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

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Background—Myocardial late gadolinium enhancement (LGE) on contrast-enhanced magnetic resonance imaging (CE-MRI) has been suggested to represent intramyocardial 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—Four hundred twenty-four patients with HCM (age = 55±16 years [range 2 to 90], 41% females), without a history of septal ablation/myectomy, underwent CE-MRI (GE 1.5 Tesla). 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 implanted cardioverter defibrillator (ICD) therapies were recorded during a mean follow-up of 43±14 months (range 16 to 94). Two hundred thirty-nine patients (56%) had LGE on CE-MRI, ranging from 0.4% to 65% of the left ventricle. Gene-positive patients were more likely to have LGE (P<0.001). The frequencies of New York Heart Association class ≥3 dyspnea and angina class ≥3 were similar in patients with and without LGE (125 of 239 [52%] versus 94 of 185 [51%] and 24 of 239 [10%] versus 18 of 185 [10%], respectively, P=NS). LGE-positive patients were more likely to have episodes of nonsustained ventricular tachycardia (34 of 126 [27%] versus 8 of 94 [8.5%, P<0.001), had more episodes of nonsustained ventricular tachycardia per patient (4.5±12 versus 1.1±0.3, P=0.04), and had higher frequency of ventricular extrasystoles/24 hours (700±2080 versus 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%/y, P=0.01 versus 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 nonsustained ventricular tachycardia (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. (Circ Heart Fail. 2010;3:51-58.)

Key Words: hypertrophic cardiomyopathy ■ magnetic resonance imaging ■ late gadolinium enhancement ■ sudden death and risk assessment

The clinical definition of hypertrophic cardiomyopathy (HCM) is myocardial hypertrophy that occurs in the absence of an obvious cause for the hypertrophy (eg, aortic stenosis or systemic hypertension) often predominantly involving the interventricular septum of a nondilated left ventricle (LV) and frequently associated with functional LV outflow obstruction.1,2 The clinical course of patients with

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HCM is highly variable in that it can be generally benign in regard to overall survival; however, 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

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patients with HCM, the actual risk is low (≈1%/y), 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 More over, 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 MRI (CE-MRI) of the heart demonstrates high accuracy in the detection of myocardial infarction and in the differentiation of variant cardiomyopathies.7 In patients with HCM, late gadolinium enhancement (LGE) on CE-MRI is presumed to represent intramyocardial 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 is 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 the 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 the Mayo Clinic in Rochester, Minn. Typical reasons for not performing MRI were MRI exclusions (eg, pacemaker/ICD), previous MRI performed elsewhere, or sufficient clinical information. This period represents 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 previous septal myectomy or ablation (n=5) (septal reduction therapies may have a significant effect on LGE measurements12), 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 patients with HCM.

MRI Acquisition

All studies were performed on a 1.5-Tesla MRI scanner (Signa Twin Speed Excite, General Electric, Waukesha, Wis). MRI data were analyzed by 2 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, and 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 pulse sequence; repetition time=3.5 ms, echo time=1.6 ms, temporal resolution=40 ms, matrix 224×160, 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 steady-state free precession 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 ≈10 minutes 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=160 to 240 ms, matrix=256×192, 8 mm section thickness with 1 mm interslice gap, field of view 32 to 44 cm, flip angle=20°, bandwidth=31.2 kHz, views per segment=24. A cine multi-inversion time inversion recovery sequence (Cine IR) was used to select the optimal inversion time 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 locations of LGE in the LV were recorded: (1) right ventricular “insertion points” (the anterior and inferior attachment vents of the right ventricle to the inlet 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 steady-state free precession 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 in which the MRI was performed. The following baseline characteristics were recorded: (1) hypertension (blood pressure of ≥140/90 or treatment with antihypertensive 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); and (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 class ≥3 dyspnea or Canadian Cardiovascular Society angina class ≥3.

Evaluation of Ventricular Arrhythmias With Holter-ECG

Holter monitoring within <6 months of MRI date was performed in 220 of 424 (52%) patients. Reports were scrutinized for the presence of total ventricular beats, presence of ventricular couplets or bigeminy, and presence and number of nonsustained 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 up for a mean duration of 43±14 months (range 16 to 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 antitachycardia overdrive pacing were considered an appropriate therapy if the device was triggered by ventricular tachycardia or fibrillation and 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 1 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 patients with HCM (161 men, 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±SD. The associations between presence of LGE as a binomial variable and MRI morphological variables, LVEF, and presence of severe symptoms were evaluated using the Pearson χ² test for categorical variables and an equal variance 2-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 were examined using the log rank test. Multivariate analysis to define independent LV morphological 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 was used to define statistical significance. Statistical analysis was performed using JMP 7 package (SAS institute Inc, Cary, NC). The study was approved by the Mayo Clinic institutional review board, and the authors had full access to data and take full responsibility for the integrity of the data.

Results

Patients’ Characteristics
Four hundred twenty-four patients were included for analysis, and baseline characteristics are presented in Table 1. Mean age was 55±16 years (range 2 to 90 years) and 173 (41%) were women.

### Table 1. Baseline Characteristics in 424 Patients With HCM Undergoing CE-MRI

<table>
<thead>
<tr>
<th>Age, y</th>
<th>55±16 (2 to 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>173 (41)</td>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

Data are presented as mean±SD (range) or n (%).

LV Functional and Morphological Cardiac MRI Findings
Mean LV ejection fraction (LVEF) was 67±9% (range 30 to 88). Twenty patients had reduced LVEF (<50%). Maximal interventricular 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) compared with all others (19±4 mm, P<0.0001). Three hundred fifty-nine (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
Two hundred thirty-nine 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%. One hundred and twelve patients (26%) had large LGE (=5% of the LV mass). The most common locations for LGE were the RV insertion points observed in 174 of 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. Twenty-three percent of patients (55 of 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 (compared with all other subtypes) with an odds ratio of 7.8 (95% CI, 3.9 to 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.
LGE was significantly associated with outcome events. Another univariate associate of events was presence of NSVT (among the subset of patients with LGE).
Holter-ECG). Of note, LGE was still predictive of events ($P=0.03$) among 211 patients without hypertension (which hypothetically may increase the degree of hypertrophy), of whom 5 had an event.

Because of 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 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 genotype-positive patients. This study is the first to demonstrate an association between the presence of LGE and SCD or appropriate ICD therapies. LGE remained significantly associated with events even after controlling for all other parameters.

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 used risk markers, the complex balance between potential benefits, and the well-described morbidity of ICD placement.

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. 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.

The presence of LGE in patients with HCM is thought to represent intramyocardial fibrosis, perhaps as a result of subendocardial ischemia. 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.

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. This 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 because 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 terms of symptom relief, and perhaps even by improving survival (for surgical myectomy), 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 after their MRI.
An association between LGE and ventricular arrhythmias and a higher rate of ventricular ectopy was recently described. 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, lend support to the hypothesis that fibrosis as detected by CE-MRI may lead to ventricular arrhythmias.

Although 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 et al, sudden death was observed in 3 of 111 patients without LGE. If events had occurred among our LGE-negative group, LGE would not have yielded a statistically significant probability 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 of 239). The incidence estimate of LGE for events (0.94%/y) was comparable to other traditional risk factors. Nonetheless, it is too early to translate our findings to all patients with HCM.

In contrast with the previous report, our data demonstrate that LGE was not more common in patients with severe (class 3 or 4) angina or heart failure, although there were differences in the definition of advanced symptoms between the 2 studies. It is also possible that symptom severity may be dependent on the degree of LV outflow obstruction or LV hypertrophy and not necessarily on fibrosis. However, fibrosis as detected by CE-MRI may still be an underlying mechanism of diastolic dysfunction and therefore of symptoms.

This 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 this study and in a previous report. Whether greater septal thickness (which may lead to chronic intramyocardial 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 with other studies that used various cutoff values of the signal intensity to define LGE. However, all studies were performed with same methodology, and all studies were reread by same 2 observers. Regardless of methodology, diagnosis of small LGE (while avoiding artifacts) may be difficult.

The study may introduce selection bias because patients presented to a tertiary referral center may differ from an unselected group of patients. In addition, the annual event rate in our cohort of patients (<1%/y) was low (even for LGE-positive patients), and perhaps lower than expected. This may have been influenced by the high rate of septal reduction therapies. 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

| Table 3. Univariate Predictors of Sudden Cardiac Death or Appropriate ICD Discharges During Follow-Up Period in 424 Patients With HCM |
|-----------------|----------------|---------|---------|----------------|
| Patients With Events | HR | 95% CI | P |
| Advancing age | 0.98 | 0.94 to 1.01 | 0.27 |
| Male gender (n=251) | 3 | 0.4 | 0.09 to 1.7 | 0.22 |
| LGE positive (n=239) | 8 | 0.002 | 0.002 |
| LVEF <50% (n=20) | 3 | 0.16 to 17.4 | 0.36 |
| Maximal septal thickness ≥30 mm (n=29) | 2 | 0.94 to 27.9 | 0.06 |
| Previous syncope (n=67) | 1 | 0.7 | 0.04 to 4 | 0.74 |
| Severe (class 3 or 4) angina or dyspnea (n=223) | 4 | 0.9 | 0.2 to 3.8 | 0.9 |
| History of coronary artery disease (n=37) | 0 | 0.06 |
| History of atrial fibrillation (any) (n=66) | 3 | 3.5 | 0.7 to 14.3 | 0.11 |
| Family history of HCM (n=79) | 3 | 2.6 | 0.53 to 10.5 | 0.22 |
| Family history of sudden death (n=27) | 2 | 2.4 | 0.13 to 13.3 | 0.47 |
| NSVT per Holter-ECG (n=42) | 3 | 6.9 | 1.14 to 52.4 | 0.04 |
| Positive genetic testing (n=62) | 3 | 3.3 | 0.8 to 13.8 | 0.1 |

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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.

Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

Myocardial late gadolinium enhancement (LGE) on contrast-enhanced magnetic resonance imaging of patients with hypertrophic cardiomyopathy has been suggested to represent intramyocardial fibrosis. We explored the relation between LGE among 424 patients with hypertrophic cardiomyopathy and their genetic testing status, presence of severe symptoms, ventricular arrhythmias, or occurrence of sudden cardiac death. Two hundred thirty-nine patients (56%) had LGE on contrast-enhanced magnetic resonance imaging, ranging from 0.4% to 65% of the left ventricle. Gene-positive patients were more likely to have LGE. The frequencies of New York Heart Association class ≥3 dyspnea and angina class ≥3 were similar in patients with and without LGE. LGE-positive patients were more likely to have episodes of nonsustained ventricular tachycardia and higher frequency of ventricular extrasystoles/24 hours. During a mean follow-up of almost 4 years, sudden cardiac death occurred in 4 patients, and additional 4 patients received appropriate defibrillator discharges. All 8 patients were LGE positive. The association of LGE with events remained significant after controlling for other risk factors. We concluded that in patients with hypertrophic cardiomyopathy, presence of LGE on contrast-enhanced magnetic resonance imaging was common, and more prevalent among gene-positive patients. LGE was not associated with severe symptoms, but LGE was strongly associated with surrogates of arrhythmia and remained a significant associate of subsequent sudden cardiac death and/or implantation of cardioverter defibrillator discharge. If replicated, LGE may be considered an important risk factor for sudden death in patients with hypertrophic cardiomyopathy.
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