



Sudden death among infants and adults: companion disorders of maladaptive sympathetic bias

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Summary Sudden infant death syndrome is the leading cause of death in infancy, but its pathophysiological mechanism has been elusive. Sudden death in adults is a common phenomenon, but the etiology in many cases remains unknown at autopsy. We hypothesize that maladaptive sympathetic bias is the explanatory mechanism that links many cases of sudden demise among adults and infants as companion syndromes. Normally, sympathetic response occurs as an adaptation to physiologic demands of the body through various autonomic reflex arcs such as chemoreceptors. Sympathetic response can become chronic and maladaptive when the normal sympathetic response fails to correct the precipitating physiologic trigger, leading to chronic activation of autonomic reflex arcs. In conditions such as infant sleep apnea or adult heart failure, a pernicious cycle of sympathetic bias may result. Chronic sympathetic bias increases susceptibility to sudden fatal arrhythmias, QT-related and otherwise, in the setting of an exaggerated adrenergic challenge. Examples of such adrenergic stressors include trauma, hypoxia, hypercapnia, acidosis, sleep arousal, illness, medical procedures, and physical activity, all of which have associations with sudden death. Our hypothesis may not only help explain the survival benefits of drugs such as beta-blockers and devices such as synchronization therapy, but also portend new application of similar therapies for many conditions of sympathetic bias.

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Introduction

Sudden death among infants is a startling event from a scientific and social perspective due to the untimely nature of the demise. Sudden death among adults, especially the elderly, is a far more common event, though it is met with greater acceptance. We hypothesize that maladaptive sympathetic bias is a distinct syndrome that mechanistically links many cases of these seem-

ingly unrelated types of demise. Normally, the sympathetic drive responds adaptively to acute physiologic demands of the body. Maladaptive, chronic sympathetic stimulation can occur when the normal sympathetic response fails to correct the precipitating physiologic trigger. In the context of chronic sympathetic bias, an acute sympathetic response to behavioral, metabolic, or physiologic stressors such as fear, injury, hypoxia, hypercapnia, acidosis, sleep arousal, and physical activity may increase the likelihood of fatal arrhythmias, QT-related and otherwise. We propose that sudden death among infants and

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adults are companion syndromes manifesting this phenomenon.

Sudden death among infants

SIDS is the most common cause of death in infancy, but its pathophysiological mechanism is still obscure [1]. The lack of a consensus hypothesis on the cause of SIDS reflects the sheer volume of implicated risk factors of varying prevalence. Thus, SIDS is perhaps better viewed as a heterogeneous disease with variable upstream causes. In this context, we hypothesize that a maladaptive shift to sympathetic bias may be the common pathway of demise among SIDS victims.

Various data supports the view that SIDS victims display sympathetic bias. Decreased heart rate variability (HRV) and tachycardia, indicators of autonomic shift to sympathetic bias seen in respiratory distress syndrome and prenatal hypoxia [2], have been observed in patients with central hypoventilation and in infants who have later succumbed to SIDS [3]. Infants who experienced near-miss SIDS demonstrate tachycardia and decreased HRV [4]. Food regurgitation and diaphoresis associated with SIDS may reflect excess sympathetic activity [5–7].

The inciting cause of sympathetic bias may be manifold. Hyperthermia, infection, inflammation, and fever, all of which have known associations with SIDS, are potential causes of sympathetic bias [5,6,8,9]. In certain situations, the adaptive chemoreceptor-mediated sympathetic response of arousal and increased respiration may fail to correct the underlying hypoxia, hypercapnia, and acidosis, leading to a maladaptive sympathetic bias. The association of prone sleeping position, obstructive sleep apnea, and other respiratory conditions with SIDS may exemplify this phenomenon [5,10,11]. In infants with OSA, as with their adult counterparts, the sympathetic bias can exacerbate sleep disturbance and can trigger insomnia, leading to a pernicious cycle [12,13].

Sympathetic bias has an ominous association with QT interval prolongation, a risk factor for sudden cardiac death in adults [14]. Sympathetic bias may predispose infants to similar risks. Recent articles have noted a significant association between prolonged QT interval and SIDS victims or those who experienced apparent life-threatening event [15,16]. Various theories for this association have been proposed, including development-related abnormalities in cardiac sympathetic innervation and genetic predisposition [17,18]. We propose a broader view that

maladaptive sympathetic response is the key determinant of SIDS.

Sudden death among adults

Sudden death is a common phenomenon among adults and a notable percentage of cases are unexplained at autopsy [19]. We propose that sudden death precipitated by maladaptive sympathetic bias, similar to those seen in infants, may account for a not insignificant proportion of these cases.

Emerging evidence suggests that aging is associated with a shift to sympathetic bias. HRV and baroreflex sensitivity decreases with aging [20]. While likely multi-factorial in mechanism, conditions such as constipation, insomnia, erectile dysfunction, and hypertension are endemic among the aged and may represent a broad physiologic bias towards sympathetic function. The mechanism of the broad shift to sympathetic bias with aging is likely manifold. The sympathetic bias may also be a maladaptive component of the aging process attributable to an inexorable functional decline in autonomic regulatory systems. As in SIDS, some cases may reflect maladaptive chemoreceptor response to hypoxia, hypercapnia, and acidosis, all of which are common conditions seen in the elderly due to myriad of diseases. Common diseases of the aged such as obstructive sleep apnea (OSA), congestive heart failure (CHF), renal failure, chronic obstructive lung disease (COPD) and chronic pain may set up pernicious cycles of sympathetic bias that fail to redress the underlying abnormality. Heightened sympathetic function is seen in many other conditions including pheochromocytoma, autoimmune conditions, and collagen vascular diseases [21]. Consistent with our hypothesis, QT interval lengthens with aging and also with other chronic conditions that promote sympathetic bias such CHF, OSA, and COPD, putting the patient at increased risk of fatal arrhythmias [22–25].

Acute and chronic sympathetic bias

While chronic sympathetic bias may be the basis of increased susceptibility to sudden death in infants and adults, superimposed acute sympathetic activity may be the cataclysmic event in many cases. Exogenous stressors, which are generally accepted to play an acute role in SIDS [26], could precipitate such a sympathetic response. In adults, QT interval prolongation is associated with an elevated risk of sudden death under stressful conditions, situations

that are typified by a sympathetic surge [27]. Experiments have shown that stress can cause sudden death in an animal model with QT prolongation [28]. Arousal from sleep, a common cause of sudden cardiac death, is characterized by sympathetic surge [29]. Any acute or sub-acute cause of hypoxia, hypercapnia, or acidosis could also precipitate an acute maladaptive adrenergic surge leading to QT-related sudden death. Positional hypoventilation, postural exacerbation of underlying respiratory compromise, and sleep apnea are among the potential inducers of sympathetic surge. The inability of the sympathetic response to correct the underlying respiratory and metabolic challenge may set up maladaptive self-propelling sympathetic cycle. Sudden surge in sympathetic discharge may also occur with physical trauma, psychological trauma, hemorrhage, shock, acute pain, physical exertion, and invasive medical procedures.

Testing the hypothesis

The development of our hypothesis was enabled by synthesizing emerging circumstantial evidence, and further studies are needed to establish maladaptive sympathetic response as the mechanistic thread that links sudden deaths among infants and adults. Such studies could include prospective longitudinal investigations, modeled after earlier SIDS studies, in which comprehensive physiologic data are collected on eventual victims of sudden death and compared to controls [5]. Continuous or serial measurements of circulating and excreted catecholamine levels, heart rate variability, QT interval, and other non-invasive physiologic methods would be useful [30]. Such measurements could be mapped to parameters such as time of day, sleep patterns, respiratory status, body position, metabolic status, level of activity, presence of physical or psychological stressors, and disease status. While these studies may reveal temporal data, microneurography and MIBG imaging studies may elucidate the spatial distribution of autonomic function relevant to our hypothesis. Similar assessment of vagal activity may add to the understanding of the role of the counterbalancing effect of the parasympathetic system. Controlled prospective studies in these population groups could also be performed to measure the impact of antiadrenergic pharmacotherapy, such as beta-blockers, or device-based synchronization therapy on preventing sudden death in adults and infants who are predisposed to sympathetic bias.

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