

Extent of Myocardial Hyperenhancement on Late Gadolinium-Enhanced Cardiovascular Magnetic Resonance Correlates with Q Waves in Hypertrophic Cardiomyopathy

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ABSTRACT

Purpose: Despite several electrocardiographic, echocardiographic, electrophysiologic and pathologic studies, the cause of abnormal Q waves in patients with HCM remains unclear. Cardiovascular magnetic resonance (CMR) is a powerful in vivo diagnostic tool for evaluating cardiac morphology and function. We hypothesized that estimation of segmental and transmural extent of myocardial enhancement by late gadolinium enhancement (LGE) CMR could clarify the basis of Q waves. The purpose of this prospective study was to evaluate the morphological basis of abnormal Q waves in hypertrophic cardiomyopathy (HCM) as assessed by CMR. **Methods:** Thirty-eight patients with HCM underwent gadolinium-enhanced CMR and 12 lead electrocardiography (ECG). Left ventricular function, volumes, segmental and transmural extent of myocardial LGE were assessed and analysed in relation to the presence of abnormal Q waves. **Results:** Twelve (31%) of the 38 patients had abnormal Q waves on the ECG. Patients with Q waves exhibited significantly more myocardial LGE segmentally as well as transmurally than patients without Q waves. As the segmental and the transmural extent of LGE increased, the probability of Q wave increased (anterior: segmental extent $\chi^2 = 10$, $p = 0.0013$, transmural extent $\chi^2 = 10$, $p = 0.0013$; inferior: segmental extent $\chi^2 = 13$, $p = 0.0003$, transmural extent $\chi^2 = 15$, $P < 0.0001$; lateral: segmental extent $\chi^2 = 10$, $p = 0.0016$, transmural extent $\chi^2 = 10$, $p = 0.0012$). Additionally, the ratio of septal to posterior wall thickness was significantly higher in patients with Q waves than in patients without Q waves (2.3 vs. 1.6, $p = 0.012$). **Conclusions:** It seems that segmental and transmural extent rather than the mere presence of myocardial LGE is the underlying mechanism of abnormal Q waves in HCM. Additionally, distribution of hypertrophy as indicated by differences in the ratio of septal to posterior wall thickness seems to play an important role.

INTRODUCTION

Patients with hypertrophic cardiomyopathy (HCM) present with various electrocardiographic (ECG) abnormalities, including increased QRS voltage, T wave changes and pathologic Q waves (1–11). Although no single ECG pattern is characteristic, abnormal Q waves are one of the most common abnormalities in HCM and can mimic myocardial infarction (5, 12–14). Despite several electrocardiographic (3, 9, 11, 15), echocardiographic (3, 15), electrophysiologic (7, 8) and pathologic studies (13, 14) the underlying mechanisms of abnormal Q waves in HCM are not yet completely understood. Generally, it has been suggested

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that Q waves in HCM result from disturbed electrical activation and depolarization of the hypertrophied ventricular septum (5, 7, 8, 13, 14). However, no clear correlation between the severity of ventricular hypertrophy and the presence of Q waves could be demonstrated in previous studies (3, 15, 16). Other investigators support the viewpoint of previous pathologic studies that Q waves may result from myocardial scarring, a common finding in patients with HCM (5, 6). In this context, Koga et al. (17) recently demonstrated that loss of electrical forces due to transmural myocardial fibrosis and altered direction of the initial QRS vector due to increased electrical forces of a disproportionately hypertrophied basal septum and/or left ventricular free wall, unopposed by apical forces, are possible mechanisms of abnormal Q waves in HCM.

Late gadolinium enhanced cardiovascular magnetic resonance (CMR) is a new technique that allows in vivo visualization of myocardial scarring (18). This technique has been primarily validated in patients with documented chronic myocardial infarction, as well as in animal models of infarct healing (18–20). Late gadolinium enhancement (LGE) is considered to occur in areas of expanded extracellular space. Since abnormal myocardial interstitium, consisting of interstitial fibrosis, myocardial disarray and small vessel disease, is also commonly present in patients with HCM, gadolinium-enhanced CMR has been increasingly used as a tool for assessing regions of myocardial LGE in these patients (21, 22).

In the present study we hypothesized that in vivo estimation of the segmental and transmural extent of LGE by CMR could contribute to the understanding of the underlying pathophysiology of Q waves in patients with HCM. Accordingly, we prospectively correlated these CMR findings to the presence of abnormal Q waves.

METHODS

Study population

Thirty-eight patients (21 males and 17 females; mean age 58 ± 15 years) with HCM were recruited between January 2003 and October 2004. The selected patients fulfilled conventional criteria for HCM with left ventricular hypertrophy ≥ 15 mm on 2D echocardiography in the absence of another disease that could account for the hypertrophy (23). Fifty-two consecutive patients were initially identified for enrollment, but patients were excluded if they had concomitant coronary artery disease ($n = 4$), previous myocardial infarction ($n = 2$) or implantation of a pacemaker or defibrillator ($n = 8$). In all thirty-eight study patients coronary artery disease could be excluded by coronary angiography. Informed consent for the CMR protocol was obtained from all subjects.

Image acquisition

All studies were performed using a 1.5 Tesla whole body imaging system (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany). A dedicated four-element, phased-array cardiac coil was used. Images were acquired during repeated

end-expiratory breath-holds. Scout images (coronal, sagittal and axial planes) were obtained for planning of the final double-oblique long-axis and short-axis views. To evaluate functional parameters, ECG-gated cine images were then acquired using a segmented steady state free precession sequence [(TrueFISP); TE/TR 1.2/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4×1.8 mm², slice thickness 5 mm, interslice gap 5 mm]. 7 to 12 short-axis views covering the whole left and right ventricle were obtained. After intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering AG, Berlin, Germany) the same views were re-scanned in identical orientation and slice position using a segmented inversion recovery gradient-echo sequence (24). Images were obtained 15 min after contrast administration. The inversion time was individually adjusted to optimally null myocardial signal (250 to 300 ms). Total examination time averaged 40 min. A complete series of short-axis late enhancement images is shown in Figure 1.

Image analysis and determination of ventricular parameters

MR images were analyzed both qualitatively and quantitatively by two experienced investigators blinded to the ECG findings. Ventricular function, end-diastolic volumes, end-systolic volumes, and myocardial mass were assessed off-line from the serial short-axis true FISP cine loops using dedicated software (ARGUS, Siemens, Erlangen, Germany). In addition to volumetric measurements, one-dimensional measurements of LV end diastolic dimensions (LVEDD), posterior wall thickness (PWT) and maximum interventricular septum wall thickness (SWT) were taken from end diastolic short-axis views. Additionally the ratio of septal to posterior wall thickness was determined.

Contrast enhanced images were analyzed using the standard left ventricular 17-segment model (25) (Fig. 2). Each segment was visually scored by the consensus of two observers for the distribution of LGE throughout the width of the segment (segmental extent of hyperenhancement) and for the maximal distribution of LGE throughout the myocardial wall (transmural extent of hyperenhancement) by using the same scoring scheme: 0 = 0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75% and 4 = 76–100% (Fig. 3). For assignment of the myocardium to each of the 16 segments, transparent charts were used which were divided into six segments for the basal and mid-cavity short axis slices and four segments for the apical short axis slices. Results for all the basal, the mid and the apical slices were averaged separately. The 17th segment is the true apex and was evaluated from the long-axis planes. Segments were grouped into three territories (anterior, inferior, and lateral) corresponding to the territories derived from ECG analysis (25). The anterior territory consists of seven segments, the inferior territory of five segments, and the lateral territory consists of five segments (Fig. 2). By summing all the 17 segmental scores the total size of myocardial hyperenhancement and transmural extent were calculated for each territory separately and for the total left ventricle. The resulting summed score for the anterior, inferior and lateral territory and

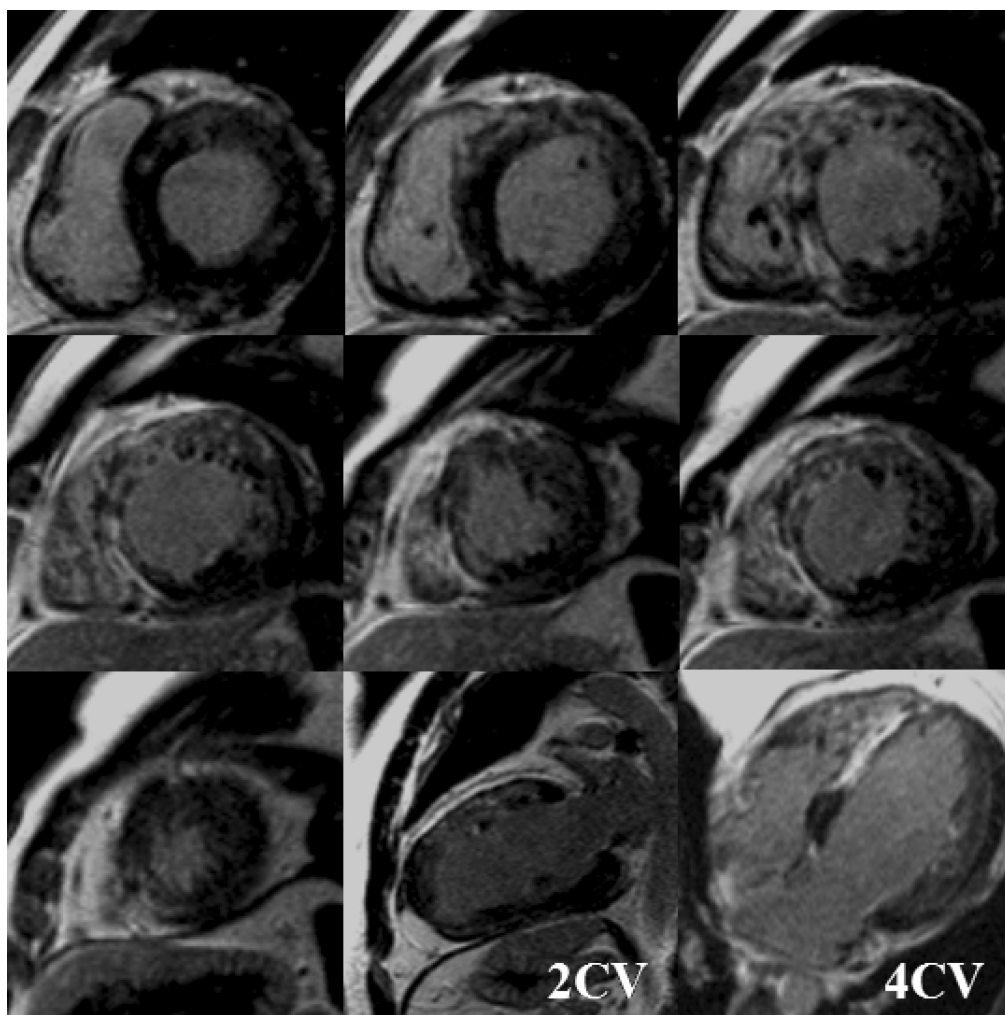


Figure 1. A complete late gadolinium enhancement study. This patient had moderately reduced left ventricular ejection fraction (38%) and history of two episodes of syncope. The myocardial scarring was assessed as 57% of the total myocardium (71% of the anterior territory, 35% of the inferior territory and 60% of the lateral territory). The myocardial scarring was transmural in five of the seven segments in the anterior territory.

total left ventricular volume ranged in theory from 0 to 28, 0 to 20, 0 to 20 and 0 to 68 respectively, and was thereafter expressed as a percentage of the maximum possible score (Fig. 1, Fig. 4). Validity of this method has been previously reported (26).

ECG analysis

A standard 12 lead ECG was performed before CMR in all subjects in the supine position. The ECGs were evaluated by consensus of two experienced investigators blinded to the CMR findings. There are currently more than one diagnostic criteria in clinical use for identification of abnormal Q waves in patients with HCM, resulting in various definitions being applied in previous studies. Recently Konno et al. (27) applied various definitions of pathologic Q-waves in 148 HCM genotyped subjects: criterion 1: Q wave $> 1/3$ of the ensuing R wave in depth and/or > 0.04 s in duration in at least two leads except aVR (28); criterion 2: Q wave $> 1/4$ of the ensuing R wave in depth and/or > 0.04 s in duration in at least two leads except aVR (29) and

criterion 3: Q wave > 3 mm in depth and/or > 0.04 s in duration in at least two leads except aVR (30). They suggested that criterion 3 may be the most accurate one. Based on these findings we also applied criterion 3.

Statistical analysis

Two-tailed t tests were used to compare continuous variables, which are expressed as means $\pm$ SD. The χ^2 test for trend was used to examine the influence of the segmental and transmural extent on the presence of Q waves. Receiver operating characteristic (ROC) curves were used to assess the relationship between classification as QW/NQW ECG and the segmental or the transmural extent of myocardial LGE. Areas under the ROC curves were compared using the technique described by DeLong et al. (31). Cut-off values were determined by receiver operating characteristics analysis. A p-value < 0.05 was considered statistically significant. The SAS software package was used for analysis.

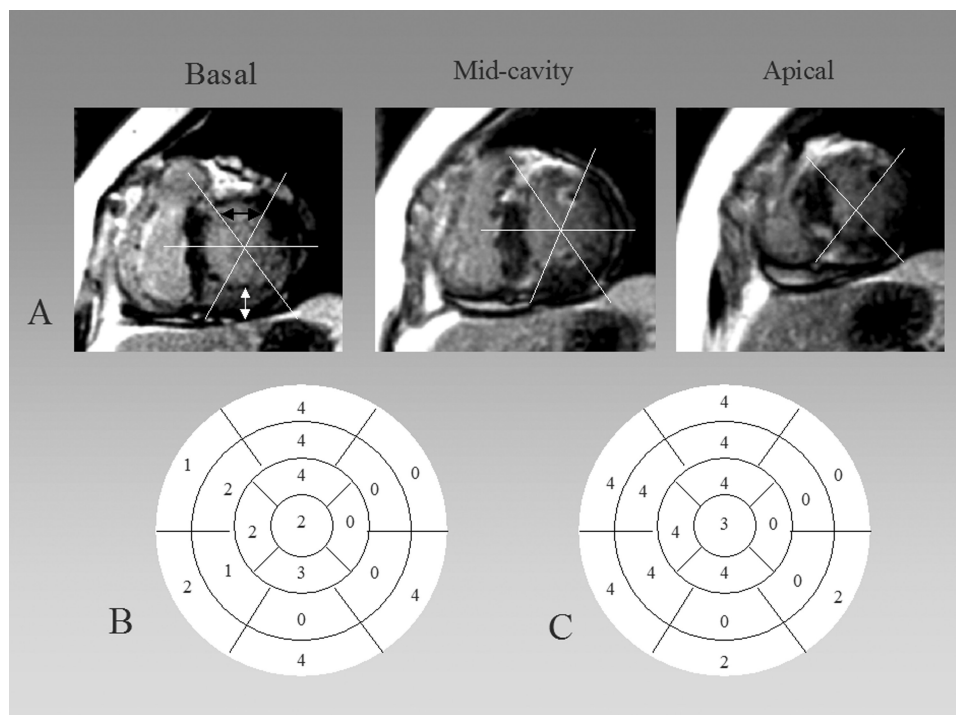


Figure 2. Distribution of LGE throughout myocardial wall (transmural extent [white arrows]) and width of segments (segmental extent [black arrow]) were scored in those segments with LGE. *A* Representative basal, mid-cavity and apical short-axis slices of a patient with HCM and LGE, divided into six, six and four segments respectively. *B* Estimation of segmental extent of LGE using a 17-segment model and a score ranging from 0 to 4. *C* Estimation of transmural extent using the same model.

RESULTS

Patient characteristics and extent of hyperenhancement

The demographics and baseline characteristics of the patients are given in Table 1. Table 2 shows the values of all LV

parameters for patients with and without Q waves as measured by CMR. There were no statistically significant differences in dimensions, volumes and mass between patients with and without Q waves. LGE was present in a total of 26 patients (68%). Of these, 12 patients exhibited Q waves and 14 patients did not have Q waves (Fig. 3). Segmental and transmural extent of myocardial LGE are presented in Table 3. Statistically significant differences

Table 1. Demographics and baseline characteristics

Characteristics	
Age (years)	58 ± 15
Male gender	21 (55%)
NYHA functional class	
I	26 (68%)
II	7 (18%)
III	5 (13%)
Family history of HCM or sudden death	7 (18%)
Syncope	1 (3%)
NSVT on holter monitor	0
Documented sustained VT/VF	5 (13%)
Maximum LV wall thickness >30 mm	4 (11%)
Echocardiographic LV outflow gradient >30 mmHg	11 (29%)

Data are presented as the mean value ± SD or number (%) of subjects. NYHA = New York Heart Association; HCM = hypertrophic cardiomyopathy; VT = ventricular tachycardia; VF = ventricular fibrillation; LV = left ventricular.

Table 2. Left ventricular parameters measured by CMR

	Patients with Q waves (n = 12)	Patients without Q waves (n = 26)	p-Value
LVM (g)	191 ± 57	180 ± 76	n.s.
LVEDD (mm)	49 ± 9	50 ± 6	n.s.
SWT (mm)	21 ± 5	17 ± 4	n.s.
PWT (mm)	10 ± 3	11 ± 3	n.s.
EDV (ml)	150 ± 46	143 ± 48	n.s.
ESV (ml)	72 ± 38	55 ± 23	n.s.
SV (ml)	78 ± 20	85 ± 34	n.s.
EF (%)	53 ± 11	62 ± 9	n.s.

Data are presented as mean ± SD; n.s. = not significant.

HCM = hypertrophic cardiomyopathy; LVM = left ventricular mass; LVEDD = left ventricular end-diastolic diameter; SWT = septal wall thickness; PWT = posterior wall thickness; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction.

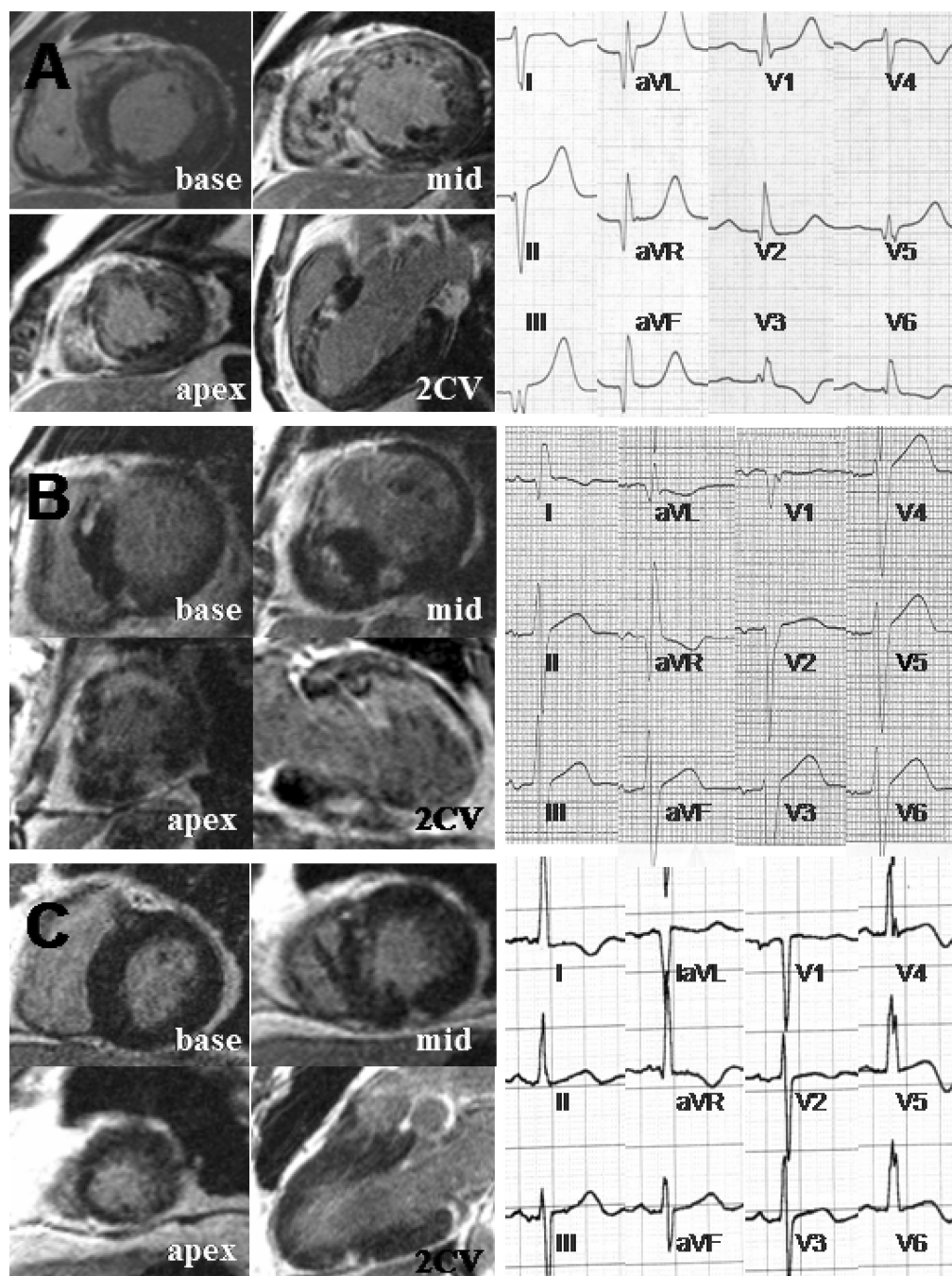


Figure 3. Three late gadolinium enhancement studies of patients with HCM: (A) A patient with excessive LGE and abnormal Q waves (III, aVL, aVF) in the 12-lead ECG (B) A patient with abnormal Q waves (I and aVL) in the 12-lead ECG. The extent of the myocardial LGE was assessed as 44% of the total myocardium (75% of the anterior territory and 45% of the inferior territory). The myocardial hyperenhancement was transmural in five of the seven segments in the anterior territory. (C) This patient showed LGE on the CMR images but no Q waves in the ECG. The extent of the myocardial LGE was assessed as 3% of the total myocardium.

between patients with and without Q waves were observed for lateral, inferior and the composite of all territories, both with regard to segmental and transmural extent of myocardial LGE. The difference for the anterior territory did not reach statistical significance.

Location of Q waves

Twelve (31%) of the 38 patients had abnormal Q waves on the 12 lead electrocardiogram. Abnormal Q waves were most frequently observed in leads I, II, aVL, V3-V6. Territorial

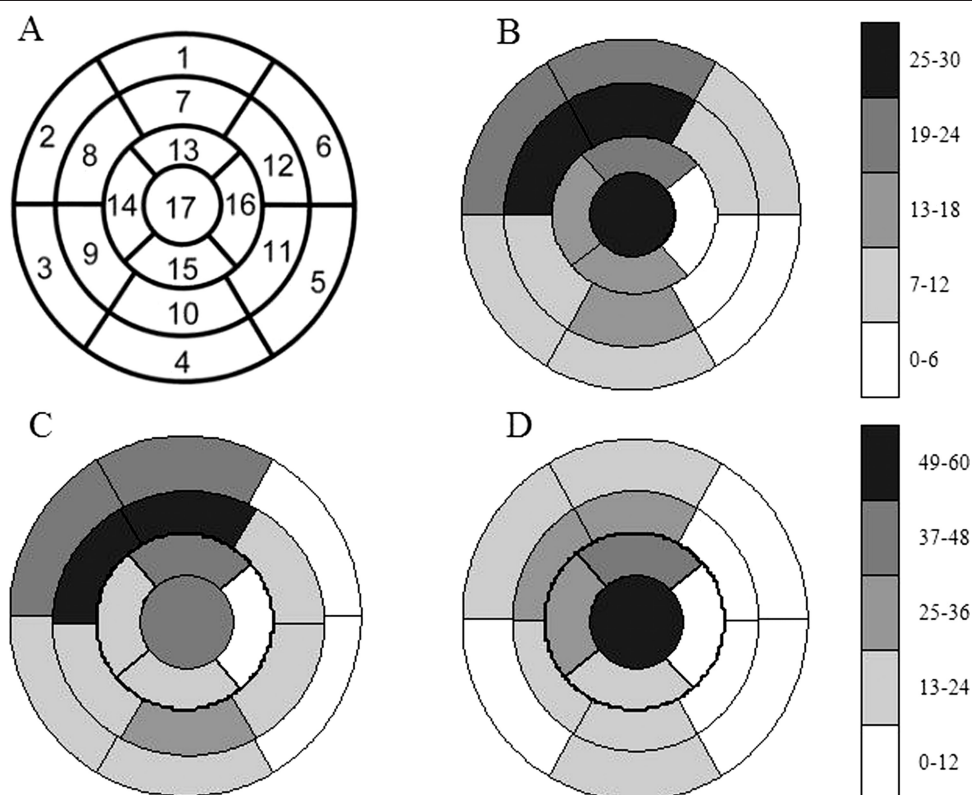


Figure 4. The 17-segment model (A) and the corresponding greyscale coded bulls-eye plots for displaying the extent of LGE in the whole population (B), in patients with Q waves (C) and in patients without Q waves (D).

distribution of Q waves on the ECG was similar to the territorial distribution of areas with LGE. All 12 patients with abnormal Q waves on the 12 lead ECG had LGE on CMR.

Q waves and segmental extent of myocardial hyperenhancement

As the segmental extent of LGE increased in the anterior, inferior and lateral territories, the probability of finding a Q

Table 3. Segmental and transmural extent of myocardial hyperenhancement expressed as a percentage maximum possible score in patients with and without Q waves

Myocardial territories	Patients with Q waves (n = 12)	Patients without Q waves (n = 14)	p-Value
Segmental Extent			
Anterior	43% ± 27%	22% ± 25	0,07
Inferior	21% ± 16%	12% ± 12%	0,03
Lateral	13% ± 19%	2% ± 3%	0,05
All territories	28% ± 18%	13% ± 14%	0,015
Transmural Extent			
Anterior	52% ± 29%	26% ± 36%	0,06
Inferior	39% ± 29%	13% ± 14%	0,006
Lateral	18% ± 25%	2% ± 4%	0,03
All territories	38% ± 22%	15% ± 18%	0,006

Data are presented as mean ± SD.

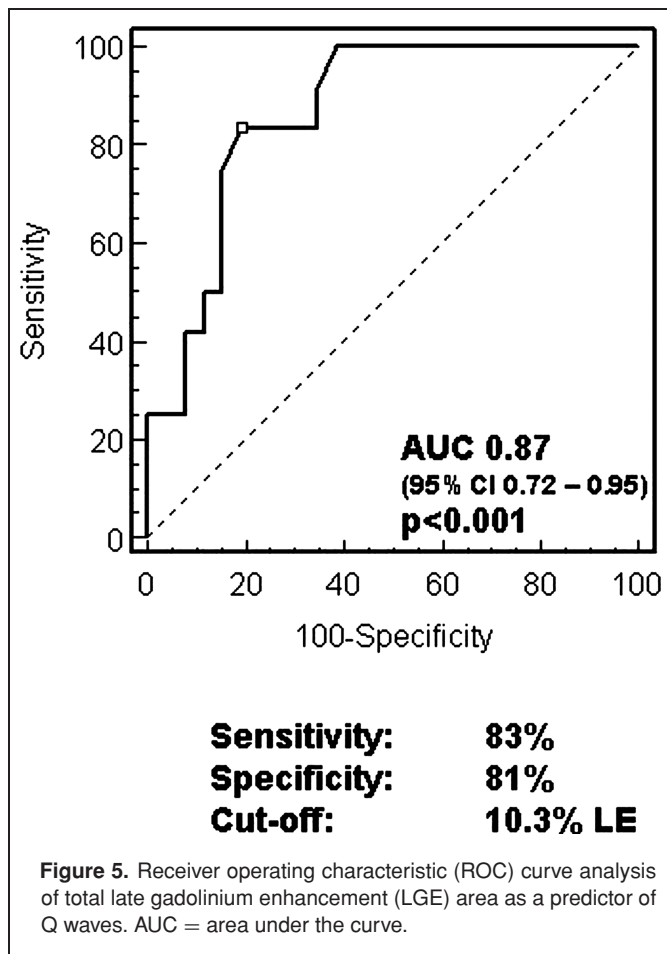
wave on the ECG increased (χ^2 ; anterior, $p = 0.0013$; inferior, $p = 0.0003$; lateral, $p = 0.0016$). Classification into Q wave/non Q wave ECG was a good diagnostic test for size of LGE; the area under the ROC curve was 0.862 for the anterior territory and 0.840 for the inferior territory. There was a moderate relationship in the lateral territory with an area under the ROC curve of 0.691. The area under the ROC curve was 0.873 for all three territories. A cut-off value of 10, 3% for total LGE area expressed as a percentage of the left ventricle for the detection of Q waves with a sensitivity of 83% and a specificity of 81% (Fig. 5) was derived from receiver operating characteristics analysis.

Q waves and transmural extent of myocardial hyperenhancement

As the extent of transmural LGE increased, the probability of classification as Q wave ECG increased (χ^2 ; anterior, $p = 0.0013$; inferior, $p < 0.0001$; lateral, $p = 0.0012$). The area under the ROC curve was 0.849 for the anterior territory, 0.846 for the inferior territory and 0.7 for the lateral territory respectively. The area under the ROC curve was 0.889 for all territories.

Segmental extent versus transmural extent and Q waves

When comparing segmental and transmural extent of LGE, there was no significant difference in terms of prediction of



QW/NQW ECG classification (anterior: area under ROC curve: 0.862 vs. 0.849, $P = \text{n.s.}$; inferior: 0.840 vs. 0.846, $P = \text{n.s.}$; lateral: 0.691 vs. 0.7, $p = \text{n.s.}$).

Septal to posterior wall thickness and Q waves

The ratio of septal to posterior wall thickness was significantly higher in patients with Q waves than in patients without Q waves (2.3 vs. 1.6, $p = 0.012$). Within the subgroup of patients with LGE there was no significant difference between patients with and those without Q waves (2.3 vs. 1.9, $p = 0.3$).

DISCUSSION

The present study demonstrates that segmental width as well as transmural extent of myocardial LGE found in patients with HCM using state-of-the-art CMR correlates to the presence of Q waves on the ECG. The larger the segmental width and transmural extent of LGE, the higher the likelihood for presence of Q waves on the ECG. These findings provide evidence in support of the hypothesis that abnormal Q waves in patients with HCM are predominantly due to the extent of myocardial fibrosis in the LV wall. Additionally, distribution of hypertrophy as indicated by differences in the ratio of septal to posterior wall thickness seems to play an important role.

The origin of Q waves in HCM has been controversially debated over the years. Early studies favoured the hypothesis that Q waves in HCM are caused by abnormal electrical activation of the markedly hypertrophied interventricular septum. Contrary to these perceptions, Maron et al. (3) reported that Q waves occur most frequently in young patients who have HCM characterized by an unusual pattern of left ventricular hypertrophy without typical asymmetric septal hypertrophy. In a further study, Lemery et al. (4) found a relationship between the presence of abnormal Q waves and an increased ratio of basal ventricular septal thickness to either right ventricular wall thickness or posterior LV wall thickness. Other investigators have suggested that Q waves are due to myocardial fibrosis, a common finding in the left ventricular wall of patients with HCM studied at necropsy (5, 6).

The present study shows, for the first time in vivo, a correlation between the presence of abnormal Q waves and abnormal myocardial interstitium as obtained by LGE CMR in patients with HCM. In our prospective study all 12 patients with abnormal Q waves on the 12 lead ECG had myocardial LGE on CMR. Fourteen of 26 patients showing myocardial LGE had no Q waves on ECG which is not surprising since LGE is a frequent finding in patients with HCM. Therefore, we can assume that the presence of LGE by itself is not indicative of the presence of Q waves. In this context our results show that patients with Q waves on the ECG exhibit significantly more myocardial LGE segmentally as well as transmurally than patients without Q waves. Thus, it seems that rather segmental as well as transmural extent of myocardial LGE is of prognostic value for the occurrence of Q waves on the ECG. In support of this view is the observation by Maron et al. (6) in a necropsy study that all patients with HCM and documented transmural fibrosis had prominent Q waves on ECG and many patients with nontransmural ventricular scarring did not have prominent Q waves. However, using autopsy to quantify myocardial scarring in patients with HCM may be biased by the fact that patients in these studies are highly selected and may not represent the majority of patients with HCM. Late gadolinium enhancement CMR has a number of advantages for investigating myocardial scarring and its relationship to the ECG. It is non-invasive with global myocardial coverage and allows visualization of even microinfarcts that cannot be detected by other imaging techniques. These characteristics suggest that LGE CMR may allow better interpretation of the anatomic and pathologic basis of the ECG in patients with HCM.

Additionally, our results show that distribution of hypertrophy as indicated by differences in septal to posterior wall thickness ratio in patients with and those without abnormal Q waves also contributes to the pathogenesis of Q waves. Similar findings were also reported by Lemery et al. (4). Recently, Koga et al. (17) also attempted to clarify the mechanisms of abnormal Q waves in HCM using intracoronary electrocardiography of the left anterior descending artery and thallium myocardial imaging in 20 patients with HCM and 10 control subjects. Consistent with the findings of the present study, two mechanisms found to be responsible for abnormal Q waves in patients with HCM were: 1) loss of local electrical forces due to transmural

myocardial fibrosis as assessed by single-photon emission computed tomography; and 2) altered direction of resultant initial QRS vector due to increased electrical forces of disproportionate hypertrophy. Different from our results however, not all patients with abnormal Q waves showed perfusion defects on thallium scintigraphy. This difference might be explained by: 1) the different ECG criteria used for identification of abnormal Q waves and 2) the different imaging techniques for detection of myocardial scarring.

Clinical implications. Data from recent studies indicate that the extent of hyperenhancement is linked with progressive disease and markers of clinical risk for sudden death. Tanaka et al. (34) quantified the amount of myocardial scarring in a necropsy study of 10 patients with HCM. Although the sample size was small, they found that all seven patients who died suddenly had a larger amount of scarring compared to the three who died from noncardiac causes ($13 \pm 3\%$ of total area vs. $6 \pm 3\%$). Recently, Moon et al. (35) reported a greater extent of hyperenhancement in patients with two or more risk factors for sudden death (15,7% vs. 8,6%, $p = 0.02$). In the present study, Q waves were associated with more extensive LGE. Since myocardial scarring seems to be related to prognosis, presence of Q waves in patients with HCM may serve as a simple novel prognostic marker of adverse outcome. However, further studies are clearly needed before any firm conclusions can be drawn.

LIMITATIONS

Although it is believed that the pathological basis of late gadolinium-enhancement in HCM is myocardial fibrosis (32), histopathological data to support this view are scarce. In fact, there have only been two case reports to date comparing in vivo late gadolinium enhancement CMR findings in patients with HCM to histopathological findings. Both case reports could demonstrate that myocardial hyperenhancement in HCM is related to the presence of replacement scarring and not to myocardial disarray or inflammation (22, 33). However, further studies are required before firm conclusions can be drawn.

Secondly, patients investigated in the present study had more advanced symptoms compared to patients in previously published reports (21, 35), as reflected by the higher incidence of patients in NYHA III. Therefore, we cannot exclude that our patient population had more advanced heart disease.

CONCLUSIONS

It seems that segmental width and transmural extent rather than the mere presence of myocardial LGE is one possible mechanism of abnormal Q waves in HCM. Additionally, distribution of hypertrophy as indicated by differences in the ratio of septal to posterior wall thickness seems to play an important role.

ABBREVIATIONS

CMR cardiovascular magnetic resonance
LGE late gadolinium enhancement

HCM hypertrophic cardiomyopathy
ECG electrocardiography
EF ejection fraction
LV left ventricular

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