

# Sudden death in hypertrophic cardiomyopathy<sup>1</sup>

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**Hypertrophic cardiomyopathy affects people of all ages, and with the advent of echocardiography, it is being recognized more frequently. Death is usually sudden and unexpected. Factors reviewed that may play a role in sudden death include anatomic, hemodynamic, and electrophysiologic mechanisms. The results of medical and surgical treatment are also discussed.**

**Index terms:** Death, sudden • Heart surgery • Myocardial diseases

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Hypertrophic cardiomyopathy (HC) is transmitted as an autosomal dominant trait or may occur sporadically. It occurs in patients of all ages, and it is recognized much more frequently since the advent of echocardiography. Patients with HC may present with symptoms of left ventricular outflow obstruction such as chest pain, dyspnea, dizziness, syncope, or sudden death or they may be completely asymptomatic and present with a heart murmur or an abnormal electrocardiogram. Mortality is 3% to 4% per year in natural history studies,<sup>1-3</sup> and death is usually sudden. We review the factors that may play a role in sudden death and discuss the medical and surgical treatment for this disease.

## Limitations of current data

Although initial studies of hypertrophic cardiomyopathy describe no clinical predictors of sudden death, a recent study by McKenna et al<sup>4</sup> suggests that a combination of (1)

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young age (less than 14 years), (2) syncope, (3) severe dyspnea, and (4) a positive family history for HC best predicts sudden death. The etiology of sudden death in patients with HC, however, remains a dilemma. From the outset, one must understand the limitations of the available data. First, of the three natural history studies published, the longest average follow-up is only 7.4 years.<sup>2</sup> Second, in order for a patient to participate in the earlier natural history studies, cardiac catheterization was usually required to make a definitive diagnosis, as echocardiography was not available. This tended to exclude older patients because of the reluctance to catheterize them, and to include sicker patients, as asymptomatic patients usually were not catheterized. Third, no published studies evaluate progression of the disease in a systematic fashion. Only 4 cases have been reported in which gradually worsening left ventricular outflow tract obstruction is documented.<sup>2,5,6</sup> In the natural history studies, most patients were catheterized initially and subsequent follow-up was only clinical.

### Possible etiologies

#### *Anatomic and hemodynamic factors*

Early investigators suggested obstruction of left ventricular egress as the cause of sudden death,<sup>7-9</sup> but subsequent studies have not supported this concept.<sup>1,3,4</sup> Unfortunately, most patients in these studies were not catheterized serially, and death occurred years after catheterization. In children with HC with symptoms prior to age 15, Maron et al<sup>2</sup> found that 8 of 20 with documented subaortic obstruction died, but only one of 11 patients without obstruction died during a follow-up of 7.4 years. It should be noted that among the 126 patients reported by Frank and Braunwald,<sup>10</sup> 10 died; 6 died suddenly and 4 suffered progressive deterioration. The average basal gradient was only 23 mm Hg in the group that died suddenly, but 2 of the 6 patients were not given provocative drugs such as isoproterenol or amyl nitrite. In one patient with a gradient of 4 mm Hg, a gradient of 34 developed with isoproterenol. Two of the 4 patients with progressive deterioration had subvalvular gradients at the time of initial catheterization, but only one of the remaining 2 patients without a documented gradient was given isoproterenol. If the 3 patients who had lower gradients at rest had been provoked and a more substantial gradient documented, the data would have been

entirely different. Interestingly, the patients in this study who were functional class III and IV had higher gradients and a much higher incidence of sudden death. Shah et al<sup>1</sup> and McKenna et al<sup>4</sup> demonstrated no correlation between sudden death and the measured subaortic gradient; however, the deaths were always remote in time from the catheterization. It is well known that gradients measured at catheterization vary from study to study.

One interesting case report<sup>11</sup> from Japan describes a patient who underwent cardiac catheterization because of recurrent episodes of syncope and convulsions. During catheterization, he was found to have no gradient at rest; however, with isoproterenol, he displayed a gradient of 65 mm Hg, complained of chest pain, had a "mild convulsive seizure," and lost consciousness. During this episode, he remained in sinus rhythm, and aortic pressure dropped to 40 mm Hg despite the absence of arrhythmias. This unique report of syncope during catheterization suggests that obstruction probably played a role.

Presence of a subvalvular gradient may be only one factor in the etiology of sudden death. For a number of years, Goodwin<sup>12</sup> has considered poor diastolic compliance a significant factor in functional limitation and in sudden death of patients with HC. Glancy et al<sup>13</sup> have clearly shown that with onset of atrial fibrillation and sudden loss of atrial systole in the hypertrophied, poorly compliant left ventricle, cardiac output is markedly reduced. Further, James and Marshall<sup>14</sup> have speculated that decreased ventricular compliance may provoke fatal ventricular fibrillation. Webb-Peploe et al<sup>15</sup> and Goodwin<sup>12</sup> have shown that abnormalities of diastolic function are aggravated by adrenergic stimulation and ameliorated by beta blockade. These factors may further compromise the patient with HC in whom sudden tachycardia develops. As the inotropic state of the heart increases, compliance decreases, the diastolic filling time is shortened, and, consequently, cardiac output is further compromised.

#### *Electrophysiologic factors*

Patients with HC are prone to arrhythmias.<sup>15</sup> There are individual case reports of heart block,<sup>16</sup> asystole,<sup>17</sup> and cases of sudden death associated with an accessory pathway.<sup>18</sup> James and Marshall<sup>14</sup> studied the conduction system in detail in 22 patients who died suddenly of HC and found a number of structural abnormalities.

Twelve patients had significant sinus node fibrosis, and 13 had marked fragmentation or division of the A-V node or His bundle. This fragmentation is typical of fetal hearts and has been associated with pre-excitation syndromes. There were also areas of focal fibrosis in the A-V node and His bundle in 4 patients, and multiple cysts in the central fibrous body in 4 patients. James and Marshall<sup>14</sup> speculated that these structural abnormalities could lead to significant atrial arrhythmias, which in turn, might result in fatal ventricular arrhythmias.

Many authors have documented that atrial arrhythmias lead to rapid clinical deterioration in patients with HC. Glancy et al<sup>13</sup> studied 16 patients with HC who had atrial fibrillation. Clinical deterioration was marked: congestive heart failure developed in 11, syncope or presyncope in 7, and hypotension in 5. Five patients were studied both in atrial fibrillation and sinus rhythm, and a consistently higher cardiac output was documented in sinus rhythm. However, the subvalvular gradients were also slightly higher during sinus rhythm. These authors emphasized that atrial fibrillation causes large variations in stroke volume. After a short diastole, there is little or no ejection of blood. With a beat that occurs after a longer pause, there is an increase in stroke volume and an accentuation of the subvalvular gradient similar to that seen after a premature ventricular contraction. In addition, with the loss of synchronous atrial contraction, a noncompliant ventricle ejects less blood. These factors together significantly reduce cardiac output.

Many authors have attempted to correlate the prevalence of arrhythmias in patients with HC and their prognoses. All have found Holter recordings to be more sensitive than exercise testing. In 83 consecutive patients, McKenna et al<sup>19</sup> documented paroxysmal supraventricular tachycardia in 21 and atrial fibrillation in 12. Sixty-two percent of the patients had ventricular arrhythmias. Eighteen of 20 patients with frequent premature ventricular beats also had high-grade arrhythmias, but only 35% of patients with multiform or paired premature ventricular beats had frequent extrasystoles. Twenty-four patients had at least one episode of ventricular tachycardia. Ventricular tachycardia, as well as the combination of multiform and paired premature ventricular contractions, strongly correlated with sudden death. Of 7 patients in McKenna's series who died suddenly, 5 had ventricular tachycardia during Holter recording. Supraventricular arrhyth-

mias, on the other hand, did not correlate with sudden death. Maron et al<sup>20</sup> studied 84 patients by Holter recording. Ventricular tachycardia was found in 17 patients. In this series, 4 patients died suddenly, and 2 were resuscitated from ventricular fibrillation. Of these 6 patients, 4 had previously documented ventricular tachycardia on a 24-hour Holter recording. Supraventricular tachycardia again did not correlate with sudden death. Combining the studies, 9 of the 13 patients who died suddenly had previously documented ventricular tachycardia.

In an attempt to determine prospectively what types of arrhythmias patients with HC may be prone to, Schiavone et al<sup>21</sup> studied 8 patients with HC using electrophysiologic techniques. All patients had syncope or presyncope. Two patients had had sustained atrial fibrillation from the onset of the study. All patients underwent two-dimensional echocardiography, cardiac catheterization, 24-hour Holter monitoring, resting electrocardiography, and atrial and ventricular programmed electrical stimulation. Echocardiography revealed a mean left atrial size of 47 mm and a mean septal thickness of 24 mm, and 6 patients had systolic anterior motion at rest. During cardiac catheterization, the mean resting left ventricular outflow tract gradient was 37 mm Hg, and with provocation, the mean peak gradient increased to 89 mm Hg. Twenty-four hour Holter recordings revealed chronic atrial fibrillation in 2, paroxysmal supraventricular tachycardia in one, and paroxysmal atrial fibrillation in one. Unsustained ventricular tachycardia was present in 2 patients.

Programmed atrial stimulation in the 6 patients without chronic atrial fibrillation produced sustained atrial fibrillation in 2, sustained atrial flutter in 2 others, and no atrial arrhythmias in the last 2. Ventricular fibrillation could be provoked in only one patient with use of double extrastimuli in the right ventricular apex. These patients were therefore much more susceptible to sustained atrial arrhythmias than to sustained ventricular arrhythmias.

Anderson et al<sup>22</sup> used programmed ventricular stimulation in the operating room prior to myectomy. With two extra stimuli, they found that sustained ventricular tachycardia developed in 3 of 17 patients, while with three extra stimuli, sustained ventricular tachycardia developed in 11. No attempt was made to induce atrial arrhythmias. Although the numbers of patients in these studies are small, such evaluations do indi-

**Table 1.** Mortality in patients with HC treated with beta blockers

	No. of patients	Deaths due to HC	Mean follow-up (yr.)	Annual mortality (% yr.)
Swan et al <sup>26</sup> London	47	5	3.0	3.5
Adelman et al <sup>27</sup> Toronto	18	2	2.0	5.5
Shah et al <sup>1</sup> Rochester, NY	101	19	4.7	4.0
Canedo et al <sup>*29</sup> Augusta, GA	24	0	4.4	0
				3.4 Weighted Mean

\* High dose propranolol.

HC = Hypertrophic cardiomyopathy.

cate the potential usefulness of programmed electrical stimulation prospectively to determine the types of arrhythmias for which the patient is at risk.

Although arrhythmias had been noted in a large percentage of patients who died suddenly, a recent case report by McKenna et al<sup>23</sup> suggests that other factors are involved. A 52-year-old woman with HC and a resting subvalvular gradient of 50 mm Hg had experienced repeated episodes of syncope. Holter recordings revealed numerous asymptomatic short episodes of ventricular tachycardia. On one occasion when she experienced a syncopal episode while wearing a Holter recorder, she maintained a sinus rhythm. When her heart rate increased from 70 to 130 beats/min, she lost consciousness. There was no ventricular tachycardia throughout the episode. However, in the recovery period, marked ST depression developed with atrioventricular dissociation and a junctional rhythm at 50 beats/min. This episode implicates a hemodynamic cause for syncope and suggests obstruction or poor ventricular filling as a result of the tachycardia, rather than the arrhythmia alone. Using simultaneous echocardiographic indices of out-flow obstruction and Holter monitoring, Shah and Lever<sup>24</sup> found a positive correlation between gradient and serious ventricular or supraventricular arrhythmias in a group of 30 patients with HC. However, Doi et al<sup>25</sup> in a similar study found no correlation between echocardiographic indications of obstruction and arrhythmias.

### Treatment

Since the causes for syncope and sudden death in HC are probably multifactorial and related to

anatomic, hemodynamic, and electrophysiologic factors, treatment is complex. Patients treated with beta blockers reported in previous series<sup>1,26,27</sup> have a sudden death rate similar to that in the natural history studies (Table 1). McKenna et al,<sup>28</sup> using a mean dose of 280 mg/day of propranolol, did not demonstrate any reduction in ventricular or supraventricular arrhythmias. On the other hand, Candeo et al<sup>29</sup> suggest that sudden death can be reduced by rigid control of documented arrhythmias. They recommend large doses of propranolol alone or in conjunction with quinidine, disopyramide, or diphenylhydantoin. No deaths occurred in their group of 33 patients. McKenna et al<sup>30</sup> recently suggested that amiodarone is helpful in controlling supraventricular and ventricular arrhythmias, but there have been no long-term studies to prove this. Calcium channel-blocking agents may be helpful in some patients with supraventricular arrhythmias, but offer little or no help for ventricular arrhythmias. Digitalis is contraindicated except when no other agent slows the ventricular response to atrial fibrillation.

Septal myectomy, as described by Cleland<sup>31</sup> and popularized by Morrow et al<sup>32</sup> at the NIH, has become the standard surgical procedure. Numerous studies have clearly documented that patients with the severe symptoms associated with HC are markedly improved after surgery. The natural history study of Shah et al<sup>1</sup> suggested that survival might be better with surgery; however, the 26% operative mortality was unacceptable. A recent study by Beahrs et al<sup>33</sup> also suggests that surgery may prolong life. Their early mortality for patients after myectomy was only 1.9% per year. Other groups are summarized in Table 2.<sup>1,34-36</sup> In late survival, myectomy patients do better than unoperated, natural history patients, and far better than those treated with beta blockers alone. Surgery, however, does not uniformly protect patients from sudden death, and continued close follow-up and medical management are mandatory. It appears that patients with HC who have a resting or provokable gradient greater than 50 mm Hg and severe symptoms despite a good medical regimen should undergo surgery. Patients who have a mild degree of obstruction at rest or with provocation should be managed medically and monitored for the development of arrhythmias and the progression of disease. Patients with severe subvalvular gradient at rest or with provocation, but with few symptoms present

**Table 2.** Mortality among survivors of septal myectomy or myotomy for HC

	No. of patients	Surgical survivors	Deaths due to HC	Mean follow-up (yr.)	Annual mortality (% yr.)
Maron et al <sup>34</sup> Bethesda 1960–75	120	110	12	5.6	1.9
Agnew et al <sup>35</sup> New Zealand 1962–76	49	47	6	7.4	1.7
Reis et al <sup>36</sup> Miami 1971–76	30	30	1	3.1	1.1
Shah et al <sup>1</sup> Rochester, NY 1960–73	58	43	4	5.2	1.8
					1.8 Weighted Mean

HC = Hypertrophic cardiomyopathy.

a difficult management problem. Some authors recommend surgical intervention in this group; however, this remains uncertain.

### Summary

A number of factors, anatomic and hemodynamic as well as electrophysiologic, apparently contribute to sudden death in patients with HC. How these factors interact is yet to be determined. In the future, careful prospective evaluation of patients with HC may elucidate the mechanism of sudden death.

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