustrates the different patterns found in central, obstructive, and mixed apneas. In each example, the presence of apnea is confirmed by the cessation of airflow at the nose and mouth (top), and the consequence of apnea—namely, hypoxemia—is demonstrated by the development of oxygen desaturation on the continuous record of arterial oxygen saturation ($S_pO_2$) (bottom). The three types of apnea are distinguished by the respiratory efforts made during the episode (middle). In central apnea, no respiratory efforts are made; in obstructive apnea, diaphragmatic contractions continue and often intensify during the episode; and in mixed apnea, a period of absent respiratory efforts is followed by active inspiratory muscle contractions against an occluded upper airway.
intrathoracic pressure changes, which result in preload and afterload effects on the heart.25

EVALUATING SLEEP DISTURBANCES

Monitoring a person with electrodes during sleep results in a classification of sleep into two states: non–rapid eye movement, or NREM, sleep and rapid eye movement, or REM, sleep. NREM sleep can be further subdivided into stages I and II (light or transitional sleep) and stages III and IV (deep sleep), depending on the frequency and amplitude of brain waves. States are distinguished by recording electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) measurements. The combination of these measures and the cardiopulmonary monitoring of airflow, respiratory effort, oxygen saturation, and heart rate—along with identification of body position—constitute polysomnography, which is a common test used to diagnose sleep apnea.

Respiratory Disturbance

Various measurements are used to quantify respiratory disturbances during sleep.15 The apnea-hypopnea index (AHI) is the total number of apneas and hypopneas occurring during sleep divided by the hours of sleep time. Values of AHI can be computed for the different stages of sleep. Another term for AHI is the respiratory disturbance index (RDI). The term desaturation index, also called oxygen desaturation index, refers to the number of times per hour that O₂ saturation falls by more than 3% to 4%, and it may be reported as an independent measure of cardiorespiratory instability. The snoring index (SI) is the percentage of time spent snoring during sleep.

The arousal index (AI) is computed as the number of transient awakenings per hour, and it is defined by a change in state from sleep to waking that is longer than 2 seconds but less than 3 minutes.13 This number is used to estimate individual exposure to transient arousals from sleep, and it is distinguished from nocturnal awakenings by the length of the bout of wakefulness. Included in this index are spontaneous brief awakenings caused by external and internal stimuli (e.g., noises and leg jerks, respectively). The AI may differ from the AHI or RDI because many (approximately 20%) apneas or hypopneas are not accompanied by arousals, and because the AI count includes arousals that are not apnea-induced.

Oxygen Saturation

Various measurements of O₂ saturation, as plotted over time, indicate the extent of exposure to hypoxemia during sleep. One measure is the O₂ saturation profile, in which values of O₂ saturation are presented in the frequency domain, which plots the pattern and extent of O₂ deficiency during sleep.26 Values reported include estimations of the lowest O₂ saturation and the length of time spent below a specific O₂ saturation (e.g., 90%, 85%, 80% O₂ saturation of hemoglobin). In addition, recordings can be examined in the time domain to estimate the degree to which O₂ saturation exhibits periodic behavior.

Hypoventilation

Hypoventilation is not directly measured during routine sleep studies, because tests for arterial blood gases are uncomfortable and incur an unfavorable risk-to-benefit ratio. Markers for PₐCO₂ include end-tidal values of CO₂ or transcutaneous estimates of CO₂. Both are qualitative. The former makes the assumption of adequate sampling of alveolar gas, and the latter provides trends rather than precise numbers. Neither is used routinely during sleep studies in adults.

Sleep-Disordered Breathing

Healthy individuals may exhibit obstructive or central apneas at sleep onset or during periods of REM sleep.27 Episodes are usually less than 15 seconds in duration and are not repetitive.
Occasionally, longer periods of apnea (lasting 30 seconds or more) are seen during REM sleep. These episodes may not be accompanied by arousal or sleep-state changes.

Healthy young men have more frequent apneas during sleep than young women, but after the sixth decade of life, respiratory disturbances during sleep increase in number and occur with equal frequency in men and women. Patients with a clinically important sleep apnea may be distinguished from patients with normal respiratory disturbances by the presence of repetitive apneas longer than 10 to 15 seconds that occur during stages I and II of NREM sleep and during REM sleep and that are frequently accompanied by daytime sleepiness. If treated, patients with significant apnea show improvement in daytime symptoms and general performance.

DEFINITION OF SLEEP-DISORDERED BREATHING

In the United States, 9% to 12% of women and 27% to 35% of men may have an AHI greater than 5, a number often quoted as a threshold value for normality; however, many people with an AHI greater than 5 have no clinically apparent illness. If the definition of illness is the presence of daytime sleepiness or cardiovascular complications such as hypertension, it is estimated that about 2% of women and about 4% of men have symptomatic SDB. Studies suggest that patients with symptomatic SDB who drive are at increased risk for vehicular accidents in which they may incur substantial disability. Medical practitioners often fail to recognize the presence of sleep apnea syndrome.

ETIOLOGY OF SLEEP-DISORDERED BREATHING

Predisposing Factors

Snoring is generally considered a predisposing feature in the development of SDB and symptoms of sleep apnea. Snoring increases with age; approximately 44% of men and 30% of women 65 years of age or older are said to snore. Persons who snore are two or three times more likely to have hypertension and 1.5 times more likely to have diabetes than people who do not snore, even after age and obesity are taken into account as risk factors for these diseases.

Genetic Factors

Sleep apnea has a genetic component. Symptoms relating to apnea occur two to four times more often in family members of affected patients than in a control population. Sleep apnea events occur more often in first-degree relatives of sleep apnea patients than in control subjects matched for age, sex, and socioeconomic status. Such studies reveal that the symptomatic sequelae of multiple apneas are quite variable, probably because of an interaction between both genetics and the environment.

Patients with sleep apnea exhibit a twofold increase in a polymorphism for apolipoprotein E associated with cardiovascular disease and Alzheimer disease. Using a statistical approach to estimate inheritance, the Cleveland Family Study found that 27% of the variation in AHI in the community could be accounted for by perhaps only a few genetic factors. Transmission patterns in both the white and the African-American patients were consistent with mendelian inheritance. Adjustment for body mass index (BMI) significantly reduced the significance of a genetic effect in whites but not in African Americans. Thus, an underlying genetic basis for sleep apnea could be independent of the contribution of BMI to the disease in African Americans.

Specific craniofacial morphology (e.g., a short mandible and round head) are predisposing factors for the development of snoring, apneas, or both. It is also known that there are familial traits in hypercapnic and hypoxic sensitivity; these could relate to the tendency to breathe periodically during sleep. In addition, obesity and alcoholism (factors associated with SDB) can be family traits and, to the extent that these factors are causally related to apneas, may account for the familial clustering of sleep apnea. It is not known whether there is a familial trait involving the respiratory coordination of muscles of the chest wall and upper airway. A role for genetic transmission of ventilatory behavior (respiratory frequency, tidal volume, and minute ventilation) is directly supported by reports of nearly absent respiratory depression in several gene knockout models and by studies of inbred rat and mouse strains. Given the current evidence, sleep apnea does not appear to be the result of a single mutation or protein action.

Central Sleep Apnea

PATHOPHYSIOLOGY

The instability of breathing that occurs with central apnea or hypopnea reflects brain stem interplay between the sensitivity to CO2 and the hypocapnic-apneic threshold. The inhibitory effects of sleep on ventilatory responsiveness are offset by neural mechanisms that stabilize ventilation. One such mechanism is short-term potentiation (STP), or a transient increase in ventilation occurring after a large breath (a sigh) or an apnea. STP may be abolished by prolonged hypoxia, which may explain the development of periodic breathing in patients at high altitudes or in patients with cardiopulmonary disease who have modest hypoxemia. Finally, upper airway obstruction may reflexly inhibit central ventilatory output and provoke central apnea in some patients.

The occurrence of a central apnea or, for that matter, any apnea appears to set in motion events that conspire to promote further breathing instability [see Figure 6]. First, time delays in the ventilatory control system prevent resumption of rhythmic breathing after apnea until arterial CO2 levels increase by 4 to 6 mm Hg above the set point. Second, central apnea is associated with narrowing or occlusion of the pharyngeal airway. Resumption of ventilation thus requires opening of a narrowed or occluded airway, which involves overcoming mucosal adhesion and gravitational forces. (This narrowing of the upper airway may explain the overlap between central and obstructive apnea, or mixed apnea, and the successful use of nasal continuous positive airway pressure [CPAP] in some patients with central sleep apnea.) Third, a combination of hypoxia, hypercapnia, and transient arousal results in ventilatory overshoot, subsequent hypocapnia, and further apnea or hypopnea.

Mathematical models and studies in humans have focused on statistical correlations between the incidence of periodic breathing and the incidence of hypoxic sensitivity. Such periodic breathing during sleep occurs more frequently in individuals with higher peripheral chemosensitivity. Alternative explanations for repetitive apneas during sleep are that (1) patients with repetitive apneas have the same oscillations as normal individuals, but excitatory stimuli contribute to a larger amplitude of these oscillations in sleep apnea, or (2) recurrent apneas result from an intrinsic property of the feedback control of breathing in regard to either stability or instability in ventilation over time.
Several factors predispose persons to sleep apnea, and some of these factors are more selective for central apnea than for obstructive events [see Table 1].

Central sleep apnea is also more common in stroke patients than in control subjects matched for age, weight, and BMI.45 Interestingly, there is no difference between the prevalence of sleep apnea in patients with hemispheric involvement and that in patients with brain stem involvement. Although central sleep apnea is associated with stroke, the natural history and consequences of central sleep apnea in stroke patients remain uncertain. Available data on the effects of sleep apnea on blood pressure and sympathetic motor output suggest that it is prudent to identify and treat sleep apnea in the poststroke period.46

Patients with hypothyroidism and renal failure have an unexpectedly high prevalence of both central and obstructive sleep apnea (OSA).47,48 Similarly, patients with acromegaly have a high rate of central and obstructive apnea, which correlates with higher biochemical markers of disease activity and higher chemoresponsiveness.49-51

### Diagnosis

**Clinical Presentation**

Cheyne-Stokes respiration, or CSR, is the signature feature of central apnea. CSR is marked by a crescendo-decrescendo pattern of breaths, followed by central apneas or central hypopneas, some lasting as long as 30 seconds [see Figure 7]. Patients are often hypocapnic during wakefulness and sleep. CSR commonly seen in healthy persons at high altitude results from hypoxic stimulation of breathing and resultant hypocapnia. Conditions that promote CSR at normal altitude include hypoxia, decreased lung volume, decreased metabolic rate, renal failure, and cerebrovascular disease.

CSR occurs in 25% of congestive heart failure (CHF) patients. A seemingly minor ventilatory disturbance may initiate an appropriate change in ventilation and overcompensation. Then, a change in ventilation in the opposite direction occurs, with overshoot, and an oscillating breathing pattern is established.

**Diagnostic Testing**

The severity of central apneas during sleep is determined by a polysomnographic study of the frequency of respiratory events per hour of sleep (i.e., the apnea-hypopnea index or respiratory disturbance index), the severity and frequency of O₂ desaturation or hypercapnia, changes in sleep-stage distribution, and clinical symptoms produced by the disorder.

**Treatment**

Central apneas in otherwise healthy persons are usually not treated. Approximately 25% of patients with CHF, even those who are well compensated, have clinically significant central sleep apnea.52 CHF patients with CSR have a higher mortality and a greater need for cardiac transplantation than CHF patients without CSR events.53,54 The clinical management of CSR in the setting of CHF is well documented, and data indicate CPAP as the recommended therapy.

In a randomized study, CHF patients with CSR and central sleep apnea who received treatment with CPAP for up to 6 hours a night had a significantly greater rate of transplant-free survival than control subjects, who did not receive CPAP.55 In patients with stable chronic CHF who have CSR, CPAP has been shown to reduce CSR, left ventricular afterload, plasma catecholamine

### Table 1  Risk Factors for Sleep Apnea with Associations to Apnea Type

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Apnea Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>CSA, OSA</td>
</tr>
<tr>
<td>Male gender predominance</td>
<td>CSA, OSA</td>
</tr>
<tr>
<td>Family history of apnea or snoring</td>
<td>OSA</td>
</tr>
<tr>
<td>Head form (craniofacial morphology)</td>
<td>OSA</td>
</tr>
<tr>
<td>Poor physical fitness</td>
<td>OSA</td>
</tr>
<tr>
<td>BMI</td>
<td>CSA (lower BMI); OSA (higher BMI)</td>
</tr>
<tr>
<td>Alcohol ingestion</td>
<td>OSA</td>
</tr>
<tr>
<td>Smoking exposure</td>
<td>OSA</td>
</tr>
<tr>
<td>Sleep restriction</td>
<td>OSA</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>CSA, OSA</td>
</tr>
</tbody>
</table>

BMI—body mass index  CSA—central sleep apnea and Cheyne-Stokes respiration  OSA—obstructive sleep apnea
levels, and sympathetic nervous system activity and to improve left ventricular ejection fraction and quality of life. Application of CPAP therapy is discussed elsewhere [see Obstructive Sleep Apnea, Continuous Positive Airway Pressure, below].

Supplemental O2 has also been shown to reduce the severity of CSR, decrease urinary catecholamine levels, and improve exercise capacity. Theophylline reduces the severity of central sleep apnea; however, long-term use of theophylline is associated with proarrhythmic effects, and sustained benefits are unproven. Thus, further study is necessary before theophylline or O2 therapy can be recommended over CPAP.

Nonhypercapnic idiopathic central sleep apnea without CSR may improve with supplemental O2 therapy or treatment with acetazolamide. Treatment for hypercapnic central sleep apnea, a disorder of the ventilatory control system, should be aimed at improving alveolar ventilation. Noninvasive ventilation or tracheostomy and mechanical ventilation should be aimed at improving alveolar ventilation. Noninvasive ventilation or tracheostomy and mechanical ventilation should improve P_{CO2}, cor pulmonale, and symptoms of daytime hypersomnolence.

Obstructive Sleep Apnea

The fundamental feature of obstructive apneas and hypopneas, including snoring, is a functional narrowing or collapse of the upper airway. Illness occurs in the context of repetitive events.

PATHOPHYSIOLOGY

The presence of an anatomic abnormality is not sufficient or necessary to produce overt disease. Nevertheless, there is evidence that persons with OSA have a smaller-caliber pharyngeal airway during wakefulness than the airway in persons without OSA. In addition, the pharyngeal airway in patients with OSA syndrome has an elliptical anterior-posterior configuration, in contrast to a more circular configuration in normal persons. This asymmetry seems to predispose patients to anterior-posterior collapse.

A collapsing transmural pressure is generated either by a negative intraluminal pressure or a collapsing surrounding pressure; however, pharyngeal obstruction does not require negative pressure, because complete upper airway collapse occurs during central apnea. The occurrence of upper airway obstruction in the absence of negative intraluminal pressure is consistent with the hypothesis that the intrinsic properties of the upper airway (e.g., stiffness of the pharyngeal wall) will or will not permit collapse to occur.

Another factor in airway collapse is the mechanical independence of the upper airway and the thoracic cage and mediastinum. An increased lung volume is associated with increased upper airway caliber in awake humans, independent of muscle dilatation in the upper airway. Caudal traction may stiffen the pharyngeal airway and permit greater dilating force or, at the very least, prevent inspiratory collapse, both of which effects have been demonstrated in model systems. Therefore, a reduction in functional residual capacity could also contribute to a reduction in upper airway patency during sleep.

Proposed mechanisms for the pathophysiology of OSA involve alterations in the neuromuscular control of upper airway muscle, the resting size of the upper airway, and the degree of stiffness of the upper airway wall. The underlying defect is a pharynx that is susceptible to narrowing and collapse. The change in respiratory drive that occurs with sleep onset leads to reduced ventilatory motor output to upper airway muscles, which triggers the cascade of events leading to pharyngeal obstruction during sleep. Upper airway obstruction often occurs during experimentally induced periodic breathing at the lowest point of respiratory drive. Central ventilatory control instability is a key mechanism for repetitive obstructive apnea.

RISK FACTORS

Obesity is the strongest risk factor for OSA [see Table 1], and the prevalence of OSA substantially increases with age. OSA has a strong familial component that likely involves multiple genetic influences. Several anatomic abnormalities may predispose a patient to OSA; in men, a large neck size (>17 in) may be a risk factor for OSA. Additional risk factors include ethanol and nicotine use, because these agents promote airway collapse.

OSA-ASSOCIATED MORBIDITY AND MORTALITY

The mortality associated with sleep apnea has not been satisfactorily explained. Early reports suggested mortality from cardiorespiratory failure, pulmonary embolus, and renal failure. Death has been reported to result from sedative drug use, particularly preoperative medications, which suppress breathing and the arousal response to an obstructive apnea. Automobile acci...
Dents related to excessive daytime sleepiness may have a substantial impact on morbidity and mortality. Taking a broader view, sleep quantity and quality are associated epidemiologically with hypertension, all-cause cardiovascular risk, and early mortality.62,64

The occurrence of sleep apnea with the features of syndrome X—hypertension, obesity, diabetes, and hyperlipidemia—has prompted a call to rename this disorder syndrome Z.65 This cluster of diseases and disorders may occur through a common set of neuroendocrine factors, genetic predispositions, or both. Both the physiologic plausibility that sleep problems relate to insulin resistance66 and the epidemiologic association between snoring and cardiovascular risk factors offer a rationale to explore the pathogenesis of OSA as it relates to obesity, race, and cardiovascular disease and the pathogenesis of central apnea as it relates to aging, cardiovascular disease, and stroke. It may be that prevention of disease progression in sleep apnea may be nested within the factors that increase cardiovascular risk—namely, obesity, hypertension, lack of exercise, and alcohol use.

DIAGNOSIS

Clinical Presentation

Self-reported snoring and excessive daytime sleepiness are the major presenting symptoms of OSA. One might suspect that the bed partner rather than the patient would report snoring more reliably; however, reports by the patient and bed partner are similar.67 Other complaints include apneas, choking during sleep, restless sleep, and, in some patients, insomnia-like symptoms along with excessive daytime sleepiness.

Diagnostic Testing and Imaging

Overnight polysomnography is the current gold standard for the diagnosis of OSA and should be considered in any patient suspected of having this disorder [see Figure 8]. Split night polysomnograms provide adequate time for both diagnosis and proper CPAP prescription. Home-based studies provide data comparable to data from laboratory studies; however, devices vary substantially. Oximetry alone cannot be recommended as a screening tool for OSA. Nasal-pressure changes detected during inspiration and expiration reflect changes in airflow with greater accuracy than thermistors.

TREATMENT

OSA patients should be counseled about the risk of sleepiness and offered therapy when it is clinically indicated.68 Therapy for sleep apnea is diverse and includes correction of associated medical conditions (e.g., cardiopulmonary disease) and treatment of SDB by specific interventions (e.g., surgery or use of mechanical aids). The principles of management are directed toward improvement in gas exchange, sleep continuity, and chronic cardiopulmonary symptoms during wakefulness. Management approaches start with consideration of mechanical devices; when mechanical devices prove inadequate, surgery to remove nasal or pharyngeal obstruction is considered.

Treatment is customized to the individual patient and may require avoidance of agents that provoke apneic episodes (e.g., alcohol, sedatives, and androgens). Obese patients with OSA who are treated for obesity may show improvement in the severity of sleep apnea, but long-term weight reduction is often difficult to achieve. Dietary management alone is effective in producing long-term weight reduction in a small minority of morbidly obese patients. However, even modest weight reduction achieved by dieting can improve SDB. Gastric stapling can achieve weight reduction in approximately 60% of patients who undergo the procedure, and appears to be effective in improving or reversing sleep apnea in most morbidly obese patients.

Continuous Positive Airway Pressure

Indication CPAP is considered the first choice of treatment for OSA.69 Treatment with CPAP improves vigilance and cognitive function in persons who report hypersomnolence; however, patients who do not have daytime hypersomnolence may not experience substantial improvement of cognitive function with CPAP.70 Treatment with CPAP will reduce blood pressure in normotensive and hypertensive patients; in the latter patients, control of blood pressure with drugs may become easier, or

Figure 8 A fragment of a polysomnogram shows a series of obstructive apneas during sleep. Each episode of absent flow is accompanied by continued thoracoabdominal efforts. Apneas are terminated by arousals. Obstructive sleep apnea has this pattern as its signature.
drugs may no longer be needed. Contraindications include bronchopleural fistula, acute pneumothorax, and sinus-communicating pneumocephalus. A relative contraindication is nasal or pharyngeal obstruction, which must be managed before CPAP treatment is attempted.

**Application** Nasal CPAP is immediately effective in reversing airway obstruction in most patients with OSAS. The patient is outfitted with a nasal mask, which is attached to a blower that applies an adjustable positive pressure. The amount of pressure required to relieve upper airway obstruction (usually 5 to 20 cm H2O) is most often determined empirically during a sleep study. Effective CPAP is defined as the pressure required to prevent inspiratory collapse of the upper airway when the patient is in the supine position and during all stages of sleep. Positive pressure applied to the nose presses the soft palate to the back of the tongue and thereby prevents leakage of air out of the mouth. If the apparatus fails, the patient is free to breathe through the oral cavity. Full-face masks or chinstraps may be needed for patients in whom air escapes through the mouth. Monitoring of pressure can be used to document the hours of use of CPAP and the effectiveness of CPAP in maintaining airway patency. Heated-humidification devices may increase patient compliance and reduce symptoms of nasal obstruction. For patients in whom standard CPAP is unsuccessful or intolerable, bilevel or self-adjusting modes may be attempted.

The routine use of bilevel therapy (i.e., devices that sense inspiration efforts and apply a higher positive pressure during inhalation) does not improve patient adherence; however, bilevel pressure is able to eliminate apneas with lower expiratory pressure and mean airway pressure in patients who are unable to tolerate high pressures. Devices that sense and then automatically tritrurate pressure to eliminate apneas operate in a way similar to personal titration; the routine use of unattended devices in the home is currently under study.

**Oral Appliances**

Intraoral devices to reposition the mandible are increasingly being used in the management of sleep apnea, both as primary therapy for heavy snoring and as an alternative therapy for patients who cannot tolerate CPAP. An oral appliance will reduce the hypopnea index and the arousal index and will improve O2 saturation even in patients with mild to moderate OSA. Oral appliances are modestly preferred over CPAP; however, CPAP is more effective than oral appliances in reducing the apnea-hypopnea index.

**Surgery**

Surgical management of OSA encompasses several strategies: (1) bypass of the anatomic obstruction by way of tracheostomy, (2) alteration of the bony structural support of the upper airway, and (3) alteration of the soft tissue attachments or deposits to improve airway patency. Of the surgical options, only tracheostomy is routinely effective in eliminating OSA. Central apneas may persist after tracheostomy. Despite the development of a new flap-type tracheostomy and low-profile tracheostomy tubes, local stoma problems are relatively common. Infections, local discomfort, formation of granulation tissue, and the distortions of self-image produced by tracheostomy have limited the use of this procedure to relatively few patients. Adaptation to a tracheostomy often takes a year or more.

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**Pharmacologic Therapy**

Pharmacologic therapy plays a very limited role in the management of upper airway obstructions during sleep. Modafinil is the only drug approved by the Food and Drug Administration for treatment of OSA, and it is effective for the management of residual sleepiness after treatment with CPAP. Use of modafinil may be considered when CPAP compliance is acceptable and other behavioral issues, such as sleep restriction, have been addressed.

Medroxyprogesterone is not effective therapy for OSA in patients with normal levels of Pco2, but it may be used in the management of obesity hypoventilation syndrome. Acetazolamide therapy is not effective treatment for OSA, but it will reduce the CO2-apneic threshold and thus may improve central sleep apnea. Protriptyline (a nonselecting antidepressant) increases alertness and may modestly reduce the apnea-hypopnea index, but its anticholinergic side effects limit its routine use. Nicotine may modestly reduce the apnea-hypopnea index in patients with OSA; however, current delivery methods and available doses do not have clinical utility. Serotonin agonists do not generally affect the apnea-hypopnea index or the neurocognitive deficits associated with sleep apnea. Thus, these agents are not currently recommended for management of OSA, but they can be used to treat comorbid depression or mood disorders.

**Other Conditions Associated with Sleep-Disordered Breathing**

**ASTHMA**

Cough and cough-induced arousals from sleep may be the presenting complaint of patients with reactive airway disease. Cough may be caused by changes in airway smooth muscle tone during NREM sleep and by bronchoconstriction during REM sleep. Gastroesophageal reflux may contribute to awakenings and bronchoconstriction. Nighttime cough occurring in a patient with uncomplicated asthma may indicate inadequate therapeutic effect of asthma medication or exacerbation of airway disease by exposure to allergens [see 14:II Asthma]. Morning dipping refers to the fall in lung function that occurs in the early morning hours and represents an extreme form of diurnal variation in lung function present in most patients with airway reactivity. Reports describing morning dipping emphasize that lung function measured at midday may be normal, whereas nighttime values may show moderately severe airway obstruction.

**UPPER AIRWAY DISEASE**

Patients with disease of the nose, larynx, and pharynx may be disturbed during sleep by apnea or aspiration of secretions caused by excessive production of mucus (e.g., chronic allergic rhinitis) or by impaired swallowing (e.g., bilateral recurrent laryngeal nerve paralysis). In both instances, frequent arousals from sleep are associated with cough or a choking sensation. During sleep, particularly REM sleep, the cough response is less than it is during wakefulness. As a result, greater amounts of secretions are tolerated before a cough ensues. After awakening, this larger amount of material may precipitate paroxysmal cough. Patients who are being treated with hypnotic medications may tolerate greater amounts of secretions before cough-induced arousal from sleep, which increases the likelihood of aspiration injury to the lungs. Hypnotic medications used to manage insomnia should be used with caution in these patients.
Patients with COPD may present with a variety of sleep problems. Nocturnal cough can be related to bronchitis. Insomnia may be the consequence of therapy with methylxanthines (e.g., aminophylline). Hypoxemia during sleep may occur as a consequence of a mechanical airway impairment present during wakefulness that is exacerbated during sleep by the normal fluctuations in gas exchange. Hypoxemia that occurs only during sleep in patients with moderately severe COPD is associated with the development of cor pulmonale. In these persons, complications attributed to hypoxemia and hypercapnia are associated neither with a severe mechanical defect (forced 1-second expiratory volume of less than 1 L) nor with symptomatic apnea. Other diagnostic entities, such as recurrent pulmonary emboli or chest wall muscle weakness, should certainly be considered.

The combination of COPD and sleep apnea is called the overlap syndrome in the European literature, and it is estimated to be present in 20% to 25% of patients presenting with moderate and moderately severe COPD. There is usually historical evidence for snoring, pauses during sleep, and arousals from sleep, and the patient should be treated for OSA [see Obstructive Sleep Apnea, Treatment, above]. Patients with SDB that is not caused by OSA may experience a good sleep response to supplemental O2. Symptoms persisting after nocturnal O2 may warrant a sleep study.

INTERSTITIAL LUNG DISEASE

Respiratory disturbances during sleep for patients with interstitial lung disease include cough and hypoxemia. Patients also may have a concomitant sleep apnea. Sleep hypoxemia may be a factor in the development of pulmonary hypertension. A restrictive defect on pulmonary function testing and interstitial fibrosis on chest roentgenogram may reflect a history of chronic aspiration. In patients with interstitial lung disease, during sleep, the tone of the gastroesophageal junction relaxes, allowing stomach contents to regurgitate to the level of the pharynx. In such patients, it may be useful to measure pH levels in the pharynx and esophagus during sleep.

NEUROMUSCULAR DISORDERS

Respiratory disturbances caused by OSA during sleep may occur because the underlying disease process affects upper airway muscles. Sleep disturbances associated with cough, choking, or aspiration and with SDB may be the first indications of ventilatory problems in patients with neuromuscular disease. Occasionally, sleep fragmentation and the effects of sleep deprivation dominate the clinical presentation of the patient with neuromuscular disease. After treatment for SDB, the clinical manifestations of the primary neuromuscular disorder may no longer appear so severe.

KYPHOSCOLIOSIS

Treatment of hypopacnic respiratory failure by tracheostomy with or without positive-pressure ventilator support during sleep can reverse cor pulmonale and improve the appearance of the chest roentgenogram.

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References


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Figure 1 Seward Hung.

Figures 5, 7, and 8 Courtesy of M. Safwan Badr, M.D.