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Sleep-Related Hypoventilation/Hypoxemic Syndromes*

Kenneth R. Casey, MD, MPH, FCCP; Kathia Ortiz Cantillo, MD; and Lee K. Brown, MD, FCCP

The latest edition of The International Classification of Sleep Disorders: Diagnostic and Coding Manual subsumes a broad range of disorders under the heading “Sleep Related Hypoventilation/Hypoxemic Syndromes.” Some are quite common, such as COPD with worsening gas exchange during sleep; while some are exceedingly rare, such as congenital central hypoventilation syndrome. All share the attribute of abnormal gas exchange that worsens, or may only be present, during sleep. The sleep state, the sleeping posture, and the circadian rhythm driving sleep all may affect respiration by altering control of breathing and/or pulmonary mechanics. These changes are largely inconsequential in the normal individual but interact with respiratory, neurologic, or neuromuscular disease to manifest as the sleep-related hypoventilation/hypoxemic syndromes. In addition to optimal treatment of the underlying disorder (when known and when possible), treatment usually involves nocturnal ventilatory support that is now most commonly provided by noninvasive positive pressure ventilation. (CHEST 2007; 131:1936–1948)

Key words: chest wall disease; control of breathing; hypercapnia; hypoventilation; hypoxemia; hypoxia; neuromuscular disease

Abbreviations: BMI = body mass index; CCHS = central congenital hypoventilation syndrome; CF = cystic fibrosis; FRC = functional residual capacity; HD = Hirschsprung disease; ICSD-2 = second edition of The International Classification of Sleep Disorders, Diagnostic and Coding Manual; NIPPV = noninvasive positive pressure ventilation; NREM = non-rapid eye movement; OHS = obesity-hypventilation syndrome; OSAS = obstructive sleep apnea syndrome; PAP = positive airway pressure; REM = rapid eye movement; SCD = sickle-cell disease

The availability of new technology, applied in original ways, has often been responsible for rapid advances in a variety of medical disciplines. This been particularly apparent in sleep medicine, in which the introduction of equipment capable of continuously monitoring oxyhemoglobin saturation and PaCO₂ has permitted detailed study of gas exchange during sleep in both health and disease. Indeed, the linkage of technologies for continuous measurement of gas exchange with the technology of EEG essentially created the contemporary field of sleep medicine. This review will set forth the mechanisms thought to be responsible for sleep-induced hypoventilation and hypoxemia, and then discuss recent developments related to sleep-induced hypoventilation and hypoxemic syndromes reflecting a portion of the recently published second edition of The International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD-2) [Table 1].¹

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Mechanisms of Sleep-Induced Hypoventilation and Hypoxemia

Sleep-induced hypoventilation is characterized by elevated levels of PaCO₂ while asleep, defined in the ICSD-2 as a level > 45 mm Hg or "disproportionately increased relative to levels during wakefulness."¹ Sleep-induced hypoxemia in the ICSD-2 is defined as "an SpO₂ [oxyhemoglobin saturation] during sleep of < 90% for more than five minutes with a nadir of at least 85%" or "> 30% of total sleep time with an SpO₂ of < 90%."¹ Other sources define these gas exchange conditions differently, and the literature is sufficiently controversial in this regard that space limitations prevent any detailed discussion.

Nocturnal hypoventilation can be attributed to either decreased ventilatory drive ("won’t breathe") or worsening mechanics ("can’t breathe"). Nocturnal hypoxemia follows due to the displacement of oxygen in the alveoli from rising carbon dioxide levels, as predicted by the alveolar air equation. Alternatively, arterial hypoxemia alone may be the product of worsening ventilation/perfusion mismatch with greater effective shunt.

Ventilatory Drive

Several studies²,³ have demonstrated a reduction in inspiratory muscle drive following sleep onset, independent of any changes in upper airway mechanics. At least part of this change is usually attributed to a state-dependent increase in the medullary "set point" for PCO₂ of approximately 2 mm Hg.²,⁴ An older body of literature⁵,⁶ has documented reductions in the slope of ventilatory response to hypoxemia and hypercapnia that are profound during rapid eye movement (REM) sleep but more modest in non-REM (NREM) sleep; indeed, there

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<th>Table 1—ICSD-2 Sleep-Related Hypoventilation/Hypoxemic Syndromes With Examples of Associated ICD-9 Diagnoses*</th>
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<td>ICSD-2 Diagnosis</td>
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<td>Sleep-related nonobstructive alveolar hypoventilation, idiopathic CCHS</td>
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*ICD-9 = International Classification of Diseases, ninth revision; n/a = not applicable.
Dempsey et al.8) and lead to an unstable breathing irregularity of tidal volume and respiratory rate.10

Sometimes called common in REM sleep, particularly the phasic portion of REM. These include conditions that increase ventilatory responsiveness to CO$_2$ in the domain between the apneic threshold and eupnea, including hypoxia or pulmonary vascular engorgement.8,9

Another type of ventilatory control perturbation is common in REM sleep, particularly the phasic portion of REM. Sometimes called a**taxic breathing** or respiratory dysrhythmia, this phenomenon consists of shallow breathing, pauses in breathing, and/or irregularity of tidal volume and respiratory rate.10 Orem and coworkers$^{11,12}$ demonstrated in cats that REM-related excitatory and inhibitory effects on individual ventral respiratory group neurons may be the underlying cause of the irregular breathing. Interestingly, Orem and coworkers maintain that ventilatory drive is generally increased in REM,12 and his group as well as others have demonstrated REM-related breakthrough of ventilatory effort during post-hyperventilation apnea in cats,$^{11}$ or absence of an apneic threshold entirely during REM in dogs.$^{13}$ However, the overall effect of this REM-related dysrhythmic breathing may be to reduce alveolar ventilation by altering minute ventilation or dead space/tidal volume ratio, or both.$^{14}$

**Respiratory Mechanics**

Respiratory mechanics may change during sleep and thereby worsen gas exchange, particularly in obstructive airways disease or neuromuscular disease. REM sleep is accompanied by widespread skeletal muscle hypotonia. The diaphragm is spared; the accessory muscles of respiration (scalenes, intercostals, sternomastoids, and muscles of the abdominal wall) are not.$^{15}$ Gas exchange may be adversely affected if the individual requires the assistance of these muscles to maintain normal ventilation. Johnson and Remmers$^{16}$ demonstrated this effect in six patients with COPD, wherein dropout of scalene and sternomastoid electromyographic activity during REM sleep coincided with decreases in chest wall excursion and oxyhemoglobin saturation.

REM sleep also appears to reduce functional residual capacity (FRC), probably due to the loss of accessory muscle tone and consequent alterations in chest wall movement.$^{17}$ Since FRC also declines in normal individuals when assuming a reclining position,$^{18}$ the combination may result in a decline in FRC to below closing capacity. When this occurs, dependent lung zones will remain unventilated during part of each tidal breath, effectively resulting in a shunt.$^{19}$ It is questionable whether the degree of FRC change that occurs in normal individuals is sufficient to cause hypoxemia. However, this mechanism appears to be a *bone fide* mechanism for sleep-related hypoxemia in obstructive pulmonary disease (when closing capacity is already elevated due to pathologic narrowing of the small airways) and in obesity (which contributes an additional decrement in FRC that may well bring it to below closing capacity).

Upper airway patency during inspiration depends on a variety of muscles acting alone or in concert (e.g., tensor palatini, genioglossus, geniohyoid). All of these skeletal muscles participate in the phenomenon of REM-related hypotonia. They are also known to become less active during NREM sleep compared to wakefulness, albeit to a more modest degree. This has been demonstrated indirectly by measurement of state-related increases in supraglottic resistance,$^{20}$ as well as by electromyography of individual dilator muscles.$^3$

Finally, ventilation may be impaired by virtue of the postures adopted during sleep. The supine position, especially, burdens the inspiratory muscles of ventilation by imposing the weight of the abdominal contents as an additional load on these muscles. This is almost certainly apparent only when respiration is already compromised by disease, rather than in normal individuals.

**Sleep-Related Nonobstructive Alveolar Hypoventilation, Idiopathic**

Patients with a variety of neurologic conditions, such as Arnold-Chiari malformation, brainstem tumors, space occupying lesions, vascular malformations, CNS infection, stroke, or neurosurgical procedures, may demonstrate central hypoventilation.$^{21}$ However, a small number of patients demonstrate hypoventilation even after all of these conditions have been excluded. The condition of decreased alveolar ventilation resulting in sleep-related hypoxemia in patients with normal mechanical properties
of the lung and chest wall (no apparent primary lung disease, skeletal malformations, or neuromuscular disorder) is, by definition, idiopathic. This entity is uncommon and not well characterized. It seems probable that many of these patients have subtle or incipient manifestations of known causes of hypoventilation.

**Sleep-Related Hypoventilation/Hypoxemia Due to Neuromuscular and Chest Wall Disorders**

In the ICSD-2, this category subsumes a variety of disparate entities referred to in pulmonary medicine as *chest wall restrictive disorders*, all of which may result in ventilatory muscle failure during sleep with hypoventilation, hypercapnia, and/or hypoxemia. Surprisingly, there is no separate category in the ICSD-2 for obesity-hypoventilation syndrome (OHS). In respiratory medicine, OHS is recognized in the morbidly obese individual with hypoventilation and hypercapnia that is not only sleep related but extends into wakefulness as well. This review will concentrate on OHS as defined in respiratory medicine, and will separately discuss other chest wall restrictive disorders with hypoventilation/hypoxemia specifically during sleep.

**OHS**

In 1956, Burwell et al coined the term *Pickwickian syndrome* to describe patients with obesity, diurnal hypercapnia and hypoxemia, hypersomnia, polycythemia, and right ventricular failure based on the character “Joe” in Charles Dickens’ *The Posthumous Papers of the Pickwick Club*: “a fat and red-faced boy in a state of somnolency.” A less eponymous term was later popularized for what was then thought to be a fairly homogenous group of patients: *obesity hypoventilation syndrome*. A common definition of OHS consists of chronic diurnal alveolar hypoventilation (PO₂ <70 mm Hg, PaCO₂ >45 mm Hg) in an obese patient (body mass index [BMI] > 30 kg/m²; other authors used > 35 kg/m²) with no other identifiable cause of hypoventilation.

As the field of sleep medicine has developed, so has our concept of OHS. It is now recognized that OHS in most (but not all) cases is associated with obstructive sleep apnea syndrome (OSAS), an entity poorly recognized in Burwell’s time. In part, the importance of OHS lies in the dramatically increasing prevalence of obesity in developed countries, both in the United States and worldwide. In data from 2003 and 2004, 17% of US children and adolescents were overweight, and 32% of adults were obese; the prevalence of extreme or morbid obesity (BMI > 40 kg/m²) was 2.8% in men and 6.9% in women. Overweight patients have an increased risk of pulmonary, cardiovascular, GI, metabolic, and joint disorders, all of which may shorten life expectancy, diminish quality of life, and increase their use of health-care resources. Adding to this health burden, the frequently inadequate identification and treatment of OHS has significant medical and public health implications.

While obesity and unexplained hypoventilation and hypoxemia are the primary features of OHS, a variety of secondary features are common. These include hypersomnia, disturbed sleep, awakenings with headache or nausea, depressive symptoms, polycythemia, and signs of pulmonary hypertension or cor pulmonale. The prevalence of OHS in the general population is unknown. One study of 4,332 consecutive admissions to an internal medicine service revealed approximately 1% who met the definition of OHS among the 6% with a BMI ≥ 35 kg/m²; however, 75 patients meeting the BMI criterion refused to participate in the study, and of course an inpatient study is hardly representative of the general population. One study investigating the close association of OHS with OSAS reported that 37% of 111 consecutive patients with an apnea-hypopnea index > 10 had PaCO₂ > 45 mm Hg. Most reviews estimate the prevalence of OHS in OSAS at 10 to 15%. One could extrapolate these data, combined with the measured prevalence of OSA in the adult population, to estimate that approximately 0.5% of women and 1% of men have OHS, figures that seem higher than clinical experience would suggest. Mortality in this disorder is difficult to estimate given the advances in therapy that have occurred over the last decade. The report of inpatients with OHS previously cited suggests an 18-month mortality rate of 23%, although only 11 of their 47 subjects with OHS were recognized as such at discharge and considered for treatment.

The pathogenesis of OHS is now known to be multifactorial. Most early theories concentrated on the many effects of obesity on pulmonary mechanics. Obesity acts as a mass load on the respiratory system, which implies both a weight placed on the respiratory apparatus as well as an increase in respiratory inertance. Respiratory compliance is reduced, some or all of which may be attributable to changes in lung volume from mass loading. More recent data suggest that obesity also results in a degree of obstructive ventilatory impairment. These mechanical loads result in a measurable increase in the work of breathing and a defect in excitation/contraction coupling of the inspiratory muscles; that is, greater ventilatory drive is necessary to achieve normal levels of ventilation. The presence of increased ventilatory...
drive without concomitant increased ventilation has been well demonstrated in the eucapnic obese. Consequently, early thinking on OHS pathogenesis postulated that at some point, the ventilatory apparatus was no longer capable of maintaining normal levels of ventilation without excessive work of breathing, and some unknown mechanism resulted in a change in ventilatory response in order to accept a degree of hypercapnia. Why this would occur in some individuals with morbid obesity and not others of the same weight was not known until OSAS emerged in the medical literature as an important sleep disorder. Rapoport and colleagues studied a group of patients with OHS who also had severe OSAS, and determined that some of these patients regained diurnal eucapnia when their OSAS was treated. The work of Rapoport et al thus demonstrated several possible mechanisms for the development of OHS in patients with OSAS: (1) the stress of repeated obstructive sleep apneas causing inspiratory muscle fatigue directly; (2) elevated PaCO₂ from apneas leading to depression of inspiratory muscle function and/or central ventilatory control; and (3) sleep deprivation from recurrent apneas resulting in depressed central ventilatory control. A separate group of OHS patients can then be inferred in which diurnal hypoventilation appears to be purely due to the mechanical load of obesity and its effect on ventilatory control, the inspiratory muscles, or both.

An intriguing component of OHS pathogenesis concerns the metabolic consequences of obesity and consequent effects on ventilatory control. Leptin, a protein of 167 amino acids, is produced in white adipose tissue, increases in direct proportion to the degree of obesity, and acts in the hypothalamus to inhibit appetite. In the leptin-deficient mouse, absence of this metabolic messenger is associated with severe obesity, hypoventilation, and decreased ventilatory responsiveness to hypercapnia, which corrects after exogenous leptin infusion. In contrast to this experimental animal, obese humans demonstrate very high levels of leptin that do not seem to suppress appetite, suggesting that human obesity may be a leptin-resistant state. Thus, it is postulated that central leptin resistance in some obese individuals may lead to depressed ventilatory drive and consequent OHS. Phipps and coworkers reported that leptin levels, after controlling for the degree of obesity, are higher in OHS patients compared with eucapnic individuals. Additionally, Yee and collaborators demonstrated that serum leptin decreases in patients with OHS when treated with noninvasive ventilation, further suggesting a relationship between OHS pathogenesis and leptin signaling.

Early diagnosis and appropriate therapy are critically important for patients with OHS. Diagnostic polysomnography is an essential part of the evaluation of any patient with OHS in order to determine if OSAS is present. Weight loss readily comes to mind as the definitive therapy, and has proven efficacy. A reduction of 5 to 10% of body weight can result in a significant fall in PaCO₂. Unfortunately, weight loss by diet alone is difficult to achieve and sustain; thus, bariatric surgery has been advocated. Sugerman et al demonstrated that after weight reduction surgery in 31 patients with OHS who had initial and follow-up (1 year) arterial blood gas data, BMI fell from 56 ± 13 to 38 ± 9 kg/m², and PaCO₂ fell from 53 ± 9 to 44 ± 8 mm Hg. However, operative mortality (defined as occurring within 30 days) was 4% in the total of 126 OHS patients subjected to a variety of bariatric surgical techniques, compared to 0.2% in the 884 eucapnic patients. It is possible that laparoscopic bariatric surgery may be more broadly, and safely, utilized in the future.

When obstructive sleep apnea is associated with OHS, a considerable body of literature now exists demonstrating the effectiveness of positive airway pressure treatment (PAP), either continuous PAP or bilevel PAP. The latter modality, of course, has the advantage of providing a measure of ventilatory support that can be continued into wakefulness when needed and is presumably the treatment of choice when OHS is not associated with significant OSAS. Masa et al reported treatment of 22 “pure” OHS patients (apnea-hypopnea index < 20) with nocturnal noninvasive mechanical ventilation, using either a volume-cycled ventilator or bilevel PAP; 11 patients also required supplemental oxygen. Symptoms of daytime somnolence and dyspnea improved as did respiratory failure, with PaCO₂ falling from 58 ± 10 to 45 ± 5 mm Hg after 4 months. When OHS is associated with OSAS, either continuous PAP or bilevel PAP have proven effective, with improvement in diurnal hypercapnia seen in as little as 24 h. Measures of central respiratory control (hypercapnic and hypoxic ventilatory drive) have also been demonstrated to improve in OHS patients treated with either modality.

Progesterone is responsible for the hyperventilation associated with pregnancy, has been shown to stimulate ventilation in normal subjects, and has produced some benefit in OHS patients by improving hypercapnia. However, PAP has proven to be more effective in these patients, partly because it will treat any coexisting OSAS and partly because, if bilevel PAP is used, it will also augment ventilation. In contrast, progesterone by itself does not usually improve OSAS, and often has unacceptable side effects such as decreased libido in men, and increased risk of pulmonary thromboembolic disease.
Finally, oxygen treatment alone is ineffective for OSAS and is mainly used as an adjunct to PAP in patients with OHS plus OSAS; even in pure OHS, oxygen does not correct the underlying ventilatory insufficiency and is therefore not indicated without PAP or other definitive therapy.

Neuromuscular Disorders

This category reflects a diverse group of conditions affecting both adults and children, characterized by dysfunction of respiratory motor innervation or impairment of respiratory muscles. These conditions include amyotrophic lateral sclerosis, spinal cord injury, diaphragmatic paralysis, myasthenia gravis, Eaton-Lambert syndrome, toxic or metabolic myopathies, post-polio syndrome, and Charcot-Marie-Tooth syndrome. While the pathogenesis of each of these conditions is quite different, the impact of the changes in respiratory mechanics and control of breathing related to sleep can be profound in all of them. As with other conditions discussed in this review, these patients are often at particular risk during REM sleep.

Supplemental oxygen alone may be appropriate for milder cases, but nocturnal mechanical ventilation appears to improve parameters of sleep quality and may promote improved muscular performance during the daytime in some circumstances. Many of these conditions are characterized by progressive deterioration. Consequently, one of the challenges of management is the determination of the most appropriate time of initiation of mechanical ventilation. In one trial, patients with mild daytime hypoxemia (PaO2, 56 to 69 mm Hg) and sleep-related desaturation had 93% nocturnal desaturation, while none with awake saturations > 95% were hypoxemic at night; another study found a high correlation between diurnal PaCO2 > 50 mm Hg and nocturnal hypoxemia.

Sleep-Related Hypoventilation/Hypoxemia

Due to Lower Airways Obstruction

COPD

The phenomenon of nocturnal hypoxemia complicating COPD has been recognized for at least 50 years. It has also long been recognized that, in comparison to their nonhypoxic brethren, hypoxic COPD patients have greater degrees of pulmonary hypertension and cor pulmonale, require more frequent hospitalizations, and sustain higher mortality rates. Not surprisingly, sleep-related hypoxemia in the COPD patient is most frequently associated with awake oxyhemoglobin desaturation and diurnal hypercapnia, both of which may be quite modest in degree, and individuals who are already significantly hypoxic while awake are more likely to exhibit profound desaturation during sleep.

In one study, all patients with diurnal oxyhemoglobin saturations < 93% had nocturnal desaturation, while none with awake saturations > 95% were hypoxemic at night; another study found no improvement in mortality but did demonstrate a hemodynamic benefit when...
patients with normal daytime oxygenation but nighttime hypoxemia received oxygen during sleep. Both studies involved relatively small numbers of subjects, and the latter study had a high dropout rate. Increased ventricular ectopy during sleep has also been shown to occur in COPD when saturations fall to $< 80\%$. The correlation of ventricular ectopy with the degree of hypoxemia provides one possible explanation for the peak in COPD mortality that occurs in the early morning hours, when longer periods of REM sleep occur and saturations would tend to be the lowest. Finally, COPD is a cause of sleep-related symptoms, with insomnia complaints leading the list. For instance, the Tucson Epidemiologic Study of Obstructive Airways Disease reported on a cohort of 202 patients with chronic bronchitis, chronic bronchitis with asthma, or emphysema, and detected a high prevalence of insomnia (53 to 75\%, depending on diagnosis) and excessive daytime sleepiness (about 25\% for all three diagnoses) in these patients. Furthermore, insomnia complaints are associated with either abnormal pulmonary function with or without symptoms, or normal pulmonary function with respiratory symptoms, in patients with COPD.

Any discussion of sleep-related hypoventilation and hypoxemia in COPD must necessarily mention the "overlap syndrome." Flenley originated this term to apply to patients with coexisting COPD and OSAS, thus provoking research into two important issues: whether COPD is a risk factor for OSAS, and whether outcome in patients with both disorders is worsened. Both COPD and OSAS are common, and both become more prevalent with age and male gender. Cigarette smoking, responsible for most cases of COPD, has also been identified as a risk factor for OSAS; and COPD may be associated with disordered control of breathing that could increase the likelihood of OSAS. However, two investigations appear to have settled this issue in favor of the association occurring merely by chance. In an analysis of data from 5,954 subjects enrolled in the Sleep Heart Health Study, as well as a population study involving 676 Eastern Europeans, both failed to demonstrate a statistical relationship between the two disorders.

The combination of obstructive sleep apnea and COPD does have implications with respect to outcome. The "overlap syndrome" is associated with lower and longer nocturnal oxyhemoglobin desaturations, and produces more severe pulmonary hemodynamic complications. Patients with the overlap syndrome have been reported to exhibit diurnal hypercapnia more frequently, and concomitant COPD appears to be an important cause of acute ventilatory failure in patients with severe obstructive sleep apnea, a so-called critical care syndrome.

Oxygen remains the mainstay of treatment for the hypoxemia of COPD, both diurnal and nocturnal. Early studies established that continuous administration of oxygen was capable of ameliorating pulmonary hypertension and improving survival in patients with both daytime and nocturnal hypoxemia. However, it remains controversial whether COPD patients with isolated nocturnal hypoxemia should receive oxygen therapy. Chaouat and coworkers, in a randomized controlled trial of nocturnal oxygen treatment in this situation, failed to demonstrate any improvement in pulmonary hemodynamic outcome compared to no treatment. NIPPV has also been evaluated as a treatment modality in COPD patients with nocturnal desaturation. However, a metaanalysis of clinical trials has not supported this form of therapy, and a more recent trial did not furnish compelling evidence to change this point of view. Finally, the clinician should consider the use of pharmacologic agents that can maintain bronchodilation during the night in those patients with an element of bronchospasm. A variety of drugs have been used for this purpose, including controlled-release theophylline, long-acting  \( \beta \)-agonists, and long-acting inhaled anticholinergic agents. Theophylline itself can disrupt sleep, and has in general fallen out of favor for the treatment of COPD. There are ongoing controversies concerning the safety of long-acting  \( \beta \)-agonists, and therefore the inhaled, long-acting anticholinergics may represent the best choice of nocturnal therapy for COPD patients at the present time.

**Bronchial Asthma**

It has long been recognized that asthma often worsens at night. Turner-Warwick, in a study of 7,729 asthmatics, reported that 74\% awoke with asthma symptoms at least once per week, 64\% reported symptoms at least 3 nights per week, and 40\% had symptoms every night. It has been reported that 53\% of asthma deaths occur between midnight and 8:00 AM. Lung function and airway responsiveness vary in a circadian rhythm, with a nadir in lung function occurring at approximately 4:00 AM. The definition of nocturnal asthma as a distinct entity requires an exaggerated increase in this variation, which nominally measures 15 to 20\%. The factors responsible for this circadian variability in airway function are incompletely understood. The number of inflammatory cells and the levels of inflammatory mediators in the lung appear to increase during the night, and there is speculation that the underlying circadian rhythm of cortisol, histamine, or glucocor-
ticoid receptor-binding affinity may be responsible. A study by Sutherland et al demonstrated that melatonin levels are higher in subjects with nocturnal asthma compared to asthmatics without nocturnal symptoms and normal control subjects, but not enough is known relative to melatonin function to provide more insight. Investigators have also implicated lowered airway temperature during sleep and gastroesophageal reflux as factors contributing to nocturnal asthma.

Nocturnal symptoms such as cough and dyspnea disrupt sleep. Patients with asthma are more likely to experience daytime sleepiness and much more likely to complain of difficulty falling asleep or awakening early than subjects without asthma. Polysonography in nocturnal asthma patients demonstrates a reduction in sleep efficiency and increased awakenings.

Patients with nocturnal asthma are generally considered to be suboptimally controlled and the intensity of treatment should be increased according to published guidelines. Long-acting β-agonists have been shown to improve asthma-specific quality of life and pulmonary function in the morning and to increase the percentage of nights free of awakening. These agents should be used in combination with inhaled corticosteroids. Currently available inhaled anticholinergics seem to have little effect on pulmonary function to provide more insight. Investigators have demonstrated that the factors doubtless relate to the mechanisms discussed at the beginning of this article; minor changes in control of breathing and respiratory mechanics previously discussed, and any increase in PaCO2 with sleep onset, even if still within the normal range, must result in a corresponding fall in oxyhemoglobin saturation. Diseases known to cause nocturnal hypoxemia and/or hypoventilation include cystic fibrosis (CF), interstitial pneumonitides, hypersensitivity pneumonitis, pulmonary hypertension (primary, or due to other causes such as recurrent pulmonary emboli), and hemoglobinopathies such as sickle-cell anemia. Of all of these disorders, CF and sickle-cell anemia have been studied most extensively with respect to gas exchange during sleep.

CF is a chronic progressive disorder that encompasses mucus hypersecretion, reduced clearance of secretions, recurrent and/or chronic respiratory tract infection, bronchiectasis, lower airway obstruction, and destruction of pulmonary parenchyma. It has been suggested that nocturnal hypoxemia contributes to cor pulmonale and progressive functional decline in these patients. Sleep disturbances have been demonstrated in many patients with CF, particularly when more severe pulmonary functional abnormalities are present; although there are conflicting results. Dancy et al reported polysomnographic studies of CF patients demonstrating reduced sleep efficiency, more frequent awakenings, and lower mean arterial oxyhemoglobin saturations. This group of CF patients also demonstrated daytime hypersomnia as measured by multiple sleep latency testing, which can lead to neurobehavioral dysfunction. Furthermore, it has been shown that infectious exacerbations of CF are associated with worsening neurobehavioral function, perhaps mediated to some degree by sleep fragmentation.

Several factors may contribute to the loss of sleep and poor quality of sleep in CF patients. Episodes of cough, when present, result in fragmentation of sleep and perhaps halt the progress of sleep through cycles of REM during the night. Upper airway obstruction related to infection or nasal polyps, GI symptoms, and side effects of medications all may interfere with sleep continuity.

Not all of the pathophysiologic mechanisms underlying the development of hypoxemia and hypoventilation in CF patients are understood. Some of the factors doubtless relate to the mechanisms discussed at the beginning of this article; minor changes in ventilation and gas exchange accompanying transition to sleep, which are of minimal consequence in normal subjects, may result in dramatic alteration of ventilation/perfusion matching in CF patients. These changes are often most striking when supine and while sleeping in REM. Discrete apneic events are not often present, but episodes of hypopnea with associated hypoxemia are sometimes prominent in REM sleep. Respiratory failure develops in advanced disease and NIPPV, including nocturnal ventilatory support, may provide short-term benefit to these patients.

Sickle-cell disease (SCD) results from a point mutation in the β-globin gene. Individuals who
are homozygous for this mutation produce sickle hemoglobin, which when deoxygenated is less soluble than normal hemoglobin. In addition, deoxygenated sickle hemoglobin β-chains tend to polymerize, forcing the erythrocyte to assume the characteristic rigid, sickle shape that is unable to properly traverse the postcapillary venule. Acute, widespread sickling in different tissues results in the vaso-occlusive phenomenon known as a crisis, while recurrent crises or ongoing vaso-occlusion eventually can manifest as chronic pathology. Pulmonary vaso-occlusive phenomena, including recurrent pulmonary infarction, are particularly common; as a result, abnormal pulmonary function (restrictive physiology with or without reduced diffusing capacity) is found in as many as 90% of SCD adults.104

Given that profound pulmonary vascular and parenchymal abnormalities are so common in SCD, it is not surprising that nocturnal oxyhemoglobin desaturation is also frequently recognized.105 The mechanisms leading to sleep-related abnormalities in gas exchange already discussed in the introductory sections of this article have been implicated in the pathogenesis of nocturnal hypoxemia in SCD.106 However, it has also been suggested that obstructive sleep apnea plays a significant role because the progressive development of functional asplenia during the first 5 years of life frequently leads to adenotonsillar hypertrophy.107 Adenotonsillar hypertrophy in this age group is a significant risk factor for OSAS, and a high prevalence of OSAS in children with SCD has indeed been demonstrated in some studies.108 In addition to the usual clinical implications of OSAS in children, it has been hypothesized that nocturnal hypoxemia from OSAS may increase the incidence of painful crises in SCD, since hypoxemia promotes sickling and also increases erythrocyte adhesion.109 A relationship between nocturnal hypoxemia and sickle crises has been demonstrated in one study,110 but that same study and an earlier case-control study111 failed to link OSAS with more frequent crises in SCD. Furthermore, adenotonsillectomy carries increased risk in SCD (including the risk of provoking vaso-occlusive crisis) and should not be undertaken lightly. Patient selection and preoperative preparation (eg, vigorous hydration and transfusion to reduce sickle hemoglobin to < 40% of total hemoglobin) are of paramount importance.112

Congenital Central Alveolar Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare condition characterized by dysfunction of automatic control of breathing, most dramatically during sleep, and was first described by Mellins et al113 in 1970. The term Ondine’s curse was originally used to describe this syndrome, based on a literary reference to the unfaithful husband of the daughter of Poseidon, but is now largely out of favor. At present there are a few hundred known cases worldwide. The estimated incidence varies widely in different reports, from 1 in 10,000 to 1 in 200,000 live births.114 The clinical manifestations of CCHS appear to be related to a spectrum of neural crest disorders.115 Between 15% and 20% of patients have aganglionic megacolon (Hirschsprung disease [HD]),106 and 2 to 5% acquire neural crest tumors such as neuroblastoma, ganglioneuroblastoma, and ganglioneuroma.116

CCHS is a heterogeneous condition with regard to severity. Diagnostic criteria generally require persistent evidence of hypoventilation during sleep with Paco2 > 60 mm Hg. Onset of symptoms typically is in the first year of life,116,117 and may present in the neonate.118 To be certain of the diagnosis, it is necessary to rule out primary cardiac or pulmonary disease as well as neuromuscular dysfunction. Polysomnographic recordings of patients with CCHS demonstrate the most severe hypoventilation in deep NREM sleep during which automatic or homeostatic control of breathing normally predominates.119 Ventilation is less dramatically affected in REM sleep, when some degree of cortical stimulation of respiration is present, but is generally still abnormal.119 Interestingly, hypoventilation in CCHS is most often related to decreased tidal volume rather than respiratory rate. These patients do not exhibit a normal ventilatory response to hypoxia or hypercapnia, but they may demonstrate an arousal response to hypercapnia.120

Impairment of respiration during wakefulness is variably abnormal.121 Pulmonary function is normal unless there has been injury as a result of infection or complications of mechanical ventilation. The majority of these patients can increase ventilation appropriately with exercise and some can breathe essentially normally while awake;122 responsiveness to hypoxemia and hypercapnia is somewhat variable during wakefulness.123 Many of these patients fail to appreciate symptoms of dyspnea when challenged;124 Taken as a whole, these findings have been interpreted as suggesting a defect in the brainstem integration of respiratory control inputs.124

While respiratory control abnormalities are the dominant feature of CCHS, it is now clear that these patients demonstrate a wide variety of disorders of the autonomic nervous system, including decreased heart rate variability, decreased breath-to-breath interval variability, baseline bradycardia, vagally mediated syncope or asystole, and impaired swallowing.
Ocular manifestations are common, such as miosis, anisocoria, and abnormal responsiveness to light, as well as abnormal irides, strabismus, and lack of tears. Other common complications are gastroesophageal dysmotility and reflux, hypotonia, profuse sweating, absence of fever with infection, and recurrent pneumonia.

The clinical features present in a given patient depend in large part on how early the condition is detected. Untreated, these patients have complications of chronic hypercapnia and hypoxemia, with cyanosis, cor pulmonale, edema, developmental retardation, seizures, and death. Early diagnosis and institution of ventilatory support may prevent these problems. Virtually all of these patients require mechanical ventilatory support during sleep, while some require additional support during the daytime, up to 24 h/d. Respiratory support has traditionally been delivered via tracheotomy. In recent years, there has been an increased use of noninvasive ventilation with a nasal or oronasal interface; in selected patients, diaphragmatic pacing can also be utilized. Mortality is largely related to complications of long-term respiratory support or from complications of bowel disease if HD is present.

A genetic basis for CCHS has long been suspected. In 2003, Amiel et al implicated mutations in the PHOX2B gene as responsible for CCHS. Subsequent studies have shown that the great majority of CCHS patients have mutations in polyalanine expansion related to this gene, and the identification of multiple alleles provides an explanation for the variation in severity of CCHS manifestations. A different mutation of the same gene appears to greatly increase the likelihood of HD and development of neural crest tumors.

Most studies have indicated that these mutations occur de novo. Cases of siblings and twins with CCHS suggest that transmission could occur in an autosomal dominant pattern with variable penetration. Genetic analysis of family members of CCHS patients has demonstrated a small number of adults with previously undetected, milder cases of CCHS. Investigations into how this mutation may be responsible for loss of integrated ventilatory control may provide a unique understanding of the neural mechanisms involved in the control of breathing, and could provide insight into the pathogenesis of other syndromes of sleep-disordered breathing.

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