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Original Article

Anatomopathological changes of the cardiac conduction system in sudden cardiac death, particularly in infants: advances over the last 25 years☆,☆☆

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ABSTRACT

Sudden cardiac death (SCD) is defined as the unexpected death without an obvious noncardiac cause that occurs within 1 h of witnessed symptom onset (established SCD) or within 24 h of unwitnessed symptom onset (probable SCD). In the United States, its incidence is 69/100,000 per year. Dysfunctions of the cardiac conduction and autonomic nervous systems are known to contribute to SCD pathogenesis, even if most clinicians and cardiovascular pathologists lack experience with detailed examination of the cardiac conduction system and fail to recognize lesions that are crucial to explain the SCD itself. In this review, we sought to describe the advances over the last 25 years in the study of the anatomopathological changes of the conducting tissue, in SCD, in mature hearts and particularly in sudden infant death syndrome (SIDS) and sudden intrauterine unexpected death syndrome (SIUDS), through the articles published in our journal *Cardiovascular Pathology* (*CVP*). We carried out an extensive Medline search to retrieve and review all articles published in *CVP* in which the sudden unexpected death of one or more subjects believed healthy was reported, especially if associated with lesions of the conducting tissue in settings that revealed no other explained causes of death, particularly in infants and fetuses. The cardiac conduction findings of resorptive degeneration, His bundle dispersion, Mahaim fibers, cartilaginous metahyperplasia, persistent fetal dispersion, left-sided His bundle, septation of the bifurcation, atrioventricular node dispersion, sinus node hypoplasia, Zahn node, His bundle hypoplasia, atrioventricular node, and His bundle dualism were similarly detected in SIDS and SIUDS victims.

1. Introduction

Sudden cardiac death (SCD) can hit human individuals of any age, gender, nationality, and ethnicity. According to Horace [1], "*Pallida mors pulsat aequo pede alterno pauperum tabernas regumque turres*" (Pale death knocks with impartial footstep at the cottages of the poor and the palaces of kings).

For the whole of its 25 years, medical literature on SCD has filled the pages of *Cardiovascular Pathology* (*CVP*) [2–41]. This literature has been growing from newborn child to fully grown 25-year-old adult, as investigators have been increasingly eager to solve the centuries-old mystery of the *mors subitanea sine materia*, the sudden death without a substance, i.e., autopsy negative. In 25 years, over 100 articles on the topics of arrhythmias, the conduction system, and SCD have been published in *CVP* [42].

Over the years, increasing attention has been given to research on sudden death in fetuses, newborns, and infants, mostly addressed to the pathological study of the cardiac conduction system. Sudden death strikes savagely not only at infants but also at the parents of the young victims. Parents of victims of sudden infant death syndrome (SIDS), besides suffering the emotional consequences of their loss, are also surrounded by juridical suspicions worthy of further clarifications. Parents are immediately questioned to determine if the death of their child was natural or nonnatural [43]. Then, the corpse of their child is autopsied. Studies of this form of death may also focus on the electrophysiological structure and function of the conduction system of these little hearts, such as the research on long-QT syndrome (LQTS).

Abbreviations: AF, atrial fibrillation; ARVD, arrhythmogenic right ventricular dysplasia; AV, atrioventricular; *CVP*, *Cardiovascular Pathology*; HCMP, hypertrophic cardiomyopathy; LQTS, long-QT syndrome; PVT, polymorphic ventricular tachycardia; SCD, sudden cardiac death; SQTS, short-QT syndrome; SIDS, sudden infant death syndrome; SIUDS, sudden intrauterine unexpected death syndrome; VF, ventricular fibrillation.

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In SCD, the lethal event is not only sudden but also unexpected, tragic, dynamic, and unexplained, with little, if any, hope for survival. The inherent emotional consequences among families of the young victims are devastating. The social costs for the early loss of many potentially productive individuals and for programs of psychological support and/or adaptation therapies are particularly heavy.

In order to fulfill the general intent of the *CVP* 25th Anniversary Special Review series, we aim to provide a general overview of SCD. A second aim is to include in this review a perspective on SIDS and sudden intrauterine unexpected death syndrome (SIUDS), which is a topic often not included in reviews of SCD and one with particular interest for the authors. Therefore, we carried out an extensive Medline search to retrieve and review all articles published in *CVP* in which the sudden unexpected death of one or more subjects believed healthy was reported, especially if associated with lesions of the cardiac conduction system in the absence of any explained cause of death, particularly in infants and fetuses.

1.1. Overview of sudden death and SCD

Sudden death is a general category that includes both sudden cardiac and noncardiac deaths. Recently, Thiene et al. [44] defined sudden death as a natural unexpected fatal event occurring within 6 h of the beginning of symptoms in an apparently healthy subject or in one whose disease was not so severe that such an abrupt outcome could have been predicted.

The chances of dying from sudden death decline with age. The overall death rate is higher in blacks compared to whites and higher in males than in females, largely given that women before menopause are protected from coronary heart disease [20].

According to the American Heart Association [45], SCD is defined as unexpected death without an obvious noncardiac cause that occurs within 1 h of symptom onset (witnessed) or within 24 h of last being observed in normal health (unwitnessed). According to the definition of the working group of the National Heart, Lung, and Blood Institute and the Heart Rhythm Society [46], a case of *established SCD* is an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse, or if unwitnessed, occurring within 1 h after the onset of symptoms; a *probable SCD* is an unexpected death without obvious extracardiac cause that occurred within the previous 24 h. Virmani et al. [20] defined SCD as a natural, nonviolent, unexpected, and witnessed death within 6 h of the onset of symptoms from a stable medical condition, or within 24 h for unwitnessed deaths, after having ruled out any potentially lethal noncardiac cause.

According to the 2016 report from the American Heart Association [45], in the United States, the estimated risk-adjusted incidence of SCD, excluding a noncardiac cause, is 69/100,000 per year. Epidemiological data on SCD are mostly limited to the United States and Europe [47,48], with a general lack of data worldwide. Over the last 25 years, the modern major medical advances have produced a significant reduction in coronary heart disease mortality but have not significantly changed the SCD rates, which not only have not decreased but are even increasing [48], so that increased awareness and prevention of SCD have become essential.

Usually SCD occurs at home, unwitnessed, and unexpected. In the minority of subjects that benefit from resuscitation attempts performed in emergency facilities, the overall survival rate is only 7.9% [48].

Two thirds of sudden deaths are from natural causes. The most common form of sudden death is SCD. Extracardiac causes of sudden death are mostly thrombotic, embolic, and hemorrhagic in nature [7]. Among cardiac deaths, the rate of SCD is approximately 50%, and this rate decreases with age. The causes of SCD are certainly different in relation to different ages [20]. The search for these causes has always been of particular interest even if they are often uncertain. Fetuses and infants die suddenly mostly from SIUDS and SIDS; in children and adolescents, coronary anomalies, hypertrophic cardiomyopathy (HCMP), and myocarditis are frequent substrates for lethal arrhythmias; adults die suddenly mostly from coronary atherosclerosis and acquired forms of cardiomyopathy. In infancy, sudden deaths for congenital vascular malformations, although rare, are far more frequent than deaths from degenerative vascular disease whose frequency increases with advancing age [11].

According to the most recent report from the American Heart Association [45], atrial fibrillation (AF) accounts for 1.6% of global deaths in men and 1.7% in women. The prevalence, incidence, and mortality of AF have been increasing over the last years. In 5 years, hospitalizations for AF as a first-listed diagnosis have increased by 34%. In AF, SCD accounts for the majority of deaths for cardiac causes (22.25%), followed by progressive heart failure (15.1%) and stroke (7%), although noncardiac causes (35.8%) account for the majority of AF deaths. The prevalence of AF in ventricular fibrillation (VF) is 15.4% versus 2.6% in the community control subjects. Individuals with AF, without comorbidities, myocardial infarction, or antiarrhythmic or QT-prolonging drugs, had an overall adjusted threefold increased risk for VF regardless of age and gender. After accounting for baseline and time-varying confounders, AF is associated with double risk for SCD.

Polymorphic ventricular tachycardia (PVT) has been detected in 30%–43% of patients who developed SCD during ambulatory cardiac monitoring. In subjects with a normal QT interval, PVT is most frequently seen in acute ischemia and myocardial infarction [45].

At the end of the 1800s and early 1900s, renowned anatomists [49–51] filled proceedings of scientific societies with very accurate notes on the conduction system of the heart. Less fruitful was the pathological research mostly comparing cardiac alterations with electrocardiograph correlation. These studies documented clinical aspects, such as the LQTS [52–54].

SCD is explained especially as electrical arrhythmogenic instability, although there is some variation among authors. To date, the study of the patient at risk for sudden death in the post-myocardial-infarction setting is of particular importance to understanding the development of cardiac arrhythmias. In the acute, subacute, or chronic phases of myocardial infarction, the development of a subsequent infarction due to a reentrant tachycardia circuit is often regarded as an important arrhythmogenic factor.

SCD is mostly due to VF as a result of electrical instability of the working myocardium [39]. SCD is a phenomenon of cardiac electrical dysfunction and cardiac arrest through at least three pathways: (a) ischemia induced by a perturbation in a coronary artery with rapid development of VF; (b) arrhythmia occurring in an early stage of acute myocardial infarction associated with coronary thrombosis; and (c) primary ventricular arrhythmia not associated with new-onset ischemia, related to a cardiomyopathy or channelopathy [55]. For years, there has been abundant evidence for a link between alterations of the conduction system and the development of lethal ventricular arrhythmias. Impaired electrical impulse propagation through an abnormal atrioventricular (AV) junctional conducting tissue can predispose to bradyarrhytmias and tachyarrhythmias due to ectopic arrhythmic foci [56–61].

Clinical history and genetic studies do not offer certainty concerning the development of arrhythmias. Our recent studies [62,63] have searched for anatomopathologic and hemodynamic features both in congenital heart diseases and in various well-documented ischemic and nonischemic cardiomyopathies analyzed in explanted hearts in patients suffering from end-stage heart failure undergoing heart transplantation.

SCD has recently attracted researchers eager to document changes in the cardiac conduction system and autonomic nervous system with genetic research. Unfortunately, coordination of this research at the international level has been lacking even though, over the years, more and more researchers [57,59,60,64–72] have been attracted to this thorny problem. The prediction, detection, investigation, and prevention of SCD are enormous public health issues. Yet, over the years, too little