Sudden cardiac death in the young: causes and prevention

Abstract
Sudden cardiac death (SCD) in the young is a tragic event that can occur in infants, children, adolescents and young adults alike. In a lot of cases, sudden death is the first manifestation of an undetected fatal heart abnormality, with no previous symptoms or warning signs during the victim’s life. Although we know many pathological heart conditions that give rise to SCD in the young, the frequently ‘silent’ nature of these conditions means that identifying individuals who are susceptible is difficult. Strategies aimed at reducing the incidence of SCD in the young mainly focus on risk stratification through screening programmes, followed by the institution of preventive management in those discovered to be at risk. The role of genetic testing in SCD is constantly advancing, particularly in screening relatives of young people with known heart conditions, or of young people who have tragically succumbed to SCD. This paper gives a broad overview of the causes of SCD in the young, with extra consideration given to infants and young athletes. This is followed by discussion of both current and future prevention strategies.

Key words: Sudden cardiac death, sudden infant death syndrome, young adult, adolescent, children.

Introduction
Sudden cardiac death (SCD) in the young is a rare but tragic event that deeply affects families and communities. It is broadly defined as death from a cardiac cause or no identifiable cause occurring within one hour of symptom onset, in individuals at or under 35 years. SCD in the young may include sudden infant death syndrome (SIDS), which is defined as sudden unexpected death occurring without identifiable abnormality on post-mortem in an individual less than one year. In Ireland in 2005, there were 69 post-mortem confirmed cases of SCD in the young, while in the UK it is estimated that there are at least eight cases per week.

Causes of SCD in the young
The final event in SCD is usually a fatal arrhythmia such as ventricular fibrillation or ventricular tachycardia. The pathophysiological processes leading up to such an event are frequently complex. While a causative structural heart abnormality is usually identified at post-mortem, no structural defect can be found in 10-30% of cases. Sudden death in these instances is potentially due to a primary electrical condition such as an ion channel disorder or an accessory pathway. Structural abnormalities most frequently identified are hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), coronary artery anomalies, and myocarditis. Where no structural defect is found, potential causes include long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). In 69 confirmed cases of SCD in the young in Ireland in 2005, the most common autopsy findings were: no detectable heart abnormality (41.4%); and, HCM (14.5%).

Hypertrophic cardiomyopathy
HCM is the most common cause of SCD in young athletes and non-athletes in the USA and is the leading structural cause of SCD in the young in Ireland. In most cases inheritance is autosomal dominant, involving gene mutations of cardiac sarcomere proteins. The pathophysiology of sudden death in HCM involves a complex arrhythmogenic substrate formed by myocyte disarray, fibrosis, and calcium regulation abnormalities, which predisposes the individual to fatal ventricular fibrillation.

Arrhythmogenic right ventricular cardiomyopathy
ARVC is characterised by fibro-fatty replacement of ventricular myocardium (usually the right ventricle), resulting in ventricular dysfunction and arrhythmias. Inheritance is usually autosomal dominant with variable phenotype. Up to 20% of SCD may be attributable to ARVC.
Coronary artery anomalies
In addition to cardiomyopathies, anatomical anomalies of the coronary circulation are frequently implicated in SCD in the young, and have been described in detail.9 Ventricular arrhythmia leading to sudden death is usually linked to sudden myocardial ischaemia or to scarring.9

Ion channelopathies
No structural abnormalities can be identified at autopsy in 10-30% of sudden deaths in previously healthy children and adolescents.4,10 The finding of a morphologically normal heart at post-mortem therefore suggests an ion channelopathy, such as LQTS, Brugada syndrome, and CPVT.

LQTS comprises a distinct group of cardiac channelopathies, which usually follow autosomal dominant inheritance.8 Approximately 75% of LQTS cases are caused by mutations in five specific ion channel genes.11 The characteristic features are delayed myocardial repolarisation and QT prolongation, with increased risk for syncope, seizures and SCD.11

Brugada syndrome is an inheritable arrhythmia syndrome associated with sodium channel mutations. It poses an inherent risk of SCD due to episodes of polymorphic ventricular arrhythmias. It is more common in young males; however, it can occur in children.8 CPVT, which usually involves mutations in a ryanodine receptor gene, is increasingly recognised as a cause of SCD in the young.4 This condition closely mimics LQTS but appears to be far more lethal.12

Other causes of SCD in the young
Various other causes of SCD in the young have been described including short QT syndrome,8 Wolff-Parkinson-White (WPW) syndrome,13 myocarditis,1 restrictive cardiomyopathy,14 congenital heart disease,1,15 coronary atherosclerosis,15 valvular disease,2 and blunt chest trauma (commotio cordis).16

Sudden infant death syndrome
While the causes of sudden death in infants under one year are multifactorial,17 molecular studies have shown that 10% of cases of SIDS may result from an ion channelopathy,18,19,20 of which LQTS is the most widely reported. In recent studies, post-mortem testing has revealed LQTS-associated mutations in 9.5% of 201 SIDS victims,19 and in 8.3% of 200 SIDS victims.20 The pathophysiological mechanisms of SIDS remain poorly understood, and discovery of currently unknown cardiac causes may represent the greatest challenge for researchers of SCD in the young.

SCD in young athletes
The sudden death of a young athlete often receives increased publicity, perhaps because athletes are perceived as one of the healthiest subpopulations of society. The risk of SCD in young athletes has been estimated as 2.8 times greater than the risk in non-athletes.21 HCM is considered the most frequent cause of SCD in young competitive athletes,22,23 and is implicated in one-third of fatal cases in the USA.21,24,25 However, geographical variations exist, as the leading cause of SCD in young athletes in Veneto, Italy, is ARVC.26 Other causes of SCD in young athletes include coronary anomalies, premature atherosclerotic coronary disease, mitral valve prolapse, WPW syndrome,13 and ion channelopathies.26

It is believed that intense exercise may act as an external trigger of SCD in athletes who harbour an underlying structural or arrhythmogenic heart disease. Exercise imposes a combination of physical, metabolic and endocrine stresses on the heart, which could trigger a fatal arrhythmia.22 Evidence exists to support this idea,24,25,27 including a recent study of SCD in UK athletes in which over 80% of fatal events occurred during or immediately following exercise.22 Specific sports have been pinpointed in certain instances; for example, SCD due to LQTS and CPVT has been strongly associated with swimming.28,29,30

Exercise, however, is by no means a prerequisite for SCD. Nearly 20% of athletes in the UK study who died suddenly were not exercising at the time,22 while some reports have found that SCD due to HCM often occurs during mild or sedentary activity.31,32,33 The role of exercise in triggering SCD is highlighted when considering preventive measures to reduce the incidence of SCD in the young.
Prevention of SCD in the young

Sudden death is often the first symptomatic manifestation of cardiovascular disease, which makes prevention of SCD in the young very difficult. The key to minimising the incidence of SCD in the young lies in identifying those individuals who are at risk for sudden fatal arrhythmias, thus allowing directed preventive management to be instituted. Major prevention strategies can be divided broadly into two main areas: the first is a national or population-based screening programme for specific groups; and, the second involves screening in families with suspected or known genetic cardiac abnormalities.

Population screening

There is currently no population screening for heart disease in the young in Ireland. Research on screening programmes is limited, and to date has largely focused on young competitive athletes in the USA and Europe. Currently, the American Heart Association recommends that history and physical examination alone should constitute basic pre-participation screening of young athletes, while ECG testing remains optional. However, in Italy a landmark study showed that a screening programme consisting of history, physical examination and 12-lead ECG reduced the incidence of SCD in young athletes by 89% over a 26-year period. The addition of ECG was viewed as pivotal to the success of this screening programme, being deemed a “lifescaping strategy”. The European Society of Cardiology has duly adopted the recommendation that the 12-lead ECG be included in the pre-participation screening for young athletes. ECG is a relatively cheap and simple test, and should form the basis of any screening programme for SCD in both athletes and non-athletes. ECG changes, for example, are evident in 85% of cases of HCM, with specific ECG predictors of sudden death identified. ECG screening also has the potential to unmask other undetected heart conditions such as coronary anomalies, SQTS, ARVC and Brugada syndrome. With regard to SIDS prevention, the knowledge that 10% of SIDS may be due to ion channelopathies such as LQTS has strengthened the case for infant screening. Accordingly, some European countries are considering the introduction of national neonatal ECG screening programmes, with some authors recommending screening between two and four weeks of age. Such programmes can be cost effective, and can successfully identify asymptomatic infants as well as guide further investigation of family members for ‘silent’ LQTS.

Family screening and genetic testing

In the 10-30% of SCD cases that reveal no obvious structural explanation at autopsy, identifying a possible arrhythmogenic cause is the next step. The role of genotyping in this instance is constantly advancing, and has been advocated in the analysis of cases of sudden death where the post-mortem was inconclusive. Identification of disease-causing mutations in the deceased can enable screening of family members, and initiate preventive management in relatives with mutations. One recent study established an identifiable mutation in over 30 relatives of a cohort of 49 SCD victims with LQTS. However, a major hurdle in genetic testing is that many inherited cardiac disorders have incomplete penetrance and variable expressivity, and thus may escape detection.

Preventive management

Preventive measures in those young people with known risk of SCD vary depending on the underlying condition. In addition to anti-arrhythmic medications and invasive techniques, restriction of activity and use of defibrillation devices form the cornerstone of preventive management. Exercise curtailment is an obvious prevention strategy, considering the significant incidence of SCD that occurs during or immediately after physical activity. The diagnosis of HCM, for example, generally necessitates disqualification from most competitive sports, with some individual exceptions made. However, this approach is certainly not exhaustive because many cases of SCD occur during mild or sedentary activity. Indeed, rather than unnecessarily exclude participation in all sports, the goal should be to adapt the activity in accordance with each individual’s specific risk.

The advent of implantable cardioverter-defibrillator (ICD) devices has prompted huge advances in SCD prevention in the young, particularly in HCM where ICD implantation is recommended for patients who satisfy particular criteria. ICD therapy may also have a preventive role in coronary disease, congenital heart disease and LQTS. Additionally, the presence of automated external defibrillator (AED) devices at sporting events has been advocated. This, along with an increased provision of AEDs in all public places, may reduce the time between an event and life-saving intervention, and therefore potentially reduce SCD rates.
Implications for the future

In addition to screening programmes for the young, much of the scope for preventing SCD lies in the genetic screening of surviving relatives of young victims. Provision of cardiac genetic services, where families can avail of screening as well as education and genetic counselling, should be a major focus for national health departments. In Ireland, the Family Heart Screening Clinic was set up in the Mater Hospital in Dublin in 2007, providing such services to the relatives of young SCD victims. Prevention of SCD may also be facilitated by the increased availability of national epidemiological data on SCD incidence, trends and post-mortem findings. To this end there is a need to implement national SCD registries. Cardiac arrest registries could aid the improvement of cardiac arrest response strategies, while prospective post-mortem registries have also been advocated. Comprehensive epidemiological information may strengthen the case for funding of national SCD screening programmes, and allow better risk stratification across various cohorts.

Future success in reducing the burden of SCD in the young depends on several factors, not least the implementation of screening programmes in at-risk populations, and the availability of formalised epidemiological data. Furthermore, as research increases our understanding of the genetic basis of SCD in the coming years, improved management and prevention of SCD in the young can surely be expected.

References

Making Europe a better place for our children

“By spending itself for the benefit of its children, the human race ensures the progressive development of all.”

James Connolly

The true measure of a nation’s standing is how well it attends to its children; their health and safety, their education, and their sense of being loved, valued and included in the society into which they are born.\(^1,2,3,4,5\)

Child poverty rates vary from under 3% to more than 25% in Europe. Whether measured by physical and mental development, health and survival rates, educational achievements or job prospects, incomes or life expectancies, those who spend their childhood in poverty of income and expectation are at a marked and measurable disadvantage. They are more likely to have learning difficulties, to drop out of school, to resort to drugs, to commit crimes, to be out of work, to become pregnant at an early age, and to live lives that perpetuate poverty and disadvantage into succeeding generations.\(^6\)

Indicators of health and safety of children across Europe

The infant mortality rate (IMR) is a standard indicator of child health. IMR ranges from under three per 1,000 births in Iceland to over six per 1,000 in Hungary and Poland. A society that can effectively reduce infant mortality to below five per 1,000 live births is one that has the capacity and commitment to deliver critical components of child health (Figure 1).\(^7\)

Immunisation rates serve as a measure of national commitment to primary healthcare for children. Failure to reach high levels of immunisation reduces herd immunity, which means that more children may fall victim to disease.

Furthermore, immunisation rates may be indicative of the effort made by each nation to provide each child, and particularly the children of marginalised groups, with basic preventive health services (Figure 2).\(^8\)

Sweden, the United Kingdom, the Netherlands and Italy are the four countries that have reduced the incidence of deaths from accidents and injuries to a remarkably low level, fewer than 10 per 100,000. The likelihood of a child being injured or killed is also associated with poverty, single parenthood, low maternal education, low maternal age at birth, poor housing, weak family ties, and parental drug or alcohol abuse (Table 1).

Other indicators of child well-being (Table 2) include:

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