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Progressive Left Ventricular Remodeling in Patients With Hypertrophic Cardiomyopathy and Severe Left Ventricular Hypertrophy

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OBJECTIVES The aim of this study was to determine the natural history of patients with hypertrophic cardiomyopathy (HCM) and severe left ventricular hypertrophy (LVH) (i.e., maximal left ventricular wall thickness [MLVWT] ≥30 mm) and whether changes in cardiac morphology influence the course of the disease.

BACKGROUND Severe LVH is common in young and rare among elderly patients with HCM. This has been explained by a high incidence of sudden death. We hypothesized that this age-related difference might be explained by left ventricular wall thinning.

METHODS A total of 106 (age 33 ± 15 years; 71 males) consecutive patients with severe LVH underwent history taking, examination, electrocardiography, echocardiography, cardiopulmonary exercise testing, and Holter analysis. Survival data were collected at subsequent clinic visits or by communication with patients and their general practioners. In order to assess morphologic and functional changes, 71 (67.0%) patients (mean age 31 ± 15 years; 47 males) followed at our institution underwent serial (≥1 year) assessment.

RESULTS Of the 106 patients, the majority (78 [71.6%]) were <40 years of age. During follow-up (92 ± 50 months [range 1 to 169]), 18 (17.0%) patients died or underwent heart transplantation (13 sudden cardiac deaths, 2 heart failure deaths, 1 heart transplantation, 1 stroke, 1 postoperative death). Five-year survival from sudden death was 90.1% (95% confidence interval [CI] 84.0% to 96.3%), and that from heart failure death or transplantation was 97.7% (95% CI 94.5 to 100). In patients serially evaluated over 85 ± 51 months, there was an overall reduction in MLVWT of 0.6 mm/year (95% CI 0.31 to 0.81, $p = 0.00004$). Wall thinning ≥5 mm was observed in 41 patients (57.7%; age 35 ± 13 years; 28 males). On multivariate analysis, the follow-up duration only predicted wall thinning (0.6 mm/year, 95% CI 0.38 to 0.85, $p < 0.00001$).

CONCLUSIONS Left ventricular remodeling is common in patients with severe LVH and contributes to the low prevalence of severe LVH seen in middle age and beyond. (J Am Coll Cardiol 2004; 44:398–405) © 2004 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac condition characterized by unexplained myocardial hypertrophy. Approximately 10% of patients have severe left ventricular hypertrophy (LVH), defined as maximal left ventricular wall thickness (MLVWT) of 30 mm or more (1,2). Recent studies have indicated that this level of

See page 406

hypertrophy is relatively common in young patients and rare among elderly patients (1–4). The suggested explanation for these age-related differences is that young patients with severe LVH do not survive into middle age and beyond because of the high incidence of sudden cardiac death (1). An alternative explanation is that patients with severe LVH undergo left ventricular (LV) wall thinning.

The aims of this study were to investigate the natural history of patients with severe LVH by using serial M-mode and two-dimensional echocardiography and to determine whether changes in cardiac morphology can explain the low prevalence of severe LVH in elderly patients.

METHODS

Patients. The study cohort consisted of 106 consecutive patients (mean age 33 ± 15 years; 71 males and 35 females) with HCM and severe LVH (≥30 mm on two-dimensional echocardiography), who were assessed prospectively at St. George's Hospital, London, United Kingdom, between 1988 and 2002. Patients with other cardiac or systemic

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Abbreviations and Acronyms

FS	= fractional shortening
HCM	= hypertrophic cardiomyopathy
ICD	= implantable cardioverter-defibrillator
LV	= left ventricular
LVEDD	= left ventricular end-diastolic diameter
LVESD	= left ventricular end-systolic diameter
LVH	= left ventricular hypertrophy
LVOTG	= left ventricular outflow tract gradient
MLVWT	= maximal left ventricular wall thickness
NSVT	= nonsustained ventricular tachycardia

diseases known to produce hypertrophy, such as hypertension, aortic valve disease, and metabolic or storage disorders (e.g., Anderson Fabry disease and glycogen storage disease) were excluded. Hypertrophic cardiomyopathy was diagnosed after successful resuscitation from an out-of-hospital cardiac arrest in 2 patients (1.9%), after presentation with symptoms in 58 (54.7%), and during familial assessment in 18 (17.0%). The diagnosis was an incidental finding in 28 patients (26.4%). The reasons for referral to St. George's Hospital were clinical management (44 [41.5%]), risk stratification (24 [22.6%]), family screening (12 [11.3%]), diagnostic clarification (3 [2.8%]), and genetic counseling or referral for a second opinion (23 [21.7%]).

Clinical evaluation. Patients were entered into the study at the time that severe LVH (MLVWT ≥30 mm) was first recorded by echocardiography. All patients underwent a history, examination, 12-lead electrocardiography, echocardiography, cardiopulmonary exercise testing with measurement of blood pressure response, and 48-h Holter analysis at the initial evaluation. Patients also underwent risk stratification; severe LVH was considered a risk marker for sudden cardiac death (1,2), along with nonsustained ventricular tachycardia (NSVT, defined as one or more runs of 3 or more consecutive ventricular extrasystoles at a rate of >120 beats/min, lasting for <30 s [4,5]), abnormal blood pressure response during upright exercise (failure of systolic blood pressure to rise by >25 mm Hg from baseline values, or a fall of >10 mm Hg from the maximal blood pressure during upright exercise in patients under the age of 40 years [4,6,7]), family history of sudden cardiac death (8,9), and unexplained syncope (9).

Echocardiography. Two-dimensional, M-mode, and Doppler echocardiography were performed using Acuson 128 XP/10 (Mountain View, California), GE Vingmed System V (GE Ultrasound Europe, Horten, Norway), or Hewlett-Packard Sonos 1000 (Hewlett-Packard, Andover, Massachusetts). The magnitude and distribution of LVH were assessed in the parasternal short-axis view and confirmed from the parasternal long-axis and apical views. The ventricle was divided into four regions: anterior septum, posterior septum, lateral wall, and posterior walls. Wall thickness was measured at the level of the mitral valve and papillary muscles in each of the four myocardial segments and at the apical level in the anterior and posterior segments. The MLVWT was defined as the greatest thickness in any segment. Patterns of hypertrophy were defined in accordance with previously published methods. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured from two-dimensional and M-mode images obtained from the parasternal long-axis views and percent fractional shortening (%FS), calculated using the formula: FS = ([LVEDD − LVESD]/LVEDD) × 100. Systolic impairment was defined as FS < 25%. The left ventricular outflow tract gradient (LVOTG) was calculated from continuous wave Doppler imaging, using the modified Bernoulli equation: $\Delta P = 4V^2$, where ΔP is the instantaneous pressure gradient (mm Hg) and V is the measured maximal flow velocity (m/s). An LVOTG ≥30 mm Hg was considered significant (10).

All images were stored on 5-inch videotape and reviewed independently by two experienced investigators. The mean of three measurements was taken for each segment or diameter. A third experienced echocardiographer was asked to adjudicate when there was a discrepancy of more than 10%. Differences between observers occurred in <5% of cases and were <2 mm; a consensus value was reached in all cases.

Survival analysis. Data on survival and clinical status were collected at subsequent clinic visits in those patients followed up at our institution and by direct communication with patients and their general practitioners when followed elsewhere.

End points for survival analysis were: 1) sudden cardiac death: witnessed sudden death with or without documented ventricular fibrillation, death within 1 h of new symptoms, or nocturnal death with no antecedent history of worsening symptoms; 2) progressive heart failure death: death preceded by signs and symptoms of heart failure or cardiogenic shock; 3) other cardiovascular death: deaths due to stroke, pulmonary or systemic embolism, and myocardial infarction; 4) noncardiovascular death: deaths caused by known noncardiovascular events; and 5) orthotopic heart transplantation.

Serial evaluation. To assess morphologic and functional changes, patients followed at our institution underwent serial (at least 2, 1 or more years apart) echocardiographic and clinical assessment. Patients who underwent myectomy (n = 1) or alcohol septal ablation (n = 1) or who had not completed 12 months of follow-up (n = 17) were excluded from this part of the study. Patients with typical angina or risk factors for coronary artery disease underwent coronary arteriography, and one patient with coronary artery disease was also excluded. The results of serial evaluation in the remaining 71 patients (67.0%; mean age 31 ± 15 years; 47 males and 24 females) are reported.

Statistical analysis. Statistical analysis was performed using SPSS statistical software (version 10.0; SPSS Inc., Chicago, Illinois). All data are expressed as the mean value ± SD or

JACC Vol. 44, No. 2, 2004
July 21, 2004:398–405

frequency (percentage). Differences between mean values were determined using the unpaired or paired Student *t* test, where appropriate. The chi-square test was used for comparisons between dichotomous variables. Survival estimates were calculated by the Kaplan-Meier method, and their relation to changes in left ventricular wall thickness was tested by log-rank. Five-year survival values are expressed together with their 95% confidence interval (CI), defined as survival ± 1.96 × SE. Cox regression analysis was used to investigate the relationship between significant variables, survival, and changes in MLVWT.

Patients who underwent serial evaluation were classified into three groups based on changes in MLVWT: ≥5 mm reduction (group 1); 2 to 4 mm reduction (group 2); and no change (<2 mm reduction or increase) in MLVWT (group 3). For statistical purposes, comparisons were made between patients from group 1 and patients with lesser degrees or no wall thinning (i.e., groups 2 and 3). Two patients who had an increase in MLVWT ≥2 mm were included in group 3 for statistical analysis. The relationship between a change in MLVWT (as a continuous variable) and other clinical variables was also investigated by using linear regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

Initial evaluation. The results of the initial clinical assessment in the 106 patients with severe LVH are shown in Table 1. The majority (n = 78 [71.6%]) of patients studied were less than 40 years of age (Fig. 1). The mean MLVWT was 32 ± 3 mm (range 30 to 45); 87 patients (90.6%) had asymmetric septal hypertrophy, 8 (8.3%) had concentric hypertrophy, and 1 (1.0%) had apical hypertrophy. No patient had FS <25%. Thirty-four patients (32.1%) had a significant resting LVOTG, and 60 patients (57.0 %) had left atrial enlargement (>40 mm). Five patients (4.7%) were in atrial fibrillation, 3 (2.8%) had a DDDR pacemaker (for treatment of outflow tract obstruction), and 2 (1.9%) had an implantable cardioverter-defibrillator (ICD; 1 for primary and 1 for secondary prevention). The presence or absence of symptoms and other clinical variables at the initial evaluation are shown in Table 1.

Survival. Follow-up was complete in 103 patients (97.2%), and the mean follow-up time was 92 ± 50 months (range 1 to 169). During this time, 14 patients underwent ICD implantation (11 for primary and 3 for secondary prevention) and 10 patients (9.4%) required a pacemaker (4 for treatment of symptomatic outflow tract obstruction, 4 for conduction disease, 1 for chronotropic incompetence, and 1 for treatment optimization). Eighteen patients (17.0%) died or underwent orthotopic heart transplantation (13 sudden cardiac deaths, 2 heart failure–related deaths, 1 heart transplantation, 1 stroke-related death, 1 postoperative death). None of the 14 patients with ICDs experienced a device discharge. The five-year cumulative survival rate from sudden cardiac death was 90.1% (95% CI 84.0 to 96.3); the five-year cumulative survival rate from heart failure death or transplantation was 97.7% (95% CI 94.5 to 100); and the five-year cumulative survival rate from all-cause mortality and transplantation was 86.8% (95% CI 79.8 to 93.8) (Fig. 2). The majority of patients (8 [66.6%]) who died were younger than the age of 30 years. There was a significant association between survival from sudden death and the number of risk markers present. Twelve (85.7%) of the 13 patients who died suddenly had one or more additional recognized risk markers; the five-year survival rate from sudden death in patients with one or more additional risk markers was 87.4% (95% CI 79.2 to 95.7), as compared with 96.5% (95% CI 89.7 to 100; p = 0.07 by log-rank) in patients with severe LVH and no other recognized risk markers (Fig. 3).

Table 1. Baseline Characteristics of Study (n = 106) Patients

Male/female	71/35
Age (yrs)	33 ± 15
Age at diagnosis (yrs)	28 ± 16
Clinical follow-up (months)	92 ± 50
VF	2 (1.9%)
AF	5 (4.7%)
Exertional chest pain	32 (30.5%)
NYHA dyspnea class	
I	66 (62.3%)
II	37 (34.9%)
III/IV	4 (3.8%)
FHSCD	31 (29.2%)
FHHCM	43 (57.3%)
Syncope	23 (21.9%)
ABPR	38 (40.9%)
NSVT	17 (17.2%)
Pattern	
ASH	87 (90.6%)
Concentric	8 (8.3%)
Apical	1 (1.0%)
MLVWT (mm)	32.1 ± 3.0
LVEDD (mm)	38.5 ± 5.7
LVESD (mm)	20.3 ± 4.9
FS (%)	47.1 ± 10.2
LAD (mm)	42.2 ± 8.1
LVOTG	34 (32.1%)
MR	
Moderate	3 (2.8%)
Severe	0
Vo_2 max (%)	63.8 ± 16.8
Medication taken during follow-up	
Beta-blocker	51 (48.1%)
Calcium antagonist	37 (34.9%)
ACE inhibitor	8 (7.5%)

Data are presented as the mean value ± SD or number (%) of patients.

ABPR = abnormal blood pressure response during upright exercise; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ASH = asymmetric septal hypertrophy; FHHCM = family history of hypertrophic cardiomyopathy; FHSCD = family history of sudden cardiac death; FS = fractional shortening; LAD = left atrial diameter; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVOTG = left ventricular outflow tract gradient (≥30 mm Hg); MLVWT = maximal left ventricular wall thickness; MR = mitral regurgitation; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; VF = ventricular fibrillation; %Vo_2 max = %predicted maximal oxygen consumption during upright exercise.

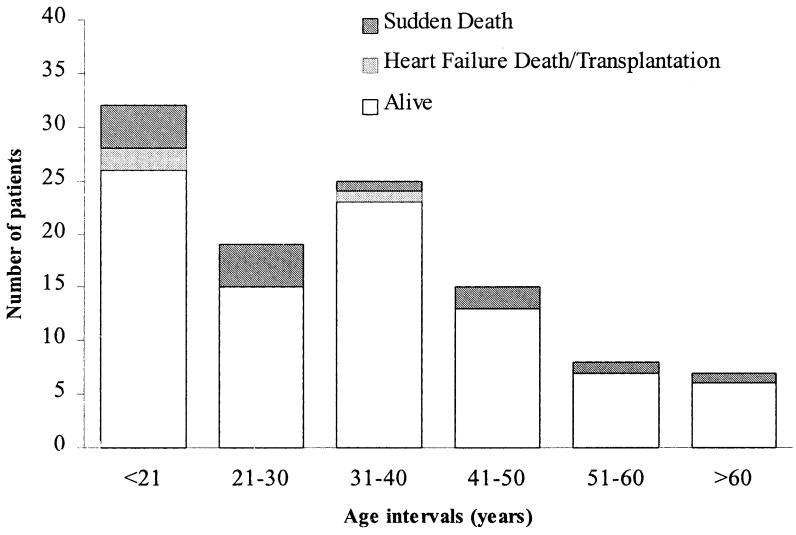
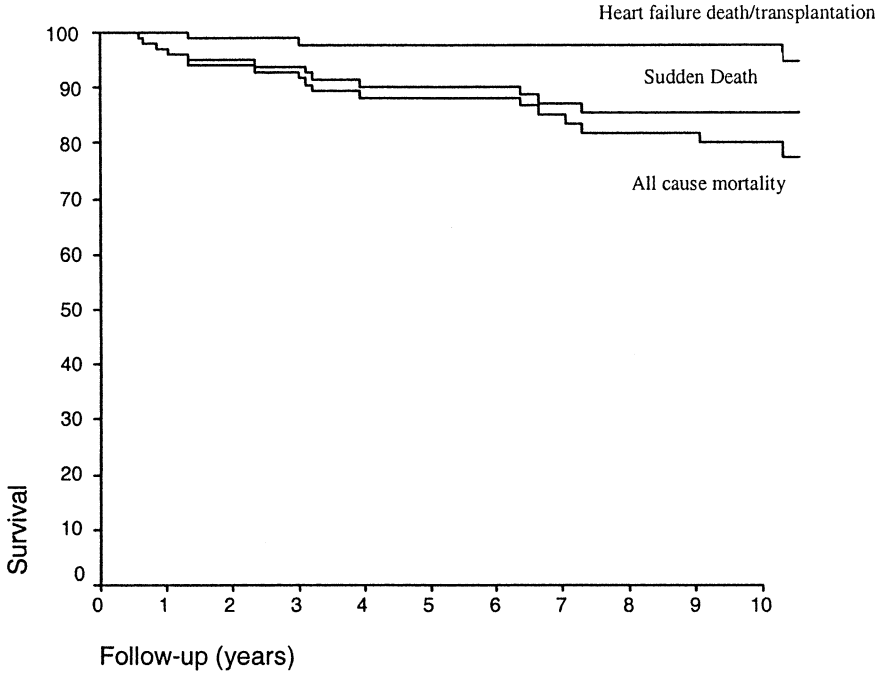


Figure 1. Age distribution of the 106 patients studied and sudden death (**darker shading in bars** represents sudden deaths).

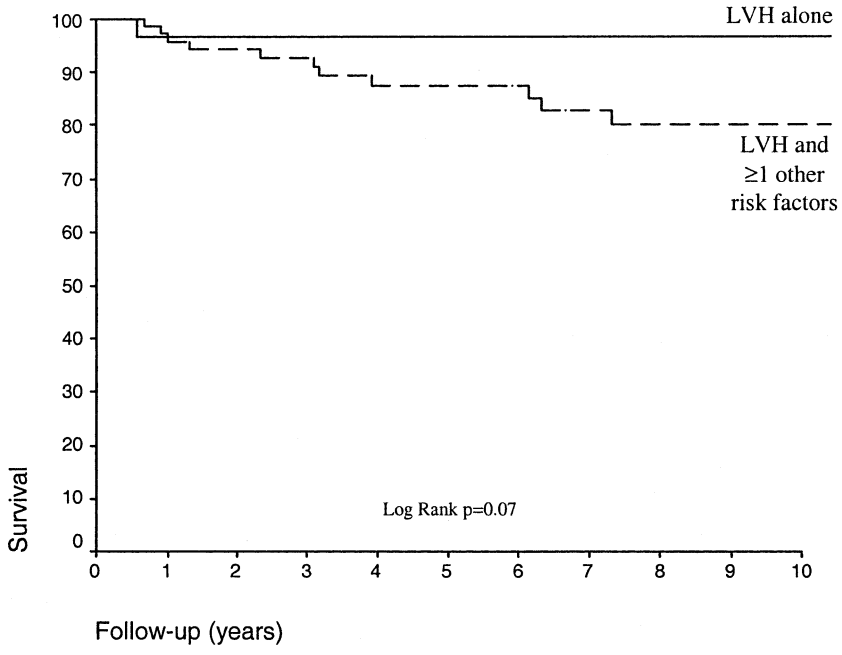
Results of serial evaluation. The mean follow-up time in the 71 patients who underwent serial clinical and echocardiographic evaluation was 85 ± 51 months (range 12 to 186). In these patients, there was a decrease in MLVWT from 32 ± 3 to 27 ± 5 mm, corresponding to a reduction in MLVWT of 0.6 mm/year (95% CI 0.31 to 0.81, p = 0.00004). At final follow-up, only 23 patients (32%) had MLVWT ≥30 mm. Changes in maximal wall thickness in the different myocardial segments are shown in Table 2.

Wall thinning of 5 mm or more was observed in 41 patients (57.7%; age 35 ± 13 years; 28 males and 13 females), of whom 35 (85.4%) had asymmetric septal hypertrophy, 5 (12.2%) had concentric hypertrophy, and 1 (2.4%) had apical hypertrophy. Wall thinning occurred



Number of patients at risk			
0 year	3 years	6 years	9 years
103	79	58	40

Figure 2. Kaplan-Meier survival estimates free from sudden cardiac death, heart failure/transplantation, and all-cause mortality in the study population.



Number of patients at risk				
0 year	3 years	6 years	9 years	
30	25	19	13	LVH alone
73	54	39	27	LVH and ≥1 other risk factors

Figure 3. Kaplan-Meier survival estimates free from sudden cardiac death for patients with one or more risk factors. LVH = left ventricular hypertrophy.

predominantly in the anterior septum at the level of the mitral valve and papillary muscle and was accompanied by an increase in LV cavity size (from 38.4 ± 5.0 to 44.6 ± 6.8 mm for LVEDD [$p < 0.00001$] and from 20.7 ± 5.0 to 26.7 ± 7.9 mm for LVESD [$p < 0.00001$]), left atrial size (from 43.0 ± 8.1 to 47.7 ± 7.9 mm, $p < 0.00001$), and reduction in FS (from 46.2 ± 11.1% to 40.8 ± 11.2%, $p = 0.01$). Three patients (7.3%) progressed to systolic impairment (FS ≤25%), and there was a reduction in the number of patients with significant LVOTG (from 10 [24.4%] to 7 [17.9%], $p = 0.05$).

Table 2. Changes in Echocardiographic Measurements During Follow-Up

		95% CI		
	Mean ± SD	Lower	Upper	p Value*
LVEDD (mm)	5.5 ± 6.6	7.1	4.0	<0.00001
LVESD (mm)	5.0 ± 6.8	6.6	3.4	<0.00001
FS (%)	−3.9 ± 11.9	−1.1	−6.7	0.008
LAD (mm)	4.3 ± 6.5	5.8	2.7	<0.00001
MLVWT (mm)	−5.2 ± 4.4	−4.1	−6.2	<0.00001
Mitral valve				
Anterior septum	−3.8 ± 4.5	−2.7	−4.8	<0.00001
Posterior septum	−2.6 ± 4.6	−1.5	−3.7	0.00002
Posterior wall	−0.5 ± 2.8	0.2	−1.2	0.1
Lateral wall	−1.2 ± 2.8	−0.5	−2.0	0.002
Papillary muscle				
Anterior septum	−4.4 ± 4.5	−3.3	−5.5	<0.00001
Posterior septum	−2.9 ± 4.3	−1.8	−4.0	<0.00001
Posterior wall	−0.2 ± 2.7	0.5	−0.8	0.6
Lateral wall	−1.1 ± 3.2	−0.3	−2.0	0.01
Apex				
Anterior wall	−1.5 ± 3.8	−0.5	−2.6	0.005
Posterior wall	−0.4 ± 2.1	0.2	−1.0	0.2

*Two-tailed.
CI = confidence interval; other abbreviations as in Table 1.

A reduction in MLVWT of 2 to 4 mm was observed in 15 patients (21.1%; age 30 ± 16 years; 10 males and 5 females), of whom 14 (93.3%) had asymmetric septal hypertrophy and 1 (6.7%) had concentric hypertrophy. Wall thinning also occurred predominantly in the anterior septum at the level of the mitral valve and papillary muscles. Left ventricular cavity size increased (from 37.8 ± 5.8 to 43.7 ± 3.6 mm [$p < 0.00001$] for LVEDD and from 19.2 ± 4.3 to 23.1 ± 5.9 mm [$p = 0.02$] for LVESD), and left atrial size increased (from 40.8 ± 8.3 to 46.2 ± 9.0 mm, $p = 0.0008$). No significant change in %FS or the number of patients with significant LVOTG was observed.

A minimal or no change in wall thickness (<2 mm reduction or increase) was observed in 13 patients (18.3%; age 23 ± 16 years; 8 males and 5 females). In these patients, small but significant changes in cavity size (from 39.3 ± 7.7 to 41.8 ± 9.7 mm [$p = 0.4$] for LVEDD and from 20.5 ± 4.8 to 23.1 ± 8.2 mm [$p = 0.1$] for LVESD), left atrial size (from 38.8 ± 9.4 to 40.9 ± 9.4 mm, $p = 0.3$), and %FS (from 46.5 ± 12.2% to 45.5 ± 9.2%, $p = 0.6$) were

Table 3. Differences in Baseline Clinical Characteristics in Relation to Changes in Wall Thickness

	Reduction			
	≥5 mm	2–4 mm	Change* <2 mm	p Value†
Number (%) of patients	41 (57.7%)	15 (21.1%)	15 (21.1%)	
Age (yrs)	35 ± 13	30 ± 16	22 ± 12	0.02
Age (yrs) at diagnosis	29 ± 16	24 ± 14	16 ± 13	0.01
Gender (male/female)	28/13	10/5	9/6	0.7
Echocardiographic follow-up (months)	90 ± 41	61 ± 50	39 ± 31	<0.0001
FHSCD	13 (31.7%)	4 (26.7%)	1 (6.7%)	0.2
FHHCM	27 (65.9%)	8 (53.3%)	2 (13.3%)	0.003
NYHA class				
I	24 (58.5%)	7 (46.7%)	11 (73.3%)	1
II	15 (36.6%)	8 (53.3%)	3 (20.0%)	1
III/IV	2 (4.9%)	0	1 (6.7%)	—
Exertional chest pain	14 (34.1%)	6 (40.0%)	2 (13.3%)	0.5
Syncope	9 (22.0%)	4 (26.7%)	1 (6.7%)	0.5
ABPR	18 (43.9%)	4 (26.7%)	7 (46.7%)	0.7
Vo_2 max (%)	66.0 ± 17.6	62.9 ± 15.0	63.5 ± 17.2	0.5
NSVT	11 (26.8%)	1 (6.7%)	1 (6.7%)	0.04
LVEDD (mm)	38.4 ± 5.0	37.8 ± 5.8	38.1 ± 7.8	0.7
LVESD (mm)	20.7 ± 5.0	19.2 ± 4.3	19.7 ± 5.1	0.3
FS (%)	46.2 ± 11.1	49.1 ± 8.7	47.5 ± 11.8	0.4
MLVWT (mm)	32.7 ± 3.1	31.9 ± 2.6	32.4 ± 4.1	0.5
LAD (mm)	43.0 ± 8.1	40.8 ± 8.3	38.7 ± 9.1	0.1
Pattern				
ASH	35 (85.4%)	14 (93.3%)	15 (100%)	0.2
Concentric	5 (12.2%)	1 (6.7%)	0	0.4
Apical	1 (2.4%)	0	0	—
LVOTG (mm Hg)				
MR	10 (24.4%)	2 (13.3%)	7 (46.7%)	0.9
Moderate	0	1 (6.7%)	0	—
Severe	0	0	0	—
Medication taken during follow-up				
Beta-blocker	17 (41.5%)	8 (53.3%)	11 (73.3%)	0.07
Calcium antagonist	17 (41.5%)	7 (46.7%)	4 (26.7%)	0.7
ACE inhibitor	7 (17.1%)	0	0	0.02

*Two patients who had increased MLVWT 4 and 5 mm are included in this group. †Relates to comparison between patients with significant wall thinning and patients with mild or no change in wall thickness. Data are presented as the number (%) of patients or mean value ± SD.

Abbreviations as in Table 1.

observed. An increase in MLVWT of >2 mm was observed in two individuals (2.8%): MLVWT increased by 4 mm in one and by 5 mm in the other. These patients were 17 and 8 years old, respectively, at the initial evaluation, and the changes were not accompanied by any significant change in cavity size, left atrial size, or LVOTG.

Clinical characteristics and survival in patients serially evaluated. Age, gender, and other clinical features at the initial evaluation in the three groups of patients are shown in Table 3. Patients with wall thinning of ≥5 mm were older (35 vs. 26 years old, p = 0.02) and had a higher prevalence of NSVT (11 [26.8%] vs. 2 [6.7%], p = 0.04) at the initial evaluation, as compared with patients with lesser amounts of wall thinning. There were no other differences in baseline symptoms, clinical features, exercise capacity (percent maximal oxygen consumption), or medications taken. Compared with the initial evaluation, no significant changes in symptoms, New York Heart Association functional class, or exercise variables were observed during follow-up in the three groups. However, seven patients (17.1%) who underwent wall thinning of ≥5 mm were commenced on angiotensin-converting enzyme inhibitors for symptoms of congestive cardiac failure or systolic dysfunction, as compared with no patients with lesser amounts of wall thinning. There were no other significant differences in medications taken during follow-up.

There were no significant differences in survival between patients with ≥5 mm or lesser amounts of wall thinning: five patients (12.2%) with wall thinning ≥5 mm died (three sudden cardiac deaths, two heart failure deaths), compared with five patients (16.7%; four sudden cardiac deaths, one procedure-related death) with lesser or no wall thinning. The five-year cumulative survival rate from all-cause mortality was 83.8% (95% CI 69.2 to 98.5) for patients with ≥5 mm wall thinning, compared with 97.4% (95% CI 92.5 to 100) for patients without significant wall thinning (p = 0.2).

Predictors of wall thinning. Patients who developed significant wall thinning were older (35 ± 13 vs. 26 ± 16 years, p = 0.02), had a longer follow-up duration (90 ± 41 vs. 50

JACC Vol. 44, No. 2, 2004
July 21, 2004:398–405

± 43 months, p = 0.0002), and were more likely to have a family history of HCM (27 [65.9%] vs. 10 patients [33.3%], p = 0.007) than patients with mild or no change in wall thickness. Using multivariate analysis, only the follow-up duration predicted the development of wall thinning (0.6 mm reduction in MLVWT per year [95% CI 0.38 to 0.85], p < 0.00001).

DISCUSSION

This study shows that wall thinning significantly contributes to the lower incidence of severe LVH in middle and older age. Previous studies have reported wall thinning in up to 15% of patients with HCM (11). In this study, wall thinning of ≥5 mm occurred in nearly 60% of patients with severe LVH, and only 32% of patients had severe LVH at the final evaluation. Wall thinning occurred predominantly at the anterior interventricular septum at the mitral valve and papilliary muscle levels (i.e., areas of maximal hypertrophy in the majority of patients studied) and was accompanied by an increase in LV cavity size and a reduction in LVOTG and FS. Three patients (4.2%) progressed to "end-stage" disease with cavity dilation and severe systolic impairment.

Mechanisms responsible for LV wall thinning. The mechanisms responsible for remodeling in HCM are unknown. In dilated and ischemic cardiomyopathy, myocardial load or injury results in changes at the cellular, molecular, and interstitial levels. These changes include myocardial ischemia, necrosis, apoptosis, increased collagen synthesis, and fibroblast proliferation and eventually result in alterations in the size, shape, and function of the heart (12,12–25). It is likely that similar processes occur in HCM, modified by hemodynamic load, neurohormonal activation, oxidative stress, cytokines, and myocardial ischemia, all of which may play a greater role in patients with severe LVH (26–28).

Predictors of wall thinning. On univariate analysis, significant wall thinning was related to age and follow-up duration. Wall thinning was more common in patients older than the age of 40 years, and there was a linear correlation between the amount of wall thinning and follow-up duration. After correcting for age, only follow-up duration was significantly related to wall thinning, suggesting that the remodeling process is a time-related phenomenon.

Clinical implications of severe LVH and remodeling. In this study, survival was related to the number of risk markers present, rather than to progressive thinning. Patients with significant wall thinning did, however, have a higher prevalence of NSVT at baseline, compared with patients with lesser amounts or no wall thinning, possibly reflecting a greater disruption of myocardial structure or fibrosis in these patients. Although patients with wall thinning were no more likely to have a sudden cardiac death, they had a greater tendency toward other adverse outcomes, including progression to severe systolic impairment and heart failure-related death.

Study limitations. The main limitation to this study was that we were unable to study patients independently of medication; however, this is one of the inherent difficulties when performing studies of this nature. In patients receiving treatment, the effect of medication was also difficult to assess, as patients often require more than one medication and for variable periods of time. Although some earlier studies have shown a possible effect of calcium antagonists on LV remodeling (29), this has not been confirmed in more recent larger studies (2,30,31). In this study, no effect of medication on wall thinning was identified. Randomized trials in larger populations, to evaluate the possible effects of medication on cardiac remodeling in HCM, will be welcomed. Medication may have led us to underestimate certain echocardiographic variables such as LVOTG, although a significant effect on wall thickness measurements is unlikely. The natural history of patients studied may also have been altered by other interventions such as myectomy or septal alcohol ablation, and we therefore excluded these patients from serial evaluation. Patients with pacemakers and ICDs, however, were not excluded. The effect of intervention on survival of the original study cohort could not be established because of a small number of terminal events. Finally, the process of wall thinning may relate to the underlying mutation; however, we are unable to present this data, as genetic testing was not routinely performed in the study cohort.

Conclusions. Left ventricular remodeling is common in patients with severe LVH and may account for the low prevalence of severe LVH in middle age and beyond. Remodeling was not associated with an increased sudden death risk, but may be associated with increased risk from other disease-related complications.

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