Sudden Cardiac Death With Autopsy Findings of Uncertain Significance
Potential for Erroneous Interpretation

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Background—The sudden death of young individuals is commonly attributed to inherited cardiac disorders, and familial evaluation is advocated. The identification of pathognomonic histopathologic findings, or the absence of cardiac pathology (sudden arrhythmic death syndrome [SADS]) at postmortem, directs familial evaluation targeting structural disorders or primary arrhythmogenic syndromes, respectively. In a proportion of autopsies, structural abnormalities of uncertain significance are reported. We explored the hypothesis that such sudden cardiac deaths represent SADS.

Methods and Results—Families (n=340) of index cases of sudden cardiac deaths who underwent postmortem evaluation were evaluated in specialist cardiogenetics clinics. Families in whom the deceased exhibited structural abnormalities of uncertain significance (n=41), such as ventricular hypertrophy, myocardial fibrosis, and minor coronary artery disease, were included in the study. Results were compared with 163 families with normal postmortem (SADS). Relatives underwent comprehensive cardiac evaluation. Twenty-one families (51%) with autopsy findings of uncertain significance received a diagnosis based on the identification of an inherited cardiac condition phenotype in ≥1 relatives: 14 Brugada syndrome; 4 long-QT syndrome; 1 catecholaminergic polymorphic ventricular tachycardia; and 2 cardiomyopathy. A similar proportion of families (47.2%) received a diagnosis in the SADS cohort (P=0.727). An arrhythmogenic syndrome was the predominant diagnosis in both cohorts (46% versus 45%; P=0.863).

Conclusions—Familial evaluation after sudden cardiac deaths with autopsy findings of uncertain significance identified a similar proportion of primary arrhythmogenic syndromes to a contemporary series of SADS. Our study highlights the need for accurate interpretation of autopsy findings to avoid erroneous diagnoses, with potentially devastating implications. (Circ Arrhythm Electrophysiol. 2013;6:588-596.)

Key Words: cardiac arrhythmia ▪ cardiomyopathies ▪ death, sudden cardiac ▪ pathology ▪ ion channel

The majority of sudden cardiac deaths (SCDs) are attributable to atherosclerotic coronary artery disease and are manifest in the older population, whereas cardiomyopathies predominate in the young (<35 years).1 In a proportion of SCDs, a cardiac abnormality cannot be identified despite detailed histopathologic examination and toxicology screen; such cases are classified as sudden arrhythmic death syndrome (SADS).1 The recognition of SADS is imperative, because evaluation of blood relatives of the deceased identifies a hereditary arrhythmogenic syndrome in ≥50% of families, thereby providing a likely cause of death and identifying surviving relatives at risk from the same fate.3,4

Clinical Perspective on p 596

The interpretation of the results of postmortem evaluation of SCD cases is a complex task and uncertainty may exist about the causal relationship between the pathological findings and the sudden death.4 The significance of myxoid degeneration of the mitral valve with prolapse, stable atherosclerotic coronary plaque with limited (<50%) luminal stenosis and focal myocarditis, which are relatively prevalent in the general population, may be erroneously overestimated. Not infrequently, postmortem diagnoses of hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy are based solely on the presence of left ventricular hypertrophy (LVH) and fatty infiltration of the right ventricular wall, respectively, in the absence of pathognomonic histological changes. Left ventricular hypertrophy, however, is a recognized feature of...
physiological adaptation to exercise, and fatty infiltration of the right ventricle is commonly present in obese individuals. The distinction between pathology and normal variants may, therefore, be challenging in the context of SCDs.

This study explored the hypothesis that a proportion of SCDs with autopsy findings of uncertain significance may represent part of the SADS spectrum and, in particular, inherited arrhythmogenic syndromes.

**Methods**

**Setting**

The SCDs of several young individuals prompted the United Kingdom government to commission the 8th chapter of the National Service Framework for heart disease, aimed at facilitating early identification of individuals at risk of SCD. St George’s Hospital and University Hospital Lewisham (London, UK) have implemented dedicated inherited cardiac diseases clinics, serving relatives of individuals who experienced SCD, from throughout the United Kingdom. Family members undergo comprehensive cardiac evaluation aimed at identifying those at risk and preventing further tragedies.

**Study Cohort**

Between 2003 and 2009, 368 families of cases of premature SCDs (aged between 4 and 64 years) were evaluated in our inherited cardiac diseases clinics. Criteria for inclusion in the study comprised the following: (1) unexpected death of an apparently healthy individual; (2) death from natural causes; (3) last seen alive and well within 12 hours; (4) complete postmortem report; (5) the absence of an extracardiac cause of death; and (6) negative toxicology screen. Twenty-eight families were excluded from further analysis based on the absence of a complete postmortem report (n=4), positive toxicology (n=14), and the presence of documented past medical history before death (n=10).

Postmortem reports of the 340 SCD cases were scrutinized by 2 authors and divided into the following 3 groups: Group 1, autopsy findings highly suggestive of structural cardiac pathology accounting for the SCD (n=136); Group 2, no identifiable structural cardiac pathology, consistent with an SADS death (n=163); and Group 3, autopsy findings with structural abnormalities of uncertain causal effect (n=41). In cases of disagreement a third, senior author was consulted. The main study cohort consisted of 41 families, comprising 157 blood relatives, where the postmortem report was classified into group 3. The 163 families in group 2 (SADS cohort) were used as controls for comparison (Figure 1).

**Autopsy Evaluation**

All cases of SCDs included in the study had undergone a full coroners’ pathologist postmortem, and in 39% of cases a specialist cardiac pathologist had performed additional assessment. The diagnostic criteria for specific structural cardiac diseases and examples of autopsy findings of uncertain significance are outlined in Table 1.

**Familial Cardiological Evaluation**

All relatives underwent comprehensive cardiac evaluation according to a previously published protocol. Baseline ECG, echocardiography, holter monitoring, and exercise tolerance testing were performed routinely. Ajmaline provocation testing to identify the type-1 Brugada phenotype was performed in the event of normal ECG recordings and echocardiograms or in the presence of type-2 or type-3 Brugada ECG patterns. Ajmaline testing was performed by placing leads V1 and V2 in the conventional 4th intercostal space as well as the higher 3rd and 2nd intercostal spaces. Ajmaline testing was not performed in relatives ≤16 years of age (n=28) who did not have sinister cardiac symptoms or in patients (n=7) who refused consent.

Cardiac MRI (CMR) with gadolinium was performed in all relatives with ECG or echocardiographic features suggestive of cardiomyopathy. All relatives diagnosed with an arrhythmogenic syndrome where the deceased’s postmortem findings could be interpreted to...
Table 1. Pathological Criteria for Defining Cardiac Pathology and Certainty of Causal Effect in Sudden Cardiac Death Autopsies

<table>
<thead>
<tr>
<th>Post-mortem findings highly suggestive of causal effect</th>
<th>Post-mortem findings of uncertain significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>Left ventricular wall thickness</td>
<td>Myocyte hypertrophy</td>
</tr>
<tr>
<td>≥15 mm and/or heart weight</td>
<td>disarray + interstitial fibrosis</td>
</tr>
<tr>
<td>≥500 g</td>
<td>+/- abnormal intra-myocardial small vessels</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>Right ventricular thinning + fatty replacement + fibrosis</td>
<td>Fat + fibrosis of the wall of the right and/or left ventricle</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>Heavy heart with dilated ventricles and absence of coronary artery disease</td>
<td>Absence of inflammatory myocardial disease</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>Atherosclerosis with estimated luminal narrowing &gt;75%</td>
<td>Acute or chronic infarction in the left ventricle</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td></td>
</tr>
<tr>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>Normal or dilated ventricles</td>
<td>Inflammation with myocyte necrosis</td>
</tr>
<tr>
<td>Mitral valve papillary muscle or chordae tendineae rupture with marked ballooning of both leaflets above the atrioventricular junction</td>
<td>Floppy mitral valve with mild ballooning between chordae in one or both leaflets</td>
</tr>
<tr>
<td>Aortic stenosis with left ventricular hypertrophy</td>
<td>Isolated bicuspid aortic valve</td>
</tr>
</tbody>
</table>
represent a cardiomyopathy (LVH, myocardial fibrosis, ventricular dilatation, and fatty infiltration of the myocardium) also underwent CMR. Further investigations were based on clinical need.

Genetic Testing

Mutation analysis was offered to all relatives with phenotypic abnormalities suggestive of inherited arrhythmogenic syndromes or cardiomyopathies, after appropriate counseling. After consent, targeted mutation analysis was performed in 1 phenotypically affected member of each family, dependent on the suspected clinical condition: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in long-QT syndrome (LQTS); SCN5A in Brugada syndrome (BrS); selected exons (7–9, 13–16, 43–50, 82–84, and 87–105) of ryanodine receptor 2 gene (RYR2) in catecholaminergic polymorphic ventricular tachycardia (CPVT). Exons and flanking intronic regions were amplified from genomic DNA, and bidirectionally sequenced to identify coding variants. Variants were labeled as pathogenic if they were previously reported to be associated with disease susceptibility, in-frame or frameshift-causing insertions or deletions; affecting splice sites; missense mutations likely to be pathogenic, as identified by 2 in silico models (affect protein function by a tolerating splice sites; missense mutations likely to be pathogenic, as classified probably damaging by polymorphism phenotyping [PolyPhen]). If a pathogenic mutation was identified in a phenotypically affected member, other family members were offered cascade screening. Segregation analysis was used to confirm mutation pathogenicity.

Pathogenesis of SCD

An inherited condition was deemed the most likely cause of SCD if ≥1 blood relatives of the deceased exhibited phenotypic evidence of the disease. Standard criteria for the diagnosis of LQTS were used. The second consensus criteria for the diagnosis of BrS were used. Only the presence of the type-1 Brugada pattern (coved ST-segment elevation ≥2 mm followed by a negative T-wave) in >1 right precordial leads, in addition to standard evaluation, to exclude coexistent myocardial disease. All CMR scans were reported as normal. Of interest, in the 19 SCD cases where LVH or myocardial fibrosis was reported at postmortem, (isolated LVH; n=10; myocardial fibrosis alone: n=6, or in conjunction with LVH: n=3) evaluation of family relatives identified an arrhythmogenic syndrome phenotype underwent CMR scans, in addition to standard evaluation, to exclude coexistent myocardial disease.

Results

Characteristics of Cases of SCDs and Blood Relatives

The characteristics of the cases of SCDs are depicted in Table 2. Of the 157 blood relatives evaluated, 48% were male, with a mean age of 33.7±17.9 years (range, 9–70 years). Almost a quarter (23%) of the evaluated relatives reported cardiac symptoms with 10% having experienced ≥1 episode of syncope in the past.

Autopsy Findings and Results of Familial Evaluation

The postmortem findings of uncertain pathological significance in 41 cases are illustrated in Figure 2. After familial evaluation, 21 (51%) out of the 41 SCD cases were considered to have died from a definite or probable inherited cardiac disorder (Figure 1). Of the 157 relatives who underwent cardiac evaluation, 36 (23%) were diagnosed with a cardiac condition, which had not been previously identified.

Diagnosis of Arrhythmogenic Syndromes

A hereditary arrhythmogenic syndrome was diagnosed in 19 of 21 families in whom an underlying inherited cardiac condition was identified. Brugada syndrome (n=14) was the predominant diagnosis, followed by LQTS (n=4) and a single case of CPVT.

After familial evaluation, an arrhythmogenic syndrome was detected in 42% (11/26) of cases where the autopsy findings were suggestive of a possible cardiomyopathy (LVH, myocardial fibrosis, ventricular dilatation, myocardial fatty infiltration; Figure 2). In these cases, all relatives with an arrhythmogenic syndrome phenotype underwent CMR scans, in addition to standard evaluation, to exclude coexistent myocardial disease. All CMR scans were reported as normal. Of interest, in the 19 SCD cases where LVH or myocardial fibrosis was reported at postmortem, (isolated LVH; n=10; myocardial fibrosis alone: n=6, or in conjunction with LVH: n=3) evaluation of family relatives identified an arrhythmogenic syndrome in ≥50% of families (5 out of 10 cases with isolated LVH and 4 out of 9 cases with myocardial fibrosis). A cardiomyopathy was diagnosed in only 1 case in either group. In the remaining 8 (42%) cases, we were unable to identify any features of inherited cardiac pathology.

Brugada syndrome was also diagnosed in 1 of the 3 families whose proband exhibited isolated fatty infiltration of the right ventricle (Figure 3.4). One of the families where the pathologist reported marked right ventricular dilatation was subsequently diagnosed with CPVT, based on the identification of typical bidirectional ventricular tachycardia on exercise testing in 2 relatives.

Moreover, 2 out of the 6 families whose probands exhibited atheromatous disease at postmortem were diagnosed with BrS. Both probands were young, aged 28 and 34 years, respectively, and exhibited up to 50% coronary artery lesions in the left anterior descending and right coronary arteries (Figure 3.1). In 1 of the 2 families where an inflammatory infiltrate commonly attributed to myocarditis was present, BrS was diagnosed during Ajmaline provocation testing in the deceased’s father. In similar fashion, 1 of the 3 families whose proband exhibited pathological features of mitral valve prolapse was subsequently diagnosed with BrS based on the presence of type-1 Brugada ECG in 2 relatives.

Diagnosis of Cardiomyopathy

Only 2 families were diagnosed with an inherited cardiomyopathy; 1 dilated cardiomyopathy and 1 HCM. The first case was of a 17-year-old boy who died in his sleep. The postmortem revealed circumferential subendocardial hemorrhage with extensive myocardial fibrosis of the left ventricle. Evaluation of his relatives revealed a dilated, globally hypokinetic left ventricle in his mother and 1 of his sisters. The second case was of a 20-year-old male who died at rest. The postmortem revealed a heavy heart (>500 g) with LVH but no evidence of myocardial fibrosis or myocyte disarray. There was no history of hypertension or regular exercise. Familial evaluation revealed asymmetrical septal hypertrophy in the context of a nondilated left ventricular cavity in his father, raising suspicion of HCM. Unfortunately, the father declined further investigations.
Mutation Analysis

We had the opportunity to undertake mutation analysis in relatives with phenotypes suggestive of inherited cardiac conditions in 17 out of the potential 21 families. In 2 families (1:HCM, 1:BrS), individuals declined genetic testing after counseling. In 2 LQTS families, genetic testing was performed by their local geneticist. Because of the absence of coexisting atrioventricular block, mutation analysis was not performed in the dilated cardiomyopathy family. Of the 13 families with BrS who underwent genetic testing, 3 carried pathogenic SCN5A mutations (R376H, H558fs, A1680T). Pathogenic mutations were also identified in the 2 LQTS families tested (E1784K and G840R in SCN5A) and in the CPVT family (A4556T in RYR2). Four of the identified mutations are previously reported as disease-associated (SCN5A R376H, A1680T, E1784K, and RYR2 A4556T). One novel SCN5A mutation (H558fs) is a deletion, resulting in a frameshift, whereas the other (G840R) is a missense mutation with in-silico confirmation of disease causation. A detailed description of the 6 families with a positive genotype is tabulated in the Table in the online-only Data Supplement.

Immediate Management

All relatives affected received appropriate lifestyle modification and drug avoidance advice. Eleven patients were prescribed β-blockers and 2 angiotensin-converting enzyme inhibitors. Prophylactic cardioverter defibrillators were implanted in 5 patients: 3 BrS; 2 LQTS, and 2 LQTS patients received a pacemaker.

Comparison of Diagnostic Yield With the SADS Cohort

The SADS cohort consisted of 163 families, comprising 463 relatives. The characteristics of the SADS victims are described in Table 2. The diagnostic yield in the SADS cohort

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**Table 2. Characteristics of Victims of Sudden Cardiac Death With Autopsy Findings of Uncertain Significance. A Comparison Is Made With Victims With Normal Postmortem (SADS)**

<table>
<thead>
<tr>
<th></th>
<th>Uncertain Significance (n=41)</th>
<th>SADS Deaths (n=163)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range, y)</td>
<td>29.9±14.4 (4–59)</td>
<td>27.6±11.1 (1–56)</td>
<td>0.267</td>
</tr>
<tr>
<td>Sex: male</td>
<td>80%</td>
<td>67%</td>
<td>0.128</td>
</tr>
<tr>
<td>Ethnicity: white</td>
<td>93%</td>
<td>91%</td>
<td>1.000</td>
</tr>
<tr>
<td>Mode of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asleep/at rest</td>
<td>61%</td>
<td>61%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>During/postexertion</td>
<td>37%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Reported antecedent cardiac symptoms*</td>
<td>37%</td>
<td>27%</td>
<td>0.250</td>
</tr>
<tr>
<td>Syncope</td>
<td>15%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Previous family history of premature (&lt;55 y)</td>
<td>25%</td>
<td>17%</td>
<td>0.369</td>
</tr>
</tbody>
</table>

**sudden cardiac death**

*Chest pain, palpitations, shortness of breath, presyncope, syncope.

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**Figure 2.** Histogram depicting the diagnostic yield of familial evaluation in victims of sudden cardiac death. The x-axis represents the number of families, and the y-axis represents the pathology identified in the deceased during postmortem evaluation of the heart. The different colors in the columns represent the diagnosis established after cardiac evaluation of surviving relatives with absolute numbers of families stated within the relevant color. CPVT indicates catecholaminergic polymorphic ventricular tachycardia; and LVH, left ventricular hypertrophy.
was similar to that of individuals with autopsy findings of uncertain significance (47.2% versus 51%; \( P=0.727 \)). In both cohorts, the predominant diagnosis was of a primary arrhythmogenic syndrome (Figure 4). A similar proportion of the relatives who were evaluated in the SADS and the autopsy findings of uncertain significance cohorts were diagnosed with a cardiac condition (24.6% versus 22.9%; \( P=0.715 \)).

**Discussion**

SCDs in young, previously healthy individuals instigates cardiac evaluation of first-degree relatives aimed at identifying potentially inherited cardiac pathology to minimize the risk of further tragedies.\(^2\)\(^,\)\(^3\) In a significant proportion of SCDs, the pathologist may observe findings that are relatively common in the general population, or findings that partially fulfill diagnostic criteria for structural cardiac disease, leaving uncertainty about causality and management of surviving relatives. In this study of 41 families with postmortem findings of uncertain significance, \( \approx 50\% \) were diagnosed with a hereditary arrhythmogenic syndrome, and the causes of SCD were similar to those observed in a true SADS cohort. This finding is of particular importance because by convention the absence of any cardiac pathology is considered a prerequisite for the definition of a death as SADS.\(^1\)
Implications of Autopsy Findings of Uncertain Significance

The causal effect of the autopsy findings is unclear. The authors offer 4 plausible hypotheses:

(a) Innocent Bystander

Bicuspid aortic valve and floppy mitral valve are present in 1% to 2% of the general population and may represent innocent bystanders. Likewise, coronary atherosclerosis without significant narrowing of the arterial lumen and without evidence of acute or chronic ischemia is common. Moreover, it is well documented that the degree of coronary artery stenosis can be overestimated by the pathologists as a result of postmortem collapse of the vessel wall.17 Finally, foci of lymphocytes are common in the normal heart, and a degree of myocardial inflammation may be the effect of prolonged resuscitation efforts rather than evidence of myocarditis resulting in SCDs.18

(b) Primary Cause of SCDs

Most of the conditions identified at autopsy in our cohort have been associated with ventricular arrhythmias and sudden death.8 Similarly, the absence of severe luminal narrowing of the coronary arteries does not preclude ventricular arrhythmias attributable to myocardial ischemia, particularly as a result of coronary artery vasospasm,19 and isolated fatty infiltration involving the cardiac conduction system has been implicated in SCD of obese people.20

(c) Trigger in the Context of an Arrhythmogenic Syndrome

Consideration must also be given to the fact that structural cardiac disorders may serve as triggers for arrhythmias in the context of a coexistent inherited arrhythmogenic syndrome. One third of SCDs in our cohort with minor coronary disease were subsequently attributed to an arrhythmogenic syndrome. Current evidence suggest that the presence of coronary artery disease is an independent risk factor for LQTS-related symptomatic events.21 It seems likely that transient ischemia alters the arrhythmic substrate by reducing the threshold for afterdepolarizations or increasing transmural dispersion of repolarization, both recognized mechanisms for arrhythmogenesis in ion-channel disease.22

(d) Spectrum of Arrhythmogenic Syndromes

There is mounting evidence that individuals with ion-channel defects may exhibit structural cardiac changes.22 Although the majority of BrS patients possess a structurally normal heart, a small proportion, seems to exhibit evidence of ventricular wall motion abnormalities, ventricular dilatation, and fibrosis.23,24 Such structural abnormalities may be subtle, requiring sophisticated diagnostic tools.25 Several theories have been postulated to correlate ion-channel dysfunction with structural abnormalities, ranging from impaired excitation–contraction coupling and energy production, to a hibernation-like state which over time may even lead to intracellular lipid accumulation.22 Support for potential structural abnormalities in patients with BrS is also provided by the study of Nademanee et al26 where the authors identified the anterior aspect of the RVOT epicardium as the substrate for the Brugada ECG pattern.

Additionally, there are reports in the literature of identical mutations presenting with either a cardiomyopathy or an arrhythmogenic syndrome phenotype, suggesting that structural and ion-channel defects may be part of a spectrum incorporating myocardial disease and primary arrhythmogenic syndromes. Mutations in the cardiac ryanodine receptor gene, commonly implicated in CPVT, have been reported in individuals exhibiting an arrhythmogenic right ventricular cardiomyopathy phenotype.27 Mutations in the SCN5A gene, implicated in BrS, may present with arrhythmia, conduction disease, and atrial or ventricular dilatation.28 Heritable SCN5A defects have also been associated with early-onset dilated cardiomyopathy and atrial fibrillation.29

LVH and Myocardial Fibrosis

In our cohort, isolated LVH and myocardial fibrosis were the most prevalent findings. Idiopathic LVH is an increasingly recognized entity in cases of SCDs. It remains unclear whether it represents an innocent bystander, a pathological variant of physiological LVH in genetically predisposed individuals or part of the HCM spectrum.5 Although LVH is a well-recognized feature of cardiovascular adaptation to exercise, in our study, only 4 out of the 10 individuals exhibiting isolated LVH exercised on a regular basis. Data from the Framingham study also indicate that LVH confers a 4-fold risk of sudden death.30 In addition, experimental studies suggest that LVH alters ion-channel expression and function predisposing to reentry arrhythmias and ventricular fibrillation.31 Although in the majority of individuals such adaptations are unlikely to result in increased risk of arrhythmias, the development of LVH in an
individual with an underlying arrhythmogenic syndrome may exacerbate electric instability and predispose to sudden death.

The amount of myocardial fibrosis and the collagen texture seem to play a role in vulnerability to arrhythmia. Moreover, myocardial fibrosis may represent incomplete expression of underlying cardiomyopathy. Myocardial fibrosis has also been reported in marathon runners and in cases of SCDs in athletic individuals, raising concerns whether prolonged arduous exercise can lead to repeated myocardial injury, necrosis, and subsequent fibrosis. Finally, animal models have demonstrated that SCN5A mutations cause progressive impairment of atrial and ventricular conduction associated with myocardial rearrangements and fibrosis.  

The Role of the Cardiac Pathologist

This study highlights the importance of accurate interpretation of the autopsy findings because false conclusions may misguide familial evaluation or offer false reassurance to surviving relatives and dissuade physicians from initiating familial screening. Given the relative rarity of SCDs from inherited conditions and the challenges associated with their diagnosis, the authors propose that all cases of SCDs and, particularly, SCDs in young (≤35 years) individuals, where an inherited condition is suspected or diagnostic uncertainty remains as to the cause of death, should be referred for further evaluation to an expert cardiac pathologist.

Limitations

The predominant diagnosis in our cohort was of BrS, reflecting the victims’ demographics (80% males, mean age of 30 years), predominant mode of death (60% asleep at rest), and the routine use of Ajmaline provocation testing. It is plausible that some Ajmaline-based diagnoses may be erroneous. Although currently there are no large series of normal subjects undergoing Ajmaline test, existing literature in SCN5A positive families suggests that the specificity of the Ajmaline challenge exceeds 94%. Therefore, in the absence of an alternative gold standard, provocation testing with a sodium channel blocker remains an integral part of the evaluation of individuals with suspected BrS.

The authors also concede that given the relative novelty of the condition and the association of the Brugada phenotype with several structural cardiac abnormalities, it is possible that some of the relatives exhibiting the Brugada phenotype did not have a genuine arrhythmogenic syndrome. However, all individuals who were diagnosed with BrS underwent comprehensive evaluation, including a detailed echocardiogram, and a significant proportion were subjected to CMR, and none exhibited any evidence, suggesting structural cardiac anomalies. Further support for the presence of BrS is underscored by the genetic yield (23%) of pathogenic SCN5A mutations, similar to existing literature.

In the 6 families in whom a pathogenic mutation was identified in evaluated relatives, we were unable to perform post-mortem analysis in the tissues of the victims for confirmation of the genotype because no tissue was available by the time the relatives were evaluated in our clinic. In the United Kingdom, the Human Tissue Act does not permit retention of tissue as part of a deceased patient’s record, and retention for research requires familial consent at the time of postmortem. As such, in the majority of cases, histological slides are prepared, reported, and imaged at the time of the postmortem examination, allowing early return of the tissue for burial or cremation.

Conclusion

The current study underscores the need for accurate interpretation of autopsy findings in cases of SCDs to avoid erroneous diagnoses with potentially devastating implications for surviving relatives. Our data suggest that all SCDs with inconclusive autopsy findings should be considered as potential SADS deaths, and comprehensive evaluation of family relatives for both inherited primary arrhythmogenic syndromes and structural cardiac abnormalities should be advocated.

Acknowledgments

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Disclosures

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References


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/content/6/4/e67.full.pdf

Data Supplement (unedited) at:
http://circep.ahajournals.org/content/suppl/2013/05/13/CIRCEP.113.000111.DC1

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In the article “Sudden Cardiac Death With Autopsy Findings of Uncertain Significance: Potential for Erroneous Interpretation” by Papadakis et al, which was published in the June 2013 issue (Circ Arrhythm Electrophysiol. 2013;6:588–596), corrections were needed.

The in-text figure citation of Figure 3.4 was erroneously referenced as Figure 4D; the in-text figure citation of Figure 3.1 was erroneously referenced as Figure 4A.

The panel labels in the Figure 3 legend have been corrected.

A more complete Figure 4 has been updated, indicating “DCM” and “None.”

The compositor apologizes for these errors.

The online version of the article has been corrected.
**Supplemental Table:** Detailed presentation of the characteristics of victims of sudden cardiac death and relatives diagnosed with a condition in families where the presence of an inherited arrhythmogenic syndrome was confirmed by the presence of a pathogenic mutation in the relatives.

<table>
<thead>
<tr>
<th>Victims age, gender, mode of death</th>
<th>Post-mortem findings</th>
<th>Clinical phenotype</th>
<th>Clinical findings in relatives diagnosed with a hereditary arrhythmogenic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 years Female At rest</td>
<td>Septal subendocardial fibrosis</td>
<td>LQTS SCN5A:p.G840R</td>
<td>QTc (Bazett) of 479ms&lt;sub&gt;½&lt;/sub&gt; (65bpm) and non-sustained VT in father, in context of family history (Schwartz score 4.5). Brother has QTc of 460ms&lt;sub&gt;½&lt;/sub&gt; (84bpm) with prolongation late in recovery post-exercise (Schwartz score 3).</td>
</tr>
<tr>
<td>34 years Male At rest</td>
<td>Lipomatous hypertrophy of atrial septum</td>
<td>LQTS SCN5A:p.E1784K</td>
<td>Resting QT prolongation in 2 daughters (Bazett QTc 497ms&lt;sub&gt;½&lt;/sub&gt; at 70bpm and 490ms&lt;sub&gt;½&lt;/sub&gt; at 71bpm) with syncope in one consistent with Schwartz score 4 in both.</td>
</tr>
<tr>
<td>17 years Male</td>
<td>Marked right ventricular dilatation</td>
<td>CPVT RYR2:p.A4556T</td>
<td>Exertional polymorphic non-sustained ventricular tachycardia in mother; bidirectional ventricular tachycardia</td>
</tr>
<tr>
<td>Age</td>
<td>Gender</td>
<td>Position</td>
<td>Clinical Features</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>39 years Male Cycling</td>
<td>Mitral valve prolapse (floppy mitral valve with mild ballooning)</td>
<td>BrS</td>
<td>SCN5A:p.H558fs</td>
</tr>
<tr>
<td>30 years Male At rest</td>
<td>Left ventricular Hypertrophy. Maximal wall thickness 18mm No significant disarray</td>
<td>BrS</td>
<td>SCN5A:p.R376H</td>
</tr>
<tr>
<td>37 years Male Asleep</td>
<td>Calcified atrial mass</td>
<td>BrS</td>
<td>SCN5A:p.A1680T</td>
</tr>
</tbody>
</table>
Early Repolarisation Patterns in Relatives of Individuals with Autopsy Findings of Uncertain Significance

All ECG recordings were reviewed retrospectively for the presence of early repolarization (ER), based on the results of recent studies which indicate that early repolarization in the inferior and lateral leads may represent a potentially heritable marker of malignant arrhythmias,\(^1\) particularly in the context of SADS.\(^2\) Inferior (II, III, AVF) and lateral (I, AVL, V4-V6) leads were assessed for the presence of J-point elevation defined as ≥0.1 mV in ≥2 leads in the same territory. The ER pattern was further classified according to the morphology of the terminal QRS in the majority of the leads as notched, slurred or indeterminate. In the presence of ER, the ST-segments were assessed for the presence of ST-segment elevation and a distinct ST-segment morphology (ascending or horizontal/descending).\(^1\)

The prevalence of ER pattern in the inferior and/or lateral leads in our cohort was lower than that observed by Nunn et al., and comparable to the prevalence reported in healthy controls.\(^2\) Of the 157 relatives evaluated, 10.2% (n=16) exhibited the ER pattern in the inferior and/or lateral leads and less than 2% (n=3) demonstrated a slurred terminal QRS complex with a descending ST-segment, which is the ER pattern predominantly linked to the risk of sudden death in the general population.\(^1\) Although the prevalence of ER was higher in relatives without a diagnosis of arrhythmogenic syndrome or cardiomyopathy compared to relatives with a diagnosis, the difference did not achieve statistical significance (11.6% versus 5.6%, p=0.366). Only one family
consisted of ≥2 relatives who exhibited ER offering little support to the theory of a potentially inheritable pro-arrhythmia trait. In that particular family the deceased’s post-mortem revealed mitral valve prolapse and no diagnosis was established after comprehensive cardiac evaluation of blood relatives.

References
