Sudden Cardiac Death in Genetic Heart Diseases and the Promise of Prevention

Barry J. Maron

Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota, USA

Genetic heart diseases are responsible for a substantial proportion of sudden unexpected deaths in young people. The most common among this diverse group of conditions is hypertrophic cardiomyopathy (HCM), also the single leading cause of sudden death in young people in the U.S., including competitive athletes. In addition, less common inherited diseases in the general population such as ion channelopathies (ie, long or short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia) and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) also account for a considerable proportion of these deaths.

The phenotypic expression of these genetic cardiomyopathies (responsible for life-threatening sustained ventricular tachyarrhythmias) is notably heterogeneous. HCM and ARVC/D constitute structural abnormalities predominantly of the left and right ventricles, respectively. Alternatively, the ion channelopathies are characterized by absence of gross and histopathologic abnormalities with the primary life threatening ventricular tachyarrhythmias due to causative mutations in genes encoding proteins regulating the transport of ions across the cell membrane (eg, sodium, potassium, and calcium).

Given the youthful ages of the victims, with the potential for many decades of future productive life, these genetic conditions constitute a public health issue with considerable societal impact—perhaps not yet fully appreciated in the medical or lay communities. Indeed, in this issue of Revista Española de Cardiología, Gimeno et al substantiate this risk for sudden unexpected death by reporting a substantial number of 152 such events (mean age 43 [18] years), comprising 18% of 846 largely asymptomatic members in 103 families, predominantly with HCM, ARVC/D, and ion channelopathies.

Fortunately, over the last 30 years, cardiovascular medicine has seen the development of the implantable cardioverter-defibrillator (ICD) with the power to effectively impact these catastrophes and prevent sudden deaths from occurring (Figure). In the seminal 1980 ICD paper, Mirowski et al reported 3 exceptionally high risk patients who had survived 2 or more cardiac arrests. For the first time, the implanted defibrillator was shown to operate spontaneously and automatically to abort ventricular fibrillation (VF). Notably, although the ICD was not originally designed for young patients with genetic heart diseases (but rather for ischemic heart disease), 2 of the 3 initial patients appear to have HCM. However, for the ensuing 2 decades, patients with HCM (and other inherited heart diseases) were largely ignored as ICD therapy evolved with these devices penetrating the marketplace worldwide, largely in older patients with coronary artery disease.

Nevertheless, over the last decade, ICD therapy has been applied to increasing numbers of younger patient populations with genetic heart diseases. The most substantial impetus has been in HCM, a disease constituting 60% of deaths in the report of Gimeno et al. Indeed, the largest and most robust ICD series in inherited heart disease is an international, multicenter retrospective/prospective registry with >500 HCM patients, each judged to be at unacceptably high risk and implanted for primary or secondary prevention by cardiovascular specialists at 42 institutions in the U.S., Europe, and Australia (Figure). This ICD registry is comprised predominantly of patients with no or only mild limiting heart failure symptoms who were relatively young (average age, 41 years at time of implant), and similar to the age at death in the Gimeno et al report. Over an average follow-up of only 3.7 years, appropriate device discharges for VF or rapid ventricular tachycardia (VT) occurred in 20% of the patients (Figure), with an implant-to-life...

SEE ARTICLE ON PAGES 268-76
more extensive and successful defibrillator use in that disease and similarly in young patients with ARVC/D, Brugada and long QT syndromes. Unfortunately, Gimeno et al do not report whether their patients with these diseases were considered for ICD therapy.

Of note, primary prevention in genetic heart diseases, usually in young asymptomatic patients with conventional risk factors, is conceptually different from primary prevention in ischemic heart disease following myocardial infarction with reduction in ejection fraction. Furthermore, risk stratification strategies directed toward selection of patients for primary prevention ICDs differ considerably among the inherited cardiac diseases, given the evident heterogeneity in phenotypic expression and the

served ratio of 5:1. Appropriate ICD discharge rate was 5.5%/year at a mean age of only 44 years. Of those particularly young patients ≤20 years of age when receiving ICDs largely for primary prevention, almost 30% had appropriate ICD interventions at an average age of 18 (4) years of age (ie, 7% per year). Appropriate ICD intervention rate for secondary prevention (implant after cardiac arrest) was 11% per year and for primary prevention (based only on risk factors) was 4% per year (Figure), similar to the sudden death rate reported from tertiary referral centers in the pre-ICD era. Now, several other ICD studies of in single center HCM populations have also shown the life-saving capability of this strategy for both primary and secondary prevention. Indeed, the initial ICD experience with HCM triggered

Fig. 1. Prevention of sudden death in hypertrophic cardiomyopathy. Top left: intracardiac electrogram obtained at 1:20 AM while asleep, 5 years after implant. From 35-year-old man with hypertrophic cardiomyopathy who received prophylactic implantable cardioverter-defibrillator (ICD) because of family history of sudden death and extreme ventricular septal thickness. A: ventricular tachycardia (VT) begins abruptly, apparently unprovoked, at 200 beats/minutes. B: defibrillator senses VT and charges. C: VT deteriorates in ventricular fibrillation (VF). D: defibrillator issues 20-J shock (arrow) immediately restoring sinus rhythm. A virtually identical sequence occurred 9 years later, also during sleep; patient is now 53 years old and asymptomatic. From Maron BJ et al13 reproduced with permission of Massachusetts Medical Society. Top right: flow-diagram summarizing ICD-related outcome in 506 high-risk HCM patients from international multicenter ICD registry.12 Bottom left: ICD intervention rates in patients implanted prophylactically for only one risk factor. In hypertrophic cardiomyopathy, one major risk factor within the individual patient’s clinical profile is sufficient to consider a primary prevention ICD. Bottom right: cumulative rates for first appropriate ICD intervention in patients implanted for primary prevention with 1, 2, or ≥3 risk factors. From Maron et al,12 reproduced with permission of American Medical Association.
mechanisms of arrhythmogenicity.\textsuperscript{2,3,6,7} Because HCM is the most common of these diseases, and oldest in terms of clinical recognition, its risk stratification algorithm can probably be regarded as more mature and settled (Figure).\textsuperscript{17} However, each of the inherited arrhythmogenic diseases lack a single predominant and quantitative risk factor (in contrast to coronary artery disease) due to their variability in expression, and the inability to assemble highly powered randomized trials with such relatively uncommon conditions.\textsuperscript{17}

Nevertheless, there is little or no debate concerning secondary prevention ICDs following cardiac arrest in any of the inherited heart diseases. While prophylactic ICDs are most commonly the primary treatment strategy for sudden death prevention when risk is judged to be unacceptably high in HCM, ARVC and Brugada syndrome, medical therapy with beta-blockers still assumes a major role as a first line prophylactic therapy for many high-risk patients with long QT syndrome.\textsuperscript{7}

It should be noted that overall ICD implant rates differ considerably with regard to country and healthcare system, due to a number of cultural, societal and economic factors, a fact that unavoidably influences strategies for primary prevention of sudden death in HCM and other inherited heart diseases.\textsuperscript{25} Overall implant rates in the U.S. far exceed those in Western European countries (2- to 5-fold), and are much higher than in Far East, Middle-Eastern, and Eastern European nations. Although these gaps are closing, such differences in ICD utilization raise the distinct possibility that patients with genetic heart disease and the same level of risk, living in different countries, may not have the same access to prophylactic ICDs and the opportunity for sudden death prevention.

In the year 2010, it is 30 years after the introduction of the ICD to clinical practice by Mirowski and Mower,\textsuperscript{9} and 10 years after the ICD was first promoted and used systemically (as well as successfully) in young patients with HCM.\textsuperscript{13,17} The ICD is now widely regarded as one of the most significant advances in cardiovascular medicine of this era. Introduction of ICDs to patient populations with HCM and other genetic arrhythmogenic heart diseases represents a new paradigm for clinical practice. ICDs offer the only absolute protection against sudden death by virtue of effectively terminating ventricular tachycardia/fibrillation. In the process, ICDs alter the natural history of the disease, providing the potential opportunity for many young patients to achieve normal or near-normal longevity, and legitimately aspire to the possibility of long and productive lives despite the presence of an unpredictable underlying arrhythmogenic substrate.

REFERENCES


