Review

Sudden Cardiac Death in the Young: Advances in Risk-stratification and Treatment

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Sudden cardiac death (SCD) is an uncommon but extremely tragic event in pediatric patients. In this review, we discuss recent advances in this problem, focusing on the cardiovascular diseases associated with SCD and the management of patients who are identified as being at high risk for SCD. The most significant advances have occurred in the following areas: 1) definition of the causes and treatments of genetic cardiovascular diseases; 2) advances in risk assessment for SCD in patients with congenital heart disease (CHD); and 3) treatment strategies for SCD risk reduction in patients with cardiomyopathies. Based on recent advances, our understanding of the causes and risk factors for SCD as well as management of children at risk has improved. This includes clinical criteria for SCD risk stratification as well as optimal management strategies such as the judicious use of anti-arrhythmic medications and implantable device therapy.

Introduction

Sudden cardiac death (SCD) is defined as a death which is abrupt, unexpected and due to a cardiovascular cause, occurring in the absence of other potentially fatal conditions.[1] The term *sudden* refers to an interval of less than 1 hour from the onset of symptoms to biologic death or irreversible neurologic injury. Although SCD is most frequently an event in adults with coronary artery disease, it may also occur in young patients with diverse forms of cardiovascular disease. These include individuals with cardiomyopathies, prior repair of congenital heart defects, and primary arrhythmic disorders such as the long QT syndromes and other genetic channelopathies.[2]

Although some diseases associated with SCD in the young are clinically obvious, cardiovascular collapse may be the first symptom in others. Studies of SCD therefore focus on the identification of patients with the subtle diseases known to cause SCD as well as risk stratification for SCD in those with recognized heart disease. The identification of young individuals at risk for SCD remains a crucial public health challenge, as the probability of survival without neurologic disability following an out-of-hospital cardiac arrest is between 2% and 17%, depending on the cardiac rhythm at the time of initial resuscitation.[3] However, the very low incidence of SCD among those < 21 years of age (generally estimated at 1 : 100,000 patient-years) has precluded the performance of systematic clinical studies which would allow the development of criteria for the prospective identification of young patients at risk for SCD.

In spite of these challenges, recent advances in school screenings, genetic testing and implantable devices have stimulated efforts to define individuals who are at risk for SCD prior to a first event. This discussion will focus on recent advances in these areas, based on the types of underlying cardiovascular disease responsible for the risk of SCD in young patients.

Genetic Cardiovascular Diseases

Tremendous progress has been made in the current decade in the diagnosis and treatment of primary arrhythmic disorders, which are now recognized to be due to gene mu-

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tations resulting in cardiac ion channel dysfunction and ultimately cardiac arrhythmias. To summarize and categorize the rapid advances in this area, a 2007 Consensus Committee of the National Heart, Lung and Blood Institute proposed the following classification for inheritable electrical cardiomyopathies: 1) sodium channelopathies; 2) potassium channel mutations, responsible for most long QT syndrome (LQTS) variants; and 3) arrhythmias due to other ionic mechanisms, primarily involving abnormal calcium transport.[4] The molecular and clinical advances in these genetic diseases will be summarized using this classification system.

1. Sodium channel mutations

The clinical phenotypes of sodium channelopathies include the Brugada syndrome, familial conduction system disease, and congenital sick sinus syndrome. These diagnoses have all been linked to mutations in the SCN5A gene, which has been mapped to chromosome 3p21, resulting in loss of function in the sodium channel.[4]

Although Brugada syndrome was initially described over 15 years ago, the clinical course of this disease in pediatrics was only recently reported.[5] In a study of 30 children (mean age 8 $\pm$ 4 years) with Brugada syndrome, the diagnosis was based on clinical symptoms in 13 patients (10 with syncope) and was an incidental discovery in 17 others during family screening. All symptomatic patients displayed spontaneous ST segment elevation; conversely symptoms were only reported in 1 of 13 patients who required drug provocation to unmask the typical electrocardiogram (ECG) findings of Brugada syndrome. A very important finding was that syncope and cardiac arrhythmias in young patients with Brugada syndrome were most commonly precipitated by fever. During 37 $\pm$ 23 months of follow-up, 1 patient died suddenly and 2 received appropriate implantable cardioverter defibrillator (ICD) therapies. The authors concluded that *symptomatic* pediatric patients with *spontaneous* Brugada ECG pattern are at high risk, particularly during a febrile illness; conversely the prognosis of Brugada syndrome in asymptomatic children in whom the Brugada ECG pattern is present only following drug provocation is favorable. The ECG diagnosis of Brugada syndrome remains a challenge in young patients because the precordial ST segment elevation may be intermittent, a right bundle block pattern may be present in up to 5% of all young individuals, and the presenting arrhythmia may be either an atrial or ventricular tachycardia (VT), sinus bradycardia or an unexplained seizure.[6]

2. Potassium channel mutations

The clinical phenotype of diverse potassium channel mutations are represented by the LQTSs. Clinically, the term LQTS refers to a group of disorders with the common features of prolongation of the corrected QT interval on the surface ECG and associated syncope, polymorphic VT or familial SCD.[7] In fact, this is a heterogeneous group of disorders, which may be either congenital or acquired, with an autosomal dominant pattern of transmission usually seen in individuals with the congenital form of this disorder. In the current era of commercially available genetic testing, a specific mutation is identified in nearly 75% of families with LQTS, with 90-95% of these mutations involving abnormalities of potassium channel function.[4] At least ten different long QT gene mutations have been identified, with the site of the defect (transmembrane versus pore region) an important determinant of the clinical manifestations.[8]

In spite of these molecular advances, the diagnosis of a prolonged QT interval by the surface ECG remains challenging in children. This is due to the presence of sinus arrhythmia, uncertainty regarding the inclusion of “U” waves, and the transient prolongation of the QT interval frequently observed in newborns.[9] These difficulties in diagnosis were highlighted by Taggart et al. in a study describing the misdiagnosis of LQTS.[10] Of 176 patients referred with a preliminary diagnosis of LQTS, 73 patients (41%) were ultimately categorized as normal, 56 (32%) as possible and only 47 (27%) as definite LQTS. Errors in diagnosis were most often overestimation of the QTc (corrected QT) and misinterpretation of vasovagal events as cardiac arrhythmias.

Due to the imprecision inherent in measurement of the ECG and diverse clinical presentations, criteria were proposed in 1993 for the diagnosis of the long QT syndrome based on the ECG and clinical events.[11] Patients with 4 or more points were categorized as having a high probability, 2-3 points as intermediate and one or less as low probability of having the LQTS. More recently, the clinical course and risk for life-threatening events for adolescents was reported by the international long QT registry.[12] In this analysis, a QTc $\geq$ 530 ms was the critical value, with a hazard ratio (HR) of 2.3 for life-threatening events compared to those with a QTc < 530 ms. Syncope within the prior 2 years had an adjusted HR of 11.7-18.1 for events compared to those

Table 1 LQTS - risk stratification

Risk of event	Highest risk (>50%)	Intermediate risk (30-50%)	Low risk (<30%)
Males	LQT 1,2,3 with QTc >500	LQT 3 with QTc <500	LQT 1,2 with QTc <500
Females	LQT 1,2 with QTc >500	LQT 2 with QTC <500 Any LQT3	LQT 1 with QTc <500

Estimated lifetime risk of an event in an individual with long QT syndrome (LQTS) based on corrected QT interval (QTc), gender and LQTS genetic subtype. For LQT 1 patients, the risk of events is greater for mutations located in the transmembrane regions.[8,13)]

without syncope.

With the addition of genetic testing to clinical events and ECG criteria, further attempts at risk stratification in LQTS have been developed.[13)] These include a composite evaluation based primarily on the degree of QTc prolongation, the gender and age of the patient and the specific type of genetic mutation (Table 1). The potential benefit of beta-blockade in the prevention of events has also been elucidated, based on the specific type of LQTS: a 66% relative risk reduction has been demonstrated in LQTS-1, compared to a 33% relative risk reduction in LQTS-2 and no benefit in LQTS-3.[14)] Although these beta-blockade efficacy data are from adults with LQTS, it is reasonable to anticipate a similar benefit ratio in young patients with LQTS.

The initial recommended treatment of minimally symptomatic patients with LQTS continues to be beta-blockade, with the exception of those with a SCN5A mutation. Combined treatment with a pacemaker and pharmacologic therapy has not proven to provide effective prophylaxis against SCD in symptomatic patients.[15)] Therefore, LQTS patients who are SCD survivors or with recurrent syncope on medication generally require implantation of an ICD.

As a related topic, there continues to be debate regarding whether some cases of sudden infant death syndrome (SIDS) may be due to the presence of LQTS which is unrecognized. Interest in this area was renewed when Schwartz reported in 1998 that a large proportion of SIDS victims had a prolonged QT (> 440 ms) during ECG screening in the first week of life.[16)] The hypothesis that some cases of SIDS are caused by a cardiac ion channel defect has been further supported by recent genetic studies. Arnestad et al. reported on post-mortem molecular screening of seven genes associated with LQTS in 201 consecutive cases of SIDS from Norway.[17)] Significant mutations were identified in 19 of the 201 cases, including 13 cases with SCN5A mutations. The clinical implications of these studies are that 1) cases of *recurrent* familial SIDS require consideration of an inherited ion channelopathy and 2) 5-10% of all cases of SIDS may be due to a cardiac ion channel mutation. This issue remains a topic of debate, but does not appear to explain the majority of deaths from SIDS.[18)]

Prolongation of the QT interval may also be “acquired” secondary to electrolyte abnormalities, hypothermia, central nervous system injury, liquid protein diets, and starvation. A number of antiarrhythmic medications, non-sedating antihistamines, and macrolide antibiotics have been associated with QT interval prolongation.[19)] There is increasing evidence that some individuals are genetically predisposed to QT prolongation, and that these drugs may unmask this disorder.

3. Calcium-dependent arrhythmia syndromes

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is increasingly recognized as a cause of unexplained SCD in young individuals. Most cases of CPVT are due to mutations in the calcium receptor RyR2 gene, which results in uncontrolled calcium release during electrical diastole.[4)] The mean age of onset of symptoms in CPVT is 8 years, with 30% of probands having a family history of unexplained SCD.[20)] Atrial arrhythmias as well as sinus node dysfunction have been recognized as part of the CPVT phenotype, and the possibility has been raised that SVT (supraventricular tachycardia) may trigger the ventricular arrhythmias.[21)] In spite of a very large genome, successful genotyping is reported in 55-60% of CPVT patients. The efficacy of beta-blockade remains in debate, with a recent study demonstrating a role for calcium channel blockers in augmenting beta-blockade.[22)] Therapeutic guidelines are based on limited data, with ICDs indicated for patients with aborted SCD or CPVT during exercise.

Table 2 Risk score for appropriate ICD shocks in primary prevention of TOF patients[27)]

Variable	Points attributed
Left ventricular end-diastolic pressure ≥ 12 mmHg	3
Non-sustained ventricular tachycardia	3
Inducible sustained ventricular tachycardia	2
Prior palliative shunt	2
Ventriculotomy incision	2
QRS duration ≥ 180 ms	1
Total points	0-12

4. Post-mortem genetic testing

No abnormalities are identified at autopsy in up to 30% of sudden deaths in previously healthy children and adolescents. These cases, which are referred to as sudden unexplained death (SUD) when SCD occurs after the first year of life, have led forensic pathologists to speculate that the causes of death may be arrhythmic. Three recent studies have recently been reported regarding gene testing in the autopsy-negative victims and their first degree relatives.[23–25)] A defined or probable cause of SUD was established in 39% of victims, with genetic findings suggesting CPVT nearly as common as LQTS. These results indicate the need for extended family screening after SUD in a child.

Congenital Heart Disease (CHD)

Survival following surgical repair of congenital heart defects has continued to improve in recent decades due to advances in surgical and post-operative care. However, late death after surgical treatment of CHD continues to pose a challenge, with identification of the causes and risk factors for SCD a topic of ongoing research.

1. Incidence and risk factors

In a long-term population-based study in Finland, Nieminen et al. provided insight into the causes of late deaths following CHD surgery.[26)] Of 6,024 patients studied, there were a total of 592 (9.8%) deaths during the 45-year follow-up period. Sudden death occurred in 88 patients (22% of 400 cardiac deaths) at a mean age of 19.3 years. Most sudden deaths (84%) were classified as *arrhythmic* due to lack of other structural abnormalities, along with a prior history of arrhythmias in most patients. In patients with tetralogy of Fallot (TOF) and D-transposition of the great arteries (d-TGA), SCD accounted for 30% of all CHD-related deaths, with males with TOF or d-TGA at significantly higher risk for SCD than females (relative risk of 3.9).

SCD risk stratification is crucial for long-term survivors of surgery for CHD, both to determine optimal medical or surgical therapies and to identify the highest risk patients who may be candidates for ICD therapy. Insights into risk factors for SCD for patients with TOF were provided by a multi-center study of ICD discharges by Khairy et al.[27)] In this study of 121 TOF patients with ICDs, the observed annual rates of ICD discharges were 9.8% in patients with an ICD for secondary prevention of SCD compared to a 7.7% annual rate of appropriate ICD discharges in primary prevention patients. For primary prevention, an elevated left ventricular end-diastolic pressure and non-sustained VT independently predicted appropriate ICD discharges. Based on this data, these authors devised a risk score for TOF patients and defined low risk (0-2 points), intermediate risk (3-5 points) and high risk (6-12 points) patients (Table 2). Annualized rates of appropriate ICD shocks were 0%, 3.8%, and 17.5% for low, intermediate and high risk patients, respectively. Of note, although not included in this analysis, appropriate anti-tachycardia pacing for termination of VT also occurred at an annual rate of 2.4% in the low risk group.

A recent report regarding the use of ICDs in patients with prior Mustard or Senning (atrial baffle) repairs of d-TGA evaluated 37 patients (age 28 ± 7.6 years).[28)] ICDs were implanted in 23 patients for primary prevention and 14 for secondary prevention of SCD. The annual rates of appropriate ICD shocks were 0.5% for primary and 6.0% for secondary prevention, with intra-cardiac electrograms documenting supraventricular tachycardia preceding or co-existing with VT in 50% of shocks. Inducible VT at electrophysiology study was not predictive of future events; however, the use of

beta-blockers was associated with a reduced incidence of appropriate ICD therapies.

2. Catheter ablation of VT

Investigation continues into the role of catheter ablation in the treatment of VT in CHD patients. Kriebel et al. performed non-contact mapping in 10 patients with TOF and hemodynamically unstable VT.[29] Ablation was attempted in eight patients, with no radiofrequency lesions in 2 patients due to a high risk for atrioventricular block. In all eight patients undergoing ablation, VT was not inducible at the end of the case, with recurrence of VT in 2 patients during a mean follow-up of 35.4 months. Regardless, ICD's were recommended in all patients post-ablation, with successful termination of VT in one patient.

Zeppenfeld et al. reported the results of electroanatomical contact mapping and catheter ablation in 11 patients with VT after repair of CHD, including nine with TOF repair.[30] Detailed arrhythmia mapping in the TOF patients revealed that reentrant VT was due to four distinct conduction regions between 1) the tricuspid annulus and scar/patch in the anterior right ventricular outflow tract; 2) the pulmonary annulus and the right ventricular free wall scar/patch; 3) the pulmonary annulus and septal scar/patch: and 4) the septal scar/patch and tricuspid annulus. Ablation of the appropriate conduction isthmus abolished VT in all patients. During 30.4 months of follow-up, there was one recurrence of VT. ICDs were implanted in 5 patients, one for a subsequent resuscitated cardiac arrest and one for unexplained syncope.

These studies suggest a role for continued investigation of VT ablation in patients after repair of congenital heart disease. The long-term outcomes after ablation are improving although recurrences after ablation demonstrate the continued need for ICD protection in these patients. The current role of VT ablation may be that of an adjunct to ICD therapy, particularly in patients with recurrent shocks.

3. Impaired ventricular function as a risk factor for SCD in CHD

Several multi-center randomized clinical trials in adults have established that impaired left ventricular systolic function, i.e., an ejection faction < 30-35%, is a significant independent risk factor for SCD.[31] Whether these findings are relevant to patients with CHD remains an unresolved matter, but will likely become an important issue in the future. This is due to the increasing long-term survival of patients with complex CHD and the observed decline in systemic ventricular function with increasing age in these patients, most notably after age 40 years.[32] Additional factors which are concerning to the older CHD populations are the increasing prevalence of patients with systemic right or single ventricular physiology, complicated by complex coronary artery anatomy variants and decades of pathologic ventricular hypertrophy and maladaptive remodeling.

Programmed electrical stimulation has been advocated as a method to further determine the risk of SCD among CHD patients with impaired ventricular function. There is some basis for this recommendation, as a multi-center study of electrophysiology testing in CHD patients did demonstrate significant predictive value for subsequent events when sustained ventricular arrhythmias were inducible.[33] The risk of SCD in older patients with prior repair of CHD and impaired ventricular function as well as the role of programmed electrical stimulation in further definition of risk stratification will be important issues to address with prospective clinical trials in the near future.

Cardiomyopathy

1. Hypertrophic cardiomyopathy (HCM)

Risk stratification for SCD in young patients with HCM remains at the forefront of clinical research. A recent evaluation of prolonged QRS duration (≥ 120 ms) as a marker of risk for cardiovascular death revealed a relative risk of 5.2 in adults with HCM.[34] Over an 8-year follow-up, cumulative risks for HCM-related death were 55% for those with a QRS duration ≥ 120 ms compared to 7% in those with QRS duration < 120 ms. In multivariate analysis, QRS duration remained an independent risk factor for SCD. Although further study in children will be necessary to validate the risk of QRS prolongation, this study suggests that QRS duration should be considered when assessing risk for SCD in HCM.

Anti-arrhythmic medications have traditionally been considered to reduce the risk of life-threatening events in HCM patients. However, a study by Melacini et al. demonstrated no reduction in the rate of SCD among patients taking anti-arrhythmic medications.[35] SCD occurred in 20% of patients taking amiodarone (6 of 30), 9% of patients taking verapamil (4 of 46) or beta-blockers (7 of 76), and none of 21 patients taking sotalol. Mortality was not statistically different when compared to 120 HCM patients not treated with anti-arrhythmic medications ($p = 0.08$). HCM patients on anti-arrhythmic medications therefore remain at risk for

Table 3 Gene mutation, clinical phenotype and risk of SCD in hypertrophic cardiomyopathy[36]

Gene mutation / protein involved	LV hypertrophy	Risk of SCD
MYH7 / β-myosin heavy chain	mild-severe	variable
MYPBC3 / Myosin-binding protein C	mild-moderate	low
TNNT2 / Troponin-T	mild	high
TNNI3 / Troponin-I	mild-moderate	low
TPM1 / Tropomyosin 1α	variable	moderate-high

SCD, with ICD implantation the most reasonable option for the highest risk patients.

Genetic testing for HCM variants has recently become available, and may provide great benefit in the pre-symptomatic diagnosis of the disease as well as providing counsel regarding the risk of SCD and the probability of transmission of the disease to offspring.[35] Current genetic testing will identify a specific mutation in 50-60% of patients with a high clinical index of suspicion for HCM. The most notable finding is that troponin-T mutations, which are associated with mild or no clinical evidence of left ventricular hypertrophy, may nonetheless confer a high risk of SCD (Table 3). Conversely, myosin-binding protein mutations, which are associated with significant left ventricular hypertrophy, may be associated with only a limited risk of SCD. Further validation of these preliminary findings will be required, but suggest that in the near future, risk stratification for SCD may be based as much on the specific genetic mutation responsible for HCM as the clinical phenotype of the disease.

2. Other cardiomyopathies

Rhee et al. studied the incidence of sudden death in young patients awaiting heart transplantation.[37] Of 2,392 patients in the Pediatric Heart Transplant Study Registry, 420 (17.6%) died prior to heart transplantation. SCD occurred in only 32 patients, representing 7.6% of all deaths. This relatively low rate of sudden death suggests that ICD therapy may not be warranted for young patients with advanced ventricular dysfunction awaiting heart transplant. However, two aspects of the study deserve comment. First, patients with ischemic cardiomyopathy, defined as having an abnormal coronary artery substrate, had an increased SCD relative risk of 6.92; therefore, this subgroup may need to be considered separately for primary prevention ICDs. Second, the average time to transplant was only 6 months in the group studied. The risk for SCD may increase with time, and patients expected to have longer wait times may also need to be considered separately.

Restrictive cardiomyopathy is extremely rare in childhood, but associated with a very poor prognosis. A study by Hayashi et al. described the clinical characteristics of restrictive cardiomyopathy in 12 children.[38] A characteristic ECG pattern of marked ST segment depression was noted in these patients. Four died suddenly and three others died of right heart failure. Using this small data sample, the probability of survival at 1, 2 and 3 years was 78%, 52% and 26% respectively. While the utility of ICD therapy for these patients remains uncertain, the extremely low survival rates underscore the need for early consideration of heart transplantation.

Schools and Athletic Participation

Pre-participation screening of athletes and school-age children remains a topic of great debate. There was renewed focus on the issue after the American Heart Association in 2007 restated its position that pre-participation screening should include the history and physical examination with any further testing, including a 12-lead ECG, remaining optional.[39] This reiteration of the previous 1996 guidelines for pre-participation screening differs from the recommendations of the European Society of Cardiology and International Olympic Committee that a 12-lead ECG be included in all pre-participation screenings.[40] After thorough re-evaluation of new considerations and data from the last decade, the conclusion of the American Heart Association was that a routine pre-participation ECG “is probably impractical.” These recommendations remain controversial with ongoing debate in the medical literature and diverse standards of practice in various countries.

Conclusion

SCD in pediatrics is a significant problem due to the enormous consequences of each death. Progress has been made in the study of SCD in children, both in identifying the diseases known to cause SCD and in elucidating the most relevant risk factors. A major advance has been establishment of the profound role of genetics in SCD. As our understanding of the molecular underpinnings of these diseases continues, significant progress can be expected in both identification of the highest risk patients and better definition of the optimal treatment(s) in order to minimize these catastrophic events.

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