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

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Genetic heart diseases are responsible for a substantial proportion of sudden unexpected deaths in young people.[1] 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.[2-4] 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.[1,5]

The phenotypic expression of these genetic cardiomyopathies (responsible for life-threatening sustained ventricular tachyarrhythmias) is notably heterogeneous.[2,3,6,7] 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).[5]

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[8]

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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[9] 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.[9] 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.[10,11]

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.[8] 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).[12] 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.[8] 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
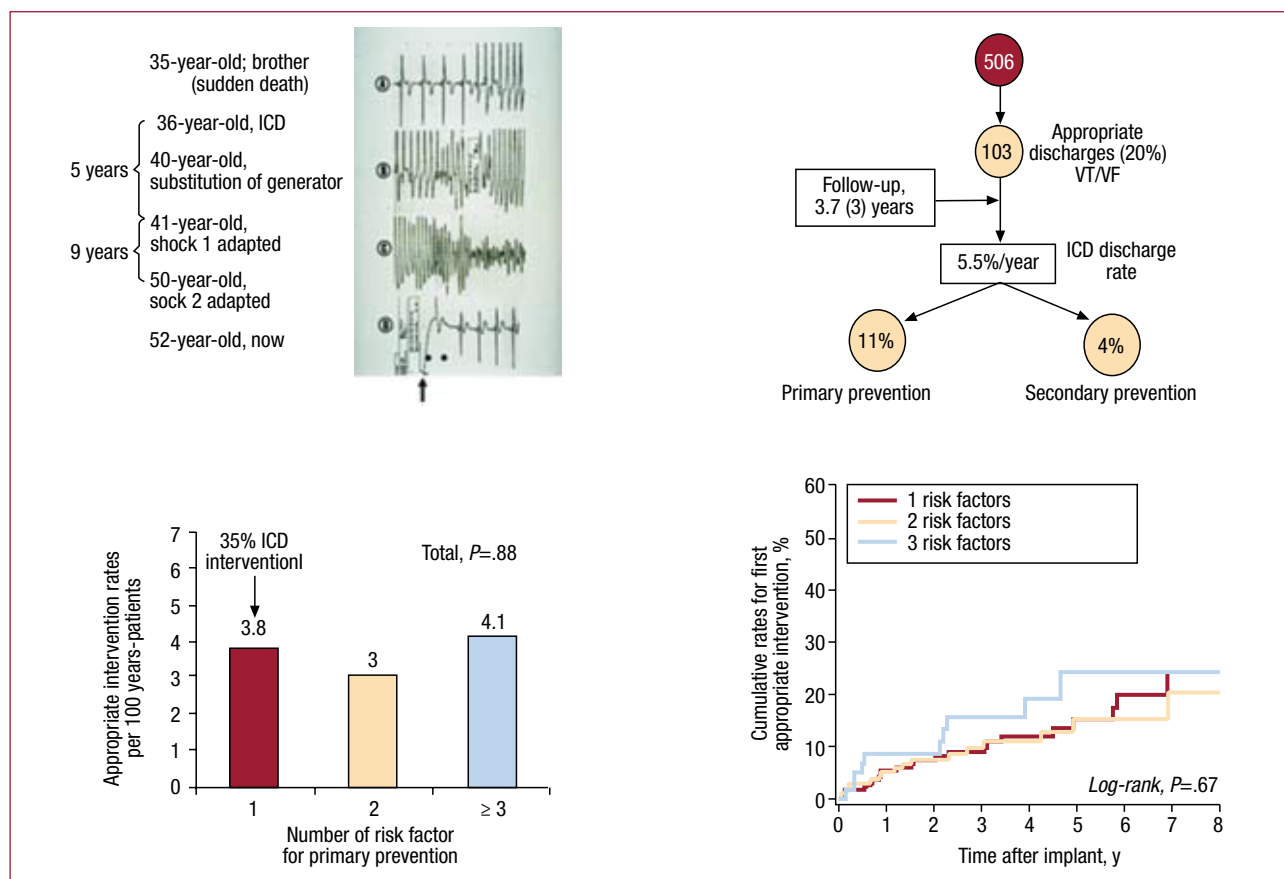
Fig. 1. Prevention of sudden death in hypertrophic cardiomyopathy. Top left: intracardiac electrogram obtained at 1:20 AM while asleep, 5 years after implant. From 35-year-old man with hypertrophic cardiomyopathy who received prophylactic implantable cardioverter-defibrillator (ICD) because of family 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 al[13;] 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.

saved 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.[2,3] 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.[14-17] Indeed, the initial ICD experience with HCM[13] triggered more extensive and successful defibrillator use in that disease[14-17] and similarly in young patients with ARVC/D, Brugada and long QT syndromes.[18-24] Unfortunately, Gimeno et al[8] 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.[10,11] 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

mechanisms of arrhythmogenicity.[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).[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.[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.[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.[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,[9] and 10 years after the ICD was first promoted and used systematically (as well as successfully) in young patients with HCM.[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

1. Maron BJ, Chaitman B, Ackerman MJ, Bayés de Luna A, Corrado D, Crosson JE, et al. American Heart Association Scientific Statement: Recommendations for Physical Activity and Recreational Sports Participation for Young Patients with Genetic Cardiovascular Diseases. Circulation. 2004;109:2807-16.
2. Maron BJ. Hypertrophic cardiomyopathy: A systematic review. JAMA. 2002;187:1308-20.
3. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines Committee to Develop an Expert Consensus Document on Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2003;42:1687-713 and Eur Heart J. 2003;24:1965-91.
4. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the U.S., 1980-2006. Circulation. 2009;119:1085-92.
5. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies. An American Heart Association Scientific Statement from the Council of Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113:1807-16.
6. Basso C, Corrado D, Marcus F, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. Lancet. 2009;373:1289-300.
7. Viskin S, Halkin A. Treating the long-QT syndrome in the era of implantable defibrillators. Circulation. 2009;119:204-6.
8. Gimeno JR, Oliva MJ, Lacunza J, Alberola AG, Sabater M, Martínez-Sánchez J, et al. Características de la muerte súbita en las cardiopatías hereditarias. Rev Esp Cardiol. 2010;63:268-76.
9. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, et al. Termination of malignant ventricular arrhythmias with an implantable automatic defibrillator in human beings. N Engl J Med. 1980;303:322-4.
10. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al; for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med. 1996;335:1933-40.
11. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber D, Cannom D, et al; for the MADIT II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877-83.
12. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Outcomes of patients with implantable cardioverter-defibrillators for prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405-12.
13. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy N Engl J Med. 2000;342:365-73.
14. Jayatilleke I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, et l. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. Am J Cardiol. 2004;93:1192-4.
15. Woo A, Monakier D, Harris L, Shah P, Wigle ED, Rakowski H, et al. Determinants of implantable defibrillator discharges

in high-risk patients with hypertrophic cardiomyopathy. Heart. 2007;93:1044-5.

16. Maron BJ, Spirito P. Implantable defibrillators and prevention of sudden death in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2008;19:1118-26.

17. Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Circulation. 2009. [In press].

18. Corrado D, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation. 2003;108:3084-91.

19. Sacher F, Probst V, Iesaka Y, Jacon P, Labordeire J, Mizon-Gérard F, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada Syndrome. A multicenter study. Circulation. 2006;114:2317-24.

20. Roguin A, Bomma CS, Nasir K, Tandri H, Tichnell C, James C, et al. Implantable cardioverter-defibrillators in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol. 2004;43:1843-52.

21. Sarkozy A, Boussy T, Kourgiannides G, Chierchia G-B, Richter S, De Potter T, et al. Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. Eur Heart J. 2007;28:334-44.

22. Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion C, Drenckhahn J, Norman MW, et al. The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). J Am Coll Cardiol. 2005;45:400-8.

23. Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson MS, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. J Cardiovasc Electrophysiol. 2003;14:337–41.

24. Proclemer A, Ghidina M, Facchin D, Rebellato L, Corrado D, Gasparini M, et al. Use of implantable cardioverter-defibrillator in inherited arrhythmogenic diseases: data from Italian ICD registry for the years 2001-6. PACE. 2009;32: 434-45.

25. Camm A, Nisam S. The utilization of the implantable defibrillator – a European enigma. Eur Heart J. 2000;21:1998-2004.