

MAGNITUDE OF LEFT VENTRICULAR HYPERTROPHY AND RISK OF SUDDEN DEATH IN HYPERTROPHIC CARDIOMYOPATHY

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ABSTRACT

Background Sudden death is a possible consequence of hypertrophic cardiomyopathy. Quantification of the risk of sudden death, however, remains imprecise for most patients with this disease.

Methods We assessed the relation between the magnitude of left ventricular hypertrophy and mortality in 480 consecutive patients with hypertrophic cardiomyopathy. The patients were categorized into five subgroups according to maximal wall thickness: 15 mm or less, 16 to 19 mm, 20 to 24 mm, 25 to 29 mm, and 30 mm or more. Their ages ranged from 1 to 89 years (median, 47).

Results Over a mean follow-up period of 6.5 years, 65 of the 480 patients (14 percent) died: 23 suddenly, 15 of heart failure, and 27 of noncardiac causes or stroke. The risk of sudden death increased progressively and in direct relation to wall thickness ($P=0.001$), ranging from 0 per 1000 person-years (95 percent confidence interval, 0 to 14.4) for a wall thickness of 15 mm or less to 18.2 per 1000 person-years (95 percent confidence interval, 7.3 to 37.6) for a wall thickness of 30 mm or more and almost doubling from each wall-thickness subgroup to the next. The cumulative risk 20 years after the initial evaluation was close to zero for patients with a wall thickness of 19 mm or less but almost 40 percent for wall thicknesses of 30 mm or more. As compared with the other subgroups, patients with extreme hypertrophy were the youngest (mean age, 31 years), and most (41 of 43) had mild symptoms or no symptoms; of the 12 patients who were less than 18 years old at the initial evaluation, 5 died suddenly.

Conclusions In hypertrophic cardiomyopathy, the magnitude of hypertrophy is directly related to the risk of sudden death and is a strong and independent predictor of prognosis. Young patients with extreme hypertrophy, even those with few or no symptoms, appear to be at substantial long-term risk and deserve consideration for interventions to prevent sudden death. The majority of patients with mild hypertrophy are at low risk and can be reassured regarding their prognosis. (N Engl J Med 2000;342:1778-85.)

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SUDDEN death has been recognized as a possible consequence of hypertrophic cardiomyopathy since the first modern descriptions of the disease.^{1,2} However, despite 40 years of investigation, the search for a way to identify patients who have a high risk of dying suddenly has been frustrated by certain features of this disorder, including

the frequent absence of symptoms before sudden death,²⁻⁵ the great variation in clinical presentation and prognosis,³⁻⁵ the relatively low prevalence of the disease,^{6,7} and the difficulty of enrolling large study populations without bias due to referral of patients at tertiary centers.⁸⁻¹⁰

Several factors are known to be strong indicators of a high risk of sudden death in patients with hypertrophic cardiomyopathy, including a previous aborted cardiac arrest, one or more episodes of sustained ventricular tachycardia, and a history of sudden death in two or more young family members.³⁻⁵ However, these features are uncommon in the overall population of patients with hypertrophic cardiomyopathy. Other indicators of increased risk, such as the presence of nonsustained ventricular tachycardia on ambulatory electrocardiographic monitoring or an abnormal blood-pressure response during exercise, have a low positive predictive value.^{4,5,11-14} The limitations of risk stratification have recently acquired particular relevance because of the increasing availability of implantable cardioverter-defibrillators and their proven efficacy in preventing sudden death in patients with hypertrophic cardiomyopathy.¹⁵

Although there is circumstantial evidence that young patients with extreme left ventricular hypertrophy may be at increased risk for sudden death,¹⁶⁻¹⁸ the importance of the magnitude of hypertrophy as a risk factor remains unresolved. The purpose of our study was to assess the relation between the magnitude of left ventricular hypertrophy and survival in a large and relatively unselected series of consecutive patients with hypertrophic cardiomyopathy.

METHODS

Study Population

Each of the 490 consecutively enrolled patients with hypertrophic cardiomyopathy who were evaluated at the Ente Ospedaliero Ospedali Galliera in Genoa, Italy, from January 1983 to December 1997 (213 patients) or at the Minneapolis Heart Institute Foundation in Minneapolis from January 1981 to December 1996 (277 patients) were initially considered for inclusion in the study.

The initial evaluation (base line) at the center in Genoa was de-

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defined as taking place at the time of the first visit and at the center in Minneapolis as taking place at the initial diagnosis of hypertrophic cardiomyopathy (for a minority of patients as early as 1966). Eight patients had only a single evaluation and were excluded from subsequent analysis. Two patients had a history of aborted cardiac arrest before their initial evaluation and were also excluded from the analysis. Therefore, the final study population comprised a total of 480 patients (210 in Genoa and 270 in Minneapolis). Six of these 480 patients had an aborted cardiac arrest or had ventricular tachycardia or fibrillation interrupted by the discharge of an implantable cardioverter-defibrillator after enrollment; follow-up of these patients was terminated at the time of their most recent evaluation. Six other patients underwent heart transplantation, and follow-up was terminated at that time.

Echocardiography

The magnitude of left ventricular hypertrophy was assessed with two-dimensional echocardiography according to previously published criteria.^{17,18} The greatest thickness measured at any site in the left ventricular wall was considered to represent the maximal wall thickness.¹⁷⁻¹⁹ In the analysis of data, the maximal wall thickness was not corrected for body size, either in adults or in children. The study population was divided into five subgroups according to maximal wall thickness: 15 mm or less, 16 to 19 mm, 20 to 24 mm, 25 to 29 mm, and 30 mm or more. These arbitrary cutoff points are consistent with criteria used in previous studies.^{4,5,16-19}

The echocardiographic measurements in each of the 210 patients evaluated at the center in Genoa were made by a single investigator, and in each of the 270 patients evaluated in Minneapolis these measurements were made by a single, different investigator. The correlation between these two investigators' measurements of left ventricular wall thickness in patients with hypertrophic cardiomyopathy has been reported.^{20,21}

The same investigators repeated their measurements of maximal wall thickness independently and without knowledge of the identity of the patients or of the previous findings in 48 echocardiograms selected at random from the echocardiograms of the 480 patients (24 were from the Italian cohort and 24 from the U.S. cohort, and 18 others were from the 43 patients with a wall thickness of 30 mm or more). The correlation between the two sets of measurements was high (Pearson correlation coefficient, 0.94), and there was good concordance between the two sets with respect to classification into the five wall-thickness subgroups (weighted kappa for ordered categories, 0.91).

Left ventricular outflow obstruction under basal conditions was considered present when a peak outflow gradient of 30 mm Hg or more was identified by Doppler echocardiography.²² The left atrial and left ventricular end-diastolic cavity dimensions were assessed by M-mode echocardiography in a standard fashion.

Definitions

Hypertrophic cardiomyopathy was diagnosed when there was echocardiographic evidence of a nondilated and hypertrophied left ventricle (defined as a wall thickness of ≥ 15 mm in adult index patients or the equivalent wall thickness relative to body-surface area in children) in the absence of another cardiac or systemic disease that could produce a similar degree of hypertrophy.^{10,13,19} In adult relatives of the patients with hypertrophic cardiomyopathy, a wall thickness of 13 mm or more was considered a criterion for diagnosis.²³

Sudden death of cardiac origin was defined as instantaneous and unexpected death within minutes after a witnessed collapse in patients previously in stable clinical condition. Death was also classified as sudden if it occurred unexpectedly but was unwitnessed, such as death occurring in bed overnight.¹³

Death due to congestive heart failure was defined as death occurring in the context of long-standing cardiac decompensation with progression of disease during the previous year, with the development of pulmonary edema or evolution to end-stage disease.

A history of sudden death in the family was considered present if one or more family members with hypertrophic cardiomyopa-

thy had died suddenly, according to the definition of sudden death given above, or if one or more close relatives without a documented diagnosis of hypertrophic cardiomyopathy had died suddenly at less than 50 years of age.

Statistical Analysis

To estimate mortality rates, the number of patients who died during follow-up was divided by the total number of person-years accumulated during follow-up in the study population or in each wall-thickness subgroup. For the calculation of overall rates of death, follow-up time was considered to be the interval from the date of the initial evaluation to the time of death or (among surviving patients) to the time of the most recent evaluation. For the calculation of rates of sudden death, follow-up data for patients who died from congestive heart failure or from noncardiac causes were censored at the time of death. For the calculation of rates of death due to heart failure or noncardiac causes, follow-up data for patients who died suddenly were censored at the time of death.

Ninety-five percent confidence intervals for mortality rates were calculated with the assumption of an underlying Poisson distribution of rare events. Rates were compared among subgroups of patients by means of the chi-square test for heterogeneity, Fisher's test, or the chi-square test for trend, as appropriate. Survival curves were constructed according to the Kaplan-Meier method.

To assess the role of wall thickness as an independent predictor of death, three multivariate Cox proportional-hazards models were fitted to the data. In each model, patients were stratified according to age (into one of four categories), and variables significantly associated with outcome were entered in a stepwise procedure based on the likelihood-ratio test. The results of the multivariate analyses should be interpreted cautiously in view of the relatively small number of events and the large number of strata. All P values are two-sided. SPSS statistical software (SPSS, Chicago) was used for most calculations.

RESULTS

Base-Line Clinical Characteristics

The clinical features of the overall study population and of the five wall-thickness subgroups at base line (the initial evaluation) are summarized in Table 1. The duration of follow-up ranged from 1 month to 31 years (mean, 6.5 years; median, 4.6). The 480 study patients ranged in age from 1 to 89 years (mean, 47; median, 47); 288 of the patients (60 percent) were male. Of the 480 patients, 446 (93 percent) were asymptomatic or had only mild symptoms (New York Heart Association functional class I or II), and 34 (7 percent) had severe symptoms (class III or IV); 133 patients (28 percent) had left ventricular outflow obstruction (an outflow gradient of ≥ 30 mm Hg under basal conditions).

At the time of the first visit, the maximal left-ventricular-wall thickness ranged from 7 to 40 mm (mean, 21 ± 5); 448 patients had a left-ventricular-wall thickness of 15 mm or more, and 32 had a wall thickness of less than 15 mm. Of these 32 patients, 10 were children 15 years of age or younger; 3 were patients with progression to end-stage disease with wall thinning, cavity dilatation, and systolic dysfunction²¹; and 19 were adult members of families affected by hypertrophic cardiomyopathy.

Among the five wall-thickness subgroups, patients with wall thicknesses at the two extremes of the morphologic spectrum (maximal wall thickness, ≤ 15 or

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO THE MAGNITUDE OF LEFT VENTRICULAR HYPERTROPHY.*

VARIABLE	LEFT-VENTRICULAR-WALL THICKNESS					P VALUE†	
	ALL PATIENTS	≤15 mm	16–19 mm	20–24 mm	25–29 mm		≥30 mm
No. of patients	480	69	138	184	46	43	—
Age — yr							<0.001
Mean	47	42	52	49	42	31	
Median	47	40	55	50	41	28	
Male sex — no. (%)	288 (60)	43 (62)	82 (59)	105 (57)	30 (65)	28 (65)	0.77
NYHA functional class III or IV — no. (%)	34 (7)	3 (4)	10 (7)	15 (8)	4 (9)	2 (5)	0.79
Left ventricular outflow obstruction — no. (%)	133 (28)	7 (10)	35 (25)	65 (35)	17 (37)	9 (21)	0.001
Maximal wall thickness — mm	21±5	14±2	18±1	21±1	28±1	32±2	—
Left ventricular end-diastolic cavity dimension — mm	44±7	46±8	45±7	44±7	45±7	40±7	0.002
Left atrial cavity dimension — mm	43±9	40±10	42±8	44±8	44±8	44±11	0.03

*Plus–minus values are means ±SD. NYHA denotes New York Heart Association.

†P values for the comparisons among the five wall-thickness subgroups to detect differences in mean age, left ventricular end-diastolic cavity dimension, and left atrial cavity dimension were calculated by one-way analysis of variance. P values for the comparisons among the five subgroups to detect differences in sex, NYHA functional class, and left ventricular outflow (proportions) were calculated by the chi-square test for heterogeneity, with 4 df.

≥30 mm) were the youngest ($P<0.001$) and had the lowest frequency of outflow obstruction ($P=0.001$) (Table 1). Sex distribution and New York Heart Association functional class were similar among the five subgroups ($P=0.77$ and $P=0.79$, respectively), and the proportion of patients with moderate or severe symptoms in each subgroup was low (4 to 9 percent).

During follow-up, 65 of the 480 study patients (14 percent) died: 23 suddenly, 15 of heart failure, and 27 of noncardiac causes or stroke. The overall incidence of death from any cause was 20.9 per 1000 person-years (95 percent confidence interval, 16.1 to 26.6), that of sudden death was 7.4 per 1000 person-years (95 percent confidence interval, 4.7 to 11.1), that of death due to heart failure was 4.8 per 1000 person-years (95 percent confidence interval, 2.7 to 8.0), and that of death from noncardiac causes or stroke was 8.7 per 1000 person-years (95 percent confidence interval, 5.7 to 12.6). The mean age at the time of death was 44 ± 24 years among those who died suddenly, 63 ± 21 years among those who died of heart failure, and 74 ± 12 years among those who died of noncardiac causes or stroke. Of the 23 patients who died suddenly, 21 had no symptoms or mild symptoms (New York Heart Association class I or II) and 2 had severe symptoms (class III) at the time of death.

At the time of the initial evaluation or shortly thereafter, 151 (31 percent) of the study patients were not taking any cardioactive medications, 300 (62 percent) were taking beta-blockers or calcium antagonists, and 29 (6 percent) were taking amiodarone either because of ambulatory electrocardiographic evidence of non-sustained ventricular tachycardia or because of paroxysmal atrial fibrillation. Of the 29 patients taking

amiodarone, 5 (17 percent) died suddenly during follow-up; each was taking amiodarone at the time of death.

Of the 480 study patients, 26 underwent a septal myotomy–myectomy operation, and 8 were given a pacemaker in an attempt to reduce the left ventricular outflow gradient and to improve symptoms.²⁴ Thirteen patients had a cardioverter–defibrillator; three of them had an appropriate discharge for ventricular tachycardia or fibrillation during follow-up.

Relation between Maximal Left-Ventricular-Wall Thickness and Mortality

Mortality in the five wall-thickness subgroups is reported in Table 2. The risk of sudden death increased significantly and progressively in direct relation to wall thickness ($P=0.001$) (Fig. 1). The risk of sudden death was 0 (95 percent confidence interval, 0 to 14.4) per 1000 person-years in patients with a wall thickness of 15 mm or less, 2.6 per 1000 person-years (95 percent confidence interval, 0.3 to 9.6) in those with a wall thickness of 16 to 19 mm, 7.4 per 1000 person-years (95 percent confidence interval, 3.5 to 13.6) in those with a wall thickness of 20 to 24 mm, 11.0 per 1000 person-years (95 percent confidence interval, 3.0 to 28.2) in those with a wall thickness of 25 to 29 mm, and 18.2 per 1000 person-years (95 percent confidence interval, 7.3 to 37.6) in those with a wall thickness of 30 mm or more.

Kaplan–Meier estimates of the proportion of patients without sudden death in each of the five wall-thickness subgroups are shown in Figure 2. Twenty years after the initial evaluation, patients with a wall thickness of 19 mm or less had a cumulative risk

TABLE 2. RISK OF DEATH ACCORDING TO THE MAGNITUDE OF LEFT VENTRICULAR HYPERTROPHY.*

LEFT-VENTRICULAR-WALL THICKNESS	DEATH FROM ANY CAUSE		SUDDEN DEATH		DEATH DUE TO HEART FAILURE	
	NO. OF PATIENTS (%)	INCIDENCE PER 1000 PERSON-YR (95% CI)	NO. OF PATIENTS (%)	INCIDENCE PER 1000 PERSON-YR (95% CI)	NO. OF PATIENTS (%)	INCIDENCE PER 1000 PERSON-YR (95% CI)
≤15 mm (n=69)	3 (4.3)	11.7 (2.4–34.3)	0	0 (0–14.4)	0	0 (0–14.4)
16–19 mm (n=138)	12 (8.7)	15.9 (8.2–27.8)	2 (1.4)	2.6 (0.3–9.6)	2 (1.4)	2.7 (0.3–9.6)
20–24 mm (n=184)	29 (15.8)	21.4 (14.4–30.8)	10 (5.4)	7.4 (3.5–13.6)	9 (4.9)	6.6 (3.0–12.6)
25–29 mm (n=46)	10 (21.7)	27.5 (13.2–50.6)	4 (8.7)	11.0 (3.0–28.2)	2 (4.3)	5.5 (0.7–19.9)
≥30 mm (n=43)	11 (25.6)	28.6 (14.3–51.3)	7 (16.3)	18.2 (7.3–37.6)	2 (4.7)	5.2 (0.6–18.8)
Chi square for trend		3.66		10.62		1.22
P value		0.06		0.001		0.27

*CI denotes confidence interval. Comparisons among the five subgroups were made by the chi-square test for trend.

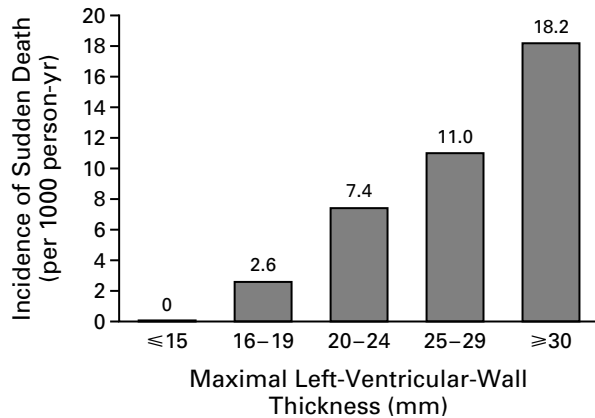


Figure 1. Relation between Maximal Left-Ventricular-Wall Thickness and the Risk of Sudden Death in 480 Patients with Hypertrophic Cardiomyopathy.

The incidence of sudden death increased progressively and in direct relation to maximal wall thickness (P=0.001 by the chi-square test for trend).

close to zero, whereas those with a wall thickness of 30 mm or more had a risk of close to 40 percent.

The highest rate of sudden death was observed in the youngest patients with a wall thickness of 30 mm or more; of the 12 patients who were younger than 18 years of age at base line 5 died suddenly (incidence of sudden death, 37.9 per 1000 person-years; 95 percent confidence interval, 12.8 to 88.5). Of the five patients younger than 13 years of age at base line, three died suddenly.

Univariate Analysis

The results of univariate analyses of the relation between clinical variables (other than wall thickness) and mortality are reported in Table 3. A significant univariate association with death due to heart failure was identified for several variables: age at base line

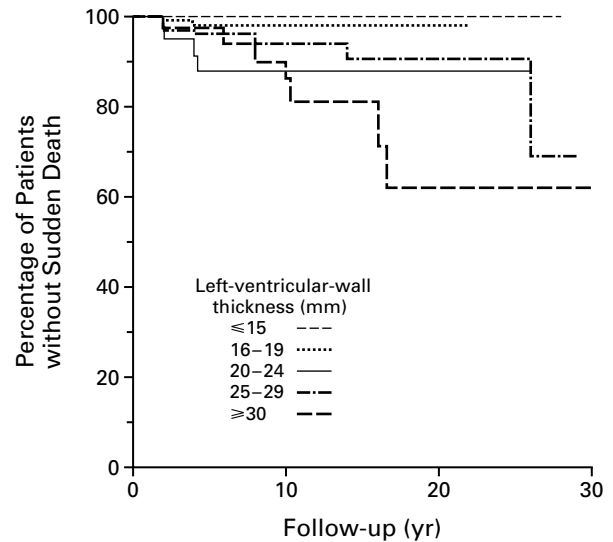


Figure 2. Kaplan–Meier Estimates of the Proportions of Patients without Sudden Death among the 480 Patients with Hypertrophic Cardiomyopathy, According to the Magnitude of Left Ventricular Hypertrophy.

(P=0.003), New York Heart Association functional class (P=0.001), the presence or absence of outflow obstruction (P=0.006), and left atrial cavity dimension (P=0.03). A univariate association with sudden death was identified for left ventricular end-diastolic cavity dimension (P=0.002). No relation was identified between the incidence of sudden death or of death due to heart failure and a history of sudden death in the family (P=0.23 and P=0.48), respectively).

Multivariate Regression Analysis

In a Cox regression model that included age as a stratification factor (Table 4), left-ventricular-wall

TABLE 3. RESULTS OF UNIVARIATE ANALYSIS OF THE RELATION BETWEEN BASE-LINE CLINICAL VARIABLES OTHER THAN LEFT-VENTRICULAR-WALL THICKNESS AND THE RISK OF DEATH.*

VARIABLE	No. OF PATIENTS	SUDDEN DEATH		DEATH DUE TO HEART FAILURE		DEATH FROM ANY CAUSE		DURATION OF FOLLOW-UP person-yr
		NO. OF PATIENTS	INCIDENCE PER 1000 PERSON-YR (95% CI)	NO. OF PATIENTS	INCIDENCE PER 1000 PERSON-YR (95% CI)	NO. OF PATIENTS	INCIDENCE PER 1000 PERSON-YR (95% CI)	
Age								
<20 yr	64	8	14.2 (6.1–28.0)	0	0 (0–6.5)	8	14.2 (6.1–28.0)	563
20–39 yr	120	3	4.0 (0.8–11.6)	3	4.0 (0.8–11.6)	7	9.3 (3.7–19.2)	754
40–59 yr	154	6	5.5 (2.0–11.9)	3	2.7 (0.6–8.0)	18	16.4 (9.7–26.0)	1094
≥60 yr	142	6	8.6 (3.1–18.7)	9	12.9 (5.9–24.4)	32	45.8 (31.3–64.6)	699
P value			0.39		0.003		<0.001	
NYHA functional class								
I or II	446	21	7.1 (4.4–10.9)	10	3.4 (1.6–6.2)	55	18.7 (14.1–24.3)	2945
III or IV	34	2	12.1 (1.5–43.7)	5	30.3 (9.8–70.6)	10	60.5 (29.0–111.3)	165
P value			0.35		0.001		0.002	
History of sudden death in family								
Present	70	1	2.1 (0–11.9)	3	6.4 (1.3–18.8)	8	17.2 (7.4–33.8)	466
Absent	410	22	8.3 (5.2–12.6)	12	4.5 (2.3–7.9)	57	21.6 (16.3–27.9)	2643
P value			0.23		0.48		0.54	
Left ventricular outflow obstruction								
Present	133	7	8.6 (3.5–17.9)	9	11.1 (5.1–21.1)	27	33.4 (22.0–48.5)	809
Absent	347	16	6.9 (4.0–11.3)	6	2.6 (1.0–5.7)	38	16.5 (11.7–22.7)	2301
P value			0.63		0.006		0.005	
Left atrial cavity dimension								
<40 mm	150	11	11.8 (5.9–21.2)	0	0 (0–4.0)	14	15.0 (8.2–25.3)	930
40–50 mm	257	7	4.4 (1.8–9.1)	11	6.9 (3.4–12.4)	37	23.2 (16.4–32.1)	1591
>50 mm	73	5	9.0 (2.8–19.8)	4	7.2 (1.8–17.4)	14	25.1 (13.0–39.9)	589
P value			0.30		0.03		0.20	
Left ventricular end-diastolic cavity dimension								
<40 mm	106	11	14.4 (7.2–25.8)	6	7.9 (2.9–17.1)	27	35.4 (23.4–51.6)	761
40–50 mm	287	12	6.7 (3.5–11.7)	8	4.5 (1.9–8.8)	29	16.2 (10.9–23.3)	1790
>50 mm	87	0	0 (0–6.6)	1	1.8 (0–10.0)	9	16.1 (7.4–30.6)	558
P value			0.002		0.11		0.009	

*P values for the comparisons among the subgroups with respect to age, left atrial cavity dimension, and left ventricular end-diastolic cavity dimension were calculated by the chi-square test for trend. P values for the comparisons among the subgroups with respect to NYHA functional class, the presence or absence of a history of sudden death in the family, and the presence or absence of left ventricular outflow obstruction were calculated by Fisher's exact test. CI denotes confidence interval, and NYHA New York Heart Association.

TABLE 4. RESULTS OF MULTIVARIATE COX PROPORTIONAL-HAZARDS ANALYSIS OF THE RELATION BETWEEN BASE-LINE CLINICAL VARIABLES AND THE RISK OF DEATH, ADJUSTED FOR AGE.*

VARIABLE	No. OF SUBGROUPS	SUDDEN DEATH (N=23)		DEATH DUE TO HEART FAILURE (N=15)		DEATH FROM ANY CAUSE (N=65)	
		RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Left-ventricular-wall thickness	5	1.76 (1.19–2.60)	0.003	1.92 (1.04–3.55)	0.04	1.41 (1.09–1.81)	0.008
NYHA functional class	2	—	0.47	9.48 (2.61–34.42)	0.001	2.55 (1.26–5.18)	0.02
Left ventricular outflow obstruction	2	—	0.76	5.52 (1.55–19.65)	0.005	1.85 (1.08–3.19)	0.03
Left atrial cavity dimension	3	—	0.21	—	0.10	—	0.61
Left ventricular end-diastolic cavity dimension	3	0.48 (0.23–0.98)	0.04	—	0.22	0.70 (0.47–1.04)	0.07

*All models included age (<20, 20–39, 40–59, and ≥60 years) as a stratification factor. The subgroups for each variable are provided in Tables 2 and 3. For variables with more than two subgroups, subgroup-specific estimates of the coefficients could not be calculated, because of the small number of events, which precluded convergence of the coefficients. Relative risks were calculated from the Cox model. For variables with more than two subgroups, P values were calculated with the likelihood-ratio test, which must be interpreted as a test for linear trend of increasing (or decreasing) hazard across subgroups of the variable in question. Dashes denote variables that were removed from the final model. CI denotes confidence interval, and NYHA New York Heart Association.

thickness was found to be independently and directly related to the incidence of sudden death ($P=0.003$), and left ventricular end-diastolic cavity dimension was, as a consequence, inversely related to this end point ($P=0.04$). Wall thickness was also independently related to the incidence of death due to heart failure ($P=0.04$). The New York Heart Association functional class and the presence or absence of outflow obstruction at base line showed no relation to the incidence of sudden death ($P=0.47$ and $P=0.76$, respectively), but they were independently related to the incidence of death due to heart failure ($P=0.001$ and $P=0.005$, respectively).

To assess whether the associations between wall thickness and mortality were similar in the populations of patients at the Italian and U.S. institutions, a term to represent interaction between the institution and the wall-thickness subgroup was introduced into the multivariate models. The interaction term was not significantly different from zero with regard to sudden death ($P=0.54$), death due to heart failure ($P=0.14$), or death from any cause ($P=0.48$), indicating no difference between the two populations in the relation between wall thickness and mortality.

DISCUSSION

Our results show that the magnitude of left ventricular hypertrophy, as measured by echocardiography and expressed in terms of maximal wall thickness, is a strong and independent predictor of the risk of sudden death in patients with hypertrophic cardiomyopathy. Though relatively low overall, the rate of sudden death in our study population increased progressively and significantly in direct relation to left-ventricular-wall thickness, almost doubling from each wall-thickness subgroup to the next.

About 10 percent of our patients were at the high end of the morphologic spectrum of disease (maximal wall thickness, ≥ 30 mm). In these patients, the cumulative risk of sudden death was almost 20 percent 10 years after the initial evaluation and was almost 40 percent at 20 years. Most of these patients were young, had no outflow obstruction under basal conditions, and had few or no symptoms. The possibility that life expectancy in this subgroup is substantially reduced is supported by previous findings that patients with extreme hypertrophy who are older than 50 are rarely encountered.¹⁶⁻¹⁸

The rate of sudden death that we identified in patients with extreme left ventricular hypertrophy should be considered in the context of their youth, particularly in an era in which the implantable cardioverter-defibrillator is available and can provide effective protection from lethal ventricular tachyarrhythmias in patients with hypertrophic cardiomyopathy.¹⁵

Admittedly, we cannot predict the future clinical course of young patients with extreme phenotypic expressions of this condition after sudden death has

been prevented by a cardioverter-defibrillator. Other unfavorable patterns of disease could emerge later in life, such as progression to heart failure or development of atrial fibrillation.^{3-5,10} Nevertheless, since sudden death often occurs in the absence of clinically important symptoms and systolic dysfunction in hypertrophic cardiomyopathy, it is reasonable to expect that prevention of sudden death in patients with this disease will prolong life substantially. Therefore, we believe that young patients with extreme hypertrophy (including those with no other risk factors) should be informed about the option of the implantable cardioverter-defibrillator.

Treatment with amiodarone has been considered an effective method for the prevention of sudden death in patients with hypertrophic cardiomyopathy.^{3-5,25} This conclusion, however, is based principally on a single retrospective study that included historical control subjects who were treated with potentially proarrhythmic medications.²⁵ The finding that almost 20 percent of our patients who died suddenly were taking amiodarone at the time of death casts doubt on the efficacy of this drug in preventing sudden death in patients with hypertrophic cardiomyopathy. Furthermore, the toxic effects often associated with long-term amiodarone treatment limit its use in young patients.

Our findings also have implications for the identification of patients at low risk for sudden death. In patients with mild hypertrophy (maximal wall thickness, ≤ 19 mm), the rate of sudden death was close to zero 10 years after the initial evaluation and was less than 3 percent at 20 years. These findings are consistent with previous hypotheses suggesting that the majority of patients with mild hypertrophy and without strong predictors of risk should be reassured that they have a favorable prognosis.^{4,5,8,10} These recommendations have far-reaching implications, since patients with mild hypertrophy represent a large proportion of those with this disease⁸⁻¹⁰ and, indeed, constituted more than 40 percent of our study population.

Because virtually all the data in the literature on hypertrophic cardiomyopathy rely on measurements of left-ventricular-wall thickness uncorrected for body-surface area, we were concerned that results based on values that took body size into account would be inconsistent with all previous findings and would therefore be meaningless in the clinical arena. Consequently, we used absolute wall thickness, a reliable and easily obtained measurement with which there has been extensive experience in studies of hypertrophic cardiomyopathy. Inevitably, this method raises the problem of how to relate our findings with precision to the risk of death among children of various body sizes. Unfortunately, the number of children in our study population was insufficient to address this issue in detail. Nevertheless, our observations clearly indicate that children with extreme hypertrophy in

absolute terms (which would be even greater if wall thickness were corrected for body size) are at particularly high risk and require treatment to prevent sudden death. Children whose hypertrophy can be classified at the high end of the morphologic spectrum with respect to body size are likely to be at increased risk, but we currently recommend that treatment be based on an evaluation of their overall risk profile.

The clinical implications of a marked outflow gradient in patients with hypertrophic cardiomyopathy have been a subject of debate since the early 1960s.²⁶ However, for more than 40 years, the lack of systematic data from large populations of consecutively enrolled patients has precluded definitive conclusions on this issue. A recent study of a regional cohort of patients with hypertrophic cardiomyopathy identified a relation between the presence or absence of basal outflow obstruction and the risk of death from cardiovascular causes.¹⁰ Because of the small number of events in that investigation, however, sudden death and death related to heart failure could not be examined as separate end points. In the current study, we found a relation between the presence of outflow obstruction and the risk of death due to heart failure, but not the risk of sudden death. This finding substantiates the view that interventions designed to lower the gradient, such as septal myotomy–myectomy, pacing, or alcohol septal ablation,²⁷ cannot be expected to decrease the risk of sudden death. Also, the relation we identified between the presence of an outflow gradient and the risk of death related to heart failure should not be interpreted as a reason to abolish or reduce the gradient by invasive means in the absence of severe symptoms, since there is no evidence that such interventions improve survival.

A history of sudden death at a young age in affected family members has generally been regarded as an indicator of increased risk in patients with hypertrophic cardiomyopathy.³⁻⁵ In the current study, this variable was not related to the risk of sudden death. However, only a minority of our patients had a history of sudden death in two or more family members less than 50 years old. Therefore, our findings should not obscure previous data suggesting that affected persons from such families are at increased risk.^{4,5,28,29}

Despite our previous findings that two-dimensional echocardiographic measurements of left-ventricular-wall thickness in patients with hypertrophic cardiomyopathy are highly reliable,¹⁶⁻²¹ as also supported by the analysis of reproducibility in the current study, we wish to sound a note of caution regarding the capability of echocardiography to measure wall thickness within 1 to 2 mm.³⁰ This limitation may be more relevant to left ventricles with particularly marked hypertrophy. Therefore, we believe that for borderline measurements of extreme hypertrophy, clinical decisions regarding treatment to prevent sudden death should also be based on the evaluation of other poten-

tial risk factors, as well as on the physician's overall clinical judgment. For measurements of wall thickness that are clearly at the high end of the morphologic spectrum of hypertrophic cardiomyopathy, this phenotype alone identifies high risk and justifies intervention for the primary prevention of sudden death.¹⁵

Our results show that the magnitude of left ventricular hypertrophy is a strong and independent predictor of prognosis in patients with hypertrophic cardiomyopathy, a finding that has important implications for patient care. In the absence of other generally accepted risk factors, patients at the low end of the morphologic spectrum of this disease (maximal left-ventricular-wall thickness, ≤ 19 mm) are at low risk for sudden death. Conversely, young patients with extreme hypertrophy (maximal wall thickness, ≥ 30 mm), although they usually have few or no symptoms, appear to be at substantial long-term risk. Such patients, in consideration of their youth and the potential for a near-normal life expectancy if sudden death is prevented, should be informed about the lifesaving protection afforded by the implantable cardioverter–defibrillator.

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