

## Sudden cardiac death in the young

*Identifying people at highest risk of sudden death, using the most effective therapies and working to develop new therapies, are essential strategies*

FEW EVENTS ARE HARDER TO DEAL WITH than sudden death in young people. Each year in the United States, about one in 200 000 high school or college athletes will die suddenly, the vast majority without any prior symptoms,<sup>1</sup> and these devastating events are often the first clinical manifestation of an underlying cardiovascular disorder. Indeed, about 90% of sudden deaths, defined as death occurring within one hour of the onset of symptoms, are found to be caused by cardiac *structural* pathology in autopsy-based series. The remaining 10% relate to other cardiac *electrical* disorders, such as long-QT syndrome and Wolf-Parkinson-White syndrome, or commotio cordis (the result of sudden sharp chest blows), as well as complications of asthma, substance misuse, and sudden infant death syndrome (SIDS).<sup>2</sup>

The single most common disorder causing sudden cardiac death in people aged less than 35 years, including competitive athletes, is the genetically inherited cardiac disorder hypertrophic cardiomyopathy (HCM).<sup>1</sup> HCM is characterised by cardiac hypertrophy, usually of the left ventricle, in the absence of other loading conditions such as hypertension or hyperthyroidism. This disease occurs in approximately one in 500 people. It is clinically heterogeneous, with most affected individuals having few or no symptoms, while others develop serious complications, including heart failure, arrhythmias, and sudden death.<sup>3</sup> In a series of 158 sudden deaths in young competitive athletes (median age, 17 years), 36% were found to have HCM and an additional 10% had evidence of increased cardiac mass suggestive of HCM.<sup>1</sup> In Australia, 34 sudden deaths in people with HCM were reported to the HCM clinic at Sydney's Royal Prince Alfred Hospital over a five-year study period.<sup>4</sup> A substantial proportion of patients with HCM die during or immediately after vigorous physical activity, but sudden death during rest or sleep is also common. The mechanism of death relates to ventricular arrhythmias in over 90% of known cases.

Over the past decade, major advances have been made in understanding the genetic basis of many of the disorders which cause sudden death. DNA defects in disease-causing genes have been identified in HCM, as well as the long-QT syndrome, Marfan syndrome, dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia. Over 200 mutations in at least 10 genes, all encoding proteins of the sarcomere (the basic contractile element of the heart), have been identified.<sup>5</sup> Not only have such discoveries thrown light on the molecular pathogenesis of this disorder, but they have also enabled us to predict an apparently favourable or unfavourable clinical course.<sup>6,7</sup> For example, many people in families with the Arg403Gln mutation in the beta-myosin heavy chain gene develop severe symptoms and even die by age 45 years. In contrast, individuals with the Val606Met

### Risk stratification and screening in sudden cardiac death

#### Risk factors for sudden cardiac death

- Family history of premature sudden death
- Individuals with a family history of an inherited disorder associated with sudden death (eg, hypertrophic cardiomyopathy, long-QT syndrome)
- Previous cardiac arrest
- Previous episodes of documented ventricular tachycardia
- Recurrent syncope
- A known "malignant" gene mutation
- Specific risk factors for a disease (eg, left ventricular wall thickness greater than 30 mm in hypertrophic cardiomyopathy)

#### Screening tests for family members at risk of sudden cardiac death

- History
- Physical examination
- 12-lead electrocardiogram
- Echocardiogram
- Other tests, such as Holter monitoring and exercise testing

mutation in the same gene usually appear to experience minimal symptoms and have a normal life expectancy.<sup>7</sup> Clearly, understanding the molecular mechanisms by which gene defects lead to the clinical phenotype is important. To this end, the recent sequencing of the human genome<sup>8</sup> offers the potential to identify more causative genes in HCM and other medical disorders. It also provides the possibility of understanding the mechanisms and signalling processes with which these genes regulate and modify gene expression (either by second disease-causing or modifying genes or environmental factors), leading to recognition of therapeutic targets important in the pathogenesis of sudden death (eg, ion-channel genes and genes regulating cardiac collagen formation).

Pharmacological agents ranging from  $\beta$ -blockers to amiodarone, while frequently used, have not been shown to be effective in preventing sudden death in HCM. However, the implantable cardioverter-defibrillator has emerged as a proven therapy.<sup>9</sup> Patients should be selected for implantable cardioverter-defibrillator implantation based on risk-stratification parameters. Proven predictors of sudden death which should identify patients who would most benefit from an implantable cardioverter-defibrillator are shown in the Box. Further, providing automatic external defibrillators in public places where crowds are present and where people may be at higher risk (eg, sporting venues) might be of significant benefit in reducing sudden cardiac death in this setting.

In HCM, sudden death has been the most visible and devastating consequence of the disease since the original

report by Teare over 40 years ago.<sup>10</sup> Accurately identifying individuals at highest risk and initiating the most effective therapy to prevent this complication are clearly the ultimate goals. Understanding the genetic basis and molecular mechanisms underlying the cardiovascular disorders that cause sudden death, using this knowledge to identify potential new therapeutic targets, coupled with the use of established therapies such as implantable defibrillators, will go a long way to achieving these goals.

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**Competing interests:** None declared.

**Acknowledgement:** Christopher Semsarian is supported by a National Heart Foundation of Australia fellowship.

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