

Myocardial Fibrosis Predicts Appropriate Device Therapy in Patients With Implantable Cardioverter-Defibrillators for Primary Prevention of Sudden Cardiac Death

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Objectives	The purpose of this study was to evaluate the association between regional myocardial fibrosis and ventricular arrhythmias in patients with cardiomyopathy.
Background	Patients with heart failure are at risk of sudden cardiac death (SCD). Current guidelines recommend implantable cardioverter-defibrillator (ICD) devices for a subgroup based on impaired left ventricular function. A significant proportion of devices never discharge, hence a more accurate method for targeting those at risk is desirable.
Methods	We prospectively enrolled 103 patients meeting criteria for ICD implantation for primary prevention of SCD. Cardiac magnetic resonance imaging was performed before device implantation. Regional fibrosis was identified with late gadolinium enhancement (LGE).
Results	Median follow-up was 573 days (interquartile range: 379 to 863 days). The LGE identified regional fibrosis in 31 of 61 (51%) patients with nonischemic cardiomyopathy (NICM) and in all 42 patients with ischemic cardiomyopathy (ICM). There was a 29% (9 of 31) discharge rate in the NICM group with LGE compared with a 14% (6 of 42) discharge rate in the ICM group ($p = \text{NS}$). There were no ICD discharges in the NICM group without LGE, which was significantly lower than the rate observed in both the ICM patients ($p = 0.04$) and the NICM patients with LGE ($p < 0.01$). Left ventricular ejection fraction was similar in patients with and without device therapy ($24 \pm 12\%$ vs. $26 \pm 8\%$, $p = \text{NS}$) and those with or without LGE ($25 \pm 9\%$ vs. $26 \pm 9\%$, $p = \text{NS}$).
Conclusions	Patients with advanced cardiomyopathy and myocardial fibrosis demonstrated by LGE on cardiac magnetic resonance imaging have a high likelihood of appropriate ICD therapy. Correspondingly, absence of LGE may indicate a lower risk for malignant ventricular arrhythmias. (J Am Coll Cardiol 2011;57:821-8) © 2011 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) is a major cause of mortality in patients with advanced heart failure (1), and implantation of an automatic implantable cardioverter-defibrillator (ICD) has been found to significantly reduce arrhythmic death in this population (2,3). Consequently, current clinical guide-

lines recommend ICD insertion for primary prevention of SCD in a subgroup of patients with heart failure based on reduced left ventricular ejection fraction (LVEF) (4). Specifically, ICD therapy is indicated for those with nonischemic cardiomyopathy (NICM) with LVEF $<35\%$ and New York Heart Association (NYHA) functional class II or III,

See page 829

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and also for those with ischemic cardiomyopathy (ICM) with LVEF $<35\%$ or 30% depending on NYHA functional class. These guidelines have been predicted to result in as many as 500,000 Medicare beneficiaries becoming eligible for ICD implantation in the U.S. alone (5). In this context, the estimated cost is as high as U.S. \$100,000 per quality-adjusted life year (6). However, the majority of patients with

**Abbreviations
and Acronyms****CMRI** = cardiac magnetic resonance imaging**ICD** = implantable cardioverter-defibrillator**ICM** = ischemic cardiomyopathy**IQR** = interquartile range**LGE** = late gadolinium enhancement**LV** = left ventricular**LVEF** = left ventricular ejection fraction**NICM** = nonischemic cardiomyopathy**NYHA** = New York Heart Association**SCD** = sudden cardiac death

ICD implantation for primary prevention never receive device therapy, with the average rate of appropriate ICD shocks estimated at 5.1% per year (3). Moreover, there appear to be a group of patients with low LVEF who remain at low risk of SCD, although predictive measures are not well validated (7,8). Therefore, strategies to improve cost effectiveness of ICD therapy may reduce the population exposed to unnecessary device implantation while perhaps also driving earlier implantation in high-risk patients, which would be highly desirable.

Recent studies have shown that presence of myocardial fibrosis identified by cardiac magnetic resonance imaging (CMRI)

is associated with a poor prognosis in patients with heart failure (9,10), using a composite end point of cardiovascular morbidity and overall mortality. While these studies add important information regarding the significance of myocardial fibrosis, they do not answer the clinical question of whether myocardial fibrosis predicts likelihood of ICD therapy. Although the mechanism for pathogenesis of ventricular arrhythmias in patients with cardiomyopathy is not well elucidated, there is evidence to suggest it is linked to presence of myocardial fibrosis, both in ischemic and nonischemic groups (11–13). Areas of late gadolinium enhancement (LGE) visualized on CMRI are presumed to represent macroscopic regions of myocardial fibrosis (14), and are present in approximately 30% of patients with NICM (15). We have, therefore, hypothesized that absence of LGE on CMRI predicts a lower risk of requiring ICD therapy in patients with devices implanted for primary prevention of SCD.

Methods

Study design and patient selection. The present study was performed at the Alfred Hospital, Melbourne, Australia, between July 2003 and October 2009. Subjects with advanced heart failure planned for implantation of ICD according to international guidelines (4) for primary prevention of SCD were invited to participate. Subjects were excluded if they suffered from claustrophobia, uncontrolled arrhythmias, or had a history of a metallic prosthetic implant contraindicating CMRI. No patient with previous ventricular arrhythmia causing hemodynamic compromise or requiring treatment was considered for this study. Patients with recent myocardial infarction (<3 months) or myocarditis were also excluded.

Only subjects with successful device implantation and a minimum of 6 months of follow-up and/or an event (appropriate device therapy, death, or heart transplantation) were included in the data analysis. The primary end point of the study was appropriate device therapy, with a pre-specified composite secondary end point of appropriate device therapy, all-cause mortality, and heart transplantation. The study was carried out with approval of the Alfred Hospital Ethics Review Committee. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

CMRI protocol. MRI SEQUENCES. We performed CMRI on 103 subjects with impaired left ventricular (LV) function on a clinical 1.5-T CMRI scanner (Signa 1.5-T, GE Healthcare, Waukesha, Wisconsin). All sequences were acquired during a breath-hold of 10 to 15 s. The LV function was assessed by a steady-state free precession pulse sequence (TR = 3.8 ms, TE = 1.6 ms, 30 phases, slice thickness 8 mm).

Delayed hyperenhancement was obtained 10 min after a bolus of gadolinium-DTPA (0.2 mmol/kg, BW Magnevist, Schering, Berlin, Germany) to identify regional fibrosis using an inversion-recovery gradient echo technique (TR = 7.1 ms; TE = 3.1 ms; TI individually determined to null the myocardial signal, slice thickness 8 mm, matrix 256 × 192, number of acquisitions = 2).

All cine CMRI sequences were performed in 3 standard long-axis and short-axis slices, kept identical for each sequence throughout the CMRI examination (16). From an end-diastolic 4-chamber long-axis view, 5 equally spaced slices were planned, so that the 2 outer slices lined up exactly either with the tip of the apex or the mitral annulus. The 2 outer slices were then deleted, leaving 3 slices corresponding to typical basal, mid, and apical short-axis views. Delayed enhancement imaging was performed in both long-axis and short-axis views.

EVALUATION OF LV FUNCTION AND REGIONAL FIBROSIS. The LV function was evaluated globally utilizing the bi-plane area-length method using 2- and 4-chamber long-axis views.

Regional fibrosis was identified by delayed enhancement within the myocardium, defined quantitatively by myocardial post-contrast signal intensity greater than 2 SD above that within a reference region of remote noninfarcted myocardium within the same slice. Myocardial delayed enhancement was assessed in all cases by 2 independent blinded expert readers and was defined as being present only if it was identified in both long-axis and short-axis views (Fig. 1). Ambiguous cases were reviewed using a third expert reader blinded to patient clinical status and ICD follow-up details.

ICD implantation and follow-up. All devices were implanted using standard surgical technique: choice of device was at the discretion of the implanting physician and the device was activated at completion of implantation. Defi-

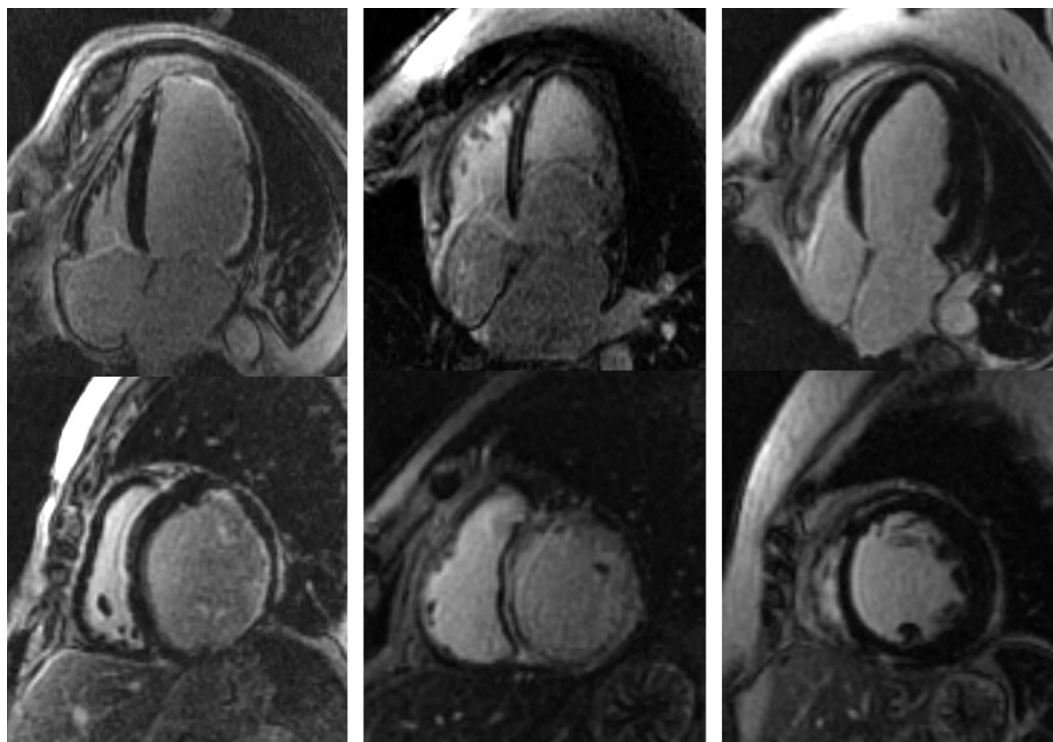


Figure 1 Determining Presence of Myocardial Delayed Enhancement

Four-chamber long-axis views (**top images**) and mid-ventricular short-axis views (**bottom images**) are shown. Examples depict ischemic cardiomyopathy with regional sub-endocardial delayed enhancement (**left**), dilated cardiomyopathy with septal mid-wall fibrosis (**center**), and dilated cardiomyopathy without delayed enhancement (**right**).

brillation threshold was routinely assessed immediately post-implant unless the patient was in atrial fibrillation and not receiving anticoagulation therapy. Initial programming of the defibrillator at time of implant was for shock only at a detection rate of >180 beats/min.

During follow-up antitachycardia pacing was only programmed after an episode of ventricular tachycardia, which may or may not have resulted in device shock. Device activation was defined as any therapy including antitachycardia pacing or shocks delivered by the device for ventricular tachyarrhythmias.

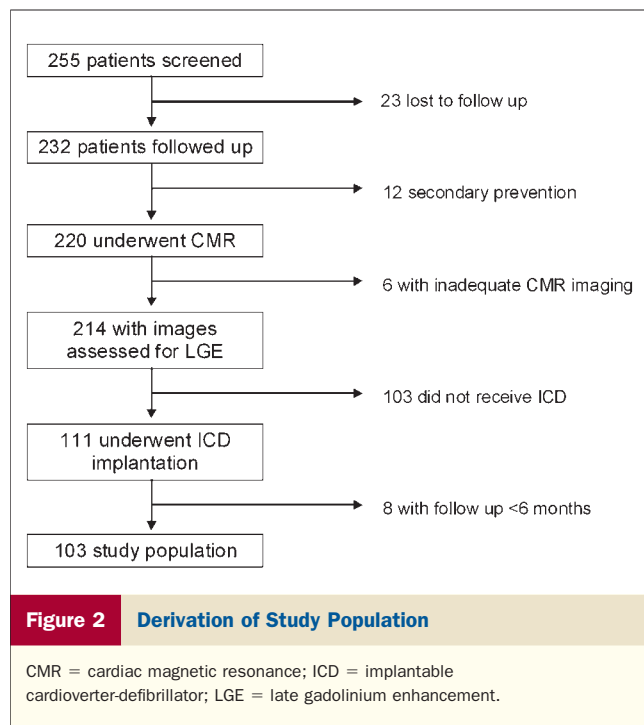
Each patient had appropriate sensing confirmed, and each device was interrogated for recorded events and device therapy before hospital discharge and at each follow-up. Device therapy was assessed by an experienced cardiologist (blinded to CMRI findings and clinical status) and classified as appropriate if it was a result of ventricular tachyarrhythmia according to established criteria (17–20). Patients were reviewed according to routine clinical schedule, with regular follow-up visits at 1 and 6 months after implantation, and every 6 months thereafter. Additional reviews were performed if clinically indicated. Pharmacological management and ICD parameter settings were at the discretion of the treating physician.

Statistics. All data are expressed as mean \pm 1 SD unless otherwise indicated. Comparison between 2 groups using

continuous variables utilized unpaired Student *t* test. For ordinal data, the Mann-Whitney *U* test was used. Analysis of variance was used for comparison between >2 groups using continuous variables. Comparison between groups using categorical variables utilized the chi-square test or Fisher exact test for small group sizes. The log-rank test was used to compare Kaplan-Meier survival curves. Results from multiple comparisons were adjusted using the Bonferroni correction. All analyses were conducted using SPSS software (version 17, SPSS, Chicago, Illinois) or SigmaStat software (version 3.5, Systat Software, San Jose, California). Event (or censoring) times for all patients were measured from time of ICD implantation. Patients who had appropriate device therapy, received a heart transplant, or died were censored at the time of first event. For all comparisons, a *p* value <0.05 was considered significant, and all reported *p* values are 2-tailed.

Results

Clinical and demographic data. A total of 103 subjects with successful CMRI and ICD implantation were evaluated (derivation of study population in Fig. 2). Median follow-up was 573 days (interquartile range [IQR]: 379 to 863 days). Table 1 shows baseline characteristics of patients before and after stratification by etiology of cardiomyopathy



and presence of LGE on CMRI. The study population was divided into 3 groups: ICM, NICM with LGE (NICM+) and NICM without LGE (NICM-). At CMRI patients were age 54 ± 13 years with a mean LVEF of $26 \pm 9\%$. There was no significant difference in LVEF or medication use between groups; however, a nonsignificant trend to younger age in the NICM+ cohort was observed. The study population contained 61 subjects with NICM (31 NICM+, 30 NICM-) and 42 subjects with ICM.

CMRI findings. LGE was present in 73 of the 103 (71%) subjects. All images were assessed by 2 blinded expert readers with agreement in 99 of 103 (96%) cases, with adjudication in the remaining 4 by a senior expert blinded reader. As expected, LGE was identified in all 42 subjects with ICM, and was present in 31 of 61 (51%) patients with NICM. In patients with ICM, 28 of 42 (67%) patients had subendocardial LGE and 36 of 42 (86%) had transmural

LGE (22 of 42 [52%] had both). Myocardial LGE was single vessel in distribution in 22 of 42 (52%) patients and was multivessel in distribution in 20 of 42 (48%) patients. In patients with NICM, 19 of 31 (61%) had midwall LGE and 12 of 31 (39%) had patchy LGE in a nonvascular distribution. There were more males in the ICM group, with borderline statistical significance ($p = 0.05$). Mean LVEF and left ventricular end diastolic volume (indexed to body surface area) did not vary significantly between groups (Table 1).

ICD follow-up data. During the follow-up period, 15 subjects (6 with ICM, 9 with NICM) received appropriate device therapies with a median time from device implantation to first therapy of 211 days (IQR: 86 to 370 days). Of these 15 patients, 12 (80%) received defibrillation (7 for ventricular fibrillation and 5 for sustained ventricular tachycardia), with the remaining 3 receiving antitachycardia pacing for sustained ventricular tachycardia. The average rate of ventricular tachycardia was 199 beats/min (range 150 to 227 beats/min). All therapies occurred in subjects with LGE on CMRI (LGE+), which resulted in a significant increase in rate of device therapy in the LGE+ group compared with patients without LGE (21% in LGE+ patients vs. 0% in LGE- patients, $p = 0.01$). Death occurred in 2 subjects in the LGE- group and 1 in the LGE+ group, whereas 8 LGE+ patients received heart transplantation at a median time of 328 days (IQR: 210 to 459 days) after ICD implantation. When subjects were stratified by device therapy, there was no difference in age, LVEF, or medication use (Table 2).

Analysis of ICD discharge rate by etiology and CMRI findings. To further evaluate patient risk, we analyzed the data in 3 separate groups. In the NICM subgroup, 31 of 61 (51%) had LGE identified on CMRI and 30 of 61 (49%) had no LGE. These 2 groups were compared to the 42 patients with ICM (all with LGE on CMRI). There was a 29% (9 of 31) discharge rate in the NICM+ group compared with a 14% (6 of 42) discharge rate in the ICM group ($p = NS$). There was a 0% (0 of 30) discharge rate in the NICM- group, which was significantly lower than the

Table 1 Baseline Characteristics

	All (n = 103)	ICM (n = 42)	NICM+* (n = 31)	NICM-* (n = 30)	p Value
Age, yrs	54 ± 13	56 ± 11	50 ± 14	55 ± 14	0.09
LVEF, %	26 ± 9	27 ± 8	25 ± 10	25 ± 9	0.45
LVEDVI, ml/BSA	170 ± 51	167 ± 38	176 ± 69	169 ± 46	0.75
NYHA functional class†	2 (2-3)	2 (2-3)	3 (2-3)	2 (2-3)	0.18
Male, %	77	88	74	63	0.05
Amiodarone, %	24	21	29	23	0.97
ACE inhibitor/ARB, %	95	100	94	90	0.13
Beta-blocker, %	92	95	90	90	0.64
Spironolactone, %	56	52	61	57	0.75

*Nonischemic cardiomyopathy (NICM) with (+) and without (-) late gadolinium enhancement on cardiac magnetic resonance imaging. †Expressed as median with interquartile range.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BSA = body surface area; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index. NYHA = New York Heart Association.

Table 2 Stratification of Patients by Device Therapy

	All (n = 103)	No Device Therapy (n = 88)	Device Therapy (n = 15)	p Value
Age, yrs	54 ± 13	55 ± 13	49 ± 13	0.13
LVEF, %	26 ± 9	26 ± 8	24 ± 12	0.49
LVEDVI, ml/BSA	170 ± 51	166 ± 43	196 ± 81	0.19
NYHA functional class*	2 (2-3)	2 (2-3)	2 (2-3)	0.05
Ischemic cardiomyopathy, %	41	41	40	0.83
Male, %	77	74	93	0.19
Amiodarone, %	24	22	40	0.23
ACE inhibitor/ARB, %	95	94	100	0.77
Beta-blocker, %	92	92	93	0.73
Spironolactone, %	56	53	73	0.25

*Expressed as median with interquartile range.
Abbreviations as in Table 1.

rate observed in both ICM ($p = 0.04$) and NICM+ patients ($p < 0.01$). Kaplan-Meier analysis again showed a significant difference between groups for both device therapy and the composite secondary end point ($p < 0.01$) (Figs. 3 and 4, respectively). Analysis between groups found a lower rate of device therapy and the composite secondary end point in the NICM- group compared with both the NICM+ group ($p < 0.01$) and the ICM group ($p < 0.05$). After Bonferroni correction, the observed differences between NICM- patients and NICM+ patients with respect to ICD discharge rate and the composite secondary end point remained significant. There was a nonsignificant trend to a lower rate of device therapy and composite end point in the ICM group compared with the NICM+ group ($p = 0.08$ and $p = 0.09$, respectively).

Of 15 administered ICD therapies (7 for ventricular fibrillation and 8 for ventricular tachycardia), 4 of 15 (27%) had midwall LGE, 5 of 15 (33%) had patchy LGE in a nonvascular distribution, 3 of 15 (20%) had subendocardial LGE in a vascular distribution, and 3 of 15 (20%) had transmural LGE in a vascular distribution. There was no association between type of LGE morphology and ICD therapy ($p = \text{NS}$, chi square), nor between any type of scar morphology and type of arrhythmia (ventricular tachycardia versus ventricular fibrillation).

Discussion

The present study of patients with advanced heart failure undergoing ICD insertion for primary prevention of SCD

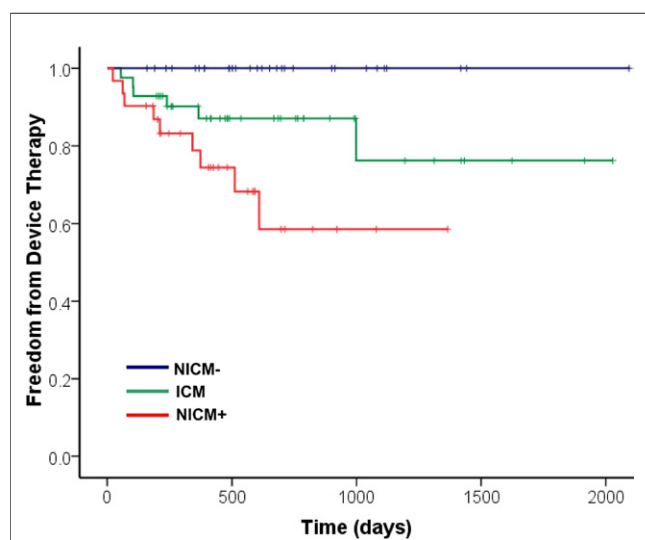


Figure 3 Freedom From Device Therapy

Kaplan-Meier analysis of patients with ischemic cardiomyopathy (ICM) (green line) and patients with nonischemic cardiomyopathy with (NICM+) (red line) and without (NICM-) (blue line) late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging shows a significant difference in device therapy, with all events occurring in patients with LGE ($p < 0.01$).

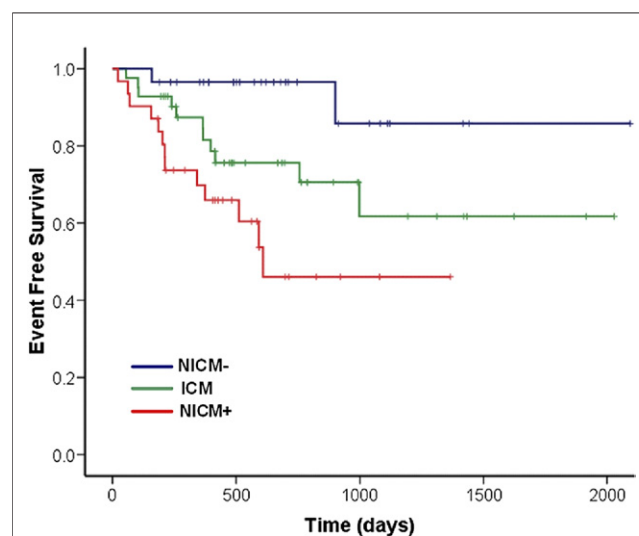


Figure 4 Event-Free Survival

Kaplan-Meier analysis using the composite end point of appropriate device therapy, all-cause mortality, and cardiac transplantation for patients with ischemic cardiomyopathy (ICM) (green line), nonischemic cardiomyopathy (NICM) with (NICM+) (red line) and without (NICM-) (blue line) late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging shows improved event-free survival for patients without LGE ($p < 0.01$).

demonstrates a strong association between presence of regional fibrosis demonstrated by CMRI and appropriate ICD therapy. Our data not only support a mechanistic link between regional fibrosis and malignant ventricular arrhythmias, they also suggest that absence of regional fibrosis predicts a low risk of ICD therapy. Assessment of patients with NICM who had LGE on CMRI revealed an ICD discharge rate at least as high as patients with ICM, with both groups experiencing a significantly higher risk than those without LGE on CMRI (with no events occurring in this subgroup). These findings were independent of LVEF, left ventricular end diastolic dimensions, or medication use. Additionally, the difference remained significant when death and cardiac transplantation were included in the composite secondary end point, implying our results were not due to increased mortality/transplantation among patients without LGE on CMRI.

The pathophysiology of ventricular arrhythmias has been extensively studied and is thought to have a number of contributing mechanisms (21). With ICM, the predominant mechanism is thought to be scar-based re-entry. The arrhythmogenic substrate in NICM is less well defined; however, prior studies have demonstrated increased myocardial collagen content as well as regional scarring in NICM (14,21). In addition, electrophysiological evidence suggests there is a greater degree of myocardial fibrosis in patients with sustained monomorphic ventricular tachycardia than in patients without sustained arrhythmias, and that the site of origin of ventricular tachycardia corresponds to regions of basal electrogram abnormalities (22). Recently, it has been demonstrated that myocardial scarring (identified by CMRI) is associated with ventricular arrhythmias in a cohort of patients with NICM referred for catheter ablation (23).

Prior studies have correlated myocardial fibrosis detected by CMRI with ventricular arrhythmias and/or adverse prognosis (9,10,13). These studies have used combined primary end points (9,10), inducible arrhythmias (13), or Holter monitoring data (24). While these studies add important information regarding the significance of myocardial fibrosis, they do not answer the clinical question of whether myocardial fibrosis predicts likelihood of ICD therapy. Our study demonstrated a strong and direct correlation between presence of myocardial fibrosis and appropriate device therapy, which to our knowledge has not been previously shown.

Current clinical guidelines recommend ICD implantation in a large number of patients with advanced heart failure using systolic dysfunction as the main criterion. Risk stratification based on LVEF alone is an inexact method, as evidenced by the finding that the majority of patients with ICD implantation never receive appropriate therapy (25). There has been incomplete translation of these recent guidelines into clinical practice (26). The reason is probably multifactorial but is due at least in part to the economic implications of such widespread device implantation. Cost-

benefit analysis, while complex, suggests that in most cases, the cost comes under the commonly used cut-off point of U.S. \$100,000 per quality-adjusted life year (6,27–29). However, even with more conservative estimates this would correspond to an expenditure of several billions of dollars per year in the U.S. alone (6), a figure that may be unsustainable.

With these considerations in mind, a technique to accurately identify a subgroup at particularly high risk and optimize device implantation in this most vulnerable population would be highly advantageous. That would need to be considered in conjunction with other clinical factors, as discussed previously (30). In our study, there were no events in the LGE– group, suggesting this subgroup may have a low risk of SCD. However other recent studies (9,10) have demonstrated a small number of ICD events even in patients without LGE; therefore, we would not at this stage suggest applying this method to stratify ICD implantation in patients in whom ICD therapy is currently both available and indicated. Larger multicenter studies are required to demonstrate the predictive value of delayed enhancement on risk stratification in cardiomyopathy. That would require ongoing review, including serial CMRI assessment to detect subsequent development of regional fibrosis. Recent evidence also supports a role for a clinical risk prediction model for assessment of likely benefit from ICD (31). Although our results are promising, rather than advocating a single test, we would favor a combination of clinical factors, including scar imaging, to provide the best assessment of risk for SCD in this vulnerable population.

Our study contained a population with multiple etiologies of cardiomyopathy, including a number with coronary artery disease. Although this could potentially lead to a bias in favor of the LGE+ group (due to inclusion of all those with ICM in this subgroup), it is pertinent to note that the rate of device therapy did not differ significantly between patients with ICM and patients with NICM and LV scar. We also found a very high rate of LGE in our nonischemic subgroup, perhaps because of a population with more advanced disease, as a number of our study participants were being considered for cardiac transplantation. Previous studies have reported rates of LGE in NICM in the order of 30% (9,15,32), compared with 51% in our study. Possibly, the mechanism of ventricular arrhythmias in advanced heart failure is similar in ischemic and nonischemic groups, and the presence of regional fibrosis is an important substrate in all etiologies, explaining both the high incidence of LGE and device therapy in this study. That is also supported by a recent study of patients with hypertrophic cardiomyopathy, demonstrating an association between LGE on CMRI and ventricular arrhythmias (33). Structural remodeling is common to all types of cardiomyopathy with associated fibrosis, providing an arrhythmogenic focus in susceptible patients. This theory deserves further explo-

ration as it may prove useful in identifying patients with less severe systolic dysfunction (measured by LVEF), who are also at increased risk of SCD. Presently, methods to risk stratify this subgroup are limited and subsequently we remain unable to accurately identify which patients would benefit from ICD implantation.

LGE also only assesses fibrosis distributed in a patchy/regional pattern and does not give any information on diffuse myocardial fibrosis, which is also likely to have a significant effect on clinical outcome. Quantification of diffuse fibrosis has thus far been difficult; however, recent work from our group (34) proposes a CMRI method to address this problem, and we hope future studies will be able to assess the prognostic impact of both regional and diffuse myocardial fibrosis in this patient population.

Study limitations. Assessment of myocardial fibrosis by LGE as performed in our study has a number of limitations. We used standard clinical sequences with long-axis and short-axis views and did not quantify fibrosis volumetrically. Our sequences did not include coverage of the entire myocardium, and hence, we could have missed small areas of fibrosis. However, given the absence of ICD therapy in the LGE– group, such small areas of LGE potentially missed by our CMRI protocol would be of uncertain clinical relevance. Furthermore, recent studies (10,24) suggest it is the presence, not volume, of myocardial fibrosis which is the important prognostic factor. Therefore, we propose our method allows for a more practical clinical application of assessing myocardial fibrosis. Our study was also performed in a heterogeneous group that included patients with ICM. Although the utility of myocardial fibrosis as detected with CMRI as a discriminator for appropriate ICD implantation is perhaps best suited to patients with NICM, our results suggest patients with NICM who are found to have LGE on CMRI may have a risk similar to that of patients with ischemic pathology. This finding would need to be confirmed in a larger study before translation into clinical practice, as our sample size is small and the rate of device therapy is relatively low.

Conclusions

In this single-center study, we demonstrated a strong association between myocardial LGE and appropriate ICD therapy, supporting the assertion that ventricular scar is an important arrhythmic substrate in cardiomyopathy. In addition, patients without LGE had no appropriate device therapies, suggesting it may be possible to identify a low-risk patient subgroup that could be managed conservatively.

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