Sudden cardiac death: history, aetiology and management

Despite being a relatively common medical condition, sudden cardiac death suffers a widespread lack of knowledge and understanding among general physicians. This article fills this knowledge gap, outlining risk factors, causes and preventative strategies.

Sudden cardiac death – defined as an unexpected death from cardiac causes occurring in a short time period (generally within 1 hour of symptom onset) in a person who has no previously diagnosed fatal non-cardiac condition (Myerberg and Catellanos, 1997) – continues to represent a major challenge for the entire medical profession, and for cardiologists in particular. For the families of affected individuals, sudden cardiac death comes as a devastating and shocking experience as it often claims the lives of young previously fit adults. Preventing sudden cardiac death requires identifying people at risk, and for this an understanding of the underlying pathologies is crucial. This article provides a brief historical perspective of sudden cardiac death and discusses its risk factors, causes and preventative management strategies.

Historical background

Understanding the mechanism of death and appreciating the central role that the heart plays in blood circulation has occupied the thoughts and works of many ancient philosophers. Huang Ti, the Yellow Emperor of China (2698–2598 BC), wrote in *Nei Ching* (Canon of Inner Medicine): 'The blood current flows continuously in a circle without a beginning or end and never stops' and 'all the blood is under control of the heart'. Hippocrates (470–410 BC) provided a concise, but historically compelling, description of sudden cardiac death in his Aphorisms II, 41: 'Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly' (Mirchandani and Phoon, 2003). Avicenna of Persia (Ibn Sina 980–1037) stated that: 'fast heart beats cause palpitations, faster heart beats cause fainting, and extremely fast heart beats result in sudden death'.

In 1775 Peter Christian Abildgaard, a Danish veterinarian and physician, performed the first successful defibrillation through conducting experiments on electrical counter-shock on animals. Using direct current (DC) derived from a Leyden jar he succeeded in first rendering fowl lifeless by an electric shock and then reviving them by a counter-shock applied to the chest. In 1887 Augustus Desiré Waller made the first ever recording of the electric activity of the human heart, the electrocardiogram (ECG) (Waller, 1887). In 1931 Dr Albert Hyman invented the first artificial cardiac pacemaker, which stimulated the heart by using a transthoracic needle.

In 1947 Claude Beck et al reported the first case of successful defibrillation of the human heart during cardiac surgery with full recovery. The patient was a 14-year-old boy. In 1956 Paul Zoll, a cardiologist, managed to perform closed-chest defibrillation in a human. In 1960, Smirk and Palmer described the 'R-on-T' phenomenon, and they also recognized its role in sudden cardiac death causation through initiating ventricular fibrillation. In 1966 François Dessertenne of Paris published the first case of 'Torsade de pointes' polymorphic ventricular tachycardia. In 1992, Pedro and Josep Brugada published a series of eight cases of sudden death, right bundle–branch block pattern and ST segment elevation in V1–V3 in apparently healthy individuals. Known as Brugada syndrome, this is now believed to be the commonest cause of sudden cardiac death in individuals aged less than 50 years in South Asia (Brugada and Brugada, 1992).

Epidemiology

Sudden cardiac death is a major cause of adult mortality in the developed world. Its annual incidence is 3 000 000 deaths worldwide. Of these, 400 000 deaths occur in western Europe and 340 000 in the United States (Mirchandani and Phoon, 2003). In the UK alone, sudden cardiac death causes 75 000–100 000 deaths each year (Camm, 1989). Most patients have either poor left ventricular ejection fraction (<35%) with or without coronary disease, or inherited cardiac conditions that predispose to malignant ventricular arrhythmia. The Sudden Arrhythmic Death Syndrome study group estimated the incidence of unexplained sudden cardiac deaths in England, in healthy people aged between 16 and 64 years, as 11 per 100 000 (3500 deaths per year). This constitutes 4.1% of the total UK sudden cardiac death annual incidence (Behr et al, 2003). Worldwide, less than 1% of those who experience sudden cardiac arrest manage to survive. The greatest incidence occurs in cohorts with identifiable risk factors, but most events

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(in absolute numbers) occur in individuals without prior known risk factors (Crawford et al, 2004). Sudden cardiac death is the commonest – and often the first – manifestation of coronary heart disease (Huikuri et al, 2001) and accounts for approximately 50% of cardiovascular disease mortality in the developed world. In developing countries, sudden cardiac death rates are lower. Several population-based studies have documented a 15–19% decline in sudden cardiac death incidence since the 1980s. However, the increasing incidence of congestive cardiac failure may adversely affect this decline in the future (Reddy and Yusuf, 1998).

Risk factors for sudden cardiac death

Multiple epidemiological studies showed that conventional risk factors for ischaemic heart disease are also predictive of sudden cardiac death. In one study, elevated heart rate, heavy drinking and arrhythmia emerged as factors that were specific to sudden cardiac death (Wannamethee et al, 1995). Furthermore, age and blood cholesterol level were found to be associated with an increased risk of sudden cardiac death in men both with and without pre-existing coronary disease. Physical activity, systolic blood pressure and active smoking were associated with sudden cardiac death only in men without pre-existing coronary disease, whereas high-density lipoprotein cholesterol level and haematocrit were found to be strong predictors of sudden cardiac death only in men with pre-existing ischaemic heart disease. Malignant ventricular arrhythmias – ventricular fibrillation and haemodynamically unstable ventricular tachycardia – are the direct cause of sudden cardiac death. Patients with congenital heart disease or certain genetic disorders (e.g. channelopathies) are much more likely to experience ventricular arrhythmias.

Mechanism and aetiology of ventricular arrhythmias

Mechanism

Arrhythmogenesis can be caused by disorders of impulse conduction, disorders of impulse formation or both (Levy and Wiseman, 1991).

Disorders of impulse conduction (re-entry)

For re-entry to occur there needs to be an area of non-excitable myocardium (ischaemic or scar tissue) surrounded by a ring of excitable tissue that has a short refractory period and a sufficient length of ring circumference. This allows antegrade conduction through one arm of the ring before retrograde propagation of the depolarization wavelet proceeds through the other ring arm, thereby resulting in self-sustaining (re-entry) circus movement phenomenon.

Disorders of impulse formation (increased automaticity)

Automaticity is a measure of the propensity of an area of tissue to initiate an impulse spontaneously. Factors such as hypoxia promote automaticity by causing a net gain in the intracellular positive charge during diastole. This occurs as a result of raised external concentration of potassium, decreased intracellular concentration of potassium, increased permeability to sodium or decreased permeability to potassium. Therefore, the maximum diastolic potential becomes less negative and lies closer to the threshold potential.

Triggered activity

Depolarizing oscillations in the membrane voltage are induced by preceding action potentials and are called afterdepolarizations. All afterdepolarizations may not reach threshold potential, but if they do they can trigger another afterdepolarization and thus self perpetuate resulting in ventricular tachycardia or ventricular fibrillation.

Aetiology

Ventricular arrhythmias can be induced or precipitated by a number of cardiac or non-cardiac disorders. If untreated, sustained ventricular tachycardia often degenerates into ventricular fibrillation and then asystole. Apart from fascicular and right ventricular outflow tract tachycardias, monomorphic ventricular tachycardia generally tends to affect abnormal or damaged myocardium. Some of the other causes of monomorphic ventricular tachycardia include:

- Acute myocardial infarction or ischaemia
- Previous myocardial infarction (scar-related ventricular tachycardia)
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular dysplasia
- Valvular heart disease (e.g. mitral valve prolapse)
- Post-cardiac surgery (e.g. repair of tetralogy of Fallot)
- Severe left ventricular dysfunction (from any cause).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a widely heterogeneous, autosomally dominant inherited condition (Maron et al, 1995). Some of the sporadic forms of the disease may be caused by spontaneous mutations. At least six different genes on four chromosomes are associated with hypertrophic cardiomyopathy, with more than 50 different mutations discovered thus far. The abnormality results in disarray of the ventricular myocardial cells causing asymmetrical ventricular wall hypertrophy and creating a substrate for re-entrant ventricular tachycardia.

Dilated cardiomyopathy

Dilated cardiomyopathy is congestive cardiac failure secondary to dilatation and systolic dysfunction of the ventricles in the absence of congenital, valvular or coronary artery disease (Felker et al, 1999). There are numer-

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ous causes of dilated cardiomyopathy, including myocardial microbial infections (e.g. coxsackie virus B, diphtheria, toxoplasmosis), neuromuscular disorders (e.g. Friedreich ataxia), glycogen storage diseases, carnitine deficiency, and drugs (e.g. cyclophosphamide, chloroquine). However, in the vast majority of cases no cause is found (idiopathic dilated cardiomyopathy).

Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia is an unusual, often familial, condition characterized by the replacement of myocardial tissue by fat and fibrous tissue in the right ventricle (Burke et al, 1998). Arrhythmogenic right ventricular dysplasia has a wide spectrum of clinical presentations, including mechanical dysfunction and various forms of ventricular arrhythmias. It is a cause of sudden death, mostly in young people and in athletes.

On the other hand, polymorphic ventricular tachycardia tends to result from genetic, electrical or even non-cardiac disorders in otherwise structurally normal hearts. Some of the causes of polymorphic ventricular tachycardia include:

- Bradycardia as a result of sick sinus syndrome or atrioventricular nodal block
- Congenital long QT syndrome
- Brugada syndrome
- Short QT syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Electrolyte imbalance (e.g. hypokalaemia or hypomagnesaemia)
- Most antiarrhythmic drugs (e.g. quinidine, sotalol, amiodarone, flecainide)
- Other non-cardiac drugs (e.g. tricyclic antidepressants, erythromycin, tetrafenadine)
- Anorexia nervosa.

Congenital long QT syndrome

This is a congenital disorder characterized by a prolongation of the QT interval on ECG and a propensity to ventricular arrhythmias (Schwartz et al, 1993). Torsade de pointes is thought to be triggered by reactivation of calcium channels, reactivation of a delayed sodium current, or a decreased outward potassium current that results in early afterdepolarizations. So far, ten different genes have been identified: six types of Romano–Ward syndrome, one type of Andersen syndrome, one type of Timothy syndrome, and two types of Jervell–Lang–Nielsen syndrome.

Brugada syndrome

This is an arrhythmogenic cardiac disorder of sodium channels characterized by coved or saddle-shaped ST segment elevation in leads V1 to V3 on ECG along with complete or incomplete right bundle–branch block and T-wave inversion (Priori et al, 2002). Although initially believed to affect structurally normal hearts, this has been challenged as some underlying histological abnormalities have subsequently been observed on endomyocardial biopsies (Frustaci et al, 2005). The ECG abnormality may not be evident until it is unmasked by infusion of a sodium-channel blocker such as flecainide or procainamide. Brugada syndrome is genetically determined (autosomal dominant inheritance in about 50% of familial cases).

Short QT syndrome

This is a genetic cardiac channelopathy with autosomal dominant inheritance. The condition is characterized by a short QT interval on the ECG (<300 ms) that does not significantly change with heart rate, tall and peaked T waves, and a structurally normal heart.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia is a genetically determined arrhythmogenic condition that affects the release of calcium from the sarcoplasmic reticulum. While the resting ECG of affected individuals is often normal, exercise stress testing precipitates the typical pattern of the arrhythmia. As the exercise protocol progresses, ventricular ectopics become more frequent and more complex until polymorphic or bidirectional ventricular tachycardia is recorded (80% of cases). Upon termination of exercise, arrhythmias progressively diminish until they disappear.

Management of ventricular arrhythmias

Terminating an arrhythmia and preventing its recurrence is the mainstay of treatment. Termination is achieved by DC cardioversion, transvenous overdrive pacing or intravenous administration of antiarrhythmic drug therapy. Prophylactic therapy includes oral antiarrhythmic drugs, radiofrequency ablation, surgery and implantable cardioverter defibrillators. An acute episode of ventricular fibrillation or haemodynamically unstable ventricular tachycardia is often easily treatable with DC cardioversion; this should be delivered urgently if a fatal outcome is to be avoided. The chance of successful resuscitation declines by about 7–10% each minute (Cummins, 1993). In the setting of recurrent or persistent haemodynamically stable ventricular tachycardia, intravenous antiarrhythmic drug therapy may be preferred over DC cardioversion, as the latter is then neither urgently required nor likely to help prevent arrhythmia recurrence.

Antiarrhythmic drugs

A number of randomized controlled clinical trials have evaluated the use of antiarrhythmic drugs. Of these, only the use of acute intravenous and long-term beta-blockers, independently and in combination, have been shown to reduce mortality.

The Cardiac Arrhythmia Suppression Trial (CAST) studied placebo *vs* encainide, flecainide or moricizine. It was stopped early because there were excess deaths in the antiarrhythmic arms (Obias-Manno et al, 1996). Crystal et al (2003) showed that amiodarone reduced arrhythmic but not overall mortality when studied by the European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Trial (CAMIAT). When studied in heart failure patients, amiodarone was associated with a neutral overall survival and a statistically non-significant trend towards improved survival in non-ischaemic cardiomyopathy patients (Naccarelli et al, 2000). When compared with other antiarrhythmic agents (CASCADE study), amiodarone was shown to better reduce arrhythmia recurrence rates but arrhythmic death rates remained high in both arms of the study (Greene, 1993).

Beta-blockers were shown in many randomized trials to significantly reduce sudden cardiac death incidence as well as all-cause mortality in post-myocardial infarction patients and in patients with heart failure. Propranolol was associated with a 26% reduction in mortality in the Beta Blocker Heart Attack Trial (BHAT) (Gheorghiade et al, 1990) and timolol provided a 39% reduction in mortality in the Norwegian Multi-centre Study group (Andersen, 1981).

In the post-myocardial infarction Implantable cardioverter defibrillator trials, Antiarrhythmic Versus Implantable Defibrillator (AVID) and Multicenter Unsustained Tachycardia Trial (MUSTT), beta-blockers were independently associated with improved overall survival with the exception of those treated with Implantable cardioverter defibrillators (Ellison and Gandhi, 2005). Extended-release metoprolol reduced all-cause mortality by 34% in the Metoprolol controlled-release/Extended-Release randomized Intervention Trial in Heart Failure (MERIT-HF) (Wilkstrand et al, 2002). Bisoprolol was associated with a 34% mortality benefit in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) and carvedilol was associated with a 35% mortality reduction in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (Eichhorn and Bristow, 2001). Intravenous atenolol given early in acute myocardial infarction has been shown to reduce chest pain, enzyme release and incidence of arrhythmias. Data published before the first report of the International Studies of Infarct Survival (ISIS-1) group showed a 12% decrease in the probability of death using intravenous beta-blockade albeit with large confidence limits (Sleight, 1987).

Besides the poor efficacy of antiarrhythmic drugs, their use is further limited by a multitude of side effects and contraindications. Nearly all class I antiarrhythmic agents can induce polymorphic ventricular tachycardia, particularly in patients with underlying left ventricular dysfunction or structural heart disease. Non-pharmacological forms of therapy have been sought to overcome some of the limitations of antiarrhythmic drugs.

Interventional treatment

Various radiofrequency catheter ablation techniques have been developed in the last two decades. They were shown in some small studies to significantly reduce arrhythmia recurrence rate (Borger van der Burg et al, 2002). Further advances in catheter ablation techniques are underway, which will further improve procedural success rates. Despite such advances, technical challenges, complications (3% mortality was observed in a study of 69 patients who underwent cooled radiofrequency ablation; Stevenson et al, 2002), and arrhythmia recurrence remain a major problem. At present, procedures are offered at experienced centres only, with an estimated success rate of 80% when a substrate-based mapping method is used (Verma et al, 2005). Recurrence rates were quoted in some studies to be as high as 40–50% after 3 years follow up (Segal et al, 2005).

Surgical treatment

Many surgically-based techniques for ventricular tachycardia treatment have been developed in recent years. They all involve destruction of tissue at the border-zone between scar and viable muscle. The results, however, are variable depending on patient selection, use of mapping data, and type and extent of ablation technique used. As postoperative mortality remains high at 5–10% (Mickleborough et al, 1992), this option is only used when other strategies have failed to control the arrhythmia.

Implantable cardioverter defibrillators

Implantable cardioverter defibrillators are the cornerstone in the management of ventricular arrhythmias. Patients who survive sudden cardiac arrest (not occurring within the context of acute myocardial infarction and without identifiable reversible precipitants) and those who are at a significantly increased risk of ventricular arrhythmias because of underlying structural or genetic disorders should all be offered Implantable cardioverter defibrillator implantation (National Institute for Health and Clinical Excellence, 2006).

Evidence base

Most primary prevention randomized controlled trials have shown consistent superiority of implantable cardioverter defibrillators over pharmacological therapy alone in reducing mortality from ventricular arrhythmias and sudden cardiac death.

Two trials, the Coronary Artery Bypass Graft (CABG) Patch Trial (Block and Breithardt, 1999) and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) (Cleland et al, 2004), found that prophylactic implantation of an implantable cardioverter defibrillator did not reduce the risk of death in patients undergoing coronary artery bypass graft and in those experiencing ventricular arrhythmias within 40 days of myocardial infarction respectively. It is accepted that, in

these two cohorts of patients, implantable cardioverter defibrillator implantation is more expensive and less effective than control therapy, unless they have severely reduced ejection fraction (the Multi-centre Automatic Defibrillator Implantation Trial (MADIT II); Moss, 2003).

Six other primary prevention trials – MADIT I (Nisam and Adrago, 1997), MADIT II (Moss, 2003), the Multicentre Unsustained Tachycardia Trial (MUSTT) (Klein and Reek, 2000), the Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation trial (DEFINITE) (Schaechter and Kadish, 2003), the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial (COMPANION) (Cleland et al, 2003), and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (Borggrefe and Wolpert, 2006), have all demonstrated unequivocal superiority of implantable cardioverter defibrillators over optimal pharmacological therapy in reducing overall cardiovascular mortality and arrhythmic death in cohorts of patients with impaired left ventricular function whose ejection fraction ≤35% with or without underlying coronary disease.

Secondary prevention trials – AVID, the Canadian Implantable Defibrillator Study and the Cardiac Arrest Study Hamburg – have all demonstrated the superiority of implantable cardioverter defibrillator therapy over empirical amiodarone in improving overall survival in cohorts of patients who survived episodes of primary ventricular arrhythmias (Oseroff et al, 2004).

Limitations of implantable cardioverter defibrillator therapy

Although better than conventional antiarrhythmic medical therapy in reducing mortality, implantable cardioverter defibrillators still have significant limitations. Procedural complications have generally become less common in recent years (risk <1%) (Grimm et al, 1999) and may occur at times of implantation or later on; these include pneumothorax, haemothorax, system infection, lead displacement or fracture. Other problems related to device programming can occur, the commonest of which is inappropriate shock delivery affecting approximately 12–25% of patients (Swerdlow et al, 2002); this is mainly triggered when implantable cardioverter defibrillators sense atrial arrhythmias (commonly atrial fibrillation) and interpret them as ventricular tachycardia and consequently deliver DC cardioversion or high-energy shock therapy while patients are fully awake and haemodynamically stable. If it becomes recurrent, inappropriate shocking can lead to patients adopting major lifestyle restrictions and, in some cases, can result in severe psychological disturbances (Sweeney et al, 2005). The problem persists even with fourth generation dual chamber implantable cardioverter defibrillators (Sinha et al, 2000).

The addition of antiarrhythmic drugs to decrease the incidence of inappropriate shocks has only helped slightly, but the bulk of the problem remains yet to be solved. Various physiological parameters – such as right ventricular and atrial pressures, coronary sinus blood temperature and intracardiac impedance – have been investigated for their potential use as haemodynamic sensors by implantable cardioverter defibrillator technology, albeit with rather limited success. A successful haemodynamic sensor should reliably discriminate haemodynamically stable from unstable arrhythmias, thereby allowing an implantable cardioverter defibrillator to provide tiered therapy for stable arrhythmias but reserve DC shocks for ventricular fibrillation and haemodynamically unstable ventricular tachycardia only.

Conclusions

Sadly, sudden death is often the first symptom in affected sudden cardiac death victims. Not uncommonly, retrospective history taking reveals either an underlying risk factor such as previous unexplained and unreported syncope, or a positive family history of sudden death. Developing a clear understanding of the problem among physicians, coupled with measures to raise public awareness, will help identify and treat at risk individuals and greatly avoid sudden cardiac death. **BJHM**

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KEY POINTS

- Sudden cardiac death was identified and accurately linked to cardiac arrhythmias many centuries ago.
- Sudden cardiac death still constitutes a major challenge, mainly affecting young, seemingly fit adults who have no previously known health problems.
- People mostly at risk of sudden cardiac death are those with underlying structural or genetic cardiac conditions. Identifying populations with known risk factors, and screening those with positive family history of sudden cardiac death or sudden cardiac arrest is an essential first step in the management process.
- Currently available antiarrhythmic drugs decrease arrhythmia recurrence, but do not seem to reduce mortality. Surgical and radiofrequency catheter ablation techniques can both be successfully used to treat some forms of monomorphic ventricular tachycardia but high arrhythmia recurrence rates remain a problem.
- Implantation of implantable cardioverter defibrillators is the mainstay of management and has already been proven to be of prognostic benefit in many randomized clinical trials. However, implantable cardioverter defibrillator therapy has some limitations, the most prominent of which is the delivery of inappropriate direct current shocks. If implantable cardioverter defibrillator technology successfully develops a reliable haemodynamic sensor in the future, this problem may be greatly reduced.

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