Sleep Apnea In Infants And Children

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Introduction.

For nearly 3,000 years, it has been recognized that apparently healthy infants could die suddenly and unexpectedly during their sleep [1]. Throughout most of history, it was believed that these infants somehow suffocated, implying that these babies died a respiratory death. Nearly one infant per thousand live births continues to die suddenly and unexpectedly from sudden infant death syndrome (SIDS). The cause of SIDS remains unknown, but most SIDS research has focused on some failure of cardiorespiratory regulation as the cause of death. Similarly, infants are at increased risk for apneas and other respiratory disorders during sleep due to immaturity of their cardiorespiratory system. As with older children and adults, sleep has a profound effect on ventilation and cardiorespiratory control. These can manifest as important clinical respiratory problems during sleep.

Development Of The Infant Respiratory System.

The ability to sustain spontaneous ventilation requires adequate function of the mechanisms which control ventilation, ventilatory muscle function, and lung mechanics. Significant dysfunction of any of these three components of the respiratory system may impair the ability to breathe spontaneously. Apnea or respiratory failure occur when central respiratory drive and/or ventilatory muscle power are inadequate to overcome the respiratory load.

SIDS and other disorders of cardiorespiratory regulation occur at a time when the infant respiratory system is developmentally immature and rapidly changing. From an engineering perspective, a rapidly changing system is intrinsically unstable [2]. Lung mechanics are different in infants than in older children. This makes the infant's respiratory system more vulnerable to respiratory failure in the event of lung disease. The rapid growth and development of the lungs during infancy also makes the respiratory system vulnerable to the effects of lung injury. During late fetal life and early post-natal life, the lungs grow by adding alveoli. Only ten percent of alveoli are present at birth. Thus, relatively few alveoli are available for gas exchange. In addition, the walls of alveoli contain elastic tissue. The role of elastic tissue in the lungs is to provide support for intrapulmonary structures: alveoli, airways, blood vessels, and lymphatics. As lung volume increases, elastic tissue stretches, increasing the pull on the walls of these structures, increasing their caliber, and preventing collapse. The decreased number of alveoli is accompanied by decreased elastic support of intrapulmonary structures. Because of decreased chest wall stability in infants, there is a tendency for decreased lung volume. Thus, in infants undergoing any disease or stress to the lungs, this decreased elastic support causes a tendency toward atelectasis, airway obstruction, increased pulmonary vascular resistance, and increased lung water or pulmonary edema. Further, the upper airway is predisposed to collapse, causing obstructive apnea during sleep [3,4].

The diaphragm is the major muscle of breathing. Ventilatory muscles can fatigue, resulting in respiratory failure, when either the muscle is too weak (decreased strength or endurance) and/or the respiratory load is too great. Infants have a decreased proportion of fatigue-resistant muscle fibers in their diaphragms compared to older children or adults [5]. Thus ventilatory muscle endurance is severely decreased in infants, making ventilatory muscle fatigue, and resulting respiratory failure, more likely. Diaphragm strength is also decreased in infants compared to older children [6].

Neurologic control of breathing must insure adequate ventilation to meet the metabolic needs of the body during sleep, rest, and exercise [7,8]. Ventilation varies with the state of the individual. It becomes less adequate during sleep, and it is nearly unresponsive to modulation by chemoreceptor input during active (REM) sleep. It is not surprising that sleep is the most vulnerable period for the development of inadequate ventilation in disorders of respiratory control [7,8]. Even in healthy infants, neurologic control of breathing is unstable. Ventilation is depressed by hypoxia, and immature reflexes cause apnea [7]. Further, the infant spends 40-70% of sleep time in active or REM sleep, in contrast to 15-20% in the adult, and sleeps for a longer portion of the day [9]. Active sleep is associated with greater variation in respiratory timing and amplitude, resulting in periods of inadequate gas exchange [8].

Therefore, infants and children are predisposed to apnea and respiratory dysfunction compared to adults, because of differences in the control of sleep and breathing, decreased ventilatory muscle strength and endurance, and immature lung mechanics. Even normal infants frequently have respiratory pauses during sleep, which last up to 30-seconds, and hypoxic events, which cause arterial oxygen desaturations to as low as 80% [10,11]. While these developmental aspects of respiratory dysfunction are present in all infants during the peak age range for SIDS and other respiratory disorders, most infants survive and do not die or suffer significant morbidity. Thus, it is controversial whether the respiratory dysfunction seen in all infants is enough to cause morbidity or mortality.

Effect Of Sleep On Cardiorespiratory Regulation.

Chemical and neurological control of breathing in infants are related to sleep state [12]. During quiet (NREM) sleep, breathing is regulated primarily by automatic ventilatory control, located in the brainstem. Thus, breathing is regular with respect to timing and amplitude [13]. Breathing is responsive and tightly linked to chemoreceptor input [7,8]. However, during active (REM) sleep, breathing is controlled primarily by the voluntary or behavioral system, and it is not tightly regulated by chemoreceptor input. Thus, breathing is irregular with respect to timing and amplitude. Periodic breathing occurs frequently in wakefulness, quiet sleep, and active sleep, but its prevalence is greater in active (REM) sleep [14]. Periodic breathing tends to be more regular in quiet (NREM) sleep than in active (REM) sleep [15,16]. However, minute ventilation is increased in REM sleep due to an increase in respiratory rate, with little change in tidal volume, compared to NREM sleep [14,15,16].

	Quiet (NREM) Sleep	Active (REM) Sleep
Neurologic Control	Automatic (Metabolic)	Behavioral (Voluntary)
Chemoreceptor Regulation	Tight	Poor
Timing of Ventilation	Regular	Irregular
Amplitude of Ventilation	Regular	Irregular
Periodic Breathing	Decreased; Regular	Increased; Irregular

At the peripheral chemoreceptors, hypoxia and hypercapnia act synergistically to stimulate ventilation. Centrally, hypoxia and hyperoxia have opposing effects. Hypoxia increases cerebral bloodflow, which decreases brain tissue Pco_2, and thus decreases ventilation. Hyperoxia causes cerebral vasoconstriction, which increases tissue Pco_2, and thus increases ventilation.

	Hypoxia	Hyperoxia
Metabolic Rate	Decreases	Normal or Increases
Brain Tissue	Depresses	Stimulates
Peripheral Chemoreceptor	Stimulates	Inhibits
Cerebral Blood Flow	Increases	Decreases
Brain Tissue Pco_2	Decreases	Increases
Lung Compliance	Decreases	No Effect

Thus, sleep has influence on cardiorespiratory regulation in infants. The pattern of breathing is regular during quiet (NREM) sleep and irregular during active (REM) sleep. This may relate to the tighter coupling of ventilation of chemoreceptor function in quiet (NREM) sleep. This difference is less pronounced in the newborn, and becomes more significant with maturation into infancy. The newborn ventilatory response to hypoxia is characterized by a late depression of ventilation, possibly due to direct hypoxic depression of central respiratory centers.

Effect Of Sleep On Chest Wall Mechanics And Work Of Breathing.

Active (REM) sleep decreases intercostal muscle tone, which results in a reduction in lung volume compared to wakefulness or NREM sleep [17.]. Therefore, not only is the neonate's ventilatory control more susceptible to ventilatory depression from hypoxia [7.], but the decreased functional residual capacity also decreases oxygen reserves, making hypoxia more likely.

Chest wall stability is maintained primarily by intercostal muscle tone, as the rib cage is cartilaginous [7,17.]. Therefore, when intercostal muscle tone is decreased in REM sleep, there is inward distortion of the rib cage during inspiration, with resulting loss of lung volume. Thus, in REM sleep, the infant must either accept hypoventilation and relative hypoxia and hypercapnia from sucking in rib cage instead of fresh air, or increase work of breathing to generate sufficient minute ventilation [7,17.]. However, the infant is poorly equipped to perform increased work of breathing. Infants have a decreased proportion of fatigue-resistant muscle fibers in their diaphragms compared to older children or adults [5.]. Thus ventilatory muscle endurance is severely decreased in infants, making ventilatory muscle fatigue, and resulting respiratory failure, more likely. Diaphragm strength is also decreased in infants compared to older children

[6]. Thus, during REM sleep, when ventilatory control is less tightly coupled to blood gases, mechanical instability of the chest wall also increases work of breathing. Ventilation, then, is most likely to become inadequate in infants during active (REM) sleep.

Ventilatory Pattern And Oxygenation In Infants During Sleep.

Infants with bronchopulmonary dysplasia (BPD) have spontaneous episodes of hypoxia, not associated with apnea or cyanosis, which are worse during sleep and during feeding [18]. Further, these preterm infants with BPD are not able to rescue themselves from hypoxia [19]. As a group, these infants had an arousal response to the hypoxia, but a substantial proportion developed apnea and/or bradycardia. Though less common or severe, some hypoxia is also seen in normal infants [18].

Results from home recordings of respiratory inductance plethysmography, ECG, and pulse oximetry (CHIME Study) suggest that the normal infant's control of ventilation and oxygenation is not precise [10,11]. Normal infants commonly have prolonged central, obstructive, or mixed apneas up to 30-seconds duration in the home. Approximately 2%-3% of healthy term infants demonstrated prolonged apneas exceeding 30-seconds, with both central and obstructive components, which were associated with oxygen desaturation [11]. Prolonged obstructive apneas were recorded in a few normal infants with a simple upper respiratory infection. These extreme events were seen in 15%-30% of preterm infants. The risk of a preterm infant having such an event was 20-30 times increased over healthy term infants at comparable post-gestational age until 43-weeks post-conception. Thirty-five percent of preterm infants who had clinically observed apneas within five-days of NICU discharge had one or more extreme event [11]. Siblings of SIDS victims and infants with idiopathic ALTE were 2-3 times more likely to have such events, but the difference was not statistically significant.

In the CHIME Study, healthy term infants had an average baseline arterial oxygen saturation at home of 97.9%, and this did not change with age [10]. However, hypoxia (S_pO_2 <90%) occurred in 59% of term infants, and in 0.6% of recorded epochs [10]. Acute desaturations were most common during periodic breathing, or during short apneas. Occasionally, normal infants had spontaneous arterial oxygen desaturations to the low 70%-80% range [10]. Thus, even normal infants do not control their oxygenation precisely. Levels of hypoxia, previously thought to be pathological, are commonly recorded at home in normal infants.

Therefore, infants and children with underlying respiratory disorders will have worse exacerbation of gas exchange due to the influence of sleep on breathing. Those patients who have adequate, but marginal, oxygenation while awake, may experience profound hypoxia during sleep. Similarly, CO_2 retention is more likely to occur during sleep, than during wakefulness. Thus, children with lung disease are especially vulnerable to the normal disruption of breathing which occurs during sleep.

Apparent Life-Threatening Events.

The diagnosis of an ALTE is made if an infant has a convincing history of an episode of sudden onset characterized by color change (cyanosis or pallor), tone change (limpness, rarely stiffness), and apnea, which requires significant intervention (vigorous shaking, mouth to mouth breathing, or full cardiopulmonary resuscitation) to revive the infant and restore normal breathing [20]. ALTE are often frightening to the observer, who may believe that the infant is in the process of dying [20]. ALTE are severe episodes. Mild episodes, which require little or no intervention,

probably do not have the same prognostic significance, and may be treated with parental reassurance. Episodes occurring during wakefulness are more likely to be secondary to a treatable etiology, such as a seizure disorder or gastroesophageal reflux. The diagnosis is made on the basis of the history of the event, as there are currently no diagnostic tests which accurately confirm the presence of ALTE [20,21,22.]. The physician usually has not witnessed the ALTE, and infants often appear entirely normal by the time they reach medical attention. The most important initial diagnostic step is to obtain a careful history from a person witnessing the event. One should specifically ask about the infant's color, tone, apnea, and the need for intervention.

Previously healthy infants may present with an ALTE, and the incidence of ALTE in the general population may be as high as 3% [20.]. ALTE describes a clinical syndrome which may have many causes, some of which can be identified and some of which can not. The respiratory system of infants is immature, and many systemic conditions include apnea as a presenting sign; including seizures, anemia, sepsis, metabolic disorders, pneumonia, lung disease, upper airway obstruction, pertussis, and heart disease [23.]. Optimal care of the infant presenting with an ALTE requires a thorough diagnostic evaluation to detect treatable causes of the event. We recommend hospital admission for protective monitoring, to facilitate the diagnostic evaluation, and for parental training. When no treatable cause for the ALTE is found, these infants may be at increased risk of subsequently dying from SIDS [21,25,26,27.].

Sleep Studies: Overnight polysomnography [28.] is particularly useful in the evaluation of infants with atypical presentation, a prolonged clinical course, or severe events. Normal polysomnography does not rule out a diagnosis of ALTE or unexplained apnea, nor does it reduce the risk of recurrent apneic episodes. In fact, there are no diagnostic tests which are consistently abnormal in, or diagnostic of, ALTE or unexplained apnea [21,22,27,29,30.].

Management: Treatable etiologies for ALTE are found in approximately 30% of infants presenting with ALTE to our referral center [21.]. The diagnosis of apnea of infancy (AOI) is made when an identifiable cause for the ALTE can not be found. There are presently no specific treatments for AOI, thus home apnea-bradycardia monitoring is recommended for these infants [21,24,31.]. Although scientific studies have not been performed to prove the efficacy or lack of efficacy of home apnea-bradycardia monitoring in saving the lives of these infants, they have a high risk for subsequent apneas, and home monitoring is used to detect these episodes [21,24,31.].

Parents or caregivers are instructed to use home monitors whenever the infant is not being otherwise observed. Alarms are set to sound for central apneas >20-seconds and/or bradycardias <80 beats/min in the first month of life, <60 beats/min from 1-12 months, and <50 beats/min thereafter. These monitors do not sound an alarm for obstructive apneas, unless an accompanying bradycardia sounds an alarm. Tachycardia alarms are not useful.

Home monitors only alert the caregiver that a potential episode is occurring. The caregiver must then respond to evaluate and/or terminate the episode. Parents and caregivers must be trained in the proper operation of the monitor, a graded response to monitor alarms, and infant cardiopulmonary resuscitation. Thorough education of the parents and psychosocial support of monitoring families are important for successful home apnea-bradycardia monitoring [32.].

Documented Monitoring (Event recordings): It may be difficult for parents or caregivers to distinguish true apnea or bradycardia alarms from loose lead alarms or alarms for nonsignificant events. Documented monitoring, with event recorders built into the monitors, provide objective recordings of apnea and bradycardia alarms, and may be helpful in making these distinctions [33]. In addition, it provides information regarding compliance with monitor use, because the length of time the monitor was turned on each day is recorded. Compliance with monitoring may be enhanced with documented monitoring because the physician has access to data on monitor use.

Outpatient Management: After discharge, the usual clinical pattern of AOI is that true alarms will decrease in both frequency and severity with time. Infants whose alarms become more frequent or severe, those infants with multiple alarms requiring intervention, and those infants who continue to have true alarms after 6-8 months of monitoring require further diagnostic evaluation, including overnight polysomnography. With severe episodes, these infants may require hospitalization for observation and further diagnostic evaluation [25]. Sometimes the character of the events may change, suggesting the presence or development of other clinical problems, such as a seizure or metabolic disorder [23], which also require specific evaluation.

Discontinuing Monitors: Home apnea-bradycardia monitoring can be discontinued after 3-months of no apnea or bradycardia alarms that require intervention [20]. Tolerating a physical stress (upper respiratory infection or other intercurrent illness) without an apnea or bradycardia is reassuring information, but not required. Most infants with ALTE require 4-6 months of home monitoring, indicating that they had subsequent apneas for 1-3 months after the initial ALTE.

Even with the above diagnostic evaluation and home monitoring, AOI infants have twice the risk of dying from SIDS than the general population [21]. AOI infants have died when home monitor function and response to the alarms appeared to be appropriate [21,25]. Infants with AOI who have received full CPR on more than one occasion are at high risk of dying [21,25]. There is also a high risk of metabolic disorder sin this group [23]. Some infants continue to die in temporal association with noncompliance or with errors in home monitoring technique [21], emphasizing the importance of parental teaching and reinforcement of monitoring skills.

Munchausen Syndrome by Proxy: SIDS and AOI represent true organic disease; they are not a form of child abuse. However, child abuse exists and may masquerade as SIDS and/or AOI. Munchausen syndrome by proxy is a disorder of parenting and a form of child abuse, where the parent creates a factitious illness in the child [34,35]. Most parents afflicted with this syndrome do not harm their children, but rather the factitious illness is created by providing a fabricated history. However, Munchausen Syndrome by proxy may involve inflicted physical injury to the child with suffocation used to induce "apneic spells", or even death, which can mimic SIDS.

Apnea Of Prematurity.

As a group, preterm infants are at statistically increased risk for SIDS [36]. However, at present, there is no way to accurately identify which preterm infants will die from SIDS [21,22]. Apnea of prematurity is defined as a respiratory pause 20-seconds in duration or longer, or any respiratory pause associated with bradycardia or cyanosis, in an infant less than 37-weeks post-conception. A large epidemiologic study of SIDS indicated that apnea of prematurity was not, in and of itself, a precursor or predictor of subsequent SIDS death [37]. Therefore, the optimal management of preterm infants, in order to prevent SIDS, is unclear. Apnea of prematurity is a natural consequence of immaturity, and it improves with maturation.

Preterm infants who continue to exhibit symptomatic apnea when they would otherwise be ready for hospital discharge should have their oxygenation carefully evaluated, since hypoxia can cause apnea in preterm infants, and relieving it may resolve the problem [18]. In the absence of hypoxia or chronic lung disease, preterm infants who are still having clinically apparent episodes of apnea can be discharged on home apnea-bradycardia monitoring. If theophylline or caffeine reduce the frequency of apneic episodes, then these infants can be treated in addition to the home apnea-bradycardia monitor. However, if theophylline or caffeine have no clinical effect, these infants should be discharged on home apnea-bradycardia monitoring alone. Theophylline, if used, may be stopped after 40-weeks post-conceptional age. If there is no recurrence of apnea, home monitoring can be discontinued one-month later. If theophylline is not used, home monitoring is continued until one-month post-term, and discontinued if the child has had no real apnea or bradycardia alarms. If the child has had real apnea alarms, then the infant is managed in the same way as Apnea of Infancy.

Obstructive Sleep Apnea Syndrome.

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of complete inspiratory upper airway (extrathoracic) obstruction during sleep, defined as cessation of airflow at the nose and mouth with continued respiratory effort [38,39,40,41]. In addition, repetitive or persistent partial upper airway obstruction without apnea may result in hypoventilation or hypoxia during sleep.

OSAS is most common between the ages of 2 and 6 years, when tonsils and adenoids reach maximal size, but can occur at any age [38,42]. Unlike adults, boys and girls appear to be equally affected. The factors that determine airway patency are airway size, neuromuscular tone, and neuromuscular coordination. Symptoms of obstructive apnea are usually only present during sleep because of sleep-related changes that occur in respiratory control and neuromuscular tone of the upper airway [40]. These are often more pronounced during rapid eye movement (REM) sleep. Termination of obstructive apnea depends upon arousal from sleep to restore the tone of the pharyngeal dilating musculature. Frequent obstructive sleep apneas and resulting arousals cause sleep disruption, deprivation, and fragmentation which can lead to alterations in daytime function (excessive daytime sleepiness, school difficulties) [38,43].

Hypertrophic tonsils and/or adenoids are the most common cause of OSAS in children [38,39,40]. Infants and children with craniofacial abnormalities are at very high risk for obstructive sleep apnea syndrome. Any evidence for respiratory difficulty during sleep in children with craniofacial abnormalities should prompt an evaluation for OSAS. Eighty percent of children with Down syndrome have OSAS [44]. Infants with severe laryngomalacia may also have sleep disordered breathing with obstructive apnea, hypoventilation, and hypoxemia during sleep [45].

Obesity should be considered a risk factor for OSAS [38,39,40,42,46]. Factors that promote OSAS in obese individuals include anatomical narrowing of the airway due to fat deposition, mechanical loading of the respiratory muscles which will decrease lung volumes and decrease airway patency, and perhaps abnormalities of central respiratory control [46,47,48]. However, not all morbidly obese children will have OSAS. Evaluation should be performed in those children with snoring and disrupted sleep. Patients with waking hypoventilation and excessive daytime sleepiness are likely to have very abnormal respiration during sleep.

Diagnosis: Snoring, agitated arousals, and respiratory distress during sleep are the hallmarks of OSAS [38,39.40.]. Questions regarding these symptoms should be asked as part of well child care. Complaints that increase the likelihood of OSAS include: mouth-breathing, swallowing difficulty, and poor speech articulation. The family may be able to describe obstructive apneas during sleep. Unusual sleep postures or enuresis may be present. Sleep fragmentation and deprivation may lead to excessive daytime sleepiness, but more commonly there will be complaints of hyperactivity, school failure, and behavioral difficulties [43,49.]. In children with multiple congenital malformations or cerebral palsy OSAS may contribute to developmental delay.

The signs and symptoms of OSAS are more subtle in the infant than in the adult, thus the diagnosis is more difficult to make, and should be confirmed by polysomnography. During infancy, snoring, which is characteristic of adult OSAS, may not be present [38,39,40,41.]. Infants more commonly present with stridor or inspiratory retractions on physical examination. However, these signs may be absent if the infant is examined during wakefulness. Infants do not manifest excessive sleepiness. However, if the resulting hypoxia is severe, infants may be lethargic or hypotonic while awake. Failure to thrive is not uncommonly seen, and may be the only presenting sign.

Infants with OSAS usually have some congenital anomaly of the upper airway associated with increased upper airway resistance, such as choanal atresia or stenosis, mid-face hypoplasia, micrognathia, Pierre Robin syndrome, Down syndrome, or cleft palate. A severe upper respiratory infection or chronic allergic rhinitis may cause transient obstructive sleep apnea.

Because this diagnosis can be missed for extended periods of time, children with severe OSAS may present with frank respiratory failure and right heart failure. This type of severe presentation is more common in children with associated problems such as craniofacial abnormalities, cerebral palsy, or obesity. Life-threatening OSAS secondary to hypertrophic tonsils and adenoids is rarely seen in otherwise normal children.

On physical examination, hypertrophic tonsils and/or adenoids are the most common finding. Failure to thrive may be present. Unlike adults, systemic hypertension is not a common finding in pediatric OSAS [50.]. The pulmonic component of the second heart sound may be accentuated suggesting pulmonary hypertension. However, the physical examination may be normal.

Polysomnography: A polysomnogram (PSG; cardiopulmonary sleep study) is required to diagnose OSAS. Generally, these should be performed overnight [51,52.]. Abnormal polysomnograms are characterized by obstructive apneas, partial obstructions (hypopneas), agitated arousals, paradoxical breathing, hypoventilation, and desaturation. Normal children may have up to one obstructive event per hour of sleep [51.]. It should be noted that the upper limit of normal for obstructive events in adults in 5 to 10 per hour of sleep emphasizing the need for age appropriate normal PSG values [51.].

The most reliable polysomnographic technique for making the diagnosis of OSAS is a tight fitting face mask with a pneumotachograph to measure airflow and an intraesophageal balloon to measure intrathoracic pressure swings. However, these measures are not well tolerated by infants and children, who often will not sleep with them in place. Many infants with OSAS demonstrate chronic hypercapnia or hypoxia during sleep. Polysomnographic tracings, under

most circumstances, will confirm the diagnosis of OSAS, though a daytime nap may be too brief to reveal obstructive sleep apneas [52].

Normal Overnight Polysomnography Values [51]

	Mean SD	*Range*	*Recommended Normal Values* [a]
Apnea Index (N/hour)	0.1 0.5	0 -3.1	≤ 1
Maximum $P_{ET}CO_2$ [b] (mm Hg)	46 4	38 - 53	≤ 53
Minimum $P_{ET}CO_2$ [b] (mm Hg)	38 3	28 - 44	---
Duration of Hypoventilation ($P_{ET}CO_2$ [c] >45 mm Hg [% TST [c]])	6.9% 19.1%	0% - 90.5%	≤ 45%
Maximum S_aO_2 (%)	100 1	98 - 100	---
Minimum S_aO_2 (%)	96 2	89 - 98	92%
Fall in S_aO_2 (%)	4 2	0 - 11	≤ 8

[a] Recommended normal values are defined by the mean 2 SD for polysomnographic parameters derived from the study of a population of normal children and adolescents.

[b] $P_{ET}CO_2$; end-tidal carbon dioxide tension.

[c] TST; total sleep time.

Other Diagnostic Tests: Other useful laboratory investigations may include a lateral neck film for soft tissues of the nasopharynx, an electrocardiogram and/or echocardiogram to evaluate for pulmonary hypertension, and a chest radiograph. Lateral neck x-rays (high KV), which visualize the upper airway, may show tonsillar or adenoidal hypertrophy, or other causes of upper airway narrowing. Chest x-ray may show cardiomegaly or pulmonary edema in severe cases. Electrocardiogram (ECG) and echocardiogram (right ventricular dimensions, pulmonic valve systolic time intervals, septal morphology, pulmonic valve "a" dip, pulmonic valve early systolic closure, and acceleration time of pulmonary artery flow [doppler]) may show evidence of pulmonary hypertension.

In children with severe OSAS, arterial blood gases during wakefulness may be normal, but can show hypercapnia and hypoxia. Elevated hemoglobin and hematocrit may indicate polycythemia from chronic intermittent hypoxia.

More sophisticated radiographic assessment of the upper airway such as cine CT scans, MRI, or cephalometry may be indicated in complicated cases such as craniofacial abnormalities or OSAS that persists following adenotonsillectomy.

Treatment: Progression of obstructive sleep apnea syndrome may be slow or rapid. Once complications develop, especially pulmonary hypertension, progression is accelerated. However, many infants and children never reach that point. The development of pulmonary hypertension and cor pulmonale can cause death.

Treatment is directed toward relieving the airway obstruction [38,40]. Adenotonsillectomy is indicated for OSAS secondary to hypertrophic tonsils and adenoids. Children with craniofacial abnormalities or obesity may also improve after adenotonsillectomy. Adenoidectomy in children with a history of previous cleft palate repair must be balanced with the risk of creating velopharyngeal incompetence and hypernasal speech. Children with OSAS who are not candidates for surgery, or who do not respond to surgery, may benefit from nasal continuous

positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) delivered via mask during sleep. Supplemental oxygen may offer some benefit [53]. The safety and efficacy of supplemental oxygen during sleep must be titrated by polysomnographic monitoring [53]. Uvulopalatopharyngoplasty has been used extensively in adults with OSAS and results in improvement in some patients. Experience in children is limited, but this procedure can be considered by experienced centers in cases unresponsive to standard therapies. A tracheostomy is always effective in relieving upper airway obstruction in OSAS, but not frequently required.

A repeat PSG should be performed six weeks post-operatively in patients with craniofacial abnormalities, obesity, and in those who had severely abnormal studies pre-operatively. Repeat investigations should be performed in any child with persistent symptoms. Pediatric follow-up of associated complications is critical.

The Collaborative Home Infant Monitoring Evaluation (Chime) Study.

Although many monitors are in use in the United States, no prospective controlled clinical trial has been conducted to assess the efficacy of home monitoring to prevent deaths, either in symptomatic or asymptomatic high risk infant populations. Before data can be interpreted for mortality rates in monitoring programs and the usefulness of monitors in managing high risk infants, information is needed on compliance, the reliability of alarms as measuring true events, and the causes of infant death.

The purpose of this CHIME study was to employ state of the art technology to determine the frequency, duration, and type of respiratory and cardiac alteration in infants at risk for life-threatening events that are recorded preceding, during, and following an alarm event [54].

Methods. Infants were recruited from five clinical sites between May 1994 and February 1998. The following groups of infants were studied:

- Healthy Term Group: Full term with birthweight 10th-90th percentile, enrolled in the first month. These infants were clinically well without any personal history of apnea, heart or lung disease, and without a family history of apnea.
- Term Idiopathic ALTE Group: History of an unexplained, sudden episode of color change (cyanosis or pallor), tone change (limpness, stiffness) or apnea, that required mouth-to-mouth resuscitation or vigorous stimulation, which was unexplained following a thorough diagnostic evaluation.. [1]
- Preterm Idiopathic ALTE Group: as above except born <37 weeks PCA.
- Term SIDS-SIB Group: full or half sibling of one or more previous SIDS infants (documented by autopsy).
- Preterm SIDS-SIB Group: as above except born <37-weeks PCA.
- Asymptomatic Preterm Group: Ineligible for other groups and □34 weeks gestation at birth, with <1750 g birth weight. No apnea or bradycardia associated with cyanosis observed by NICU staff within five days of discharge.
- Symptomatic Preterm Group: as above except apnea or bradycardia associated with cyanosis *was* observed by NICU staff within five days of discharge.

CHIME Home Monitor: Following enrollment, each infant had cardiorespiratory waveforms recorded in the home using the CHIME monitor.[54.] Rib cage (RC) and abdominal (AB) movement were recorded by respiratory inductance plethysmography (RIP) bands and a third signal, proportional to tidal volume, was calculated from the weighted algebraic sum (sum channel). The monitor recognizes a *breath* whenever there is an excursion on the sum channel that is <25% of the amplitude determined during a calibration period (first 5 minutes each time monitor turned on). The monitor is capable of determining central apneas (no respiratory excursions) or obstructive apneas (out of phase abdominal and rib cage motion, previously documented by comparison with polysomnography). Heart rate was measured. Hemoglobin oxygen saturation by pulse oximetry, SpO_2 oximeter, and transthoracic impedance (TTI) signals were also monitored, but were not used to define recording or alarm thresholds.

The monitor had the capability to initiate recording and storage of physiologic data at a preset duration (threshold) for low heart rate and apnea; the duration for initiating an alarm was longer and could be set independently. All events stored in memory included the 75 s preceding onset of the event, the event, and 30 s after resolution of the event. The thresholds for recording physiologic events were identical for all groups of subjects: apnea >16 s in duration, or a heart rate <80 or 60 beats/min for >5 s for infants <44 or >44 weeks post-conceptional age (PCA), respectively. The alarm thresholds in the Healthy Term group were set at >40 s for apnea and <40 bpm for heart rate since they had no clinical indication for the audible alarm. For all other infants, the monitor was set to sound an audible alarm for apnea 20 s, or a heart rate <80 beats/min for 5 s for infants <44, or <60 for those >44 weeks PCA.

Families received standardized training and ongoing support of home monitoring, and were instructed to use the monitor whenever the infant was sleeping or unobserved. The intended duration of home monitoring was through 66 weeks PCA (6-months post-term) for the Healthy Term and SIDS-Sib groups, 56 weeks PCA (4-months post-term) for the preterm groups, and 4 months from enrollment for the ALTE groups. In addition, infants remained on the monitor until they were free of events exceeding alarm thresholds for at least 3 months.

For the purposes of data analysis, events were categorized as *conventional* or *extreme events. Conventional* events were defined as: 1. Apnea >20 s; 2. if < 44 wk PCA, heart rate < 60 bpm for >5s or < 80 bpm for >15s; or 3. if > 44 wk PCA, heart rate < 50 bpm for >5s or < 60 bpm for >15s. *Extreme* events were defined as: 1. Apnea >30 s; 2. if < 44 wk PCA, heart rate < 60 bpm for >10s; or 3. if >44 wk PCA, heart rate < 50 bpm for >10s.

Results. 1079 infants participated in the study, and provided 718,358 hours of home monitoring data. Six infants died during the study, but none was using the monitor at the time of death. 21,647 events exceeded recording thresholds. Of these, 6,958 events exceeded conventional thresholds in 41% of infants, and 653 events exceeded extreme thresholds in 10% of infants. SpO_2 were available and of sufficient quality for assessment in 84% of conventional events and 67% of extreme events.

Types of Events: Apnea without bradycardia occurred in three-quarters of conventional events, and in nearly half of extreme events. Bradycardia without apnea only occurred in 12% of conventional events, and in 22% of extreme. In general, the degree of hypoxemia increased with increasing duration of apnea or bradycardia. One-fourth of all extreme events were associated with <10% decrease in SpO_2. Among all extreme events with apnea >30 seconds, 70% included

>3 obstructed breaths. Among all conventional events with apnea □20 seconds, 50% of the apneas included >3 obstructed breaths.

Risk of Events: Risk ratios for each study group compared with Healthy Term infants for the occurrence of at least one extreme event and at least one conventional event during the first 180 days on the monitor were calculated. Only the four preterm groups had significantly increased risk of an extreme event. Symptomatic preterm infants were nearly 20-times more likely to have extreme events than controls, and asymptomatic preterm infants were 10-times more likely, and these declined over time ($p<0.01$). For example, symptomatic preterm infants were 34-times more likely to have extreme events than controls at day seven of monitoring, compared to 14-times at day 28 of monitoring. Similarly, asymptomatic preterm infants were 17-times more likely to have extreme events at day seven of monitoring than controls, compared to 8-times at day 28 of monitoring. For both groups, the risk of at least one extreme event remained significantly higher than the Healthy Term group for approximately the first seven weeks of monitoring (until 43-weeks PCA). Similarly, the symptomatic and asymptomatic preterm groups also had the highest risk ratios for conventional events. However, the occurrence of at least one conventional event was very common in all groups, including the Healthy Term group (cumulative incidence 43%). The risk of conventional events for the Preterm groups declined with time, and by seven weeks of monitoring were not significantly higher than the Healthy Term group.

Relationship of Events to Age: The likelihood of experiencing at least one extreme event decreased with age (PCA). After 43 weeks PCA, all groups had similarly low rates of having extreme events. Compared to the Healthy Term group (at 42-45 weeks PCA), the number of 34-37 week PCA symptomatic preterm infants having $\geq$1 extreme event per 4 weeks of monitoring time was nearly 20-times higher ($p<0.001$). Similarly, the number of asymptomatic preterm infants having $\geq$1 extreme event per 4 weeks of monitoring time was nearly 10-times higher ($p<0.01$) than controls. At 38-41 weeks PCA, all four preterm groups also demonstrated significantly higher rates than the healthy term controls. After 42-weeks PCA, no group had a rate of extreme events that was significantly higher than the controls.

Discussion. The CHIME Study is the first large, longitudinal study comparing risk of cardiorespiratory events between infants commonly placed on home monitors and healthy term infants. These data show that events previously described as pathologic are actually quite common, even in healthy term infants [54]. Further, groups of preterm infants have higher risks of extreme events. However, the increased risk of at least one extreme event occurs only in preterm infants and only until about 43 weeks PCA. By using RIP to detect breaths, a high frequency of obstructed breaths was observed in our subjects. This suggests that many events would have been missed by techniques commonly used in clinical practice.

The high proportion of apnea containing >3 obstructed breaths could be observed because we used respiratory inductance plethysmography (RIP) to detect breaths. For this reason, TTI (which only detects central apneas) may miss many of these apneas, and currently available home monitors may have detected less apnea than we observed. Thus, the distribution of events might vary between our subjects and those reported using other technology. Although detection of bradycardia theoretically provides an alternative opportunity to detect obstructed events, fully half of extreme events had no bradycardia, even if associated with desaturation.

CHIME was not designed to address the question whether infants who experience extreme cardiorespiratory events are more likely to die from SIDS. The six deaths are too few to derive conclusions. However, the highest rates of events were observed among infants who were < 43 weeks PCA, whereas the peak incidence of SIDS generally occurs at older mean PCAs of 44, 47, and 53 weeks for infants born at 24-28, 29-32, and >37 weeks, respectively.[54] These differences in timing suggest that extreme events are not likely to be direct precursor to SIDS, although it does not eliminate the possibility that they are markers of vulnerability..

Summary.

The infant respiratory system is immature. Pulmonary mechanics lead to certain vulnerabilities, which predispose to lung disease. Ventilatory muscles lack sufficient endurance to perform increased work of breathing, and therefore are subject to fatigue, especially in the face of increased demands. Sleep has a profound effect on the ventilatory pattern. Sleep is much more irregular in active (REM) sleep. Chemoreceptor function is decreased in infants and in sleep. Infants have a unique respiratory depression from hypoxia. Active (REM) sleep with decreased intercostal muscle tone, causes chest wall instability, reduced lung volume, and increased work of breathing. Infants, especially, are predisposed to respiratory disorders during sleep.

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