Hypertrophic cardiomyopathy (HCM) is a common genetic disease with an estimated prevalence of 1 in 500 of the population.1 The natural history of this cardiomyopathy is varied, ranging from a benign, asymptomatic course to the development of heart failure or sudden cardiac death.2–4 Several unique features of the myocardium and its vascular supply have been identified in patients with HCM that may be integral to its phenotypic and clinical expression. For example, histopathology studies invariably demonstrate myocyte disarray with varying degrees of interstitial fibrosis5–10 within the hypertrophied myocardial segments. In addition, intramural arteriolar dysplasia11–14 is commonly identified within the same segments, leading to a reduction in the luminal area of intramural arterioles. Colocalization of these phenomena leads to a plausible hypothesis that ischemia may be a dominant contributor to the development of fibrosis in this population, a theory motivated by several noninvasive imaging studies, identifying a high prevalence of ischemia in thickened myocardial segments.15–18 Although highly relevant to understanding the pathophysiology of HCM, the relative distribution of inducible hypoperfusion and tissue injury remains poorly examined.

Clinical Perspective on p 238

Cardiovascular magnetic resonance (CMR) imaging offers combined evaluations of each phenomenon at sufficiently high resolution to examine transmural spatial distribution. In this prospective cohort study, we examine the spatial distribution of stress perfusion abnormalities and tissue injury in patients with hypertrophic cardiomyopathy.

Methods and Results—One hundred consecutive patients with hypertrophic cardiomyopathy underwent cardiovascular magnetic resonance imaging. Cine, stress perfusion, late gadolinium enhancement, and T2-weighted imaging techniques were used. Each was spatially coregistered according to predefined segmental and subsegmental models and was blindly analyzed for abnormalities using validated techniques. Spatial associations among stress perfusion, late gadolinium enhancement, and T2 imaging were made at segmental and subsegmental levels. Of the 100 patients studied, the phenotype was septal in 86 and apical in 14. Late gadolinium enhancement imaging was abnormal in 79 patients (79%). Eighty-six patients met prespecified safety criteria to undergo stress perfusion, and ischemia was identified in 46 patients (57%). T2 imaging was available in 81 patients and was abnormal in 19 (29%). The dominant distribution of all 3 findings was to segment with hypertrophy. Subsegmental analysis revealed geographic dominance of ischemia within the subendocardial zones. However, this zone was most commonly spared from late gadolinium enhancement and T2 abnormalities, typically seen in midwall and subepicardial zones.

Conclusions—Inducible hypoperfusion is a common finding in hypertrophic cardiomyopathy and is typically identified within segments exhibiting imaging markers of tissue injury. However, the respective transmural dominance of these phenomena seems distinct. Alternate factors contributing to a regional susceptibility to tissue injury are deserving of further study. (Circ Cardiovasc Imaging. 2013;6:229-238.)

Key Words: fibrosis ■ hypertrophic cardiomyopathy ■ ischemia ■ MRI ■ tissue edema
patients with HCM. In this prospective cohort study, we exploit the superior signal-to-noise ratio of 3-T MRI to perform high-resolution CMR imaging in an aim to discriminate and systematically compare transmural spatial distributions of inducible hypoperfusion (ie, ischemia) and tissue injury. The latter is evaluated using both late gadolinium enhancement (LGE) fibrosis imaging and T2-weighted edema imaging.

Methods

Patient Population

One hundred patients with HCM were identified and enrolled from outpatient cardiology clinics within a tertiary care referral center. Study inclusion criteria consisted of: age ≥16 years and the presence of echocardiographically diagnosed HCM, defined as the presence of a wall thickness ≥15 mm (or ≥13 mm, if a first-degree relative with HCM) in the absence of chamber dilation and with no history of systemic or cardiac disease sufficient to explain the hypertrophy. Patients were excluded if they had standard contraindications to MRI or a glomerular filtration rate ≤30 mL/min per 1.73 m². All patients provided written informed consent, and the study protocol was approved by the Health Research Ethics Board at the University of Western Ontario.

CMR Imaging Protocol

All patients were scanned using a 3-T MRI scanner (TRIO or Verio; Siemens Medical Systems, Germany) and underwent a standardized CMR imaging protocol, inclusive of cine imaging, T2-weighted imaging, first-pass SP imaging, and LGE imaging. The SP component of this protocol was performed only when the resting left-ventricular (LV) outflow tract gradient was documented at the time of CMR to be ≤40 mmHg using phase-contrast velocity mapping, a requirement stipulated to alleviate safety concerns in this population. T2-weighted imaging was added after the initiation of the study (after patient 27), when the presence of T2-weighted imaging abnormalities in HCM was first described. Cine imaging was performed using a standard SSFP-based pulse sequence in sequential short-axis slices from the aortoventricular anulus to apex at 10-mm intervals, as well as in the 4-, 3-, and 2-chamber orientations (typical parameters: slice thickness, 6 mm; gap, 4 mm; matrix, 256×208; TE, 1.5 ms; temporal resolution, 35–40 ms). T2-weighted imaging was performed in sequential short-axis orientations using a triple inversion recovery fast spin echo sequence, performed both with and without the use of body surface coils. Typical imaging parameters were: voxel size, 1.4×1.4 mm; slice thickness, 8 mm; and TE, 55 ms. Phase-contrast imaging was performed to determine maximal systolic left-ventricular outflow tract velocity according to a previously published protocol. First-pass perfusion imaging was performed for eligible patients using a saturation recovery TurboFLASH pulse sequence in 3 to 4 short-axis planes. Typical imaging parameters were: voxel size, 1.9×1.9×6 mm; TE, 1.51 ms; and duration, 120 cardiac cycles. SP imaging was performed 2 minutes after the intravenous administration of dipyridamole at 0.156 mg/kg over 3 minutes during bolus infusion of 0.05 mmol/kg gadolinium contrast (Gadovist, Bayer Inc, Canada) at a rate of 3.5 to 5 mL/s. Patients were routinely given 125 mg of aminophylline immediately after SP imaging, and rest perfusion imaging was performed 10 minutes later. Finally, LGE imaging was performed in sequential short-axis orientations using a standard inversion recovery gradient echo pulse sequence. Typical imaging parameters were: voxel size, 1.4×1.4; slice thickness, 8 mm; gap, 2 mm; and TE, 1.93 ms. Manual adjustment of the inversion time was performed, as previously described.

CMR Image Analysis

Image analysis was performed by a trained CMR expert using a standardized segmental scoring interface that equally divided an American Heart Association 16-segment model into 4 transmural zones, as shown in Figure 1 (CMRDb, QStatistic.com). Any of these subsegments having ≥50% of its area occupied by a relevant abnormality was scored as abnormal (and assigned a value of 1), resulting in summed segmental scores from 0 to 4. To avoid memory bias, each CMR imaging technique was blindly scored on separate days.

Quantitative analysis was incrementally performed by trained core laboratory personnel using commercially available software (CMR42 Version 3.4; Circle Cardiovascular Inc, Calgary, Canada) for the assessment of LV volumes, LV ejection fraction, LV mass, segmental wall thickness, and segmental wall thickening.

Cine Imaging: Segmental and Global Systolic Function

HCM phenotype was visually scored by identifying the predominant location of hypertrophy. Quantitative wall thickness measures were performed using semiautomated contour tracing of the endocardial and epicardial borders (Figure 2) and were reported in accordance with a 16-segment model. For each segment, the mean length of 10 evenly spaced radial measurements was used to measure the end-diastolic and end-systolic wall thickness. Papillary muscle architecture was carefully excluded for all wall thickness measures but was included for the calculation of LV end-diastolic volume, end-systolic volume, and LV mass. LV volumes and mass were indexed to body surface area.

SP Imaging: Myocardial Ischemia

First-pass SP imaging was visually scored for the presence of myocardial hypoperfusion. Significant reductions in contrast enhancement, defined as the presence of a visual reduction in signal relative to remote areas of myocardium for ≥5 cardiac cycles and not related to artifact, were coded as abnormal, as shown in Figure 1. Quantitative time signal intensity curves were generated for each myocardial segment using semiautomated tracking of the endocardial and epicardial borders. Corresponding time signal intensity curves were derived for each myocardial segment, and the maximal slope of these curves was reported for each of the 16 myocardial segments. This analysis was repeated for rest perfusion imaging and a myocardial perfusion reserve (MPR) calculated for each segment, where MPR=stress max slope/rest max slope. In addition, this analysis was independently performed for the endocardial and epicardial half of each myocardial segment, as shown in Figure 3. The aim of the latter analysis was to provide objective validation for visually scored transmural distributions of blood flow abnormalities.

LGE Imaging: Myocardial Fibrosis

Visual scoring of fibrosis was performed for all sequential short-axis LGE image data sets using the same reporting interface, as shown in Figure 1. Fibrosis was considered to be present if the myocardial signal seemed to exceed that of the blood pool and was not associated with image artifact. Computer-based signal analysis was performed using commercially available software (CMR42, Version 3.4; Circle Cardiovascular Inc, Calgary, Canada). Manual endocardial and epicardial contour tracing was performed for all short-axis LGE images and a signal threshold versus reference myocardium technique was used to define myocardial fibrosis volume. Myocardial tissue with signal ≥5 SD above the mean signal of normal myocardium (largest contiguous region of visually nulled myocardium) was defined as fibrosis. Total LV fibrosis volume was expressed as a percentage of the LV mass.

T2-Weighted Imaging: Myocardial Inflammation

Sequential short-axis T2-weighted images, acquired with the surface coil, were visually evaluated for regional signal enhancement. In those patients with identified regional abnormalities, the same imaging plane prescribed without the use of surface coils was evaluated and the region of enhancement was manually circled in addition to a reference region of skeletal muscle on the same image. If the mean myocardial signal exceeded 1.9-fold than that of skeletal muscle, as previously
described, then the myocardial signal was considered definitely abnormal. Those regions with homogeneous signal not exceeding this threshold were considered normal. The distribution of this regional enhancement was then scored using the same visual scoring interface, as shown in Figure 1. Confirmation of abnormal signal was performed using T2-weighted images acquired without the surface coil in an effort to avoid influences of coil-related signal gradients.

Statistical Analysis

Continuous data are expressed as mean±SD, and categorical data, in frequencies and percentages. Respective differences between patient groups were compared using the independent samples $t$ test for continuous data, and $\chi^2$ test for categorical data. Paired $t$ tests were used for all within-patient comparisons. All tests were 2-sided with a level of statistical significance set at $P \leq 0.05$. All statistical tests were performed using a commercially available statistical program (GraphPad Prism, Version 5.0; GraphPad Software, CA).

Results

Baseline Patient Characteristics

Baseline patient characteristics are shown in Table 1. The mean age of the population was 56±13 years with 32 (32%) being female. The distribution of hypertrophy (ie, HCM phenotype) among the 100 patients was septal in 75, concentric in 11, and apical in 14. A resting LV outflow tract gradient of $\geq 20$ and $\geq 40$ mm Hg was documented in 27 and 19 patients, respectively. Any cardiac symptoms were reported in 67 patients, inclusive of exertional chest pain in 29, dyspnea in 58, prior syncope in 8, and symptomatic ventricular tachycardia in 3. One patient had a prior cardiac arrest. Genetic testing was performed on 29 patients, identifying pathogenic mutations in 13 patients and a variant of unknown significance in 5 patients. Of the former group, there were 7 patients with MYPC3 mutations, 3 with MYH7 mutations, 3 with TPM1 mutations, and 2 with TNNT2 mutations.

Cardiovascular MRI

All patients successfully completed CMR inclusive of cine and LGE imaging. On the basis of prespecified eligibility,
LV end-diastolic volume of 61.9±13.1 mL/m² and a mean LV mass of 183±62 g/m². Segmental systolic thickening was inversely correlated with increased diastolic wall thickness both by visual wall motion scoring and by quantitative analysis of wall thickening (Figure 4). The mean percent wall thickening of myocardial segments in the lower, middle, and upper tertiles of end-diastolic wall thickness was 130±7%, 80±4%, and 44±3%, respectively (P<0.0001). Patients with septal HCM phenotype showed significantly lower mean wall thickening values for the septal versus nonseptal wall segments (54.9±7.7% versus 95.8±2.0%, P<0.0001). In contrast, patients with an apical HCM phenotype showed no significant difference in thickening between the apical and nonapical segments (80.4±4.9% versus 84.1±5.2%; P=0.6).

SP Imaging: Myocardial Ischemia
SP imaging was interpretable in all patients. Subsegmental visual scoring identified the presence of an inducible perfusion abnormality (ie, perfusion abnormality in the absence of concurrent fibrosis) in 46 patients (57%), a finding that was not associated with any measured clinical characteristic other than the prevalence of New York Heart Association class I status (Table 3). When analysis was performed using a standard 16-segment model (Figure 4), the mean summed stress scores were significantly higher for the septal wall segments in those with a septal phenotype and for the apical segments in those with an apical phenotype. The mean diastolic wall thickness of segments with and without inducible hypoperfusion was 11.3±0.3 and 9.5±0.1 mm, respectively (P<0.0001). When raw subsegmental scoring data were plotted, they demonstrated inducible hypoperfusion to be a common finding within the subendocardial zone of hypertrophied myocardial segments, irrespective of the disease phenotype (Figure 5). Patient examples are shown in Figure 6A.

Quantitative analysis of MPR was performed for the epicardial versus endocardial zones and confirmed a spatial dominance of inducible hypoperfusion in the subendocardial zone. Comparing MPR measures from all segments, the mean MPR was significantly lower for the endocardial versus epicardial zones (1.52 versus 1.88 respectively; P<0.0001). As shown in Figure 7, this relationship was driven by MPR reductions within hypertrophied myocardial segments that disproportionately affected the subendocardial zone.

LGE Imaging: Myocardial Fibrosis
LGE imaging was interpretable in all patients. Any LGE abnormality was visually identified in 79 patients. Fibrosis was quantified to be ≥5% of the LV mass (ie, significant fibrosis) in 67 patients, with this group not demonstrating any significant difference in clinical characteristics other than the prevalence of New York Heart Association class I status (Table 3). The mean volume of fibrosis identified in all patients and those with septal versus apical phenotypes is shown in Table 2. The segmental distribution of LGE findings is shown in Figure 4. Again, the predominant distribution of these abnormalities was to the respective hypertrophied segments of those with septal versus apical phenotypes. The mean diastolic wall thickness of segments with versus without LGE abnormalities was 12.3±0.2 and 8.4±0.1 mm, respectively (P<0.0001). The

Cine Imaging: Global Ventricular Measures and Segmental Wall Thickening
Global ventricular measures are shown in Table 2. The mean LV ejection fraction was 74.4±10.9% with a mean indexed
Table 2. MRI Variables Presented for the Total Population and According to Dominant Cardiomyopathy Phenotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=100)</th>
<th>Septal (N=86)</th>
<th>Apical (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²</td>
<td>90.3±26.7</td>
<td>88.5±26.5</td>
<td>100.6±20.4</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>74.4±10.9</td>
<td>73.9±11.4</td>
<td>77.2±6.8</td>
</tr>
<tr>
<td>LV EDV index, mL/m²</td>
<td>61.9±13.1</td>
<td>62.1±12.9</td>
<td>60.5±14.4</td>
</tr>
<tr>
<td>LV ESV index, mL/m²</td>
<td>16.3±8.7</td>
<td>16.7±9.0</td>
<td>14.0±6.1</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>65.9±10.6</td>
<td>65.7±10.8</td>
<td>67.0±9.4</td>
</tr>
<tr>
<td>RV EDV index, mL/m²</td>
<td>56.7±16.8</td>
<td>55.7±16.0</td>
<td>62.6±20.4</td>
</tr>
<tr>
<td>RV ESV index, mL/m²</td>
<td>19.5±9.1</td>
<td>19.4±9.2</td>
<td>20.5±8.8</td>
</tr>
<tr>
<td>Total fibrosis, % LV mass</td>
<td>9.4±11.2</td>
<td>10.0±11.7</td>
<td>4.9±4.5</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean±SD, categorical data as n (%). EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricle; and RV, right ventricle.

P<0.001). Stratification of the former group according to low or intermediate versus high fibrosis volume showed no significant difference in their respective summed stress scores (P=0.5 by ANOVA), suggesting that the presence, but not the burden, of fibrosis was associated with inducible hypoperfusion.

T2-Weighted Imaging: Myocardial Inflammation

T2-weighted imaging was interpretable in 61 patients (84%). Of these patients, a definite signal abnormality was identified in 19 patients (29%), a finding that was not associated with any measured clinical characteristic other than the prevalence of New York Heart Association class I status (Table 3). These abnormalities reliably localized to the hypertrophied segments of patients with septal and apical HCM (Figure 4). The mean diastolic wall thickness of segments with and without T2-signal abnormalities was 14.6±0.8 and 9.6±0.1 mm, respectively (P<0.0001). The raw subsegmental scoring of T2-signal abnormalities is shown in Figure 5. This identified a predominant transmural distribution within the midwall and subepicardial zones, matching that of LGE abnormalities. In each case, T2-signal abnormalities were spatially matched to regions of abnormal LGE. Patient examples are shown in Figure 6B.

Discussion

This prospective cohort study describes the prevalence and respective transmural distributions of inducible hypoperfusion, myocardial fibrosis, and myocardial T2-signal abnormalities in patients with HCM. Our findings support that inducible hypoperfusion and tissue injury are common and colocalize to hypertrophied myocardial segments in this population. Inducible hypoperfusion seems to burden the subendocardial zone reliably, whereas tissue injury predominantly develops within the midwall and subepicardial zones.

The identification of endocardial-dominant inducible hypoperfusion in this study is not unexpected. Indeed, several recognized mechanisms of ischemia are anticipated to contribute to this phenomenon in HCM as follows: (1) diffuse microvascular disease resulting from arteriole dysplasia,8,12,13,29 (2) reduced coronary vasodilator response,29–31 (3) dynamic systolic compression of the epicardial vessels resulting from an intramuscular course,20,33 and (4) supply–demand mismatch in the setting of marked tissue hypertrophy.34 In combination, these are anticipated to provide substantial reductions in myocardial blood flow at the most remote endocardial zone.

Previous studies evaluating the regional distribution of myocardial blood flow abnormalities in HCM are limited; however, they do provide consistent findings. Two small studies using MRI have evaluated stress hypoperfusion at a segmental level.15,16 The largest of these studies, performed by Peterson et al.,15 used first-pass SP imaging at 1.5 T in 35 patients with HCM and demonstrated that myocardial blood flow reserve reductions were most notable within the subendocardial zone. A similar description has been reported using positron emission tomography.17,18 For example, in a study by Knaapen et al.,17 rest and stress imaging was performed in 18 patients with HCM, and the endocardial/epicardial myocardial blood flow ratio was calculated for both. They demonstrated that this ratio fell significantly at stress in patients with HCM (1.2 to
but no change was seen in a control population (1.4 to 1.3). Among these studies, no comparison with the transmural distribution of fibrosis or tissue injury was performed. The dominant distribution of myocardial fibrosis within the midwall and subepicardial zones found in this study is highly consistent with the findings of previous studies. Gross and microscopic histopathology of ex vivo HCM hearts has reliably identified a predilection for fibrosis accumulation within the midmyocardium,10,11,35,36 a finding now reproduced by numerous in vivo studies using LGE-CMR. 6,9,37 In a study by Bohl et al, 37 the prevalence of fibrosis by LGE imaging was found to be 9%, 61%, and 21% in the subendocardial, midmyocardial, and subepicardial zones, respectively. Similarly, Choudhury et al.7 described a significantly higher prevalence of fibrosis within the midmyocardial zone versus the subendocardial zone. None of these studies performed SP or T2-weighted imaging.

Only 2 small studies have previously explored T2-signal abnormalities in patients with HCM. 22,23 A study by Abdel-Aty et al identified 9 of 27 HCM patients (33%) to have visually apparent T2-signal abnormalities, a prevalence similar to the current study. They also identified spatial matching to regions of dense fibrosis. Although the second study by Melacini et al35 showed a slightly higher prevalence (≈50%), they similarly identified that this prevalence was in regions of dense fibrosis. Neither study reported the transmural location of these abnormalities; however, both included illustrative cases that confirm midwall and subepicardial dominance. The mechanism for regional T2-signal enhancement in HCM is unknown. However, several theories can be envisioned.

<table>
<thead>
<tr>
<th>Table 3. Clinical and CMR Characteristics Presented for Patients With Normal vs Abnormal Findings From Respective Imaging Sequences</th>
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<tbody>
<tr>
<td>Fibrosis Imaging (N=100)</td>
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<tr>
<td><strong>Clinical characteristics</strong></td>
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<td>Age, y</td>
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<tr>
<td>Male</td>
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<tr>
<td>White</td>
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<tr>
<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<td>Hyperlipidemia</td>
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<td>Smoking</td>
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<tr>
<td>Syncope</td>
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<tr>
<td>Prior PCI/CABG</td>
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<tr>
<td>Chest pain</td>
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<tr>
<td>Systolic BP, mm Hg</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
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<tr>
<td>Heart rate</td>
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<tr>
<td>GFR, mL/min per 1.73 m²</td>
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<tr>
<td>LBBB</td>
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<tr>
<td>ORS duration, ms</td>
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<td>NYHA class</td>
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<td>Class I</td>
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<td>Class II</td>
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<td>Class III–IV</td>
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<tr>
<td><strong>CMR Characteristics</strong></td>
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<tr>
<td>LV mass index, g/m²</td>
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<td>LVEF, %</td>
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<tr>
<td>LV EDV index, mL/m²</td>
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<td>LV ESV index, mL/m²</td>
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<tr>
<td>RVEF, %</td>
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<tr>
<td>RV EDV index, mL/m²</td>
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<td>RV ESV index, mL/m²</td>
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</table>

Data are presented for patients with successful and interpretable image acquisitions: fibrosis imaging (N=100), stress perfusion imaging (N=81), and T2-weighted imaging (N=61). Continuous data are expressed as mean±SD, categorical data as n (%).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BP, blood pressure; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CMR, cardiovascular magnetic resonance; EDV, end-diastolic volume; EF, ejection fraction; eGFR, glomerular filtration rate; ESV, end-systolic volume; LBBB, left bundle branch block; LV, left ventricle; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and RV, right ventricle.

*P ≤ 0.05.
First, T2 signal has been associated with tissue edema, resulting from acute ischemic and inflammatory myocardial injury, and may therefore represent an atypical distribution of one or both of these phenomena. This would suggest the potential for T2 imaging to be a marker of increased disease activity in HCM, a purely speculative hypothesis at this time.

**Figure 5.** Bulls-eye plots illustrating the subsegmental spatial distribution of myocardial fibrosis, inducible hypoperfusion, and T2-signal enhancement among patients with (A) septal phenotype (N=86) and (B) apical phenotype (N=14) hypertrophic cardiomyopathy. Subsegmental values represent relative prevalence for each subsegment (ie, indexed to maximal prevalence value).

**Figure 6.** A. Case examples—spatial comparison of fibrosis vs stress hypoperfusion: 4 case examples illustrating a spectrum of spatial relationships between fibrosis by late gadolinium enhancement (LGE) imaging and stress inducible hypoperfusion. Patient A shows dense subepicardial-based fibrosis in the setting of marked, subendocardial inducible hypoperfusion of the septum. Patient B shows multifocal subepicardial fibrosis in the setting of marked subendocardial inducible hypoperfusion of the anterolateral wall. Patient C shows subendocardial and midwall fibrosis of the anteroseptal and inferoseptal walls in the setting of subendocardial hypoperfusion extending beyond the same regions. Patient D shows dense subepicardial and patchy midwall and subendocardial fibrosis within the anteroseptum, whereas stress perfusion imaging shows marked subendocardial and midwall hypoperfusion of all septal segments. B. Case examples—spatial comparison of fibrosis vs T2-signal enhancement: 4 case examples illustrating typical spatial relationships between fibrosis by LGE imaging and T2-signal enhancement. Patient A shows midwall fibrosis of the inferoseptal and anteroseptal walls with T2-signal enhancement identified within the same regions. Patient B shows subepicardial fibrosis of the anteroseptal wall with associated T2-signal enhancement of the same region. Patient C shows midwall fibrosis of the anteroseptal and inferoseptal walls with T2-signal enhancement of the same regions. Patient D shows extensive subepicardial and midwall fibrosis with T2-signal enhancement of the same regions.
However, the findings of the current study do raise important considerations with respect to an apparent susceptibility of the midwall and subepicardial zones to developing tissue injury. From our findings, this does not seem to be adequately explained by the presence of inducible ischemia because this phenomenon burdens a relatively injury-spared subendocardial zone. Accordingly, ongoing exploration of factors contributing to tissue injury in HCM is warranted because this may lead to novel therapeutic targets.

**Limitations**

As a single-center cohort study, our findings require confirmation within a multicenter setting. As mentioned previously, definitions used for inducible hypoperfusion inherently lead to its disparate geographic distributions versus fibrosis (ie, once the latter exists, the former can no longer exist). We addressed this in 2 ways. First, analysis was performed at a population level, evaluating the mean prevalence of respective findings over a range of disease maturity. It is therefore assumed that if phenomena are associated, their geographic distribution should, in general, be similar. Second, we incrementally performed quantitative segmental analysis of myocardial blood flow at rest and stress to corroborate visually identified spatial dominance of inducible hypoperfusion. Because this represents an objective comparison of myocardial blood flow reserve between respective zones, any bias related to regional tissue fibrosis is minimized.

The first 27 patients recruited in this study did not have T2 imaging performed because this predated the first description of this technique’s use in HCM. However, no statistical differences were identified in baseline characteristics of those receiving and not receiving T2 imaging. The signal thresholds used in this study for defining abnormal T2 signal were extrapolated from studies at 1.5 T. Further validation of optimal thresholds at 3-T field strengths is required.

No control population was used in this study because the aim of this study was to evaluate the relative prevalence and distribution of abnormal findings among patients with known HCM. It was not an aim to identify the prevalence of such findings relative to normal individuals because this has been addressed by previous studies. Of particular note, T2 abnormalities are recognized to be rare in healthy controls.

### Conclusions

In this study, we confirm that inducible hypoperfusion and myocardial injury are common findings in patients with HCM and colocalize to hypertrophied wall segments. It is interesting that although inducible hypoperfusion is highly prevalent in the subendocardial zone, relevant markers of tissue injury are typically identified in the midwall and subepicardial zones. Therefore, factors contributing to injury vulnerability in these latter zones require investigation and may offer novel therapeutic targets.

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Disclosures
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References


**CLINICAL PERSPECTIVE**

Patients with hypertrophic cardiomyopathy commonly demonstrate abnormal vascular and tissue findings by histological examination, inclusive of arteriole dysplasia and myocardial fibrosis. These are thought to represent important contributors to clinical disease expression and may be of importance for the occurrence of future cardiovascular events. However, relationships among tissue ischemia, injury, and repair (fibrosis) remain poorly understood in this population. Contemporary cardiovascular magnetic resonance offers a validated toolset to explore such associations. In the current study, we spatially examine the presence of stress-induced hypoperfusion, current tissue injury (edema), and irreversible tissue injury (fibrosis) in 100 patients with hypertrophic cardiomyopathy. Several important findings are highlighted as follows: (1) stress hypoperfusion was seen in more than half of the patients and was predominantly found in the subendocardial zones; (2) established fibrosis was seen in two thirds and predominantly found in midwall and subepicardial zones; and (3) current tissue injury was suggested in a third of patients and was reliably found in regions of established fibrosis. These data support that inducible ischemia commonly exists in myocardial segments burdened by tissue injury and fibrosis. However, the transmural distribution of these respective phenomena suggest greater complexity with a vulnerability to tissue injury (in midwall and subepicardial zones) that is not adequately explained by cardiovascular magnetic resonance–based measures of tissue hypoperfusion alone. Such factors remain of particular interest, given their potential to provide novel therapeutic targets in this condition.
Stress Hypoperfusion and Tissue Injury in Hypertrophic Cardiomyopathy: Spatial Characterization Using High-Resolution 3-Tesla Magnetic Resonance Imaging

Chung Chun Tyan, Sarah Armstrong, David Scholl, John Stirrat, Kimberly Blackwood, Omar El-Sherif, Terry Thompson, Gerald Wisenberg, Frank S. Prato, Aaron So, Ting Yim Lee, Maria Drangova and James A. White

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