Chapter 10

Myocardial Scar Predicts Monomorphic VT but not Polymorphic VT or VF in Non-ischemic Dilated Cardiomyopathy

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ABSTRACT

Background

The relation between myocardial scar and different types of ventricular arrhythmias in patients with non-ischemic dilated cardiomyopathy (NIDCM) is unknown.

Objectives

To analyze the effect of myocardial scar, assessed by late gadolinium enhancement (LGE)-CMR, on the occurrence and type of ventricular arrhythmia in patients with NIDCM.

Methods

Consecutive patients with NIDCM who underwent LGE-CMR and ICD implantation at two centers were included. LGE was defined by signal intensity ≥35% of maximal signal intensity, subdivided into core and border zone (≥50% and 35-50% of maximal signal intensity, respectively), and categorized according to (non)basal location and transmurality. ICD recordings and ECGs were reviewed to determine the occurrence and type of ventricular arrhythmia during follow-up.

Results

Of 87 patients (age 56±13 years, 62% male, LVEF 29±12%), 55 (63%) had LGE (median 6.3g, interquartile range 0.0–13.8g). During a median follow-up of 45 months, monomorphic VT occurred in 18 (21%) patients, and polymorphic VT/VF in 10 (11%). LGE predicted monomorphic VT (Log-rank, $p<0.001$), but not polymorphic VT/VF (Log-rank, $p=0.40$). The optimal cut-off value for LGE to predict monomorphic VT was 7.2g (area under curve 0.84). Features associated with monomorphic VT were core extent, basal location, and area with 51-75% LGE transmurality.

Conclusions

Myocardial scar assessed by LGE-CMR predicts monomorphic VT, but not polymorphic VT/VF in NIDCM. The risk for monomorphic VT is particularly high when LGE shows a basal transmural distribution and a mass ≥7.2g. Importantly, patients without LGE on CMR remain at risk for potentially fatal polymorphic VT/VF.

INTRODUCTION

The presence of myocardial scar, as assessed by late gadolinium enhancement (LGE)-CMR, is an independent predictor of appropriate ICD therapy, sudden cardiac death and all-cause mortality in patients with non-ischemic dilated cardiomyopathy (NIDCM).[1-4] Ventricular arrhythmias do however occur in patients without LGE and may be caused by a different underlying substrate.[1,2,4]

Sustained monomorphic ventricular tachycardias (VTs) in patients with NIDCM undergoing catheter ablation are often due to scar-related fixed re-entry. Slow-conducting parts of these re-entry circuits are found in regions with myocardial scar, as demonstrated by integrating LGE-CMR data with 3D electroanatomical maps during VT ablation.[5-8] Several mechanisms for monomorphic VT have however been proposed[9] and the association between LGE and monomorphic VT has never been systematically analyzed in the general population of patients with NIDCM.

In contrast to sustained monomorphic VT, polymorphic VT and VF are thought to be related to multiple wavelet re-entry or a mother rotor fractionating to daughter wave fronts, resulting in continuously changing activation.[10] Although normal myocardium can sustain VF, different cardiac fibrosis patterns may contribute to the initiation and maintenance of polymorphic VT/VF.

The aims of the present study were (1) to analyze the effect of myocardial scar, as assessed by LGE-CMR, on the occurrence and type of ventricular arrhythmias in patients with NIDCM and (2) to evaluate the predictive value of LGE presence, extent and characteristics, for monomorphic VT.

METHODS

Patients

All patients with NIDCM who underwent LGE-CMR before ICD implantation at Leiden University Medical Centre (n=46) and Maastricht University Medical Centre (n=41), the Netherlands, between 2004 and 2012 were included. Patients who were implanted at the Maastricht University Medical Centre but followed at another center were excluded. The diagnosis of NIDCM was based on World Heart Organization definitions[11] and on CMR findings, requiring increased LV end-diastolic volume index and decreased LV ejection fraction (LVEF) compared with published 95% reference ranges normalized for gender, age and body surface area.[12] Significant coronary artery disease (≥70% stenosis in a major coronary artery) was excluded by coronary angiography or MDCT in all patients. Patients with sarcoidosis, amyloidosis or subendocardial LGE in a coronary artery perfusion territory were excluded.

The Dutch Central Committee on Human-related Research (CCMO) allows use of anonymous data without prior approval of an institutional review board provided that the data is acquired for patient care. All data used for this study was acquired for clinical purposes and handled anonymously.

LGE-CMR acquisition

CMR was performed on a 1.5T Gyroscan ACS-NT/Intera MR system (Philips Medical Systems, Best, the Netherlands) at the two centers. A standardized protocol was followed, including cine imaging in long-axis (two- and four-chamber) views, and in short-axis view covering the complete LV.

Approximately 15 minutes after bolus injection of gadolinium (Magnevist; Schering, Berlin, Germany; 0.15 mmol/kg) a look-locker sequence was acquired in short axis orientation at mid-ventricular level. T1-weighted LGE images were acquired with an inversion-recovery 3D turbo-field echo sequence with parallel imaging. Typical scan parameters were: average TR/TE 3.7/2.4ms, Flip angle 15°, FOV 400mm, matrix 256×206, acquired and reconstructed voxel size 1.56x1.94x5mm. The inversion time was optimized to null normal appearing myocardium. The heart was imaged in long-axis two- and four-chamber views (between 5-10 slices), and short-axis views (between 20-24 slices). Signal outside the field of view was suppressed using two saturation slabs to avoid fold-over artifacts.

CMR image analysis

All CMR analyses were performed using Mass software (research version 2012; LKEB; Leiden University Medical Centre, the Netherlands). The LV and RV end-diastolic and end-systolic endocardial contours were traced on cine images to calculate LV mass, end-diastolic volumes, end-systolic volumes and ejection fractions. Volumes and LV mass were indexed to body surface area.

To measure post-contrast T1-values, LV endocardial and epicardial contours were semi-automatically traced on look-locker images. Signal intensity was plotted against time and fitted to an exponential curve to obtain T1-values for the six midventricular segments, according to the American Heart Association (AHA) 17-segment model. The overall T1-value was defined as the average of these T1-values, excluding segments with LGE, to analyze the effects of myocardial scar and diffuse fibrosis separately. Similar to the method reported by Gai et al.[13], T1-values were normalized to a heart rate of 60 bpm using the following formula: T1 corrected = T1 uncorrected + α*(60–heart rate), where α equals -3.409, i.e. the slope of the regression line of heart rate vs. T1 of nonenhanced segments. Shorter T1 values indicate more diffuse myocardial fibrosis.[14]

Myocardial scar was assessed while the observer was blinded to clinical data and outcome, and was only considered to be present if LGE was visible in 2 orthogonal views. LGE was defined by signal intensity ≥35% of maximal myocardial signal intensity,

and subdivided into core (≥50% of maximal signal intensity) and border zone (35-50% of maximal signal intensity).[15] To assess the predictive value of LGE location, intensity and transmurality for monomorphic VT, the following parameters were calculated using Mass research software:

1. Extent of LGE (≥35% of maximal signal intensity, in grams) in basal and nonbasal segments (American Heart Association segments 1-6 and 7-17, respectively);
2. Extent of LGE (in grams) according to pre-defined signal intensity categories (30-40%, 40-50%, 50-60%, 60-70% and >70% of maximal signal intensity)
3. Endocardial surface area of myocardial regions with LGE (≥35% of maximal signal intensity, in cm^2) according to pre-defined transmurality categories (1-25%, 26-50%, 51-75% and 76-100% transmurality).

ICD programming and follow-up

ICDs were typically programmed to include 3 zones: monitor zone (150-188bpm, antitachycardia pacing [ATP] if clinically indicated), fast VT zone (188-210bpm, ATP and shock), VF zone (>210bpm, if available ATP during charging, and shock). Patients were followed at 6-monthly intervals. Intracardiac recordings were analyzed by an experienced observer who was blinded to clinical and CMR data when reviewing the recordings. The combined endpoint of any ventricular arrhythmia consisted of monomorphic VT and polymorphic VT/VF. Monomorphic VT was defined as VT with ≤30ms beat-to-beat variation in cycle length and stable far-field electrogram morphology, lasting >30 seconds or treated with ATP and/or shock. Polymorphic VT/VF was defined as any ventricular arrhythmia with >30ms beat-to-beat variation in cycle length and unstable far-field electrogram morphology, lasting >30 seconds or treated with ATP and/or shock. If ICD recordings and/or 12-lead ECGs were not available for some of the episodes, the missing episodes were considered to be of the same type as the documented episodes provided that the cycle length was similar. When ICD recordings and/or 12-lead ECGs were missing for all episodes, patients were excluded from all analysis involving the type of arrhythmia.

Statistical analysis

Categorical variables are displayed as number (percentage) and compared using the χ^2 test or the Fisher's exact test. Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), and compared using the Student's *t* test or the Mann-Whitney *U* test when appropriate. The LGE extent in basal and nonbasal segments was compared using the Wilcoxon signed rank test.

Kaplan Meier survival analysis and Cox proportional hazard analysis were performed to identify predictors for arrhythmic events during follow-up. Multivariable Cox proportional hazard analyses were performed to analyze the independent predictive value of LGE and

specific LGE features, adjusting for other predictors with a p-value<0.10 in univariable analyses and for other LGE features of interest, respectively. A maximum of 1 variable per ~10 endpoints was included in the models. Receiver operating characteristic curve analysis was performed to determine the optimal cut-off values of LGE for prediction of monomorphic VT, which were defined as the values maximizing the sum of sensitivity and specificity. All analyses were performed with SPSS version 20.0 (IBM, Somers, New York, USA). All tests are two-sided and p-values<0.05 were considered significant.

RESULTS

Patients

Of the 87 patients (age 56±13 years, 62% male), 64 (74%) underwent ICD implantation for primary prevention, 10 (11%) after presentation with sustained monomorphic VT and 13 (15%) after out-of-hospital cardiac arrest with VF as the initial recorded rhythm (OHCA-VF)(Table 1). Forty-six patients (53%) were implanted with a cardiac resynchronization therapy-defibrillator.

CMR parameters and presenting arrhythmia

Patients presenting with OHCA-VF and in particular patients presenting with sustained monomorphic VT had lower LV end-diastolic and end-systolic volume indexes and higher LVEF, compared to primary prevention patients (Table 1).

Overall, LGE was present in 55 patients (63%, examples in Figure 1A-F), with a median LGE extent of 6.3 g (IQR, 0.0–13.8). LGE was observed in 9 of 10 patients (90%) presenting with sustained monomorphic VT and in only 4 of 13 patients (31%) with OHCA-VF, compared to 42 of 64 primary prevention patients (66%). The LGE extent was substantially higher in patients presenting with sustained monomorphic VT compared with primary prevention patients. In contrast, patients presenting with OHCA-VF tended to have less LGE than primary prevention patients.

The corrected T1 did neither differ between groups (Table 1) nor between patients with and without LGE (340±64 vs. 336±50, respectively, p=0.78).

Ventricular arrhythmias during follow-up

One patient (1%) was lost to follow-up after ICD implantation. During a median follow-up of 45 months (IQR, 23–67 months), 392 episodes of ventricular arrhythmia occurred in 28 patients (32%) (examples in Figure 1G-H). The ICD tracings or 12-lead ECGs could be reviewed for 298 episodes (76%), with at least one reviewed episode in 26 of 28 patients (93%). Of the 2 remaining patients, one had a dislocated RV lead and was resuscitated because of OHCA-VF, with VF as the first recorded rhythm, and the other had one single

episode with ATP, with no available tracings. These 2 patients were excluded from all analysis involving the type of arrhythmia.

Monomorphic VT occurred in 18 patients (median 5, IQR 3–23 episodes per patient; mean cycle length 308±47ms). At least one episode was terminated by ATP in 15 patients

Table 1. Baseline characteristics according to presenting arrhythmia

	All patients (n=87)	Primary prevention (n=64)	SMVT (n=10)	p†	OHCA (n=13)	p†
Age	56±13	56±13	61±12	0.30	51±15	0.20
Male	54(62%)	37(58%)	8(80%)	0.30	9(69%)	0.44
NYHA functional class						
I	28(32%)	11(17%)	7(70%)	**0.001**	10(77%)	**< 0.001**
II	32(37%)	26(41%)	3(30%)		3(23%)	
III-IV	27(31%)	27(42%)	0(0%)		0(0%)	
History of AF/atrial flutter	14(16%)	12(19%)	0(0%)	0.20	2(15%)	1.00
History of hypertension	25(29%)	18(28%)	3(30%)	1.00	4(31%)	1.00
Diabetes mellitus	6(7%)	4(6%)	2(20%)	0.18	0(0%)	1.00
eGFR, mL/min/1.73m^2	72±24	69±22	74±12	0.51	86±31	**0.027**
QRS duration, ms	132±32	130±31	128±35	0.84	142±31	0.21
LV volumes and function						
LVEDV, mL	288 (231–358)	318 (248–376)	219 (180–241)	**0.001**	244 (213–302)	**0.033**
LVESV, mL	209 (145–279)	228 (170–309)	119 (102–147)	**< 0.001**	150 (128–197)	**0.004**
LVEF, %	29±12	25±11	44±7	**< 0.001**	37±11	**0.001**
LV mass, g	147 (111–176)	150 (114–177)	135 (102–155)	0.31	138 (93–194)	0.45
RV volumes and function						
RVEDV, mL	158 (129–204)	153 (129–208)	160 (126–192)	0.90	166 (133–182)	0.83
RVESV, mL	80 (57–118)	80 (57–125)	75 (54–129)	0.68	71 (55–84)	0.16
RVEF, %	47±15	44±15	49±14	0.40	56±11	**0.004**
T1 corrected	339±59	335±54	341±79	0.80	355±74	0.27
LGE						
LGE presence	55(63%)	42(66%)	9(90%)	0.16	4(31%)	**0.019**
LGE extent						
Total LGE, g	6.3 (0.0–13.8)	5.8 (0.0–12.8)	16.6 (9.5–24.3)	**0.007**	0.0 (0.0–10.9)	0.14
Core, g	2.8 (0.0–5.8)	2.6 (0.0–4.8)	10.0 (5.6–15.3)	**0.002**	0.0 (0.0–3.3)	0.094
Border zone, g	3.0 (0.0–7.7)	2.5 (0.0–7.6)	5.9 (4.0–10.0)	0.070	0.0 (0.0–7.6)	0.14

Data are expressed as number (percentage), mean ± standard deviation or median (interquartile range). AF indicates atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; NYHA, New York Heart Association; OHCA, out-of-hospital cardiac arrest; RV, right ventricular; SMVT, sustained monomorphic ventricular tachycardia. † vs. primary prevention.

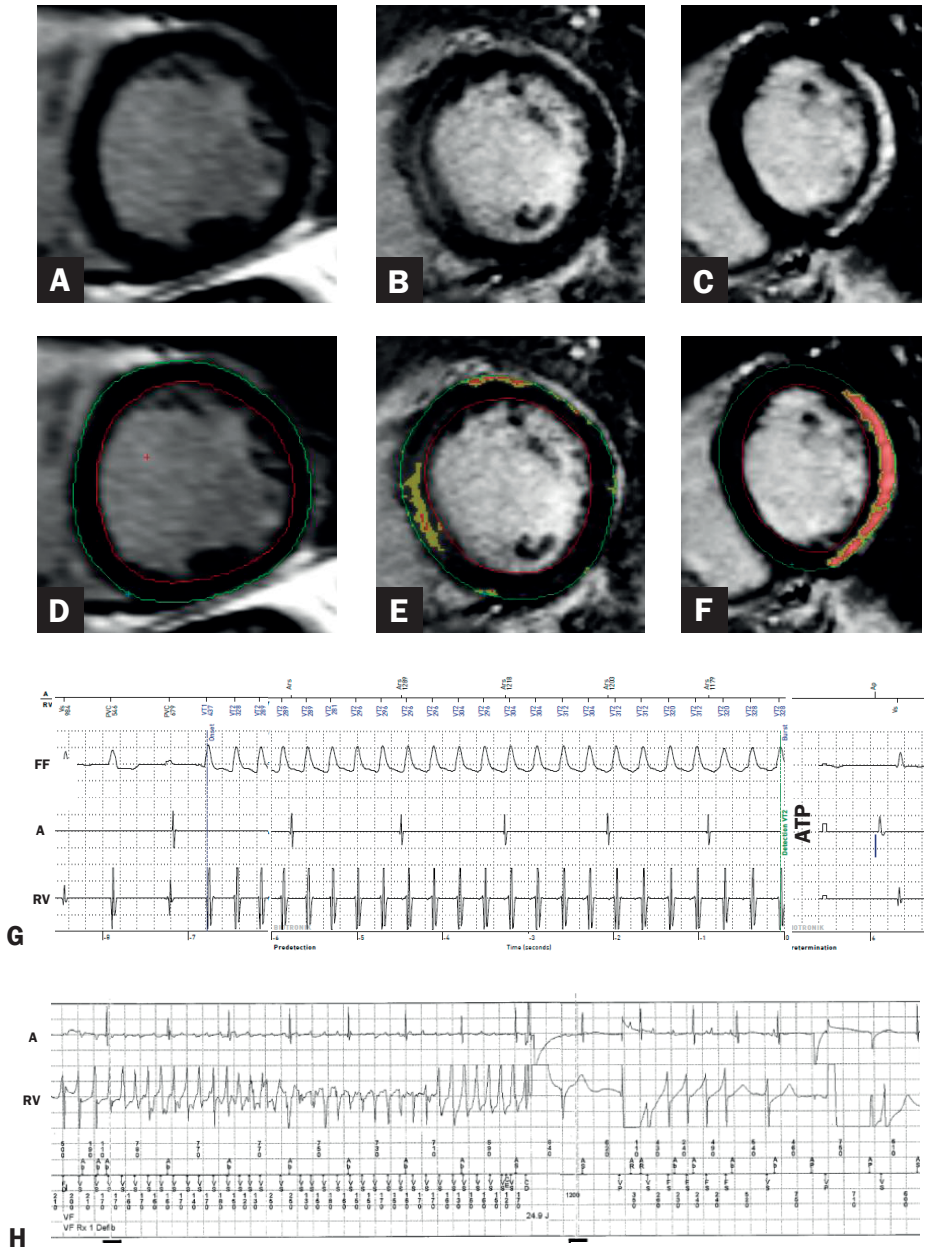

Figure 1. Examples of LGE-CMR and ventricular arrhythmias

Examples of a patient without LGE (panels A&D), small amount of LGE (panels B&E) and extensive LGE (panels C&F). Red indicates LGE core and yellow border zone. Monomorphic VT was related to LGE and frequently terminated by antitachycardia pacing (panel G), whereas polymorphic VT/VF was not related to LGE and typically terminated by an ICD shock (panel H).

(83%) and ≥1 episode by an ICD shock in 9 (50%). Seven patients (39%) had ≥1 episode lasting >30 seconds in the monitor zone or below detection rate.

Polymorphic VT/VF occurred in 10 patients (one episode in 8 patients (80%), 2 and 4 episodes in the remaining 2 patients). Nine of 10 patients (90%) only had episodes terminated by an ICD shock, while one patient had 4 episodes of polymorphic VT that stopped after a single burst of ATP.

Of note, only 2 patients had both monomorphic VT and polymorphic VT/VF – the other 26 patients with ventricular arrhythmias during follow-up had only one type of ventricular arrhythmia.

Predictors of different types of ventricular arrhythmia during follow-up

Predictors of monomorphic VT and polymorphic VT/VF were remarkably different. The presence of myocardial scar, as assessed by LGE-CMR, predicted the occurrence of monomorphic VT ($p<0.001$), but not of polymorphic VT/VF ($p=0.41$) (Figure 2, Table 2, Supplemental Table 1). Accordingly, the total LGE extent was a strong predictor of monomorphic VT ($p<0.001$), but not of polymorphic VT/VF ($p=0.66$).

Monomorphic VT was also predicted by male gender, presentation with sustained monomorphic VT, hypertension, diabetes mellitus, LVEF and corrected T1 values. The LGE extent remained an independent predictor for monomorphic VT when adjusted for each of these parameters separately (Supplemental Table 2), and also when only primary prevention patients were analyzed (Supplemental Table 3 and supplemental Figure 1).

The only predictor of polymorphic VT/VF during follow-up was presentation with OHCA-VF (Table 2). Of importance, LV and RV volumes and function, and LGE presence and extent were not associated with the occurrence of polymorphic VT/VF.

The combined endpoint of any ventricular arrhythmia was predicted by the presence and extent of LGE, male gender, hypertension, diabetes mellitus, LVEF and corrected T1 values (Figure 3, Table 2, Supplemental Table 1). The LGE extent remained an independent predictor when adjusted for each of these parameters separately, except diabetes mellitus (Supplemental Table 2), which may be due to the small number of patients with diabetes mellitus.

Myocardial scar characteristics and monomorphic VT

Receiver operating characteristic curve analysis of the association between the total LGE, core and border zone extent and monomorphic VT during follow-up yielded areas under the curve of 0.84, 0.86 and 0.78, respectively. The optimal cut-off values for prediction of monomorphic VT were 7.2g for total LGE extent (sensitivity 94%, specificity 67%), 3.0g for core (sensitivity 94%, specificity 64%) and 2.3g for border zone (sensitivity 100%, specificity 58%). Patients with LGE <7.2g were at very low risk for monomorphic VT (Figure 2) and at relatively low risk for any ventricular arrhythmia during follow-up (Figure 3).

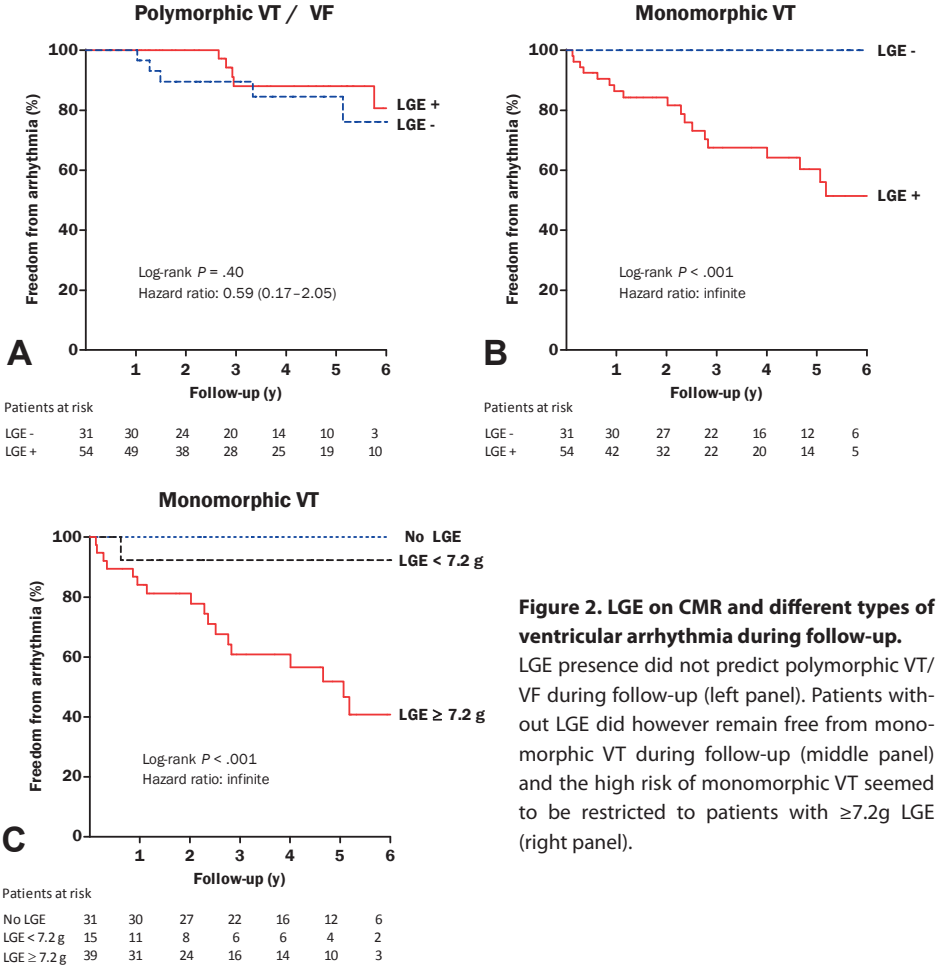

Figure 2. LGE on CMR and different types of ventricular arrhythmia during follow-up. LGE presence did not predict polymorphic VT/VF during follow-up (left panel). Patients without LGE did however remain free from monomorphic VT during follow-up (middle panel) and the high risk of monomorphic VT seemed to be restricted to patients with ≥7.2g LGE (right panel).

The LGE extent was larger in basal segments than in nonbasal segments (basal median 2.0g (IQR 0.0-7.7g), vs. nonbasal median 1.1g (IQR, 0.0-4.0g), p=0.011). The LGE extent in basal segments was a stronger predictor for monomorphic VT than the extent in nonbasal segments (Table 3). When both were included in a single model, only the LGE extent in basal segments remained an independent predictor of monomorphic VT (Supplemental Table 4).

When subdivided into 5 signal intensity categories, categories with LGE >60% of maximal signal intensity carried stronger prognostic information than categories with LGE 30-60% of maximal signal intensity (Table 3). When the two categories of LGE 30-60% and >60% of maximal signal intensity were included in a single model, only LGE >60% of maximal signal intensity remained associated with monomorphic VT (Supplemental Table 4).

Table 2. Predictors of ventricular arrhythmia during follow-up

Univariate analyses	Any ventricular arrhythmia		Monomorphic VT		Polymorphic VT/VF	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age, per 5 years↑	1.03 (0.90–1.19)	0.65	1.17 (0.96–1.42)	0.13	0.88 (0.71–1.10)	0.27
Male gender	3.59 (1.24–10.35)	**0.018**	2.89 (0.83–9.99)	0.094	4.42 (0.56–34.92)	0.16
Presenting arrhythmia						
OHCA vs. none	2.29 (0.82–6.39)	0.12	0.68 (0.08–5.43)	0.71	7.77 (1.90–31.69)	**0.004**
SMVT vs. none	6.54 (2.75–15.54)	**< 0.001**	11.52 (4.22–31.42)	**< 0.001**	3.01 (0.55–16.51)	0.21
Symptomatic heart failure	0.66 (0.31–1.40)	0.28	0.62 (0.24–1.57)	0.31	0.55 (0.16–1.89)	0.34
History of AF / atrial flutter	1.04 (0.39–2.74)	0.94	0.98 (0.28–3.40)	0.98	0.47 (0.06–3.76)	0.48
History of hypertension	2.36 (1.11–5.02)	**0.025**	4.81 (1.86–12.47)	**0.001**	1.04 (0.26–4.07)	0.96
Diabetes mellitus	7.27 (2.56–20.60)	**< 0.001**	12.29 (3.94–38.34)	**< 0.001**	1.70 (0.21–13.43)	0.62
eGFR, per 10mL/min/1.73m^2↓	1.04 (0.88–1.22)	0.69	1.06 (0.87–1.31)	0.56	0.91 (0.71–1.16)	0.45
QRS duration, per 10ms↑	0.93 (0.82–1.05)	0.23	0.94 (0.81–1.09)	0.41	0.89 (0.72–1.11)	0.30
Class III AAD at discharge	1.36 (0.55–3.36)	0.51	1.47 (0.48–4.46)	0.50	0.47 (0.06–3.71)	0.47
LV volumes and function						
LVEDV index, per 10mL/m^2↑	1.00 (0.93–1.06)	0.91	0.93 (0.83–1.04)	0.18	0.98 (0.87–1.10)	0.70
LVESV index, per 10mL/m^2↑	0.99 (0.92–1.06)	0.71	0.90 (0.80–1.02)	0.086	0.97 (0.87–1.09)	0.64
LVEF, per 10%↓	0.74 (0.54–1.01)	0.054	0.55 (0.36–0.83)	**0.005**	0.85 (0.51–1.41)	0.52
LV mass index, per 10g/m^2↑	0.88 (0.73–1.07)	0.20	0.89 (0.72–1.11)	0.31	0.75 (0.51–1.10)	0.14
RV volumes and function						
RVEDV index, per 10mL/m^2↑	1.04 (0.94–1.16)	0.45	1.04 (0.91–1.18)	0.59	1.04 (0.87–1.24)	0.65
RVESV index, per 10mL/m^2↑	1.01 (0.90–1.14)	0.83	0.99 (0.85–1.15)	0.92	1.00 (0.82–1.23)	0.98
RVEF, per 10%↓	1.01 (0.79–1.30)	0.92	0.94 (0.68–1.29)	0.68	0.94 (0.61–1.45)	0.78
T1 corrected, per 50ms↓	0.65 (0.45–0.93)	**0.020**	0.58 (0.37–0.92)	**0.020**	1.22 (0.66–2.26)	0.53
LGE						
LGE presence	2.71 (1.10–6.69)	**0.031**	∞	**< 0.001**	0.59 (0.17–2.05)	0.41
LGE extent						
Total LGE, per 10g↑	1.47 (1.10–1.97)	**0.010**	1.90 (1.35–2.67)	**< 0.001**	0.87 (0.48–1.59)	0.66
Core, per 10g↑	2.38 (1.34–4.22)	**0.003**	4.28 (2.15–8.51)	**< 0.001**	0.74 (0.22–2.49)	0.63
Border zone, per 10g↑	1.79 (1.03–3.10)	**0.039**	2.59 (1.38–4.86)	**0.003**	0.80 (0.26–2.48)	0.70

Abbreviations as in Table 1. When events only occurred in one subgroup, hazard ratios were infinite(∞) and p-values were derived from Kaplan-Meier analyses.

Finally, the area with 51-75% transmural LGE was a particularly strong predictor for monomorphic VT, whereas the area with 1-25% transmural LGE was not significantly associated with monomorphic VT (Table 3). Only the area of 51-75% transmural LGE remained an independent predictor when adjusted for each of the other transmurality categories (Supplemental Table 4).

Table 3. Specific LGE characteristics predicting monomorphic VT

Univariate analyses	Amount of LGE	Predictive value for monomorphic VT	
	Median (IQR)	Hazard ratio (95% CI)	p
LGE location †			
LGE in basal segments, g	2.0 (0.0–7.7)	3.82 (2.11–6.93)†	**< 0.001**
LGE in nonbasal segments, g	1.1 (0.0–4.0)	2.17 (1.13–4.17)†	**0.020**
LGE according to % of maximal signal intensity			
>70%, g	0.6 (0.0–1.8)	1.55 (1.29–1.85)	**< 0.001**
60-70%, g	0.7 (0.0–1.6)	1.66 (1.28–2.13)	**< 0.001**
50-60%, g	1.2 (0.0–2.4)	1.29 (1.11–1.50)	**0.001**
40-50%, g	1.8 (0.0–4.3)	1.21 (1.07–1.36)	**0.003**
30-40%, g	2.9 (0.0–7.0)	1.12 (1.03–1.21)	**0.006**
LGE transmurality areas ‡			
76-100%, cm^2	1.6 (0.0–7.0)	1.05 (1.01–1.10)	**0.029**
51-75%, cm^2	1.6 (0.0–4.6)	1.22 (1.11–1.34)	**< 0.001**
26-50%, cm^2	3.4 (0.0–9.5)	1.09 (1.02–1.16)	**0.007**
1-25%, cm^2	4.8 (0.0–12.1)	1.04 (0.99–1.08)	0.092

† per 10g † ‡ based on total LGE (≥35% of maximal SI)

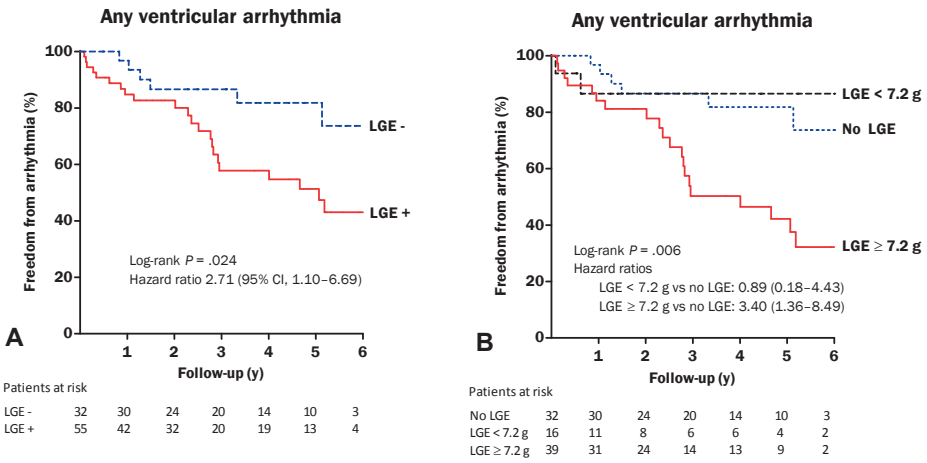

Figure 3. LGE on CMR and any ventricular arrhythmia during follow-up.
LGE presence predicted any ventricular arrhythmia during follow-up. The risk for ventricular arrhythmia was only increased in patients with ≥7.2g LGE.

DISCUSSION

In this study we analyzed the impact of myocardial scar, assessed by LGE-CMR, on different types of ventricular arrhythmias in NIDCM. We found that LGE was an important predictor for monomorphic VT, but not for polymorphic VT/VF. The optimal cut-off value for the extent of LGE to predict monomorphic VT was 7.2g. Patients with LGE extent <7.2g were at very low risk for monomorphic VT. Specific LGE characteristics associated with a high risk for monomorphic VT were LGE extent in basal segments, extent with >60% of maximal signal intensity and area with 51-75% transmural scar. Of importance, patients without LGE remain at risk for potentially lethal polymorphic VT/VF, and the only predictor for polymorphic VT/VF was a history of OHCA-VF.

Myocardial scar and type of ventricular arrhythmia

The presence of LGE on CMR has been reported to predict combined arrhythmic endpoints.[2-4,16] The present study is the first to analyze the predictive value of clinical and CMR parameters separately for monomorphic VT and polymorphic VT/VF. Patients presenting with sustained monomorphic VT had a substantially larger extent of LGE compared to patients without prior arrhythmias. Remarkably, the smallest LGE extent was observed in patients after OHCA-VF and accordingly, the predictive value of LGE for ventricular arrhythmias during follow-up was entirely explained by LGE predicting monomorphic VT, but not polymorphic VT/VF. This strong association between LGE and monomorphic VT is supported by studies on integration of CMR-derived data during VT ablation in patients with non-ischemic LV cardiomyopathy.[5,7,8]

The optimal cut-off for LGE extent to predict monomorphic VT was 7.2g. Patients with <7.2g LGE were at very low risk for monomorphic VT. Prior studies have identified 4–6.1% LGE as the optimal cut-off value for different combined endpoints (cardiovascular death and appropriate ICD therapy[1]; all-cause mortality and hospitalization for cardiovascular event;[4] cardiac death, hospitalization for decompensated heart failure and appropriate ICD discharge[16]). To the best of our knowledge, none has analyzed cut-off values for prediction of arrhythmic endpoints.

When LGE extent was analyzed separately in basal or nonbasal segments, the basal LGE extent appeared to be a stronger predictor for monomorphic VT. This finding is consistent with VT ablation studies reporting predominantly basal substrates for monomorphic VT in non-ischemic LV cardiomyopathy.[8] Similar to observations in post-infarct patients, basal scars and mitral/aortic annuli may serve as un-excitable barriers that can define parts of the re-entry circuit of monomorphic VT.

Other LGE features strongly associated with monomorphic VT were >60% of maximal signal intensity and 51-75% transmurality. This is in line with our prior findings during VT ablation procedures, demonstrating that the critical VT isthmus sites are typically

located close to the core-border zone transition (i.e., the 50% of maximal signal intensity cut-off value) and to >75% transmural scar.[17] These more specific LGE features may facilitate identification of NIDCM patients at risk for monomorphic VT.

Diffuse fibrosis and ventricular arrhythmias

The present study also analyzed post-contrast T1 values, which have been shown to correlate with the amount of diffuse fibrosis in biopsy specimens.[14] T1 values were similar between patients presenting with sustained monomorphic VT, OHCA-VF and no prior ventricular arrhythmias. In the latter group T1 values did not predict any type of ventricular arrhythmia during follow-up. Prior studies using endomyocardial biopsy specimens could also neither demonstrate a correlation between fibrosis content and history of ventricular arrhythmias,[18] inducible sustained monomorphic VT,[19] and LGE on CMR,[20] nor between the amount of interstitial tissue and arrhythmic events during follow-up.[21] Of interest, some data suggest that the microscopic pattern of fibrosis, rather than the amount may be important for arrhythmias.[22] Future studies are required to evaluate whether T1 mapping may contribute to the identification of specific arrhythmogenic substrates.

Predicting polymorphic VT/VF

Although we could identify clinical and CMR characteristics with predictive value for monomorphic VT, the only predictor for polymorphic VT/VF was a history of OHCA-VF. Neither LV and RV volumes and function, nor LGE presence and extent were associated with polymorphic VT/VF. It therefore appears that polymorphic VT/VF cannot be predicted with the same methods/parameters that apply for monomorphic VT. More insights are required into the substrate and related mechanisms of polymorphic VT/VF in patients with NIDCM to identify predictors for these arrhythmias, which may include parameters that are beyond the scope of imaging techniques.

Limitations

Not all patients with NIDCM underwent CMR before ICD implantation, and although patient characteristics were similar to prior studies in patients with NIDCM undergoing CMR and ICD implantation,[1,3] we cannot exclude a selection bias. T1 measurement is considered to be a marker for diffuse fibrosis, but is validated only to a limited extent by histology in patients with NIDCM.[14] The LGE core, but not the border zone definition has been validated by histopathology in NIDCM.[2] Also, core and border zone may not be comparable between patients after myocardial infarction and NIDCM due to differences in maximal LGE signal intensity. The present study did not allow differentiation between VTs based on scar-related re-entry or other mechanisms such as triggered activity. Follow-up was relatively long (median 45 months), but the sample size was limited and the multivariable models therefore had to be restricted to 2-3 variables.

CONCLUSIONS

The present study provides evidence that different types of ventricular arrhythmias are due to different underlying substrates in patients with NIDCM. The presence and extent of LGE on CMR identifies patients who are at risk for monomorphic VT, but not those at risk for potentially fatal polymorphic VT/VF. Only patients with a significant amount of myocardial scar (i.e., ≥7.2g) appeared to be at high risk for monomorphic VT. In addition, specific LGE features (extent in basal segments, LGE with >60% of maximal signal intensity, LGE area with 51-75% transmurality) further indicate a predisposition for monomorphic VT. Although patients without LGE are at relatively low risk for ventricular arrhythmias during follow-up, they still remain at risk for potentially fatal polymorphic VT/VF.

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CLINICAL PERSPECTIVES

Myocardial scar, assessed by LGE-CMR, has been shown to predict appropriate ICD therapy and sudden cardiac death in patients with NIDCM. However, ventricular arrhythmias encompass monomorphic VT, polymorphic VT and VF which may be related to different underlying substrates. The present study is the first to evaluate the relation between myocardial scar and different types of arrhythmia in NIDCM. Importantly, it is demonstrated that LGE predicts monomorphic VT, but not polymorphic VT/VF. Specific LGE features (including mass ≥ 7.2g, basal location, higher signal intensity, and area with 51-75% transmurality) were associated with a high risk for monomorphic VT. Although patients without LGE were at relatively low risk for ventricular arrhythmias, they still remained at risk for polymorphic VT/VF. Despite the availability of advanced measures of LV and RV volumes and function and of LGE indices, the only predictor for polymorphic VT/VF was a history of out-of-hospital cardiac arrest.

These novel insights may have important implications for risk stratification and therapeutic interventions. The risk for monomorphic VT in patients with NIDCM can be predicted by the presence, location and geometry of LGE on CMR, which may be useful for selection of patients that benefit from VT ablation at the time of ICD implantation. It is important to recognize that patients without LGE remain at risk for potentially fatal polymorphic VT/VF. More insights are required into the substrate and mechanisms of the different ventricular arrhythmias in patients with NIDCM to also identify those at risk for polymorphic VT/VF.

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Supplemental Table 1. Baseline characteristics and ventricular arrhythmias during follow-up.

	No arrhythmia (n=59)	Monomorphic VT (n=18)		Polymorphic VT/VF (n=10)	
			p*		p*
Age	55±14	60±9	0.17	52±13	0.45
Male gender	30 (51%)	15 (83%)	**0.014**	9 (90%)	**0.035**
Presenting arrhythmia					
OHCA	8 (14%)	1 (6%)	0.68	4 (40%)	0.064
SMVT	1 (2%)	9 (50%)	**< 0.001**	2 (20%)	0.053
Symptomatic heart failure	43 (73%)	10 (56%)	0.17	5 (50%)	0.16
History of AF / atrial flutter	9 (15%)	3 (17%)	1.00	1 (10%)	1.00
History of hypertension	13 (22%)	11 (61%)	**0.002**	3 (30%)	0.69
Diabetes mellitus	1 (2%)	5 (28%)	**0.002**	1 (10%)	0.27
eGFR, mL/min/1.73m^2	73±22	67±20	0.31	75±36	0.90
QRS duration, ms	134±32	129±33	0.57	125±27	0.41
Class III AAD at discharge	8 (14%)	4 (22%)	0.46	1 (10%)	1.00
LV volumes and function					
LVEDV index, 10mL/m^2	154 (123–176)	124 (100–165)	0.056	128 (116–195)	0.71
LVESV index, 10mL/m^2	113 (82–139)	72 (61–103)	**0.008**	74 (66–160)	0.38
LVEF, %	27±11	37±13	**0.001**	33±13	0.18
LV mass index, g/m^2	75 (60–93)	68 (62–81)	0.77	67 (49–91)	0.41
RV volumes and function					
RVEDV index, mL/m^2	77 (64–95)	81 (70–115)	0.33	98 (72–103)	0.19
RVESV index, mL/m^2	39 (28–59)	41 (31–58)	0.66	42 (33–54)	0.61
RVEF, %	46±16	49±12	0.58	48±16	0.73
T1 corrected, ms	332±55	362±78	0.082	322±62	0.64
LGE					
LGE presence	33 (56%)	18 (100%)	**0.001**	5 (50%)	0.75
LGE extent					
Total LGE, g	2.3 (0.0–10.2)	15.8 (9.7–24.3)	**< 0.001**	6.9 (0.0–15.7)	0.60
Core, g	1.0 (0.0–3.8)	9.4 (3.8–14.5)	**< 0.001**	2.0 (0.0–9.3)	0.67
Border zone, g	0.8 (0.0–6.6)	6.9 (4.7–10.7)	**< 0.001**	2.6 (0.0–9.8)	0.72

Data are expressed as number (percentage), mean ± standard deviation or median (interquartile range). AF indicates atrial fibrillation; eGFR, estimated glomerular filtration rate; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; OHCA, out-of-hospital cardiac arrest; RV, right ventricular; SMVT, sustained monomorphic ventricular tachycardia.

* vs. no arrhythmia

Supplemental Table 2. Extent of LGE adjusted for other predictors of any ventricular arrhythmia and monomorphic VT

Multivariate analyses	Any ventricular arrhythmia		Monomorphic VT	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Model 1				
Total LGE, per 10g ↓	1.42 (1.05–1.93)	0.023	1.87 (1.32–2.66)	< 0.001
Male gender	3.24 (1.12–9.39)	0.030	2.46 (0.71–8.53)	0.16
Model 2				
Total LGE, per 10g ↓	1.36 (1.00–1.85)	0.049	1.63 (1.14–2.32)	0.007
History of hypertension	1.87 (0.84–4.14)	0.12	3.26 (1.18–8.96)	0.022
Model 3				
Total LGE, per 10g ↓	1.25 (0.90–1.74)	0.18	1.52 (1.03–2.25)	0.035
Diabetes mellitus	4.80 (1.44–16.01)	0.011	5.49 (1.43–21.18)	0.013
Model 4				
Total LGE, per 10g ↓	1.52 (1.12–2.05)	0.007	2.08 (1.42–3.03)	< 0.001
LVEF, per 10% ↓	0.72 (0.53–0.98)	0.034	0.55 (0.37–0.80)	0.002
Model 5				
Total LGE, per 10g ↓	1.46 (1.08–1.98)	0.014	1.97 (1.35–2.86)	< 0.001
T1 corrected, per 50ms ↓	0.65 (0.45–0.93)	0.018	0.57 (0.37–0.90)	0.016

LGE indicates late gadolinium enhancement; LVEF, LV ejection fraction.

Supplemental Table 3. Predictors of any ventricular arrhythmia and monomorphic VT in primary prevention patients.

Univariate analyses	Any ventricular arrhythmia		Monomorphic VT	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	P
Age, per 5 years ↓	1.04 (0.84–1.28)	0.74	1.17 (0.85–1.60)	0.33
Male gender	9.87 (1.29–75.53)	0.028	5.11 (0.63–41.55)	0.13
Symptomatic heart failure	1.52 (0.34–6.78)	0.59	1.76 (0.22–14.34)	0.60
History of AF / atrial flutter	1.47 (0.46–4.69)	0.52	1.23 (0.25–6.14)	0.80
History of hypertension	4.40 (1.52–12.75)	0.006	∞	< 0.001
Diabetes mellitus	18.69 (4.08–85.69)	< 0.001	41.69 (6.79–256.14)	< 0.001
eGFR, per 10mL/min/1.73m^2 ↓	1.30 (1.00–1.68)	0.052	1.27 (0.90–1.80)	0.18
QRS duration, per 10ms ↓	0.91 (0.76–1.09)	0.32	1.02 (0.82–1.28)	0.85
Class III AAD at discharge	1.36 (0.38 - 4.88)	0.64	0.71 (0.09 - 5.78)	0.75
LV volumes and function				
LVEDV index, per 10mL/m^2 ↓	1.06 (0.99–1.13)	0.11	1.01 (0.90–1.13)	0.85
LVESV index, per 10mL/m^2 ↓	1.06 (0.99–1.14)	0.098	1.00 (0.90–1.13)	0.94
LVEF, per 10% ↓	1.23 (0.72–2.10)	0.44	0.81 (0.42–1.55)	0.53
LV mass index, per 10 g/m^2 ↓	1.10 (0.89–1.37)	0.37	1.06 (0.80–1.41)	0.67
RV volumes and function				
RVEDV index, per 10mL/m^2 ↓	1.05 (0.91–1.21)	0.51	1.04 (0.85–1.25)	0.73
RVESV index, per 10mL/m^2 ↓	1.05 (0.92–1.20)	0.47	1.01 (0.83–1.23)	0.89
RVEF, per 10% ↓	1.23 (0.87–1.73)	0.24	1.03 (0.66–1.63)	0.89
T1 corrected, per 50ms ↓	0.79 (0.47–1.32)	0.37	0.78 (0.40–1.55)	0.48
LGE				
LGE presence	2.41 (0.67–8.66)	0.18	∞	0.024
LGE extent				
Total LGE, per 10g ↓	1.46 (0.97–2.22)	0.072	1.84 (1.12–3.03)	0.016
Core, per 10g ↓	2.14 (0.88–5.20)	0.094	3.43 (1.19–9.91)	0.023
Border zone, per 10g ↓	1.98 (0.95–4.13)	0.069	2.96 (1.22–7.17)	0.016

AF indicates atrial fibrillation; eGFR, estimated glomerular filtration rate; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; RV right ventricular; RVEF, RV ejection fraction.

Supplemental Table 4. Specific LGE characteristics predicting monomorphic VT – multivariable models.

Multivariable analyses	Monomorphic VT	
	Hazard ratio (95% CI)	p
Model 1: LGE in basal and nonbasal segments		
Basal segments, per 10g	3.95 (1.88–8.32)	< 0.001
Nonbasal segments, per 10g	0.93 (0.35–2.46)	0.88
Model 2: Signal intensity categories		
>60% of maximal SI, per g	1.36 (1.16–1.61)	< 0.001
30–60% of maximal SI, per g	0.97 (0.91–1.04)	0.40
Model 3: Transmurality categories (A)		
51–75% transmural LGE, per cm^2	1.25 (1.12–1.40)	< 0.001
1–25% transmural LGE, per cm^2	0.98 (0.93–1.03)	0.45
Model 4: Transmurality categories (B)		
51–75% transmural LGE, per cm^2	1.31 (1.11–1.55)	0.001
26–50% transmural LGE, per cm^2	0.94 (0.84–1.06)	0.31
Model 5: Transmurality categories (C)		
51–75% transmural LGE, per cm^2	1.22 (1.09–1.37)	0.001
76–100% transmural LGE, per cm^2	1.00 (0.93–1.07)	0.95

LGE indicates late gadolinium enhancement; SI, signal intensity.