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Sudden cardiac death: prevention and treatment

Sudden cardiac death remains a major health issue in western countries as well as in Hong Kong. Despite increasing knowledge of the mechanisms and risk factors of sudden cardiac death, methods for identifying high-risk candidates and predicting the efficacy of measures to prevent sudden cardiac death are still inadequate. A significant proportion of patients have known heart disease but are generally considered to be at low risk for this event. More efforts are needed to improve the success rate of out-of-hospital resuscitation through better warning systems, the use of amiodarone for refractory arrhythmias, and the widespread availability of automated defibrillation devices to allow early defibrillation. It is likely that these measures could increase the number of survivors following cardiac arrest. In survivors of sudden cardiac death episodes, treatment of the underlying cardiac disease, especially early revascularisation for myocardial ischaemia, is required. In the majority of patients, implantation of an implantable cardioverter defibrillator, with or without the use of an anti-arrhythmic drug such as amiodarone, would then be used to maintain survival. Furthermore, for individuals at significant risk of sudden cardiac death, primary prevention of sudden cardiac death through the placement of an implantable cardioverter defibrillator is increasingly being used.

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Sudden death can be defined as either: (1) an unexpected natural death within a short time period, generally 1 hour or less from the onset of symptoms; or (2) a non-witnessed death discovered within 24 hours in someone without prior symptoms, or any prior condition that would appear fatal. Such a rapid death is often attributed to a cardiac cause, but it is now well recognised that classification based on clinical circumstances is often not possible, and can be misleading, as up to 40% of sudden deaths are non-witnessed ones. Prodromal symptoms are often non-specific, and those taken to indicate ischaemia (chest pain), tachyarrhythmia (palpitations), or congestive heart failure symptoms (dyspnoea), should only be seen as suggesting the diagnosis. Sudden cardiac death can be prevented if high-risk patients are identified and referred to a cardiologist. Recently, implantable cardioverter defibrillators (ICD) have been shown to be effective in preventing sudden cardiac death in 99% of cases. Furthermore, automated external defibrillators (AED) have been increasingly accessible.
to non-medical personnel, significantly improving survival rates in patients at immediate risk of sudden cardiac death.

**Epidemiology**

In the United States, sudden cardiac death episodes affect 250 000 to 350 000 people every year, with an average survival rate of only 5%. Cardiovascular disease accounts for up to 89% of cases of sudden death in western populations, as shown in Table 1. Sudden cardiac death is often the first manifestation of coronary heart disease, and is responsible for approximately 50% of the mortality from cardiovascular disease in the United States and other developed countries. In less-developed countries, the rates of sudden cardiac death are parallel to the rates of ischaemic heart disease as a whole, and therefore are lower. According to a 1997 survey in Hong Kong, the incidence of sudden cardiac deaths was 1.8 per 100 000 population. Even when adjusted for the population incidence of coronary artery disease, the incidence of sudden cardiac death is still significantly lower than the western figure. The reason for this difference remains unclear.

**Risk factors**

As the majority of individuals who suffer sudden cardiac death have coronary heart disease, the epidemiology of sudden cardiac death parallels that of coronary heart disease to a large extent. Anatomic findings at autopsy include acute changes in coronary plaque morphology, such as thrombus, plaque disruption, or both, in more than 50% of cases of sudden coronary death. However, up to 50% of patients at immediate risk of sudden cardiac death due to coronary artery disease have no manifestations of their disease prior to that acute episode. Risk factors for sudden cardiac death are similar to those for coronary artery disease, and include age, hypertension, elevated serum cholesterol levels, glucose intolerance, and smoking.

The clinical history can assist in identification of patients at risk of sudden cardiac death. Patients with a history of a sudden cardiac death episode, and with haemodynamically significant ventricular tachyarrhythmias are at risk of sudden cardiac death. A prior history of myocardial infarction can be identified in as many as 75% patients, and raises the 1-year risk of sudden cardiac death by 5%. In patients with a history of previous myocardial infarction, the risk of sudden death is further increased if they present with syncope, with New York Heart Association class III or IV, and have ventricular tachycardia/fibrillation early after myocardial infarction (3 days-2 months). For patients with heart failure due to either ischaemic or non-ischaemic cardiomyopathy, the presence of left ventricular systolic dysfunction (ejection fraction, <30%) is a major independent predictor of total and sudden cardiac mortality. About half of all deaths in patients with heart failure are characterised as sudden death due to arrhythmias, and the risk of sudden cardiac death increases as the left ventricular ejection fraction deteriorates.

<table>
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<tr>
<th>Table 1. Underlying causes of sudden cardiac death</th>
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<td>Prevalence (%)</td>
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<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>Ruptured aneurysm</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Valvular heart disease</td>
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<tr>
<td>Other cardiovascular causes</td>
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<tr>
<td>Non-cardiac causes</td>
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In some patients, family history of cardiac diseases or sudden cardiac death can be important. The prevalence of hypertrophic cardiomyopathy is about 0.2% in the general population, and about 10% of these patients are considered to be at high risk for sudden cardiac death. Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in athletes younger than 35 years. Idiopathic long QT syndrome is a congenital disorder that may lead to unexplained syncope, seizures, and sudden cardiac death. Patients may either remain asymptomatic, or be prone to potentially lethal arrhythmias. For the purposes of risk stratification, a young age at presentation, a family history of sudden cardiac death, and a personal history of cardiac arrest are powerful markers of sudden cardiac death risk. A positive family history is present in 60% of patients with long QT syndrome.

Brugada syndrome was first described in 1991, and has since been recognised as another important cause of sudden cardiac death in patients without structural heart disease. It can be identified by a typical electrocardiographic (ECG) pattern—coved-type, or less commonly, saddleback-type ST segment elevation in precordial leads V1, and V2. There may be associated T wave inversion and right bundle branch block. Sudden cardiac death in patients with Brugada syndrome is caused by fast, polymorphic ventricular tachycardia. Sodium channel blockers, such as procainamide, can unmask these ECG patterns in those with apparently normal baseline ECG findings. In some patients, this syndrome has been shown to be genetically determined, with an autosomal dominant transmission, linking to mutations in the cardiac sodium channel gene SCN5A in chromosome 5, the same gene that causes long QT syndrome. It has long been recognised that some South-East Asian countries, such as Thailand, have a high incidence of sudden death in males (26-38 per 100 000 people per year), known as sudden unexpected death syndrome. It was recently discovered that this syndrome and Brugada syndrome share a defect in a similar gene, indicating that they are allelic diseases, if not the same disease. In Hong Kong, Brugada syndrome is not uncommon, and a case series of 40 patients has been reported. However, the precise genetic defects causing Brugada syndrome in Hong Kong patients remain unclear. Certain ECG abnormalities can help to identify patients at increased risk for sudden cardiac death. These include the presence of atrioventricular block or intraventricular conduction defects and QT prolongation, an increase in resting heart rate to higher than 90 beats per minute, and the presence of complex ventricular arrhythmias, such as non-sustained ventricular tachycardia.
Mechanisms

A number of arrhythmias have been identified as being the underlying mechanism leading to sudden cardiac death (Fig 1)—ventricular tachycardia (62% of cases), bradycardia (17%), primary ventricular fibrillation (8%), and torsades de pointes (13%). In the majority of cases, sudden cardiac death is thus due to a life-threatening ventricular tachyarrhythmia that develops in individuals with underlying anatomic and functional substrates and is precipitated by transient events (Table 2). The interplay between anatomic and functional substrates and transient events leads to disruption of the normal state of balance. The impact of all three on the underlying potential arrhythmia mechanisms intrinsic to all hearts precipitates sudden cardiac death. Understanding this is critical to understanding the pathophysiology of sudden cardiac death. Cardiac arrest due to severe bradycardia, asystole, or pulseless electrical activity (electromechanical dissociation), appears to be more common in severely diseased hearts, probably representing more global myocardial dysfunction. The outlook for patients exhibiting these disturbances at the time of attempted resuscitation is poorer than for patients who exhibit ventricular fibrillation.

Table 2. Anatomic/functional and transient factors that modulate potential arrhythmogenic mechanisms associated with sudden cardiac death

<table>
<thead>
<tr>
<th>Anatomic/functional substrate</th>
<th>Transient initiating events</th>
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<tbody>
<tr>
<td>Coronary artery disease</td>
<td>Neurological events, e.g. stroke</td>
</tr>
<tr>
<td>Cardiomyopathy-dilated or hypertrophic</td>
<td>Endocrine events, e.g. diabetic ketoacidosis</td>
</tr>
<tr>
<td>Right ventricular dysplasia</td>
<td>Electrolytes imbalance</td>
</tr>
<tr>
<td>Valvular diseases</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Primary electrophysiological diseases, e.g. long QT syndrome</td>
<td>Myocardial ischaemia/reperfusion</td>
</tr>
<tr>
<td>Neurohumoral</td>
<td>Haemodynamic stress</td>
</tr>
<tr>
<td>Development</td>
<td>Stress</td>
</tr>
<tr>
<td>Inflammatory, infiltrative, neoplastic, degenerative, toxic</td>
<td>Sleep</td>
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Management

Treatment of patients at immediate risk of sudden cardiac death

Treatment and prognosis depend on the type of underlying cardiac rhythm. Furthermore, different electrophysiological mechanisms are present in different types of cardiac disease. The management of patients includes:

1. initial emergency care to stabilise haemodynamic status;
2. investigation of the underlying causes and precipitating factors; and
3. prevention of recurrence.

Ventricular fibrillation is the type of arrhythmia most responsive to defibrillation. However, ventricular fibrillation tends to rapidly deteriorate into asystole, for which defibrillation is ineffective. Furthermore, the success rate of resuscitation reduces by 8% to 10% after each minute of arrest. Hence, the key for successful resuscitation in patients at immediate risk of sudden cardiac death due to ventricular fibrillation is early defibrillation. This has led to the development of AEDs, which allow early defibrillation for such patients. Preliminary data published support this option. Studies using AEDs to achieve rapid defibrillation (that is, within 4 minutes of cardiac arrest) have demonstrated improved survival in a variety of settings and situations, including by police rescuers trained in early defibrillation, casino security personnel trained with AEDs, airport personnel and non-trained members of the public in airports using AEDs, in-flight airline personnel, and from a broad community-based defibrillation programme that included lay rescuers, police, and public AEDs. Collectively, the effectiveness of early defibrillation is well established, resulting in survival rates approaching 50%. However, the actual impact of AED in reducing mortality remains unclear. As up to 80% of sudden cardiac deaths occur at home, many would not appear to be prevented by placement of AEDs in public places. Therefore, the cost-effectiveness of AED in the community is still subject to further evaluation.

Until recently, no anti-arrhythmic agents administered during cardiopulmonary resuscitation (CPR) have been shown to be effective in shock-refractory ventricular fibrillation. Amiodarone was recently shown to improve
survival to hospital admission during CPR, in patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.\textsuperscript{17,18} Recent guidelines have recommended the use of amiodarone as an alternative to lidocaine in shock-refractory ventricular fibrillation or pulseless ventricular tachycardia forms of cardiac arrest.

All patients resuscitated following sudden cardiac arrest should be stabilised and closely monitored in an intensive care setting, where continuous cardiac monitoring and defibrillation equipment are available. In general, prophylactic anti-arrhythmic therapy is not required, unless the patient develops persistent or recurrent arrhythmia. Disorders of electrolytes (particularly potassium, calcium, and magnesium) should be checked and corrected. Serial surface ECG and cardiac enzyme measurements are required, to exclude an acute myocardial infarction. The QT interval should be noted. Transthoracic echocardiography is useful in assessing ventricular function and structural heart disease. Transoesophageal echocardiography should be reserved for cases where a transthoracic approach is inadequate. As coronary artery disease is an important cause of sudden cardiac arrest, coronary angiography is indicated in the majority of patients who survive. Significant coronary disease should be treated by revascularisation before an electrophysiology study is performed. Aggressive therapy, using thrombolysis in acute ischaemic syndromes, or intracoronary interventions resulting in reduction of myocardial damage and scar formation and the prevention of ventricular remodelling will diminish the occurrence of some of the mechanisms that play a role in a fatal arrhythmia. Coronary revascularisation is protective against ventricular arrhythmia of ischaemic origin. An electrophysiology study is helpful in the diagnosis of a number of important arrhythmias, including sinus and atrioventricular nodal dysfunction, conduction abnormalities, accessory pathways, and inducibility of ventricular tachycardia.

**Pharmacological treatment**

After comprehensive evaluation and the management of underlying causes, structural heart disease, found in the majority of cases, must be addressed. Of the different drugs that have been evaluated, only β-blockers and amiodarone have been shown to reduce sudden death in those surviving myocardial infarction. Other classes of anti-arrhythmic agents either failed to reduce or increased the incidence of sudden cardiac death after a myocardial infarction. A meta-analysis from 13 trials of 6500 patients treated with amiodarone after myocardial infarction or with heart failure, showed a reduction in all-cause mortality, death from arrhythmia, and sudden death.\textsuperscript{19} In patients with diminished left ventricular function and/or ventricular arrhythmias, β-blockade reduced all-cause mortality by 25%.\textsuperscript{20}

Prevention of coronary artery disease through the use of statins and aspirin are probably useful in also preventing sudden cardiac death. The role of angiotensin-converting enzyme inhibitors, angiotensin II blockers, and spironolactone in the prevention of sudden cardiac death is more controversial.

**Implantable cardioverter defibrillators: indications and contra-indications**

An ICD is currently the most effective therapy for primary and secondary prevention of sudden cardiac death, in patients with ventricular tachycardia as the underlying cause. An ICD is a small device, implanted at the pectoral site via transvenous access. The implantation procedure can be performed under local anaesthesia, with conscious sedation. In general, it requires only a short hospital stay and carries a low complication rate. Perioperative mortality is below 1%. A modern ICD can provide a number of therapy options, including bradycardia sensing, bradycardia pacing, anti-tachycardia pacing, cardioversion, and defibrillation.

**Indications**

Current indications for an ICD are summarised in Fig 2. **Secondary prevention**

Secondary prevention refers to prevention of sudden cardiac arrest in those with a known history of this event. A number of trials (AVID [The Antiarrhythmics versus Implantable Defibrillators], CASH [Cardiac Arrest Study Hamburg], and CIDS [Canadian Implantable Defibrillator Study])\textsuperscript{21-23} have confirmed that an ICD is superior to anti-arrhythmic drug treatment (mainly amiodarone) in preventing sudden cardiac arrest in patients with previous ventricular tachycardia or fibrillation and coronary artery disease. The only current indication for ICD implantation in patients with non-ischaemic cardiomyopathy, is secondary prevention after an episode of resuscitated sudden death, or the presence of ventricular tachycardia-induced syncope. The decision-making process for secondary prevention of sudden cardiac death in Brugada or long QT syndromes and for hypertrophic cardiomyopathy is very simple—an ICD is indicated. Research to date indicates that an ICD should be the initial treatment of choice for patients resuscitated from documented ventricular fibrillation that is not related to a reversible or transient cause, such as an acute myocardial infarction. It should also be the initial treatment of choice for patients with haemodynamically poorly tolerated ventricular tachycardia, and probably also for patients with a history of unexplained syncope in the presence of impaired ventricular function, in whom sustained ventricular arrhythmia can be induced during electrophysiological testing.\textsuperscript{24}

**Primary prevention**

Primary prevention of sudden cardiac arrest is indicated in patients without a history of sudden cardiac arrest but who are at high risk of the event. Recent clinical trials (MADIT [Multicenter Automatic Defibrillator Implantation Trial] I and II, MUSTT [Multicenter Unsustained Tachycardia Trial]) have demonstrated that use of an ICD is associated with a 30% to 54% risk reduction for sudden cardiac arrest in patients with prior myocardial infarction, and a low left
ventricular ejection fraction (<30%), with or without an inducible ventricular tachyarrhythmia during electrophysiological study. The indications for an ICD as prophylactic therapy for sudden cardiac death in patients with non-ischaemic dilated cardiomyopathy are still uncertain. The identification of high-risk patients with Brugada or long QT syndrome and hypertrophic cardiomyopathy is more problematic, as screening tests used in other organic heart disease for potentially lethal ventricular arrhythmia (electrophysiology study, signal-averaged ECG, heart rate variability, continuous ambulatory ECG monitoring, and T-wave alternans) have poor predictive values. For patients with hypertrophic cardiomyopathy, the presence of two or more of the following risk factors should prompt the decision for ICD placement: (1) family history of sudden death; (2) unexplained syncope; (3) younger than 40 years; (4) presence of an abnormal blood response during exercise; (5) severe and diffuse left ventricular hypertrophy; and (6) a positive electrophysiology study, with an inducible ventricular tachyarrhythmia demonstrated.

A more difficult decision with respect to patients with ECG manifestation of Brugada or long QT syndrome in the absence of symptomatic arrhythmia, and/or a family history of sudden cardiac death has to be made. Although the threshold for ICD implantation for primary prevention is decreasing, there is no widely accepted single or uniform approach to these syndromes. An individual approach, with participation in the final decision by a well-informed patient and family, is indicated in high-risk patients with Brugada or long QT syndrome and hypertrophic cardiomyopathy.
Contra-indications
An ICD is contra-indicated in the following patients:
1. patients with syncope of undetermined aetiology, and without a documented or inducible sustained ventricular tachycardia;
2. patients whose arrhythmias are due to a transient or reversible disorder, such as acute myocardial infarction, or electrolyte abnormalities;
3. patients with incessant ventricular tachyarrhythmia;
4. patients with specific arrhythmias that have a definitive cure with catheter or surgical ablation, eg verapamil-sensitive ventricular tachycardia, and Wolff-Parkinson-White syndrome, and
5. patients with a projected life expectancy of less than 6 to 12 months, including patients with drug-refractory heart failure, who are not candidates for cardiac transplantation.

Conclusion
Sudden cardiac death is a common and serious medical problem. While effective treatment is available, it is costly and can only be applied to a small percentage of those at risk. Currently, non-invasive methods that allow early and accurate identification of individuals who are at risk of sudden cardiac death are still lacking. Existing methods—including ambulatory ECG monitoring, heart rate variability, signal-averaged ECG, QT dispersion, and T wave alternans—have poor positive predictive value for identifying patients at risk of sudden cardiac death. Although AED has proven effective in saving lives, its cost-effectiveness in the community is still unclear.

Therefore, other alternative approaches to preventing sudden cardiac death should focus on measures to reduce the burden of coronary artery disease. Public education to increase the awareness of sudden cardiac death, to promote learning of CPR, and to develop an effective community resuscitation service will hopefully also act to reduce the incidence of sudden cardiac death.

References