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CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Sleep-Related Hypoventilation/Hypoxemic Syndromes*

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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-hypoventilation 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 $Paco_2$ 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 $Paco_2$ 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 Spo_2 [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 Spo_2 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 studies[2,3] 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 Pco_2 of approximately 2 mm Hg.[2,4] An older body of literature[5,6] 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

Table 1—*ICSD-2 Sleep-Related Hypoventilation/Hypoxemic Syndromes With Examples of Associated ICD-9 Diagnoses

ICSD-2 Diagnosis	ICD-9 Sleep Diagnosis	ICD-9 Classifiable Condition (Examples Only; Not All Inclusive)	ICD-9 Sleep Diagnosis Code	ICD-9 Classifiable Condition Code
Sleep-related nonobstructive alveolar hypoventilation, idiopathic	Idiopathic sleep-related nonobstructive alveolar hypoventilation	n/a	327.24	
CCHS	CCHS	n/a	327.25	
Sleep-related hypoventilation/ hypoxemia due to pulmonary parenchymal or vascular pathology	Sleep-related hypoventilation/ hypoxemia in conditions classifiable elsewhere		327.26	
		Desquamative interstitial pneumonia		516.8
		Idiopathic fibrosing alveolitis		516.3
		Extrinsic allergic alveolitis		495
		Primary pulmonary hypertension		416.0
		Other chronic pulmonary heart diseases (pulmonary hypertension, secondary)		416.8
		Sickle-cell anemia		282.6
		CF		277.0
Sleep-related hypoventilation/ hypoxemia due to lower airways obstruction	Sleep-related hypoventilation/ hypoxemia in conditions classifiable elsewhere		327.26	
		Obstructive chronic bronchitis		491.2
		Emphysema, pulmonary		492.8
		Asthma		493
		Bronchiectasis		494
Sleep-related hypoventilation/ hypoxemia due to neuromuscular and chest wall disorders	Sleep-related hypoventilation/ hypoxemia in conditions classifiable elsewhere		327.26	
		Obesity		278
		Kyphoscoliosis and scoliosis		737.3
		Amyotrophic lateral sclerosis		335.20
		Multiple sclerosis		340
		Myasthenia gravis		358.0

*ICD-9 = *International Classification of Diseases*, ninth revision; n/a = not applicable.

may be no change at all in the ventilatory response to hypoxia during NREM in women.[7] In this age of polypharmacy, the clinician must also be on the lookout for the use of respiratory depressant medications (opiates; benzodiazepines or other sedative medications that depress ventilatory drive) that can further exacerbate any sleep state-related depression of respiratory drive.

Recent work has focused on ventilatory instability at the transition between wakefulness and sleep. It appears that the apneic threshold (the $PaCO_2$ level below which ventilation ceases) exists only slightly below measured $PaCO_2$ during drowsiness but before sleep onset.[8,9] A variety of factors can narrow the difference between the apneic threshold and $PaCO_2$ during this transition (termed *CO_2 reserve* by Dempsey et al[8]) and lead to an unstable breathing pattern. 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 *ataxic 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 (*eg*, 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,[1] 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).[1] 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[22] 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."[23] 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 (Po_2 <70 mm Hg, $Paco_2$ >45 mm Hg) in an obese patient (body mass index [BMI] > 30 kg/m^2; other authors used > 35 kg/m^2) with no other identifiable cause of hypoventilation.[24]

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/m^2) was 2.8% in men and 6.9% in women.[25] 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.[26] Adding to this health burden, the frequently inadequate identification and treatment of OHS has significant medical and public health implications.[27]

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.[28] The prevalence of OHS in the general population is unknown. One study[29] 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/m^2; 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[30] investigating the close association of OHS with OSAS reported that 37% of 111 consecutive patients with an apnea-hypopnea index > 10 had $Paco_2$ > 45 mm Hg. Most reviews[21] 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,[30] 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[29] 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[31] as well as an increase in respiratory inertance.[32] Respiratory compliance is reduced, some or all of which may be attributable to changes in lung volume from mass loading.[33] More recent data suggest that obesity also results in a degree of obstructive ventilatory impairment.[34] 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.[35] 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[36] 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[36] 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 $Paco_2$ 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.[37]

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.[38] 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.[39] 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[40] reported that leptin levels, after controlling for the degree of obesity, are higher in OHS patients compared with eucapnic individuals. Additionally, Yee and collaborators[41] 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 $Paco_2$.[42] Unfortunately, weight loss by diet alone is difficult to achieve and sustain; thus, bariatric surgery has been advocated. Sugerman et al[43] 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/m^2, and $Paco_2$ 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.[43] 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[44] 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 $Paco_2$ 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.[45,46] Measures of central respiratory control (hypercapnic and hypoxic ventilatory drive) have also been demonstrated to improve in OHS patients treated with either modality.[36,46,47]

Progesterone is responsible for the hyperventilation associated with pregnancy, has been shown to stimulate ventilation in normal subjects,[48] and has produced some benefit in OHS patients by improving hypercapnia.[49] 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 amyotropic lateral sclerosis, spinal cord injury, diaphragmatic paralysis, myasthenia gravis, Eaton-Lambert syndrome, toxic or metabolic myopathies, post-polio syndrome, and Charcot-Marie-Tooth syndrome.[50–53] 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.[54] 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.[55] In recent years, the use of noninvasive intermittent positive pressure ventilation (NIPPV) such as bilevel PAP has increased in popularity because it avoids the ethical dilemmas and potential medical complications of positive pressure ventilation via tracheotomy.

Other Chest Wall Disorders

Patients with chest wall disorders impacting the bellows function of the respiratory system, such as kyphoscoliosis, ankylosing spondylitis, limitation of chest expansion related to trauma, or pleural conditions, may be significantly compromised during sleep. The changes in control of breathing and respiratory mechanics described in the opening section of this review make it difficult for the patient to sustain adequate gas exchange during sleep, and they may demonstrate diurnal as well as nocturnal hypoventilation and hypoxemia as their condition worsens. These patients are subject to the development of atelectasis, further worsening hypoxemia. Also, deformities of the rib cage may lead to changes in the length and orientation of the diaphragm resulting in impairment of diaphragmatic function.[56] As with many of the conditions discussed in this review, the relative atonia of both intercostal and accessory muscles of respiration during REM sleep often produces dramatic decompensation, particularly in those patients with coexisting diaphragmatic dysfunction. The additional burden of pregnancy may cause great difficulty for these patients.

NIPPV in patients with kyphoscoliotic ventilatory insufficiency improves daytime and nighttime oxyhemoglobin saturation, respiratory muscle performance, symptoms of hypoventilation, and quality of life.[57] The combination of NIPPV plus oxygen appears to result in greater improvement and survival than oxygen alone.[58]

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 nonhypoxemic brethren, hypoxemic 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[59,60]; and individuals who are already significantly hypoxemic while awake are more likely to exhibit profound desaturation during sleep.[59–61] In one study,[61] all patients with diurnal oxyhemoglobin saturations $< 93\%$ had nocturnal desaturation, while none with awake saturations $> 95\%$ were hypoxemic at night; another study[59] found a high correlation between diurnal $Paco_2 > 50$ mm Hg and nocturnal hypoxemia.

Awake hypoxemia in COPD is well known to be associated with a variety of cardiac complications (pulmonary hypertension/cor pulmonale; rhythm disturbances) and uncommonly with secondary polycythemia; untreated hypoxemic COPD patients also tend to require more frequent hospitalizations and have high mortality rates. However, it is unclear whether exclusively nocturnal hypoxemia in these patients will be deleterious, and therefore whether isolated sleep-related hypoxemia should be treated. In one trial,[62] patients with mild daytime hypoxemia (Pao_2, 56 to 69 mm Hg) and sleep-related desaturation did not benefit from nocturnal oxygen treatment in terms of pulmonary hemodynamics or mortality. Fletcher et al[63] 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[62,63] involved relatively small numbers of subjects, and the latter study[63] had a high dropout rate. Increased ventricular ectopy during sleep has also been shown to occur in COPD when saturations fall to $< 80\%$.[64] 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.[65] Finally, COPD is a cause of sleep-related symptoms, with insomnia complaints leading the list.[66] For instance, the Tucson Epidemiologic Study of Obstructive Airways Disease[67] 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.[66]

Any discussion of sleep-related hypoventilation and hypoxemia in COPD must necessarily mention the "overlap syndrome." Flenley[68] 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,[69] as well as a population study involving 676 Eastern Europeans,[70] 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,[70] and produces more severe pulmonary hemodynamic complications.[71] Patients with the overlap syndrome have been reported to exhibit diurnal hypercapnia more frequently,[72] 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*.[73]

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,[62] 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[74] of clinical trials has not supported this form of therapy, and a more recent trial[75] 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 inhaled β-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 β-agonists, and therefore the inhaled, long-acting anticholinergics may represent the best choice of nocturnal therapy for COPD patients at the present time.[76]

Bronchial Asthma

It has long been recognized that asthma often worsens at night. Turner-Warwick,[77] 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.[78] 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%.[79] 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,[80] and there is speculation that the underlying circadian rhythm of cortisol, histamine, or glucocor-

ticoid receptor-binding affinity may be responsible.[81,82] A study by Sutherland et al[83] 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[84] and gastroesophageal reflux as factors contributing to nocturnal asthma.[85]

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.[86] Polysomnography in nocturnal asthma patients demonstrates a reduction in sleep efficiency and increased awakenings.[87]

Patients with nocturnal asthma are generally considered to be suboptimally controlled and the intensity of treatment should be increased according to published guidelines.[88] 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.[89] These agents should be used in combination with inhaled corticosteroids. Currently available inhaled anticholinergics seem to have little effect on the nocturnal decrement in pulmonary function of asthmatics.[90] Although currently out of favor, theophylline is generally regarded as an effective treatment for nocturnal asthma, particularly if the dosing schedule is constructed to reach peak levels at the time of night when airflow limitation is greatest.[91] Theophylline itself, however, may disrupt sleep.

Sleep-Related Hypoventilation/Hypoxemia Due to Pulmonary Parenchymal or Vascular Pathology

Any respiratory system disorder that produces hypoxemia may potentially worsen during sleep. Compensatory hyperventilation may not be sustainable as a result of the state-dependent and postural changes in control of breathing and respiratory mechanics previously discussed, and any increase in $Paco_2$ 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.[92] It has been suggested that nocturnal hypoxemia contributes to cor pulmonale and progressive functional decline in these patients.[93] Sleep disturbances have been demonstrated in many patients with CF, particularly when more severe pulmonary functional abnormalities are present; although there are conflicting results.[94] Dancy et al[95] 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.[96] Jankelowitz et al[97] demonstrated poor sleep quality in CF patients even in the presence of normal sleep latency and apparently normal sleep efficiency. In one study,[98] there was a close relationship between worsening sleep variables and declining FEV_1.

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 progression of sleep through cycles of REM during the night.[99] Upper airway obstruction related to infection or nasal polyps, GI symptoms, and side effects of medications all may interfere with sleep continuity.[100]

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.[100] Respiratory failure develops in advanced disease and NIPPV, including nocturnal ventilatory support, may provide short-term benefit to these patients.[101,102]

Sickle-cell disease (SCD) results from a point mutation in the β-globin gene.[103] 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 study[111] 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 al[113] 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 $Paco_2 > 60$ 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.[121] Many of these patients fail to appreciate symptoms of dyspnea when challenged.[123] 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.[125] Other common complications are gastroesophageal dysmotility and reflux, hypotonia, profuse sweating, absence of fever with infection, and recurrent pneumonia.[126]

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.[127] 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.[128]

A genetic basis for CCHS has long been suspected. In 2003, Amiel et al[129] 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,[130] and the identification of multiple alleles provides an explanation for the variation in severity of CCHS manifestations.[131] A different mutation of the same gene appears to greatly increase the likelihood of HD and development of neural crest tumors.[132]

Most studies[133] 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.[134] Genetic analysis of family members of CCHS patients has demonstrated a small number of adults with previously undetected, milder cases of CCHS.[135] 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.

References

1 American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual; 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005; 165–167

2 Simon PM, Dempsey JA, Landry DM, et al. Effect of sleep on respiratory muscle activity during mechanical ventilation. Am Rev Respir Dis 1993; 147:32–37

3 Worsnop C, Kay A, Pierce R, et al. Activity of respiratory pump and upper airway muscles during sleep onset. J Appl Physiol 1998; 85:908–920

4 Morrell MJ, Harty HR, Adams L, et al. Changes in total pulmonary resistance and pCO_2 between wakefulness and sleep in normal human subjects. J Appl Physiol 1995; 78:1339–1349

5 Berthon-Jones M, Sullivan CE. Ventilatory and arousal responses to hypoxia in sleeping humans. Am Rev Respir Dis 1982; 125:632–639

6 Douglas NJ, White DP, Weil JV, et al. Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 1982; 126:758–762

7 White DP, Douglas NJ, Pickett CK, et al. Hypoxic ventilatory response during sleep in normal women. Am Rev Respir Dis 1982; 126:530–533

8 Dempsey JA, Smith CA, Przybylowski T, et al. The ventilatory responsiveness to CO_2 below eupnoea as a determinant of ventilatory stability in sleep. J Physiol 2004; 560:1–11

9 Thomson S, Morrell MJ, Cordingley JJ, et al. Ventilation is unstable during drowsiness before sleep onset. J Appl Physiol 2005; 99:2036–2044

10 Gould GA, Gugger M, Molloy J, et al. Breathing pattern and eye movement density during REM sleep in man. Am Rev Respir Dis 1988; 138:874–877

11 Orem J, Lovering AT, Dunin-Barkowski W, et al. Endogenous excitatory drive to the respiratory system in rapid eye movement sleep in cats. J Physiol 2000; 527:365–376

12 Orem JM, Lovering AT, Vidruk EH. Excitation of medullary respiratory neurons in REM sleep. Sleep 2005; 28:801–807

13 Xi L, Smith CA, Saupe KW, et al. Effects of rapid-eye-movement sleep on the apneic threshold in dogs. J Appl Physiol 1993; 75:1129–1139

14 Millman RP, Knight H, Kline LR, et al. Changes in compartmental ventilation in association with eye movements during REM sleep. J Appl Physiol 1988; 65:1196–1202

15 Duron B, Marlot D. Intercostal and diaphragmatic electrical activity during wakefulness and sleep in normal unrestrained adult cats. Sleep 1980; 3:269–280

16 Johnson MW, Remmers JE. Accessory muscle activity during sleep in chronic obstructive pulmonary disease. J Appl Physiol 1984; 57:1011–1017

17 Hudgel DW, Martin RJ, Johnson B, et al. Mechanics of the respiratory system and breathing pattern during sleep in normal humans. J Appl Physiol 1984; 56:133–137

18 Hewlett AM, Hulands GH, Nunn JF, et al. Functional residual capacity during anesthesia: II. Spontaneous respiration. Br J Anaesth 1974; 46:486–494

19 Muller NL, Francis PW, Gurwitz D. Mechanism of hemoglobin desaturation during rapid-eye-movement sleep in normal subjects and patients with cystic fibrosis. Am Rev Respir Dis 1980; 121:463–469

20 Tangel DJ, Mezzanotte WS, White DP. The influence of sleep on tensor palatini EMG and upper airway resistance in normal subjects. J Appl Physiol 1991; 70:2574–2581

21 Phillipson EA, Duffin J. Hypoventilation and hyperventilation syndromes. In: Mason RJ, Broaddus VC, Murray JF, et al, eds. Murray and Nadel's textbook of respiratory medicine, 4th ed. Philadelphia, PA: Saunders, 2005; 2069–2090

22 Burwell CS, Robin ED, Whaley RD, et al. Extreme obesity associated with alveolar hypoventilation: a Pickwickian syndrome. Am J Med 1956; 21:811–818

23 Dickens C. The posthumous papers of the Pickwick Club. London, UK: Chapman & Hall, 1837

24 Olson AL, Zwillich C. The obesity hypoventilation syndrome. Am J Med 2005; 11:948–956
25 Odgen C, Carroll M, Lester C, et al. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006; 295:1549–1555
26 Raebel MA, Malone DC, Conner DA, et al. Health services use and health care costs of obese and nonobese individuals. Arch Intern Med 2004; 164:2135–2140
27 Berg G, Delaive K, Manfreda J, et al. The use of health-care resources in obesity-hypoventilation syndrome. Chest 2001; 120:377–383
28 Strumpf DA, Millman RP, Hill NS. The management of chronic hypoventilation. Chest 1990; 98:474–480
29 Nowbar S, Burkart KM, Gonzales R, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med 2004; 116:1–7
30 Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230–1235
31 Lopata M, Onal E. Mass loading, sleep apnea, and the pathogenesis of obesity hypoventilation. Am Rev Respir Dis 1982; 126:640–645
32 Sharp JT, Henry JP, Sweany SK, et al. Total respiratory system inertance and its gas and tissue components in normal and obese men. J Clin Invest 1964; 43:503–509
33 Waltemath CL, Bergman NA. Respiratory compliance in obese patients. Anesthesiol 1974; 41:84–85
34 Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function: the normative aging study. Chest 1997; 111:891–898
35 Sampson MG, Grassino AE. Load compensation in obese patients during quiet tidal breathing. J Appl Physiol 1983; 55:1269–1276
36 Rapoport DM, Garay SM, Epstein H, et al. Hypercapnia in the obstructive sleep apnea syndrome: a reevaluation of the "Pickwickian syndrome." Chest 1986; 89:627–635
37 Kessler R, Chaouat A, Schinkewitch P, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest 2001; 120:369–376
38 Klein S, Coppack SW, Mohamed-Ali V, et al. Adipose tissue leptin production and plasma leptin kinetics in humans. Diabetes 1996; 45:984–987
39 O'Donnell CP, Schaub CD, Haines AS, et al. Leptin prevents respiratory depression in obesity. Am J Respir Crit Care Med 1999; 159:1477–1484
40 Phipps PR, Starritt E, Caterson I, et al. Association of serum leptin with hypoventilation in human obesity. Thorax 2001; 57:75–76
41 Yee B, Cheung J, Phipps P, et al. Treatment of obesity hypoventilation syndrome and serum leptin. Respiration 2006; 73:209–212
42 Tirlapur VG, Mir MA. Effect of low calorie intake on abnormal pulmonary physiology in patients with chronic hypercapneic respiratory failure. Am J Med 1984; 77:987–994
43 Sugerman HJ, Fairman RP, Sood RK, et al. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. Am J Clin Nutr 1992; 55:597S–601S
44 Masa JF, Celli BR, Riesco JA, et al. The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. Chest 2001; 119:1102–1107
45 Shivaram U, Cash ME, Beal A. Nasal continuous positive airway pressure in decompensated hypercapnic respiratory failure as a complication of sleep apnea. Chest 1993; 104: 770–774
46 Lin C-C. Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnoea syndrome. Eur Respir J 1994; 7:2005–2010
47 de Lucas-Ramos P, de Miguel-Diez J, Santacruz-Siminiani A, et al. Benefits at 1 year of nocturnal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Respir Med 2004; 98:961–967
48 Zwillich CW, Natalino MR, Sutton FD, et al. Effects of progesterone on chemosensitivity in normal men. J Lab Clin Med 1978; 92:262–269
49 Sutton FD, Zwillich CW, Creagh CE, et al. Progesterone for outpatient treatment of Pickwickian syndrome. Ann Intern Med 1975; 83:476–479
50 Goldstein RS. Hypoventilation: neuromuscular and chest wall disorders. Clin Chest Med 1992; 13:507–521
51 Mellies U, Dohna-Schwake C, Voit T. Respiratory function assessment and intervention in neuromuscular disease. Curr Opin Neurol 2005; 18:543–547
52 Polkey MI, Lyall RA, Moxham J, et al. Respiratory aspects of neurological disease. J Neurol Neurosurg Psychiatry 1999; 66:5–15
53 David WS, Bundlie SR, Madhavi Z. Polysomnographic studies in amyotrophic lateral sclerosis. J Neurol Sci 1997; 152:S29–S35
54 Ward S, Chatwin M, Heather S, et al. Randomized controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax 2005; 60:1019–1024
55 Lo Coco D, Marchese S, Corrao S, et al. Development of chronic hypoventilation in amyotrophic lateral sclerosis patients. Respir Med 2006; 100:1028–1036
56 Muirhead A, Conner A. The assessment of lung function in children with scoliosis. J Bone Joint Surgery Br 1985; 67:699–702
57 Gonzales C, Ferris G, Diaz J, et al. Kyphoscoliotic ventilatory insufficiency: effects of long-term intermittent positive-pressure ventilation. Chest 2003; 124:857–862
58 Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? Eur Respir J 2003; 22:525–528
59 De Angelis G, Sposato B, Mazzei L, et al. Predictive indexes of nocturnal desaturation in COPD patients not treated with long term oxygen therapy. Eur Rev Med Pharmacol Sci 2001; 5:173–179
60 Little SA, Elkholy MM, Chalmers GW, et al. Predictors of nocturnal oxygen desaturation in patients with COPD. Respir Med 1999; 93:202–207
61 Douglas NJ, Calverley PMA, Leggett RJE, et al. Transient hypoxemia during sleep in chronic bronchitis and emphysema. Lancet 1979; 1:1–4
62 Chaouat A, Weitzenblum E, Kessler R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 1999; 14:1002–1008
63 Fletcher EC, Luckett RA, Goodnight-White S, et al. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime Pa_{O_2} above 60 mm Hg. Am Rev Respir Dis 1992; 145:1070–1076
64 Shepard JW, Garrison MW, Grither DA, et al. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. Am J Med 1985; 78:28–34
65 McNicholas WT, Fitzgerald MX. Nocturnal deaths among patients with chronic bronchitis and emphysema. BMJ 1984; 289:878
66 Phillips B, Mannino D. Correlates of sleep complaints in adults: the ARIC study. J Clin Sleep Med; 1:277–283

67 Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 1987; 91:540–546
68 Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985; 6:651–661
69 Sanders MH, Newman AB, Haggerty CL, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003; 167:7–14
70 Bednarek M, Plywaczewski R, Jonczak L, et al. There is no relationship between chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: a population study. Respiration 2005; 72:142–149
71 Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995; 151:82–86
72 Bradley TD, Rutherford R, Lue F, et al. Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. Am Rev Respir Dis 1986; 134:920–924
73 Fletcher EC, Shah A, Qian W, et al. "Near miss" death in obstructive sleep apnea: a critical care syndrome. Crit Care Med 1991; 19:1158–1164
74 Wijkstra PJ, Lacasse Y, Guyatt GH. A meta-analysis of nocturnal noninvasive positive pressure ventilation in patients with stable COPD. Chest 2003; 124:337–343
75 Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 2002; 20:529–538
76 McNicholas WT, Calverley PMA, Lee A, et al. Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. Eur Respir J 2004; 23:825–831
77 Turner-Warwick M. Epidemiology of nocturnal asthma. Am J Med 1988; 85(suppl 1B):6–8
78 Robertson CE, Rubinfeld AR, Bowej G. Deaths from asthma in Victoria: a 12-month study. Med J Aust 1990; 152–511-517
79 Calhoun WJ. Nocturnal asthma. Chest 2003; 123:399S–405S
80 Kraft M, Djukanovic R, Wilson S, et al. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996; 154:1505–1510
81 Barnes P, Fitzgerald G, Brown M, et al. Nocturnal asthma and changes in circulating epinephrine, histamine, and cortisol. N Engl J Med 1980; 303:263–267
82 Kraft M, Vianna E, Martin RJ, et al. Nocturnal asthma is associated with reduced glucocorticoid receptor binding affinity and decreased steroid responsiveness at night. J Allergy Clin Immunol 1999; 103:66–71
83 Sutherland ER, Ellison MC, Kraft M, et al. Elevated serum melatonin is associated with the nocturnal worsening of asthma. J Allergy Clin Immunol 2003; 112:513–517
84 Chen WY, Chai H. Airway cooling and nocturnal asthma. Chest 1982; 81:675–680
85 Feld SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux: a critical review of the literature. Chest 1998; 114:275–283
86 Janson C, De Backer W, Gislason T, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. Eur Respir J 1996; 9:2132–2138
87 Stores G, Ellis AJ, Wiggs L, et al. Sleep and psychological disturbance in nocturnal asthma. Arch Dis Child 1998; 78:413–419
88 Sutherland ER. Nocturnal asthma. J Allergy Clin Immunol 2005; 116:1179–1186
89 Lockey RF, DuBuske LM, Friedman B, et al. Nocturnal asthma: effect of salmeterol on quality of life and clinical outcome. Chest 1999; 115:666–673
90 Coe CI, Barnes PJ. Reduction of nocturnal asthma by an inhaled anticholinergic drug. Chest 1999; 115:666–673
91 Barnes PJ, Greening AP, Neville L, et al. Single-dose slow-release aminophylline at night prevents nocturnal asthma. Lancet 1982; 1:299–301
92 Milross MA, Piper AJ, Dobbin CJ, et al. Sleep disordered breathing in cystic fibrosis. Sleep Med Rev 2004; 8:295–308
93 Fraser KL, Tullis DE, Sasson Z, et al. Pulmonary hypertension and cardiac function in adult cystic fibrosis. Chest 1999; 115:1321–1328
94 Milross MA, Piper AJ, Norman M, et al. Night-to-night variability in sleep in cystic fibrosis. Sleep Med 2002; 3:213–219
95 Dancy DR, Tullis ED, Heslegrave R, et al. Sleep quality and daytime function in adults with cystic fibrosis and severe lung disease. Eur Respir J 2002; 19:504–510
96 Dobbin CJ, Bartlett D, Melehan K, et al. The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis. Am J Respir Crit Care Med 2005; 172:99–104
97 Jankelowitz L, Reid KJ, Wolfe L, et al. Cystic fibrosis patients have poor sleep quality despite normal sleep latency and efficiency. Chest 2005; 127:1593–1599
98 Amin R, Bean J, Burklow K, et al. The relationship between sleep disturbance and pulmonary function in stable pediatric cystic fibrosis patients. Chest 2005; 128:1357–1363
99 Stokes DC, McBride JT, Wall MA, et al. Sleep hypoxemia in young adults with cystic fibrosis. Am J Dis Child 1980; 134:741–743
100 Francis PW, Muller NL, Gurwitz D, et al. Hemoglobin desaturation: its occurrence during sleep in patients with cystic fibrosis. Am J Dis Child 1980; 134:734–740
101 Serra A, Polese G, Braggion C, et al. Non-invasive proportional assist and pressure support ventilation in patients with cystic fibrosis and chronic respiratory failure. Thorax 2002; 57:50–54
102 Gozal D. Nocturnal ventilatory support in patients with cystic fibrosis: comparison with supplemental oxygen. Eur Respir J 1997; 10:1999–2003
103 Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med 1997; 337:762–769
104 Klings ES, Wyszynski DF, Nolan VG, et al. Abnormal pulmonary function in adults with sickle cell anemia. Am J Respir Crit Care Med 2006; 173:1264–1269
105 Castele RJ, Strohl KP, Chester CS et al. Oxygen saturation with sleep in patients with sickle cell disease. Arch Intern Med 1986; 146:722–725
106 Needleman JP, Franco ME, Varlotta L, et al. Mechanisms of nocturnal oxyhemoglobin desaturation in children and adolescents with sickle cell disease. Pediatr Pulmonol 1999; 28:418–422
107 Powars DR. Natural history of sickle cell disease: the first ten years. Semin Hematol 1975; 12:267–285
108 Samuels MP, Stebbens VA, Davies SC, et al. Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. Arch Dis Child 1992; 67:925–929
109 Setty BN, Stuart MJ, Dampier C, et al. Hypoxaemia in sickle cell disease: biomarker modulation and relevance to pathophysiology. Lancet 2003; 362:1450–1455
110 Hargrave DR, Wade A, Evans JPM, et al. Nocturnal oxygen saturation and painful sickle cell crises in children. Blood 2003; 101:846–848
111 Brooks LJ, Koziol SM, Chiarucci KM, et al. Does sleep-disordered breathing contribute to the clinical severity of

sickle cell anemia? J Pediatr Hematol Oncol 1996; 18:135–139
112 Halvorson DJ, McKie V, McKie K, et al. Sickle cell disease and tonsillectomy: preoperative management and postoperative complications. Arch Otolaryngol Head Neck Surg 1997; 123:689–692
113 Mellins RB, Balfour HH Jr, Turino GM, et al. Failure of autonomic control of ventilation (Ondine's curse). Medicine (Baltimore) 1970; 49:487–526
114 Trang H, Dehan M, Beaufils F, et al. The French congenital central hypoventilation syndrome registry: general data, phenotype, and genotype. Chest 2005; 127:72–79
115 Bolande RP. The neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. Hum Pathol 1974; 5:409–429
116 Weese-Mayer DE, Shannon DC, Keens TG, et al. Idiopathic congenital central hypoventilation syndrome: diagnosis and management. Am J Respir Crit Care Med 1999; 160:368–373
117 Gozal D, Gaultier C. Proceedings from the first international symposium on the congenital central hypoventilation syndrome. Pediatr Pulmonol 1997; 23:133–168
118 Dejhalla M, Parton P, Golombek SG. Case report of Haddad syndrome in a newborn: congenital central hypoventilation syndrome and Hirschsprung's disease. J Perinatol 2006; 26:259–260
119 Gaultier C, Trang-Pham H, Praud JP, et al. Cardiorespiratory control during sleep in the congenital central hypoventilation syndrome. Pediatr Pulmonol 1997; 23:140–142
120 Marcus CL, Bautista DB, Amihyia A, et al. Hypercapnic arousal responses in children with congenital central hypoventilation syndrome. Pediatrics 1991; 88:993–998
121 Paton J, Swaminathan S, Sargent C, et al. Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. Am Rev Respir Dis 1989; 140:368–372
122 Paton J, Swaminathan S, Sargent C, et al. Ventilatory response to exercise in children with congenital central hypoventilation syndrome. Am Rev Respir Dis 1993; 147:1185–1191
123 Shea SA, Andres LP, Shannon DC, et al. Respiratory sensations in subjects who lack a ventilatory response to CO_2. Respir Physiol 1993; 93:203–219
124 Spengler CM, Gozal D, Shea SA. Chemoreceptive mechanisms elucidated by studies of congenital central hypoventilation syndrome. Respir Physiol 2001; 129:247–255
125 Weese-Mayer DE, Silvestri JM, Huffman AD, et al. Case/control family study of autonomic nervous system dysfunction in idiopathic congenital central hypoventilation syndrome. Am J Med Genet 2001; 100:237–245
126 Chen ML, Keens TG. Congenital central hypoventilation syndrome: not just another rare disorder. Pediat Respir Rev 2004; 5:182–189
127 Vanderlaan M, Holbrook CR, Wang M, et al. Epidemiologic survey of 196 patients with congenital central hypoventilation syndrome. Pediatr Pulmonol 2004; 37:217–229
128 Weese-Mayer DE, Silvestri JM, Menzies LJ, et al. Congenital central hypoventilation syndrome: diagnosis and management, and long-term outcome in thirty-two children. J Pediatr 1992; 160:381–387
129 Amiel J, Laudier B, Attié-Bitach T, et al. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene *PHOX2B* in congenital central hypoventilation syndrome. Nat Genet 2003; 33:459–461
130 Weese-Mayer DE, Berry-Kravis EM. Genetics of congenital central hypoventilation syndrome: lessons from a seemingly orphan disease. Am J Respir Crit Care Med 2004; 170:16–21
131 Berry-Kravis EM, Zhou L, Rand CM, et al. Congenital central hypoventilation syndrome PHOX2B mutations and phenotype. Am J Respir Crit Care Med 2006; 174:1139–1144
132 Hamilton J, Bodurtha JN. Congenital central hypoventilation syndrome and Hirschsprung's disease in half-sibs. J Med Genet 1989; 26:272–274
133 Gaultier C, Amiel J, Dauger S, et al. Genetics and early disturbances of breathing control. Pediatr Res 2004; 55:729–733
134 Trochet D, O'Brien LM, Gozal D. PHOX2B genotype allows for prediction of tumor risk in congenital central hypoventilation syndrome. Am J Hum Genet 2005; 76:421–426
135 Antic NA, Malow BA, Lange N, et al. PHOX2B mutation-confirmed congenital central hypoventilation syndrome: presentation in adulthood. Am J Respir Crit Care Med 2006; 174:923–927