Advances in the prevention of sudden cardiac death in the young

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Ther Adv Cardiovasc Dis
(2009) 3(2) 145–155
DOI: 10.1177/1753944708100181

Abstract: Sudden cardiac death (SCD) is a tragic and devastating complication of a number of cardiovascular diseases. Although coronary artery disease accounts for a majority of these deaths across all ages, many other aetiologies contribute to this problem when it occurs in the young (age $\leq$ 35 years), where coronary artery disease is far less common. Specifically, genetic heart disorders are an important cause of SCD in the young. While pharmacological therapies have made some impact on prevention of SCD, the introduction of implantable cardioverter-defibrillator (ICD) therapy has been the single major advance in the prevention of SCD in the young. In addition, the awareness that most causes of SCD in the young are inherited, means family screening of relatives of young SCD victims allows identification of previously unrecognised at-risk individuals thereby enabling prevention of SCD in relatives. The role of genetic testing, both in living affected individuals and in the setting of a 'molecular autopsy', is emerging as a key factor in early diagnosis of an underlying cardiovascular genetic disorder. Understanding the genetic basis of SCD, investigating the molecular mechanisms that lead from the gene defect to the clinical phenotype, and elucidating the specific environmental triggers for SCD, will most likely lead to further key improvements in the prevention of SCD in the young.

Keywords: sudden cardiac death, screening, genes, family, multidisciplinary

Introduction

Sudden cardiac death (SCD) is a tragic and devastating complication of a number of cardiovascular diseases. SCD is defined as an unexpected death occurring usually within an hour of the onset of symptoms. The prevalence of SCD is significant, with an estimated 3 million people dying suddenly each year [Priori *et al.* 2001; Zipes and Wellens, 1998]. In the United States, SCD occurs in up to 450 000 people each year, translating to over 1000 deaths per day or one death every 1.5 minutes [Zheng *et al.* 2001]. Although coronary ischaemic heart disease accounts for a majority of these deaths across all ages, many other aetiologies contribute to this problem when it occurs in the young, defined as those aged $\leq$35 years, where coronary artery disease is far less common than in older age groups [Doolan *et al.* 2004]. Specifically, genetic heart disorders are an important cause of SCD in the young, as a consequence of both structural abnormalities and primary arrhythmogenic predisposition [Semsarian and Maron, 2002].

This review will focus particularly on SCD in the young. Specifically, an update will be provided on the causes of SCD in the young, and key aspects of prevention of SCD will be discussed, including lifestyle factors, pharmacotherapy, the role of implantable cardioverter defibrillator (ICD) therapy, and the importance of family evaluation and screening. For the purposes of this review, we will focus on two diseases which represent the most common structural and arrhythmogenic causes of SCD; that is, hypertrophic cardiomyopathy (HCM) and familial long QT syndrome (LQTS).

Causes of SCD in the young

SCD can broadly be categorised into disorders which predominantly affect the structure of the heart as well as those which affect mainly the cardiac conduction system, so-called

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arrhythmogenic disorders. The specific diseases which cause SCD within these two areas are summarised in Table 1. Up to 80% of SCD in the young has been attributed to a structural abnormality of the heart, the most common cause being HCM [Maron, 2003; Semsarian and Maron, 2002; Maron *et al.* 1996]. These cases are often diagnosed during life, or identified on pathological examination at post mortem. In contrast, arrhythmogenic disorders of the heart with no evidence of structural abnormalities at post mortem have been reported to account for less than 10% of all sudden cardiac deaths in the young. These primary arrhythmogenic disorders include LQTS, arrhythmogenic right ventricular dysplasia (ARVD), idiopathic ventricular fibrillation, and Brugada syndrome. Such cases in which no abnormalities are found at post mortem are classified as being of unknown aetiology or 'unascertained', resulting in an underestimation of the incidence of arrhythmogenic causes of SCD.

Compounding this underestimate, primary arrhythmogenic disorders can predispose to more overt causes of death. Consequently, young deaths attributed to events such as drowning and motor vehicle accidents may have been directly precipitated by a ventricular arrhythmia, as illustrated by an association between swimming and development of ventricular arrhythmias in patients with familial LQTS [Tester *et al.* 2005a]. Furthermore, studies suggest that up to 10% of sudden infant death syndrome (SIDS) deaths are associated with gene mutations known to cause familial LQTS [Tester *et al.* 2005b; Ackerman *et al.* 2001a]. Until recently, studies investigating the causes of SCD excluded deaths in which the heart appeared 'normal' at post mortem. In 2004, Doolan and colleagues reported the causes of SCD from post-mortem examinations performed in over 10 000 Australian subjects. In those aged ≤35 years, the most common cause of SCD in the young was a primary arrhythmogenic event (31%; Figure 1). In these young deaths no identifiable cause of death was found at post mortem, with the heart appearing structurally and histologically normal. The most likely cause for such deaths is by primary arrhythmogenic disorders, such as familial LQTS. Other important causes of SCD identified in this young Australian cohort included HCM, unexplained left ventricular hypertrophy, myocarditis, congenital heart disease, and other less common causes including aortic dissection, valvular heart disease and ARVD (Figure 1) [Doolan *et al.* 2004].

Genetic basis of SCD in the young

The majority of these cardiac disorders leading to SCD are either directly caused by genetic abnormalities; for example HCM, or have a genetic predisposition in the young; for example, coronary artery disease. Currently, over 40 genetic heart diseases have been described, with

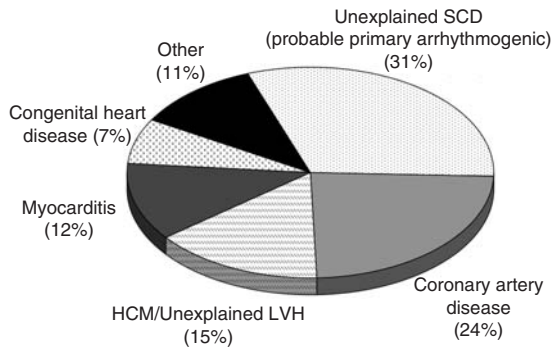

Figure 1. Causes of sudden cardiac death. Causes of sudden cardiac death (SCD) in young Australians aged ≤35 years. Unexplained SCD (probable primary arrhythmogenic event) accounts for 31% of all SCD. LVH = left ventricular hypertrophy (modified from Doolan *et al.* 2004).

Table 1. Causes of sudden cardiac death in the young.

Structural cause of SCD	Arrythmogenic cause of SCD
Abnormal post-mortem findings	'Normal' post mortem (autopsy negative)
Hypertrophic cardiomyopathy	Long QT syndrome
Coronary artery disease	Brugada syndrome
Myocarditis	Catecholaminergic polymorphic VT
Coronary anomalies	Idiopathic ventricular fibrillation
Arrhythmogenic right ventricular dysplasia	
Aortic dissection	
Congenital heart disease	

many of these disorders associated with an increased risk of SCD. The genetic basis of these cardiac genetic disorders which can lead to SCD is briefly summarised in Table 2. The two genetic heart diseases studied in most detail to date are HCM and familial LQTS.

Hypertrophic cardiomyopathy (HCM)

HCM was the first cardiac disease in which a genetic basis was identified and remains the most common cardiovascular genetic disorder, occurring in at least 1 in 500 of the general population [Chung *et al.* 2003; Maron *et al.* 1995]. HCM is a primary inherited disorder of the myocardium characterised by hypertrophy, usually of the left ventricle, in the absence of other loading conditions such as hypertension. Individuals with HCM exhibit marked diversity in their morphological features and clinical manifestations, ranging from no symptoms to heart failure and sudden death [Maron, 2002a]. This clinical heterogeneity reflects the complex pathophysiology underlying the disorder, which includes not only diastolic dysfunction, but also arrhythmogenic substrates leading to ventricular arrhythmias, small vessel disease leading to subendocardial ischaemia, and left ventricular outflow tract obstruction. Therefore, HCM is a disease in which a multitude of potential cardiac pathologies and outcomes exist, including severe heart failure and SCD [Lind *et al.* 2006; Chung *et al.* 2003].

Since 1990, over 400 mutations in at least 13 genes have been identified in patients with HCM (summarised in Table 2) [Lind *et al.* 2006].

Table 2. Genetic causes of sudden cardiac death.

Disease	Gene name	Encoded protein	% of disease
HCM	βMHC	β-myosin heavy chain	30–35
	MyBP-C	Myosin binding protein C	20–30
	cTnT	Cardiac troponin T	10–15
	TPM	Tropomyosin	5–15
	cTnI	Cardiac troponin I	<5
	CSRP3	Cardiac muscle LIM protein	<5
	TCAP	Telethonin	<2
	MYL2	Regulatory light chain	<1
	MYL3	Essential light chain	<1
	ACTC	Actin	<0.5
	TTN	Titin	<0.5
	MYH6	α-myosin heavy chain	<0.5
	TNNC1	Cardiac troponin C	<0.5
LQTS1	KCNQ1	I_{Ks} potassium channel a-subunit	35–40
LQTS2	HERG	I_{Kr} potassium channel a-subunit	30–35
LQTS3	SCN5A	I_{Na} sodium channel a-subunit	5–10
LQTS4	ANKB	Ankyrin B	<1
LQTS5	KCNE1/minK	I_{Ks} potassium channel b-subunit	<1
LQTS6	KCNE2/MiRP1	I_{Kr} potassium channel b-subunit	<1
LQTS7 (Andersen–Tawil syndrome)	KCNJ2	Inwardly rectifying potassium channel	50
LQTS8 (Timothy Syndrome)	CACNA1C	Voltage-dependent L-type calcium channel	<1
LQTS9	CAV3	Caveolin-3	<1
LQTS10	SCN4B	I_{Na} sodium channel b4-subunit	<1
Short QT syndrome-1	HERG	I_{Kr} potassium channel a-subunit	Unknown
Short QT syndrome-2	KCNQ1	I_{Ks} potassium channel a-subunit	Unknown
Brugada syndrome	SCN5A	I_{Na} sodium channel a-subunit	15–30
CPVT1	RyR2	Cardiac ryanodine receptor	65
CPVT2	CASQ2	Calsequestrin	5
ARVD	PKP2	Plakophilin-2	15–45
	DSP	Desmoplakin	15
	DSG2	Desmoglein-2	10
	TGFβ-3	Transforming growth factor-β3	2.5
	RyR2	Cardiac ryanodine receptor	Unknown
Naxos Disease	JUP	Junction plakoglobin	Unknown

*rarer genetic causes of disease excluded from table.

Approximately 70% of all mutations are identified in the two most common genes; β-myosin heavy chain (*βMHC*) and myosin-binding protein C (*MyBP-C*). All mutations are inherited in an autosomal dominant pattern and encode proteins of the sarcomere, or are associated with sarcomere-related structures. As with the clinical features, genetic heterogeneity is an important characteristic of HCM [Seidman and Seidman, 2001]. The explanation for the clinical variability observed in patients with HCM remains unclear. A number of possibilities exist, which include the actual gene involved, the type and location of the gene mutation, and the presence of both genetic (second gene) and environmental modifying factors that interact with the primary gene defect [Tsoutsman *et al*. 2006].

SCD in HCM is a relatively uncommon but important complication of the disease. The prevalence of sudden death ranges from 0.5% to 5% in various reported studies, most of which are derived from tertiary referral centres and therefore have an inherent tertiary referral bias of more severe cases [Maron, 2002a]. SCD in HCM is often associated with exercise, and in some cases, related to high-level, high-profile competitive sports [Maron *et al*. 1996]. Over recent years, a number of risk stratification factors have been identified in patients with HCM. Specifically, a positive family history of HCM, a previous resuscitated cardiac arrest, a left ventricular wall thickness $\geq$30 mm, syncope, and nonsustained ventricular tachycardia on Holter monitoring, are all considered important risk factors for SCD in HCM [Maron *et al*. 2003a; Maron, 2002b]. Other factors associated with an increased risk of SCD in HCM include an abnormal blood pressure response to exercise, significant left ventricular outflow tract obstruction, and the presence of specific 'malignant' gene mutations [Maron *et al*. 2003a].

Familial long QT syndrome (LQTS)

Prolongation of the QT interval most commonly occurs in the setting of drug therapy side effects; that is, acquired causes of LQTS. In the young, inherited or familial LQTS is responsible for the majority of cases in which SCD occurs [Goldenberg and Moss, 2008]. The prevalence of familial LQTS is reported to be 1 in 5000 although this is likely to be an underestimate given the increasing numbers of genetically proven familial LQTS patients in which traditional 'normal' measures of QT interval are observed.

Patients with familial LQTS are usually identified by QT prolongation on an ECG during clinical evaluation of unexplained syncope. The syncope that occurs in this disorder is due to a transient, rapid, polymorphic ventricular tachycardia described as 'torsade de pointes', which can deteriorate into ventricular fibrillation. A family history of SCD, or unexplained deaths due to 'epilepsy' or 'drowning' may also be present. The clinical course of patients with familial LQTS is variable and is influenced by factors such as the length of the corrected QT interval, gender, environmental modifiers, genotype and therapy [Roden, 2008].

Genetic studies over the last decade have identified familial LQTS as a disease of ion channels (so-called 'ion channelopathies'), predominantly involving K^+ and Na^+ channels (for a review see Goldenberg and Moss, 2008). At least 10 causative genes have been identified. Mutations in these ion channel genes lead to abnormal channel function, with alterations in cardiac repolarisation (early and/or delayed after depolarisations) resulting in QT prolongation and susceptibility to ventricular arrhythmias and sudden death. Approximately 80% of all family members with LQTS studied to date have been found to have mutations in the *KCNQ1*, *HERG* and *SCN5A* genes (Table 2) [Tester *et al*. 2006; Van Langen *et al*. 2003].

A number of factors have been identified that correlate with an increased risk of SCD in familial LQTS. The most powerful predictor is the corrected QT (QTc) interval, with a QTc interval >500 ms associated with an increased risk of SCD. Other important risk stratifying factors include a previous resuscitated cardiac arrest, syncope (particularly syncope while on beta blocker therapy), and a family history of premature SCD [Priori *et al*. 2003].

Other SCD syndromes in the young

Several less common genetic heart disorders have been identified in which SCD is an important and relatively common complication. A recent collection of diseases has been reported in families where exercise-induced SCD is a feature. Mutations in these families have been detected not only in K^+ or Na^+ ion channel genes, but also in genes related to Ca^{2+} homeostasis.

Two clinically distinct forms of SCD in children and young adults have recently been linked to autosomal-dominant mutations in the ryanodine receptor gene (*RyR2*; Table 2). These disorders, known as catecholaminergic polymorphic ventricular tachycardia (CPVT1) and arrhythmogenic right-ventricular dysplasia (ARVD) share the clinical characteristics of exercise-induced ventricular arrhythmias and SCD (Table 2) [Dalal *et al.* 2006; Tester *et al.* 2005b; Laitinen *et al.* 2003; Priori *et al.* 2002; Rampazzo *et al.* 2002]. ARVD is usually evident at post mortem by fatty deposits in the right ventricular wall, and although relatively uncommon in most reported series of SCD in the young, is the commonest cause of SCD in parts of Northern Italy amongst young athletes [Corrado *et al.* 1990]. Apart from *RyR2*, mutations in a number of structural/cytoskeletal genes have been identified to cause ARVD (Table 2) [Dalal *et al.* 2005; Rampazzo *et al.* 2002]. Furthermore, autosomal recessive mutations in the sarcoplasmic Ca^{2+} storage protein calsequestrin (*CASQ2*) have also been described in families with catecholamine-induced ventricular tachycardia (CPVT2; Table 2) [Di Barletta *et al.* 2006; Eldar *et al.* 2003].

Mutations in genes which cause familial LQTS, have also been implicated in other arrhythmogenic SCD syndromes. The Brugada syndrome defines a subgroup of patients at risk of ventricular arrhythmias who also have no definable structural heart disease. These patients classically have a right bundle branch pattern and ST elevation in leads V1 to V3 on electrocardiography, and tend to die during sleep, secondary to ventricular fibrillation [Priori *et al.* 2002a]. Interestingly, autosomal dominant mutations in the *SCN5A* gene have been found in approximately 25% of patients with the Brugada syndrome. Mutations in *HERG* and *KCNQ1* have also been identified in patients with short QT syndrome (Table 2), as well as in up to 5% of deaths reported to be due to SIDS [Tester *et al.* 2005b; Bellocq *et al.* 2004; Ackerman *et al.* 2001a].

Prevention strategies for SCD in the young

SCD in the young is always a tragedy. One of the most difficult and challenging problems for a clinician is sitting down face-to-face with a parent who has just experienced the death of his or her son or daughter. SCD in the young is always unexpected, is frequently unexplained, is usually in a previously healthy young person, and is a tragedy that is never fully overcome by the family. It is therefore not surprising that managing a family in which an SCD has occurred involves many aspects of clinical medicine [Ingles and Semsarian, 2007]. Prevention of further SCD events is the key goal of the management of families in which an SCD has occurred.

There are two common clinical presentations in which prevention of SCD in the young is of paramount importance: (1) the individual patient with no family history of SCD who presents for treatment and prevention (i.e. the affected individual); and (2) the family who presents after a SCD event in a young relative (i.e. the SCD family). In both these clinical presentations, a number of common approaches are required, and often involve a number of professional and allied health personnel in a multidisciplinary approach to care.

The affected individual

Avoiding SCD triggers

In many genetic cardiac disorders which cause SCD, observational studies have indicated environmental triggers which may precipitate ventricular arrhythmias and SCD. In the two diseases that are the focus of this review, both HCM and familial LQTS have been associated with potentially avoidable triggers. In HCM, up to 70% of SCD events occur during, or immediately after, high-level exercise, including competitive sports. The association of SCD with high-level exercise in HCM has led to the universal recommendation of avoiding competitive sports in all patients with HCM [Semsarian, 2007; Maron *et al.* 2004, 2003b; Maron, 2003b].

Environmental triggers are more complex in familial LQTS. Based on a number of reported cohorts, it appears certain LQTS genotypes are associated with different triggers [Goldenberg and Moss, 2008; Bunch and Ackerman, 2006; Schawrtz *et al.* 2001]. Specifically, LQTS types 1, 2 and 3 are linked to variable triggers, in addition to differences in ECG morphology and responses to pharmacological therapy (Table 3). SCD in LQTS1 is more commonly triggered by exertional activities, including emotional and physical stress, as well as swimming. In contrast, in LQTS2, sudden loud noises, such as being awoken by an alarm clock, can trigger SCD. In patients with LQTS3 (also causing the

Table 3. Triggers and drug responses in familial LQTS types 1–3.

Feature	LQTS1	LQTS2	LQTS3
Causative gene	KCNQ1	HERG	SCN5A
Triggers for SCD	Swimming, emotional or physical stress	Sudden loud noise, emotional or physical stress	Sleep, rest
Response to beta-blockers	Yes	Yes, but less than for LQTS1	Uncertain

Brugada syndrome), SCD often occurs at rest or during sleep [Priori *et al*. 2002a].

Avoidance of such triggers, where feasible, is indicated. Clearly patients need to sleep, but avoiding emotional and physical stressors, which may include various behavioural and relaxation therapies, as well as avoiding involvement in competitive sports, are important lifestyle measures aimed at reducing the triggers for SCD.

Pharmacological therapies

Overall, pharmacological therapy to prevent SCD has been disappointing in cardiac genetic diseases. The mainstay of pharmacological SCD prevention has been beta-blockers and amiodarone. Both are associated with significant side-effects, particularly in this target population in which therapy is frequently commenced within the first two decades of life.

In HCM, no definitive randomised trials have been performed to show any pharmacological therapy can prevent SCD in the young. Beta-blockers and amiodarone have both been used on an empirical basis with some evidence of reduction in arrhythmic events [Ostman-Smith *et al*. 1999; McKenna *et al*. 1985], but neither has been identified to prevent SCD in HCM.

In patients with familial LQTS, the mainstay of pharmacological therapy has been beta-blockers. While beta-blockers *per se* do not reduce the QT interval, largely observational studies have indicated familial LQTS patients on beta-blockers have less syncopal events and an improved survival [Hobbs *et al*. 2006]. In recent studies, which take into account the underlying genotype, patients with the LQTS1 genotype respond particularly well to beta-blockers in terms of reduced syncope and improved survival when compared with patients with LQTS2 and LQTS3 (Table 3) [Priori *et al*. 2004]. This favourable response in LQTS1 patients is consistent with the adrenergic dependence of LQTS1.

Sodium-channel blockers such as mexiletine and flecanide have been shown to normalise the QT interval in patients with LQTS3, but there are significant concerns in those who have overlapping Brugada syndrome. Specifically, treatment with these sodium-channel blockers in this setting may increase the risk of SCD, and therefore the role of this group of drugs remains uncertain [Moss *et al*. 2005; Priori *et al*. 2000].

Importantly, in patients with familial LQTS, drugs known to prolong the QT interval must be avoided. Patients need to be educated that such QT-prolonging drugs are numerous and are used in the treatment of a diverse group of clinical disorders. Commonly used QT-prolonging drugs include amiodarone, albuterol, cisapride, erythromycin, pseudoephedrine and sotalol.

Implantable cardioverter-defibrillator (ICD) therapy

The most significant advance in the prevention of SCD in the young has been the introduction of ICD therapy. While the focus of ICD therapy has been on older patients with coronary artery disease and heart failure, the use of ICD therapy for both primary and secondary prevention in young people with inherited heart disorders at risk of SCD has been a major strategy in preventing SCD.

In HCM, ICD therapy has been shown to be of benefit in a number of studies published predominantly over the last decade [Jayatilleke *et al*. 2004; Maron *et al*. 2003a, 2000]. The largest of these, a 42-centre international study involving 506 unrelated patients with HCM, showed ICD therapy was successful in reducing SCD events at a rate of 10.6% per year for secondary prevention and 3.6% per year for primary prevention [Maron *et al*. 2007]. The key indications for

ICD therapy, listed previously, were again confirmed in this study and further highlighted the notion that having only one of the risk factors alone was sufficient to warrant ICD therapy [Maron *et al.* 2007].

In familial LQTS, as well as other arrhythmogenic disorders such as Brugada syndrome, CPVT and ARVD, ICD therapy is emerging as a cornerstone for prevention of SCD. The use of ICD therapy in familial LQTS is considered in patients at high risk for SCD [Goel *et al.* 2004; Zareba *et al.* 2003]. These high-risk patients include those with symptoms in early life (age < 12 years), those with a previous resuscitated cardiac arrest, those with a markedly prolonged QTc interval (QTc > 500 ms), and those with recurrent syncope despite beta-blocker therapy. The benefits of ICD therapy have also been reported in patients with Brugada syndrome, CPVT and ARVD. Potential complications of ICD therapy, including inappropriate shocks, 'multiple shocks', psychological effects regarding fear of the device being activated, are all relevant issues which need to be discussed with patients prior to initiation of ICD therapy.

The sudden cardiac death family

Investigating the cause of SCD

An increasingly common presentation in genetic heart disease clinics is the family who present after a SCD in a young relative. In beginning to clinically evaluate the surviving relatives, a critical first step is to pursue all available avenues to determine the exact cause of death. Such an investigation should include obtaining any premorbid medical information (e.g. symptoms, ECG, etc.), and investigating the circumstances of the death, including whether the death occurred during activity or at rest, and talking to any witnesses (including information from ambulance and police reports). Investigation of the information from the post-mortem examination is crucial, and should include evaluation of the post-mortem report, with a particular focus on the macroscopic and histological evaluation of the heart, as well as in some cases a direct discussion with the attending forensic pathologist.

Unfortunately, as previously reported (Figure 1) [Doolan *et al.* 2004], in approximately one-third of young SCD cases, the post mortem is negative. The availability of post-mortem tissue for subsequent DNA analysis should therefore be considered, as genetic testing strategies in post-mortem negative cases is emerging as an important aspect of identifying the cause of unexplained SCD (the 'molecular autopsy') [Doolan *et al.* 2008; Ingles and Semsarian, 2007; Tester *et al.* 2006]. As the correct diagnosis and therefore cause of SCD in the young will have major implications for clinical screening and management of the surviving relatives, every effort should be made to investigate the cause of death.

The surviving family

As the majority of causes of SCD in the young have a genetic basis, investigation of the surviving relatives is crucial in identifying further affected individuals, who may themselves be at an increased risk of SCD. The majority of genetic heart diseases show autosomal dominant inheritance and marked clinical heterogeneity. This means the probability of other family members being affected is high, but the variability in presenting phenotypes can often make a diagnosis very difficult. Clinical screening of family members should be tailored based on the suspected underlying disease. The cardiac investigation of surviving family members should include a thorough clinical history, physical examination, 12-lead resting ECG, M-mode and 2D echocardiography, and in most instances, an exercise ECG stress test. Additional tests may be required for specific cardiac genetic diseases. For example, if Brugada syndrome is suspected, flecainide challenge should be performed, while if ARVD is suspected then cardiac MRI is most informative.

In the first instance, clinical screening of first-degree relatives should be carried out. Family members who are clinically screened and found to have no evidence of disease should be followed up at regular intervals. The frequency of follow-up is largely dependent on the disease in question and the age of the individual. Clinical screening of surviving family members after an SCD is not only useful in identifying affected individuals, but particularly in the case of a unexplained SCD, can provide useful insight into the cardiac disease affecting the family, and therefore the cause of death in the young deceased individual. Clinical assessment of surviving family members after an unexplained SCD has recently been reported to lead to the diagnosis of the underlying cardiac disease, and likely cause of death, in 40% of cases [Tan *et al.* 2005].

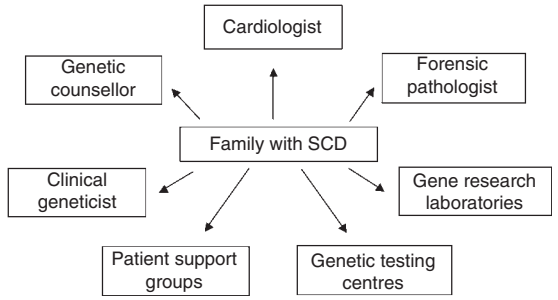

Figure 2. Key components of a specialised cardiac genetics clinic. A critical aspect of the care of families where a young SCD has occurred is the integrated involvement of a number of key health and allied health professionals.

Multidisciplinary approach to care in SCD families

In addition to establishing the cause of the SCD, and performing clinical screening of surviving relatives, there are many other medical issues that need to be addressed in this complex medical presentation. The family experience a range of emotions from grief following the death of a loved one, to fear that it will happen again in the family, to a feeling of hopelessness not knowing why their loved one died, to anger over why it happened to them. These normal psychological responses need to be managed sensitively and appropriately. Furthermore, with the major advances in our knowledge of the genetic basis of many cardiovascular diseases which can lead to SCD in the young, informed discussions relating to genetic counselling and testing need to be part of the overall management strategy of the family. Therefore, the investigation and appropriate management of a family with a young SCD requires a dedicated multidisciplinary team, in the form of a Cardiac Genetic Clinic (Figure 2). Recent evidence suggests such specialised clinics significantly reduce anxiety and worry levels in families with a genetic heart disease [Ingles *et al.* 2008].

The role of genetic testing in prevention of SCD in the young

The role of genetic testing in cardiovascular medicine is emerging as an important tool for early diagnosis and therefore the opportunity to initiate potential treatment and prevention strategies earlier in life. This is similarly the case in evaluating both individuals and families at risk of SCD. The majority of genetic heart diseases predisposing to SCD are autosomal dominant, meaning there is a 1 in 2 (50%) chance of passing the gene mutation on.

Commercial genetic testing for a number of these diseases; for example, genetic testing for HCM and LQTS, is now readily available. Specifically, any family member can have a gene test to determine if they too carry the genetic abnormality. This can prove extremely useful in family members who have a borderline phenotype; for example, a young person with an 'athlete's heart'. Genetic testing should be performed in the setting of a cardiac genetics clinic, with appropriate pretest counselling provided. The process of genetic testing can be both time consuming and costly, and due to the large number of genes implicated in inherited cardiac disease, it is not feasible to screen every gene in every case of young SCD. Therefore, a targeted approach to genetic testing is more cost-effective and informative when a clinical diagnosis is first made, allowing the list of potential causative genes to be narrowed down. It should be noted that in every inherited cardiac disease listed in Table 2, there exists a proportion of patients who have no gene mutation identified in the known causative genes. In addition, where a clinical diagnosis of LQTS or HCM is made, genetic testing can uncover a more complex genotype, involving the identification of more than one disease-causing mutation, leading to compound and double heterozygotes. This has important implications for recurrence risk and further highlights the need for discussion at a cardiac genetics clinic.

In the specific example where there has been an unexplained SCD in the young; that is, where the post mortem is negative, the current hypothesis is that these deaths were caused by an underlying arrhythmogenic disorder, and if genetic testing is considered, a focus should be on mutations in genes which cause LQTS (LQTS1-5) and CPVT (RyR2) [Doolan *et al.* 2008; Tester *et al.* 2006, Ackerman *et al.* 2001a, 2001b]. The concept of a 'molecular autopsy'; that is, genetic analysis, targeted at the possible causes of death is performed as part of the routine post-mortem examination in order to determine a specific cause of SCD, is currently mainly at a research level but will likely become an important part of the routine forensic examination of SCD in the young.

Conclusions

SCD is a tragic and devastating complication of a number of cardiovascular diseases. In the young, SCD is frequently caused by an underlying genetic heart disorder. Major advances have been made in our understanding of both the clinical and genetic basis of SCD in the young. While pharmacological therapies have made some impact on prevention of SCD, the introduction of ICD therapy has been the single major advance in the prevention of SCD in the young. In addition, the awareness that most causes of SCD in the young are inherited, means family screening of relatives of young SCD victims allows identification of previously unrecognised at-risk individuals thereby enabling prevention of SCD in relatives. The role of genetic testing, both in living affected individuals and in the setting of a 'molecular autopsy', is emerging as a key factor in early diagnosis of an underlying cardiovascular genetic disorder. Understanding the genetic basis of SCD, investigating the molecular mechanisms that lead from the gene defect to the clinical phenotype, and elucidating the specific environmental triggers for SCD, will most likely lead to further key improvements in the prevention of SCD in the young.

Acknowledgements

CS is the recipient of a co-funded National Health and Medical Research Council (NHMRC) and National Heart Foundation of Australia (NHFA) Practitioner Fellowship, in addition to a research grant from the RT Hall Foundation, Sydney, Australia.

Conflict of interest statement

None declared.

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