Sudden Death in Hypertrophic Cardiomyopathy
Assessment of Patients at High Risk
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The incidence of sudden death in hypertrophic cardiomyopathy is 2–4% a year in adults and 4–6% a year in children and adolescents.1 These data have been generated from referral cardiac centers and may reflect a bias to the more severe patients.2 The identification and management of patients with hypertrophic cardiomyopathy who are at increased risk of sudden death remains a major problem, particularly in younger patients.

Identification of High-Risk Adults
During the 1960s and 1970s, routine characterization of patients with hypertrophic cardiomyopathy included clinical, angiographic, and hemodynamic assessment with measurement of left ventricular gradients and filling pressures. Retrospective analysis of this information reveals that this extensive characterization failed to provide a clinical profile that would identify the majority of patients who subsequently died suddenly (Table 1).3,4 The additional value of M-mode and two-dimensional echocardiographic wall thickness measurements to this clinical profile has not been rigorously assessed but would not be expected to be of great predictive value.5 In Maron et al’s study of 78 patients with hypertrophic cardiomyopathy who died suddenly, the severity of left ventricular hypertrophy was similar in those who died suddenly and in an age- and gender-matched group who survived.6

The single most useful marker of the high-risk adult is the finding of episodes of nonsustained ventricular tachycardia during 48-hour ECG monitoring.6,7 These episodes appear benign: they are usually slow, follow periods of relative bradycardia, and are not associated with ST segment or QT interval change. Their significance, however, lies in the simultaneous observation from two independent centers that adults with nonsustained ventricular tachycardia have increased mortality from sudden death. Of 170 consecutive uneoperated patients from the National Institutes of Health, Bethesda, Maryland, and the Hammersmith Hospital, London, 13 died suddenly during 3 years; nine of these 13 had nonsustained ventricular tachycardia. In both studies, this arrhythmia was significantly more common in those who died suddenly.6,7 This does not prove a causal relation but does establish that ventricular tachycardia is a marker of the adult who is at particular risk of sudden death.

How useful is the finding of nonsustained ventricular tachycardia during electrocardiographic monitoring as a marker of sudden death? It has a sensitivity of 69%, a specificity of 80%, and a positive predictive accuracy of 22% for the prediction of sudden death8 (Table 1). The reduced sensitivity in part reflects the inclusion of an adolescent who did not have ventricular tachycardia but died suddenly. A more recent study reveals that spontaneous arrhythmias are rare in children and adolescents with hypertrophic cardiomyopathy and that other clinical features are of greater predictive value in the young.9 In addition, all four of the patients who did not have nonsustained ventricular tachycardia but died suddenly (two from the National Institutes of Health and two from the Hammersmith Hospital) had only 24 hours of electrocardiographic monitoring and, thus, a sampling error is possible, particularly as ventricular arrhythmias in hypertrophic cardiomyopathy are known to exhibit marked biologic variability.10 The finding of nonsustained ventricular tachycardia during 48-hour electrocardiographic monitoring identifies adults at high risk with a sensitivity that is probably more than 69%.

Identification of High-Risk Children and Adolescents
Patients with a family history of multiple sudden deaths are recognized to be at particular risk.3,11 Children and adolescents without such a malignant family history still have an annual mortality from sudden death of more than 4%.12 Apart from syn-
TABLE 1. Prediction of Sudden Death in Adults with Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Adult (&gt;21 years old)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive accuracy</th>
<th>Negative predictive accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical-hemodynamic</td>
<td>70</td>
<td>68</td>
<td>24</td>
<td>94</td>
</tr>
<tr>
<td>Angiogram at diagnosis</td>
<td>82</td>
<td>72</td>
<td>32</td>
<td>96</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>69</td>
<td>80</td>
<td>22</td>
<td>97</td>
</tr>
</tbody>
</table>

Clinical assessment from a retrospective series of 254 patients of whom 23 died suddenly during 6 years (McKenna et al). Angiographic assessment at diagnosis from a retrospective series of 88 patients of whom 11 died suddenly during 7 years (Newman et al).

Nonsustained ventricular tachycardia was assessed from two independent series (see text for data) (Maron et al and McKenna et al).

Sudden episodes that are associated with sudden death, other clinical features and electrocardiographic and hemodynamic measurements are similar in those who die suddenly and survive and do not help identify the high-risk young patient. The majority of children and adolescents who die suddenly neither have any limitation of exercise tolerance nor have experienced syncope; when syncope does occur, this is ominous. In a retrospective analysis of 37 patients, it was 86% specific for subsequent sudden death. In addition, arrhythmias during electrocardiographic monitoring are uncommon in children and adolescents and do not appear to be of predictive prognostic value. Thus, in the patients with hypertrophic cardiomyopathy who are at greatest risk, many of whom are not only young but also asymptomatic, current clinical and hemodynamic evaluation is of limited value in the identification of most of those who died suddenly. This underscores the need to better characterize patients with hypertrophic cardiomyopathy in relation to likely mechanisms of sudden death.

Mechanisms of Sudden Death

There are many potential mechanisms of sudden death to consider in the identification of high-risk patients. Both impaired and accelerated atrioventricular conduction have been documented. It is well recognized that a tachycardia, whether physiologic or secondary to an arrhythmia, may be associated with hypotension, ischemia, symptoms of angina, or impaired consciousness. A recent case report by Stafford et al is of interest in this regard.

A 15-year-old youth, who presented with cardiac arrest and documented ventricular fibrillation, was found to have nonobstructive hypertrophic cardiomyopathy with diffuse left ventricular hypertrophy. Electrophysiologic study demonstrated inducible sustained atrial fibrillation with a ventricular response of 180–190 beats/min. This rhythm, which was associated with hypotension and evidence of myocardial ischemia, degenerated into ventricular fibrillation. There was no evidence of an accessory pathway, and no ventricular arrhythmias were inducible during programmed ventricular stimulation. It has long been claimed that patients with hypertrophic cardiomyopathy are unable to maintain stroke volume and increase cardiac output during exercise or tachycardia, presumably because of the shortened time for filling of a poorly relaxing and noncompliant left ventricle. Recently, we have demonstrated hypotension during exercise in a third of more than 100 consecutive patients with falls in blood pressure of 20–110 mm Hg (median, 40 mm Hg), from peak pressure recorded. A possible cause of these findings is that during exercise these patients are unable to increase or maintain stroke volume. To test this hypothesis, invasive hemodynamic studies were performed in 10 hypotensive responders and 10 normal blood pressure responders. Cardiac output increased appropriately and similarly in both groups, but there was an exaggerated fall in systemic vascular resistance that was observed to take place in association with the fall in blood pressure. This indicates abnormal peripheral vascular responses, which may be an important determinant of not only exercise blood pressure but also the hemodynamic response to arrhythmias in the condition. The prognostic significance of exercise hypotension and abnormal control of peripheral blood flow remains to be determined.

In addition to hemodynamic factors, the electrical stability of the myocardium must also be an important determinant of sudden death. In the adult, nonsustained ventricular tachycardia during electrocardiographic monitoring may be a marker of this, whereas in children and adolescents no such marker has been identified. The extent and severity of myocardial disarray may influence the electrical stability of the myocardium. Myocardial disarray is greater in young patients who die suddenly than in adults who die suddenly or from other causes, but the severity and distribution of disarray is not closely related to the severity and distribution of hypertrophy and at present can only be reliably assessed at postmortem examination.

What is the role of programmed ventricular stimulation in the identification of high-risk patients with hypertrophic cardiomyopathy? The study by Pananapazir et al reports the results of right ventricular and, in some, left ventricular stimulation in a consecutive but predominantly high-risk subset of patients with hypertrophic cardiomyopathy. Sustained ventricular arrhythmias of “more than 30 beats” were induced by an aggressive stimulation protocol in 66 of 155 patients (43%). In 64 of these, tachycardia was associated with “marked and prompt systemic arterial hypotension and loss of consciousness,” and in 31, it degenerated into ventricular fibrillation. The significance of short episodes of polymorphic ventricular tachycar-
dia, a nonspecific response in other clinical settings, that results in hypotension is problematic. Does this finding provide a marker of primary electrical instability, of hemodynamic instability, or is it merely a nonspecific artifact of an aggressive stimulation protocol in patients with myocardial hypertrophy who tolerate heart rates in excess of 250 beats/min poorly? The prognostic significance of these findings will be uncertain until the clinical outcome has been determined and compared with a larger number of low-risk patients than was reported by Fananapazir et al. The association of “higher risk patients” with inducible sustained ventricular arrhythmia is of interest. This may reflect a protocol that was not consistently applied with the possibility of systematic error related to more vigorous testing of patients with cardiac arrest or recurrent syncope. The clinical relevance of Fananapazir et al’s finding of sustained ventricular arrhythmia will depend on the reproducibility of the findings and, ultimately, on prospective evaluation.

What is the potential for programmed electrical stimulation to improve on the sensitivity (≥69%) of electrocardiographic monitoring for the identification of the high-risk adult with hypertrophic cardiomyopathy? As electrocardiographic monitoring identifies most of the adults who are at high risk, electrophysiologic studies may be more profitably performed in selected “high risk” patient populations. As discussed above, the predictive accuracy of ventricular tachycardia is low (22%). Programmed stimulation as well as assessment of left and right ventricular function may provide measurements that will improve the predictive accuracy and identify those patients with episodes of nonsustained ventricular tachycardia during electrocardiographic monitoring who are at greatest risk and warrant more vigorous treatment. A broader application of programmed ventricular stimulation in adults with hypertrophic cardiomyopathy, however, does not seem warranted.

The cause of sudden death in hypertrophic cardiomyopathy is uncertain. The low incidence of spontaneous arrhythmias in the young suggests that in this subgroup of patients, a primary arrhythmia is unlikely. We speculate that in some adults, but particularly in the young, the precipitating event is most often hemodynamic with hypotension in relation to emotion or exercise-related tachycardia. In addition, ischemia may be an important cause or consequence of tachycardia. Coincident ambulatory electrocardiographic monitoring in a young man who died suddenly documented sinus tachycardia with several minutes of marked ST-segment depression preceding a brief period of junctional escape rhythm and a fatal ventricular tachyarrhythmia. A primary supraventricular tachyarrhythmia as the cause of the tachycardia is also possible but less likely. The outcome, survival versus sudden death, is then determined by the vulnerability of the myocardium to sustain ventricular fibrillation.

In the assessment of adults and, particularly, children and adolescents with hypertrophic cardiomyopathy, future studies should evaluate patients in relation to likely mechanisms of sudden death. This should include an assessment of both propensity for hemodynamic collapse as well as the vulnerability of the myocardium to life-threatening arrhythmias. The optimal method of acquiring this information has not been determined and may differ in patient subgroups, particularly in relation to age and perhaps in relation to the severity of both left ventricular hypertrophy and functional impairment. Noninvasive tests that simulate or record events during normal daily life, such as stress testing, response to physiologic maneuvers, and electrocardiographic monitoring, can be broadly applied, whereas invasive investigations, particularly electrophysiologic studies, are more appropriate in selected subgroups. It is important that patients with hypertrophic cardiomyopathy are better characterized in relation to likely mechanisms of sudden death as the pharmacologic and surgical treatments may significantly improve prognosis if they are applied appropriately.

References


(Circulation 1989;80:1489–1492)
Sudden death in hypertrophic cardiomyopathy. Assessment of patients at high risk.
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Circulation. 1989;80:1489-1492
doi: 10.1161/01.CIR.80.5.1489

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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