Sudden unexpected death is the most devastating feature of the natural history of hypertrophic cardiomyopathy and is the most devastating feature of the natural history of the disease. Left ventricular hypertrophy appears to be an important determinant of many clinical features of hypertrophic cardiomyopathy, but the relation between its magnitude and the occurrence of sudden cardiac death has not been clearly defined. In this study, the magnitude of hypertrophy was assessed with two-dimensional echocardiography in 29 asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy who subsequently died suddenly or experienced cardiac arrest with documented ventricular fibrillation. Findings were compared with those obtained in a control group of 95 patients of similar age and asymptomatic state.

Maximal left ventricular wall thickness was significantly greater in patients with sudden death (26 ± 7 mm) than in control patients (21 ± 5 mm, p < 0.001). Left ventricular wall thickness index, a quantitative expression of the overall extent of hypertrophy, was also greater in patients with sudden death (76 ± 20 mm) than in surviving control patients (62 ± 13 mm, p < 0.001). Particularly marked and diffuse hypertrophy, with maximal wall thickness ≥30 mm or wall thickness ≥25 mm in two or more of the four segments into which the left ventricle had been divided, was eight times more common in patients with sudden death (11 [38%] of 29) than in control patients (5 [5%] of 95, p < 0.001). The prevalence of mild and localized hypertrophy, with maximal wall thickness ≤17 mm involving only one segment, was similar in patients with sudden death (4 [14%] of 29) and in control patients (23 [24%] of 95, p > 0.05); however, of the four patients with sudden death and mild hypertrophy, only one was an adult; three were preadolescent children whose hypertrophy would have been considered to be more substantial if corrected for body surface area.

It is concluded that most asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy who die suddenly have marked and diffuse left ventricular hypertrophy, and that a relation exists between the extent of hypertrophy and the occurrence of sudden and unexpected death in this disease. Sudden cardiac death is uncommon in asymptomatic or mildly symptomatic adult patients with hypertrophic cardiomyopathy and relatively mild left ventricular hypertrophy.

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form the present study group. Sudden death was defined as instantaneous collapse with subsequent death within minutes or documented ventricular fibrillation.

In each patient, the diagnosis of hypertrophic cardiomyopathy had been established by the echocardiographic demonstration of a nondilated and hypertrophied left ventricle in the absence of another cardiac or systemic disease that could produce left ventricular hypertrophy of the magnitude observed (8). Patients ranged in age from 11 to 62 years (mean 30); 17 (60%) were male. For convenience, we will refer to the study patients who either died suddenly or survived cardiac arrest as patients experiencing sudden cardiac death.

Each of the 29 patients met the following selection criteria: 1) no or only mild symptoms (New York Heart Association functional class I or II) before their catastrophic and unexpected event, and 2) a two-dimensional echocardiogram of sufficient technical quality to permit reliable assessment of the extent and distribution of left ventricular hypertrophy. The time interval between the two-dimensional echocardiogram and sudden death or cardiac arrest was < 1 year (range 1 to 11 months, mean 3) in 23 patients. In the remaining six patients, the two-dimensional echocardiogram was obtained 1.9 to 4.6 years (mean 2.9) before sudden death. Patients who had undergone operation (ventricular septal myotomy-myectomy) for relief of subaortic obstruction and subsequently died suddenly were not included in the study.

By virtue of selection criteria, the 29 study patients had no or only mild symptoms before their sudden death; 15 patients (52%) were asymptomatic and 14 (48%) had mild symptoms that did not represent significant functional limitation (that is, functional class II). The most common symptoms were exertional dyspnea, fatigue, chest pain and presyncope; six patients had experienced syncope. Although patients with severe symptoms of cardiac failure can also die suddenly, we confined our study to those patients who had not had marked cardiac symptoms before their catastrophic event. We believe that data obtained in this fashion will ultimately be more pertinent to our understanding of the determinants of unexpected sudden death in hypertrophic cardiomyopathy.

**Left ventricular outflow tract obstruction under basal conditions** was assessed at cardiac catheterization in 20 patients, and estimated from the M-mode echocardiogram (on the basis of the magnitude and duration of systolic anterior motion of the mitral valve) in the remaining 9 patients (9,10). In each of the former 20 patients, cardiac catheterization was performed within 17 months (mean 3) of the two-dimensional echocardiogram used to assess the extent of left ventricular hypertrophy.

**Significant narrowing of the extramural coronary arteries** was excluded by coronary arteriography or by gross visual inspection at necropsy in 11 patients. In the other 18 study patients, the presence of coronary artery disease was considered unlikely because of their youthful age (range 9 to 37 years; mean 21).

**Control patients.** Morphologic findings in the study patients with sudden cardiac death were compared with those in a control group of surviving patients with hypertrophic cardiomyopathy. The control group represented a series of 95 patients evaluated at the National Heart, Lung, and Blood Institute between February 1982 and March 1986 who had two-dimensional echocardiograms of sufficient technical quality to permit reliable assessment of the extent and distribution of left ventricular hypertrophy. These patients were selected so that they represented a group similar in age and symptomatic status to that of the patients who died suddenly.

At the time of their echocardiographic examination, the control patients ranged in age from 9 to 61 years (mean 31); 71 (75%) were male. Forty-five patients were asymptomatic, and 50 others were mildly symptomatic (functional class II). Left ventricular outflow tract obstruction under basal conditions was assessed at cardiac catheterization in 24 patients and estimated from the M-mode echocardiogram in the other 71. The only cardioactive medication administered to the control patients was a beta-adrenergic blocking agent or verapamil.

**Echocardiography**

An Advanced Technology Laboratory Mark 500 mechanical sector scanner with a 3 MHz transducer and a Hewlett-Packard 77020A or a Varian (V-3000 or V-3400) phased-array sector scanner with 2.25 MHz transducers were used to perform the two-dimensional echocardiographic studies. Images were recorded on 1 in. (2.54 cm) reel to reel videotape. Two-dimensional echocardiographic images were obtained in the parasternal long- and short-axis views and apical two and four chamber views, using standard transducer positions (11).

**Assessment of magnitude of hypertrophy.** The extent and distribution of left ventricular hypertrophy were assessed at end-diastole, utilizing criteria previously described (12-15). Briefly, the magnitude of left ventricular hypertrophy was assessed primarily from parasternal short-axis planes; however, parasternal long-axis and apical views were also used to integrate the observations made from the short-axis views. In particular, the long-axis view was used to verify the measurements of anterior septal and posterior free wall thickness obtained from the short-axis views; the apical views were used primarily to exclude the presence of apical hypertrophy in those patients in whom, on the basis of the parasternal views, hypertrophy was considered to be mild and localized to the basal portions of the ventricle.

In the parasternal short-axis plane, the left ventricle was divided into four segments that identified the anterior and posterior ventricular septum and the lateral and posterior left ventricular free walls (Fig. 1). Wall thickness was
measured at the levels of both the mitral valve and the papillary muscles in each of the four ventricular segments. The segment of the wall that showed the greatest thickness was considered to represent the maximal left ventricular wall thickness (13-16). In addition, an index of the extent of left ventricular hypertrophy was calculated by adding the maximal wall thickness measured (at either the mitral valve or papillary muscle level) in each of the four ventricular segments (14). This index was considered representative of the overall magnitude of left ventricular hypertrophy. Measurements of maximal left ventricular wall thickness and wall thickness index have previously been shown to have satisfactory reproducibility (14,16). These measurements provide an adequate estimate of the extent of left ventricular hypertrophy and reliably separate, in quantitative terms, patients with marked and diffuse hypertrophy from those with mild and localized hypertrophy (12-15). Left ventricular end-diastolic cavity dimension was assessed from the M-mode echocardiogram, as previously described (17).

Statistical methods. Data were expressed as mean values ± SD. Differences between continuous variables were determined using the unpaired Student’s t test. Differences between proportions were determined using the chi-square test or the Fisher exact test, as appropriate.

Results

Echocardiographic findings. The 29 study patients with sudden cardiac death and the 95 control patients were compared with regard to the magnitude of left ventricular hypertrophy. Maximal left ventricular wall thickness, measured from the two-dimensional echocardiogram, was significantly greater in patients with sudden death (26 ± 7 mm) than in the control group (21 ± 5 mm, p < 0.001) (Fig. 2). The left ventricular wall thickness index, a measure of the overall extent of left ventricular hypertrophy, was also greater in patients with sudden death (76 ± 20 mm) than in control patients (62 ± 13 mm, p < 0.001). Left ventricular end-diastolic cavity dimension was similar in the two groups (42 ± 6 and 44 ± 6 mm, respectively, p > 0.05).

Furthermore, patients at the extremes of the morphologic spectrum of the disease showed a strikingly different prevalence within the two study groups. Particularly marked and diffuse left ventricular hypertrophy, with maximal wall thickness ≥30 mm or wall thickness ≥25 mm in two or more of the four segments into which the left ventricle had been divided, was eight times more common in patients with sudden death (11 [38%] of 29) than in the control patients (5 [5%] of 95, p < 0.001) (Fig. 3). Mild and localized hypertrophy, with maximal wall thickness <17 mm involving only one ventricular segment, showed a similar prevalence in the patients with sudden death (4 [14%] of 29) and in control patients (23 [24%] of 95, p > 0.05). However, only one of the four patients with sudden death and mild localized hypertrophy was an adult (Case 27). The other three were preadolescent children (Cases 5, 6 and 7) whose hypertrophy would have been classified as more substantial if corrected for body surface area. In 27 (93%) of the 29 patients with sudden death, the anterior ventricular septum was the thickest portion of the left ventricle. No patient had hypertrophy confined to the most distal apical portion of the left ventricle.

Figure 1. Patterns of left ventricular hypertrophy in two patients with hypertrophic cardiomyopathy. Parasternal short-axis plane during diastole: A, Stop-frame echocardiogram from a 21 year old woman (Case 12) shows marked hypertrophy of the anterior ventricular septum (ANT. VS), which measures up to 32 mm; wall thickening also involves the posterior septum (POST. VS) and contiguous portion of the anterior free wall (ANT. FW). B, Echocardiogram from a 14 year old boy (Case 6) shows relatively mild and localized wall thickening, primarily involving the anterior portion of the ventricular septum (15 mm). LAT. FW = lateral free wall.
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Figure 2. Comparison of maximal left ventricular (LV) wall thickness in patients with sudden cardiac death and in surviving control patients. \( \Theta \) = mean value.

Figure 3. Prevalence of severe and mild left ventricular hypertrophy (LVH) in patients with sudden cardiac death and in surviving control patients.

below papillary muscle level (that is, "apical hypertrophic cardiomyopathy") (18,19).

Clinical findings. Clinical, morphologic and functional findings in the 29 study patients with sudden death are reported in Table 1. Age at the time of the patient's catastrophic event ranged from 11 to 62 years (mean 30); eight patients were <18 years of age and four were >50 years. Seventeen (59%) of the 29 study patients were male. Sudden death occurred in 22 patients during sedentary activity and in the other 7 during moderate to severe exertion such as running, jogging or lifting weight.

Twenty-one of the 29 patients had been taking cardioactive medication in the period just before their catastrophic event, including beta-blockers (12 patients), verapamil (3 patients), both verapamil and propranolol (2 patients), amiodarone (1 patient), disopyramide and propranolol (1 patient), nifedipine and propranolol (1 patient) and digitalis and diuretic (1 patient).

In 2 of the 29 patients, hypertrophic cardiomyopathy was associated with another cardiovascular abnormality. One patient (Case 4) had an anatomically redundant floppy mitral valve with systolic prolapse but without significant mitral regurgitation, and the other (Case 14) had mild systemic hypertension. Subaortic obstruction under basal conditions (pressure gradient \( \geq 30 \) mm Hg) was present in 10 (34%) of the 29 study patients with sudden cardiac death. This prevalence of subaortic obstruction was not significantly different from that in the control group (16 [17%] of 95, \( p > 0.05 \)). Gender distribution also did not differ in the patients with sudden death (17 [59%] of the 29 study patients were male patients compared with 71 [75%] of the 95 control patients, \( p > 0.05 \)).

Discussion

Previous studies have shown that the presence of marked and diffuse left ventricular hypertrophy is an unfavorable feature in patients with hypertrophic cardiomyopathy. Patients with extensive hypertrophy have a higher prevalence of obstruction to left ventricular outflow (6,20,21) and nonsustained ventricular tachycardia on ambulatory electrocardiography (6,22), a finding associated with increased risk for sudden death (23,24). The present study extends these observations and demonstrates a relation between the extent of left ventricular hypertrophy and the occurrence of sudden death or cardiac arrest in this disease.

Relation between extent of hypertrophy and occurrence of sudden death. Both maximal left ventricular wall thickness and wall thickness index (a measure of the overall magnitude of left ventricular hypertrophy) were significantly greater in our group of patients who died suddenly or experienced cardiac arrest than in a representative control group of surviving patients with hypertrophic cardiomyopathy of similar age and functional status. Furthermore, analysis of extent of left ventricular hypertrophy in individual patients showed that particularly marked and diffuse hypertrophy, with maximal wall thickness \( \geq 30 \) mm or wall thickness \( \geq 25 \) mm in two or more left ventricular segments, was eight times more common in patients with sudden cardiac death than in the control patients. At the other extreme of the morphologic spectrum of the disease, mild and localized left ventricular hypertrophy, with maximal wall thickness \( \leq 17 \) mm involving only one ventricular segment, was uncommon in patients.
with sudden cardiac death (14%) and showed a similar prevalence in the control patients (24%). However, only one of the four patients with sudden cardiac death and mild hypertrophy was an adult. The other three were preadolescent children; thus, their left ventricular hypertrophy, although appearing mild in absolute terms, would have been more substantial if corrected for body surface area.

The findings of the present study indicate that marked and diffuse left ventricular hypertrophy is associated with an increased risk of sudden death in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. Conversely, sudden death would appear to be uncommon in adult patients with relatively mild and localized hypertrophy who have not experienced severe symptoms; indeed, only one of the adult patients who died suddenly had this pattern of hypertrophy. However, it should also be emphasized that mild left ventricular hypertrophy does not always constitute a benign morphologic feature in hypertrophic cardiomyopathy. Some patients with modest degrees of left ventricular wall thickening may have severe symptoms of cardiac failure; in such patients, the mild hypertrophy is often the consequence of diffuse and progressive left ventricular wall thinning and is associated with a poor prognosis (13-15).

Clinical implications. Our findings do not imply that left ventricular hypertrophy is an independent determinant of sudden death in patients with hypertrophic cardiomyopathy. Indeed, both the determinants and the mechanisms of sudden death in this disease have not yet been fully defined. They are likely to be complex, involving the interaction of multiple factors, and may differ in individual patients. However, an association has been previously demonstrated (6,22) between magnitude of left ventricular hypertrophy and the occurrence of nonsustained ventricular tachycardia in hypertrophic cardiomyopathy. Thus, the relation that we identify...
tified in this study between extent of hypertrophy and sudden cardiac death suggests, by inference, that complex ventricular arrhythmias may constitute the mechanism for sudden cardiac death in many patients with particularly marked left ventricular hypertrophy.

The present investigation is based on a retrospective analysis of data and thus has the intrinsic limitations of such a study design. Moreover, left ventricular morphology in the study patients who died suddenly was compared with that of control patients who were alive at the time of the investigation but could subsequently die suddenly. Thus, although our findings support the concept that more severe left ventricular hypertrophy conveys a greater risk for sudden death, our data do not permit definitive conclusions regarding the risk of dying suddenly in individual patients with different extent of hypertrophy. Therefore, caution should be exercised in utilizing these observations for prospective assessment of prognosis in patients with hypertrophic cardiomyopathy.

Conclusions. Our findings show that particularly marked and diffuse left ventricular hypertrophy is common in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy who die suddenly. Our results also suggest that asymptomatic adult patients with only relatively mild and localized hypertrophy are probably at low risk of dying suddenly. Although these observations demonstrate a relation between the magnitude of left ventricular hypertrophy and the occurrence of sudden death in hypertrophic cardiomyopathy, a prospective investigation is necessary to define more conclusively the risk of sudden death in individual patients with this disease and different magnitudes of left ventricular hypertrophy.

References