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Sudden cardiac death

K Jennings
Consultant, Cardiology Department, Aberdeen Royal Infirmary, Aberdeen, Scotland

ABSTRACT The majority of the approximately 100,000 sudden cardiac deaths each year in the UK are associated with coronary heart disease, but most sudden deaths in those under 30 years of age are caused by inherited cardiomyopathies and arrhythmias. In those aged 16–64 years, a coroner's post mortem examination is unable to identify a structural cardiac abnormality in 4·0%. The cause of death is therefore uncertain. These deaths are termed 'sudden arrhythmic death syndrome' or 'sudden unexpected death syndrome'.

KEYWORDS Coronary artery disease, drugs, defibrillation, inherited disease, re-synchronisation, screening

LIST OF ABBREVIATIONS Electrocardiogram (ECG), implantable cardiac defibrillator (ICD), myocardial infarction (MI), New York Heart Association (NYHA), sudden arrhythmic death syndrome (SADS), sudden unexpected death syndrome (SUDS)

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Correspondence to **K Jennings, Cardiology Department, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN**

tel. **+44(0)1224 681 818**

fax. **+44 (0)1224 550692**

e-mail
jennings@cardiac-concerns.com

INHERITED DISEASE AND SUDDEN CARDIAC DEATH

Sudden death can occur in those with structurally normal hearts who have abnormalities of the cardiac ion channels which prevent sodium, calcium and potassium ions, important in regulating cardiac activity, from crossing the cell membranes of cardiac muscle cells appropriately (see Table 1).

These are inherited conditions and the relatives of the victim may therefore be at risk of dying suddenly from potentially reversible disease. Also, it may only be by identifying the abnormality in relatives that the cause of death in the victim might be identified. In one study, 43 families where young adults had died suddenly were investigated; 151 carriers of pre-symptomatic disease were identified, and the likely cause of death of the victim was identified in 17 (40%) of the 43 families studied.[1]

There are rare, also genetic, conditions associated with structural cardiac disease which have been identified in relatives of a victim, but not detected at post mortem examination (see Table 2). This may reflect variable penetrance of these conditions.

Families of victims of sudden cardiac death must be assessed for inherited disease. Histories should be obtained of previous unexplained syncope, family history of sudden death, congenital deafness (Jervill–Lange–Nielson syndrome) and muscle weakness. First-degree relatives should have an ECG, a signal averaged ECG (a computer interrogation of the ECG seeking afterpotentials which are arrhythmogenic), an echocardiogram, a holter monitor and an exercise test. Thereafter some will require additional testing using cardiac magnetic resonance imaging, adenosine provocation (to reveal QT prolongation) and electrophysiological study.

Interventions with, for example, implantable defibrillators can prevent sudden death. The DEBUT study,[2] compared implantable defibrillators with beta blockade in a SUDS study. In this study patients with structurally normal hearts who had survived an episode or who had an ECG pattern of SUDS were randomised to either beta blockade or defibrillator therapy. Over a two-year follow up, four died in the medical treatment arm, whilst seven people with defibrillators experienced an event successfully terminated by the device and no patient with a defibrillator died.

THE AUTONOMIC NERVOUS SYSTEM AND LIABILITY TO SUDDEN CARDIAC DEATH

There is accumulating evidence of a close association between abnormalities in the autonomic nervous system and sudden cardiac death. This autonomic imbalance reflects either a relative or absolute decrease in vagal activity or an increase in sympathetic stimulation. One of the measurable manifestations of this is heart rate variability. It has been suggested that low heart rate variability is associated with sudden death in patients with cardiovascular disease. Bigger *et al.*[3] determined normal values for healthy middle-aged persons and compared them with those of patients soon after and late after MI. He found that all measures of heart rate variability were significantly and substantially higher in healthy subjects than in those with chronic or sub-acute coronary disease. The

TABLE 1 Cardiac diseases associated with abnormal cardiac ion channels.

- Long QT interval syndrome (on electrocardiogram).
- Brugada syndrome (right bundle-branch block and ST elevation in leads V1-3).
- Progressive cardiac conduction disease.
- Catecholaminergic polymorphic VT.

TABLE 2 Genetic structural diseases of the heart.

- Arrhythmogenic right ventricular dysplasia.
- Hypertrophic cardiomyopathy.
- Dilated cardiomyopathy.
- Dystrophia myotonica.
- Wolff–Parkinson–White syndrome.

difference from normal values was much greater two weeks after MI than one year after MI. The authors concluded that values of heart rate variability previously reported to predict death in patients known to have coronary disease are rarely (approximately 1%) found in healthy middle-aged people. Thus, if heart rate variability is used to screen middle-aged individuals who might be at risk of sudden arrhythmic death, misclassification of healthy middle-aged persons should be rare. Another study demonstrated significantly lower heart rate variability in depressed patients who were at excess risk for all cause mortality after adjusting for confounding factors (hazard ratio: 2·8 P<0·003).[4] However, a large study of 5,713 men aged 42–53 years without overt coronary disease has shown that exercising heart rate variables do predict risk of sudden death in this apparently healthy population. The resting heart rate, the increase in rate to the peak exercise level and rate decrease from peak exercise to the level one minute after exercise were recorded. During a remarkable 23 year follow up, 81 patients died suddenly. The risk of sudden death from MI was increased in subjects with a resting heart rate that was more than 75 beats per minute (relative risk 3·92). In those with a heart rate increase during exercise that was less than 89 beats per minute (relative risk 6·18) and in subjects with a heart rate decrease of less than 25 beats per minute (relative risk 2·20). After adjustment for confounding variables, these three factors remained strongly associated with an increased risk of sudden death.[5]

SUDDEN DEATH IN CARDIAC DISEASE

In patients with cardiac disease, sudden cardiac death occurs more frequently in those with advanced left ventricular dysfunction. In the MADIT-2 study,[6] 1,232 patients with left ventricular ejection fractions below 30% (normal 60%) and an MI on average five years earlier, were randomised to receive conventional, optimal medical therapy alone or, in addition to an ICD. At two years follow-up the defibrillator group had a 31% reduction in risk from all cause mortality compared with those receiving only medical therapy. This mortality reduction was entirely due to a reduction in sudden cardiac death. Similarly in the SCD-HeFT study,[7] in patients with ischaemic and non-ischaemic left ventricular dysfunction and a median ejection fraction of 25%, there was a 23% mortality reduction with ICD therapy at a median follow up of 45 months (hazard ratio 0·77, P<0·007). In this study, patients were randomised to optimal therapy plus placebo, optimal therapy plus amiodarone or optimal therapy plus an ICD. Amiodarone and placebo were associated with a similar risk of death (hazard ratio 1·06, P<0·53).

Patients with advanced cardiac failure have a mortality risk in the range usually associated with aggressive malignant disease. Many have conduction abnormalities which leads to dyssynchrony of contractility. Re-synchronisation therapy in the form of bi-ventricular pacing promotes synchronous and more efficient contractility in patients with threatening cardiac dysfunction. The COMPANION study tested the theory that re-synchronisation therapy with and without ICD would reduce death and hospitalisation in patients with advanced chronic heart failure. One thousand, five hundred and twenty patients with NYHA III or IV heart failure due to ischaemic and non-ischaemic cardiomyopathy and who had on ECG a QRS interval of at least 120 msec, were recruited. They were randomly assigned to receive optimal medical therapy alone or in combination with re-synchronisation therapy with either a pacemaker or pacemaker-defibrillator. The primary end-point was time to death or hospitalisation. As compared with medical therapy alone, cardiac re-synchronisation therapy with a pacemaker reduced the risk of the primary endpoint (hazard ratio 0·81, P<0·014), as did treatment with a pacemaker-defibrillator (hazard ratio 0·80, P<0·01). A pacemaker reduced the risk of death by 24% (P<0·059) and a pacemaker-defibrillator reduced the risk by 36% (P<0·003).[8] The CARE-HF study confirms but extends these findings by showing a significant reduction in all cause mortality for cardiac re-synchronisation therapy without ICD provision. This study enrolled 813 patients with NYHA III or IV heart failure, an ejection fraction of less than 35% and QRS duration of at least 120 msec. Those with a QRS interval of less than 150 msec were required to have echo evidence of ventricular dyssynchrony.[9] They were randomly assigned to

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optimal medical therapy or re-synchronisation and were followed for a mean 29 months. Again the primary end-point was time to death or hospitalisation. The primary end-point was reached by 39% of the group receiving re-synchronisation compared with 55% of the medically treated patients (hazard ratio 0·63, P<0·001). Twenty percent of the instrumented group died compared with 30% of the conventional therapy patients (hazard ratio 0·64, P<0·002). The authors have concluded that a reduction in cardiac dyssynchrony has resulted in favourable left ventricular modelling and thereby reduced risk.

DRUGS AND SUDDEN CARDIAC DEATHS

Finally, we need to acknowledge that some drugs are able to precipitate threatening rhythm disturbances: one study has shown a three-fold increase in sudden cardiac death with non-cardiac agents which prolong the QTc (the rate corrected QT interval).[10] In this study, 775 cases of sudden cardiac death were identified between 1995 and 2003 with more than 6,000 matched controls. After adjustment for known confounders, current use of QTc prolonging drugs was associated with a significantly increased risk of sudden cardiac death (odds ratio 2·7). These drugs were cisapride, domperidone, chlorpromazine, haloperidol and pimozide and the macrolide antibiotics erythromycin and clarithromycin.

CONCLUSION

We can now identify some patients who are at risk of sudden cardiac death. First-degree relatives of patients who have died young from unexplained sudden death should be screened for identifiable, life-threatening disease for which there may be a therapy. We must avoid using drugs which are pro-arrhythmic without good indications. Patients with advanced cardiac dysfunction are at excess risk of sudden arrhythmic death and this is significantly reduced by bi-ventricular pacing and/or implantable defibrillators where appropriate.

KEYPOINTS

- Most sudden cardiac death is due to coronary artery disease.
- Sudden cardiac death under 30 years of age is usually due to inherited heart disease.
- Autopsy fails to reveal a cause in about 4% of sudden cardiac deaths.
- Relatives of young victims of sudden cardiac death, particularly first-degree relatives, should be investigated as this may identify the cause of victim deaths and allow effective preventative treatment for relatives.
- Autonomic nervous abnormalities identified from heart rate variability can identify those at increased risk of sudden cardiac death.
- Patients with advanced heart disease are at increased risk of sudden cardiac death and this may be prevented by cardiac resynchronisation and defibrillation therapy.
- Drugs recognised as precipitating serious cardiac arrhythmias should be avoided whenever possible.

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