

# Proposal for mechanisms of protection of supine sleep against sudden infant death syndrome: an integrated mechanism review

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Supine sleep decreases sudden infant death syndrome (SIDS) incidence, however the mechanisms for this are unclear. The triple risk model for SIDS requires that one or more underlying abnormalities of breathing or autonomic control are present; these are rare, but brainstem defects are found in most SIDS cases. Supine sleep increases sympathetic nervous system tone, and level of state organization, and may therefore act as a stressor. This is evidenced by physiological arousal, and by delayed neurodevelopment in supine compared to prone sleepers. It is argued here that prone sleep position is the biological normative standard in healthy infants, supporting autonomic regulation. During rapid eye movement (REM) sleep (and other circumstances), a parasympathetic-mediated adverse autonomic event (AAE) may be spontaneously triggered. In healthy infants, gasping initiates autoresuscitation and recovery. Hypothesis: the underlying vulnerability to SIDS is specific to autoresuscitation from an AAE, the initial serotonin-dependent gasp is commonly compromised. Serotonin metabolism defects also influence sleep architecture, increasing the likelihood of AAE. The mechanism whereby supine sleep decreases SIDS may therefore be a stressor effect, disturbing sleep architecture to decrease REM and AAEs, and increasing sympathetic tone, which may prevent and counteract the purely parasympathetic-mediated AAE, thereby decreasing the risk of SIDS.

## AAP POLICY AND TRIPLE RISK MODEL

The prone sleeping position is identified as a risk factor in sudden infant death syndrome (SIDS). In the 2011 American Academy of Pediatrics (AAP) Technical Report “Expansion of recommendations for a safe infant sleeping environment” (1), the need for supine sleep is stressed very strongly, as summarized in the “Back to Sleep” campaign. The arguments for supine sleep are based on epidemiological association to SIDS. These are well supported by international data from 13 countries that implemented supine sleep campaigns (2).

There is however inadequate understanding of the underlying pathophysiological etiology for SIDS (2), and hence for the protective mechanism conferred by supine sleep. One currently accepted explanation for SIDS is the “Triple Risk Model”

proposed by Filiano and Kinney (3), based on pathological studies of brainstems from SIDS victims. Kinney *et al.* (4) state that “many cases result from defects in brainstem-mediated protective responses to homeostatic stressors occurring during sleep in a critical developmental period”. Kinney and Thach emphasize the importance of this in stating that according to the Triple Risk Model (5), SIDS occurs “only in infants with an underlying abnormality” (page 797). This applies regardless of safe or unsafe potentially asphyxiating sleeping environment (6). In 70% of SIDS cases, the abnormality or defect involves serotonin (5-HT) metabolism (5), ~10–20% have cardiac ion channelopathy defects (7), and other more rare defects have been found. No defects have been reported in control cases (5,6). Secondly, there is a “vulnerable period”, reflecting the epidemiological peak of cases in the 2nd and 3rd month of life. Thirdly, a risk factor, whether extrinsic or intrinsic, is necessary: the combination of all three is believed to trigger a cascade of events leading to death. Genetic factors and defects that contribute to the “underlying abnormality” are included as intrinsic factors. A common feature seen in rare instances where recordings are available during the death, is profound bradycardia with inadequate gasps (8,9), an adverse autonomic event from which there is a failure to autoresuscitate (10,11). The deficiency in serotonin and other related neurotransmitters and pathways are implicated in this failure (5), with effective gasping being “vulnerable to disruption by much smaller defects in multiple neurotransmitter systems” (page 533) (4).

## RE-EXAMINATION OF RESEARCH ON PRONE AND SUPINE SLEEP

Since prone sleep is associated with an increased risk of SIDS, with odds ratio 2.3–13.1 (1,12), prone sleep is identified as “not safe” (1). Studies comparing prone and supine sleep do show significant differences, from which possible harmful mechanisms through physiological compromise of prone sleep are postulated (1). However, I propose that in interpreting such significant differences, it is valid to relate them to a “biologically normative standard”. The fact that supine sleep reduces the risk of SIDS, a rare event, I suggest is not sufficient in itself to make it normative. In biology, the vast majority of mammals sleep

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prone, excepting those in specific ecological niches, such as bats and sloths. The labyrinthine righting reflex to prone is evident prenatally in the cat (13), nesting newborns huddle prone to conserve heat. Neonates in supine are more like to startle, as in the Moro reflex (14). Togari *et al.* (15) studied age of first roll over from initial sleep position compared to preferred final sleep position, and conclude “the healthy human infant tends to sleep in the prone rather than the supine position”. This infant preference or tendency to prone sleep is acknowledged by those recommending supine sleep (1), infants learn “to roll over, which generally happens at 4 to 6 months of age” (1); this preference is also recognized by many parents as justification for prone sleep (16–18).

There is in addition a body of evidence that the prone sleeping position supports neonatal and infant physiology. A non-systematic selection of studies supporting prone sleep as the biological normative state is presented in **Table 1**. The strongest evidence comes from clinical trials in preterm infants, where prone position provides greater physiological regulation than supine, with respect to respiration, cardiac function, metabolism, and state organization. Though some studies report no difference (19), prone sleep is recommended in preterm intensive care (20–22). The Cochrane review on position in mechanically ventilated infants states prone position will “slightly improve the oxygenation” (23). It is possible that the primary effect of position is on sleep state (24,25), ventilatory

**Table 1.** Studies reporting support for prone sleep: results and comments (ranked by age at first exam)

Reference <sup>a</sup>	Context	Prone	Supine	Author comment
(1)	Own control, <i>n</i> 28; born 25–36 wk postmenstrual age, exam at 7 d old	Quiet sleep 68% Active sleep 24% Crying 6% Stress responses 10.1	Quiet sleep 40% Active sleep 43% Crying 12% Stress responses 32.0	Chang: “Prone positioning improves the quality of sleep, decreases stress for ventilated preterm infants.” This author: 5–7 stress responses /20 min in supine—normal hourly sleep cycling highly unlikely.
(2)	Own controls, <i>n</i> 55; chronic lung disease in birth weight below 1,000 g	Oxygen saturation 94% Decreased hypoxemia episodes	Oxygen saturation 92%	McEvoy: “Our findings support prone positioning for the extremely low birth weight infant with chronic lung disease.”
(3)	Own control, <i>n</i> 42, (66 studies); 920–1,760 g neonates, exam at 12–57 d old	(Results presented as supine–prone difference)	Energy expenditure increased +3.1 Energy expend. active sleep increased +2.4 Time awake increased +5.7 Quiet sleep decreased	Masterson: “Data suggest that prone is the position of choice for the low birth weight infant.” This author: Poorer quality sleep in supine.
(4)	Own control, <i>n</i> 18; weight 750–2,100, age at exam 27–36w PMA	Moderate desaturation 2.0 Severe desaturation 0.0 Heart rate (per minute) 153	Moderate desaturation 4.5 Severe desaturation 1.5 Heart rate (per minute) 150	Heimann: “Supine is associated with higher frequency of ... desaturations as compared to prone.”
(5)	Own control, <i>n</i> 31; low-birth-weight infants	Perfusion index “good non-invasive estimate of tissue perfusion”; prone perfusion 3.7	Supine perfusion 3.1	This author: Prone position—better perfusion in quiet and active sleep.
(6)	Own control, <i>n</i> 29; born 1,915 ± 939 g, exam at 36 wk postmenstrual age	Heart rate variability total power (high frequency plus low freq.): TP 25.87; LF 9.79	TP 32.60; LF 13.82	Jean-Louis: “Prone ... decreased HRV and ... decreased sympathetic tone, implies decreased autonomic stability.” This author: In term infants Morgan (2011) attributes same results to “anxious arousal,” supine sleep may as likely be increasing the normal autonomic tone.
(7)	Prospective, own control, <i>n</i> 20; born 25–32 wk, exam at 36 wk postmenstrual age and 6 wk later	At 36 wk Oxygen saturation 98% Compliance 3.0 FRC (capacity) 26 Six wk later Oxygen saturation 98% Compliance 3.7 FRC (capacity) 35	At 36 wk Oxygen saturation 96% Compliance 2.4 FRC (capacity) 24 Six wk later Oxygen saturation 97% Compliance 2.5 FRC (capacity) 31	Saiki: “Lung function impairment does not explain why prematurely born infants are at increased risk of sudden infant death syndrome in the prone compared with the supine position.”

<sup>a</sup>Supplementary Reference list (online).

frequency, and measures of cardioventilatory coupling were more sensitive to sleep state than to position. The above findings may be due to increased active sleep caused by supine position.

A selection of articles reporting support for supine sleep, and quoted in the AAP policy, is provided in **Table 2**, with key results for prone and supine sleep, along with comments from this author derived from a biologically determined normative standard for sleep. Articles stating support for supine sleep, when reinterpreted according to a biologically based normative standard (**Table 2**), actually provide support for prone sleep with respect to respiration, cardiac function, metabolism, and state organization. Note that this is evident both when examined at preterm age, and when re-examined at 2–3 mo of adjusted age.

The epidemiological association of prone sleep to SIDS has made supine sleep the normative standard, with no further consideration for a possible physiological or biological alternative, or potential side-effects. The research articles in **Table 2** begin with the premise that supine sleep is normative, the reported physiological compromise from prone sleep is thus potentially harmful. However, none establish such harm, harm is assumed *a priori*, and mechanisms by *post hoc* attribution and inference. Tuffnell *et al.* (**Table 2**), for example, state that prone sleep results in “inability to lose heat”, prone sleep could equally be credited with “increased ability to preserve warmth”, biologically beneficial in preserving calories for growth. Decreased cerebral oxygenation during prone sleep is proposed as a “new insight into potential risks of prone sleeping”, while not providing any objective normative standard. Supine sleep may be causing an abnormally high cerebral oxygenation, or be simply due to the arousal identified in **Tables 1** and **2**. All the differences reported in **Table 2** are essentially within normal limits of physiology, being within the parameters for healthy homeostatic adjustment to the environment. The findings cannot therefore legitimately be attributed as alarming or potentially harmful to the normal infant sleeping prone.

Jean-Louis *et al.* (**Table 1**) calculated total power of heart rate variability, a measure of autonomic activity, in prone and supine low-birth-weight infants, reporting decreased sympathetic tone in prone. However, in a separation paradigm study, Morgan *et al.* (26) argued that the very same higher total power was due to anxious arousal, and this was concomitant with an 86% reduction in quiet sleep. Since all other studies in **Table 1** (and **Table 2** as argued) show improved physiological regulation in prone, the “decreased sympathetic tone in prone” is likely to be physiologically optimal. Therefore, the autonomic tone in supine sleep could be regarded as elevated.

Galland *et al.* (27) review a number of prone vs. supine studies related to SIDS. The abstract states: “The majority of findings suggest a reduction in physiological control related to respiratory, cardiovascular and autonomic control mechanisms, including arousal during sleep in the prone position” (page 32), which findings are interpreted as potentially harmful, justifying continued supine sleep recommendations (27). The findings are equally consistent with the conclusion that

supine sleep causes an “increase in physiological activation mechanisms”, where the decreased arousal threshold in supine sleep is consistent with a response to threat, hence attributing a potential state of stress, as in the “anxious arousal” reported by Morgan *et al.* (26).

Most important however, for infants sleeping supine maturational delays are reported during later infant development, as summarized in **Table 3**. In all of these studies, using four different methods, delays are reported in the motor domain, evident from 2 mo through 6 mo. Most show no differences after 12 mo of age, only one (Majnemer) shows sleep position continued to predict motor performance at 15 mo.

These reports acknowledge the findings as statistically significant, but declare the findings as clinically insignificant (since they are not apparent at 1 y), stating that infants should continue sleeping supine and parents be reassured. Some advise “compensatory strategies”, (such as providing awake supervised “prone for play” opportunities, Ratliff-Schaub), which would not be necessary if there was no clinical significance in the findings. The question could be asked whether this assurance to parents comes from loyalty to the medical recommendations for supine sleep, rather than a biological understanding of sleep and development. There does appear to a developmentally detrimental mechanism or process operating in infants sleeping supine. With the tests used, such delay has been shown primarily in the motor domain, and to be temporary. But if the factors influencing early development are operating in other domains and neural networks, the impact may not be detected until later. A parallel could be drawn from the recent realization that infants born late preterm have significant learning problems when they start school, despite having normal developmental tests in earlier years (28,29).

A number of independent extrinsic factors may impose risk for SIDS and other unexpected death to a prone sleeping infant, but this author argues that for the infant without the defects described by Kinney (5), prone sleep is not a “risk”. Prone sleep as the biological normative standard supports normal physiology and early motor development. In the majority of research papers cited, the effect of supine sleep is totally consistent with increased stress and level of arousal. Supine sleep may be a stressor.

#### NEONATAL NEURODEVELOPMENT: ROLE OF SLEEP, ALLOSTATIC LOAD

Sleep plays a fundamental role in neurodevelopment. A current hypothesis for the primary purpose of sleep “pertains to the consolidation of memory” (30), fundamental to development. This requires the building of specific circuits at specific times from cortical and subcortical areas through limbic brain centers and back (30), and the coupling of these circuits into networks. Sleep cycling is essential for brain wiring (30,31), including receptor systems, pathway processing, cortical processing, learning, cognition, and memory (31). Each part of the sleep–wake cycle has fundamental importance for brain wiring and neurodevelopment (31); it is not merely sleep, but the quality of sleep that matters. A full sleep cycle of ~1 h is

**Table 2.** Studies reporting support for supine sleep (and quoted in AAP policy): results and alternative interpretations (ranked by age at exam)

Reference <sup>a</sup>	Context	Prone	Supine	Author comment
(8)	Own control, <i>n</i> 32; low-birth-weight infants (805–1,590 g), exam when 33–38 postmenstrual age	Temperature higher Increased heart rate Increased respiratory rate Lower oxygen consumption Lower CO <sub>2</sub> production	Supine defined as standard	Ammari <i>et al.</i> speculate on relationship to sudden infant death syndrome, assuming supine is normative.  This author: Results consistent with prone as biologically normative standard.
(9)	Own control, <i>n</i> 16; exam at 36 wk postmenstrual age		More awakenings supine After feed, quiet sleep shorter  Increased heart rate variability	Goto: “These data support ... “Back to Sleep” for asymptomatic preterm infants because more awakenings and lower threshold for arousal may provide some benefit for the infant responding to a life-threatening event.”  This author: Above true for infant with defect, but findings <i>per se</i> not necessarily beneficial.
(10)	Own control, <i>n</i> 24; 2–3 wks, then 2–3 mo, then 5–6 mo	Arousal threshold air-jet stimulation: 2–3 w higher than supine; 2–3 m higher than supine; 5–6 m no difference	Supine is assumed to be normal state	Horne: In prone “impairment in arousability ... with no clinically significant changes in cardiorespiratory variables or body temperature.”  This author: Results equate also to “increased arousability in supine.”
(11)	Descriptive study, <i>n</i> 17; 2–4 wks, then 2–3 mo, then 5–6 mo	Tissue oxygenation index (TOI, cerebral) lower in quiet and active sleep: 5 and 4% (MAP higher at 2–3 wk) (temperature higher)	Supine assumed to be optimal or normative	This author: The TOI values in the supine position are not proved to be normative, a 3 to 5% difference may well be physiological.
(12)	Own control, <i>n</i> 20; full term, 2–4 wks, 2–3 mo, then 5–6 mo	Heart rate (HR) and arterial pressure (MAP) changes minimal	HR and MAP increased, then decreased, then returned to baseline	This author: Interpretation could equally be that prone position is more stable: the tilt in supine produced an excessive autonomic response.
(13)	Observation, <i>n</i> 21; exam at 5–24 wk old	Single 87% desaturation		Descriptive, infants face down in corrugated foam mattress.  This author: Despite provocation, little adverse effect.
(14)	Descriptive study, <i>n</i> 43; 4–29 wk old	Heat loss coefficient 60%	Supine defined as standard	Tuffnell: “Inability to lose heat.”  This author: Biologically equivalent with better heat retention, and increased heat loss from supine.
(15)	Own controls, <i>n</i> 37; 2–4 mo infants	Prone heart rate variability reduced  Full awakening to 60° tilt during active sleep 15%	Full awakening to 60° tilt during active sleep 54%	Galland: “Blunted arousal responses and/or altered autonomic function ... prone sleeping position.”  This author: Since a severe tilt did not wake prone babies: argument could be they were sleeping better, supine sleepers in higher level of state organization.
(16)	Descriptive, <i>n</i> 24; 10–19 wk old	REM sleep 21.6  Cortical arousals in REM 15.2  Sleep efficiency 80.2%	REM sleep 30.4  Cortical arousals in REM 23.0  Sleep efficiency 72.2%	Kato: “Prone sleep position decreased the frequency of cortical arousals during REM” interpreted as “impairment of arousal process.”  This author: No biologically normative standard provided: supine sleep may have increased frequency of cortical arousals.
(17)	Descriptive matched, <i>n</i> 80; 3 mo olds, each prone and supine in 3 h spells	Increased sleep duration (+16%) Increased non-REM sleep (25%) Decrease in arousals (–40%) Duration of arousals (–43%)		Kahn: “No explanation has been found for the sleep-promoting effect of prone body positioning.”

<sup>a</sup>Supplementary Reference list (online).

**Table 3.** Studies reporting developmental delay following supine sleep: results and comments (ranked by age at exam)

Reference <sup>a</sup>	Context	Prone		Supine		Author comment
(18)	Cross sectional sample, 2m 22/23 supine, 4 m 25/26 supine, 6m 12/17 supine	Not tested (normative provided)		Denver II GMS		Compared against “normative population” prior to back to sleep era. Significant differences on all three gross motor milestones at 2 mo, no difference 4 and 6m.
		2m head up 45°	75%	2m head up 45°	55%	
		Head up 90°	50%	Head up 90°	18%	
		Sit—head steady	50%	Sit—head steady	24%	
(19)	CHIME study <i>n</i> 213, born <1,750 g; seen 6 and 13 mo	Bayley (BSID-II)				Psychomotor and Mental, 6 and 13m no difference
		6m head up 45°	94% <i>P</i> 0.021	6m head up 45°	81% <i>P</i> 0.021	Ratliff-Schaub: “Compensatory strategies while awake may be needed to avoid delayed acquisition of head control.”
		Head up 90°	80% 0.001	Head up 90°	52% 0.001	
(20)	<i>N</i> 343; 4 and 6 mo checkups	Denver developmental screening				Jantz: “Sleep position significantly influences the age of achieving the gross motor developmental milestone of rolling over.”
		Rolls over	76.9% <0.01	Rolls over	59.8%	
		Pull to sit no lag	92.9% (NS)	Pull to sit no lag	87.8%	
(21)	Descriptive study <i>n</i> 83 + 72; recruited 4 mo, exam at 4, 6, and 15 mo	6m Alberta Infant Motor Scale		4m: motor scores lower		Majnemer: “Infants sleeping supine may exhibit early motor lags, associated with less time in prone while awake.”
		Prone 60		Supine 44.5		
		6m Peabody Development Motor Scale		6m Peabody development Motor Scale		
		Supine 90.2		Prone 85.7		
		“At 15m sleep position continued to predict motor performance.”		“Motor delays were documented in 22% of babies sleeping supine.”		
(22)	Prospective practice study, <i>n</i> 351; recruited <2 mo, exam at 6 mo age	Denver developmental screening		Supine sleepers = significant “difference = “delay” in achieving key milestones.		Davis: “Prone sleepers acquired motor milestones at an earlier age than supine sleepers.”
		Significant difference in the age of attainment of:				
		rolling prone to supine,				
		tripod sitting, creeping,				
		crawling, pulling to stand				
(23)	ALSPAC study UK, <i>n</i> 9,663; tested 6 and 18 mo	Denver developmental screening		At 18 mo		Dewey: At 6 mo “increased ability on the gross motor scale ( <i>P</i> , 0.0001), the social scale ( <i>P</i> , 0.05), and the total score ( <i>P</i> , 0.0001) when compared with back sleepers.”
		At 6 mo		No difference		
		Gross motor scale 0.38 SD higher				
		Social skills scale 0.11 SD higher				
		Total development 0.20 SD higher				

<sup>a</sup>Supplementary Reference list (online).

required (31). Sleep cyclicity is evident at 30 wk postmenstrual age in the majority of preterm infants (32). Rapid eye movement (REM) sleep is predominant in the fetus (33), and produces “spontaneous synchronous firing” of fetal sensory receptors necessary for brain wiring (33). By term age, slow wave sleep or quiet sleep is evident, and 1 h sleep cycling between REM and slow wave sleep is usually apparent, with mature cyclicity showing more slow wave sleep than REM starting at 3 mo (34). During infancy, such sleep cycles begin to block together, and resemble adult sleep at 6 mo (34). This maturation period coincides with the critical period for SIDS.

That supine sleep could be a stressor is not part of current thinking, nor has it been considered as a possible mechanism for protection against SIDS. Neurologically, a stressor results in a neuroendocrine response, with activation of the sympathetic nervous system and numerous hormonal and chemical mediators, and subsequent activation of the parasympathetic

system to restore homeostasis. When this response is able to return physiological systems to baseline, allostatic state is maintained (35). However, when the stress is repeated, prolonged, or excessive, a cumulative burden, termed “allostatic load”, begins to affect multiple organ systems, including the brain. This causes epigenetic changes through stress mediators such as cortisol (36,37). Homeostasis is maintained, as an adjustment to a more demanding environment, but this comes at a higher cost, with increased “wear and tear” of the systems that maintain it (35). An early prediction is made (38), that alters gene expression of physiological set points, when there is a mismatch with future conditions, disruption, or maladaptation follows (39). Such disruptions will be most severe when gene expression in particular critical periods of development is taking place (40), thereby affecting quite specific aspects of development. Stress capable of causing such change is termed “toxic stress”, a defining feature of which is also the “absence



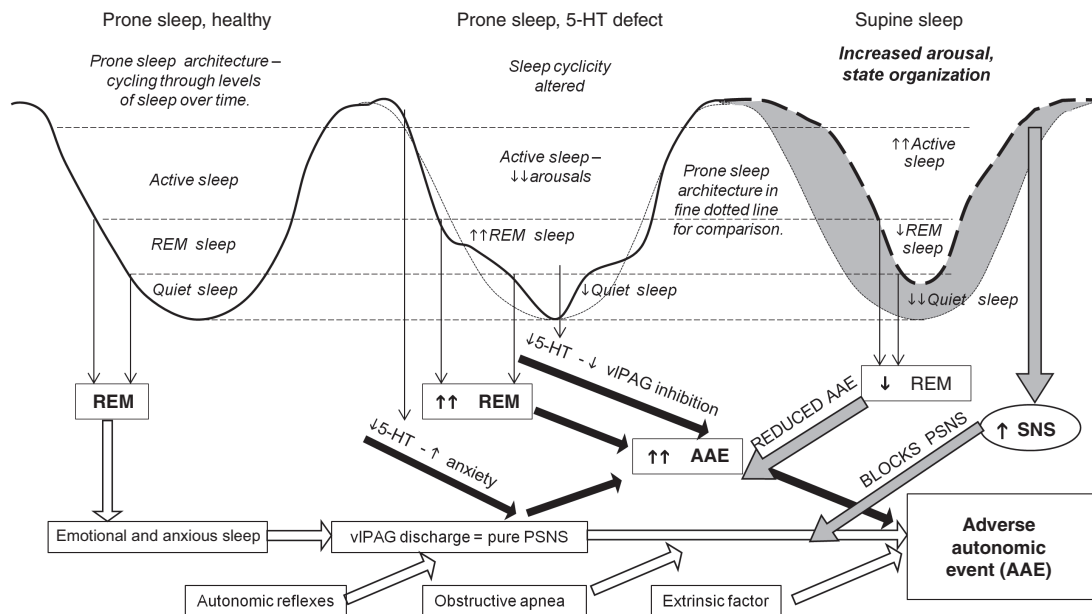
of the buffering protection of a supportive, adult relationship”, from the AAP Technical Report entitled “The lifelong effects of early childhood adversity and toxic stress” (40). While the term “toxic stress” was coined in the context of attachment behavior and social stressors, the same mechanisms of mediator-induced epigenetic changes that was first identified in the neonatal period (36) was earlier described as “fetal programming” (41), but continues from soon after conception until late adolescence, hence now more broadly named Developmental Origins of Health and Adult Disease (39).

Research data on supine sleep (as in Tables 1 and 2) shows increased autonomic tone, changes in sleep architecture, and disruption of sleep cyclicality, with subsequent motor developmental delays (Table 3). Reinterpreted in the light of the above neuroscience, this could equate to a stressor effect of supine sleep causing increased allostatic load (35), coupled with impaired quality of sleep, impacting development negatively (31), and possible maladaptation of early critical neural circuitry (40). If this were indeed so: supine sleep would qualify as a stressor, with potential for future harm.

## HYPOTHESIZED MECHANISM FOR SIDS PROTECTION BY SUPINE SLEEP

That supine sleep reduces incidence of SIDS is not disputed. The mechanism of supine sleep in reducing mortality in SIDS may however be precisely because a stressor is operating to raise the level of arousal, or state organization, and/or by increasing autonomic nervous system tone. This integrated mechanism review for SIDS protection by supine sleep is summarized as a “model” in Figure 1.

Healthy sleep that promotes development is characterized by cycling (31), and on the premise that prone sleep is the biologically normative standard, Figure 1 depicts this as “Prone Sleep, healthy”. REM sleep is a state of autonomic instability even in healthy infants (42,43), with a role in processing negative emotional memory (44). Such negative emotion includes fear, threat, and anxiety, and memory processing takes place under protective cover of atonia, and higher levels of cortisol (30). The amygdala is the point of convergence from higher hierarchical networks that assess safety and threat (45), the central nucleus of the amygdala then projects appropriately selected responses to the periaqueductal gray (PAG), hypothalamus, and brainstem, expressed as various orchestrated defensive programs (45). The ventrolateral PAG (vlPAG) is the most caudal and ventral (hence the most primitive), expressing a passive coping strategy comprising quiescence, hyporeactivity, hypotension, and bradycardia (46). This is also described as a “co-ordinated immobilization and dissociation defence response” (47), akin to the primitive reptilian defense response (48). In adults, the vlPAG mediates panic and anxiety (49), as a most extreme and severe response to threat. The vlPAG outflow is intensely and purely parasympathetic (47). The above, and aspects of it, are described in various terms: neurocardiogenic syncope (50), vagal bradycardia (51), loss of cardiovagal baroreflex during vasovagal syncope (52), hypotension from decreased renal, and iliac vascular resistance (53). Prenatal nicotine exposure increases parasympathetic control of heart rate (54). I propose the term “Adverse Autonomic Event” (AAE) as a generic term for all the above, and as the common starting point for autore-suscitation mechanisms. An intrinsic vlPAG generated AAE



**Figure 1.** Model for mechanisms of supine sleep’s protective effect on sudden infant death syndrome. “Prone sleep, healthy” displays normal sleep architecture and sleep cycling; this is contrasted with “Prone sleep, 5-HT defect” with altered cyclicality and increased rapid eye movement (REM) sleep, and thirdly “Supine sleep” (heavy dashed line) with reduction in REM sleep. Grey-shaded area represents degree of increased arousal. White block arrows depict mechanisms producing an adverse autonomic event (AAE), probably occurring in most normal infants. Black block arrows depict possible contributors to increased AAE. Grey block arrows show effect of sympathetic blocking of AAE, and increased arousal decreasing REM and thereby AAE. PSNS, parasympathetic nervous system; SNS, sympathetic nervous system; vlPAG, ventrolateral periaqueductal gray.

accounts for SIDS cases that occasionally occur in the absence of external risk factors. The AAE can arise from many other causes, not least obstructive apnoea and identified intrinsic and extrinsic risk factors (4).

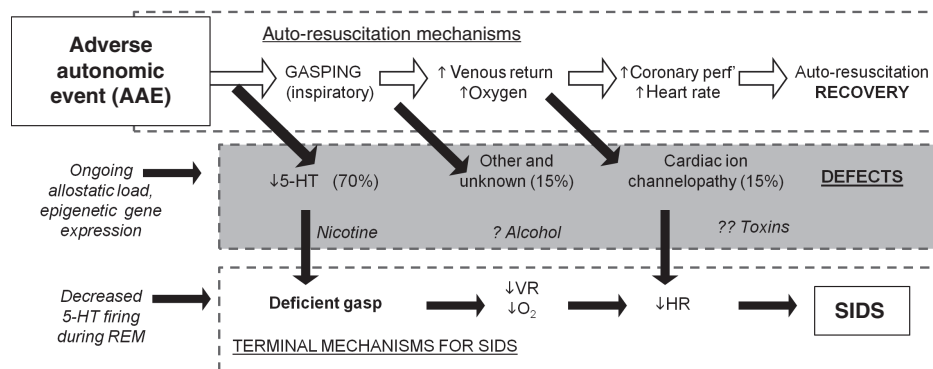
Autoresuscitation starts with a gasp that is purely inspiratory (55), and needs to be sufficient to decrease intrathoracic pressure to the extent that there is an increased venous return (56). The rebound expiration that follows allows for coronary perfusion of blood with some oxygenation, which allows for safe increase in heart rate (56). Increased heart rate and coronary perfusion without oxygenation increases cardiomyocyte damage and mortality (47). A period of compensatory tachycardia usually follows successful autoresuscitation. It is likely that such AAEs occur in many normal healthy infants (57), but in these, autoresuscitation is effective in restoring normal breathing, heart rate, and blood pressure, see **Figure 2**.

Serotonin has complex effects on sleep architecture (58), but specifically, the 5-HT(1A) neuron is involved in regulation of sleep and REM, knockout mice without 5-HT(1A) have increased REM sleep (59). Kohyama identifies the inhibitory phase of REM sleep as being the key period of risk in SIDS and ALTE (apparent life-threatening event) subjects (60); in polygraphic sleep recordings of future SIDS victims Kahn found that 78% of events with apnoeas and bradycardia occurred during REM sleep (9). A feature of REM sleep is an almost complete absence of medullary 5-HT firing; this may be implicated in failure of autoresuscitation (4,61). Future SIDS victims showed significant alterations in sleep architecture compared to controls (**Figure 1**, “Prone Sleep, 5-HT defect”), with more REM in early life (62), and increased subcortical arousals during REM sleep and decreased cortical arousals (9,63). Sleep architecture itself may be subject to epigenetic adaptation in development: infants with previous ALTE had disturbances in “cyclic alternating pattern” of sleep (64). Serotonin has anxiolytic effects; knockout mice show increased anxiety (65). In vulnerable infants with poor serotonin function, REM sleep anxiety may be enhanced, increasing the risk for vLPAG discharge leading to a potentially lethal AAE. Serotonin specifically inhibits discharge of the vLPAG (66); deficiency of serotonin may predispose the vLPAG

to discharge. Overall, the presence of a defect in serotonin metabolism may increase the likelihood of AAE.

The inspiratory gasping mechanism that initiates autoresuscitation from the AAE is dependent on specific 5-HT(2A) receptors (67,68), SIDS victims have altered and deficient gasping (8), and some have defects of these receptors (5,6) (see **Figure 2**, black arrows). The gasp therefore may be inadequate to achieve venous return, maintaining coronary hypoxia and reflex vagal bradycardia. The hypoxic induced bradycardia, mediated by the vagal nerve from nucleus ambiguus and the dorsal motor complex is protective for the heart, blocking the vagus decreases survival (47). Failure to inhibit the dorsal motor complex may be underlying QT syndromes identified as contributing to some cases of SIDS (7). Reduced 5-HT(1A) receptor binding density is one of several specific features seen only in SIDS cases, not in controls (69), and is implicated in the failure of autonomic regulation of respiration, blood pressure, and arousal. Though protective to the heart, the hypoxia is lethal to the brain. The AAE and failure to autoresuscitate can be augmented by nicotine and other factors; Dergecheva *et al.* (47) state “exaggeration of protective response to hypoxia could be detrimental ... fatal events are augmented cardiorespiratory responses” (page 9). Note that serotonin defects may both predispose to AAE, and contribute to failure to recover from them. A severe cardiac channelopathy can however lead to failure to autoresuscitate from an AAE, whatever triggered it, and with no serotonin defect. In the absence of a defect, SIDS would not occur in the model proposed, in agreement with Kinney *et al.* (4). In the presence of an underlying vulnerability, or defect, in any of these autoresuscitation mechanisms, SIDS may follow. There is evidence to suggest that SIDS victims have had earlier episodes of autoresuscitation prior to the terminal event (4). The brainstem gliosis seen in SIDS victims suggests a progressive failure of resuscitation mechanisms prior to death (70,71). Compounding effects of several risk factors, and findings of more than one underlying defect, suggest possible convergence of more than one factor in triggering SIDS (70,71).

Two specific mechanisms for supine sleep protection against SIDS are proposed (**Figure 1**, grey arrows). First, by raising



**Figure 2.** Pathway to autoresuscitation, and proposed terminal mechanisms for sudden infant death syndrome (SIDS). An adverse autonomic event (AAE) leads to a robust autoresuscitation pathway, white arrows. Shaded area summarizes “defects” in mechanisms for autoresuscitation. Black block arrows represent pathways resulting from such underlying abnormalities, with hypothesized mechanisms for failure to autoresuscitate as leading to SIDS. SIDS occurs only in response to an AAE, and when autoresuscitation fails due to presence of defect. HR, heart rate; O<sub>2</sub>, oxygenation; VR, venous return.

the general level of state organization, increasing arousal (27), supine sleep decreases the amount of time spent in REM sleep (62,72,73), which may decrease the likelihood and frequency of AAE, and thereby contribute to SIDS reduction.

Perhaps more importantly, supine sleep provides a higher level of ongoing sympathetic tone (27), preventing the purely parasympathetic override that characterizes vIPAG discharge, or individual parasympathetic components of this. The more ventral and caudal column of the PAG (dorsolateral) evokes a freeze response (74), in which intense discharge of parasympathetic is balanced by equally intense sympathetic discharge. The first 2 mo are a “critical period of organization of the amygdalar–hypothalamic system” (75), the stronger this becomes the less risk for a purely parasympathetic AAE. Other protective stressor mechanisms are possible.

In the presence of an underlying defect (5), maintaining the infant with a vulnerability in a higher arousal and autonomic state (increased sympathetic tone) may in this way be protective through the critical period of risk, thus preventing the onset of the cascade that leads to the AAE, from which the defect in serotonin leads to failure of auto-resuscitation and finally SIDS. Essentially, this paper proposes that supine sleep has reduced the incidence of SIDS because it is a stressor.

## EPIDEMIOLOGICAL ASPECTS OF SIDS ASSOCIATION TO SUPINE SLEEP

The vulnerability caused by the underlying defects may be severe, as a few infants appear to die of SIDS despite sleeping supine and in the absence of any risk factors. The lethality of the defect is likely to be at least “moderate”, as it is modifiable by supine sleep. Based on extrapolations by this author (almost all cases show a defect, none yet found in controls), perhaps a 2/1,000 incidence of the defect with a 50% lethality (1/1,000 SIDS rate) has been modified by the “Back to Sleep” campaign from 1.2 to the current level of 0.6/1,000 in the USA (2). There may also be increasing allostatic load over time (35), as well as known risk factors such as nicotine (54), increasing the severity of the defect, as evidenced by further reduced serotonin gene expression in older SIDS cases (76). This is consistent also with the findings of multiple risk factors (acting as contributors to allostatic load) in the majority of SIDS cases. Invoking the allostatic load concept, including effects of fetal and early neonatal exposure to nicotine and alcohol, provides a rationale for the gender difference observed in SIDS (69), female estrogens provide an early protective effect against fetal and neonatal stress (77,78).

## IMPLICATIONS OF THE HYPOTHESIS

This model suggests that further reduction in SIDS incidence will not be achieved by intensified supine sleep campaigns. In the USA, Hauck *et al.* (2) demonstrate that increased compliance to supine sleep recommendations could lower SIDS rates by 47%; however, the same data demonstrate that even if supine sleep was absolute, the USA SIDS rate would still be between 0.28 and 0.39/1,000, (compared to 0.10 in Netherlands). More progress will almost certainly be made with a broader approach addressing other risk factors. Added to such could

be a developmentally supportive approach that decreases stress and allostatic load, improves the quality of sleep cycling, and decreases the likelihood and frequency of AAE.

This model may also provide direction to research elucidating the proposed “critical periods”; space does not allow discussion of these, but they include sleep maturation, sympathetic and parasympathetic ontogeny, and measures of allostatic load with epigenetic markers. The hypothesis also highlights the urgent need to research and develop a practical means to identify infants that are at risk, allowing for a more nuanced and focused preventive strategy.

To parents who experience the terrible tragedy of SIDS, the triple risk model as interpreted here is of some slight solace: there is a very rare but very severe neurological defect, and they should not be blamed, nor take blame, for anything they did or did not do.

## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/pr>

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