Myocardial delayed enhancement (DE) by gadolinium cardiac magnetic resonance (CMR) in hypertrophic cardiomyopathy (HCM) has emerged as a highly informative biomarker with implications for diagnosis and prognosis. Case reports have shown agreement between location and quantity of myocardial fibrosis in postmortem/explanted hearts and DE extent on antemortem/pretransplant CMR, suggesting that DE could reflect fibrosis in HCM.1,2 However, any process that increases extracellular fluid volume in the myocardium will result in DE. Hence, edema, inflammation, and myocyte disarray may also result in DE.3,4 The presence of DE on CMR has been associated with markers of sudden cardiac death5 and higher incidence of adverse cardiovascular events, including disease progression,2,5 heart failure symptoms,6 ventricular arrhythmias,7 and all-cause and cardiac mortality8 in HCM patients.

Myocardial ischemia has been proposed as an important contributor to fibrosis in HCM.9 Abnormalities in intramural coronary arterioles coupled with increased demand by the hypertrophied myocardium can result in microvascular dysfunction, ischemia, edema, myocyte death, and fibrosis in HCM patients.10,11 However, increased transcription of profibrotic genes has been detected even in the prehypertrophic stage of the left ventricular (LV) myocardium in transgenic mouse models of HCM, indicating that factors other than ischemia may be playing a role in the induction of fibrosis in HCM.12

Positron emission tomography (PET) is the gold standard for noninvasive quantification of myocardial perfusion and myocardial blood flow (MBF)13 and has been shown to predict heart failure, sustained ventricular arrhythmias, and myocardial ischemia.9,10,13 PET data have shown that decreased MBF is associated with worse clinical outcomes in HCM.11,13

**Background**—Presence of delayed enhancement (DE) on cardiac magnetic resonance (CMR) is associated with worse clinical outcomes in hypertrophic cardiomyopathy. We investigated the relationship between DE on CMR and myocardial ischemia in hypertrophic cardiomyopathy.

**Methods and Results**—Hypertrophic cardiomyopathy patients (n=47) underwent CMR for assessment of DE and vasodilator stress ammonia positron emission tomography to quantify myocardial blood flow and coronary flow reserve. The summed difference score for regional myocardial perfusion was also assessed. Patients in the DE group (n=35) had greater left ventricular wall thickness (2.09±0.44 versus 1.78±0.34 cm; P=0.03). Stress myocardial blood flow (2.25±0.46 versus 1.78±0.43 mL/min per gram; P=0.01) and coronary flow reserve (2.78±0.32 versus 2.01±0.52; P<0.001) were significantly lower in DE-positive patients. Summed difference score (median, 5 versus 0; P<0.0001) was significantly higher in patients with DE. A coronary flow reserve <2.00 was seen in 18 patients (51%) with DE but in none of the DE-negative patients (P<0.0001). CMR and positron emission tomography showed visually concordant DE and regional myocardial perfusion abnormalities in 31 patients and absence of DE and perfusion defects in 9 patients. Four DE-positive patients demonstrated normal regional myocardial perfusion, and 3 DE-negative patients had (apical) regional myocardial perfusion abnormalities.

**Conclusions**—We found a close relationship between DE by CMR and microvascular function in most of the patients studied. However, a small proportion of patients had DE in the absence of perfusion abnormalities, suggesting that microvascular dysfunction and ischemia are not the sole causes of DE in hypertrophic cardiomyopathy patients. (Circ Cardiovasc Imaging. 2013;6:210-217.)

**Key Words:** cardiac MRI ◆ fibrosis ◆ HCM ◆ ischemia ◆ PET

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Clinical Perspective on p 217

Myocardial ischemia has been proposed as an important contributor to fibrosis in HCM.9 Abnormalities in intramural coronary arterioles coupled with increased demand by the hypertrophied myocardium can result in microvascular dysfunction, ischemia, edema, myocyte death, and fibrosis in HCM patients.10,11 However, increased transcription of profibrotic genes has been detected even in the prehypertrophic stage of the left ventricular (LV) myocardium in transgenic mouse models of HCM, indicating that factors other than ischemia may be playing a role in the induction of fibrosis in HCM.12

Positron emission tomography (PET) is the gold standard for noninvasive quantification of myocardial perfusion and myocardial blood flow (MBF)13 and has been shown to predict heart failure, sustained ventricular arrhythmias, and
cardiovascular-related death in HCM.\textsuperscript{14,15} Measurement of basal and vasodilator-induced MBF permits calculation of coronary flow reserve (CFR), which is primarily determined by the coronary microvasculature in the absence of epicardial coronary artery disease. Hence, a reduction in CFR, which is often observed in patients with HCM, is an indicator of microvascular dysfunction.\textsuperscript{16} However, it is not known whether microvascular dysfunction is a prerequisite for the development of fibrosis and DE in HCM patients.

Therefore, the purpose of our study was to investigate the relationship between DE and coronary microvascular function assessed by PET.

**Methods**

**Patients**

We enrolled patients from the Johns Hopkins HCM Clinic who fulfilled the standard diagnostic criteria for HCM and underwent cardiac PET and CMR for clinical indications between June 2009 and May 2012. The diagnosis of HCM was based on the presence of unexplained LV hypertrophy ($\geq$15-mm wall thickness by echocardiography) in the absence of other conditions capable of producing a similar degree of hypertrophy (eg, moderate to severe valvular disease).\textsuperscript{17} We excluded patients with a history of coronary artery disease, including surgical or percutaneous coronary revascularization, and those with prior septal myectomy or alcohol septal ablation. Echocardiography was used to measure LV wall thickness, ejection fraction, and outflow tract gradients (resting and provoked).

A total of 62 patients underwent PET and CMR during this interval; however, 8 patients had history of coronary artery disease, 5 patients had prior myectomy/alcohol ablation, and 2 patients showed artifacts during DE-CMR phase and were excluded. The final study population consisted of 47 patients. The Johns Hopkins Medicine Institutional Review Boards approved this study. All participants gave informed consent.

**Cardiac Magnetic Resonance**

CMR imaging was performed using a 1.5-T MR imaging unit (Avanto, Siemens, Erlangen, Germany). Cine and DE sequences were acquired in the short axis slices and covered the entire LV.

**Cardiac Cine Acquisition and Analysis**

Retrospective, ECG-gated, steady-state free precession segmented cine images were acquired in the short-axis, 2-chamber, 4-chamber, and 5-chamber views. Myocardial wall thickness was measured at end diastole in the short axis.

**DE Sequence and Analysis**

DE images were acquired at end diastole during breath holding using a segmented inversion-recovery gradient-echo turbo fast low-angle shot sequence obtained 10 to 15 minutes after injection of 0.2 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer) contrast medium. The inversion time was selected to obtain maximal nulling of the signal from the LV. Images were visually scored for the presence or absence of DE. Subsequently, the extent of DE in the LV was quantitatively measured using dedicated software (QMass version 6.2, Medis, Leiden, The Netherlands). DE was defined by a threshold signal intensity of 6 SD above the mean signal intensity of remote normal myocardium (region without DE on visual assessment).\textsuperscript{18} This threshold was chosen owing to overall good agreement with visual evaluation. The extent of DE was expressed as a percentage of total LV mass with DE.

**Cardiac PET**

All patients were imaged using a GE Discovery VCT PET/computed tomography system (GE Healthcare) equipped with an integrated Lutetium Yttrium Orthosilicate scintillator system.

**Rest Acquisition**

$^{13}$N-$\text{NH}_3$ ($\approx$370 MBq [10 mCi]) was injected at baseline, and 2 dimensional listmode PET images were acquired for 20 minutes.

**Stress Acquisition**

Dipyridamole or regadenoson was administered for vasodilator stress followed by second injection of $^{13}$N-$\text{NH}_3$ (20 minutes of 2 dimensional listmode PET stress acquisition). We have previously demonstrated that dipyridamole- and regadenoson-induced hyperemia (peak-MBF) is equivalent in patients with HCM.\textsuperscript{19} In the present study, peak-MBF was highly comparable between dipyridamole and regadenoson in HCM patients without DE ($2.20\pm0.41$ versus $2.28\pm0.52$; $P=0.8$) and those exhibiting DE ($1.79\pm0.36$ versus $1.77\pm0.47$; $P=0.9$).

**Quantification of Absolute Flow**

Volumetric sampling of the myocardial tracer activity was performed on static images (Munich Heart software). Then, polar map-defined segments were reapplied 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. MBF was calculated by fitting the arterial input function and myocardial time–activity curves from the dynamic polar maps to a 2-tissue compartment tracer kinetic model as previously described.\textsuperscript{20} MBF of the LV during peak-MBF and rest was measured in milliliter per minute per gram. CFR was determined as the ratio of the peak-MBF to rest MBF. Regions of interest were applied to each flow polar map to obtain regional analysis between the LV septum and lateral wall. Interobserver agreement for global ($R^2=0.88$) and regional ($R^2=0.85$) flow data was very good.

**Regional Myocardial Perfusion**

Regional myocardial perfusion was semiquantitatively assessed by the standard 17 American Heart Association segmentation, 5-point visual score method based on the level of tracer activity (normal=0, mildly decreased=1, moderately decreased=2, severely abnormal=3, and absent perfusion=4) using the CardIQ Physio package (GE Healthcare). The summed stress score and summed rest score consisted of the summation score of the 17 LV segments during vasodilator stress and rest perfusion imaging respectively. Summed difference score (SDS) was the difference between summed stress score and summed rest score. Abnormal regional myocardial perfusion (rMP) was defined as an SDS$\geq$2 in this study.\textsuperscript{14} Interobserver ($R^2=0.80$) agreement for global SDS was very good.

**Statistical Analysis**

We analyzed the data using SPSS (version 19.0). Paired $t$ test was used to evaluate statistical differences between 2 continuous measurements or variables of the same individuals. An independent-measures $t$ test was used to assess continuous variables differences between 2 groups. One-way ANOVA combined with Scheffe test for post hoc analysis and correction for multiple comparisons was performed to compare mean values of $>2$ groups. Continuous variables are presented as mean$\pm$SD. The Mann–Whitney $U$ test was used to test for statistical differences of continuous variables that had a skewed distribution, and results are given in median in addition to their mean values. Categorical variables were compared between groups using $\chi^2$ tests and are presented as percentages. A $P$ value $<0.05$ was considered statistically significant.

**Results**

**Patient Characteristics**

A total of 47 patients were studied; they were divided into 2 groups: patients without DE (n=12) and patients with evidence of DE (n=35) on CMR (mean DE, 10$\pm$10%; range 1%–37% of LV mass). DE-positive patients had a higher septal wall thickness and were more likely to have nonobstructive HCM (Tables 1 and 2). There was no difference in ejection fraction between the DE-negative and DE-positive groups.

**Global and Regional Absolute Flow Quantification, CFR, and DE-CMR**

Baseline hemodynamics including the rate-pressure product and vasodilator-induced hemodynamics were similar in both
groups as shown in Table 3. Consequently, MBF and CFR were not corrected by the rate-pressure product.

At rest, global MBF showed a trend for higher values in the DE-positive compared with DE-negative group. However, during vasodilator stress, both peak-MBF and CFR were significantly lower in the DE-positive group (Table 3). A global CFR <2.00 was seen in 18 DE-positive patients (51%) but in none of the DE-negative subjects ($P<0.0001$).

A regional analysis was conducted to investigate MBF differences based on the severity of hypertrophy in patients from both groups (Figure 1); we compared MBF in the septum, the wall that showed the maximum amount of hypertrophy, with the lateral wall that showed a lesser degree of hypertrophy. Within the DE-negative group, the septum showed no significant differences in peak-MBF compared with the lateral wall. In contrast, in the DE-positive group the septum exhibited a significantly lower peak-MBF in comparison with the lateral wall. Peak-MBF was significantly lower within the lateral wall of the DE-positive than DE-negative group (Figure 1).

Global peak-MBF ($r=-0.44; P=0.002$) and CFR ($r=-0.40; P=0.005$) showed a weak correlation with the extent of DE in the LV in the entire cohort ($n=47$). However, when DE-positive patients ($n=35$) were divided into tertiles based on the extent of DE in the LV, there were no significant differences in peak-MBF ($P=0.6$) and CFR ($P=0.5$) across the different tertiles, whereas septal wall thickness ($P=0.015$) significantly augmented at higher degrees of DE in the LV (Figure 2).

**rMP and DE-CMR**

The SDS was undertaken to assess for flow heterogeneity or regional CFR differences, which could be missed by global evaluation of CFR in the LV. The overall SDS was significantly higher in the DE-positive group compared with DE-negative patients. A total of 31 patients had both abnormal rMP ($SDS\geq2$) and evidence of DE on CMR, with the majority of the reversible perfusion abnormalities visually matching the myocardial region with DE (Figure 3). On the contrary, 9 patients demonstrated normal rMP and no evidence of DE on CMR, for an overall agreement between rMP by PET and DE by CMR of 85%.

**Discussion**

Our study demonstrates a close relationship between DE on CMR and regional and globally impaired hyperemic MBF and CFR in DE-positive patients.

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**Table 1. Baseline Characteristic of HCM Patients With and Without Evidence of DE on Cardiac Magnetic Resonance**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>No DE (n=12)</th>
<th>DE Present (n=35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>49±16</td>
<td>51±16</td>
<td>0.7</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>6 (50)</td>
<td>20 (57)</td>
<td>0.7</td>
</tr>
<tr>
<td>Chest pain and dyspnea, n (%)</td>
<td>10 (83)</td>
<td>28 (80)</td>
<td>0.8</td>
</tr>
<tr>
<td>NYHA class I, n (%)</td>
<td>7 (58)</td>
<td>14 (40)</td>
<td>0.4</td>
</tr>
<tr>
<td>NYHA class II, n (%)</td>
<td>3 (25)</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
<td>2 (17)</td>
<td>5 (14)</td>
<td></td>
</tr>
<tr>
<td>Lightheadedness, n (%)</td>
<td>5 (42)</td>
<td>15 (43)</td>
<td>0.9</td>
</tr>
<tr>
<td>Palpitations, n (%)</td>
<td>1 (8)</td>
<td>6 (17)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (42)</td>
<td>16 (46)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (8)</td>
<td>4 (11)</td>
<td>0.8</td>
</tr>
<tr>
<td>Family history of HCM, n (%)</td>
<td>3 (25)</td>
<td>6 (17)</td>
<td>0.5</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>10 (83)</td>
<td>27 (77)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

DE indicates delayed enhancement; HCM, hypertrophic cardiomyopathy; and NYHA, New York Heart Association.

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**Table 2. Echocardiography and CMR Characteristics in HCM Patients With and Without Evidence of DE**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No DE (n=12)</th>
<th>DE Present (n=35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Interventricular septum thickness, cm</td>
<td>1.78±0.34</td>
<td>2.09±0.44</td>
<td>0.03</td>
</tr>
<tr>
<td>2. Left ventricular posterior wall thickness, cm</td>
<td>0.96±0.12</td>
<td>1.17±0.31</td>
<td>0.03</td>
</tr>
<tr>
<td>3. Left ventricle septum/posterior wall ratio</td>
<td>1.94±0.79</td>
<td>2.15±2.09</td>
<td>0.7</td>
</tr>
<tr>
<td>4. Rest LOVTG, mm Hg</td>
<td>14±12</td>
<td>27±27</td>
<td>0.1</td>
</tr>
<tr>
<td>5. Peak provoked LOVTG, mm Hg</td>
<td>46±25</td>
<td>60±59</td>
<td>0.4</td>
</tr>
<tr>
<td>6. Nonobstructive HCM, n (%)</td>
<td>3 (25)</td>
<td>17 (49)</td>
<td>0.01</td>
</tr>
<tr>
<td>7. Obstructive HCM, n (%)</td>
<td>1 (8)</td>
<td>11 (31)</td>
<td></td>
</tr>
<tr>
<td>8. Latent HCM, n (%)</td>
<td>8 (67)</td>
<td>7 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>CMR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Left ventricular ejection fraction, %</td>
<td>72±9</td>
<td>72±7</td>
<td>0.7</td>
</tr>
<tr>
<td>2. Interventricular septum thickness, cm</td>
<td>1.66±0.28</td>
<td>2.03±0.40</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise specified. CMR indicates cardiac magnetic resonance; DE, delayed enhancement; HCM, hypertrophic cardiomyopathy; and LOVTG, left ventricular outflow tract gradient.
CFR by PET in a well-characterized HCM cohort. A small proportion of patients (8%) had evidence of DE by CMR but normal rMP and flow parameters, indicating that DE may exist in the absence of myocardial ischemia in HCM patients.

**Microvascular Ischemia in HCM**

Our results are concordant with the results of a number of studies using different imaging modalities, such as PET, CMR, and echocardiography, which have revealed that HCM patients often demonstrate an impaired response to vasodilator stress, translating into abnormal peak-MBF and CFR. In the absence of obstructive coronary artery disease, failure to increase MBF during vasodilator stress is considered evidence for microvascular dysfunction. In HCM, this is believed to be in part secondary to structural alterations in the intramural arterioles (the main source of coronary resistance), characterized by thickening of the small vessel wall and decreased luminal size. Ex vivo studies of hearts from a few HCM patients who died of various causes have found that these microvascular changes are more common in tissue sections demonstrating concomitant significant myocardial fibrosis than in those with mild or absent fibrosis. Similarly, most of our patients showed evidence of reduced regional perfusion, presumably owing to microvascular disease.

**DE by CMR and Myocardial Ischemia in HCM**

Our clinical study reveals that patients with evidence of DE had a significantly lower global peak-MBF and CFR in comparison with patients without DE, which implies that microvascular dysfunction and ischemia are more common in this subgroup. Importantly, no patient in the DE-negative group exhibited a global CFR <2.00, a cutoff value that has consistently being associated with a higher incidence of adverse cardiovascular events, including mortality in a number of PET studies.

However, 17 patients (49%) who had evidence of DE by CMR had preserved global CFR (≥2.00), and despite the obvious significant flow differences of DE-positive compared with DE-negative patients, we observed no definite correlation between the extent of myocardial DE and myocardial flow.
in HCM (Figure 2). These findings suggest the existence of significant global and regional flow heterogeneity in the presence of DE. For example, in the absence of myocardial DE, peak-MBF was similar in the septum and lateral wall, whereas it was significantly lower in the septum of patients with DE. Moreover, myocardial flow in the lateral wall (which showed a lesser degree of hypertrophy) was significantly lower in DE-positive compared with the DE-negative group (Figure 1). These findings indicate that the presence, rather than the extent, of myocardial DE is associated with myocardial flow impairment in HCM.

Some of our regional results are in agreement with Petersen (n=35) and Sotgia (n=34) who observed that peak-MBF (assessed by perfusion-CMR and 13NH3-PET, respectively) was significantly lower in myocardial segments with DE and higher in those segments without DE. However, neither of these studies evaluated patients demonstrating preserved myocardial flow in the presence of overt myocardial DE or the influence of myocardial DE extent on CFR. Moreover, both Sotgia and Peterson seem to support the thesis that DE (fibrosis markers) is the consequence of myocardial ischemia. Our findings demonstrate that DE as marker of fibrosis can exist without evidence of corresponding reductions in perfusion (see below).

Mismatch Between DE and Regional Ischemia in HCM

It is conceivable that in some instances, CMR may detect areas of DE that correspond to perfusion defects that are undetectable by PET given the superior spatial resolution of CMR. This could theoretically result in underreporting by PET of perfusion defects caused by small patchy areas of replacement fibrosis. In our study, the size of DE and the wall thickness were similar in DE+PET+ patients compared with DE+PET− patients as shown in Table 4. Therefore, the likelihood of an artifactual underreporting of PET abnormalities owing to differences in resolution seems low. All patients in our study had LV wall thicknesses of at least 1.5 cm (range, 1.5–3.0 cm), a cutoff that is at least 2 times the spatial resolution of PET (5–7 mm). Consequently, any area of DE occupying one third or

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**Figure 2.** Patients with hypertrophic cardiomyopathy and delayed enhancement (DE)-positive cardiac magnetic resonance (n=35) were divided into tertiles based on the extent of DE in the left ventricle (LV). Please note that peak myocardial blood flow (MBF) and coronary flow reserve (CFR) are not significantly different across the different tertile groups, whereas septum thickness increases at higher levels of DE in the LV.
more of the LV wall thickness would be, presumptively, within the resolution and detection capabilities of PET and should translate into a myocardial perfusion defect if this area of DE were related to derangement of the coronary microvasculature. This was not the case in a small proportion of the patients (8%) in whom, despite significant DE involvement of thickened regions of the heart, myocardial perfusion (as well as quantitative flow) remained unaffected as depicted in Figure 4.

**Significance of DE in HCM**

Whether or not these regions of DE in patients with HCM represent fibrosis is still unclear. Unlike ischemic heart disease, where DE has been proven to result from replacement fibrosis using animal models,29 no detailed histopathologic correlates of DE in HCM are available. DE is nonspecific, resulting from an expansion of extracellular fluid volume in the myocardium, which may be due to fibrosis, myonecrosis/edema, or myocyte disarray—all of which frequently occur in HCM patients.

It has been previously postulated that fibrosis may be the result of repetitive episodes of myocardial ischemia owing to coronary microvascular disease in HCM.13,28 Alternatively, fibrosis and disarray may be secondary to specific genotypes, advanced disease, and the expression of a severe phenotype. Furthermore, preclinical and clinical data suggest that the stimulus for fibrosis can predate hypertrophy,12,29 and in fact, we believe that fibrosis may occur in the absence of coronary microvascular changes in some cases. This is supported by the following data: ≈8% of DE-positive subjects had normal myocardial perfusion in our cohort, and in a necropsy study of 7 HCM individuals with evidence of myocardial replacement fibrosis but no significant atherosclerosis of the epicardial coronaries, abnormal intramural coronary arteries typical of HCM were noted in all but one of these patients. The authors concluded that the causal relation between ischemia and fibrosis cannot be considered definitive.31 In addition, Kwon et al32 observed that histologically proven small-vessel changes were present in 35 of 38 (92%) postmyectomy specimens of HCM patients who exhibited DE in the basal septum before surgery, indicating that a small proportion (8%) of individuals had fibrosis without concomitant small-vessel disease. These findings support our conclusion that myocardial ischemia is not a prerequisite for the development of DE in HCM patients.

**Clinical Implications**

HCM individuals with evidence of DE-CMR have been reported to be at higher risk for adverse events.2,8 Current American College of Cardiology Foundation/American Heart Association guidelines recommend the use of DE-CMR in selected patients with known HCM when sudden death risk stratification is inconclusive after documentation of the conventional risk factors (Class: IIb; Level of Evidence: C).17 Studies have consistently showed that more than half of HCM patients referred for CMR have DE, but only a fraction of these patients will eventually experience cardiovascular events.2,6,8,33 The apparent inconsistency with which DE predicts clinical events could be partially explained by the presence or absence of concomitant ischemia. Fibrosis markers and perfusion abnormalities can separate the overall HCM population into several subgroups that may better segregate high-risk patients. It remains to be prospectively explored whether HCM patients with DE on CMR and evidence of concomitant ischemia are at higher risk for adverse events, such as sudden cardiac death, because the combination of intermittent ischemia, fibrosis, and disarray can be highly proarrhythmic.34–37

**Limitations**

We were unable to obtain histopathologic correlates for DE in our HCM patient cohort because we did not perform myocardial biopsies or use molecular imaging agents that directly bind collagen. Furthermore, our cross-sectional, observational study cannot address whether microvascular dysfunction precedes the development of DE in HCM patients. Availability of genotype and histopathology would permit a more detailed analysis of the gene-pathology–ischemia relationship. Others have shown that the prevalence of DE is higher and myocardial flow significantly lower in genotype-positive (for sarcomeric protein mutations) compared with genotype-negative individuals with HCM.38 Lastly, we want to point out that given the relatively small size and potential for variability of regional measurements of our cohort, no definite conclusions can be drawn regarding the relationship between DE and myocardial flow; rather, this is a hypothesis-generating study, and larger studies are needed to evaluate the complex implications of DE and microvascular dysfunction/ischemia, including on the risk of developing ventricular arrhythmias and heart failure in HCM patients.

**Conclusions**

This study demonstrates a close relationship between DE by CMR and microvascular ischemia by PET in HCM in most of the patients. However, DE can also occur in the absence of coronary flow impairment, indicating that perfusion abnormalities are important but are not the sole cause of myocardial DE in HCM. Prospective studies are needed to assess the combined use of perfusion and DE imaging for predicting cardiovascular events in HCM.

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**Table 4. Imaging Characteristics Between Patients With Concordant and Discordant PET-MR Scans**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DE-Positive PET-Positive (n=31)</th>
<th>DE-Positive PET-Negative (n=4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Range</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>DE extent in LV, %</td>
<td>10.7±10</td>
<td>1–37</td>
<td>8.0±6.4</td>
</tr>
<tr>
<td>Septum thickness, cm</td>
<td>2.07±0.42</td>
<td>1.50–2.90</td>
<td>2.18±0.59</td>
</tr>
<tr>
<td>SDS (median)</td>
<td>6.0</td>
<td>2–32</td>
<td>1.0</td>
</tr>
<tr>
<td>CFR</td>
<td>1.90±0.42</td>
<td>1.19–3.06</td>
<td>2.89±0.33</td>
</tr>
</tbody>
</table>

CFR indicates coronary flow reserve; DE, delayed enhancement; LV, left ventricle; PET, positron emission tomography; and SDS, summed difference score.
Acknowledgments

We thank the staff of the Nuclear Medicine laboratories, in particular Jennifer Merrill-Warne and Judy Buchanan, and the staff of the Johns Hopkins Hypertrophic Cardiomyopathy Center of Excellence, especially the sonographers and nurses of the Johns Hopkins Hospital Echocardiography Laboratories, and General Electric Ultrasound, Horten, Norway (Glenn Lie and Gunnar Hansen), for providing the software and support for echocardiography analysis. We also thank the staff of the Johns Hopkins Clinical MRI Laboratories for their assistance.

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Disclosures

None.

References


ClinicaL PeRsPecTive

In the present study, we examined the relationship of microvascular ischemia by ammonia positron emission tomography with markers of fibrosis (delayed enhancement [DE]) by cardiac magnetic resonance. Our results indicate that the presence, not extent, of DE by cardiac magnetic resonance was closely but not exclusively related to impaired microvascular perfusion by ammonia positron emission tomography, suggesting that fibrosis markers are not always associated with ischemia as previously thought. We found hypertrophic cardiomyopathy (HCM) patients with DE in the setting of normal positron emission tomography flow/perfusion, indicating that, at least in a subgroup, the process of fibrosis is not related to ischemia. Ischemia–fibrosis profiling of HCM resulted in 3 subgroups: ischemia plus fibrosis, ischemia only, and fibrosis only. This ischemia–fibrosis nexus may better explain the apparent inconsistency with which DE alone predicts clinical events in HCM. For instance, HCM patients with DE on cardiac magnetic resonance and evidence of microvascular ischemia may be at higher risk for adverse events such as sudden cardiac death because the combination of intermittent ischemia, fibrosis, and disarray can be highly proarrhythmic. Larger prospective studies are needed to clarify if this hypothesis is true and if ischemia–fibrosis profiling offers superior risk prediction information in HCM compared with DE alone.
Relationship of Delayed Enhancement by Magnetic Resonance to Myocardial Perfusion by Positron Emission Tomography in Hypertrophic Cardiomyopathy


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