

**Sudden Infant Death Syndrome: implications of altered physiological control during sleep.**

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## **Abstract**

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 development 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 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, the major risk factors for SIDS (prone sleeping and maternal smoking), together with three "protective" factors (breastfeeding, pacifiers and swaddling), and cardiovascular control and arousability from sleep in infants, and discusses their potential involvement in SIDS.

**Keywords:** infant, sleep, SIDS, cardiovascular control, arousal

## **Introduction**

Despite intensive research over the past decades, the mechanisms which lead to the Sudden Infant Death Syndrome (SIDS) still remain elusive. SIDS is presumed to occur in an apparently healthy infant during a period of sleep [1]. Sleep has a marked influence on respiratory and cardiovascular control in both adults and infants, although sleep states, sleep architecture and arousal from sleep processes in infants are very different from those of adults [2-5].

Arousal from sleep involves both physiological and behavioural responses and has long been considered a vital survival response for restoring homeostasis in response to various life-threatening situations, such as prolonged hypoxia or hypotension [2]. There are two distinct arousal types defined in infants, sub-cortical activation and full cortical arousal, which reflect the hierarchical activation from the brainstem (including heart rate, blood pressure and ventilation changes) to the cortex [3]. Any impairment of these protective responses may render an infant vulnerable to the respiratory and cardiovascular instabilities that are common during infancy and have been postulated to occur in SIDS. In support of this possibility, extensive physiological and neuropathological studies have provided compelling evidence that impaired cardiovascular control, with a concomitant failure to arouse from sleep are involved in the final events leading to SIDS [8-17].

The first 6 months of life are a critical period of development when rapid maturation of the brain, cardiorespiratory system and sleep state organisation are all taking place [18-21]. Thus, the investigation of sleep physiology in healthy infants during this high-risk period may provide important insights into the likely mechanisms involved in the pathogenesis of SIDS.

## **SIDS Risk Factors and Autonomic Control**

It is currently believed that SIDS is not due to a single factor, but is multi-factorial in origin. Over the past four decades several models have been proposed to explain the multifactorial nature of SIDS, including the three inter-related causal spheres of influence model [4], the quadruple risk model [5] and the triple risk model [6]. The most widely accepted model is the “Triple Risk Model” for SIDS which provides useful means for organising SIDS knowledge. This model proposes that SIDS occurs when three factors occur simultaneously: (1) a vulnerable infant; (2) a critical developmental period for homeostatic control and (3) an exogenous stressor [6] (Figure 1).

### *Vulnerable Infant*

Neuropathological findings from SIDS victims show significant deficits in brainstem and cerebellar structures [7-12] involved in the regulation of both respiratory drive, cardiovascular control, sleep/wake transition and arousal from sleep [13, 14]. Furthermore, genetic polymorphisms have been identified in SIDS victims which affect genes involved in autonomic function, neurotransmission, energy metabolism, and the response to infection [15-18]. Infants with certain genetic polymorphisms are believed to be more vulnerable to SIDS, particularly when these are associated with challenges caused by suspected sub-optimal intra-uterine and postnatal environments [19].

Prenatal and/or postnatal exposure to cigarette smoke is one factor which increases infant vulnerability to SIDS [11, 20], with over 40 studies showing a positive association with risk ratios of between 0.7 and 4.85 [21-24]. This increased SIDS risk is likely to be due to the effects of nicotine exposure on autonomic control and arousal. In support of this idea Duncan and colleagues [25] 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 [25]. Studies in infants exposed to maternal smoking have demonstrated altered heart rate and blood pressure control compared with control infants [26-32]. 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 [33-39]. Few mothers change their smoking behaviour post-partum [40], 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 [41, 42]. A more recent study, however, showed that before discharge home from hospital, preterm infants of smoking mothers already exhibited disruptions in sleep patterns, prior to any postnatal smoke exposure [43]. 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 intra-uterine growth restriction (IUGR) [44-47], which likely result from suboptimal intrauterine environments. Impaired heart rate control, manifested 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 [48, 49]. 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 [66-71]. Recently, it has been reported that preterm infants exhibited lower blood pressure and delayed blood pressure recovery following head-up tilting across the first 6 months corrected age, when compared with term infants [50, 51].

When compared with term infants at matched conceptional ages, preterm infants also exhibit decreased frequencies and durations of spontaneous arousals from sleep [52, 53], together with decreased heart rate responses following arousal [54]. Furthermore, preterm infants exhibited longer arousal latencies after exposure to mild hypoxia (15% inspired O<sub>2</sub>), reaching significantly lower oxygen saturations than term infants [55]. Cardiorespiratory complications commonly associated with prematurity, apnoea and bradycardia, have also been shown to suppress total arousability when these infants were compared to preterm infants with no history of apnoea [56].

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 pre-existing 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 [19, 57]. 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 to 4 month period, in particular, has been described as a “developmental window of vulnerability” [58, 59], and coincides with the age where a distinct peak in SIDS incidence occurs [19, 57]. The age of peak SIDS incidence has been reported to have remained constant at 2-4 months of age following the introduction of safe sleeping campaigns in some studies [57, 60]. However, other studies have reported that the peak SIDS incidence may now occur at an earlier age [61], with a decrease in the median peak age from 80 to 64 days in Sweden [62] and 91 to 66 days in south west England [63] since the initiation of “back to sleep” campaigns.

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 [51] and term [64] infants have identified a nadir in basal blood pressure during sleep at 2-3 months of age, when compared to both earlier (2-4 weeks) and later (5-6 months) ages studied; a nadir in physiological anaemia also occurs at this age. Thus, the 2-3 month age could represent a critical time period when effects of low blood pressure could accentuate decrements in oxygen carrying capacity and delivery to critical organs [64]. 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 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 (QS), whilst remaining unchanged in active sleep (AS) [65-67]. Following the introduction of standard scoring criteria for sub-cortical activation and cortical arousal as separate entities, a recent study

noted that spontaneous sub-cortical activations decreased with increasing postnatal age, whilst cortical arousals increased [68]. Conversely, another study analysed 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 [69]. 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 [39, 69]. 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, over-heating and recent infection, which may disrupt homeostasis [78, 86-93].

The prone sleeping position has long been considered the major risk factor for SIDS [46, 70-73], with some studies suggesting a causal relation between prone sleep and SIDS [74, 75]. Several physiological changes ensue when infants sleep prone, including increased peripheral skin temperature, and increased baseline heart rate, together with decreased heart rate variability [64, 76-84]. 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 [85, 86]. Furthermore, sympathetic effects on blood pressure and vasomotor tone are decreased in the prone sleeping position [11, 102, 107, 114]. 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 [11, 107, 114]. In addition, prone sleeping infants exhibit reduced cardiac and respiratory responses when arousing from sleep, when compared to sleeping in the supine position [85, 86]. 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 [87-90]. Furthermore, in other studies the prone sleeping position depressed arousal responses provoked by postural change [76], auditory [91] and somatosensory challenges [38, 77, 92]. We have previously 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 [93]. Despite this well-documented decrease in total arousability, examining sub-cortical and cortical responses separately has produced conflicting results. Although one study reported a decreased frequency of spontaneous cortical arousals in the prone position [90], more recent studies have found an increased proportion of cortical arousals (of total responses) in both non-smoking and smoking exposed infants when sleeping prone [39, 69]. 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 [94]. 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 [95-97]. Skadberg and Markstead observed decreased variation in behaviour and respiratory pattern, increased heart rate, and increased peripheral skin temperature during prone compared with supine sleep [96]. These studies suggest that infants are less able to maintain adequate respiratory and metabolic homeostasis during prone sleep.

Increased sweating occurs in SIDS victims, regardless of whether infants slept prone or supine; these cases were predominantly associated with a covered face [57, 98]. 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 [99]. 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 [100] and the suggestion that future SIDS victims may have had atypical temperature regulation [101]. 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 [102], whilst infants sleeping in warmer environments (28 °C vs. 24 °C) exhibited increased arousal thresholds to auditory stimuli [103]. Furthermore, based on studies assessing blood pressure control in infants [11, 102, 107], 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.

Head covering has been identified as a major risk for SIDS with between 16-28% of SIDS infants found with their heads covered. Although a causal relationship with SIDS has not been established [104, 105], 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 [104, 106]. Head covering in healthy infants has profound effects on autonomic control during sleep [107]. Franco and colleagues [107] found that infants sleeping supine with their head covered by a bed sheet 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 [108].

Bed-sharing or co-sleeping has also been reported to significantly increase the risk of SIDS, particularly when the mother smokes with more than 50% of SIDS deaths occurring in this situation between 1997 and 2006 [109, 110]. There have been few studies investigating the physiology behind this risk factor. In infants from non-smoking 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 [111]. 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 [112]. 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 [113-115]. 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 [61, 116]. 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 [117], 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 amongst 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 [113, 118]. This apparent protection may be a biological effect, given that breastfeeding has been associated with a decreased incidence of diarrhoea, vomiting, colds and other infections; in addition, breast milk is rich in antibodies and many micronutrients [113, 119, 120]. 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 [121]. 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 [122]. In a more recent study, 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 [123]. Although there is a general consensus that breastfeeding should be encouraged, a causal relationship between breastfeeding and SIDS has not been established.

### *Pacifier/Dummy Use*

The finding that 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) [57,

124-128]. One study suggested that a likely mechanism for this protection against SIDS was increased heart rate variability which has been demonstrated during sucking periods [129]. 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 [130, 131]. In addition, pacifier sucking has been shown to elicit increases in blood pressure in quietly awake or sleeping term infants when assessed prior to feeding [132]. 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 [133]. In contrast, another study 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 pacifier in the mouth [134]. It has also been hypothesized that sucking on a pacifier during sleep may assist in maintaining airway patency, thus preventing a pharyngeal vacuum and the consequent sealing of the airway [135, 136]. Thus the risk of oropharyngeal obstruction may be reduced due to the forward positioning of the tongue when sucking on a pacifier [136]. Although epidemiological studies have provided strong support for dummy use to be protective for SIDS; however, 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 [137]. Low incidences of SIDS in populations where swaddling is common has led to the proposal that swaddling may be protective [138, 139]. Several studies have documented a “tranquil” behavioural state with longer sleep periods in swaddled infants; therefore, despite a disparity between studies on the risk for SIDS [63, 116, 140], swaddling has become increasingly popular as a soothing technique throughout the world [141, 142]. 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. The average duration of swaddling has been reported to be 35 days in infants in Yunnan Province in China [143] and to be for the entire first year of life in rural Turkish children [144]. The age of initiation of swaddling also varies, with reports of commencing swaddling in the first month of life in Mongolia [145] and immediately after birth in Russia [146].

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 [147-149]. No significant effects have been documented on baseline heart rate, skin temperature or oxygen saturation in term infants during sleep [148, 150]. 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 [137, 151]. One study reported

that when infants were swaddled, fewer startle responses progressed to a full awakening, indicating an inhibition of the cortical arousal process [152]. A more recent study 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 [148]. 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 [150]. The authors attributed these effects of swaddling on arousal to the greater autonomic changes found after auditory stimulation in swaddled conditions [153]. As with the other protective factors discussed above, the mechanisms whereby swaddling is protective for SIDS remain unclear, and further research is required.

## **Conclusions**

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 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 [154-156]. 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, whilst minimising the incidence of SIDS with close monitoring and early intervention.

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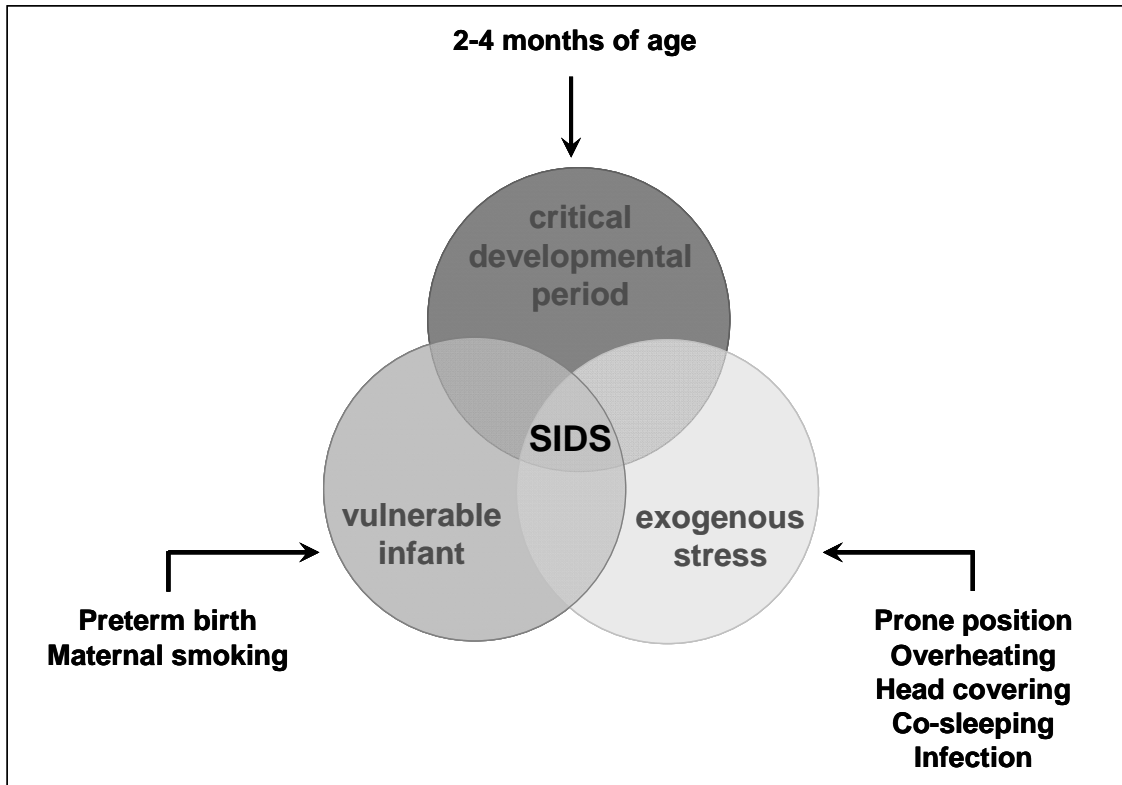
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**Figure 1:** Triple Risk Model for SIDS, illustrating the three overlapping factors: (1) a vulnerable infant; (2) a critical developmental period; and (3) an exogenous stress (Adapted from Filiano and Kinney, 1994).