Published in final edited form as:
J Am Coll Cardiol. 2003 March 19; 41(6): 994–996.

On Predictors of Sudden Cardiac Death in Hypertrophic Cardiomyopathy*

Ali J. Marian, MD
Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, Texas.

Abstract

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

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

Reprint requests and correspondence: Dr. Ali J. Marian, Section of Cardiology, One Baylor Plaza, 519D, Houston, Texas 77030. amarian@bcm.tmc.edu..

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 an earlier onset, more severe cardiac hypertrophy, and a higher incidence of SCD than those in the MyBP-C (26–28). The phenotype of patients with mutations in cTnT is characterized by relatively mild hypertrophy but a high incidence of SCD and extensive disarray (19,29). While the diversity of causal genes and mutations is partially responsible for the variability of clinical phenotype, there is a significant degree of phenotypic variability among the affected individuals within a family and among members of families with identical causal mutations. Overall, the existing data suggest mutations exhibit highly variable clinical, electrocardiographic, and echocardiographic manifestations and no particular phenotype is mutation-specific (30).

In this issue of the *Journal*, Jongbloed et al. (31) describe a large family with HCM caused by a novel missense mutation (E62Q) in the gene coding for alpha-tropomyosin. The phenotype is characterized by a high incidence of SCD, affecting 9 out of the 18 mutation carriers, at a relatively young age and a variable degree of cardiac hypertrophy (31). Because mutations in the alpha-tropomyosin are uncommon causes of HCM, only a few genotype-phenotype correlation studies have been reported previously. The results showed variable phenotypic expression but predominantly mild-to-moderate degree of cardiac hypertrophy and a relatively benign prognosis (32,33), with the exception of one report that described a high incidence of SCD, despite a mild degree of cardiac hypertrophy (34). The E62Q mutation described by Jongbloed et al. (31) is clearly associated with a malignant phenotype in this particular family. However, what remains unknown and will likely remain unknown (given the low frequency of individual causal mutations in HCM), is whether the observed association is unique to this family or could be generalized to additional HCM families. While HCM is a classic single-gene disorder, its clinical phenotypes, including hypertrophy and SCD, are complex phenotypes. No HCM phenotype is strictly genetic or entirely environmental but is the result of complex interplay between genetic and nongenetic factors. Specific factors that account for the variability of the clinical and pathological phenotypes in HCM are not well understood.

Diverse causal genes and mutations, by imparting different effects on the structure and function of contractile sarcomeric proteins, account for part of the variability of clinical phenotypes. In addition, modifier genes, epigenetic factors (such as deoxyribonucleic acid methylation and imprinting), epistasis (interactions between genes), post-transcriptional and post-translation modifications of gene products, presence of concomitant diseases (e.g., hypertension), compound heterozygosity, and environmental factors are expected to affect phenotypic expression of HCM. Therefore, based on the results of genotype-phenotype correlation study in a single family, one cannot conclude that the high incidence of SCD reflects the impact of the E62Q mutation. As authors suggest, topography of the causal mutation (on the encoded protein) could significantly impact the severity of the phenotype. This is best exemplified in the case of mutations in sarcomeric proteins leading to contrasting phenotypes of either hypertrophic or dilated cardiomyopathy (35,36). Variability in the clinical phenotype among individuals within a family implicate factors other than the causal mutation, such as the modifier genes, in influencing expression of clinical phenotypes in HCM (37). Thus, association of the E62Q mutation with the risk of SCD, while an important initial observation, should be considered provisional pending confirmation in additional families.

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 need. The ultimate goals are to establish a consensus in delineating the prognostic significance of the causal mutations, modifier genes, and nongenetic factors.

Acknowledgments

This work is supported in part by a grant from the National Heart, Lung, and Blood Institute, Specialized Centers of Research (P50- HL42267-01) and R01-HL68884.

REFERENCES

1. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation 1995;92:785–9. [PubMed: 7641357]
2. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA 1996;276:199–204. [PubMed: 8667563]

3. McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981;47:532–8. [PubMed: 7193406]
4. Hardarson T, De la Calzada CS, Curiel R, Goodwin JF. Prognosis and mortality of hypertrophic obstructive cardiomyopathy. Lancet 1973;2488:1462–7. [PubMed: 4129311]
5. Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. Circulation 1968;37:759–88. [PubMed: 5689584]
6. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. N Engl J Med 1989;320:749–55. [PubMed: 2646539]
7. Kofflard MJ, Waldstein DJ, Vos J, ten Cate FJ. Prognosis in hypertrophic cardiomyopathy observed in a large clinic population. Am J Cardiol 1993;72:939–43. [PubMed: 8213552]
8. Cannan CR, Reeder GS, Bailey KR, Melton LJ III, Gersh BJ. Natural history of hypertrophic cardiomyopathy. A population-based study, 1976 through 1990. Circulation 1995;92:2488–95. [PubMed: 7586349]
9. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000;102:858–64. [PubMed: 10952953]
10. Kofflard MJM, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol 2003;41:987–93. [PubMed: 12651046]
11. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20. [PubMed: 11886323]
12. Nienaber CA, Hiller S, Spielmann RP, Geiger M, Kuck KH. Syncope in hypertrophic cardiomyopathy: multivariate analysis of prognostic determinants. J Am Coll Cardiol 1990;15:948–55. [PubMed: 2312980]
13. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high-risk patients. J Am Coll Cardiol 2000;365:2212–8. [PubMed: 11127463]
14. Fananapazir L, Chang AC, Epstein SE, McAreavey D. Prognostic determinants in hypertrophic cardiomyopathy. Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiological findings. Circulation 1992;86:730–40. [PubMed: 1516184]
15. Maron BJ, Lipson LC, Roberts WC, Savage DD, Epstein SE. “Malignant” hypertrophic cardiomyopathy: identification of a subgroup of families with unusually frequent premature death. Am J Cardiol 1978;41:1133–40. [PubMed: 149494]
16. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000;342:1778–85. [PubMed: 10853000]
17. Elliott PM, Gimeno B Jr. Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet 2001;357:420–4. [PubMed: 11273061]
18. Yetman AT, Hamilton RM, Benson LN, McCrindle BW. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. J Am Coll Cardiol 1998;326:1943–50. [PubMed: 9857876]
19. Varnava AM, Elliott PM, Mahon N, Davies MJ, McKenna WJ. Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. Am J Cardiol 2001;88:275–9. [PubMed: 11472707]
20. Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. J Am Coll Cardiol 2000;35:36–44. [PubMed: 10636256]
21. Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell 1990;62:999–1006. [PubMed: 1975517]
22. Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. J Mol Cell Cardiol 2001;338:655–70. [PubMed: 11273720]

23. Arad M, Seidman JG, Seidman CE. Phenotypic diversity in hypertrophic cardiomyopathy. Hum Mol Genet 2002;1108:2499–506. [PubMed: 12351586]
24. Watkins H, Rosenzweig A, Hwang DS, et al. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. N Engl J Med 1992;326:1108–14. [PubMed: 1552912]
25. Fananapazir L, Epstein ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy. Insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. Circulation 1994;89:22–32. [PubMed: 8281650]
26. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998;338:1248–57. [PubMed: 9562578]
27. Charron P, Dubourg O, Desnos M, et al. Genotype-phenotype correlations in familial hypertrophic cardiomyopathy. A comparison between mutations in the cardiac protein-C and the beta-myosin heavy chain genes. Eur Heart J 1998;1995:139–45. [PubMed: 9503187]
28. Erdmann J, Raible J, Maki-Abadi J, et al. Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. J Am Coll Cardiol 2001;38:322–30. [PubMed: 11499719]
29. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995;332:1058–64. [PubMed: 7898523]
30. Marian AJ. On genetic and phenotypic variability of hypertrophic cardiomyopathy: nature versus nurture. J Am Coll Cardiol 2001;38:331–4. [PubMed: 11499720]
31. Jongbloed RJ, Marcelis CL, Doevendans PA, et al. Variable clinical manifestation of a novel missense mutation in the alpha-tropomyosin (TPM1) gene in familial hypertrophic cardiomyopathy. J Am Coll Cardiol 2003;41:981–6. [PubMed: 12651045]
32. Coviello DA, Maron BJ, Spirito P, et al. Clinical features of hypertrophic cardiomyopathy caused by mutation of a “hot spot” in the alpha-tropomyosin gene. J Am Coll Cardiol 1997;299:635–40. [PubMed: 9060904]
33. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995;332:1058–64. [PubMed: 7898523]
34. Karibe A, Tobacman LS, Strand J, et al. Hypertrophic cardiomyopathy caused by a novel alpha-tropomyosin mutation (V95A) is associated with mild cardiac phenotype, abnormal calcium binding to troponin, abnormal myosin cycling, and poor prognosis. Circulation 2001;103:65–71. [PubMed: 11136687]
35. Gerull B, Gramlich M, Atherton J, et al. Mutations of TTN, encoding the giant muscle filament titin, cause familial dilated cardiomyopathy. Nat Genet 2002;304:201–4. [PubMed: 11788824]
36. Kamisago M, Sharma SD, DePalma SR, et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. N Engl J Med 2000;343:1688–96. [PubMed: 11106718]
37. Marian AJ. Modifier genes for hypertrophic cardiomyopathy. Curr Opin Cardiol 2001;17:242–52. [PubMed: 12015473]
38. Maron BJ, Shen WK, Link MS, 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. [PubMed: 10666426]
39. Lim DS, Lutucuta S, Bachireddy P, et al. Angiotensin II blockade reverses myocardial fibrosis in a transgenic mouse model of human hypertrophic cardiomyopathy. Circulation 2001;103:789–91. [PubMed: 11171784]
40. Patel R, Nagueh SF, Tsybouleva N, et al. Simvastatin induces regression of cardiac hypertrophy and fibrosis and improves cardiac function in a transgenic rabbit model of human hypertrophic cardiomyopathy. Circulation 2001;104:317–24. [PubMed: 11457751]
41. Ho CY, Lever HM, DeSanctis R, Farver CF, Seidman JG, Seidman CE. Homozygous mutation in cardiac troponin T: implications for hypertrophic cardiomyopathy. Circulation 2000;102:1950–5. [PubMed: 11034944]

42. Jeschke B, Uhl K, Weist B, et al. A high risk phenotype of hypertrophic cardiomyopathy associated with a compound genotype of two mutated beta-myosin heavy chain genes. Hum Genet 1998;102:299–304. [PubMed: 9544842]

Table 1

Potential Risk Factors for SCD in HCM

History of SCD
Family history of premature death
“Malignant” causal mutations
“Malignant” modifier genes
History of syncope
Magnitude of left ventricular hypertrophy
Extent of myocyte disarray
Extent of interstitial fibrosis
Early onset of the disease
Myocardial ischemia on perfusion tomography
Abnormal blood pressure response to exercise
Presence of nonsustained VT on Holter

HCM = hypertrophic cardiomyopathy; SCD = sudden cardiac death; VT = ventricular tachycardia.