The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths

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Aims

Post-mortem examination of the heart in young sudden cardiac death (SCD) is vital as the underlying aetiology is often an inherited cardiac disease with implications for surviving relatives. Our aim is to demonstrate the improvement in diagnostic quality offered by a specialist cardiac pathology service established to investigate SCD with fast-track reporting on hearts sent by pathologists in cases of SCD.

Methods and results

A tertiary centre prospective observational study was conducted. Detailed histopathological examination was performed in a tertiary centre specialized in the investigation of cardiac pathology in SCD. Hearts from 720 consecutive cases of SCD referred by coroners and pathologists from 2007 to 2009 were included. A comparison was drawn with diagnoses from referring pathologists. Most SCDs occurred in males (66%), with the median age being 32 years. The majority (57%) of deaths occurred at home. The main diagnoses were a morphologically normal heart (n = 321; 45%), cardiomyopathy (n = 207, 29%), and coronary artery pathology (n = 71; 10%). In 158 out of a sample of 200 consecutive cases, a cardiac examination was also performed by the referring pathologist with a disparity in diagnosis in 41% of the cases (κ = 0.48). Referring pathologists were more inclined to diagnose cardiomyopathy than normality with only 50 out of 80 (63%) normal hearts being described correctly.

Conclusion

Expert cardiac pathology improves the accuracy of coronial post-mortem diagnoses in young SCD. This is important as the majority of cases may be due to inherited cardiac diseases and the autopsy guides the appropriate cardiological evaluation of blood relatives for their risk of sudden death.

Keywords

Autopsy • Cardiomyopathy • Morphologically normal heart • Sudden arrhythmic death syndrome • Sudden cardiac death • Young

Introduction

Inherited cardiac diseases are common causes of young sudden cardiac death (SCD) and the family must not only contend with the grief of their loss but also with the possibility that SCD may strike the family again. The UK reports at least 10 cases of SCD occurring per week or 1.8 per 100 000 persons-year, with several cases misclassified under drowning or epilepsy. In the UK, national guidelines have outlined the need for specialist cardiological evaluation for families who have suffered an unexplained SCD (sudden arrhythmic death syndrome, SADS) and expert post-mortem examination is a critical first diagnostic step required to guide clinical evaluation of surviving relatives. This aims to identify individuals at the risk of SCD, in whom medical intervention is likely to prevent further tragedies.

Best practice guidelines set by the Royal College of Pathologists and the Association for European Cardiovascular Pathology recommend referral of whole hearts to specialist centres with high volume and recognized expertise. In the UK, all sudden unexpected
What’s new?

- The pathological investigation of sudden cardiac death (SCD) poses significant diagnostic challenges, particularly in the young where inherited cardiac diseases predominate.
- There is a considerable variability in the interpretation of autopsy findings between general and specialist cardiac pathologists, which can lead to alternative diagnoses in 40% of the cases.
- General pathologists are likely to overestimate the significance of autopsy findings and attribute deaths to cardiomyopathy at the expense of diagnosing a morphologically normal heart.
- Isolated left ventricular hypertrophy is present in a considerable proportion of SCDs and its significance remains unclear, warranting further research.
- Investigation of SCD by an experienced cardiac pathologist is essential when an inherited cause is suspected, to ensure diagnostic accuracy, given the potential implications for surviving relatives.

Deaths have an autopsy carried out by a pathologist, whereas in the rest of Europe there is widespread variation as to the rate of autopsies for SCD even within the same country. Most British pathologists have limited exposure to cases of young SCD as well as few resources and time constraints to perform the autopsy. Moreover, the introduction of the Human Tissue Act in 2004 has limited preservation of tissue at autopsy. All these factors translate to either the introduction of the Human Tissue Act in 2004 has limited preservation of tissue at autopsy. The charity Cardiac Risk in the Young (CRY) launched a Centre for Cardiac Pathology, CRY CCP, established in the National Lung and Heart Institute (Imperial College) and Royal Brompton Hospital (RBH) in March 2007 to address the need for detailed histopathological evaluation of cases of SCD from potentially inherited conditions by an expert cardiac pathologist at no cost to the family, coroner, or health service. We report the diagnostic results of this innovative service.

Methods

Population inclusion and exclusion criteria

This study was completed with ethical approval from the Brompton, Harefield and National Heart and Lung Institute: Ref 07/Q040. A total of 753 cases, referred between March 2007 and December 2009 for expert cardiac pathological assessment to the CRY CCP service, were considered for this prospective observational study. Inclusion criteria were as follows: referral by a coronial pathologist of a witnessed instantaneous death; or a suspected sudden death when the individual was seen alive and well up to 24 h prior to death; and where non-cardiac causes had been excluded at initial autopsy. All ages were included to demonstrate the wide age range of referrals received at the centre.

Cases were excluded from the study if the death occurred in the context of deteriorating heart failure (n = 26), was non-sudden (n = 4), or if subsequent toxicology provided an explanation for the death (n = 3). Data on age, sex, and location/circumstances of death of the deceased were obtained from the referring pathologist or coroner. Subjects were divided into two groups based upon their age at death: (i) ≤35 years and (ii) >35 years.

Specimen referral process

A specific protocol was established for handling an SCD referral and is summarized in Figure 1.

Referrals

The total numbers of SCD referrals were calculated before and after the launch of the CRY CCP in March 2007. To examine trends over time, SCD referrals were grouped into two time bands: 1999–2006 and 2007–09.

Heart specimen handling

Sudden cardiac death victims were examined by local pathologists in 45 counties within the UK. Following the exclusion of extra-cardiac causes for the death, the hearts were referred to CRY CCP with the consent of the coroner and the family of the deceased. Established macroscopic and histological criteria for the diagnosis of cardiac pathology were used and are summarized in Supplementary material online, Table S1. For all cases, observations and dimensions were consistently recorded. Ten to twenty tissue sections were routinely taken according to agreed national and international criteria and included: the RV outflow tract; a right lateral cut containing right atrium, posterior leaflet of the tricuspid valve, and lateral RV; a left lateral cut containing left atrium, mitral valve and lateral LV; circumferential RV and LV samples; the anterior and posterior septum; the three major coronary arteries; the ascending aorta; and the conduction system. Extra tissue sections were taken to confirm pathology when this was detected macroscopically and/or microscopically. Sections were fixed in formalin, embedded in paraffin, and stained with haematoxylin and eosin stain or elastic Van Gieson to highlight myocardial fibrosis.

The results were reported in categories: (i) morphologically normal heart, (ii) cardiomyopathies, (iii) coronary artery pathology, (iv) complex congenital heart disease (CHD), (v) inflammatory disease, (vi) valve disease, (vii) aortic disease, (viii) tumour, and (ix) other cardiac pathology.

Comparison with referring pathologist opinion

A sample of 200 consecutive cases of SCD referred from March 2007 onwards were examined to find out whether the referring pathologists had performed pathological examination of the heart and provided a potential cardiac cause of SCD. Cardiac diagnoses were compared between the referring pathologist and M.N.S. using the kappa (κ) coefficient.

Statistical methods

Data were analysed using the statistical software Stata version 10.1 (Statacorp). Categorical data were presented as percentages and differences between groups, including changes, over time were assessed with the use of the χ² or Fisher’s exact test. The kappa (κ) coefficient was used as a measure of agreement. Numerical data were presented as means ± SD or as median [interquartile range (IQR)]. A value P < 0.05 was considered statistically significant.
Results

Referral patterns
A total of 720 cases of SCD were included in the period from March 2007 to December 2009. There was a progressive increase in the number of SCD referrals over time (Figure 2), with a statistically significant upward trend when comparing the periods before and after the CRY CCP launch ($P = 0.014$).

Demographics
The cohort was predominantly male ($n = 475, 66\%$) and young. The median age was 32 years, age range $1\text{–}98$ years, and $58\%$ were $\leq 35$ years of age (Figure 3).

Location and circumstance of death
The majority of deaths occurred at home ($57\%$) (see Supplementary material online, Table S2) of whom most died at rest ($n = 244, 34\%$), including those found dead in bed ($n = 197, 27\%$). Sudden cardiac death occurred during or immediately after exertion in $14\%$ of the total cohort, most of whom were young with a median age of 24 years. Sudden cardiac death in the community occurred in 144 (20%) cases, with 66 of the 144 (46%) occurring during exertion, mostly on sport pitches and in leisure centres. Subjects with a
normal heart were more likely to die at rest whereas a higher proportion of deaths in individuals with a cardiomyopathy were related to exertion ($P = 0.0121$) (see Supplementary material online, Table S3).

**Causes of sudden cardiac death**

The main causes of SCD and their representation in the cohort are presented in Tables 1, 2, and Supplementary material online, Figure S1. The most common finding was a morphologically normal heart implying SADS ($n = 321, 45\%$), which was also the leading cause in those aged $\leq 35$ years ($228$ of $422, 54\%$). Although males predominated ($197$ of $321, 61\%$), female SCD victims were proportionately more likely to have a normal heart ($51\%$ vs. males; $41\%, P = 0.019$). The group with a morphologically normal heart was also significantly younger compared with cases with structurally abnormal hearts ($P < 0.0001$): median age as $28$ years (IQR $20, 38$) compared with $36$ years (IQR $26, 47$).

Just under one-third of the cohort ($n = 207$) had cardiomyopathy. Males were proportionately more commonly affected by cardiomyopathy than females. The most common cardiomyopathies included: idiopathic left ventricular hypertrophy (ILVH) ($26\%$), of which $42\%$ were associated with fibrosis; hypertrophic cardiomyopathy (HCM) ($20\%$); arrhythmogenic right ventricular cardiomyopathy (ARVC) ($14\%$); and obesity cardiomyopathy ($14\%$).

Coronary artery pathology was the third main cause of death identified in $10\%$ of all subjects. The most common aetiologies were atheroma ($56$ of $71, 79\%$, mean age $49.8 \pm 18.1$ years) of whom $13$ were $\leq 35$ years including an $11$-year-old with known familial hypercholesterolaemia. Non-atheromatous causes occurred in younger individuals ($15$ of $71, 21\%$, mean age $36.2 \pm 13.5$ years) and included myocardial infarction with normal coronary arteries ($n = 7$); anomalous origin of the coronary artery ($n = 5$); and left coronary artery and left anterior descending artery (LAD) from the pulmonary trunk ($n = 2$); coronary artery bridging of the LAD ($n = 1$); and spontaneous coronary dissection found only in two females.

Myocardial inflammation was noted in $4\%$ of the patients. The inflammatory types were: lymphocytic ($n = 9$), toxic ($n = 8$), eosinophilic and lymphocytic ($n = 5$), granulomatous cardiac sarcoid ($n = 4$), neutrophilic ($n = 3$), eosinophilic ($n = 2$), and acute rheumatic fever ($n = 1$).

Valvular pathology totalled $24$ cases ($3\%$) with a predominance of mitral valve prolapse ($14$ of $24, 58\%$), which was associated with LV fibrosis in $11$ cases, followed by bicuspid aortic valve ($n = 7$). There were $23$ cases of SCD with CHD, of which $17$ ($74\%$) had surgical correction for their conditions in early life. Mild to extensive fibrosis of the LV and/or RV was detected in the majority of CHD cases ($14$ of $23, 61\%$). Aortic dissection or rupture accounted for $13$ ($2\%$) sudden deaths that were mostly in the young males.

With the exception of two atrioventricular (AV) nodal tumours, examination of the conduction system did not establish accessory pathways, fibrosis, or inflammation within the AV nodal tissue. Overall, there were $587$ of $720$ cases ($80\%$): $321$ normal hearts, $207$ cardiomyopathy, $23$ complex CHD, $24$ valve disease, and $12$ aortic dissections, where death could be attributed to a potentially genetic disorder and therefore may require evaluation of the family.

**Specialist cardiac pathology compared with coronial pathology**

From a sample of $200$ consecutive cases examined by M.N.S., in $158$ ($79\%$), a provisional diagnosis had been made by the referring pathologist. This matched the diagnosis of M.N.S. in only $94$ of $158$
Importance of specialist cardiac pathology

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ARVC was isolated fatty infiltration of the RV (agreement in only 2 cases. The main observation misattributed to ARVC. In contrast, seven of the hearts described as normal by the referring pathologist were thought to have signs of cardiomyopathy, the majority being normal hearts being described as such. Of the 30 normal hearts, inflammation was focal with no myocyte necrosis. Remaining cases were in fact ARVC (63%) was over-reported by the referring pathologist. In the majority of cases, inflammation was focal with no myocyte necrosis. Histological images of these common confounders are shown in Supplementary material online, Figure S2.

Table 1 Cardiac causes of SCD stratified by age

<table>
<thead>
<tr>
<th>Cardiac cause of death</th>
<th>n</th>
<th>%</th>
<th>Median age (IQR)</th>
<th>Age range, years</th>
<th>≤35 years n</th>
<th>%</th>
<th>≤35 years n</th>
<th>%</th>
<th>&gt;35 years n</th>
<th>%</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>Normal heart</td>
<td>321</td>
<td>45</td>
<td>28 (20, 38)</td>
<td>&lt;1–82</td>
<td>228</td>
<td>54</td>
<td>93</td>
<td>31</td>
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<td>Cardiomyopathy</td>
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<td>36 (26, 47)</td>
<td>&lt;1–98</td>
<td>97</td>
<td>23</td>
<td>110</td>
<td>36</td>
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<td>Idiopathic left ventricular hypertrophy</td>
<td>54</td>
<td>8</td>
<td>25 (34, 39)</td>
<td>4–69</td>
<td>30</td>
<td>7</td>
<td>24</td>
<td>8</td>
<td>–</td>
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<tr>
<td>Obesity CM</td>
<td>29</td>
<td>4</td>
<td>30 (40, 47)</td>
<td>9–64</td>
<td>10</td>
<td>2</td>
<td>19</td>
<td>6</td>
<td>–</td>
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<td></td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>42</td>
<td>6</td>
<td>28 (37, 52)</td>
<td>7–98</td>
<td>19</td>
<td>5</td>
<td>23</td>
<td>8</td>
<td>–</td>
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<td></td>
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<tr>
<td>Arrhythmogenic right ventricular CM</td>
<td>29</td>
<td>4</td>
<td>30 (37, 46)</td>
<td>10–56</td>
<td>12</td>
<td>3</td>
<td>17</td>
<td>6</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>Idiopathic fibrosis</td>
<td>17</td>
<td>2</td>
<td>34 (26, 42)</td>
<td>&lt;1–51</td>
<td>9</td>
<td>2</td>
<td>8</td>
<td>3</td>
<td>–</td>
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<td></td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>17</td>
<td>2</td>
<td>38 (21, 49)</td>
<td>15–81</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>–</td>
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<td></td>
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<tr>
<td>Other CM</td>
<td>9</td>
<td>1</td>
<td>48 (11, 55)</td>
<td>&lt;1–71</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>–</td>
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<tr>
<td>CM NOS</td>
<td>10</td>
<td>1</td>
<td>35 (27, 46)</td>
<td>14–64</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>Coronary artery pathology</td>
<td>71</td>
<td>10</td>
<td>45 (34, 63)</td>
<td>11–82</td>
<td>21</td>
<td>5</td>
<td>50</td>
<td>17</td>
<td>&lt;0.0001</td>
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<tr>
<td>Atheroma</td>
<td>56</td>
<td>8</td>
<td>46 (37, 66)</td>
<td>11–82</td>
<td>13</td>
<td>3</td>
<td>43</td>
<td>14</td>
<td>–</td>
<td></td>
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<tr>
<td>Non-atheromatous</td>
<td>15</td>
<td>2</td>
<td>35 (23, 45)</td>
<td>16–63</td>
<td>8</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>Inflammation</td>
<td>32</td>
<td>4</td>
<td>21 (14, 36)</td>
<td>&lt;1–67</td>
<td>24</td>
<td>5</td>
<td>8</td>
<td>3</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>Complex congenital heart disease</td>
<td>23</td>
<td>3</td>
<td>23 (16, 30)</td>
<td>&lt;1–44</td>
<td>19</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>–</td>
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<tr>
<td>Valvular disease</td>
<td>24</td>
<td>3</td>
<td>33 (23, 45)</td>
<td>12–79</td>
<td>14</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>Aortic disease</td>
<td>13</td>
<td>2</td>
<td>34 (34, 43)</td>
<td>13–59</td>
<td>8</td>
<td>2</td>
<td>5</td>
<td>2</td>
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<td></td>
<td></td>
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<tr>
<td>Tumour</td>
<td>5</td>
<td>1</td>
<td>25 (22, 40)</td>
<td>7–43</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>–</td>
<td></td>
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<tr>
<td>Hypertensive heart disease</td>
<td>12</td>
<td>2</td>
<td>48 (38, 61)</td>
<td>35–85</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>4</td>
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<tr>
<td>Other cardiac pathology&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12</td>
<td>2</td>
<td>23 (18, 85)</td>
<td>&lt;1–98</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>720</td>
<td>100</td>
<td>32 (22, 43)</td>
<td>&lt;1–98</td>
<td>422</td>
<td>54</td>
<td>93</td>
<td>31</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CM, cardiomyopathy; NOS, not otherwise specified.

Decimal values were rounded to the nearest whole number for ease of interpretation. Values are expressed as percentage (number/total number) or median (range).

<sup>a</sup>Other miscellaneous causes were: non-toxic alcohol/drug-related myocardial damage (n = 4), amyloid (n = 2), transplant rejection due to coronary allograft vasculopathy (n = 1), post-chemotherapy fatty replacement of the LV (n = 1), subendocardial fibroelastosis (n = 2), and arrhythmia (supraventricular tachycardia) related ischaemic damage (n = 1).

Discussion

This study reports the results of a unique specialist cardiac pathology service dedicated to the pathological investigation of predominantly young SCD. Eighty per cent of deaths had pathological evidence to support potentially inherited cardiac diseases including Marfan’s syndrome, cardiomyopathy, and a morphologically normally heart (SADS). Evaluation of first-degree relatives of victims with SADS syndrome, cardiomyopathy, and a morphologically normally heart (<sup>1,4,5,18</sup>) identifies inherited heart diseases in up to half of the families. It is therefore vital that SADS deaths and other deaths due to potentially inherited heart diseases are recognized accurately at post-mortem to trigger this process. Cardiac familial investigation is, however, a time-consuming and expensive process that can be distressing to relatives. For these reasons, clinicians need accurate (59%) of the cases (Table 3). The k coefficient as a statistical measure of concordance was moderately significant at 0.48. Referring pathologists were more inclined to diagnose pathology rather than designate the heart as morphologically normal with only 50 out of 80 (63%) normal hearts being described as such. Of the 30 normal hearts, myocarditis (5 of 9, 55%) was also over-reported by the referring pathologist. In the majority of cases, inflammation was focal with no myocyte necrosis. Histological images of these common confounders are shown in Supplementary material online, Figure S2.

Consensus was greatest, however, in the diagnosis of dilated cardiomyopathy (6 of 8, 75%). In two out of five (40%) cases of valvular disease, over-interpretation of floppy mitral was noted, especially in older patients where slight ballooning of the mitral leaflet edges is a normal finding. Finally, coronary artery atheroma was considered a significant cause of death in three cases but was determined to be non-significant by M.N.S. due to over-interpretation of collapsed coronary arteries at autopsy.

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The importance of a specialist cardiac pathology service

Erroneous autopsy interpretation may mislead clinicians and cause missed diagnostic opportunities that could result in further tragedies within the same family. This is particularly pertinent to primary care physicians and cardiologists who are required to interpret a post-mortem report, often without any guidance, as well as initiate referral of family members and plan cardiological evaluation. Our study thus highlights the importance of an experienced cardiac pathology service dedicated to providing a thorough cardiac autopsy and ensuring a higher probability of accurate interpretation.

Pathological findings and their implications

In the under 35 age group, 54% were normal heart/SADS cases. At autopsy, it is a diagnosis of exclusion where the heart is structurally normal and toxicology is negative. This is a higher proportion than other recent series, where proportions of structurally normal hearts in similar-aged groups of sudden death victims range from 26 to 43%. This may reflect referral bias (see limitations), but nonetheless reinforces the importance of normal heart/SADS and its genetic implications. Among the cardiomyopathies, ILVH without the evidence of disarray was the most common structural abnormality in our cohort. Idiopathic LVH is an increasingly recognized entity in cases of SCD in athletic and non-athletic individuals. Although its exact significance remains unclear, a recent study from our group suggested a number of plausible hypotheses including innocent bystander, pathological variant of physiological LVH in genetically predisposed individuals, part of the HCM spectrum, and a trigger of arrhythmia in the context of an inherited arrhythmogenic syndrome. Other processes can mimic inherited cardiomyopathies. For example, ARVC was over-diagnosed by coroners’ pathologists based upon RV fatty infiltration alone, a common finding in an increasingly obese population and in subjects with a history of alcohol misuse or inherited myopathies. Variable amounts of intramyocardial fat in the RV have also been documented in individuals dying of non-cardiac causes. The presence of fibrosis in association with fat is necessary to diagnose ARVC, reinforcing the need for detailed histological examination including the taking of further blocks by an experienced cardiac pathologist.

Gender and risk of sudden cardiac death

Male gender accounted for two-thirds of SCDs in our cohort. This observation is consistent with existing literature which unanimously reports a male predominance in SCD, in both athletic and sedentary individuals. This also correlates with the higher incidence of male SCDs observed in cardiomyopathies in general and in arrhythmia syndromes such as long QT 1 (LQT1) (prepubescent males), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome. Female gender, on the other hand, has only been associated with a higher risk in long QT syndrome, particularly drug-induced torsade-de-pointes LQT2 in young female adults.

Causes of sudden cardiac death by circumstance of death

Normal hearts occurred twice as often as cardiomyopathy in SCD under rest with a comparative tendency for cardiomyopathy to be more associated with SCD under exertion. This is in line with other studies. Individuals that die during sleep commonly have a...
normal heart and are likely to be affected by circadian rhythm and autonomic nervous system factors. Sudden cardiac death in athletes during or shortly after exertion is mostly attributed to an underlying cardiomyopathy, where adrenergic surges are thought to be important. Other arrhythmia syndromes such as LQT1 and CPVT that are likely to underlie morphologically normal heart SCD are also associated with sudden death on exertion. This is supported by the study of Behr et al., where most of the SADS victims died at rest/during sleep.

Limitations
The CRY CCP offers a nationally recognized service and is more likely to attract challenging cases or cases where a morphologically normal heart is suspected. It does not, however, receive all SCD referrals in the country. For these reasons, conclusions drawn from this study, with particular reference to the prevalence of different causes of SCD, may not reflect the whole of the UK because of selection bias. The aim of this study was, however, to investigate the importance of expert opinion in the diagnosis of SCD. It is plausible that some referring pathologists intended to send the heart for specialist review from the outset and performed only limited histopathological evaluation. Discrepancies between the autopsy conclusions of our specialist centre and that of local pathologists may have been overestimated.

The over-diagnosis of ARVC by referring pathologists may, in part, be explained by the use of older contemporaneous task force criteria that proposed fatty replacement alone as indicative of ARVC disease. New guidelines emphasize that histology must confirm the presence of fibrosis, alone or in combination with fatty infiltration. Our centre adhered to the new criteria throughout the study, long before their official acknowledgement.

The CRY CCP service is based upon analysis undertaken by a single pathologist, albeit an acknowledged international expert. Having an additional pathologist to corroborate the cardiac pathological interpretation would be desirable, but single centres cannot justify more than one pathologist doing cardiac work full-time. There are also few cardiac pathology specialists in the UK, posing a limitation on double reporting. This issue is being addressed by the UK Cardiac Pathology Network by establishing cardiac pathology pathways in the country to support and train general pathologists.

The use of imaging has been proposed to replace the conventional autopsy and was not included in our study. It is clear, however, from our experience that these are currently unsuitable for the accurate diagnosis of cardiac causes of death.

Finally, we acknowledge the lack of post-mortem genetic testing, ‘molecular autopsy’, to support the diagnosis of possible genetic conditions. Although genetic testing can be a useful tool, accurate conventional pathological findings remain the cornerstone of the diagnosis of conditions predisposing to SCD and subsequent guidance of familial evaluation and genetic analysis.

Conclusions
This study demonstrates the value of specialist cardiac pathological analysis in SCD, particularly in the young, and highlights that pathological diagnoses consistent with underlying cardiac genetic disease may account for a majority of cases. Accurate and reliable diagnoses

<table>
<thead>
<tr>
<th>Agreement in cardiac diagnoses</th>
<th>Referring pathologist opinion</th>
<th>Expert opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARVC</td>
<td>HCM</td>
</tr>
<tr>
<td>ARVC</td>
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<td>HCM</td>
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<td>LVH</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>DCM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CM NOS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other CM</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Other pathology</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>

ARVC, arrhythmogenic right ventricular cardiomyopathy; CM NOS, cardiomyopathy not otherwise specified; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; other CM, other cardiomyopathy. Shaded boxes indicate those cases where there was agreement.
are therefore invaluable for coroners’ pathologists, primary care, cardiologists, and ultimately the deceased’s families. The large and increasing number of referrals to the CRY CCP reflects a demand for fast-track expert cardiac diagnostic service for SCD in the UK. We propose that this should be considered an ideal model for future service provision in the UK and abroad.

Supplementary material
Supplementary material is available at Europace online.

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Conflict of interest: All authors have completed the International Committee of Medical Journal Editors disclosure of potential conflicts of interest form at the time of manuscript submission, and declare: S.V.N. was funded by a research grant from the charitable organization, Cardiac Risk in the Young (CRY) UK. E.R.B. receives research funds from CRY, the British Heart Foundation (BHF), European Union, Biotronik, St Jude Medical, and the International Serious Adverse Events Consortium. M.P. has received a clinical research grant from CRY. K.O., an honorary visited cardiologist from Japan, was funded by the Great Britain Saskawa Foundation. W.B. is a medical statistician employed by the NHS, J.W. was funded by a grant from CRY. S.C. is Deputy Chief Executive of CRY. A.C. is the founder and Chief Executive of CRY. S.S. has been a co-applicant on research grants with CRY and receives research grants from the BHF. M.N.S., expert cardiac pathologist receives research grants from CRY. There are no financial relationships with commercial entities that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work other than their involvement in current primary research in the topic area (S.V.N., K.O., M.P., E.R.B., S.S., M.N.S.), and clinical practice in tertiary healthcare (E.R.B., M.P., S.S., M.N.S.).

Ethical approval
Ethical approval was obtained from the local research ethics committee.

Ethical clearance
Research is conducted according to the Declaration of Helsinki and local research ethics committee approval.

Ethical statement
Research is conducted in agreement with the Scottish Government, Scottish Human Research Authority and the Caldicott Guardian.

Ethical approval
Research is conducted according to the Declaration of Helsinki and local research ethics committee approval.

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Correlation of inflammation due to cardiac sarcoidosis by positron emission tomography-computed tomography imaging and endocardial voltage mapping in a patient with recurrent ventricular tachycardia

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A 48-year-old man with cardiomyopathy and sarcoidosis presented with ventricular tachycardia (VT). He underwent an electrophysiology study with mapping which demonstrated low voltage (red regions in panel A, left) along the mitral, tricuspid annulus and septum. Catheter ablation was performed at sites with fractionation, diastolic potentials and excellent pace maps (red dots in panel A, left).

Cardiac positron emission tomography (PET)-computed tomography scan with N-13 ammonia and F-18 fluorodeoxyglucose (FDG) radiotracers was performed 2 weeks post-ablation. Areas of active sarcoid disease with increased inflammation and decreased perfusion by PET (panel A, right) correlated with low voltage regions encountered during mapping. At 10 months following ablation, the patient underwent cardiac transplantation. Tissue pathology of areas targeted for VT ablation (panel B, left) revealed multinucleated giant cells and lymphocytic infiltration (panel B, right).

Our case illustrates correlation between low voltage associated with VT and areas of active inflammation identified by PET imaging. Using dual radiotracer PET imaging, early-stage cardiac sarcoid lesions demonstrate normal or decreased perfusion and increased F-18 FDG uptake while late-stage lesions show matched decreases in both perfusion and F-18 FDG uptake. Metabolic cardiac PET imaging may have a role in guiding ablation of VT due to sarcoidosis.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Correlation-of-Inflammation-due-to-cardiac-sarcoidosis.pdf.