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Brouwer, W.P.

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IV

Multiple myocardial crypts on modified long-axis view are a specific finding in pre-hypertrophic HCM mutation carriers.

Wessel P Brouwer, Tjeerd Germans, Maaike C Head, Jolanda van der Velden, Martijn W Heymans, Imke Christiaans, Arjan C Houweling, Arthur A Wilde, Albert C van Rossum

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex genetic heart disease affecting the myocardium, mitral leaflets and small arterioles, and is clinically recognized as unexplained left ventricular (LV) hypertrophy in the absence of increased loading conditions such as hypertension or aortic valve stenosis [1]. With high resolution imaging techniques, such as cardiovascular magnetic resonance imaging (CMR), inferoseptal crypts were frequently (70-80%) discerned in a small group of hypertrophic HCM mutation carriers without LV hypertrophy (carriers) [2]. Besides, examples of heavily disrupted myocardium with high numbers of crypts (>3) were shown in these carriers, using a modified two-chamber view through the inferoseptum [2]. However, in approximately 6% of patients with other cardiovascular disease and healthy volunteers single or paired crypts were recognized when using standard long-axis views [3,4]. Thus, it is currently unknown whether the reported differences in prevalence and morphology of crypts in carriers, patients with other cardiovascular disease and even healthy individuals is solely attributable to the use of different image planes, or to specific alterations of the inferoseptal myocardium in carriers, being indicative of HCM mutation carriernesship.

To investigate whether morphology and frequency of crypts are specific for HCM mutation carriernesship, we performed a modified two-chamber view and standard two and four chamber long-axis views in carriers and consecutive CMR control patients with various cardiac pathologies (controls). Firstly, we compared crypt-morphology focussing on the number and depth of the crypts into the myocardium. Secondly, we compared the sensitivity of a modified two-chamber view with standard long-axis views for the detection of crypts. Thirdly, we evaluated whether crypt detection can be used in family screening to predict positive mutation status among unaffected
family members with otherwise normal LV morphology and function (assessed with CMR).

Methods

Patient selection

The study population consisted of HCM mutation carriers who were identified in a family screening program at the cardiogenetic outpatient clinics of the Academic Medical Center and the VU University Medical Center in Amsterdam. Genetic testing was performed according to the sequencing protocols described previously [5,6]. The carriers harbored mutations in genes encoding either for cardiac myosin binding protein C (MYBPC3) or for the alpha-tropomyosin (TPM1) protein. All carriers included had no signs of LV hypertrophy (i.e. LV wall thickness <13mm assessed with CMR). The control group consisted of consecutive CMR patients enrolled between October 2008 and March 2009 at our institute. In order to minimize the inclusion of potential carriers of mutations that encode sarcomeric proteins in the control group, we excluded control patients with phenotypic HCM and patients with a positive family history for HCM. In general, subjects were excluded from the study if they met any of the following criteria: implanted pacemaker or internal cardioverter defibrillator, claustrophobia and insufficient image quality due to excessive (supra)ventricular ectopy. Also, we included a separate group of healthy family members of carriers, without the familial mutation. The study was performed according to the declaration of Helsinki, and written informed consent was obtained from all carriers and family members.
**Crypt definition**

LV crypts were pre-defined as abrupt sharp-edged disruptions of normally compacted myocardium penetrating the LV wall ≥30% and showing total or subtotal obliteration during systole by surrounding tissue.

**CMR image acquisition**

Studies were performed on a 1.5 Tesla scanner, using a six-channel phased-array body coil (Magnetom Avanto or Sonata, Siemens, Erlangen, Germany). After standard localizing scouts, a retrospective gated, steady state free precession (SSFP) gradient-echo sequence was used for cine imaging. In addition to standard four, three and two-chamber cines, a modified two-chamber cine was performed by angulating the image plane of the regular two-chamber cine through the inferoseptum, as previously described [2]. A stack of standard short-axis cine images fully covering the LV was performed to allow off-line CMR analysis of LV volumes, ejection fraction, mass and maximal LV wall thickness (WT). Typical scan parameters were: slice thickness of 5 mm and 5 mm gap between each short-axis slice, a temporal resolution of 30-40 ms, echo time 1.54 ms, flip angle 70 degrees and an image plane resolution of 1.3*1.6mm. When appropriate, patients underwent late gadolinium enhancement imaging (LGE), which was performed approximately ten minutes after the infusion of a bolus of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Scheringen, Berlin, Germany or Dotarem, Guerbet, Roissy CdG, France).

**Off-line CMR analysis**

Dedicated analysis software (Mass, Medis, Leiden, The Netherlands) was employed for off-line LV analysis. LV volumes and LV mass was determined by drawing endo-
and epicardial contours and the contours of papillary muscles. Papillary muscles were included in the calculation of LV mass and excluded from LV volumes. In all patients, assessment of crypts was performed by careful evaluation of long-axis, short-axis and the complementary end-diastolic modified two-chamber cine images. Crypt-morphology was subsequently characterized by number and percentage of penetration in the myocardium. For comparison of crypt-penetrance between groups, the crypt with highest extent of penetration was selected. LGE-images were visually assessed for the presence of areas with increased signal intensity, indicative for replacement fibrosis within the myocardium [7].

**Statistical Analysis**

Data are presented as means with standard deviations (SD). Continuous data were compared using an unpaired Student’s t-test or a Mann Whitney test as appropriate. Proportions were compared using a Chi-square test. Two-sided p-values <0.05 were considered statistically significant. Receiver Operating Characteristic (ROC) curves with area under the curve (AUC) were constructed for the number of crypts and crypt-penetrance, and optimal sensitivity and specificity were calculated. All statistical analyses were performed in SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).
Results

Patient characteristics

Initially, 56 carriers were included in the study, of which 13 individuals were excluded since maximal regional LV wall thickness exceeded 13mm. The mean age was 40±14 years and the majority was female (67%). One carrier displayed subtle intramyocardial fibrosis on the LGE-images. The control group consisted of 279 consecutive CMR patients, of whom 27 patients were excluded, yielding a total of 252 eligible controls. Twelve patients were excluded because they had phenotypic HCM, three patients had a positive family history for HCM and the remaining twelve subjects had insufficient image quality or claustrophobia. Table 1 displays the baseline characteristics of both carriers and controls. The control group was slightly older than the mutation carrier group. Global LV dimensions and ejection fraction (EF) were comparable between both groups. The group of genotype-negative HCM family members consisted of 15 individuals with normal LV dimensions and function, which were comparable to findings in carriers (data not shown).

<table>
<thead>
<tr>
<th>Carriers (n=43)</th>
<th>Controls (n=252)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>40±14</td>
<td>52±16</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>14/29</td>
<td>146/106</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>164±33</td>
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<tr>
<td>LVESV (mL)</td>
<td>72±21</td>
<td>88±53</td>
</tr>
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<td>LVEF (%)</td>
<td>57±6</td>
<td>53±12</td>
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<tr>
<td>Cardiac pathology:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (n,%)</td>
<td>(115, 46)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension (n,%)</td>
<td>(1, 0.4)</td>
<td></td>
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<td>(3, 1)</td>
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<tr>
<td>NICM (n,%)</td>
<td>(57, 23)</td>
<td></td>
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<tr>
<td>ARVC (n,%)</td>
<td>(15, 6)</td>
<td></td>
</tr>
<tr>
<td>Chemotoxicity (n,%)</td>
<td>(2, 1)</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy (n,%)</td>
<td>(12, 5)</td>
<td></td>
</tr>
<tr>
<td>Non-compaction (n,%)</td>
<td>(4, 2)</td>
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<td>(1, 0.4)</td>
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<td>Post-partum cardiomyopathy (n,%)</td>
<td>(1, 0.4)</td>
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<tr>
<td>Cardiomyopathy NFS (n,%)</td>
<td>(7, 3)</td>
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<tr>
<td>ECG-abnormalities with normal hearts (n,%)</td>
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<td></td>
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<tr>
<td>Storage diseases (n,%)</td>
<td>6, 2</td>
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<td>Sarcoidosis (n,%)</td>
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<td>Haemochromatosis (n,%)</td>
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<tr>
<td>Myocarditis (n,%)</td>
<td>(9, 4)</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease (n,%)</td>
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<tr>
<td>Aortic disease (n,%)</td>
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<tr>
<td>Valve pathology (n,%)</td>
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<tr>
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<td>Congenital (n,%)</td>
<td>(10, 4)</td>
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</tr>
<tr>
<td>Miscellaneous (n,%)</td>
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Carriers = HCM mutation carriers; ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; m/f = male/female; NFS = not further specified; NICM = non-ischemic cardiomyopathy.
Initially, 56 carriers were included in the study, of which 13 individuals were excluded since maximal regional LV wall thickness exceeded 13 mm. The mean age was 40 ± 14 years and the majority was female (67%). One carrier displayed subtle intramyocardial fibrosis on the LGE-images. The control group consisted of 279 consecutive CMR patients, of whom 27 patients were excluded, yielding a total of 252 eligible controls. Twelve patients were excluded because they had phenotypic HCM, three patients had a positive family history for HCM and the remaining twelve subjects had insufficient image quality or claustrophobia. Table 1 displays the baseline characteristics of both carriers and controls. The control group was slightly older than the mutation carrier group. Global LV dimensions and ejection fraction (EF) were comparable between both groups. The group of genotype-negative HCM family members consisted of 15 individuals with normal LV dimensions and function, which were comparable to findings in carriers (data not shown).

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- Systemic hypertension (n, %) (3, 1)
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**Crypt-morphology**

Crypts were identified in 70% of carriers (n=30) and in 12% of controls (n=31), p<0.001. The median number of crypts identified was significantly larger in carriers compared to controls (3±1 versus 1±1, p<0.01). The distribution of crypts within carriers and controls is presented in Figure 1. The maximal penetration of crypts into the myocardium was higher in crypt-positive carriers compared to crypt-positive controls (74±21% versus 59±22%, p<0.01), see Figure 2B. Within the controls, 1 out of 3 patients with hypertension (33%) showed crypts, 5 out of 16 with aorta pathology (31%), 2 out of 9 with myocarditis (22%), 9 out of 57 with non-ischemic cardiomyopathy (16%), 2 out of 15 with valve pathology (13%) and 10 out of 115 with ischemic cardiomyopathy (9%). Among genotype-negative HCM family members, 1 out of 15 subjects had a single crypt, penetrating the myocardium for 60%.

![Figure 1: Distribution of the number of crypts in carriers (black bars) and controls (open bars). Over two-thirds (70%) of HCM mutation carriers show two or more crypts, and over half (57%) of carriers three or more crypts, in contrast to controls, who predominantly display only one or two crypts.](image-url)
Crypt morphology

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Image plane selection for optimal visualization of crypts

The modified two-chamber view was most sensitive for crypt visualization, since only 15 of 30 carriers (50%) who showed crypts on the modified two-chamber view also showed crypts on the standard long-axis cine images, see Figure 4. Of note, in a subset of carriers, subtle disruptions of normally compacted myocardium could also be detected on short-axis cine images. Then, blood containing crypts appeared as a triangular shaped bright area located at the inferior insertion point of the right ventricle into the septum, due to partial volume effects (Figure 4C). Taking controls and mutation-negative family members together, 31 of 32 crypts (97%) were visualized on the modified two-chamber view, whereas one control displayed one crypt at the anteroseptal LV wall on a three-chamber view. Of the 31 crypts demonstrated in the control subjects on the modified two-chamber cine, only 15 (48%) were also detected on regular long-axis views.

Figure 4: Different end-diastolic cine views of a HCM mutation carrier with crypts. Standard short-axis view (A), two-chamber view (B), modified two-chamber view (C). On short-axis view (A), note the subtle triangular shaped bright inferoseptal area due to partial volume effects induced by the presence of crypts. The cut-lines of image B (continuous line) and C (dashed line) are indicated on the short-axis view. The extensive crypt-formation in the inferoseptum, indicated by arrowheads (C) is not detected on standard two-chamber view in this patient (B).
Diagnostic value of crypts

**Carriers vs controls**

To explore the diagnostic potential of crypts for assessing HCM mutation carriership, we calculated the sensitivity and specificity for different numbers of crypts. When comparing carriers with controls, the presence of any crypt had a sensitivity and specificity of 70% (95% CI 54% - 82%) and 88% (95% CI 83% - 91%) respectively. Two or more crypts had a sensitivity of 51% (95% CI 36% - 66%) and specificity of 94% (95% CI 91% - 97%), while three or more crypts showed a sensitivity of 40% (95% CI 25% - 56%) and a specificity of 99% (95% CI 96% - 100%). A finding of 5 crypts or more had 9% sensitivity (95% CI 3% - 23%) and reached 100% specificity (95% CI 98% - 100%) for HCM mutation carriership. The constructed ROC curve for the number of crypts is shown in Figure 3, demonstrating good predictive ability (AUC=0.80). The optimal cut-off value for crypt-penetrance was 48.5%, which was associated with a sensitivity and specificity of 48% (95% CI 30% - 67%) and 93% (95% CI 78% - 99%), respectively. The area under the ROC curve was 0.72 (Figure 2A). However, there was considerable overlap in crypt-penetrance between carriers and controls, as shown in Figure 2B.
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Figure 2: Penetration of crypts in carriers and controls. (A) Receiver operating characteristic curve and area under the curve (AUC) for diagnosis of HCM mutation carriership using crypt-penetration. The optimal cut-off value was at 48.5%, with an area under the curve (AUC) of 0.72. (B) Scatter plots depicting the difference in crypt-penetration between carriers (green) and controls (red). Although the penetration of crypts is significantly larger (p<0.01) in carriers, there is considerable overlap in values between both groups.

Figure 3: The receiver operating characteristic curve (ROC) of crypts in HCM mutation carriers and controls. This ROC curve is based on the number of crypts detected in HCM mutation carriers and consecutive CMR control patients. The number in the proximity of each dot represents the number of crypts detected. The area under the curve = 0.80.
**Crypts in family screening**

To evaluate the diagnostic value of crypts to discriminate HCM mutation carriers from mutation-negative family members with structural and functional normal hearts, we compared the number of crypts in carriers with mutation-negative family members (n=15). Since only one family member showed a single crypt, the presence of any crypt had a specificity of 93% (95% CI 66% - 100%). The detection of two or more crypts had a 100% positive predictive value in predicting HCM mutation carriership, while the optimal cut-off for crypt-penetrance was <61.5%, associated with a sensitivity of 100% and a specificity of 70%.

**Discussion**

In this study, we used a tailored CMR protocol and found that crypts were more prevalent and occurred in higher numbers in carriers compared to controls (Figure 1). Furthermore, crypts in carriers showed deeper penetrance into compact myocardium, although there was considerable overlap in values between both groups (Figure 2B). In addition, we demonstrated that the use of a modified two-chamber view through the inferoseptal area doubled the sensitivity to detect crypts compared to the standard long-axis views. When employed in family screening, visualization of crypts was highly specific for HCM mutation carriership, but sensitivity was moderate. To definitely establish the predictive potential of crypts in family screening however, our study results should be prospectively repeated in larger study populations.

A direct comparison of crypt prevalence in our study with previously conducted studies is challenging, since both predefined criteria and nomenclature of crypts are not uniform. Srichai et al named any out pouching of the LV cavity embedded
between myocardium ‘ventricular diverticula’ and found these in 2.2% of a cohort of patients with predominantly suspected coronary artery disease undergoing MDCT angiography [8]. Johansson et al used the term ‘clefts’ for V-shaped extensions of blood signal, penetrating the myocardium for >50% [4] on standard long-axis views. Clefts at the basal inferior LV wall were detected in approximately 7% of patients, while septal clefts were described in 24 of 399 (6%) of studied individuals. In contrast to Johansson et al., we used a 30% penetrance cut-off value in our definition of crypts, since we observed that invaginations with less than 50% penetrance were still often denoted as ‘morphological abnormal’ by cardiologists. Notwithstanding, the prevalence of crypts in the abovementioned study is in line with our study, since we also detected crypts in approximately 6% of controls when using standard long-axis views only. However, using the modified two-chamber view we found the detection-rate to be increased by twofold and therefore advocate its use when screening for crypts. Importantly, short-axis cines lacked the ability to determine the number of crypts involved.

The histological background of extensive crypt formation in carriers is still unclarified, since histological specimens are lacking. It is likely that a key component in the formation of crypts in carriers is myocardial disarray, which is extensively encountered at the inferoseptum in post-mortem manifest HCM hearts [9]. In a post-mortem study from Kuribayashi et al. [9], deep tissue clefts were detected at the interventricular junction in hearts with overt HCM phenotype in areas with extensive myocardial disarray. Mild forms of myocardial disarray at the interventricular junctions have also been found in post-mortem studies of patients with congenital heart disease and even in patients without apparent cardiac disease.
This would explain why carriers display substantially, but not exclusively, more crypts than patients with other cardiac pathologies or healthy subjects [5].

Although crypts represent a disruption of normally compacted myocardium, it is important to discriminate LV crypts from (isolated) non-compaction cardiomyopathy [11]. Crypts can be discriminated from isolated non-compaction cardiomyopathy based on three criteria. First, crypts penetrate compacted myocardium perpendicular to the endocardial border, while non-compaction is characterized by a non-compacted layer of myocardium that is aligned parallel to compact myocardium (Figure 5) [12]. Secondly, the localization of crypts is different from the localization of the non-compacted area; crypts are located predominantly at the basal and mid inferoseptal area, while non-compaction is located at the apical and mid ventricular LV wall segments. Finally, the clinical course between patients with crypts and with non-compaction cardiomyopathy varies importantly, since patients with crypt-formation have typically normal LV ejection fraction, while non-compaction cardiomyopathy is associated with a reduced LV ejection fraction, and LV dilation. This differentiation is clinically relevant since non-compaction cardiomyopathy might require treatment for heart failure and the use of anticoagulation, whereas this is not indicated for HCM mutation carriership [13].

Our data indicate that the assessment of crypts by CMR may be of additional value to standard cardiological evaluation with ECG and echocardiographic evaluation in HCM family screening, especially when no mutation is found in the HCM proband, or when genetic screening is unavailable. In a previous study, we found that crypts were present in approximately 30% (4/13) of carriers in whom echocardiography and ECG were normal. These carriers would remain unidentified when evaluated only by echocardiography and ECG. In this study, we showed that the presence of...
multiple crypts indicates a high likelihood of HCM mutation carriermship in otherwise phenotype-negative individuals, underscoring the additional value of CMR for this indication. However, asymptomatic family members with unknown genotype, otherwise normal LV morphology and absence of multiple crypts should not yet be refrained from clinical follow-up, since approximately 30% of carriers is devoid of crypts by CMR. Future prospective studies with long-term follow-up are needed to evaluate the prognostic value of crypts in the pathogenesis of overt HCM.

Figure 5. Morphological comparison of crypt formation and non-compaction cardiomyopathy. The image on the left (A) is an end-diastolic CMR cine with modified two-chamber view and represents a typical example of inferoseptal crypts intersecting the myocardium perpendicular to the endocardial border (indicated by white arrows). The white asterisk at image B is located at a region of apical hypertrabecularisation/non-compaction, which runs parallel to the endocardial border and is located in the mid and apical LV segments.

Limitations

Screening for mutations in genes encoding for proteins of the sarcomeric apparatus was solely performed in carriers and in family members, and not in the remainder of consecutive MRI patients. Therefore, we cannot rule out that some control patients might harbour mutations in sarcomeric genes, thereby influencing study results. The prevalence of these genetic defects in the general population is considered rather
low however [1]. A second limitation of our study is that the group of HCM mutation carriers and the control population of consecutive CMR patients were not matched for age and gender. A previous study however reported no evidence of relationships between crypt (e.g. ‘cleft’) visibility and age or sex in both healthy subjects and various patient groups [4]. Thirdly, we predominantly included carriers with founder mutations that are known to occur with high frequency in the Netherlands [5]. To what extend our findings apply to other HCM populations remains to be elucidated. Finally, we cannot exclude that deviations of the angle of intersection of the modified two-chamber view through the inferoseptum influence the number of crypts visualized and the relative penetrance of these invaginations. All short-axis cine images were carefully assessed however for local disruptions of normally compacted myocardium, and perpendicular imaging planes were optimally aimed through these areas.

**Conclusions**

The presence of multiple crypts in the absence of LV hypertrophy is highly specific for HCM mutation carrier ship and warrants clinical follow-up. A modified two-chamber view has superior sensitivity compared to the use of standard long-axis cines for crypt detection. CMR may be of additional value to identify carriers in family screening.
IV

References


