

Prediction of Life-Threatening Arrhythmic Events in Patients With Chronic Myocardial Infarction by Contrast-Enhanced CMR

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OBJECTIVES We hypothesized that infarct transmuralty assessed with late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) predicts arrhythmic events in patients with chronic myocardial infarction.

BACKGROUND Patients with decreased left ventricular function due to chronic myocardial infarction are at increased risk for life-threatening arrhythmias related to infarcted tissue. LGE-CMR accurately detects infarct morphology.

METHODS We prospectively enrolled 52 patients with chronic myocardial infarction referred for primary preventive implantable cardioverter-defibrillator (ICD) implantation following MADIT (Multi-center Automatic Defibrillator Implantation Trial) study criteria. Using LGE-CMR, left ventricular volumes, function, and infarct morphology were assessed including calculation of total and relative infarct mass, infarct border, infarct border zone, and infarct transmuralty.

RESULTS Patients were followed for $1,235 \pm 341$ days. The primary combined endpoint including appropriate device therapy (ICD discharge or antitachycardia pacing) or death from cardiac cause occurred in 16 individuals resulting in an annual event rate of 4.7%. Six patients received an appropriate shock, 7 patients received recurrent appropriate antitachycardia pacing for sustained ventricular tachycardia, and 3 patients died of cardiac cause. There was a significant association to relative infarct mass ($38 \pm 8\%$ vs. $28 \pm 14\%$, $p = 0.02$), infarct transmuralty (24 ± 8 g vs. 16 ± 12 g, $p = 0.02$), and relative infarct transmuralty (RIT) ($63 \pm 12\%$ vs. $48 \pm 23\%$, $p = 0.01$). In separate logistic regression models, no variable emerged as significant when combined with RIT. As a single effect, RIT emerged as a predictor of the primary endpoint ($p = 0.02$). A RIT cutoff at 43% resulted in a sensitivity of 88%, a specificity of 50%, a positive predictive value of 44%, and a negative predictive value of 90%.

CONCLUSIONS In patients with chronic myocardial infarction scheduled for primary preventive ICD implantation, infarct transmuralty as defined by LGE-CMR identifies a subgroup with increased risk for life-threatening arrhythmias and cardiac death. (J Am Coll Cardiol Img 2011;4:871–9) © 2011 by the American College of Cardiology Foundation

Spontaneous ventricular arrhythmias are considered to be critically involved in the pathophysiology of sudden cardiac death (1), one of the leading causes of mortality worldwide, causing an estimated 184,000 to 462,000 deaths/year in the United States alone (2). In particular, patients with heart failure due to a previous myocardial infarction are at very high risk with an annual sudden cardiac death rate of 4% to 7% (3). Insertion of implantable cardioverter-defibrillators (ICDs) as primary preventive therapy in this patient population was shown to significantly reduce mortality when compared with standard medical therapy (4–6). Although of proven efficacy, ICD therapy is associated with survival benefit in only a small fraction of patients. Specifically, it has been estimated that to save 1 life, 18 patients would

have to get an ICD inserted, resulting in an enormous burden on national health systems (4). Moreover, only approximately one-third of these patients receive adequate therapy from the ICD within 3 years after implantation (7). Furthermore, despite considerable improvements in device technology in the past years, there is still a fairly high rate of adverse events (3,7). These considerations demonstrate the need for an effective risk-stratifying strategy to identify patients who will most/least likely benefit from this therapy. Non-invasive risk stratification in this patient population has achieved unsatisfactory results to date (2). In particular, the use of left ventricular (LV) ejection fraction has limitations, and relying on electrocardiogram provocation tests such as programmed ventricular stimulation in electrophysiology studies (EPS) yielded controversial results (8). One aspect that may show promise is to target the focal substrate, that is, the infarct scar initiating the arrhythmic cascade that leads to sudden cardiac death. Currently, late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) is a well-established and accurate method to assess scar morphology in the clinical setting (9), and there are

first results describing its relation to inducible arrhythmias (10). We hypothesized that infarct transmural assessed with LGE-CMR prior to ICD insertion would independently predict life-threatening arrhythmias in a cohort of patients with chronic myocardial infarction and clinical characteristics similar to the MADIT (Multicenter Automatic Defibrillator Implantation Trial) study population (4,6).

METHODS

Patients. This prospective study was conducted between May 2004 and August 2009 in a single tertiary referral center. All patients referred to our department for ICD implantation between May 2004 and June 2007 ($n = 140$) were screened and consecutively included if they fulfilled primary prevention criteria for sudden cardiac death following MADIT I or II: documented previous myocardial infarction (adapted to current guidelines: more than 40 days of age [11]); LV ejection fraction, by non-CMR method, below 30% or LV ejection fraction below 35% and documented nonsustained ventricular tachycardia (VT) in conjunction with a positive EPS. The screening procedure is shown in Figure 1. Baseline study group characteristics are given in Table 1. All patients gave informed consent, and the study was approved by the institutional ethics committee.

CMR protocol. Patients underwent a CMR study using a 1.5-T clinical CMR system (Avanto or Sonata, Siemens Healthcare, Erlangen, Germany) 36 ± 78 days before ICD implantation. The imaging protocol comprised state-of-the-art electrocardiogram-gated cine steady-state free-precession acquisitions for the analysis of cardiac dimensions and function in 2 long-axis planes as well as a stack of contiguous short-axis slices (6-mm slice thickness) covering the left ventricle from base to apex without gap (parameters: matrix 256×224 , field of view 340 mm, flip angle 75° , echo time 1.2 ms, repetition time 3 ms, and a temporal resolution of 30 ms). Approximately 10 to 15 min after intravenous injection of 0.2 mmol/kg gadolinium diethylenetriamine pentaacetate (Magnevist, Bayer Schering Pharma, Berlin, Germany), late enhancement imaging was per-

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

EPS = electrophysiology study

IB(Z) = infarct border (zone)

ICD = implantable cardioverter/defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

RIM = relative infarct mass

RIT = relative infarct transmural

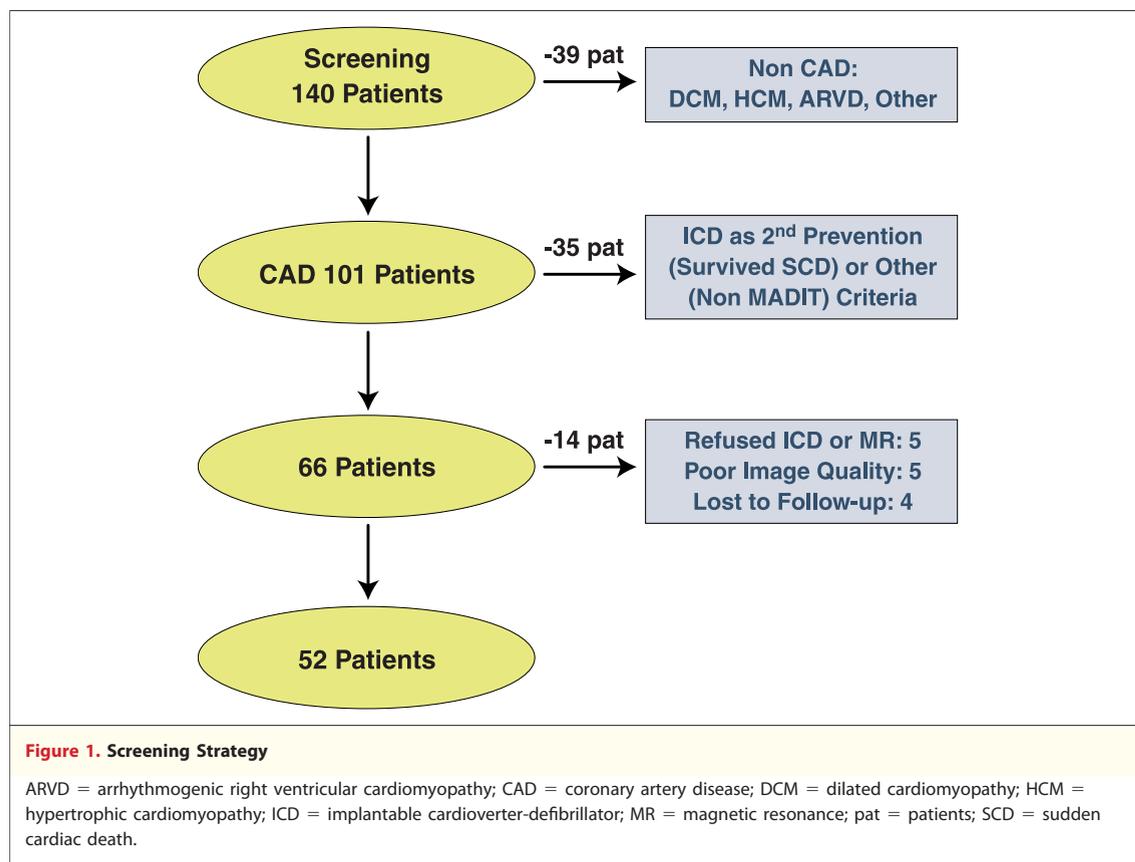
ROC = receiver-operator characteristic

ROI = region of interest

VT = ventricular tachycardia

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formed in the same slice orientation as the cine images using a standard 2-dimensional inversion-recovery gradient-echo sequence. The inversion time was manually adjusted to achieve optimal suppression of signal from normal myocardium (parameters: matrix 256×192 , field of view 350×262 mm, flip angle 30° , echo time 4.3 ms, repetition time 500 ms, inversion time 250 to 300 ms).

CMR image post-processing and data analysis. Images and data were analyzed by an experienced cardiologist blinded to clinical and electrophysiology data using a research version of MASS (Leiden University Medical Center, the Netherlands). Left ventricular dimensions and function were calculated from the cine images. In LGE images, epicardial and endocardial contours as well as a region of interest (ROI) within remote myocardium were traced manually in each slice. Images were analyzed semiautomatically: areas of LGE were defined as a signal intensity of more than 5 standard deviations (SD) above remote myocardium as previously described (12). Each slice was segmented in 100 chords starting from the anterior right ventricular insertion point, and for each chord, the amount of LGE was calculated as well as the amount of transmural extent (above 75% wall thickness). Ad-

ditionally, for each chord, the presence of an interface between remote myocardium and LGE was assessed, and if present, the corresponding surface area was included in the infarct border (IB) (Figs. 2 and 3) calculation. Infarct border zone (IBZ) was defined as areas with signal intensity of more than 2 or 3 SD above remote myocardium but below 3, 4, or 5 SD and below 4 or 5 SD, respectively (reflecting infarct core and heterogeneity, adapted from previously described studies) (13,14). These measurements resulted in 6 different border zone measures (Table 2).

The evaluated parameters included LV mass and end-diastolic volume, calculation of LV ejection fraction, infarcted mass, relative infarct mass (RIM: percent of LV mass), the amount of transmurally infarcted mass normalized to LV mass (infarct transmural) and normalized to total infarct mass (RIT). To further evaluate infarct morphology, IB (mm^2) and IBZ (g) were calculated as described in the previous text (Figs. 2 and 3).

ICD implantation and clinical follow-up. All ICDs were programmed in a standardized fashion. Detection criteria for VT and ventricular fibrillation were as follows: VT was considered if 12 of 16 consecutive heart beats were at a heart rate within

Table 1. Baseline Characteristics

	With Event (n = 16)	Without Event (n = 36)	p Value
Clinical data			
Age, yrs	73 ± 10	69 ± 10	0.28
Body mass index, kg/m ²	27 ± 3	27 ± 4	0.36
Infarct age, months	117 ± 79	80 ± 73	0.19
NYHA functional class			0.95*
I	2	5	
II	10	22	
III	4	9	
IV	0	0	
Hypertension	13 (81%)	33 (92%)	0.36
Hypercholesterolemia	13 (81%)	27 (75%)	0.73
Diabetes	6 (38%)	17 (47%)	0.56
Current smoker	1 (6%)	7 (19%)	0.41
Medication			
Beta-blocker	15 (94%)	35 (97%)	0.52
ACE inhibitor	16 (100%)	35 (97%)	1.00
Statin	14 (88%)	34 (94%)	0.58
Amiodarone	3 (19%)	6 (17%)	1.00
Other antiarrhythmic agent	1 (6%)	3 (17%)	1.00
Diuretics	13 (81%)	23 (64%)	0.33
Electrocardiogram			
QRS duration, ms	131 ± 35	112 ± 27	0.14
Left bundle branch block	5 (31%)	5 (14%)	0.25
Right bundle branch block	3 (19%)	4 (11%)	0.66
Atrial fibrillation	6 (38%)	5 (14%)	0.07
<small>Values are mean ± SD, n, or n (%). The Fisher exact test for categorical and Mann-Whitney <i>U</i> test for continuous variables were used. *Mann-Whitney <i>U</i> test on differences in NYHA functional classes. ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.</small>			

176 and 201 beats per minute (beats/min). Ventricular fibrillation was considered if 8 of 12 consecutive heart beats were at a heart rate of at least 202 beats/min. After ICD implantation, patients were followed up, including ICD interrogation, after 3 months and then every 6 months or as clinically indicated. The primary endpoint of the study was the occurrence of an appropriate discharge, anti-tachycardia pacing, or death from cardiac cause. Data were analyzed by an experienced electrophysiologist blinded to the CMR results.

Statistical analysis. The analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute, Cary, North Carolina). Continuous variables are expressed as mean ± SD. Baseline characteristics were compared between patients that reached the endpoint and those that did not using Fisher exact test for categorical and Mann-Whitney *U* test for continuous variables. The evaluation of potential predictors for life-threatening ventricular arrhythmia and cardiac mortality was performed using

multiple separate logistic regression models. The following variables were tested: age, LV ejection fraction, LV end-diastolic volume, LV mass, total infarct mass and RIM, parameters of infarct morphology (IB, IBZ, infarct transmural, RIT), and all baseline clinical characteristics. The variables were tested in separate models with RIT as a second explaining factor to select only variables in the final model that add significantly to the RIT. Receiver-operator characteristic (ROC) analysis was performed on significant predictors to calculate the accuracy and other diagnostic parameters and to determine a cutoff point at the maximum sum of sensitivity and specificity using the Youden index. Clopper-Pearson 95% confidence intervals were calculated for the diagnostic parameters. The 95% confidence interval for the area under the ROC curve was calculated by bootstrapping. Kaplan-Meier curves were calculated for the RIT to evaluate the performance of the predictor on the primary endpoint. Two-sided *p* values <0.05 were regarded as statistically significant.

RESULTS

Baseline characteristics. Fifty-two patients were enrolled in the present study. Their baseline characteristics are shown in Table 1, and the screening/inclusion strategy is illustrated in Figure 1. Medical therapies at baseline and basic risk factors were not different between patients who did or did not meet the combined endpoint (Table 1).

Electrophysiological and mortality data. The mean follow-up was 1,235 ± 341 days. Endpoint criteria were met in 16 patients, resulting in an annual event rate of 4.7%. Events occurred 714 ± 382 (70 to 1,516) days after ICD placement. Six patients received an appropriate shock, 7 patients received recurrent appropriate antitachycardia pacing for sustained VT, and 3 patients died of cardiac cause (2 patients died of advanced heart failure in hospital, 1 patient of presumable sudden cardiac death at home during sleep). All 6 patients with ICD shocks as well as 2 patients with an episode of antitachycardia pacing presented to the emergency room within 1 week after the event. In these patients, acute myocardial infarction as a trigger for arrhythmic events was ruled out by electrocardiogram and negative troponin levels. The remaining 5 patients with antitachycardia pacing presented to our outpatient clinic more than 1 week after the events and did not report episodes of acute chest pain or dyspnea.

CMR data. The baseline CMR values of the study population were as follows: mean LV mass 153 ± 39 g; LV end-diastolic volume 274 ± 93 ml; and mean LV ejection fraction $30 \pm 9\%$. LGE was observed in all patients included in the study with a mean infarct mass of 39 ± 21 g.

LGE extent and primary endpoint. Analysis of the CMR data showed that RIM, infarct transmural, and RIT were significantly associated with the endpoint ($p = 0.02$ each) (Table 2). All other parameters showed no significant association with the endpoint criteria, including LV ejection fraction, LV mass, LV end-diastolic volume, infarct mass, IB, and IBZ defined as areas of moderately increased signal (Table 2).

In separate multiple logistic regression models of RIT with one of the effects LV ejection fraction, LV mass, LV end-diastolic volume, infarct mass, RIM, IB, IBZ, infarct transmural, RIT, and all baseline characteristics, only RIT alone emerged as an independent predictor of the primary endpoint ($p = 0.02$). The odds ratio for RIT was 22.1 (95% confidence limits: 1.64 to 297.58). ROC analysis of RIT as a predictor for events (arrhythmic events and cardiac mortality) showed an area under the curve of 0.70 (95% confidence interval [CI]: 54% to 85%), that is, an accuracy of 70%. A cutoff at 43% for the RIT resulted in a sensitivity of 88% (14 of 16, 95% CI: 61% to 98%), a specificity of 50% (18 of 36, 95% CI: 33% to 67%), a positive predictive value of 44% (14 of 32, 95% CI: 26% to 62%), and a negative predictive value of 90% (18 of 20, 95% CI: 68% to 99%).

Using this cutoff, the study population was divided into 2 groups ($<43\%$ and $\geq 43\%$ RIT), and a Kaplan-Meier curve for event-free survival was calculated (Fig. 4). Only 2 of 16 (12%) patients in the group with less than 43% RIT showed an event compared with 14 of 16 (88%) in the group with $\geq 43\%$ RIT ($p = 0.04$). Separating the study population by LV ejection fraction (LV ejection fraction $<30\%$ vs. 30% to 35%) showed no significant difference between the MADIT populations (LV ejection fraction $<30\%$: 25 patients total, 17 patients with no event, 8 patients with an event; LV ejection fraction 30% to 35%: 27 patients total, 19 no event, 8 with an event; Fisher exact test $p = 1.00$).

DISCUSSION

The main result of our prospective study is that RIT seems to be a strong predictor for a composite endpoint of spontaneous life-threatening ventricu-

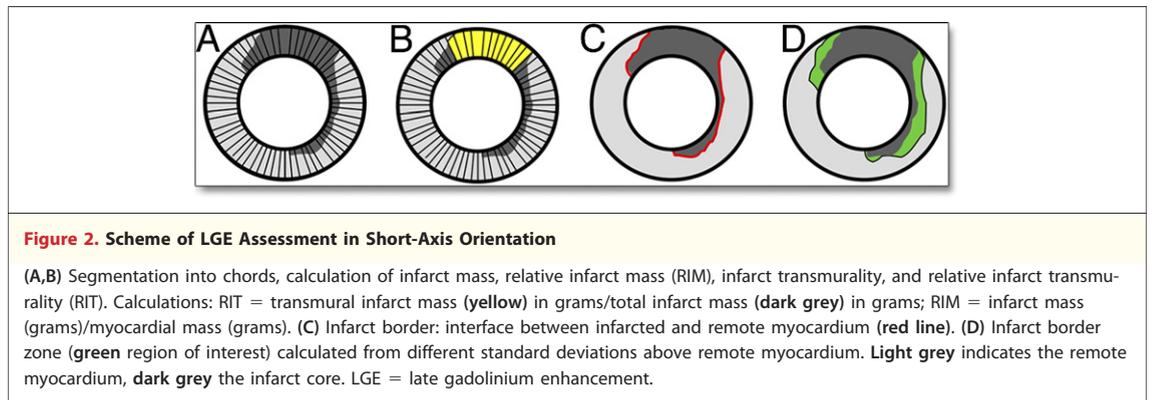
Table 2. Analysis of CMR Parameters as Predictors of the Study Endpoint

	With Event (n = 16)	Without Event (n = 36)	p Value
LV ejection fraction, %	28 ± 6	30 ± 8	0.31
LV end-diastolic volume, ml	286 ± 123	271 ± 78	0.61
LV mass, g	152 ± 27	154 ± 45	0.84
Infarct mass, g	46 ± 22	35 ± 20	0.09
RIM, % of LV mass	30 ± 14	21 ± 11	0.02*
Infarct border, mm ²	950 ± 404	952 ± 496	0.99
IBZ, g (LGE: 2-3 SD)	7.9 ± 2.2	8.6 ± 1.7	0.23
IBZ, g (LGE: 2-4 SD)	13.8 ± 4.2	13.6 ± 4.8	0.93
IBZ, g (LGE: 2-5 SD)	17.4 ± 5.1	19.2 ± 4.0	0.23
IBZ, g (LGE: 3-4 SD)	5.9 ± 2.3	5.4 ± 3.3	0.66
IBZ, g (LGE: 3-5 SD)	9.6 ± 3.1	10.6 ± 4.6	0.52
IBZ, g (LGE: 4-5 SD)	3.7 ± 1.6	5.1 ± 4.3	0.28
Infarct transmural, g	21 ± 13	12 ± 10	0.02*
RIT, % of infarct mass	64 ± 26	43 ± 26	0.01*

Values are mean \pm SD. * $p < 0.05$.
 CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricular; IBZ = infarct border zone; RIM = relative infarct mass; RIT = relative infarct transmural.

lar arrhythmias and cardiac mortality in chronic infarct patients scheduled for primary preventive ICD implantation. This finding was found to be independent of each of the established markers of adverse outcome like LV ejection fraction, LV end-diastolic volume, total infarct mass and RIM, and age as tested in separate logistic regression models and may therefore have implications for the risk stratification of chronic infarct patients. The limited sample size, however, did allow for testing RIT with only 1 other potential marker in a single model so we could not evaluate combinations of RIT with more than 1 other potential marker.

Several studies have documented a survival benefit with primary preventive implantation of ICD in heart failure patients, using LV ejection fraction as a determinant for risk stratification (4-6). Therefore, LV ejection fraction has become a major criterion for prophylactic ICD implantation despite being a poor indicator of treatment benefit. Recently, there is increased interest in characterizing infarct scar morphology as a potential candidate for better risk stratification strategies. Phenomena such as re-entry or distortion of intramyocardial sympathetic innervation play a key role in post-infarct arrhythmogenesis and are substantially affected by scar morphology (15). Specifically, earlier studies demonstrated a close relationship between scar size or transmural involvement and the risk of arrhythmia in animal models of myocardial infarction (16). LGE-CMR allows precise assessment of myocardial scar morphology with an accuracy matching that of histopathology (17,18). Additionally, LGE-



CMR is of increasing importance for risk stratification in cardiomyopathies (19) as well as coronary artery disease (20). Recently, LGE-CMR was shown as the strongest predictor of all-cause mortality in a large retrospective setting (21). In chronic myocardial infarction, infarct morphology as defined by LGE-CMR was also shown to be associated with inducibility of sustained VT in humans (10,13,22) as well as in animal models (23). Specifically, Bello et al. (10) found that infarct mass and IB size were better predictors of inducibility of VT in EPS than LV ejection fraction. However, inducibility of VT in EPS is only a surrogate parameter and seems to be of limited use in the prediction of

spontaneous VT, especially in patients meeting the MADIT criteria (24).

There is increasing interest in infarct tissue heterogeneity, specifically infarct border zone assessment, as a potential origin of arrhythmic triggers. Several studies showed an association between IBZ size and inducibility of ventricular arrhythmias in EPS (13,22), and recently, it was shown that LGE-driven infarct tissue heterogeneity is associated with spontaneous ventricular arrhythmias in patients after myocardial infarction (25). Unfortunately, infarct tissue heterogeneity and border zone suffers from different definitions today, making direct comparisons difficult. Some investigators use

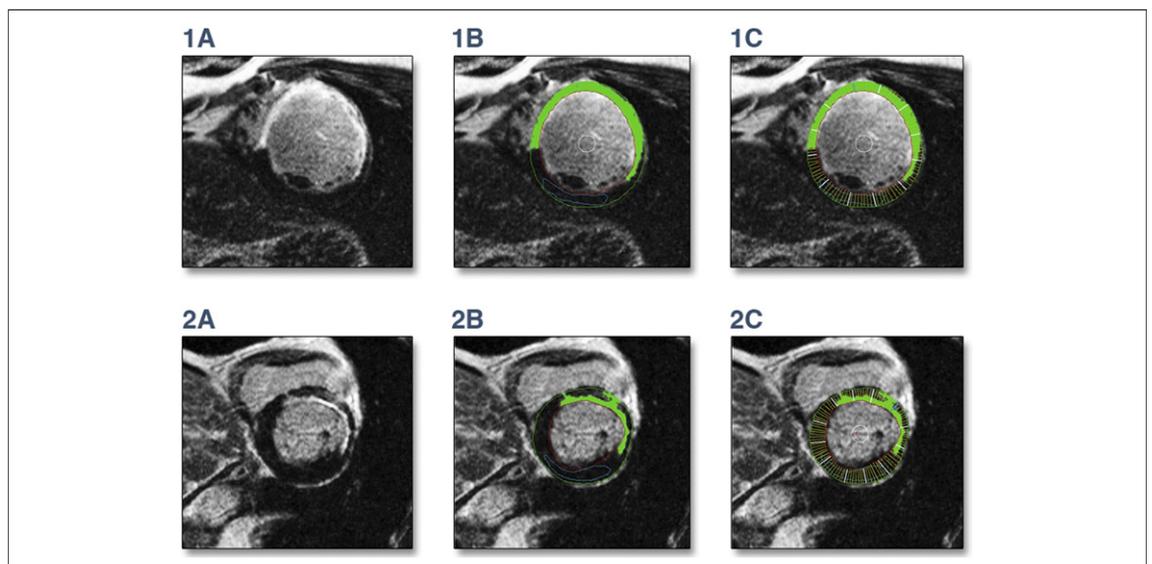


Figure 3. Assessment of LGE Parameters

(A) Typical end-diastolic mid-cavity LGE images of 2 patients with previous myocardial infarction (bright region) showing high (1) and low (2) RIT (overall RIT: Patient #1 = 76%, Patient #2 = 30%; LV ejection fraction: Patient #1 = 29%, Patient #2 = 21%; Patient #1 had sustained ventricular tachycardia terminated by ICD 121 days after implantation). (B) Semiautomated quantification of LGE defined as signal intensity (SI) greater than average SI +5 SD of remote myocardium. Transmural involvement is defined as LGE-extent >75% of wall thickness. Green contour indicates epicardial circumference, red contour indicates endocardial circumference, blue ROI indicates remote myocardium, and green ROI = +5 SD. (C) Segmentation into 100 chords (yellow lines). LV = left ventricular; ROI = region of interest; other abbreviations as in Figures 1 and 2.

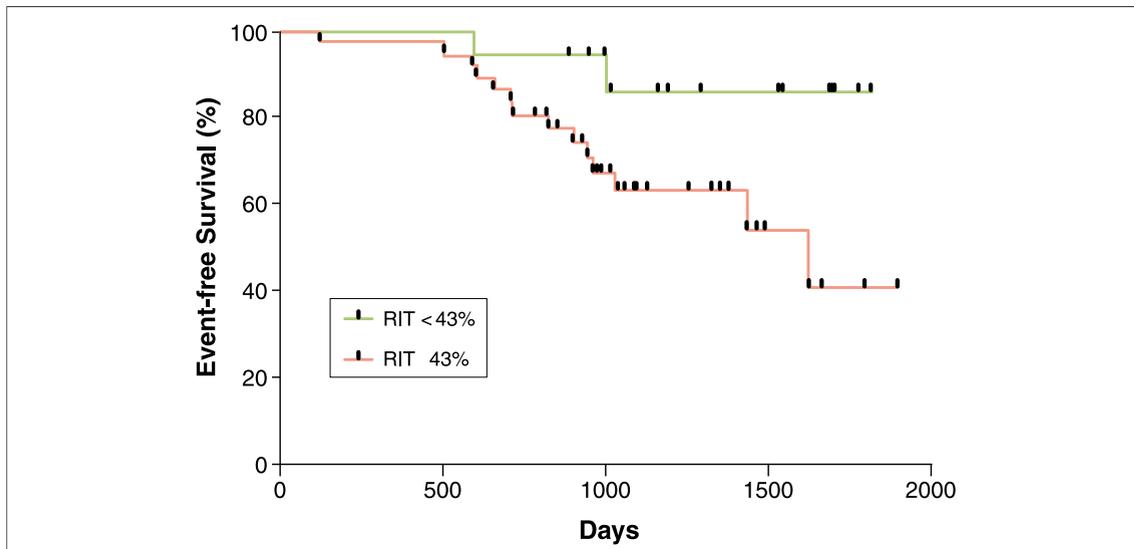


Figure 4. Kaplan-Meier Analysis Showing the Differences in Event-Free Survival

The patient population was divided according to a relative infarct transmural (RIT) cutoff value of 43% (derived from receiver-operator curve analysis).

the full-width half-maximum approach to define infarct core and periphery, whereas others defined infarct core and periphery according to differences in SD above remote myocardium using different cutoff values (13,14,22,25). In the present study, we did not find a significant association between any of our infarct periphery measures and the occurrence of the combined endpoint. This may be a result of population differences, as we strictly focused on patients matching MADIT criteria as well as differences in LGE-CMR assessment. Specifically, we used a thin-slice thickness, which could have led to less partial volume effects with a more precise IBZ definition and therefore to fundamental differences in IBZ assessment.

Kelle et al. (26) found total infarct size to be a strong predictor of future events in coronary artery disease patients with positive LGE-CMR. These data are consistent with our findings that RIM is a predictor of the composite endpoint of spontaneous VT and death in univariate analysis. Interestingly, the authors did not find an association between infarct transmural and cardiac events as presented in this study. This may be due to differences in the study populations (consecutive LGE-positive coronary artery disease patients with a mean LV ejection fraction of 45% vs. “MADIT patients” with a mean LV ejection fraction of 30% in our population) and due to methodological disparities in LGE assessment. A recent study by Desjardins et al. (17) fused electroanatomic mapping results with CMR images

in post-infarct patients with recurrent ventricular arrhythmia and showed that VT circuits are mainly located in the center of the LGE-CMR-defined infarcts. Even in cases with VT circuit detection in infarct periphery, these patients had mainly transmural infarct extensions (17), and electric instability was particularly increased in scar regions with a high transmural involvement and large infarct cores (17). These findings match former studies that found an association between infarct transmural and ventricular arrhythmias in animal models of myocardial infarction (16,27) and our results showing that infarct transmural is associated with life-threatening arrhythmias and mortality in post-infarct patients. Taken together, these different findings, including the present study, indicate it might not be infarct size that causes vulnerability to cardiac arrhythmia but rather the transmural infarct extension with alteration of sympathetic cardiac innervation. Large infarction with consecutively severely reduced ejection fraction are associated with increased mortality from cardiac arrhythmia, but considering the previously stated findings, this might only reflect a higher proportion of transmurally infarcted tissue, and transmural might be the more promising parameter for adequate risk assessment in post-myocardial infarction patients.

Study limitations. The present study was conducted at a single center with a relatively small sample size; the number of events was small, so that only strong effects can be detected besides effects that show

significance by chance only. The statistical power with regard to confirmative statistical testing was low. These results should therefore be interpreted with care and can only be regarded as a pilot study to provide basic data for the adequate planning of a confirmatory sufficiently powered multicenter study. This would also enable the verification and validation of the value of RIT as a biomarker, the cutoff point, and the performance of the presented marker on an independent dataset.

CONCLUSIONS

The extent of transmural scar formation, as assessed with LGE-CMR, seems to be a predictor of the composite endpoint of spontaneous life-threatening arrhythmias and cardiac death in post-infarct patients scheduled for primary preventive ICD im-

plantation. This finding needs to be confirmed by a larger multicenter clinical study.

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