Contemporary considerations for risk stratification, sudden death and prevention in hypertrophic cardiomyopathy

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For patients with hypertrophic cardiomyopathy, the likelihood of receiving primary prevention for sudden death with an ICD may depend in part on the country of residence

Sudden death has been the most devastating, unpredictable and recognisable complication of hypertrophic cardiomyopathy (HCM), since the modern description of the disease by Teare over 40 years ago. HCM is now recognised as the most common cause of sudden cardiac death in young people, including trained athletes, although only a minority of all HCM patients are susceptible to the risk of sudden death (perhaps 10–15%). Nevertheless, the identification of this patient subset has been a priority, and the subject of a considerable body of literature. Because of the power and availability of the implantable cardioverter-defibrillator (ICD) for both primary and secondary prevention of sudden death, and its recent application to HCM, it now more important than ever to identify those patients within this broad disease spectrum who are at high risk for a catastrophic event.

RISK STRATIFICATION PROFILES

Defining reliable clinical markers for sudden death, and isolating the minority of HCM patients who are at high risk, has been an imposing task. This has been due largely to the relatively low prevalence of HCM within cardiology practice and its striking heterogeneity in clinical expression and outcome. Indeed, there is not yet a single test which is generally accepted as capable of assessing the risk level in all HCM patients with precision.

Because HCM patients who are at risk for sudden death are often asymptomatic, risk factors assessed non-invasively have been most practical in clinical terms. The highest risk profiles in HCM are presently identified by one or more clinical markers: (1) prior cardiac arrest; (2) family history of HCM related death; (3) otherwise unexplained syncope; (4) frequent or prolonged bursts of non-sustained ventricular tachycardia on Holter; (5) abnormal blood pressure response to exercise; and (6) extreme left ventricular hypertrophy.

It has been proposed, based on genotypetype correlations, that disease causing mutations in genes encoding sarcomeric proteins could also be unfavourable (or favourable) primary determinants of sudden death. While such a molecular based treatment strategy is attractive, caution is warranted in translating the “good gene/bad gene” hypothesis to the practical clinical management of HCM patients. Available epidemiologic-genetic data are based on relatively small numbers of genotyped families; each of the 10 known disease causing HCM mutant genes (and approximately 200 individual mutations) occur infrequently in the general population of this genetically heterogeneous disease. Furthermore, genotyping involves complex, time consuming, and expensive laboratory techniques which are presently confined to only a select few research oriented laboratories.

Other non-invasive indices such as signal averaged ECG and QT dispersion have not proven to be useful for the stratification of risk. Therefore, there is a continuing aspiration to develop additional tests to better define the high risk HCM patient. The recently reported study by Butera and colleagues, comprising a relatively small series of children with HCM who demonstrated a high rate of sudden death, is timely by raising the possibility that substantial heart rate variability (reflecting autonomic imbalance) may be predictive of high risk in this disease. Whether heart rate variability will ultimately achieve inclusion into the risk stratification armamentarium of HCM will require confirmatory studies in larger patient populations.

PREVENTION OF SUDDEN DEATH

Historically, treatment strategies to reduce the likelihood of sudden death in HCM have been largely pharmacologic, predicated on prophylactic administration of β blockers, verapamil, type IA antiarrhythmic agents (that is, quinidine, procainamide), and amiodarone to patients judged to be at unacceptably high risk. However, these drugs have never been shown to mitigate sudden death risk convincingly, usually cannot be tolerated over the long periods of risk incurred by young HCM patients because of their potential toxicity, and therefore seem outdated compared to the power of the ICDs.

When sudden death risk is judged by available clinical evidence to be unacceptably high in HCM patients, the ICD has proven to be the most effective and reliable treatment option, harbouring the potential to alter the natural history of this disease. In a multicentre retrospective study, which has been a stimulus to many device implants in HCM since its publication in February 2000, ICDs aborted potentially lethal ventricular tachyarrhythmias in almost 25% of the patients.
Indeed, it may be very difficult in a heterogeneous and relatively uncommon disease such as HCM to establish practice guidelines for ICD related decisions based solely on the construction of strict algorithms and arbitrary cut-points. Such a strategy could result in the under treatment of some HCM patients truly at risk for sudden death. For example, in formulating a risk level for surviving relatives in a family affected by HCM, how many sudden deaths are sufficient to constitute a risk factor? One or two? If two deaths are required, as proposed by some investigators, should one relative be required to wait until another relative dies before an ICD is considered? In an HCM family with two young affected brothers (one who has already died suddenly of HCM), would it not be appropriate to offer the option of a prophylactic ICD to the surviving brother, even in the absence of any other independent risk factors? These are just a few of the innumerable and difficult (if not impossible) questions which commonly arise in contemplating primary prevention of sudden death in individual HCM patients.

It is also of note that physician and patient attitudes toward ICDs (and access to such devices within the respective health care system) can vary considerably among countries and cultures (fig 1), thereby impacting importantly on clinical decision making and specifically the threshold for prophylactic implants in HCM patients. For example, employment of ICDs relative to population size is much higher in the USA, accounting for about 75% of all implants worldwide—fivefold greater than in Europe and 10 times that of the UK (fig 1). Such disparity in implant rates suggests that for HCM patients with equivalent levels of risk, the likelihood of receiving primary prevention for sudden death with an ICD would be highly dependent on the patient’s country of residence.

REFERENCES


ICDs per million population

Figure 1. Defibrillator implants worldwide in the year 2001, shown by country (per one million population). The rates shown are for all ICD indications, but largely represent implants in patients with coronary artery disease.
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