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Original article

The value of cardiac magnetic resonance and distribution of late gadolinium enhancement for risk stratification of sudden cardiac death in patients with hypertrophic cardiomyopathy

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ABSTRACT

Background: The presence of late gadolinium enhancement (LGE) in hypertrophic cardiomyopathy (HCM) is associated with worse clinical outcome and the extent of LGE predicts the increased risk of sudden cardiac death (SCD). Limited data exist regarding the distribution of LGE. We attempted to verify whether the presence of LGE outside the interventricular insertion points carries additional risk for patients with HCM.

Methods: In this prospective study, 328 patients with HCM, who underwent cardiac magnetic resonance (CMR) were enrolled. Five major risk factors for SCD were assessed in all patients. The median follow-up was 37 months.

Results: LGE was detected in 226 (68.9%) patients. In 70 (21.3%) patients it was present only at the interventricular insertion points – LGE (+) group, while in 156 (47.6%) it was noted in other locations – LGE (++) group. Primary endpoint defined as SCD or appropriate implantable cardioverter-defibrillator intervention occurred in 14 (4.3%) patients, one in LGE (+) and 13 in LGE (++). In multivariable analysis including five traditional risk factors and left ventricular ejection fraction <50%, only the presence of LGE outside the insertion points was a significant predictor of SCD/aborted SCD (HR 10.01, 95% CI 1.21–83.86, $p = 0.033$). The performance of the multivariable sudden cardiac death risk model was improved by the addition of LGE (++) to the traditional risk factors (likelihood ratio $p = 0.005$). The Kaplan–Meier curves showed better event-free survival in the LGE (−) and LGE (+) patient groups compared to the LGE (++) group.

Conclusions: In HCM patients, presence of LGE outside interventricular insertion points is associated with increased risk of sudden cardiac death or its equivalent as well as overall mortality. Cardiac fibrosis as a substrate for SCD in HCM may be identified on CMR and serve as an imaging biomarker of increased risk.

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Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most frequently occurring genetic disorders of the heart muscle [1]. It is typically defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions [2,3]. In the past years, HCM was regarded as a rare disease with serious prognosis [4]. Numerous reports have shown, however, that it is much more frequent and characterized by variable outcome [5]. The majority of patients have near-normal life span without special treatment requirements [6]. Average mortality in HCM patients is around 1% per year. On the other hand in some, often asymptomatic, patients the risk of sudden cardiac death (SCD) may be significantly greater [7,8]. A lot of research over the past decades has gone into effort aimed at elucidating this group and defining risk factors associated with increased mortality [9–13]. As most SCD episodes in HCM are due to ventricular fibrillation (VF), the most effective way of reducing increased mortality associated with high-risk HCM is implanting the patient with an implantable cardioverter-defibrillator (ICD) [14]. This is recommended for secondary SCD prevention. Less obvious is selecting the patients for primary prevention, as ICD implantation is not free from risk of complications, patient discomfort, psychological burden, and costs [15]. Previous research has shown that the presence of at least one of the so-called large risk factors of SCD in HCM should lead to considering ICD implantation [2,16]. The negative predictive value of this strategy is excellent, but the positive predictive value poor. In effect, the vast majority of patients implanted with ICD will never need a shock. In a paper analyzing 2190 patients with ICD implanted for SCD prevention 14% of patients received appropriate lifesaving shocks; the frequency of inappropriate shocks was 20%, while the complication rate reached 15% [15].

In the European Society of Cardiology (ESC) Guidelines published recently the authors update the decision-making process postulating the use of a novel risk calculator [17]. The clinical and risk factors represented in this novel risk model are those that are generally recognized: age, LV wall thickness, non-sustained ventricular tachycardia (nsVT), family history of SCD, syncope, left atrial diameter, left ventricular outflow tract (LVOT) obstruction. The risk factor left out from the formula is the inappropriate exercise blood pressure response. It seems a great attempt at simplifying the decision-making process, but this empirical risk model is based on a large multicenter, but retrospective analysis [18].

Two studies published recently show that the extent of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) study in HCM patients may be an independent predictor of SCD but previous studies did not analyze all five large risk factors in conjunction with LGE assessment [19,20]. The new guidelines acknowledge the value of CMR, but at the same time, due to limited data, do not support the use of gadolinium contrast-enhanced CMR in SCD risk assessment [17].

The aim of this study was to elucidate the prognostic value of LGE along with full standard SCD risk assessment in prospectively analyzed unselected HCM patients. Specifically, we attempted to verify whether the presence of LGE outside the interventricular insertion points carries additional risk for patients with HCM.

Methods

Study population

Included in the study were 328 consecutive HCM patients with no contraindications to CMR, followed at a single center – the Institute of Cardiology in Warsaw, over the years 2008–2013. CMR imaging was supported financially by a grant from the Polish Ministry of Science and Higher Education. HCM was diagnosed according to standard criteria published in clinical guidelines. From this group we excluded patients with concomitant factors that may have induced significant myocardial fibrosis or scarring. These were patients with known previous myocardial infarction, previous alcohol septal ablation, and myocarditis. Patients with diagnosed Fabry disease and Noonan syndrome were also excluded. CMR images of patients who due to renal impairment had no gadolinium contrast given and of those with incomplete studies due to claustrophobia or arrhythmia were not analyzed either. The study was approved by the Institutional Ethics Committee, with written informed consent obtained from all patients agreeing to the use of their medical information for research purposes. Major risk factors were defined at baseline as: (1) family history of SCD, i.e. one or more cases of SCD among first degree relatives under the age of 40 years (irrespective of HCM diagnosis); one or more SCD/aborted SCD at any age among first-degree relatives diagnosed with HCM; one or more cases of SCD/aborted SCD among second-degree relatives under the age of 50 years and if previously diagnosed with HCM; (2) syncope; history of otherwise unexplained syncope at any time in the past; (3) extreme hypertrophy of the LV muscle (30 mm or more) as assessed by echocardiography; (4) abnormal exercise blood pressure response: increase in systolic blood pressure less than 20 mmHg from baseline to peak exercise or fall by over 10 mmHg at peak exercise; (5) nsVT on 24-h electrocardiogram (ECG) Holter monitoring diagnosed when an episode of at least three consecutive ventricular beats over 120 beats per minute, lasting less than 30 s, was noted. All patients under follow-up had at least one cardiopulmonary or standard exercise test performed (except two with clear symptomatic LVOT obstruction) and at least one 24-h Holter ECG. An nsVT episode in any Holter ECG was sufficient to include this risk factor. Left ventricular wall thickness and LVOT obstruction gradient were measured by echocardiography according to the guidelines. Standard or cardiopulmonary treadmill exercise tests were performed using the modified Bruce protocol.

CMR acquisition and image analysis

All CMR studies were performed on a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany) as previously described [21]. In brief, ECG-gated breath-hold steady state free precession (SSFP) cine images were acquired in the LV long axis (2-, 3- and 4-chamber views) and short axis, covering both ventricles from the base to the apex. LV mass (LVM), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV stroke volume (LVSV), and LV ejection fraction (LVEF) were calculated with the use of the dedicated software (Mass 6.2.1; Medis, Leiden, the Netherlands) on the basis of manual delineation of epicardial and endocardial contours in end-diastole and end-systole. Volume and mass parameters were indexed for body surface area. The acquisition of LGE images was performed 10–15 min after intravenous administration of gadobutrol (Gadovist, Bayer, Berlin, Germany) with the inversion time chosen in order to null normal myocardium. The presence of LGE was divided into three categories: (1) LGE (−) – none LGE; (2) LGE (+) – LGE localized in the right ventricle-left ventricle insertion points only; (3) LGE (++) outside the insertion points (with or without insertion points involvement) (Fig. 1).

Study endpoints and follow-up

The primary endpoint of the study was SCD or its equivalent (aborted SCD) in the form of resuscitated ventricular fibrillation

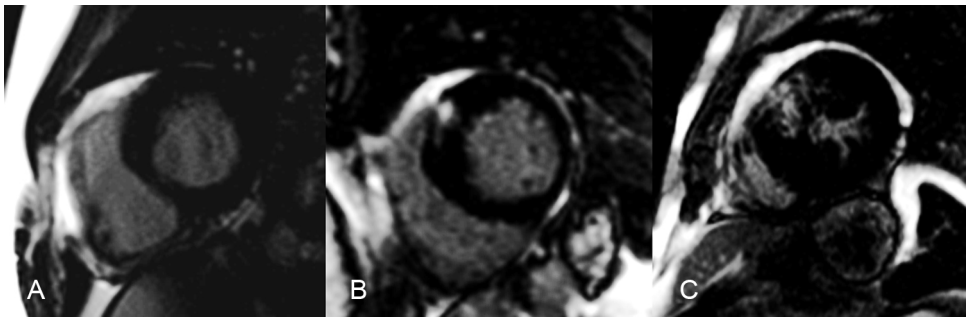

Fig. 1. Representative patterns of LGE distribution in HCM patients identified by CMR. *Left ventricular short-axis images* obtained by CMR from three HCM patients presenting diverse locations of LGE: (A) without LGE, (B) LGE at right ventricular insertion into the anterior septum, LGE (+), and (C) LGE in the anterior ventricular septum and at right ventricular insertion point, LGE (++). LGE, late gadolinium enhancement; HCM, hypertrophic cardiomyopathy; CMR, cardiac magnetic resonance.

(VF) or hemodynamically unstable sustained ventricular tachycardia (VT), or appropriate lifesaving ICD intervention. There were two composite secondary endpoints: (1) primary endpoint and cardiovascular death; (2) primary endpoint and death of any cause. SCD was defined as unexpected death either within 1 h of cardiac symptoms or in a patient who previously had a relatively uneventful clinical course. Aborted SCD was diagnosed in patients who received an appropriate ICD discharge for ventricular arrhythmia or had a non-fatal episode of VF or spontaneous sustained ventricular tachycardia (VT) (>30 s in duration) causing hemodynamic compromise and/or requiring cardioversion.

The date and cause of death were determined using a combination of death certificates and communication with patients' family and hospital records. Final follow-up was performed in July and August 2014. The start of follow-up was defined as the date of initial CMR evaluation. Patients were censored at the time of their last clinical follow-up. All patients were directly contacted at 3- to 12-month intervals during follow-up. No patient was lost to follow-up.

Statistical analysis

The patient population is described using medians and quartiles with respect to quantitative variables. Subgroups of patients were compared with non-parametric Kruskal–Wallis test followed by post hoc Dwass–Steel–Critchlow–Fligner test for multiple comparisons. Counts and percentages were used to describe categorical variables. Exact Fisher–Freeman–Halton test or χ^2 test and test for two proportions with Bonferroni adjustment for multiple comparisons were used to assess relationships between these variables or endpoints and LGE. Kaplan–Meier survival curves were used to visually describe cumulative events of patients categorized by LGE. Multivariable Cox proportional hazard model was used to analyze associations of five major conventional risk factors with SCD/aborted SCD. Assumption of proportional hazard was checked by visually assessing shape of Kaplan–Meier curves. To investigate additional predictive value of LGE two separate multivariable models were formulated (with and without LGE assessment). The fit of these models was compared using likelihood-ratio test. Differences between the sensitivities and specificities of two diagnostic approaches [single major factor or in combination with LGE (++)] were calculated as described previously [22]. The additional value of LGE in predicting SCD/aborted SCD risk was calculated using area under the receiver operating characteristic curves. Statistical analyses were performed with IBM SPSS Statistics package (IBM Corp. Released 2011, IBM SPSS for Windows, Version 20.0, IBM, Armonk, NY, USA). *p*-Values smaller than 0.05 were considered statistically significant. All provided *p*-values relate to two-tailed tests.

Results

Study population

The baseline demographic and clinical characteristics of the study population are summarized in Tables 1 and 2. The median duration of follow-up was 37 months (IQR 24–48 months) amounting to 1048 patient-years. The median age at study entry was 45 years. More than half of the patients were male (58.0%) and the majority were minimally symptomatic. Patients without LGE were classified as the LGE (−) group. LGE was detected in 226 (68.9%) patients. In 70 (21.3%) of patients it was present only at the interventricular insertion points [LGE (+) group], while in 156 (47.6%) it was noted in other locations, either solely or apart from insertion points [LGE (++) group]. Patients with LGE were more likely to have massive hypertrophy (LV wall thickness ≥30 mm), nsVT, and abnormal blood pressure response during exercise (ABPR) at baseline, were older, were on average in higher New York Heart Association (NYHA) class, had higher N-terminal prohormone brain natriuretic peptide (NT-proBNP) serum concentrations, and more often suffered from atrial fibrillation. LGE (++) patients had thicker interventricular septum than LGE (+) patients. The proportion of patients with nsVT and massive left ventricular hypertrophy (≥30 mm) was significantly higher in the LGE (++) group than in LGE (+) and LGE (−) group ($p < 0.05$), but similar in the LGE (+) and LGE (−) groups. In addition, there were more patients with LVOT gradient >30 mmHg in the LGE (+) group compared to the LGE (++) group ($p < 0.05$).

CMR findings

The CMR data are presented in Table 1. LGE (+) and LGE (++) patients showed more pronounced LV hypertrophy than LGE (−) patients.

The results of clinical follow-up

All primary study endpoints occurred in the LGE (+) and LGE (++) groups. None occurred in the LGE (−) group. During follow-up 14 (4.27%) out of 328 patients experienced a primary endpoint. There were 4 sudden deaths and 10 appropriate ICD interventions. Only one patient out of these was in the LGE (+) group. A summary of primary endpoints is presented in Table 3. As for secondary endpoints, two patients died of thrombo-embolic complications in the course of AF [1 in LGE (+) and 1 in LGE (++) group]. Two patients died of heart failure. One had LVOT obstruction and severe pulmonary hypertension [LGE (+)], while in the other HCM evolved to end-stage congestive heart failure [LGE (++)]. Three patients died of complications of oncologic surgery [1 LGE (+), 2 LGE (++)].

Table 1
Baseline demographic, clinical, and cardiovascular magnetic resonance data according to LGE in 328 HCM patients.

	All patients $n=328$ (100%)	LGE (−) $n=102$ (31.1%)	LGE (+) $n=70$ (21.3%)	LGE (++) $n=156$ (47.6%)	*p*-Value
Median FU (month)	37 [24–48]	36 [24–48]	45 [30–48]	38 [24–48]	0.146
Median age (years)	45 [29–58]	34 [24–55]	49 [37–60]	47 [34–57]	0.003*
LV wall thickness (mm)	20 [17–25]	18 [14–20]	20.5 [18–25]	22 [20–27]	<0.001**
NT-proBNP (pg/ml)	732 [240–1516]	206 [75–862]	938 [477–1532]	1026 [420–1533]	<0.001***
Male sex (*n*)	192	58	37	97	0.387
LVEF <50% (*n*)	11	0	1	10	0.001
Hypertension (*n*)	43	8	11	24	0.154
NYHA class					<0.001
I	63	22	11	30	
II	149	29	28	92	
III	43	9	21	13	
IV	0	0	0	0	
CMR parameter					
EDV (ml)	162 [133–190]	166 [133–191]	157 [124–191]	161 [133–191]	0.629
EDV/BSA (ml/m^2)	84 [73–95]	86 [74–95]	84 [72–94]	84 [74–94]	0.845
ESV (ml)	51 [37–66]	52 [38–67]	49 [34–60]	49 [37–64]	0.358
ESV/BSA (ml/m^2)	27 [19–32]	27 [22–33]	26 [19–33]	27 [19–32]	0.402
SV (ml)	109 [90–127]	110 [90–129]	110 [89–128]	109 [91–124]	0.905
SV/BSA (ml/m^2)	56 [50–64]	57 [51–64]	57 [51–67]	56 [50–63]	0.975
LVEF (%)	69 [63–75]	68 [63–73]	70 [64–75]	68 [63–75]	0.384
LV mass (g)	167 [128–222]	151 [116–206]	171 [132–242]	179 [134–224]	0.018****
LV mass/BSA (g/m^2)	87 [67–114]	77 [61–105]	93 [71–128]	90 [71–114]	0.003*****

* LGE (−) vs. LGE (+) $p=0.009$, LGE (−) vs. LGE (++) $p=0.011$, LGE (+) vs. LGE (++) $p=0.656$.
** LGE (−) vs. LGE (+) $p=0.001$, LGE (−) vs. LGE (++) $p=0.001$, LGE (+) vs. LGE (++) $p=0.044$.
*** LGE (−) vs. LGE (++) $p=0.001$, LGE (−) vs. LGE (++) $p=0.001$, LGE (+) vs. LGE (++) $p=0.986$.
**** LGE (−) vs. LGE (+) $p=0.093$, LGE (−) vs. LGE (++) $p=0.019$, LGE (+) vs. LGE (++) $p=0.998$.
***** LGE (−) vs. LGE (+) $p=0.018$, LGE (−) vs. LGE (++) $p=0.007$, LGE (+) vs. LGE (++) $p=0.812$.
Data are expressed as median and interquartile range or numbers. FU, follow-up; LGE, late gadolinium enhancement; LV, left ventricle; EF, ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone brain natriuretic peptide; CMR, cardiac magnetic resonance; EDV, end diastolic volume; BSA, body surface area; ESV, end systolic volume; SV, stroke volume.

One patient died in a motor accident [LGE (+)]. Neither primary nor secondary endpoints occurred in the LGE (−) group. The data are summarized in Table 4.

In univariable analysis, the independent predictors of the primary endpoint occurrence were the presence of nsVT, massive LV hypertrophy (at least 30 mm), and two parameters acquired with CMR: LGE (++) and LVEF <50% (Table 5).

In multivariate analysis calculated using only the five classic major risk factors the independent predictors of SCD or its equivalent were the presence of nsVT and LV hypertrophy (Table 5). When two CMR-derived predictors, LGE (++) and LVEF<50%, were included in the two-way analysis, the only independent SCD predictor that remained significant was LGE (++). Next, we compared two primary endpoint prediction models, one consisting of traditional risk factors only and the other supplemented by LGE (++) in addition. The model taking into account LGE (++) was significantly more precise [log-likelihood $p = 0.005$, HR for LGE (++) 10.45, 95% CI 1.26–86.4, $p = 0.029$]. However, no prediction improvement was noted when adding any LGE or CMR-derived LVEF <50% instead.

Table 2
Risk factors for sudden cardiac death and treatment of 328 hypertrophic cardiomyopathy patients.

	All patients $n=328$ (100%)	LGE (−) $n=102$ (31.1%)	LGE (+) $n=70$ (21.3%)	LGE (++) $n=156$ (47.6%)	*p*-Value
Major risk factors for SCD					
LV wall thickness ≥30 mm (*n*)	34 (10.4%)	1	3	30	<0.001
Syncope (*n*)	42 (12.8%)	10	9	23	0.521
FHSCD (*n*)	68 (20.7%)	16	15	37	0.29
ABPR (*n*)	48 (14.6%)	2	10	36	<0.001
nsVT (*n*)	120 (36.6%)	14	18	120	<0.001
Minor risk factors for SCD					
Atrial fibrillation (*n*)	62 (18.9%)	9	18	35	0.007
LVOTG >30 mmHg (*n*)	111 (33.8%)	34	32	45	0.048
Treatment					
ICD (*n*)	100 (30.5%)	11	21	68	<0.001
Beta-blockers (*n*)	262 (79.9%)	61	63	138	<0.001
Calcium-blockers (*n*)	15 (4.6%)	6	2	7	0.697
ACE-inhibitors, ARB (*n*)	85 (25.9%)	17	21	47	0.053
Spironolactone (*n*)	27 (8.2%)	3	7	17	0.047
Amiodarone (*n*)	31 (9.5%)	3	5	23	0.004

LGE, late gadolinium enhancement; SCD, sudden cardiac death; LV, left ventricle; FHSCD, family history of sudden cardiac death; ABPR, abnormal blood pressure response during exercise; nsVT, non-sustained ventricular tachycardia on Holter monitoring; LVOTG, left ventricular outflow tract gradient; ICD, implantable cardioverter defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 3
Characteristics of 14 patients experiencing primary endpoint.

Pts.	Sex	Age (years)	Max. wall thickness (mm)	LV mass (g/m^2)	LGE	LVOTG (mmHg)	EF (%)	AF	Risk factors	Event
1	M	13	20	58	++	–	66	–	ABPR	Sudden death
2	F	58	19	125	+	60	69	–	ABPR	Sudden death
3	M	58	16	79	++	–	66	–	Syncope, nsVT	Sudden death
4	M	48	34	148	++	–	68	–	IVS ≥30 mm	Sudden death
6	M	50	35	93	++	–	69	–	nsVT, IVS ≥30 mm	VF/ICD discharge
7	M	55	31	129	++	60	47	+	nsVT, IVS ≥30 mm	VF/ICD discharge
8	M	62	22	142	++	85	63	+	nsVT	VT/ICD discharge
9	M	19	32	114	++	–	73	–	IVS ≥30 mm	VF/ICD discharge
10	M	44	23	142	++	–	35	–	FHSCD, nsVT	VF/ICD discharge
11	M	57	25	123	++	–	72	–	FHSCD, nsVT	VT/ICD discharge
12	M	54	22	132	++	–	71	+	nsVT	VF/ICD discharge
13	F	73	20	49	++	–	60	–	FHSCD, nsVT, syncope	VT/ICD discharge
14	F	64	21	65	++	–	75	–	nsVT	VT/ATP pacing

LV, left ventricle; LGE, late gadolinium enhancement; LVOTG, left ventricular outflow tract gradient; EF, ejection fraction; AF, atrial fibrillation; ABPR, abnormal blood pressure response during exercise; nsVT, non-sustained ventricular tachycardia on Holter monitoring; IVS, interventricular septum; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; FHSCD, family history of sudden cardiac death; ATP, antitachycardia pacing.

When combining LGE (++) with any of the traditional risk factors, the specificity increased significantly for nsVT ($p < 0.001$), family history of SCD ($p < 0.001$), and history of syncope ($p < 0.01$) with no deterioration of sensitivity. No significant improvement was noted for extreme LV hypertrophy (at least 30 mm) ($p = 0.134$). These data, accuracy, positive predictive value, and negative predictive value are summarized in Table 6.

The Kaplan–Meier curves show better event-free survival in the LGE (−) and LGE (+) patient groups compared to the LGE (++) group (Fig. 2).

When the five traditional major risk factors were supplemented by LGE (++), the area under the curve (AUC) of receiver operating characteristic (ROC) increased from 0.738 (95% CI 0.641–0.835) to 0.786 (95% CI 0.697–0.874).

Discussion

The main finding of this study is that the presence of LGE in CMR beyond the interventricular insertion points is an independent predictor of SCD or its equivalents (primary study endpoint) in the analyzed group of HCM patients. LGE positive patients are also more likely to develop one of the secondary endpoints (composite of SCD or equivalent and CV mortality; composite of SCD or equivalent and total mortality).

It has long been known that cardiomyocyte disarray and fibrosis are the pathophysiological mechanisms underlying the risk of SCD in HCM [4]. While it is difficult to assess the extent of disarray, CMR with gadolinium is a sensitive tool for the assessment of the extent of fibrosis, correlating well with the extent of LGE [23–25]. In view of this, the results we obtained may not be surprising. Previous research, although generally supporting the prognostic value of LGE in HCM, yielded promising but inconclusive data. Hence, the evaluation of LGE is not advocated in the SCD risk assessment in the new clinical guidelines [17]. In a metaanalysis there was only a trend toward LGE predicting the risk of SCD in HCM [26]. However, despite doubts and technical differences in assessing the extent of LGE, there are data supporting the use of LGE assessed by CMR as a predictor of SCD in HCM patients [19,20].

First, there is a group of four studies on which the aforementioned metaanalysis is based. In the study by Maron et al. the annual cardiovascular event rate was higher in the LGE group, although there were no differences in the extent of LGE [27]. Bruder et al. showed that LGE was an independent predictor of general and cardiovascular mortality [28]. In a group of 217 patients O'Hanlon et al. demonstrated that 63% of this group had fibrosis on CMR and it correlated with the occurrence of primary composite outcome of cardiovascular death, unplanned cardiovascular hospital stay, sustained ventricular tachycardia or ventricular fibrillation, and appropriate ICD discharge [25]. Rubinshtein et al. in a group of 424 patients, out of whom 8 experienced SCD or appropriate ICD discharge, showed that all 8 had LGE [29]. Six-year survival was better in patients without LGE compared to patients with LGE. Furthermore, Hen and colleagues demonstrated significantly higher annual cardiovascular events rate in 345 HCM patients with late gadolinium enhancement on CMR and the presence of LGE was one of the independent predictors of worse prognosis [30]. Second, there are newer studies looking more closely into the extent of LGE. Recent research of Chan et al. (1293 patients, 7 centers) and Ismail et al. (711 patients, single center) have also proven that the extent of LGE is a strong predictor of SCD [19,20]. However, in the second of these studies the effect of LGE was eliminated after adjusting for LVEF [19].

A possible drawback of most of these studies was lack of full risk stratification, evaluating all known SCD risk factors in the whole group under follow-up. In general, our results are consistent with previous observations [19,20,29]. The patient group was similar.

Table 4
Patients' outcomes according to the presence and location of LGE.

Event	All patients $n = 328$ (100)	LGE (−) $n = 102$	LGE (+) $n = 70$	LGE (++) $n = 156$	p-Value*
Sudden cardiac death and aborted SCD	14	0	1	13	0.001
Sudden cardiac death and aborted SCD and cardiovascular mortality	18	0	3	15	0.001
Sudden cardiac death and aborted SCD and overall mortality	22	0	5	17	0.001

* Chi-square test for trend.
LGE, late gadolinium enhancement; SCD, sudden cardiac death.

Table 5
Predictors of sudden cardiac death or aborted sudden cardiac death in univariate and multivariate analyses.

	HR	95% CI	*p*-Value
Univariate analysis			
LV wall thickness ≥30 mm	3.46	1.08–11.01	0.036
Syncope	1.79	0.50–6.41	0.373
FHSCD	2.25	0.75–6.72	0.166
ABPR	0.99	0.22–4.41	0.986
nsVT	3.88	1.21–12.40	0.022
LGE (++)	14.35	1.88–109.7	0.010
LVEF <50%	4.93	1.10–22.22	0.037
Multivariate analysis			
Five conventional major risk factors			
LV wall thickness ≥30 mm	3.65	1.08–12.39	0.038
Syncope	1.81	0.46–7.10	0.395
FHSCD	2.14	0.66–6.88	0.204
ABPR	0.89	0.19–4.12	0.876
nsVT	3.29	1.01–10.69	0.048
After adjustment for LGE (++) and EF <50%			
LV wall thickness ≥30 mm	2.14	0.63–7.37	0.225
Syncope	2.20	0.57–8.62	0.254
FHSCD	2.30	0.73–7.25	0.153
ABPR	0.52	0.10–2.41	0.384
nsVT	2.00	0.53–6.14	0.347
LGE (++)	10.01	1.21–83.86	0.033
LVEF <50%	2.47	0.51–2.48	0.262

HR, hazard ratio; CI, confidence interval; LV, left ventricle; ABPR, abnormal blood pressure response during exercise; FHSCD, family history of sudden cardiac death; nsVT, non-sustained ventricular tachycardia on Holter monitoring; LGE, late gadolinium enhancement; EF, ejection fraction.

The presence of LGE at right ventricle (RV) insertion points in our study was noted in 21% of patients. This varied between 7.5% and 28% in previous works [19,25,29]. LGE was observed more frequently in cases with large hypertrophy, nsVT, higher NYHA class, or atrial fibrillation. We also showed that larger LGE correlated with higher NT-proBNP. As in previous studies, the presence of LGE was associated with increased frequency of non-sustained ventricular tachycardia on ambulatory Holter ECG [24,31,32]. Our results may additionally indicate that nsVT is more frequently seen in patients with LGE located beyond the RV insertion points. Increasing the practical implications of this work is the fact that all patients had full SCD risk stratification performed with respect to the five classic risk factors. We have shown that LGE beyond the RV insertion points is an independent risk factor of SCD or its equivalents. There were no events in the group without LGE, while only one occurred in the group with LGE

Table 6
Specificity, sensitivity, accuracy, negative and positive predictive value of major risk factors alone or when combining LGE (++).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
nsVT	71.4	65.0	8.3	98.1	65.2
nsVT with LGE (++)	71.4	75.2	11.4	98.3	75.0
Syncope	21.4	87.6	7.1	96.2	84.8
Syncope with LGE (++)	21.4	93.6	13.0	96.4	90.5
ABPR	14.3	85.3	4.2	95.7	82.2
ABPR with LGE (++)	7.1	88.9	2.8	95.5	85.3
FHSCD	35.7	79.9	7.4	96.5	78.0
FHSCD with LGE (++)	35.7	89.8	13.5	96.9	87.5
LVWT ≥30 mm	28.6	90.4	11.8	96.6	87.8
LVWT ≥30 mm with LGE (++)	28.6	91.7	13.3	96.6	89.0

PPV, positive predictive value; NPV, negative predictive value; LGE, late gadolinium enhancement; nsVT, non-sustained ventricular tachycardia on Holter monitoring; ABPR, abnormal blood pressure response during exercise; FHSCD, family history of sudden cardiac death; LV, left ventricle; WT, wall thickness.

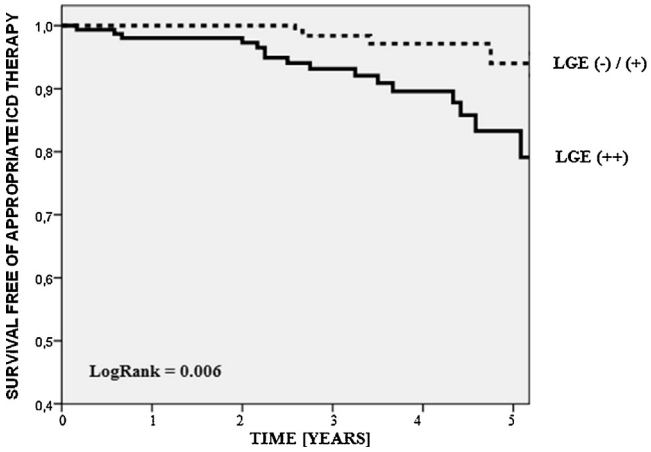

Fig. 2. LGE and clinical outcome. Kaplan–Meier curve presenting survival free of sudden cardiac death or appropriate ICD discharge in patients with hypertrophic cardiomyopathy in relation to presence and location of late gadolinium enhancement on cardiac magnetic resonance. LGE, late gadolinium enhancement; ICD, implantable cardioverter defibrillator.

limited to the interventricular insertion points. An interesting result obtained in this study is the observation that in case of the presence of just one classic risk factor, which was particularly evident for nsVT, identifying LGE beyond insertion points allows for better identification of patients that will actually benefit from ICD implantation. Considering recent European guidelines and new risk calculator, one may speculate that at least in case of patients with calculated intermediate SCD risk, CMR may help to decide whether to implant ICD, especially if the patient falls into our LGE (++) group, meaning the presence of LGE outside RV insertion points [17]. Fibrosis limited to insertion points is generally considered low risk and is not HCM specific [33,34]. It has been seen in other pathologies and may simply be secondary to overload conditions [35,36].

As confirmed by this work one can reasonably assume that no LGE is safe for the patient; its presence solely at the insertion points probably carries not much higher risk. On the other hand, in the work of Rubinshtein there were endpoints also in the group of patients with LGE limited to the insertion points [29]. It is also only a guess that in many patients LGE may increase over time. When is the time to repeat CMR?

Future research should focus on protocol standardization and precision of LGE assessment, as not only the extent, but also the location of LGE seems relevant. A risk score should likely be developed taking into the account the presence of LGE, its extent, and location.

In our group of patients ABPR brought no further relevant information. It may be that this risk factor is only important in a younger HCM population. The only adolescent patient in our group who experienced SCD had one classic risk factor – ABPR, but also had LGE beyond RV insertion points. Risk stratification and decision-making regarding ICD implantation are much more difficult in young HCM patients [5,17,37]. The median age in our group was 45 years and LGE is less pronounced in younger patients. However, in a study involving 71 children with HCM all adverse events occurred in those with LGE [38]. In the work of Chan et al. low-risk patients on classic risk evaluation who experienced events also had LGE [20]. Similarly, all events in our study occurred in the group of LGE patients.

Study limitations

Most of the highest risk patients were not included as they were previously implanted with an ICD, which precluded CMR. LGE

analysis was qualitative, assessing the presence of LGE at insertion point and beyond, but not its precise extent. On the other hand, this simplified the assessment and reduced variability. As there were no events in the LGE (−) group and just one in the LGE (+), we could not perform a valid multivariable Cox regression analysis. Also, this was a comparatively modest sample from a single tertiary center with only 14 primary endpoints occurring overall. The sub-analysis assessing the outcome of patients with LGE outside insertion points only was not performed. Our definitions of several risk factors were also a little different. We adjudicated as a risk factor SCD in young, second-degree relatives with diagnosed HCM, as well as syncope occurring more than 5 years in the past. This could influence analysis.

Conclusions

Cardiac fibrosis is a crucial substrate for life-threatening ventricular arrhythmia in HCM, and may be evaluated on magnetic resonance. This study confirms the value of CMR and LGE assessment in predicting the risk of SCD in HCM patients. It also shows that the location of LGE may be of paramount importance. The novel paradigm of risk evaluation in HCM based on the identification of biomarkers for the substrate for SCD has the potential to significantly improve current models or SCD risk assessment in HCM patients. Despite robust pathophysiological background and significant results of the current study, the occurrence of just 14 primary endpoints may influence the significance of the results. Therefore, more research is needed to confirm these findings in large multicenter prospective observations.

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Conflict of interest

The authors declare that there is no conflict of interest.

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References

[1] Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation 1995;92:785–9.
[2] Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:2703–38.
[3] Minami Y, Haruki S, Hagiwara N. Phenotypic overlap in hypertrophic cardiomyopathy: apical hypertrophy, midventricular obstruction, and apical aneurysm. J Cardiol 2014;64:463–9.
[4] McKenna WJ, Deanfield JE. Hypertrophic cardiomyopathy: an important cause of sudden death. Arch Dis Child 1984;59:971–5.
[5] Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013;381:242–55.
[6] Maron BJ, Casey SA, Hauser RG, Aeppli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. J Am Coll Cardiol 2003;42:882–8.
[7] Maron BJ, Olivotto 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;102:858–64.
[8] Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart 2006;92:785–91.
[9] 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;36:2212–8.
[10] 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;42:873–9.
[11] Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi O, Maro BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation 2009;119:1703–10.
[12] Dimitrow PP, Chojnowska L, Rudzinski T, Piotrowski W, Ziólkowska L, Wojtarowicz A, Wycisk A, Dabrowska-Kugacka A, Nowalany-Kozielska E, Sobkowicz B, Wróbel W, Aleszewicz-Baranowska J, Rynkiewicz A, Loboz-Grudzien K, Marchel M, et al. Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up. Eur Heart J 2010;31:3084–93.
[13] Gimeno JR, Tome-Esteban M, Lofiego C, Hurtado J, Pantazis A, Mist B, Lambiase P, McKenna WJ, Elliott PM. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Eur Heart J 2009;30:2599–605.
[14] Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes 3rd NA, Favale S, Piccininno M, Winters SL, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405–12.
[15] Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy. Circ Heart Fail 2012;5:552–9.
[16] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006;48:e247–346.
[17] Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733–79.
[18] O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis 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). Eur Heart J 2014;35:2010–20.
[19] Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, et al. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart 2014;100:1851–8.
[20] Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484–95.
[21] Spiewak M, Malek LA, Misko J, Chojnowska L, Milosz B, Klopotowski M, Petryka J, Dabrowski M, Kepka C, Ruzyllo W. Comparison of different quantification methods of late gadolinium enhancement in patients with hypertrophic cardiomyopathy. Eur J Radiol 2010;74:149–53.
[22] Hawass NE. Comparing the sensitivities and specificities of two diagnostic procedures performed on the same group of patients. Br J Radiol 1997;70:360–6.
[23] 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;43:2260–4.
[24] 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;54:242–9.
[25] O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867–74.
[26] Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2012;5:370–7.
[27] 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;1:184–91.
[28] 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;56:875–87.
[29] 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;33:51–8.
[30] Hen Y, Iguchi N, Utanohara Y, Takada K, Machida H, Takayama M, Sumiyoshi T. Prognostic value of late gadolinium enhancement on cardiac magnetic resonance imaging in Japanese hypertrophic cardiomyopathy patients. Circ J 2014;78:927–37.
[31] Fujita T, Konno T, Yokawa J, Masuta E, Nagata Y, Fujino N, Funada A, Hodatsu A, Kawashiri MA, Yamagishi M, Hayashi K. Increased extent of myocardial fibrosis in genotyped hypertrophic cardiomyopathy with ventricular tachyarrhythmias. J Cardiol 2015;66:63–8.
[32] Magri D, De Cecco CN, Piccirillo G, Mastromarino V, Serdoz A, Muscogiuri G, Ricotta A, Gregori M, Marino L, Cauti FM, Pagannone E, Musumeci MB, Maruotti A, Autore C. Myocardial repolarization dispersion and late gadolinium enhancement in patients with hypertrophic cardiomyopathy. Circ J 2014;78:1216–23.
[33] Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennel DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol 2003;41:1561–7.
[34] Chan RH, Maron BJ, Olivotto I, Assenza GE, Hass TS, Lesser JR, Gruner C, Crean AM, Rakowski H, Rowin E, Udelson J, Lombardi M, Tomberli B, Spiroto P, Formisano F, et al. Significance of late gadolinium enhancement at right ventricular attachment to ventricular septum in patients with hypertrophic cardiomyopathy. Am J Cardiol 2015;116:436–41.
[35] Spiewak M, Malek LA, Petryka J, Mazurkiewicz L, Marczak M, Biernacka EK, Kowalski M, Hoffman P, Demkow M, Miśko J, Rużyłło W. Determinants of left- and right-ventricular ejection fractions in patients with repaired tetralogy of Fallot: a cardiac magnetic resonance imaging study. Pol Arch Med Wewn 2013;12:539–46.
[36] Rudolph A, Abdel-Aty H, Bohl S, Boyé P, Zagrosek A, Dietz R, Schulz-Menger J. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. J Am Coll Cardiol 2009;53:284–91.
[37] Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes 3rd NA, Shannon KM, Ashley EA, Day SM, Pacileo G, Formisano F, Devoto E, Anastasakis A, Bos JM, Woo A, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;61:1527–35.
[38] Chaowu Y, Shihua Z, Jian L, Wei F. Cardiovascular magnetic resonance characteristics in children with hypertrophic cardiomyopathy. Circ Heart Fail 2013;6:1013–20.