State of the Art

Sleep-disordered Breathing in Children

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CONTENTS

INTRODUCTION

"To know even one life has breathed easier because you lived. This is to have succeeded."

—Ralph Waldo Emerson

Sleep is a major physiological drive. The average child spends almost one-half of his or her life asleep. A newborn will sleep for as much as 16 h a day. Thus, respiratory disorders during sleep are of particular importance during childhood. Although some respiratory disorders, such as sleep apnea, occur only during sleep, virtually all respiratory disorders—including upper airway obstruction, central hypoventilation, and chronic lung disease—are worse during sleep than wakefulness. It is therefore incumbent upon the pulmonologist to understand the effects of sleep upon breathing. Despite this, it is only recently that the medical community has started to scientifically evaluate sleep, and there are still large gaps in our knowledge.

This review will not attempt to provide a comprehensive description of all aspects of pediatric sleep-disordered breathing. Rather, it will focus on the differences in these disorders between children and adults, from a developmental perspective. Due to space limitations, disorders limited to infancy, such as apnea of prematurity, apparent life-threatening events, and sudden infant death syndrome, will not be discussed.

NORMAL PHYSIOLOGY DURING SLEEP: CHANGES WITH MATURATION AND DEVELOPMENT

Changes in Respiration during Sleep

We all breathe better awake than asleep. During sleep, there is a decrease in minute ventilation. In adults, minute ventilation decreases by approximately 13–15% compared with the value during wakefulness; respiratory rate tends to remain constant and the decrease is due primarily to a decrease in tidal volume (1). In contrast, studies of infants, children, and adolescents have shown that the respiratory rate decreases during sleep (2–4). Data on sleep-related changes in tidal volume in the pediatric age group are scarce, although one study in adolescents confirmed a decrease in tidal volume (4). The functional residual capacity (FRC) decreases with sleep (5), and upper airway resistance doubles (6). The ventilatory drive decreases, particularly during rapid eye movement (REM) sleep (7, 8). During REM sleep, breathing is erratic, with variable respiratory rate and tidal volume and frequent central apneas. REM sleep is also associated with a decrease in intercostal and upper airway muscle tone. Thus, breathing is impaired during sleep compared with wakefulness, and is further impaired during REM sleep. This is especially important in children, as they sleep more than adults, and have relatively more REM sleep. In neonates, active sleep (a REM-like state) can occur for up to two-thirds of total sleep time (9), as compared with 20–25% of sleep time in adults (10).

Thoracic Mechanics

The chest wall and upper airway change during infancy and childhood in order to respond to the physiological needs of the developing organism. The compliant chest wall of the newborn allows for compression during the birth process. In addition, this compression aids in expelling pulmonary fluid. After birth, however, the compliant chest wall places the infant at a mechanical disadvantage during respiration. In infants, chest wall compliance is three times the lung compliance (11). This causes paradoxical inward rib cage motion during inspiration, with resultant increased work of breathing, particularly during REM sleep when intercostal muscle activity is decreased. Ossification of the sternum and vertebrae begins *in utero* and continues until 25 yr of age, resulting in a stiffer chest wall. Although chest wall compliance equals lung compliance by age

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2 yr (11), paradoxical inward rib cage motion during inspiration is seen in normal children during REM sleep until at least 31 mo of age (12). Children with upper airway obstruction have relatively more paradoxical breathing during sleep than adults. By adolescence, paradoxical inward rib cage motion during inspiration is not seen in normal subjects (4).

The shape of the rib cage also changes during early childhood. In infants, the ribs are orientated horizontally, resulting in a circular thorax with little potential for further expansion. The zone of apposition of the diaphragm is smaller. Thus, the rib cage contribution to tidal breathing during quiet/non-REM sleep is only one-third at 1 mo of age (13), as compared with two-thirds in older subjects (4). As the child begins to assume a more upright posture over the first 2 yr of life, the muscle forces act on the ribs to produce the adult configuration (14).

Muscle mass develops progressively through childhood to adulthood. Although infants can produce high inspiratory pressures, they tend to function close to the diaphragmatic fatigue threshold (15). They are therefore more likely to decompensate if they develop cardiopulmonary disease, including upper airway obstruction.

Upper Airway

During development, the upper airway changes in both structure and function. Because of the increased compliance of their chest wall, infants have a lower FRC and are prone to atelectasis. To maintain their FRC, they employ a mechanism termed laryngeal braking (active glottic narrowing) until 6–12 mo of age. In infants, the larynx is located relatively cephalad, such that the epiglottis may overlap the soft palate (16). This enables the infant to make a better seal for suckling. However, it predisposes the infant to upper airway obstruction if the nasopharynx is partly occluded. Previously, it was thought that infants were obligate nasal breathers. It has since been shown that they have the ability to breathe through their mouth, but breathe preferentially through their nose (17).

In males, the larynx increases in size and changes shape at puberty (18). Although pubertal changes in other upper airway structures have not been well studied, one study demonstrated that pubertal and postpubertal males have larger tongues than females (19). Unfortunately, this was not controlled for overall body size; thus, further study is needed. Theoretically, testosterone-induced changes in upper airway morphology may partly explain the increased risk for obstructive sleep apnea syndrome in adolescent (20) and adult males compared with females, in contrast to the equal risk noted in prepubertal children (21).

The lymphoid tissue of the upper airway increases from birth until approximately 12 yr of age (22). Simultaneously, there is gradual growth in the size of the skeletal boundaries of the upper airway. Thus, between 2 and 8 yr of age, the tonsils and adenoid are the largest in relation to the underlying airway, resulting in a relatively narrow upper airway (23). Nevertheless, children have a less collapsible upper airway than adults (24). Studies suggest that they compensate for the narrow upper airway by activation of the upper airway muscles, secondary to the increased central ventilatory drive present during childhood (24).

Ventilatory Control

Growth and development are associated with sexual maturation, changes in body size and composition, and changes in the metabolic rate, all of which would be expected to affect ventilatory control. Although studies have attempted to compare the ventilatory drive in infants with adults, it is difficult due to the differences in technique (e.g., mouthpiece versus mask). Of note, however, is that infants have an exaggerated biphasic response to hypoxia compared with adults, with an initial increase in ventilation followed by a depression of ventilation below baseline levels, sometimes resulting in apnea (25). Infants have an active Hering–Breuer reflex that decreases with age but is still present during early childhood (26). Clinically, this can be a problem for children receiving continuous positive airway pressure (CPAP), who sometimes develop central apnea during positive pressure application (27).

When corrected for body size, school-aged children have a higher ventilatory drive than adults (28–30). The ventilatory drive declines with age through childhood and adolescence, is stable during young adulthood, and then declines with older age (28, 31–37).

Arousal

Arousal is an important defense mechanism against sleep-disordered breathing, as one breathes better awake than asleep. In general, children have a higher arousal threshold than adults; the younger the child, the higher the arousal threshold (38). Numerous studies have shown that moderate hypoxemia is a poor stimulus to arousal in infants (39), prepubertal children (40), and adults (8), with only 25–50% of subjects arousing. In contrast, hypercapnia and increased upper airway resistance are both potent stimuli to arousal in all age groups (40–44). Children appear to have fewer spontaneous arousals than adults. Using the American Academy of Sleep Medicine criteria (45) with some minor alterations, the spontaneous arousal index has been noted to be 7–9/h in infants, 7 ± 2/h in prepubertal children, 14 ± 2/h for adolescents, 16–18/h for younger adults, and 31 ± 3/h in the elderly (46–49). However, one study reported significantly lower arousal indices for both older children and adults (50).

Apnea

Central apneas are common in infants and children, particularly during REM sleep (3, 51). Traditionally, central apneas in children have been considered significant if they were greater than 20 s in length, or if they were associated with desaturation, bradycardia, or arousal. However, central apneas > 20 s are commonly seen in normal children, particularly after movement or sighs, and associated transient desaturation is not uncommon (3, 52, 53). Recent data on normal infants have shown central apneas up to 25 s duration, associated with desaturation to $< 81\%$ (54). Thus, the clinical significance of these central apneas is dubious (55), unless they occur very frequently or are associated with prolonged gas exchange abnormalities.

In contrast to central apneas, obstructive apneas are rare in normal children. A study of more than 1,000 infants found a median obstructive apnea index of zero (range 0–4/h) (51). A study of 50 normal children aged 1–18 yr found that only 18% had even a single obstructive apnea during the night, and all obstructions were $\leqslant 10$ s duration. The mean obstructive apnea index was 0.1 ± 0.5/h (52). These data apply to complete apneas only; there are no normative data for hypopneas in children. The only study evaluating hypopneas did not publish the hypopnea data separately, but found a total respiratory disturbance index (i.e., central apneas, obstructive apneas, and hypopneas) of 1.1/h (50).

Gas Exchange

Baseline arterial oxygen saturation during sleep is 96–100% during infancy (56, 57) and childhood (52, 53), with neonates

having the lowest levels (56). These values are similar to adults (58). However, as mentioned previously, transient desaturation in association with central apnea or periodic breathing is common during childhood, especially in infants. A study of 64 normal infants monitored for 6 mo found that 59% had at least one episode of desaturation $< 90\%$ (59); desaturation into the 50s has been reported in normal infants (56).

During sleep, there is relative hypercapnia compared with wakefulness, although data are scanty in the pediatric age group. In infants, transcutaneous P_{CO_2} increases 1–3 mm Hg from wakefulness to sleep (60). In a study of children aged 1–18 yr, end-tidal P_{CO_2} increased 7 ± 3 mm Hg from wake to sleep (52). In adults, P_{CO_2} increases by 3–7 mm Hg (1).

OBSTRUCTIVE SLEEP APNEA SYNDROME

The obstructive sleep apnea syndrome (OSAS) is common in childhood, occurring approximately one-third as often as asthma. In symptoms, pathophysiology, polysomnographic findings, and treatment, it differs significantly from the condition in adults (Table 1). In fact, it is not clear whether OSAS in childhood is the same condition as in adults, or whether these are two distinct diseases.

Epidemiology

OSAS occurs in children of all ages, from neonates to adolescents. It is commonest in the preschool age group, due to adenotonsillar hypertrophy (*see below*); younger or older children are more likely to have other underlying etiological factors. Three studies (from Britain, Iceland, and the United States) have shown similar prevalence rates of approximately 2% (21, 61, 62). These studies either used sampling methods, did not use conventional polysomnography, or used adult rather than pediatric polysomnographic criteria; thus, a definitive demographic study has not yet been performed. In contrast to adults, where the disease occurs primarily in males, in children it appears to occur equally among the sexes (21). This may be because of the lack of hormonal influences in the prepubertal child. One study suggests that it is more common in African American children, due to either structural differences or socioeconomic factors (21).

Pathophysiology

The etiology of childhood OSAS is quite different from the adult condition. In adults, OSAS is usually associated with obesity. Obese children are also at risk for OSAS, and the degree of OSAS is proportional to the degree of obesity (63). However, most children with OSAS are not obese. In fact, they may have failure to thrive. Instead, the vast majority of cases of OSAS in children are associated with adenotonsillar hypertrophy. The peak prevalence of childhood OSAS occurs at 2–8 yr, which is the age when the tonsils and adenoid are the largest in relation to the underlying airway size; endoscopy has shown that the site of collapse is most often at the level of the adenoid (64); and most children with OSAS improve following tonsillectomy and adenoidectomy (T&A) (65). OSAS also occurs in children with upper airway narrowing due to craniofacial anomalies, or those with neuromuscular abnormalities such as hypotonia (e.g., muscular dystrophy [66]) or muscular incoordination (e.g., cerebral palsy [67]).

Although childhood OSAS is associated with adenotonsillar hypertrophy, it is not caused by large tonsils and adenoid alone. Several facts suggest that it is due to a combination of structural and neuromuscular factors. First, patients with OSAS do not obstruct during wakefulness, showing that structural factors alone cannot be the cause. Second, studies have failed to show a correlation between upper airway or adenotonsillar size and OSAS (68–70). Third, a small percentage of children with adenotonsillar hypertrophy but no other known risk factors for OSAS are not cured by T&A (65). Finally, Guilleminault and colleagues reported a cohort of children who were cured of their OSAS by adenotonsillectomy, but developed a recurrence during adolescence (20). Thus, it appears that childhood OSAS is a dynamic process resulting from a combination of structural and neuromotor abnormalities, rather than from structural abnormalities alone. These predisposing factors occur as part of a spectrum: in some children (e.g., those with craniofacial anomalies), structural abnormalities predominate, whereas in others (e.g., those with cerebral palsy), neuromuscular factors predominate. In otherwise healthy children with adenotonsillar hypertrophy, neuromuscular abnormalities are probably subtle. Current research is aimed at defining these abnormalities. It has been shown that children with OSAS have overall normal ventilatory responses both awake (71)

TABLE 1. OBSTRUCTIVE SLEEP APNEA SYNDROME IN CHILDREN VERSUS ADULTS

	Children	Adults
Clinical characteristics		
Peak age	Preschoolers	Elderly
Sex ratio	Equal	Predominantly males Females postmenopause
Etiology	Adenotonsillar hypertrophy	Obesity
Weight	Failure to thrive, normal, obese	Obese
Excessive daytime somnolence	Uncommon	Very common
Neurobehavioral	Hyperactivity, developmental delay	Cognitive impairment, impaired vigilance
Polysomnographic characteristics		
Obstruction	Cyclic obstruction or prolonged obstructive hypoventilation	Cyclic obstruction
Sleep architecture	Normal	Decreased delta and REM sleep
State with OSA	REM	REM or non-REM
Cortical arousal	$< 50\%$ of apneas	At termination of each apnea
Treatment		
Surgical	T&A (majority of cases)	UVPP (selected cases)
Medical	CPAP occasionally	CPAP

Definition of abbreviations: CPAP = continuous positive airway pressure; REM = rapid eye movement; T&A = tonsillectomy and adenoidectomy; UVPP = uvulopharyngopalatoplasty.

and asleep (40), although subtle differences exist in their response to repeated hypercapnic challenges (72). It is suspected, however, that children with OSAS may have abnormal centrally mediated activation of their upper airway muscles, leading to a more collapsible upper airway (73).

Children with OSAS appear to have a deficit in arousal mechanisms. Studies have shown that these patients have elevated arousal thresholds in response to hypercapnia (40) and increased upper airway resistance (43). Unlike adults, children with OSAS often do not have EEG arousals following obstructive apneas (Figure 1). McNamara and coworkers (46) found that obstructive apneas were associated with arousal in less than half of the apneas in children, and only 18% of apneas in infants. As a result, sleep architecture is preserved in children with OSAS (74, 75), and therefore excessive daytime sleepiness, the cardinal symptom of OSAS in adults, is uncommon (76). However, although apnea-related EEG arousals are less common in children than adults, subcortical arousals, as demonstrated by movement (77, 78) or autonomic changes (79), occur frequently. It is also possible that subtle disturbances in sleep architecture, which cannot be detected on routine polysomnography, are present (80). These factors may contribute to neurobehavioral and autonomic complications.

In adults, OSAS is more common during non-REM sleep (81), although some patients do have events primarily during REM sleep. Conversely, in children OSAS is very much a REM-related disease. One study showed a median apnea index of 56/h in REM sleep versus 9/h in non-REM sleep (74). This indicates a state-specific deficit in upper airway/central nervous system function. Furthermore, apneas were longer and more numerous during later REM periods than during REM periods earlier in the night. The clinical ramification is that abnormalities can be missed during nap studies if sufficient REM sleep is not obtained.

Complications

Untreated OSAS can result in serious morbidity. Early reports documented such complications as failure to thrive, cor pulmonale, and mental retardation (82). These severe sequelae are less common now, due to earlier diagnosis and treatment.

Even though failure to thrive is the exception these days, children with OSAS still tend to have a growth spurt following T&A (75, 83). This does not appear to be due to increased caloric intake postoperatively, but rather to decreased work of breathing (75). A recent study found an increase in insulin-like growth factor-I following T&A, suggesting that endocrine factors play a role in postoperative catch-up growth (83).

Cor pulmonale with heart failure used to be a common mode of presentation for children with OSAS but is now rare. Although overt failure occurs less often, asymptomatic degrees of pulmonary hypertension may be common. Tal and coworkers showed a reduced right ventricular ejection fraction in 37% of children with clinically diagnosed OSAS, although only 7% had clinical evidence of pulmonary hypertension (84). When cor pulmonale does develop, it can be reversed by treating the OSAS (82, 84–87). Systemic hypertension is a well-described complication of OSAS in adults, and has been reported in a few pediatric case series (88, 89). A systematic study showed elevated diastolic blood pressure in children with OSAS, which could be predicted by apnea index, body mass index, and age (90).

Many reports have suggested that children with OSAS have neurocognitive deficits, such as poor learning, behavioral

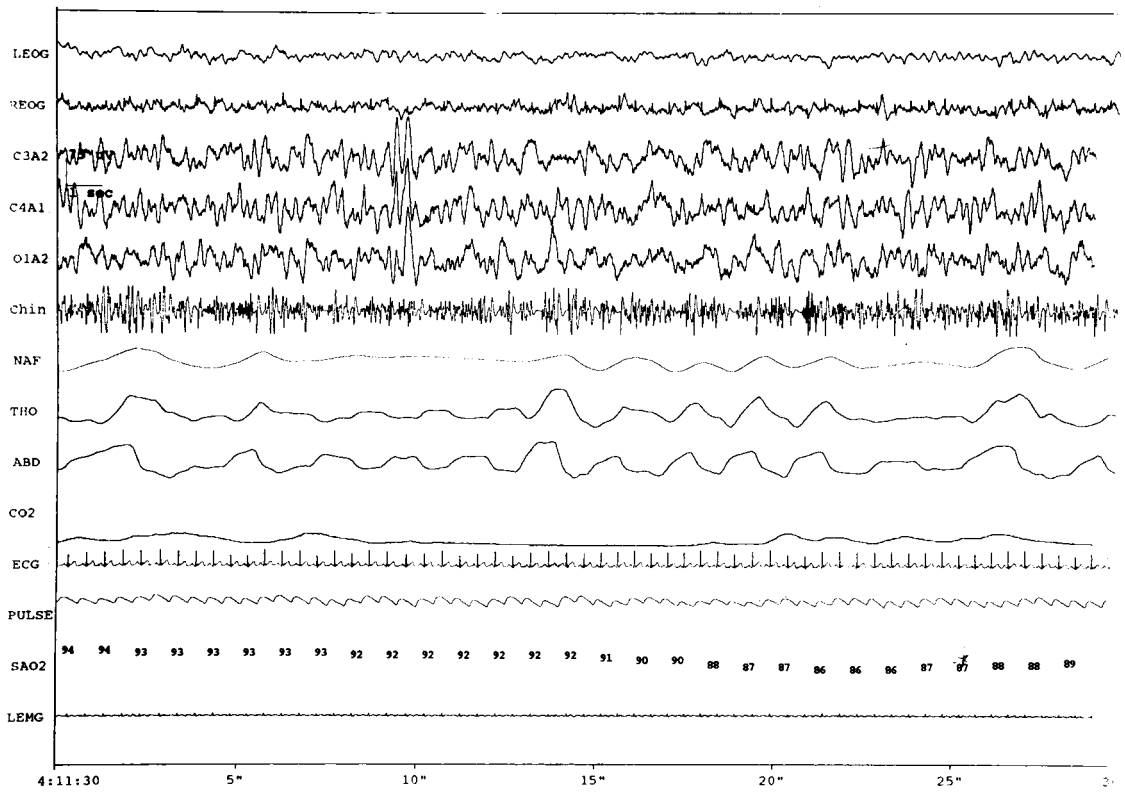

Figure 1. Portion of a polysomnogram from an 18-mo-old girl with OSAS. The patient has a short obstructive apnea of 8 s duration. Despite the brevity of the event, it is associated with significant desaturation (86%). Note also the lack of EEG arousal in response to the obstruction. The Sa_{O_2} at the beginning of the event is slightly low due to a preceding apnea. A second, single-breath obstruction is also seen. The end-tidal P_{CO_2} channel is partially obstructed and not picking up well in this epoch. LEOG and REOG, left and right electrooculograms; C3A2, C4A1, and O1A2, EEG channels; Chin, submental EMG; NAF, oronasal airflow; THO, thoracic movement; ABD, abdominal movement; CO_2, end-tidal P_{CO_2}; Pulse, oximeter pulse waveform; Sa_{O_2}, arterial oxygen saturation; LEMG, tibial EMG.

problems, and attention deficit hyperactivity disorder. Most of these studies were based on histories obtained from parents of snoring children (91–94). A recent study was one of the first to objectively evaluate the effect of sleep-disordered breathing on intellectual function (95). Gozal performed screening for sleep-disordered breathing in first-grade students who were performing in the lowest 10th percentile of their class academically. An amazingly high proportion (18%) had home studies suggestive of sleep-disordered breathing. Children treated with T&A had a significant improvement in their grades the following year, whereas untreated children showed no change (95).

If untreated, OSAS may result in death. The early OSAS literature described children who presented in cardiorespiratory failure or coma, some of whom died (96–98). A link to the sudden infant death syndrome (SIDS) has also been proposed. A polysomnographic study of infants who subsequently died of SIDS showed an increased amount of obstructive apnea in those who died, although the degree of obstruction did not appear to be clinically significant (99). There is an increased family history of SIDS in adults with OSAS (100, 101). Clearly, more data are needed. However, the dramatic drop in SIDS incidence in response to a change to supine positioning (102) suggests that obstructive apnea does not play a role in most SIDS deaths.

Evaluation

Screening studies. As with adults, the gold standard for diagnosing childhood OSAS is polysomnography. Because of the shortage of pediatric sleep centers, however, several studies have evaluated the use of screening techniques. History, otolaryngological examination and audiotapes of snoring have been shown to have a low sensitivity and specificity for diagnosis (65, 103–109). Other screening tests, such as nocturnal videotaping (110), pulse oximetry (111), or nap polysomnograms (112), have limited utility, in that they are indicative of OSAS if positive, but have a high false-negative rate. Thus, they may be useful for initial testing if polysomnography is not readily available, but polysomnography is recommended if the studies are negative or if the patient has other significant medical conditions. Cost efficacy would be dependent on the cost of performing screening studies, and the number of patients with indeterminate studies who required polysomnography.

Polysomnography. Full polysomnography can be successfully performed in infants and children of any age, provided that appropriate equipment and well-trained staff are available. Pediatric studies must be scored and interpreted using age-appropriate criteria. The American Thoracic Society has published a consensus statement outlining the requirements for pediatric polysomnography, some of which are described below (103). There are some important differences in the pattern of upper airway obstruction in children compared with adults. Children often desaturate with short apneas, as they have a lower FRC and a faster respiratory rate than adults (Figure 1). Therefore, obstructive apneas of any length are scored when interpreting pediatric sleep studies, as compared with the 10-s duration in adults (103, 113). Children may develop clinical sequelae with what appears to be relatively mild OSAS. Thus, an apnea index of 10 is considered to be severe by most pediatric pulmonologists, whereas it is considered only mildly abnormal in adults. One reason why a low apnea index can be associated with severe clinical disease is that the apnea index, the parameter used most often to characterize disordered breathing in adults, does not give an accurate picture of the nature of the breathing disturbance in children. Many children, particularly those younger than 3 yr of age, have a pattern of persistent, partial upper airway obstruction associated with hypercapnia and/or hypoxemia, rather than cyclic discrete obstructive apneas (Figure 2). This has been

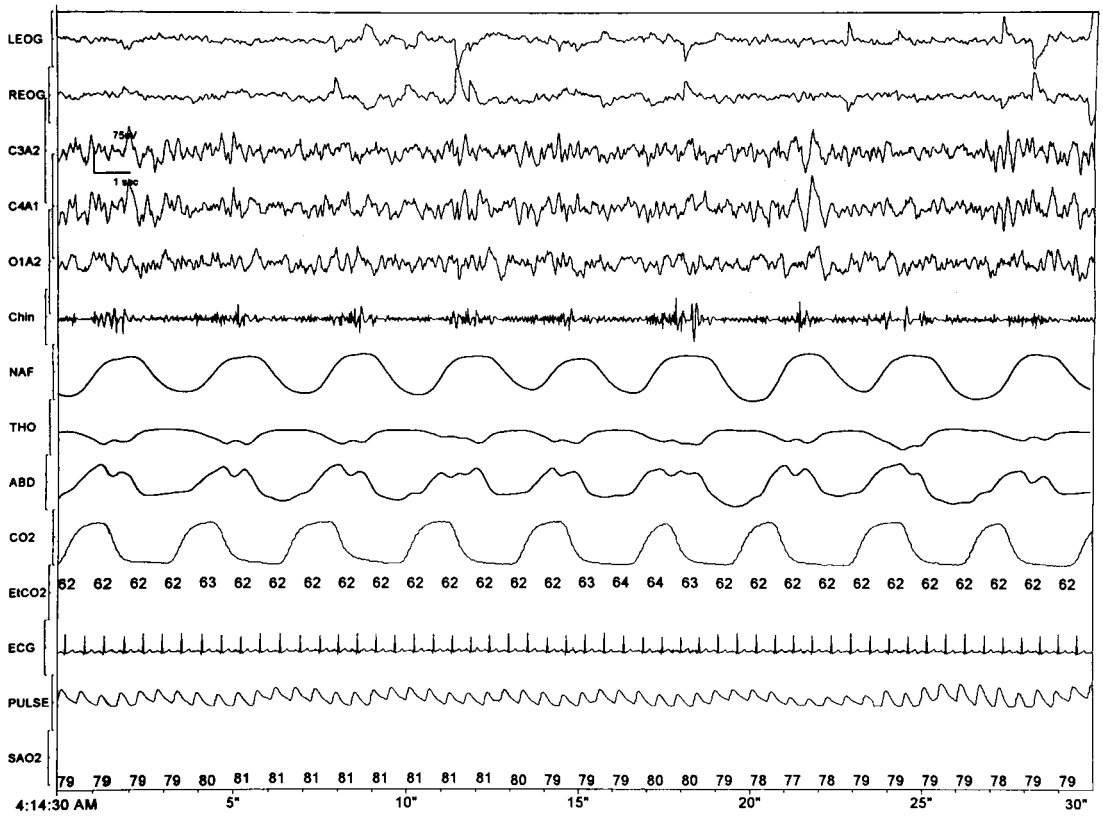

Figure 2. Example of obstructive hypoventilation during REM sleep in a 7-yr-old boy. Airflow channels show no evidence of obstruction. However, paradoxical inward chest wall motion during inspiration, associated with hypercapnia (end-tidal P_{CO_2} in the 60s) and desaturation (Sa_{O_2} in the 70s), is present. Abbreviations as in Figure 1. $EtCO_2$, peak end-tidal P_{CO_2} value, averaged over several breaths.

termed "obstructive hypoventilation" (103), and can result in a misleadingly low apnea index. Unfortunately, there are no studies correlating polysomnographic parameters with clinical outcome in children, and it is not known what degree of polysomnographic abnormalities requires treatment (114).

Over the past few years, a new syndrome, the upper airway resistance syndrome (UARS), has been described in both children (115) and adults. Patients with UARS have snoring and daytime sleepiness associated with increased work of breathing during sleep, but no discrete obstructive apneas or gas exchange anomalies. Thus, UARS can be diagnosed only by measuring the work of breathing during sleep, using an esophageal pressure manometer. Further study is required to determine the prevalence and clinical sequelae of UARS, as well as the best method for diagnosis. Less invasive techniques for diagnosis, such as nasal pressure transducers, quantification of respiratory effort, and pulse transit time (116), are currently under study.

Treatment

The overwhelming majority of children with OSAS will have both symptomatic and polysomnographic resolution following T&A (65). OSAS results from the relative size and structure of the upper airway components, rather than the absolute size of the adenotonsillar tissue. Thus, even children with associated medical conditions, such as Down syndrome (117) or obesity (118), tend to improve following T&A, although additional treatment may be needed. Children with OSAS are at risk for respiratory compromise postoperatively, due to upper airway edema, increased secretions, respiratory depression secondary to analgesic and anesthetic agents, and postobstructive pulmonary edema (119). Postoperative respiratory compromise has been reported to occur in 16–27% of children with OSAS (120–122). Particularly high-risk children include those younger than 3 yr of age, those with severe OSAS, and those with additional medical conditions (120, 121, 123); these patients should not undergo outpatient surgery. Postoperative polysomnograms 6–8 wk following surgery are recommended for patients with additional risk factors for OSAS, or those with a high apnea index, to ensure that additional treatment is not required.

Additional treatment options are available for those children who do not respond to T&A, or the small minority in whom T&A is contraindicated. Nasal CPAP is not approved by the Federal Drug Administration for children weighing less than 30 kg. Nevertheless, it has now been reported to be both effective and well-tolerated in hundreds of infants and older children (27, 124, 125), with side effects similar to those seen in adults. Nonetheless, the institution of CPAP therapy in young or developmentally delayed children can be challenging. Developmentally appropriate behavioral techniques are necessary for it to be successful. Another limiting factor is the lack of adequate pediatric interfaces and other equipment designed for children. For example, young or weak children frequently do not trigger bilevel ventilators. Children may develop central apneas or hypoventilation at higher pressure levels (27). This is presumably due to activation of the Hering–Breuer reflex by stimulating pulmonary stretch receptors. It can be remedied by placing the patient on bilevel ventilation with a backup rate. There is also concern among pediatric practitioners that the current nasal masks can cause midfacial depression when used in very young patients; this has been described anecdotally in one case report (126). Nasal deformities have also been noted in premature infants receiving CPAP via nasal prongs (127).

Two studies have evaluated the effects of supplemental oxygen in children with OSAS. Supplemental oxygen resulted in improved oxygenation during sleep, without worsening of the degree of obstruction (128, 129). In one study, P_{CO_2} levels did not change for the group as a whole. However, a few individuals showed a marked increase in P_{CO_2} when breathing supplemental oxygen (128). There were no apparent predictive factors for which patients would develop hypercapnia. Supplemental oxygen does not address many of the pathophysiological features associated with OSAS, such as arousal from sleep or increased work of breathing. However, these studies suggest that it may be useful in selected individuals as a temporizing measure, or when other treatments fail, for example, in neonates with mild craniofacial anomalies who are expected to improve rapidly with growth; or patients who do not respond to T&A, do not tolerate CPAP, but refuse tracheostomy. Supplemental oxygen should never be administered in patients with OSAS without first measuring their change in P_{CO_2} in response to oxygen.

Uvulopharyngopalatoplasty has been reported to be successful in children with cerebral palsy and hypotonic upper airway muscles (130); it has not been studied in the uncomplicated pediatric patient. Craniofacial surgery is appropriate for some children with craniofacial anomalies (131). The use of oral appliances has not been reported in children, partly due to the concern that the appliances may adversely affect the facial configuration of the growing child.

Long-term Outcome

The natural course and long-term prognosis of childhood OSAS are not known. Specifically, it is not known whether childhood OSAS is a precursor of adult OSAS, or whether these are two diverse diseases affecting discrete populations. Only one study has looked at the long-term outcome. Guilleminault and colleagues reevaluated adolescents who had been successfully treated with T&A during childhood (20). Thirteen percent of those evaluated had recurrence of OSAS. This study leads to the hypothesis that children at risk for OSAS, due to such factors as a small pharyngeal airway or decreased upper airway neuromuscular tone, develop OSAS when they reach the age of maximal adenotonsillar hyperplasia. The adenotonsillar hypertrophy results in an increased mechanical load on a marginal upper airway, thus precipitating OSAS. Following surgical treatment, patients may become asymptomatic. While data are lacking on the natural history of the illness, it is possible that these high-risk children will develop a recurrence of OSAS during adulthood if they acquire additional risk factors, such as androgen secretion at puberty, weight gain, or excessive alcohol ingestion.

CENTRAL HYPOVENTILATION SYNDROMES

Definition

Central alveolar hypoventilation is defined as an increase in arterial carbon dioxide tension due to a decrease in central nervous system ventilatory drive. Patients with central hypoventilation fail to breathe normally, despite having normal lungs, chest wall, and upper airway. Classically, a $P_{CO_2} > 45$ mm Hg has been considered abnormal. However, as we all hypoventilate during sleep compared with wakefulness, this value cannot be used when assessing for hypoventilation during sleep. One study showed that a P_{CO_2} up to 53 mm Hg is normal in children during sleep, although the percent of sleep time with $P_{CO_2} > 50$ mm Hg should be $< 9\%$ (52). Central hypoventilation syndromes can be primary (congenital central hypoventilation syndrome and late-onset central hypoventilation syndrome) or secondary (Table 2).

TABLE 2. CAUSES OF CENTRAL HYPOVENTILATION

Primary
Congenital central hypoventilation syndrome (CCHS)
Late-onset central hypoventilation syndrome
Secondary
Obesity hypoventilation syndrome
Central hypoventilation associated with brainstem lesions
Arnold–Chiari malformation Type I or II
Hydrocephalus
Achondroplasia with stenosis of the foramen magnum
Hypoxic–ischemic encephalopathy
Trauma
Hemorrhage
Tumor
Congenital anomalies (including Moebius sequence)
Meningoencephalitis
Poliomyelitis
Central hypoventilation associated with other neurological syndromes
Autonomic neuropathies (including familial dysautonomia)
Mitochondrial defects (e.g., subacute necrotizing encephalomyelopathy)
Neurodegenerative syndromes
Miscellaneous
Drugs
Hyperthermia
Hypothyroidism
Metabolic dysfunction, inborn errors of metabolism

Etiology

Congenital central hypoventilation syndrome. Congenital central hypoventilation syndrome (CCHS) is a congenital form of severe central hypoventilation of undetermined etiology. The original term, "Ondine's Curse," is no longer used due to its negative connotations. The prevalence of CCHS is unknown, but registries suggest that there are, at minimum, 160–180 living children worldwide with the condition (132). Patients with congenital central hypoventilation usually present with cyanosis, respiratory failure, or occasionally apnea at birth. Rarely, infants present later with apparent life-threatening events or cor pulmonale. It is quite possible that some cases of sudden infant death syndrome are actually due to CCHS.

Patients with CCHS have intact voluntary control of ventilation, but lack automatic control. During sleep, they will hypoventilate to the point where they need ventilatory support. Patients usually have a decreased tidal volume and respiratory rate during sleep (133–135); frank central apnea is uncommon (Figure 3). Although most patients breathe adequately during wakefulness, a subset requires ventilatory support 24 h/d. Even those who breathe adequately awake have been shown to have mild hypoventilation in association with increased metabolic demands such as exercise (136). CCHS may be associated with other abnormalities, including Hirschsprung's disease (16% of 33 cases in one study [137]), autonomic dysfunction (e.g., decreased heart rate variability [138, 139], hypotension), neural tumors (e.g., ganglioneuromas [138, 140], ganglioneuroblastomas [138]), swallowing dysfunction when young (138, 141, 142), and minor ocular abnormalities (143).

The underlying pathophysiology of CCHS is unclear. Radiological and pathological studies have failed to demonstrate significant structural abnormalities (134, 137, 138), although a few case reports have found isolated abnormalities, such as small carotid bodies (132, 144). In contrast to almost all types of sleep-disordered breathing, children with CCHS breathe slightly better during REM than non-REM sleep (133, 134, 137, 145), perhaps because ventilation during REM sleep is less related to metabolic control. Physiological studies have shown that children with CCHS have decreased or absent ventilatory chemosensitivity in response to progressive hypoxia and hypercapnia during wakefulness (146) and sleep (133, 134, 145). However, they do have intact peripheral chemoreceptor responses to acute hypoxia, hypercapnia, and hyperoxia (147). Although they often do not arouse in response to chronic hypercapnia when asleep, they have been demonstrated to arouse when exposed to a superimposed hyperoxic hypercapnic stimulus, albeit at a higher arousal threshold than control subjects (148). These studies have been interpreted to suggest that the primary physiological defect in CCHS may be in the area of the brainstem where afferent impulses from the central and peripheral chemoreceptors are integrated (148). One reason why children with CCHS may breathe better awake than asleep is the presence of the wake nonchemical drive to breathe (149). Another possibility may be related to movement, rather than sleep per se. Mechanoreceptors in the limbs stimulate ventilation, and are thought to play a role in exercise-induced hyperpnea. Studies have shown that ventilation during exercise in children with CCHS is related primarily to the rate of movement (i.e., stepping pace) rather than metabolic demands (136). Passive motion of the lower extremities resulted in increased ventilation (150). Recently, Gozal showed that passive limb motion during sleep resulted in normalization of ventilation (151). Further study is required, particularly as this study evaluated patients for only several minutes at a time. However, it raises the exciting possibility that future patients will be able to be treated with motion devices rather than mechanical ventilation.

The association of CCHS with Hirschsprung's disease, autonomic dysfunction, and neural tumors has led to the hypothesis that it is due to a defect in neural crest migration. An alternative hypothesis is that it is due to a defect in serotonin metabolism, as serotonin is present in the myenteric plexus of the intestine, and also affects ventilatory control (138). There appears to be a genetic component; CCHS has occurred in sib-

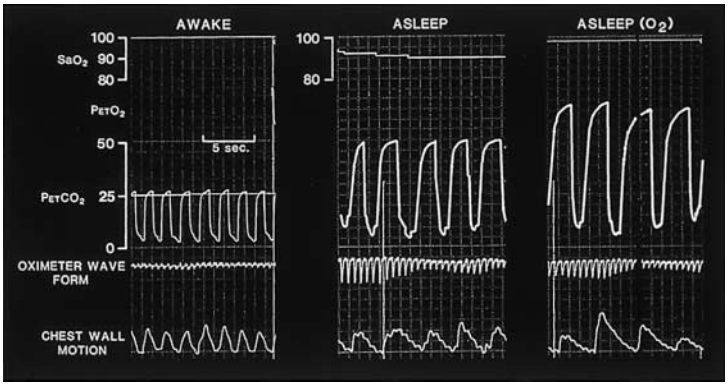

Figure 3. Portions of a sleep study from an infant with congenital central hypoventilation syndrome. In the *left panel*, the infant is awake, has a normal arterial oxygen saturation (Sa_{O_2}), and is actually hyperventilating slightly. At sleep onset (*middle panel*), Sa_{O_2} begins to drop (to 90%) and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) begins to rise (to 50 mm Hg). At that point, the patient was placed on supplemental oxygen (*right panel*), resulting in normalization of Sa_{O_2}. However, $P_{ET_{CO_2}}$ has increased to 68 mm Hg. Note that in this particular patient the hypoventilation is due primarily to a decrease in respiratory rate. There are no central apneas.

lings (138, 152) and monozygotic twins (153), and segregation analysis suggests that it is familial (154). However, although isolated genetic mutations have been found in a few cases, a distinct genetic etiology has not been determined (132). No teratogens or perinatal risk factors have been determined; most infants with CCHS are born at term, following an uneventful pregnancy.

The older literature described a high morbidity and mortality in children with CCHS, with death resulting from cor pulmonale, aspiration, or sepsis (138, 141). Recent reports from centers experienced with CCHS show prolonged survival with a good quality of life. In the three centers reporting long-term outcome in patients with CCHS, mortality was 0% of 6 patients (155), 8% of 13 patients (142), and 31% of 32 patients (137), respectively. Patients continue to need ventilatory support, and do not "outgrow" their disease. Reversible episodes of pulmonary hypertension may occur with infections or with hypoventilation due to inadequate ventilatory support. Intelligence is usually in the normal or low-normal range; children with mental retardation and above average intelligence have been reported (142). Cognitive outcome appears to be related to the adequacy of control of the hypoventilation. The first surviving generation of patients with CCHS is now reaching adulthood, and issues such as pregnancy and childbirth will need to be addressed. The CCHS Family Network Newsletter describes one patient who gave birth to a child with CCHS; other pregnancies have not been reported.

Late-onset central hypoventilation syndrome. A form of late-onset central hypoventilation syndrome has been described in at least 11 cases in the literature (summarized in Katz and coworkers [156]). Typically, these children present at an older age (2–4 yr) and have sleep-related hypoventilation and hypothalamic abnormalities. The hypothalamic abnormalities may include hypothalamic endocrinopathies and/or obesity. Interestingly, a number of these patients have been reported to have neural tumors such as ganglioneuromas and ganglioneuroblastomas (156), suggesting an etiological link with CCHS.

Myelomeningocele. Central apnea/hypoventilation is relatively common in patients with Arnold–Chiari malformations, due to compression and/or dysplasia of the brainstem. In children, the most commonly encountered Arnold–Chiari malformation is a type II malformation associated with a myelomeningocele. Indeed, this is probably the commonest cause of central hypoventilation encountered in pediatric practice. In addition to central hypoventilation, patients may also have obstructive apnea (157), due to collapse at the level of the larynx (158). Bilateral vocal cord paralysis can occur as a result of traction on the vagal nerve roots (159). Although breathing during wakefulness is usually normal, severe breath-holding spells may occur, indicating further abnormalities of central control of ventilation (159, 160). In addition to sleep-disordered breathing, patients with myelomeningocele are predisposed to other pulmonary problems. Patients may have restrictive lung disease, secondary to ventilatory muscle weakness or scoliosis (161). Concomitant pharyngeal abnormalities can occur secondary to bulbar paralysis (162). These factors, especially when combined with central hypoventilation or vocal cord paralysis, place patients at risk for aspiration, atelectasis, and pneumonia. Interestingly, the presence of ventilatory control abnormalities in patients with the Arnold–Chiari malformation is not necessarily associated with cognitive impairment. Many patients with severe ventilatory control dysfunction have normal intellectual function, and can lead fulfilling lives once appropriate treatment is provided.

Physiological studies have shown that children with myelomeningocele have decreased ventilatory (163) and arousal (164) responses to hypercapnia, suggesting an abnormality of central chemoreceptor function or of brainstem processing of central chemoreceptor signals. Peripheral chemoreception is depressed in a subset of patients (163, 165), again suggesting an abnormality of central integration of chemoreception, or perhaps abnormalities of the glossopharyngeal nuclei (which innervate the carotid body) or other chemoreceptive areas.

Waters and coworkers (157) studied 76% of the 109 myelomeningocele patients followed in their clinic, and demonstrated sleep-disordered breathing in 62%. Despite this high prevalence, and the known risk for death either during sleep or during cyanotic/apneic spells in infants with myelomeningocele (166), the problem remains underrecognized. A survey of spina bifida clinics in Canada and the United States revealed that 13% of deaths were attributed to sleep-disordered breathing, 11% to respiratory failure, and a further 9% to sudden, unexplained death during sleep (167). Despite this, only 8% of patients had been evaluated for sleep-disordered breathing.

Prader–Willi syndrome. Prader–Willi syndrome (PWS) is a congenital disorder typified by hypothalamic obesity, mental retardation, hypotonia, and hypogonadism. The vast majority of patients have abnormalities of chromosome 15 (168). Although patients with PWS do not have classic central hypoventilation, they are included here as physiological testing has shown abnormalities of ventilatory control.

When evaluating patients with PWS, it is difficult to separate the effects of obesity from the effects of the underlying syndrome. Obstructive sleep apnea and REM-associated desaturation are seen commonly (169, 170). Patients tend to have restrictive lung disease based on obesity and muscle weakness (171), which can explain the tendency to desaturate. Excessive daytime sleepiness is common, and it has not been well established whether this is due entirely to sleep-disordered breathing or also to a central nervous system component. Patients appear more predisposed to REM-onset sleep, although published studies have not excluded confounding factors such as sleep deprivation or partial upper airway obstruction/UARS (169, 170, 172).

Physiological studies in PWS have shown blunted hypercapnic ventilatory responses secondary to obesity; patients in whom weight has been controlled have a normal hypercapnic drive (173). However, the ventilatory response to hypoxia (173), as well as other tests of peripheral chemoreception (174), indicate a marked decrease in peripheral chemoreceptor function. Although this suggests carotid body dysfunction, the other symptoms of PWS are due to central nervous system dysfunction. In addition, patients with PWS have evidence of autonomic dysfunction (175). A unifying hypothesis, therefore, is that the abnormalities of ventilatory control are due to central processing of chemoreceptor input. Interestingly, a recent study shows that baseline ventilation and ventilatory drive (measured by CO_2 rebreathing and $P_{0.1}$) increase following growth hormone administration, despite an unchanged body mass index (176).

Other causes of central hypoventilation. Obesity–hypoventilation syndrome may occur in morbidly obese children, and is similar to the adult condition. Other causes of central hypoventilation are listed in Table 2.

Evaluation

The diagnosis of central hypoventilation is usually based on clinical findings and polysomnography (including capnometry). Standard rebreathing ventilatory responses can be performed via a mouthpiece in school-aged children, although it may be useful to modify the volume used in the rebreathing

bag in accordance with body size (177). We have performed this technique successfully in children as young as 4 yr of age (28). In infants, it is easiest to measure steady-state responses via a head hood during sleep. Evaluation for the cause of hypoventilation should include a cranial MRI. Muscle weakness (including diaphragmatic paralysis) and metabolic disorders should be excluded. The diagnosis of congenital central hypoventilation syndrome is one of exclusion.

Treatment

Whenever possible, the cause of secondary hypoventilation should be treated. Patients with Arnold–Chiari malformation frequently improve following the relief of elevated intracranial pressure by ventriculoperitoneal shunting (159). The role of posterior fossa decompression in patients who do not respond to simple shunting is controversial, and controlled studies have not been performed. Review of available studies suggest that a proportion of patients improves (178, 179), particularly those treated early (180). Patients with dysplastic changes or necrosis of the brainstem will not improve postoperatively (178).

For those patients without a treatable cause, the mainstay of treatment is chronic ventilatory support. Although respiratory stimulants such as caffeine are helpful in treating central apnea in preterm infants, pharmacotherapy has not proved to be successful in patients with other forms of central hypoventilation (137, 138, 152, 155). The aim of long-term ventilation is to provide adequate gas exchange, leading to normal neurocognitive development, growth, and cardiac function, in the home environment. Noninvasive ventilation (both negative pressure [142] and positive pressure via face mask [181]) has been used successfully, but great care must be taken with this method in young infants, as strict control of ventilation is crucial for normal neurocognitive development. Diaphragm pacers are useful for mobility in patients with CCHS who require ventilatory support both awake and asleep.

Unfortunately, a tracheostomy is usually required in order to prevent upper airway obstruction, as there is no synchrony between vocal cord and diaphragmatic motion. In addition, diaphragm pacers require surgical implantation and are prone to infection and malfunction (182). Therefore, they are not recommended for patients requiring nocturnal ventilation only.

CHRONIC PULMONARY DISEASE AND SLEEP

Obstructive Lung Disease

The normal changes in ventilation associated with sleep were described in an earlier section. These changes are magnified in children with chronic lung disease. Patients with a low FRC have little functional reserve, and are more likely to desaturate as a result of REM-related intercostal muscle hypotonia, and increased ventilation–perfusion mismatch. Thus, patients with adequate oxygenation during wakefulness may desaturate during sleep, particularly REM sleep (183, 184). Sleep-related desaturation has been reported in pediatric patients with cystic fibrosis (184, 185), bronchopulmonary dysplasia (183), asthma (186), and other causes of chronic obstructive pulmonary disease (187). Other physiological factors that will exacerbate sleep-disordered breathing in children with chronic lung disease include increased bronchoconstriction during sleep, reduced mucociliary clearance (188), and decreased cough. During sleep, tracheal irritation is more likely to cause arousal or apnea than cough (189). Thus, sleep architecture is disrupted, and awakenings are frequent (185). Patients with chronic lung disease may also have abnormalities in ventilatory control that can adversely affect their respiration during sleep. Patients with life-threatening episodes of asthma have been shown to have impaired peripheral chemoreceptor function (190) and impaired perception of respiratory loads (191). This could lead to a worsening of hypoxemia, as well as abnormal arousal responses to respiratory stimuli.

Infants with bronchopulmonary dysplasia (BPD) who are normoxic during wakefulness may desaturate during sleep (183). In patients with BPD, hypoxemia during sleep has been shown to cause severe central apnea and bradycardia (192). This has been postulated as a mechanism for the increased rate of sudden death in these patients (193). This central apnea may result from the marked biphasic hypoxic response present during infancy (*see* VENTILATORY CONTROL). In addition, it has been shown that infants with BPD have impaired peripheral chemoreceptor responses (194, 195). Central apnea decreases significantly when supplemental oxygen is provided (196).

Restrictive Lung Disease: Pulmonary and Chest Wall

Few studies have examined the effect of restrictive lung disease, other than that due to ventilatory muscle weakness, on sleep in children, although there is a growing literature on the topic in adults. In adults, restrictive lung disease due to kyphoscoliosis has been studied the most. The FVC correlates linearly with the degree of spinal curvature (197), so patients with severe kyphoscoliosis may develop respiratory failure. As with other patients with chronic lung disease, adults with kyphoscoliosis breathe worse asleep than awake. Hypoventilation and desaturation are worst during REM sleep, in association with decreased chest wall motion (198). The diaphragm in patients with kyphoscoliosis is at a mechanical advantage and they are therefore more dependent on intercostal and accessory muscles of respiration, which become hypotonic during REM. No studies have specifically looked at the pediatric population with kyphoscoliosis, to determine whether they differ from adults.

There are a number of congenital chest wall deformities that can affect respiration. These can range from mild to lethal (such as Jeune's asphyxiating thoracic dystrophy). Again, there are few data on breathing during sleep in these patients, although it would be anticipated that desaturation and hypercapnia would be worse during sleep. One group that has been studied is children with achondroplasia. Patients with achondroplasia are at high risk for sleep-disordered breathing. One study of 88 children with achondroplasia found that 48% had sleep-disordered breathing, and 44% had at least one episode of desaturation to $< 90\%$ (199). These patients have a high prevalence of OSAS (due in part to midfacial hypoplasia) and may also develop central apnea or vocal cord paralysis due to stenosis of the foramen magnum with resultant brainstem compression. However, in this study many of the patients had isolated hypoxemia, and seven patients required supplemental oxygen. This was not a population-based study, and many of these patients had additional lung disease. However, their hypoxemia appeared out of proportion to the degree of lung disease, suggesting a restrictive component. This is consistent with pulmonary function tests showing restrictive lung disease in this population (200).

Restrictive Lung Disease: Ventilatory Muscle Weakness

Most studies of children with ventilatory muscle weakness have concentrated on patients with Duchenne muscular dystrophy (DMD). Patients with DMD have a fairly predictable course of increasing weakness with age, and, if left untreated, usually die of either respiratory or cardiac failure as adolescents or young adults. Prior to the advent of awake respiratory failure, patients hypoventilate during sleep, particularly dur-

ing REM sleep, when muscle tone decreases (201–203). Significant desaturation during REM sleep can occur in patients with normal waking Sa_{O_2} (66, 204, 205). Patients with DMD tend to desaturate with central apneas (66, 204, 205). In addition, they have a high incidence of obstructive apnea, presumably due to upper airway muscle weakness (66, 202, 204, 205). Sleep may be fragmented, in part due to physical factors such as the need to be turned. A number of studies have attempted to predict sleep-disordered breathing on the basis of pulmonary function during wakefulness, with conflicting results (203–205). In one study, the nocturnal Sa_{O_2} nadir, in addition to the vital capacity and awake P_{CO_2}, correlated with survival from the time of sleep study (206). However, only vital capacity correlated with age at death.

A number of other studies have documented nocturnal desaturation and apnea in children with other forms of muscular dystrophy, such as spinal muscular atrophy and myotonic dystrophy (207, 208). Young children with ventilatory muscle weakness have increased compliance of their chest wall (209). This predisposes them to paradoxical breathing that is less efficient. Patients with spinal muscular atrophy have craniofacial anomalies, including a long face, short mandible, and long palate (210). Although this has not been studied, these changes would be expected to predispose subjects to obstructive apnea. The craniofacial changes may be secondary to weakness of the muscles of mastication, and thus may be present in other forms of early-onset muscular dystrophy.

Treatment

Supportive therapy. Good supportive therapy is essential in patients with chronic lung disease and nocturnal hypoxemia. Medical management should be maximized with bronchodilators (including long-acting agents, when appropriate), antiinflammatory agents, diuretics, etc. Nutrition should be optimized. In patients with ventilatory muscle weakness, chest physical therapy and devices to enhance coughing and secretion clearance are useful. Prevention of aspiration (in patients with bulbar muscle weakness) and treatment of scoliosis will help prevent further deterioration in lung function.

Supplemental oxygen. In adults, supplemental oxygen is usually administered to asymptomatic patients with chronic obstructive pulmonary disease if their P_{O_2} is < 55 mm Hg (211). In children, supplemental oxygen is routinely given for milder nocturnal hypoxemia, although strict guidelines have not been developed (193). Although few studies have objectively evaluated the long-term effects of supplemental oxygen, it is thought that adequate oxygenation is necessary for neurocognitive development, cardiac function, and optimal growth. Correction of sleep-related hypoxemia has been demonstrated to improve growth in infants with BPD if Sa_{O_2} is maintained $\geq$ 92–93% (183, 193). It has been recommended that Sa_{O_2} be maintained at least $\geq$ 93% in infants with chronic lung disease in order to optimize health (193).

Although supplemental oxygen is used frequently in patients with cystic fibrosis (212), and clinicians are convinced that it is effective, there are few objective published data on its use. It has not been shown to improve sleep quality (185). There has been one controlled, double-blind study of nocturnal oxygen use in hypoxemic cystic fibrosis patients (213). The study was small (14 subjects received supplemental oxygen and 14 received room air placebo). Subjects had a mean age of 23 yr, and follow-up was approximately 2 yr. Oxygen use averaged 7 h per night. There was no significant effect of oxygen on mortality, pulmonary hypertension, or rate of hospitalization. However, patients using oxygen maintained school/work attendance, whereas the placebo group did not.

Noninvasive positive pressure ventilation. The use of noninvasive positive pressure ventilation (NIPPV) for both acute and chronic respiratory failure in children has been increasing rapidly in recent years (214, 215). NIPPV is being used frequently in children with advanced cystic fibrosis, either as supportive therapy or as a bridge to transplantation (214, 216–219). Studies over months to years of use have shown an improvement in oxygenation, ventilation, and vital capacity, as well as subjective symptomatic improvement (217, 219). Chronic sinusitis may be a limiting factor in its use. NIPPV has also been used successfully to treat respiratory failure secondary to kyphoscoliosis in adults (220).

NIPPV via nasal mask has been used widely in children and adolescents with ventilatory muscle weakness, including Duchenne muscular dystrophy and spinal muscular atrophy (214, 221–223). Negative pressure ventilation is less useful, as patients may develop a worsening of upper airway obstruction (224), and will not be discussed further in this review. Several studies have shown that patients with ventilatory muscle weakness and chronic respiratory failure, treated by nocturnal NIPPV, have improved gas exchange during spontaneous breathing while awake (203, 214, 225). NIPPV is thought to rest the respiratory muscles, and adequate nocturnal ventilation may result in resetting of the central ventilatory drive. Most studies have not shown an improvement in pulmonary function tests (203, 226). In a study of adults with muscular dystrophy, sleep efficiency and sleep architecture improved on NIPPV (226). Many studies report symptomatic improvement, and one study showed a reasonable quality of life with NIPPV (227). Patients receiving NIPPV have fewer hospitalizations (214). A few studies have evaluated whether NIPPV prolongs life in patients with Duchenne muscular dystrophy. Vianello and colleagues (222) compared five patients treated with NIPPV to five nonventilated controls. At 2 yr, all ventilated patients were still alive, whereas 80% of the nonventilated patients had died. Simonds and coworkers (227) showed a 73% 5-yr survival for hypercapnic patients placed on NIPPV, which well exceeds the historic survival for such patients. NIPPV has not been shown to be helpful in patients with DMD prior to the onset of respiratory failure (228). In fact, the study evaluating this reported an increased death rate in patients using NIPPV compared with controls (8 versus 2 deaths, $p < 0.05$). However, this study has been criticized for a number of reasons, including the fact that analysis on the basis of intent to treat meant that two of the deaths in the NIPPV group were patients who did not actually receive NIPPV, and three of the deaths resulted from surgical complications.

The decision to institute NIPPV is a personal one, to be made by the patient and his or her family, in conjunction with medical advice. However, it is important that treatment options be discussed electively, prior to the advent of a respiratory crisis (229). Side effects and complications of NIPPV are similar to those of CPAP (*see* Obstructive Sleep Apnea Syndrome—Treament). Some children with ventilatory muscle weakness will ultimately require a tracheostomy and positive pressure ventilator for secretion clearance, if other mucus-clearing techniques (230) are unsuccessful. In addition, ventilation via tracheostomy is the most practical mode of ventilation in children requiring ventilatory support 24 h/d, in order to facilitate eating and speech.

RESEARCH QUESTIONS/AREAS OF UNCERTAINTY

Pediatric sleep-disordered breathing is a relatively new field, and a myriad of questions remain unanswered. We do not fully understand the pathophysiology, including genetic and

basic mechanisms, underlying conditions such as OSAS and CCHS. Neither do we know the natural history of many of these conditions. One of the most important questions in pediatric sleep-disordered breathing is the outcome of patients with OSAS. We know that severe OSAS can result in severe sequelae. However, we do not know the clinical correlates of mild obstructive apnea, or what degree of OSAS warrants treatment. In the short term, primary snoring does not appear to progress to OSAS (47, 91). However, the long-term relationship between primary snoring, UARS, and OSAS has not been studied. In particular, the effect of pubertal changes on upper airway collapsibility and obstructive apnea needs to be elucidated. Further longitudinal studies evaluating the recurrence of childhood OSAS are required.

Polysomnography is our primary tool for evaluating sleep-disordered breathing. However, it is not a perfect tool. We are still lacking normative data on such basic parameters as hypopneas or esophageal pressure in children. Although polysomnography is widely used, we still do not know which polysomnographic parameters predict morbidity. The recent development of standard criteria for performing and scoring pediatric polysomnography is a major step in ensuring consistency between different centers, so that data from various studies can be compared, and the pool of knowledge increased (103). Adherence to these standards is crucial if the field is to be advanced.

In the past 25 yr, since Dr. Guilleminault's landmark article describing OSAS in eight children (88), there have been major advances in our knowledge of pediatric sleep-disordered breathing. Hopefully, the burgeoning interest in this area in the past few years will lead to answers to some of our questions, and result in improved patient care.

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