

Prognostic Value of Quantitative Contrast-Enhanced Cardiovascular Magnetic Resonance for the Evaluation of Sudden Death Risk in Patients With Hypertrophic Cardiomyopathy

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Background—Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the young, although not all patients eligible for sudden death prevention with an implantable cardioverter-defibrillator are identified. Contrast-enhanced cardiovascular magnetic resonance with late gadolinium enhancement (LGE) has emerged as an in vivo marker of myocardial fibrosis, although its role in stratifying sudden death risk in subgroups of HCM patients remains incompletely understood.

Methods and Results—We assessed the relation between LGE and cardiovascular outcomes in 1293 HCM patients referred for cardiovascular magnetic resonance and followed up for a median of 3.3 years. Sudden cardiac death (SCD) events (including appropriate defibrillator interventions) occurred in 37 patients (3%). A continuous relationship was evident between LGE by percent left ventricular mass and SCD event risk in HCM patients ($P=0.001$). Extent of LGE was associated with an increased risk of SCD events (adjusted hazard ratio, 1.46/10% increase in LGE; $P=0.002$), even after adjustment for other relevant disease variables. LGE of $\geq 15\%$ of LV mass demonstrated a 2-fold increase in SCD event risk in those patients otherwise considered to be at lower risk, with an estimated likelihood for SCD events of 6% at 5 years. Performance of the SCD event risk model was enhanced by LGE (net reclassification index, 12.9%; 95% confidence interval, 0.3–38.3). Absence of LGE was associated with lower risk for SCD events (adjusted hazard ratio, 0.39; $P=0.02$). Extent of LGE also predicted the development of end-stage HCM with systolic dysfunction (adjusted hazard ratio, 1.80/10% increase in LGE; $P<0.03$).

Conclusions—Extensive LGE measured by quantitative contrast enhanced CMR provides additional information for assessing SCD event risk among HCM patients, particularly patients otherwise judged to be at low risk. (*Circulation*. 2014;130:484-495.)

Key Words: cardiomyopathies ■ heart arrest ■ magnetic resonance imaging

More than 50 years after its contemporary description, hypertrophic cardiomyopathy (HCM) remains the most common cause of sudden death in the young.¹⁻⁶ Although

several clinical markers have proved to be useful guides for risk stratification,^{3-5,7} current strategies do not identify all HCM patients at risk for sudden death.^{3,5,8,9} Over the last

Received October 23, 2013; accepted May 2, 2014.

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Guest Editor for this article was Judith S. Hochman, MD.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.007094/-DC1>.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.113.007094

decade, implantable cardioverter-defibrillators (ICDs) have been effective in the primary prevention of sudden death in HCM,^{7,10-12} underscoring the importance of more precise identification of those patients at highest risk.

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Ventricular tachyarrhythmias, emanating from regions of structurally abnormal myocardium (including areas of disorganized architecture and myocardial fibrosis), represent the likely mechanism of sudden death in HCM.^{3,7,10,13-16} Contrast-enhanced cardiovascular magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) is capable of noninvasive identification of myocardial fibrosis in coronary artery disease and cardiomyopathies,¹⁷⁻²⁰ including HCM.²¹⁻²⁴ Although recent investigations in HCM have demonstrated an association between LGE and ambulatory ventricular tachyarrhythmias,^{14,25-27} available data do not resolve the clinical utility of LGE in sudden death risk stratification.^{28,29} Therefore, we have assembled a large, multicenter HCM cohort, defined by eligibility for CMR, to investigate the prognostic value of LGE with respect to sudden cardiac death (SCD) events and other adverse disease consequences, including in those patients otherwise judged to be at low risk for sudden death in the context of current practice.

Methods

Study Patients

We evaluated 1669 HCM patients who were initially considered for CMR study at 7 HCM centers between November 2001 and February 2010. A total of 376 patients were excluded from the cohort on the basis of these criteria: prior implantation of an ICD (or other incompatible device), history of sustained ventricular tachycardia/ventricular fibrillation, claustrophobia, known associated obstructive coronary artery disease (including history of myocardial infarction or acute coronary event associated with increased cardiac enzymes or Q waves), other myocardial diseases, septal myectomy or alcohol ablation (before CMR), and incomplete follow-up (n=7). Therefore, the final study group comprised 1293 patients referred and eligible for CMR.

The date of the first evaluation (ie, study entry) was the time of the initial CMR examination. Median follow-up from study entry to the most recent evaluation (clinic visit or telephone interview) or death (as of January 2012) was 3.3 years (quartile 1-3, 2.3-4.5 years). Selected data from 270 patients in the present study cohort have been part of previous analyses.^{30,31}

All patients signed statements approved by the Internal Review boards of participating institutions, agreeing to the use of their medical information for research. All authors had full access to and take responsibility for the integrity of the data and have agreed to the manuscript as written.

Definitions

HCM Diagnosis

HCM diagnosis was defined as CMR documentation of a hypertrophied and nondilated left ventricle (LV; wall thickness ≥ 15 mm in adults and the equivalent relative to body surface area in children) at some point during their clinical course in the absence of another cardiac or systemic disease capable of producing similar magnitude of hypertrophy.^{2,4}

SCD Events

Sudden death was defined as unexpected sudden collapse occurring within 1 hour from the onset of symptoms in patients with a previously stable or uneventful clinical course. Additionally, potentially

lethal cardiovascular events in which patients were successfully resuscitated from cardiac arrest (with documented ventricular fibrillation) or received appropriate defibrillation interventions from an ICD were regarded as equivalent to sudden death and are included in all references to SCD events. Stored intracardiac electrograms were analyzed independently at each center by expert electrophysiologists blinded to CMR results; ICD discharges were characterized as appropriate if triggered by ventricular fibrillation or rapid ventricular tachycardia (rate, ≥ 180 bpm).^{7,10}

Risk Stratification

At study entry, each patient was assessed for the conventional primary prevention sudden death risk factors described in HCM^{3-5,32}: (1) history of HCM-related sudden death in ≥ 1 first-degree or other relatives < 50 years of age; (2) massive LV hypertrophy (maximum wall thickness ≥ 30 mm); (3) nonsustained ventricular tachycardia (≥ 3 consecutive ventricular beats, ≥ 120 bpm) on 24-hour ambulatory (Holter) ECG monitoring; and (4) unexplained syncope, inconsistent with neurocardiogenic origin, occurring within 5 years before CMR evaluation. Hypotensive blood pressure response to exercise was excluded from this analysis because exercise testing for risk stratification was customary practice in only a minority of patients.^{7,10,12} The conventional risk factors were then collapsed into a score ranging from 0 to 4, depending on the number of risk factors.

Ambulatory (Holter) ECGs were obtained in 1034 patients at the discretion of investigators at each of the participating HCM centers. In 259 patients, this test was not performed as a result of patient refusal or advanced age or was not judged necessary with high-risk status already established by other risk markers. Low-risk status was judged to be present in 598 study patients in whom all 4 risk factors were tested and were negative and in 184 patients in whom 3 risk factors were tested (exclusive of the Holter ECG) and were negative.

Heart Failure

Adverse heart failure-related events and mortality were defined as symptom progression during follow-up period to New York Heart Association functional class III or IV.³³ Patients with refractory heart failure and heart transplantation were considered equivalent to HCM-related heart failure death. End-stage phase of HCM with LV remodeling was defined by a CMR-derived LV ejection fraction (EF) $< 50\%$.³⁴

CMR Imaging

CMR imaging was performed with a 1.5-T scanner (Philips, Best, the Netherlands; or Siemens, Erlangen, Germany) using steady-state, free-precession breath-hold cines in 3 long-axis planes and sequential short-axis slices from the atrioventricular ring to the apex.^{19,29} LGE images were acquired 10 to 20 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA with breath-hold 2-dimensional segmented inversion-recovery sequence or phase-sensitive inversion-recovery sequences in identical planes as in cine images. Inversion time was optimized to null normal myocardial signal. For phase-sensitive sequences, uncorrected magnitude images were used.

CMR Analysis

Images from all centers were transferred to a core laboratory (PERFUSE, Boston, MA) for central, blinded analysis. LV volume, mass, and EF were measured by use of standard volumetric techniques and analyzed with commercially available software (QMASS version 7.4, Medis Inc). LV chamber was assessed according to the American Heart Association 17-segment model.³⁵ LV endocardial and epicardial borders on cine images were manually planimetered to define the myocardium, taking care to exclude papillary muscles and the intertrabecular blood pool. Maximal LV wall thickness was defined as the greatest dimension at any site within the LV myocardium.

The LV short-axis stack of LGE images was first assessed visually for the presence of LGE by 2 experienced readers (R.H.C. and E.A.) blinded to patient profiles and clinical outcome, with any disagreement adjudicated by a third expert reader (W.J.M.). Quantification of LGE was then performed by 1 expert reader (R.H.C.) on all

LGE-positive studies by manually adjusting a gray-scale threshold to define areas of visually identified LGE (see the online-only Data Supplement text and video). These areas were then summed to generate a total volume of LGE and expressed as a proportion of total LV myocardium (%LGE). Therefore, in this study, LGE was used as an imaging risk marker for clinical outcome and events (presumably representing myocardial fibrosis).^{21,23,24}

At PERFUSE, the visual LGE quantitation method used here for assessment of LGE has been previously reported and validated with high reproducibility with strong correlation to the gray-scale threshold method of ≥ 6 SDs exceeding the mean of normal myocardium ($r=0.9$, $P<0.001$; see the online-only Data Supplement).³⁶ In addition, high gray-scale thresholding methods have recently been validated by histopathology and have been shown to provide the best representation of total fibrosis burden (ie, replacement and interstitial).^{37,38} Therefore, we want to underscore that the results presented here pertaining to the extent of LGE in predicting SCD events are reliable only when the same quantification technique used in this study is applied. The time required for quantification using the visual gray-scale threshold method averaged 10 minutes per study. The software required to perform this analysis is now available on a number of commercial imaging platforms. For additional methods, please see the online-only Data Supplement.

To test interobserver agreement (R.H.C. and E.A.), LGE was quantified using the visual thresholding on 24 randomly selected studies. Intraobserver agreement (R.H.C.) was analyzed 12 months after the initial image analysis. For interobserver and intraobserver agreement measurements, endocardial and epicardial borders were retraced, and the amount of LGE was recalculated using visual gray-scale method.

Statistical Analysis

Continuous and categorical data are expressed as mean \pm SD, median (quartiles 1–3), or n (%) as appropriate. Comparisons of characteristics between groups were made with the unpaired Student *t* test, χ^2 test, or Fisher exact test as appropriate. All reported *P* values are 2 sided. The prespecified primary clinical end point was SCD events and included the composite of sudden death, aborted cardiac arrest, or appropriate ICD discharge for ventricular tachycardia/ventricular fibrillation.

Survivor curves comparing patients with and without LGE were constructed by the Kaplan-Meier method, and differences between groups were examined by use of a log-rank test for equality of survivor functions. The relationship between the presence or amount of LGE and the likelihood of subsequent clinical events was further evaluated through the use of univariate and multivariable Cox proportional hazards model. The proportional hazards assumption was tested graphically and with time-dependent covariates before proceeding.

The multivariable model was constructed to adjust for possible confounders using a stepwise selection method with an entrance and stay criteria of $P<0.20$, forcing the number of conventional sudden death risk factors into all models a priori. Variables entered into the multivariable model for SCD events thus include %LGE, conventional SCD risk factors (all 4 risk markers collapsed into analysis as 1 continuous variable), and maximal LV thickness. After the model was completed, the remaining candidate variables (ie, age, LV mass, EF, LV outflow tract gradient at rest, and septal reduction therapies performed after CMR) were retested individually with a sensitivity analysis to examine their influence on effect estimates. Separate multivariable models were constructed and retested in a similar fashion for death resulting from any cause and the development of end-stage HCM.

The incremental value of LGE in predicting 5-year SCD event risk was assessed in the overall cohort and the prespecified subgroup without conventional sudden death risk factors using area under the receiver-operating characteristics curve, integrated discrimination improvement, and net reclassification improvement (NRI).^{39,40} For NRI, the 5-year predicted risk for SCD was divided into 3 risk categories, defined as low ($\leq 0.5\%/y$, $2.5\%/5 y$), high ($\geq 1.5\%/y$, $7.3\%/5 y$), and intermediate ($0.6\%–1.4\%/y$, $2.6\%–7.2\%/5 y$).⁵ To account for sampling variability, confidence intervals (CIs) for all measures were obtained by bootstrapping with 1000 resamples. Results were internally validated with the bootstrap approach, and degree of overoptimism was calculated for each performance metric.⁴¹ The optimism

for the performance of the final multivariable risk prediction model is estimated by calculating the average difference between model performance (as measured by the area under the receiver-operating characteristics curve) in 500 bootstrap samples and the model performance of the original sample (ie, the full data set). All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Clinical and demographic characteristics of the study population are summarized in Table 1. At CMR, the mean patient age was 46 ± 17 years (range, 7–87 years), 815 (63%) were male, and initial New York Heart Association class was 1.6 ± 0.7 . Resting LV outflow tract obstruction (gradient ≥ 30 mmHg) was present in 302 patients (23%), with no difference in the prevalence of rest obstruction between patients with and without LGE ($n=119$ [22%] versus $n=183$ [24%]; $P=0.42$).

Clinical Outcome

During follow-up, SCD events occurred in 37 patients (3%): 14 died suddenly, 6 survived an aborted cardiac arrest, and 17 had appropriate primary prevention ICD therapy for ventricular tachycardia/ventricular fibrillation (cumulative SCD events incidence, 0.9%/y; Table 2). There was no difference in SCD event risk between patients taking cardioactive medications (ie, β -blockers, calcium channel blockers, disopyramide, or amiodarone) and those not taking these medications ($P=0.37$). In addition, 118 patients experienced adverse HCM-related heart failure events: 99 survivors with progressive heart failure symptoms to New York Heart Association class III/IV and 19 patients who died of heart failure or embolic stroke or underwent heart transplantation; 17 patients died of noncardiac causes, most commonly cancer and sepsis.

Distribution of LGE

Of the 1293 study patients, LGE was present in 548 (42%; Figure 1). Of those with LGE, the extent was $9\pm 10\%$ of the LV myocardial mass: $\leq 10\%$ of the LV ($n=381$, 29%), 11% to 19% ($n=94$, 7%), and $\geq 20\%$ ($n=73$, 6%). Among 37 patients with SCD events, LGE was present in 26 (70%; Table 2), occupying $13\pm 14\%$ of the LV myocardium.

Association of %LGE and SCD

During follow-up, SCD event risk was significantly greater among HCM patients with LGE compared with patients without any evidence of LGE (log-rank $P=0.002$). Notably, the unadjusted SCD event incidence per 1000 person-years increased in direct relation to the extent of LGE: 4 without LGE (95% CI, 2–8), 10 with LGE $\leq 10\%$ (95% CI, 6–18), 18 with 11% to 19% (95% CI, 7–39), and 24 with $\geq 20\%$ (95% CI, 9–51; $P=0.001$ for trend; Figure 2). The absence of LGE was associated with lower risk for SCD events (adjusted hazard ratio [HR_{adj}], 0.39; 95% CI, 0.18–0.84; $P=0.02$; Figure 2). In addition, in a subgroup analysis of 1008 patients, SCD events were not significantly increased in HCM patients with minimal LGE (1%–5%) compared with those with no LGE ($P=0.09$).

Table 1. Demographic and Clinical Characteristics of 1293 HCM Patients With CMR

Variable	All Patients (n=1293)
Age, y	46±17
Male, n (%)	815 (63)
Body surface area, g/m ²	1.9±0.3
NYHA class, n (%)	
Mean	1.6±0.7
I	735 (57)
II	380 (29)
III/IV	178 (14)
Atrial fibrillation, n (%)	159 (12)
Basal LVOT gradient ≥30 mm Hg	302 (23)
CMR variables	
LVED dimension, mm	54±7
LVEF %	67±9
Maximum LV thickness, mm	20±5
LV mass, g	163±71
LV mass index, g/m ²	83±34
LGE, n (%)	548 (42)
LGE, median (Q1–Q3), g	9 (4–21)
%LGE, median (Q1–Q3)	5 (3–13)
Location of LGE, n (%)	
Septum	275 (51)
LV free wall	143 (26)
Septum and LV free wall	89 (16)
Apex	187 (34)
Only at RV insertion into LV	134 (25)
Risk factors (0–4), n (%)	
Mean	0.5±0.6
0/1/2/3/4 risk factors	782 (60)/415 (32)/90 (7)/6 (0.5)/0 (0)
Nonsustained VT on ambulatory Holter*	204 (20)
Unexplained syncope	122 (9)
Family history of SCD	219 (17)
Maximum LV wall thickness ≥30 mm	68 (5)
Drugs, n (%)	
β-Blockers	741 (57)
Calcium channel antagonists	257 (20)
ACE-I/ATII	194 (15)
Amiodarone	42 (3)
Disopyramide	73 (6)
Diuretics	146 (11)
ICD implantation after initial CMR	259 (20)
Genetic testing, n (%)†	
MYBPC3	99 (24)
MYH7	77 (19)
TNNT2	16 (4)
TPM1	3 (0.7)
ACTC	1 (0.2)
Others	11 (5)

(Continued)

Table 1. Continued

Variable	All Patients (n=1293)
Duration of follow-up, median (Q1–Q3), y	3.3 (2.3–4.5)
Major clinical events during follow-up, n (%)	
HCM-related Sudden Death	14 (1.0)
Aborted arrest	6 (0.5)
ICD discharge (VT/VF)	17 (1.3)
Heart failure death	6 (0.5)
Heart transplantation	9 (0.7)
End-stage HCM‡	87 (7)
Progression to NYHA class III/IV§	99 (9)
Noncardiac death	21 (1.6)

ACE-I indicates angiotensin-converting enzyme inhibitor; ACTC, α -cardiac actin; ATII, angiotensin receptor blocker; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVED, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MYBPC3, cardiac myosin binding protein C; MYH7, β -myosin heavy chain; NYHA, New York Heart Association; Q1, quartile 1; Q3, quartile 3; RV, right ventricular; SCD, sudden cardiac death; TNNT2, troponin T; TPM1, α -tropomyosin; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*By convention, ambulatory 24-hour Holter monitors were ordered at the discretion of the investigators at each HCM center, with Holter monitoring performed in 1034 of 1293 study patients.

†Four hundred fourteen patients (32%) underwent genetic testing for HCM.

‡Fifty-eight had end-stage HCM at study entry; 26 others developed end-stage HCM during follow-up.

§Includes only 1115 patients who were in NYHA class I/II at study enrollment.

Prediction of SCD Events by %LGE

Notably, adjusted SCD event risk increased in a continuous and direct manner with respect to the extent of LGE (Table 3 and Figure 3). The extent of LGE was a strong predictor of SCD events in that each 10% increase in LGE was associated with 40% increase in relative SCD events risk (HR_{adj} , 1.46/10% increase in LGE; 95% CI, 1.12–1.92; Wald $\chi^2=9.6$; $P=0.002$; Table 4 and Figure 2), independently of patient age ($P=0.89$ for interaction). In addition, even when we consider those 184 HCM patients who did not undergo Holter ECG monitoring (and who had none of the other conventional risk factors) as theoretically having a positive Holter with nonsustained ventricular tachycardia, the relative risk of LGE in predicting SCD for the total cohort of 1293 patients remained essentially unchanged (HR_{adj} , 1.45/10% LGE; 95% CI, 1.11–1.90; Wald χ^2 , 7.5; $P=0.006$).

Compared with patients without LGE, the HR_{adj} of SCD events related to %LGE was as follows: 10%, $HR_{adj}=1.46$; 15%, $HR_{adj}=1.77$; and 20%, $HR_{adj}=2.14$ (Figure 3 and Table 3). The estimated risk of SCD events at 5 years increased incrementally with respect to %LGE, ranging from 4.9% in patients with 10% LGE to 6.9% in patients with 20% LGE (Figure 3 and Table 3).

In addition, the extent of LGE remained a significant predictor of SCD events, even after the exclusion of HCM patients with an EF <50% at study entry (HR_{adj} , 1.61/10% LGE; 95% CI, 1.21–2.16; $P=0.002$). The extent of LGE was also a predictor of SCD events when expressed as total grams (HR_{adj} , 1.13 per 10 g LGE; 95% CI, 1.01–1.28; $P=0.04$).

Table 2. Clinical and Demographic Characteristics of 37 Patients Experiencing SCD Events

Patient	Age, y	Sex	NYHA Class	LVEF, %	Maximum Wall Thickness, mm	LV Mass Index, g/m ²	LVOT Gradient	LGE	LGE, g (% of LV mass)	24-Hour Holter	Risk Factors	Event
Low-risk patients												
1	13	F	1	62	22	62	4	–	0 (0)	Y	...	Sudden Death
2	14	M	1	72	13	83	0	–	0 (0)	Y	...	Sudden Death
3	15	M	1	69	16	80	0	–	0 (0)	Y	...	Sudden Death
4	19	F	2	31	20	106	0	+	80 (40)	Y	...	Sudden Death
5	20	M	2	59	27	83	0	+	7 (5)	Y	...	Alive, ICD shock
6	22	F	1	57	22	57	6	+	1 (1)	Y	...	Alive, aborted arrest
7	30	M	2	63	26	71	0	+	17 (10)	Y	...	Alive, aborted arrest
8	35	M	1	71	25	129	0	+	15 (7)	Y	...	Alive, aborted arrest
9	35	F	2	51	14	48	5	+	53 (54)	Y	...	Alive, ICD shock
10	37	M	2	63	23	96	8	+	41 (26)	Y	...	Alive, ICD shock
11	39	F	1	66	20	103	0	+	6 (4)	Y	...	Sudden Death
12	47	M	1	60	19	54	5	–	0 (0)	Y	...	Alive, aborted arrest
13	48	M	1	54	24	120	35	+	3(1)	N	...	Alive, aborted arrest
14	55	M	2	60	22	104	8	+	87(36)	Y	...	Alive, ICD shock
15	57	F	2	52	16	62	9	+	11(11)	N	...	Sudden Death
16	59	M	2	79	27	142	0	+	8(3)	Y	...	Sudden Death
17	61	F	2	75	22	108	60	–	0 (0)	Y	...	Sudden Death
18	64	M	3	82	21	117	70	+	2(1)	Y	...	Sudden Death
19	66	F	3	74	23	80	0	–	0 (0)	Y	...	Sudden Death
20	72	M	1	70	22	127	0	–	0 (0)	Y	...	Alive, aborted arrest
21	73	M	2	71	20	91	10	–	0 (0)	Y	...	Sudden Death
Patients with ≥1 risk factor												
22	15	F	1	59	20	95	0	+	5 (3)	N	FH	Alive, ICD shock
23	21	M	1	73	26	175	0	+	21 (6)	Y	NSVT	Alive, ICD shock
24	27	F	1	66	16	65	0	–	0 (0)	Y	Syncope	Alive, ICD shock
25	48	F	2	70	22	89	0	+	12 (7)	Y	NSVT	Alive, ICD shock
26	54	M	1	58	28	117	0	+	25 (10)	Y	NSVT	Alive, ICD shock
27	58	M	1	65	17	48	0	+	2 (2)	Y	FH	Sudden Death
28	58	M	1	65	19	43	0	+	5 (2)	Y	FH	Sudden Death
29	61	F	1	66	16	46	0	+	17 (23)	Y	NSVT	Alive, ICD shock
30	65	M	3	35	20	86	5	+	27 (17)	Y	NSVT	Alive, ICD shock
31	78	M	3	66	22	69	0	–	0 (0)	N	Syncope	Alive, ICD shock
32	25	F	1	69	18	71	0	+	10 (10)	Y	FH, NSVT	Alive, ICD shock
33	31	M	1	65	50	138	16	+	43 (19)	Y	NSVT, extreme LVH	Alive, ICD shock
34	45	F	2	77	32	90	0	+	50 (31)	Y	NSVT, extreme LVH	Alive, ICD shock
35	49	F	3	77	25	78	0	–	0 (0)	Y	Syncope, FH	Alive, ICD shock
36	66	M	3	81	22	101	0	+	9 (5)	Y	FH, NSVT	Sudden Death
37	36	F	1	62	22	107	8	+	28 (12)	Y	Syncope, FH, NSVT	Alive, ICD shock

FH indicates family history of sudden death resulting from hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; and SCD, sudden cardiac death.

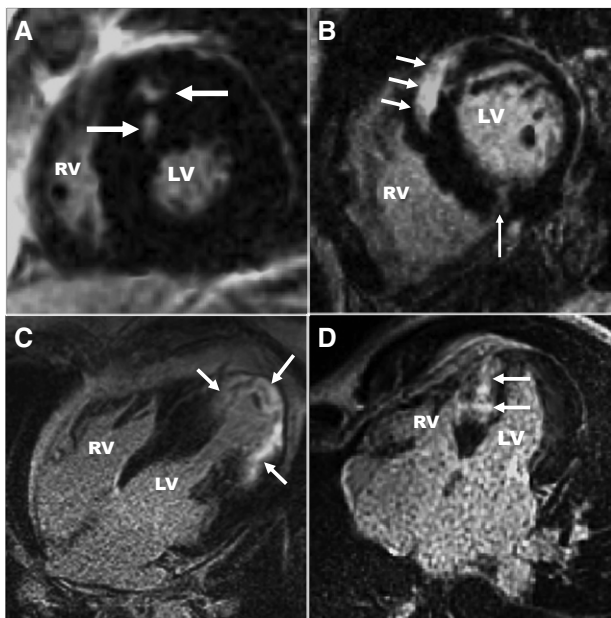


Figure 1. Contrast-enhanced cardiovascular magnetic resonance images in 4 patients with hypertrophic cardiomyopathy. **A**, Basal left ventricular (LV) short-axis image from an asymptomatic 29-year-old man without conventional risk factors. Focal areas of late gadolinium enhancement (LGE) are confined to the midmyocardial anterior wall (arrows), encompassing 4% of the LV mass. **B**, Mid-LV short-axis image from a 61-year-old woman with substantial LGE (23% of LV mass) involving the basal anterior septum and contiguous anterolateral free wall (thick arrows), as well as focally at the intersection of right ventricular (RV) free wall and posterior septum (thin arrow). A 12-beat nonsustained ventricular tachycardia (VT; 180 bpm) run on 24-hour ambulatory ECG was the only evidence of increased sudden cardiac death (SCD) risk. Extensive LGE was the arbitrator for the decision to implant a cardioverter-defibrillator (ICD) for primary prevention, which 5 months later terminated an episode of rapid VT. **C**, A 4-chamber long-axis image from mildly symptomatic 54-year-old man without conventional SCD risk factors and normal ejection fraction (EF; 60%) but with transmural LGE involving the distal posterior septum, apex, and lateral free wall (arrows) encompassing 36% of the LV mass. One year after ICD implantation, this patient received a shock for rapid monomorphic VT (180 bpm). **D**, A 4-chamber long-axis image from 29-year-old man with extensive LGE involving large portions of the ventricular septum (arrows) encompassing 32% of the overall LV mass. Over follow-up, he developed end stage with systolic dysfunction (EF, 40%) associated with progressive heart failure (New York Heart Association class III) and currently awaits heart transplantation.

Furthermore, LGE was an independent predictor of all-cause mortality ($P=0.006$; Table 4).

Relation of LGE to SCD Event Risk in Patients With Conventional Risk Factors

Sixteen HCM patients with ≥ 1 risk factors experienced SCD events (Table 2). A strong trend was present between sudden death risk and extent of LGE (unadjusted hazard ratio, 1.32/10% LGE; 95% CI, 0.93–1.86). %LGE was a stronger predictor of SCD events compared with each of the individual risk factors (univariate analysis global Wald statistic for %LGE=13.8 versus 0.1 for massive LVH, 0.9 for syncope, 0.1 for family history of SCD, and 3.3 for nonsustained ventricular tachycardia; $P \leq 0.001$ for each comparison; Table 5). In

addition, when %LGE is considered together with each of the risk markers, the incremental prognostic value in predicting SCD events is increased significantly (Table 5).

LGE in Low-Risk Patients

Of the 37 patients with SCD events, 21 (57%) were considered to be at lower risk for SCD using current clinical parameters.⁸ Among these patients, SCD event risk increased in direct proportion to extent of LGE (HR_{adj} , 1.66/10% LGE; 95% CI, 1.24–2.23; Wald $\chi^2=11.56$; $P=0.0007$). Therefore, compared with patients without LGE, the relative risk of SCD event in patients judged at lower risk related to %LGE was 10% (HR_{adj} , 1.66), 15% (HR_{adj} , 2.14), and 20% (HR_{adj} , 2.76; Table 3). The estimated risk of SCD event at 5 years also increased in an incremental manner with respect to %LGE, ranging from 4.9% in patients with 10% LGE to 8.1% in patients with 20% LGE (Table 3). In addition, when the analysis was restricted to the 598 low-risk patients with all 4 conventional risk factors assessed (and with negative results), the relative risk of SCD events remained essentially unchanged (HR per 10% LGE, 1.62; 95% CI, 1.21–2.37, Wald $\chi^2=9.39$; $P=0.002$).

Enhanced SCD Event Risk Model by LGE

The performance of the multivariate SCD event risk model was improved by the addition of LGE (likelihood ratio $P=0.0075$). The area under the receiver-operating characteristics curve increased from 0.710 (95% CI, 0.632–0.788) to 0.741 (95% CI, 0.664–0.818); the relative integrated discrimination improvement was 0.565 (95% CI, 0.019–3.564); and the NRI was 0.129 (95% CI, 0.003–0.383). This change in the model resulted from patients with SCD events being reclassified from a lower to higher SCD risk category (event NRI, 0.130; nonevent NRI, -0.001). When confined to the low-risk patient subgroup, the relative integrated discrimination improvement was 1.737 (95% CI, 0.044–19.19) and NRI was 0.295 (95% CI, 0.120–0.543; event NRI, 0.172 versus nonevent NRI, 0.123). Internal validation of the risk model using bootstrapping suggested limited degrees of optimism (<8% for all risk factor performance metrics).

Relation of LGE to Systolic Dysfunction (End Stage)

At study entry, 1235 patients had preserved systolic function (EF $\geq 50\%$) and 58 were in the end stage of HCM, characterized by systolic dysfunction (EF $< 50\%$). Twenty-six of those 1235 patients with normal EF evolved to end-stage HCM during follow-up, including 13 with progression to New York Heart Association class III/IV, transplantation, stroke, or heart-failure death.

Amount of LGE at study entry was greater in the 26 patients who developed end-stage HCM during follow-up compared with the 1209 HCM patients in whom systolic function remained within the normal range ($13 \pm 15\%$ versus $3 \pm 6\%$ LGE; $P < 0.0001$; Figure 1). Therefore, the extent of LGE was a strong independent predictor of the development to end-stage HCM (HR_{adj} , 1.80/10% increase in LGE; 95% CI, 1.40–2.40; $P=0.03$; Figure 3 and Table 4). %LGE was not a determinant of adverse heart failure events/mortality in HCM patients with preserved EF ($\geq 50\%$; $P=0.23$).

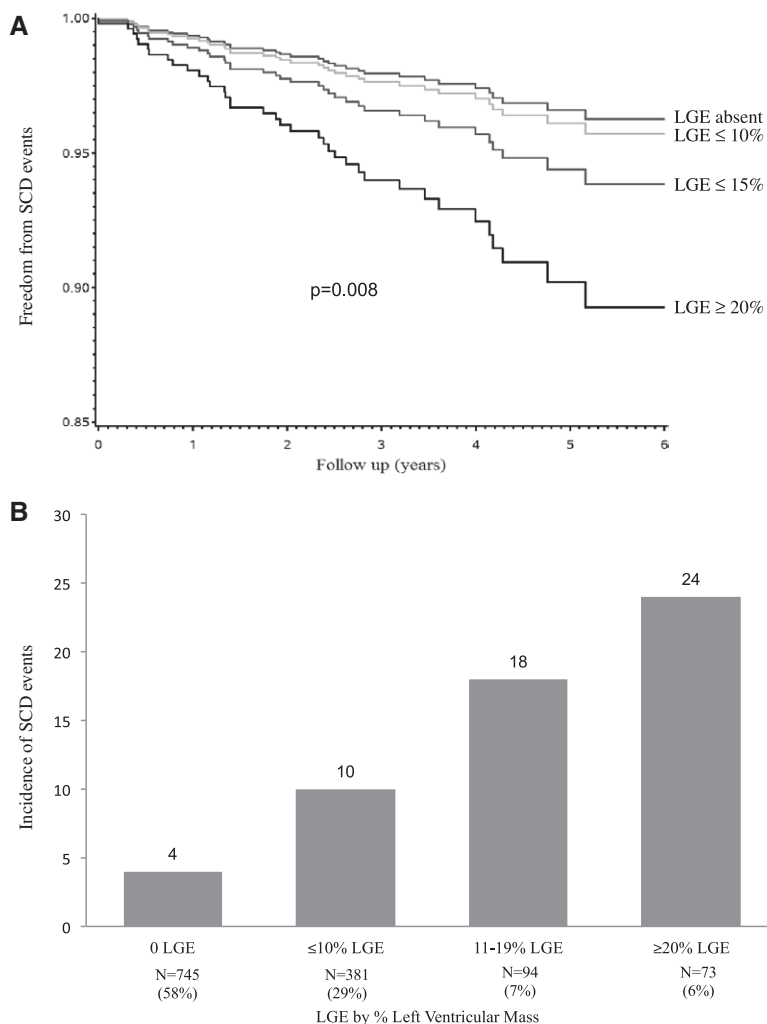


Figure 2. Relation between extent of late gadolinium enhancement (LGE) and sudden cardiac death (SCD) events in 1293 patients with hypertrophic cardiomyopathy. **A**, Hazard plot based on multivariable Cox regression analysis ($P=0.008$). **B**, Incidence of SCD events increased progressively and in direct relation to the extent of LGE ($P<0.001$).

Reproducibility

The visual gray-scale thresholding method was associated with good reproducibility: intraobserver coefficient of variation, $5.9\pm 1.1\%$; interobserver coefficient of variation, $6.3\pm 1.2\%$; and concordance correlation coefficient (ρ_c), 0.996, with minimal bias (bias, $-0.1g$; 95% CI, -3.5 to 3.3).

Discussion

Although effective in promoting the prevention of SCD, current risk stratification strategies in HCM patients do not identify all at-risk patients, largely as a result of the substantial heterogeneity in clinical and phenotypic expression of this genetic disease.^{2,3,5,8,42} Because SCD can occur in HCM patients considered to be at low risk, identification of additional markers to allow more precise selection of those patients who may benefit from primary prevention ICD therapy represents a major clinical aspiration.^{3,28} Recently, considerable interest in using contrast-enhanced CMR to improve the risk stratification model has emerged.⁴³⁻⁴⁸ However, available data on the prognostic value of CMR do not provide an opportunity to specifically predict SCD risk for individual HCM patients.^{28,29} In the present large, multicenter HCM cohort,

we have investigated LGE as a predictor of SCD and other adverse disease consequences among a predominantly lower-risk cohort of HCM patients.

Our data show that in the overall HCM study cohort ($n=1293$), extensive LGE remained an important marker of increased risk for SCD, even after adjustment for other relevant disease variables, including EF. Notably, a continuous relationship between risk of SCD and amount of LGE emerged as a general principle. Compared with patients without LGE, SCD risk increased substantially across the range of LGE amounts, with LGE $\geq 15\%$ of the LV mass conferring a >2 -fold risk in patients otherwise considered low risk. The 3 model performance metrics we used (ie, area under the receiver-operating characteristics curve, integrated discrimination improvement, and NRI) demonstrated an improvement in the SCD risk model after the addition of LGE, substantiating LGE as a risk marker for SCD in HCM and providing information which exceeded that currently available.^{39,40} In addition, we found that the association between SCD risk and LGE was independent of patient age, although underrepresentation of young patients in our cohort could have influenced this observation.

Perhaps the most important and novel finding of this multicenter study was the unique opportunity to identify SCD

Table 3. Adjusted HRs and Estimated 5-Year Sudden Cardiac Death Event Rates for the HCM Cohort and the Low-Risk Subgroup Without Conventional Risk Markers

%LGE	Adjusted HR Point Estimate*	95% CI	Estimated 5-y SCD event rate (%)	95% CI
Total cohort				
0	1.0	...	3.4	2.0–4.8
1	1.04	1.01–1.06	3.5	2.1–5.0
5	1.21	1.07–1.34	4.1	2.5–5.6
10	1.46	1.12–1.92	4.9	3.0–6.7
15	1.77	1.22–2.43	5.8	3.4–8.1
20	2.14	1.30–3.26	6.9	3.7–10.0
25	2.59	1.40–4.39	8.2	3.8–12.4
30	3.13	1.49–5.90	9.8	3.7–15.4
40	4.59	1.70–10.65	15.0	2.7–25.7
Low risk				
0	1.0	...	3.0	1.4–4.6
1	1.05	1.02–1.08	3.2	1.5–4.8
5	1.29	1.11–1.49	3.8	2.0–5.7
10	1.66	1.24–2.23	4.9	2.6–7.3
15	2.14	1.38–3.32	6.3	3.1–9.4
20	2.76	1.54–4.95	8.1	3.4–12.5
25	3.56	1.71–7.38	10.3	3.5–16.6
30	4.58	1.91–11.01	13.0	3.0–22.1
40	7.61	2.36–24.5	20.7	0–37.6

CI indicates confidence interval; HR, hazard ratio; LGE, late gadolinium enhancement; and SCD, sudden cardiac death.

*Adjusted for number of conventional sudden death risk factors and left ventricular ejection fraction.

risk among an important but underrecognized subgroup of predominantly asymptomatic HCM patients previously considered (from current clinical criteria) to be at low risk for lethal ventricular tachyarrhythmias. Without the application of contrast-enhanced CMR to HCM, these patients would potentially remain unprotected against SCD, with no impetus to implant ICDs for primary prevention.^{7,10} Because a substantial portion of clinically identified HCM patients do not demonstrate acknowledged risk factors sufficient to be definitely regarded at increased risk,^{4,5} CMR alone could identify some of these unrecognized high-risk patients who could potentially benefit from this enhanced risk stratification model.⁷

However, we would like to emphasize that an essential element of these data is the linear relation between %LGE and SCD event risk, which avoids the imposition of a single and rigid LGE cut point (eg, $\geq 15\%$). Indeed, using graded risk levels (depicted in Table 3) is a more realistic and clinically useful strategy for estimating relative risk. It allows prophylactic ICD decisions to be resolved in the context of the continuous relation between %LGE and SCD risk, in accord with the wishes of the fully informed and autonomous patient and the managing cardiologist and in agreement with what constitutes an unacceptable level of risk.⁴⁹

In addition, our results support a role for %LGE with contrast-enhanced CMR as a novel imaging marker to aid in more accurately identifying patients at risk for SCD who otherwise may have some evidence of enhanced risk.⁵⁰ For example, 15% LGE was associated with an almost 2-fold increase in SCD event risk in patients with ≥ 1 risk factors compared with patients with risk factors (but without LGE). This consideration becomes a useful clinical tool for those HCM patients situated in the ambiguous gray zone of HCM risk stratification because, not uncommonly, a single risk marker may be poorly or incompletely defined. In such cases, extensive LGE can act as a potential arbitrator for resolving otherwise ambiguous ICD decisions.

Previous contrast-enhanced CMR studies in HCM have focused largely on the association between the presence of LGE and SCD.^{45–48} However, evidence of any amount of LGE per se cannot be regarded as a risk marker because this designation attributes equal predictive weight to a broad spectrum of LGE amounts (eg, from minimal to extensive). Furthermore, assigning increased risk to HCM patients on the basis of solely the presence of LGE per se conveys an impractical and clinically imprudent message, given that most CMR studies report some LGE in $>50\%$ of HCM patients.^{29,43,44,47} By inference, most such HCM patients could theoretically be regarded as potential candidates for primary prevention ICDs, including a very large proportion who would not benefit from this therapy and could be exposed only to potential device complications.^{3,4,7}

On the other hand, the absence of LGE itself was associated with lower risk of SCD events, which may serve to influence decision making against ICD implantation in those patients for whom high-risk status remains uncertain on the basis of conventional risk stratification. Nevertheless, we should note that the absence of LGE was not absolutely protective against SCD risk in this cohort, suggesting that susceptibility to potentially lethal ventricular tachyarrhythmias in HCM can be influenced by factors other than myocardial fibrosis.¹⁴ We also recognize that although focal LGE can be assessed reliably in the vast majority of patients, technical limitations occasionally make precise quantification of small amounts of LGE challenging. However, the incremental increase in absolute SCD event risk associated with very small amounts of LGE (ie, in the range of 1%–5%) is trivial and does not differ significantly from that in patients without LGE. Greater insights into this issue of LGE and SCD risk could be achieved through the emergence of novel CMR techniques (eg, T1 mapping), which could provide an even more robust assessment of the abnormal myocardial substrate in HCM.⁵¹

Our data also identify an association between extensive LGE (presumably a marker for replacement fibrosis) and progressive heart failure with systolic dysfunction (ie, end-stage HCM).⁵² In the present study, we have also shown prospectively that in patients with preserved systolic function at study entry, extensive amounts of LGE can be predictive of subsequent remodeling and evolution to the end stage.³⁴ Indeed, a continuous relationship between future development of end-stage HCM and %LGE was demonstrated, with $\geq 20\%$ LGE conveying a >3 -fold increase in risk (compared with patients without LGE).

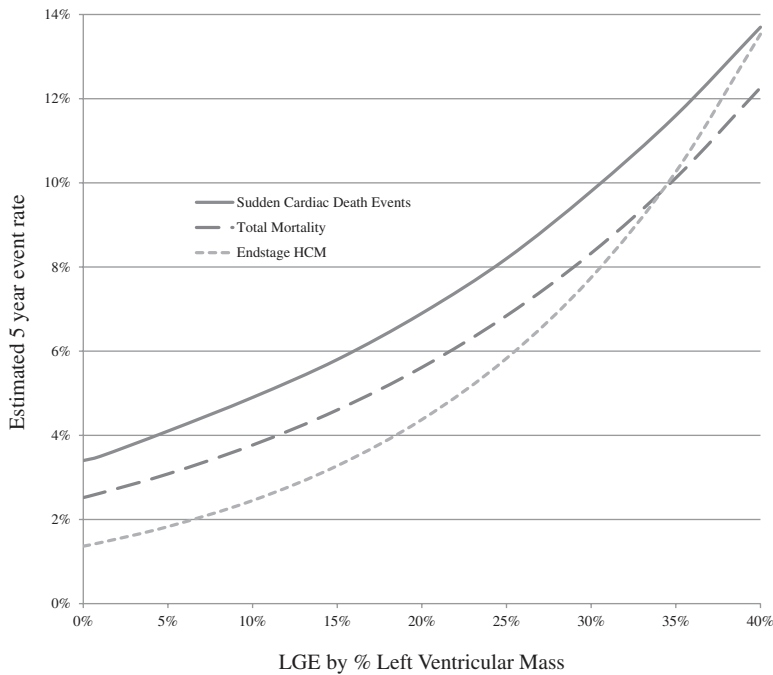


Figure 3. Predicted 5-year event rates relative to late gadolinium enhancement (LGE) by percent left ventricular mass for risk of end-stage HCM with systolic dysfunction, sudden cardiac death events, and total mortality.

The capability to prospectively identify patients who will progress to the end stage is clinically relevant by permitting anticipation of changes in clinical course and management strategies, including tailored drug administration and early consideration for heart transplantation and prophylactic defibrillators.^{3,4,34}

Limitations

A certain degree of preference with respect to patient selection was unavoidable within our study design because of the exclusion of some high-risk patients in whom ICDs were implanted before CMR. As a result, the present large,

Table 4. Results of Univariate and Multivariable Cox Proportional-Hazards Analyses of the Relation Between Baseline Clinical Variables and Outcome

Variable	Sudden Death Event, Univariate Analysis		Sudden Death Event, Multivariable Analysis*		Death Resulting From Any Cause, Univariate Analysis		Death Resulting From Any Cause, Multivariable Analysis†		Development of End-Stage HCM, Univariate Analysis		Development of End-Stage HCM, Multivariable Analysis‡	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
%LGE (per 10% increase)	1.50 (1.22–1.85)	0.0001	1.46 (1.12–1.92)	0.002	1.35 (1.07–1.71)	0.01	1.51 (1.13–2.01)	0.006	1.89 (1.47–2.43)	<0.0001	1.80 (1.40–2.40)	0.03
Age (per decade increase)	0.93 (0.77–1.12)	0.44	NA	NA	1.67 (1.37–2.05)	<0.0001	1.67 (1.34–2.08)	<0.0001	1.01 (0.82–1.26)	0.91	NA	NA
Sudden death risk factors	1.39 (0.89–2.16)	0.15	1.17 (0.74–1.85)	0.80	0.64 (0.37–1.09)	0.10	0.48 (0.26–0.89)	0.02	0.90 (0.50–1.63)	0.41	1.04 (0.68–1.58)	0.87
LV mass (per 10 g increase)	1.01 (0.97–1.05)	0.76	NA	NA	1.00 (0.96–1.04)	0.79	NA	NA	0.99 (0.94–1.05)	0.79	NA	NA
LVEF (per 10% decrease)	1.26 (0.82–1.72)	0.14	0.99 (0.69–1.42)	NA	1.41 (1.06–1.84)	0.02	1.22 (0.90–1.65)	0.20	4.29 (2.46–7.46)	<0.0001	2.63 (2.12–3.23)	NA

LGE indicates late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; left ventricular outflow tract obstruction; and NA, not applicable. *Adjusted for number of conventional sudden death risk factors and LVEF. Sensitivity analysis using age, LV mass, maximal LV wall thickness, left ventricular outflow tract obstruction, and septal reduction therapy did not change effect estimates. †Adjusted for age, conventional sudden death risk factors, and LVEF. Sensitivity analysis using LV mass, maximal LV wall thickness, left ventricular outflow tract obstruction, and septal reduction therapy did not change effect estimates. ‡Adjusted for conventional sudden death risk factors and LVEF. Sensitivity analysis using age, LV mass, left ventricular outflow tract obstruction, and septal reduction therapy did not change effect estimates.

Table 5. Univariate and Bivariate Analyses of the Extent of LGE Versus Conventional Sudden Death Risk Factors Among 1293 HCM Patients

	Univariate HR (95% CI)	Model Global Wald χ^2	P Value	Bivariate HR (95% CI)	P	Model Global Wald χ^2	P Value	P Value, Univariate vs Bivariate
Massive LVH	0.92 (0.22–3.84)	0.0122	0.91	0.72 (0.17–2.99)	0.65	14.478	0.0007	0.0001
%LGE (per 10% increase)	1.50 (1.22–1.85)	13.894	<0.001	1.50 (1.22–1.85)	<0.001			
Syncope	1.18 (0.42–3.32)	0.0945	0.76	1.07 (0.38–3.06)	0.90	14.023	0.0009	0.0001
%LGE (per 10% increase)	1.50 (1.22–1.85)	13.894	<0.001	1.49 (1.21–1.84)	<0.001			
Family History of SCD	1.19 (0.52–2.70)	0.164	0.686	1.05 (0.45–2.43)	0.91	13.966	0.0009	0.0002
%LGE (per 10% increase)	1.50 (1.22–1.85)	13.894	<0.001	1.49 (1.20–1.85)	<0.001			
Non sustained VT	1.97 (0.95–4.07)	3.349	0.0672	1.61 (0.77–3.36)	0.21	14.741	0.0006	0.0007
%LGE (per 10% increase)	1.50 (1.22–1.85)	13.894	<0.001	1.46 (1.17–1.82)	<0.001			
Sudden death risk factors (per risk factor)	1.37 (0.88–2.14)	1.896	0.17	1.17 (0.74–1.85)	0.51	14.373	0.0008	0.0004
%LGE (per 10% increase)	1.50 (1.22–1.85)	13.894	<0.001	1.46 (1.17–1.82)	0.0009			

CI indicates confidence interval; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; and VT, ventricular tachycardia.

multicenter HCM cohort was made up predominantly of patients at low risk for sudden death. In addition, HCM is generally a low-event-rate disease,^{3,5,6} contributing to the relatively small number of patients with sudden death in this study cohort. These notable features of our study design and patient selection may also have influenced our analysis supporting LGE as statistically a stronger predictor of SCD events than each of the individual conventional risk factors used in HCM. Therefore, these data should not obscure the time-honored efficacy of the current conventional risk factor model for identifying high-risk patients documented to have substantial benefit for prevention of sudden death with prophylactic ICD therapy, which has served the HCM patient population so well over the last 15 years. Finally, although the present data were assembled by necessity in HCM referral centers, the results should nevertheless have implications for the broader HCM disease spectrum, given that the clinical profile of our cohort is similar to that reported in the HCM literature with respect to demographics, %LGE, and outcome rates.^{2,4,43–45} Furthermore, with the growing penetration of CMR into clinical cardiovascular practice,¹⁷ our referral center–derived data should become increasingly applicable to patient decision making. Notably, in 17 of our 37 sudden death events, the ICD detected arrhythmias that may not have been fatal in the absence of an ICD, based on inferences from randomized defibrillator trial data in patients with coronary artery disease.⁵³

Conclusions

Although the present data do not resolve all remaining questions in the arena of risk stratification for the HCM patient population, the capability of contrast-enhanced CMR to identify extensive LGE advances the risk stratification strategy in this disease by providing the opportunity to potentially recognize additional patients at increased risk for SCD events. Conversely, the absence of LGE was associated with lower risk of SCD events. In addition, extensive LGE was

predictive of adverse LV remodeling with systolic dysfunction (end-stage HCM) and therefore proved to be associated with 2 diverse consequences of HCM.

Disclosures

None.

References

- Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J*. 1958;20:1–8.
- Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687–1713.
- Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. *Circulation*. 2010;121:445–456.
- Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rawkowski H, Seidman CE, Towbin JA, Udelsman JE, Yancy CW. 2011 ACCF/AHA guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol/Circulation*. 2011;58:212–260.
- Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol*. 2000;36:2212–2218.
- Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet*. 2013;381:242–255.
- Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA 3rd, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;298:405–412.
- 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.
- Bongioanni S, Spirito P, Masi AS, Chiribiri A, Bonamini R, Conte MR. Extensive myocardial fibrosis in a patient with hypertrophic cardiomyopathy and ventricular tachycardia without traditional high-risk features. *Circ Cardiovasc Imaging*. 2009;2:349–350.

10. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, Estes NA 3rd, Spirito P. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:365–373.
11. Jayatilake I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, Semsarian C. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. *Am J Cardiol*. 2004;93:1192–1194.
12. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes NA 3rd, Shannon KM, Ashley EA, Day SM, Pacileo G, Formisano F, Devoto E, Anastakis A, Bos JM, Woo A, Autore C, Pass RH, Boriani G, Garberich RF, Almquist AK, Russell MW, Boni L, Berger S, Maron MS, Link MS. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2013;61:1527–1535.
13. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol*. 2003;42:873–879.
14. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;45:697–704.
15. Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. *J Am Coll Cardiol*. 2000;35:36–44.
16. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol*. 2000;31:988–998.
17. Pennell DJ. Cardiovascular magnetic resonance. *Circulation*. 2010;121:692–705.
18. Rochitte CE, Tassi EM, Shiozaki AA. The emerging role of MRI in the diagnosis and management of cardiomyopathies. *Curr Cardiol Rep*. 2006;8:44–52.
19. Moon JC, McKenna WJ. The emerging role of cardiovascular magnetic resonance in refining the diagnosis of hypertrophic cardiomyopathy. *Nat Clin Pract Cardiovasc Med*. 2009;6:166–167.
20. Alpendurada F, O'Hanlon R, Prasad SK. Cardiovascular magnetic resonance of cardiomyopathies. *Curr Cardiol Rep*. 2009;11:61–69.
21. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, Petrou M, Pennell DJ. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;43:2260–2264.
22. Kim RJ, Judd RM. Gadolinium-enhanced magnetic resonance imaging in hypertrophic cardiomyopathy: in vivo imaging of the pathologic substrate for premature cardiac death? *J Am Coll Cardiol*. 2003;41:1568–1572.
23. Kwon DH, Smedira NG, Rodriguez ER, Tan C, Setser R, Thamilarasan M, Lytle BW, Lever HM, Desai MY. Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy: correlation with histopathology and prevalence of ventricular tachycardia. *J Am Coll Cardiol*. 2009;54:242–249.
24. Papavassiliu T, Schnabel P, Schröder M, Borggrefe M. CMR scarring in a patient with hypertrophic cardiomyopathy correlates well with histological findings of fibrosis. *Eur Heart J*. 2005;26:2395.
25. Kwon DH, Setser RM, Popović ZB, Thamilarasan M, Sola S, Schoenhagen P, Garcia MJ, Flamm SD, Lever HM, Desai MY. Association of myocardial fibrosis, electrocardiography and ventricular tachyarrhythmia in hypertrophic cardiomyopathy: a delayed contrast enhanced MRI study. *Int J Cardiovasc Imaging*. 2008;24:617–625.
26. Fluechter S, Kuschyk J, Wolpert C, Doesch C, Veltmann C, Haghi D, Schoenberg SO, Sueselbeck T, Germans T, Streitner F, Borggrefe M, Papavassiliu T. Extent of late gadolinium enhancement detected by cardiovascular magnetic resonance correlates with the inducibility of ventricular tachyarrhythmia in hypertrophic cardiomyopathy. *J Cardiovasc Magn Reson*. 2010;12:30.
27. Aquaro GD, Masci P, Formisano F, Barison A, Strata E, Pingitore A, Positano V, Spirito P, Lombardi M. Usefulness of delayed enhancement by magnetic resonance imaging in hypertrophic cardiomyopathy as a marker of disease and its severity. *Am J Cardiol*. 2010;105:392–397.
28. Salerno M, Kramer CM. Prognosis in hypertrophic cardiomyopathy with contrast-enhanced cardiac magnetic resonance: the future looks bright. *J Am Coll Cardiol*. 2010;56:888–889.
29. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Cardiovasc Magn Reson*. 2012;14:13.
30. Maron MS, Appelbaum E, Harrigan CJ, Buros J, Gibson CM, Hanna C, Lesser JR, Udelson JE, Manning WJ, Maron BJ. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2008;1:184–191.
31. Biagini E, Lorenzini M, Olivetto I, Rocchi G, Lovato L, Lai F, Rosmini S, Pazzi C, Pasquale F, Reggiani ML, Fattori R, Rapezzi C. Effects of myocardial fibrosis assessed by MRI on dynamic left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy: a retrospective database analysis. *BMJ Open*. 2012;2:e001267.
32. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. 2002;287:1308–1320.
33. Maron BJ, Olivetto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation*. 2000;102:858–864.
34. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation*. 2006;114:216–225.
35. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.
36. Harrigan CJ, Peters DC, Gibson CM, Maron BJ, Manning WJ, Maron MS, Appelbaum E. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. *Radiology*. 2011;258:128–133.
37. Maron MS. Contrast-enhanced CMR in HCM: what lies behind the bright light of LGE and why it now matters. *JACC Cardiovasc Imaging*. 2013;6:597–599.
38. Moravsky G, Ofek E, Rakowski H, Butany J, Williams L, Ralph-Edwards A, Wintersperger BJ, Crean A. Myocardial fibrosis in hypertrophic cardiomyopathy: accurate reflection of histopathological findings by CMR. *JACC Cardiovasc Imaging*. 2013;6:587–596.
39. Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176:473–481.
40. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172.
41. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
42. Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivetto I, Biller L, Lesser JR, Udelson JE, Manning WJ, Appelbaum E. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2009;54:220–228.
43. O'Hanlon R, Grasso A, Roughton M, Smith G, Alpendurada FD, Wong J, Dahl A, Oxborough D, Godfrey R, Sharma S, Roughton M, George K, Pennell DJ, Whyte G, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:867–874.
44. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, Nassenstein K, Schlosser T, Sabin GV, Sechtem U, Mahrholdt H. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:875–887.
45. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, Bos JM, Tajik AJ, Valeti US, Nishimura RA, Gersh BJ. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail*. 2010;3:51–58.
46. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging*. 2012;5:370–377.
47. Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy

- with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2003;41:1561–1567.
48. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, Bonow RO, Judd RM, Kim RJ. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:2156–2164.
 49. Hauser RG, Maron BJ. Lessons from the failure and recall of an implantable cardioverter-defibrillator. *Circulation*. 2005;112:2040–2042.
 50. O'Mahony C, Jichi F, Pavlou M, Monserrat C, Anastakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott, PM. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD) [published online ahead of print October 14, 2013]. *Eur Heart J*. doi: 10.1093/eurheartj/eh439. <http://eurheartj.oxfordjournals.org/content/early/2013/10/14/eurheartj.eht439.long>. Accessed September 26, 2013.
 51. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2011;57:891–903.
 52. Olivetto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, Udelson JE, O'Donnell C, Lesser JR, Manning WJ, Maron MS. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;106:261–267.
 53. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. *J Am Coll Cardiol*. 2008;52:1111–1121.

CLINICAL PERSPECTIVE

Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death (SCD) in young patients, although identifying all at-risk patients remains challenging. Recently, contrast-enhanced cardiovascular magnetic resonance with late gadolinium enhancement (LGE) has emerged as an important imaging marker of myocardial fibrosis, a structural nidus for the generation of potentially lethal ventricular tachyarrhythmias. Therefore, we assessed whether extent of LGE provided additional prognostic information in assessing cardiovascular outcome among a large cohort of 1293 patients with hypertrophic cardiomyopathy eligible for cardiovascular magnetic resonance. Amount of LGE was associated with an increased risk of SCD events (including appropriate defibrillator interventions), with every 10% increase in LGE associated with a 40% increase in relative risk of SCD events, even after adjustment for relevant clinical variables, including the conventional sudden death risk factors. In addition, among the subgroup of patients with hypertrophic cardiomyopathy judged otherwise to be at lower risk, extensive LGE ($\geq 15\%$ of the left ventricular mass) identified a 2-fold greater risk of SCD events with an estimated likelihood of SCD events of 6% at 5 years. In addition, the absence of LGE was associated with a lower risk of SCD events (adjusted hazard ratio, 0.39; $P=0.02$). These findings demonstrate that extensive LGE is a novel imaging marker that may identify patients with hypertrophic cardiomyopathy at increased risk for SCD events who otherwise would not be considered high risk on the basis of the conventional risk stratification strategy and who may become candidates for primary prevention of SCD with an implantable defibrillator. The absence of LGE is associated with low risk, providing a measure of reassurance for patients.

SUPPLEMENTAL MATERIAL

Visual LGE Quantification Method

First, the short-axis LGE images should be manually segmented for epicardial and endocardial borders to define the myocardial volume, taking care to exclude the papillary muscles and blood pool (Supplemental Figure 1A). This is performed in a manner identical to that used when quantifying LV morphologic parameters on the cine short-axis stack. Next, as the intensity threshold slider is activated, a “grayscale” threshold (red, in this example) will automatically appear in the myocardium (Supplemental Figure 1B). Adjust the grayscale intensity threshold slider so that all visually apparent hyperintense (bright areas) are completely filled in by the grayscale threshold (Supplemental Figure 1C). The image should then be inspected to confirm that only areas of high signal intensity within the LV myocardial borders are included by the grayscale threshold. Particular attention should be given to make sure that no portion of the bright blood pool of the LV cavity has been included. The LGE image can be compared to the cine image in the same imaging plane to help differentiate areas of myocardial LGE (which should be included) from that of blood pool (which should not be included). If necessary, using a separate set of editing tools, additional minor adjustments to the image analysis can be performed such as including areas of LGE not identified using the intensity threshold slider (Supplemental Figure 1D) or excluding areas of the myocardium which should not be included. The same process should be repeated for each LV short-axis slice, after which the analysis program will automatically calculate the total amount of LGE (in grams) which can also be expressed as a % of the total LV myocardium. The process can also be viewed using the on-line video supplement.

Rational for Visual LGE Quantification Method

For the purposes of this study, we chose a method in which visually identified areas of increased signal intensity within the myocardium were used to define LGE. Based on our previous study¹ and also that of other investigators^{2,3} the visual grayscale technique results in an amount of LGE that is nearly identical to that obtained using a grayscale threshold ≥ 6 SD above the mean SI of normal myocardium ($r=0.913$; $p=0.001$). We have provided additional data derived from the present cohort in the form of a Bland Altman plot (Supplemental Figure 2) and dot plot and regression line equation (Supplemental Figure 3), which substantiates good correlation between the 2 methods for %LGE (mean bias of +1.2%; 95% CI -4.3 to +6.6% and $R^2 = 0.88$, respectively). Furthermore, we found no difference in terms of patient outcome (including sudden death events), when the amount of LGE in our current dataset was analyzed using a 6SD threshold in comparison to visual determination. In this regard, the Supplemental Table 1 below compares the hazard ratios for sudden death using visual and 6SD methods of defining LGE, and the effect estimates are remarkably similar.

The visual method provides a number of unique advantages over the 6SD threshold, including the opportunity for the individual reader to adjust the threshold (“hands on and in real time”) in order to identify LGE (See Video Supplement), while in the process excluding areas of signal intensity which can result from incomplete nulling or image artifact. On the other hand, 6SD is solely dependent on an automated calculation of LGE, after the ROI is drawn, which can result in underestimation of the amount of LGE, particularly if the ROI is placed in a region of myocardium with even a small amount of hyperenhanced pixels (rather than a completely normal area) or if there is incomplete “nulling” of the myocardium.⁴ The visual method also requires less time to perform (<10 minutes on average).

Finally, we have previously demonstrated an association between intermediate signal intensity LGE (ie., “grey-zone”; subtracting the amount of myocardium at ≥ 6 SD from that at ≥ 4 SD) and ambulatory nonsustained VT.⁵ In this study we also quantified the “grey-zone” but found intermediate LGE was *not* a better predictor of actual sudden death events compared to the visual quantification technique. For all these reasons, we concluded that the visual LGE quantification method was the most applicable strategy for our data and to promote to the practicing community.

Supplemental Table 1. Adjusted Hazard Ratios by extent of LGE for visual and 6SD

%LGE	VISUAL METHOD			6SD METHOD		
	Adjusted HR (p<0.01)	95% C.I.		Adjusted HR (p=0.03)	95% C.I.	
0%	1.00	-	-	1.00	-	-
1%	1.04	1.01	1.07	1.03	1.00	1.06
5%	1.21	1.06	1.38	1.17	1.02	1.32
10%	1.46	1.12	1.92	1.38	1.04	1.75
15%	1.77	1.18	2.65	1.62	1.05	2.32
20%	2.14	1.25	3.67	1.90	1.07	3.07
25%	2.59	1.32	5.08	2.23	1.09	4.06
30%	3.13	1.40	7.04	2.61	1.11	5.37
40%	4.59	1.56	13.48	3.59	1.15	9.41

Abbreviations: CI = confidence interval; LGE = late gadolinium enhancement; HR = hazard ratio; SD = standard deviation

Supplemental Table 2. Demographic and Clinical Characteristics of 1293 HCM Patients by Center

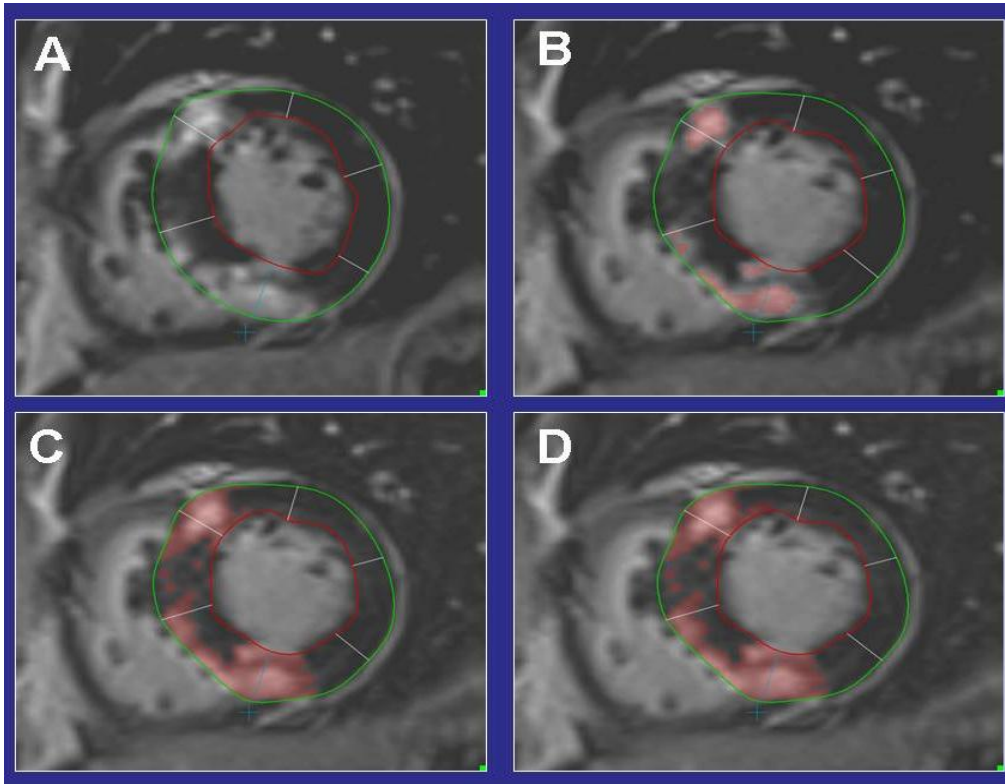
	Minnesota Heart Institute Foundation	Tufts Medical Center	Genoa	Rome	Florence	Bologna	Toronto
No. Patients	484	248	64	49	165	64	219
Male, n (%)	334(69)	170(69)	43(67)	27(55)	92(56)	38(59)	154(70)
Age, yr	44±18	47±18	42±14	48±17	45±16	52±15	51±15
Duration of follow-up, yr (median, IQR)	3.7 (2.2-5.2)	2.8 (2.1-3.9)	4.9 (4.0-5.4)	2.9 (2.3-3.2)	3.3 (2.5-4.2)	3.1 (2.5-3.9)	3.1 (2.3-3.9)
Risk factors Mean 0/1/2/3 risk factors	0.48 288(60)/163(34)/ 32(7)/1(0.2)	0.33 179(72)/59(24)/ 8(3)/2(0.8)	0.36 43(67)/19(30)/ 2(3)/0(0)	0.62 25(51)/18(37)/ 6(12)/0(0)	0.54 92(56)/58(35)/ 14(8)/1(0.6)	0.73 29(45)/24(38)/ 10(16)/1(1.6)	0.51 126(58)/74(34)/ 18(8)/1(0.5)
NYHA class, mean	1.5±0.7	1.8±0.8	1.5±0.7	1.5±0.6	1.6±0.8	1.5±0.7	1.6±0.7
SD events, n	16	10	2	2	1	1	5
Maximum wall thickness (mm)	20±5	20±5	19±5	19±5	20±6	20±5	19±6
LV mass index (g/m ²)	90±35	80±29	82±22	77±29	79±36	89±31	76±36
LVOT gradient >30mmHg, n (%)	103 (21)	88(36)	17 (27)	12 (24)	36 (22)	20 (31)	41(19)
LGE, n(%)	202 (42)	98 (42)	38(60)	13 (28)	72 (46)	30 (48)	97 (46)
LGE, g (median, IQR)	10 (4-21)	4 (2-13)	11 (6-29)	18 (12-23)	9 (3-25)	10 (6-21)	10 (4-24)
%LGE (median,	5	3	6	8	6	7	6

IQR)	(2-11)	(2-6)	(4-16)	(6-12)	(3-15)	(3-13)	(3-15)
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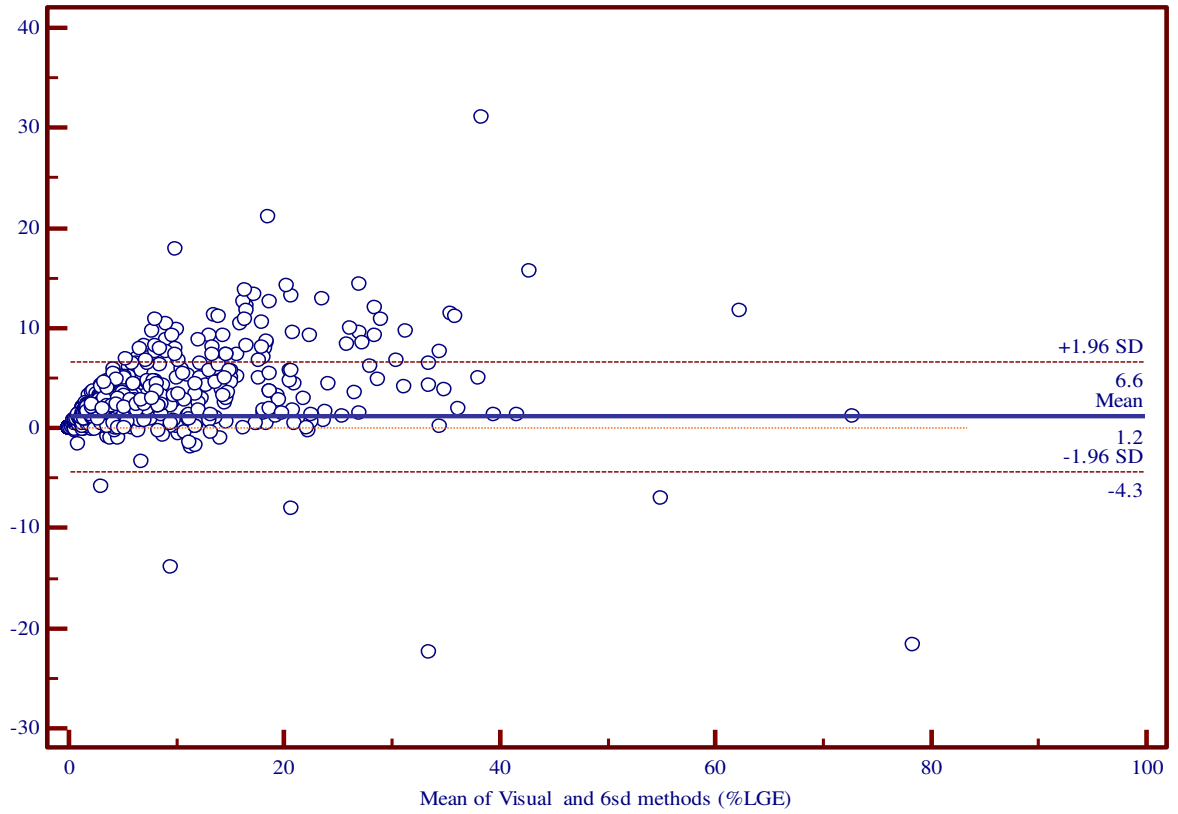
Abbreviations:

IQR = Inter-quartile range; NYHA = New York Heart Association; LGE = late gadolinium enhancement; LV = left-ventricular; LVOT = left ventricular outflow tract; HCM=hypertrophic cardiomyopathy; SD = sudden death.

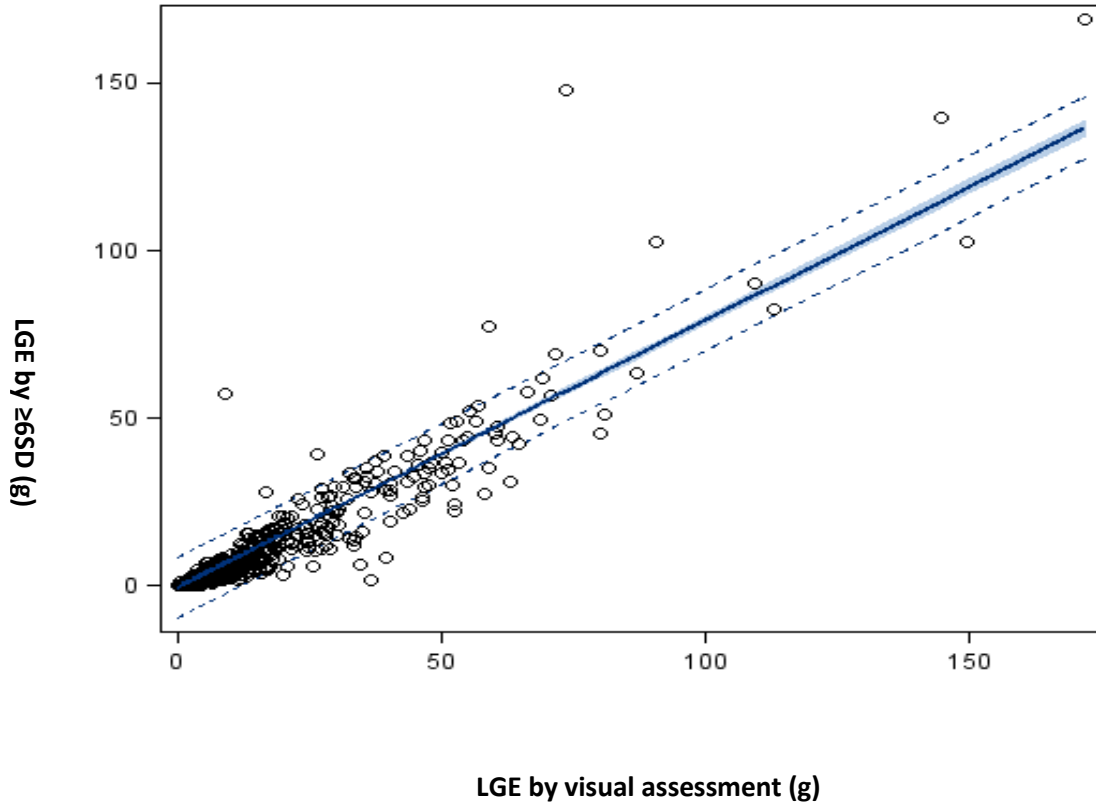
Supplemental Figure 1. Visual Quantification of Late Gadolinium Enhancement



Supplemental Figure 2. Bland Altman plot showing relation between LGE quantified at ≥ 6 SD threshold compared to visual technique



Supplemental Figure 3. Relation between LGE quantified at ≥ 6 SD threshold compared to visual technique



Legend

Supplemental Figure 1. Visual Quantification of Late Gadolinium Enhancement

Supplemental Figure 2. Bland Altman plot showing relation between LGE quantified at ≥ 6 SD threshold compared to visual technique

Supplemental Figure 3. Relation between LGE quantified at ≥ 6 SD threshold compared to visual technique

Video. Visual late gadolinium enhancement quantification method in hypertrophic cardiomyopathy.

Supplemental References

1. Harrigan CJ, Peters DC, Gibson CM, et al. Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. *Radiology* 2011;258:128-33.
2. Flett AS, Hasleton J, Cook C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2011;4:150-6.
3. Spiewak M, Malek LA, Misko J, et al. Comparison of different quantification methods of late gadolinium enhancement in patients with hypertrophic cardiomyopathy. *European journal of radiology* 2010;74:e149-53.
4. Kwong RY, Farzaneh-Far A. Measuring myocardial scar by CMR. *JACC Cardiovasc Imaging* 2011;4:157-60.
5. Appelbaum E MB, Adabag S, Hauser TH, Lesser JR, Haas TS, Riley A, Harrigan CJ, Delling F, Udelson JE, Gibson CM, Manning WJ, Maron MS. Extent of Intermediate Signal Intensity Late Gadolinium Enhancement Predicts Ventricular Tachyarrhythmias in Patients with Hypertrophic Cardiomyopathy. *Circ Cardiovasc Imaging* 2012;5:78-85.

Prognostic Value of Quantitative Contrast-Enhanced Cardiovascular Magnetic Resonance for the Evaluation of Sudden Death Risk in Patients With Hypertrophic Cardiomyopathy

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Circulation. 2014;130:484-495

doi: 10.1161/CIRCULATIONAHA.113.007094

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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