Intermediate-Signal-Intensity Late Gadolinium Enhancement Predicts Ventricular Tachyarrhythmias in Patients With Hypertrophic Cardiomyopathy

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Background—In hypertrophic cardiomyopathy (HCM), the arrhythmic potential associated with a variety of left ventricular myocardial signal intensities evident on contrast-enhanced cardiovascular magnetic resonance with late gadolinium enhancement (LGE) is unresolved.

Methods and Results—In 145 HCM patients (43±15 years old), visually identified areas of LGE in left ventricle were analyzed quantitatively for intermediate (≥4 but <6 SD) and high (≥6 SD above the mean signal intensity of normal myocardium) LGE signal intensity (LGE-SI). Ambulatory Holter ECGs were obtained within 7.8±8.3 weeks of cardiovascular magnetic resonance. HCM patients with nonsustained ventricular tachycardia, ventricular couplets, and premature ventricular contractions showed greater amounts of intermediate LGE-SI (17±7 versus 10±10 g, 16±10 versus 10±11 g, and 13±8 versus 10±13 g, respectively; P=0.003 to <0.001) and greater amounts of high LGE-SI (15±6 versus 10±8 g, 14±9 versus 10±12 g, and 12±7 versus 10±8 g, respectively; P=0.02–0.003) than patients without these arrhythmias. In HCM patients with either nonsustained ventricular tachycardia, couplets, or premature ventricular contractions, the extent of intermediate LGE-SI exceeded that of high LGE-SI (17±7 versus 15±6 g, 16±10 versus 14±9 g, and 13±8 versus 12±7 g, respectively; P=0.01–0.04). In addition, the receiver operating characteristic area under the curve established intermediate LGE-SI as a better discriminator of patients with nonsustained ventricular tachycardia than was high LGE-SI, with 7 additional patients with this arrhythmia identified.

Conclusions—In patients with HCM, intermediate LGE-SI is a better predictor of ventricular tachyarrhythmias (including nonsustained ventricular tachycardia, a risk factor for sudden death) than is high LGE-SI. Longitudinal studies in larger HCM cohorts are justified to define the independent prognostic impact of intermediate LGE-SI. (Circ Cardiovasc Imaging. 2012;5:78-85.)

Key Words: magnetic resonance imaging ■ cardiomyopathy, hypertrophic ■ gadolinium ■ tissues ■ arrhythmias, cardiac

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease and the leading cause of sudden cardiac death in young people.1–7 Despite considerable advances, risk stratification in HCM remains challenging, and not all at-risk patients are appropriately identified by use of contemporary strategies.6,8–10 Ventricular tachyarrhythmias emanating from a structurally abnormal left ventricular (LV) myocardium with substantial areas of replacement fibrosis have emerged as a potential mechanism responsible for sudden death in HCM.11–14 Recently, late gadolinium enhancement (LGE; ie, likely myocardial fibrosis) identified by contrast-enhanced cardiovascular magnetic resonance (CMR) has been associated with an increased risk of ventricular tachyarrhythmia and adverse outcome, which suggests that LGE may represent a novel marker of risk in HCM.15–31

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Most contrast-enhanced CMR studies in HCM have considered only those areas of LV myocardium with high LGE...
signal intensity (LGE-SI) as clinically relevant with respect to outcome. However, regions of mixed intermediate and high LGE-SI detected in patients with HCM have been shown to correlate with increased myocardial collagen on postmortem analysis, yet their independent clinical significance and relation to ventricular tachyarrhythmias remain unresolved. In patients with atherosclerotic coronary artery disease who have experienced a prior myocardial infarction, areas of intermediate LGE-SI (ie, regions of "tissue heterogeneity") identify patients at increased risk for ventricular tachyarrhythmias and cardiovascular death. Therefore, in the present study of a large HCM cohort, we have assessed the prevalence, extent, and relationship of intermediate LGE-SI to a number of important demographic and clinical variables, including nonsustained ventricular tachycardia (NSVT, an established risk factor for sudden death in HCM) and other ventricular tachyarrhythmias on ambulatory Holter monitoring.

Methods

Study Patients

Inclusion Criteria
From April 2003 to January 2007, consecutive HCM patients eligible for magnetic resonance imaging were evaluated with contrast-enhanced CMR and 24-hour ambulatory Holter ECGs (n = 288) at the Minneapolis Heart Institute Foundation (Minneapolis, MN; n = 176) and Tufts Medical Center (Boston, MA; n = 112). Median interval between the 2 studies was 2 months (≤3 months in 81% of patients, ≤6 months in 98%, and maximum interval of 7 months in 1.3%).

Diagnosis of HCM was based on the demonstration by echocardiography and/or CMR of a hypertrophied LV (wall thickness ≥13 mm) associated with a nondilated cavity in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy and/or arrhythmia evident. Patients included in the analysis were those with visual evidence of LGE (145/288, or 50% of the cohort) on contrast-enhanced CMR imaging (see "CMR Analysis"). Selected patients in the present study cohort (n = 72) have been part of other analyses.

Exclusion Criteria
During the same time period, those HCM patients with implanted pacemakers or defibrillators (n = 10), end-stage patients (LV ejection fraction <50%; n = 15), and those with a history of cardiac arrest or sustained ventricular tachycardia (n = 5), a family history of sudden cardiac death (n = 10), an abnormal blood pressure response to exercise (<20-mm Hg increase in systolic blood pressure from rest to peak; n = 6), or any other contraindication to magnetic resonance imaging (n = 5) were excluded from the study.

Cardiovascular Magnetic Resonance
CMR was performed on a Philips Gyroscan ACS-NT 1.5T (Philips Medical Systems, Amsterdam, Netherlands) or Siemens Sonata or Avanto 1.5T (Siemens Medical Systems; Erlangen, Germany) whole-body CMR scanner with a commercial cardiac-surface coil. Cine images were acquired in contiguous LV short-axis orientation with an ECG-gated, breath-hold, steady state free-precession sequence with full LV coverage (8-mm slice thickness, 2-mm interslice gap, in-plane spatial resolution 2×2 mm, 30-ms temporal resolution). LGE was performed 15 minutes after the intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnetevis; Schering, Berlin, Germany) with a 2-dimensional breath-hold, segmented inversion-recovery sequence (inversion time optimized by the Look-Locker sequence [inversion time scout] to null normal myocardium) acquired in the same orientation (short-axis stack) as the cine images, with the following imaging parameters: 8-mm slice thickness, 2-mm interslice gap, repetition time 4.3 ms, echo time 2.1 ms, flip angle 15°, field of view 320 mm, matrix 160×160, and spatial resolution 2×2×2×8 mm.

CMR Analysis
All CMR analyses were performed with commercially available software (QMassMR version 7.1.0; Medis Inc, Leiden, Netherlands). LV endocardial and epicardial borders on both cine and LGE images were measured by planimetry, with special care taken to exclude papillary muscles and intertrabecular blood pool. LV wall thickness, volumes, mass, and ejection fraction were measured from the cine short-axis images by standard techniques.

The LV short-axis stack of LGE images was first assessed visually for the presence of LGE by 2 independent, blinded, experienced readers (E.A., C.J.H.), with any disagreement adjudicated by a senior observer with >10 years of CMR experience (W.J.M.). Areas of LV LGE were identified visually by consensus in 145 (50%) of the 288 HCM patients, who constituted the final study cohort. The mean grayscale signal intensity (SI) and SD for normal LV myocardium were measured for each patient, with a region of interest placed in a portion of nulled myocardium (ie, without LGE on visual inspection) on 3 consecutive midventricular short-axis slices and averaged (Figure 1).

To determine the optimal grayscale threshold for the identification of intermediate LGE-SI versus normal myocardium, we performed an analysis on the first 50 HCM patients with LGE, comparing the signal intensity of areas of normal and intermediate signal intensity by visual measurement versus a series of semiautomated grayscale thresholds. In this a priori analysis, we determined that values ≥5 SD but <6 SD above the mean signal intensity of normal myocardium demonstrated the most robust correlation to visual assessment for intermediate LGE-SI compared with an SD threshold of ≥5 but <6 SD (r = 0.904, P < 0.0001). Pixels that were <4 SD above the mean of normal (low signal intensity) correlated best with visually nulled myocardium (r = 0.911, P < 0.0001) and were therefore considered within a signal intensity range for normal myocardium. We previously have demonstrated a grayscale threshold of ≥6 SD above normal myocardium to have the strongest correlation with that of high LGE-SI quantified by visual assessment. To avoid partial volume averaging, areas of intermediate LGE-SI were required to be >1 pixel width (≥2 mm) if contiguous with high LGE-SI.

With these semiautomated grayscale threshold signal intensity cutoff values, areas of LGE were analyzed in 2 groups: (1) High LGE-SI (ie, the amount of LV myocardium with a grayscale threshold ≥6 SD above the mean signal intensity of normal myocardium) and (2) intermediate LGE-SI (ie, calculated by subtracting the amount of myocardium at ≥6 SD from that at ≥4 SD; Figure 1). In addition, we analyzed the combination of intermediate and high LGE-SI. The amount of LGE for each group was expressed in grams of myocardium and as a proportion (percentage) of total LV myocardial mass.

The location of intermediate and high LGE-SI within LV myocardium was classified as follows: Ventricular septum, LV free wall, and points of insertion of the right ventricle into the septum. In addition, LGE was considered transmural if it involved ≥75% wall thickness in any segment. Intermediate LGE-SI was considered contiguous with high LGE-SI when the vast majority of intermediate LGE-SI was localized to the periphery of regions of high LGE-SI, as visualized on both the short- and long-axis imaging planes. Intermediate LGE-SI was considered remote from high LGE-SI when these 2 areas of LGE were separated by normal myocardium. Intermediate LGE-SI and the combination of the 2 were correlated with clinical and functional/morphological CMR imaging parameters.

Ambulatory Holter ECGs
Ambulatory Holter ECG recordings were obtained in a standard fashion with a portable tape recorder and modified V1 and V5 leads. Holter ECG recordings were scanned on a DelMar Reynolds AccuPlus (model 403) Holter Analysis System (Del Mar Reynolds Medical, Irvine, CA). In patients with >1 Holter ECG, the recording closest to the CMR study was analyzed. NSVT was defined as 3 or more consecutive premature complexes at a heart rate ≥100 bpm.
Statistical Analyses
Continuous data are expressed as mean±SD. Categorical variables are presented as counts and percentages. Clinical and demographic characteristics of the LGE groups were compared with a 2-sample t test for continuous variables and Fisher exact tests for categorical variables expressed as proportions. Paired comparisons were performed with the Wilcoxon signed rank test. ANOVA was used to determine differences in means between multiple groups, with post hoc testing with the Bonferroni correction for multiple testing. The ability of intermediate LGE-SI, high LGE-SI, or their combination to discriminate patients with NSVT on Holter ECG was assessed with the receiver operating characteristic (ROC) area under the curve with 95% confidence intervals. The optimal cutoff in each ROC was determined by maximizing the accuracy of the test. ROC areas under the curve were compared by use of methods for correlated data. All comparisons were 2-tailed, with P<0.05 considered significant. SPSS software version 10.0 (SPSS Inc, Chicago, IL) or SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses.

Results
Study Population
Baseline demographics for the 145 study patients are presented in Table 1. The majority were male (56%) and in New York Heart Association class 1 (n=93; 64%); 40 patients (28%) were in class 2, and 12 (8%) had class 3 symptoms. Maximum LV wall thickness was 24±5 mm (range 13–36 mm). A minority of patients (n=24; 17%) had an LV outflow tract gradient at rest ≥30 mm Hg.

Ambulatory Holter ECG
On 24-hour ambulatory Holter monitoring, 120 patients (83%) with LGE had ventricular arrhythmias, including 119 (82%) with isolated premature ventricular contractions (range 1–5800, median 191), 58 (40%) with ventricular couplets (range 1–110, median 6), and 46 (32%) with NSVT. The number of NSVT runs was 1 to 6, with 3 to 58 beats in the

Table 1. Baseline Clinical and CMR Characteristics in 145 HCM Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43±15</td>
</tr>
<tr>
<td>Male, %</td>
<td>56</td>
</tr>
<tr>
<td>Maximal LV wall thickness, mm</td>
<td>24±5</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Mean NYHA class</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>LV outflow tract obstruction at rest (≥30 mm Hg), n (%)</td>
<td>24 (17)</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>83 (57)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>33 (23)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>4 (3)</td>
</tr>
<tr>
<td>CMR measurements, mean±SD</td>
<td></td>
</tr>
<tr>
<td>LV mass, g</td>
<td>210±87</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>107±34</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>70±11</td>
</tr>
<tr>
<td>High LGE-SI, g (%)</td>
<td>11±15 (5.5±7.2)</td>
</tr>
<tr>
<td>Intermediate LGE-SI, g (%)</td>
<td>13±8 (6.5±4.6)</td>
</tr>
<tr>
<td>Combination of high and intermediate LGE-SI, g (%)</td>
<td>24±23 (12.1±11.9)</td>
</tr>
</tbody>
</table>

CMR indicates cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; LV, left ventricular; NYHA, New York Heart Association; LGE-SI, late gadolinium enhancement signal intensity.
longest burst at ventricular rates of 130±28 per minute (range 109–235 per minute).

Late Gadolinium Enhancement
Intermediate and high LGE-SI was present in all 145 HCM study patients, with intermediate LGE-SI occupying 13±8 g (6.5±4.6% of LV myocardium), high LGE-SI 11±15 g (5.5±7.2%), and both combined 24±23 g (12.1±11.9%; Table 1). In most patients (n=105; 72%), intermediate LGE-SI exceeded high LGE-SI (1.4±10.7 g or 1.0±5.3%; P<0.001).

Location of LGE
In most patients (n=84; 58%), areas of intermediate LGE-SI were evident at the periphery of (and contiguous with) high LGE-SI and were present in a variety of areas of the LV chamber: Ventricular septum (n=8), LV free wall (n=20), junction of right ventricular wall with ventricular septum (n=16), or a combination of these sites (n=40; Figure 2). In 61 patients (42%), areas of intermediate LGE-SI were contiguous with high LGE-SI and also were found in (often multiple) regions remote from high LGE-SI (Figure 3).

Figure 2. Intermediate late gadolinium enhancement signal intensity (LGE-SI) contiguous with high LGE-SI. A, Cardiac magnetic resonance midventricular short-axis LGE image showing hyperenhancement (white arrows) at the junction of the right ventricular (RV) free wall with ventricular septum and a designated region of interest (ROI; orange circle) encircling normal, nulled myocardium in the posterior (inferior) portion of septum. LV indicates left ventricle. B, Automated grayscale threshold ≥6 SDs above the mean SI of normal myocardium of the ROI, representing high LGE-SI (arrows; red shading). C, Grayscale threshold ≥4 SDs above normal myocardium representing intermediate and high LGE-SI (red shading). D, Intermediate LGE-SI (red shading) identified by subtracting LGE quantified at ≥6 SD from that of ≤4 SD, with most intermediate LGE-SI being contiguous with regions of high LGE-SI.

Figure 3. Intermediate late gadolinium enhancement signal intensity (LGE-SI) contiguous with and remote from high LGE-SI. A, Cardiac magnetic resonance midventricular short-axis LGE image showing hyperenhancement (white arrow) in the anterior ventricular septum and a designated region of interest (ROI; orange circle) encircling normal, nulled myocardium in the posterior septum. RV indicates right ventricle; LV, left ventricle. B, Automated grayscale threshold ≥6 SDs above the mean signal intensity of the ROI indicating high LGE-SI (arrows; red shading). C, Grayscale threshold ≥4 SDs above normal myocardium identifying intermediate and high LGE-SI (red shading), remote from (white arrow) and contiguous with high LGE-SI. D, Subtraction of LGE at ≥6 SD from that quantified at ≤4 SD, indicating intermediate LGE-SI (red shading) remote from (white arrow) and contiguous with the regions of high LGE-SI.
ROC analysis (intermediate LGE-SI optimal cutoff for extent of LGE relative to NSVT from the high LGE-SI (30 of 46), and 2 more than the combination of additional HCM patients with NSVT (37 of 46) compared with and their combination interval 0.56–0.80;)

of intermediate and high LGE-SI (0.68 [95% confidence interval 0.52–0.77];

ence of intermediate LGE-SI to the severity of ventricular arrhythmias on 24-hour ambulatory (Holter) ECG in 145 patients with hypertrophic cardiomyopathy. LGE indicates late gadolinium enhancement; None, no ventricular arrhythmia; PVC, premature ventricular contractions; Couplet, ventricular couplets; and NSVT, nonsustained ventricular tachycardia.

Relation of Extent of LGE to Ventricular Tachyarrhythmias

Premature Ventricular Contractions

The extent of intermediate and high LGE-SI was greater among HCM patients with premature ventricular contractions than among those without them (13±8 versus 10±10 g, P<0.001, and 12±7 g versus 10±8 g, P=0.003, respectively; Figure 4). In patients with premature ventricular contractions, the extent of intermediate LGE-SI exceeded that of high LGE-SI (13±8 versus 12±7 g; P=0.01).

Ventricular Couplets

The amount of intermediate and high LGE-SI was greater among HCM patients with ventricular couplets than among those without them (16±10 versus 10±10 g, P<0.001, and 14±9 versus 10±8 g, P=0.02, respectively; Figure 4). In patients with ventricular couplets, the extent of intermediate LGE-SI exceeded that of high LGE-SI (16±10 versus 14±9 g; P=0.04).

Nonsustained Ventricular Tachycardia

The amount of intermediate and high LGE-SI was greater among HCM patients with NSVT than among those without NSVT (17±7 versus 10±10 g, P=0.003, and 15±6 versus 10±8 g, P<0.001, respectively). In patients with NSVT, the amount of intermediate LGE-SI exceeded that of high LGE-SI (17±7 versus 15±6 g, P=0.01; Figure 4).

With ROC analysis, the area under the curve demonstrated a trend for intermediate LGE-SI to be a better discriminator for identifying HCM patients with NSVT (0.72 [95% confidence interval 0.60–0.83]) than high LGE-SI (0.65 [95% confidence interval 0.52–0.77]; P=0.174) or the combination of intermediate and high LGE-SI (0.68 [95% confidence interval 0.56–0.80]; P=0.129; Figure 5). By determining the optimal cutoff for extent of LGE relative to NSVT from the ROC analysis (intermediate LGE-SI ≥12 g, high LGE-SI ≥8 g, and their combination ≥19 g), intermediate LGE-SI identified 7 additional HCM patients with NSVT (37 of 46) compared with high LGE-SI (30 of 46), and 2 more than the combination of high and intermediate LGE-SI (35 of 46; Table 2; Figure 6). Within each LGE-SI group, there was no significant relationship between the occurrence of ventricular tachyarrhythmias and the location of LGE or transmural distribution.

Association of LGE With CMR and Clinical Characteristics

There was no significant relationship between the extent of intermediate or high LGE-SI and maximal LV wall thickness (best r=0.03; P=0.09), LV mass index (best r=0.02; P=0.4), or ejection fraction (best r=−0.3; P=0.07). In addition, there was no difference in age, use of cardioactive drugs, New York Heart Association functional class, presence of LV outflow tract obstruction, or history of syncope among patients with greater than the median compared with those with less than the median of LGE for intermediate or high LGE-SI (P=0.22 and 0.30, respectively).

Discussion

Contrast-enhanced CMR has emerged as a novel imaging technique to identify myocardial fibrosis in patients with HCM.11,15,16,25,27 Several recent CMR studies have demonstrated an increased risk of ventricular tachyarrhythmias and adverse outcome among HCM patients with LGE, which suggests that hyperenhancement may be a marker for an unstable electric substrate.11,15,16,25,27 These earlier studies primarily considered areas of myocardium with high LGE-SI as most relevant for the generation of potentially life-threatening ventricular arrhythmias. Areas of intermediate LGE-SI are also present in HCM patients,34 but despite their relationship to increased myocardial collagen on postmortem analysis, they remain of uncertain clinical significance. Therefore, we thought it timely to focus on determining the prevalence of intermediate LGE-SI and its association with ventricular tachyarrhythmias in HCM.
We found regions of both intermediate and high LGE-SI present in all HCM patients demonstrating LGE. In patients with ventricular tachyarrhythmias, including NSVT (a recognized risk factor for sudden death in HCM), the amount of intermediate LGE-SI exceeded that of high LGE-SI. Furthermore, based on our ROC analysis, the magnitude of intermediate LGE-SI proved to be the most reliable LGE discriminator for identifying HCM patients with ambulatory NSVT. Indeed, after we determined the optimal cutoff value for identifying NSVT in each LGE subgroup, intermediate LGE-SI identified 7 additional HCM patients with NSVT who would not otherwise have been recognized if the CMR images had been analyzed only with respect to high LGE-SI. Finally, intermediate LGE-SI alone was even a stronger predictor of NSVT than the combination of intermediate and high LGE-SI.

Therefore, the present observations introduce 2 novel principles with respect to the interpretation of LGE in patients with HCM: (1) Not all LGE is equivalent as a clinical marker of risk for ventricular tachyarrhythmias, because our data suggest that intermediate LGE-SI identifies an abnormal myocardial substrate more prone to ventricular tachyarrhythmias than high LGE-SI. This principle represents a paradigm shift from the strategy currently exercised in analyzing LGE on CMR images, in which areas of lesser LGE-SI have been largely ignored. (2) The magnitude of LGE-SI indicates late gadolinium enhancement signal intensity; HCM, hypertrophic cardiomyopathy; %LV, percent of left ventricle; NSVT, nonsustained ventricular tachycardia; PVCs, premature ventricular contractions.

*Statistically significant with respect to absence of the arrhythmia; \( P<0.003 \).

†Statistically significant with respect to absence of the arrhythmia; \( P<0.02 \).

‡Statistically significant with respect to absence of the arrhythmia; \( P<0.005 \).

Table 2. Relation of Ventricular Arrhythmia to LGE-SI in 145 HCM Patients

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients (%)</th>
<th>Intermediate LGE-SI, g (%LV)</th>
<th>High LGE-SI, g (%LV)</th>
<th>Combined Intermediate and High LGE-SI, g (%LV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSVT</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Present</td>
<td>46 (32)</td>
<td>17±7 (8.2±3.3)*</td>
<td>15±6 (7.2±2.4)†</td>
<td>32±11 (15.1±5.5)‡</td>
</tr>
<tr>
<td>Absent</td>
<td>99 (68)</td>
<td>10±10 (4.8±3.8)</td>
<td>10±8 (4.2±3.3)</td>
<td>21±16 (9.1±6.3)</td>
</tr>
<tr>
<td>Ventricular couplets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>58 (40)</td>
<td>16±10 (7.5±4.2)*</td>
<td>14±9 (5.5±2.1)†</td>
<td>28±9 (13.3±4.5)‡</td>
</tr>
<tr>
<td>Absent</td>
<td>87 (60)</td>
<td>10±11 (4.8±3.9)</td>
<td>10±12 (4.2±4.0)</td>
<td>22±16 (9.2±6.1)</td>
</tr>
<tr>
<td>PVCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>119 (82)</td>
<td>13±8 (6.2±3.9)*</td>
<td>12±7 (4.7±3.0)†</td>
<td>26±16 (11.1±7.2)‡</td>
</tr>
<tr>
<td>Absent</td>
<td>26 (18)</td>
<td>10±13 (4.8±4.1)</td>
<td>10±8 (4.2±3.3)</td>
<td>21±17 (8.1±6.4)</td>
</tr>
</tbody>
</table>

Figure 6. A 54-year-old male patient with hypertrophic cardiomyopathy with nonsustained ventricular tachycardia (NSVT) on ambulatory Holter ECG monitor predicted by the quantity of intermediate late gadolinium enhancement signal intensity (LGE-SI) but not high LGE-SI or their combination. A, Cardiac magnetic resonance LGE short-axis image (midventricle) showing enhancement (white arrow) in the interventricular septum. RV indicates right ventricle; LV, left ventricle. B, Extensive regions of intermediate LGE-SI (red shading) amounting to 12.4 g or 7.9% (greater than optimal receiver operating characteristic [ROC] cutoff). C, Small area high LGE-SI (red shading) amounting to 3.2 g or 1.8% (less than optimal ROC cutoff). D, The combination of intermediate and high LGE-SI amounting to 15.6 g or 9.6% (less than optimal ROC cutoff). E, Holter monitor showing a 10-beat run of NSVT (the patient had 6 such bursts of NSVT in a 24-hour period).
LGE may be more important for the identification of patients at risk for the generation of ventricular tachyarrhythmias than only the presence of LGE.

Indeed, when we compared the present data with those of Adabag et al.15 (based on the presence of high-signal-intensity LGE in HCM), the extent of intermediate signal intensity in patients in the present study was associated with a 2-fold increase in NSVT. Whether or not recognition of intermediate LGE-SI myocardium on contrast-enhanced CMR studies can be extrapolated into the clinical arena to identify individual HCM patients at risk of potentially lethal arrhythmias and sudden death is unresolved at this time and beyond the scope of the present investigation.

Nevertheless, these data establish a new concept with respect to the interpretation of LGE in HCM, which now appears to be a more heterogeneous entity in which areas of lesser signal intensity should also be taken into consideration. The potential impact of lower LGE-SI has been explored in other disease states, most extensively in ischemic cardiomyopathy, in which such areas (termed “border zones”) appear on the periphery but contiguous with the high-signal-intensity core myocardial infarction.37 Indeed, the extent of the “border zone” area identifies patients with ischemic cardiomyopathy at increased risk for ventricular tachyarrhythmias and adverse outcome, with histopathological studies demonstrating these regions to be composed of substantial tissue heterogeneity, including a mixture of isolated myocytes and fibrosis.35,36,38,39 The present data may extend this concept to patients with HCM. However, several obstacles to clarifying the histopathological basis of either high or intermediate LGE-SI in the typical HCM phenotype with preserved LV systolic function remain, including (as in the present cohort) (1) lack of an HCM animal model suitable for study by CMR and (2) the impracticality associated with coordinating the comparison of postmortem HCM hearts with contrast-CMR studies previously obtained in the same patients.

It is possible that these early observations may ultimately lead to enhanced identification of the HCM subset with increased susceptibility to sudden death. However, at this juncture, the role of intermediate LGE in risk stratification and selection of patients for primary prevention implantable cardioverter-defibrillators is unresolved given the lack of long-term follow-up data in this cohort. Nevertheless, our data underscore the potential value of assessing the extent and character of LGE (rather than only the presence of LGE) for predicting outcome in HCM. The study of larger patient cohorts followed up for long periods of time will be necessary to acquire the robust statistical power necessary to clarify the independent prognostic impact that intermediate LGE-SI may have as a risk-stratification strategy in HCM.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

A number of recent cardiac magnetic resonance studies have demonstrated an increased risk of ventricular tachyarrhythmias and adverse outcome among patients with hypertrophic cardiomyopathy with late gadolinium enhancement (LGE), which suggests that it may be a marker for an unstable electric substrate. These studies primarily considered areas of myocardium with high LGE signal intensity as most relevant for generating potentially life-threatening ventricular arrhythmias. Our present observations introduce 2 novel principles with respect to the interpretation of LGE in patients with hypertrophic cardiomyopathy: (1) Not all LGE is equivalent as a clinical marker of risk for ventricular tachyarrhythmias, because our data suggest that intermediate signal intensity identifies an abnormal myocardial substrate more prone to ventricular tachyarrhythmias than high-intensity LGE. This principle represents a paradigm shift from the strategy currently exercised in analyzing LGE on cardiac magnetic resonance images, in which areas of lesser signal intensity have been largely ignored. (2) The magnitude of LGE may be more important for identifying patients at risk for generating ventricular tachyarrhythmias than merely the presence of LGE. Despite these important observations, the role of LGE in risk stratification and selection of patients for primary prevention implantable cardioverter-defibrillators is unresolved, given the lack of amply powered outcome studies. Nevertheless, the present data underscore the potential importance of assessing the extent and character of LGE (rather than only the presence of LGE) for predicting outcome in hypertrophic cardiomyopathy and should therefore be measured in a larger patient study designed to clarify the incremental prognostic value of LGE.
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