

LETTER TO THE EDITOR

The SIDS–critical diaphragm failure hypothesis revisited

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Dear Sir,

Since the publication of the sudden infant death syndrome (SIDS)–critical diaphragm failure (CDF) hypothesis in 2011 (1), it has attracted the attention of several investigators active in the field (2,3). In addition to the published commentary, the author has corresponded with several colleagues regarding the potential role of critical diaphragm failure in SIDS. In several of these communications, I have been asked about three salient characteristics of SIDS that were not discussed in the original article. They relate to the inverse correlation between SIDS and breast-feeding, and the positive correlations between the male gender and cigarette smoke and SIDS. In this letter, I will briefly describe how the SIDS–CDF hypothesis would approach these questions and highlight implications for future SIDS research.

The SIDS–CDF hypothesis postulates that the cause of death in SIDS is respiratory failure precipitated by the failure of the primary respiratory muscle, the diaphragm. Several factors can reduce the force-generating capacity of the diaphragm, and in certain circumstances the cumulative effect of these factors can lead to a self-reinforcing cycle that results in death that has no single identifiable cause.

As discussed in our original article, SIDS is saliently associated with infections, the prone sleeping position, low birth weight and prematurity, sleep, non-monotonic death rate (low at age 0–1 month, peak at age 2–4 months, and rare after age 6 months), the male gender, cigarette smoke, and absence of breast-feeding (1). The SIDS–CDF hypothesis postulates that when several of these factors manifest simultaneously, infants can suffer critical diaphragm and respiratory failure that has *no single* cause. It is well established that even trivial infections can cause a

rapid and significant reduction in the diaphragm force generation capacity. It is also well known that the prone sleeping position significantly increases the respiratory load of the diaphragm. It is similarly well established that during REM sleep, the secondary respiratory muscles (intercostals) that stabilize the highly compliant rib-cage of the infant and support the primary respiratory muscles, as well as the muscles of the upper airway, are partially or totally inactive. Likewise it has been shown that the respiratory force and endurance of a neonate diaphragm correlates with its birth weight and term maturity, and that the diaphragm reaches full force generation capacity and endurance by approximately 6 months of age. It is also established that during the first month of life when SIDS is rare, the infants enjoy the immunological benefit of passive maternal antibodies (that rapidly wane after the first month *post partum*) and that during the first 6 months of life the innate immune function is underdeveloped. Finally, we draw attention to the obvious physiological reality that compromised respiratory function can lead to diminished oxygen supply required for normal muscle function, including that of the diaphragm. The causal links between these features and SIDS are addressed in detail in our original article (1). However, the possible connection between male gender, absence of breast-feeding, and cigarette smoke and SIDS has not been previously examined in the context of CDF.

I will address the 60/40 male preponderance among SIDS victims first. Here I would like to thank Professor Goldwater for highlighting this enigmatic aspect of SIDS in his recent article (2). Males and females display significant differences in their immune responses, and as Fish notes in her comprehensive review article titled ‘The X-files in immunity’,

there is ‘accumulating evidence in support of sex-based differences in innate and adaptive immune responses’ (4). Compelling evidence from this and numerous other publications (5–7) shows that testosterone can significantly attenuate the immune function in humans, and that it is a critical factor in explaining why males and females display disparate immune responses. There is a detailed discussion on the interplay between testosterone and the immune function in the article by Muehlenbein and Bribiescas (8). This would suggest that if young male infants have higher testosterone levels than females during the first 6 months of life, they would be more susceptible to infections and, critically, also to infection-induced diaphragm weakness. Forest and colleagues show that male infants indeed have significantly higher testosterone levels than females between the ages of 1 and 6 months, and others have reported similar results (9,10). Hence, these well-documented data, when combined with the evidence that testosterone can significantly attenuate the immune response, offer a compelling explanation as to why young male infants are more vulnerable to infections and infection-induced diaphragm weakness. However, considering that the detailed longitudinal data were reported some 40 years ago, it would be important to conduct a robust study that measures the testosterone levels of male infants during the first 6 months of life and assesses their possible impact on the immune function in the context of SIDS.

There is compelling evidence that suggests a significant inverse correlation between breast-feeding and SIDS (11,12). The SIDS–CDF hypothesis postulates that, as with the role of male gender/testosterone, this inverse correlation is related to the immune function of the infant. As we discussed in our article, infants enjoy the benefits of passive maternal immune factors during the first month of their life (1). However, this passive immune protection wanes relatively quickly after the first month *post partum*, well before the innate immune function is fully developed. Numerous studies have shown that breast-feeding extends both the duration and effect of this passive immune protection (13–15). Thus, infants who are breast-fed benefit from a more robust immune function during the period when their diaphragms are most vulnerable (the first 1–6 months of life). They would thus also be less susceptible to infections that can result in the reduction of the diaphragm force-generating capacity.

Finally, we turn to cigarette smoke (CS) as a risk factor for SIDS. CS is a complex risk factor, partly due to its chemical complexity and partly because it may be a proxy for other environmental risk factors such as poor neonatal care. However, studies on

the effect of CS on skeletal muscles and specifically the diaphragm offer a possible biomechanical explanation for this correlation. A study from 2010 notes: ‘the present investigation is the first to provide evidence of the posttranslational oxidative modifications induced by both ROS and RNS [reactive oxygen and nitrogen species, respectively] on muscle proteins in human smokers and in animals chronically exposed to CS’. The authors go on to note that CS ‘led to the significant increase in oxidative modifications of proteins involved in glycolysis, energy production and distribution, carbon dioxide hydration, and muscle contraction in both humans and guinea pigs [and] the reduction in creatine kinase activity in both respiratory and limb muscles of guinea pigs’ (16). These authors conclude that CS can significantly affect the energy metabolism of the diaphragm without producing visible signs of inflammation. Considering evidence from this and other studies on CS and muscle function (17,18) and the potential vulnerability of young infant diaphragms discussed earlier, the effects of environmental CS on the function of respiratory muscles should be further investigated.

The diaphragm muscle has been completely ignored in the study of SIDS. By itself, the obvious correlation between the prone sleeping position and increased diaphragm work-load should raise serious questions about the role of the diaphragm in SIDS. Similarly, the extensive research showing that even relatively minor infections can cause a rapid and significant reduction in diaphragm force-generating capacity should not be ignored by SIDS researchers. The numerous links between the salient SIDS risk factors and diaphragm function can and should be tested experimentally. It is only by combining insights from diverse fields of research, such as infection-induced diaphragm dysfunction, the effect of REM sleep and sleep position on respiratory muscles, the infant respiratory muscle structure and development, and the infant immune system, that we can hope to understand the underlying mechanism of this complex syndrome.

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References

1. Siren PMA, Siren MJ. Critical diaphragm failure in sudden infant death syndrome. *Ups J Med Sci.* 2011;116:115–23.
2. Goldwater PN. A perspective on SIDS pathogenesis. The hypotheses: plausibility and evidence. *BMC Med.* 2011;9:64.
3. Eisenhut M. Features of diaphragmatic myositis in a case of sudden infant death. *Ups J Med Sci.* 2011;116:220.
4. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol.* 2008;8:737–44.

5. Oertelt-Prigione S. The influence of sex and gender on the immune response. *Autoimmun Rev.* 2012;11:A479–85.
6. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. *J Autoimmun.* 2012;38:J282–91.
7. Bird MD, Karavitis J, Kovacs EJ. Sex differences and estrogen modulation of the cellular immune response after injury. *Cell Immunol.* 2008;252:57–67.
8. Muehlenbein MP, Bribiescas RG. Testosterone-mediated immune functions and male life histories. *Am J Hum Biol.* 2005;17:527–58.
9. Forest MG, Sizonenko PC, Cathiard AM, Bertrand J. Hypophyso-gonadal function in humans during the first year of life. 1. Evidence for testicular activity in early infancy. *J Clin Invest.* 1974;53:819–28.
10. Bolton NJ, Tapanainen J, Koivisto M, Vihko R. Circulating sex hormone-binding globulin and testosterone in newborns and infants. *Clin Endocrinol (Oxf).* 1989;31:201–7.
11. Task Force on Sudden Infant Death Syndrome. Moon RY. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. *Pediatrics.* 2011;128:1030–9.
12. Young J, Watson K, Ellis L, Raven L. Responding to evidence: breastfeed baby if you can—the sixth public health recommendation to reduce the risk of sudden and unexpected death in infancy. *Breastfeed Rev.* 2012;20:7–15.
13. Goldman AS. Evolution of immune functions of the mammary gland and protection of the infant. *Breastfeed Med.* 2012;7:132–42.
14. Garofalo R. Cytokines in human milk. *J Pediatr.* 2010;156: S36–40.
15. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. *Pediatr Res.* 2007;61:2–8.
16. Barreiro E, Peinado VI, Galdiz JB, Ferrer E, Marin-Corral J, Sánchez F, et al. Cigarette smoke-induced oxidative stress: a role in chronic obstructive pulmonary disease skeletal muscle dysfunction. *Am J Respir Crit Care Med.* 2010;182:477–88.
17. Rinaldi M, Maes K, De Vleeschauwer S, Thomas D, Verbeken EK, Decramer M, et al. Long-term nose-only cigarette smoke exposure induces emphysema and mild skeletal muscle dysfunction in mice. *Dis Model Mech.* 2012;5: 333–41.
18. Barreiro E, del Puerto-Nevaldo L, Puig-Vilanova E, Pérez-Rial S, Sánchez F, Martínez-Galán L, et al. Cigarette smoke-induced oxidative stress in skeletal muscles of mice. *Respir Physiol Neurobiol.* 2012;182:9–17.