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# Low-intensity late gadolinium enhancement predominates in hypertrophic cardiomyopathy ☆

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## ARTICLE INFO

## ABSTRACT

**Aim:** Assess the extent of low- versus high-intensity late gadolinium enhancement (LGE) in hypertrophic cardiomyopathy (HCM).
**Methods:** Low- versus high-intensity LGE indexed volumes in 19 HCM patients were compared to 23 myocardial infarction (MI) patients.
**Results:** Total, low-, and high-intensity LGE volumes in HCM vs. MI were 7.6 ml/m$^2$, 4.7, and 2.4 vs. 11.2, 2.5, and 7.1, respectively. Total LGE volume did not differ ($P=.13$), though low- and high-intensity did ($P=.05, .004$). 67% versus 26% of all LGE was low-intensity in HCM versus MI ($P<.001$).
**Conclusions:** LGE in HCM is predominantly low-intensity, so a low threshold may be the most appropriate.

## 1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent genetic disease affecting the heart [1], characterized by myocardial hypertrophy out of proportion to the hemodynamic load. HCM is a heterogeneous disease with significant variation in severity and morphologic forms [2]. HCM can result in lethal arrhythmias and is the number one cardiovascular killer among young patients. The risk of arrhythmias and poor clinical outcomes in HCM is associated with LV mass [1,3,4] as well as late gadolinium enhancement (LGE) demonstrated by cardiac magnetic resonance imaging (MRI) [5–14].

LGE is seen in approximately 80% of HCM patients [13] and is thought to correlate to areas of fibrosis [15]. Particularly in cases with focal LGE, "replacement" fibrosis is responsible, a form in which fibrosis replaces large areas of damaged or necrotic myocytes [16,17]. A component of diffuse interstitial fibrosis is also present in this disease [17,18], though it is not readily apparent on cardiac MRI without using advanced T1 mapping techniques [19]. The LGE seen on routine cardiac MRI of HCM has only been limitedly characterized in the literature as to the absolute amounts of different intensity LGE [20]. To our knowledge the LGE in HCM has not previously been evaluated comparing the low-versus intermediate-to-high-intensity LGE, and it has not previously

been directly compared to a reference disease with a well-established pattern of LGE such as myocardial infarction. Information regarding the distribution of LGE could guide new cardiac MRI readers as to the patterns expected in HCM compared to other disorders with LGE, and may correspond to different types of myocardial fibrosis seen in this disease.

The aim of this study was to characterize the low- versus intermediate/high-intensity LGE in HCM, both in terms of volume (indexed) of myocardium and proportionately, by employing a method of LGE analysis that has previously been used in patients with myocardial infarction. To provide a frame of reference, the indexed volumes of different intensity LGE in HCM were compared to a group of patients with MI.

## 2. Materials and methods

### 2.1. Subjects

This study was approved by the institutional review board and is Health Insurance Portability and Accountability Act compliant. Informed consent was waived. All clinical cardiac MRI reports from Jan 1995 to Oct 2009 from a single institution were searched for the keywords "hypertrophic," "cardiomyopathy," and "HCM", yielding 277 unique reports. Each study was assessed for the presence of a LGE sequence, a short axis cine, and imaging findings compatible with HCM. The medical chart was reviewed to confirm the absence of a pressure overload lesion and to confirm the diagnosis of HCM had also been made clinically. In patients evaluated repeatedly, only the first study was included. Twenty-three unique studies remained after this process, of which 19 (83%) demonstrated LGE per the image analysis described below.

A keyword search for "infarct," "infarction," or "MI" over the same time frame yielded 156 unique MR reports which were reviewed for the presence of a short axis LGE sequence, a short axis cine, and imaging findings compatible with an acute or chronic MI. Of note, the work-up algorithm of MI patients at our institution uncommonly included MR, whereas HCM was commonly imaged through our HCM-focused subspecialty clinic. The medical chart was reviewed to confirm the clinical diagnosis of MI. Eight patients with apical MIs (both acute and chronic) were excluded due to either marked thinning of the apex limiting LGE evaluation (3 patients) or inadequate image quality (5 patients). Four patients with complex congenital heart disease were also excluded. Twenty-three patients were included in the final MI cohort.

## 2.2. Imaging parameters

Images were acquired on a 1.5-T Intera CV MRI scanner (Philips Medical Systems, Best, The Netherlands) with a phased-array cardiac coil. Steady-state free precession (SSFP) cine images were obtained in the short-axis plane encompassing the entire heart with a slice thickness of 8 mm and no gap. Eighteen phases in the cardiac cycle were obtained (repetition time [TR]=R-R interval, echo time [TE]=1.4–3.2 ms, flip angle [FA]=45°). Late gadolinium enhancement images were obtained approximately 15 minutes after the administration of a double dose (0.2 mmol/kg) of chelated gadolinium intravenous contrast. 3D inversion-recovery turbo field echo images were obtained with the following parameters: inversion time=220–300 ms, TR=7.6 ms, TE= 2.0 ms, FA=15°, field of view=260 mm, number of excitations=1, matrix 256×256). The inversion recovery time was optimized for myocardial nulling and slice thickness was 12 mm with no gap.

## 2.3. Image analysis

The image analysis was performed using the freely available software Segment, version 1.8 R1145 [21]; two authors worked together in a consensus fashion to derive all measurements. A third reader was omitted given the marked similarity in measurements from the two readers and the ease of consensus formation. Endocardial and epicardial contours were manually drawn on short axis cine images at end-diastole and end-systole to obtain LV myocardial volume (and mass), end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction. The volumes were indexed to the body surface area. End-diastolic wall thickness was measured in the anterior, inferior, lateral, and septal walls at the mid-ventricle. Late gadolinium enhancement was identified using the "S.D. from Remote Mode" analysis, which analyzes the signal intensity of each myocardial pixel compared to the mean/standard deviation measured in a region of remote myocardium [22].

The preferential location for the remote myocardium region of interest (ROI) was the lateral wall given it is generally the least affected by LGE in HCM; this area was successfully selected in 17 of the 19 HCM subjects. The anterolateral and anteroseptal walls were chosen in two subjects to avoid a definitive focus of LGE in the lateral wall in the first subject and due to a thin lateral wall in the second. Remote areas were semi-automatically drawn to encompass 30 degrees of the ventricular circumference and the middle 80 percent of the wall thickness (to avoid artifact from the endocardial and epicardial interfaces). In MI patients, the lateral wall was also preferentially chosen, though other segments had to be selected more commonly to avoid areas of LGE; in 12 of 23 subjects, the remote ROI was in the lateral or anterolateral wall (52%), 6 of 23 in the anterior or anteroseptal wall (26%), and 5 of 23 in the septum or inferior walls (22%).

The threshold values selected to define low- versus intermediate/ high-intensity LGE regions were based on multiple prior studies in the MI literature which characterized a low-intensity "border zone" versus a higher intensity "core" [23], specifically areas with signal intensities between 2–3 and >3 S.D. above remove myocardium, respectively. Mechanistically, obtaining the low-intensity LGE measurement

required subtracting the intermediate/high-intensity LGE (>3 S.D.) volume from the total LGE (>2 S.D.) volume (Fig. 1A and B). High-intensity only volumes (>6 S.D.) were also measured. The parameters used in the Segment algorithm include a beta (curvature weight) of 0.2 and a minimum value (volume that an area of LGE must exceed) of 0.5 ml. All LGE volumes were indexed to body surface area.

LGE images were reviewed for areas of non-LGE in the center of dense LGE. Such areas are considered to be regions with compromised blood flow (if in a patient who has not been revascularization) or microvascular obstruction (if in a patient who was recently revascularized) and were defined a priori to be part of the intermediate/high-intensity LGE.

## 2.4. Statistical analysis

Statistics were calculated using Stata, version 11.0 (College Station, TX). A p-value threshold for statistical significance of 0.05 was used for all analyses. Data are reported as percentages for categorical variables and as medians with an interquartile or absolute range for continuous variables. Two group comparisons were made using the Wilcoxon rank-sum test for continuous variables and the $\chi^2$ test for dichotomous variables.
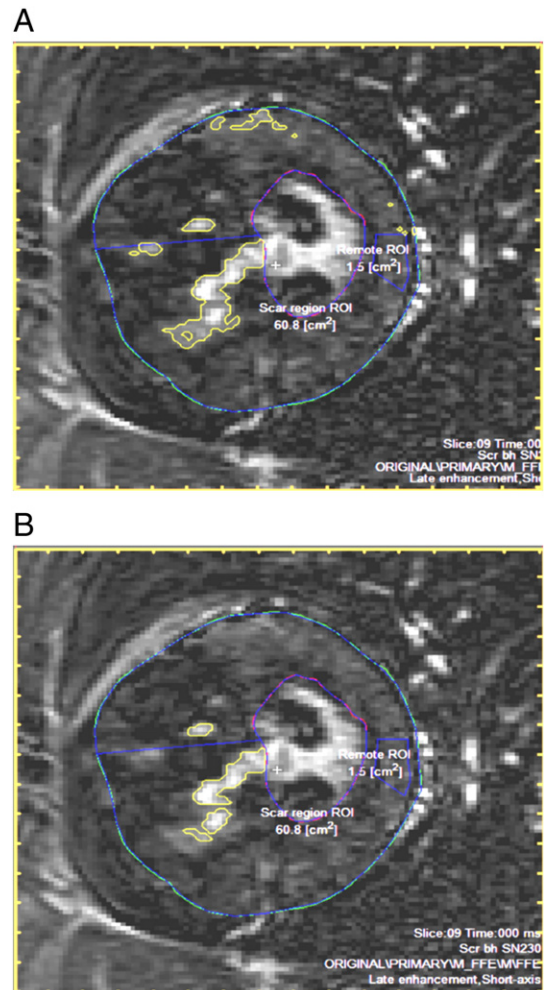


**Fig. 1.** LGE Quantification by *Segment* Software. Epicardial and endocardial boundaries were drawn manually and a region of remote myocardium was defined via a semi-automated technique that preferentially assigned a region of the lateral wall (labeled "Remote ROI"). Pixels with signal intensities greater than 2 (A) and 3 (B) standard deviations above the remote myocardium correspond to the "total LGE" and "intermediate/high-intensity LGE", respectively. The mathematical difference represents the low-intensity LGE volume.

# 3. Results

## 3.1. Subject characteristics

Patients' characteristics are summarized in Table 1. Of note, the MI cohort included 10 acute and 13 chronic MI subjects, thereby constituting a cross-section of MI subjects. Nine of the 10 acute MI subjects were imaged without a prior revascularization; 1 subject received percutaneous coronary angioplasty one day prior to cardiac MRI. None of the thirteen chronic MI subjects had revascularization immediately prior to imaging.

HCM patients demonstrated a normal median end-diastolic volume index (70.6 ml/m$^2$), though a small median end-systolic volume index (22.7 ml/m2) and a high median ejection fraction (69%). These two abnormal parameters were statistically significantly different than the comparison group of MI patients, $P=.001$, $P<.001$, respectively. HCM patients demonstrated an abnormally large LV mass index (105 g/m$^2$) and thickened LV walls, most prominent in the septum (median, 19 mm), parameters that statistically significantly differed from subjects with MI ($P$ values of 0.02 to <0.001). Seventeen of the 19 HCM (89%) subjects demonstrated a septum to lateral wall ratio of 1.5 or greater and were considered to have asymmetric septal HCM. The remaining two subjects demonstrated concentric thickening indicative of concentric HCM.

## 3.2. Late gadolinium enhancement

The majority of our HCM cohort demonstrated more than one focus of LGE; 2 foci were observed in 5/19 subjected (26%) and 3 or more foci in 10/19 (53%). LGE was most commonly observed in the septum and least commonly in the lateral wall and generally was seen in the mid-myocardium.

Table 2 summarizes the volumes of LGE of different intensities observed in HCM. Total LGE in our cohort of HCM comprised a median of 6% of the myocardium, with a median indexed volume of 7.6 ml/m$^2$. A median of 67% of the LGE was low-intensity. The LGE in some HCM subjects was entirely low-intensity, which was not true for any MI subject.

By comparison, MI subjects total LGE comprised a median of 22% of the myocardium ($P=.004$ compared to HCM), with a median indexed volume 11.2 ml/m$^2$ ($P=.13$ compared to HCM). A median of 26% of the LGE was low intensity. Indexed low-intensity LGE volume (Fig. 2A), intermediate/high-intensity LGE volume, high-intensity only LGE volume, and percent LGE that is low-intensity (Fig. 2B) were all statistically significantly different compared to the HCM group ($P=.05$, .004, <.001, <.001, respectively).

There was no difference in the low-intensity, intermediate/high-intensity, and total volumes (indexed) of LGE between the acute and chronic infarcts subjects ($P=.5$, .95, .98, respectively). Eight of the 23 (35%) and 15 of 23 (65%) MI subjects demonstrated subendocardial

and transmural myocardial infarcts (Fig. 3), respectively. Four (27%) of the transmural infarct patients demonstrated more than one discrete foci of LGE. One transmural infarct subject 5 days after MI (which was not revascularized) demonstrated a sizeable low signal region within an area of high signal intensity, suggesting a central area of compromised blood flow (volume index = 10 ml/m$^2$, which was included in the "intermediate/high-intensity" LGE volume measurement of 38 ml/m$^2$).

The remote (normal) myocardium regions of interest were comparable in intensity between the two groups (Table 2).

# 4. Discussion

Our study demonstrated that low-intensity LGE predominates in patients who have demonstrable LGE in the setting of HCM. A comparison was made to subjects with MI, a common LGE-positive abnormality frequently evaluated by cardiac MRI, which demonstrated that the proportion of low-intensity LGE is greater in HCM compared to MI. Indexed volumes of total LGE were not statically different between the two groups, though the total amount of LGE in HCM represented a much smaller percentage of the myocardium given the hypertrophy inherent to the disease.

In myocardial infarction patients, the different intensities of LGE seen by cardiac MRI correspond to very specific histologies. Namely, low-intensity LGE, approximately 2–3 S.D. above remote myocardium, corresponds to a border zone around infarcts comprised of viable myocytes interspersed within fibrosis [24–26], where as more the intermediate/high-intensity LGE corresponds to completely necrotic or fibrotic tissue. Given the entirely different pathophysiology of HCM, the significance of different intensities of LGE cannot be inferred from the MI literature.

In multiple early studies of LGE in HCM, LGE was shown to represent only a portion of the fibrosis known to exist in patients with HCM. Areas of "replacement" fibrosis result in a sufficient enlargement of the extracellular space such that macroscopically visible accumulation of gadolinium can be detected on delayed images [17,27]. Subsequent studies have shown an extensive diffuse interstitial fibrosis also occurs affecting nearly the entire ventricle, but does not have a clear correlate on LGE, particularly when higher thresholds are used; the extent of this more diffuse fibrosis can result in diastolic dysfunction and can be demonstrated by advanced post-gadolinium T1 mapping techniques [15,19,28].

The body of literature evaluating the detectable, but low-to-intermediate-intensity, LGE in HCM is limited. A few studies have specifically examined the association of low-intensity LGE to histopathology [29] and visual assessment [30]. Compared to high intensity LGE, intermediate intensity LGE better associated with the total volume of fibrosis seen by pathology, including the dense (replacement) and less dense (interstitial) fibrosis detected. The lowest intensity LGE in the Moravsky et al. paper, seemed to overestimate the extent of fibrosis

**Table 1**
Subject characteristics, LV morphology, and LV function

|  | Hypertrophic cardiomyopathy ($n=19$) Median (IRQ) | Myocardial infarction ($n=23$) Median (IRQ) | Statistical significance (Wilcoxon rank-sum test) |
|---|---|---|---|
| Age, years | 48 (17–60) | 59 (47–68) | $P=.03$ |
| Male | 13/19 (68%) | 17 / 23 (74%) | $P=.7$ (Chi-2) |
| Body surface area (m$^2$) | 1.8 (1.8–2) | 1.8 (1.7–2.0) | $P=.9$ |
| End-diastolic volume index, ml/m$^2$ | 70.6 (60.5–81.8) | 78.4 (66.3–104) | $P=.4$ |
| End-Systolic Volume Index, ml/m$^2$ | 22.7 (17–36.8) | 56.8 (31.1–76.5) | $P=.001$ |
| Stroke volume index, ml/m$^2$ | 44.4 (38.4–52.6) | 26.9 (21.6–37.3) | $P<.001$ |
| Ejection Fraction, % | 69 (60–72) | 31 (25–55) | $P<.001$ |
| LV mass index, g/m$^2$ (LV mass=LV volume x 0.9533) | 105 (75–119) | 60 (49–71) | $P<.001$ |
| Mid-ventricle, end-diastolic wall thickness |  |  |  |
| Septum, mm | 19 (15–23) | 10 (9–12) | $P<.001$ |
| Anterior, mm | 11 (7–19) | 7 (6–9) | $P<.001$ |
| Lateral, mm | 10 (7–11) | 7 (6–8) | $P=.02$ |
| Inferior, mm | 10 (8–11) | 7 (6–9) | $P=.001$ |

IRQ=interquartile range.

**Table 2**
Late gadolinium enhancement measurements

| | Hypertrophic cardiomyopathy (n=19) Median (IRQ) | | Myocardial infarction (n=23) Median (IRQ) | | Statistical significance (Wilcoxon rank-sum) |
| --- | --- | --- | --- | --- | --- |
| | Volume index, ml/m2 | Percent myocardium, % | Volume index, ml/m2 | Percent myocardium, % | Volume index |
| Total LGE | 7.6 (2.8-12.8) | 6 (4–11) | 11.2 (6.0-20.3) | 22 (8–34) | $P=.13$ |
| Low-intensity LGE (2–3 S.D.) | 4.7 (2.3-7.9) | 4 (3–7) | 2.5 (1.8-4.8) | 5 (3–8) | $P=.05$ |
| Intermediate/high-intensity LGE (>3 S.D.) | 2.4 (0.7-5.6) | 2 (1–4) | 7.1 (3.2-16.2) | 14 (4–26) | $P=.004$ |
| High-intensity LGE (>6 S.D.) | 0 (0–0.65) | 0% (0–0.3) | 3.5 (1.1-8) | 6% (2–16) | $P<.001$ |
| Low-intensity LGE (% of total) | 67% (50–80%) | | 26% (17–38%) | | $P<.001$ |
| Remote myocardium intensity | 0.084 (0.05–0.12) | | 0.099 (0.06–0.15) | | $P=.06$ |

IRQ=interquartile range.

seen in resection specimens. We intentionally selected a low threshold for analysis, in part because our cohort of HCM patients lacked high-intensity LGE, and also to maintain maximal sensitivity for any abnormal myocardium. Our study benefited from a comparison group – therefore any artifacts or processing abnormalities causing increased signal theoretically would affect imaging in both groups. We demonstrated more low-intensity LGE in HCM compared to an MI group scanned on the same equipment and analyzed in the same manner, suggesting a true underlying abnormality. While we lack pathologic correlation for this low-intensity LGE, one possible explanation is this abnormality represents an early manifestation of disease that eventually would become more intense on LGE later in the disease process.

Our analysis employed the S.D. above remote myocardium technique given its sensitivity to low-intensity LGE and its success in the border zone MI literature [23]. Techniques that define levels of intensity in reference to the highest signal intensity [31,32] may not be well suited to evaluate a disease with an overall low-intensity, highly variable LGE.

Using a slightly higher threshold for analysis than ours, namely intermediate versus high intensity, Appelbaum and colleagues evaluated the potential clinical relevance of intermediate-intensity predominant LGE in HCM [20]. This study specifically interrogated the association between intermediate- versus high-intensity LGE (4–6 S.D. above remote myocardium versus >6 S.D.) and electrophysiological makers of poor outcomes. Their study demonstrated the intermediate LGE volume was a better predictor of nonsustained ventricular tachycardia compared to higher-intensity LGE. In 72% of their subjects, there was more intermediate-intensity LGE than high-intensity, similar to our finding of predominant low intensity LGE (2–3 S.D.) compared to higher level-intensity LGE (>3 S.D.).

Given low-intensity LGE predominates in HCM, relatively low thresholds for detection of LGE may be the most appropriate for clinical interpretations and in future research studies such that sensitivity may be maintained. In addition, cardiac MRI sequences capable of characterizing diffuse interstitial fibrosis, such as T1 mapping, may be useful in further characterizing the extent of fibrosis and predicting poor outcomes in HCM.

Our study has a number of limitations. First is the relatively small sample size, which limits the confidence that our cohort is broadly representative. This was a retrospective study, which can result in certain biases, including biases resulting from only a subset of HCM or MI patients being referred for cardiac MRI. Our comparison group, MI
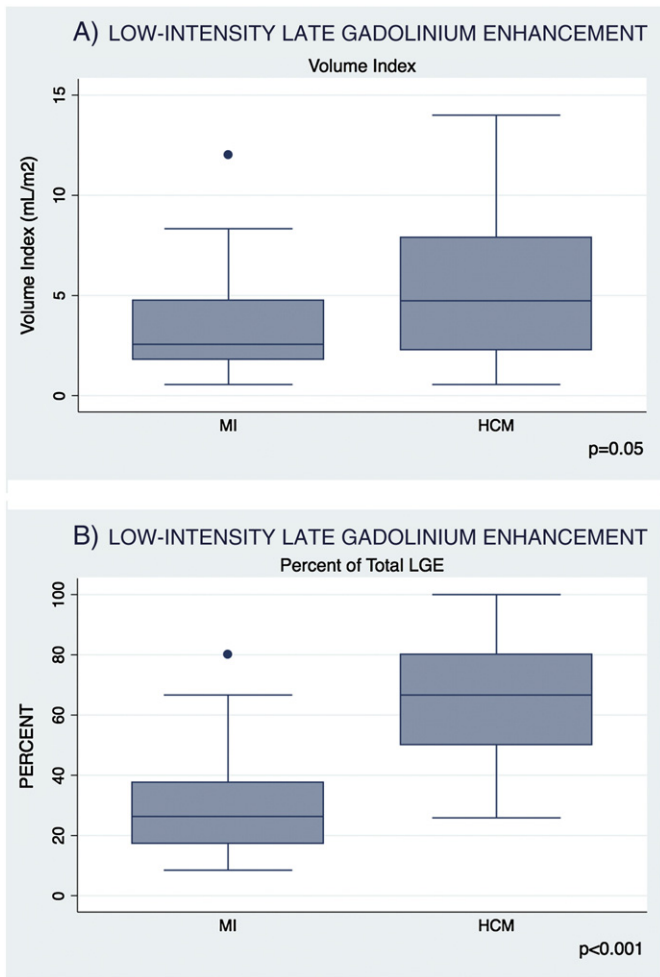


**Fig. 2.** Low-intensity LGE in HCM vs. MI subjects. Boxplots depict low-intensity LGE by volume index (A) and percent of total LGE (B). Statistically significantly more low-intensity LGE was demonstrated in the myocardium of HCM subjects, *P*=.05. The median percent LGE that was low-intensity was 67% vs. 26% in HCM vs MI subjects, respectively, *P*<.001.
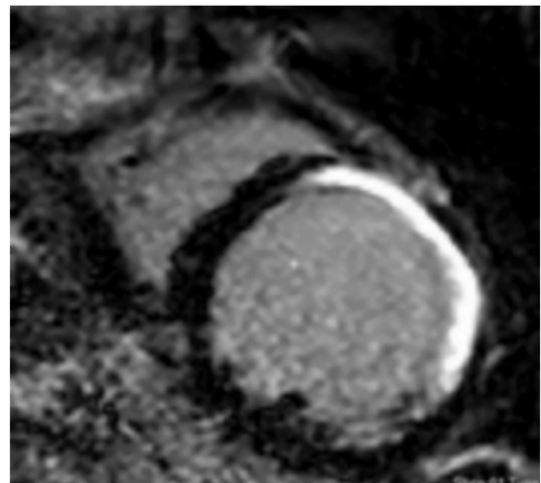


**Fig. 3.** LGE in myocardial infarction. A LGE image of a 73-year-old patient initially suspected of having a left ventricular aneurism. MR imaging demonstrates a perfusion defect on dynamic post gadolinium images (not shown), akinesis on cine images (not shown), and intermediate/high-intensity LGE involving the anterior wall, findings consistent with a transmural myocardial infarction.

subjects, was chosen given the extensive understanding of LGE mechanisms and multiple prior studies applying LGE quantification techniques in this disease; though our specific group of MI patients was mixture of MI subjects and was inherently heterogonous. Only a single set of LGE measurements were obtained, but the measurements were derived from two investigators working together in a consensus fashion. Prior research has suggested high levels of reproducibility in LGE measurements [31]. Finally, pathologic analysis and sufficient clinical follow up was not available to allow for assessing associations with LGE.

In conclusion, low-intensity LGE is the predominant form of LGE in HCM patients. In the clinical evaluation of HCM patients, relatively low visual and/or quantitative thresholds may be appropriate in an effort to maintain sensitivity. Future research can explore the clinical significance of low-intensity LGE, thereby helping inform the selection of a clinically meaningful threshold for detecting LGE.

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