EDITORIAL COMMENT
On Predictors of Sudden Cardiac Death in Hypertrophic Cardiomyopathy*
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The clinical diagnostic hallmark of hypertrophic cardiomyopathy (HCM) is unexplained cardiac hypertrophy, commonly found on an echocardiogram and in unfortunate occasions, in an autopsy. The latter is most tragic as HCM, a relatively common disease (1) often presenting with sudden cardiac death (SCD) in apparently healthy young individuals (2,3). Indeed, HCM is considered the most common cause of SCD in young competitive athletes (2). The unexpected SCD of young athletic individuals in conjunction with the results of earlier studies from major referral centers, reporting an annual mortality rate of approximately 2% to 6% (3–5), led to the impression that HCM is a relatively malignant disease. Population-based studies, however, suggested a more benign course with an annual mortality rate of approximately 1% (6–9). In the largest series comprised of 744 patients, the annual mortality rate was 1.2% of which approximately half were sudden unexpected deaths (9).

In this issue of the Journal, Kofflard et al. (10) extend their previous report (7) and present data on the clinical outcome of 225 patients with HCM that were followed up for a mean period of 8 years. The overall annual cardiac mortality rate was 0.8% with SCD comprising the majority of deaths. Among the potential predictors, only syncope was associated with the risk of SCD. The results suggest a less malignant course for HCM in the setting of conventional therapy that may include surgical septal myectomy and pacemaker implantation and are in accordance with the result of previous population-based studies (6–9). Collectively, the existing data suggests an annual cardiac mortality rate of patients with HCM is about 1% with SCD comprising at least half and heart failure and stroke comprising the remainder (9,11).

Death due to HCM, while uncommon, is often catastrophic, as it is often unexpected in young, apparently healthy, athletic individuals. The challenges facing physicians and patients alike are to identify those who are at risk and to intervene to prevent SCD. Since HCM is a genetic disease with a simple Mendelian inheritance and variable penetrance, risk stratification often extends to the offspring of an affected individual as well. During the past several years, significant efforts have been made to accurately identify those who are at a high risk of SCD. The results have been complicated by the clinical and genetic heterogeneity of HCM as well the relatively small number of cases in the studies. Nevertheless, several potential risk factors have been identified (Table 1). In the Kofflard et al. (10) study, only history of syncope was associated with SCD, a finding that corroborates the results of previous studies (3,12–14). In contrast, several other indices, previously associated with the risk of SCD, such as age (3,9), family history of SCD (3,13,15), magnitude of left ventricular hypertrophy (16,17), and presence of ventricular tachycardia on Holter monitoring (14,18) were not independent predictors of SCD. The apparent discrepancy may reflect the relatively small number of SCD in the present study. There were only 27 cardiovascular deaths of which 20 were SCD. In addition, the results largely reflect the clinical practice experience of the Thoraxcenter and, as often is the case in such studies, no a priori criteria were implemented for phenotypic characterization and interventions. As such, Holter monitoring data were available in two-thirds of the patients and invasive electrophysiologic studies were not part of the study. Furthermore, patients received a variety of pharmacologic and nonpharmacologic interventions, as deemed clinically indicated, which may or may not confound the results of the study with regard to identification of predictors of SCD. Finally, pathologic phenotypes, such as myocyte disarray and interstitial fibrosis, previously associated with the risk factors for SCD (14,19,20), were not included in the report. Nevertheless, the results are useful and probably relevant to the day-to-day experience of many clinicians who manage patients with HCM.

The seminal discovery of a R403Q mutation in the beta-myosin heavy chain (MyHC) in a family with HCM approximately 12 years ago (21) led to elucidation of molecular genetic basis of HCM and subsequent identification of a large number of mutations in 10 different sarcomeric proteins (22). Today, the causal genes and mutations have been identified for approximately two-thirds of HCM cases (22,23). Mutations in genes encoding beta-MyHC, myosin binding protein-C (MyBP-C) and cardiac troponin T (cTnT) account for the vast majority of HCM cases and the remainder are uncommon (22). Elucidation of molecular genetic basis of HCM brought forth the possibility of genetic risk stratification, independent of and prior to the development of clinical phenotypes. The results of genotype-phenotype correlation studies suggest that specific mutations impart a significant impact on phenotypic expression of HCM including the risk of SCD (24,25). In general, mutations in the beta-MyHC are associated with

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Table 1. Potential Risk Factors for SCD in HCM

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<thead>
<tr>
<th>Factor</th>
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<tr>
<td>History of SCD</td>
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<tr>
<td>Family history of premature death</td>
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<tr>
<td>&quot;Malignant&quot; causal mutations</td>
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<tr>
<td>&quot;Malignant&quot; modifier genes</td>
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<tr>
<td>History of syncope</td>
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<tr>
<td>Magnitude of left ventricular hypertrophy</td>
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<tr>
<td>Extent of myocyte disarray</td>
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<tr>
<td>Extent of interstitial fibrosis</td>
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<tr>
<td>Early onset of the disease</td>
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<tr>
<td>Myocardial ischemia on perfusion tomography</td>
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<td>Abnormal blood pressure response to exercise</td>
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<td>Presence of non sustained VT on Holter</td>
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HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death; VT = ventricular tachycardia.

The collective results of studies reported in this issue of the Journal and the previous studies identify several potential predictors of SCD, albeit each has limited positive and negative predictive values (Table 1). Despite the imperfectness of the current data in predicting the risk of SCD, those with syncope or multiple risk factors, which comprise about one-fifth of patients with HCM (10,13) are considered at a high risk of SCD and may benefit from prophylactic interventions. Because ventricular fibrillation is likely to constitute the primary mechanism of SCD in high-risk individuals, implantation of an automatic internal cardioverter-defibrillator (AICD) could prove to be effective. The results of a recent retrospective study support the potential effectiveness of AICD implantation in prevention of SCD in selected patients with HCM (38). Experimental data also have raised the possibility of attenuation and reversal of the arrhythmogenic substrate (i.e., cardiac hypertrophy and fibrosis, in animal models of HCM) (39,40).

These advances further underscore the need for accurate risk identification and identification of those who are at risk of SCD. The clinical utility of genotype-phenotype correlation studies has been limited for various reasons, including confounding effects of small size of the families, small number of families with identical mutations, modifier genes, nongenetic factors, and sometimes compound homozygosity for the causal mutations (41,42). Studies in single families, despite their limitations, could provide the initial impetus for performing large-scale studies. In order to extend the results of genotype-phenotype correlation studies to clinical practice aiming to prevent SCD, large-scale studies in multiple families are needed. The ultimate goals are to establish a consensus in delineating the prognostic significance of the causal mutations, modifier genes, and nongenetic factors.
REFERENCES


