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Assessment and Significance of Left Ventricular Mass by Cardiovascular Magnetic Resonance in Hypertrophic Cardiomyopathy

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Objectives Our aim was to assess the distribution and clinical significance of left ventricular (LV) mass in patients with hypertrophic cardiomyopathy (HCM).

Background Hypertrophic cardiomyopathy is defined echocardiographically by unexplained left ventricular wall thickening. Left ventricular mass, quantifiable by modern cardiovascular magnetic resonance techniques, has not been systematically assessed in this disease.

Methods In 264 HCM patients (age 43 ± 18 years; 75% men), LV mass by cardiovascular magnetic resonance was measured, indexed by body surface area, and compared with that in 606 healthy control subjects.

Results The LV mass index in HCM patients significantly exceeded that of control subjects (104 ± 40 g/m^2 vs. 61 ± 10 g/m^2 in men and 89 ± 33 g/m^2 vs. 47 ± 7 g/m^2 in women; both $p < 0.0001$). However, values were within the normal range (≤ mean +2 SDs for control subjects) in 56 patients (21%), and only mildly increased (mean +2 to 3 SDs) in 18 (16%). The LV mass index showed a modest relationship to maximal LV thickness ($r^2 = 0.38$; $p < 0.001$), and was greater in men (104 ± 40 g/m^2 vs. 89 ± 33 g/m^2 in women; $p < 0.001$) and in patients with resting outflow obstruction (121 ± 43 g/m^2 vs. 96 ± 37 g/m^2 in nonobstructives; $p < 0.001$). During a 2.6 ± 0.7-year follow-up, markedly increased LV mass index proved more sensitive in predicting outcome (100%, with 39% specificity), whereas maximal wall thickness >30 mm was more specific (90%, with 41% sensitivity).

Conclusions In distinction to prior perceptions, LV mass index was normal in about 20% of patients with definite HCM phenotype. Therefore, increased LV mass is not a requirement for establishing the clinical diagnosis of HCM. The LV mass correlated weakly with maximal wall thickness, and proved more sensitive in predicting outcome. (J Am Coll Cardiol 2008;52:559–66) © 2008 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, characterized by marked clinical and morphologic heterogeneity (1–3). Diagnosis is usually based on the echocardiographic finding of unexplained left ventricular (LV) hypertrophy, defined by increased wall thickness in 1 or more LV segments (2,4). LV mass is generally assumed to be increased in patients with phenotypically expressed HCM, based largely on early pathological studies (5,6). However, in vivo assessment of LV mass by echocardiography has been judged unreliable in HCM, due to the asymmetric distribution of hypertrophy and heterogeneous chamber morphology (4). Therefore, the distribution and clinical correlates of LV mass have not been previously assessed in this disease.

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Cardiovascular magnetic resonance (CMR), by virtue of its high-resolution volumetric reconstruction of the LV chamber, currently affords a highly accurate and reproducible quantitative assessment of mass (7,8). In the present cross-sectional

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Abbreviations and Acronyms

BSA = body surface area
CMR = cardiovascular magnetic resonance
HCM = hypertrophic cardiomyopathy
LV = left ventricle/ventricular
OR = odds ratio

study, we sought to examine whether CMR contributes to our understanding of the morphology and clinical correlates of the HCM phenotype, with respect to echocardiographic measures, in a large multicenter cohort.

Methods

Study population. HCM PATIENTS. The study population comprised 264 patients with HCM (age 43 ± 18 years; 75% men, body surface area [BSA] 2.0 ± 0.3 m^2 for men and 1.7 ± 0.2 m^2 for women) consecutively referred for CMR at 4 participating institutions: Minneapolis Heart Institute Foundation, Minneapolis, Minnesota (n = 95); Azienda Ospedaliera Careggi, Florence, Italy (n = 80); Tufts-New England Medical Center, Boston, Massachusetts (n = 49); and Ospedale S. Andrea, Rome, Italy (n = 40) (Table 1). All HCM patients were probands, had an expressed phenotype permitting an unequivocal clinical diagnosis (2), and were referred specifically for disease evaluation; family members identified solely by virtue of pedigree studies were not included.

Diagnosis of HCM was based on 2-dimensional echocardiographic evidence of a hypertrophied, nondilated LV (maximal wall thickness ≥15 mm, or the equivalent relative to BSA in children), in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident (1,2). CMR examinations were performed in all patients within 2 weeks of echocardiography. The study protocol was approved by the respective internal review board or research ethics committees of each institution, and written inform consent was obtained from each subject.

CONTROL SUBJECTS. A total of 606 healthy adult participants in the Framingham Heart study (239 men; 367 women) without systemic hypertension or evidence of cardiovascular disease were studied by CMR, using a scanning protocol similar to that reported here for patients with HCM (8). Mean age was 61 ± 8 years for both men and women. BSA was 2.0 ± 0.2 m^2 for men and 1.7 ± 0.2 m^2 for women.

Echocardiography. Echocardiographic studies were performed with commercially available instruments. LV hypertrophy was assessed with 2-dimensional echocardiography, and the site and extent of maximal wall thickness were identified (4). Maximal end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the LV chamber (4). Peak instantaneous LV outflow gradient was estimated with continuous wave Doppler under basal conditions (9). LV outflow obstruction, due to mitral valve systolic anterior motion and mitral-septal contact, was identified by a peak instantaneous outflow gradient ≥30 mm Hg (9).

CMR. All CMR examinations were performed using commercially available scanners (Philips ACS-NT 1.5 T Gyroscan-Intera, Best, the Netherlands or Siemens Sonata 1.5 T, Erlangen, Germany) and a commercial cardiac coil. Electrocardiographic-gated, steady-state, free precession breath-hold cines in sequential 10-mm short-axis slices (no gap) were acquired starting parallel to the atrioventricular ring and covering the entire ventricle. LV end-diastolic and end-systolic volumes, LV mass, and wall thickness were calculated with commercially available work-stations (Easy Vision 5.0, and View Forum, Philips Medical System, Best, the Netherlands; or Argus, Siemens, Erlangen, Germany). Post-processing and analysis of LV volumes and mass were performed according to criteria previously agreed upon by investigators from each center.

For the calculation of LV mass, the endocardial and epicardial borders of the LV myocardium were manually planimetered on successive short-axis cine images at end-diastole. The most basal slice at end-diastole was visually inspected, and, if ventricular myocardium was present, it was planimetered and included in the mass calculation. If myocardium but no intracavitary blood pool was present on the most apical slice, it was included in the mass calculation by planimetering only the epicardial border. Particular care was taken to avoid including papillary muscles in the LV mass calculation. The LV mass was derived by the summation of discs method and multiplying myocardial muscle volume by 1.05 g/cm^3 (10,11). The LV mass was indexed to BSA. Maximum end-diastolic LV wall thickness was taken as the dimension of greatest magnitude at any site within the LV wall. The CMR measurements were performed by an experienced investigator at each center, blinded to the results of echocardiography.

Finally, the presence of delayed enhancement was assessed by visual inspection 15 min after intravenous administration of 0.2 mmol/kg gadolinium-diethylenetriamine penta-acetic acid (Magnevist, Schering, Berlin, Germany) with a breath-held segmented inversion-recovery sequence (inversion time 240 to 300 ms), which was acquired in the same views as the cine images (7).

Statistical methods. Data were expressed as mean ± SD. For the comparison of 2 and more than 2 normally distributed variables, we employed the Student *t* test and 1-way analysis of variance (ANOVA) followed by Bonferroni's post-hoc test, respectively. The chi-square test was utilized to compare noncontinuous variables expressed as proportions; however, the Fisher exact test was employed when 1 or more cells in the comparison table had an expected frequency of <5. Intraobserver and interobserver variability for CMR measurement of LV mass index were assessed in 100 randomly selected patients, using Pearson's correlation method.

Independent predictors of normal LV mass index were assessed by stepwise (forward conditional) multivariate logistic regression analysis. The relationship between echocardiographic and CMR-derived LV wall thickness values was assessed by linear regression analysis. The relationship between LV wall thickness and mass values was assessed by

Table 1 Clinical Features in 264 Patients With HCM and CMR

		LV Mass Index (g/m²)*			
	Overall	Normal* (Males <81 g/m²; Females <62 g/m²)	Mildly Increased (Males 81–91 g/m²; Females 62–69 g/m²)	Markedly Increased (Males >91 g/m²; Females >69 g/m²)	p Value
No. of patients	264	56 (21%)	41 (16%)	167 (63%)	
Male	197 (75%)	49 (87%)†	31 (74%)	117 (70%)	0.04
Age at study entry (yrs)	43 ± 18 (8–86)	41 ± 19	45 ± 19	43 ± 18	0.57
Age at diagnosis (yrs)	38 ± 18	37 ± 18	40 ± 18	38 ± 19	0.74
Body surface area (m²)	1.9 ± 0.3	1.9 ± 0.3	2.0 ± 0.2	1.9 ± 0.3	0.43
Family history of HCM-related sudden death	39 (15%)	11 (20%)	6 (14%)	22 (13%)	0.49
NYHA functional class	1.5 ± 0.7	1.4 ± 0.6	1.5 ± 0.6	1.5 ± 0.7	0.36
I	159 (60%)	37 (66%)	22 (52%)	100 (60%)	
II	83 (31%)	17 (30%)	17 (41%)	49 (30%)	
III/IV	22 (9%)	2 (4%)	3 (7%)	17 (10%)	
Angina	67 (25%)	14 (25%)	9 (21%)	44 (27%)	0.79
End-stage (ejection fraction <50%)	8 (3%)	1 (2%)	0	7 (4%)	0.16
Medical treatment	176 (67%)	33 (59%)	32 (76%)	111 (68%)	0.19
Beta-blockers	144 (54%)	29 (52%)	23 (55%)	92 (56%)	0.87
Verapamil	41 (15%)	6 (11%)	7 (17%)	28 (17%)	0.53
Amiodarone	14 (5%)	2 (4%)	5 (12%)	7 (4%)	0.11
Disopyramide	8 (3%)	2 (4%)	1 (2%)	5 (3%)	0.94
Diabetes mellitus	10 (4%)	0 (0%)	2 (5%)	8 (5%)	0.58
Systemic hypertension	54 (20%)	9 (16%)	11 (27%)	34 (20%)	0.57
Echocardiography					
Left atrium (mm)	43 ± 8	41 ± 8§	45 ± 8	44 ± 8	0.03
Maximal LV wall thickness (mm)	21 ± 6	18 ± 4	19 ± 4	23 ± 6	<0.001
Maximal LV thickness ≥30 mm	29 (11%)	3 (5%)	1 (2%)	25 (15%)	0.02
LV end-diastolic dimension (mm)	45 ± 6	46 ± 5	44 ± 5	45 ± 7	0.49
LV end-systolic dimension (mm)	26 ± 6	27 ± 6	26 ± 6	26 ± 7	0.69
LV outflow obstruction at rest (≥30 mm Hg)	47 (18%)	1 (2%)†‡	9 (21%)	37 (22%)	0.002
LV end-diastolic volume (ml)	105 ± 35	112 ± 29	101 ± 33	96 ± 37	0.18
LV end-systolic volume (ml)	37 ± 11	40 ± 14	36 ± 12	34 ± 11	0.62
Ejection fraction (%)	65 ± 8	64 ± 8	64 ± 7	65 ± 9	0.52
Moderate-to-severe mitral regurgitation	11 (4%)	2 (4%)	1 (2%)	8 (5%)	0.25
CMR					
Maximal LV wall thickness	21 ± 6	18 ± 5‡	21 ± 5	23 ± 6	<0.001
Maximal LV thickness ≥30 mm	26 (10%)	2 (4%)	2 (5%)	22 (13%)	0.036
LV mass (g)	193 ± 84	133 ± 30	159 ± 34	222 ± 91	N/A
LV mass index (g/m²)	101 ± 39	68 ± 11	81 ± 10	118 ± 40	N/A
LV end-diastolic volume (ml)	135 ± 44	127 ± 40	131 ± 45	138 ± 46	0.21
LV end-diastolic volume index (ml/m²)	70 ± 18	65 ± 16	66 ± 16	73 ± 19†	0.005
LV end-systolic volume (ml)	40 ± 21	38 ± 18	36 ± 17	41 ± 23	0.25
LV end-systolic volume index (ml/m)	21 ± 10	20 ± 9	18 ± 7	22 ± 11	0.09
Ejection fraction (%)	71 ± 10	70 ± 9	73 ± 8	70 ± 10	0.35
LV mass/volume ratio	1.5 ± 0.7	1.1 ± 0.3	1.3 ± 0.3	1.7 ± 0.7§	<0.001
Post-contrast delayed enhancement	169 (64%)	29 (52%)	24 (57%)	116 (70%)§	0.031

*Normal left ventricular (LV) mass index is defined as < mean +2 SD in normal control group (according to gender), mildly increased is defined as between mean +2 SD and mean +3 SD, and markedly increased is defined as > mean +3 SD; †p < 0.05 versus each of the other 2 groups by chi-square or Fisher exact test (‡); §p < 0.05 versus the other 2 groups by Bonferroni's post-hoc test after analysis of variance.

CMR = cardiovascular magnetic resonance; HCM = hypertrophic cardiomyopathy; N/A = not applicable; NYHA = New York Heart Association.

regression analysis using a cubic model, to account for the comparison of a linear with tridimensional (volumetric) variable. The survival curve was constructed according to the Kaplan-Meier method. All p values are 2-sided and considered significant when <0.05. Calculations were performed with SPSS 12.0 software (SPSS Inc., Chicago, Illinois).

Results

Assessment of LV mass. CONTROL SUBJECTS. LV mass indexed to BSA was 53 ± 8 g/m², and was significantly greater in men than women (61 ± 10 g/m² vs. 47 ± 7 g/m², respectively, p < 0.001). The upper limit of normal (mean +2 SDs) was 81 g/m² for men and 61 g/m² for women.

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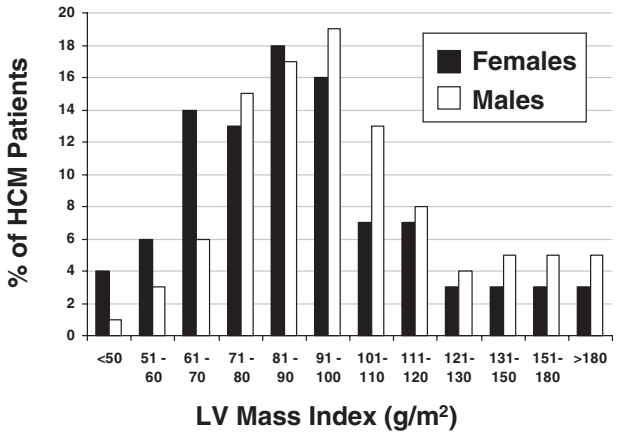

Figure 1 **Distribution of LV Mass Index in the 264 Study Patients With HCM**

The **bars** represent the percentage of patients in each subgroup according to gender. HCM = hypertrophic cardiomyopathy; LV = left ventricular.

HCM PATIENTS. LV mass index was 100 ± 39 g/m^2, and was significantly greater in men than women (104 ± 40 g/m^2 vs. 89 ± 33 g/m^2, respectively; $p < 0.001$) (Fig. 1, Table 2), despite identical maximal echocardiographic LV wall thickness (21 ± 6 mm vs. 21 ± 5 mm; $p = 0.65$), and was similar among the 4 participating centers (Florence, 104 ± 50 g/m^2; Boston, 102 ± 28 g/m^2; Minneapolis, 99 ± 39 g/m^2; Rome, 96 ± 27 g/m^2; overall ANOVA p value = 0.69). Intraobserver and interobserver reproducibility was high; the average difference in LV mass index was 5 ± 7 g/m^2 and 7 ± 9 g/m^2, respectively; the Pearson correlation coefficient was 0.967 and 0.959, respectively ($p < 0.001$ for both).

The LV mass index in HCM patients markedly exceeded that of normal control subjects ($p < 0.0001$ for both genders). However, 56 (21%) HCM patients (49 men; 7 women) had CMR LV mass values within 2 SDs from the mean of the control group (i.e., <95th percentile for normal individuals) (Fig. 2), and were regarded as within the normal range. An additional 42 (16%) HCM patients (31 men; 11 women) showed only mildly increased LV mass (i.e., were 2 to 3 SDs from the mean for the control group or 95th to 99th percentile for normal individuals). The remaining 167 (63%; 117 men and 50 women) had markedly increased LV mass index (Fig. 2, Table 1).

Clinical correlates of LV mass. Independent predictors of normal LV mass index at multivariate analysis were male gender (odds ratio [OR] vs. women: 4.3; $p = 0.008$), lesser maximal LV wall thickness (OR per mm increment: 0.79; $p < 0.001$), smaller end-diastolic volume (OR per ml increment: 0.98; $p < 0.001$) and absence of outflow obstruction at rest (OR vs. obstructive patients: 10.9; $p = 0.02$).

LV mass index was greater in obstructive than in nonobstructive patients (121 ± 43 g/m^2 vs. 96 ± 37 g/m^2, respectively; $p < 0.001$), despite similar maximal LV thickness (23 ± 7 mm vs. 21 ± 6 mm, respectively; $p = 0.06$). Only 1 (2%) of 47 patients with a resting outflow tract gradient ≥30 mm Hg had a normal LV mass index

Table 2 **CMR Findings According to Gender in 264 HCM Patients**

	Men	Women	p Value
n	197	67	
Age at enrollment (yrs)	42 ± 18	47 ± 19	0.09
Body surface area (m^2)	2.0 ± 0.3	1.7 ± 0.2	<0.001
Maximal LV wall thickness	22 ± 3	21 ± 5	0.69
Maximal LV thickness ≥30 mm	21 (11%)	5 (8%)	0.63
LV mass (g)	207 ± 81	152 ± 60	<0.001
LV mass index (g/m^2)	104 ± 40	89 ± 32	0.009
LV end-diastolic volume (ml)	143 ± 45	111 ± 31	<0.001
LV end-diastolic volume index (ml/m^2)	72 ± 19	66 ± 15	0.007
LV end-systolic volume (ml)	42 ± 22	32 ± 18	0.001
LV end-systolic volume index (ml/m)	21 ± 10	19 ± 11	0.15
Ejection fraction (%)	70 ± 10	72 ± 10	0.34
LV mass/volume ratio	1.5 ± 0.7	1.4 ± 0.5	0.06
Post-contrast delayed enhancement	128 (65%)	41 (61%)	0.65

Comparison of normally distributed variables by Student *t* test; comparison of noncontinuous variables expressed as proportions by chi-square.
Abbreviations as in Table 1.

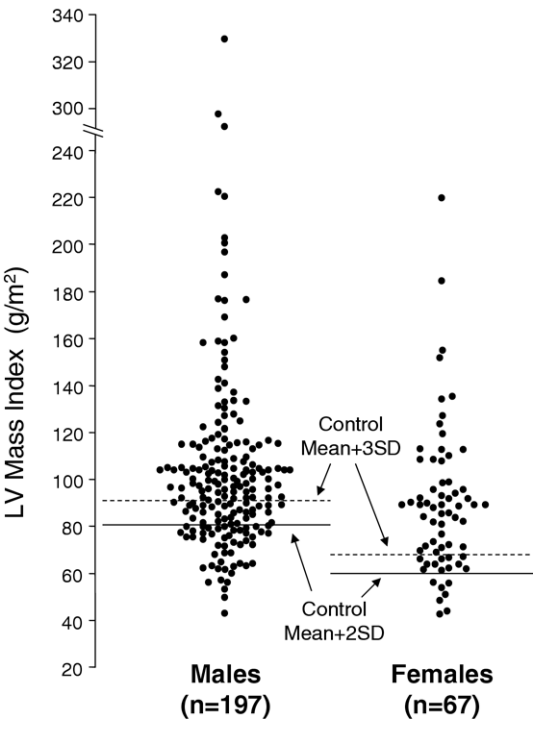

Figure 2 **Distribution of LV Mass Index According to Gender**

Mean left ventricular (LV) mass index +2 SD **(solid lines)** and +3 SD **(dashed lines)** of the reference control population are reported. The LV mass in hypertrophic cardiomyopathy patients was defined as normal when <2 SD, mildly increased when within 2 to 3 SD, and markedly increased when >3 SD of control subjects. Higher reference values in male subjects account for the greater number of male patients with normal LV mass index compared with female patients.

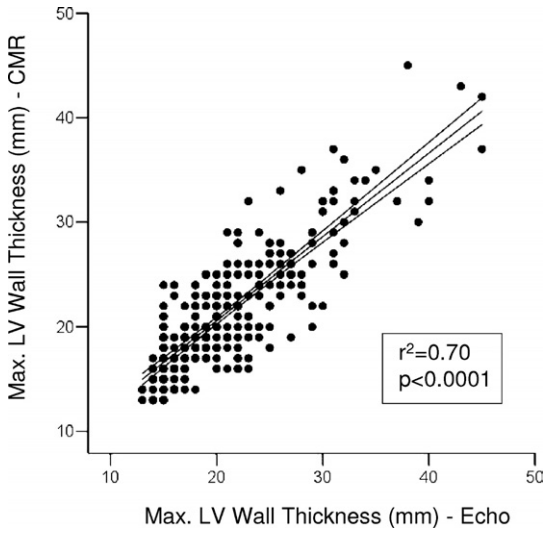

Figure 3 **Comparison of Different Techniques to Assess Maximum LV Wall Thickness**

Scatterplot illustrating the linear relationship between maximal left ventricular (LV) wall thickness measured by echocardiography (echo) and by cardiovascular magnetic resonance (CMR) in 264 hypertrophic cardiomyopathy patients.

compared with 55 (25%) of 217 patients without obstruction ($p < 0.001$). In addition, patients with markedly increased LV mass showed a greater prevalence of delayed enhancement as compared with patients from the other 2 groups (Table 1).

Conversely, LV mass index was unrelated to age (103 ± 47 g/m^2, 98 ± 29 g/m^2, and 101 ± 35 g/m^2, among patients <40, 40 to 60, and >60 years of age, respectively; ANOVA $p = 0.67$), or severity of heart failure symptoms (98 ± 31 g/m^2, 104 ± 51 g/m^2, and 105 ± 44 g/m^2 for patients in New York Heart Association functional classes I, II, and III/IV, respectively; ANOVA $p = 0.42$). Seven of 8 patients with end-stage progression (ejection fraction <50%) had increased LV mass index (up to 283 g/m^2); as a group, however, end-stage patients did not differ significantly from those with preserved LV systolic function (125 ± 77 g/m^2 vs. 99 ± 38 g/m^2, respectively; $p = 0.11$).

Maximum LV wall thickness. ECHOCARDIOGRAPHY. Maximal LV wall thickness in HCM patients was 21 ± 6 mm (range 13 to 45 mm), including 29 individuals ≥30 mm (11%). The location of maximal wall thickness was the ventricular septum in 230 patients (87%), anterolateral free wall in 25 (9%), and apex in 9 (4%).

CMR. Maximal LV wall thickness was 21 ± 6 mm (range 13 to 45 mm), closely related to that measured by echocardiography ($r^2 = 0.70$, $p < 0.0001$; average difference in individual patients 0.3 ± 3.4 mm) (Fig. 3), and included 26 patients (9%) with a thickness ≥30 mm. Also, similar to echocardiography, CMR identified predominant LV wall thickness in the septum of 230 patients (87%), anterolateral free wall in 25 (9%), and apex in 9 (4%).

Maximal LV wall thickness by echocardiography exceeded CMR by ≥2 mm in 88 patients (33%; range 2 to 8 mm). Maximal CMR wall thickness exceeded that with echocardiography by ≥2 mm in 71 patients (27%; range 2 to 9 mm). In the remaining 105 patients (40%), differences between the 2 techniques were negligible (≤1 mm).

RELATION TO LV MASS. A cubic relationship was present between maximal LV wall thickness by echocardiography and CMR LV mass index ($r^2 = 0.38$, $p < 0.001$). Despite achieving statistical significance, this relationship was modest, due to the substantial variability of mass values with respect to individual LV thicknesses (Fig. 4). For example, 15 patients with an identical echocardiographic LV wall thickness of 21 mm showed LV mass index that ranged widely from 64 to 220 g/m^2, including 3 within normal

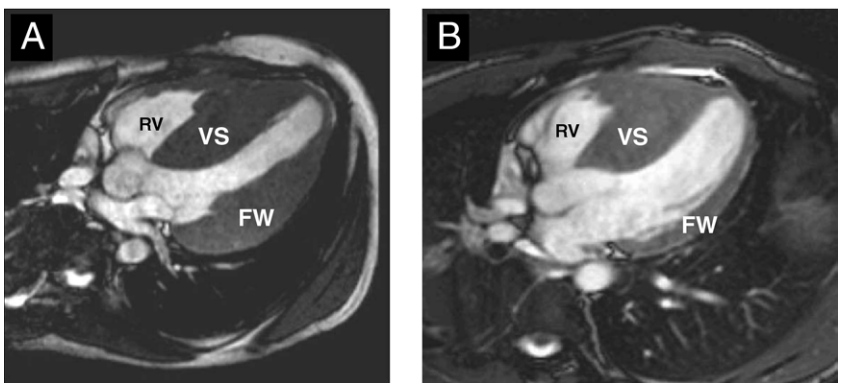

Figure 4 **Individual LV Mass Variability in Patients With HCM**

Cardiovascular magnetic resonance 4-chamber end-diastolic images from 2 HCM patients with identical maximal LV wall thickness (i.e., 33 mm in the anterior ventricular septum), but markedly different LV mass index values (**A** = 184 g/m^2; **B** = 92 g/m^2). The difference in mass is due to the extensive distribution of increased LV thickness beyond the ventricular septum and into the LV free wall in **A**, while the patient in **B** shows hypertrophy confined to the septum. FW = free left ventricular wall; RV = right ventricular cavity; VS = ventricular septum; other abbreviations as in Figure 1.

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limits, 1 with mildly increased, and 11 with markedly increased mass.

As a group, the 29 patients with extreme LV wall thickness by echocardiography (≥30 mm) showed a marked increase in LV mass index (145 ± 62 g/m^2). However, the range was considerable (43 to 329 g/m^2) and included 3 male patients with relatively localized LV hypertrophy and normal LV mass values (i.e., 43, 68, and 78 g/m^2) (Fig. 4).

Outcome. Over a 2.6 ± 0.7-year follow-up, there were 10 HCM-related deaths: 5 sudden death events (including 1 resuscitated cardiac arrest and 2 appropriate implantable cardioverter-defibrillator discharges), 3 due to heart failure, and 2 after surgical septal myectomy. Patients who died of HCM had significantly greater LV mass index than survivors (128 ± 62 g/m^2 vs. 99 ± 38 g/m^2; p = 0.02). All 10 HCM patients who died were in the subgroup of 167 patients with markedly increased LV mass index (6%), while no events occurred among the 97 patients with normal or mildly increased LV mass (Kaplan-Meier survival analysis p = 0.019) (Fig. 5).

Conversely, 4 HCM-related deaths occurred among the 29 patients with echocardiographic maximal LV thickness ≥30 mm (14%), compared with 6 (of which 4 were sudden) among the 235 patients <30 mm (Kaplan-Meier survival analysis p = 0.016). As a result, a markedly increased LV mass (>91 g/m in men and >69 g/m in women) index proved to be more sensitive with regard to HCM-related death (100%, with 39% specificity), whereas a maximal wall thickness >30 mm was more specific (90%, with 41% sensitivity).

Discussion

In this large multicenter cohort of 264 patients presenting with an echocardiographic phenotype diagnostic of HCM, CMR has added new perspectives to the morphologic expression of the disease. Based on early necropsy studies, HCM has been generally regarded as a condition characterized by greatly increased cardiac mass (5,6). With the introduction of echocardiography, increased LV wall thickness became the *sine qua non* of the HCM phenotype, and the large heterogeneity of the extent and distribution of hypertrophy became evident (1–4). By inference, these findings suggested a broad spectrum of LV mass in this disease (4). Nevertheless, quantitative assessment of mass with 2-dimensional echocardiography has been generally regarded as unreliable in HCM, due largely to nontomographic cross-sectional planes, as well as the heterogeneous geometry of the LV chamber (4). By providing high-resolution volumetric reconstruction of the LV (7,8,10), CMR is superior to 2-dimensional echocardiography for quantitative assessment of LV mass (12), and consequently offers a unique opportunity to revisit and characterize more definitively the phenotypic expression of HCM in vivo. To this purpose, we have prospectively assembled a large cohort of HCM patients studied with both CMR and echocardiography, to clarify the extent to which this genetic disease increases LV mass, and the interaction of mass and wall thickness.

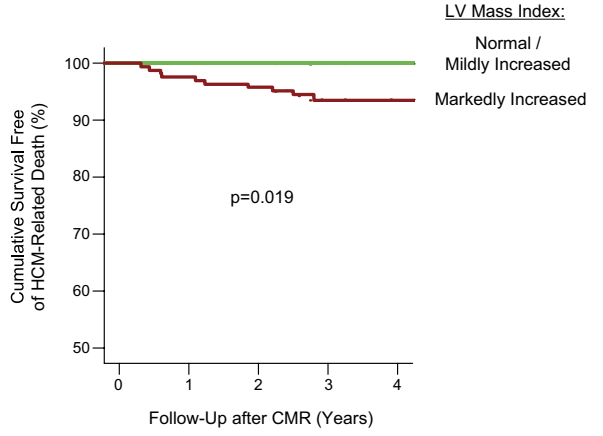

Figure 5 LV Mass and Outcome

Kaplan-Meier curve showing the cumulative survival free from cardiovascular mortality with respect to LV mass index. CMR = cardiovascular magnetic resonance; other abbreviations as in Figure 1.

First, in distinction to prior perception, we found that an increased LV mass is not invariably present in patients with HCM, and therefore cannot be considered a requirement to establish this clinical diagnosis. When compared with >600 healthy adult participants in the Framingham Heart study, serving as normal control subjects, over 20% of our study patients from hospital-based cohorts had CMR-calculated LV mass index values that fell within the normal range (i.e., <95th percentile of normal subjects), and another 16% had only mildly increased mass (95th to 99th percentile of normal subjects). In systematic HCM pedigree analyses, affected individuals frequently exhibit mild phenotypes, which may be associated with normal LV mass (13–16). Consequently, it is reasonable to speculate that in the general HCM population (i.e., including referred and nonreferred patients), the proportion of patients with normal LV mass may substantially exceed the 20% reported here (16). These observations underscore the novel principle that LV mass may not be augmented in HCM, and defines a heretofore unrecognized subset of patients with normal LV mass (13–17). Of note, prior studies employing CMR in HCM patients were often based on selected cohorts of limited size, predominantly comprised of patients with severe disease expression and obstruction to LV outflow (18,19). This selection bias probably accounts for the higher LV mass values reported in those studies, compared with those in our present patient group.

Second, LV mass was distinctively increased in specific subgroups of HCM patients. Specifically, LV mass index was substantially greater in male than female patients. This finding differs from echocardiographic measurements of

maximal wall thickness (as an estimate of LV hypertrophy), reporting little difference between the genders (9,20–26). Moreover, LV mass index was greater in patients with LV outflow obstruction at rest, probably the result of the increased intraventricular systolic pressure load (18,19), despite a comparable magnitude of LV wall thickness between the obstructive and nonobstructive patients. This observation supports the hypothesis of secondary hypertrophy in HCM caused by impedance to LV outflow, and also contrasts sharply with prior echocardiographic studies (9,18,19,22,23).

Third, maximal LV wall thickness often proved to be an unreliable estimate of total LV mass index, despite a statistically significant relationship between these 2 parameters. For example, HCM patients with an echocardiographic wall thickness of 21 mm (the mean in this cohort, similar to that of other HCM populations) (9,22–25) showed adjusted mass values that ranged from normal (64 g/m^2) to greatly increased (220 g/m^2). In addition, a considerable proportion of patients with extreme LV wall thickness (≥30 mm) (25,27,28) did not show a marked increase in LV mass, and 3 of these patients were actually within the normal range. Such mismatches between absolute LV wall thickness and mass reflect the heterogeneity of the HCM phenotype, due primarily to the variable distribution of hypertrophy in regions of the LV chamber remote from the site of maximal thickness (4).

This latter observation raises potentially important management considerations. Current risk stratification strategies for young HCM patients have used extreme LV wall *thickness* (≥30 mm) to represent the overall burden of hypertrophy (23–25). However, the present analysis suggests that calculated LV mass could prove more relevant to the assessment of risk in HCM. Over the available follow-up, markedly increased LV mass index by CMR was associated with HCM-related mortality with greater sensitivity (although lower specificity) than maximal LV thickness. Nevertheless, revising risk stratification guidelines in HCM, currently based on echocardiography (2,3), in accord with calculated LV mass, will require new prospective CMR-driven studies with long periods of observation, which are well beyond the scope of the present investigation.

Conclusions

The LV mass index was normal in a substantial subset of patients with HCM. Therefore, normal LV mass does not exclude the diagnosis of HCM in the presence of increased segmental wall thickness. Left ventricular mass correlated weakly with maximal wall thickness, and proved more sensitive in predicting HCM-related mortality. In this complex and heterogeneous disease, CMR affords the opportunity to achieve enhanced phenotypic characterization and, possibly, to improve risk stratification.

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