Central Sleep Apnea in Infants

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KEYWORDS

• Central sleep apnea • Infants • Oxygen supplementation • Apnea • Polysomnography

KEY POINTS

- Central apnea (CA) and periodic breathing are common in infants, and are much more common in preterm than term infants.
- Irregular breathing is seen in both active and quiet sleep. It tends to improve with increasing gestational age, and is presumed to be due to maturity of the respiratory control centers and chest-wall mechanics.
- In-laboratory polysomnography is the study of choice for the evaluation of CA in infants. Most therapies directed at treatment of CA are meant to stabilize the breathing pattern and prevent oxygen desaturation.
- Most of these therapies are temporary, and are used for a brief period in preterm and term infants until the breathing matures.

INTRODUCTION

Sleep-disordered breathing encompasses a wide variety of breathing disorders including obstructive sleep apnea, central apnea (CA), and nonobstructive sleep related hypoventilation. Central sleep apnea results from absent respiratory drive from breathing centers in the brainstem during sleep. The criteria that meets the definition of CA differ between children and adults. The American Academy of Sleep Medicine (AASM) defines CA in children as cessation of breathing during sleep without any breathing effort for a duration of 20 seconds or longer, or lasting at least 2 breaths' duration with 3% oxygen desaturation or arousal.[1] In infants, the CA is at least 2 breaths in duration and is associated with a decrease in heart rate to less than 50 beats per minute for at least 5 seconds, or less than 60 beats per minute for 15 seconds. Periodic breathing is a form of CA that has been described as greater than 3 episodes of CA lasting 3 seconds separated by no more than 20 seconds of normal breathing.[1] Apnea following a sigh is not considered pathologic unless it is associated with arousal or desaturation. Isolated central sleep apnea (**Fig. 1**A), CA following sigh breathing (see **Fig. 1**B), CA following body movements, and periodic breathing patterns (see **Fig. 1**C) can be seen in healthy infants and children.[2] It is common to see CA in healthy infants, but on rare occasions it can be a harbinger of ominous pathologic consequences, such as congenital central hypoventilation syndrome or Arnold-Chiari malformation.[3] The severity of CA can be characterized using the apnea-hypopnea index (AHI), the total number of events overnight divided by hours of sleep. There is no clear description in the literature of pathologic central AHI, but studies have considered a central AHI from greater than 0.9 to AHI greater than 5 as abnormal.[4–6] The adverse consequences of moderate and severe CA are well known, but those of CA of milder degree is still debated.[7] The mild CA seen in otherwise healthy infants tends to improve with age, and older children can have rare CAs.[5,8] The improvement in apnea frequency can be considered as maturation of respiratory control and chest-wall mechanics.

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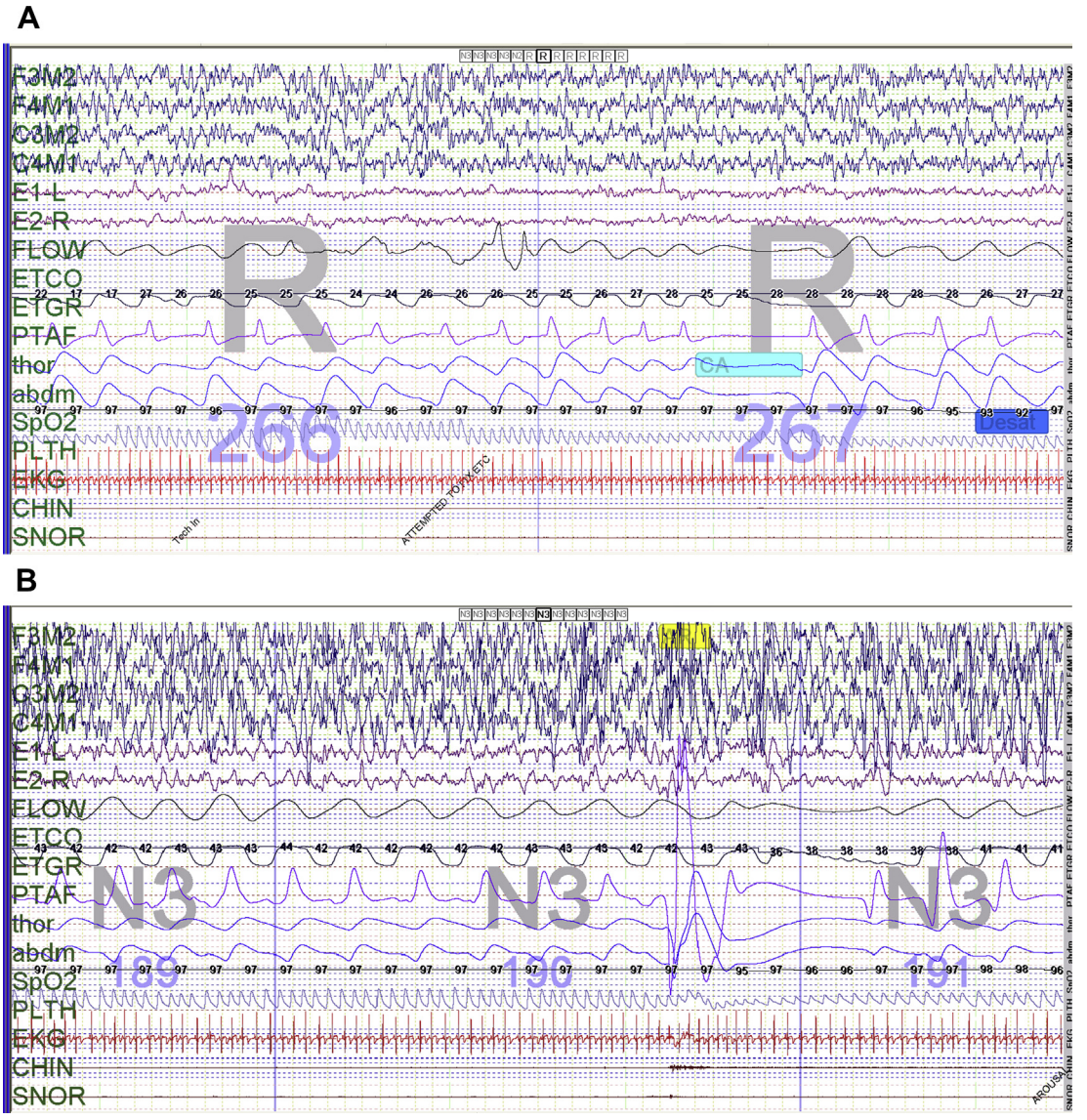

Fig. 1. (*A–C*) Sixty-second-long epoch of the polysomnography of a 21-month-old child born at full term, referred for evaluation of sleep apnea because of a family history of sudden infant death syndrome. (*A*) Central sleep apnea without arousal. (*B*) Central sleep apnea after arousal during stage 3 non–rapid eye movement sleep. (*C*) Periodic breathing during rapid eye movement sleep. abdm, abdominal plethysmography; C3, C4, central electroencephalogram leads; CHIN, chin electromyogram; E1, left eye electromyogram; E2, right eye electromyogram; EKG, electrocardiogram; ETCO, end-tidal carbon dioxide tracing; ETGR, End tidal graphical representation; F3, F4, frontal electroencephalogram leads; FLOW, tracing of oral thermistor; PLTH, Plethysmography; PTAF, for measurement of nasal air flow; SNOR, snore micrograph; SpO2, continuous pulse oximetry; thor, thoracic plethysmography.

APNEA IN HEALTHY NORMAL INFANTS

Brief CA in full-term infants is very common, especially in the early months of life. The duration and frequency of CA improves with age.[9,10] Several studies have focused on defining the prevalence of CA in healthy infants. Each study has used different criteria to define CA, different monitoring techniques, and different testing environments such as home versus in-laboratory polysomnography, which makes it difficult to make comparisons between the studies. As already noted, standardization of the definition of CA has been achieved, which will make interstudy comparisons in the future much easier and more fruitful. Home monitoring provides an opportunity to collect data in infants during sleep for a long

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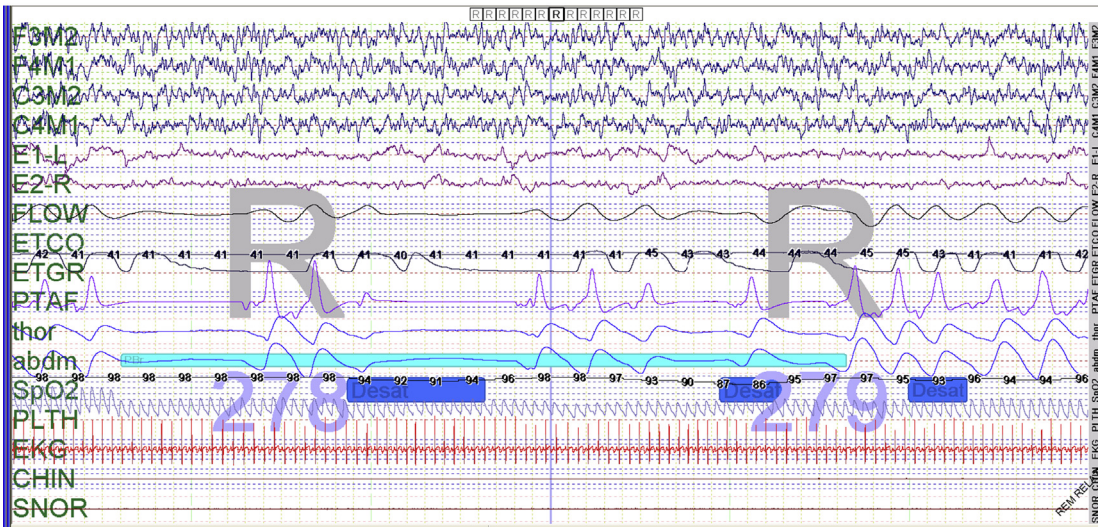

Fig. 1. (*continued*)

period in familiar surroundings. The limitations of home monitoring include inability to assess the exact duration of apnea caused by lack of airflow, and reliance on breathing pattern and heart rate to differentiate between sleep and wakefulness. The Collaborative Home Infant Monitoring Evaluation (CHIME) study is perhaps the most comprehensive study allowing comparison of breathing patterns during sleep in healthy term infants, siblings of infants with a family history of sudden infant death syndrome (SIDS), healthy preterm infants, and infants with apparent life-threatening events (ALTE) in both term and preterm subjects.[11] The study was conducted in almost 1100 infants over 6 months' duration in their home environment. The investigators concluded that conventional events, described as apnea of 20 seconds' duration not associated with bradycardia, are not uncommon in otherwise healthy term infants. The study also reported that extreme events, described as apneas longer than 30 seconds associated with bradycardia, are more common in premature infants and tend to reduce in frequency after 43 weeks gestational age (GA). A strength of the study is the ability to potentially differentiate between central, obstructive, and mixed apneas.[12] In another smaller study, breathing was monitored in the home environment in healthy term infants for a shorter period.[9] Electrocardiography (ECG) and abdominal-wall movement was used to define apnea in 110 subjects, and subjects were monitored at 2, 6, 12, and 24 weeks of age. It was concluded that CAs of longer than 20 seconds are common in first 2 weeks of life, and rare afterward. Periodic breathing was seen in all age groups studied, and improved with age.

In another study of 46 full-term healthy infants, the investigators used pneumograms, overnight recording of the respiratory pattern by impedance and heart-rate monitoring, to define the incidence of CA in the nursery and home settings.[13] The recordings were made at birth, 1 month, and 3 months of age. A modified definition of CA, with duration of 5 seconds, was used. There was no mention of desaturation association with apnea, nor was there any characterization of sleep and wakefulness. The investigators relied on parents' descriptions of sleep and wakefulness, and reported that apnea of longer than 15 seconds at birth and 4 weeks of age is rare. Moreover, there was significant intersubject and intrasubject variability in terms of apnea frequency, pattern of apnea, and change in pattern of apnea over the first 4 weeks of life.

In-laboratory monitoring for sleep-disordered breathing is also associated with limitations and advantages. The data collected during this monitoring is for a shorter duration but has better ability to characterize events such as non–rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and wakefulness. In a smaller study of 9 full-term infants, the investigators studied subjects in a laboratory setting at monthly intervals until 6 months of age,[10] using slightly different criteria to define apnea and periodic breathing. CA was defined as of at least 6 seconds' duration, while periodic breathing was at least 2 CAs alternating

with regular breathing of at least 3 seconds in a 20-second period. The investigators reported that CA is common until 3 months of age and that it is rare to see CA of 15 seconds' duration afterward. The frequency of apnea decreases after 3 months. Most apneas were in active sleep (ie, REM sleep). It was further reported that periodic breathing remained stable across the ages and was mostly seen in active sleep.

In an attempt to describe normative data of breathing patterns during sleep in older children, Uliel and colleagues[5] studied 70 subjects between the ages of 1 and 15 years who underwent a single-night sleep study in the laboratory. CA was defined as of at least 10 seconds' duration or any duration associated with desaturation of greater than 4% compared with baseline. The investigators confirmed that CA is rare in children, and stated that CA with desaturation is even rarer. The study was conducted with a modern computer-based recording system and was manually scored by visual inspection.

On review of the literature, it can be suggested that CA is common in early infancy and improves with age. It is also rare to see CA not following a sigh breath in older healthy children beyond infancy. One should keep in mind that these studies used different monitoring techniques, variable duration of monitoring periods, different testing environments, and variability in describing CA in the population tested. These differences limit the ability to compare studies.

APNEA OF PREMATURITY

Central apnea and periodic breathing in premature infants is a rule rather than an exception. With the technological advancement in the neonatal intensive care unit (NICU) and the availability of newer and improved medications, extremely premature infants are surviving. The etiology of premature birth is multifactorial, but results in the birth of an infant who is not fully equipped to transition to an independent life. The premature birth results in significant comorbidity and mortality later in life that compounds the difficulty in transition to postnatal life. In premature infants, the breathing pattern is not fully developed at the time of birth.[14] This situation may be complicated with the development of bronchopulmonary dysplasia with limited respiratory reserves, and/or cerebral palsy with associated poor neuromuscular control of upper airway.[15] Thus, prematurity predisposes to both central and obstructive sleep apnea. Most studies performed in premature infants to assess the maturation of breathing are retrospective in nature.

In a retrospective study, Eichenwald and colleagues[16] reviewed the medical records of 457 subjects born between 24 and 28 weeks GA to assess the natural history of recurrent apnea and bradycardia in premature infants. The nursing documentation of apnea alarms and the infants' condition were reviewed. The monitor alarm was set for apnea duration of 20 seconds, and bradycardia for a heart rate less than 100 beats/min in infants younger than 35 weeks GA and less than 80 beats/min thereafter. The investigators found that apnea and bradycardia were reported in all infants. The time to resolution of apnea was longer for infants born at lower GA. Infants born between 24 and 27 weeks GA had recurrent apnea and bradycardia at 36 and 38 weeks but not beyond 40 weeks GA, compared with those born at 28 weeks GA. Later resolution of recurrent apnea and bradycardia was strongly correlated with higher incidence of chronic lung disease, but not with severity of head ultrasonographic abnormalities. The study is limited because of its inability to characterize types of apnea based on the NICU monitor and to differentiate sleep and wakefulness, and its retrospective nature.

In yet another retrospective study, investigators reviewed the charts of 865 infants born between 24 and 32 weeks GA to assess the maturity of different body functions including breathing patterns.[17] Nurse-documented monitor events were used to characterize apnea and bradycardia. The monitor alarm was set for an apnea duration of 20 seconds and bradycardia of less than 80 beats/min. The investigators reported that at 31 weeks GA 25% of patients were free of apnea and bradycardia, and by 36 weeks GA all were without apnea or bradycardia. Furthermore, infants born at less than 26 weeks GA demonstrated a delay in becoming apnea free by a mean of 2.3 weeks when compared with infants born at 31 and 32 weeks GA. Bronchopulmonary dysplasia and necrotizing enterocolitis were associated with a delay in becoming apnea and bradycardia free.

Periodic breathing is also common in premature infants (**Fig. 2**). In an attempt to describe the prevalence of periodic breathing in relatively mature preterm infants (30–35 weeks GA) in comparison with full-term infants, Glotzbach and colleagues[18] recorded pneumograms in 66 preterm infants before discharge. The investigators reported a higher mean percentage value of periodic breathing per quiet sleep and number of episodes of periodic breathing per 100 minutes of quiet sleep, and the longest episode of periodic breathing was higher in preterm infants than in full-term controls. Moreover, percentage and episodes of

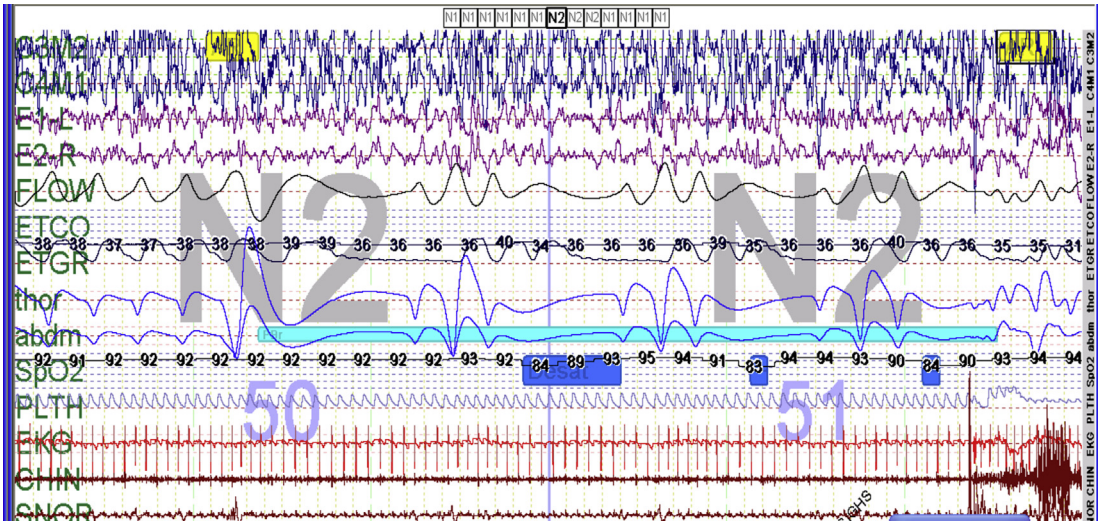

Fig. 2. Sixty-second-long epoch of the polysomnography in a 6-month-old child with periodic breathing born at 26 weeks gestational age. abdm, abdominal plethysmography; C3, C4, central electroencephalogram leads; CHIN, chin electromyogram; E1, left eye electromyogram; E2, right eye electromyogram; EKG, electrocardiogram; ETCO, end-tidal carbon dioxide tracing; ETGR, End tidal graphical representation; FLOW, tracing of oral thermistor; PLTH, Plethysmography; SNOR, snore micrograph; SpO2, continuous pulse oximetry; thor, thoracic plethysmography.

periodic breathing during sleep decreased as infants reached 39 to 41 weeks postgestational age. The study suggests that periodic breathing is common in premature infants and decreases as infants approach term GA. Periodic breathing is also seen in full-term infants.

APPARENT LIFE-THREATENING EVENT

ALTE has been described as an episode that is frightening to the observer and characterized by some combination of apnea, color change, marked change in muscle tone, choking, and/or gagging. The pathophysiology of ALTE is multifactorial; occasionally it is a single event, and no significant pathologic features may be discovered despite extensive investigation.[19] In the past, it was proposed that some infants who die of SIDS had recurrent ALTE, but most patients with ALTE do not die.[20–24] The true prevalence of ALTE is difficult to assess because of the wide range of definitions used to describe ALTE, geographic variations in care, and different patient populations studied.[25,26] It is further complicated because the definition involves the caregiver response to the particular event, which is variable; some parents perhaps ignore the event completely, whereas others may misperceive normal physiologic body function as abnormal.

There are various of causes for ALTE, and it is difficult to focus on a single system function.[27] Several retrospective studies have focused on different organ systems involved in infants who survived ALTE and underwent extensive workup. Most of these studies failed to show any significant abnormalities discovered during the initial workup, but some studies have suggested that patients with ALTE should have close follow-up, as the chances of missing any neurologic disease may be high on initial workup.[28,29–31] Child abuse has been reported as a cause of ALTE Munchausen by proxy, and these children are at higher risk of death subsequently.[32,33] A few studies highlight that the autonomic nervous system may be abnormal in infants who have suffered ALTE.[34–36]

Apnea may not necessarily be part of the presentation in infants who present with ALTE. The AASM recommends performing polysomnography in infants with clinical suspicion of sleep-disordered breathing.[37] The studies that have assessed sleep-disordered breathing as an etiologic factor in ALTE have used various techniques and different populations of subjects, which make it difficult to draw conclusions. The early studies implicated CA as a major cause of SIDS but only in a very limited number of patients studied.[13] In a study of 340 infants who experienced an ALTE a pneumogram was performed, with subsequent home monitoring in infants with abnormal pneumograms. Rahilly[23] reported that 8% of subjects had abnormal findings, and most these infants had CA on home monitoring.

In a study of infants who were admitted with ALTE, extreme respiratory events, described as CA of 30 seconds' duration or bradycardia of longer than 20 seconds, are more likely to be associated with upper respiratory infection, premature birth, and GA of less than 43 weeks.[38] To delineate the relationship between gastroesophageal reflux (GER) and apnea, Khan and colleagues[39] studied both central and obstructive apnea in 50 infants with ALTE and 50 control subjects. It was concluded that there is no temporal association between GER in the middle esophagus and apnea/bradycardia in both populations. Periodic breathing has also been shown in excessive amounts in patients with ALTE.[40] It is unclear whether CA or periodic breathing is associated with or is a cause of ALTE in infants, and the relationship between ALTE and SIDS is less than tenuous at best.[41]

In a recent prospective study of 300 infants who presented with ALTE and underwent pneumography, Mittal and colleagues[42] showed that the presence of abnormal pneumographic findings does not predict recurrent ALTE.

PATHOPHYSIOLOGY OF CENTRAL APNEA IN INFANTS

The exact timing of the start of breathing movements in the human fetus is unclear, but most of the data derived from animal models show that it starts fairly early in fetal life. It is suggested that fetal breathing movement in most mammals starts in the second trimester.[43] The role of breathing is not gas exchange in fetal life, this being achieved via the circulatory system and placenta. The fetal breathing movement is noncontinuous, rhythmic, and nonsynchronized.[44] During periods of high-voltage, low-frequency activity, electrocorticography of the fetus is apneic (similarly to REM sleep).[45] Perhaps an important aspect of breathing rhythm in the fetus is that it is vital for lung development during fetal life.[46] The control of breathing in fetal life is complex, and involves several inhibitory and excitatory stimuli. Some of the important modulators of breathing include central rhythm generators, central and peripheral chemoreceptors, sleep and wake states, and various neurotransmitters.[47,48]

Based on the animal model of respiratory control, there are 2 distinct groups of respiratory centers that function in harmony. The first, the parafacial nucleus, is located at the ventral surface of the hindbrain while the second, the pre-Bötzinger complex, is on the dorsal aspect. Both groups of neurons develop independently from each other in the hindbrain.[49] The parafacial nucleus predominantly controls expiration and functions by phasic inhibition of tonic background inspiratory activity via glutamatergic neurons.[50] The pre-Bötzinger complex predominately works as the inspiratory control. The development of these respiratory centers and the interaction between them is beyond the scope of this review.

Fetal breathing is stimulated with elevated carbon dioxide during low-voltage high-frequency electrocorticography, suggestive of awake state, and during both high-voltage and low-voltage electrocorticography with exposure to cold and carbon dioxide.[51,52] Responses to hypoxia and hypercapnia in fetal life suggest that carotid chemoreceptors are already active in fetal life.[53] A powerful inhibitory effect of the upper lateral pons may be responsible for the episodic nature of fetal breathing.[54] The other inhibitory stimuli for breathing in fetal life include adenosine and the placenta.[55,56] Removal of placenta after birth may be a stimulus for continuous breathing.[57] Fetal breathing is also under behavioral control. It is stimulated during high-frequency, low-voltage electrocorticographic activity, which is characteristic of awake and REM sleep, and is inhibited during low-frequency, high-voltage electrocorticographic activity, with apnea being present.[45]

Transition from fetal to neonatal life is probably the most complex transition in human life.[58] In a preterm infant, the transition is difficult because of the immaturity of organ systems, such as an immature breathing pattern and limited lung development that can adapt to an independent life. The intermittent breathing pattern noted in fetal life persists in premature infants and even extends into the age at which they reach term gestation.[59] The irregular breathing pattern in preterm and term infants is also exacerbated by immature lung mechanics at the time of birth. Infants have low functional residual capacity, which results in hypoxemia even with brief CA and periodic breathing.

In premature infants the breathing is irregular, and is characterized by apnea and periodic breathing. Irregular breathing is most commonly seen in active sleep/REM sleep, with breathing becoming more regular during quiet or NREM sleep.[60] The breathing irregularities increase from 30 to 36 weeks GA and then decrease. In full-term infants, breathing irregularities persist during 60% to 70% of the sleep time and decrease by 3 months of age.[61] Warm temperature induces apnea in term infants, and loss of body heat stimulates breathing.[62]

Periodic breathing in premature infants is related to the carbon dioxide level and its relationship to the apnea threshold. Reduction in serum

carbon dioxide below a certain point causes apnea during sleep, and this level is termed the apneic threshold. In premature infants, the apnea threshold is much closer to the eucapnia level in comparison with adults.[63] The apnea threshold is therefore frequently reached with common maneuvers such as an augmented breath, resulting in recurrent apnea that is seen in periodic breathing. Another concept in understanding periodic breathing may be related to loop gain, an engineering term. Loop gain is described as a negative feedback system in which a disturbance (u) increases alveolar ventilation from a steady state. This increase in ventilation in turn reduces carbon dioxide, which evokes a negative corrective action (e) to suppress the disturbance. The ratio of e/u will define the loop gain of the system. In the high loop-gain system, the response is greater or equal to the disturbance, which results in an unstable system. For example, a sigh produces a sudden reduction of carbon dioxide levels, which evokes an exaggerated response from the central respiratory center and induces apnea, which in turn results in elevated levels of carbon dioxide. This process causes resumption of breathing but in an exaggerated fashion, leading to washout of carbon dioxide, bringing it below the apneic threshold; the cycle will thus repeat itself, resulting in the characteristic breathing pattern seen in periodic breathing.

DIAGNOSIS

Premature infants often have a prolonged stay in the NICU after birth for respiratory support and nutritional needs. CA and periodic breathing are seen after invasive ventilation has been discontinued. The apnea events may be noticed by the health care staff during routine care and mostly during sleep. Alternatively, the alarm at the bedside will show apnea, bradycardia, and/or desaturation.[64] The accuracy of diagnosis of CA based on nursing documentation is debatable.[65] Patients may have skin-color change and may lose muscle tone. Typically, stimulation will restore breathing in most of the infants. Sometimes the apnea and periodic breathing may be significant enough to require invasive and noninvasive ventilation or oxygen supplementation. After discharge, the premature infants may present with ALTE. Infants with chronic lung disease attributable to prematurity are more likely to have desaturations and apnea events, probably related to the limited respiratory reserves in such infants.[66] The CA is most likely noticed during sleep and rarely during wakefulness. Young infants take frequent naps during the day, so CA is more likely to be noticed by parents during the day than at night.

Polysomnography is considered a test of choice to diagnose sleep-disordered breathing in infants and children. The study requires in-laboratory testing, which is well tolerated by patients and family members.[67] A recent study has shown that a shorter 4-hour evening study is comparable with an overnight sleep study in the diagnosis of sleep-disordered breathing in children younger than 2 years.[68] A nap study, even shorter than a 4-hour study, is not considered to be equivalent to a full-night study and may miss sleep-disordered breathing.[69] The advantage of in-laboratory polysomnography includes accurate diagnosis of the nature of sleep-disordered breathing, assessment of additional sleep-related physiologic parameters such as sleep-related hypoventilation, and ability to intervene during the study as indicated. The disadvantages include the short period of data collection, expensive testing, and long waiting time for the study because of the shortage of child-friendly sleep laboratories.

Home monitoring has been used in several research studies to document sleep-disordered breathing in infants,[11] but has not been widely accepted as a tool for clinical use. There are various portable testing modalities available for the assessment of sleep-disordered breathing in infants, including home pulse oximetry, pulse transit time, and multichannel unattended sleep studies.[70,71] Portable monitoring provides the advantage to collect data in a patient's familiar surroundings and for an extended period of time. It is also inexpensive and readily available. The disadvantages include difficulty in accurate differentiation of sleep and wake stages, and multiple artifacts during the data collection. Despite these disadvantages, home monitoring for sleep apnea is a valuable tool in certain circumstances.

MANAGEMENT OF CENTRAL APNEA IN INFANTS

Management of CA in infants is aimed at normalization of breathing and stabilization of fluctuation in oxygen saturation. Various therapies are available for the treatment of apnea in infants, but all serve as temporary therapies while awaiting maturity of the breathing apparatus of premature and full-term infants.

Supplemental oxygen is probably the most widely prescribed therapy for CA and periodic breathing in both premature and full-term infants. In a small study of 15 preterm infants, supplemental oxygen improved apnea and periodic

breathing.[72] Oxygen therapy prevents desaturation and improves breathing stability in infants. Despite widespread use of supplemental oxygen, there is no clear guideline for its use in the treatment of CA in infants.

Another widely accepted therapy for CA and periodic breathing in preterm and term infants is theophylline or caffeine. In premature infants, the use of caffeine to stimulate breathing is targeted toward adenosine-induced breathing suppression that is normally seen in fetal life.[55] A meta-analysis of 6 clinical trials looking at the efficacy of methylxanthine in the treatment of apnea of prematurity reported a reduction in apnea severity and utilization of intermittent positive pressure therapy in the first 2 to 7 days.[73] In a randomized placebo-controlled trial of 2000 infants born at preterm and with apnea of prematurity, caffeine reduced the need for positive pressure ventilation and reduced the use of supplemental oxygen.[74] The same investigators studied the long-term effect of caffeine used for the treatment of apnea of prematurity, and showed that it reduces the incidence of cerebral palsy and cognitive delay.[75] Caffeine therapy is generally not indicated beyond 33 weeks GA.[76]

Other available nonconventional therapies for the treatment of CA have been researched in preterm infants. A small study of 24 premature infants born at 27 weeks GA with apnea of prematurity compared supine versus prone positioning, and concluded that more CA and less arousal was noted during prone sleeping position, whereas infants had more awakening and arousals per hour in a supine sleeping position.[77] However, a prone sleeping position is a risk factor for SIDS, so this therapy cannot be recommended. In a short, randomized controlled trial of 87 preterm infants born between 27 and 32 weeks GA, Alvaro and colleagues[78] compared theophylline and 1% inhaled carbon dioxide for the treatment of apnea of prematurity. The investigators concluded that theophylline, which was better in reducing the severity of apnea, and carbon dioxide should not be considered as a therapy at this time. In another prospective, randomized controlled study of 27 preterm infants of similar GA, the short-term inhalation of 0.8% carbon dioxide had efficacy similar to that of theophylline in reducing the apnea.[79] Both of these trials were based on the fact that inhaled carbon dioxide will increase the carbon dioxide levels and prevent the apnea threshold being reaching in preterm infants, thus stabilizing breathing.

Positive pressure ventilation has been widely used in the treatment of CA and periodic breathing in preterm and term infants. Continuous positive airway pressure (CPAP) is one such modality. The underlying mechanism of improvement of CA was recently studied by Edwards and colleagues[80] in a lamb model of periodic breathing. CPAP reduced CA and mixed apnea in a dose-dependent manner, most likely by reducing the loop gain via an increase in the lung volume.

Other therapies that have been studied in preterm infants for treatment of CA and periodic breathing, but not yet available for clinical use, include stochastic mechanosensory stimulation (vibrotactile stimulation to stimulate breathing). In a small study of 10 relatively mature preterm infants (33 weeks), a low level of exogenous stochastic stimulation stabilized breathing during sleep and helped to reduce the incidence of apnea and periodic breathing.[81] Acetazolamide, a carbonic anhydrase inhibitor, has been used in treatment of CA and periodic breathing. In a small study of 12 infants with recurrent hypoxemia, acetazolamide reduced the CA index and improved oxygen saturation.[82] Treatment of anemia of prematurity with blood transfusion has also been shown to reduce central apnea in preterm infants.[83]

SUMMARY

CA and periodic breathing are common in infants, and are much more common in preterm than in term infants. The irregular breathing is seen in both active and quiet sleep. Irregular breathing tends to improve with increasing GA, and is presumed to be due to maturity of the respiratory control centers and chest-wall mechanics. In-laboratory polysomnography is the study of choice for the evaluation of CA in infants. Most therapies directed at the treatment of CA are aimed at stabilizing the breathing pattern and preventing oxygen desaturation. Most of these therapies are temporary, and are used for a brief period in preterm and term infants until the breathing matures.

REFERENCES

1. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 15;8(5):597–619.
2. Fukumizu M, Kohyama J. Central respiratory pauses, sighs, and gross body movements during sleep in children. Physiol Behav 2004;82(4):721–6.
3. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: congenital central hypoventilation syndrome: genetic

basis, diagnosis, and management. Am J Respir Crit Care Med 2010;181(6):626–44.
4. Ng DK, Chan CH. A review of normal values of infant sleep polysomnography. Pediatr Neonatol 2013;54(2):82–7.
5. Uliel S, Tauman R, Greenfeld M, et al. Normal polysomnographic respiratory values in children and adolescents. Chest 2004;125(3):872–8.
6. Kritzinger FE, Al-Saleh S, Narang I. Descriptive analysis of central sleep apnea in childhood at a single center. Pediatr Pulmonol 2011;46(10):1023–30.
7. O'Driscoll DM, Foster AM, Ng ML, et al. Central apnoeas have significant effects on blood pressure and heart rate in children. J Sleep Res 2009;18(4):415–21.
8. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992;146(5 Pt 1):1235–9.
9. Richards JM, Alexander JR, Shinebourne EA, et al. Sequential 22-hour profiles of breathing patterns and heart rate in 110 full-term infants during their first 6 months of life. Pediatrics 1984;74(5):763–77.
10. Hoppenbrouwers T, Hodgman JE, Harper RM, et al. Polygraphic studies of normal infants during the first six months of life: III. Incidence of apnea and periodic breathing. Pediatrics 1977;60(4):418–25.
11. Ramanathan R, Corwin MJ, Hunt CE, et al. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. JAMA 2001;285(17):2199–207.
12. Weese-Mayer DE, Corwin MJ, Peucker MR, et al. Comparison of apnea identified by respiratory inductance plethysmography with that detected by end-tidal CO(2) or thermistor. The CHIME Study Group. Am J Respir Crit Care Med 2000;162(2 Pt 1):471–80.
13. Steinschneider A. Prolonged apnea and the sudden infant death syndrome: clinical and laboratory observations. Pediatrics 1972;50(4):646–54.
14. Robertson CM, Watt MJ, Dinu IA. Outcomes for the extremely premature infant: what is new? And where are we going? Pediatr Neurol 2009;40(3):189–96.
15. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357(19):1946–55.
16. Eichenwald EC, Aina A, Stark AR. Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. Pediatrics 1997;100(3 Pt 1):354–9.
17. Bakewell-Sachs S, Medoff-Cooper B, Escobar GJ, et al. Infant functional status: the timing of physiologic maturation of premature infants. Pediatrics 2009;123(5):e878–86.
18. Glotzbach SF, Baldwin RB, Lederer NE, et al. Periodic breathing in preterm infants: incidence and characteristics. Pediatrics 1989;84(5):785–92.
19. Samuels MP, Poets CF, Noyes JP, et al. Diagnosis and management after life threatening events in infants and young children who received cardiopulmonary resuscitation. BMJ 1993;306(6876):489–92.
20. Infantile Apnea and Home Monitoring. NIH Consens Statement Online 1986 Sep 29-Oct 1;6(6):1-10. Available at: http://consensus.nih.gov/1986/1986InfantApneaMonitoring058html.htm.
21. Rahilly PM. Review of 'near-miss' sudden infant death syndrome and results of simplified pneumographic studies. Aust Paediatr J 1986;22(Suppl 1):53–4.
22. Esani N, Hodgman JE, Ehsani N, et al. Apparent life-threatening events and sudden infant death syndrome: comparison of risk factors. J Pediatr 2008;152(3):365–70.
23. Rahilly PM. The pneumographic and medical investigation of infants suffering apparent life threatening episodes. J Paediatr Child Health 1991;27(6):349–53.
24. Kant S, Fisher JD, Nelson DG, et al. Mortality after discharge in clinically stable infants admitted with a first-time apparent life-threatening event. Am J Emerg Med 2013;31(4):730–3.
25. Semmekrot BA, van Sleuwen BE, Engelberts AC, et al. Surveillance study of apparent life-threatening events (ALTE) in the Netherlands. Eur J Pediatr 2010;169(2):229–36.
26. Ponsonby AL, Dwyer T, Couper D. Factors related to infant apnoea and cyanosis: a population-based study. J Paediatr Child Health 1997;33(4):317–23.
27. McGovern MC, Smith MB. Causes of apparent life threatening events in infants: a systematic review. Arch Dis Child 2004;89(11):1043–8.
28. Claudius I, Keens T. Do all infants with apparent life-threatening events need to be admitted? Pediatrics 2007;119(4):679–83.
29. Mittal MK, Shofer FS, Baren JM. Serious bacterial infections in infants who have experienced an apparent life-threatening event. Ann Emerg Med 2009;54(4):523–7.
30. Hoki R, Bonkowsky JL, Minich LL, et al. Cardiac testing and outcomes in infants after an apparent life-threatening event. Arch Dis Child 2012;97(12):1034–8.
31. Bonkowsky JL, Guenther E, Filloux FM, et al. Death, child abuse, and adverse neurological outcome of infants after an apparent life-threatening event. Pediatrics 2008;122(1):125–31.
32. Guenther E, Powers A, Srivastava R, et al. Abusive head trauma in children presenting with an apparent life-threatening event. J Pediatr 2010;157(5):821–5.

33. Parker K, Pitetti R. Mortality and child abuse in children presenting with apparent life-threatening events. Pediatr Emerg Care 2011;27(7):591–5.
34. Harrington C, Kirjavainen T, Teng A, et al. Altered autonomic function and reduced arousability in apparent life-threatening event infants with obstructive sleep apnea. Am J Respir Crit Care Med 2002;165(8):1048–54.
35. Tirosh E, Ariov-Antebi N, Cohen A. Autonomic function, gastroesophageal reflux in apparent life threatening event. Clin Auton Res 2010;20(3):161–6.
36. Edner A, Ericson M, Milerad J, et al. Abnormal heart rate response to hypercapnia in boys with an apparent life-threatening event. Acta Paediatr 2002;91(12):1318–23.
37. Aurora RN, Zak RS, Karippot A, et al. Practice parameters for the respiratory indications for polysomnography in children. Sleep 2011;34(3):379–88.
38. Al-Kindy HA, Gelinas JF, Hatzakis G, et al. Risk factors for extreme events in infants hospitalized for apparent life-threatening events. J Pediatr 2009;154(3):332–7, 337.e1–2.
39. Kahn A, Rebuffat E, Sottiaux M, et al. Lack of temporal relation between acid reflux in the proximal oesophagus and cardiorespiratory events in sleeping infants. Eur J Pediatr 1992;151(3):208–12.
40. Kelly DH, Shannon DC. Periodic breathing in infants with near-miss sudden infant death syndrome. Pediatrics 1979;63(3):355–60.
41. Fleming P, Tsogt B, Blair PS. Modifiable risk factors, sleep environment, developmental physiology and common polymorphisms: understanding and preventing sudden infant deaths. Early Hum Dev 2006;82(12):761–6.
42. Mittal MK, Donda K, Baren JM. Role of pneumography and esophageal pH monitoring in the evaluation of infants with apparent life-threatening event: a prospective observational study. Clin Pediatr (Phila) 2013;52(4):338–43.
43. Jansen AH, Chernick V. Development of respiratory control. Physiol Rev 1983;63(2):437–83.
44. Johnston BM, Gunn TR, Gluckman PD. Surface cooling rapidly induces coordinated activity in the upper and lower airway muscles of the fetal lamb in utero. Pediatr Res 1988;23(3):257–61.
45. Dawes GS, Fox HE, Leduc BM, et al. Respiratory movements and rapid eye movement sleep in the foetal lamb. J Physiol 1972;220(1):119–43.
46. Wallen-Mackenzie A, Gezelius H, Thoby-Brisson M, et al. Vesicular glutamate transporter 2 is required for central respiratory rhythm generation but not for locomotor central pattern generation. J Neurosci 2006;26(47):12294–307.
47. Corcoran AE, Hodges MR, Wu Y, et al. Medullary serotonin neurons and central CO_2 chemoreception. Respir Physiol Neurobiol 2009;168(1–2):49–58.
48. Wong-Riley MT, Liu Q. Neurochemical development of brain stem nuclei involved in the control of respiration. Respir Physiol Neurobiol 2005;149(1–3):83–98.
49. Bouvier J, Thoby-Brisson M, Renier N, et al. Hindbrain interneurons and axon guidance signaling critical for breathing. Nat Neurosci 2010;13(9):1066–74.
50. Janczewski WA, Feldman JL. Distinct rhythm generators for inspiration and expiration in the juvenile rat. J Physiol 2006;570(Pt 2):407–20.
51. Rigatto H, Lee D, Davi M, et al. Effect of increased arterial CO2 on fetal breathing and behavior in sheep. J Appl Physiol 1988;64(3):982–7.
52. Kuipers IM, Maertzdorf WJ, De Jong DS, et al. The effect of hypercapnia and hypercapnia associated with central cooling on breathing in unanesthetized fetal lambs. Pediatr Res 1997;41(1):90–5.
53. Blanco CE, Dawes GS, Hanson MA, et al. The response to hypoxia of arterial chemoreceptors in fetal sheep and new-born lambs. J Physiol 1984;351:25–37.
54. Gluckman PD, Johnston BM. Lesions in the upper lateral pons abolish the hypoxic depression of breathing in unanaesthetized fetal lambs in utero. J Physiol 1987;382:373–83.
55. Adamson SL, Kuipers IM, Olson DM. Umbilical cord occlusion stimulates breathing independent of blood gases and pH. J Appl Physiol 1991;70(4):1796–809.
56. Koos BJ, Maeda T, Jan C. Adenosine A(1) and A(2A) receptors modulate sleep state and breathing in fetal sheep. J Appl Physiol 2001;91(1):343–50.
57. Alvaro R, de Almeida V, al-Alaiyan S, et al. A placental extract inhibits breathing induced by umbilical cord occlusion in fetal sheep. J Dev Physiol 1993;19(1):23–8.
58. Hillman NH, Kallapur SG, Jobe AH. Physiology of transition from intrauterine to extrauterine life. Clin Perinatol 2012;39(4):769–83.
59. Rigatto H. Regulation of fetal breathing. Reprod Fertil Dev 1996;8(1):23–33.
60. Don GW, Waters KA. Influence of sleep state on frequency of swallowing, apnea, and arousal in human infants. J Appl Physiol 2003;94(6):2456–64.
61. Parmelee AH, Stern E, Harris MA. Maturation of respiration in prematures and young infants. Neuropadiatrie 1972;3(3):294–304.
62. Tourneux P, Cardot V, Museux N, et al. Influence of thermal drive on central sleep apnea in the preterm neonate. Sleep 2008;31(4):549–56.
63. Khan A, Qurashi M, Kwiatkowski K, et al. Measurement of the CO_2 apneic threshold in newborn infants: possible relevance for periodic

breathing and apnea. J Appl Physiol 2005;98(4):1171–6.
64. Vergales BD, Paget-Brown AO, Lee H, et al. Accurate automated apnea analysis in preterm infants. Am J Perinatol 2013. [Epub ahead of print].
65. Amin SB, Burnell E. Monitoring apnea of prematurity: validity of nursing documentation and bedside cardiorespiratory monitor. Am J Perinatol 2013;30(8):643–8.
66. McGrath-Morrow SA, Ryan T, McGinley BM, et al. Polysomnography in preterm infants and children with chronic lung disease. Pediatr Pulmonol 2012;47(2):172–9.
67. Das S, Mindell J, Millet GC, et al. Pediatric polysomnography: the patient and family perspective. J Clin Sleep Med 2011;7(1):81–7.
68. Kahlke PE, Witmans MB, Alabdoulsalam T, et al. Full-night versus 4h evening polysomnography in children less than 2 years of age. Sleep Med 2013;14(2):177–82.
69. Marcus CL, Keens TG, Ward SL. Comparison of nap and overnight polysomnography in children. Pediatr Pulmonol 1992;13(1):16–21.
70. Kirk VG, Bohn SG, Flemons WW, et al. Comparison of home oximetry monitoring with laboratory polysomnography in children. Chest 2003;124(5):1702–8.
71. Foo JY, Parsley CL, Wilson SJ, et al. Detection of central respiratory events using pulse transit time in infants. Conf Proc IEEE Eng Med Biol Soc 2005;3:2579–82.
72. Weintraub Z, Alvaro R, Kwiatkowski K, et al. Effects of inhaled oxygen (up to 40%) on periodic breathing and apnea in preterm infants. J Appl Physiol 1992;72(1):116–20.
73. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev 2010;(1):CD000273.
74. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354(20):2112–21.
75. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357(19):1893–902.
76. Finer NN, Higgins R, Kattwinkel J, et al. Summary proceedings from the apnea-of-prematurity group. Pediatrics 2006;117(3 Pt 2):S47–51.
77. Bhat RY, Hannam S, Pressler R, et al. Effect of prone and supine position on sleep, apneas, and arousal in preterm infants. Pediatrics 2006;118(1):101–7.
78. Alvaro RE, Khalil M, Qurashi M, et al. CO(2) inhalation as a treatment for apnea of prematurity: a randomized double-blind controlled trial. J Pediatr 2012;160(2):252–7.e1.
79. Al-Saif S, Alvaro R, Manfreda J, et al. A randomized controlled trial of theophylline versus CO_2 inhalation for treating apnea of prematurity. J Pediatr 2008;153(4):513–8.
80. Edwards BA, Sands SA, Feeney C, et al. Continuous positive airway pressure reduces loop gain and resolves periodic central apneas in the lamb. Respir Physiol Neurobiol 2009;168(3):239–49.
81. Bloch-Salisbury E, Indic P, Bednarek F, et al. Stabilizing immature breathing patterns of preterm infants using stochastic mechanosensory stimulation. J Appl Physiol 2009;107(4):1017–27.
82. Philippi H, Bieber I, Reitter B. Acetazolamide treatment for infantile central sleep apnea. J Child Neurol 2001;16(8):600–3.
83. Zagol K, Lake DE, Vergales B, et al. Anemia, apnea of prematurity, and blood transfusions. J Pediatr 2012;161(3):417–21.e1.