Chapter 8
Sleep Disorders in Newborns and Infants

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Abstract During infancy, sleep is at a lifetime maximum, and the maturation of sleep is one of the most important physiological processes occurring during the first year of life, particularly the first 6 months. Sleep has a marked effect on cardiorespiratory control which is also rapidly maturing during infancy. Immaturity of cardiorespiratory control frequently leads to respiratory instability and prolonged pauses in breathing as manifest in apnea of prematurity and periodic breathing. During infancy, central apneas are common and obstructive apnea is rare. Although currently believed to be benign during this early period of development, there is growing evidence that they may be associated with developmental deficits in neurocognition. A failure of cardiorespiratory control mechanisms, together with an impaired arousal from sleep response, is believed to play an important role in the final event of the sudden infant death syndrome (SIDS). The "triple-risk model" describes SIDS as an event that results from the intersection of three overlapping factors: (1) a vulnerable infant, (2) a critical developmental period in homeostatic control, and (3) an exogenous stressor. In an attempt to understand how the triple-risk hypothesis is related to infant cardiorespiratory physiology, many researchers have examined how the known risk and protective factors for SIDS alter infant physiology and arousal, particularly during sleep. This review discusses the association between the three components of the triple-risk hypothesis and major risk factors for SIDS, such as prone sleeping and maternal smoking, together with three "protective" factors, and cardiovascular control and arousability from sleep in infants, and discusses their potential involvement in SIDS.

Keywords Pediatric obstructive sleep apnea • Periodic breathing • Apnea of prematurity • Sudden infant death syndrome • Sleeping position • Maternal smoking • Prematurity

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Development of Sleep

The maturation of sleep is one of the most important physiological processes occurring during the first year of life and is particularly rapid during the first 6 months after birth [1]. Behavioral states are defined by physiological and behavioral variables that are stable over time and occur repeatedly in an individual infant and also across infants [2]. The emergence of sleep states is dependent on the central nervous system and is a good and reliable indicator of normal and abnormal development [3]. Sleep states and sleep architecture in infants are quite different to those in adults. In infants, sleep states are defined as active sleep (AS) and quiet sleep (QS), which are the precursors of adult rapid eye movement sleep (REM sleep) and non-rapid eye movement sleep (NREM sleep), respectively. QS is characterized by high-voltage low-amplitude electroencephalogram activity, the absence of eye movements, and regular heart rate and respiration. In contrast, AS is characterized by low-amplitude high-frequency electroencephalogram activity, eye movements, and irregular heart rate and respiration (Fig. 8.1). In addition a third state, that of indeterminate sleep (IS), is defined when criteria for AS and QS are not met. IS is usually considered a sign of immaturity and the incidence decreases with increasing postnatal age.

Rhythmic cyclical rest activity patterns can be observed in the human fetus from 28 weeks of gestation [4]. In infants born preterm, the infant sleep states cannot be distinguished in infants younger than 26 weeks of gestation [5]. By 28–30 weeks of gestation, AS can be recognized by the presence of eye movements, body movements, and irregular breathing and heart rate. At this gestational age, QS is
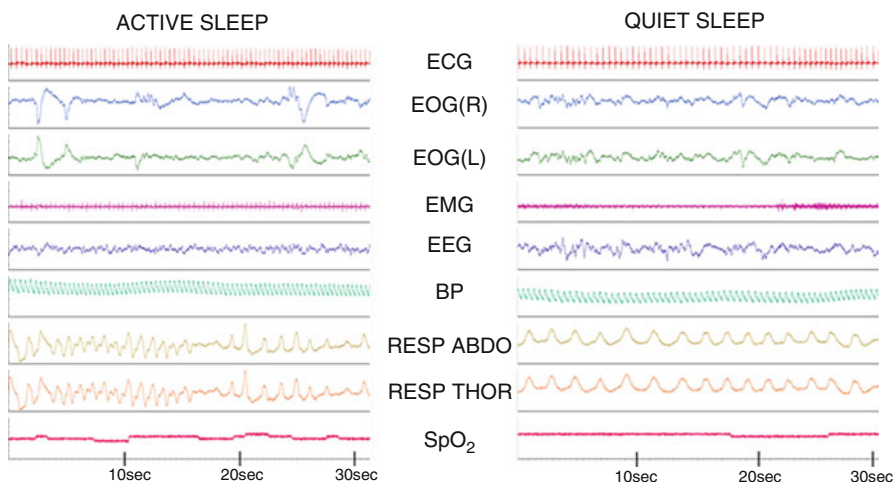
Fig. 8.1 Cardiorespiratory parameters in active and quiet sleep in an infant. *ECG* electrocardiograph, *EOG* electrooculograph, *EMG* electromyograph, *EEG* electroencephalograph, *BP* blood pressure, *RESP ABDO* abdominal respiratory effort, *RESP THOR* thoracic respiratory effort, *SpO2* oxygen saturation, *HR* heart rate. Note regular breathing and heart rate in quiet sleep compared to active sleep

difficult to identify as chin hypotonia is difficult to evaluate, and the majority of the sleep period is spent in AS. QS does not become clearly identifiable until about 36 weeks of gestational age [4]. The percentage of time spent in QS increases, and by term equal amounts of time are spent in both AS and QS with the two states alternating throughout each sleep period. The proportion of AS decreases across the first 6 months to make up approximately 25 % of total sleep time similar to that in adults [6]. In contrast, the proportion of QS increases with age to make up about 75 % of total sleep time by 6 months [6].

At term, infants sleep for about 16–17 h out of every 24 [4]. There is a gradual decrease in total sleep time with infants sleeping 14–15 h at 16 months of age and 13–14 h by 6–8 months of age. In the neonatal period, infants awaken every 2–6 h for feeding, regardless of the time of day, and stay awake for 1–2 h [7]. The major change in sleep/wake pattern occurs between 6 weeks and 3 months post term age [7]. During the first 6 months after term, consolidation and entrainment of sleep at night develops and sleep periods lengthen. At 3 weeks of age, the mean length of the longest sleep period has been reported to be 211.7 min, increasing to 358.0 min by 6 months of age [8]. The longest sleep period was randomly distributed between daytime and nighttime at 3 months but had moved to nighttime by 6 months [8].

Dramatic changes in the sleep electroencephalographic (EEG) patterns of infants occur during early infancy as the brain matures. The EEG patterns of QS and AS differ with a relatively continuous pattern in AS and a relatively discontinuous pattern in QS. A continuous pattern is defined by the presence of background activity throughout each 30 s epoch scored, and a discontinuous pattern is defined by the presence of higher amplitude EEG waves during <50 % of each epoch [9]. A semi-discontinuous EEG pattern of depressions and continuous delta activity during ≤70 % each epoch is called a *tracé alternant* pattern and can be identified at 32–34 weeks of gestational age [9]. This pattern is prominent in preterm infants but also occurs in infants born at term and disappears after 1 month after term equivalent age. Sleep spindles appear coincidentally with the disappearance of *tracé alternant* [10]. True continuous delta frequency does not appear until 8–12 weeks of age, and it is not until this age that adult criteria for determining the stages of NREM sleep can be used [11].

In summary, during infancy, sleep is at a lifetime maximum, and significant changes occur in the maturation of sleep which reflect maturation of the central nervous system. Sleep has a marked effect on cardiorespiratory control. Cardiorespiratory disturbances occur predominantly in AS sleep, so the predominance of AS in early infancy may increase the risk of cardiorespiratory disturbances during this period of development.

Apnea of Prematurity

One of the major problems facing preterm infants after birth is the immaturity of their cardiorespiratory system which often leads to repeated apneic events. Apnea of prematurity is defined as the cessation of breathing for >20 s, or if the breathing

pause is shorter in duration, it is associated with bradycardia, cyanosis, marked pallor, or hypotonia [12]. Apnea of prematurity is extremely common, occurring in more than 85 % of infants born prior to 34 weeks of gestation. The incidence of apnea of prematurity is inversely related to gestational age: 3–5 % of term-born infants, 7 % of infants born at 34–35 weeks, 15 % of infants born at 32–33 weeks, 54 % of infants born at 30–31 weeks, and nearly 100 % of infants born less than 29 weeks experience episodes of apnea of prematurity [13, 14]. There are also marked changes in apnea frequency with postnatal age, with few events in the first week of life, then a progressive increase in weeks 2–3 which plateau in weeks 4–6, and then decrease in weeks 6–8 [15].

Frequently, the magnitude and frequency of the apneic events are underestimated due to the current clinical settings of pulse oximeter monitors, which often are set with long averaging times and to alarm at events longer than 20 s duration. In a study which used a 2 s averaging time and which counted apneas where oxygen saturation fell to ≤80 % for between 3 and 10 s, between 50 and 100 events/day were recorded [16]. It has recently been recommended that to take these frequent apneas which are associated with significant desaturation into account, that all events longer than 5 s should be recorded [17].

Studies have shown that excessive or persistent apnea and bradycardia are associated with long-term neurodevelopmental problems [18]. It is well known that obstructive sleep apnea in children and adults is associated with neurocognitive deficits, and the repetitive hypoxic events associated with this condition have been proposed as the primary mechanism. It is also possible that postnatal intermittent hypoxia can affect cardiovascular control beyond the neonatal period with studies in both rodent models [19] and human infants [20] demonstrating this.

Methylxanthines have been used since the 1970s for the treatment of apnea of prematurity and also to facilitate extubation and weaning off mechanical ventilation [21, 22]. Methylxanthines cross the blood-brain barrier [23], and their primary action is to antagonize the A_1/A_{2a} adenosine receptors in the CNS. Methylxanthines improve apnea of prematurity by increasing minute ventilation and improving both hypercapnic and hypoxic ventilatory drive [24, 25].

Today, caffeine is the most commonly used methylxanthine in neonatal units worldwide. Caffeine's universal acceptance followed the 2006 CAP (caffeine for apnea of prematurity) randomized control trial, which compared caffeine citrate (20 mg/kg loading dose of caffeine citrate followed by 5 mg/kg/day) with placebo in very low birth weight preterm infants. The study demonstrated both significant short-term benefits of reduced incidence of bronchopulmonary dysplasia, medically and surgically treated ductus arteriosus, and long-term benefits of improved rates of survival without neurodevelopmental delay and significantly reduced incidences of cerebral palsy at 18–21 months [26, 27]. Improved microstructural development of white matter has been demonstrated in a subsample of these children who underwent brain magnetic resonance imaging (MRI) at term equivalent age, a finding which may explain the improved neurodevelopmental outcomes [28]. However, when reassessed at 5 years of age, there was no longer any difference in rate of survival without disability between children treated with caffeine and those that were not [29].
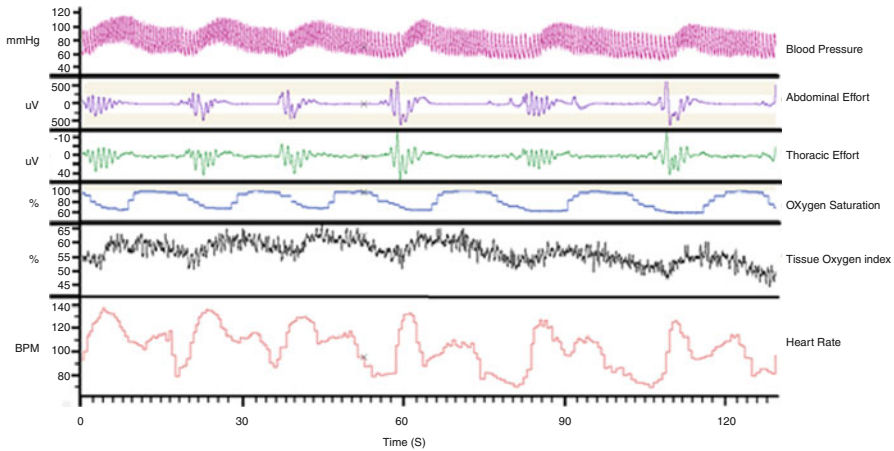
Fig. 8.2 Polysomnographic example of the effects of periodic breathing in an infant born at 27 weeks of gestational age and studied at 2–4 weeks corrected age after discharge home. Periodic breathing is associated with repetitive oxygen desaturations, marked falls in cerebral tissue oxygenation index as measured with near-infrared spectroscopy, and repetitive bradycardias which worsen over time. This infant spent 28 % of his total sleep time in periodic breathing

Apneas can occur in isolation or in a repetitive pattern termed periodic breathing. Repetitive short central apneas are termed periodic breathing (defined as three or more sequential central apneas each lasting ≥3 s) and are common in term babies in the first 2 weeks of life but significantly decrease with age [30]. In term babies, the frequency of periodic breathing is low, making up <1 % of total sleep time [30, 31]. Periodic breathing is significantly more prevalent in ex-preterm infants compared to term-born infants at term equivalent age [32]. Because of its high prevalence, and the fact that it is not usually associated with life-threatening hypoxia or bradycardia, the traditional view of periodic breathing is that it is simply due to immaturity of respiratory control and is benign [33]. However, recent studies have shown that periodic breathing can be associated with significant deficits in cerebral oxygenation [34] (Fig. 8.2), although any link to neurocognitive deficits has yet to be elucidated.

Sleep Apnea in Infants

Apneas are characterized as central, obstructive, or mixed. *Central* apneas are defined as a cessation of nasal and oral airflow in conjunction with an absence of respiratory effort. *Obstructive* apneas are defined as the cessation of nasal and oral airflow in the presence of continued respiratory effort against airway obstruction. Central apneas are common in infancy and can occur spontaneously but occur more frequently after a movement [35, 36]. Traditionally, they are considered benign as

they are not associated with significant desaturation and occur in healthy infants [36]. The frequency of central apneas declines with age. In a study by Brockmann et al., the median number of events per hour declined from 5.5 (minimum 0.9; maximum 44.3) at 1 month of age to 4.1 (minimum 1.2; maximum 27.3) at 3 months [31]. The authors suggested these high rates of central apnea may be simply due to the fact that the current definitions for central apneas used for older children are not appropriate for young infants.

Obstructive apneas are reported to be rare in infancy [31, 37]. However, snoring is reported to be common, with prevalence rates ranging from 5.6 to 26 % [38–41]. These wide ranges in prevalence may have been due to confounders, with some studies including infants with colds and others studying different ethnicities. In a study of healthy predominantly Caucasian children aged 0–3 months, a prevalence of 9 % has been reported [42]. A significantly greater proportion of 2–3-month-old infants were reported to snore habitually than 0–1-month-old infants [42]. Cognitive ability at 6 months of age was found to be lower in those infants who began snoring frequently (≥3 nights/week) within the first month of life [43].

In summary, central apnea is common in infants but obstructive apnea is rare. Both forms of apnea have been considered benign during infancy, but there is growing evidence that they may be associated with neurological deficits.

Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is defined as "the sudden and unexpected death of an infant under 1 year of age, with the onset of the lethal episode apparently occurring during sleep, that remains unexplained after a thorough investigation including performance of a complete autopsy and review of the circumstances of death" [44]. The incidence of SIDS was more than halved after public health campaigns publicized the known major risk factors of prone sleeping, maternal smoking, and overheating [45]. However, SIDS still remains the leading cause of unexpected death in infants in Western countries, contributing to almost 50 % of all postneonatal deaths [46, 47].

As SIDS is a diagnosis of exclusion, there has been considerable research into the underlying mechanisms which may underpin known risk factors. SIDS has long been believed to be multifactorial in origin. The triple-risk hypothesis [48] proposes that when a vulnerable infant, such as one born preterm or exposed to maternal smoking, is at a critical but unstable developmental period in homeostatic control and is exposed to an exogenous stressor, such as being placed prone to sleep, then SIDS may occur. The model proposes that infants will die of SIDS only if all three factors are present and that the vulnerability lies dormant until they enter the critical developmental period and are exposed to an exogenous stressor. SIDS usually occurs during sleep, and the peak incidence is between 2 and 4 months of age, when sleep patterns are rapidly maturing. The final pathway to SIDS is widely believed to involve immature cardiorespiratory control, in conjunction with a failure of arousal

from sleep [45]. Support for this hypothesis comes from numerous physiological studies showing that the major risk factors for SIDS (prone sleeping, maternal smoking, prematurity, head covering) have significant effects on blood pressure and heart rate and their control [49] and impair arousal from sleep [50].

Vulnerable Infant

Neuropathologic findings from SIDS victims show significant deficits in brainstem and cerebellar structures involved in the regulation of respiratory drive, cardiovascular control, sleep/wake transition, and arousal from sleep [51–58]. Furthermore, genetic polymorphisms have been identified in SIDS victims which affect genes involved in autonomic function, neurotransmission, energy metabolism, and the response to infection [59–63].

Prenatal and/or postnatal exposure to cigarette smoke is one factor which increases infant vulnerability to SIDS [64, 65], with over 40 studies showing a positive association with risk ratios of between 0.7 and 4.85 [66–69]. This increased SIDS risk is likely to be due to the effects of nicotine exposure on autonomic control and arousal [58, 70–72]. In support of this idea, Duncan and colleagues [73] found that chronic exposure to nicotine in the prenatal baboon fetus altered serotonergic and nicotinic acetylcholine receptor binding in regions of the medulla, critical to cardiorespiratory control. Furthermore, they identified that these alterations were associated with abnormalities in fetal heart rate variability, indicating altered cardiovascular control [73]. Studies in infants exposed to maternal smoking have demonstrated altered heart rate and blood pressure control compared with control infants [74–80]. Maternal tobacco smoking also decreases both total arousability and the proportion of cortical arousals. Arousal impairment was observed for both spontaneous arousals from sleep and responses induced by various stimuli [81–87]. Few mothers change their smoking behavior postpartum [88]; therefore, it is difficult to ascertain whether these physiological effects are caused by prenatal or postnatal smoke exposure. Environmental smoke (in the same room) independently increases the risk of SIDS [89, 90]. Importantly, a recent study has shown that before discharge home from hospital, preterm infants of smoking mothers already exhibited disruptions in sleep patterns, prior to any postnatal smoke exposure [91]. Thus, there is considerable evidence from both animal and human studies suggesting that prenatal exposure to cigarette smoke has deleterious effects on the developing brain and cardiorespiratory system. It is suggested that these effects increase infant vulnerability to SIDS.

Maternal smoking may also be a confounding risk factor for SIDS due to its association with other risk factors, such as preterm birth and intrauterine growth restriction (IUGR) [92–95], which likely result from suboptimal intrauterine environments. Impaired heart rate control, manifest as shorter cardiac R-R intervals and higher resting sympathetic tone, has been reported in term-born IUGR infants when compared with infants of appropriate size for gestational age [96, 97]. Similarly,

preterm infants demonstrated impaired autonomic control compared with term infants studied at or before term equivalent age, and this pattern was inversely related to gestational age at birth [98–103]. Longitudinal studies after term equivalent age have identified that preterm infants exhibited lower blood pressure, delayed blood pressure recovery following head-up tilting, and impaired baroreflex control of blood pressure and heart rate across the first 6 months corrected age, when compared with age-matched term infants [104–108]. Furthermore, maturation of baroreflex control of blood pressure during sleep is affected by gestational age at birth, with infants born very preterm (<32 weeks of gestation), having reduced increases in baroreflex sensitivity compared to both preterm and term infants [109]. Recently, studies have also identified that cerebral oxygenation is also lower in preterm compared to term infants across the first 6 months corrected age [110] and that cerebrovascular control after a head-up tilt is more variable [111], indicating immature or impaired control.

When compared with term infants at matched conceptional ages, preterm infants also exhibit decreased frequencies and durations of spontaneous arousals from sleep [112–114], together with decreased heart rate responses following arousal [115]. Furthermore, preterm infants exhibited longer arousal latencies after exposure to mild hypoxia (15 % inspired O_2), reaching significantly lower oxygen saturations than term infants [116]. Cardiorespiratory complications commonly associated with prematurity, apnea, and bradycardia have also been shown to suppress total arousability when these infants were compared to preterm infants with no history of apnea [117].

In summary, these alterations in cardiorespiratory control and arousability during sleep support the classification of prenatal smoke exposure and preterm birth as factors strongly linked with the idea of a preexisting vulnerability to SIDS. Such physiological disturbances may be further exacerbated during a critical developmental period within infancy and by exposure to exogenous stressors.

Critical Developmental Period

Approximately 90 % of SIDS deaths occur in infants aged less than 6 months [45, 118]. During this period, the central nervous system undergoes dramatic maturational changes which are reflected in extensive alterations to sleep architecture, electroencephalogram characteristics, and autonomic control. The 2–4-month period, in particular, has been described as a "developmental window of vulnerability" [119, 120] and coincides with the age where a distinct peak in SIDS incidence occurs [45, 118].

A number of other significant developmental factors may make an infant more vulnerable to a cardiorespiratory challenge during this critical developmental period. Studies in both preterm [105, 110] and term [121] infants have identified a nadir in basal blood pressure during sleep at 2–4 months of age, when compared to both earlier (2–4 weeks) and later (5–6 months) ages studied; a nadir in physiological

anemia also occurs at this age. Blood pressure responses to a cardiovascular challenge (head-up tilting) are also impaired at 2–4 months compared to younger (2–4 weeks) and older (5–6 months) ages [122]. The maturational reduction in cerebral oxygenation is most marked between 2–4 weeks and 2–4 months of age, which may be due to limited or inadequate flow-metabolism coupling at this age [123]. Thus, the 2–4-month age represents a critical time period when the effects of low blood pressure could accentuate decrements in oxygen-carrying capacity and delivery to critical organs [124]. These studies suggest that there is a postnatal age effect on cardiovascular control, with critical maturational changes occurring when the risk of SIDS is greatest.

Infant arousal responses from sleep are also affected by postnatal age, although these maturational effects are sleep state dependent. Previous studies have demonstrated that in response to respiratory (mild hypoxia), tactile (nasal air-jet), and auditory stimulation, total arousability is reduced with increasing age during quiet sleep while remaining unchanged in active sleep [124–126]. Following the introduction of standard scoring criteria for subcortical activation and cortical arousal as separate entities, a recent study noted that spontaneous subcortical activations decreased with increasing postnatal age, while cortical arousals increased [127]. Conversely, another study analyzed both spontaneous and nasal air-jet-induced arousability during supine sleep and found no change in the percentage of cortical arousals (from total responses) throughout the first 6 months of life [128]. Interestingly, when the same infants slept in the prone position, an increased propensity of cortical arousal was identified at 2–3 months, the age when SIDS is most common [87, 128]. This increase in cortical arousals may reflect an innate protective response to ensure an appropriate level of arousal for restoring homeostasis, not only during a vulnerable period of development but also in the presence of an exogenous stressor (e.g., the prone sleeping position).

Exogenous Stressor(s)

An exogenous stressor constitutes the third aspect of the triple-risk model for SIDS. Epidemiological studies have identified numerous factors common to SIDS victims, such as the prone sleeping position, overheating, and recent infection, which may disrupt homeostasis [45, 59, 129, 130].

The prone sleeping position has long been considered the major risk factor for SIDS [94, 131–134], with some studies suggesting a causal relation between prone sleep and SIDS [135, 136]. Several physiological changes ensue when infants sleep prone, including increased peripheral skin temperature and increased baseline heart rate, together with decreased heart rate variability [121, 137–145]. In an effort to identify changes in autonomic cardiovascular control with sleeping position, studies examining heart rate responses to auditory and nasal air-jet stimuli have suggested an increase in sympathetic and a decrease in parasympathetic tone in the prone sleeping position [146, 147]. Furthermore, sympathetic effects on blood

pressure and vasomotor tone are decreased in the prone sleeping position. Lower resting blood pressure and altered cardiovascular responses to head-up tilting have also been identified in term infants when sleeping in the prone position, compared with the supine position [121, 122]. Furthermore, cerebral oxygenation is reduced and cerebrovascular control impaired in the prone position in both term [123, 148] and preterm infants [110, 149]. In addition, prone sleeping infants exhibit reduced cardiac and respiratory responses when arousing from sleep, when compared to sleeping in the supine position [146, 147]. Previous studies of both term and preterm infants have consistently identified increases in sleep time, with significant reductions in spontaneous arousability, associated with prone sleeping when compared with the supine position [150–153]. Furthermore, in other studies, the prone sleeping position depressed arousal responses provoked by postural change [137] and auditory [154] and somatosensory challenges [86, 138, 155]. It has been demonstrated that both spontaneous and induced arousal responses are similarly affected by sleep state and SIDS risk factors, suggesting that they are mediated through the same pathways [156]. Despite this well-documented decrease in total arousability, examining subcortical and cortical responses separately has produced conflicting results. Although one study reported a decreased frequency of spontaneous cortical arousals in the prone position [153], more recent studies have found an increased proportion of cortical arousals (of total responses) in both nonsmoking and smoking exposed infants when sleeping prone [87, 128]. This apparent promotion of full cortical arousal, demonstrated for both spontaneous and stimulus-induced responses, may protectively compensate against the threat of altered autonomic control and the already blunted total arousability imposed by the prone position.

The prone sleeping position also potentiates the risk of overheating, by reducing the exposed surface area available for radiant heat loss and reducing respiratory heat loss when the infants face is covered [157]. Both physiological studies in healthy infants and theoretical model studies of heat balance have observed a decreased ability to lose heat when in the prone position [158–160]. Early studies observed decreased variation in behavior and respiratory pattern, increased heart rate, and increased peripheral skin temperature during prone compared with supine sleep [159]. These studies suggest that infants are less able to maintain adequate respiratory and metabolic homoeostasis when sleeping prone.

Increased sweating occurs in SIDS victims, regardless of whether infants slept prone or supine; these cases were predominantly associated with a covered face [118, 161]. A history of profuse sweating in SIDS victims has been postulated to be a phenomenon representing an abnormality of function of the autonomic nervous system [162]. The involvement of thermal stress with SIDS is further supported by the finding of similar odds ratios for both too much and too little bedding [163] and the suggestion that future SIDS victims may have had atypical temperature regulation [164]. Infant arousability is also affected by body and room temperature; decreased sleep continuity and increased body movements have been associated with exposure to cooler temperatures [165], while infants sleeping in warmer

environments (28 °C vs. 24 °C) exhibited increased arousal thresholds to auditory stimuli [166]. Furthermore, based on studies assessing blood pressure control in infants [139, 144], it has been suggested that in response to the increased peripheral skin temperature when infants sleep prone, thermoregulatory vasodilatation of the peripheral microvasculature occurs, resulting in a decrease in blood pressure and a reduction in vasomotor tone. Recent studies in preterm infants have shown that increased ambient temperature led to significant changes in autonomic control with elevated heart rates and lower heart rate variability compared to thermoneutral or cooler temperature [167].

Head covering has been identified as a major risk for SIDS with between 16 % and 28 % of SIDS infants found with their heads covered. Although a causal relationship with SIDS has not been established [168, 169], it appears likely that rebreathing and impaired arousal are involved. It has been suggested that the increased SIDS risk associated with head covering may result from hypoxia and hypercapnia via rebreathing of expired air [168, 170]. Head covering in healthy infants has profound effects on autonomic control during sleep [171]. Franco and colleagues [171] found that infants sleeping supine with their head covered by a bedsheet exhibited decreased parasympathetic activity, increased sympathetic activity, and increased body temperature when compared with head-free periods. In addition, arousal responses in active sleep were also depressed when the head was covered [172].

Bed-sharing or co-sleeping has also been reported to significantly increase the risk of SIDS, particularly when the mother smokes [118, 173–175] with more than 50 % of SIDS deaths occurring in this situation between 1997 and 2006 [176, 177]. There have been few studies investigating the physiology behind this risk factor. In infants from nonsmoking families who were studied on successive bed-sharing and solitary sleeping nights, bed-sharing was associated with increased awakenings and transient arousals during slow wave sleep compared to solitary nights [178]. In contrast, another study found that bed-sharing infants spent less time moving and were more likely to have their heads partially or fully covered by bedding than cot-sleeping infants [179]. Thus more studies are required to identify the exact physiological changes which occur during bed-sharing.

Other external stressors, such as infection, fever, and minor respiratory and gastrointestinal illnesses, commonly occur in the days to weeks preceding death of SIDS victims [180–182]. Although not identified as an independent risk factor for SIDS, minor infections have been associated with an increased likelihood of SIDS when combined with head covering or prone sleeping [183, 184]. In the prone sleeping position, minor infection, in combination with fever, could further exacerbate thermoregulatory effects on peripheral vasculature, which could increase the susceptibility of a hypotensive episode. Thus, hypotension, in combination with a decreased ability to arouse from sleep, which has been documented in term infants immediately following an infection [185], could potentially further impair an infant's ability to appropriately respond to a life-threatening challenge such as circulatory failure or an asphyxial insult.

SIDS "Protective" Factors and Autonomic Control

Some studies have suggested that infant care practices, such as breastfeeding, dummy/pacifier use, and swaddling (tight wrapping), decrease the risk of SIDS. These potentially protective factors for SIDS have all been associated with alterations to both cardiovascular autonomic control and arousal responses during sleep. However, results are often inconsistent, and supporting evidence is less extensive than for the risk factors discussed above; thus, these potentially preventative factors remain controversial among researchers.

Breastfeeding

Breastfeeding reduces the incidence of SIDS by approximately half (OR 0.52, 95 % CI: 0.46–0.60), even after multivariate analyses accounted for potentially confounding socioeconomic factors [180, 186, 187]. This apparent protection may be a biological effect, given that breastfeeding has been associated with a decreased incidence of diarrhea, vomiting, colds, and other infections; in addition, breast milk is rich in antibodies and many micronutrients [180, 188, 189]. Only one study has assessed the effects of breastfeeding on the cardiovascular system during sleep in term infants, and this study found that heart rate was significantly lower in breast-fed infants when compared with formula-fed infants [190]. Although little is known about the effects of breastfeeding vs. formula feeding on cardiovascular control in infants, physiological studies have demonstrated an apparent promotion of arousal from sleep associated with breastfeeding. One study found that breast-fed infants spent more time awake during the night, thus requiring more frequent parental visits [191]. Another study showed that healthy breast-fed infants aroused more readily from active sleep than formula-fed infants in response to nasal air-jet stimulation at 2–3 months postnatal age [192]. Although there is a general consensus that breastfeeding should be encouraged, the relationship between breastfeeding for SIDS prevention remains unclear.

Pacifier/Dummy Use

The finding that the use of a dummy/pacifier has a protective effect for SIDS has consistently emerged from epidemiological studies, with significant associations being described for both usage during the final sleep and "dummy ever used" (OR: 0.46. CI 0.36–0.59) [118, 193–198]. Studies have suggested that a likely mechanism for this protection against SIDS is increased heart rate variability which has been demonstrated during sucking periods [199, 200]. Conversely, dummy sucking has also been shown to have no effect on heart rate, heart rate variability, respiratory frequency, or oxygen saturation in term infants [201, 202]. In addition, dummy sucking has been shown to elicit increases in blood pressure in quietly awake or

sleeping term infants [203]. Another potential mechanism for the protective nature of dummy use against SIDS is an enhanced arousability from sleep. However, results of the few studies which have been conducted are conflicting, with one study reporting decreased arousal thresholds to auditory stimulation observed in infants who regularly used a dummy, when compared with those who did not use a dummy [204]. In contrast, other studies have reported no effect of dummy use on either the frequency or duration of spontaneous arousals in sleeping infants, when studied both with and without a dummy in the mouth [205, 206]. It has also been hypothesized that sucking on a dummy during sleep may assist in maintaining airway patency, thus preventing a pharyngeal vacuum and the consequent sealing of the airway [207, 208]. Thus, the risk of oropharyngeal obstruction may be reduced due to the forward positioning of the tongue when sucking on a dummy [208]. Although epidemiological studies have provided strong support for dummy use to be protective for SIDS, the physiological mechanisms responsible for this protection remain uncertain.

Swaddling

Swaddling, or firm wrapping, is a traditional infant care practice which, according to an extensive historical review, has been used in some form or another by various cultures since medieval times [209]. Low incidences of SIDS in populations where swaddling is common have led to the proposal that swaddling may be protective [210, 211], and on this basis, a number of SIDS prevention organizations recommend it. Several studies have documented a "tranquil" behavioral state with longer sleep periods in swaddled infants; therefore, despite a disparity between studies on the risk for SIDS [174, 183, 212], swaddling has become increasingly popular as a soothing technique throughout the world [213, 214]. Swaddling is a common practice in infants throughout the first 6 months of life, during the period of increased SIDS risk. The duration of swaddling and the age of initiation of the practice vary widely. Currently, it is unclear if swaddling is protective against SIDS or is indeed a risk. In the United Kingdom during the mid-1990s, swaddling during the last sleep was more common among SIDS infants than age-matched controls (14 % vs. 9 %); furthermore, a more recent study showed that this difference has since become more marked (19 % vs. 6 %) [174].

Studies investigating the effect of swaddling on cardiovascular control are limited. Swaddling elicits a mild increase in respiratory frequency, most likely due to restricted tidal volumes imposed by the firm wrapping [215–217]. No significant effects have been documented on baseline heart rate, skin temperature, or oxygen saturation in term infants when swaddled during sleep [216, 218]. Studies which compared infants who were routinely swaddled to those who were unused to this practice found that sleep time and heart rate variability were only altered in those naïve-to-swaddling infants [219]. Several studies investigated the effects of swaddling in relation to infant arousability; however, divergent results have been published. The commonly observed decreases in spontaneous movements and startle responses with swaddling are in contrast to effects of other protective factors for

SIDS [209, 220]. One study reported that when infants were swaddled, fewer startle responses progressed to a full awakening, indicating an inhibition of the cortical arousal process [221]. More recent studies reported that swaddled infants exhibited increased arousal thresholds in response to nasal air-jet stimulation; furthermore, a decreased frequency of full cortical arousals was observed primarily in infants who were unaccustomed to being swaddled, at 3 months of age [216]. Spontaneous cortical arousals were also decreased in those infants unaccustomed to being swaddled, at 3 months of age [219]. These arousal differences between routinely swaddled and naïve-to-swaddling infants, only at this age of peak SIDS risk, may explain the contradictory findings of another group which found decreased auditory arousal thresholds in swaddled infants when compared to infants who were free to move [218]. The authors attributed these effects of swaddling on arousal to the greater autonomic changes found after auditory stimulation in swaddled conditions [222]. As with the other protective factors discussed above, the mechanisms whereby swaddling is protective for SIDS remain unclear, and further research is required.

Conclusions

In summary, the assessment of cardiovascular control and arousal processes during sleep is important in understanding sleep-related pathologies such as SIDS. In otherwise healthy infants, studies have demonstrated impairment of these physiological mechanisms in association with all three aspects of the triple-risk model, thus demonstrating the heterogeneous nature of SIDS. Altered cardiovascular and cerebrovascular control, in conjunction with a failure to arouse from sleep, could potentially impair an infant's ability to appropriately compensate for life-threatening challenges, such as prolonged hypotension or asphyxia during sleep. The concept of a close relationship between SIDS and autonomic dysfunction becomes more compelling with the demonstration of an apparent promotion of arousal from sleep by protective factors for SIDS. Despite successful public awareness campaigns dramatically reducing SIDS rates, this decline in SIDS incidence may have stabilized [223–226]. Thus, further research is imperative to elucidate the exact mechanisms involved in the final events of SIDS, allowing identification of "at-risk" infants in the future. The ability to identify these infants would have the potential to increase awareness of both parents and clinicians while minimizing the incidence of SIDS with close monitoring and early intervention.

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