Structural Abnormalities of the Inferoseptal Left Ventricular Wall Detected by Cardiac Magnetic Resonance Imaging in Carriers of Hypertrophic Cardiomyopathy Mutations

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OBJECTIVES

The purpose of this study was to evaluate whether structural left ventricular (LV) abnormalities can be observed in hypertrophic cardiomyopathy (HCM) mutation carriers who have not yet developed echocardiographic signs of hypertrophy by using cardiac magnetic resonance imaging (CMR).

BACKGROUND

Hypertrophic cardiomyopathy is caused by mutations of genes encoding for sarcomeric proteins. Myocyte disarray and interstitial fibrosis precede the development of regional hypertrophy in HCM mutation carriers (carriers). No macroscopic LV structural abnormalities have been observed in carriers without LV hypertrophy.

METHODS

A CMR, echocardiogram, and electrocardiogram (ECG) were performed in 16 carriers. Delayed contrast enhancement imaging was used with CMR to detect fibrosis. In 16 age- and gender-matched control subjects, CMR and ECG were performed and an echocardiogram was made when structural abnormalities were detected with CMR. All carriers had an LV wall thickness <13 mm in the year before the study, measured by echocardiography.

RESULTS

In 13 carriers (81%), crypts were discerned with CMR in the basal and mid inferoseptal LV wall, not detected by routine echocardiography and not observed in healthy volunteers. In 4 of the crypt-positive carriers, both the echocardiogram and ECG were normal. Two HCM carriers revealed regional hypertrophy of the inferoseptum not detected by echocardiography, and in both carriers, focal fibrosis was present.

CONCLUSIONS

In carriers who have not yet developed frank hypertrophy, crypts can be detected with CMR in the inferoseptal LV wall, even when echocardiography and ECG are normal. The crypts might represent one of the early pathological alterations of myocardium in carriers that ultimately progress into manifest HCM. (J Am Coll Cardiol 2006;48:2518–23) © 2006 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a common disease, occurring in 1 in 500 in the general population, and clinically diagnosed by the presence of left ventricular (LV) hypertrophy in the absence of a disease likely to cause this hypertrophy (1).

Hereditary HCM is caused by mutations in genes, most of which encode for sarcomeric proteins (2). Genetic screening of families of index HCM patients enables the identification of HCM mutation carriers, whose echocardiographic dimensions of the LV might still be within the normal range. It is yet unclear how mutations in sarcomeric proteins, which presumably affect all cardiac myocytes, give rise to the usually regional myocardial hypertrophy.

Earlier studies in animals and human subjects have shown that myocyte disarray, fibrosis, relaxation abnormalities, and concomitant left atrial enlargement precede the development of frank hypertrophy in HCM mutation carriers (3,4). We hypothesized that HCM mutation carriers exhibit local structural abnormalities before hypertrophy can be discerned.

Cardiac magnetic resonance imaging (CMR) has a high spatial resolution, is considered the gold standard for in vivo determination of mass and volumes of the LV, and enables precise quantification of wall thickness and dimensions (5). Also, CMR with delayed contrast enhancement (DCE) imaging can be used to detect foci of collagen deposition in the myocardium of HCM patients (6).

Therefore, we used CMR to evaluate whether structural LV abnormalities can be observed in HCM mutation carriers who have not yet developed echocardiographic signs of hypertrophy.

METHODS

Patient selection. Hypertrophic cardiomyopathy mutation carriers with an LV wall thickness <13 mm as measured by 2-dimensional echocardiography in the year before the study were selected. The HCM mutation carriers had either a 2373insG mutation in the gene encoding for cardiac...
myosin-binding protein C (MYBPC3), which is found in at least 25% of HCM patients in the Netherlands (7), or a Glu62Gln missense mutation in the gene encoding for alpha-tropomyosin (TPM1) (8).

CMR image acquisition. The CMR studies were performed on a 1.5-T whole body scanner (Magnetom Sonata, Siemens, Erlangen, Germany), with a 6-channel phased-array body coil. After survey scans, long-axis 4-, 3-, and 2-chamber cines were acquired with a retro-triggered, balanced steady-state free precession gradient-echo (true-FISP) sequence.

Scan parameters were: 5-mm slice thickness with 5-mm gap between short-axis slices, temporal resolution <50 ms, repetition time 3.2 ms, echo time 1.54 ms, flip angle 70°, and typical image resolution 1.3 × 1.6 mm. A stack of 10 to 12 short-axis slices was used to cover the LV, as described previously (9). Acquiring additional cine images was left to the discretion of the attending cardiologist, a CMR specialist.

The DCE images were obtained 10 min after injection of 0.2 mmol/kg gadolinium-DTPA. An inversion recovery turbo Fast Low Angle Shot (FLASH) sequence was used to obtain images with 6-mm slice thickness planned at the same position as the long- and short-axis cines in end-diastole. All images were obtained during breath holding in mild expiration. The LV volumes and mass were obtained as described previously (9). The LV volumes and mass were indexed to body surface area. End-systolic left atrial dimensions were measured on 3-chamber view as the distance between the aortic root and posterior wall of the left atrium. The presence of fibrosis and the structure of the LV were evaluated by a cardiologist experienced in CMR (A.C.vR.) and blinded to the genotype.

Echocardiography. Two-dimensional and Doppler echocardiography were performed on a Vivid-7 (General Electric Vingmed Ultrasound, Horten, Norway). Left ventricular structure and function were evaluated on parasternal and apical views. Acquiring additional images was left to the discretion of the echocardiographer. Left ventricular structure and function were evaluated by a cardiologist (O.K.) experienced in echocardiography and blinded to the genotype.

### Table 1. Baseline Characteristics and Dimensions Measured by Cardiac Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th></th>
<th>HCM Mutation Carriers (n = 16)</th>
<th>Healthy Volunteers (n = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>40.7 ± 12.7</td>
<td>40.1 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/10</td>
<td>6/10</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>114.8 ± 12.7</td>
<td>122.7 ± 12.7</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>65.2 ± 9.1</td>
<td>70.3 ± 7.0</td>
<td>NS</td>
</tr>
<tr>
<td>LV EDV (ml/m²)</td>
<td>92.0 ± 11.0</td>
<td>92.5 ± 11.0</td>
<td>NS</td>
</tr>
<tr>
<td>LV ESV (ml/m²)</td>
<td>34.3 ± 4.9</td>
<td>36.3 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>LV EF</td>
<td>62.3 ± 3.7</td>
<td>60.8 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass (ml/m²)</td>
<td>56.2 ± 11.0</td>
<td>52.3 ± 10.0</td>
<td>NS</td>
</tr>
<tr>
<td>SWT (mm)</td>
<td>9.2 ± 2.8</td>
<td>7.5 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>7.3 ± 1.6</td>
<td>7.0 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>LA dimension (mm)</td>
<td>28.3 ± 6.1</td>
<td>29.8 ± 5.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP = blood pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HCM = hypertrophic cardiomyopathy; LA = left atrial; LV = left ventricular; PWT = maximal left ventricular lateral wall thickness; SWT = maximal septal wall thickness.
**ECG.** Standard 12-lead ECG was performed. Conduction intervals were measured, and LV hypertrophy was evaluated with the Romhilt-Estes criteria (10). The ST-segments were defined as normal or abnormal and, in addition, an R-wave in V1 > 3 mm was considered abnormal. The ECGs were analyzed by 2 observers blinded for the genotype (T.G. and A.A.M.W.).

**Genetic screening.** Genomic deoxyribonucleic acid was isolated from blood samples. Sequencing protocols are given in Alders et al. (7) and Jongbloed et al. (8).

**Statistical analysis.** An independent Student t test was used to compare groups. A p value of < 0.05 was considered significant.

**RESULTS**

The group of HCM mutation carriers comprised 5 TPM1 mutation carriers (3 men) and 11 MYBPC3 mutation carriers (3 men) from 7 different families. No HCM mutation carriers were excluded. Sixteen age- and gender-matched healthy volunteers were included (6 men).

**Dimensions and global LV function.** Baseline characteristics and global LV and left atrial dimensions measured with CMR did not differ between HCM mutation carriers and healthy volunteers (Table 1).

The CMR showed inferoseptal basal hypertrophy that was not detected previously by echocardiography in 2 carriers with a septal wall thickness of 17 and 13 mm, respectively (Table 2). In all other HCM mutation carriers, maximal septal wall thickness, maximal lateral wall thickness, LV mass, and left atrial dimensions were within normal limits. In the HCM mutation carrier with regional hypertrophy, LV mass exceeded normal limits of 64.7 ± 9.3 g/m² (11).

**Structure.** In the majority of HCM mutation carriers (13 of 16; 81%), CMR revealed an abnormal structure of the myocardium consisting of profound crypts in the basal and mid segment of the inferoseptal LV myocardium, at the junction of the right and left ventricle (Fig. 1). The crypts were only visible at end-diastole (Video [see Appendix]). On LV short-axis images, they appeared as triangular, blood-containing bright spots (Fig. 1). Importantly, the myocardial segments surrounding the crypts were considered normokinetic, both on CMR and echocardiography. Best visualization was obtained on subsequently acquired dedicated long-axis slices, slightly modified from the 2-chamber view, cutting through the inferior septum (Fig. 1).

In HCM mutation carriers with an LV septal wall thickness < 9 mm, the crypts could be visualized within the inferoseptal LV wall up to the subepicardium (Fig. 1). In those HCM mutation carriers with an LV wall thickness ranging from 9 to 12 mm, the crypts could be visualized only throughout 70% of the inferoseptal LV wall. The 1 HCM mutation carrier who had 17-mm LV wall thickness revealed only 1 remnant crypt at the border of the regionally hypertrophied segment. The 3 HCM mutation carriers who

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**Table 2. Detailed Description of HCM Mutation Carriers**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Group</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>SWT (mm)</th>
<th>PWT (mm)</th>
<th>LV Mass (g/m²)</th>
<th>LA (mm)</th>
<th>DCE Crypt Location</th>
<th>Pen.</th>
<th>RE Score</th>
<th>ECG Cond.</th>
<th>ST-Segment V 1R (mV)</th>
<th>ECG Concl.</th>
<th>Penetration</th>
<th>CR Score</th>
<th>Overall ECG Concl.</th>
<th>LA Mass (g/m²)</th>
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<td>22.3</td>
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<td>Abnormal</td>
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<td>4.5</td>
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<td>70.7</td>
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<td>70.7</td>
<td>3</td>
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<td>0</td>
<td>0</td>
<td>70.7</td>
<td>70.7</td>
<td>3</td>
</tr>
</tbody>
</table>

**Age** indicates the age at cardiac evaluation. **AS** = anteroseptal; **DCE** = delayed contrast enhancement; **ECG Conc.** = overall ECG conclusion; **IS** = inferoseptal; **LA** = left atrial dimension; **LV Mass** = left ventricular mass indexed to body surface area; **Pen.** = penetration of LV wall; **RE score** = degree of LV ventricular hypertrophy score according to Romhilt and Estes; **TPM1** = Glutathione T1 mutation carrier in alpha-tropomyosin 1 gene; other abbreviations as in Table 1.
had no discernable crypts were all women and were MYBPC3 mutation carriers.

All healthy volunteers had normal LV myocardium without the structural abnormalities described in the preceding text.

Focal fibrosis within the septal wall was present in the 2 HCM mutation carriers with regional hypertrophy. Fibrosis was absent in all other HCM mutation carriers and healthy volunteers. However, the crypts did mimic focal fibrosis by partial volume effects on short-axis DCE images (Fig. 2).

**ECG.** None of the HCM mutation carriers met the criteria for LV hypertrophy (Table 2). In 2 (15%) crypt-positive carriers, ST-segments were abnormal. An R-wave in V1 ≥3 mm was found in 9 of the crypt-positive carriers. In total, 63% of the crypt-positive carriers had an abnormal ECG. Of the 3 HCM mutation carriers who had no detected crypts, 2 had a normal ECG and 1 had an abnormal ECG.

### DISCUSSION

Hypertrophic cardiomyopathy is characterized by a large interfamilial and intrafamilial variety of clinical presentations, ranging from sudden cardiac death at young age to mild symptoms of heart failure at advanced age, even if a single mutation is involved. Therefore, research is often focused on early identification of HCM mutation carriers who are at increased risk for developing heart failure or potentially life-threatening arrhythmias (12–14).

This study is the first to report that structural abnormalities consisting of crypts that can be detected in the LV myocardium of many asymptomatic HCM mutation carriers, in whom no hypertrophy has developed yet, no fibrosis is present, and no ECG abnormalities occur. The crypts were best visualized in end-diastole with CMR, not with routine echocardiography. When LV wall thickness was <9 mm, crypt penetration could be visualized up to the subepicardial layer. In 1 HCM mutation carrier who had developed overt regional hypertrophy, only a single crypt was visible at the border of the hypertrophied area, suggesting that this might be a remnant of crypts that have been compressed by surrounding hypertrophied myocardium. This might also explain why crypts have never been described previously in pathology studies. So far, pathology studies have described in detail the macroscopy, microscopy, and histology of the myocardial structure in patients with overt HCM but not in carriers without hypertrophy (15,16). Furthermore, post-mortem analyzed hearts are always to some extent in a contracted state, which makes detection of the crypts more difficult. In vivo study by CMR, however, allows detailed analysis of the myocardium in the non-contracted, end-diastolic state. Thus, the recent availability of genetic identification of pre-symptomatic HCM mutation carriers, in combination with the tomographic precision provided by CMR, resulted in the discovery of macroscopic abnormalities in this patient group.

Although the HCM mutation carriers in our study were asymptomatic, the crypts might induce regional function abnormalities and conduction disorders. If one assumes that crypts are the result of regional ischemia due to coronary microvascular dysfunction and/or myocyte disarray, both hallmarks of HCM (1), then the presence of crypts might lead to loss of contractility within the area of myocardium where the crypts are located (17). This assumption is in
agreement with the results of a clinical study performed by Nagueh et al. (4), who evaluated myocardial function with tissue Doppler imaging in asymptomatic HCM mutation carriers. They found that early diastolic myocardial velocities were reduced in HCM mutation carriers who had not yet developed hypertrophy. Thus, one might hypothesize that crypts lead to a loss of contractility, which in turn serves as a trigger to develop hypertrophy (18). However, we found the myocardium surrounding the crypts to be normokinetic on both cine imaging and routine echocardiography, which does not support this hypothesis. Whether more subtle systolic or diastolic abnormalities of the myocardial segments surrounding the crypts can be detected with more advanced functional imaging techniques, such as tissue Doppler imaging by echocardiography or myocardial tissue tagging by CMR, needs to be further evaluated.

In this study, regional fibrosis was observed within the hypertrophied region of 2 HCM mutation carriers. This is in accordance with the results of a study performed by Moon et al. (19), who found that fibrosis was not present in carriers of troponin I mutations who had no LV hypertrophy or electrocardiographic abnormalities. Nevertheless, the location of the crypts is similar to the typical location of the DCE in HCM patients. This suggests that crypts as well as formation of focal replacement fibrosis, which is the histological counterpart of DCE (6,20), might both reflect 2 different stages of the same disease process that ultimately results in manifest HCM. However, investigating the role of the crypts on regional myocardial function and development of regional hypertrophy with subsequent focal fibrosis requires a long-term follow-up study with a large variety of HCM mutation carriers. In addition, acquiring histology of myocardium surrounding the crypts might enable researchers to learn more about the histopathological background of the crypts.

We found that CMR was more sensitive in detecting structural abnormalities than routine echocardiography; whether the use of contrast agents might increase the sensitivity of echocardiography in detection of crypts has yet to be evaluated. Furthermore, CMR identified regional hypertrophy in 2 HCM mutation carriers, which was not detected by echocardiography. This is consistent with a previous report (21). Importantly, the crypts were only visualized within the basal and mid segments of the inferoseptal LV wall. Therefore, the awareness for the need of making dedicated modified imaging planes through the

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**Figure 2.** Delayed contrast enhancement images of hypertrophic cardiomyopathy (HCM) mutation carriers. (A) Modified 2-chamber view of HCM mutation carrier with regional hypertrophy. White arrowhead indicates focal fibrosis; dashed line indicates the cutline of image plane C. (B) Modified 2-chamber view of HCM mutation carrier without regional hypertrophy; dashed line indicates the cutline of image D. (C) Short-axis view of HCM mutation carrier with regional hypertrophy. White arrowhead indicates focal fibrosis in inferoseptum; dashed line indicates cutline of image A. (D) Short-axis view of HCM mutation carrier without regional hypertrophy. Black arrowhead indicates partial volume effect of blood-containing crypts. Dashed line indicates cutline of image B.
inferoseptum to detect the crypts might increase the sensitivity to identify HCM mutation carriers.

Thus, CMR might indeed serve as a valuable additional tool to identify HCM mutation carriers in an early stage of disease, thereby allowing timely initiation of risk stratification and therapy.

**Study limitations.** We studied 2 groups of common mutations in the Netherlands, and sample size was limited. However, whether the crypts can be found in all HCM-related mutation carriers who have not developed hypertrophy and the role of the crypts in the development of HCM have yet to be determined. We used a gap of 5 mm between the LV short-axis slices. Therefore, we did not cover the entire LV myocardium to screen for structural abnormalities. Acquiring a stack of LV short-axis slices with no gap between the slices might increase the sensitivity to detect crypts.

**Conclusions.** The integrity of the inferoseptal LV wall is interrupted by crypts in many HCM mutation carriers, whose LV wall thickness is within normal limits and whose routine echocardiography and ECG show little or no abnormalities.

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**REFERENCES**


**APPENDIX**

To view the video referenced in the text, please see the online version of this article.