Late gadolinium enhancement confined to the right ventricular insertion points in hypertrophic cardiomyopathy: an intermediate stage phenotype?

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Received 9 February 2015; accepted after revision 23 May 2015; online publish-ahead-of-print 14 June 2015

Aims

To investigate whether hypertrophic cardiomyopathy (HCM) patients with late gadolinium enhancement (LGE) confined to the right ventricular insertion points (RVIP) differ phenotypically from patients without LGE or intramural LGE in the left ventricle (LV).

Methods and results

Sixty-two HCM patients underwent cardiac magnetic resonance for quantification of LGE (% LV mass) and were classified as group (i) no-LGE (n = 18), group (ii) LGE-RVIP (n = 19), and group (iii) intramural LGE (n = 25). All patients also underwent vasodilator N-13 ammonia PET to quantify myocardial blood flow (MBF) and myocardial flow reserve (MFR), and echocardiography to measure longitudinal LV strain. LGE extent (17 ± 11% vs. 4 ± 4% vs. 0%; P < 0.001) and LV thickness (21.7 ± 3.4 vs. 18.8 ± 3.9 vs. 16.3 ± 2.8 mm; P < 0.001) were significantly greater in group 3, intermediate in group 2, and lower in group 1. In contrast, stress MBF (1.62 ± 0.44 vs. 1.90 ± 0.37 vs. 2.22 ± 0.48 mL/min/g; P < 0.001); MFR (1.92 ± 0.47 vs. 2.15 ± 0.52 vs. 2.71 ± 0.52; P < 0.001), and longitudinal LV strain (−11.4 ± 3.8 vs. −12.6 ± 3.2 vs. −14.4 ± 4.1%; P = 0.04) were lower in group 3, intermediate in group 2, and higher in group 1.

Conclusions

From an imaging viewpoint, patients with LGE confined to only the RVIP appear to represent an intermediate-stage phenotype between patients with no LGE and intramural LGE in the LV.

Keywords CMR • LGE • RV insertion points

Introduction

Left ventricular (LV) late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) imaging in hypertrophic cardiomyopathy (HCM) has emerged as a highly informative biomarker with implications for diagnosis and prognosis.

Individuals with HCM and LGE on CMR have more markers associated with sudden cardiac death (SCD), and higher incidence of adverse cardiovascular events, including disease progression, heart failure symptoms, ventricular arrhythmias, and all-cause and cardiac mortality. Two major distribution patterns of LGE have been described: intramural LGE, within the hypertrophied segments of LV, and LGE located at the anterior and/or posterior right ventricular insertion points (RVIPs). Intramural LGE is traditionally thought to correspond to areas of focally increased collagen content, a major component of fibrosis, whereas LGE at the RVIP has been proposed to represent focal plexiform fibrosis (associated with myocardial disarray) rather than replacement fibrosis. Interestingly, patients with LGE limited to only the RVIP have been found to have less heart failure symptoms and a lower risk profile for SCD as opposed to HCM individuals with intramural LGE.
LGE. Recent data from Chan et al.\textsuperscript{6} and Ismail et al.\textsuperscript{11} indicate that the extent of LGE is probably a more important predictor of SCD events than just the presence of LGE (based on univariate and multivariate analyses in Chan’s study, but only as a univariate predictor in Ismail’s work),\textsuperscript{10} which could help explain the lower risk profile reported in patients with LGE confined to the RVIP.

However, it remains unclear whether in addition to having lower degrees of LGE, there are additional differences in the imaging characteristics of HCM patients with LGE confined to the RVIP.

Previous studies have independently revealed that myocardial flow reserve (MFR),\textsuperscript{12–14} an indirect measure of coronary microvascular function, and myocardial longitudinal strain,\textsuperscript{15} a parameter of regional systolic and diastolic function, are more affected in patients with LGE compared with those without LGE. In contrast, the relationship of left ventricular outflow tract gradients (LVOTGs) and LGE is less predictable or intuitive.\textsuperscript{16}

Therefore, in this multi-modality imaging study, we aimed at investigating whether HCM patients with LGE confined to the RVIP differ phenotypically from patients with no-LGE or intramural LGE by measuring LGE extent and LV hypertrophy by CMR, myocardial flow by PET, and LV longitudinal strain, and LVOTG by echocardiography. Short-term outcomes were also investigated.

**Methods**

**Subjects**

We enrolled consecutive patients from the Johns Hopkins Hypertrophic Cardiomyopathy Clinic who fulfilled the standard diagnostic criteria for HCM, and who underwent cardiac PET (primarily for evaluation of symptoms) and CMR (for risk stratification). The diagnosis of HCM was based on standard criteria.\textsuperscript{17} Patients with history of epicardial coronary artery disease, including surgical or percutaneous coronary revascularization, and those with prior alcohol septal ablation therapy were excluded from the study. This study was approved by the institutional review board.

**Echocardiography**

A standard clinical scanning protocol was implemented in all subjects using a GE Vivid 7 ultrasound machine (GE Ultrasound, Milwaukee, WI, USA). Conventional analysis included measurements of septum and posterior wall thickness at basal and mid wall regions, LV ejection fraction (LVEF), LVOTG at rest and during provocation tests with Val-salva, and inhaled nitrate. A peak (resting and/or provoked) LVOTG of 30 mm Hg or more was considered obstructive.

Defrangement analysis based on speckle-tracking imaging was performed offline using dedicated GE Echopac software, v. 7.1.1 (GE Ultrasound, Norway).\textsuperscript{18} Three consecutive cardiac cycles with a frame rate of 70–90/s were recorded. The endocardial border of the RV and LV was traced manually from a still frame image and automatically tracked throughout the cardiac cycle by the software. If necessary, the tracing was repeated or adjusted to optimize the endocardial border tracking. Longitudinal systolic strain and strain rate were determined.

**Cardiac magnetic resonance**

Cardiac magnetic resonance imaging was performed using a 1.5-T MR imaging unit (Siemens, Germany). Cardiac cine acquisition and analysis: retrospective, ECG-gated steady-state free precession (SSFP) segmented cine images were acquired in the short axis, two-, four-, and five-chamber views. Myocardial wall thickness was measured at end-diastole.

in the short axis view. LGE acquisition and analysis: LGE images were acquired at end-diastole during a single breath-hold using a segmented inversion-recovery gradient-echo turbo fast low angle shot (FLASH) sequence 10 min after injection of 0.2 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer) contrast medium. An inversion scout sequence was used to select the optimal inversion time for maximal nulling of normal myocardial signal.

The presence and location of LGE was visually assessed. Patients were divided into three groups as following: (i) no visual evidence of LGE in the LV, (ii) LGE confined to the anterior and/or posterior RVIP into the interventricular septum, and (iii) intramural LGE in the LV with or without involvement of the RVIP (Figure 1). In patients with visual evidence of LGE, the extent of LGE in the LV was quantitatively assessed using Qmass 7.4 software (Medis, Leiden, The Netherlands). The LV endocardial and epicardial borders were manually contoured in all short axis images. LGE regions were determined using a threshold signal intensity of 6 standard deviations (SDs) above the mean signal intensity of remote normal myocardium. This threshold has been shown to have the closest correlation with visual assessment.\textsuperscript{19} Patients with no visible myocardial LGE were given a score of zero. The computer software automatically quantified areas of enhancement. The extent of LGE was expressed as a percentage (%) of total LV mass.

**Cardiac PET**

All patients were imaged using a GE Discovery VCT PET/CT. Rest acquisition: 13N-NH₃ (≏ 370 MBq [10 mCi]) was injected at baseline and PET images acquired for 20 min. Stress acquisition: dipiridamole or regadenoson was administered for vasodilator stress followed by second injection of 13N-NH₃ and a 20 min-stress acquisition.\textsuperscript{20}

Flow quantification: volumetric sampling of the myocardial tracer activity was performed on static images (Munich Heart software). Then, polar map-defined segments were reemployed to the dynamic imaging series to create myocardial time–activity curves. A region of interest was positioned in the LV cavity to obtain the arterial input function. Myocardial blood flow (MBF) was calculated by fitting the arterial input function and myocardial time–activity curves from the dynamic polar maps to a two-tissue-compartment tracer kinetic model as previously described.\textsuperscript{21} Flow is recorded in millilitres/minute/gram (mL/min/g). MFR was determined as the ratio of the peak MBF to rest MBF (unitless).

**Outcomes analysis**

Sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate implantable cardioverter defibrillator (ICD) discharge, heart failure progression defined as worsening symptoms to New York Heart Association (NYHA) functional class III or IV and death were recorded.

**Statistical analysis**

Statistical analyses were performed using SPSS (version 21.0). Continuous variables are presented as mean ± SD. One-way, factorial ANOVA combined with Scheffe’s test for post hoc analysis and correction for multiple comparisons was performed to compare the means of the three study groups. Categorical variables were compared between groups using Chi-square ($\chi^2$) tests and presented as percentages. Multiple stepwise regression analysis (with stepping method criteria of probability of $F$ to enter 0.05 and to remove 0.10) was used to determine predictors as appropriate.

**Results**

A total of 18 patients showed no evidence of LGE (group 1), 19 patients had LGE confined to the RVIP (group 2), and 25 patients...
intramural LGE in the LV (group 3). All patients from group 3 also had evidence of LGE at the RVIP. Baseline characteristics were not statistically significantly different between groups, although atrial fibrillation appeared to be more common in patients with LGE (Table 1).

From an imaging perspective, LVOTGs were comparable at baseline and during provocation between patients with no-LGE and intramural LGE, whereas, both resting and provoked LVOTG were significantly higher in patients with LGE confined to the RVIP (Table 2). Yet, the majority of patients without LGE had latent LVOT obstruction (67%), whereas most patients with intramural LGE were mostly non-obstructive (60%). Patients with LGE confined to the RVIP had a combination of obstructive (47%) and non-obstructive HCM (37%). LGE extent and maximal LV wall thickness were greater in patients with intramural LGE, intermediate in patients with LGE confined to the RVIP and lowest in patients without LGE (Table 2, Figure 2). In contrast, longitudinal systolic strain, systolic strain rate, early and late diastolic strain rates, peak MBF, and MFR were lower in patients with intramural LGE, intermediate in patients with LGE confined to the RVIP and greater in patients without LGE (Table 2, Figure 2). LVEF and resting MBF were comparable between groups.

In an attempt to adjust for differences in baseline characteristics between groups, logistic regression analyses were performed. In the first analysis, the presence and location of LGE (categorical variable), was the only independent predictor of impaired peak MBF ($P < 0.001$) and MFR ($P < 0.001$), whereas LGE extent (continuous variable), maximal LV wall thickness, myocardial strain, and LVOTG were not independent predictors of abnormal myocardial flow. In contrast, the main (and only) independent predictor of myocardial strain was maximal LV wall thickness ($P < 0.001$), whereas presence, location, and extent of LGE, peak MBF, MFR, and LVOTG were not independent predictors of impaired myocardial strain. In a third logistic regression analysis, where only patients with LGE ($n = 44$) were included, LGE location (RVIP vs. intramural) remained an independent predictor of peak MBF ($P = 0.036$), but did not reach statistical significance for MFR.

**Outcomes data**

Clinical follow-up information was available for 92% of patients ($n = 57$) with a median follow-up of 20 months (interquartile range 10–46). No one in the study presented with sustained ventricular...
Table 1  Baseline characteristic of HCM patients depending on the presence and location of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 19)</th>
<th>Group 3 (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>51 ± 14</td>
<td>55 ± 14</td>
<td>46 ± 18</td>
<td>0.2</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>8 (44)</td>
<td>9 (47)</td>
<td>19 (76)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dyspnoea and/or chest pain, n (%)</td>
<td>16 (89)</td>
<td>16 (84)</td>
<td>19 (76)</td>
<td>0.5</td>
</tr>
<tr>
<td>Pre-syncpe, n (%)</td>
<td>8 (44)</td>
<td>8 (42)</td>
<td>11 (44)</td>
<td>0.9</td>
</tr>
<tr>
<td>Palpitations, n (%)</td>
<td>4 (22)</td>
<td>6 (32)</td>
<td>4 (16)</td>
<td>0.5</td>
</tr>
<tr>
<td>Unexplained syncope, n (%)</td>
<td>1 (6)</td>
<td>3 (16)</td>
<td>4 (16)</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history of SCD, n (%)</td>
<td>3 (17)</td>
<td>6 (32)</td>
<td>8 (32)</td>
<td>0.5</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>15 (83)</td>
<td>14 (74)</td>
<td>22 (88)</td>
<td>0.5</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>3 (17)</td>
<td>7 (37)</td>
<td>5 (20)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (50)</td>
<td>11 (58)</td>
<td>11 (44)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (11)</td>
<td>2 (11)</td>
<td>3 (12)</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>0</td>
<td>2 (11)</td>
<td>4 (16)</td>
<td>0.2</td>
</tr>
<tr>
<td>Family history of HCM, n (%)</td>
<td>3 (17)</td>
<td>3 (16)</td>
<td>3 (13)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Group 1 corresponds to patients without LGE on CMR; group 2, patients with LGE limited to the right ventricular insertion points (RVIP); group 3, patients with intramural LGE; SCD, sudden cardiac death.

Table 2  Imaging characteristics of HCM patients depending on presence and location of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 19)</th>
<th>Group 3 (n = 25)</th>
<th>ANOVA P-value</th>
<th>P 1 vs. 2</th>
<th>P 2 vs. 3</th>
<th>P 1 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
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<tr>
<td>Resting LVOTG, mmHg</td>
<td>13 ± 10</td>
<td>37 ± 31</td>
<td>16 ± 16</td>
<td>0.001</td>
<td>0.004</td>
<td>0.008</td>
<td>0.9</td>
</tr>
<tr>
<td>Provoked LVOTG, mmHg</td>
<td>45 ± 24</td>
<td>84 ± 65</td>
<td>41 ± 40</td>
<td>0.007</td>
<td>0.04</td>
<td>0.01</td>
<td>0.9</td>
</tr>
<tr>
<td>LVOTG change, mmHg</td>
<td>32 ± 22</td>
<td>48 ± 44</td>
<td>25 ± 34</td>
<td>0.1</td>
<td>0.4</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-obstructive HCM, n (%)</td>
<td>5 (28)</td>
<td>7 (37)</td>
<td>15 (60)</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Obstructive HCM, n (%)</td>
<td>1 (5)</td>
<td>9 (47)</td>
<td>3 (12)</td>
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<tr>
<td>Latent obstruction, n (%)</td>
<td>12 (67)</td>
<td>3 (16)</td>
<td>7 (28)</td>
<td></td>
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<tr>
<td>Longitudinal systolic strain, %</td>
<td>−14.4 ± 4.1</td>
<td>−12.6 ± 3.2</td>
<td>−11.4 ± 3.8</td>
<td>0.043</td>
<td>0.3</td>
<td>0.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Systolic strain rate, s⁻¹</td>
<td>−0.98 ± 0.34</td>
<td>−0.76 ± 0.20</td>
<td>−0.77 ± 0.23</td>
<td>0.025</td>
<td>0.06</td>
<td>0.9</td>
<td>0.055</td>
</tr>
<tr>
<td>Early diastolic strain rate, s⁻¹</td>
<td>1.05 ± 0.34</td>
<td>0.81 ± 0.27</td>
<td>0.74 ± 0.32</td>
<td>0.008</td>
<td>0.08</td>
<td>0.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Late diastolic strain rate, s⁻¹</td>
<td>0.95 ± 0.46</td>
<td>0.67 ± 0.29</td>
<td>0.70 ± 0.32</td>
<td>0.046</td>
<td>0.08</td>
<td>0.9</td>
<td>0.1</td>
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<tr>
<td>Cardiac magnetic resonance</td>
<td></td>
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<tr>
<td>LV ejection fraction, %</td>
<td>71 ± 9</td>
<td>73 ± 6</td>
<td>69 ± 8</td>
<td>0.3</td>
<td>0.8</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Maximal LV thickness, mm</td>
<td>16.3 ± 2.8</td>
<td>18.8 ± 3.9</td>
<td>21.7 ± 3.4</td>
<td>&lt;0.001</td>
<td>0.075</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>0</td>
<td>4 ± 4</td>
<td>17 ± 11</td>
<td>&lt;0.001</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Positron emission tomography</td>
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<tr>
<td>Rest MBF, mL/min/g</td>
<td>0.84 ± 0.19</td>
<td>0.92 ± 0.21</td>
<td>0.87 ± 0.21</td>
<td>0.5</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Stress MBF, mL/min/g</td>
<td>2.22 ± 0.48</td>
<td>1.90 ± 0.37</td>
<td>1.62 ± 0.44</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial flow reserve</td>
<td>2.71 ± 0.52</td>
<td>2.15 ± 0.52</td>
<td>1.92 ± 0.47</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P-value derived from χ², not ANOVA. Values are mean ± SD. Group 1 corresponds to patients without LGE on CMR; group 2, patients with LGE limited to the right ventricular insertion points (RVIP); group 3, patients with intramural LGE; LVOTG, left ventricular outflow tract gradients; MBF, myocardial blood flow.
arrhythmias or aborted SCD, but after risk-stratification, 21/57 (37%) patients underwent ICD placement for primary prevention (Table 3).

On follow-up, although uncommon, appropriate ICD shock(s) for sustained ventricular arrhythmias (n = 1), and death (n = 1) only occurred in patients with intramural LGE. Similarly, progression to NYHA functional class III or IV (n = 5) was more commonly seen in patients with intramural LGE (n = 4) than patients with LGE at the RVIP (n = 1) or no-LGE (Table 3).

Discussion

The main finding of this study is that HCM patients with LGE confined to only the RVIP appear to represent an intermediate stage phenotype between individuals with no LGE and intramural LGE in the LV as summarized in Table 4. We also found no definite association between LGE extent (% of LV mass) and myocardial flow and strain, which suggests that the flow and strain differences seen between groups are not necessarily due to the extent of LGE involvement. Lastly, although the number of adverse cardiovascular events was generally low, we did observe a trend for worse outcomes in patients with intramural LGE.

Frequency of late gadolinium enhancement

Several studies have documented that between 40 and 60% of patients with HCM show evidence of myocardial LGE at different locations including the RVIP, interventricular septum, LV apex, and...
In this sense, the RVIP is the most common location of LGE in HCM reported in 73% of patients (174 of 239) in one large series (n = 424) and in all cases (19 of 19) in a small case series (n = 21). Now, the prevalence of LGE confined to only the RVIP has been estimated at 11–25% previously. Compared with other studies, in general we observed a higher prevalence of LGE (70%), and specifically of cases with LGE confined to the RVIP (44%). But similar to the report of Choudhury et al. all of our patients were symptomatic for the most part as well as diagnostic criteria (e.g. definition of RVIP) may account for some of these differences between studies.

Myocardial blood flow evaluation

A number of studies have revealed that HCM individuals have an impaired response to vasodilator stress, translating into lower peak MBF and MFR than non-HCM individuals. In the absence of obstructive coronary disease, failure to increase MBF during vasodilator stress is considered as evidence for coronary microvascular dysfunction. In HCM, this is believed to be in part secondary to structural alterations in the intramural arteries (the main source of coronary resistance), characterized by thickening of the small vessel wall and decreased luminal size. Ex vivo studies of hearts from patients who died of sudden death, progressive heart failure, peri-operative complications, and other extra-cardiac causes, have found that these microvascular changes are more common in tissue sections that demonstrate concomitant significant myocardial fibrosis (particularly in the septum) than in those with mild or absent fibrosis. Similarly, our group and others have previously shown in vivo, that patients with evidence of LGE have significantly lower MFR in comparison with those without LGE.

In this study, we further expanded our knowledge of the inter-relationship of LGE with myocardial flow by unmasking differences in flow based on the location of LGE in the myocardium. In this regard, the presence of LGE confined to the RVIP appeared to be phenotypically different from patients with no-LGE and intramural LGE. First, patients with LGE confined to the RVIP showed lower peak MBF and MFR compared with HCM patients without LGE, whereas myocardial flow was higher (although not statistically significant) in patients with LGE confined to the RVIP compared with those with intramural LGE. In aggregate, these results imply that coronary vasodilator reserve is less affected in patients with no-LGE, immediately impaired in those with LGE confined to only the RVIP, and more affected in HCM patients with intramural LGE. Finally, we found no definite association between LGE extent and coronary vasodilator reserve, suggesting that the differences in myocardial flow seen between patients with varying degrees of LGE are not necessarily related to LGE extent.

Assessment of myocardial longitudinal strain

Myocardial strain derived from speckle tracking imaging is a sensitive parameter of regional LV function. Previous studies have shown that LV strain is influenced by both LV hypertrophy and presence of myocardial LGE in HCM. In this respect, Popovic et al. found that both LV wall thickness and LGE extent were predictors of abnormal longitudinal strain in patients with HCM. Moreover, Saito et al. suggested that global longitudinal myocardial strain may be used as a surrogate marker of myocardial fibrosis, and potentially correlate with cardiac events. In agreement with this data, we did observe a stepwise decrease in myocardial strain in patients with...
no-LGE, LGE confined to the RVIP, and intramural LGE. However, in our study, the differences in myocardial strain between groups appeared to be primarily driven by the degree of LV hypertrophy rather than by the extent of LGE.

**Differences in left ventricular outflow tract gradients**

Another interesting finding was the fact that most patients without LGE had latent LVOT obstruction, whereas those with intramural LGE were mostly non-obstructive. Patients with LGE confined to the RVIP had a combination of obstructive and non-obstructive HCM. At present, we do not have a satisfactory explanation for these findings; however, somewhat similar observations were made by Biagini and co-workers in a study where they evaluated 76 HCM patients with CMR (LGE prevalence 71%) and stress echocardiography, and reported that patients with higher exercise-induced LVOTG had lesser degrees of LGE, and vice versa. They hypothesized that fibrosis probably affected myocardial contractility recruitment, and consequently, its ability to increase LVOTG during exercise. This is an interesting hypothesis that in part correlates with our findings, because patients with intramural LGE had the lowest myocardial strain parameters and concomitantly the majority of them (60%) showed LVOTG in the non-obstructive range both at rest and upon provocation. In contrast, patients without LGE had higher myocardial strain and 67% of them exhibited latent LVOT obstruction. The exact mechanism of LVOT obstruction remains incompletely understood, but there seems to be consensus that it is partly related to morphologic and dynamic changes of the mitral valve apparatus resulting from excessive leaflet tissue, chordal abnormalities, and/or anterior displacement of the mitral apparatus against the hypertrophied septum during systole. Consequently, the implications of myocardial fibrosis in the genesis of LVOT obstruction will require further consideration in future studies.

**Clinical implications**

We observed that HCM patients with LGE limited to the RVIP showed more favourable imaging profiles, including higher myocardial flow and strain and less LV hypertrophy and fibrosis than patients with intramural LGE, but at the same time, less favourable in comparison with patients without LGE.

Clinically, albeit the number of adverse events was low after a median follow-up of 20 months, except for one patient with LGE at the RVIP who progressed to NYHA functional class III, all adverse outcomes seemed to occur in the group of patients with intramural LGE, whereas no adverse events were recorded in patients without LGE (Table 3).

Similarly, Chan et al. investigated the clinical significance of LGE limited to the RVIP in a significantly larger HCM population (n = 1293) with longer follow-up (3.4 ± 1.7 years). In this work, a total of 37 (2.9%) SCD events occurred, as following: 11 (1.5%) in patients with no-LGE (n = 745), 4 (3%) in patients with LGE confined to the RVIP (n = 134), and 33 (8%) in patients with intramural LGE (n = 414). After adjustment for conventional SCD risk factors, LGE confined to the RVIP was associated with low risk for SCD and no different than HCM patients without LGE (HRadj: 0.38; 95% CI: 0.19 – 0.74, P = 0.005). Also, LGE confined to the RVIP did not predict risk for adverse heart failure events. The authors hypothesized that the low risk of SCD and adverse heart failure events seen in patients with LGE limited to the RVIP may be related to the absence of replacement myocardial fibrosis at these sites.

On the other hand, new evidence indicates that HCM is potentially an evolving disease as shown by Todiere et al. who performed a study in which 55 HCM patients underwent two CMR evaluations separated in average 2.0 ± 1.1 years apart, and observed that the extent of LGE increased in the majority of patients, and more importantly eight individuals, previously classified as without LGE, were subsequently found with LGE (authors do not specify location) on follow-up examinations.

All things considered, we feel that the outcome data from Chan and co-workers, and to a lesser extent our study (due to underpower) support the argument that patients with LGE confined to only the RVIP may represent a phenotype with a seemingly lower risk profile than patients with intramural LGE. Nonetheless, future research will be required to further explore any potential sequence and/or mechanism(s) of disease progression between patients with no-LGE, LGE limited to only the RVIP, and intramural LGE.

Finally, it is worth emphasizing that being HCM a heterogeneous disorder with complex pathophysiology, and diverse clinical expression, the presence, location, and extent of LGE, as a marker of myocardial fibrosis, is not sufficient to explain the different phenotype characteristics (e.g. myocardial flow, strain, hypertrophy) and/or adverse clinical outcomes seen in HCM.

**Limitations**

This is an observational study, and suffered from all the limitations of similar study designs. We evaluated a relatively small sample size with a short follow-up, which affected the statistical power for the post hoc test and outcomes analyses. Consequently, it is possible that many of the reported trends may become significant in a larger study sample with longer follow-up. This was also a cross-sectional study and, as thus, does not permit to evaluate for disease progression, or to know if some or all of these cases do or do not reflect an intermediate stage before the development of more significant myocardial fibrosis. Lastly, the use of genetics, T1 mapping by CMR, a novel technique that allows detection and quantification of diffuse or interstitial myocardial fibrosis, and serial follow-up CMR-LGE imaging may further improve our understanding and the definition of individuals with LGE limited to the RVIP in comparison with other subtypes of HCM. This remains to be clarified in future studies.

**Conclusion**

In summary, our data suggest that HCM patients with LGE confined to only the RVIP may represent an intermediate stage between individuals with no LGE and intramural LGE as evidenced by a more favourable imaging profile, compared with individuals with intramural LGE, but at the same time, less favourable in comparison with patients without LGE. Future studies will be required to evaluate the potential dynamic behaviour of myocardial fibrosis, and its relationship with the different event risk profiles observed between HCM subgroups.

**Conflict of interest:** None declared.
Funding
This work was supported in part by a grant from the National Institutes of Health (HL098046).

References