Hospital Autopsy for Prevention of Sudden Cardiac Death

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Abstract. In the past 20 years, cardiovascular mortality has decreased in high-income countries in response to the adoption of preventive measures to reduce the burden of coronary artery disease and heart failure. Despite these encouraging results, cardiovascular diseases are responsible for approximately 17 million deaths every year in the world, approximately 25% of which are sudden cardiac death. The risk of sudden cardiac death is higher in men than in women, and it increases with age due to the higher prevalence of coronary artery disease in older age. Accordingly, the sudden cardiac death rate is estimated to range from 1.40 per 100 000 person-years in women to 6.68 per 100 000 person-years in men. Sudden cardiac death in younger individuals has an estimated incidence of 0.46–3.7 events per 100 000 person-years, corresponding to a rough estimate of 1100–9000 deaths in Europe and 800–6200 deaths in the USA every year. Cardiac diseases associated with sudden cardiac death differ in young vs. older individuals. In the young there is a predominance of channelopathies and cardiomyopathies, myocarditis and substance abuse, while in older populations, chronic degenerative diseases predominate. In younger persons, the cause of sudden cardiac death may be elusive even after autopsy, because conditions such as inherited channelopathies or drug-induced arrhythmias that are devoid of structural abnormalities are epidemiologically relevant in this age group. Identification of the cause of an unexpected death provides the family with partial understanding and rationalization of the unexpected tragedy, which facilitates the coping process and allows an understanding of whether the risk of sudden death may extend to family members. Accordingly, author present their experience with autopsies of unexplained sudden death young victims in which a cardiac origin was suspected and the relevance of a standardized protocol for heart examination and histological sampling, as well as for toxicology and molecular investigation.

Keywords: Sudden cardiac death · Hospital autopsy · Prevention

1 Introduction

Sudden death is defined as non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy subject (unexplained). If death is not witnessed, the definition applies when the victim was in good health 24 h before the event [1]. Sudden cardiac death is a tragic complication of a number of cardiovascular

diseases. More precisely, the term "sudden cardiac death" is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life, or autopsy has identified a cardiac or vascular anomaly as the probable cause of the event, or no obvious extra-cardiac causes have been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death. The prevalence of sudden cardiac death is significant, with at least 3 million people worldwide dying suddenly each year. In the United States, sudden cardiac death occurs in up to 350,000 people each year, translating to 950 deaths per day, or 1 death every 1.5 min. The death can occur at all ages but is significantly more common in older age groups, and the incidence in young people aged less than 40 years is generally low. Although sudden unexplained death (SUD) in the young is statistically uncommon, affecting <5 per 100.000 persons per year, the sudden and unanticipated loss of an apparently healthy child or young adult remains a great tragedy with disastrous implications for the surviving family and the society. The public health burden of premature death for men and women is greater for sudden cardiac death than for all individual cancers and most other leading causes of death [2, 3]. The best estimate of the incidence of sudden cardiac death in the general population aged 20–75 years is 1 in every 1000 individuals, accounting for 18.5% of all deaths [4]. Estimates in studies of the incidence of sudden cardiac death in the young vary widely owing to differences in the age range of the study populations, sample size and study designs. Is reported that in the 1–40 age group, the incidence is up to 8.5 per 100,000 person years, including competitive athletes.

1.1 Causes of Sudden Cardiac Death

The causes of SCD can be broadly divided into structural and arrhythmogenic etiologies. Over the last two decades, our understanding of the cardiac causes of sudden unexplained death has increased importantly by the discovery of a genetic basis for a number of various cardiac diseases and the identification of the same genetic substrates in a significant portion of sudden cardiac death cases, including at least one-third of cases with structural cardiac changes at autopsy and up to one-third of cases where no cause of death is identified at post-mortem, so-called sudden arrhythmia death syndrome (SADS). The most common cause of sudden cardiac death is coronary artery disease in the elderly. In subjects over the age of 40 years, coronary artery disease and acute myocardial infarction account for over 90% of sudden cardiac death cases [5, 6]. In younger persons aged 1 to 40 years, sudden cardiac death is more likely to be caused by a variety of inherited heart diseases and cardiac arhythmia syndromes, and most are autosomal dominant disorder [7, 8]. **Of note, surviving family members with the same genetic substrate as their deceased relative may be at increased risk**. Structural causes of SCD in the young include inherited cardiomyopathies, such as hypertrophic cardiomyopathy (HCM), dilated and restrictive cardiomyopathies, arhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction. HCM is the most common inherited heart disease with a prevalence of 1 in every 200 people. HCM remains the most common structural cause of SCD in the young, including competitive athletes. Other structural causes of SCD in the young include myocarditis, aortic dissection, congenital heart diseases and coronary artery

disease. The main inherited arrhythmogenic causes of SCD in the young are arrhythmogenic disorders include familial long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), idiopathic ventricular fibrillation, early repolarization syndromes, and short QT syndrome. These disorders rarely cause any structural changes to the heart; often are associated with sudden cardiac death and a structurally normal heart. The underlying mechanism of these cardiac arrhythmia syndromes is dysfunction of the cardiac sodium, potassium and calcium ion-channel subunits and accessory proteins, which is not evident at the macroscopic or microscopic level. Therefore, arrhythmogenic causes of sudden cardiac death are difficult to identify at autopsy investigation and the cause of death is often unascertained. Unexplained sudden cardiac death is therefore a diagnosis of exclusion of all other possible causes of death, but is often presumed to have an arrhythmogenic basis.

1.2 Role of Post Mortem in the Investigation of Sudden Cardiac Death in the Young

Autopsy is a crucial step in defining the causes of sudden cardiac death, which are broadly categorized as having either a structural or arrhythmogenic basis [9, 10]. According to the 2015 ESC guidelines, identification of the cause of an unexpected death provides the family **with partial understanding and rationalization of the unexpected tragedy, which facilitates the coping process and allows an understanding of whether the risk of sudden death may extend to family members**. Accordingly, it appears reasonable that all unexplained sudden death victims undergo post-mortem expert examination to investigate whether a cardiac origin should be suspected. Overall, a properly conducted autopsy should provide answers to the following issues: (I) whether the death is attributable to a cardiac disease, (II) the nature of the cardiac disease (if present), (III) whether the mechanism of death was arrhythmic, (IV) whether there is evidence of a cardiac disease that may be inherited and thus requires screening and counselling of relatives and (V) the possibility of toxic or illicit drug use or other causes of unnatural deaths. Collectively, in all structural causes of SCD, often associated with severe atherosclerosis, chamber dilatation or left ventricular hypertrophy, the post mortem examination has a high probability of identifying the cause of death. In a three-year prospective study of sudden cardiac death in persons aged 1 to 35 years, a structural abnormality of the heart was found in 60% of cases [11]. However, the death remains unexplained in up to 40% of cases. Up to 12% of sudden cardiac death in the young have autopsy findings of uncertain significance, such as minor coronary artery disease, mild cardiac hypertrophy or minor myocardial fibrosis, which pose a challenge for the interpretation of the autopsy investigation [12, 13]. Such pathological findings may lead to the death being attributed to structural disease in some cases. Infact, clinical screening of the first-degree relatives of patients with inconclusive autopsy findings revealed an inherited arrhythmia syndrome in almost half of the families. A further challenge to the interpretation of the autopsy investigation is that sudden cardiac death due to structural causes can occur without characteristic pathology [14, 15]. In particular, hypertrophic cardiomyopathy caused by pathogenic variants in troponin T may have a high risk of sudden death with only mild hypertrophy

and fibrosis. Furthermore, non-cardiac conditions can cause unexplained sudden death that is indistinguishable from unexplained sudden cardiac death. For example, patients with epilepsy have a higher mortality rate than patients without epilepsy and the leading cause of epilepsy related death is sudden unexpected death in epilepsy, so called SUDEP. This is of particular concern to the surviving family who do not know why their relative died or the risk of sudden death in other family members. It is important to define the precise cause of death, as this is relevant to the risk of sudden cardiac death and timely implementation of potential life-saving interventions in the relatives of the deceased. Important aspects of the postmortem include the proper and detailed conduct of the postmortem examination it self, collection of appropriate samples for subsequent analysis (including DNA analysis), careful evaluation of the findings, and a precise and accurate final conclusion are important aspects of the role of the postmortem. A comprehensive and detailed postmortem process can not only define the exact cause of death in a young sudden cardiac death case, but the results also have farreaching effects in identifying at risk relatives of the decedent. This information can thereby provide a therapeutic window for disease and sudden death prevention in at risk relatives.

1.3 Molecular Autopsy

Genetic studies over the last 20 years have shown that many inherited cardiac arrhythmia syndromes are caused by defective cardiac ion-channel subunits that regulate the cardiac action potential. Long QT syndrome is characterised by QT prolongation, T wave abnormalities, torsades de points, and a predisposition to syncope and sudden cardiac death. Approximately 75% of long QT syndrome is caused by pathogenic variants in the potassium ion channel subunits KCNQ1 (LQT1, 35%) and KCNH2 (LQT2, 30%), and the sodium ion channel subunit SCN5A (LQT3, 10%). An additional 5% of patients have a copy number variant in the KCNQ1 and KCNH2 genes. Genetic testing of a further 10 genes implicated in long QT syndrome increases the diagnostic yield by 5%. Brugada syndrome is associated with conduction delays, potentially lethal arrhythmias and a family history of sudden cardiac death. In a substantial portion of patients, Brugada syndrome is sporadic, but in some families follows an autosomal dominant inheritance pattern. At least eight genes are implicated in Brugada syndrome, and although pathogenic variants in SCN5A account for over 75% of genetically proven cases, they account for 20–25% of patients. Therefore, genetic testing of SCN5A in Brugada syndrome is useful, but of low yield. Catecholaminergic polymorphic ventricular tachycardia is a rare, adrenergically stimulated ventricular arrhythmia syndrome associated with syncope and sudden cardiac death, typically occurring during physical exertion or emotional stress. A highly penetrant autosomal dominant form accounts for 65% of cases and is caused by pathogenic variants in the very large calcium release channel, cardiac ryanodine receptor, encoded by RYR2. A rare recessive form of catecholaminergic polymorphic ventricular tachycardia is caused by pathogenic variants in CASQ2, encoding cardiac calsequestrin; an accessory protein of the ryanodine receptor. This genetic testing process has been termed the "molecular autopsy", and involves DNA extraction from postmortem blood, followed by DNA analysis of selected candidate genes responsible for the main inherited

arrhythmogenic diseases [16, 17]. Guidelines for post-mortem evaluation of sudden cardiac death in the young recommend collecting blood as a source of DNA for the molecular autopsy. The major problem of genetic testing and the molecular autopsy is establishing genetic causality or pathogenicity. Determining the pathogenicity of the variants identified in the post mortem setting is complicated by the absence of a true "phenotype" in the deceased. Many factors need to be considered in determining pathogenicity including the type of mutation, the frequency of the variation in genetic population databases, the type of aminoacid change and its conservation, the predicted damaging effect using in silico tools, supportive functional data, and evidence of cosegregation of the variant within a family [18, 19]. Taking such factors in to account, the genetic variant is classified as pathogenic (disease-causing), benign, or variant of uncertain significance (VUS). The key consideration for the clinician seeing the surviving family of the decedent is that cardiac genetic results are "probabilistic".

2 A Post Mortem Protocol for Sudden Cardiac Death Prevention in Relatives: Lucca's Triennal Experience

According to specific guidelines for autopsy investigation of sudden unexpected death published by several scientific societies we developed a methodological approach in order to fulfil the basic requirements for an appropriate post-mortem assessment and to ensure standardization of the autopsy practice, including adequate ancillary testing and collection of suitable materials (i.e., blood and/or frozen sections of highly cellular tissues) for DNA extraction and genetic testing in the decedent if inheritable structural or non-structural cardiac disease are suspected.

2.1 Materials and Methods

A comprehensive postmortem study by an experienced team of pathologists was performed in all sudden cardiac cases in the young (0–40 years). A complete premorbid medical history was collected, including a history of syncopal episodes, exertional symptoms, intercurrent illnesses, recent pharmacological therapies, previous ECGs, and other relevant studies. The investigation was focused to detect any family history of cardiac disease, premature sudden death, or suspicious deaths (e.g. SIDS cases or drowning). Other relevant family history information included family members with epilepsy, identifying "fainters", and any other unusual symptoms or clinical presentations. Circumstances of sudden cardiac death were investigated in all cases when possible, including activity at the time of death, the level of physical activity, and the symptoms immediately preceding the death obtaining information from available ambulance and police reports, as well as talking to witnesses or those who found the deceased. Postmortem examination included a detailed macroscopic and histological evaluation of all organs with the purpose of identifying any non-cardiac causes of death, before focusing on specific cardiac pathologies. Heart was fixed in 10% buffered formalin and MNR was performed in all cases before macroscopic and histological examination. A standard histological examination of the heart includes mapped labelled blocks of myocardium from representative transverse slices of both ventricles. A 5–

10 mL blood sample was collected for subsequent toxicological analysis and DNA extraction and analysis. In addition, frozen sections of brain, liver, spleen, which are highly cellular and therefore rich in DNA, were collected and stored at a temperature of −20 °C. If a structural or non-structural genetic cardiac disease is rendered likely, blood or tissue samples suitable for future DNA extraction and genetic testing are procured and specialized analysis by an expert cardiac pathologist is requested. Cases in which this process results in a definite clinical diagnosis of structural genetic disease (e.g., HCM, ARVC, or DCM) were referred to a specialized Inheritable Cardiac Diseases Clinic (ICDC) for genetic testing using a candidate gene approach (i.e., phenotype-driven sequencing of a gene or a panel of genes previously associated with a certain genetic cardiac disease). In the cases in which no cause of death was found after thorough post-mortem analysis, genetic testing of the decedent's blood or tissue was performed by ICDC to identify a genetic cause for the sudden cardiac death. After establishing a clinical and/or genetic diagnosis of an inheritable cardiac disease as the underlying cause of sudden cardiac death, necessary actions to initiate the screening of the family members of the decedent were considered.

2.2 Results

The Azienda Toscana Nord Ovest includes a population of over one million two hundred thousand inhabitants with thirteen hospitals and twelve territorial areas. Since 2015, Department of Legal Medicine of Lucca performed 190 hospital autopsies in cases of sudden unexpected death. 20 cases occurred in young between 1–40 years (Table 1).

Table 1. Demographic characteristics of hospital autopsies performed on sudden unexpected deaths

Years	Hospital autopsies (n)	Sex (M/F)	Age (1–40 y.o.)
2015	34	24/10	1
2016	43	30/13	6
2017	76	54/22	7
2018 (Jan–May)	37	20/17	6
Tot.	190	128/62	20

In 75% of cases death was untestified and the deceased was found lifeless at bed, in the morning by relatives. In 25% of cases a sudden collapse occured in apparent well being. In three cases toxicological investigations revealed acute intoxication of drugs (neuropleptics) or cocaine and further analysis were excluded. In four cases coronary artery disease was indicated as the cause of death because of stenosis of one or more coronary arteries. Non cardiac pathologies (ab ingestis pneumonia, cerebral haemorrhage, post traumatic haemorrhagic shock) were diagnosed as relevant for death and excluded from molecular analysis as well as cases in which acute myocarditis and LAD artery myocardial bridging were observed. Dilatative cardiomypathy (1) and hypertrophic (1) cardiomyopathy were diagnosed at gross examination of the heart and

Table 2. Cases of sudden unexpected death in young between 1–40 year old.

Years	Sex	Age	Circumstances	Medical history	Toxicoloy	Cause of death after hospital autopsy	Molecular autopsy
2015	♂	38	Untestified	Negative	cocaine	Cocaine abuse in CAD	No
2016	♂	36	Untestified	Negative	Neuroleptics	Drug abuse	No
	♂	33	Sudden collapse	Past myocarditis	Negative	Acute myocarditis	No
	♀	35	Untestified	Negative	Negative	Dilatative cardiomyopathy	Ongoing on relatives
	♂	39	Untestified	Negative	Negative	Hypertrophic cardiomyopathy	Ongoing on relatives
	♀	38	Untestified	Mental retard	Negative	Ab ingestis pneumonia	No
	♂	32	Untestified	Negative	Negative	LAD artery myocardial bridging	No
2017	♂	34	Sudden collapse	Hypertension	Negative	Cerebral haemorrhage	No
	♂	39	Sudden collapse	Diabetes	Negative	Unexplained	Brugada Sdr (VUS)
							Ongoing on relatives
	♂	25	Untestified	Negative	Negative	Unexplained	Brugada Sdr (VUS)
							Ongoing on relatives
	♀	38	Sudden collapse	Recidivant syncopal episodes	Negative	Unexplained	Hypertrophic cardiomyopathy
							Ongoing on relatives
	♂	37	Untestified	Negative	Cocaine	Cocaine abuse	No
	♂	40	Untestified	Negative	Negative	CAD	No
	♂	40	Untestified	OSAS	Negative	Unexplained	Ongoing
2018	♂	40	Untestified	Negative	Negative	CAD	No
	♂	28	Untestified	Negative	Negative	Post traumatic haemorrhagic shock	No
	♂	39	Sudden collapse	Negative	Negative	CAD	No
	♂	40	Untestified	Negative	Negative	Unexplained	Ongoing
	♀	31	Untestified	Negative	Negative	Unexplained	Ongoing
	♀	32	Untestified	Negative	Negative	Unexplained	Ongoing

histopathological investigation; in these two cases relatives allowed for genetic test to verify inheritable cardiac structural disease. In 35% of cases (7/20) at both autopsy and toxicology investigations were inconclusive and frozen blood samples were referred to a specialized Inheritable Cardiac Diseases Clinic (ICDC) for genetic testing. In one

case, mutation on LMNA gene "likely pathogenic" for dilated cardiomyopathy was detected and relatives (mother, father and 2 y.o. daughter) were immediately involved in genetic test to exclude inheritable cardiac structural disease. In two cases genetic variant for Brugada syndrome of uncertain significance was detected and relatives were invited to ICDC for explanation more explanation about risks. In last four cases, genetic test are still ongoing (Table 2).

3 Discussion

The term "sudden cardiac death" is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life, or autopsy has identified a cardiac or vascular anomaly as the probable cause of the event, or no obvious extra-cardiac causes have been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death. A recent three-year prospective study of sudden cardiac death across Australia and New Zealand recorded an annual incidence of 1.3 cases per 100,000 persons aged 1 to 35 years [7]. A review of death certificates in England and Wales placed the annual sudden cardiac death incidence at 1.8 per 100,000 persons aged 1 to 34 years [20]. A retrospective study of sudden cardiac death in persons 1 to 35 years of age in Denmark showed a higher incidence of 2.8 per 100,000 person-years, or 1.9 per 100,000 person-years when only autopsied cases were considered [8]. These unselected, nationwide, patient cohorts likely provide the most accurate estimates of the incidence of sudden cardiac death in the young. The true overall incidence of sudden cardiac death is likely to be an underestimate, since primary arrhythmogenic disorders can predispose people to more overt causes of death, such as drowning and motor vehicle accidents and a complete methodological post mortem study is still far to be performed in all cases in which cause of death remains unknown. Autopsy is a crucial step in defining the causes of sudden cardiac death, which are broadly categorized as having either a structural or arrhythmogenic basis [21]. Identification of the cause of an unexpected death provides the family **with partial understanding and rationalization of the unexpected tragedy, which facilitates the coping process and allows an understanding of whether the risk of sudden death may extend to family members**. According to the 2015 ESC guidelines all unexplained sudden death victims undergo post-mortem expert examination to investigate whether a cardiac origin should be suspected. Up to 12% of sudden cardiac death in the young have autopsy findings of uncertain significance, such as minor coronary artery disease, mild cardiac hypertrophy or minor myocardial fibrosis, which pose a challenge for the interpretation of the autopsy investigation. Guidelines for post-mortem evaluation of sudden cardiac death in the young recommend collecting blood as a source of DNA for the molecular autopsy to investigate inherited cardiac arrhythmia syndromes. The major problem of genetic testing and the molecular autopsy is establishing genetic causality or pathogenicity. Determining the pathogenicity of the variants identified in the post mortem setting is complicated by the absence of a true "phenotype" in the deceased. This is an important consideration in family management and highlights the need to consider the genetic findings of the molecular autopsy with caution, and in conjunction with clinical findings derived from screening family

relatives. These complexities highlight both the need for ongoing collaborative efforts to improve the ways we determine pathogenicity and the key role of the specialized multidisciplinary model of care for SCD and families with genetic heart diseases. This is especially important and relevant in the setting of SADS, where there is no phenotype in the decedent in up to 40% of cases. Finding a relevant clinical cardiac phenotype in family relatives of the decedent may significantly help in the determination of pathogenicity of genetic variants identified in young SADS cases. Given the possibility of an inherited cardiac disease as a cause of sudden cardiac death, appropriate evaluation and management of the surviving family is essential. The care of families in which sudden cardiac death has occurred aims to establish the cause of death in the victim and to clinically screen the surviving family members. In fact, a clinical diagnosis of an inherited cardiac disease can be made in up to half of families. Therefore, first-degree relatives and symptomatic relatives should have a comprehensive medical and family history, physical examination, resting and exercise ECGs and a standard transthoracic echocardiogram. Depending on the clinical situation, further second tier investigations may include CMR imaging, 24-h ECG monitoring and signal averaged ECG, and pharmacological challenge tests. Clinical evaluation alone in families with a sudden unexplained death may identify an underlying cause in up to 50% of selected and comprehensively evaluated families in tertiary centers [22, 23].

A common challenge with clinical evaluation is that not every at-risk family member will be revealed since arrhythmia syndromes display incomplete penetrance and variable expressivity. For example, incomplete penetrance is common in long QT syndrome with up to 40% of gene carriers having a normal QT interval. Therefore, asymptomatic relatives are generally screened up to age 40 years, as many genetic heart diseases most commonly manifest clinical disease in the second decade of life. Furthermore, given the challenges, genetic counselling as part of a multidisciplinary clinic is an important part of family management. Identification of a clearly pathogenic (disease causing) variant in a previously defined unexplained sudden cardiac death has high diagnostic value with at least two major clinical implications. First, the genetic confirmation of a cause of death has a major influence in families in coming to terms as to why their child or spouse died suddenly and brings some level of closure in this respect. Second, the pathogenic variant provides the family with a diagnostic test for screening other at-risk family members, in conjunction with clinical screening approaches. Offering cascade genetic testing to asymptomatic relatives should always be performed in conjunction with clinical evaluation, and only alongside comprehensive pre- and post-test genetic counseling. Defining the precise cause of death allows accurate identification of at-risk relatives and prudent initiation of therapeutic strategies, such as lifestyle modification, beta-blocker therapy and implantation of a cardioverter-defibrillator. Family management in the setting of sudden cardiac death of a young person is complex and ideally suited for a multidisciplinary specialized approach [24, 25].

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