Clinical Course of Hypertrophic Cardiomyopathy With Survival to Advanced Age

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OBJECTIVES

This study was designed to clarify and resolve the clinical profile of older patients with hypertrophic cardiomyopathy (HCM).

BACKGROUND

Adverse consequences of HCM such as sudden death and incapacitating symptoms have been emphasized for the young and middle-aged.

METHODS

Long-term outcome of HCM was assessed in a community-based cohort not subject to tertiary center referral bias.

RESULTS

Of 312 patients, 73 (23%) achieved normal life expectancy (≥75 years; range to 96); 44 (14%) were ≥80 years old. Most patients ≥75 years (47; 64%) experienced no or only mild limiting symptoms and lived virtually their entire lives with few HCM-related clinical consequences; 26 patients (36%) experienced severe progressive symptoms. In elderly patients with HCM, diagnosis and symptom onset were considerably delayed to 74 ± 8 and 70 ± 11 years, respectively. For patients ≥50 years at diagnosis, the probability of survival for 5, 10, and 15 years was 85 ± 3%, 74 ± 4%, and 57 ± 6%, respectively, and did not significantly differ from a matched general population (p = 0.20). Patients ≥75 years were predominantly women, had less marked wall thickness and more frequently showed basal outflow obstruction ≥30 mm Hg (compared with those <75 years; p < 0.01 and 0.001, respectively).

CONCLUSIONS

Hypertrophic cardiomyopathy is frequently well tolerated and compatible with normal life expectancy, and may remain clinically dormant for long periods of time with symptoms and initial diagnosis deferred until late in life. These observations afford a measure of reassurance to many patients with HCM, a disease for which clinical course is often unfavorable and unpredictable. (J Am Coll Cardiol 2003;42:882–8) © 2003 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a relatively common familial cardiac disease with a broad clinical spectrum for which the risk of premature cardiovascular death and incapacitating symptoms in young patients has been repeatedly emphasized (1–16). These unfavorable aspects of the natural history of HCM, although applicable only to some patient subsets, have nevertheless contributed importantly to the mistaken perception that HCM is a generally adverse disease that inevitably leads to sudden or heart failure-related death or profound disability (5–10,12–15).

Although HCM has been regarded largely as a disease of the young, its occurrence in elderly patients has been acknowledged (17–21). However, the probability and frequency with which HCM is consistent with extended survival is not generally appreciated. Therefore, we have analyzed a large HCM cohort not subject to tertiary center-related referral bias (22), in order to develop a clinical profile of the subset of patients with HCM notable for achieving advanced age.

METHODS

Selection of patients. The Minneapolis Heart Institute is a large community-based clinic and hospital service sup-
with either beta-blockers or verapamil and occasionally disopyramide. Amiodarone was administered in 18 patients (6%), usually for control of atrial fibrillation.

**Echocardiography.** Echocardiographic data were taken from the clinical assessment at or near the time of the initial diagnostic evaluation. Studies were performed with commercially available Hewlett-Packard Nos. 500, 2000, and 5500 instruments. Extent and distribution of LV hypertrophy were assessed as previously reported (23). In the parasternal short axis, the LV was divided into four regions: anterior and posterior ventricular septum and lateral and posterior free wall (23).

Peak instantaneous LV outflow gradient was estimated under basal conditions with continuous-wave Doppler (23). Calcium accumulation in the mitral annular space was graded qualitatively (1 to 4+). Echocardiographic measurements in each patient were made prospectively by one observer (B.J.M.).

**Statistical analysis.** Data are expressed as mean ± SD or in proportions, where appropriate. Subgroups were compared by Student t test for continuous variables, and by chi-squared with the continuity (Yates) correction for categorical variables.

Estimation of survival in a sample of the general U.S. population was based on U.S. mortality rates (24). Age- and gender-appropriate risk rates were used to compute the probability of death within each successive five-year interval for each patient, or part thereof in the case of censoring within that interval. The sum of these probabilities for patients alive at the beginning of the respective intervals represents the expected number of deaths, which was then used to construct a survival curve according to the actuarial method. The expected number of deaths during the follow-up period was compared to the observed number by the chi-squared test for a Poisson distribution (25).

The probability of survival (taking into account all-cause mortality) 5, 10, 15, and 20 years after initial HCM diagnosis was calculated for the overall cohort and for those patients <50 years or ≥50 years old at diagnosis and compared with the general population. In addition, the specific influence of a history of systemic hypertension on survival was tested, after adjustment for patient age at HCM diagnosis, by Cox-regression analysis. P values of ≤0.05 were considered indicative of a significant difference; all tests were two-sided.

**RESULTS**

**Patients <75 years old. DEMOGRAPHICS.** Of the 312 patients, 239 (77%) were <75 years of age at the most recent evaluation or death (Table 1, Fig. 1); 156 (65%) were men. Most patients (203; 85%) had experienced no or only mild symptoms and were in New York Heart Association functional classes I and II at most recent evaluation; only 36 (15%) had severe symptoms (classes III/VI). Age at initial HCM diagnosis was 38 ± 18 years (Table 1, Fig. 1).

**OUTCOME.** Of the 239 patients <75 years, 195 (83%) survived to the end of the follow-up period. The remaining 41 patients died (17%), including 24 that were HCM-related (Table 1).

**LEFT VENTRICULAR HYPERTROPHY.** Average maximum LV wall thickness was 22 ± 6 mm, including 81 (34%) ≤20 mm and 34 (14%) ≥30 mm (Table 1). Patients commonly showed hypertrophy localized to one LV segment (88%, 37%); 151 patients (63%) had more diffuse LV hypertrophy involving two to four segments.

**Patients ≥75 years old. DEMOGRAPHICS.** Of the 312 study patients, 73 (23%) had survived to age 75 and beyond; 44 of these 73 patients achieved ≥80 years of age (ranging to 96 years), comprising 14% of the overall study group (Table 1, Fig. 1). Age of the patients in this subset was 83 ± 5 years at most recent evaluation or death. Age at initial HCM diagnosis was considerably delayed to 74 ± 8 years (range 47 to 91).

Age at the onset of HCM-related symptoms was also delayed to 70 ± 11 years (range 25 to 91), including 44 (60%) after age 70 (Table 1). At most recent evaluation, 47 patients (64%) were asymptomatic or mildly symptomatic (classes I/II) and 26 (36%) had severe symptoms (classes III/IV).

Most older patients were women (78%), significantly exceeding that in younger study patients (35%; p < 0.001) (Table 1). Clinical presentation and the trigger for the diagnostic echocardiographic study was onset of symptoms in 65 (90%), a heart murmur in 6 (8%), and family history of HCM in 1 (2%).

Outflow obstruction (gradient ≥30 mm Hg) was present at or near the initial diagnostic evaluation in 35 of 73 patients (48%), exceeding that in patients <75 years of age (25%; p = 0.001) and was ≥50 mm Hgg in 27 of these, with range to 140 mm Hg (Fig. 2). Atrial fibrillation showed a trend toward greater frequency in older patients ≥75 years (25% vs. 17%, respectively; p = ns).

There was no consistent relation between the presence of mitral annular calcium and outflow obstruction. Of the 27 patients with large subaortic gradients ≥50 mm Hg, only 12 (45%) had moderate-to-severe annular calcium; most of the 27 patients (15/27; 55%) showed either no or mild calcium accumulation.

**OUTCOME.** Of the 73 study patients who had achieved age 75 or more, 46 (63%) were alive at the end of the follow-up period; for 27 patients (37%) the follow-up ended with their death, including 8 that were HCM-related: sudden in 2, HF-related in 2, and the consequence of embolic stroke in 4 (Table 1).

**Abbreviations and Acronyms**

- HCM = hypertrophic cardiomyopathy
- HF = heart failure
- LV = left ventricle
Table 1. Comparison of Clinical, Demographic, and Echocardiographic Features With Respect to Age in 312 Patients With HCM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age*</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥75 Years</td>
<td>&lt;75 Years</td>
</tr>
<tr>
<td>Patients</td>
<td>73 (23%)</td>
<td>239 (77%)</td>
</tr>
<tr>
<td>Male gender</td>
<td>16 (22%)</td>
<td>156 (65%)</td>
</tr>
<tr>
<td>Age, initial HCM diagnosis</td>
<td>74 ± 8</td>
<td>38 ± 18</td>
</tr>
<tr>
<td>Age, most recent evaluation (or death)</td>
<td>83 ± 5</td>
<td>49 ± 18</td>
</tr>
<tr>
<td>Family history HCM</td>
<td>4 (5%)</td>
<td>68 (28%)</td>
</tr>
<tr>
<td>NYHA functional class (most recent evaluation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13 (18%)</td>
<td>126 (53%)</td>
</tr>
<tr>
<td>II</td>
<td>34 (46%)</td>
<td>77 (32%)</td>
</tr>
<tr>
<td>III/IV</td>
<td>26 (36%)</td>
<td>36 (15%)</td>
</tr>
<tr>
<td>Age—at onset symptoms</td>
<td>70 ± 11</td>
<td>37 ± 18</td>
</tr>
<tr>
<td>Symptom onset &gt; 70 years</td>
<td>44 (60%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>LV outflow gradient (≥ 30 mm Hg)</td>
<td>35 (48%)</td>
<td>60 (25%)</td>
</tr>
<tr>
<td>Maximum LV wall thickness (mm)</td>
<td>20.6 ± 3</td>
<td>22.0 ± 6</td>
</tr>
<tr>
<td>LVID</td>
<td>42 ± 7</td>
<td>43 ± 8</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>43 ± 8</td>
<td>42 ± 10</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18 (25%)</td>
<td>40 (17%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>4 (6%)</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (34%)</td>
<td>27 (11%)</td>
</tr>
</tbody>
</table>

Deaths

HCM-related

Sudden                                      | 2 | 19 | — |
Heart failure                                | 2 | 3 | — |
Stroke                                      | 4 | 2 | — |
Other cardiac/noncardiac                     | 19 | 17 | — |

Major interventions

Septal myectomy/MVR                          | 8 | 26 | — |
Pacemaker                                    | 12 | 9 | — |
ICD                                          | 0 | 14 | — |
Heart transplant                             | 0 | 5 | — |

*Obtained at most recent evaluation or death, with exception of the echocardiographic measures which were obtained at or near the time of the initial diagnostic evaluation.

HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVID = left ventricular internal dimension at end-diastole; MVR = mitral valve replacement; NYHA = New York Heart Association.

Figure 1. Distribution of ages (at last evaluation or death) in 312 patients with hypertrophic cardiomyopathy (HCM), showing those patients who survived, died of HCM-related causes, or died of causes unassociated with HCM.
Figure 2. Presence of basal left ventricular outflow tract gradient (LVOT) (at or near the time of initial diagnostic evaluation) shown separately for subaortic gradients of 30 to 49 mm Hg and 50 mm Hg. Expressed as the proportion of patients in each age subgroup with outflow obstruction, and depicted with respect to age at last evaluation (or death).

LEFT VENTRICULAR HYPERTROPHY. Left ventricular wall thickness was significantly less than in younger patients <75 years (20.6 ± 3 vs. 22.0 ± 6 mm; p = 0.01), including 30 (41%) ≤20 mm; only one patient (1.4%) was ≥30 mm in thickness versus 34 patients (14%) <75 years old (p = 0.002) (Table 1). Patients achieving ≥75 years of age commonly showed hypertrophy confined to one LV segment (31; 42%); 42 patients (58%) had more diffuse LV hypertrophy involving two to four segments (all p = 0.5 vs. patients <75 years).

Survival probabilities. Probability of actuarial survival (with respect to total all-cause mortality) was calculated from the time of initial HCM diagnosis for all patients in the study cohort (Table 2, Figs. 3 and 4). Likelihood of survival after 5, 10, 15, and 20 years was 90 ± 2, 82 ± 2, 73 ± 3, and 64 ± 4 years, respectively, and the probability of death during the study period was significantly reduced compared to that of the general population (p = 0.001) (Table 2, Fig. 3).

Probability of survival was assessed separately in those patients <50 years (mean 29 ± 14) and ≥50 years (mean 66 ± 10) at HCM diagnosis (Table 2, Fig. 4). For patients identified earlier in life (<50 years) survival at 5, 10, 15, and 20 years was 95 ± 2, 90 ± 3, 86 ± 3, and 77 ± 5, reduced respectively compared to the general population (p < 0.001). However, for those patients diagnosed later in life (≥50 years), the expectation for survival was 85 ± 3, 74 ± 4, 57 ± 6, and 48 ± 7 years, respectively, which did not differ significantly from the general population and the overall risks of living (p = 0.20).

HCM patients with hypertension. Of the 312 study patients, 52 (27 were <75 years and 25 were ≥75 years) had a history of systemic hypertension, predominantly mild in degree (<150/90 mm Hg) (Table 3). Each of these patients also had at least one other independent, objective clinical marker most consistent with HCM to substantiate this clinical diagnosis (Table 3). A history of systemic hypertension had no significant influence on survival in the analysis of the overall study group (p > 0.05).

DISCUSSION

Disability and premature sudden death have been established as important consequences of HCM, with the occurrence of major disease complications emphasized for young patients (5–16). Although survival to older ages has been reported (17–21), the frequency and probability with which HCM patients achieve advanced longevity (and the clinical profile of such patients) remain incompletely defined.

Most published data on the clinical course of HCM have emanated from tertiary center referral cohorts often comprised of highly selected patients (2,4,5–8,12–16, 18–20,22,26,27). Indeed, such referral bias has importantly influenced our perceptions of the overall HCM clinical spectrum (1–4,16), owing to patient enrollments skewed to younger high-risk individuals and those requiring specialized interventions such as surgery (1–4,16,22,26). For these reasons, the subset of elderly patients with HCM, many without substantial symptoms, has probably been underestimated in prior reports (22).

We have attempted to compensate for such prior deficits in describing the overall HCM disease spectrum by offering the present cross-sectional analysis in our large community-based cohort of more than 300 patients with HCM not subject to tertiary referral bias, and focusing on those patients of advanced age. Such a HCM population is particularly suitable for this purpose, and largely represen-

Table 2. Survival Probabilities in HCM Study Population

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Years From HCM Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>All patients*</td>
<td>90 ± 2 (86, 93)</td>
</tr>
<tr>
<td>General population (expected)</td>
<td>94</td>
</tr>
<tr>
<td>&lt; 50 years at diagnosis*</td>
<td>95 ± 2 (91, 98)</td>
</tr>
<tr>
<td>General population (expected)</td>
<td>99</td>
</tr>
<tr>
<td>≥50 years at diagnosis†</td>
<td>85 ± 3 (78, 91)</td>
</tr>
<tr>
<td>General population (expected)</td>
<td>88</td>
</tr>
</tbody>
</table>

Mean ± SD; 95% confidence limits appear in parentheses. *Survival significantly different vs. general population; p = 0.001. †Survival did not differ significantly vs. general population; p = 0.20.

HCM = hypertrophic cardiomyopathy.
tative of the overall disease state (1,3,16,21,22) by virtue of minimal skewing toward high-risk patients.

We have made a number of observations in older patients that support the view that HCM does not invariably or usually infer adverse prognosis. First, a substantial proportion of our cohort (almost 25%) achieved normal life expectancy of at least 75 years of age, and remarkably about 60% of these patients survived well beyond to particularly advanced ages of 80 to 96 years. Indeed, HCM patients with diagnosis later in life (>50 years; mean age 66 ± 10) survived 5, 10, and 15 years with a probability of 85%, 74%, and 57%, respectively, an expectation not substantially different from that of the general population given the overall risks of living (24). Furthermore, about two-thirds of our patients ≥75 years old experienced little or no symptoms of functional disability and achieved their extended survival and quality of life without major interventions (1–4,16,26,27). These observations underscore the diverse natural history of HCM, which includes clinical presentation at virtually any age from infancy to the elderly and compatibility with normal life expectancy.

We wish to emphasize, however, that because our cohort is unavoidably hospital-based, the identification of all patients with HCM in our geographic region who achieved

Figure 3. Actuarial curves showing survival probabilities with respect to all causes of death for the hypertrophic cardiomyopathy (HCM) study population from the time of initial diagnosis, compared to expected survival probabilities of an age- and gender-matched cohort from the U.S. general population (Gen. Pop.) (24).

Figure 4. Actuarial curves showing survival probabilities with hypertrophic cardiomyopathy (HCM) with respect to all causes of death, from the time of initial diagnosis. Shown separately for patients with HCM diagnosis <50 years and ≥50 years, and compared to expected survival probabilities of an age and gender-matched cohort from the U.S. general population (Gen. Pop.) (24).
advanced age was not possible. Also, we are not able to ascertain the number of patients who died prematurely at young ages and before clinical diagnosis (and potentially would have been part of this cohort) (11,16,28). Consequently, a precise calculation for the number of elderly patients represented in our population of patients with HCM at any particular cross-sectional point in time is beyond the scope of the present investigation.

Second, whereas HCM is regarded as a genetic disorder caused by sarcomeric protein mutations (1,3,16,29–31,34), our data suggest that disease manifestations may nevertheless remain dormant for particularly long periods of time, with clinical diagnosis frequently delayed until very late in life. Therefore, it is possible for patients with HCM to live virtually their entire lives without clinical evidence of their disease. For example, almost one-half of our patients who survived to at least 75 years developed HCM-related symptoms for the first time only after age 70. This long period of clinical dormancy is striking, suggesting the alternative possibility that phenotypic expression of HCM may evolve later during adulthood, in midlife and beyond, as recently reported with cross-sectional (28,29) and serial echocardiographic analyses (30,32).

Third, survival to particularly advanced age was associated with relatively mild morphologic expression of the HCM phenotype. This was demonstrable by the modest degrees of LV wall thickening usually confined to only one segment of the wall (<20 mm, predominantly the anterior septum), as well as the uncommon occurrence of extreme LV hypertrophy with wall thickness ≥30 mm in only 1% of our patients; the latter phenotypic expression is largely confined to young patients, for whom it may represent a risk factor for sudden death (11,12,15).

Fourth, of note, a substantial proportion of our HCM patients of advanced age demonstrated outflow obstruction under basal conditions with subaortic gradients ≥30 mm Hg (33), including almost 50% of those ≥75 years and 33% of those ≥80 years. Indeed, subaortic obstruction was significantly more common in our older patients, of whom about one-half were also free of marked symptoms. This observation suggests that although LV outflow obstruction has been associated with deleterious long-term consequences such as progressive HF and death (33), it may also be well tolerated over substantial periods of time in some patients.

Because we cannot be certain regarding the duration over which these outflow gradients have been present (given the unavailability of serial echocardiographic studies spanning many years), it is possible that, alternatively, outflow obstruction could develop late in life and represent a delayed disease feature of HCM. However, the lack of correlation between mitral annular calcium and subaortic obstruction suggests that such accumulation of calcium with aging is not a determinant of outflow gradients developing in elderly patients with HCM (20).

The determinants of extended survival in some patients with HCM are largely unresolved. It is possible that benign genetic substrates may convey favorable prognosis and normal life expectancy (29,30,34). However, at present, genotype data are available for only a limited number of elderly patients with HCM, with mutations in cardiac myosin-binding protein C and troponin-I genes predominating (31).

Finally, we are cognizant of the potential ambiguities that may surround the diagnostic assignment of nonobstructive HCM to those patients of advanced age with modest LV hypertrophy, because of the frequency with which systemic hypertension occurs in this age group (35). However, in the present study, each of the patients with a history of hypertension also had ≥1 independent and objective markers characteristic of clinically expressed HCM and inconsistent with the modest level of hypertension observed (3). Therefore, it is unlikely that the present HCM study cohort is contaminated significantly by patients with hypertensive heart disease unrelated to HCM.

**Table 3. HCM-Related Clinical Markers in Study Patients With Systemic Hypertension**

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>≥75 Years</th>
<th>&lt;75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>HCM family history</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(including premature death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCM mutation identified</td>
<td>1‡</td>
<td>0</td>
</tr>
<tr>
<td>Maximum LV wall thickness ≥20 (with mild hypertension)</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>LV outflow obstruction at rest§</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>HCM-related stroke</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>HCM-related sudden death</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>(or appropriate ICD discharge)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Each patient had ≥1 independent objective HCM marker; therefore, the additive data exceed 100%. †Obtained at most recent evaluation (or death). ‡-myosin heavy chain gene. §≥30 mm Hg gradient, moderate SAM or mitral-septal contact; or prior septal myectomy.

**REFERENCES**