Sudden Death in Hypertrophic Cardiomyopathy: A Profile of 78 Patients

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SUMMARY The clinical profile of 78 patients with hypertrophic cardiomyopathy who died suddenly (or experienced cardiac arrest and survived) was analyzed. At the time of cardiac catastrophe, 71% of the patients were younger than 30 years of age, 54% were without functional limitation and 61% were performing sedentary or minimal physical activity. Nineteen of the 78 patients (24%) were taking propranolol in apparently adequate dosages, indicating that this drug does not provide absolute protection against sudden death.

No clinical or morphologic variable was particularly reliable in identifying patients at risk for sudden death. Forty-eight of 62 patients (77%) who died suddenly had a markedly increased ventricular septal thickness of 20 mm or more; however, mean septal thickness was similar in patients who died suddenly (25.2 ± 0.9 mm) and in age- and sex-matched control patients with hypertrophic cardiomyopathy who have survived (23.6 ± 0.8 mm). An abnormal ECG was present as often in patients who died suddenly as in control patients who have survived, (51 of 53, 96%). In addition, no particular cardiac symptom or hemodynamic variable (such as the magnitude of left ventricular outflow tract obstruction under basal conditions or left ventricular end-diastolic pressure) was characteristic of the patients with hypertrophic cardiomyopathy who died suddenly.

PREMATURE SUDDEN DEATH is not uncommon in patients with hypertrophic cardiomyopathy.\textsuperscript{1-10} Groups of patients with hypertrophic cardiomyopathy who died suddenly have been described,\textsuperscript{6,9} but a detailed clinical and morphologic analysis of a large series of such patients is not available. It is not known whether certain clinical measurements can predict which patients with hypertrophic cardiomyopathy are at increased risk of sudden death. Thus, the present clinical profile of 78 patients with hypertrophic cardiomyopathy who died suddenly was assembled and is the subject of this report.

Patients

Autopsy records of the Pathology Branch and the patient records of the Cardiology Branch, 1960–1980, were reviewed. Sixty-six nonoperated patients with hypertrophic cardiomyopathy who died suddenly and unexpectedly were identified. Sudden death was defined as instantaneous collapse with subsequent death or documentation of ventricular fibrillation within minutes. Five of the 66 patients had survived a previous cardiac arrest with documented ventricular fibrillation 3 weeks to 26 months (median 20 months) before death.

Twelve other patients who experienced a cardiac arrest (with documented ventricular fibrillation), but who were successfully resuscitated and have survived to date were included in the study group and were considered to represent sudden deaths. These 12 patients have survived for 7 months to 15 years (mean 3.8 years) after their arrest, although one has had two subsequent occurrences of ventricular fibrillation; 10 of these 12 patients have also undergone ventricular septal myotomy-myectomy since the cardiac arrest.\textsuperscript{11}

Of the 78 study patients, 29 had been evaluated at the National Heart, Lung, and Blood Institute before their death or cardiac arrest; the other 49 were either evaluated at institutions other than the National Heart, Lung, and Blood Institute or were never evaluated clinically. Fifteen patients had been chronically conditioned competitive athletes; seven of these 15 were initially identified because they were athletes who had died suddenly and were found to have hypertrophic cardiomyopathy only after examination of the heart at necropsy.\textsuperscript{12}

The diagnosis of hypertrophic cardiomyopathy was based on the presence of a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing left ventricular hypertrophy.\textsuperscript{13} The presence of a hypertrophied, nondilated left ventricle was documented at necropsy in 45 patients, by echocardiography in 17 patients, by echocardiography and at necropsy in eight patients, and by left ventricular angiography in eight patients. Three patients in the study group had associated systemic hypertension, but are included because they demonstrated clinical or hemodynamic features consistent with hypertrophic cardiomyopathy\textsuperscript{14} or because the extent of left ventricular hypertrophy clearly exceeded that which would have been expected to result from hypertension alone.\textsuperscript{15,18}

Sixteen other patients with hypertrophic cardiomyopathy who died suddenly were excluded from the present study group: Five had associated, hemodynamically significant coronary artery disease documented at necropsy (i.e., atherosclerotic luminal narrowing greater than 75% of the cross-sectional area of at least one major extramural coronary artery). In six, death was clearly related to a cerebrovascular accident or other embolic phenomena, including one with a pulmonary embolus. In five, the presence of coronary heart disease could not be definitively excluded; each of these patients was older than 40 years of age and did not undergo coronary arteriography during life or have a necropsy examination.

Fifteen of the 78 study patients did not undergo coronary arteriography or necropsy examination to

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definitively exclude coronary heart disease. However, based on patient age and clinical history, we believe that it is highly unlikely that any of these 15 patients with hypertrophic cardiomyopathy had associated hemodynamically significant coronary arterial narrowing, and therefore they have been included in the study group. Seven of the 15 patients were younger than 18 years of age; five others (three men and two women) were 21–37 years old, and had never experienced chest pain. The other three (two men and one woman) had experienced episodes of chest pain but were 29, 38 and 37 years of age.

Methods

Echocardiography

The echocardiographic technique used in this study has been described.\(^1^\) Echocardiograms were obtained with a 2.25-MHz, 1.2-cm-diameter Aerotech transducer connected to either a modified Ekoline 20A or a Hoffrel 201 ultrasound unit. The ultrasonic signal was connected by means of a custom-built video amplifier to a Honeywell 1856 Visicorder and recorded continuously on light-sensitive paper. The thickness of the ventricular septum was measured below the tips of the mitral valve leaflets just before atrial systole; the posterior left ventricular wall thickness was measured at the level of the tips of the mitral valve leaflets during the same phase of the cardiac cycle. The left ventricular outflow gradient (in mm Hg) was estimated from the M-mode echocardiogram based on the magnitude and duration of systolic anterior motion of the anterior mitral leaflet.\(^2^\)

Necropsy

Measurements of ventricular wall thicknesses were made at necropsy in the ventricular septum, just below the tips of the mitral leaflets, usually about one-half the distance between the base of the aortic valve and the apex of left ventricle; and in the posterior left ventricular wall, behind the midpoint of the posterior mitral leaflet, at a level corresponding to the tips of the mitral leaflets. In measuring ventricular wall thicknesses, we avoided including trabeculae, papillary muscles or cristae supraventricularis. Two patients in whom transmural scarring of the ventricular septum and left ventricular free wall\(^3^\) was identified at necropsy (although significant atherosclerosis of the extramural coronary arteries was absent) were excluded from the analysis of left ventricular wall thicknesses.

Electrocardiograms

Electrocardiograms were obtained in 53 patients. The ECG analyzed for each patient was that obtained closest to the time of death or cardiac arrest (range 1 week to 6 years, median 10 months, and during the last year of life in 32). Criteria used for the electrocardiographic diagnosis of left ventricular hypertrophy were those of Cassel and Ziegler\(^4^\) for patients younger than 18 years of age and those of Romhilt and Estes\(^5^\) for patients 18 years and older; a score of five or more points by the Romhilt-Estes system was considered evidence for left ventricular hypertrophy. QT intervals (measured in standard lead II) were corrected for heart rate and compared with normal standards.\(^6^\) Criteria used for identification of other electrocardiographic abnormalities have been summarized.\(^7^\)

Control Patients

Certain clinical, hemodynamic and morphologic findings in the study patients with sudden cardiac death (or cardiac arrest) were compared with a control group of surviving patients with hypertrophic cardiomyopathy. The control patients represented a consecutive series evaluated at the National Heart, Lung, and Blood Institute from February 1979 to April 1981, in whom a technically satisfactory one- or two-dimensional echocardiogram identified or confirmed the diagnosis of hypertrophic cardiomyopathy.

The presence and frequency of cardiac symptoms in 76 study patients who had died suddenly (exclusive of two infants) were compared with those in 76 surviving control patients with hypertrophic cardiomyopathy, matched for age and sex. Of the 76 surviving controls, 22 had no functional limitation, 27 had mild symptoms (New York Heart Association functional class II) and 27 had substantial functional limitation (class III). Fifty-four of the 76 controls had been taking propanolol for at least 1 year, within 5 years of the time of this study; 43 of these 54 were taking a daily dosage of propranolol that was considered clinically appropriate (120 mg/day or more in adults or 2 mg/kg/day or more in children). In addition, nine patients were taking quinidine, two Propranolol, 17 verapamil, and seven digitalis.

Left ventricular wall thicknesses in the 62 patients who died suddenly were compared with those in the first 62 patients of the control group who could be matched for age and sex. Similarly, electrocardiographic patterns in 53 patients and hemodynamic data (left ventricular outflow gradient under basal conditions and left ventricular end-diastolic pressure) in 46 patients who died suddenly were compared with age- and sex-matched surviving control patients.

Statistical Analysis

Where appropriate, the t test, chi-square test or the Fisher exact test were used to assess statistical significance.

Results

Age at Death

The age at death (or cardiac arrest) ranged from 2 months to 58 years (median 19 years) (fig. 1). Sixty-seven of these 78 patients (89%) were younger than 40 years of age and 55 (71%) were younger than 30 years. Forty-nine (63%) of the patients were male and 29 were female. The 12 patients who experienced a cardiac arrest but survived were significantly older at the time of their arrest (mean age 32 ± 4 years [± SEM]) than the 66 patients who died (23 ± 8 years) (p < 0.05).
Functional State Before Death

The functional state before death or cardiac arrest was assessed in 71 patients. Seven patients who were initially referred to us because they were athletes who had died suddenly and unexpectedly were excluded from this analysis because they could not have performed as competitive athletes unless they had been asymptomatic.

Thirty-eight of 71 patients (54%) had experienced no functional limitation (fig. 2). Of these 38 patients, 22 had been completely asymptomatic and 11 had experienced rare, transient symptoms that could have been due to hypertrophic cardiomyopathy (e.g., light-headedness, palpitations and nonspecific chest pain). Hence, in 33 patients, sudden death was the first definitive manifestation of underlying cardiac disease. The remaining five patients without functional limitation, however, had demonstrated probable evidence of cardiac disease; i.e., they had experienced one or two episodes of syncope, supraventricular tachycardia, or both.

Thirty-three of the 71 patients (46%) had functional limitation, including 22 who were considered to be in New York Heart Association functional class II and 11 who had substantial limitation and were in class III (fig. 2); three of these latter 11 patients had had overt clinical manifestations of pulmonary congestion in the presence of a nondilated left ventricle and normal ejection fraction. Eight of the 33 patients with functional limitation had also had supraventricular tachycardia, including five with atrial fibrillation.

The symptoms manifested by the study patients are summarized in table I. No symptom was significantly more common among patients who died suddenly (or experienced cardiac arrest) than in surviving controls.

Circumstances of Death

Activity at the time of sudden death or cardiac arrest was assessed in 75 patients (fig. 3). Excluded from this analysis were one patient in whom the precise circumstances of death could not be determined and the two patients who died in infancy.

In 58 of the 63 patients who died suddenly (exclusive of the 12 patients who survived cardiac arrest), death was virtually instantaneous. Five other patients lived for 1 hour to 6 weeks after resuscitative measures were instituted. After the initial collapse, two of these five patients had hypotension, low cardiac output and pulmonary edema and died within 24 hours; two others had recurrent ventricular tachycardia followed by a terminal arrest; and one lived for 6 weeks in coma with evidence of cerebral anoxia before dying.

At the time of the cardiac catastrophe, 46 of 75 patients (61%) were engaged in sedentary activities (e.g., lying, sitting or standing, usually in the home but while in the hospital in three patients), or participating in activities that required mild exertion (e.g., walking, shopping, throwing or performing mild calisthenics); four of these 46 patients were known to be asleep. The other 29 patients were performing moderate-to-severe exertion (e.g., running, jogging, hiking, lifting, riding a horse or diving) at the time of death, including...
TABLE 1. Cardiac Symptoms in 76* Patients with Hypertrophic Cardiomyopathy and Sudden Death (or Cardiac Arrest) and in 76 Surviving Control Patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of patients</th>
<th>Sudden death</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightheadedness</td>
<td>36</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>24</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Exertional dyspnea or fatigue</td>
<td>24</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>20</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>14</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Orthopnea</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachyarrhythmia producing symptoms</td>
<td>8†</td>
<td>10‡</td>
<td></td>
</tr>
</tbody>
</table>

*Two infants were excluded from this analysis.
†Includes five patients with paroxysmal atrial fibrillation.
‡Includes eight patients with paroxysmal atrial fibrillation and two with chronic atrial fibrillation; three of these 10 also had other supraventricular arrhythmias.

four who died during or just after a competitive athletic contest. Sixty-eight of the 75 patients with sudden death or cardiac arrest had had no premonitory symptoms just before death; however, apparent “warning” symptoms occurred in six patients (fatigue in two and chest pain, syncope, presyncope, and combined chest pain and syncope in one each) from seconds to 2 hours before death.

Electrocardiograms

Electrocardiograms were obtained in 53 patients 1 week to 6 years (median 10 months) before death or cardiac arrest. They were abnormal in 51 patients and normal in two (table 2). No electrocardiographic pattern was characteristic of the study group. ST-segment and T-wave alterations were present in 42 patients, left ventricular hypertrophy in 40 and abnormal Q or QS waves in 21.

The prevalence of abnormal ECGs in the 53 patients who died suddenly (51 of 53, 96%) was the same as that in an age- and sex-matched control population of 53 surviving patients with hypertrophic cardiomyopathy (table 2). Electrocardiographic patterns among patients who died suddenly or had cardiac arrest did not differ from those in surviving controls.

Left Ventricular Wall Thicknesses

Ventricular septal thicknesses, assessed at necropsy in 45 patients and by echocardiography in 17, ranged from 12 to 44 mm (mean 25 mm) (fig. 4). In 48 of the 62 patients (77%), septal thickness was 20 mm or greater; in the other 14, it was less than 20 mm. Six of the patients with septal thickness less than 20 mm were chronically conditioned competitive athletes (including two who were also younger than 15 years old) and one was a member of a family with “malignant” hypertrophic cardiomyopathy. However, ventricular septal thicknesses in the 62 patients with hypertrophic cardiomyopathy who died suddenly (mean 25.2 ± 0.9 mm) did not differ significantly from those in control.
patients with hypertrophic cardiomyopathy who have survived (mean 23.6 ± 0.8 mm) (fig. 4).

Posterior left ventricular free wall thicknesses (mean 14.5 ± 0.6 mm, range 7–26 mm) were significantly greater than in controls (mean 11.8 ± 0.4 mm) (p < 0.001). Ventricular septal-to-posterior free wall thickness ratios ranged from 1.0 to 3.5 (mean 1.8 ± 0.1); in 58 of the 62 patients (94%), the septal-free wall ratio was 1.3 or greater and therefore met our criteria for asymmetric septal hypertrophy;\(^1\) septal-free wall ratios in the controls (2.0 ± 0.1) were significantly greater (p < 0.01) than those in the patients with sudden death or cardiac arrest. The differences between control patients and patients who died suddenly with regard to posterior free wall thickness and septal-free wall ratio are probably due primarily to discrepancies inherent in comparing ventricular wall thickness measurements made at necropsy and those obtained by echocardiography during diastole.\(^2\)

**Hemodynamic Findings**

The magnitude of the left ventricular outflow gradient was measured at cardiac catheterization in 46 patients and was estimated from the M-mode echocardiogram in three others who did not undergo catheterization. These 49 studies were performed 1 week to 10 years (median 15 months) before death and during the last year of life in 23 patients.

Left ventricular outflow tract gradients were present under basal conditions in 37 patients, and ranged from 5–120 mm Hg; in 12 other patients, no outflow gradient was present at rest (fig. 5). Eight of the patients who had no outflow obstruction or only a small gradient (less than 30 mm Hg) under basal conditions, had a gradient of more than 30 mm Hg with provocative interventions (Valsalva maneuver, isoproterenol infusion or amyl nitrite inhalation). Seven patients had no obstruction or a small gradient both under basal conditions and with provocative maneuvers. Patients who died suddenly and surviving control patients did not differ significantly with regard to the magnitude of the left ventricular outflow gradient measured at cardiac catheterization at rest (41 ± 5 mm Hg vs 39 ± 5 mm Hg). Only three patients had right ventricular outflow gradients of greater than 10 mm Hg (15, 47 and 55 mm Hg).

Left ventricular end-diastolic pressures ranged from 5 to 40 mm Hg (average 21 mm Hg) and were abnormal (more than 12 mm Hg) in 36 of the 46 patients. Patients who died suddenly and controls did not differ significantly with regard to the magnitude of left ventricular end-diastolic pressure (21 ± 1.2 mm Hg vs 18 ± 0.9 mm Hg) (fig. 5).

**Cardiac Medications**

Twenty-nine of the 78 patients had been taking propranolol in the period just before death. Nineteen of the 29 patients were reliably taking a daily dose that was considered clinically appropriate (120 mg/day or more in adults or 2 mg/kg/day or more in children) and the other 10 patients were taking less-than-ade-
quate dosages. Two of the patients taking appropriate dosages of propranolol also received either quinidine (1200 mg/day) or Norpace (400 mg/day). Nine patients were receiving digitalis, including three with clinical evidence of elevated pulmonary venous pressure and two with atrial fibrillation.

No cardiac medication regimen was characteristic of the 12 study patients who experienced ventricular fibrillation but were successfully resuscitated. Five of the 12 patients were taking no cardioactive medications before cardiac arrest. Of the remaining seven patients, five were taking propranolol (one in less-than-adequate dosages), one was taking a combination of propranolol and Norpace and one was taking digitalis.

Discussion

This study describes the clinical profile of patients with hypertrophic cardiomyopathy who experienced premature sudden death or cardiac arrest. Most of these patients were young, had experienced no or mild cardiac symptoms before death and were usually participating in sedentary or mild activity at the time of death.

The data show a particular predilection of sudden death for patients younger than 30 years of age and suggest that patients older than 40 years may be at low risk for sudden death. However, certain factors related to the selection of our patients could have influenced these data. For example, older patients who die suddenly outside the hospital are commonly assumed to have had coronary heart disease; often, a necropsy examination is not performed, and hence, the diagnosis of hypertrophic cardiomyopathy is unlikely to be made. In addition, older patients with hypertrophic cardiomyopathy who die suddenly often have associated coronary heart disease, making it difficult to be certain which of the cardiac diseases was primarily responsible for death. In fact, our data suggest that the combination of hypertrophic cardiomyopathy and coronary heart disease may be particularly lethal; five of the 16 patients (30%) we evaluated with hypertrophic cardiomyopathy older than age 40 years who died suddenly had associated significant coronary arterial narrowing from atherosclerosis.

The fact that death usually occurred during sedentary or mild activity suggests that severe exertion may not per se be a substantial risk factor for sudden death in patients with hypertrophic cardiomyopathy. Nevertheless, since the proportion of the day during which most persons perform moderate-to-severe exertion is relatively small, the fact that about 40% of our patients died during or just after vigorous activity is impressive. Therefore, we continue to recommend that patients with hypertrophic cardiomyopathy not engage in competitive athletics or particularly strenuous physical exertion.

However, the patient with hypertrophic cardiomyopathy who died suddenly was not identified by the clinical, hemodynamic or morphologic measurements analyzed in this study, i.e., occurrence of a particular cardiac symptom, magnitude of left ventricular outflow tract obstruction under basal conditions or left ventricular end-diastolic pressure, electrocardiographic pattern or prevalence of an abnormal ECG, or degree of ventricular septal thickening. In particular, we found no significant increase in the incidence of syncope in patients with sudden death (or cardiac arrest) compared with surviving controls with hypertrophic cardiomyopathy. This finding is different from that of McKenna et al., who reported that syncope was more common among patients with hypertrophic cardiomyopathy who died suddenly. The present data also confirm our impression that the risk of sudden death in patients with hypertrophic cardiomyopathy is not related to severity of left ventricular outflow obstruction.

Ventricular septal thickness also did not differ substantially between patients who died suddenly and the surviving controls. Therefore, absolute ventricular septal thickness cannot be used to predict sudden death in a population of patients with hypertrophic cardiomyopathy. However, in seven of our 14 patients who had a relatively thin ventricular septum (less than 20 mm), other factors were present that could have contributed to the occurrence of a premature cardiac catastrophe: a family history of "malignant" hypertrophic cardiomyopathy or a competitive athletic lifestyle.

While the variables investigated in this study were not reliable in identifying that subgroup of patients with hypertrophic cardiomyopathy who are at increased risk for sudden death, two other clinical variables may be of more value. First, a familial predilection for sudden premature death may constitute a risk factor in certain families with unusually virulent expressions of hypertrophic cardiomyopathy. Therefore, the occurrence of premature (younger than 50 years of age) sudden death in more than one first-degree relative of a person with known hypertrophic cardiomyopathy probably places that patient at an increased risk of sudden death. Second, preliminary data suggest that 24-hour ambulatory electrocardiographic monitoring may be useful in identifying certain patients with hypertrophic cardiomyopathy who are at increased risk for sudden death. Two prospective investigations of patients with hypertrophic cardiomyopathy, studied by 24- or 48-hour ambulatory ECGs, have shown a significant relationship between the presence of asymptomatic ventricular tachycardia on the ambulatory ECG and the subsequent occurrence of sudden cardiac death. In our study, sudden cardiac catastrophe was significantly more common in patients with ventricular tachycardia on 24-hour ECG (four of 17, 25%) than in patients without ventricular tachycardia (two of 66, 3%) (p < 0.02). However, the fact that 13 of the 17 patients with ventricular tachycardia did not experience a catastrophic cardiac event suggests that other variables must coexist in patients with hypertrophic cardiomyopathy for ventricular instability to evolve into a terminal arrhythmia.

Patients with hypertrophic cardiomyopathy may die suddenly even while taking usual clinical dosages
of propranolol. About one-fourth of the patients in this study were receiving apparently adequate amounts of propranolol during the period just before death. Thus, although propranolol does not eliminate the possibility of sudden death, well-controlled prospective studies have not, as yet, been performed to determine definitively whether patients with hypertrophic cardiomyopathy who are at high risk for sudden death and are receiving propranolol therapy have a lower mortality than untreated patients.

In the present study, surviving patients with hypertrophic cardiomyopathy had more often taken clinically appropriate dosages of propranolol than did the patients who died suddenly (43 of 78, 55%, vs 19 of 78, 24%). However, based on these data, we are hesitant to attribute to propranolol a role in enhancing survival of our patients with hypertrophic cardiomyopathy. The present study was not designed to critically determine whether propranolol reduced mortality rate. For example, patients with hypertrophic cardiomyopathy frequently may undergo alterations in their drug regimen. For the present investigation, we considered a patient in the control group to be treated with propranolol if the drug had been taken in clinically appropriate dosages for at least 1 year in the preceding 5 years, but the period these patients had actually been taking propranolol varied considerably, as did the drug dosage.

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