Prevalence and Clinical Profile of Myocardial Crypts in Hypertrophic Cardiomyopathy

Maron et al: Myocardial Crypts in HCM

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Abstract

**Background**—In hypertrophic cardiomyopathy (HCM), cardiovascular magnetic resonance (CMR) can detect morphologic abnormalities of the left ventricle (LV) not visualized with echocardiography. Although myocardial crypts (ie., narrow, blood-filled invaginations within the LV wall) have been recognized in HCM, all clinical implications of these structural abnormalities within the broad clinical HCM spectrum are not completely resolved. Therefore, we sought to characterize the prevalence and diagnostic significance of myocardial crypts in patients with HCM.

**Methods and Results**—Cine and late gadolinium enhancement (LGE) CMR and 2-dimensional echocardiography were obtained in 292 consecutive HCM patients including: 31 genotype positive/phenotype negative (G+ P-) family members without LV hypertrophy (28±16 years; 51% male), and 261 patients with LV hypertrophy (46±18 years; 60% male). 98 subjects without cardiovascular disease were controls. Myocardial crypts (1-6/patient) were identified only by CMR in 19/31 G+ P- patients (61%), compared to only 10/261 (4%) HCM patients with LV hypertrophy (p<0.001), and were absent in controls. 12-lead ECGs were normal in 10 (53%) of the G+ P- patients with crypts. Crypts were confined to the basal LV, most commonly in ventricular septum (n=21) or posterior LV free wall (n=4), and associated with normal LV contractility and absence of LGE in all but one patient.

**Conclusions**—LV myocardial crypts represent a distinctive morphologic expression of HCM, occurring with different frequency in HCM patients with or without LV hypertrophy. Crypts are a novel CMR imaging marker, which may identify individual HCM family members who should also be considered for diagnostic genetic testing. These data support an expanded role for CMR in early evaluation of HCM families.

**Key Words:** hypertrophic cardiomyopathy, cardiovascular magnetic resonance, crypts
Abbreviations:

CMR = cardiovascular magnetic resonance
G+/P- = Genotype positive/phenotype negative
HCM = hypertrophic cardiomyopathy
ICD = implantable cardioverter defibrillator
LGE = late gadolinium enhancement
LV = left ventricle
LVH = left ventricular hypertrophy
SAM = systolic anterior motion
Cardiovascular magnetic resonance (CMR), with its high spatial resolution and sharp contrast between blood and myocardium, provides a unique opportunity to characterize left ventricular (LV) morphology with precision in patients with HCM.\textsuperscript{1-7} Indeed, recent CMR studies have expanded our appreciation for the diverse myocardial structure characteristic of this disease, including unique patterns of LV wall thickening, apical aneurysms and papillary muscle architecture.\textsuperscript{1-3, 7, 8}

More recently, CMR studies have identified a unique structural abnormality in patients with HCM, consisting of narrow, deep blood-filled invaginations within LV myocardium.\textsuperscript{9-12} However, the clinical and prognostic significance of these myocardial “crypts” (or clefts) within the broad heterogeneous disease spectrum of HCM is incomplete.\textsuperscript{10, 11} Therefore, we have systematically applied CMR to clarify the prevalence, clinical profile and outcome associated with myocardial crypts in a large and diverse cohort of HCM patients with LV hypertrophy, as well as in family members who carry a disease-causing sarcomere mutation without LV hypertrophy (ie., genotype positive/phenotype negative, [G+ P-]).

**Methods**

**Selection of patients**

We prospectively studied 261 consecutive HCM patients with CMR and 2-dimensional echocardiography who presented to HCM referral centers at Tufts Medical Center (Boston, MA) and the Minneapolis Heart Institute Foundation (Minneapolis, MN) for clinical evaluation from December 2005 to April 2011. Diagnosis of HCM was based on CMR and echocardiographic demonstration of a hypertrophied and nondilated LV (maximum wall thickness $\geq 15$ mm), in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy
evident. In addition, 98 patients referred to the Minneapolis Heart Institute for evaluation over the same time period, in whom clinical and CMR evidence of cardiovascular disease were absent, comprised the normal control group. Clinical follow-up duration for study patients with crypts with or without LVH was from the time of initial assessment during which a CMR study was obtained, extending to the most recent evaluation ascertained in the clinic or by telephone interview.

An independent group of 31 asymptomatic G+ P- relatives (28±16 years; range: 7-63 years; 51% male) identified in HCM families was assembled from the participating centers; each was genotyped to one or more HCM disease-causing sarcomere protein mutations: myosin binding protein C [MYBPC3] in 17, β-myosin heavy chain [MYH7] in 8, troponin T [TNNT2] in 2, α-tropomyosin [TPM1] in 2, α-actin [ACTC1] in 1 and both MYBPC3 and ACTC1 in 1.

Maximal LV wall thickness was ≤12 mm (and within the normal range relative to body surface area and age), in the absence of systolic anterior motion (SAM) of mitral valve and LV outflow tract obstruction.

Written informed consent was obtained from all study patients as approved by the Investigational Review Board (IRB) of the respective participating institutions, agreeing to use their medical information for research purposes. All authors had full access to the data, take full responsibility for its integrity, and have agreed to the manuscript as written.

**Cardiovascular magnetic resonance (CMR)**

CMR imaging was performed (Tufts Medical Center: Philips Gyroscan ACS-NT 1.5T, Best, The Netherlands; Minneapolis Heart Institute: Siemens Avanto 1.5T, Erlangen, Germany) using an ECG gated steady-state, free precession breathhold cine in 3 long-axis planes and sequential 10 mm short-axis slices from the atrioventricular ring to apex. LV volumes, mass and
ejection fraction were measured using standard volumetric techniques, and analyzed with commercially available software (MASS®, version 6.1.6 Medis, Inc., The Netherlands). LV volume and mass data were indexed to body surface area (BSA). Maximum end-diastolic LV wall thickness measurements in each of the 16 segments were automatically calculated by commercially available software.

Late gadolinium enhancement (LGE) images were acquired 10-15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering; Berlin, Germany) with breath-held segmented inversion-recovery sequence, acquired in the same orientations as the cine images. A threshold ≥6 SD exceeding the mean for non-enhanced myocardium was used to define areas of LGE.14

Crypts were defined on a 2 or 4-chamber long-axis diastolic image as one (or more) narrow and deep blood-filled invaginations contiguous with the LV cavity, extending by visual assessment ≥50% of wall thickness (but not fully penetrant), adjacent to normal appearing myocardium, and not visible at end-systole.9,10

Echocardiograms

Standard 2-dimensional echocardiographic cross-sectional planes were obtained under basal conditions with commercially available instruments. LV outflow tract obstruction was defined by continuous-wave Doppler echocardiography as a peak instantaneous outflow gradient of ≥30 mmHg under resting conditions due to marked SAM with mitral-septal contact.13

Reproducibility

Interobserver and intraobserver variability for the presence or absence of LV myocardial crypts was assessed in a subset of 30 randomly selected CMR studies from the HCM cohort of 261 patients and 30 randomly selected CMR studies from controls and G+P- patients. For
interobserver variability, 2 readers (EJR and MSM) independently assessed for the presence or absence of crypts without prior knowledge of the clinical data, and were blinded to the previous results. For intraobserver variability, one reader (EJR) independently assessed for the presence or absence crypts in an identical fashion on 2 occasions (10 months apart), also blinded to the clinical data.”

Statistical analysis

Data are expressed as mean ± SD or median (inter-quartile range) where appropriate. For comparison of data, Student’s t-test, Kruskal-Wallis test or one-way ANOVA (with Shaffer’s correction) were employed. Due to small sample sizes, Fisher’s exact tests were utilized to compare non-continuous variables expressed as proportions. All p-values are two-sided and considered significant when <0.05.

Results

Patient characteristics

Clinical and demographic characteristics of the 31 G+ P- relatives, 261 HCM patients with LV hypertrophy and 98 controls are summarized in Table 1. HCM patients (and normal controls) were older and had larger body surface area than G+ P- relatives.

Characteristics of myocardial crypts

*HCM patients with LV hypertrophy.* Myocardial crypts, identified only by CMR, were present in 10 of the 261 (4%) phenotypically affected HCM patients and significantly less common than in G+ P- patients (61%; p<0.001)(Figure 1). Among these patients, 5 had one crypt and 5 had ≥ 2 crypts, including one patient with 4 (Figure 2; Table 2). All crypts were
confined to the basal one-half of the LV chamber, and most commonly located in posterior septum (n=7), but also posterior (inferior) free wall (n=2), and anterior septum (n=1).

HCM patients with crypts had greater maximal LV wall thickness compared to those without crypts (24 ± 5 vs. 20 ± 5 mm; p=0.03), but did not differ with respect to age, gender, LV mass, ejection fraction, outflow tract gradient or NYHA functional class (p>0.05). LGE was present in the majority of HCM patients with LVH (n=140; 53%) including 9 of the 10 patients with crypts (90%). In each of these 9 patients LGE was located remote from and not in the same LV myocardial segment in which crypts were situated. Global and segmental wall motion was normal in all patients with crypts. 12-lead ECGs were normal in 2 of the 10 (20%) patients with phenotypically expressed HCM and crypts, while the other 8 (80%) showed abnormalities including criteria for LVH, abnormal Q wave patterns and conduction abnormalities.

**Genotype-positive/phenotype-negative [G+/P-] HCM patients.** Crypts were identified by CMR in 19 of the 31 (61%) G+ P- relatives (Figure 1), but in none of the normal controls (p<0.001). Most of the G+ P- patients had ≥ 2 crypts (n=11; 58%), including one patient with 6, while 8 (44%) patients had one crypt (Figure 3; Table 2). All myocardial crypts were present in the basal one-half of the LV chamber, most common in the posterior septum (n=7) or anterior septum (n=5), but also posterior (inferior) wall (n=2), or anterior free wall (n=2), and both the anterior and posterior septum in one patient.

In 8 of the 19 G+ P- patients with crypts (42%) a bright triangular region was identified at the junction of the right ventricular wall and posterior septum in the short-axis plane that appeared to represent the location of crypts visualized in the posterior (inferior) wall on the 2-chamber long-axis (Figure 4).
LGE was present in 3 G+ P- patients including one patient with both LGE and crypts, in whom the focal area of fibrosis was confined to the posterior septum remote from the crypts in anterior LV free wall. G+ P- patients with or without crypts did not differ with regard to age, gender, maximal LV wall thickness, mass, or particular sarcomere gene mutation (p>0.05). Wall motion was normal in all LV segments with crypts. 12-lead ECGs were normal in 10 of the 19 (53%) G+ P- patients with crypts, while 9 others were abnormal including voltage criteria for LVH and abnormal Q waves.

Echocardiograms

Careful review of 2-dimensional echocardiograms did not identify myocardial crypts in any of the 31 G+ P- relatives, 261 HCM patients with LVH or 98 normal controls.

Clinical follow-up

At the end of the follow-up period of 1.5 ± 1.7 years, each G+ P- or phenotypically expressed HCM patient with crypts was alive. In addition, none had developed heart failure symptoms, atrial fibrillation, underwent surgical septal myectomy or alcohol ablation, or experienced an appropriate ICD intervention (4 patients with and 3 without LVH had primary prevention ICDs).

Reproducibility of crypts

Interobserver variability showed 100% concordance in identifying the presence or absence of crypts between the 2 observers. Analysis of intraobserver variability also showed 100% concordance in identifying the presence or absence of crypts between the baseline and 10 month assessment.
Discussion

CMR provides an advanced imaging tool to characterize the phenotypic expression of HCM.\textsuperscript{1-6, 8-12} With high spatial resolution and sharp contrast between blood and myocardium, CMR has led to an expanded appreciation of the diverse structural morphology of the LV wall, particularly the striking heterogeneity evident in patterns of LV wall thickening.\textsuperscript{1-6} Recently, these CMR-based morphologic observations have been expanded to include narrow blood-filled invaginations within LV myocardium which have been termed crypts.\textsuperscript{9-12} Therefore, in the present investigation, we used CMR to define the prevalence as well as clinical course and diagnostic significance of crypts across the broad HCM spectrum.

Our data support the principle that myocardial crypts represent a distinct morphologic component of HCM expression, present in over 50\% of G+P- HCM patients without LV hypertrophy, although in a much smaller proportion of HCM patients with expressed LV hypertrophy (<5\%). In addition, crypts were not observed in our controls without cardiovascular disease reported here, although previous investigators have identified these structures in a small proportion of control subjects. Nevertheless, we also wish to be cautious in explicitly extrapolating our data regarding prevalence of crypts to that of the general HCM population because of the patient selection bias unavoidably operative in tertiary centers as well as that implicit with genetic testing in which many patients decline or do not have access to this testing.

Our reported prevalence of myocardial crypts among G+P- HCM family members is somewhat less than previously published by Germans et al.\textsuperscript{10} It is possible that our data underestimate the true prevalence of crypts in the overall HCM population, as other investigators have used non-standard imaging planes not employed here (such as modified two-chamber long-axis images) to identify these small structural abnormalities. However, it was our preference to
characterize the prevalence of crypts only using routine CMR imaging planes, as most centers do not acquire additional imaging planes routinely during diagnostic CMR studies in patients suspected of HCM. Nevertheless, it would certainly be reasonable to also consider incorporating nonstandard views as part of the routine CMR assessment of G+P- patients to optimize identification of crypts. The observation that crypts were comparatively uncommon in HCM patients with LV hypertrophy suggests the possibility that such invaginations of the wall may regress associated with subsequent LV wall thickening and remodelling.

The high prevalence of crypts among G+ P- patients (ie., about 60%) underscores the important principle that crypts in the absence of LVH are a potential CMR morphologic marker associated with genetically-affected status. These observations raise a number of scenarios and clinical implications that support an expanded role for CMR in earlier diagnosis of relatives within HCM families. For example, identification of myocardial crypts by CMR in relatives for whom genetic testing is impractical due to cost or other considerations (or when the mutation remains undefined or of unknown significance after testing), should prompt prudent surveillance with imaging studies to monitor potential development of the phenotype. Likewise, identification of a crypt in a HCM family member underscores the importance of obtaining genotyping to achieve a potentially definitive HCM diagnosis.

Our data expand the current understanding and appreciation of diverse HCM expression, particularly with respect to G+ P- patients. Myocardial crypts must be included among a number of other clinical and cardiac morphologic abnormalities previously reported in G+ P- patients, including 12-lead ECG abnormalities, elongated mitral valve leaflets, late gadolinium enhancement (as well as 3 patients in the present study), serum biomarkers of myocardial fibrosis and echocardiographic indices of diastolic dysfunction.
In this study, myocardial crypts were identified only by CMR, as two-dimensional echocardiography is often not capable of detecting such small structural abnormalities. The observation that two-dimensional echocardiography is not reliable in imaging crypts is consistent with Germans et al.\textsuperscript{10} and reminiscent of other observations by CMR in HCM in which identification of regional hypertrophy confined to the anterolateral LV free wall or apex,\textsuperscript{21} are often undetected by echocardiography.\textsuperscript{1, 2, 3, 5, 6} Notably, recognition of myocardial crypts in HCM has not been confined to contemporary imaging methodologies, as early post-mortem studies\textsuperscript{22,23} reported the presence of deep invaginations within the LV wall of HCM patients, including the initial pathologic description by Teare.\textsuperscript{24}

Given their location confined to the basal one-half of the LV chamber, crypts should not be confused with the trabeculations (ie., sinusoids) characteristic of LV noncompaction, which are situated solely in the distal portion of the chamber and unlike crypts do not penetrate the wall of normal (ie., compact) myocardium.\textsuperscript{25} Myocardial crypts are also distinguishable from ventricular septal defects as they do not communicate directly between the left and right ventricles, and are frequently situated in LV free wall.

In conclusion, LV myocardial crypts were identified by CMR across the broad HCM clinical spectrum, but most frequently in genetically affected relatives without LV hypertrophy. Crypts nevertheless represent a novel and distinctive CMR marker associated with genotype-positive status in the absence of LV hypertrophy (and often as the only structural abnormality), constituting an impetus to perform genetic testing to achieve definitive diagnosis. These observations also expand our appreciation for the heterogeneous phenotypic expression of HCM, and the emerging principle that non-hypertrophied LV myocardium may be otherwise structurally abnormal.
Disclosures

Martin Maron, MD: Consultant PGx Health

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John R. Lesser, MD: None

Jana Lindberg, RN: None

Tammy S. Haas, RN: None

James E. Udelson, MD: None

Warren J. Manning, MD: None

Barry J. Maron, MD: Consultant GeneDx

References


Table 1. Clinical Characteristics and CMR Findings in HCM Patients with LV Hypertrophy, Genotype (+)/Phenotype (-) Relatives and Normal Control Subjects.

<table>
<thead>
<tr>
<th></th>
<th>HCM with LVH</th>
<th>Genotype (+)/Phenotype (-)</th>
<th>Control Subjects</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>261</td>
<td>31</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>48 (34, 60)</td>
<td>21 (16, 21)</td>
<td>46 (33,56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>182 (60%)</td>
<td>16 (51%)</td>
<td>56 (57%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Body surface area (g/m²)</td>
<td>2.0 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.9 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>71 ± 7.4</td>
<td>69 ± 5.2</td>
<td>66 ± 5</td>
<td>0.06</td>
</tr>
<tr>
<td>NYHA Class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>186 (71%)</td>
<td>31 (100%)</td>
<td>98 (100%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>42 (16%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>33 (13%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV obstruction at rest</td>
<td>66 (25%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>(≥30mm Hg); n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Max. LV wall thickness, mm</td>
<td>20 ± 5.1</td>
<td>10.4 ± 1.6</td>
<td>10 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>LV mass, g</td>
<td>178 ± 65</td>
<td>94 ± 36</td>
<td></td>
<td></td>
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<tr>
<td>LV mass index, g/m²</td>
<td>89±32</td>
<td>54±14</td>
<td></td>
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<tr>
<td>LV EDV dimension, ml/m²</td>
<td>81 ± 18</td>
<td>75 ± 15</td>
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<td>LV ESV, ml/m²</td>
<td>23 ± 9</td>
<td>24 ± 8</td>
<td></td>
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<tr>
<td>LA dimension, mm</td>
<td>55 ± 7.7</td>
<td>33 ± 7.1</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crypts, n (%)</td>
<td>10 (4%)</td>
<td>19 (61%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* values as median (quartiles)

Abbreviations: CMR = cardiovascular magnetic resonance; ESV = end-systolic volume; EDV = end-diastolic volume; LA = left atrium; LV = left ventricular; LVH = left ventricular hypertrophy; Max. = maximum; NYHA = New York Heart Association;
## Table 2. Clinical Characteristics and CMR Findings in HCM Patients with Myocardial Crypts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>BSA (g/m²)</th>
<th>Mutations</th>
<th>NYHA Class</th>
<th>Max. LV wall thickness (mm)</th>
<th>LV mass index (g/m²)</th>
<th>LA size (mm)</th>
<th>EF (%)</th>
<th>ECG</th>
<th>FH of SCD</th>
<th>No. Crypts</th>
<th>Location of Crypt(s)</th>
<th>LGE</th>
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<td>G + P. HCM Patients</td>
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<td></td>
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<tr>
<td>1</td>
<td>13</td>
<td>M</td>
<td>1.7</td>
<td>MYBPC3 Arg502Trp</td>
<td>1</td>
<td>12</td>
<td>59</td>
<td>30</td>
<td>63</td>
<td>LVH; Q waves: II, III, aVF</td>
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<td>2</td>
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<td>F</td>
<td>1.6</td>
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<td>8</td>
<td>47</td>
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<td>24</td>
<td>65</td>
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<td>8</td>
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<td>12</td>
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<tr>
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<td>Mid AVS</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>M</td>
<td>1.7</td>
<td>MYBPC3 Ala747Thr + ACTC1 Ala323Val</td>
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<td>11</td>
<td>59</td>
<td>37</td>
<td>69</td>
<td>LVH</td>
<td>Y</td>
<td>3</td>
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<td>Basal AFW</td>
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### Abbreviations
- ACTC1 = alpha cardiac actin protein mutation
- AVS = anterior ventricular septum
- AFW = anterior free wall
- BSA = body surface area
- ECG = electrocardiogram
- EF = ejection fraction
- FH = family history
- G+/P- = genotype positive-phenotype negative
- IVCD = intraventricular conduction delay
- LA = left atrium
- LAFB = left anterior fascicular block
- LPFB = left posterior fascicular block
- LV = left ventricle
- LVH = left ventricular hypertrophy
- Max. = maximum
- MYBPC3 = myosin binding protein C mutation
- MYH7 = β-myosin heavy chain mutation
- PFW = posterior (inferior) free wall
- PRWP = poor R wave progression
- PVS = posterior ventricular septum
- TNNT2 = troponin T mutation
- TPM1 = alpha tropomysin mutation
- RBBB = right bundle branch block
- SCD = sudden cardiac death
- VS = ventricular septum

### Symbols
- --- = data not available

### Table: HCM Patients with LVH

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 19 | 17 | F | 1.7 | MYBPC3 | Arg502Trp | 1 | 8 | 34 | 26 | 66 | LVH; Q waves II, III, aVF | N | 6 | Basal to Mid PVS and Basal AVS | N |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 17 | 51 | M | 2.3 | --- | 1 | 19 | 60 | 43 | 73 | Normal | N | 1 | Basal PVS | Y |
| 18 | 39 | M | 2.2 | TPM1 | E02V1 | 1 | 29 | 45 | 39 | 59 | LAFB | Y | 4 | Basal AVS | Y |
| 19 | 52 | M | 2.3 | --- | 2 | 23 | 66 | 29 | 69 | LVH, LAFB | N | 2 | Basal PVS | Y |
| 20 | 21 | F | 1.6 | --- | 2 | 27 | 153 | 47 | 69 | IVCD | N | 3 | Basal PVS | Y |
| 21 | 25 | F | 1.6 | None detected | 1 | 23 | 73 | 46 | 75 | Q waves: II, III, aVF, V1, V2, V3 | Y | 2 | Basal PVS | Y |
| 22 | 46 | F | 1.7 | --- | 1 | 26 | 63 | 35 | 72 | LVH, Q waves: I, aVL | N | 1 | Basal PVS | Y |
| 23 | 73 | F | 1.6 | --- | 1 | 17 | 59 | 33 | 63 | RBBB | N | 1 | Basal PVS | Y |
| 24 | 24 | M | 1.9 | --- | 1 | 20 | 91 | 10 | 70 | Normal | N | 2 | Mid PFW | N |
| 25 | 18 | M | 1.8 | --- | 1 | 32 | 128 | 33 | 75 | Q waves in II, III, aVF | N | 1 | Mid PFW | Y |
| 26 | 40 | M | 2.1 | TPM1 | ASP175ASN | 1 | 23 | 85 | 50 | 61 | LVH | N | 1 | Basal PVS | Y |
Figure Legends

Figure 1. Prevalence of myocardial crypts in HCM and controls. Left ventricular myocardial crypts were identified more commonly among genotype positive-phenotype negative HCM patients (G+ P-)(61%), compared to 261 HCM patients with LV hypertrophy (4%) and were absent in 98 normal controls.

Figure 2. Diverse spectrum of myocardial crypts in HCM patients with LV hypertrophy. Shown in end-diastolic long-axis CMR images. A. Single crypt (arrow) penetrating almost entire thickness of basal posterior (inferior) wall; left atrium (LA) is greatly enlarged; B. Three deep crypts (arrows) involving the posterior (inferior) free wall in basal and mid-LV levels in a patient with massive LV hypertrophy (maximal wall thickness, 32 mm); C. Three crypts (arrows) in basal anterior septum; D. Two deep crypts (arrows) penetrating virtually the entire thickness of basal posterior septum in a patient also with LV apical aneurysm; E. Single crypt (arrow) in the posterior (inferior) free wall at mid-LV level; F. Two crypts (arrows) in the basal posterior free wall. Ao = aorta, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle

Figure 3. Diverse spectrum of myocardial crypts in asymptomatic genotype-positive HCM patients without LV hypertrophy. Shown in end-diastolic long-axis CMR images. A. 17-year-old female with extensive crypts including: 3 crypts penetrating more than one-half the transmural thickness of basal inferior wall (thick arrows), 2 crypts in the anterior wall (thin
arrows) and 1 crypt penetrating virtually the entire thickness of the inferior wall at the mid-LV level (arrow head); B. Single LV crypt (arrow) in a 41-year-old women penetrating virtually the entire thickness of basal anterior ventricular septum; C. Similar to patient in panel B., 17-year-old boy patient with single deep crypt (arrow) at mid-septal level; D. 13-year-old boy with 3 crypts (arrows) in anterior septum at mid-LV level; E. Multiple crypts (arrows) in mid-anterior ventricular septum in a 13-year-old boy patient; F. 63-year-old male with 2 deep narrow crypts (arrows) in basal posterior (inferior) LV free wall. Ao = aorta, LA = left atrium, LV = left ventricle

**Figure 4. Crypts in short and long-axis CMR planes.** 7-year-old asymptomatic genotype positive/phenotype negative HCM girl with basal end-diastolic short-axis image (A.) showing bright triangular area at the insertion area of the right ventricular wall with posterior septum (arrows). Crypts are best identified in the 2-chamber long-axis plane (B.). LV = left ventricle, RV = right ventricle
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Gibson, John R. Lesser, Jana Lindberg, Tammy S. Haas, James E. Udelson, Warren J. Manning and
Barry J. Maron

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