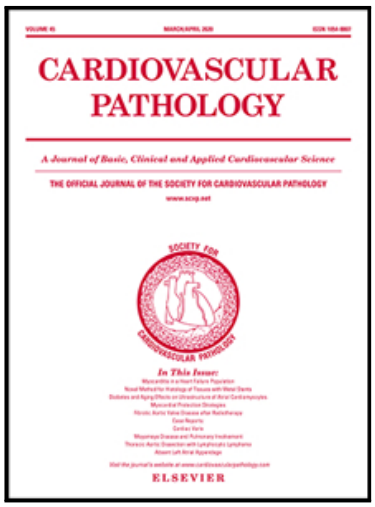

Pathology of Unexpected Sudden Cardiac Death: Obstructive Sleep Apnea is Part of the Challenge

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Editorial

Pathology of Unexpected Sudden Cardiac Death: Obstructive Sleep Apnea is Part of the Challenge

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Abstract

Unexpected sudden cardiac death (SCD), sudden infant death syndrome (SIDS) and sudden intrauterine unexplained death (SIUD) are major unsolved, devastating forms of death that occur frequently. Obstructive sleep apnea (OSA) has been associated with increased cardiovascular and cerebrovascular morbidity and mortality, including sudden cardiac death (SCD). This editorial will review the pathology of SCD, including sudden infant death syndrome (SIDS) and sudden intrauterine unexplained death (SIUD); OSA with its cardiovascular consequences; the possible link between SCD and OSA, discussing the potential mechanisms underlying these two frequent, but yet overlooked pathologies. Finally, the possible preventive benefits of treating OSA and identifying patients at common risk for OSA and SCD and SIDS-SIUD to prevent unexpected deaths will be discussed. Post-mortem examination is of great importance in every case of SCD *sine materia*, with examination of the brainstem and cardiac conduction system on serial sections, when general autopsy fails, but it should be stressed that also the investigations of patients suffering from OSA should focus on the possibility of pathological findings in common with cases of SCD.

Key words: unexpected sudden cardiac death; obstructive sleep apnea, sudden infant death syndrome; sudden intrauterine unexplained death; post-mortem examination.

1. Introduction

Unexpected sudden cardiac death (SCD), sudden infant death syndrome (SIDS) and sudden intrauterine unexplained death (SIUD) are major unsolved, devastating forms of death that occur frequently. SIDS and SIUD occur in about 1% of apparently normal pregnancies and healthy infants, and are the leading form of fetal-infant mortality in developed countries, not predicted by medical history, and unexplained after detailed death scene investigation and general autopsy [1–3].

Obstructive sleep apnea (OSA) is a frequent sleep and breathing disorder characterized by blockage of the airway, snoring, daytime sleepiness, fatigue, restlessness and gasping for air during sleep, and fatigue. OSA has been associated with increased cardiovascular and cerebrovascular morbidity and mortality, including SCD [4].

The common SCD-OSA' s etiology is largely unknown due to lack of specialized genetic, laboratory, and post-mortem studies, and to yet undetermined environmental co-factor. In this issue of *Cardiovascular Pathology*, in a Letter to the Editor, Mormile [5] raises the intriguing hypothesis that SCD and OSA are linked by inflammatory mechanisms, including elevated levels of interleukin-6 (IL-6) and other inflammatory mediators.

This editorial will review and discuss, first, the pathology of SCD, including SIDS and SIUD; second, OSA with its cardiovascular consequences; third, the possible link between SCD

and OSA, discussing the potential mechanisms underlying these two frequent, but yet overlooked pathologies. Finally, the possible preventive benefits of treating OSA and identifying patients at common risk for OSA, SCD and SIDS-SIUD to prevent unexpected deaths will be discussed.

2. Sudden cardiac death, including sudden arrhythmic death (SAD)

Sudden cardiac death (SCD) is the unexpected cardiac arrest with unsuccessful resuscitation attempts, without an obvious noncardiac cause that occurs, if witnessed within one hour of symptom onset, or, if unwitnessed, within 24 hours of last being observed in normal health [4,6].

In the USA, 1 every 7.4 (13.51%) deaths are from SCD. The incidence of SCD peaks in infancy and, in adults, it increases exponentially with age, surpassing the risk for infants by 35-39 years of age [4].

SCD can occur at any age and very frequently occurs before birth. SCD includes the sudden unexpected death of fetuses, infants, young athletes, adults and of course the elderly. There is a broad spectrum of SCD, due to mechanical lesions and those putatively linked to arrhythmia, i.e., sudden arrhythmic death syndrome (SADS) and non-SADS [7].

The incidence of SCD in young athletes aged 12-45 years, during competitive sports is 0.76 per 100,000 per year [4]. The abnormalities of the cardiac conduction system, could be the

morphological bases of arrhythmic event triggering reentry mechanisms, leading to ventricular tachycardia, fibrillation, and SCD [6].

Sudden infant death syndrome (SIDS), or crib death, is the sudden unexpected death of an infant less than one year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history [8]. SIDS is the most frequent death-causing syndrome in the first year of life, at a death rate of 0.66 per 1,000 births [2]. Decades of SIDS research have revealed only parts of its anatomo-pathological, genetic, electrophysiological, and clinical underlying features.

Sudden intrauterine unexplained death (SIUD), or unexplained stillbirth, is the late fetal death before the complete expulsion or removal of the fetus from the mother ≥25 weeks of gestation which is unexpected by history and is unexplained after review of the maternal clinical history and the performance of a general autopsy of the fetus, including examination of the placental disk, umbilical cord and membranes, and microbiological and genetic investigations [9]. Unexpected stillbirth has a 6-8 fold greater incidence than that of the SIDS that has not significantly declined in the last 20 years despite modern advances in maternal-infant care [2,3]. Although there has been valuable anatomo-pathological research to explain SIUD, in relation with SIDS [1,7], the overall body of literature is scarce and fragmentary.

SADS, including SIDS-SIUD, prolonged QT syndromes and channelopathies, typically have hearts with no evident gross or histopathological findings. Only in SADS cases of

unexpected sudden deaths, when the general autopsy fails to find the cause of death, a complete analysis of the cardiac conduction system and brainstem on serial sections is required to document minute lesions associated with cardiorespiratory and respiratory–reflexogenic mechanisms [1,6]. Post-mortem genetic testing will also contribute significant information in determining the substrate for SCD.

3. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing (SDB), consisting on reductions or stoppages in airflow despite ongoing respiratory efforts. Increased adipose tissue in the tongue and pharynx compromises upper-airway dimensions and makes the airway more prone to collapse during sleep [10]. In the USA, OSA affects approximately 10% of the adults and 5% of children. OSA prevalence is significantly more frequent in males and increases with age, affecting 43.2% of males and 27.8% of females aged 50-70 years [4]. Risk factors for OSA include male gender, obesity, increased body mass index (BMI), metabolic syndrome, hypothyroidism, genetic predisposition [10]. Genetic studies have identified variants in clock genes such as *CRY1* and *CRY2* [4]. OSA associated to alveolar hypoventilation and altered response to hypoxemia and/or hypercarbia has been described in children with congenital central hypoventilation syndrome (CCHS). Point mutations affecting

different nucleotides of the *PHOX2B* gene were observed in 32% children with Class III mandibular malocclusion and absent in controls [11].

OSA is associated with cerebrovascular diseases, i.e., cerebral infarction, transient ischemic attack (TIA), ischemic stroke, or hemorrhagic stroke, with a pooled prevalence of 62% in moderate OSA characterized with apnea/hypopnea index (AHI) >10 events/h, and 30% in severe OSA with AHI >30 [4].

There is a relationship between OSA, hypertension, especially nocturnal hypertension, and all major cardiovascular events, including acute myocardial infarction, atrial fibrillation, sudden cardiac death, and aortic dissection. OSA is present in at least 1/3 of patients with congestive heart failure [4,12–14].

In OSA patients, recurrent episodes of airway obstructions result in hypoxia and hypercapnia, which in turn increase sympathetic neural tone, resulting in vasoconstriction and marked blood pressure (BP) increase. Even mild OSA can increase nocturnal BP through different mechanisms including hypoxemia, and sympathetic activation, determining the increased cardiovascular risk [12]. As suggest by Sekizuka et al [15], sleep apnea affected nocturnal BP elevation even in patients without hypertension. The diurnal BP showed no difference in the severity of sleep apnea; however, the severe-sleep apnea group revealed significant nocturnal BP elevation.

4. Sudden cardiac death and obstructive sleep apnea

The multifactorial pathophysiology of SCD *sine materia* has multifaceted pathological substrates. In addition to the cardiac arrhythmogenic theory, controversially based on genetic [16] and electrophysiological [17], rather than on the morphological findings of the cardiac conduction system [1,6,18,19], the respiratory apnea theory should be equally be considered. Equally, emphasis should be lay on the autonomic nervous supply to the heart and respiratory system. Although the diagnosis of SIDS-SIUD are of exclusion, on the histopathological plane, developmental changes of the cardiac conduction system and of the brainstem abnormalities have been pointed out as possible substrates of SIDS-SIUD [1,6,9,18–25].

A normal autonomic nervous system receives prompt information on a progressive hypercapnia and hypoxia event, and triggers respiration or awakening. In infants with peripheral or central chemoreception defects, these protective reflexes do not take place, and prolonged apnea can develop which may be fatal and lead to sudden death [1]. Smoke exposure acts as a triggering phenomenon for sudden death in fetuses and infants with developmental abnormalities located the in brainstem centers regulating vital functions or in the cardiac conduction system [1,22].

There is a clear risk of SCD associated with OSA [26] and the current guidelines include OSA as a risk factor in the examination panels for SCD [16]. The levels of the inflammatory

markers C-Reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and Selectins have been reported to be higher in patients with OSA compared to control group [27]. These inflammatory markers might play a role in the SCD-OSA association. In particular, IL-6 is a circulating cytokine responsible for CRP production by the liver, secreted from various cells, including activated macrophages and lymphocytes in response to inflammation, cigarette smoke, adiposity, hypoxemia [27]. IL-6 is higher in patients with OSA, with a significant correlation between IL-6, AHI and BMI [27]. Increased serum and urine levels of IL-6 have been detected also in acute heart failure and acute coronary syndrome [28].

We agree with the suggestion of Mormile [5] that detection of IL-6 might be an efficient way of stratifying OSA patients at risk for fatal arrhythmia at an early stage. In addition to inflammatory biomarkers, developmental abnormalities are likely in common to both SCD and OSA, particularly in the brainstem centers regulating vital functions and in the cardiac conduction system.

From the analysis of the conducting tissue of over 200 cases of SIDS-SIUD, several pathological findings emerged, including accessory atrio-ventricular pathways, mostly Mahaim fibers, cartilaginous hypermetaplasia, abnormal resorptive degeneration, junctional islands, persistent fetal dispersion, hypoplasia of the cardiac conduction system or of the central fibrous body, splitting of the atrio-ventricular node or of the His bundle, and the Zahn

node. In addition to the cardiac conduction anomalies, with hypoplasia, agenesis, or neuronal immaturity of vital brainstem structures were detected [1,6,9,18–25].

A novel hypothesis is the link between SCD and to CO_2- related vasoconstriction superimposed on ischemic medullary autonomic nuclei. In patients experiencing cardiac arrest, the blood circulation through the heart, lungs, and brain has essentially stopped, in a similar manner to that of patients with sleep apnea, at a much more severe degree. The solitary tract nucleus is severely ischemic, yet its capacity for blood flow is preserved to a large extent by the vasodilation in the brain associated with dramatically increased carbon dioxide levels [29].

Of interest, SCD, SIDS-SIUD usually occurs at home, unexpectedly, unwitnessed, during sleep, which is the same time in which OSA occurs.

Additional research is warranted in regard to the mechanisms by which focal medullary autonomic ischemia may be related to SCD in OSA and how it may additionally be influenced by changes in arterial CO_2 levels.

5. Prevention of SCD

The occurrence and evolution of OSA to SCD result from varying degrees of interaction between the genetic background and environmental factors surrounding the human beings, starting from the earliest stages of intrauterine development. Understanding these factors and

the extent to which they could contribute to the pathogenesis of SCD and OSA will allow better risk-based prevention strategies.

The current guidelines of the European Society of Cardiology [16] include the treatment of OSA in order to prevent SCD.

Post-mortem examination is of great importance in every case of SCD *sine materia*, with examination of the brainstem and cardiac conduction system on serial sections, when general autopsy fails, but it should be stressed that also the investigations of patients suffering from OSA should focus on the possibility of pathological findings in common with cases of SCD. More in depth, specialized anatomo-pathological studies are needed to understand the common pathological bases of SCD, SIDS and SIUDS, and one determinant for the recommendations can be a history of OSA~~, in order to enhance their prevention~~.

We believe that effective prevention and treatment of OSA is a major measure to reduce the risk for SCD, SIUDS-SIUD. In every case of sudden unexpected death, the presence of OSA in the victims and their family members should be investigated and corroborated with genetic studies.

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