Characteristics and Clinical Significance of Late Gadolinium Enhancement by Contrast-Enhanced Magnetic Resonance Imaging in Patients with Hypertrophic Cardiomyopathy

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Abstract

**Background:** Myocardial late gadolinium enhancement (LGE) on Contrast-Enhanced Magnetic Resonance Imaging (CE-MRI) of patients with hypertrophic cardiomyopathy (HCM) has been suggested to represent intra-myocardial fibrosis and as such, an adverse prognostic risk factor. We evaluated the characteristics of LGE on CE-MRI and explored whether LGE among patients with HCM was associated with genetic testing, severe symptoms, ventricular arrhythmias, or sudden cardiac death (SCD).

**Methods and Results:** 424 HCM patients [age = 55 ± 16 years (range 2–90), 41% females], without prior history of septal ablation/myectomy, underwent CE-MRI (GE 1.5T). We evaluated the relation between LGE and HCM genes status, severity of symptoms, and the degree of ventricular ectopy on Holter ECG. Subsequent SCD and appropriate defibrillator (ICD) therapies were recorded during a mean follow-up of 43 ± 14 months (range 16 – 94). 239 patients (56%) had LGE on CE-MRI, ranging from 0.4–65% of the left ventricle. Gene-positive patients were more likely to have LGE (p<0.001). The frequencies of NYHA class ≥3 dyspnea and angina class ≥3 were similar in patients with and without LGE [125/239 (52%) vs 94/185 (51%) and 24/239 (10%) vs 18/185 (10%), respectively, p=NS]. LGE-positive patients were more likely to have episodes of non-sustained ventricular tachycardia (NSVT) [34/126 (27%) vs 8/94 (8.5%), p <0.001], had more episodes of NSVT per patient (4.5±12 vs 1.1±0.3, p=0.04), and higher frequency of ventricular extrasystoles/24 hours (700 ± 2080 vs 103 ± 460, p =0.003). During follow-up, SCD occurred in 4 patients, and additional 4 patients received appropriate ICD discharges. All 8 patients were LGE-positive (event rate of 0.94%/year,
p=0.01 vs LGE negative). Two additional heart failure related deaths were recorded among LGE-positive patients. Univariate associates of SCD or appropriate ICD discharge were positive LGE (p=0.002) and presence of NSVT (p=0.04). The association of LGE with events remained significant after controlling for other risk factors.

**Conclusions:** In patients with HCM, presence of LGE on CE-MRI was common, and more prevalent among gene-positive patients. LGE was not associated with severe symptoms. However, LGE was strongly associated with surrogates of arrhythmia and remained a significant associate of subsequent SCD and/or ICD discharge after controlling for other variables. If replicated, LGE may be considered an important risk factor for sudden death in patients with HCM.

**Key words:** Hypertrophic cardiomyopathy, magnetic resonance imaging, late gadolinium enhancement, sudden death and risk assessment.
Background

The clinical definition of hypertrophic cardiomyopathy (HCM) is myocardial hypertrophy that occurs in the absence of an obvious cause for the hypertrophy (e.g., aortic stenosis or systemic hypertension) often predominantly involving the interventricular septum of a non-dilated left ventricle (LV), and frequently associated with functional LV outflow obstruction (1,2). The clinical course of patients with HCM is highly variable in that it can be generally benign in regard to overall survival, yet occurrence of adverse events such as sudden cardiac death (SCD) is higher than that observed in the general population. Although SCD is the most common mode of cardiac death in younger HCM patients, the actual risk is low (~1%/year), and the only proven method for prevention of sudden death is implantation of cardioverter-defibrillator (ICD) which can be associated with short and long-term morbidity (3-5). Moreover, risk stratification for the prediction of cardiac death is imprecise and the positive predictive value of currently recognized risk markers is low. Given the imperfections in the current risk stratification algorithms, improved methods are clearly needed (3,6).

Contrast enhanced magnetic resonance imaging (CE-MRI) of the heart demonstrates high accuracy in the detection of myocardial infarction as well as in the differentiation of variant cardiomyopathies (7). In patients with HCM, late Gadolinium enhancement (LGE) on CE-MRI is presumed to represent intra-myocardial fibrosis, and the presence of perfusion defects or LGE by CE-MRI has been shown to be associated with severe hypertrophy and regional wall motion abnormalities (8,9). Large areas of myocardium involved with LGE correlates inversely with LV function and may also help
in identifying the failing stage of HCM (10). Initial reports have also suggested a possible relationship between LGE and sudden death in patients with HCM (11).

The purpose of this study was to characterize LGE findings, and to explore whether LGE in patients with HCM is associated with positive genetic testing, severe symptoms, ventricular arrhythmias, or sudden cardiac death (SCD).

Methods

Patient selection

This study was a retrospective analysis of data acquired in patients with HCM who underwent CE-MRI at Mayo Clinic, and identified by cross matching the electronic MRI database and HCM clinic database. Between May 2001 and October 2007, 1488 patients were evaluated at the HCM clinic, and 456 patients underwent cardiac MRI for further evaluation of HCM (diagnosed by Echocardiography) at Mayo Clinic in Rochester, MN. Typical reasons for not performing MRI were: MRI exclusions (e.g. pacemaker/ICD), previous MRI performed elsewhere, or sufficient clinical information. This period represent the time from first scan with dedicated MRI protocol (2001) to late 2007 (to allow > 1 year of follow-up). The definition of HCM was based on the standard clinical and echocardiographic criteria and demonstration that there was no other systemic or local cause for hypertrophy. Thirty two patients were excluded from the current investigation on the basis of prior septal myectomy or ablation (N=5) [septal reduction therapies may have a significant impact on LGE measurements (12)], lack of research
authorization as required by Minnesota law (N=7) or an MRI scan that was performed without intravenous Gadolinium contrast agent (N=20). The final study group consisted of 424 HCM patients.

**MRI acquisition:**

All studies were performed on a 1.5 Tesla MRI scanner (Signa Twin Speed Excite, General Electric, Waukesha, WI, USA). MRI data were analyzed by two experienced observers in consensus without knowledge of clinical parameters.

LV ejection fraction (LVEF), LV end-systolic and end-diastolic diameters and volumes, LV end-diastolic mass, as well as maximal (end-diastolic) septal thickness were traced and recorded from the short axis views (8 mm slice thickness, 1 mm gap) of the standard ECG-gated steady state free precession (SSFP) pulse sequence; repetition time = 3.5 msec, echo time = 1.6 msec, temporal resolution = 40 msec; matrix 224x160, flip angle = 45°, bandwidth=125 kHz, views per segment = 8 to 16. Diagnosis of HCM morphological subtype (sigmoid, reverse curve, apical or indeterminate) (13,14), and the presence of obstructive physiology (defined as systolic anterior motion of the mitral valve leaflet) were performed from the 3-chamber SSFP pulse sequence prescribed manually from the basal short axis views. Reduced LVEF was defined as LVEF<50%.

Delayed-enhancement images for detection of hyperenhancement (fibrosis) were obtained approximately 10 min after injection of double-dose intravenous Gadodiamide (0.2 mmol/kg) using a segmented inversion recovery prepared fast gradient echo sequence (15). The prescription for this sequence was identical to the short-axis cine
sequence to ensure image registration. Typical scan parameters were as follows: repetition time = 6.5 ms, echo time = 3.1 ms, inversion time (TI) = 160 to 240 ms, matrix = 256x192, 8mm section thickness with 1mm interslice gap, field of view 32-44 cm, flip angle = 20°, bandwidth = 31.2 kHz, views per segment = 24. A Cine multi-TI inversion recovery sequence (Cine IR) was used to select the optimal TI for delayed enhancement imaging. Areas of hyperenhancement (LGE) were traced manually and presented both as a binomial variable (positive/negative) and as percentage of LV mass.

Four possible location of LGE in the LV were recorded: 1. Right ventricular "insertion points" (the anterior and inferior attachment points of the right ventricle to the inter-ventricular septum, in a short axis view). 2. Septum (all other septal hyperenhancements), 3. Apical (confined to the LV apex), and 4. All other LV locations.

Tracing for both SSFP and delayed enhancement pulse sequences were all performed and calculated using MASS 6 software (Medis Inc., Leiden, the Netherlands).

Assessment of clinical status and outcome events

Vital status was determined by review of medical records, social security death index, and review of death certificates. Clinical data were determined by an investigator blinded to MRI data. The following clinical parameters were assessed:

Baseline characteristics

We recorded baseline characteristics, risk factors and symptom status during the week during which the MRI was performed. The following baseline characteristics were
recorded: 1. Hypertension (blood pressure of >140/90 or treatment with anti-hypertensive medications), 2. Diabetes Mellitus (patient history and/or treatment with Insulin or oral hypoglycemic agents), 3. Family history of HCM in first degree relatives, 4. Coronary artery disease, which was defined as ≥1 angiographically proven >50% luminal narrowing or documented prior myocardial infarction [defined according to standard definition (serum cardiac biomarker elevation with symptoms of ischemia and/or ECG changes indicative of new ischemia/infarction)], 5. History of documented atrial fibrillation (of any duration), 6. History of syncope (transient and complete loss of consciousness), 7. History of sudden death in a first degree relative.

Presence of severe symptoms

Severe symptoms were defined as the presence of either New York Heart Association (NYHA) class ≥3 dyspnea or Canadian Cardiovascular Society (CCS) angina class ≥3.

Evaluation of ventricular arrhythmias with Holter-ECG

Holter monitoring within <6 month of MRI date was performed in 220/424 (52%) patients. Reports were scrutinized for the presence of total ventricular beats, presence of ventricular couplets or bigeminy, and for the presence and number of non-sustained ventricular tachycardia episodes (NSVT) defined as 3 or more consecutive ventricular beats. Holter results were averaged for 24 hours.

Assessment of subsequent interventions and outcome events during follow-up
All 424 patients were followed for a mean duration of 43 ± 14 months (range 16 – 94). Patient records were analyzed for the following subsequent (after MRI date) procedures: surgical septal myectomy, septal ablation, or implantation of an ICD.

Analysis of all ICD interrogation records was performed to assess ICD therapies. Defibrillator discharges or anti-tachycardia overdrive pacing were considered an appropriate therapy if the device was triggered by ventricular tachycardia or fibrillation, and which was documented by stored intracardiac electrograms in conjunction with patient’s symptoms immediately before and after device discharge. All appropriate ICD therapies were confirmed by an electrophysiologist, as previously described (16).

Death certificates were reviewed to verify the date and cause of all death events occurred during the follow-up period. SCD was defined as unexpected cardiac death (within one hour of symptoms). We defined an outcome event as the occurrence of SCD or appropriate ICD therapy.

Subset analysis comparing genetic testing and CE-MRI

A genotype-phenotype subset analysis was performed in the 245 HCM patients (161 male, mean age at diagnosis = 48 ± 17 years) who underwent both CE-MRI and genetic testing for mutations in 9 myofilament-encoding, HCM-susceptibility genes, part of commercially available HCM genetic tests as previously described (13).

Statistical analysis
We used descriptive statistics to present MRI and clinical variables. Continuous variables are presented as mean ± standard deviation. The associations between presence of LGE as a binomial variable and MRI morphologic variables, LVEF and presence of severe symptoms were evaluated using the Pearson $x^2$ test for categorical variables and an equal variance two-sample t-test for LVEF. Correlation between LVEF and extent of LGE was also performed. Continuous variables from the Holter-ECG were compared between LGE-positive and negative patients using the Wilcoxon rank-sum test. Event free survival curves were constructed using the Kaplan-Meier method and differences between groups examined using the log rank test. Multivariate analysis to define independent LV morphologic and functional predictors of LGE was performed using logistic regression analysis. Time to event univariate and serial bivariate analyses of outcome events (SCD or appropriate ICD therapies) was performed using the Cox proportional hazards fit test and the results are presented as hazard ratio (HR) and 95% confidence intervals (CI). Incidence estimate of SCD or appropriate ICD shock for 4 HCM risk factors (massive hypertrophy, family history of sudden death, syncope and NSVT) and for LGE were calculated by counting the total number of events in patients with that risk factor divided to the total follow-up years in this group.

A p value of 0.05 or less was used to define statistical significance. Statistical analysis was performed using JMP 7 package (SAS institute inc., Cary, NC, USA). The study was approved by the Mayo Clinic institutional review board and authors had full access to data and take full responsibility for the integrity of the data.

Results
Patients' characteristics

424 patients were included for analysis and baseline characteristics are presented in table 1. Mean age was 55±16 years (range: 2-90 years) and 173 (41%) were female.

LV Functional and morphological cardiac MRI findings

Mean LV ejection fraction (LVEF) was 67±9% (range 30-88). 20 patients had reduced LVEF (<50 %). Maximal inter-ventricular septal thickness was 20.5±5 mm [range: 10 (localized apical variant) to 49 mm]. The following morphological subtypes, as previously defined (12,13) were observed: 250 patients (59%) had a sigmoid septal shape, 79 had reversed curve morphology (18%), 28 patients (7%) had apical HCM, and the 67 remaining (16%) had indeterminate morphology. Patients with reversed curve morphology had increased septal thickness (26±6 mm) as compared to all others (19±4 mm, p<0.0001). 359 (85%) patients had systolic anterior motion of the anterior mitral valve leaflet apparatus evident on the MRI.

Frequency, location and MRI findings associated with LGE

239 of 424 patients (56%) had LGE on CE-MRI. LGE involved 6.2±6.4% of LV end-diastolic mass with a range of 0.4 to 65%. 112 patients (26%) had large LGE (≥5% of the LV mass). The most common locations for LGE were the RV insertion points observed in 174/239 patients (73%), followed by other septal locations in 53 (13%), the LV apex in 39 (16%) and other LV locations in 51 (21%) patients. 23% of patients
(55/239) had LGE involving more than a single LV location. No significant LGE was observed in the right ventricular free wall.

Prevalence of LGE by CE-MRI was high in patients with reversed curve morphology (87% of patients), less frequent in patients with apical HCM (60%) and indeterminate morphology (57%), and lowest in patients with a sigmoid shaped septum (46%). In fact, reversed curve morphology was an independent predictor of LGE on CE-MRI (as compared to all other subtypes) with an odds ratio of 7.8 (95% CI: 3.9-15.6, p<0.0001). Univariate associations with LGE are presented in Table 2. Multivariate regression analysis (adjusting for LV end diastolic diameter, LVEF, maximal septal thickness, and presence of reverse curve morphology) identified decreasing LVEF (p=0.001) and increased septal thickness (p<0.0001) as significant associates of positive LGE.

Relation of LGE to severity of symptoms and to LV function

Mean LVEF in 239 patients with LGE (66±10%) was slightly lower than in 185 patients without LGE (69±8%) (p=0.001). Overall, there was an inverse relationship between LGE and LVEF (r = -0.35, p<0.0001). Twenty patients had reduced LVEF (<50%), of whom 17 had LGE on CE-MRI. However, the presence of LGE was not associated with the severity of symptoms. The frequencies of severe (NYHA class ≥3) dyspnea [125/239 (52%) vs 94/185 (51%), p=NS] or CCS class ≥3 angina [24/239 (10%) vs 18/185 (10%), p=NS] were similar in both groups.

Subsequent interventions during follow-up
During mean follow-up of 43 ± 14 months (range 16 – 94), 205 (48%) patients underwent septal reduction therapies. Surgical septal myectomy was performed in 150 patients (35%) and percutaneous septal ablation was performed in 63 (15%) patients (8 patients underwent both ablation and myectomy). The decision to proceed with septal reduction therapy during follow-up period was not based upon LGE, and did not correlate with presence or extent of LGE. 41 (9.7%) patients underwent ICD implantation for primary prevention based on the presence of one or more risk markers for sudden death (and not based on LGE).

**LGE in relation to Holter monitoring**

Two hundred and twenty patients underwent Holter monitoring within 6 months of MRI. There were no differences in their baseline characteristics as compared to the 204 patients who didn’t undergo Holter monitoring, other than being less likely to undergo septal reduction therapy later (85/220 vs 120/204, p<0.001). Patients with LGE (126, 57% of patients) were more likely to have NSVT on Holter ECG [34/126 (27%) vs 8/94 (8.5%), p < 0.001], and had more episodes of NSVT per patient if NSVT was detected [4.5±12 (range 1-66 per patient) vs 1.1±0.3 (range 1-2), p=0.04].

As compared to patients without LGE, LGE positive patients had higher frequency of ventricular premature extrasystoles/24 hours (700 ± 2080 vs 103 ± 460, p = 0.003), more episodes of bigeminy per patient when detected [42±119 vs 3.8±9, p=0.009], and more ventricular couplets (24±104 per patient vs 1.5±1, p=0.0007).

**CE-MRI findings in relation to genetic testing**
Sixty two of 245 (25%) patients in whom HCM genetic testing was available, had a positive test. Among the mutation positive subset, 32 (52%) had mutations in myosin binding protein C, 22 (35%) had mutations in beta-myosin heavy chain, and 10% had mutations involving the thin myofilament. Fifty two percent of the patients with reverse curve-HCM by MRI had a positive genetic test compared to only 15% for sigmoidal-HCM and 13% for apical-HCM (p<0.001). There were no significant differences between the particular HCM gene involved and septal morphology. However, LGE by CE-MRI was more common (75%) in patients with a positive genetic test compared to 53% with a negative genetic test (p<0.001).

**LGE in relation to outcome events**

During the follow-up period, 11 patients died. Five definite non-cardiac deaths were identified among our patients. Of the five, 3 were LGE positive and 2 were LGE negative. An additional two patients died during follow-up from progressive heart failure. One with extensive LGE and reduced left ventricular systolic function (“end stage HCM”) and the other with advanced diastolic heart failure and severe pulmonary hypertension (also LGE positive by CE-MRI).

Outcome events as defined occurred in 8 patients. SCD occurred in 4 patients and appropriate ICD therapies in 4 patients (9.7% of 41 patients with ICD) (see Figure 1). All 8 patients were LGE positive. LGE in those 8 patients ranged from 1.5% to 28% of the LV mass (median=4.5%, mean=7.6% ± 8.7%), and 4 of the 8 had large LGE (involving ≥5% of LV mass). Morphologically, LGE involving the right ventricular insertion points
was present in 6 of the 8 patients with outcome event. Three patients had LGE involving the mid-septum (including one where only the mid-septum was involved).

Estimated event free survival at 6 years was 100% in patients without LGE as compared to 96% in LGE positive patients (log rank, p=0.01, Figure 2). The average annualize event rate in LGE positive patients was 0.94%/year. This was in the range of other traditional risk factors evaluated in our cohort: 0.4%/year for syncope, 1.1%/year for family history of SCD, 1.6%/year for massive hypertrophy (>30mm), and 2.2%/year for NSVT.

Interestingly, there were 4 events in patients following septal reduction therapy with an incident rate of 0.5%/year in this group. There were 2 ICD discharges for ventricular tachycardia in patients who had prior myectomy (occurring at 11 and 78 months following the operation), 1 ICD discharge for ventricular fibrillation following septal ablation at 3 months, and 1 sudden death in a patient who had undergone both septal ablation and septal myectomy.

Univariate analyses of factors associated with outcome is presented in Table 3. LGE was significantly associated with outcome events. Another univariate associate of events was presence of NSVT (among the subset of patients with Holter-ECG). Of note, LGE was still predictive of events (p=0.03) among 211 patients without hypertension (which hypothetically may increase degree of hypertrophy), of whom 5 had an event.

Due to the low number of adverse events and limited number of variables to include in any Cox model, we performed serial bivariate analysis by including LGE in a Cox model with any traditional risk factor or any other variable from table 3, and also with septal myectomy or ablation (to assess if those changed the risk associated with
LGE). Positive LGE remained significantly associated with events after controlling for all other parameters.

**Discussion**

Our results show that in patients with HCM, LGE by CE-MRI was common. LGE was not associated with severe symptoms, but was associated with indirect and direct surrogates of arrhythmic sudden death including the frequency of ventricular ectopy, NSVT, sudden cardiac death, and appropriate ICD discharges. LGE was also more common among gene-positive patients. The current study is the first to demonstrate an association between the presence of LGE and SCD or appropriate ICD discharges. LGE remained significantly associated with events even when controlling for traditional risk factors (such as massive hypertrophy) or for reduced LVEF.

The data imply that CE-MRI could play a potentially important role in the risk stratification of patients with HCM if these results can be confirmed in other independent HCM populations. Risk stratification in HCM is difficult in the individual patient given the unpredictable natural history, the low positive predictive value of currently utilized risk markers (1,17), the complex balance between potential benefits and the well described morbidity of ICD placement (3-5,18).

The rationale for using LGE for risk stratification of cardiac patients is not new. Extent of LGE in patients with coronary heart disease and previous myocardial infarction is a determinant of ventricular arrhythmias and poorer outcomes (19-22). LGE was also
shown to be of prognostic value in patients with idiopathic dilated cardiomyopathy, in whom presence of “mid wall fibrosis” is associated with poorer outcome (22,23).

The presence of LGE in patients with HCM is thought to represent intramyocardial fibrosis (8,9,24-27), perhaps as a result of subendocardial ischemia (28). Therefore, scars may represent a potential focus for re-entrant arrhythmias and it is logical to consider LGE as a new novel prognostic risk factor in addition to the other established risk factors. Intramyocardial fibrosis (in addition to myocardial disarray) is among the histopathologic characteristic of HCM, and commonly found in necropsies of young patients who experienced unexpected cardiac death (29).

In a recent study by Maron et al, reporting the relationship between CE-MRI and clinical profile of 202 patients during < 2 years follow-up, the authors noted that LGE was not an independent predictor of adverse events (30). The current study is the largest series of patients reporting the relationship between LGE and outcome. Therefore, during a longer follow up period in a larger cohort of patients we were able to detect for the first time that LGE was associated with events. Of note, hazard ratio for LGE could not be calculated as all events were in the LGE-positive group.

The association between LGE and events may be even stronger if taking into account the relatively high rate of septal reduction procedures performed in our cohort (48% of patients). Despite the beneficial effect of these procedures, in term of symptom relief, and perhaps even by improving survival (for surgical myectomy) (15,31,32), LGE was still associated with outcome events. Indeed, a septal reduction procedure did not completely eliminate risk, as 4 of the 8 patients who had an outcome event in our cohort, underwent such a procedure following their MRI.
An association between LGE and ventricular arrhythmias and a higher rate of ventricular ectopy was recently described (33). This report and the increased burden of ventricular ectopy and NSVT in the subset of our patients who underwent Holter-ECG monitoring, and were LGE-positive, lends support to the hypothesis that fibrosis as detected by CE-MRI may lead to ventricular arrhythmias (34).

While no adverse events were observed in the LGE negative patients in this study, we do not feel that this should be construed as conveying the absence of risk for arrhythmia. Notably, in the study published by Maron and colleagues, sudden death was observed in 3/111 patients without LGE (29). If 2-3 events would have occurred among our LGE negative group, LGE would not have yielded a statistically significant p-value.

However, events were observed only among LGE positive patients, and despite the overall low positive predictive value of LGE for SCD or appropriate ICD shock (3.3%, 8/239). The incidence estimate of LGE for events (0.94%/year) was comparable to other traditional risk factors. Nonetheless, it is too early to translate our findings to all HCM patients.

In contrast with the prior report (29), our data demonstrate that LGE was not more common in patients with severe (class 3 or 4) angina or heart failure, although there were difference in the definition of advanced symptoms between the two studies. It is also possible that symptom severity may be dependent on degree of LV outflow obstruction or LV hypertrophy, and not necessarily on fibrosis (35-37). However, fibrosis as detected by CE-MRI may still be an underlying mechanisms of diastolic dysfunction, and therefore of symptoms (38).
The present study also shows that LGE was more common in gene-positive patients and especially in patients with reversed curve septal morphology. A shape found to be more likely to be associated with myofilament mutations, both in the current study and in a previous report (13). Whether greater septal thickness (which may lead to chronic intra-myocardial ischemia), observed in patients with reversed curve morphology, is responsible for the higher prevalence of fibrosis by CE-MRI or whether some genes are active promoters of fibrosis in those patients is still unknown.

**Study limitations**

Prescribing an accurate delayed enhancement MRI pulse sequence (in terms of timing and selection of the optimal inversion time) is somewhat operator-dependent and patient-specific and may introduce variability to the results. Variability may also be a result of LGE tracing methodology compared to other studies which used various cut-off values of the signal intensity to define LGE. However, all studies were performed with same methodology and all studies were re-read by same two observers. Regardless of methodology, diagnosis of very small LGE (while avoiding artifacts) may be difficult.

The study may introduce selection bias, as patients presented to a tertiary referral center may differ from an unselected group of patients. Additionally, the annual event rate in our cohort of patients (<1%/year) was low (even for LGE-positive patients), and perhaps lower than expected (39). This may have been influenced by the high rate of septal reduction therapies (31). However, despite a possible selection bias and frequency of septal reduction therapies, LGE was still associated with outcome, and therefore may have incremental value to traditional risk assessment.
Conclusions

In conclusion, the presence of LGE on CE-MRI in patients with HCM was common, but was not associated with higher rates of severe angina or dyspnea. However, LGE was strongly associated with surrogates of arrhythmia and our data are the first to demonstrate that LGE remained a significant associate of subsequent SCD or appropriate ICD therapies after controlling for other factors. If these findings are confirmed in independent cohorts, LGE may be considered an additional risk factor for SCD in patients with HCM.

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References


7. Jackson E, Bellenger N, Seddon M, Harden S, Peebles C. Ischaemic and non-
ischaemic cardiomyopathies--cardiac MRI appearances with delayed 

Significance, and Genetic Basis of Hypertrophic Cardiomyopathy with 

Resonance Imaging of Delayed Enhancement in Hypertrophic Cardiomyopathy: 
Relationship with Left Ventricular Perfusion and Contractile Function. J 

Sakahara H, Hayashi H. Usefulness of Delayed Enhancement Magnetic 
Resonance Imaging to Differentiate Dilated Phase of Hypertrophic 

11. Maron BJ, Maron MS, Lesser JR, Hauser RG, Haas TS, Harrigan CJ, 
Appelbaum E, Main ML, Roberts WC. Sudden cardiac arrest in hypertrophic 
cardiomyopathy in the absence of conventional criteria for high risk status. Am 
J Cardiol 2008;101:544-547.

12. Valeti US, Nishimura RA, Holmes DR, Araoz PA, Glockner JF, Breen JF, 
Oommen SR, Gersh BJ, Tajik AJ, Rihal CS, Schaff HV, Maron BJ. Comparison 
of surgical septal myectomy and alcohol septal ablation with cardiac magnetic 
resonance imaging in patients with hypertrophic obstructive cardiomyopathy. J 
Am Coll Cardiol 2007;49:350-357.


Figure legends:

**Figure 1:** Extensive patchy areas (white arrows) of late Gadolinium enhancement (involving 25% of the left ventricle) in an MRI of a 37 year-old men with hypertrophic cardiomyopathy and mildly reduced left ventricular ejection fraction (40%). This patients experienced fast ventricular tachycardia 3 years following MRI resulted in near-syncope and appropriate DC shock by his ICD.

**Figure 2:** Survival free of sudden cardiac death or appropriate ICD therapies in patients with hypertrophic cardiomyopathy in relation to presence of late Gadolinium enhancement on CE-MRI.
### Table 1

Baseline characteristics in 424 patients with HCM undergoing CE-MRI.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 16 (range = 2-90)</td>
</tr>
<tr>
<td>Females</td>
<td>173 (41%)</td>
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<tr>
<td>Hypertension</td>
<td>213 (50%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (6%)</td>
</tr>
<tr>
<td>Family history of HCM</td>
<td>79 (19%)</td>
</tr>
<tr>
<td>Family history of sudden death</td>
<td>27 (6%)</td>
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<tr>
<td>History of coronary artery disease</td>
<td>37 (9%)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>66 (16%)</td>
</tr>
<tr>
<td>History of syncope</td>
<td>67 (16%)</td>
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</table>
Table 2

Univariate predictors of late Gadolinium enhancement (LGE) on CE-MRI in 424 patients with HCM [Odds ratio (OR) and 95% confidence intervals (95%CI)].

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Number of patients</th>
<th>Proportion of patients with LGE</th>
<th>OR</th>
<th>95% C.I</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversed curved morphology</td>
<td>79</td>
<td>69/79</td>
<td>7.8</td>
<td>3.9-15.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal thickness &gt; 20 mm</td>
<td>213</td>
<td>161/213</td>
<td>5.2</td>
<td>3.4-8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass &gt; 150 gram</td>
<td>249</td>
<td>164/249</td>
<td>2.6</td>
<td>1.7-3.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF&lt;50%</td>
<td>20</td>
<td>17/20</td>
<td>4.6</td>
<td>1.3-16</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Table 3

Univariate predictors of sudden cardiac death or appropriate ICD discharges during follow up period in 424 patients with HCM

<table>
<thead>
<tr>
<th>patients with events</th>
<th>HR</th>
<th>95% C.I</th>
<th>P value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>0.98</td>
<td>0.94-1.01</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Male gender (N=251)</td>
<td>3</td>
<td>0.4</td>
<td>0.09-1.7</td>
<td>0.22</td>
</tr>
<tr>
<td>LGE positive (N=239)</td>
<td>8</td>
<td></td>
<td>0.002</td>
<td>All events in LGE-positive patients</td>
</tr>
<tr>
<td>LVEF&lt;50% (N=20)</td>
<td>1</td>
<td>3</td>
<td>0.16-17.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Maximal septal thickness ≥30mm (N=29)</td>
<td>2</td>
<td>6.4</td>
<td>0.94-27.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior syncope (N=67)</td>
<td>1</td>
<td>0.7</td>
<td>0.04-4</td>
<td>0.74</td>
</tr>
<tr>
<td>Severe (class 3 or 4) angina or dyspnea (N=223)</td>
<td>4</td>
<td>0.9</td>
<td>0.2-3.8</td>
<td>0.9</td>
</tr>
<tr>
<td>History of coronary artery disease (N=37)</td>
<td>0</td>
<td>0.06</td>
<td>All events in patients without prior coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>History of atrial fibrillation (any) (N=66)</td>
<td>3</td>
<td>3.5</td>
<td>0.7-14.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Family history of HCM (N=79)</td>
<td>3</td>
<td>2.6</td>
<td>0.53-10.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Family history of sudden death (N=27)</td>
<td>1</td>
<td>2.4</td>
<td>0.13-13.3</td>
<td>0.47</td>
</tr>
<tr>
<td>NSVT per Holter-ECG (N=42)</td>
<td>3</td>
<td>6.9</td>
<td>1.14-52.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Positive genetic testing (N=62)</td>
<td>3</td>
<td>3.3</td>
<td>0.8-13.8</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Figure 2

Survival free of sudden cardiac death or appropriate ICD therapy

Time to event (months)

LGE negative

LGE positive

P=0.01

No. at risk

--- -- - 185

239

180

228

97

114

22

26
Characteristics and Clinical Significance of Late Gadolinium Enhancement by Contrast-Enhanced Magnetic Resonance Imaging in Patients with Hypertrophic Cardiomyopathy

Ronen Rubinshtein, James F. Glockner, Steve R. Ommen, Philip A. Araoz, Michael J. Ackerman, Paul Sorajja, J. Martijn Bos, A. Jamil Tajik, Uma S. Valeti, Rick A. Nishimura and Bernard J. Gersh

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