
Control of Breathing and Neonatal Apnea

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Key Words

Apnea of prematurity · Bradycardia · Desaturation · Chemoreceptors · Xanthines

Abstract

Great strides have been made in our understanding of developmental respiratory neurobiology. A clear picture is, therefore, emerging of the physiological mechanisms that underlie apnea of prematurity. The ventral surface of the medulla and adjacent areas play a key integrative function for central CO₂ chemosensitivity and modulation of afferent inputs from peripheral chemoreceptors and laryngeal afferents. Maturation change in medullary neurotransmitter function appears to contribute to the physiological events that characterize apnea of prematurity. Despite this greater scientific insight, therapeutic strategies for neonatal apnea have changed little in 30 years. Xanthine therapy and continuous positive airway pressure remain the mainstay of therapy while other therapeutic approaches have been inadequately studied. Our understanding of a possible relationship between the triad of apnea, bradycardia and desaturation, and impaired neurodevelopmental outcome is also limited. These are all issues that need our attention if optimal therapy and outcome are to be provided for preterm infants with immature respiratory control.

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Introduction

The transition from fetal to neonatal life requires infants to develop a stable respiratory pattern for successful gas exchange. However, in preterm infants immaturity of respiratory control almost invariably results in respiratory pauses of variable duration that may require pharmacological intervention or ventilatory support. The problem is compounded by the fact that apnea and the resultant combination of bradycardia and desaturation may not be benign, and the necessary therapeutic interventions may carry their own risks. This review will explore the pathophysiological basis for apnea of prematurity, rationale for both proven and unproven therapies, and potential long-term implications of disordered respiratory control in preterm infants.

Classification of Apnea and Respiratory Patterns

Immature Respiratory Patterns

Apnea of prematurity has been defined most widely as cessation of breathing in excess of 15 s duration, typically accompanied by desaturation and bradycardia [1]. However, shorter episodes of apnea, and even periodic breathing, may be accompanied by bradycardia or hypoxemia (fig. 1), and there is not widespread agreement on what constitutes clinically significant bradycardia or de-

saturation in such infants. In ventilated preterm infants episodic desaturation is a common concern, and almost invariably is preceded by ineffective ventilation due to loss of lung volume, lower airway closure or broncho-spasm [2, 3].

Apnea is classified traditionally into three categories based on the presence or absence of upper airway obstruction: central, obstructive, and mixed. Central apnea is characterized by total cessation of inspiratory efforts with no evidence of obstruction. In obstructive apnea, the infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow throughout the entire apneic episode. Mixed apnea consists of obstructed respiratory efforts, usually following central pauses. The site of obstruction in the upper airways is primarily in the pharynx, although it also may occur at the larynx and possibly at both sites [4, 5]. Mixed apnea typically accounts for more than 50% of long apneic episodes, followed in decreasing frequency by central and obstructive apnea. Purely obstructive spontaneous apnea in the absence of a positional problem is probably uncommon.

Ventilatory Response to Hypercapnia

It has been widely assumed that apnea of prematurity is caused by immaturity of brainstem respiratory rhythm generation that is in proximity to sites of central CO₂ che-

mosensitivity (fig. 2). Research focused on the localization of chemosensory sites has revealed that the chemosensitive neural elements of the ventrolateral surface of the medulla play a pivotal role in regulating respiratory activity and ventilatory responses to CO₂. Although more recent physiological data have demonstrated the presence of chemosensitive sites in regions outside of the ventro-

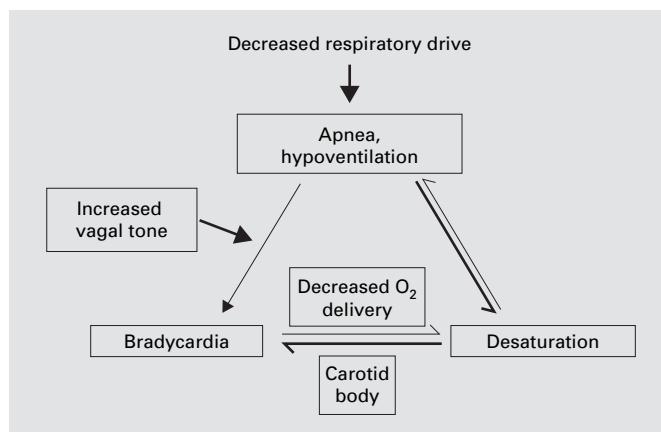
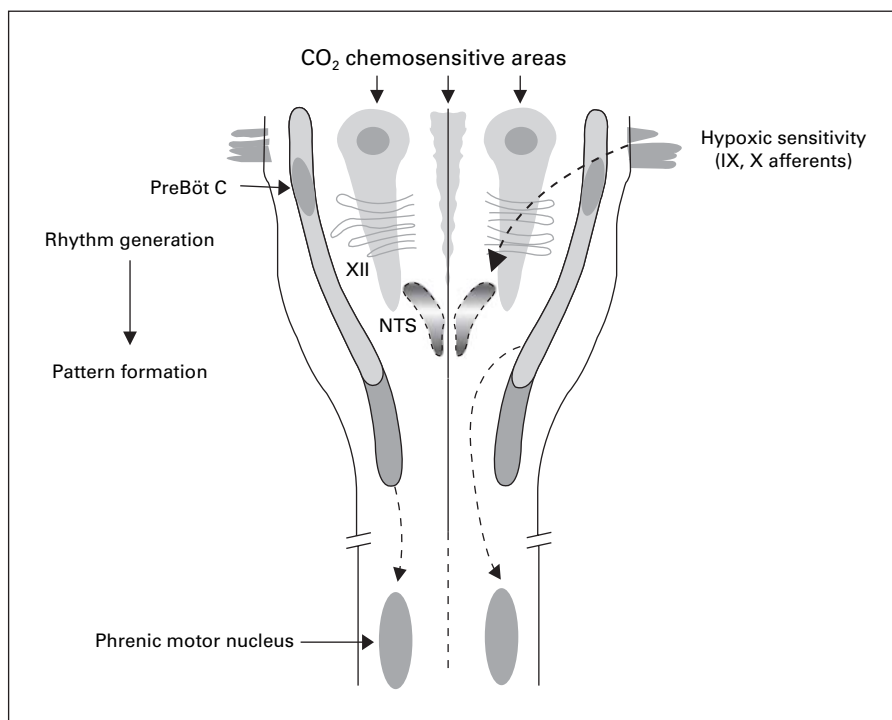


Fig. 1. A schematic representation of the sequence of events whereby apnea (or hypoventilation) results in various combinations of desaturation and bradycardia.

Fig. 2. A view of the mammalian brainstem highlighting key areas involved in respiratory control. Central CO₂ chemosensitivity occupies a broad area at or near the ventral surface and midline. The preBötzinger complex (PreBöt C) is accepted as a major site of rhythm generation that is patterned more caudally. Peripheral afferents excited by hypoxia or other (e.g., laryngeal) afferents enter the nucleus tractus solitarius (NTS). Phrenic and upper airway (e.g., hypoglossal, XII) efferents then modulate diaphragm and upper airway muscle activation.



lateral medulla oblongata, physiological studies have established primary importance for the ventral medullary chemosensitive regions (fig. 2).

The ventilatory response to CO₂ has been shown clearly to increase with advancing postnatal and gestational age in preterm human infants [6]. Furthermore, in apneic preterm infants, hypercapnic ventilatory responses are especially impaired [7]. Whereas adults increase their ventilation through an increase in both tidal volume and frequency, preterm infants do not appear to increase frequency in response to CO₂. This somewhat unique response of respiratory timing during hypercapnic exposure is associated with relative prolongation of expiratory duration. Physiological studies employing various animal models, such as rat pups and piglets, have revealed that the prolongation of expiration associated with hypercapnia is centrally mediated at the brainstem level. Furthermore, the inhibitory neurotransmitter γ -aminobutyric acid (GABA) appears to be involved [8, 9]. Future studies are required to further substantiate the role of inhibitory neurotransmitters and -modulators such as GABA, opioids, and adenosine in contributing to this predisposition to respiratory inhibition, as manifested by an impaired CO₂ response in early postnatal life [9].

Few detailed maturational studies have focused on changes in the distribution of medullary chemosensory structures that might explain the observed differences in hypercapnic ventilatory responses during development. One method of circumventing these difficulties is to examine hypercapnia-induced expression of encoding transcription factors, such as the *c-fos* gene, a member of the immediate early genes, and its product, Fos protein (Fos). This technique has been used as a cellular marker to identify activated neurons within the central nervous system, as during CO₂/H⁺ exposure. It has been demonstrated that neurons activated by increases in CO₂/H⁺ concentration appear to be well developed from the first days of postnatal life in maturing rat pups [10]. Therefore, deficiency in the neuronal network for sensing increases in CO₂/H⁺ does not appear to play a major role in the decreased CO₂ responses observed during early maturation. However, it is still possible that postnatal maturation may influence the relative importance of discrete chemosensitive sites beyond the ventrolateral medulla, such as the medullary caudal raphé nucleus, that appear to play an important role in the full expression of respiratory muscle responses to CO₂ [11].

The prominence of mixed apnea has led to comparative analysis of upper airway muscle versus diaphragm responses to chemoreceptor stimulation. Upper airway

muscles, such as the alae nasi, genioglossus, and posterior cricoarytenoid (laryngeal abductor), typically have their onset and peak of phasic activity prior to corresponding events in the diaphragm. This presumably serves to ensure upper airway patency at peak inspiratory flow. In response to hypercapnic exposure in piglets, there is a relatively linear increase in diaphragm activation. In contrast, genioglossus and the alae nasi exhibit a higher threshold, and muscle activity increases at a significantly higher level of CO₂ [12]. It is possible that, as hypercapnia develops during a central apnea (in which both diaphragm and upper airway activity are diminished), recovery of diaphragm, prior to upper airway muscle activity, may lead to obstructed inspiratory efforts and a prolonged mixed apnea.

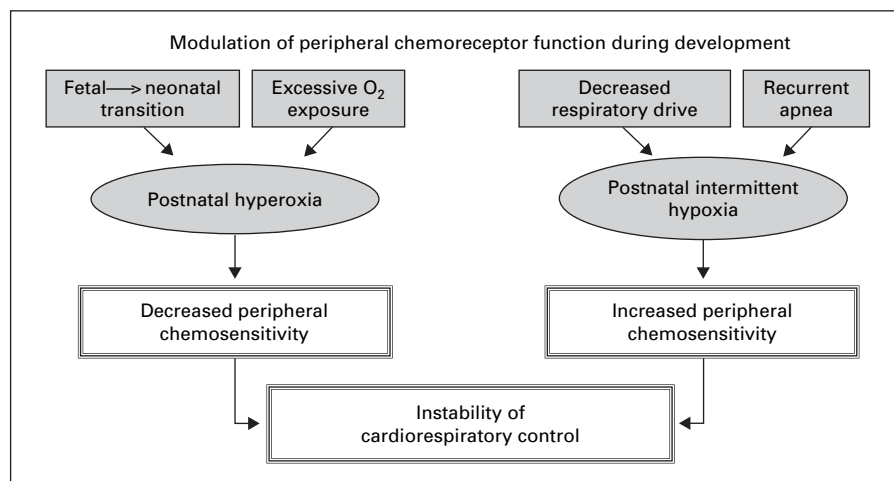
Ventilatory Response to Hypoxia

A decrease in PaO₂ and oxygen saturation is the typical response to apnea in preterm infants, although the extent of that fall varies. Presumably, the decrease in oxygenation is related directly to the duration of apnea and the initial level of PaO₂. The bradycardia that accompanies apnea and the resultant desaturation has been attributed to hypoxic stimulation of the carotid body chemoreceptors in the absence of lung inflation. However, bradycardia may also follow apnea without a measurable fall in oxygen saturation, suggesting a strong vagally mediated phenomenon that is not necessarily triggered by hypoxemia in some infants (fig. 1).

Physiological changes that occur at birth predispose to instability of neonatal respiratory control. The rise in PaO₂ (from the mid 20s mm Hg ~3 kPa) at delivery effectively silences the peripheral chemoreceptors, the major source of afferents that leads to hypoxic stimulation of breathing. This is aggravated when infants are exposed to 100% oxygen at birth, resulting in delayed onset of spontaneous breathing [13] (fig. 3).

The hypoxic ventilatory response after birth has been well characterized, especially in preterm infants [6, 14]. During exposure to hypoxia, neonates exhibit a biphasic ventilatory response that consists of an initial increase in ventilation that lasts for 1–2 min, followed by a decline in breathing, often to below baseline ventilation. This late decline traditionally has been termed hypoxic ventilatory depression. The initial increase in ventilation is caused by stimulation of peripheral chemoreceptors, primarily in the carotid body. In preterm human infants, the late decrease in ventilation is caused by a decrease in respiratory frequency, with the tidal volume remaining relatively sustained. The origin of the late depression is not well

Fig. 3. Proposed roles played by peripheral chemosensitivity (as elicited by hypoxia) in altering respiratory patterns. Relative hyperoxia, as during the transition from fetal to neonatal life, silences peripheral chemoreceptors and apnea or hypoventilation may result. In contrast, recurrent or intermittent hypoxia may upregulate peripheral chemosensitivity and, if excessive, this may also destabilize breathing in the presence of fluctuating levels of PaO₂.



understood, but it may persist for several weeks postnatally in preterm infants. In the fetal environment where levels of PO₂ are in the 20 mm Hg (2.6 kPa) range and gas exchange occurs at the placenta, hypoxic respiratory depression may be physiologic because continuous breathing is not necessary. However, postnatally when pulmonary ventilation must be continuous, hypoxia-induced respiratory depression may present a problem.

Multiple neurotransmitters have been implicated as mediators for hypoxic depression including adenosine, endorphins, and GABA. Blockers for these neurotransmitters, such as methylxanthines for adenosine, naloxone for endorphins, and bicuculline for GABA, prevent the late hypoxic depression and cause a sustained ventilatory response. Furthermore, the depressive response to hypoxia is diminished by experimental lesions in the upper brainstem and midbrain of fetal lambs, implicating the presence of descending inhibitory tracts that contribute to hypoxic ventilatory depression. While it is unclear whether hypoxic ventilatory depression plays a role in initiating apneic events, once hypoxia occurs it may aggravate apnea and result in delayed recovery.

As already indicated, silenced peripheral chemoreceptors, as during sudden hyperoxic exposure, may induce apnea. However, excessive peripheral chemoreceptor sensitivity may also destabilize breathing patterns in the face of significantly fluctuating levels of oxygenation (fig. 3). Recent data in rat pups indicate that conditioning with intermittent hypoxic exposures facilitates carotid body sensory discharge in response to subsequent hypoxic exposure [15]. This is consistent with the recent finding in preterm infants that a greater hypoxia-induced increase in ventilation correlates with a higher number of

apneic episodes [16]. Clearly, much remains to be learned about both the short- and long-term consequences of intermittent hypoxic episodes during early development [17, 18].

Ventilatory Responses to Laryngeal Afferents

Stimulation of the laryngeal mucosa, either chemically or mechanically, causes inhibition of breathing and apnea in humans and animals. This reflex-induced apnea is mediated through superior laryngeal nerve afferents. Reflex apnea has been shown in animal models to be associated with contraction of the thyroarytenoid muscle, causing closure of the glottis and swallowing movements, which signify active stimulation of expiratory-related brainstem centers [9].

There appears to be a maturational change in reflex-induced apnea. Chemical stimulation of the larynx in newborn piglets causes respiratory arrest that is not seen in older piglets. Preterm infants have an exaggerated inhibitory reflex, and they develop prolonged apnea in response to instillation of saline into the oropharynx. It has been shown that hypercapnia increases and hypocapnia decreases the threshold for superior laryngeal nerve stimulation-induced apnea. Cooling of the ventromedullary surface, a technique used to decrease central chemosensitivity by inhibiting synaptic transmission at this site, decreases the threshold for laryngeal stimulation-induced apnea [19]. Theophylline, which stimulates respiratory neural output, blocks laryngeal-induced apnea. It seems, therefore, that the exaggerated reflex-induced apnea seen in newborn infants and animals is related to decreased central neural output or a dominance of inhibitory pathways. Furthermore, blocking GABA_A receptors results in

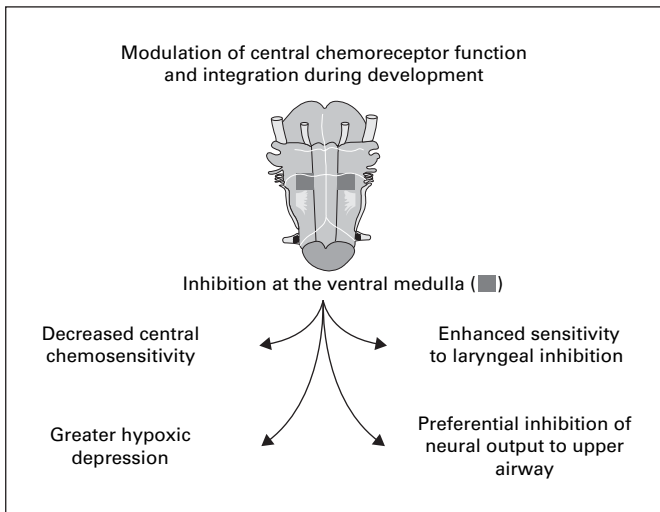


Fig. 4. Experimental inhibition at the ventral medulla, where central chemosensitivity is processed (squares), has been shown to simulate many of the physiological characteristics of apnea in early postnatal life.

complete abolition of superior laryngeal nerve stimulation-induced apnea in piglets [8].

Apnea and laryngeal adduction during laryngeal stimulation serve to protect the lungs from aspiration. While this response is assumed to be an essential protective reflex, an exaggerated response has been implicated as a cause of apnea of prematurity. This has also been implicated in gastroesophageal reflux (GER)-induced apnea in infants (see later). The mechanism responsible for the greater sensitivity of the respiratory system to the inhibitory effects of laryngeal stimulation early in development is not clear, although, as already stated, maturational changes in central chemosensitivity might contribute to postnatal alterations in the strength of this potent inhibitory reflex. As summarized in figure 4, inhibition of central chemoreceptor function at or near the ventral medullary surface can simulate many of the physiological characteristics exhibited by apneic preterm infants.

Implications for Management

Although apnea typically results from immaturity of the respiratory control system, it also may be the presenting sign of other diseases or pathophysiological states that frequently affect preterm infants. A thorough consideration of possible causes is always warranted, especially

Table 1. A partial summary of therapeutic approaches that are used, or have been proposed, to benefit apnea of prematurity

Therapeutic approaches
Accepted interventions
Xanthine therapy
CPAP
Ventilator
Interventions needing further study
‘Kangaroo’ care
Enrichment of sensory environment
Change in baseline SaO ₂ , hematocrit or ↑CO ₂
Antireflux medication

when there is an unexpected increase in the frequency of episodes of apnea or bradycardia. After exclusion of specific causes, xanthine therapy and continuous positive airway pressure (CPAP) are the most widely accepted therapeutic approaches; considerable data exist regarding their likely mechanism of action.

Xanthines

Methylxanthines have been the mainstay of pharmacological treatment of apnea of prematurity (table 1) for a long time. They were first used more than 30 years ago when given rectally by suppository [20]. Both theophylline and caffeine are used, and have multiple physiological and pharmacological mechanisms of action. Xanthine therapy increases minute ventilation, improves CO₂ sensitivity, decreases hypoxic depression of breathing, enhances diaphragmatic activity, and decreases periodic breathing. The precise pharmacological basis for these actions, which are mediated by an increase in respiratory neural output, is still under investigation. A likely major mechanism of action is through competitive antagonism of adenosine receptors. Adenosine acts as an inhibitory neuroregulator in the central nervous system via activation of adenosine A₁ receptors [21]. We have also demonstrated that activation of adenosine A_{2A} receptors appears to excite GABAergic interneurons and released GABA may contribute to the respiratory inhibition induced by adenosine [22]. Our understanding of the role of xanthines may be enhanced by future studies correlating physiological observations with labeling and localization of adenosine receptor subtypes in respiratory-related regions of the developing brainstem.

Both theophylline and caffeine are effective in reducing apnea episodes and the need for mechanical ventila-

tion in preterm infants. In many centers (including ours) xanthine therapy is employed to facilitate extubation of very low birth weight infants although studies of the long-term effects of methylxanthine treatment on growth and development are needed. These issues have been addressed in an international trial in which preterm infants were randomized to caffeine or placebo therapy with neurodevelopmental outcome as a major endpoint [23]. Evaluation of the resultant data is ongoing.

The methylxanthines have some well-documented acute adverse effects. Toxic levels may produce tachycardia, cardiac dysrhythmias, feeding intolerance and, infrequently, seizures, although these effects are seen less commonly with caffeine at the usual therapeutic doses. Mild diuresis is caused by all methylxanthines. The observation that xanthine therapy causes an increase in metabolic rate and oxygen consumption of approximately 20% suggests that caloric demands may be increased with this therapy at a time when nutritional intake already is compromised.

Continuous Positive Airway Pressure

CPAP at 4–6 cm H₂O is a relatively safe and effective therapy. Because longer episodes of apnea frequently involve an obstructive component, CPAP appears to be effective by splinting the upper airway with positive pressure and decreasing the risk of pharyngeal or laryngeal obstruction. CPAP also benefits apnea by increasing functional residual capacity, thereby improving oxygenation status. At a higher functional residual capacity, time from cessation of breathing to desaturation and resultant bradycardia is prolonged. High-flow nasal cannula therapy has been suggested as an equivalent treatment modality that may allow CPAP delivery while enhancing mobility of the infant. This approach is widely employed, although it has not been well studied. For severe or refractory episodes, endotracheal intubation and artificial ventilation may be needed. Minimal ventilator settings should be used to allow for spontaneous ventilatory efforts and to minimize the risk of barotrauma.

Other Approaches

Any approach to nursing care that optimizes the infants' well-being is clearly highly desirable. 'Kangaroo' care, or skin-to-skin nursing, has achieved widespread acceptance for stable infants, and provides an opportunity for greater parental involvement. Although the advocates of this approach have suggested a decrease in apnea rates, recent data have not supported this impression [24]. A

novel suggestion is the introduction of pleasant odors, and preliminary evidence suggests that such olfactory stimulation may diminish apnea [25]. Meanwhile, research on the biological basis of sleep and awake states needs to be translated into preventive strategies for apnea [26].

There is considerable interest in identifying the optimal target oxygen saturation (e.g., 85–89% vs. 91–95%) for preterm infants and this issue is not yet resolved. One might anticipate that desaturation accompanying apnea will be greater at lower baseline SaO₂, but this has not been well documented. It has also been assumed, although unproven, that enhanced oxygen-carrying capacity, as with red blood cell transfusion, may decrease the likelihood of hypoxia-induced respiratory depression and resultant apnea. A novel approach is supplementation of inspired air with a very low concentration of supplemental CO₂ to increase respiratory drive. While likely to be successful in decreasing apnea, it is doubtful that this would gain widespread acceptance.

GER is often incriminated in causing neonatal apnea, but such an attribution should be made cautiously [27]. Despite the frequent coexistence of apnea and GER in preterm infants, investigations of the timing of reflux in relation to apneic events indicate that they are rarely related temporally. We have also recently documented that when these events coincide, there is no evidence that GER prolongs the concurrent apnea [28]. Although physiological experiments in animal models reveal that reflux of gastric contents to the larynx induces reflex apnea, there is no clear evidence that treatment of reflux will affect the frequency of apnea in most preterm infants. Therefore, pharmacological management of reflux with agents that decrease gastric acidity or enhance gastrointestinal motility generally should be reserved for preterm infants who exhibit signs of emesis or regurgitation of feedings, regardless of whether apnea is present. Nonetheless, future studies might focus on the identification of a possible subgroup of preterm infants in whom such a therapy might decrease apnea.

Relevance to Outcome

Apnea of prematurity generally resolves by about 36–40 weeks' postconceptional age. However, in more immature infants, apnea frequently persists beyond this time. Available data indicate that cardiorespiratory events in such infants return to the baseline 'normal' level at about 43–44 weeks' postconceptional age [29]. In other words, beyond 43–44 weeks' postconceptional age, the incidence of cardiorespiratory events in preterm in-

Table 2. A summary of some of the consequences of apnea in preterm infants

Resolved

Apneic episodes may persist beyond discharge in preterm infants
After 43–44 weeks corrected age, apnea rate is comparable to
that of term infants

Apnea of prematurity is not a documented risk factor for SIDS

Unresolved

Is apnea of prematurity and associated hypoxemia of patho-
physiological significance?

Is persistent apnea implicated in impaired neurodevelopmental
outcome or later sleep disordered breathing?

Will insights derived from the genetics of congenital central
hypoventilation syndrome shed light on the apnea of prema-
turity phenotype?

infants does not significantly exceed that in term babies (table 2). For a subset of infants the persistence of cardiorespiratory events may delay hospital discharge. In these infants, apnea longer than 20 s is rare; rather, they exhibit frequent bradycardia to less than 70 or 80 beats per minute with short respiratory pauses [30]. The reason some infants exhibit marked bradycardia with short pauses is unclear, but available data suggest a vagal phenomenon and benign outcome [31]. For a few of these infants home cardiorespiratory monitoring, until 43–44 weeks' postconceptional age, is offered in the USA as an alternative to a prolonged hospital stay.

The apparent lack of a relationship between persistent apnea of prematurity and sudden infant death syndrome (SIDS) has become clearer in recent years. Significant progress in reducing the rate of SIDS is based on the observation that decreasing the incidence of prone sleeping (in conjunction with avoidance of cigarette smoke exposure and overheating of the infant) reduced the rate of SIDS. The finding of an intervention that decreased SIDS rates helped remove some of the mystery surrounding these deaths that are, by definition, unexplained. Apnea and SIDS remain epidemiologically linked because they both occur in certain population groups (e.g., preterm infants). Currently, no clinical evidence reliably links a ventilatory control abnormality to SIDS. Because idiopathic apnea is seen most often in high-risk preterm infants, separating the consequences of preterm birth from the effects of apnea of prematurity has proven difficult. Infants born prematurely often experience multiple problems during their time in the neonatal intensive care unit, and many of these conditions, particularly periventricu-

lar leukomalacia and intraventricular hemorrhage, may contribute to poor neurodevelopmental outcomes. The problem is compounded by the fact that nursing reports of apnea severity may be unreliable, and impedance monitoring techniques will fail to identify mixed and obstructive events. Despite these reservations, recent data of Janvier et al. [32] suggest a link between the number of days apnea was recorded during hospitalization and impaired neurodevelopmental outcome.

Future studies might better focus on the incidence and severity of desaturation events, as techniques for long-term collection of pulse oximeter data are now more advanced. Furthermore, it is likely that recurrent hypoxia is the detrimental feature of the breathing abnormalities exhibited by preterm infants. Finally, there are no available data on a link between apnea of prematurity and sleep-disordered breathing in children, although former preterm infants appear to be at greater risk of later sleep-disordered breathing [33]. Recurrent episodes of desaturation during early life and resultant effects on neuronal plasticity related to peripheral and/or central respiratory control mechanisms may serve as the underlying mechanisms for such a putative relationship. Ongoing investigation into the genetic background of infants with congenital hypoventilation syndrome may also serve to enhance our understanding of the problem of apnea in preterm infants [34].

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