

## Hypertrophic Cardiomyopathy

# Sudden Death in Hypertrophic Cardiomyopathy: Identification of High Risk Patients

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- OBJECTIVES** We sought to identify patients with hypertrophic cardiomyopathy (HCM) at high risk of sudden death (SD).
- BACKGROUND** Relatively low mortality rates in HCM make conventional analysis of multiple clinical risk markers for SD problematic. This study used a referral center registry to investigate a smaller number of generally accepted noninvasive risk markers.
- METHODS** We studied 368 patients (14 to 65 years old, 239 males) with HCM. There were five variables: nonsustained ventricular tachycardia (NSVT), syncope, exercise blood pressure response (BPR), family history of sudden death (FHSD) and left ventricular wall thickness (LVWT).
- RESULTS** During follow-up ( $3.6 \pm 2.5$  years [range 2 days to 9.6 years]), 36 patients (9.8%) died, 22 of them suddenly. Two patients received heart transplants. The six-year SD-free survival rate was 91% (95% confidence interval [CI] 87% to 95%). In the Cox model, there was a significant pairwise interaction between FHSD and syncope ( $p = 0.01$ ), and these were subsequently considered together. The multivariate SD risk ratios (with 95% CIs) were 1.8 for BPR (0.7 to 4.4) ( $p = 0.22$ ); 5.3 for FHSD and syncope (1.9 to 14.9) ( $p = 0.002$ ); 1.9 for NSVT (0.7 to 5.0) ( $p = 0.18$ ) and 2.9 for LVWT (1.1 to 7.1) ( $p = 0.03$ ). Patients with no risk factors ( $n = 203$ ) had an estimated six-year SD-free survival rate of 95% (95% CI 91% to 99%). The corresponding six-year estimates (with 95% CIs) for one ( $n = 122$ ), two ( $n = 36$ ) and three ( $n = 7$ ) risk factors were 93% (87% to 99%), 82% (67% to 96%) and 36% (0% to 75%), respectively. Patients with two or more risk factors had a lower six-year SD survival rate (95% CI) compared with patients with one or no risk factors (72% [56% to 88%] vs. 94% [91% to 98%]) ( $p = 0.0001$ ).
- CONCLUSIONS** This study demonstrates that patients with multiple risk factors have a substantially increased risk of SD sufficient to warrant consideration for prophylactic therapy. (J Am Coll Cardiol 2000;36:2212-8) © 2000 by the American College of Cardiology
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The identification and treatment of patients with hypertrophic cardiomyopathy (HCM) who are at risk of dying suddenly are imperative in clinical management. Although some sarcomeric protein gene mutations are associated with a high risk of sudden death (SD) (1), the heterogeneity and variable expression of gene abnormalities in HCM have limited the use of clinical genetic testing for prognostic purposes. Many clinical features are associated with an increased risk of dying suddenly (2-8), but most are associated with only modest positive predictive accuracy. Furthermore, the relatively low annual mortality rates and small size of most patient groups make conventional analysis of the interaction between multiple risk factors problematic. To overcome this limitation, we hypothesized that a smaller number of generally accepted risk markers could be used to generate a practical clinical risk stratification algorithm.

## METHODS

**Clinical characterization.** Between 1988 and 1998, 630 patients ( $37 \pm 16$  years old, 382 men) with HCM were assessed at St. George's Hospital in London. The reasons for referral were symptom management (26%), family screening (19%), confirmation of diagnosis (10%) and risk assessment (17%). Fifteen percent were referred for miscellaneous reasons, including self-referral, second opinions and genetic counseling. The reason for referral was not recorded in 15% of patients. The diagnosis of HCM was based on the presence of unexplained left ventricular hypertrophy ( $>2$  standard deviations from the normal ranges corrected for age and body size) or on the presence of unexplained electrocardiographic (ECG) and echocardiographic abnormalities in the relatives of patients with an unequivocal diagnosis of HCM, in accordance with recently proposed diagnostic criteria (9,10). Patients with Friedreich's ataxia, Noonan's syndrome and primary metabolic disorders known to cause HCM were not included.

During follow-up, six patients underwent myotomy-myectomy, three had percutaneous alcohol ablation of the

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#### Abbreviations and Acronyms

BPR	=	blood pressure response
CI	=	confidence interval
ECG	=	electrocardiogram or electrocardiographic
FHSD	=	family history of sudden death
HCM	=	hypertrophic cardiomyopathy
LVWT	=	left ventricular wall thickness
NSVT	=	nonsustained ventricular tachycardia
NYHA	=	New York Heart Association
SD	=	sudden death

interventricular septum and three had mitral valve replacement. Sixty-four patients had received pacemakers by the time of their last follow-up: 34 for refractory symptoms related to outflow tract obstruction, 28 for high degree atrioventricular block or symptomatic bifascicular or trifascicular block and 2 for chronotropic incompetence. Patients received the following cardioactive medications: beta-blockers (n = 137 [21.7%]), sotalol (n = 35 [5.6%]), calcium antagonists (n = 142 [22.5%]), diuretics (n = 66 [10.5%]), warfarin (n = 63 [10%]), angiotensin-converting enzyme inhibitors (n = 19 [3%]), disopyramide (n = 21 [3.3%]) and propafenone (n = 3 [0.5%]). One hundred and seventy-five patients (27.8%) were prescribed amiodarone for at least one day of their follow-up. The reasons for therapy were supraventricular tachycardia (including paroxysmal atrial fibrillation) (n = 34 [19.4%]), SD prophylaxis (n = 64 [36.6%]), both supraventricular tachycardia and SD prophylaxis (n = 36 [20.6%]) and rate control for atrial fibrillation (n = 5 [2.9%]). In the remaining 36 patients, amiodarone therapy had been started by referring physicians before the first assessment at St. George's Hospital.

For the purposes of this study, patients were selected from the cohort of 630 patients using the following criteria: 1) age 14 to 65 years; 2) successful completion of all noninvasive tests (echocardiography, Holter monitoring and upright exercise testing); and 3) follow-up for more than one day. Patients with documented sustained ventricular arrhythmia or out-of-hospital cardiac arrest and those who had received amiodarone for an arbitrary period of >50% of their follow-up were also excluded. A detailed pedigree analysis and clinical history were obtained from all patients. A history of syncope was defined as one or more episodes of unexplained loss of consciousness within the 12 months preceding their first visit to St. George's Hospital. Chest pain was classified as exertional or atypical if it lasted >30 min at rest in the absence of myocardial infarction. Dyspnea was coded according to the New York Heart Association (NYHA) classification (11). A family history of SD was defined as sudden cardiac death in two or more first-degree relatives <40 years old.

**Echocardiography.** Two-dimensional and M-mode echocardiography were performed using conventional methods (12,13). In summary, end-diastolic left ventricular wall thickness (LVWT) was recorded at the mitral valve and

papillary muscle level in the anterior and posterior septum, as well as in the lateral and posterior left ventricular wall using short-axis two-dimensional images. Anterior and posterior septal thickness at the apex was assessed from the apical four-chamber and the parasternal short-axis views. Left ventricular outflow tract velocities were determined using continuous wave Doppler echocardiography, and left ventricular outflow tract gradients were calculated using the modified Bernoulli equation.

**Electrocardiography.** All patients underwent 48-h ambulatory ECG monitoring while performing unrestricted daily activities, using the Marquette (Marquette Electronics Inc., Diagnostic Division, Milwaukee, Wisconsin) Holter recording system on two channels. Computer-assisted analysis was performed using the Marquette series 8000 laser Holter and laser Holter XP system. Nonsustained ventricular tachycardia (NSVT) was defined as a run of three or more consecutive ventricular beats at a rate of  $\geq 120$  beats/min, lasting <30 s.

**Exercise testing.** Patients exercised to exhaustion on a treadmill, using the Bruce or modified Bruce protocols (1988 to 1994), or on an upright bicycle ergometer (Sensormedics Ergometrics 800S, Bitz, Germany), using an incremental ramp protocol from 1994 onward. Blood pressure was measured using a mercury sphygmomanometer and auscultation of the Korotkoff sounds over the brachial artery at rest, every minute during exercise and for the first 5 min of recovery (5).

**Survival analysis.** Survival data were collected between July 1997 and January 1998, using a questionnaire sent to all patients' general practitioners. Additional information was obtained at clinic visits and by direct communication with patients and their physicians.

#### Definitions

**Initial investigations.** The initial investigations are defined as the first echocardiogram, 48-h ambulatory ECG and upright exercise test performed at our institution. Data from subsequent investigations at St. George's Hospital were not examined in this study.

**Start of follow-up.** Follow-up started with the date of completion of the initial investigations, as defined previously.

**End point classification. SUDDEN CARDIAC DEATH.** Witnessed sudden cardiac death with or without documented ventricular fibrillation or death within 1 h of new symptoms. Nocturnal deaths with no antecedent history of worsening symptoms were included in this category.

**PROGRESSIVE HEART FAILURE.** Death preceded by signs and/or symptoms of heart failure, including cardiogenic shock.

**HEART TRANSPLANTATION.** Orthotopic heart transplantation performed for end-stage disease with systolic impairment and refractory congestive symptoms.

**OTHER CARDIOVASCULAR DEATH.** Stroke, pulmonary or systemic embolism and myocardial infarction.

**NONCARDIOVASCULAR DEATH.** Death secondary to non-cardiovascular events and of unknown cause.

**Risk factors.** Five clinical risk factors were assessed: a family history of sudden cardiac death (FHSD), unexplained syncope, NSVT on ambulatory electrocardiography, abnormal blood pressure response (BPR) during upright exercise testing and maximal LVWT. Blood pressure response and LVWT were examined in a dichotomous fashion to determine the most predictive cut-off values for SD.

An abnormal BPR was defined as a failure of blood pressure to rise, or a fall in blood pressure during exercise (5). According to previously published data, BPRs were only classified as a risk factor in patients  $\leq 40$  years of age (5). The relation between SD and the change in blood pressure during exercise was determined using the Cox proportional hazards model. The statistical significance of blood pressure thresholds for a flat or hypotensive BPR in increments of 5 mm Hg (range 0 to 30) was determined, and the most significant pairing of threshold values for a rise and fall was used in subsequent analyses. The relation between maximal LVWT and time to SD was also studied in the Cox proportional hazards model. The statistical significance of wall thickness in 1-mm increments was determined, and the most significant cut-off value was used in the subsequent survival analysis.

**Statistical analysis.** All data are presented as the mean value  $\pm$  standard deviation. A  $p$  value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using SAS software, release 6.12 (SAS Institute Inc.; Cary, North Carolina). Comparison between groups was performed using the chi-square test for proportional data. The probability of survival was estimated as a function of the length of follow-up, age and the five risk factors, using the Cox proportional hazards model. All risk factors were tested for pairwise interactions.

## RESULTS

From a total of 630 patients assessed between 1988 and 1998, 368 (239 men) fulfilled the selection criteria. Sixty-eight patients were excluded because they were older than 65 years or younger than 14 years. The remaining patients were excluded because of a history of ventricular fibrillation before their first assessment ( $n = 11$ ), no verifiable Holter monitor recording ( $n = 30$ ), inability or unwillingness to perform exercise testing ( $n = 25$ ), incomplete blood pressure recordings at baseline, peak exercise and/or recovery ( $n = 38$ ) and less than one day of follow-up ( $n = 14$ ). Eleven additional patients were disqualified because they had two or more of these exclusions. When patients were excluded for these reasons, an additional 76 patients who had taken amiodarone for at least 50% of their follow-up were excluded.

**Table 1.** Clinical Characteristics at Initial Assessment

Age (yrs)	37 $\pm$ 13
Age at diagnosis (yrs)	33 $\pm$ 14
Male/female	239/129
Syncope	57 (16%)
FHSD	90 (25%)
Chest pain	
Exertional	69 (19%)
Atypical	31 (8%)
Both	40 (11%)
NYHA	
Class I	240 (65%)
Class II	117 (32%)
Class III/IV	11 (3%)
Abnormal BP	138 (38%)
NSVT	64 (17%)
AF	10 (3%)
MLVWT (mm)	20.2 $\pm$ 6.8
LVED (mm)	44.0 $\pm$ 6.5
LVES (mm)	25.2 $\pm$ 6.4
LA (mm)	41.9 $\pm$ 8.2
Gradient $> 30$ mm Hg	80 (22%)

Data are presented as the mean value  $\pm$  SD or number (%) of patients.

AF = atrial fibrillation; BP = blood pressure response during upright exercise; FHSD = family history of sudden death; Gradient = peak left ventricular out flow tract gradient; LA = left atrial diameter; LVED/LVES = left ventricular end-diastolic/systolic dimensions; MLVWT = maximal left ventricular wall thickness; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association.

The mean age at diagnosis of HCM in the 368 study patients was  $33 \pm 14$  years (range 1 to 65). Their mean age at initial evaluation at St. George's Hospital was  $37 \pm 13$  years. All patients completed their initial investigations without complications. Symptoms at initial assessment and the results of noninvasive testing in the study cohort of 368 patients are shown in Table 1. Five patients were in paced rhythm at their initial assessment. Forty-two patients (11%) were  $< 20$  years old; 84 (23%) were 20 to 29 years old; 85 (23%) were 30 to 39 years old; 90 (25%) were 40 to 49 years old; 45 (12%) were 50 to 59 years old; and 22 (6%) were 60 to 65 years old.

**Blood pressure response.** Using the Cox proportional hazards model for SD, the most predictive cut-off values for a flat or hypotensive BPR during upright exercise in patients  $\leq 40$  years old were  $< 25$  mm Hg and  $> 15$  mm Hg, respectively ( $p = 0.04$ ). The model confirmed that these blood pressure criteria were not significant at the age cut-off of  $> 40$  years ( $p > 0.05$ ), and abnormal BPR during exercise was subsequently considered a risk factor only in patients  $\leq 40$  years old. A total of 138 (38%) of the 368 patients had an abnormal BPR by these criteria. Flat or hypotensive responses were more prevalent in patients  $\leq 40$  years old than in older patients (91 [43%] of 214 vs. 47 [31%] of 154,  $p = 0.02$ ). Hypotensive but not flat responses (i.e., a fall of  $> 15$  mm Hg from baseline) were more prevalent in patients  $\leq 40$  years old than in older patients (38 [18%] of 214 vs. 13 [8%] of 154,  $p = 0.01$ ).

**Maximal wall thickness.** Using the Cox proportional hazards model for SD, the most predictive cut-off value for LVWT was 30 mm ( $p = 0.001$ ). Forty-four patients (12%)

Risk of Sudden Death in Hypertrophic Cardiomyopathy

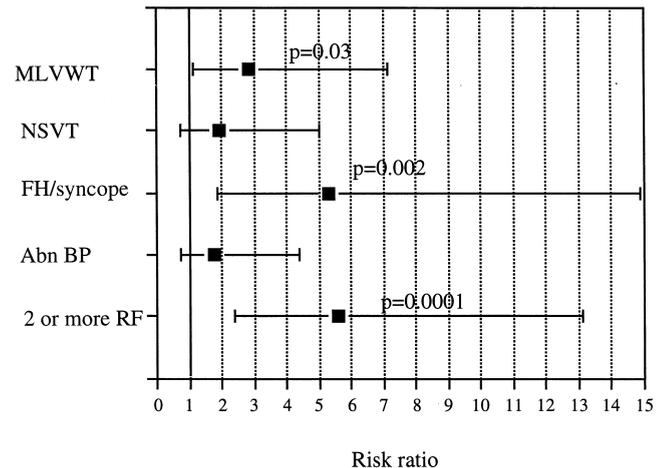
had a wall thickness  $\geq 30$  mm. Of the 368 patients studied, 229 (62%) had asymmetric septal hypertrophy (ratio  $>1.5:1$  [12]), 120 (33%) had concentric hypertrophy and 14 (4%) had hypertrophy confined to the ventricular apex. Five patients (2%) had other eccentric patterns of hypertrophy. There was no relation between the pattern of hypertrophy (asymmetric, concentric, apical or eccentric) and survival from all-cause death ( $p = 0.32$ ) or SD ( $p = 1.0$ ).

**Survival.** Mean follow-up was  $3.6 \pm 2.5$  years (range 2 days to 9.6 years). Thirty-six of the 368 patients (9.8%) died during follow-up. Twenty-two deaths (61%) were sudden, 5 (14%) were from progressive heart failure, 4 (11%) were from other cardiovascular causes and 5 (14%) were from noncardiac causes. Two patients received orthotopic heart transplants. The mean age at death or transplantation was  $39 \pm 16$  years (range 15 to 65). Of the 22 patients who died suddenly, 15 were  $<40$  years old. Sudden death occurred at rest in three patients (14%), after mild exertion in eight patients (36%) and after moderate to severe exertion in four patients (18%) and was nocturnal in three patients (14%). The circumstances preceding SD were unknown in four patients. The Kaplan-Meier estimate for six-year survival from all-cause death and transplantation for the whole group was 84% (95% confidence interval [CI] 78% to 89%). The Kaplan-Meier estimate for six-year survival from cardiovascular death (including transplantation) for the whole group was 87% (95% CI 82% to 92%). The Kaplan-Meier estimate for six-year survival from SD for the whole group was 91% (95% CI 87% to 95%).

**Univariate survival analysis.** The univariate SD risk ratios for individual risk factors were 2.4 for an abnormal exercise blood pressure (95% CI 1 to 5.5,  $p = 0.04$ ); 2.0 for syncope (95% CI 0.8 to 4.9,  $p = 0.13$ ); 1.8 for NSVT (95% CI 0.7 to 4.7,  $p = 0.21$ ); 1.9 for FHSD (95% CI 0.8 to 4.5,  $p = 0.15$ ); and 4.1 for maximal LVWT (95% CI 1.7 to 9.5,  $p = 0.001$ ).

All risk factors were tested for lack of additivity in the Cox model for SD. There was no statistical significance for the interaction term when any pair of factors was considered, except for FHSD and syncope ( $p = 0.01$ ). In the absence of the other factor, each of these two factors had a relative risk  $<1$  ( $p = \text{NS}$ ). Thus, in the subsequent multivariate analyses, these two factors were considered as a single factor (i.e., FHSD and syncope). This successfully removed all pairwise interactions and reduced the number of risk factors in the survival model to four. The univariate risk ratio for this combined risk factor was 8.2 (95% CI 3.0 to 22.4,  $p < 0.0001$ ).

**Multivariate survival analysis.** The multivariate SD risk ratios for these four risk factors were 1.8 for an abnormal exercise blood pressure (95% CI 0.7 to 4.4,  $p = 0.22$ ); 5.3 for FHSD and syncope (95% CI 1.9 to 14.9,  $p = 0.002$ ); 1.9 for NSVT (95% CI 0.7 to 5.0,  $p = 0.18$ ); and 2.9 for maximal LVWT (95% CI 1.1 to 7.1,  $p = 0.03$ ) (Fig. 1). The SD risk ratios in patients who were in NYHA functional class I were 3.3 for an abnormal exercise blood

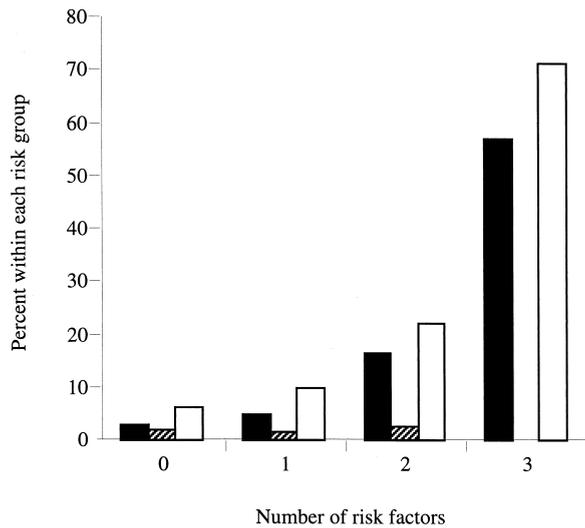


**Figure 1.** Multivariate risk ratios for each of the four risk factors and age. The bars represent the upper and lower 95% confidence intervals. Ratios  $>1$  indicate a positive association with SD. Abnormal exercise blood pressure pertains only to patients  $<40$  years old. MLVWT = maximal left ventricular wall thickness; FH = family history of SD; Abn BP = abnormal exercise blood pressure response in patients  $<40$  years old; RF = risk factors.

pressure ( $p = 0.06$ ); 5.2 for FHSD and syncope ( $p = 0.07$ ); 3.8 for NSVT ( $p = 0.04$ ); and 3.9 for maximal LVWT ( $p = 0.03$ ).

**Relation between number of risk factors and SD.** When FHSD and syncope were considered as a single risk factor, 203 patients (55%) had no risk factors. The corresponding numbers of patients with one, two and three risk factors were 122 (33%), 36 (10%) and 7 (2%), respectively. No patient had four risk factors. The numbers of SDs in patients with zero, one, two and three risk factors were 6 (3%), 6 (5%), 6 (17%) and 4 (57%), respectively. The total numbers of deaths in patients with zero, one, two and three risk factors were 13 (6%), 12 (10%), 8 (22%) and 5 (71%), respectively (Fig. 2). Patients with no risk factors had an estimated six-year survival rate from SD of 95% (95% CI 91% to 99%). The corresponding SD survival estimates (with 95% CIs) for one, two and three risk factors were 93% (87% to 99%), 82% (67% to 96%) and 36% (0% to 75%), respectively. Of the 122 patients with only a single risk factor, only four had FHSD and syncope. Patients with two or more risk factors had a significantly lower estimate of six-year survival from SD compared with patients with one or no risk factors (72% [95% CI 56% to 88%] vs. 94% [95% CI 91% to 98%],  $p = 0.0001$ ), with a risk ratio of 5.6 (95% CI 2.43 to 13.1,  $p = 0.002$ ) (Fig. 1).

Thirteen patients (8%) with none of the four risk factors, as defined earlier, died during follow-up, six of them suddenly. Of the six patients who died suddenly, two (ages 52 and 70 years, maximal wall thickness of 17 and 20 mm, respectively) had significant coronary artery disease with no resting left ventricular outflow obstruction. One patient (age 49 years) had a maximal wall thickness of 23 mm, no obstruction, refractory chest pain with angiographically normal coronary arteries and ST segment depression during



**Figure 2.** Bar graph showing the percentage of each risk factor group (zero, one, two and three risk factors) in which patients died during follow-up (black bars = sudden death; hatched bars = congestive cardiac failure or transplant; white = all deaths). The majority of deaths were sudden, and the greatest proportion occurred in patients with multiple risk factors. CCF = congestive cardiac failure; Tx = cardiac transplant.

ambulatory ECG monitoring. Two patients (ages 35 and 22 years) had FHSD, but no history of syncope, NSVT or an abnormal exercise BPR. Both had asymmetric septal hypertrophy with a maximal LVWT of 23 and 27 mm, respectively, with no rest outflow tract obstruction. One patient (age 48 years, maximal wall thickness of 24 mm) had an outflow tract gradient of 121 mm Hg and left atrial dilation.

## DISCUSSION

Many clinical features associated with an increased risk of SD have been reported in the published data. However, the relatively low annual mortality rates in most patient groups (14–24) make the study of their interaction problematic, as conventional multiple logistic regression analysis of large numbers of risk factors jeopardize the reproducibility of survival estimates. This study shows that a simpler model based on a smaller number of generally accepted risk factors can be used to identify a cohort of patients who are at a substantially increased risk of SD.

**Patient selection criteria.** The patient selection criteria in this study were designed to allow examination of a specific question—namely, can noninvasive markers be used to identify high risk patients who might benefit from prophylactic antiarrhythmic treatment? Patients with a history of sustained ventricular arrhythmia were excluded, as the risk of SD in this cohort was sufficiently high to warrant prophylactic therapy, irrespective of their other risk factors (25,26). Similarly, many patients in our group were treated with amiodarone because they were considered to be at risk of SD or for suppression of supraventricular arrhythmias, or both, and the exclusion criterion of amiodarone therapy for >50% of total follow-up was a pragmatic attempt to minimize any confounding effect that the drug may have on

survival (27,28). Patients >65 years were excluded to reduce the confounding effects of comorbidity on survival and the inability to perform all aspects of risk stratification. The five risk factors analyzed in this study were selected because they reflect the published data and are easily determined in routine clinical practice. However, they are not exclusive, and other clinical features, such as left ventricular outflow tract obstruction, atrial fibrillation, diastolic dysfunction and myocardial ischemia, could potentially be incorporated into a survival model. In several patients, there was circumstantial evidence that myocardial ischemia may have played a role in triggering a fatal rhythm disturbance, but routine screening for myocardial ischemia in patients with HCM remains problematic.

**Significance of individual risk factors.** In the univariate analysis, only BPR and maximal LVWT achieved a statistically significant association with SD. In the light of evidence describing “high risk” cardiac sarcomeric protein mutations (1), the low risk associated with FHSD alone seems counterintuitive. However, the small size of most family pedigrees, as well as the uncertain cause of SD in some individuals, can make it difficult to define a “malignant” family history and masks the undoubted importance of a family history in individuals with troponin T and high risk beta-myosin heavy-chain gene mutations. Isolated syncope is also problematic, as its multifactorial nature reduces its predictive accuracy in individual patients. An important finding in this study was the statistical interaction between FHSD and syncope. In the absence of the other, neither of these two factors was associated with an increased risk. In combination, however, they were a powerful predictor of risk. This observation may reflect a particular clinical phenotype, perhaps associated with specific high risk gene mutations.

Although several cross-sectional studies have shown that NSVT is associated with an increased incidence of SD, in this study NSVT as a single risk factor was not significantly associated with SD. A recent study in a selected “low risk” cohort has suggested that NSVT is prognostically significant only when repetitive or associated with symptoms (29). However, even in this latter report, NSVT in asymptomatic patients was associated with a relative SD risk of 2.4, with a very wide 95% CI (0.5 to 11.9). Although this ratio did not attain conventional levels of statistical significance, it was higher than that observed in the present study, and the wide confidence interval means that an association between SD and NSVT cannot be excluded.

Although abnormal exercise BPRs occurred at all ages, this study confirms the previous observation that abnormal BPRs are of prognostic significance only in patients younger than 40 years of age. Hypotensive responses were more common in the younger cohort, supporting the suggestion that the predominant mechanism of abnormal BPRs in young patients is inappropriate vasodilation in nonexercising muscles (30). In older patients, factors related to cardiac

output during exercise and impaired exercise capacity due to comorbidity may be more important.

This study confirms the findings from previous cross-sectional studies that severe left ventricular hypertrophy is associated with an increased incidence of SD (8). This relation should not, however, obscure the fact that only 12% of patients had a wall thickness >30 mm, and that the majority of SDs occurred in patients with only mild to moderate hypertrophy.

**Clinical implications.** Although the absence of risk factors identified individuals at low risk of SD, the presence of two or more risk factors (present in 12% of patients) was associated with a 4% to 5% estimated annual SD risk. This observation suggests that the estimated risk of SD associated with multiple risk factors may be high enough to justify prophylactic antiarrhythmic therapy. There is evidence to suggest that both amiodarone and implantable cardioverter-defibrillators can prevent SD in high risk patients with HCM, but their relative merits in different patient subgroups remains to be determined (26,27,31–34). Therapeutic recommendations for patients with single risk factors remain speculative, and further work on individual risk factors is necessary to determine if and when prophylactic therapy is indicated.

**Study limitations.** The overall mortality rate in this study was higher than that observed in some recently reported community studies. This may be explained by the fact that the study was performed at a tertiary referral center for the disease, but factors such as end point classification and statistical methods are probably of equal importance. Furthermore, the lack of comparable systematic risk stratification data in community-based populations makes it difficult to determine the importance, if any, of referral center bias with respect to clinical risk assessment.

The mean age of the overall study group was lower than that in many community studies. As with survival, this may be explained by referral patterns, but the routine practice of screening first-degree family members at our institution undoubtedly results in the identification of younger individuals with the disease.

The rates of surgical intervention for left ventricular outflow tract obstruction in our group are lower than those in some North American and European centers, reflecting historic practice and our participation in multicenter pacing studies. Similarly, the relatively low use of beta-blockers and calcium antagonists reflects the fact that 65% of our patients were in NYHA functional class I at their initial evaluation.

**Conclusions.** Although overall SD rates are relatively low in patients with HCM, this study shows that relatively simple, noninvasive tests can be used to identify a cohort of patients who have a substantial risk of SD and who warrant consideration for prophylactic antiarrhythmic therapy.

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