Clinical Course of Hypertrophic Cardiomyopathy in a Regional United States Cohort

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Hypertrophic cardiomyopathy (HCM) is a complex familial cardiac disease with heterogeneous clinical, morphologic, and genetic expression. Since its initial description 40 years ago, HCM has been largely regarded to be associated with substantial disability and premature death, and annual mortality rates as high as 3% to 6% have been reported. However, we believe that this rather ominous perception of HCM is likely to be skewed since available natural history data for this disease have been derived almost exclusively from a few tertiary centers in which the patterns of referral have traditionally been biased toward those patients judged as severely affected or at high risk. Such observations from highly selected populations have had an important impact on our clinical perceptions of the overall HCM disease process and continue to influence treatment strategy and risk stratification, as well as the way patients regard their disease.

Reports from Western Europe in small or non–hospital-based populations with short follow-up, suggest that the natural history of HCM may be more benign than previously reported. Consequently, we

Context Hypertrophic cardiomyopathy (HCM) has been regarded as a disease that causes substantial disability, with annual mortality rates of up to 6%, based largely on reports from tertiary referral centers.

Objective To assess the clinical course of HCM in a patient cohort more closely resembling the true disease state.

Design Retrospective cohort study.

Setting A regional cohort from Minnesota and adjoining regions, free of referral center bias, studied at Minneapolis Heart Institute.

Patients Two hundred seventy-seven consecutively studied HCM patients, none referred for specialized HCM care, managed clinically in a standard fashion.

Main Outcome Measures Mortality and clinical course of HCM.

Results During a mean (SD) follow-up of 8.1 (6.6) years, 45 patients died and 29 of these deaths were directly related to HCM; however, 8 of the 29 HCM deaths were not premature (occurring ≥75 years of age). Annual HCM mortality rate was 1.3% (0.7% for sudden cardiac death). Patients identified in adulthood (n = 234) showed no statistically significant difference in mortality when compared with expected mortality, as calculated for the general US or Minnesota populations (P = .17). Patients identified as children (n = 43) showed decreased survival compared with the general population (P < .001). At most recent clinical evaluation, 192 patients (69%) had no or mild symptoms and 69 (25%) experienced incapacitating symptoms or HCM-related death; 53 (19%) of the patients had achieved estimated life expectancy of 75 years or older. More advanced symptoms at diagnosis—occurrence of atrial fibrillation (often associated with stroke), the presence of basal outflow obstruction of at least 30 mm Hg, and marked left ventricular wall thickness of more than 25 mm—were clinically important independent predictors of HCM mortality.

Conclusions In a regionally selected patient population most closely resembling the true disease state, HCM did not significantly increase the risk of premature death or adversely affect overall life expectancy. Prevailing misconceptions of HCM as a generally unfavorable condition may largely be related to the skewed patient referral patterns characteristic of tertiary care centers. Hypertrophic cardiomyopathy is nevertheless a highly complex disease capable of serious clinical consequences and premature death in some patients.
studied a large, regional US cohort of HCM patients largely free of referral bias and more representative of the true disease state to determine the epidemiology and clinical course of HCM.

**METHODS**

**Selection of Patients**

The Minneapolis Heart Institute is a large community-based clinic and hospital service primarily supporting the Minneapolis–St Paul, Minn, metropolitan area (population, 2.5 million) and the state of Minnesota (population, 4.6 million). Between 1981 and 1997, 277 consecutively identified patients with HCM were evaluated, including 224 at the Minneapolis campus, 27 within the satellite clinic program, and 26 in the Children's Heart Clinic (Minneapolis). 273 patients were assessed clinically on at least 2 occasions.

The study cohort was assembled retrospectively after individually analyzing (during 1993 and 1994) all 131,545 medical records of patients with HCM identified at our institution. Those patients identified as having HCM were analyzed in detail, with the pertinent historical and clinical data derived from the medical record and systematically analyzed and entered as an Excel spreadsheet (PowerPoint 97, Microsoft Inc, Redmond, Wash). Recent historical information and patient outcomes were obtained during a clinic visit or, when necessary, by telephone interview with the patient or in some instances with family members (in the case of a patient’s death). To establish remote events, such as the date of HCM diagnosis and the onset of symptoms, it was often necessary to obtain records from prior referring physicians. All echocardiographic measurements were made by 1 of us (B.J.M.).

All patients resided in Minnesota (n = 243 [88%]) or the contiguous states of Wisconsin, Iowa, North Dakota, and South Dakota (n = 34 [12%]); 83 of the 243 Minnesota patients lived in Minneapolis–St Paul. None had been initially referred either to the senior author (B.J.M.) or expressly for specialized care related to HCM and only 6 were ultimately evaluated at a tertiary center (for ventricular septal myotomy-myectomy.)

Initial clinical evaluation (and time of entry into this study) was taken as the date when HCM was first diagnosed. In 133 (49%) of the 277 patients, the initial HCM diagnosis was made at or near the time of the first visit to the Minneapolis Heart Institute. Most recent clinical assessment was obtained as of August 1, 1996, either by telephone contact or clinic visit.

Diagnosis of HCM was based on the echocardiographic identification of a hypertrophied, nondilated left ventricle (wall thickness ≥15 mm in adults and the equivalent relative to body surface area in children)23 in the absence of another cardiac or systemic disease capable of producing the magnitude of wall thickening evident.1,23 In 8 patients, the initial HCM diagnosis was made before 1972 (and the advent of echocardiography) by cardiac catheterization and angiography. Cardiovascular lesions associated with HCM were relatively mild systemic hypertension usually controlled with medications (n = 44); atherosclerotic coronary artery disease (n = 19); aortic regurgitation (n = 2); and congenital heart lesions (n = 6), including atrial septal defect, Wolff-Parkinson-White syndrome, and mitral valve prolapse.

No patient was included in the study group based solely on an HCM diagnosis made during systematic pedigree analysis.4 Of the 277 patients, 241 were from separate pedigrees and unrelated; the remaining 36 patients came from 15 families.

**Echocardiography**

Echocardiographic studies were performed with commercially available Hewlett-Packard No. 500 and No. 2000 instruments (Andover, Mass). Distribution of left ventricular hypertrophy was assessed from 2-dimensional images and the site of maximum wall thickness was identified.23 Peak instantaneous outflow gradient was estimated with continuous-wave Doppler under basal conditions.24

**Statistical Analyses**

Data are expressed as mean (SD) or percentages, where appropriate. Subgroups were compared by either the t test or the Wilcoxon rank sum test for continuous variables and by χ² test for categorical measures. Observed and expected (ie, standard) survival curves for mortality from all causes were computed according to the actuarial method.25

To construct observed actuarial survival curves for the HCM patients, the number of deaths and the number of patients remaining in the study during each year following initial diagnosis were determined.25 To construct actuarial curves for expected survival, the observed number of deaths was replaced by the expected number of deaths, ascertained from US 1992 mortality tables, in which annual mortality rates are grouped by age, sex, and race.26 This allowed, for each year of follow-up, assignment to each study subject an age-, sex-, and race-appropriate mortality rate from the US population. In addition, these actuarial analyses were performed using the 1992 mortality tables for the state of Minnesota.27 The sum of the mortality rates for subjects in a given year of follow-up represents the expected number of deaths in that year. The χ² test was used to compare numbers of observed vs expected deaths.25 Standardized mortality ratios were computed as the observed divided by the expected number of deaths. Confidence intervals (95% CIs) were calculated assuming an underlying Poisson distribution for rare events.23 Survival curves were constructed according to the Kaplan-Meier method.23 When analyzing atrial fibrillation, patients were entered into the follow-up when the arrhythmia was known to occur for the first time or from the initial HCM diagnosis (if present at that time).

Thirteen clinically relevant disease variables were tested by univariate Cox regression analysis to assess possible predictors of outcome. Multivariate analysis was judged inappropriate because of a small number of HCM-related deaths, adverse events, and the large number of candidate variables that were of clinical interest in this disease. For all tests, P < .05 was considered indicative of a significant difference. SAS statistical software (SAS Institute Inc, Cary, NC) was used in most calculations.
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RESULTS

Demographics

Mean age at diagnosis was 47 (22) years (range, 1 month to 86 years). Forty-three patients (16%) were younger than 20 years while 90 patients (32%) were 60 years or older; 152 (55%) were men. All patients were white. Circumstances that led directly to the diagnosis of HCM by echocardiography were cardiac symptoms (n = 174), a newly detected heart murmur or abnormal electrocardiogram (ECG) findings (n = 82), or family history of HCM (n = 21). Duration of follow-up from initial diagnosis to the most recent clinical evaluation or death was 8.1 (6.6) years (range, 6 months to 31 years).

Mortality Data

Of the 277 study patients, 45 (13%) have died, including 16 of causes unrelated to HCM (eg, cancer, suicide or accident, or acute myocardial infarction due to advanced atherosclerotic coronary artery disease). The other 29 patients were judged to have probably or definitely died of causes directly related to HCM. Seventeen of these died suddenly and unexpectedly. 4 died of progressive heart failure, 5 died of stroke associated with atrial fibrillation, and 3 died of postoperative complications of myotomy-myectomy.

Mean age at HCM death was 56 years (range, 7-87 years); 21 deaths (72%) were considered premature, occurring before age 75 years (FIGURE 1). The other 8 patients (28%) died of HCM at age 76 to 87 years and, therefore, achieved statistical life expectancy (FIGURE 1).

Actuarial Survival Analysis

The actuarial survival curve for the 234 patients who had a diagnosis of HCM made in adulthood (≥20 years of age) was not significantly different compared with the expected survival curve derived for the general US population after adjustment for age, sex, and race. The standardized mortality ratio was 1.23 (95% CI, 0.88-1.67; P = .17) (FIGURE 2). Similar results were achieved using mortality data from Minnesota (standardized mortality ratio, 1.16; 95% CI, 0.83-1.55; P = .34). Based on these analyses, HCM did not significantly reduce overall life expectancy in those patients diagnosed as having this disease in adulthood. The latter portion of the HCM curve (after 12 years) appears to diverge from the general (control) population curve, suggesting a trend toward decreased survival for HCM patients.

The actuarial survival curve for the 43 patients in whom the diagnosis of HCM was made in childhood (<20 years of age) differed significantly and implied greater risk from that expected for the general US population (standardized mortality ratio, 12.9; 95% CI, 4.9-29.1; P < .001; FIGURE 3), although the smaller sample makes this estimate less precise. The annual mortality rate for this subset was 1.3%.

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Parameters of Survival

Based on Kaplan-Meier analyses, several clinically important variables were found to be predictors of HCM outcome: (1) more advanced symptoms at diagnosis (New York Heart Association classes III and IV); (2) presence of an outflow gradient under basal conditions (≥30 mm Hg); (3) marked left ventricular wall thickness (>25 mm); and (4) occurrence of atrial fibrillation (often associated with embolic stroke) (Figure 4). In addition to these dichotomous variables demonstrated by Kaplan-Meier analysis, univariate analysis also identified continuous variables to be associated with adverse outcome, including larger left ventricular end-diastolic dimension and greater left ventricular outflow gradient and maximal wall thickness (P = .01 to < .001). Clinical parameters that did not show a significant relationship to survival included age at diagnosis, sex, family history of premature HCM death, associated systemic hypertension, left atrial size, and syncope (P > .05). Of note, syncope occurred in 5 (17%) of 29 patients with HCM-related deaths and in 48 (19%) of the remaining 248 patients (P = .80).

Symptoms and Functional Status

At initial diagnostic evaluation, 253 patients (91%) were asymptomatic or only mildly symptomatic (functional classes I and II); 24 other patients (9%) had severe symptoms (functional classes III or IV). At the most recent evaluation, 191 patients (69%) had no or mild symptoms and 70 patients (25%) experienced severe symptoms (n = 41) or had progressed to HCM-related death (n = 29). During the period of follow-up, the most common symptoms were exertional dyspnea with or without fatigue (n = 66), chest pain (n = 31), or both (n = 69).

Thirteen of the surviving patients had a clinical course that was punctuated by periods of follow-up, the most common symptoms at initial diagnosis expressed in terms of New York Heart Association (NYHA) functional class (P = .004). 1. Occurrence of atrial fibrillation (paroxysmal or chronic) (P = .002). C. Peak instantaneous left ventricular outflow tract gradient (<30 or ≥30 mm Hg) estimated by Doppler echocardiography; preoperative gradient was used in patients undergoing myotomy-myectomy (P = .01). D. Magnitude of maximum left ventricular wall thickness (≤25 or >25 mm) from 2-dimensional echocardiogram (P < .001).

Table. Major Cardiac Events and/or Interventions Among 277 Unselected Patients With HCM*

<table>
<thead>
<tr>
<th>Event or Intervention</th>
<th>No. of Survivors</th>
<th>No. of Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCM-Related</td>
<td>Unrelated to HCM</td>
</tr>
<tr>
<td>Surgery for obstructive HCM</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Myotomy/myectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myotomy–myectomy and MVR</td>
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</tr>
<tr>
<td>AVR†</td>
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<td>0</td>
</tr>
<tr>
<td>ICD</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac arrest (HCM-related)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>35</td>
<td>11</td>
</tr>
</tbody>
</table>

*HCM indicates hypertrophic cardiomyopathy; MVR, mitral valve replacement; AVR, aortic valve replacement; and ICD, implantable cardioverter-defibrillator.
†Surgery for associated moderate-to-severe aortic regurgitation.
‡Includes 3 patients with prior aborted cardiac arrest; the other 8 ICDs were implanted prophylactically when the risk for sudden death was judged to be unacceptably high, usually due to a family history of HCM-related sudden death. Three ICDs have discharged appropriately during ventricular tachycardia or fibrillation.
§Heart transplantation for end-stage phase without outflow obstruction in 4 patients and for uncontrollable syncope in 1.
¶Heart transplantation for end-stage phase without outflow obstruction in 4 patients and for uncontrollable syncope in 1.
||Permanent pacemaker implantation was performed in the following clinical settings: sinoatrial node dysfunction in 7, high-grade heart block in 6, and an attempt to reduce drug-refractory congestive symptoms and basal left ventricular outflow tract obstruction in 7.

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chronic (n = 26) atrial fibrillation, including 24 with this arrhythmia at or near the time of diagnosis.

Treatment Strategies
In this retrospective cohort study, no standardized treatment protocol was followed and strategies sometimes differed among individual clinicians during the study period. Most patients were followed up clinically as outpatients at about 1-year intervals. Drug therapy was used as the initial measure for controlling cardiac symptoms that resulted in functional limitation. At or shortly following the initial evaluation at our institution, patients were taking the following cardioactive medications (although not in combination): β-blocking agents (n = 130), verapamil (n = 93), or disopyramide (n = 8), including 51 asymptomatic patients treated prophylactically. Thirteen patients were taking amiodarone hydrochloride, 200 mg/d, either for nonsustained ventricular tachycardia identified on Holter ECG (n = 2) or to prevent the recurrence of atrial fibrillation (n = 11). Anticoagulant (warfarin) therapy was administered selectively to the latter patients for the prevention of peripheral embolization.1,5

Severely symptomatic patients with marked basal subaortic gradients who were refractory to medical treatment underwent surgery to relieve outflow obstruction and improve functional limitation (n = 28).1-3,29 Eight high-risk patients had implantation of a cardioverter-defibrillator and 5 other patients had heart transplantation. Only 52 patients received no treatment.

Left Ventricular Morphology
Mean (SD) maximum left ventricular wall thickness was 21.7 (5) mm and was at least 35 mm in 4 patients, including 2 who died suddenly at ages 7 and 9 years. In adult patients, hypertrophy was most frequently localized (ie, confined to 1 segment of wall) (n = 92 [40%]), which, in 5 patients, was the left ventricular apex. Hypertrophy commonly involved anterior and posterior septum (n = 75 [32%]) or considerable portions of both septum and free wall (n = 65 [28%]).

COMMENT
Since the initial clinical descriptions of HCM in the early 1960s, most information regarding the natural history of this disease has come from a few referral centers, largely in the United States, Canada, and the United Kingdom.1,3-14 Although HCM encompasses an exceedingly broad clinical spectrum, severely affected or high-risk patients have been preferentially referred to tertiary care centers for evaluation and treatment,1,17 and their clinical course is likely more unfavorable than that of patients in a nonreferral population. As a consequence of this process, most published HCM reports have unavoidably incorporated a substantial degree of patient selection bias, largely confining descriptions of natural history to the most high-risk segment of the overall HCM population.

The clinical picture of HCM that has ultimately emerged, and particularly the perception of risk for sudden cardiac death, continues to be profoundly influenced by these biased referral patterns. While this circumstance is not unique to HCM, it is more substantial in this disease than in many other more common medical conditions and has undoubtedly influenced the epidemiology of HCM and clinical practice. Indeed, risk for premature HCM death may well have been exaggerated by the traditionally cited annual mortality rates of 3% to 6%,6-14 and, in the process, HCM has been characterized as a disease with a generally poor prognosis.

To overcome the shortcomings of earlier reports and create a more realistic appraisal of HCM, it is important to assess clinical course and prognosis from sizable patient cohorts that reflect the full spectrum of the disease.

The current study group of 277 patients with HCM is unique by virtue of representing a regional cohort from a distinctive geographic region of the United States, virtually confined to patients who have lived in that area for many years and uninvolved by the strong referral patterns that have predominated elsewhere.17 The relatively unselected nature of the study group is supported by the observation that only about 10% of our patients had severe symptoms at initial presentation compared with about 45% in referral populations.17

Overall, our cohort has experienced a more benign clinical course than that generally perceived for this disease. The occurrence of premature death and the annual mortality rate of only 1% were substantially less than that previously reported in the literature, based largely on the experience in tertiary institutions.2,5-14 Total mortality of HCM patients diagnosed as adults was not significantly different than that in the general population of the same age, sex, and race; therefore, HCM did not reduce life expectancy. Although not statistically significant, some divergence of the survival curve for adult HCM patients from that of the general control population is evident after 12 years, an observation that may be explained by (1) smaller numbers of patients at these later intervals (and larger 95% CIs, suggesting less precise estimates) and (2) increased late mortality from all causes among HCM patients identified early in life.

Of note, one third of our sudden and unexpected HCM-related deaths occurred in patients who were at least 60 years old, contrary to the conventional wisdom that such catastrophes are largely confined to young patients.10-14 On the other hand, our annual mortality rate of only about 1% for HCM diagnosed in childhood was just a fraction of that reported from highly selected populations.10,12,13

Furthermore, our findings are inconsistent with the characterization of HCM as a generally progressive disorder. Less than 5% of our patient cohort died of heart failure or required heart transplantation for end-stage disease,1,13,28 while about 70% showed clinical stability or even improvement. Indeed, almost 20% of the patients achieved an age of 75 years or older, substantiating that HCM is compatible with normal longevity (often with little or no disability). It is also worth considering that the favorable survival data reported here can be attributed, to some extent, to particular therapeutic measures that had emerged during the follow-up period, such as certain antiarrhythmic drugs (ie, amiodarone), the implantable cardio-

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Hypertrophic cardiomyopathy: clinical spectrum and those previously emphasized in the literature. Indeed, the heterogeneity and uncommon occurrence of HCM and patient selection factors have undoubtedly influenced these results. For example, important determinants of survival, such as family history of premature HCM death and prior cardiac arrest, did not achieve significance within our overall population but are nevertheless strong risk factors in selected HCM pedigrees. Also, nonsustained ventricular tachycardia on ambulatory Holter ECG, although previously identified as a risk factor in HCM, was not tested systematically in the present cohort. The fact that atrial fibrillation, outflow obstruction, and marked left ventricular wall thickening were unfavorable clinical markers could be important in future management and risk stratification of this disease, including more aggressive treatment of atrial fibrillation and, possibly, efforts to reduce outflow gradient, even in patients without severe symptoms.

In conclusion, while HCM can be associated with substantial morbidity and mortality, the present data from an unselected regional population show the disease to be generally less adverse than previously reported from tertiary referral centers and HCM did not significantly reduce life expectancy when compared with the general population. Clinicians should consider these results when discussing prognosis with patients.

REFERENCES

formed. All evidence of important bias should be sought and explained. As for our study, we believe no serious evidence of sponsorship bias has been presented.

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Financial Disclosure: Dr Qizilbash is currently an employee of SmithKline Beecham Pharmaceuticals. Dr Schneider and Dr Farlow have received grant support and/or have served as consultants for numerous pharmaceutical companies, including those that manufacture acetylcholinesterase inhibitors.


CORRECTION

Incorrect Figure Key: In the Clinical Cardiology article entitled “Clinical Course of Hypertrophic Cardiomyopathy in a Regional United States Cohort,” published in the February 17, 1999, issue of THE JOURNAL (1999;281:650-655), Figure 4B on page 653 was reproduced with an incorrect key. The correct designation appears in the Figure 4B below and shows that atrial fibrillation occurring in 50 patients with hypertrophic cardiomyopathy conveyed diminished longevity compared with 227 patients with this disease who were in sinus rhythm.

Figure 4. Survival According to Clinical Variables