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Hypertrophic Cardiomyopathy Phenotype Revisited After 50 Years With Cardiovascular Magnetic Resonance

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Objectives
Our purpose was to characterize the pattern and distribution of left ventricular (LV) hypertrophy by cardiovascular magnetic resonance (CMR) to more precisely define phenotypic expression and its clinical implications in hypertrophic cardiomyopathy (HCM).

Background
Based on prior pathologic and 2-dimensional echocardiographic studies, HCM has been regarded as a disease characterized by substantial LV wall thickening.

Methods
Cine and late gadolinium enhancement CMR were performed in 333 consecutive HCM patients (age 43 ± 17 years).

Results
Basal anterior LV free wall and the contiguous anterior ventricular septum were the most commonly hypertrophied segments (n = 256; 77%). LV hypertrophy was focal (involving ≤2 segments [≤12% of LV]) in 41 patients (12%), intermediate (3 to 7 segments [13% to 49% of LV]) in 112 patients (34%), and diffuse (≥8 segments [≥50% of LV]) in 180 patients (54%); 42 patients (13%) showed hypertrophied segments separated by regions of normal thickness. The number of hypertrophied segments was greater in patients with LV outflow tract obstruction (≥30 mm Hg) than without (10 ± 4 vs. 8 ± 4 per patient; p = 0.0001) and was associated with an advanced New York Heart Association functional class (p = 0.007). LV wall thickness was greater in segments with late gadolinium enhancement than without (20 ± 6 mm vs. 16 ± 6 mm; p < 0.001). We also identified 40 (12%) of HCM patients with segmental LV hypertrophy largely confined to the anterolateral free wall, posterior septum, or apex, which was underestimated or undetected by echocardiography.

Conclusions
Although diverse, patterns of LV hypertrophy are usually not extensive in HCM, involving ≤50% of the chamber in about one-half the patients, and are particularly limited in extent in an important minority. Contiguous portions of anterior free wall and septum constituted the predominant region of wall thickening, with implications for clinical diagnosis. These observations support an emerging role for CMR in the contemporary evaluation of patients with HCM. (J Am Coll Cardiol 2009;54:220–8) © 2009 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) has historically been regarded as a disease characterized by hypertrophy involving particularly substantial portions of the left ventricular (LV) wall (1–13). These perceptions regarding the morphology of HCM were derived largely from non tomographic, 2-dimensional echocardiographic imaging, as well as post-mortem studies (5–12,14). Volumetric cardiovascular magnetic resonance (CMR) offers advantages of high spatial resolution and 3-dimensional tomographic imaging thereby allowing for better characterization of the pattern and distribution of LV hypertrophy in HCM (15–21). Therefore, 50 years after the initial contemporary descriptions of HCM and its phenotypic expression, we have applied CMR to re-examine the morphologic and clinical expression of this complex disease in a large patient cohort.

Methods
Selection of patients. We prospectively studied 333 consecutive HCM patients with CMR who presented to Tufts Medical Center (Boston, Massachusetts) and the Minneapolis Heart Institute (Minneapolis, Minnesota), between

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The diagnosis of HCM was based on the CMR demonstration of a hypertrophied LV (wall thickness ≥15 mm), associated with a nondilated cavity in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident (1–3).

Echocardiographic examination was performed in all patients within 2 weeks of CMR examination. LV outflow tract obstruction was defined as a peak instantaneous gradient of ≥30 mm Hg by continuous-wave Doppler echocardiography under resting conditions (22). Due to the substantial LV remodeling associated with “end-stage” HCM (i.e., ejection fraction ≤50%), these patients were excluded from the present cohort, as well as those patients who had previously undergone alcohol septal ablation or surgical septal myectomy. Selected data from 210 study patients have been part of previous analyses (17,23,24).

All study patients signed a statement previously approved by the internal review boards of the respective participating institutions, agreeing to the use of their medical information for research purposes.

CMR. CMR imaging was performed (Philips Gyroscan ACS-NT 1.5-T, Best, the Netherlands, and Siemens Sonata 1.5-T, Erlangen, Germany) using steady-state, free precession breath-hold cine in 3 long-axis planes and sequential 10-mm short-axis slices from the atrioventricular ring to apex.

LV volumes, mass, and ejection fraction were measured using standard volumetric techniques (25), and analyzed with commercially available software (MASS, version 6.1.6, Medis, Inc., Leiden, the Netherlands). Volume and mass measurements were indexed to body surface area. Late gadolinium enhancement (LGE) images were acquired 10 to 15 min after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering, Berlin, Germany) with breath-held segmented inversion-recovery sequence, and acquired in the same orientations as the cine images. Inversion times were adjusted to null normal myocardium (typically 240 to 300 ms). All tomographic short-axis LV slices from base to apex were inspected visually to identify an area of completely nullled myocardium. Mean signal intensity (and SD) of normal myocardium was calculated, and a threshold ≥6 SD exceeding the mean was used to define areas of LGE. Areas of artifact (i.e., blood pool, incomplete nullling of fat, and pericardial fluid) were excluded from the analysis by manually adjusting the individual contours. Total volume of LGE (expressed in grams [g]) was calculated by summing the planimetered areas of LGE in all short-axis slices and was expressed as a proportion of total LV myocardium (%LGE).

The short-axis LV stack was divided into 3 approximately equal levels (basal, mid, and apical) in the longitudinal plane. Each of these 3 levels was comprised of 3 to 4 contiguous short-axis slices, with the total number of these slices usually 9 to 12 per patient.

In the short-axis plane, at the basal and mid-LV levels, each slice was divided automatically by the MASS software into 6 equal segments, while the apical level slices were divided into 4 segments. Therefore, in each patient a total of 16 LV segments were assessed according to the standard American Heart Association segmentation model (26).

For each short-axis slice, the insertion point of right ventricular wall defined the intersection of ventricular septum and anterior free wall. In the basal and mid-LV levels, the ventricular septum was divided equally into anterior septum and posterior septum (i.e., inferior septum) while the LV free wall was divided equally into anterior, anterolateral, inferolateral, and posterior (inferior) segments. The apical level was divided equally into septum, anterior, lateral, and inferior.

Maximum LV wall thickness measurements in each of the 16 segments were automatically calculated by commercially available software. In the 3 LV levels (i.e., basal, mid, apical), the greatest wall thickness measured in each of the 16 segments was recorded. The percent of the LV chamber hypertrophied was calculated by dividing the number of LV segments with increased wall thickness (≥15 mm) by the total number of LV segments.

Previous analyses have shown excellent interobserver and intraobserver agreement for similar CMR assessment of LV wall thicknesses (17,27). A patient was considered to have a pattern of noncontiguous LV hypertrophy if at least 1 LV myocardial segment of normal wall thickness was interposed between 2 or more adjacent segments of hypertrophied myocardium in either the circumferential (short-axis) or longitudinal (long-axis) cross-sectional plane.

Statistical analysis. Data are expressed as mean ± SD. Proportions and categorical data are compared across groups using the Fisher exact test. Confidence intervals for proportions are calculated using the binomial equation. Continuous data are compared across groups using the Wilcoxon rank sum test. Analyses of per-segment correlations between maximal segmental wall thickness and segmental LGE are adjusted for shared, within-patient variance using mixed-effects models. Other analyses of the same per-segment measures are summarized per patient before analysis with no other adjustment for within-patient effects. Statistical analyses were performed using Stata (version 10, Stata Corp., College Station, Texas).

Results

Patient characteristics. Clinical and demographic characteristics of the 333 study patients are summarized in Table 1. Mean age at evaluation was 43 ± 17 years (range 8 to 86 years); 240 patients (72%) were men. At the time of CMR study, 217 patients (65%) were asymptomatic in New York
Heart Association (NYHA) functional class I, 75 (23%) had mild symptoms in NYHA functional class II, and 41 patients (12%) had severe heart failure symptoms in NYHA functional class III or IV. LV ejection fraction was 72 ± 7%. LV outflow obstruction ≥30 mm Hg under resting conditions was present in 77 patients (23%).

**LV wall thickness.** For the overall study cohort, the maximal LV wall thickness was 22 ± 5 mm (range 15 to 50 mm) with a total of 2,741 LV segments hypertrophied (average per patient 8 ± 4). Distribution and extent of LV hypertrophy was diverse (Fig. 1): focal involving ≤2 segments (≤12% of LV) in 41 (12%) patients, moderate involving 3 to 7 segments (13% to 49% of LV) in 112 (34%) patients, and diffuse involving ≥8 segments (≥50% of LV) in 180 (54%) patients (Table 1, Fig. 2). Therefore, in 153 patients (46%) hypertrophy was present in <50% of the overall LV chamber.

Among the 333 study patients, the basal anterior septum showed the highest average maximal LV wall thickness (20 ± 5 mm) followed by the basal anterior free wall (19 ± 5 mm) and midposterior septum (19 ± 5 mm) (Fig. 3). However, average wall thickness was ≤15 mm in 9 other LV segments (56%).

Maximal LV wall thickness was directly related to the number of hypertrophied segments: focal (17 ± 1 mm), intermediate (20 ± 4 mm), and diffuse (25 ± 5 mm; p = 0.0001). Total LV mass index was 68 ± 13 g/m², 82 ± 17 g/m², and 120 ± 32 g/m² in patients with focal, intermediate, and diffuse hypertrophy, respectively. A significant relationship was evident between the number of hypertrophied LV segments and LV mass index (r² = 0.83; p < 0.0001).

**Location and distribution of LV hypertrophy.** Increased LV wall thickness was most commonly located in the anterior free wall (n = 266; 80%) and contiguous basal anterior ventricular septum (n = 286; 86%) (Fig. 4). In 256 of the 333 study patients (77%), hypertrophy was present in both these segments (i.e., 1 o’clock position in the short-axis plane) (Fig. 5A). Hypertrophy was commonly present in the posterior portion of septum, usually at the mid-LV level (n = 253; 76%) (Fig. 4).

Finally, among 40 (12%) of the 333 HCM study patients, CMR identified hypertrophy completely (or predominately) limited to the anterolateral free wall, posterior portion of ventricular septum, or LV apex, in whom the echocardiogram markedly underestimated (or did not detect) hypertrophy in those same regions (Fig. 6). In 5 patients (1.5% of 333), LV hypertrophy was confined to the anterior or anterolateral LV free wall (Fig. 5B).

Of the 333 patients, 42 (13%) showed a noncontiguous pattern of LV wall thickening involving ≥2 hypertrophied segments (Fig. 7). The most common locations for noncontiguous hypertrophy were combinations of basal anterior septum and apical lateral wall or basal anterior septum and mid-LV posterior septum. There were no significant differences evident between patients with a noncontiguous pattern of LV hypertrophy and other patients, with respect to age (p = 0.5), sex (male, p = 0.5), LV outflow obstruction at rest (p = 0.15), or NYHA functional class (p = 0.24).
Relation of LV hypertrophy to LGE. LV wall thickness was greater in segments with LGE compared with segments without LGE (20 ± 6 mm vs. 16 ± 6 mm; p < 0.001) (Fig. 8). In addition, maximum LV wall thickness and total LV mass index were greater in patients with LGE compared with those without LGE (24 ± 5 mm vs. 21 ± 4 mm; p < 0.0001 and 110 g/m² vs. 94 g/m²; p = 0.002, respectively). Also, LGE was more common in patients with diffuse hypertrophy (89 of 151; 59%), than with intermediate (31 of 95; 33%) or focal hypertrophy (7 of 31; 23%; p < 0.001).

The number of hypertrophied LV segments with LGE based on wall thickness tertiles was ≤15 mm, 23 of 207 (11%); 16 to 20 mm, 217 of 1,444 (15%); 21 to 25 mm, 291 of 1,615 (18%); 26 to 30 mm, 137 of 1,807 (17%); and ≥30 mm, 72 of 359 (20%) (p < 0.01). However, % LGE was unrelated to maximal LV wall thickness (r = −0.03; p = 0.7) or the number of hypertrophied segments (r = −0.03; p = 0.7) (Table 1).

Relation of LV hypertrophy to clinical and demographic variables. The number of hypertrophied LV segments was greater in patients with LV outflow tract obstruction (≥30 mm Hg at rest) compared with nonobstructed patients (10 ± 4 vs. 8 ± 4; p ≤ 0.001). In addition, patients with advanced NYHA functional class III/IV heart failure symp-
toms had a greater number of hypertrophied segments (n = 11) compared with class II minimally symptomatic (n = 9) or class I asymptomatic (n = 8) (p = 0.007) patients. However, the extent of hypertrophy was unrelated to age (p = 0.14), sex (p = 0.05), atrial fibrillation (p = 0.11), and ejection fraction (p = 0.26).

Discussion

Since its initial description 50 years ago, the phenotypic expression of HCM has often been characterized as an example of extensive LV hypertrophy, albeit with a diversity of patterns (1–12). This perception emanates from earlier autopsy observations in which LV wall thickness measurements made in rigor mortis were equivalent to those in systole (8,14), and subsequently from studies with 2-dimensional echocardiography, an imaging technique that depends on nontomographic (and often oblique) cross-sectional planes, and consequently does not image the entire LV chamber.

CMR is an important addition to the imaging armamentarium for HCM (15,18,19,21,27,28). Indeed, as a comprehensive tomographic technique with high spatial resolution, CMR provides complete reconstruction of the LV chamber.
and a more precise definition of the distribution of hypertrophy (16–18,20,29,30). Therefore, to this purpose, we have assembled here a particularly large consecutive cohort of patients with HCM imaged with CMR to permit a detailed assessment of the diverse and complex phenotypic expression in this disease.

In this cohort analysis, we found that about one-half of our HCM patients had areas of hypertrophy that were confined to <50% of the overall LV chamber, including a substantial minority with particularly focal or regional areas of increased LV wall thickness. In fact, over 10% of the study patients showed only 1 or 2 hypertrophied LV segments, a phenotypic expression that would not be expected to result in an increased calculated LV mass (24). Therefore, these results are inconsistent with the still popular notion that extensive hypertrophy represents the characteristic phenotypic expression of HCM or is a requirement for clinical diagnosis (4,5,7–10,12,13,24). Finally, among this large cohort of HCM patients, over one-half of the 16 LV segments had an average maximal wall thickness of ≤15 mm. This finding also raises important considerations with regard to the relation between the HCM genetic substrate (and disease-causing mutations) and phenotypic expression. In this regard, the observation that sarcomere protein mutations responsible for HCM (31) are not associated with hypertrophy distributed throughout most or all of the LV wall suggests that other factors, such as modifier genes or environmental triggers, may be important contributors to modification of the HCM phenotype.

A related but unexpected finding with CMR was that the predominant area of LV wall thickening in HCM involved the basal anterior free wall in continuity with the anterior ventricular septum (“1 o’clock” in the short-axis plane), rather than more centrally in the “12 o’clock” position in the anterior septum, as traditionally regarded with 2-dimensional echocardiography (6,7). Indeed, the present observation that the anterior free wall is a particularly

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Figure 2  Prevalence of Hypertrophied Segments

Prevalence of focal (1 to 2 hypertrophied segments), intermediate (3 to 7 segments), and diffuse left ventricular hypertrophy (8 to 16 segments) within the cohort of 333 patients with hypertrophic cardiomyopathy.

Figure 3  Average LV Wall Thickness per Segment

Distribution of mean left ventricular (LV) wall thicknesses in 16 segments, according to the American Heart Association model. Ant. – anterior; FW – free wall; Post. – posterior.
common, and frequently the predominant site of wall thickening within the LV, has not previously been appreciated with nontomographic imaging modalities. Furthermore, we identified an important minority of HCM patients in whom segmental LV hypertrophy was largely confined to the anterolateral wall, posterior septum, or apex and in whom the echocardiogram dramatically underestimated (or did not detect) hypertrophy in those same regions. Only CMR was capable of identifying the extent of hypertrophy and/or the diagnostic morphology (29,30).

Taken together, these observations imply that absolute LV wall thickness may have been previously underestimated in many HCM patients, as the true epicardial border of the LV free wall is often not visualized accurately with 2-dimensional echocardiography, ultimately supporting the role for CMR in providing more comprehensive and precise
diagnostic imaging in HCM. Of note, these findings not only have important implications for noninvasive HCM diagnosis, but also for planning proper operative management strategies for surgical septal myectomy candidates by recognizing the need to adjust the muscular resection to target the most hypertrophied portion of the anterior LV, thereby ensuring optimal reduction in LV outflow gradient while avoiding iatrogenic ventricular septal defect (32–35).

Another novel finding in assessing our HCM cohort with CMR was the noncontiguous distribution of segmental areas of LV wall thickening present in almost 15% of patients. This morphologic pattern consisted of hypertrophied segments separated by regions of nonhypertrophied myocardium, creating abrupt changes in wall thickness in adjacent portions of the wall and a “lumpy” hypertrophic pattern. This distribution of LV hypertrophy would seem most consistent with a genetically determined cardiomyopathic process (such as HCM) rather than forms of hypertrophy secondary to pressure overload (such as systemic hypertension), and in selected patients could possibly contribute to resolution of the differential diagnosis between primary (genetic) and secondary hypertrophy, when this distinction is otherwise ambiguous (36).

LGE imaging provides a novel, noninvasive method for in vivo identification and quantification of myocardial fibrosis, which we (17,23) and others (15,19–21,37) have previously applied to other HCM patient groups. Areas of LGE proved to be most common in those segments of the LV with the greatest magnitude of wall thickening (15,19). This observed relation between LV wall thickness and the presence of LGE was largely unanticipated. We would have expected that LGE, presumably representing the consequences of longstanding microvascular ischemia, and resulting in myocyte death and ultimately replacement fibrosis as

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**Figure 6** LV Hypertrophy Recognized by CMR But Not Reliably With 2-Dimensional Echocardiography

(A) Four-chamber image showing hypertrophy confined to the LV apex (*); (B) Mid-LV short-axis image showing increased wall thickness localized to the posterior portion of the ventricular septum (*). (C) Basal short-axis image demonstrating hypertrophy virtually limited to the anterolateral free wall (*). CMR = cardiovascular magnetic resonance; other abbreviations as in Figure 5.

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**Figure 7** Noncontiguous Areas of LV Hypertrophy

(A) End-diastolic short-axis cardiovascular magnetic resonance image from a 45-year-old man demonstrating segmental LV hypertrophy of the basal anterior septum and posterior (inferior) LV wall (*), separated by regions of normal LV thickness (arrows). (B) End-diastolic short-axis cardiovascular magnetic resonance image from a 33-year-old woman showing another noncontiguous pattern of LV hypertrophy in which there is increased thickness of the inferior (posterior) free wall and anterior septum (*) separated by areas of normal LV wall thickness (arrows). Abbreviations as in Figure 5.
expression of the cardiomyopathic process in HCM is often segmental and nondiffuse, and may also demonstrate non-contiguous patterns of wall thickness. Recognition that the anterior LV free wall is more commonly and often predominantly involved in the hypertrophic process than previously regarded (and can also be the sole area of wall thickening) represents an important principle for the noninvasive diagnosis of HCM. Taken together, these observations underscore an important role for CMR in the contemporary assessment of patients with HCM.

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