First-pass Myocardial Perfusion Defect and Delayed Contrast Enhancement in Hypertrophic Cardiomyopathy Assessed with MRI

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(Received February 3, 2003; Accepted March 26, 2003)

Background: Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) enhanced magnetic resonance imaging (MRI) is known to be useful for detecting myocardial injury. In this study, we used first-pass myocardial perfusion and delayed contrast-enhanced MRI to determine whether an abnormal signal intensity was related to the left ventricular regional contractile function in patients with hypertrophic cardiomyopathy (HCM).

Materials and Methods: Twelve patients with HCM participated in this study. Four short axial cine images of the left ventricle were acquired. Subsequently, first-pass myocardial perfusion images during the first passage of Gd-DTPA (0.1 mmol/kg), and delayed contrast-enhanced images after a 15-min delay, were acquired in the same orientation as cine imaging. Each image was divided into eight blocks and a total of 384 blocks were analyzed.

Results: First-pass myocardial perfusion defects (PD) were detected in nine patients with an average of 11.5 ± 11 blocks. Delayed contrast enhancement (DE) was detected in 11 patients with an average of 11.5 ± 10 blocks. Mean wall thickness in PD blocks (16.7 ± 4.7 mm) was larger than that in normal perfusion blocks (13.6 ± 3.9 mm, p < 0.001). Mean wall thickness in DE blocks (16.9 ± 4.9 mm) was larger than that in normal enhanced blocks (13.4 ± 3.6 mm, p < 0.001). PD were located at almost the same site as DE, but DE areas were larger than PD areas (p = 0.0021). Mean percent wall thickening of blocks with PD (63.1 ± 44.7%, p < 0.0001) and blocks with DE (75.2 ± 81.5%, p < 0.01) was lower than that in blocks with neither PD nor DE (103.5 ± 66.0%). Significant correlations were found between percent wall thickening and percent PD (r = 0.46, p < 0.0001) and between percent wall thickening and percent DE (r = 0.54, p < 0.0001).

Conclusion: Abnormal signal intensity from first-pass myocardial perfusion and delayed contrast-enhanced MRI are closely related to left ventricular regional contractile function.

Keywords: hypertrophic cardiomyopathy, magnetic resonance imaging, first-pass myocardial perfusion defect, delayed contrast enhancement, myocardial fibrosis

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by inappropriate myocardial hypertrophy and a non-dilated left ventricle with normal left ventricular ejection performance and impaired diastolic function. In addition, an impaired regional left ventricular wall thickening, via several imaging techniques, has been described in patients with HCM.1-4 Wall thickening usually deteriorates with increase of wall stress. Wall stress increases with an increase in blood pressure or left ventricular internal dimension, and decreases with the increase in wall thickness. Thus, wall stress in most patients with HCM decreases markedly.5 According to Silverman et al.,6 the catenoid shape of the septum observed in most patients with HCM may be related to septal immobility. Another cause of impaired regional left ventricular wall thickening may be the qualitative changes in the left ventricular wall in patients with HCM.
Identification of patterns of dysfunctional myocardial regions with first-pass myocardial perfusion and delayed contrast enhancement on magnetic resonance imaging (MRI) after injection of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), is a promising technique for detecting both irreversible and reversible myocardial injury and fibrosis in myocardial infarction. In patients with HCM, it is reported that regions of abnormal signal intensity in delayed contrast-enhanced MRI may be related to myocardial degeneration. However, to our knowledge no data on HCM have been obtained with first-pass myocardial perfusion MRI. In addition, the relationship between abnormal signal intensity and left ventricular regional contractile function has not been clarified. Therefore, we hypothesized that qualitative myocardial changes in patients with HCM might be revealed by first-pass myocardial perfusion and delayed contrast-enhanced MRI, and that qualitative myocardial changes would be associated with left ventricular regional contractile dysfunction.

Materials and Methods

Subjects
Twelve patients with HCM (10 men and two women, aged from 31 to 89 years, with a mean age of 57 ± 16) participated in this study after giving written informed consent. All patients were in New York Heart Association Class I (n = 9) or II (n = 3) at the time of examination. The diagnosis of HCM was made by echocardiography according to the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. Left ventricular fractional shortening evaluated by M-mode echocardiography in these patients was 43 ± 7%. Five of the 12 patients with HCM had an intraventricular pressure gradient above 30 mmHg without provocation, as determined by continuous-wave Doppler echocardiography. All patients were in normal sinus rhythm, and none had bundle-branch block, valvular, coronary or pulmonary diseases. In addition, patients with HCM and a history of congestive heart failure were excluded from this study. Drug treatment was performed with calcium-channel blockers in three patients, beta-blockers in seven patients, and antiarrhythmic Na channel blockers in six patients. We continued these cardiac medications in all patients throughout the examination.

Magnetic resonance imaging

Cine MRI studies were performed with a standard 1.5T MRI system (ACS-NT PT 3000, Gyroscan, Philips Medical Systems International, Best, The Netherlands). All scans were obtained with a whole-body coil and electrocardiographic triggering. After three rapid surveys to determine the exact position and axis of the left ventricle, four short axis slices (basal, mediobasal, medioapical and apical) were obtained with a multislice echopla-
Fig. 2. First-pass myocardial perfusion MRI in patients with HCM. This example shows one slice from a multislice acquisition. a: Prior to contrast, the heart appears dark due to T1 weighting from the saturation pulse. b: When contrast arrives in the right ventricle on the second image, the T1 of the blood becomes short enough to brighten considerably, but the rest of the heart appears dark. c: Several heartbeats later, contrast arrives in the left ventricular cavity, which therefore brightens. d: This image represents first-pass myocardial perfusion MRI. When the myocardium enhances a few heartbeats later, dark sites remain in the triangular portions of the anterior and posterior septum. e-i: A dark site gradually brightens and its area increases. j: Delayed contrast-enhanced MRI after a 15-min delay reveals DE, which appears in essentially the same site as did PD; the DE areas are clearly larger than the PD areas. The arrows in “d–e” show PD by perfusion MRI. The arrowheads in “f–i” show the so-called cores of the enhanced areas. The arrows in “j” show DE by delayed contrast-enhanced MRI. PD = First-pass myocardial perfusion defect; DE = Delayed contrast enhancement.

First-pass myocardial perfusion MRI studies were performed with an electrocardiogram-triggered, T1-weighted saturation recovery, single-shot, turbo field echo-echo planar imaging (TFE-EPI) sequence. Other parameters were as follows: saturation pulse; prepulse delay of 300 ms; acquisition duration of 125 ± 10 ms; flip angle of 15 degrees; TR of 12 ms; TE of 4.6 ms; FOV of 350 mm; and a matrix of 256 × 120. Data acquisition was performed in the same orientation used for cine imaging. During an inspiratory breath-hold, a bolus (0.1 mmol/kg body weight) of Gd-DTPA (Magnevist® Schering AG, Berlin, Germany) was injected at a rate of 4 ml/s through a 20-gauge antecubital intravenous line. Bolus injection was performed with a magnetic-resonance-compatible power injector (Spectris MR Injector Medrad, Inc.) followed by a 15-ml saline flush. The patients were instructed to hold their breath as long as possible and 27 ± 4 time frames were acquired for each patient. Subsequently, 10 time frames were acquired every minute until 10 min after Gd-DTPA administration (Fig. 2a–i).

After the first-pass myocardial perfusion study, additional Gd-DTPA was administered for a total dose of 10 mmol. After a five-minute delay, the studies were performed again with an electrocardiogram-triggered, T1-weighted inversion recovery, single-shot, turbo field echo sequence. Other parameters were as follows: inversion pulse; a prepulse delay of 400 ms; flip angle of 15 degrees; TR of 4.9 ms; TE of 1.6 ms; FOV of 350 mm; a matrix of 256 × 77; and breath-holding. Data acquisition was performed in the same orientation used for cine imaging.
ventricular pressure gradient

terventricular septal thickness; PWT

ness

wall thickening was determined by the following area assessed by a cine loop analysis. The percent w a sd eˆn e da st h eˆr s tt i m ef r a m eo ft h es t u d y w i t h end-systolic (ES) wall thicknesses. The end-diastole calculated with the absolute end-diastolic (ED) and MRI. One time frame was acquired with each as were cine and first-pass myocardial perfusion =

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as were cine and first-pass myocardial perfusion MRI. One time frame was acquired with each patient (Fig. 2j).

Image analysis

The percentage of systolic wall thickening was calculated with the absolute end-diastolic (ED) and end-systolic (ES) wall thicknesses. The end-diastole was defined as the first time frame of the study with a trigger delay to the R wave of 0 ms; the end-systole was defined as the smallest left ventricular area assessed by a cine loop analysis. The percent wall thickening was determined by the following equation: (ES thickness − ED thickness)/ED thickness × 100%. Wall thickening analysis was performed after manual segmentation of the cine data set with a commercially available analysis package (Cardiac Analysis Package™). Each single-frame image was divided into eight equiangular blocks beginning with the anterior interventricular sulcus (Fig. 1), and each block was divided into five equiangular segments. The average of the five segments was adopted as the left ventricular wall thickness of the block.

For each of these blocks, regions of myocardium with abnormally low signals—defined as less than 75% of remote normal enhanced myocardium within the same slice during the first pass of the contrast agent in the first-pass myocardial perfusion MRI study—were designated as first-pass myocardial perfusion defect (PD). In addition, regions of myocardium with abnormally high signals—defined as more than 200% of remote normal enhanced myocardium within the same slice in the delayed contrast-enhanced MRI study—were designated as delayed contrast enhancement (DE).

Statistical analysis

Values are expressed as mean ± SD. Comparisons of continuous data were made with unpaired t tests. Comparisons among three groups were performed with one-way analysis of variance with the Scheffé procedure for multiple comparisons. Correlation coefficients were calculated with linear regression analysis. The level of statistical significance was set at p < 0.05.

Results

Frequency of PD and DE

Table 1 shows the baseline characteristics of participating patients. Figure 2 shows the images of a 31-year-old male patient with HCM. Figures 2(a)–(i) show the selected myocardial perfusion MRI, while Fig. 2(d) represents first-pass myocardial perfusion MRI; PD, indicated by the arrows, were detected in the triangular portions of the anterior and posterior septum. Figure 2(j) shows delayed contrast-enhanced MRI; DE, shown by the arrows, was detected in virtually the same sites as PD. Figures 2(f)–(i) show that PD in the anterior triangular portion become enhanced gradually

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**Table 1. Echocardiographic data on 12 patients with hypertrophic cardiomyopathy**

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<th>Patient</th>
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<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>IVST (mm)</th>
<th>PWT (mm)</th>
<th>LVDd (mm)</th>
<th>LVDs (mm)</th>
<th>FS (%)</th>
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<tr>
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from without; the so-called core is indicated by the arrowheads. On the other hand, PD in the posterior triangular portion become enhanced homogeneously, in the early phase. A total of 384 blocks were analyzed, and PD were detected in nine patients, with an average of 11.5 ± 11 blocks, while DE was detected in 11 patients, with an average of 11.5 ± 10 blocks. Table 2 shows the resulting frequencies of PD and DE. Blocks one and sixty-four showed PD during the first pass, and 220 blocks had normal perfusion. Of the blocks with PD, 113 showed DE and 51 remained unchanged. Of the normal blocks during the first pass, 46 exhibited DE and 174 did not.

Areas of PD and DE

Areas of PD and DE were estimated from each slice by adding the areas of eight blocks. PD were found in almost the same sites as DE, but the mean DE area (597 ± 619 mm²) was larger than the mean PD area (390 ± 458 mm², p = 0.0021).

Wall thickness and PD and DE

Figure 3 shows the wall thickness related to PD (left) and DE (right). The wall thickness of the blocks with PD was greater than that of the blocks without PD (16.7 ± 4.7 mm vs. 13.6 ± 3.9 mm, p < 0.001), and the wall thickness of the blocks with DE was also greater than that of the blocks without DE (16.9 ± 4.9 mm vs. 13.4 ± 3.6 mm, p < 0.001). However, there was no significant difference in wall thickness between the blocks with PD and DE. Figure 4 shows the relation between wall thickness and frequency of PD and DE. The frequencies of PD and DE increased according to the severity of the wall thickness.

Percent wall thickening and PD and DE

Figure 5 shows the relation between PD or DE and percent wall thickening of the left ventricle. The percent wall thickening of blocks with PD (63.1 ± 44.7%) or DE (75.2 ± 81.5%) was lower than that of blocks having neither PD nor DE (103.5 ± 66.0%, p < 0.0001 or p < 0.01, respectively). Figure 6 shows the correlation between percent PD or percent DE and percent wall thickening. Significant correlations were seen between percent wall thickening and percent PD, and between percent wall thickening and percent DE.

Discussion

The present study demonstrates for the first time the relationship between left ventricular regional contractile function and abnormal signal intensity detected by first-pass myocardial perfusion and

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**Table 2.** Frequency of PD and DE

<table>
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<th>First-pass myocardial perfusion MRI</th>
<th>Delayed contrast enhanced MRI</th>
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<td>PD(+) (n = 164)</td>
<td>PD(-) (n = 220)</td>
<td>DE(+) (n = 159)</td>
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<tr>
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<td>113</td>
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<td>46</td>
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<td>174</td>
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PD(+) = Blocks with early perfusion defect; PD(-) = Blocks without early perfusion defect; DE(+) = Blocks with delayed contrast enhancement; DE(-) = Blocks without delayed contrast enhancement.
delayed contrast-enhanced MRI in patients with HCM. Delayed contrast-enhanced MRI with Gd-DTPA is considered useful for myocardial tissue characterization in HCM, while first-pass myocardial perfusion MRI appears to be capable of detecting microvascular perfusion abnormalities in HCM.\textsuperscript{15} Therefore, the present study demonstrates the ability to assess pathological changes of myocardium in HCM, with the dual analyses of first-pass myocardial perfusion and delayed contrast-enhanced MRI.

The pharmacokinetic behavior of intravenously delivered Gd-DTPA is similar to that of the well-known iodinated contrast agents. Gd-DTPA is rapidly distributed from the intravascular to the extracellular fluid compartment, but it cannot enter the myocyte because of its very high hydrophilicity, charge, and high molecular weight.\textsuperscript{16} It is estimated that approximately 50\% of the injected dose of Gd-DTPA is cleared from the capillaries during the first pass through the myocardium.\textsuperscript{17} The TFE-EPI MRI technique can be used to monitor the passage of a contrast medium through the central circulation and follow the first pass through the myocardium. Thus, it could estimate regional microvascular blood volume and perfusion.

Gd-DTPA, with a half-life of 20 min, is largely washed out of normal tissue within 10 to 15 min of injection.\textsuperscript{18} Gd-DTPA enhancement is determined mainly by regional Gd-DTPA concentration and by...
subsequently determined T$_1$ relaxation time on inversion recovery prepared delayed enhanced MRI. A marked difference in Gd-DTPA concentration between abnormal and normal myocardium might be created by increased delivery to, and by delayed clearance in abnormal myocardium. Thus, the effect of enhancement is determined by the amounts of vascularization and cellular damage and by the size of the extracellular space of the myocardium.

Delayed contrast-enhanced MRI after Gd-DTPA administration has been widely used for the detection of myocardial injury in myocardial infarction, hypertrophic cardiomyopathy, and secondary cardiomyopathies. In patients with HCM, delayed contrast enhancement was observed in hypertrophied myocardium on MRI after the administration of Gd-DTPA. In the histological investigation, the major focus of the disarray in HCM was noted in the septum, with asymmetric hypertrophy and triangular portions of the anterior and posterior septum. DE was detected mainly in the septum and triangular portions. Therefore, DE detected by delayed contrast-enhanced MRI may be related to myocardial disarray and fibrosis. In a histopathologic investigation of delayed contrast-enhanced MRI using hamsters with cardiomyopathy, DE was found not only in fibrosis but also at the sites of vessel proliferation, myocardial edema, and inflammatory change. DE was diminished in the late stage of myocardial fibrosis. Yamakado et al. reported two cases of dilated cardiomyopathy-like features. They showed multiple low-intensity dots in the DE area, which supposedly represented severe myocardial fibrosis.

There have been no previous reports of the use of first-pass myocardial perfusion MRI in HCM. In our study, PD was detected in 75% of patients by first-pass myocardial perfusion MRI, and the frequency of PD increased with the severity of wall thickness. PD were distributed not only in the subendocardium, but also in the epicardium. The locations of PD were almost the same as those of DE, and the image areas of PD were smaller than those of DE. PD may represent the increase in extra-cellular water fraction and perfusion abnormalities including myocardial ischemia. When the extra-cellular water fraction is increased, first-pass myocardial perfusion MRI can be abnormal, even if tissue capillary perfusion remains normal. This is due to the highly increased (extra-cellular fraction)/(intravascular fraction) ratio in such segments. Assuming tissue blood flow is preserved and the extraction fraction of Gd-DTPA is constant, the upslope of the myocardial perfusion curve can be substantially decreased in the area with substantially increased extra-cellular fraction, since the fixed amount of Gd-DTPA coming from the capillary is diluted extra-cellular water. Several explanations for myocardial ischemia in patients with HCM have been proposed. Capillary density in the hypertrophied heart may be inadequate to supply the increased myocardial mass, while increased compression of the intramyocardial coronary arteries during the systolic coronary phase may decrease the flow therein. In addition, impaired left ventricular relaxation, inadequate vasodilator flow reserve, and thickened intramural coronary arteries may also cause myocardial ischemia. Therefore, PD detected by first-pass myocardial perfusion MRI may indicate an advanced stage of the disease.

To explain this hypothesis, we examined the regional percent wall thickening among the blocks with PD or DE, as well as those with neither PD nor DE. Percent wall thickening of blocks with PD or DE was lower than that of blocks with neither PD nor DE. Percent wall thickening of blocks with PD was lower than that of blocks with DE, but the difference was not significant. One explanation for the absence of a significant difference in percent wall thickening between blocks with PD and those with DE may be that we had no patients with dilated cardiomyopathy-like features. When the blocks with PD are small and the amount of intact myocardium is sufficient, the intact myocardium may be able to compensate for dysfunctional regions; this effect might preclude the finding of a significant difference in percent wall thickening between PD and DE.

Anatomic abnormality, such as a catenoid-shaped septum, may be related to septal immobility. In addition, left ventricular regional contractile function is generally impaired in the hypertrophied regions, despite the presence of normal left ventricular ejection performance in patients with HCM; this opinion is generally shared. PD and DE are detected in the hypertrophied regions and are closely related to left ventricular regional contractile function. Therefore, left ventricular regional contractile function is impaired not only in the hypertrophied myocardium but also in regions undergoing change by fibrosis. To detect this change, first-pass myocardial perfusion MRI with delayed contrast-enhanced MRI is useful for evaluating the location and the extent of myocardial injury. In addition, it is useful for predicting left ventricular regional contractile function in patients with HCM.
Acknowledgments

We wish to thank K. Ninomiya, MD for his invaluable advice. We also thank M. Tanimoto, RT and E. Fujiwara, RT for their assistance with the MRI examinations.

References


