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Sudden arrhythmic death and cardiomyopathy are important causes of sudden cardiac death in the UK: results from a national coronial autopsy database

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Sudden arrhythmic death and cardiomyopathy are important causes of sudden cardiac death in the UK: results from a national coronial autopsy database

Aims: Sudden cardiac death (SCD) is defined as natural unexpected death in witnessed cases occurring < 1 h and in unwitnessed cases as last seen alive < 24 h. SCD due to ischaemic heart disease (IHD) is frequent in older age groups; in younger people genetic cardiac causes, including channelopathies and cardiomyopathies, are more frequent. This study aimed to present the causes of SCD from a large specialist pathology registry.

Methods and results: Cases were examined macroscopically and microscopically by two expert cardiac pathologists. The hearts from 7214 SCD cases were examined between 1994 and 2021. Sudden arrhythmic death syndrome (SADS), a morphologically normal heart, which can be underlaid by cardiac channelopathies, is most common (3821, 53%) followed by the cardiomyopathies (1558, 22%), then IHD (670, 9%), valve disease (225, 3%), congenital heart disease (213, 3%) and myocarditis/sarcoidosis (206, 3%). Hypertensive heart disease (185, 3%), aortic disease (129, 2%), vascular disease (97, 1%) and conduction disease (40, 1%) occur in smaller proportions.

Discussion: To our knowledge, this is the largest SCD cohort with autopsy findings ever reported from one country. SADS and cardiomyopathies predominate. This study highlights the importance of the autopsy in SCD, which is a significant public health concern in all age groups. Knowing the true incidence in our population will improve risk stratification and develop preventative strategies for family members. There is now a national pilot study integrating molecular autopsy and family screening into the assessment of SCD victims.

Keywords: cardiomyopathy, cause of death, family screening, molecular autopsy, sudden arrhythmic death syndrome, sudden cardiac death

Introduction

Sudden cardiac death (SCD) is defined as natural unexpected death in witnessed cases as an acute change in cardiovascular status, with time to death being < 1 h and in unwitnessed cases as person last seen alive < 24 h before being found dead.[1] SCD is frequent in older age groups due largely to ischaemic heart disease in the United States and Europe, and is also increasing in China.[2–4] The universal declining autopsy rate is highlighted in many studies, and a recent FIFA (Fédération Internationale de Football Association) report on sudden death in young footballers showed that of 617 cases from 67 countries, only 127 had had an autopsy.[5] A recent review

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within Europe highlighted that up to 40% of SCD cases in people aged < 50 years did not have an autopsy.[6] This study, however, emphasised that in the United Kingdom we have a high autopsy rate within our coronial system. It is especially important that SCD in younger people is investigated with autopsy as genetic cardiac causes, including channelopathies and cardiomyopathies, are more frequent, which have important implications for their families.[7] These cardiac diagnoses in SCD can only be made at autopsy. The almost universal decline in hospital autopsies has led to significant errors in the cause of death.[8] In a recent analysis of US death certificates from 2018, 34.7% of all death records had an unsuitable underlying cause of death while 19.8% had a non-specific underlying cause of death.[7] Correct death certification is vital to help guide public health service concerns and prevention.[9] There is still a role for the autopsy in the 21st century in determining the cause of cardiac death, which should guide future public health planning and prevention of further sudden deaths within a family when a specific genetic diagnosis is made.

In the first national autopsy-based UK study of people aged < 65 years in which Bowker *et al.* established that the estimated annual frequency of sudden unexpected death due to cardiac causes in adults was 11/100 000 (3481 annual deaths).[10] Not surprisingly, most deaths were due to coronary artery disease, but in 4.1% of sudden unexpected deaths no cause was found, and this was the first study to highlight these cases by a name: sudden adult/arrhythmic death syndrome (SADS). Following this study, a charity funded by bereaved families called Cardiac Risk in the Young (CRY) established, together with author M.N.S., a nationally available service for prospective reporting on the cardiac pathology of SCD. This work enables us to process hearts referred from coroners and pathologists from throughout the United Kingdom and report the results within 2 weeks of receipt of the heart. CRY also funded the development and maintenance of a prospective national pathology database based mainly on non-coronary atherosclerosis causes of SCD. We presented our initial results on 453 cases in 2006.[11] Since then, we have accumulated 7214 cases into this database, the largest series of autopsy sudden cardiac death in the world, and wish to expand upon our previous series and the evolution of the molecular autopsy, which is of vital importance to families and cardiologists who have developed the inherited cardiac conditions speciality within the United Kingdom.

Material and methods

All hearts are received fixed in formalin. This is the technique that M.N.S. has developed over time to examine the fixed hearts. The surface of the heart is examined and the coronary arteries are then sliced at 2–3-mm intervals to detect evidence of disease, such as significant atheroma, thrombosis, dissection, aneurysm formation or thickening, in all branches. All branches should be examined down to the apex of the heart to establish their pathway so as to exclude anomalous coronary artery. The atria are opened before looking at the ventricles. The atria are opened into the appendages. The right atrium is measured between the entrance of the superior and inferior caval vein longitudinally and transversely from the entry of the inferior vena cava to the tip of the right atrial appendage to determine right atrial size. We then check the tricuspid valve morphology to look for endocarditis, rupture or congenital abnormalities, such as Ebstein's anomaly. The inter-atrial septum is checked for fatty hyperplasia, the fossa ovalis for a patent foramen ovale and atrial septal defect. The left atrium is measured transversely between the left and right superior pulmonary veins and longitudinally from the atrioventricular junction to the superior edge to determine left atrial size. The intact mitral valve is then examined for evidence of prolapse into the left atrium, with ballooning or thickening or cordal/papillary muscle rupture into the left atrium. Once the atrioventricular valves are deemed normal macroscopically, the ventricles are sliced the transversely from the apex to mid ventricle at 5-mm intervals. The slices are examined for pathology such as hypertrophy, fatty infiltration, fibrosis and infarction. Lesions can be focal, so all levels should be examined carefully. Once the ventricles are deemed to be normal, measurements can then be made at the mid-ventricular level halfway between the atrioventricular junction and the apex of both ventricles. The cavity diameters are measured transversely, excluding the trabeculae and papillary muscles. The muscle thickness and epicardial fat of each ventricle is measured in the anterior, lateral and posterior walls. Septal muscle thickness is measured in the middle of the septum and excludes trabeculae and papillary muscle. In addition, the right ventricular outflow tract is measured 10 mm below the pulmonary valve. The epicardial fat measurement should exclude fat around the coronary arteries, where it is always prominent. The presence or absence of fibrosis, infarction or fat in the myocardium is commented upon. In the remaining heart the atrium and ventricle are opened

laterally, extending through each AV valve down to the mid-ventricle slice already made. Each atrium can then be examined closely and each appendage checked for thrombi. Both AV valves can be examined in detail and the annulus measured. The lateral left ventricular cut usually separates the anterolateral and posteromedial papillary muscles on either side. The right mid-ventricle slice is cut up into the pulmonary valve. From the left mid-ventricular slice, the aortic valve into the outflow tract is inspected and the three leaflets of the aortic valve are noted before cutting through the middle of the anterior leaflet of the mitral valve. The aortic valve can also be examined from above with a transverse ascending aortic cut. The valves are inspected for calcification and the number of leaflets are noted and annulus measured. The coronary artery ostia are examined in each sinus carefully for anomalous origin. The ascending aorta is examined for evidence of dilatation, intimal atheroma, thickening or dissection and the circumference is measured 20 mm above the valve. Following removal of any clot and attached aorta, the heart is then weighed. We have recently published on expected atrial measurements, ventricular cavity diameters, wall thicknesses, epicardial fat and valvular circumferences depending on age, sex and body measurements and provided a calculator.[12]

Cardiac sections

Blocks are taken for histology routinely from the mid-ventricular slice to include anterior, lateral (this will be a lateral cut to include right atrium above and right coronary artery as well as av junction and right ventricle) and posterior right ventricle, as well as the right ventricular outflow tract 10 mm below the pulmonary valve. Blocks are taken from the anterior, lateral (to include circumflex artery and mitral valve on lateral cut) and posterior LV as well as anterior and posterior IVS. Sections of coronary artery, atria and conduction tissue are also sampled routinely. Normally, 10 sections are examined, although more blocks will be taken if specific pathology is found. Significant stenosis or thrombosis of the coronary arteries is serially sectioned for histological analysis if observed. Following processing of the blocks, the slides are stained with haematoxylin and eosin. A picrosirius red stain is used to highlight fibrosis, if required. This sampling protocol is similar to one recommended by the UK Royal College of Pathologists, in which there is a probable cardiac cause of sudden death.[13] Table 1 shows our diagnostic criteria for cardiac causes of death and the associated figure shows examples of the histology.

The study was approved by the London–Stanmore Research Ethics Committee (10/H0724/38). Data will be made available upon reasonable request to the corresponding author.

Results

The CRY Pathology Unit has examined 7456 hearts between 1994 and 2021. Of these, 242 cases are excluded as they had a non-cardiac cause of death. We therefore have 7214 cases with cardiac causes of sudden death. Figure 1 shows the age referral pattern with a wide age distribution peaking in the 20–40-year age groups, but note that all age groups are represented. In all age groups, male predominance is striking (Figure 1).

Sudden arrhythmic death syndrome, in which the heart is morphologically normal, is the most common cause of death (3821, 53%), followed by the cardiomyopathies (1558, 22%) then ischaemic heart disease (670, 9%). Valve diseases, mainly comprising aortic stenosis and mitral valve prolapse (225, 3%), congenital heart disease (213, 3%) and myocarditis/sarcoidosis (206, 3%), are the next most common and make up similar proportions. Hypertensive heart disease (185, 3%), aortic disease, mainly acute thoracic dissection (129, 2%), and vascular disease, including ruptured peripheral aneurysms and vasculitis (97, 1%), make up smaller proportions of the cohort. Other cardiac diseases (70, 1%) include tumours, transplant and amyloidosis. Conduction disease (40, 1%) is reserved for cases of Wolff–Parkinson–White or total heart block diagnosed clinically, where often no pathological abnormality or focal fibrosis is detected in examination of the SA and AV nodal tissue. The causes of SCD are shown in Figure 2.

SCD occurs almost twice as commonly in males compared to females (4398 versus 2285, 1.9:1). This persists in most conditions underlying SCD, and is noted particularly in SADS, cardiomyopathies and ischaemic heart disease (Figure 1).

SADS is seen in all age groups, but is more frequent in the < 35-year age group, while cardiomyopathies predominate in the ≥ 35-year age group (Figure 1). Ischaemic and hypertensive heart disease is also more common in the ≥ 35-year rage group. When examining children aged < 15 years, SCD is mainly due to SADS (258, 61%), cardiomyopathy (68, 16%) and congenital heart disease (37, 9%).

Looking at the cardiomyopathies as a group, the pathological phenotype idiopathic hypertrophy (479,

Table 1. The diagnostic criteria that author M.N.S. has developed and uses to assess for the major cardiac diseases that underlie SCD

Pathology	Macroscopic criteria	Microscopic criteria
Hypertrophic cardiomyopathy	Increase in heart weight.* Right ventricular wall thickness > 5 mm or left > 15 mm. Atrial dilatation Can be normal macroscopically Absence of coronary artery disease	Left ventricular myocyte disarray (> 20% of myocardial disarray in at least two cardiac sections) and myocyte hypertrophy, with or without interstitial or replacement fibrosis and thick-walled blood vessels
Arrhythmogenic cardiomyopathy	Normal or increased heart weight.* Right or left ventricular thinning, fatty replacement, fibrosis on the epicardial surface Can be normal macroscopically Absence of coronary artery disease	Fibrosis admixed with fatty infiltration of the myocardium originating from the epicardial surface (> 20% in at least two cardiac sections)
Dilated cardiomyopathy	Increase in heart weight* with dilated left ventricle (> 40 mm chamber diameter) and thin compact wall (< 10 mm) Mural thrombi in ventricles. Dilated atria with thrombi in appendages Absence of coronary artery disease	Widespread diffuse interstitial or replacement fibrosis (> 20% in at least two cardiac sections) in the left ventricle with atrophic myocytes
Idiopathic left ventricular hypertrophy	Increase in heart weight.* Left ventricular wall thickness > 15 mm. No hypertension or coronary artery disease	Myocyte hypertrophy with or without replacement or interstitial fibrosis. Absence of myocyte disarray
Idiopathic left ventricular fibrosis	Normal heart weight and wall thickness with/without scarring macroscopically Absence of coronary artery disease. Absence of coronary artery disease	Replacement or interstitial fibrosis (> 20% in at least two cardiac sections). Absence of myocyte disarray
Hypertensive heart disease	Increase in heart weight.* Left ventricular wall thickness > 15 mm. History of hypertension No coronary artery disease	Myocyte hypertrophy with fine interstitial fibrosis in subendocardium. Absence of myocyte disarray
Myocarditis	Normal or dilated ventricles with variegated appearance Fibrinous pericarditis Can be normal macroscopically	Inflammation (> 20% in at least two cardiac sections) with associated myocyte necrosis
Coronary atherosclerosis	Atherosclerosis with luminal narrowing > 75% or lumen less than 1 mm or inability to insert 2-mm probe Infarction or scarring in myocardium Normal myocardium Rupture with haemopericardium Thrombosis in coronary artery	Acute or chronic infarction in right or left ventricle May be no infarction
Anomalous coronary artery	Anomalous origin of the coronary artery in the incorrect sinus with interarterial course or pulmonary artery origin	May have acute or chronic infarction in the right or left ventricle
Mitral valve prolapse	Prolapse of mitral valve above the atrioventricular junction with ballooning between cords in one or both leaflets. Diffuse thickening of leaflets Mitral annular dilatation Cordal thinning and/or rupture	Myxoid degeneration with expansion in spongiosa of leaflets and destruction of fibrosa layer. May be subendocardial fibrosis in posterobasal left ventricle
Aortic stenosis	Significant valve stenosis demonstrated by inability to insert a finger through the annulus Calcified valve and/or bicuspid valve Increase in heart weight* and left ventricular wall thickness > 15 mm	Myocyte hypertrophy and/or interstitial or replacement fibrosis throughout left ventricle

*Increase in heart weight is defined as greater than 450 g in females and greater than 550 g in males.

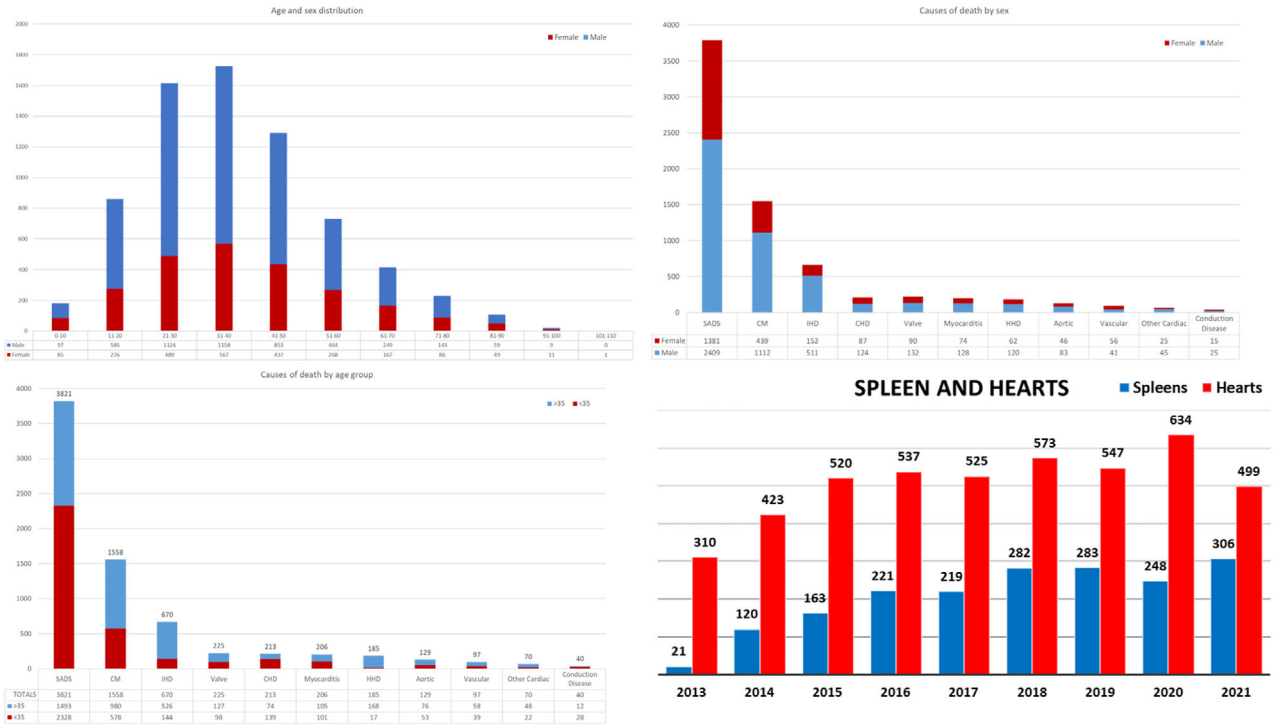

Figure 1. Demographics and numbers of referrals to the CRY cardiovascular pathology laboratories from 1994 to 2021. The upper left panel shows the age and sex distribution of the referrals, showing females in red and males in blue. The upper right panel shows the cause of death broken down by sex, showing females in red and males in blue. The lower left panel shows the causes of death broken down by less than and more than 35 years, with < 35-year-olds in red and >35-year-olds in blue. SADS = sudden arrhythmic death syndrome; CM = cardiomyopathy; IHD = ischaemic heart disease; CHD = congenital heart disease; HHD = hypertensive heart disease.

31%) is the most frequent, followed by arrhythmogenic (291, 19%), hypertrophic (284, 18%) and dilated (253, 16%) cardiomyopathies. Obesity cardiomyopathy was present in 11%. All are male-predominant and mainly occur in the ≥ 35-year age group (Figures 1 and 3).

Since 2013, the importance of taking genetic material at autopsy has been promoted by cardiologists and clinical geneticists and the so-called 'molecular autopsy' has evolved.[14,15] We developed a protocol for taking a small 1-cm square of fresh spleen and putting it into solution, called RNAlater, to preserve DNA. Since 2013 the number of spleens has risen from 21 in 2013 to 306 in 2021, reflecting that more than half the hearts are coming with material suitable for genetic analysis, which is continuing into 2022 (Figure 1).

Discussion

This study reflects the pathological phenotypes present in mainly non-ischaemic causes of SCD. It is well recognised that ischaemic heart disease is the most common overall cause of SCD, which includes our previous study.[10,16–18] This autopsy series focuses mainly upon the non-ischaemic causes of SCD; therefore, this study does not reflect the true incidence of this cause of SCD in the UK population. A large study from northern Finland of 4031 mainly older patients between 1998 and 2012 showed that, while ischaemic heart disease still predominated, it was reducing in incidence, while obesity-related, alcohol-related and hypertensive heart disease was increasing.[19] We emphasise that in younger patients the finding of significant coronary atheroma points towards the possibility of familial hypercholesterolaemia, so should be commented upon by the pathologist and the family screened accordingly.[20]

To our knowledge, this is the largest SCD cohort with autopsy findings ever reported in the literature from one country in which all cases have been autopsied and in which SADS and cardiomyopathies predominate. Comparison of SCD incidences between countries is difficult due to different age groups, autopsy rates and population, as well as regions selected and study designs. Nationwide studies in

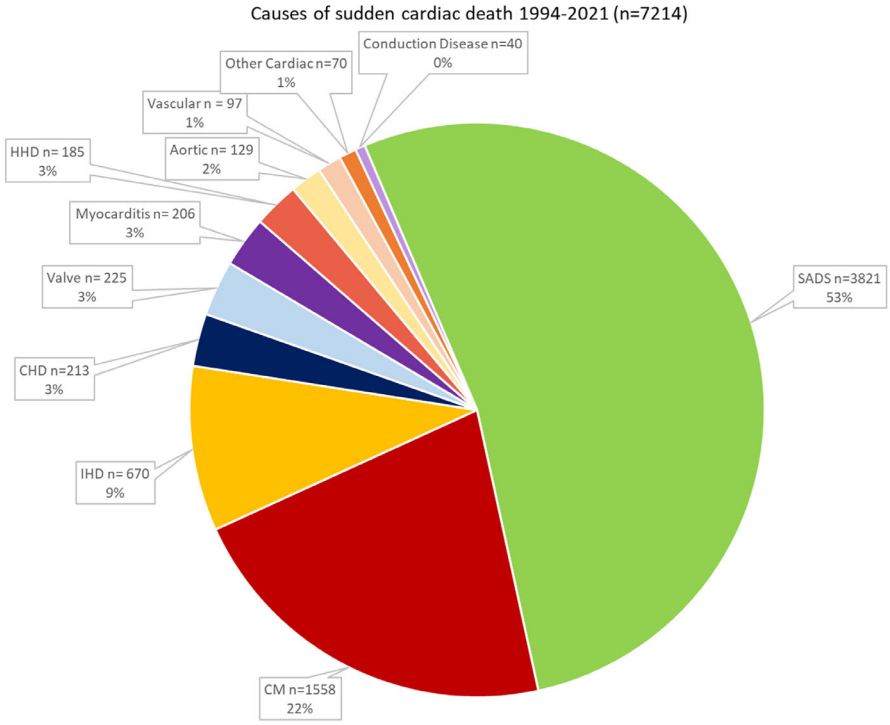

Figure 2. Pie chart showing causes of death: the causes of sudden cardiac death from 7214 referrals to the CRY cardiovascular pathology laboratories from 1994 to 2021. Sudden arrhythmic death syndrome (SADS) and cardiomyopathy (CM) account for 75% and are imperative to identify and advise family screening, as they can be heritable.

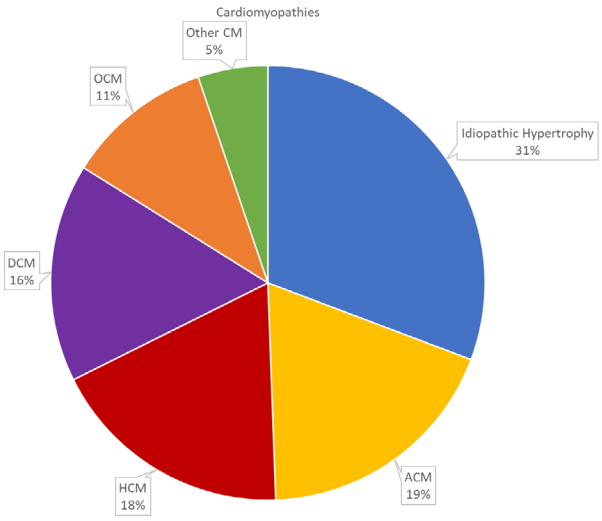

Figure 3. Pie chart showing cardiomyopathies: the breakdown of the 1558 sudden cardiac deaths with cardiomyopathy; idiopathic hypertrophy was most common. Arrhythmogenic cardiomyopathy (ACM), hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) made up similar proportions. Obesity cardiomyopathy (OCM) was less common (CM = cardiomyopathy).

Denmark, Australasia and Ireland[16,21–24] have been conducted, but not in such a wide age group, and not all had autopsies. There can be dramatic regional variation in autopsy rates even within a national legal framework, as shown in Denmark in 2012.[25]

Sudden adult death syndrome/sudden arrhythmic death syndrome (SADS)

The number of SADS which are also labelled as unexplained sudden cardiac death cases with negative autopsy and toxicology findings varies widely, depending upon age, study type and numbers (Figure 4). Previous studies have found SADS in 6–40% of cases[16,21,23,24,26–28]; all these studies confirm that SADS is more common in the younger age group. Males are more at risk for SCD in all the above studies, and our study also confirms this. Our high rate of 53% of unexplained/SADS may be due to referral bias, as a greater number of unexplained cases are more likely to be referred for a second opinion. However, we also believe that SADS is under-reported, as a study we undertook previously showed an overdiagnosis of cardiac pathology, especially HCM and ACM in normal hearts.[29] Some of the observed differences will be due to small-scale studies, regional variation, varied age ranges, select study populations and the absence of specialist examination. SADS is mainly due to

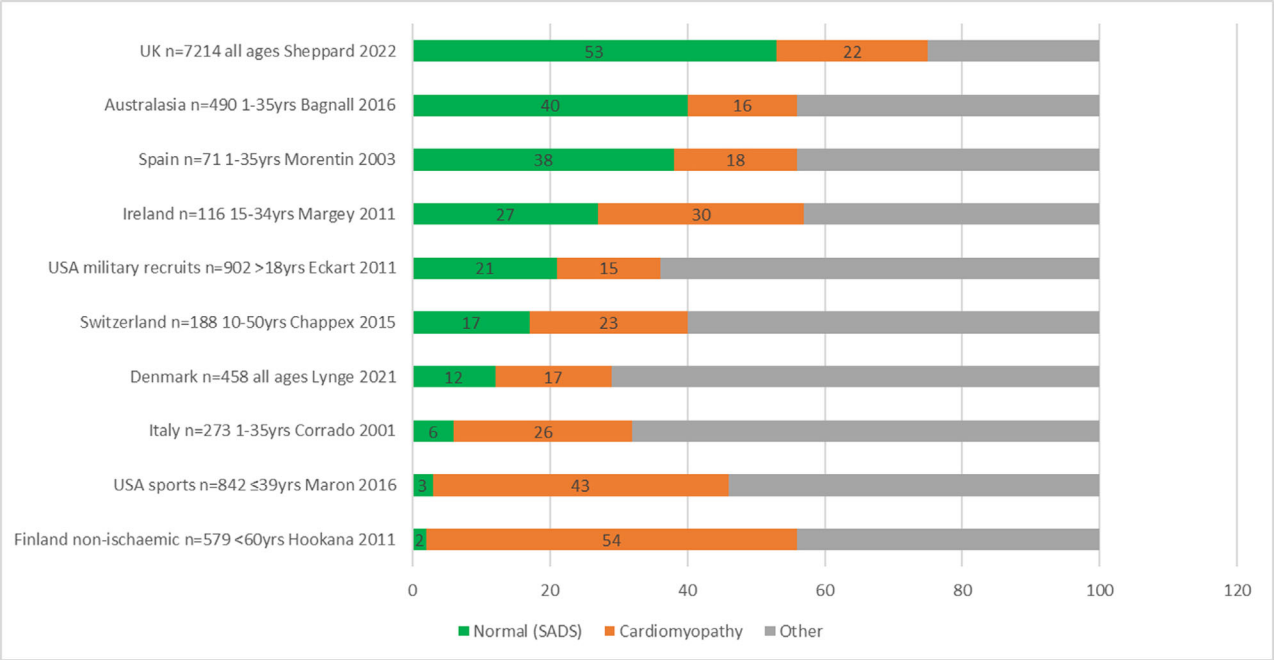

Figure 4. The proportions of sudden arrhythmic death syndrome (SADS) and cardiomyopathy from worldwide studies. This graph highlights the profound variability that exists between studies conducted in different countries from around the world.

inherited channelopathies in the majority of cases, with predominant entities being Brugada syndrome, long Q-T and catecholaminergic polymorphic ventricular tachycardia (CPVT),[30,31] and there are now clinical guidelines for their investigation in families.[32] It is thus essential that the pathologist correlates the normal heart and negative toxicology (the negative autopsy) and advises family cardiological screening. The combination of post-mortem genetic testing and family screening identifies an inherited cardiac condition in 39% of individuals diagnosed with SADS, further highlighting the importance of advising family screening and genetic testing.[31]

Cardiomyopathies

Our study identified cardiomyopathies in 22% of SCD cases, all with a male predominance and in the older age group. Other studies show cardiomyopathies ranging from 15 to 30% of SCD cases.[16,17,22,23,26–28] It is vital to diagnose these entities correctly, as most have a genetic cause and the family must undergo cardiological screening and genetic testing.[33]

When looking specifically at the types of cardiomyopathies within the cardiomyopathy category there is wide variation between our study and others. We report idiopathic hypertrophy in 32%, with ACM in 19%, HCM in 18%, DCM in 16% and obesity-related cardiomyopathy in 11%. The Danish study found a higher proportion of idiopathic hypertrophy in 60%, ACM in 29%, DCM in 7% and HCM in 4%.[22] The Irish study identified a much higher proportion of HCM at 49% and idiopathic hypertrophy in 34%, with DCM making up 9% and ACM 6%.[23] The Italian study identified a much higher proportion of ACM at 55%, with 27% being HCM and 18% being DCM with no cases of idiopathic hypertrophy.[28] HCM has been reported in 36% of 842 SCD in young US athletes, again with male predominance.[34] In a Finnish study of non-ischaemic cardiac deaths, cardiomyopathy made up 80% of cases.[35] This variation between national studies merits further investigation. The entity of idiopathic left ventricular hypertrophy is only now being included in SCD studies and on family follow-up does not appear related to HCM.[36] The entities of idiopathic cardiac fibrosis and obesity-related cardiomyopathy also need further study.

Cardiomyopathy made up a greater proportion of SCD in those aged ≥ 35 years in our study. This was also observed in the Danish and Swiss studies, particularly with regard to idiopathic left ventricular hypertrophy.[17,21] One exception to this is ACM, which presents with SCD more commonly in < 35-year-olds,[17,21] which is also noted in our cohort.

The underlying causes of the cardiomyopathy include genetic and metabolic conditions. Genes implicated in cardiomyopathy have increased considerably; a recent consensus guideline published by the European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society and Latin American Heart Rhythm Society highlights the complexity of this rapidly advancing field, with numerous genes associated with each cardiomyopathy.[37]

HCM is well recognised to be caused by mutations in sarcomere protein genes; however, it may also be mimicked by Fabry's and Danon diseases.[38] The HCM heart, which displays myocyte disarray on histology, may also be of a normal weight with no hypertrophy in approximately 30% of cases.[39]

The dilated cardiomyopathy phenotype has diverse aetiology, including metabolic causes such as inborn/mitochondrial, alcohol, diabetes and drugs and genetic, such as lamin A/C. A genetic cause is found in approximately 40–50% of cases of dilated cardiomyopathy.[40]

ACM is now recognised to be a biventricular disease and can affect solely the right or left ventricle, as well as affecting both ventricles. It is diagnosed by the presence of fibrosis in an epicardial distribution which is frequently admixed with fat. Historical reports had labelled cases with solely fat present in the right ventricle as ACM; however, it is now recognised that fatty infiltration of the right ventricle is a normal finding.[12,41]

Idiopathic hypertrophy, which is recognised to be distinct from HCM, is diagnosed on the basis of an increased heart weight in the absence of myocyte disarray.[36] We have recently published on the relationship between body measurements, sex and cardiac parameters, including heart weight, highlighting that the female heart has a lower weight, smaller atria and smaller ventricular wall thickness and cavity size but greater epicardial fat thickness.[12] The paper includes a calculator to provide expected measurements according to age, sex, height and weight.

Valve disease

Valve disease is a well-recognised cause of sudden cardiac death, incorporating entities such as aortic calcific stenosis, mitral valve prolapse and endocarditis. Other series have also highlighted it as a cause of SCD occurring at a range of less than 1% to 16%.[17,26,28] Mitral valve prolapse is important to identify as it can have a genetic aetiology, and therefore screening should be advised in blood relatives. Post-mortem studies have shown that myocardial fibrosis occurs most commonly in the posterior wall.[42] Endocarditis is a rare cause of SCD occurring in those with normal valves, valvular disease and following valve replacement surgery, and is frequently not diagnosed prior to autopsy.[43]

Congenital disease

SCD in individuals with congenital heart disease occurs frequently.[44] It has been observed to account for a similar proportion of SCD in other specialist cardiovascular pathology series.[45] There is frequently ventricular fibrosis in these individuals, which is thought to account for their SCD. However, a small proportion of individuals do not reveal a substrate for arrhythmia. Sequential segmental analysis and the 'morphological method' are important for describing these complex cases, which should be examined at a specialist centre.[46] Anomalous coronary arteries included under this category are also a well-established cause of SCD.[47]

Myocarditis and sarcoidosis

Myocarditis has been reported in 4–10% of autopsy cases in other series and has been noted to be more common in males compared to females, similar to our study.[23,24,28,48] Cardiac sarcoidosis can be a challenge to diagnose because of focal lesions. It is important to sample conduction tissue in cases of sarcoidosis, as it is frequently involved and can result in heart block.[49] It tends to occur in older individuals when compared to myocarditis.

Aortic and vascular

Aortic dissection and rare vascular causes, including peripheral ruptured aneurysms and vasculitis, are recognised within other studies which agree with our findings that it is a minor cause and generally found in fewer than 10% of cases.[23,24,27,28] It is important to advise screening in younger individuals with aortic dissection, as it is frequently familial.[50]

Conduction disease

Conduction system abnormalities are not mentioned in most other studies, but have been noted in 9% of cases in the Italian study[28] and 2% in one of the Danish studies.[21] These are higher proportions than within our cohort.

The concept of the molecular autopsy

The first such diagnosis was made in 1999 when a diagnosis of long Q-T was made in a fatal drowning. We have now proved that molecular testing with sample collection during autopsy in SCD is valuable in yielding a diagnosis.[30,31] Considering that SADS and cardiomyopathies accounts for a significant number of sudden deaths in young people and that epidemiological, clinical and now post-mortem genetic analyses all suggest a lethal cardiac channelopathy or cardiomyopathy mutation, the molecular autopsy should be viewed as the standard of care for the post-mortem evaluation of SCD.[51,52] Pathologists within the United Kingdom are already doing this by obtaining samples of spleen and fixing in RNAlater, thus avoiding the need for freezing tissue, and excellent-quality DNA can be extracted. Both the Royal College of Pathologists and European Association of Cardiovascular pathology have included this in their guidelines.[53,54]

Conclusion

This study highlights the importance of the autopsy in SCD, which is a significant public health concern in all age groups. It is important to verify the causes of SCD by autopsy, as death certification alone can be inaccurate and autopsy imaging is not yet reliable enough in detecting specific cardiac disease. We need to know the true incidence of conditions leading to SCD because, especially in the younger age group, in 75% of cases it is largely due to genetic causes. Multiple studies show that family members of young SCD victims are at risk of preventable cardiac disease. Knowing the true incidence with autopsy in a population will improve risk stratification and develop preventative strategies for family members. We have already established the molecular autopsy in a national pilot study of SCD, which is being undertaken with NHS England, Genomics England, British Heart Foundation and CRY in which all the genetic testing will be undertaken within the NHS.

Limitations

While we receive more than 500 cases annually, we obviously do not see all cases of SCD in the United Kingdom and ischaemic heart disease is not the focus of this study, which mainly deals with non-ischaemic causes.

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Conflicts of interest

We have no conflicts of interest to declare.

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