Cardiac Imaging

Late Gadolinium Enhancement by Cardiovascular Magnetic Resonance Heralds an Adverse Prognosis in Nonischemic Cardiomyopathy

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Objectives	We examined whether the presence and extent of late gadolinium enhancement (LGE) by cardiovascular magnetic resonance (CMR) predict adverse outcomes in nonischemic cardiomyopathy (NICM) patients.
Background	Morbidity and mortality is high in NICM patients. However, the clinical course of an individual patient is unpredictable and current risk stratification approaches are limited. Cardiovascular magnetic resonance detects myocardial fibrosis, which appears as LGE after contrast administration and may convey prognostic importance.
Methods	In a prospective cohort study, 65 NICM patients with left ventricular (LV) ejection fraction ≤35% underwent CMR before placement of an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death. The CMR images were analyzed for the presence and extent of LGE and for LV function, volumes, and mass. Patients were followed for an index composite end point of 3 cardiac events: hospitalization for heart failure, appropriate ICD firing, and cardiac death.
Results	A total of 42% (n = 27) of patients had CMR LGE, averaging 10 ± 13% of LV mass. During a 17-month median follow-up, 44% (n = 12) of patients with LGE had an index composite outcome event versus only 8% (n = 3) of those without LGE (p < 0.001 for Kaplan-Meier survival curves). After adjustment for LV volume index and functional class, patients with LGE had an 8-fold higher risk of experiencing the primary outcome (hazard ratio 8.2, 95% confidence interval 2.2 to 30.9; p = 0.002).
Conclusions	A CMR LGE in NICM patients strongly predicts adverse cardiac outcomes. The CMR LGE may represent the end-organ consequences of sustained adrenergic activation and adverse LV remodeling, and its identification may significantly improve risk stratification strategies in this high risk population. (Imaging Techniques for Identifying Factors of Sudden Cardiac Death Risk; NCT00181233) (J Am Coll Cardiol 2008;51:2414–21) © 2008 by the American College of Cardiology Foundation

Patients with nonischemic cardiomyopathy (NICM) comprise one-third of the heart failure (HF) population and are at risk for significant morbidity and mortality (1,2). Nonischemic cardiomyopathy is the most common indication for heart transplantation. Ten-year survival is below 60% (3), with deaths often preceded by frequent hospitalizations

for HF exacerbations (4). Forty percent of deaths are sudden cardiac death (SCD), and placement of an implantable cardioverter-defibrillator (ICD) for primary prevention reduces arrhythmic deaths in NICM patients with left ventricular (LV) ejection fraction (LVEF) ≤35% (5–7). However, risk stratification remains challenging, particularly in the individual patient in whom the clinical course frequently correlates poorly with LVEF. Better risk-stratification tools might allow earlier intervention in high-risk patients, improving both quality of life and survival.

In patients with NICM, myocardial fibrosis has been identified pathologically (8). Macroscopic regions of fibrosis have also been visualized by cardiovascular magnetic resonance (CMR), appearing as areas of late gadolinium enhancement (LGE) (9–11). Increasing amounts of fibrosis

potentially result in increased LV stiffness and reduced LV compliance, thereby progressively impairing both diastolic and systolic function, reducing cardiac output (8). Myocardial fibrosis may also form a substrate for lethal re-entrant ventricular arrhythmias (12,13). We therefore hypothesized that the presence and extent of CMR LGE are associated with a higher risk of adverse cardiac outcomes in patients with NICM and LVEF ≤35%.

Methods

Patients. We conducted this pre-specified single-center prospective cohort study between April 2004 and April 2007 as part of a larger prospective registry of both non-ischemic and ischemic cardiomyopathy patients undergoing ICD implantation for primary prevention of SCD. The present study included consecutive nonselected patients with NICM and LVEF ≤35% by a clinically indicated non-CMR study (echocardiography or nuclear), referred for ICD by their treating cardiologist. All patients had coronary angiography and were classified as nonischemic if they had no history of myocardial infarction or revascularization and no evidence of coronary artery stenoses >50% of 2 or more epicardial vessels or left main or proximal left anterior descending coronary artery stenosis >50% (14). We excluded patients with prior arrhythmic indications for ICD placement (such as a history of syncope, cardiac arrest, or ventricular arrhythmias); New York Heart Association (NYHA) functional class IV; and acute myocarditis, congenital heart disease, hypertrophic cardiomyopathy, or infiltrative heart disease. Renal insufficiency with creatinine clearance <30 ml/min was added as an exclusion in July 2006. The study protocol was approved by the Johns Hopkins Hospital Institutional Review Board. All patients gave written informed consent.

MRI protocol. Before ICD implantation, patients underwent CMR using a 1.5-T scanner (Signa CV/i, GE Healthcare Technologies, Waukesha, WI; or Siemens Avanto, Erlangen, Germany). Cine images were acquired with a steady-state free-precession pulse sequence (TR 2.5 to 3.8, TE 1.1 to 1.6, average in-plane resolution 1.5 × 2.4 mm, flip angle 45° to 60°, temporal resolution 40 to 45 ms) in long-axis planes and contiguous 8-mm short-axis slices from the mitral annulus to the apex. Fifteen to thirty minutes after intravenous administration of 0.2 mmol/kg gadodiamide (Omniscan, GE Healthcare Technologies), delayed contrast-enhanced images were acquired using inversion-recovery fast gradient-echo pulse sequences (15,16) in the same short-axis locations as the cine images. To exclude artifact, short-axis imaging was repeated in 2 different phase-encoding directions and cross-sectional long axis views were also acquired. Imaging parameters were: TR 5.4 to 8.3 ms, TE 1.3 to 3.9 ms, average in-plane spatial resolution 1.4 to 1.5 × 2.2 to 2.4 mm, 8-mm slice thickness, 2-mm gap, TI 175 to 300 ms (adjusted as needed in the delayed-enhancement image acquisitions to optimally null

the signal of normal myocardium), 1 to 2 R-R imaging, and flip angle 20° to 25°.

Data analysis. Analysis of the CMR Digital Imaging and Communications in Medicine (DICOM) images was performed using CINEtool software (GE Healthcare Technologies). Left ventricular ejection fraction, volumes, and mass were quantified from the cine images by standard methods. Left ventricular volumes and mass were normalized to body surface area. Two observers blinded to the clinical outcome independently determined the dichotomous presence or absence of LGE by reviewing all short- and long-axis contrast-enhanced images; regions of elevated signal intensity had to be confirmed in 2 spatial orientations.

If CMR LGE was present, the quantitative extent of hyperenhancement was defined as regions with abnormally increased signal intensity greater than peak remote (17). For each short-axis cross section, after the endocardial and epicardial borders were traced, a region of interest averaging 50 mm^2 was defined within the normal remote myocardium in an area with uniform myocardial suppression free of artifacts. The peak signal intensity (SI) within the remote region of interest was then determined. Total myocardial LGE was defined as abnormal myocardium with SI above peak remote SI and expressed as a percent of total LV mass and as a total volume.

Intraobserver reproducibility of the extent of LGE using the peak remote threshold was measured. In addition, comparison was made with the extent of the LGE region quantified using a threshold of >2 standard deviations above mean remote SI (11).

Clinical follow-up. Patients were followed at 3- to 6-month intervals after ICD placement via clinic visits or phone calls. The primary outcome of the study was the index combined end point of cardiac death (both sudden and nonsudden), appropriate ICD firing, and hospitalization for decompensated HF requiring intravenous diuretics with or without inotropes. No patient was lost to follow-up. Events were adjudicated by an independent committee blinded to the CMR results. Deaths were classified according to the modified Hinkle-Thaler system (18). Appropriate ICD firing was defined as a shock for sustained ventricular tachycardia above the programmed rate cutoff of the ICD (generally >180 beats/min) or ventricular fibrillation.

Statistical analysis. Continuous variables are expressed as mean ± SD. The Wilcoxon rank sum test was used to compare continuous baseline and CMR characteristics of

Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance

HF = heart failure

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

NICM = nonischemic cardiomyopathy

NYHA = New York Heart Association

SCD = sudden cardiac death

SI = signal intensity

the patients grouped by the dichotomous presence or absence of CMR LGE. The Fisher exact test was used for categoric variables. Kaplan-Meier curves and the Wilcoxon test of Breslow were used to compare univariate survivor functions (time to index composite event). Cox proportional-hazards models were developed. We included as potential covariates age, gender, baseline NYHA functional class, and LVEF, mass, and volume indexes, which are known from earlier research to affect prognosis in NICM (19). No other additional baseline characteristics were found to influence the relationship between CMR LGE and outcome. Because there was strong collinearity (correlation coefficient >0.6) between

LVEF, volumes, and mass, only left ventricular end-diastolic volume (LVEDV) was included in the models. Forward stepwise regression (p < 0.10 for entry; p > 0.05 for removal) was used to arrive at a parsimonious model (model 1). Given the well established prognostic importance of LVEDV, this was added to the parsimonious model for the final analysis of all patients (model 2). Follow-up duration was measured from the CMR study date. Bland-Altman repeatability analysis was used to compare quantification of the LGE region using the thresholds of peak remote versus 2 SD above mean remote as well as intraobserver variability. A 2-tailed p value of <0.05 defined statistical significance.

Table 1	Baseline Demographic, Clinical, and Magnetic Resonance Imaging Characteristics of the Patients		
Variable	**LGE Absent by CMR (n = 38)**	**LGE Present by CMR (n = 27)**	**p Value**
Age, yrs	55 ± 12	56 ± 9	0.99
Male gender, n (%)	19 (50)	23 (85)	0.003
Caucasian, n (%)	19 (50)	15 (58)	0.14
Duration of cardiomyopathy diagnosis, yrs	4.0 ± 4.1	4.1 ± 4.4	0.74
Entry EF (non-MRI method), %	21 ± 9	19 ± 6	0.47
Single-vessel CAD >50% (non-left main or proximal LAD vessels)	2 (5)	3 (11)	0.38
NYHA functional class			0.52
I	7 (18)	3 (11)	
II	16 (42)	15 (56)	
III	15 (39)	9 (33)	
Medication use, n (%)			
ACEI or ARB	33 (87)	25 (92)	0.46
Beta-blocker	36 (95)	24 (89)	0.64
Diuretic	22 (65)	19 (73)	0.38
Spironolactone	11 (29)	8 (30)	0.95
Digoxin	15 (39)	5 (19)	0.07
Antiarrhythmics (amiodarone)	2 (5)	4 (15)	0.19
Lipid-lowering	16 (42)	16 (59)	0.17
Received biventricular ICD, n (%)	15 (41)	8 (30)	0.37
CMR measurements			
LVEF, %	26 ± 9	22 ± 10	0.20
LVEDV index, ml/m^2			
All patients	126 ± 43	149 ± 64	0.10
Female	120 ± 37	137 ± 96	
Male	132 ± 49	151 ± 67	
LVESV index, ml/m^2			
All patients	96 ± 41	120 ± 66	0.08
Female	89 ± 36	109 ± 44	
Male	104 ± 50	122 ± 69	
LV mass, g/m^2			
All patients	78 ± 24	90 ± 43	0.16
Female	73 ± 17	71 ± 21	
Male	83 ± 29	93 ± 45	
Extent of LGE, mean ± SD	—	10 ± 13% of LV mass	—
Median extent		5%	
Interquartile range		3%–16%	
Total volume, ml		17 ± 21	

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LAD = left anterior descending coronary artery; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MRI = magnetic resonance imaging; NYHA = New York Heart Association.

Results

Baseline characteristics. We enrolled 65 patients whose baseline clinical characteristics are presented in Table 1. Median follow-up for the survivors was 17 months. Twenty-seven patients (42%) had CMR LGE with the following regional patterns: septal midwall (Fig. 1A) (n = 8), subendocardial extending to epicardial surface (Fig. 1B) (n = 7), and patchy foci (Fig. 1C) (n = 12) often including the RV-LV septal insertion points.

Patients with and without CMR LGE had similar baseline characteristics, including duration of cardiomyopathy diagnosis, entry NYHA functional class, medication usage (both at baseline and at follow-up), and biventricular ICD usage, although LGE was more frequent in men. Only 5 of the 65 patients had single-vessel coronary artery disease (CAD; not involving the left main or proximal left anterior descending coronary artery). This is consistent with cardiomyopathy "out of proportion" to CAD extent, and none of the 5 had evidence of LGE in that specific coronary distribution. The LVEF trended lower and LV volume and mass indexes were higher in those patients with LGE compared with those without LGE.

Serum sodium and creatinine values were identical in both groups. Pro–B-type natriuretic protein (BNP) values (pg/ml) were obtained in a subset of patients (n = 42) and were significantly different between the 2 groups: 1,041 ± 1,448 for patients without LGE (n = 24) versus 4,497 ± 6,519 for those with LGE (n = 18); p = 0.002.

Reproducibility of CMR LGE. For the dichotomous presence or absence of LGE, there was complete intraobserver agreement. There was only 1 case of interobserver disagreement, which was resolved by consensus with a third independent observer. For quantification of the LGE region, intraobserver variability using the peak remote threshold was extremely low, with mean difference (bias) of 0.1 ml (95% confidence interval [CI] −0.3 to 0.5 ml, limits of agreement −1.9 to 2.1 ml). Low interobserver variability of this method has previously been shown (17). Compared with the >2 SD above mean remote SI, the current methodology for quantifying LGE resulted in slightly larger regions (17.4 ± 20.8 ml vs. 16.6 ± 21.2 ml, bias 0.8, 95% CI 0.3 to 1.3, limits of agreement −1.6 to 3.2).

CMR LGE and clinical outcome. The presence of CMR LGE was associated with an increased risk of sustaining an index composite cardiac event over time. Kaplan-Meier curves (Fig. 2) for the index composite end point showed a significant difference between patients with and without CMR LGE (Wilcoxon-Breslow: p < 0.001). Twelve patients (44%) with LGE had an index composite event (8 with an HF hospitalization and 4 with an appropriate ICD firing), compared with 3 patients (8%) without LGE, all of whom had an ICD firing (Table 2). The median time to an index event was 10.2 months. Among the 12 patients with LGE and index events, additional subsequent events were common (Table 2): 3 patients died within 2 months of the
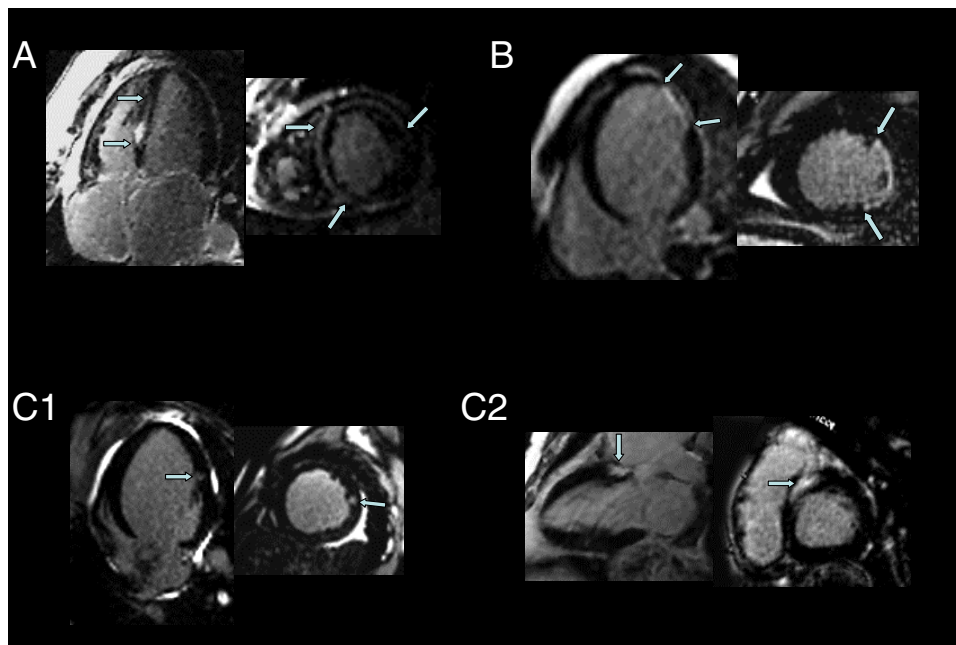

Figure 1   **CMR Late Gadolinium Enhancement Patterns Observed in the Study Group**

(A) Predominantly midwall enhancement involving the septal, anterior, and anterolateral walls. **(B)** Apical-lateral near-transmural enhancement (subendocardial to epicardial enhancement). **(C)** Patterns of patchy foci not following an epicardial coronary perfusion territory. **(C1)** There is a focus of midlateral wall enhancement. **(C2)** There is basal septal enhancement. **Arrows** indicate regions of late gadolinium enhancement.
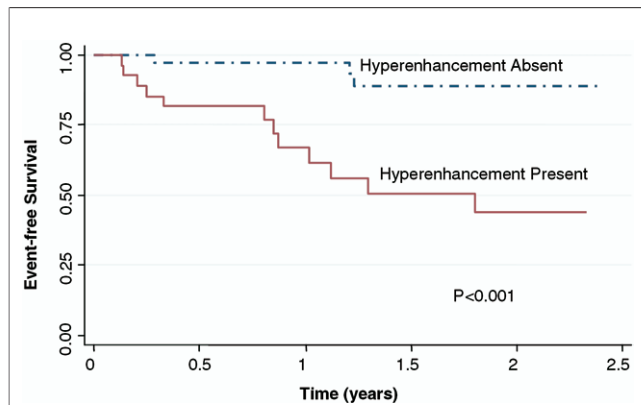
Figure 2 **Kaplan-Meier Event-Free Survival Curve for the Occurrence of an Index Composite Event**

Patients are grouped by presence or absence of cardiovascular magnetic resonance late gadolinium enhancement. Wilcoxon-Breslow: p < 0.001 for the 2 survival curves.

index event (2 patients with an initial HF hospitalization subsequently died of LV pump failure and 1 patient with an initial ICD firing died of SCD); 2 patients had multiple appropriate ICD firings on separate dates; and 3 patients with an index HF hospitalization had subsequent HF hospitalizations. There were no deaths or HF hospitalizations among patients without CMR LGE.

By univariate analysis (Table 3), the presence of CMR LGE was strongly associated with cardiac events (hazard ratio [HR] 7.1, 95% CI 2.0 to 25.3; p = 0.002). This association was unchanged in multivariate analysis: CMR LGE had a hazard ratio of 8.2 (95% CI 2.2 to 30.9; p = 0.002) for an index composite event after adjustment for HF class and LVEDV index. When the 5 patients with CAD were excluded, both univariate and multivariate results continued to show significant association between CMR LGE and adverse outcome (Table 3). Because LVEF, LV dimensions, and LV volume and mass indexes were correlated, we used only the LVEDV index in Cox proportional hazard models; the results were unchanged when LVEF was substituted for the LVEDV index or when all CMR volume and mass indexes were used and when CHF class was modeled as a categoric rather than an ordinal variable. Similarly, the addition of serum sodium and creatinine values was not predictive of outcome and did not change the multivariate results. Including whether or not a biventricular pacemaker was placed also did not change the multivariate results, and neither did medication usage. When the end point was limited to cardiac death and appropriate ICD firing, thus excluding HF hospitalization, LGE continued to predict a significantly worse outcome by Kaplan-Meier analysis (Wilcoxon-Breslow: p = 0.03): 22% (n = 6) of patients with LGE reached this secondary end point versus only 8% (n = 3) without LGE.

Among patients with LGE, even small amounts of LGE were associated with a significant risk of an index adverse

outcome: for the 13 patients whose % LV LGE mass measured below the median, the multivariate adjusted HR was 6.7 (95% CI 1.4 to 31.8; p = 0.016), compared with an HR of 11.9 (95% CI 2.1 to 66.8; p = 0.005) for those with values above the median. The rates of index adverse outcome occurrence were similar among the 3 qualitative segmental patterns of LGE: 38% of patients with a midwall pattern, 43% of those with a transmural pattern, and 50% of those with patchy LGE had an index outcome event. Excluding those with the transmural pattern did not significantly change the univariate and multivariate HRs for LGE.

Discussion

This study found that among patients with NICM, the presence of LGE on CMR, irrespective of extent or segmental pattern, is independently associated with an adverse cardiac prognosis. After controlling for LV volume, mass, or ejection fraction as well as NYHA functional class, the adjusted HR for patients with CMR LGE was 8.2 (95% CI 2.2 to 30.9; p = 0.002) for an index composite cardiac event compared with those without LGE.

The CMR LGE patterns seen in the present patients are consistent with those reported in earlier pathologic studies of NICM (9). Earlier studies examining myocardial tissue samples obtained at the time of autopsy or cardiac transplantation have shown a pattern of increasing fibrosis from the epicardium to endocardium with both septal and LV free wall involvement (20–22). Segmental and replacement fibrosis (23) have been described in as many as 57% of patients (21), and grossly visible scars have been noted in 23% (24). The frequency and pattern of CMR LGE in the present patients are consistent with those findings. The exact pathophysiology underlying the CMR abnormalities is uncertain, because NICM is the final common pathway for presumably multiple etiologies. In all likelihood, focal CMR LGE in the present patient population is a nonspecific measure of replacement and segmental fibrosis. These types

Table 2 **Number of Index and Cumulative Events Grouped by Presence or Absence of CMR LGE**

Variable	LGE Absent by CMR (n = 38)	LGE Present by CMR (n = 27)
Number of patients who experienced an index composite outcome*	3 (8%)	12 (44%)
HF hospitalization	0	8
Appropriate ICD firing	3	4
Cardiac death	0	0
Cumulative number of events over the follow-up period	3	25
HF hospitalization	0	13
Appropriate ICD firing	3	9
Cardiac death	0	3

*The primary statistical analysis in the text was performed using the number of patients experiencing an index composite outcome and time to the index event. The cumulative number of events was not used in any statistical analysis.
HF = heart failure; other abbreviations as in Table 1.

| Table 3 | Cox Proportional Hazards Analysis for the Time to Occurrence of an Index Composite Cardiac Event |

| | Univariate Analysis | | Multivariate Analysis | | | |
| | | | Model 1* | | Model 2† | |
Variable	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age (5-yr increments)	1.1 (0.9–1.5)	0.28	—	—	—	—
Gender	1.8 (0.5–6.2)	0.39	—	—	—	—
NYHA functional class	2.0 (0.8–4.5)	0.12	2.7 (1.0–7.2)	0.04	2.6 (1.0–7.0)	0.05
CMR LVEDV index (ml/m^2) (per 10-ml/m^2 increments)	1.1 (1.0–1.2)	0.08	—	—	1.0 (0.9–1.1)	0.70
Presence of CMR LGE (vs. absence)	7.1 (2.0–25.4)	0.002	8.6 (2.4–31.6)	0.001	8.2 (2.2–30.9)	0.002
Excluding Patients With CAD						
Age (5-yr increments)	1.2 (0.9–1.6)	0.17	—	—	—	—
Gender	1.9 (0.5–6.8)	0.33	—	—	—	—
NYHA functional class	1.8 (0.8–4.4)	0.17	—	—	2.1 (0.8–5.5)	0.15
CMR LVEDV index (ml/m^2) (per 10-ml/m^2 increments)	1.1 (1.0–1.2)	0.14	—	—	1.0 (0.9–1.1)	0.9
Presence of CMR LGE (vs. absence)	8.9 (2.4–32.2)	0.001	8.9 (2.4–32.2)	0.001	9.2 (2.4–35.1)	0.001

*For model 1 (parsimonious model), forward stepwise regression (p < 0.10 for entry; p > 0.05 for removal) was used to arrive at a parsimonious model. †For model 2, NYHA functional class, CMR LVEDV index, and LGE fibrosis were all entered into the multivariate model.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

of myocardial injury in NICM likely result from chronic sustained adrenergic activation that eventually leads to progressive myocyte dysfunction, apoptosis, and fibroblast hyperplasia (8). In addition, the increased wall stress caused by progressive LV remodeling can result in focal myocyte necrosis due to microvascular ischemia from augmentation of metabolic demands as well as reduced capillary density from excessive fibrosis (8,25). Current CMR techniques are less likely to detect diffuse microscopic fibrosis.

The finding of a strong association between poor cardiac prognosis and CMR LGE supports that of a more narrowly focused report by Assomull et al. (11), who specifically studied the significance of the CMR LGE pattern of midwall fibrosis in 101 patients with symptomatic NICM. That study found focal midwall fibrosis sparing the endocardium in 35% of patients, with an HR of 3.1 (95% CI 1.1 to 8.5; p = 0.03) for the combined outcome of all-cause mortality and hospitalization for any type of cardiovascular event, after adjustment for age, LV function, and chamber volumes measured by CMR. Our results suggest that adverse cardiac prognosis is specifically associated with the presence of LGE, regardless of segmental pattern. Compared with the study by Assomull et al. (11), which was performed at a regional HF referral center, the present cohort may be more generalizable to the ICD-eligible NICM population at large; our patients were older, more ethnically diverse, received cardiac care from general cardiologists, and had uniformly severe LV dysfunction. In addition, patients were classified as nonischemic by coronary angiographic findings, which is consistent with current clinical practice and an accurate definition of cardiomyopathy etiology for clinical research purposes (14). In so doing, we examined the significance of all CMR patterns in this group. Our study design was also prospective and concurrent, that is, assessment of CMR LGE preceded clinical follow-up and outcome events were pre-defined at study onset.

Although we report significantly higher rates of adverse cardiac outcomes in NICM patients with CMR LGE, the absence of LGE did not assure freedom from malignant ventricular arrhythmias: 3 patients (9%) without LGE had an appropriate index ICD firing, compared with 4 patients (15%) with LGE. Significant arrhythmic risk in NICM patients without LGE is not surprising, because ventricular arrhythmias can be caused not only by fibrosis, with focal re-entry in regions of tissue heterogeneity (13,26–28), but also in the absence of fibrosis, by bundle branch or interfasicular re-entry and by exaggerated spatial dispersion of electrophysiological properties and abnormal impulse initiation (27,28).

In addition, although the presence of LGE does predict ICD firings or cardiac death alone (p = 0.03 by Kaplan-Meier analysis), HF hospitalization was a prominent determinant of the overall outcome. Although we did not study the mechanism by which increased CMR LGE leads to worse overall or, specifically, HF prognosis, the dose-response relationship between the extent of LGE and outcome supports the hypothesis that the CMR findings reflect the transition from compensated to decompensated state which results from long-term stressors such as sustained adrenergic activation and/or the mechanical disadvantages caused by LV remodeling. The presence of even small amounts of macroscopic scar may indicate maladaption at the cellular level with myocyte apoptosis and necrosis, thus heralding the start of a progressively more symptomatic stage of the disease process. This is further suggested by the limited BNP data which indicate higher levels consistent with increased LV wall stress and interventricular pressures in patients with CMR LGE. Further investigation into the pathophysiology is required.

Study limitations. The present study has inherent limitations given its relatively small cohort size and follow-up period. Although we found a similar risk for patchy,

transmural, and midwall CMR LGE patterns, the sample size is likely too small for definitive conclusions about differential risk. Robust conclusions regarding the ability of LGE to predict each separate component of the combined end point are also limited. Patients underwent CMR at enrollment only, so the implications of temporal progression or regression of LGE or changes in regional pattern are unknown. Our CMR protocol used the inversion recovery technique, which is sensitive for replacement and segmental fibrosis but relatively insensitive for diffuse microscopic interstitial fibrosis. The present study included only patients with LVEF ≤35%, although the study by Assomull et al. (11) suggests that CMR LGE may be prognostically important for NICM patients with moderate LV systolic dysfunction as well.

Conclusions

The presence of CMR LGE identifies a subset of NICM patients with an 8-fold higher risk of an index composite outcome of HF hospitalization, appropriate ICD firings, and cardiac death compared with patients without LGE. The CMR scanning and interpretation are relatively straightforward and can be performed at many hospitals that routinely provide care for patients with heart disease. Future research will be needed to determine whether therapy guided by CMR findings can lower morbidity and mortality for patients with nonischemic cardiomyopathy and LGE, such as with intensive heart failure therapies and/or earlier consideration of cardiac transplantation or left ventricular assist device placement. In addition, extrapolation to patients with milder LV systolic dysfunction may better identify those patients at high clinical risk who are currently not recognized as such by global LV function and volumes alone.

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