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Point/Counterpoint

Family History of Sudden Death Should Be a Primary Indication for Implantable Cardioverter Defibrillator in Hypertrophic Cardiomyopathy

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See article by Watkinson and Elliott, pages 1407-1409 of this issue.

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the leading cause of sudden death in young patients. A number of noninvasive clinical markers, including family history, have formed the basis for a risk stratification strategy aimed at identifying high-risk patients with HCM. The observation that sudden death can occur in multiple relatives of the same family, and clinical studies in which a family history of HCM-related sudden death emerges as an independent predictor of sudden death, support the principle that family history should be considered a risk factor which, in the appropriate clinical scenario, can form the basis for recommending prophylactic implantable cardioverter defibrillator therapy.

RÉSUMÉ

La cardiomyopathie hypertrophique (CMH) est la cause principale de mort subite chez les jeunes patients. Plusieurs marqueurs cliniques non invasifs dont les antécédents familiaux, ont constitué la base d'une stratégie de stratification du risque visant la détection des patients atteints de CMH exposés à un risque élevé. L'observation selon laquelle la mort subite peut survenir chez de nombreux membres de la même famille, et les études cliniques selon lesquelles les antécédents familiaux de mort subite liée à la CMH apparaissent comme des prédicteurs indépendants de mort subite soutiennent le principe que les antécédents familiaux devraient être considérés comme des facteurs de risque qui, selon le scénario clinique approprié, peuvent constituer la base de la recommandation d'un traitement prophylactique à l'aide d'un défibrillateur cardioverteur implantable.

Since the original description of hypertrophic cardiomyopathy (HCM) > 55 years ago,[1] sudden death has been the most visible and devastating consequence of this disease.[2-4] Over this time, a number of noninvasive clinical risk markers, including family history, have emerged to aid in identifying patients at high risk for sudden death who may be candidates for lifesaving primary preventive therapy with an implantable cardioverter-defibrillator (ICD).[3-9] Indeed, this contemporary risk stratification strategy has now resulted in a substantial reduction in sudden death, providing the opportunity for extended longevity in the vast majority of patients with HCM.[10,11] However, what evidence supports family history as a sudden death risk marker for which to base a recommendation to implant an ICD for primary prevention?

Historical Observations

The inclusion of family history into the clinical practice of risk stratification was initially based largely on the clinical experience of HCM investigators and clinicians, who observed clusters of sudden death in select HCM families.[2,3] In fact, it was a malignant family history of several siblings who died suddenly early in life that was the impetus for referring Mr. Claude Brady to the National Institutes of Health in Bethesda, Maryland in 1958, where he became the first patient clinically diagnosed with HCM.[12] After these early observations, numerous studies and case reports have included detailed pedigrees of high-risk families in which the tragic consequence of sudden death has occurred in multiple young family members across generations and often with sudden death as the only disease manifestation incurred by these patients.[13,14] Although these highly malignant HCM families compose a small segment of the diverse HCM disease spectrum, they suggest that in select families a strong link does exist between related family members and risk of sudden death events caused by HCM.

Cohort Studies

After this early observational period, a number of longitudinal follow-up studies in large cohorts of patients with HCM have identified family history as a strong independent predictor for the risk of future sudden death in other related family members based on multivariate analysis (Table 1).[15-17] In several of these investigations, a family

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Table 1. Family history of sudden death as a predictor of sudden death events or appropriate ICD shock for VT/VF in patients with HCM

	No. patients	Age (y)	Follow-up (mo)	No. patients with family history of SD	Family history as predictor for SD, HR (95% CI)	Rate of ICD shock/100 person-years, HR (95% CI)
Elliott et al.[16]	917	43 ± 15	61 ± 10	278	1.8 (1.0-3.5)	–
D'Andrea et al.[15]	123	39 ± 6	48 ± 8	28	1.28 (1.1-1.4)	–
Maron et al.[6]	383	41 ± 16	48 ± 36	67	–	2.7 (1.1-5.1)
Bos et al.[17]	177	45 ± 14	60 ± 36	91	–	2.2 (0.6-5.6)

CI, confidence interval; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; SD, sudden death; VT/VF, ventricular tachycardia/ventricular fibrillation.

history of HCM-related sudden death was associated with a substantial (20%) relative increase in risk compared with patients with HCM with no family history of sudden death.[15,16] The totality of these studies suggest that a family history of sudden death increases risk approximately 1.0% per year for other clinically affected relatives, compared with 0.5% per year for patients with HCM with none of the conventional risk markers.

In addition, results from contemporary trials of ICD implantation for primary prevention in HCM have also provided insight into the importance of family history as a risk factor (Table 1).[5,6] Among the largest of these studies, the HCM ICD registry, 383 patients with HCM underwent ICD placement for primary prevention based on the presence of ≥ 1 of the conventional risk factors, with an appropriate intervention rate for ventricular tachycardia/ventricular fibrillation (VT/VF) of 3.6% per year over the follow-up period.[6] A substantial proportion of these patients underwent ICD implantation based on the presence of only 1 conventional risk factor, including family history of HCM-related sudden death; an important subgroup of these patients received a potentially lifesaving device intervention for ventricular tachyarrhythmia (Fig. 1A). Indeed, the rate of appropriate ICD interventions for patients undergoing implantation based only on family history was substantial (2.7 per 100 person-years) and was greater than the intervention rate for patients with HCM who underwent ICD implantation for other single risk factors, such as massive left ventricular hypertrophy, and was nearly identical to that of patients with nonsustained ventricular tachyarrhythmia on ambulatory Holter monitoring (Fig. 1B).[6] Similar results were also observed in a recent ICD study of pediatric patients with HCM in which an important subgroup of children who underwent implantation of an ICD for primary prevention based only on a family history of HCM-related sudden death received a potentially lifesaving shock for VT/VF.[7]

More recently, direct evidence has emerged for an investigation focused specifically on family history as a predictor within a large population of patients with HCM who experienced an appropriate ICD intervention for ventricular tachyarrhythmia (Table 1). In this study by Bos et al.,[17] risk of device intervention was similar for patients with HCM who underwent implantation solely for a family history of sudden death and for other patients who also experienced an appropriate shock with a single risk factor other than family history. The ICD event rate for patients with a family history of HCM-related sudden death as the sole risk factor was 2-fold greater in this select population than the sudden death rate reported in a general HCM population.[17] Of note, the highest rates of appropriate ICD interventions were in those patients with multiple risk factors, including family history. In summary, if family history had not been considered an indicator of higher risk status in these studies, an important subgroup of predominantly young asymptomatic patients with HCM may have remained unprotected from life-threatening ventricular arrhythmias without the ICD (Fig. 2).

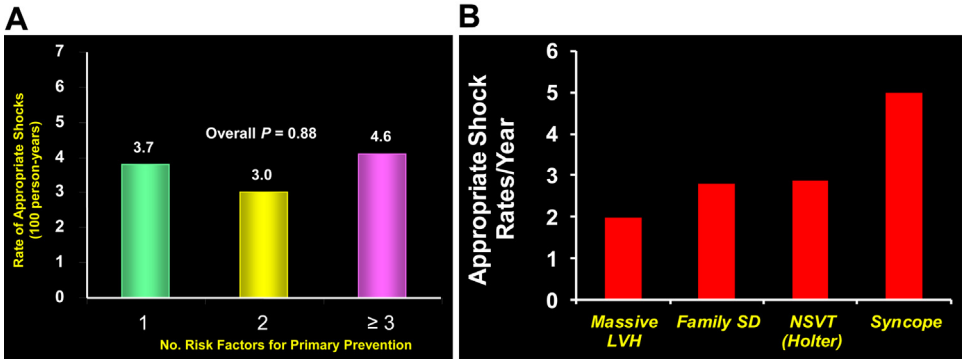

Figure 1. (**A**) Among a large cohort of patients with hypertrophic cardiomyopathy (HCM) with implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden death (SD),[6] the rate of appropriate shock for ventricular tachyarrhythmias is similar for patients who underwent implantation based on the presence of 1 conventional risk marker and patients who underwent implantation with ≥ 2 risk factors. (**B**) In the same HCM study cohort,[6] we see the rate of appropriate shocks for ventricular tachyarrhythmias among patients implanted with an ICD based on the presence of 1 risk factor, including family history of HCM-related sudden death. LVH, left ventricular hypertrophy; NSVT, nonsustained ventricular tachycardia.