

Sudden cardiac death in children

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Introduction

Sudden cardiac death (SCD) is defined as death that is abrupt, unexpected and due to a cardiac cause in the absence of other potential causes.¹ Sudden usually refers to an interval within one hour of the onset of symptoms. SCD remains a significant problem accounting for up to 350,000 deaths per annum in the US in adult and paediatric populations. The identification of children at risk for SCD is a major problem because the overall probability of survival after an out-of-hospital cardiac arrest is reported at between 2% and 19%, depending on the initial cardiac rhythm.²

Population-based studies of the incidence of SCD in paediatric patients report it at between 1.3 and 4 per 100,000 patient years.^{3,4} This compares to 300 per 100,000 patient years for adult males, three times the incidence of adult females. The paediatric data referred to above exclude patients with sudden infant death syndrome (SIDS), several of whom may have actually succumbed to an arrhythmic event not previously diagnosed.

This review will discuss some of the primary diseases responsible for SCD in children, which include (i) coronary arterial anomalies, (ii) congenital heart defects, (iii) cardiomyopathy, (iv) arrhythmias and (v) miscellaneous conditions. Obviously these groups are not mutually exclusive and there may be considerable overlap, particularly as arrhythmia may be the final manifestation of another disease process. Identification of these processes prior to a SCD event may help prevent this occurrence but risk stratification of such patients is not without difficulty.

Phases and mechanisms of SCD

There are four phases typically described in association with SCD including a prodrome, onset, cardiac arrest followed by biological death.⁵ The mechanisms of SCD may be arrhythmic (proven or presumptive) or non-arrhythmic (congestive heart failure, embolic or aneurysm). The few documented cases of arrhythmic unexpected death in children have shown atrial or ventricular tachycardia (VT) progressing to ventricular fibrillation in contrast to chronically ill children and adolescents in whom profound bradycardia typically progresses to asystole.

Coronary arterial anomalies

These anomalies may be congenital or less commonly acquired. The most common congenital anomaly is origin of the left coronary artery from the right sinus of Valsalva which courses between the aorta and the pulmonary artery.⁶ Exercise or any stimulus which increases heart rate results in pulsatile compression of the coronary artery and myocardial ischaemia. Other potential causes of myocardial ischaemia include acute take-off of either coronary artery from the ostium, an intramural origin of the coronary artery or a single coronary artery.^{6,7} Anomalous origin of the left coronary artery from the pulmonary artery may result in ischaemia in the absence of an adequate collateral circulation.⁸

Acquired coronary arterial aetiologies of SCD include Kawasaki disease, an acute idiopathic coronary vasculitis, in which 15-25% of patients may develop significant coronary ectasia if not promptly treated.⁹ Subsequent development of aneurysms and coronary artery stenosis may result in significant myocardial ischaemia. Post-transplant coronary vasculopathy and familial hyperlipidaemias may result in an accelerated form of atherosclerosis in paediatric-adolescent patients but this is quite rare.

Congenital heart disease

Certain congenital heart defects are strongly associated with SCD. Left ventricular outflow tract (LVOT) obstruction, particularly aortic valve stenosis, has been implicated in SCD (National History Study-II).¹⁰ A reduction in coronary perfusion is believed to be the underlying mechanism in LVOT obstructive lesions with myocardial ischaemia precipitating an arrhythmic event. Patients with Eisenmenger syndrome have suprasystemic pulmonary arterial pressure and may develop an acute drop in cardiac output and arrhythmic death.¹¹

Other less common lesions such as corrected transposition (or ventricular inversion with L-transposition of the great arteries, S,L,L) are associated with complete AV block, post-operative tetralogy of Fallot patients are at risk of development of VT (higher risk with QRS duration >180ms), patients following Senning or Mustard atrial switch operations are at risk of atrial flutter, and those patients with univentricular

hearts may experience SCD.¹²⁻¹⁴ In this latter group, the hypoplastic left heart syndrome group is a particularly high risk population after the Norwood procedure as the systemic and pulmonary circulations are in series and an acute increase in systemic vascular resistance or drop in pulmonary vascular resistance can induce myocardial ischaemia and arrhythmic death.¹⁵

Patients following the Fontan operation and heterotaxy patients with isomeric atria may be at particular risk of atrial, ventricular tachyarrhythmias and nodal dysrhythmia. Primary pulmonary hypertension is a potentially lethal disease and, despite aggressive therapy with prostacyclin, bosentan, sildenafil and other pulmonary vasodilators, the risk of SCD remains high.¹⁶

Cardiomyopathy

Cardiomyopathies — including hypertrophic (HCM), dilated, restrictive (RCM), arrhythmogenic right ventricular dysplasia (ARVD) and left ventricular non-compaction cardiomyopathy — are strongly associated with SCD. HCM is estimated to have an annual 2% risk of SCD and represents one of the most common causes among young patients and adolescents.¹⁷

HCM is generally defined as hypertrophy of left (LVH) and/or right ventricles (RVH), which is predominantly asymmetric (ASH) in location and associated with myocardial fibre disarray.^{17,18} Although septal hypertrophy predominates in adult and paediatric populations, mid-ventricular and apical asymmetric hypertrophy may also occur. Concentric LVH and LVH isolated to the posterior wall have also been reported in affected individuals. Over 175 independent genes coding for sarcomeric proteins including thick and thin filaments and scaffolding proteins have been identified and several mutations have been identified within the cytoskeleton and sarcomere which result in the phenotypic expression of HCM. HCM is characterised by the presence of abnormal diastolic relaxation of the LV, high LV end-diastolic pressure with or without the presence of LVOT obstruction. SCD usually results from severe LVOT obstruction, myocardial ischaemia, ventricular tachyarrhythmias or a combination of these factors.

Certain predictive factors for SCD have been reported, including maximal septal thickness, VT, specific mutations, the presence of myocardial bridging where the muscle actually compresses the coronary artery during systole and the presence of fibrosis detected by delayed contrast hyper-enhancement on magnetic resonance imaging (MRI).^{18,19}

SCD has also been reported in dilated and left ventricular non-compaction cardiomyopathy but this is less common than in the HCM group. RCM is characterised by restrictive LV physiology, high LVEDP and the development of marked bi-atrial enlargement. A prodrome of severe abdominal pain often ushers in a life-threatening arrhythmic event and SCD in this group.²⁰ ARVD deserves special mention as this is a highly lethal disease and cause of SCD. There is a high prevalence of this disease in the Italian population and it is characterised by

RV regional wall motion abnormalities, replacement of the right ventricular outflow tract by fibro-fatty infiltration and dilatation of the right ventricle and atrium.²¹ These findings are best delineated using cardiac MRI using fat saturation sequences. Familial occurrence is well recognised with an autosomal-dominant inheritance and genetic heterogeneity has been established with linkage analysis identifying four specific loci on chromosomes 14q23-q24 (ARVD 1), 1q42-q43 (ARVD 2), 14q12-q22 (ARVD 3) and 2q32.1-q32.3 (ARVD 4).²² The VT associated with this disorder has a left bundle branch morphology indicating its origin from the right ventricle. Interventions that may prevent SCD in these patients are discussed below.

Arrhythmias

Wolff-Parkinson-White syndrome (WPW)

WPW is the most common form of pre-excitation syndrome and associations with HCM, congenital heart lesions and tuberous sclerosis have been well established. Most cases are sporadic with 3% of probands having an affected first-degree relative. AD inheritance has been reported and genetic linkage to chromosome 7q3 in a family with WPW and HCM. WPW is typically associated with orthodromic conduction but also occasionally with antidromic reciprocating tachycardia.²³

The incidence of SCD in patients with WPW is estimated at 1-2 per 1,000 patient years. This usually results from rapid ventricular response to atrial fibrillation over an accessory connection. Certain medications including digoxin and verapamil may potentiate this risk by enhancing conduction via the accessory pathway.

Ventricular tachycardia (VT)

This is a broad complex (prolonged QRS duration) tachycardia with dissociation of P and QRS waves during tachycardia and is classified as sustained versus non-sustained and polymorphic versus monomorphic. Torsade de pointes is associated with LQTS and bidirectional VT is associated with digitalis toxicity, periodic paralysis or catecholaminergic VT.

There are multiple potential causes for VT including myocarditis, cardiomyopathy, myocardial tumours (Purkinje cell tumours, rhabdomyomas, fibromas), myocardial ischaemia, post-operative congenital heart disease, metabolic derangements and idiopathic VT.

Long Q-T syndrome

This syndrome is characterised by abnormal Q-T prolongation (Q-Tc >440ms in males, >450ms in females) which may result in polymorphic VT, torsade de pointes and SCD. The diagnosis is often reached following evaluation for syncopal episodes. Genetic linkage analysis has identified several loci including LQ-T1 (chromosome 11p15.5), LQ-T2 (chr 7q35), LQ-T3 (chr 3p21) and LQ-T4 (chr 4q25-27).²⁴ Mutations in KVLQ-

T1 and HERG result in LQ-T1 and 2 and mutations in SCN5a (cardiac sodium channel gene) result in LQ-T3.²⁵

Adrenergic stimulation results in the genesis of arrhythmias associated with LQTS but medications including anti-arrhythmic agents (amiodarone, quinidine, procainamide, sotalol), antihistamines (terfenadine), psychotropic drugs (haloperidol, risperidone), and other agents including cisapride, diuretics and epinephrine (for further information, visit: www.qt drugs.org) may precipitate an event.

Brugada syndrome

First reported in 1988, this syndrome is characterised by right bundle branch block, elevated ST-segments in leads V1-3 and a history of ventricular fibrillation.²⁶ It shares some similarities with ARVD and LQTS, with MRI often detecting subtle abnormalities in RV regional wall motion. Defects in SCN5A have been described in some patients.²⁷

Comotio cordis

This is an arrhythmic event with cardiac arrest and possible SCD caused by an object hitting the chest, typically a hard ball such as a baseball. Maron et al reported 128 cases, 62% of whom were involved in competitive sports with 84% of the individuals dying.²⁸ There was a 25% chance of survival if resuscitation was commenced within three minutes compared to 3% if resuscitation was delayed for greater than three minutes. Asystole-VF was documented in 73 of 82 cases in whom monitoring was retrospectively available.

Assessment of risk of patients

Aborted SCD describes a SCD episode in which resuscitative measures have obviously allowed the patient to survive. Following such episodes, it is essential that a thorough evaluation of the patient be performed to elucidate the offending aetiology. After a complete history and physical examination, electrocardiogram, Holter monitor and transthoracic echocardiography are routine investigations. In cases of coronary anomalies or cardiomyopathy, MRI is often useful to further delineate the anatomy. Stress echocardiography (dobutamine stress) and stress MRI (+perfusion scanning) allows detection of regional wall motion abnormalities.

Fat saturation sequences allow detection of fibro-fatty infiltration in the right ventricular outflow tract. Delayed contrast hyper-enhancement has been shown to correlate with areas of fibrosis within the myocardium and has been implicated as a potential prognostic factor for SCD in HCM patients.¹⁹ Electrophysiological (EP) studies may be diagnostic in determining the origin of VT in addition to allowing potential ablation of the arrhythmic focus.

Prevention of SCD

Medical therapy

For patients with obstructive cardiomyopathy, beta-blockers

and occasionally calcium channel blockers allow ventricular relaxation and alleviation of LVOT obstruction. Beta-blockers are also standard medical therapy for patients with LQTS. Certain types of LQTS may be treated with mexiletine.

In certain forms of cardiomyopathy, the prognosis is poor enough that early cardiac transplantation is offered. Restrictive cardiomyopathy is one example where, once the patient develops symptoms (abdominal or chest pain), the risk of mortality is high enough to justify immediate listing for orthotopic heart transplantation.²⁹ Certain gene mutations may have a more malevolent phenotypic expression of cardiomyopathy and ongoing studies are attempting to elucidate whether gene analysis can predict more malignant forms of cardiomyopathy. Identification of such mutations may have huge therapeutic implications regarding the need for automated implantable cardioverter-defibrillators (AICDs), potential surgical resection (HCM with LVOT obstruction) or promotion to transplantation.

AICD placement

There is ongoing debate over the exact criteria for the placement of an AICD. Patients who demonstrate LQTS with torsade de pointes, inducible sustained VT (symptomatic) or a history of an aborted SCD episode with VT-VF typically require AICDs.³⁰ HCM patients may meet criteria for placement of a device if they have syncopal episodes or sustained VT.³¹

Conclusion

In conclusion, there is a heterogeneous group of cardiac conditions which may present with SCD in children, although the final common pathway is often arrhythmia. Coronary arterial anomalies, cardiomyopathy, arrhythmia and previous surgical intervention for CHD comprise the majority of cases. A thorough investigation is essential following an aborted SCD and similarly family members should be thoroughly screened to prevent further catastrophic outcomes.

Further studies are required to delineate predictive factors for SCD in children and, most importantly, to circumvent such adverse outcomes.

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