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The Molecular Autopsy: Should the Evaluation Continue After the Funeral?

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Abstract

Sudden cardiac death (SCD) is one of the most common causes of death in developed countries, with most SCDs involving the elderly, and structural heart disease evident at autopsy. Each year, however, thousands of sudden deaths involving individuals younger than 35 years of age remain unexplained after a comprehensive medicolegal investigation that includes an autopsy. In fact, several epidemiologic studies have estimated that at least 3% and up to 53% of sudden deaths involving previously healthy children, adolescents, and young adults show no morphologic abnormalities identifiable at autopsy. Cardiac channelopathies associated with structurally normal hearts such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS) yield no evidence to be found at autopsy, leaving coroners, medical examiners, and forensic pathologists only to speculate that a lethal arrhythmia might lie at the heart of a sudden unexplained death (SUD). In cases of autopsy-negative SUD, continued investigation through either a cardiologic and genetic evaluation of first- or second-degree relatives or a molecular autopsy may elucidate the underlying mechanism contributing to the sudden death and allow for identification of living family members with the pathogenic substrate that renders them vulnerable, with an increased risk for cardiac events including syncope, cardiac arrest, and sudden death.

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Keywords

Molecular autopsy; Sudden cardiac death; Sudden unexplained death; Long QT syndrome; Catecholaminergic polymorphic ventricular tachycardia; Brugada syndrome

Sudden cardiac death (SCD) is one of the most common causes of death in developed countries. An estimated 300,000 to 400,000 individuals die suddenly each year in the United States, the vast majority of whom are the elderly [70]. In comparison, sudden death of infants, children, adolescents, and young adults is relatively uncommon, with an incidence of 1.3 to 8.5 per 100,000 patient-years [43]. However, tragically, thousands of individuals younger than 35 years die suddenly each year. Fortunately, the cause and manner of death can be explained in many cases after a comprehensive medicolegal investigation that includes an autopsy [17, 44]. However, the epidemiology of sudden death in the young often is less apparent than coronary artery disease-mediated SCD, which accounts for the majority of SCD in the elderly.

For nearly half of young victims 1 to 35 years of age, SCD occurs as the sentinel event without any apparent warning signs [43]. Therefore, the medicolegal investigation and autopsy are extremely important in determining the cause and manner of death. A postmortem examination may detect a noncardiac basis for the sudden death such as asthma, epilepsy, or pulmonary embolism. However, SCD is the most common cause of sudden death in the young, with structural cardiovascular abnormalities often identifiable at autopsy including hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), congenital coronary artery anomalies, and myocarditis [19, 44].

Not all SCD has an obvious attributable cause that can be determined at autopsy. Even after gross and histologic examination, a significant number of sudden deaths among the young with structurally normal hearts remain unexplained, and the SCD is labeled as autopsy-negative sudden unexplained death (SUD) [11, 17, 44, 46, 55].

Congenital long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and other potentially lethal and heritable channelopathies leave no trace of their presence at a comprehensive medicolegal autopsy. In fact, it is the absence of any evidence that leaves coroners, medical examiners, and forensic pathologists to speculate that a lethal arrhythmia might lie at the heart of an SUD [2, 3, 17, 34, 61, 72]. However, postmortem genetic testing or a cardiac channel “molecular autopsy” may potentially elucidate such a pathogenic mechanism and establish the probable cause and manner for the SUD [4, 5, 18, 52].

In this review, we summarize some recent population-based investigations of sudden death in the young to understand better the frequency of autopsy-negative SUD. We also review clinical and molecular observations for three of the potentially lethal arrhythmia syndromes (LQTS, CPVT, and BrS). Then, we illustrate the role played by cardiologic assessment of surviving family members and the role of a molecular autopsy in the evaluation of SUD among the young and show how such investigations can benefit those left behind.

Epidemiology of Sudden Cardiac Death in the Young: How common is SUD?

Sudden Infant Death Syndrome (age <1 year)

After a death scene and a medicolegal investigation including a complete autopsy and clinical history review [73], the sudden death of an infant younger than 1 year can be

attributed to infection, cardiovascular anomalies, child abuse or negligence, accidents, homicide, or metabolic or genetic disorders. However, 70% to 80% of SUDs involving infants have no identifiable cause after a postmortem investigation and are labeled as sudden infant death syndrome (SIDS) [7, 20]. These baffling tragedies remain the leading cause of postneonatal infant death and the third leading cause of infant mortality overall in the United States, with an estimated incidence of 0.57 per 1,000 live births [26, 39].

The pathophysiologic mechanisms responsible for SIDS remain poorly understood. A triple-risk model for SIDS was proposed suggesting a convergence of a perfect storm involving the triad of the vulnerable infant in the setting of exogenous stressors occurring in a critical developmental period [30]. Since then, several predisposing risk factors for SIDS including infection and inflammation, prone sleeping position, sleeping on a soft surface, overheating, exposure to cigarette smoke during and after pregnancy, poor prenatal care, young maternal age associated with low educational levels and social economical status, male sex, African American race, prematurity, and low birth weight have been identified [31, 32, 36, 37, 50].

Although many pathophysiologic theories have been proposed for SIDS including cardiorespiratory instability, maladaptive sympathetic bias, and coronary artery spasm, the decisive pathogenic mechanisms triggering an infant's sudden death remain unclear [35, 38, 39, 66, 76]. However, genetic factors comprising possible underlying vulnerabilities of SIDS victims have been identified in genes involved in neurotransmission, energy metabolism, autonomic response, response to infection, and duration of cardiac action potential [39, 71]. It currently is well established that an estimated 10% of SIDS stems from mutations in sudden death-predisposing, channelopathy-susceptibility genes that cause potentially lethal syndromes such as LQTS, CPVT, and BrS [4, 8, 60] (Fig. 1).

Sudden Death in the Young (ages 1–35 years)

Although the prevalence of autopsy-negative SUD in infancy (i.e., SIDS, also is described as sudden unexpected death during infancy [SUDI]) has been well defined, the exact prevalence of SUD, particularly among children, is unclear. It is estimated that at least 3% and perhaps up to 53% of sudden deaths involving previously healthy children, adolescents, and young adults have no morphologic abnormalities identifiable at autopsy (Fig. 2) [14, 19, 23, 27, 29, 44, 46, 55, 74, 75]. Large population-based explorations of SCD in the young are needed for better elucidation of the frequency and potential etiologies of such heartbreaking events.

In a 1996 study by Maron et al. [44], HCM was the most frequent cause of SCD involving young competitive athletes, with 48 (36%) of 134 SCDs attributed to HCM and an additional 10% exhibiting an unexplained increase in cardiac mass representing “possible HCM.” Only 3% of the cases were concluded to be autopsy-negative SUD (Fig. 2). The vast majority of athletes were males (90%), who had collapsed during or instantaneously after a daytime training session (90%).

In a 2001 autopsy review of 273 young Italian SCD cases (age, ≤ 35 years) from the Veneto region in north-eastern Italy, Corrado et al. [19] noted that ARVC over-shadowed HCM as the most frequent SCD-yielding cardiomyopathy among young Italians. In this study, 20% of the subjects had atherosclerotic coronary artery disease, 13% had ARVC, and 7% had HCM. Hearts were identified as macroscopically normal in 28% of the subjects, but histologic examination showed concealed pathologic sub-strates including myocarditis, regional arrhythmogenic right ventricular cardiomyopathy, and conduction system abnormalities in 79% of these apparently normal hearts. Only 6% of the 273 cases was concluded to represent autopsy-negative, structurally normal hearts (Fig. 2). Potentially due

to some sort of case ascertainment bias, it is noteworthy that these two studies had the lowest negative autopsy frequencies (3% and 6%, respectively) of all published studies.

In 2005, Puranik et al. [55] inspected the autopsy reports from 427 young victims of sudden unexpected death (ages, 5–35 years) over a 10-year period in eastern Sydney, Australia. This population-based cohort included 90% or more of all the sudden deaths that occurred in this urban population over the study period. Natural nontraumatic deaths occurring within 24 h after the onset of symptoms were included in this study cohort. Traumas, accidents, selected drownings, and drug intoxications were excluded. A cardiac origin (i.e., SCD) was determined for more than half of these unexpected sudden deaths. Compared with the previous vantage points that involved athletic field SCD and Italian SCD, autopsy-negative SUD (29%) was the leading cause of SCD (Fig. 2). Although a confirmation of primary fatal arrhythmia was not possible in all cases, slightly more than half of the cases did have documentation of a terminal arrhythmia or an account of collapse and sudden cardiac arrest. A clinical diagnosis of LQTS was made for 6 of the 70 decedents with structurally normal hearts. Cardiomyopathies explained no more than 16% of the SCD in this cohort, with only 6% of the deaths attributed to HCM.

Eckart et al. [27], in a review of autopsies performed over a 25-year period on American military recruits, showed a nontraumatic sudden death rate of 13 per 100,000 recruit-years among a monitored 6.3 million men and women ages 18 to 35 years. Of the 126 sudden deaths, 108 (86%) were related to exercise. Whereas approximately half of these sudden deaths had an identifiable cardiac abnormality at autopsy, 40% of the sudden deaths were autopsy-negative SUDs (Fig. 2) [27]. Several cases were identified as having a family history of sudden premature death, suggesting a heritable predisposition for a lethal arrhythmia [27].

Morentin et al. [46] analyzed all sudden nonviolent deaths of persons 1 to 35 years of age occurring in northern Spain from 1991 to 1998. Among the 107 cases of sudden death, 18% were considered SUDs (Fig. 2). Whereas 13 died after sudden collapse, 6 six were discovered dead in bed. Death occurred in relation to physical exertion (including swimming) or extreme emotion in one fifth of these SUDs. Interestingly, antecedent symptoms consistent with cardiac arrhythmia manifestations were evident in five SUD cases.

In more than 50% of 453 UK patients (ages 15–81 years), the victim of sudden death had a macro- and microscopically normal heart, with an equal distribution between the patients 35 years of age (53.5%, Fig. 2) or younger and those older than 35 years (46.5%) [29]. In a Swedish study among 15- to 35-year-olds with unexplained death, 21% had a normal heart (Fig. 2) [75]. An American study involving an autopsy series of 14- to 40-year-olds found that 16% had structurally normal hearts (Fig. 2) [14]. Most recently, in 2011, Winkel et al. [74] performed a nationwide study of SCD in young Danish individuals ages 1 to 35 years and determined that 29% of the SUDs were autopsy negative (Fig. 2).

The discordance in “structurally normal heart” rates observed in these epidemiology studies most likely can be attributed to the considerable variation and lack of standardization in the process whereby pathologists responsible for determining the precise cause of sudden death approach this increasingly complex task. Interpreting the epidemiologic data on sudden death is difficult [9]. For example, Di Gioia et al. [23] studied 100 consecutive SCD patients (ages 2–40 years) from the Lazio region in central Italy. In 20 cases, the gross and histologic examination ruled out the presence of significant morphologic abnormalities when more restrictive diagnostic criteria for ARVC and mitral valve prolapse were used (Fig. 2). However, if the definition of “structurally normal heart” had been restricted to cases without

even minimal, gross, or microscopic alterations, including nonspecific mild fatty infiltration of the right ventricle and mild myxomatous changes to the mitral valve, the prevalence of SUD would have been 8%. In 2008, the Association for European Cardiovascular Pathology developed guidelines representing the minimum standard required in routine autopsy practice for the adequate assessment of sudden cardiac death, including protocols for heart examination, histologic sampling, toxicology, and molecular investigations [9].

Although cardiac abnormalities evident at autopsy explain the majority of sudden deaths in the young, together these population-based studies show that a significant number of sudden deaths remain unexplained after a comprehensive postmortem investigation including full autopsy. This further suggests that a considerable number of these sudden deaths may be associated with heritable cardiac channelopathies.

Cardiac Channelopathies Associated With “Structurally Normal Heart” Sudden Death

Potentially lethal and inheritable arrhythmia syndromes described as under the umbrella of “the cardiac channelopathies,” including congenital LQTS, CPVT, BrS, and related disorders, involve electrical disturbances with the ability to produce fatal arrhythmias in the setting of a structurally normal heart. These often inconspicuous electrical abnormalities have the aptitude to cause the heart of an unsuspecting individual to develop a potentially lethal arrhythmia, leading to the sudden and early demise of an otherwise healthy individual [61]. Through molecular advances in cardiovascular genetics, the underlying genetic basis responsible for many inherited cardiac arrhythmia syndromes has been discovered.

Long QT Syndrome

Congenital LQTS is characterized by delayed repolarization of the myocardium. The incidence of LQTS may exceed 1 in 2,500 persons. Individuals with LQTS may or may not manifest QT prolongation on a resting 12-lead surface electrocardiogram (ECG) [68]. Patients with LQTS are at an increased risk for syncope, seizures, and SCD, usually after triggers such as exertion, swimming, emotion, or auditory stimuli such as an alarm clock. This repolarization abnormality almost always is without consequence. However, rarely, when caught off guard by such triggers or during the postpartum period, the heart can spiral electrically out of control into a potentially life-threatening and sometimes lethal dysrhythmia [1, 47, 69]. Although most often the heart's rhythm spontaneously returns to normal after an episode of syncope, 5% of untreated and unsuspecting individuals with LQTS succumb to a fatal arrhythmia as their first event.

As a genetically heterogeneous disorder, LQTS most often is inherited in an autosomal dominant mode. To date, hundreds of mutations have been identified in 13 LQTS-susceptibility genes, with 2 of the first 3 canonical LQTS-susceptibility genes discovered in 1995. Approximately 75% of patients with a clinically robust diagnosis of LQTS host mutations in one of these three major LQTS genes—*KCNQ1* (LQT1, ~35%), *KCNH2* (LQT2, ~30%), and *SCN5A* (LQT3, ~10%)—that encode for critical ion channel alpha subunits responsible for the orchestration of the cardiac action potential [48, 65].

Catecholaminergic Polymorphic Ventricular Tachycardia

Another heritable arrhythmia syndrome, CPVT, which typically manifests with exercise-induced syncope or sudden death, is expressed mostly in young males and closely mimics LQTS [54, 64]. Associated with a completely normal resting ECG, CPVT is electrocardiographically suspected after either exercise or catecholamine stress testing that demonstrates significant ventricular ectopy. Perturbations pursuant to mutations in the

RYR2-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT, accounting for approximately 50% to 65% of the disorder and regarded as type 1 CPVT (CPVT1) [41, 53, 54]. A rare subtype of CPVT arises in an autosomal recessive fashion with mutations in calsequestrin encoded by *CASQ2* and is deemed to be type 2 CPVT (CPVT2) [28, 40]. The lethality of CPVT is exemplified by a positive family history of juvenile (<40 years) SCD that occurs in more than one third of CPVT individuals and in as many as 60% of families with *RyR2* mutations [54, 63, 64].

Brugada Syndrome

A heritable arrhythmia syndrome, BrS is characterized by an ECG pattern consisting of coved-type ST-segment elevation (≥ 2 mm) followed by a negative T-wave in the right precordial leads V_1 through V_3 (often referred to as the type 1 Brugada ECG pattern) and an increased risk for sudden death resulting from episodes of polymorphic ventricular tachyarrhythmia [13, 16]. Like LQTS and CPVT, the penetrance and expressivity of the disorder is highly variable, ranging from lifelong asymptomatic individuals to SCD during the first year of life. Brugada syndrome is classically considered a disorder involving young male adults, with arrhythmogenic manifestation first occurring at the average age of 40 years and sudden death often occurring during sleep [56, 57]. Although BrS is inherited as an autosomal dominant trait, more than half of BrS may be sporadic. Approximately 20% to 30% of BrS is caused by loss-of-function mutations in the *SCN5A*-encoded cardiac sodium channel, classified as Brugada syndrome type 1 (BrS1).

Given their lethal and unsuspecting nature, LQTS, CPVT, and BrS represent ideal arrhythmogenic assassins able to escape suspicion, detection, and apprehension by a standard medicolegal autopsy [11, 42]. Because of the potentially devastating impact that these inheritable genetic disorders can have on living family members, the proper and thorough evaluation of an SUD is paramount.

Evaluation of SUD in the Young

The Purpose: Why Bother to Evaluate After the Funeral?

Sudden cardiac death may be the first manifestation of the aforementioned inherited arrhythmia syndromes, with the autopsy and death scene investigation perhaps representing the first opportunity for a proper diagnosis of a potentially lethal congenital disorder [22]. These tragic unforeseen deaths of the young take an overwhelming psychological toll on living family members. An autopsy may indicate an underlying pathology as the reason for the sudden death (e.g., HCM, ARVC, pulmonary embolism), but a negative autopsy leaves the family without proper closure and with wonderment of what might have led to the sudden demise of their loved one and whether other living family members are “next in line.”

In cases of autopsy-negative SUD, continued investigation through either a cardiologic and genetic evaluation of first- or second-degree relatives or a molecular autopsy may elucidate the underlying mechanism contributing to the sudden death and allow for identification of living family members with the pathogenic substrate that leaves them at an increased risk for cardiac events including syncope, cardiac arrest, and SCD.

Whereas there is global consensus on the necessity to evaluate an SUD in the young, there is extreme variability and currently a lack of guidance and standardization in the approach to such evaluations. The evaluation of an SUD should be an interdisciplinary collaboration between pathologist/medical examiner, cardiologist, and colleagues equipped with expertise in genetic counseling [45]. Multidisciplinary centralized teams guiding postmortem cardiac

genetic analysis help to minimize the risk for misinterpretation of pathology findings, genetic testing results, and borderline cardiac clinical test results [58].

Although no clear consensus statement on the clinical evaluation of surviving family members exists to date, it seems reasonable to advise that first-degree relatives of the decedent should undergo a limited cardiovascular evaluation that includes an extensive personal and family historical clinical review, a physical examination, a 12-lead electrocardiogram, a treadmill stress test, and an echocardiogram. These tests might be viewed as the minimal SUD screen. Alternatively or even simultaneously, postmortem genetic testing (i.e., a molecular autopsy) involving the major genes associated with LQTS, CPVT, and BrS should be considered as part of the “standard operating procedure” in the evaluation of autopsy-negative SUD, especially for such deaths of individuals younger than 40 years [61]. A much needed Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies published recently provides initial consensus-based guidelines and recommendations for postmortem genetic testing in sudden unexpected death cases (SUDS/SIDS) [6].

A Cardiologic Assessment of Those Left Behind

To give perspective on the overall worth and the diagnostic yield from clinical assessment of first- and second-degree relatives, we highlight some recent cardiovascular evaluation series of families faced with an SUD. In 2003, Behr et al. [11] performed a detailed cardiovascular evaluation of 109 first-degree relatives of 32 SUD cases and showed that 22% of these families had evidence of inherited cardiac disease, with the majority having clinical sequela suggestive of LQTS. Similarly, in 2005, Tan et al. [59] found after clinically assessing first-degree relatives of young SUD victims that 28% of the families had an identifiable cardiac channelopathy, including CPVT and LQTS. In a 2008 follow-up study by Behr et al. [12], a diagnosis of inheritable heart disease was rendered for 53% of the first-degree relatives of SUD victims after a more comprehensive clinical evaluation, with 70% having a diagnosis of either LQTS (53%) or BrS (17%). Strikingly, 30% of the families evaluated reported a family history of additional unexplained premature sudden deaths of family members younger than 45 years, and nearly 20% of the decedents had a history of syncope.

In 2010, van der Werf et al. [67] identified a certain or probable diagnosis in 47 (33%) of 140 families of SUD victims (ages 1–50 years) after a cardiologic clinical assessment, with 96% of the families having a diagnosis of an inherited cardiac disease (LQTS 21%, CPVT 17%, BrS 15%, and ARVC 15%). The diagnostic yield among the families depended significantly on the age of the decedent and ranged from a high of 70% when the decedent was 1 to 10 years old to a low of 21% when the decedent was 41 to 49 years old. Similar to the observations by Behr et al. [12], many of these sudden death victims had antecedent warning signs before their demise, including syncope for 15% and a family history of young sudden death for 29% of them, yet neither the decedent nor any other family member had a prior clinical diagnosis of an inherited cardiac disease.

Incomplete penetrance and variable expressivity are hallmarks of the various cardiac channelopathies that consequently lead to “concealed” forms of the aforementioned disorders [51]. For example, LQTS has a penetrance of less than 40% among families, and traditional clinical diagnostic criteria had only 38% sensitivity in correctly identifying carriers of the familial genetic defect [51]. Furthermore, 17% of *RyR2* mutation-positive subjects from CPVT families displayed no phenotype, and 75% of genetically affected parents who transmitted the disorder were asymptomatic [54]. Therefore, clinical assessment of surviving members of an SUD victim's family may not be sufficient to detect LQTS, CPVT, or BrS in unsuspecting individuals. A molecular autopsy involving postmortem

cardiac channel genetic testing may provide the much needed utility for the forensic pathologist/medical examiner/coroner to provide the answer for many unexplained deaths in the young, subsequently benefiting those left behind.

Molecular Autopsy for SUD

Since preliminary case reports of molecular autopsies [5], investigators have sought to determine the spectrum and prevalence of pathogenic cardiac ion channel mutations in unique series of SUD cases. However, to date, only 9 molecular autopsy series involving the major LQTS and CPVT genes have been reported, totaling only 207 cases (Table 1) [18, 21, 24, 25, 33, 49, 58, 62, 63].

In 2004, Chugh et al. [18] identified 12 cases of SUD after a comprehensive postmortem analysis of a consecutive series comprising 270 adult (age, ≥ 20 years) cases of SCD occurring over a 13-year period. Postmortem genetic analysis of the LQTS-susceptibility genes showed the identical *KCNH2* mutation in 2 (17%) of 12 autopsy-negative SUD cases. Similarly, Di Paolo et al. [24] performed LQTS postmortem genetic testing in 10 cases of juvenile (ages 13–29 years) SUD and identified *KCNQ1* mutations in two individuals. In 2006, Creighton et al. [21] identified putative mutations in three of nine SUD cases. In 2006, Nishio et al. [49] identified channel mutations in 24% of their 17 SUD case cohort, and in 2010, Gladding et al. [33], using DNA isolated from Guthrie (newborn blood spot) cards, identified LQTS-associated mutations in 4 (22%) of 18 SUD patients 2 to 39 years of age.

In 2007, we completed one of the largest molecular autopsy series of SUD cases to date [62]. Comprehensive mutational analysis of all 60 translated exons in the LQTS-associated genes (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2*) together with targeted analysis of the CPVT1-associated, *RYR2*-encoded cardiac ryanodine receptor was performed for a series of 49 medical examiner-referred SUD cases. As specified, most of the deaths had occurred during sleep (33%) or with exertion (24%). More than one third of SUD cases had hosted a seemingly pathogenic cardiac channel mutation, with mutations in *RYR2* alone accounting for nearly 15% of the cases [63]. Sudden death was the sentinel event in all but four mutation-positive SUD cases in this series.

In 2011, Skinner et al. [58] published a prospective, population-based long QT molecular autopsy study of postmortem negative sudden death in 1- to 40-year-olds. Over a 26-month period (2006–2008), DNA was collected at the autopsy in 52 cases of sudden unexpected death, 33 of which remained negative after a comprehensive autopsy investigation and were subjected to postmortem LQTS genetic testing. Of the 33 cases, 5 (15%) were identified as having rare possibly LQTS-predisposing missense variants.

Doolan et al. [25] completed a molecular autopsy series of 59 Australian SUD cases (38 males and 21 females; age range, 1–35 years) and did not identify any putative disease-causing mutations after a mutational analysis of *KCNQ1* and a targeted (exons 10–28) analysis of *SCN5A* using genomic DNA isolated from formalin-fixed, paraffin-embedded tissue (FF-PET). In their cohort, 57% of the individuals died while in bed, asleep, or at rest, whereas 12% died during or after exercise, and 31% died during an unknown (unwitnessed) circumstance. Based on their observations, the authors concluded that the “hit rate” of the molecular autopsy for young unexplained deaths is low. However, given the limited mutational analysis and the use of a largely unreliable source (FF-PET) of high-quality DNA for comprehensive mutation analysis, it is not too surprising that the yield of mutation detection was low.

Unfortunately, due to the ease of storing and transporting FF-PET, the vast majority of forensic and general pathologists archive it as the only source available for DNA

procurement [10]. However, DNA from paraffin-embedded tissue is error prone and should be considered largely unreliable for molecular autopsy [15]. With rare exceptions, FF-PETs constitute suboptimal sources for postmortem genetic testing to detect SUD. In contrast, blood collected in ethylenediaminetetraacetic acid (EDTA; purple-top tube) or frozen heart, liver, or spleen provides the greatest source of intact DNA, permitting the successful performance of postmortem cardiac channel genetic testing [5]. Moreover, at least 10 ml of EDTA blood or 5 g of fresh tissue should be obtained at autopsy [10]. The tissue should be stored at -80°C , until DNA can be extracted. Alternatively, 50 to 100 μl of whole blood on filter paper can be used for a molecular autopsy. However, this tends to provide a very limited amount of DNA. It is of extreme importance that guidelines central to the procurement of DNA-friendly sources be added to the standard of care for the postmortem analysis of an SUD.

Given the relatively small cohort size of these previously published molecular autopsy series, the field still needs more extensive analyses to define better the expected yield of mutation detection and perhaps to offer possible phenotype/genotype correlations that may assist in guiding phenotype-directed mutation detection efforts for future cases of SUD. For example, our 49-case series had a significant cardiac channelopathy-sex effect, with 80% of the LQTS-associated mutations detected in females compared with 6 (86%) of the 7 CPVT1-associated mutations occurring in male decedents ($p < 0.001$) [62]. Consistent with the slightly later manifestation observed in LQTS versus CPVT clinically, the decedents hosting LQTS-associated mutations tended to be older (age, 18.0 ± 11.8 years) than those with CPVT1-associated mutations (age, 13.6 ± 11.2 years), but this difference failed to achieve statistical significance due to the small sample size [62]. Accordingly, one might a priori expect a higher yield of LQTS-associated mutation detection in an adolescent or young adult woman compared with a higher expected yield of CPVT-associated mutations among young boys. Knowing the effect of sex, age, death circumstance (i.e., sleep or exertion), and personal or family history of cardiac events on the overall yield of mutation detection may help in guiding both the clinical evaluation of surviving relatives and the molecular autopsy for cases of SUD, thereby creating a more cost-effective approach to the evaluation of SUD.

Cost Effectiveness of Primary Cardiologic Evaluation of Relatives Compared With Primary Molecular Autopsy for the Sudden Death Victim

Both population studies investigating clinical evaluations of surviving relatives and postmortem genetic analyses attest that approximately one third of SUDs after the first year of life stem from a lethal cardiac channelopathy. However, the cost effectiveness of these two approaches is currently unknown. The approach that may be the most cost effective most likely will depend on several factors. The type of sudden death, whether SIDS or SUDS, will have an effect on cost effectiveness because the expected yield from the diagnosis of an underlying cardiac channelopathy through either clinical evaluation or molecular autopsy will be much lower for families with a SIDS loss than for those with an SUD.

The extensiveness of the clinical evaluation will surely influence the cost effectiveness. Does the clinician perform an ECG, Holter monitor, treadmill stress test, echocardiogram, or consultation only, or does he or she also include an epinephrine QT stress test, a procainamide Brugada challenge, and cardiac magnetic resonance imaging (MRI) in the initial evaluation of each first- or second-degree relative?

The size of the family will matter in determining the cost effectiveness of the cardiologic assessment of all first- or second-degree relatives compared with a molecular autopsy of the

SUD victim followed by mutation confirmation and genotype-directed clinical evaluation of the family members.

The strategy for molecular interrogation during molecular autopsy will determine the cost effectiveness of this approach. Is a tiered strategy such as CPVT gene analysis with reflex testing followed by LQTS genetic testing the best approach or should an all-inclusive mutational analysis strategy involving all CPVT, LQTS, and BrS genes be used when a molecular autopsy is performed?

The Role Played by Clinical Assessment of Surviving Relatives and Molecular Autopsy in the Evaluation of SUD: The New Standard of Care?

To be sure, an accurate diagnosis derived from combined clinical assessment of surviving relatives and a molecular autopsy of the decedent enables informed genetic counseling for families and guides the appropriate commencement of preemptive strategies targeted toward the prevention of another tragedy among those left behind [11]. Considering that autopsy-negative SUD accounts for a significant number of sudden deaths in the young and that inherited cardiac channelopathies may underlie many of these deaths, the clinical cardiologic assessment of surviving family members combined with a cardiac channel molecular autopsy should be viewed as the standard of care for the postmortem evaluation of SUD. Currently, the issue can no longer be whether relatives should be evaluated after an autopsy-negative SUD or whether a molecular autopsy should be performed on an autopsy-negative SUD victim. Instead, the issue must shift to focus on three key questions: What relatives should be evaluated? What cardiac tests should be performed on each of these relatives? And what kind of cardiac channel molecular autopsy should be performed?

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Sudden Infant Death Syndrome (SIDS)

Fig. 1.

The prevalence of cardiac channelopathy in sudden infant death syndrome (SIDS). The pie chart shows that approximately 10% of SIDS cases result from cardiac channelopathy sudden death-related disorders including long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT)

Prevalence of Autopsy Negative SUD in the Young

Fig. 2.

The prevalence of sudden unexplained death (SUD) in a retrospective autopsy series of individuals with autopsy-negative “structurally normal hearts.” It is estimated that at least 3% and perhaps as many as 53% of sudden deaths involve previously healthy children, adolescents, and young adults with no identifiable morphologic abnormalities found at autopsy (“structurally normal heart”), and the SCD is labeled as autopsy-negative SUD. The bar graph shows the percentage of autopsy-negative “structurally normal hearts” identified during 10 retrospective analyses of large population-based autopsy cohorts [13, 18, 22, 26, 28, 43, 45, 54, 73, 74]

Table 1

Summary of a molecular autopsy series comprising autopsy-negative sudden unexplained deaths (SUDs)

Reference	Year published	No. of cases	Age range (years)	Males/females	Gene analyzed	No. of mutations (% yield)	DNA source	Mutation analysis technique
Creighton et al. [21]	2006	9	1–43	5 M/4 F	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> , <i>RYR2</i> (target)	1 <i>KCNQ1</i> , 2 <i>RYR2</i> (33)	Frozen tissue	Direct DNA sequencing
Di Paolo et al. [24]	2004	10	13–29	5 M/5 F	LQTS genes	2 <i>KCNQ1</i> (20)	FF-PET	SSCP
Chugh et al. [18]	2004	12	NA	NA	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i>	2 <i>KCNH2</i> (17)	FF-PET	SSCP/direct DNA sequencing
Nishio et al. [49]	2006	17	12–42	13 M/4 F	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>RYR2</i> (target)	1 <i>KCNQ1</i> , 3 <i>RYR2</i> (24)	Autopsy blood	High-resolution Melt
Gladding et al. [33]	2010	18	2–39	11 M/7 F	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i>	2 <i>KCNQ1</i> , 2 <i>KCNH2</i> (22)	Guthrie (blood spot) card	DHPLC
Skinner et al. [58]	2011	33	1–40	24 M/9 F	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i>	1 <i>KCNQ1</i> , 1 <i>KCNH2</i> , 1 <i>SCN5A</i> , 2 <i>KCNE1</i> (15)	Frozen tissue or autopsy blood	DHPLC
Tester et al. [62, 63]	2004, 2007	49	1–43	31 M/18 F	<i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> , <i>RYR2</i> (target)	5 <i>KCNQ1</i> , 3 <i>KCNH2</i> , 2 <i>SCN5A</i> , 7 <i>RYR2</i> (35)	Frozen tissue or autopsy blood	DHPLC
Doolan et al. [25]	2004	59	1–35	38 M/21 F	<i>KCNQ1</i> , <i>SCN5A</i> (target)	0 (0)	FF-PET	DHPLC

F Female; M male; LQTS long QT syndrome; FF-PET formalin-fixed, paraffin-embedded tissue; SSCP single-stranded confirmation polymorphism; NA not available; DHPLC denaturing high-performance liquid chromatography