Myocardial Crypts
A Prephenotypic Marker of Hypertrophic Cardiomyopathy?

James C. Moon, MD, MRCP; William J. McKenna, MD, DSc, FRCP

It is more than 50 years since the first modern description of hypertrophic cardiomyopathy (HCM). Understanding has been driven by technology, with the first descriptions focusing on clinical examination, ECG changes, and histological changes from autopsy study. As technology evolved from ventriculography, M-mode, then 2-dimensional echocardiography, and cardiovascular magnetic resonance (CMR), understanding has evolved and the known phenotype of the disease has extended. Recent notable examples of this have been hypertrophy missed by echo, particularly but not exclusively at the apex, mitral valve abnormalities, apical aneurysms, and proposed familial criteria, where even subtle abnormalities may be adjudged significant in the context of a pretest probability of 50% of genetic mutation carriage. In this issue of Circulation: Cardiovascular Imaging, Maron et al have explored the potential significance of myocardial crypts. These “architectural abnormalities” of the left ventricle (LV) occur particularly in the septum and inferior (posterior) right ventricular (RV) insertion point and had been observed at increased frequency in HCM. Such abnormalities may be important because they may represent a “prephenotypic” marker of HCM—that is, a sign of abnormal fetal cardiogenesis triggered by the in utero consequences of the underlying sarcomeric mutation.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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markers would diminish. However, it may be that their utility may be enhanced, with the roles of more genetic modifiers being identified as a deeper understanding of cardiac morphogenesis, gene-to-phenotype pathways from cradle to grave develop, and we refine our global understanding of heart muscle in health and disease.

Disclosures
None.

References

KEY WORDS: Editorials ● hypertrophic cardiomyopathy ● magnetic resonance imaging ● structure
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Prevalence and Clinical Profile of Myocardial Crypts in Hypertrophic Cardiomyopathy

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Background—In hypertrophic cardiomyopathy (HCM), cardiovascular MR can detect morphological 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 HCM patients.

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

Conclusions—LV myocardial crypts represent a distinctive morphological expression of HCM, occurring with different frequency in HCM patients with or without LV hypertrophy. Crypts are a novel cardiovascular MR 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 cardiovascular MR in early evaluation of HCM families. (Circ Cardiovasc Imaging. 2012;5:441-447.)

Key Words: cardiovascular magnetic resonance ■ crypts ■ hypertrophic cardiomyopathy

Cardiovascular MR (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 hypertrophic cardiomyopathy (HCM). 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.

More recently, CMR studies have identified a unique structural abnormality in patients with HCM, consisting of narrow, deep blood-filled invaginations within LV myocardium. However, the clinical and prognostic significance of these myocardial “crypts” (or clefts) within the broad heterogeneous disease spectrum of HCM is incomplete. Therefore, we have systematically applied CMR to clarify the prevalence and diagnostic significance of myocardial crypts in HCM patients.

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 ≥15 mm) in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident.\textsuperscript{11} 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 was absent, comprised the normal control group. Clinical follow-up duration for study patients with crypts with or without LV hypertrophy 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 one, and both MYBPC3 and ACTC1 in one. Maximal LV wall thickness was ≤12 mm (and within the normal range relative to body surface area and age)\textsuperscript{15} in the absence of systolic anterior motion of mitral valve and LV outflow tract obstruction.

Written informed consent was obtained from all study patients as approved by the Investigational Review Board 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 article as written.

**Cardiovascular MR**

CMR imaging was performed (Tufts Medical Center: Philips Gyroscan ACS-NT 1.5 T; Best, The Netherlands; Minneapolis Heart Institute: Siemens Avanto 1.5 T, Erlangen, Germany) using an electrocardiography-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.). LV volume and mass data were indexed to body surface area. 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 to 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist; Schering, Berlin, Germany) with breathheld segmented inversion-recovery sequence acquired in the same orientations as the cine images. A threshold ≥2 SD exceeding the mean for nonenhanced myocardium was used to define areas of LGE.\textsuperscript{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.\textsuperscript{5,10}

**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 mm Hg under resting conditions due to marked systolic anterior motion with mitral–septal contact.\textsuperscript{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 control subjects and G+ P− patients. For interobserver variability, 2 readers (E.J.R. and M.S.M.) 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 (E.J.R.) 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 (interquartile range) where appropriate. For comparison of data, Student t test, Kruskal-Wallis test, or one-way analysis of variance (with Shaffer correction) was used. Due to small sample sizes, Fisher exact tests were used to compare noncontinuous variables expressed as proportions. All probability values are 2-sided and considered significant when <0.05.

**Results**

**Patient Characteristics**

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

**Characteristics of Myocardial Crypts**

**Patients With HCM With LV Hypertrophy**

Myocardial crypts, identified only by CMR, were present in 10 of the 261 (4%) phenotypically affected patients with HCM 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 half of the LV chamber and most commonly located in the posterior septum (n=7), but also posterior (inferior) free wall (n=2) and anterior septum (n=1).

Patients with HCM with crypts had greater maximal LV wall thickness compared with those without crypts (24±5 versus 20±5 mm; P=0.03) but did not differ with respect to age, sex, LV mass, ejection fraction, outflow tract gradient, or New York Heart Association functional class (P>0.05). LGE was present in the majority of patients with HCM with LV hypertrophy (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. Twelve-lead electrocardiograms were normal in 2 of the 10 (20%) patients with phenotypically expressed HCM and crypts, whereas the other 8 (80%) showed abnormalities including criteria for LV hypertrophy, abnormal Q wave patterns, and conduction abnormalities.

**Genotype-Positive/Phenotype-Negative Patients With HCM**

Crypts were identified by CMR in 19 of the 31 (61%) G+ P− relatives (Figure 1) but in none of the normal control subjects (P<0.001). Most of the G+ P− patients had ≥2 crypts (n=11 [58%]), including one patient with 6, whereas 8 (44%) patients had one crypt (Figure 3; Table 2). All myocardial
crypts were present in the basal 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, sex, maximal LV wall thickness, mass, or particular sarcomere gene mutation (P>0.05). Wall motion was normal in all LV segments with crypts. Twelve-lead electrocardiograms were normal in 10 of the 19 (53%) G+ P− patients with crypts, whereas 9 others were abnormal including voltage criteria for LV hypertrophy 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 patients with HCM with LV hypertrophy, or 98 normal control subjects.

**Clinical Follow-Up**

At the end of the follow-up period of 1.5±1.7 years, each G+ P− or phenotypically expressed patient with HCM with crypts was alive. In addition, none had developed heart

| Table 1. Clinical Characteristics and CMR Findings in Patients With HCM With LV Hypertrophy, G+ P− Relatives, and Normal Control Subjects |
|---------------------------------|----------------|----------------|----------------|
| No. of patients                 | 261            | 31             | 98             |
| Age, y*                        | 48 (34, 60)    | 21 (16, 21)    | 46 (33,56)     | <0.001          |
| Male, no. (%)                  | 182 (60%)      | 16 (51%)       | 56 (57%)       | 0.023           |
| Body surface area, g/m²        | 2.0±0.3        | 1.8±0.3        | 1.9±0.2        | <0.001          |
| Ejection fraction, %           | 71±7.4         | 69±5.2         | 66±5           | 0.06            |
| NYHA class, no. (%)            |                |                |                |
| I                              | 186 (71%)      | 31 (100%)      | 98 (100%)      |
| II                             | 42 (16%)       |                |                |
| III                            | 33 (13%)       |                |                |
| IV                             | 0 (0%)         |                |                |
| LV obstruction at rest (≥30 mm Hg), no. (%) | 66 (25%) | 0 (0%) | 0 (0%) | 0.002 |
| Maximum LV wall thickness, mm  | 20±5.1         | 10.4±1.6       | 10±1.6         | ...             |
| LV mass, g                     | 178±65         | 94±36          | ...            |
| LV mass index, g/m²            | 89±32          | 54±14          | ...            |
| LV EDV dimension, mL/m²        | 81±18          | 75±15          | ...            |
| LV ESV, mL/m²                  | 23±9           | 24±5           | ...            |
| LA dimension, mm               | 55±7.7         | 33±7.1         | ...            |
| Crypts, no. (%)                | 10 (4%)        | 19 (61%)       | 0              |
|                               |                |                | <0.001         |

CMR indicates cardiovascular MR; HCM, hypertrophic cardiomyopathy; LV, left ventricle; G+ P−, genotype-positive/phenotype-negative; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrium.

*Values as median (quartiles).
failure symptoms, atrial fibrillation, underwent surgical septal myectomy or alcohol ablation, or experienced an appropriate implantable cardioverter defibrillator intervention (4 patients with and 3 without LV hypertrophy had primary prevention implantable cardioverter defibrillators).

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.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.1-6 Recently, these CMR-based morphological observations have been expanded to include narrow blood-filled invaginations within LV myocardium, which have been termed crypts.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 morphological component of HCM expression, present in >50% of G+ P− patients with HCM without LV hypertrophy, although in a much smaller proportion of patients with HCM with expressed LV hypertrophy (<5%). In addition, crypts were not observed in our control subjects 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.10 It is possible that our data underestimate the true prevalence of crypts in the overall HCM population, because other investigators have used nonstandard imaging planes not used here (such as modified 2-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, because 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 patients with HCM with LV hypertrophy suggests the possibility that such invaginations of the wall may regress associated with subsequent LV wall thickening and remodeling.

The high prevalence of crypts among G+ P− patients (ie, approximately 60%) underscores the important principle that crypts in the absence of LV hypertrophy are a potential CMR morphological marker associated with genetically affected status.9,10 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
Myocardial crypts must be included among a number of other clinical and cardiac morphological abnormalities previously reported in G+ P− patients, including 12-lead electrocardiographic abnormalities,15,16 elongated mitral valve leaflets,13 LGE17 (as well as 3 patients in the present study), serum biomarkers of myocardial fibrosis,18 and echocardiographic indices of diastolic dysfunction.19,20 In this study, myocardial crypts were identified only by CMR, because 2-dimensional echocardiography is often not capable of detecting such small structural abnormalities. The observation that 2-dimensional echocardiography is not reliable in imaging crypts is consistent with Germans et al10 and reminiscent of other observations by CMR in HCM in which identification of regional hypertrophy confined to the anterolateral LV free wall or apex1 is often undetected by echocardiography.1–3,5,6 Notably, recognition of myocardial crypts in HCM has not been confined to contemporary imaging methodologies, because early postmortem studies21,22 reported the presence of deep invaginations within the LV wall of patients with HCM, including the initial pathological description by Teare.23 Given their location confined to the basal 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.24 Myocardial crypts are also distinguishable from ventricular septal defects because they do not communicate directly between the left and right ventricles and are frequently situated in the 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 nonhypertrophied LV myocardium may be otherwise structurally abnormal.
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Disclosures
M.S.M. is a consultant for PGx Health. B.J.M. is a consultant for GeneDx.

References

CLINICAL PERSPECTIVE
We used cardiovascular MR to define the prevalence as well as clinical course and diagnostic significance of left ventricular myocardial crypts (ie, narrow and deep blood-filled invaginations contiguous with the left ventricular cavity, extending ≥50% of wall thickness) across the broad hypertrophic cardiomyopathy spectrum. Crypts were identified in 61% of asymptomatic genotype-positive/phenotype hypertrophic cardiomyopathy family members compared with only 4% of patients with hypertrophic cardiomyopathy with left ventricular hypertrophy (P<0.001). These observations expand the appreciation of diverse hypertrophic cardiomyopathy expression, particularly with respect to genotype-positive/phenotype-negative patients, and are a potential novel cardiovascular MR imaging marker for genotype-positive status in the absence of left ventricular hypertrophy, constituting an impetus to perform genetic testing to achieve definitive diagnosis. These data support an earlier role for cardiovascular MR in the assessment of hypertrophic cardiomyopathy family members.