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Review

The physiological determinants of Sudden Infant Death Syndrome☆,☆☆

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ABSTRACT

It is well-established that environmental and biological risk factors contribute to Sudden Infant Death Syndrome (SIDS). There is also growing consensus that SIDS requires the intersection of multiple risk factors that result in the failure of an infant to overcome cardio-respiratory challenges. Thus, the critical next steps in understanding SIDS are to unravel the physiological determinants that actually cause the sudden death, to synthesize how these determinants are affected by the known risk factors, and to develop novel ideas for SIDS prevention. In this review, we will examine current and emerging perspectives related to cardio-respiratory dysfunctions in SIDS. Specifically, we will review: (1) the role of the preBötzinger complex (preBötC) as a multi-functional network that is critically involved in the failure to adequately respond to hypoxic and hypercapnic challenges; (2) the potential involvement of the preBötC in the gender and age distributions that are characteristic for SIDS; (3) the link between SIDS and prematurity; and (4) the potential relationship between SIDS, auditory function, and central chemosensitivity. Each section underscores the importance of marrying the epidemiological and pathological data to experimental data in order to understand the physiological determinants of this syndrome. We hope that a better understanding will lead to novel ways to reduce the risk to succumb to SIDS.
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1. Introduction

Sudden Infant Death Syndrome (SIDS) is the unexpected death of an infant less than twelve months of age that cannot be explained after thorough investigation, death scene examination, and review of clinical history (CDC, 2012). While the precise cause of death is unknown, it is well-established that SIDS correlates with infant sleep position and deficiencies in cardio-respiratory function. The intense efforts to better understand the etiology of SIDS has led to the development of a triple risk model involving (1) a vulnerable infant; (2) a critical period of development in homeostatic control; and (3) an exogenous stressor (Filiano and Kinney, 1994). According to this generalized model, the intersection of these risk factors leads to a significant increase in the chance of SIDS. While two of the three risk factors are intimately related to the biology of the infant, the third factor, an exogenous stressor, recognizes the important role environment plays in the pathogenesis of the syndrome. Perhaps the most recognized exogenous stressor correlating to SIDS is an infant sleeping in the prone position. In 1996, the United States launched the Back-to-Sleep campaign to better educate the public about the potential danger of infants sleeping in the prone position. This campaign dramatically reduced the occurrence of SIDS (Mage and Donner, 2009; Trachtenberg et al., 2012). However, despite the success of this campaign, SIDS remains a leading cause of infant death (CDC, 2012). Furthermore, a recent report by Trachtenberg et al. (2012) finds that although the relative contributions of risk factors for SIDS have changed, the majority of SIDS cases still involve both, intrinsic and extrinsic risk factors (Trachtenberg et al., 2012).

1.1. The prone sleeping position: an exogenous stressor of respiratory physiology in SIDS

In 1985, Davies described the exceedingly rare occurrence of cot death (i.e., SIDS) within the Hong Kong population when compared to the occurrence in western countries, and while several possible reasons were proposed for this difference, Davies recognized the potential that infant sleep position may have in SIDS (Davies, 1985). Subsequent reports found epidemiological and clinical evidence to support that the prone sleeping position correlates with increased risk of SIDS (de Jonge et al., 1989; McGlashan, 1989; Chiodini and Thach, 1993; Kemp et al., 1993; Trachtenberg et al., 2012).

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As an exogenous stressor of SIDS, a wide variety of events may occur leading to infant death when in the prone sleeping position. These events range from thermal stress (Fleming et al., 1993), to airway compression or collapse (Krous et al., 2008; Becher et al., 2012), to re-breathing of exhaled gases (Chiodini and Thach, 1993). However, a common intersection among these events appears to be the occurrence of a catastrophic life-threatening event involving cardio-respiratory distress that the SIDS victim does not successfully overcome.

It is important, however, to recognize that while the prone sleeping position is a risk factor, alone, it does not cause SIDS. SIDS occurs only when environmental challenges (i.e., extrinsic risk factors) and intrinsic risk factors intersect (Lewak, 2012). Thus, while the prone sleeping position may set the stage for SIDS, only vulnerable infants succumb to SIDS. To explore potential physiological vulnerabilities in SIDS, this review will focus on four issues derived from clinical observations and emerging perspectives from experimental models. Specifically, we will look at: (1) insights gained from studying the preBötC, an area critical for the generation of different forms of breathing; (2) gender and age distribution of SIDS etiology; (3) the persistent link between SIDS and prematurity; and (4) the intersection of SIDS, central chemosensitivity, and auditory function.

2. SIDS and central cardio-respiratory control

2.1. Sighs, gasps, and the arousal response

Recognition that the prone position is a major SIDS risk factor has not only saved lives through the Back-to-Sleep campaign but also provides critical mechanistic insights into the physiological determinants of SIDS. The insights gained are consistent with a final common pathway of cardio-respiratory distress that SIDS victims experience involving arousal and/or auto-resuscitation deficiencies. Specifically, an infant sleeping in the face-down position re-breaths exhaled gases which leads to a build-up of inspired CO_2 with a concomitant decrease in inspired O_2 (Kemp and Thach, 1991; Bolton et al., 1993; Chiodini and Thach, 1993; Kemp et al., 1993). Under normal conditions increased CO_2 (i.e., hypercapnia) is a physiological stimulus that leads to a stereotypical arousal response that relieves the build-up of end-tidal CO_2 and refreshes the inspired O_2 supply of the infant (Lijowska et al., 1997; McNamara et al., 1998; Ayas et al., 2000; Thach, 2002; Masa et al., 2003; Parslow et al., 2003; Fewell, 2005; Horne et al., 2005). This arousal response constitutes a powerful mechanism that normally protects an infant from respiratory distress associated with the prone position (Fig. 1). However, prospective studies have shown that spontaneous and induced arousals during sleep are decreased in SIDS victims indicating an innate susceptibility was present before the final event (McCulloch et al., 1982; Dunne et al., 1992; Kahn et al., 1992; Schechtman et al., 1992; Sawaguchi et al., 2005; Kato et al., 2006). Thus, any factor that blunts the initiation or effectiveness of the arousal response may increase the risk for SIDS (Franco et al., 2010).

In the case of the prone position, the stimuli evoking arousal are specifically increased CO_2 and/or decreased O_2 (Berry and Gleeson, 1997), but the same stereotypical pattern of arousal can be activated spontaneously or triggered by other sensory stimuli (Thach and Lijowska, 1996; McNamara et al., 1998). In all cases, infant arousal begins with the occurrence of a sigh (i.e., augmented breath), followed by thrashing, eye opening, and repositioning of the head which ultimately ameliorates the hypercapnic/hypoxic challenge experienced by a sleeping infant (Lijowska et al., 1997; McNamara et al., 1998). Thus, the sigh appears to be an event initiating both subcortical and cortical arousals (Lijowska et al., 1997; McNamara et al., 1998). In this context, the sigh can be considered as a central nervous system adaptation that responds to changes in blood gases and initiates a series of events that lead to arousal. Indeed, the generation of the sigh is very sensitive to hypoxic challenges (Cherniack et al., 1981; Bell and Haouzi, 2009,

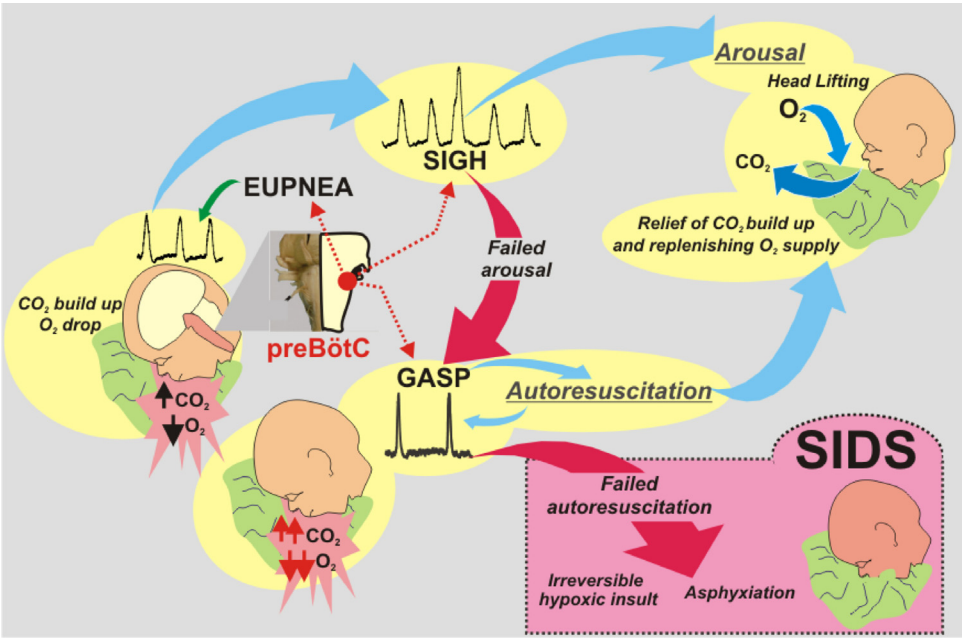

Fig. 1. Arousal and autoresuscitation follow stereotypical patterns that protect infants sleeping in the prone position from SIDS. Brainstem abnormalities, however, may alter preBötC network and impair sigh and gasp generation which may increase SIDS vulnerability. During prone sleeping, re-breathing exhaled air can increase CO_2 and decrease O_2 levels. The altered blood gas composition initiates the arousal response that begins with sigh generation during continued eupneic breathing. Successful arousal results in head lifting and repositioning which relieves the build-up of CO_2 and replenishes the O_2 supply. If arousal fails, a more severe hypoxic state is reached and eupneic breathing will transition to gasping. This transition is mediated by network reconfiguration of the preBötC (Lieske et al., 2000; Pena et al., 2004). Gasping is an autoresuscitation response that can lead to arousal and a return to normal blood gas levels. Should an infant fail to both arouse and autoresuscitate, the irreversible hypoxic insult leads to asphyxiation and the occurrence of SIDS.

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