Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Delayed Enhancement Magnetic Resonance Imaging Is a Significant Prognostic Factor in Patients With Non-Ischemic Cardiomyopathy

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Background: Delayed enhancement (DE) on cardiac magnetic resonance imaging (CMR) is a marker of myocardial fibrosis. The absence of DE in CMR is a predictor of left ventricular (LV) functional improvement in patients with non-ischemic cardiomyopathy (NICM), so in the present study it was investigated whether presence of DE has prognostic significance in patients with NICM at long-term follow-up.

Methods and Results: The 79 patients (56.4±13.5 years, 48 males) with NICM (LV ejection fraction <35%, no significant coronary artery disease) were monitored for occurrence of cardiac events. CMR was performed to assess DE. Cardiac events were defined as rehospitalization (because of worsening of heart failure), cardiac transplantation or death. There were 37 patients without and 42 patients with DE. The mean follow-up duration was 19±10 months. There was 1 event (2.7%, 1 rehospitalization) in the DE(–) group, whereas 13 events (30.9%, 1 death, 1 transplantation, 11 rehospitalizations) occurred in the DE(+) group. The event-free survival was significantly longer in the DE(–) group than in the DE(+) group (38.9±1.0 vs 28.4±2.7 months, P<0.01). Multivariate regression analysis revealed that presence of DE was the most potent, independent predictor of cardiac events (hazard ratio 8.06, confidence interval 1.03±63.41, P<0.05).

Conclusions: The presence of DE in CMR is a significant predictor of future cardiac events in patients with NICM. (*Circ J* 2010; **74:** 476–483)

Key Words: Delayed enhancement; Heart failure; Magnetic resonance imaging; Non-ischemic cardiomyopathy; Prognosis

It has been demonstrated that delayed enhancement (DE) on cardiac magnetic resonance imaging (CMR) is effective in detecting the presence, location, and extent of myocardial scarring and predicting improvement in contractile function following revascularization in patients with coronary artery disease (CAD).[1] Moreover, DE-CMR is capable of visualizing microscars (small amounts of myocardial fibrosis) that cannot be detected by other imaging techniques.[2]

We previously reported that myocardial fibrosis, as assessed by DE-CMR, is a useful predictor of functional recovery in patients with non-ischemic cardiomyopathy (NICM).[3] Dilated cardiomyopathy (DCM), a major component of NICM, is associated with increased collagen content and excessive extracellular matrix turnover, which eventually contribute to myocardial fibrosis, adverse left ventricular (LV) remodeling and poor prognosis.[4–7] Therefore, we hypothesized that the presence of DE is a long-term prognostic factor in patients with NICM.

Methods

Study Population

We enrolled 79 patients with echocardiographically proven LV systolic dysfunction (LV ejection fraction (EF) <35%). All subjects were admitted to hospital and underwent coronary angiography at initial diagnosis to exclude CAD. The baseline patient characteristics, ECG and echocardiographic variables, as well as laboratory data, were all collected and recorded. Medical treatment was then started and the patient was discharged. One month after initial admission, we performed gadolinium-enhanced CMR. The exclusion criteria were previous history of CAD, chronic renal insufficiency

Received August 5, 2009; revised manuscript received December 2, 2009; accepted December 6, 2009; released online January 30, 2010
Time for primary review: 16 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-09-0446

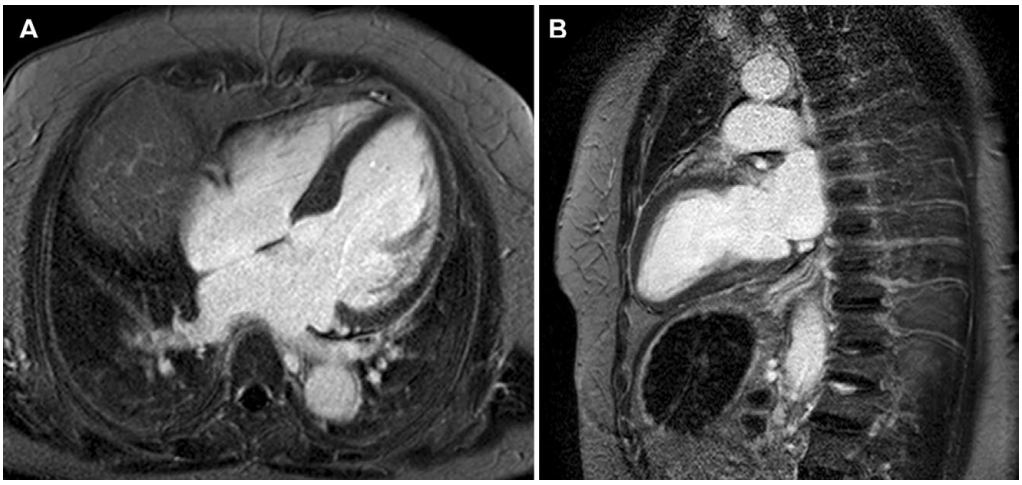

Figure 1. A 63-year-old woman who presented with dyspnea (NYHA III). Initial echocardiography shows LVEF of 22% (LVEDD/LVESD 67/59 mm). CMR revealed no DE in the entire LV myocardium. Follow-up echo 3 months later shows a slightly increased LVEF (27%, LVEDD/LVESD 63/54 mm). She had taken medications for 1 year at the outpatient clinic, with improvement of HF symptoms. CMR, cardiac magnetic resonance imaging; DE, delayed enhancement; EF, ejection fraction; HF, heart failure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF; left ventricular ejection fraction; NYHA, New York Heart Association.

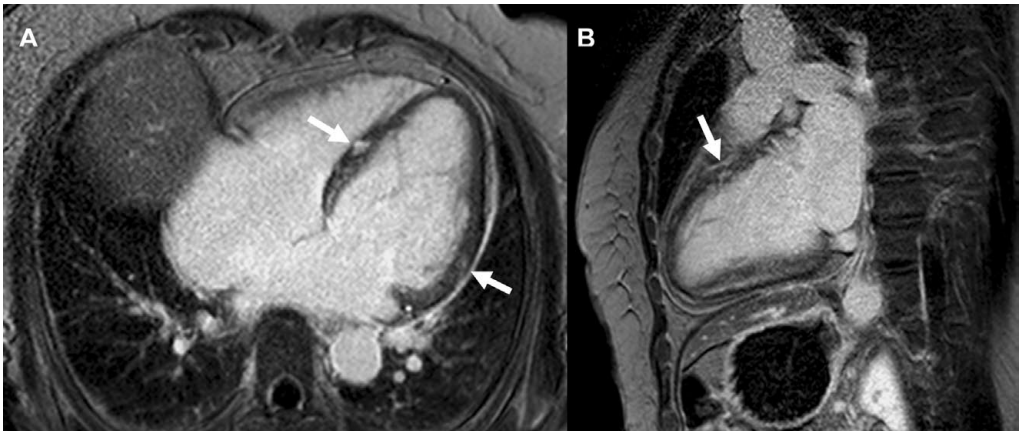

Figure 2. A 59-year-old woman who presented with dyspnea (NYHA III). Initial echocardiography shows LVEF 24% (LVEDD/LVESD 62/54 mm). CMR revealed FPE in the septum and LV free wall (**A**,**B**). After 2 years of treatment, her symptoms were much improved and follow-up echocardiography shows improved LV systolic function (LVEF 54%, LVEDD/LVESD 53/38 mm). (White arrow indicates DE in septum and LV free wall.) FPE, focal patchy enhancement. Other abbreviations see in **Figure 1**.

with serum creatinine >2 mg/dl, pregnancy, life-expectancy of less than 6 months because of other medical conditions, significant primary valvular heart disease and previous history of acute myocarditis. Patients were monitored for the occurrence of adverse cardiac events, defined as rehospitalization, because of worsening of heart failure, cardiac transplantation or death.

The study was approved beforehand by the institutional ethics committee and the procedures followed were in accordance with institutional guidelines. The study complied with the Declaration of Helsinki and informed consent was given by all patients.

CMR Procedure

The Gyroscan Intera system (Philips Medical Systems, Best, Netherlands) was used for CMR. Both cine and contrast-enhanced short-axis images were prescribed every 10 mm with a slice thickness of 10 mm from base to apex. Cine images were performed with a steady-state free precession sequence, and contrast-enhanced delayed images were obtained with an inversion recovery T1-weighted segmented gradient echo sequence 10–15 min after intravenous injection of 0.2 mmol/kg of gadolinium DTPA. We used the 'look-locker' sequence (Philips) to determine the optimal inversion time to null the enhanced normal myocardial signal, described in detail elsewhere.[3]

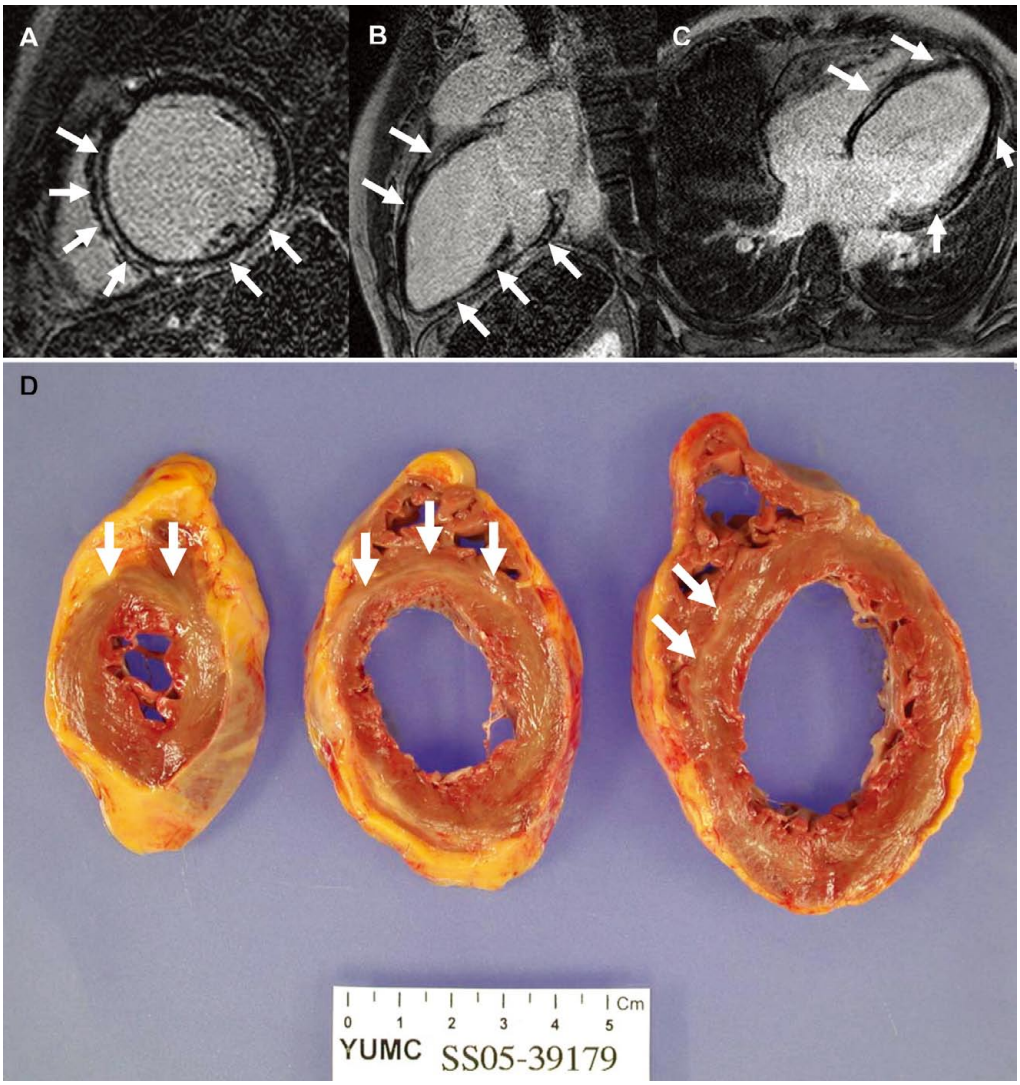

Figure 3. A 32-year-old man who presented with severe dyspnea (NYHA IV). He was a current, heavy smoker (30 pack-year). Initial echocardiography shows LVEF 14% (LVEDD/LVESD 67/62 mm). Despite intensive medical treatment, his symptoms worsened and follow-up echocardiography after 1 month showed no improvement in LVEF (12%, LVEDD/LVESD 63/59 mm). CMR revealed diffuse, mid-myocardial enhancement of the LV myocardium from base to low-mid LV (**A**–**C**) (white arrows indicate mid-myocardial DE). Eventually, he underwent cardiac transplantation. Gross specimen of the explanted heart shows linear, whitish striae (white arrow) in the mid-myocardium of the LV, suggesting mid-myocardial fibrosis, which coincides with DE-CMR findings (**D**). Abbreviations see in **Figure 1**.

Interpretation of CMR

The presence of significant DE was assessed in 12 segments per slice, with the exception of the most apical slice, which was divided into 8 segments. Regions of myocardium with abnormally high signals, as determined by 2 experienced radiologists, were determined as being positive for DE. The study population was divided into 2 groups according to the presence of DE: Group 1 comprised patients without DE (**Figure 1**) and Group 2 was the patients with DE. Group 2 was further divided into subgroups according to the pattern of DE: focal patchy enhancement (FPE) or diffuse myocardial enhancement (DME). FPE was defined as DE involving <50% of all segments (**Figure 2**) and DME was defined as DE involving >50% of all segments (**Figure 3**).

Echocardiography

Baseline and follow-up echocardiography were performed with a Hewlett-Packard Sonos 5500® Echocardiography System using a 2.5-MHz transducer to assess the recovery of LV function. The LVEF was obtained using a modified Simpson's method as described previously.[8] Standard 2-dimensional measurements (end-diastolic and end-systolic dimensions, ventricular septum and posterior wall thickness, left atrial volume index, LV mass index, LV outflow tract) were made. To estimate LV filling pressures, the ratio of mitral inflow peak velocity (E) over early diastolic tissue velocity of the mitral annulus (E') was calculated. Measurements were recorded with simultaneous ECG at a sweep speed of 50–100 mm/s. The echocardiographic data were analyzed by 2 experienced echocardiographers.

Table 1. Comparison of Baseline and Echocardiographic Characteristics According to Presence of DE

	Presence of DE		
	No (n=37)	Yes (n=42)	P value
Age (years)	55.27±14.82	57.40±12.27	0.49
Sex (M/F)	18/19	30/12	0.03*
Smoking (n)	8 (21.6%)	13 (30.9%)	0.25
Diabetes (n)	3 (8.1%)	4 (9.5%)	0.57
NYHA class ≥III	7 (18.9%)	17 (40.5%)	0.03*
QRS duration (ms)	106.43±28.04	116.71±28.37	0.11
Presence of AF (n)	9 (24.3%)	8 (19.0%)	0.38
Serum BNP (mg/dl)	4,917±8,947	5,106±6,109	0.95
Medications			
ACEI (n)	34 (91.9%)	33 (78.6%)	0.09
ARB (n)	5 (13.5%)	11 (26.2%)	0.13
β-blocker (n)	30 (81.1%)	26 (61.9%)	0.05*
Echocardiographic variables			
Time to follow-up echo (months)	6.94±5.26	7.09±4.61	0.90
Initial LVEDD (mm)	63.78±7.11	64.80±9.02	0.59
Initial LVESD (mm)	54.63±7.28	56.88±9.51	0.26
Initial LVEF (%)	28.26±7.22	25.07±9.14	0.10
Follow-up LVEDD (mm)	57.26±8.59	62.06±10.95	0.05*
Follow-up LVESD (mm)	43.55±8.80	52.53±12.04	<0.01*
Follow-up LVEF (%)	45.42±12.61	30.33±12.03	<0.01*
Functional recovery (follow-up LVEF >45%)	23 (67.6%)	3 (12.0%)	<0.01*

*P<0.05.
DE, delayed enhancement; NYHA, New York Heart Association; AF, atrial fibrillation; BNP, B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction.

Statistical Analysis

All continuous variables are expressed as mean±standard deviation. Continuous variables were compared with Student's t-test and discrete variables were compared using Fisher's exact test. Multivariate regression analysis was performed to determine the significant predictors of cardiac events. Kaplan-Meier survival analysis was performed to compare event-free survival in each group. A 2-tailed P-value <0.05 was considered statistically significant. SPSS software version 11.5 (SPSS, Chicago, IL, USA) was used.

Results

Baseline Patient Characteristics and CMR

CMR showed no DE in 37 patients (DE–) and the presence of DE in 42 patients (DE+) (Table 1). There were no statistical differences regarding age, diabetes, presence of atrial fibrillation or serum B-type natriuretic peptide (BNP level between the 2 groups (Table 1). However, there were more males in the DE(+) group than in the DE(–) group and severe (New York Heart Association (NYHA) III, IV) heart failure was more frequent in the DE(+) group than in the DE(–) group. Beta-blockers were more frequently used in the DE(–) group than in the DE(+) group. Although statistically not significant, there were trends toward longer QRS duration, less usage of angiotensin-converting enzyme inhibitors (ACEI) in the DE(+) group. In the DE(–) group, 8 patients were heavy alcoholics, 2 patients were postpartrum, 1 patient had tachycardia-induced cardiomyopathy and the remaining 26 patients had uncertain etiology. In the DE(+) group, 2 patients had LV non-compaction, 1 patient was a heavy alcoholic, 1 patient had tachycardia-induced cardiomyopathy and the remaining 38 patients had uncertain etiology. These findings showed that alcoholic cardiomyopathy was more frequent in the DE(–) group than in the DE(+) group (21.6% vs 2.4%, P<0.01), whereas idiopathic cardiomyopathy was more frequent in the DE(+) group than in the DE(–) group (70.3% vs 90.5%; P=0.02). In the comparison of cardiac event-positive (n=13) and cardiac event-negative (n=66) groups, there were no statistical differences in the baseline patient characteristics, except for a high percentage of NYHA class ≥III heart failure, longer QRS duration and less usage of β-blockers in the latter group than in the former group. Comparing the patterns of DE within group 2, there were no statistical differences regarding age, sex, diabetes, presence of atrial fibrillation and serum BNP levels. However, the usage of β-blockers was more frequent in the FPE group than in the DME group (13 (81.3%) vs 13 (50.0%); P=0.04) (data not shown).

Baseline and Follow-up Echocardiography and CMR

There were no significant difference between the DE(–) and DE(+) groups in initial LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD) and LVEF on baseline echocardiography. However, there were significant decreases in LVEDD and LVESD, as well as an increase in LVEF, in the DE(–) group, as compared with the DE(+) group, on follow-up echocardiography. In the DE(–) group, 23 of 37 patients (67.6%) showed functional recovery compared with 3 of 42 patients (13.0%) in the DE(+) group (Table 1). Between the FPE (n=16) and DME (n=26) groups there was a higher usage of β-blocker in the former group than in the latter (81.3% vs 50.0%, P=0.04). Although statistically not significant, there were trends towards higher

Table 2. Comparison of Baseline Clinical, Echocardiographic and CMR-Related Characteristics According to the Occurrence of Clinical Events

	Clinical events		
	No (n=66)	Yes (n=13)	P value
Age (years)	56.55±13.24	55.69±15.15	0.836
Sex (M/F)	35/31	7/6	0.957
Smoking (n)	14 (21.2%)	7 (53.8%)	0.015*
Diabetes (n)	5 (7.6%)	2 (15.4%)	0.365
NYHA class ≥III	15 (22.7%)	9 (69.2%)	0.001*
QRS duration (ms)	104.26±22.73	138.15±30.05	<0.001*
Presence of AF (n)	12 (18.2%)	5 (38.5%)	0.104
Plasma BNP (mg/dl)	5,199±7,977	4,094±3,237	0.785
Medications			
ACEI (n)	58 (87.9%)	9 (69.2%)	0.09
ARB (n)	10 (15.2%)	6 (46.2%)	0.011*
β-blocker (n)	50 (75.8%)	6 (46.2%)	0.032*
Echocardiographic variables			
Time to follow-up echo (months)	7.18±4.79	6.25±5.66	0.557
Initial LVEDD (mm)	63.59±8.20	67.85±7.01	0.086
Initial LVESD (mm)	55.15±8.56	59.08±8.11	0.133
Initial LVEF (%)	26.52±7.94	26.62±10.77	0.972
Follow-up LVEDD (mm)	57.93±9.41	68.90±8.43	0.001*
Follow-up LVESD (mm)	45.76±10.35	60.10±9.15	<0.001*
Follow-up LVEF (%)	40.07±14.15	25.30±8.62	<0.001*
CMR-related variables			
Presence of DE (%)	30 (45.5%)	12 (92.3%)	0.002*
Pattern of DE			<0.001*
FPE	15 (50.0%)	1 (8.3%)	
DME	15 (50.0%)	11 (91.7%)	

*P<0.05.
CMR, cardiac magnetic resonance imaging; FPE, focal patchy enhancement; DME, diffuse myocardial enhancement.
Other abbreviations see in Table 1.

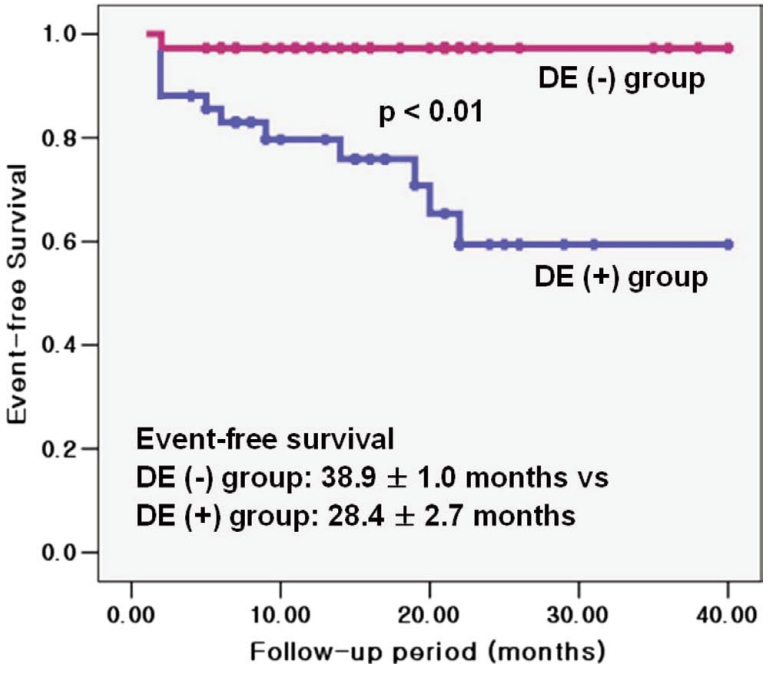

Figure 4. Event-free survival according to presence of delayed enhancement (DE) by Kaplan-Meier analysis.

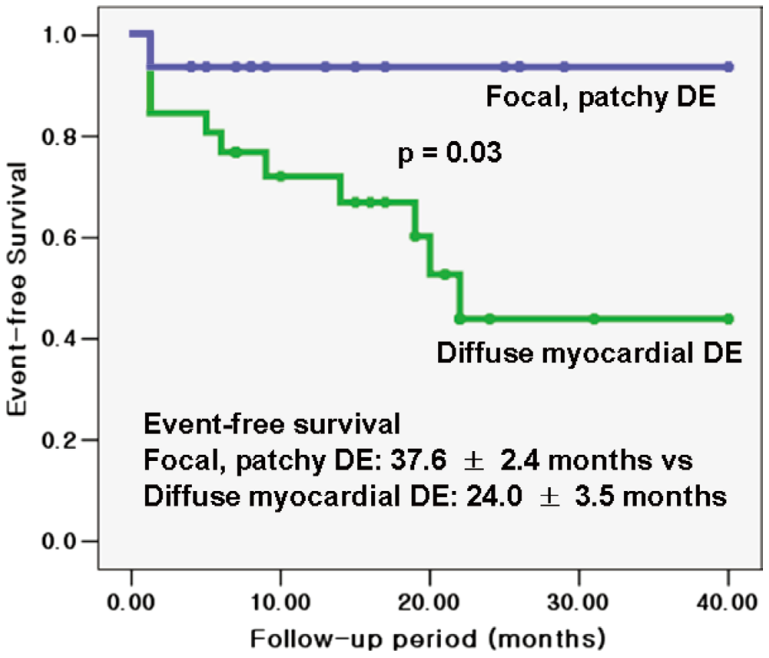

Figure 5. Event-free survival according to extent of delayed enhancement (DE) by Kaplan-Meier analysis.

percentages of patients with NYHA class ≥III, longer QRS duration and higher BNP levels in the DME group than in the FPE group at initial admission (42.3% vs 37.5%, 122.2±29.5 vs 107.9±24.9, 5,354±7,438 vs 4,651±2,891, respectively). At follow-up, there was also a numerically higher percentage of functional recovery in the FPE group than in the ME group (11.1% vs 8.3%) (data not shown).

Comparing the occurrence of cardiac events, there were no statistical differences regarding initial LVEDD, LVESD and LVEF between the 2 groups. However, there were significantly higher LVEDD and LVESD, as well as a lower LVEF, on follow-up echocardiography in the group with cardiac events, as compared with the group with no cardiac events (Table 2).

CMR and Cardiac Events

The mean duration of clinical follow-up was 33.4±1.7 months. There was 1 event (2.7%, 1 rehospitalization) in the DE(–) group, and 13 events (30.9%, 1 death, 1 transplantation, 11 rehospitalizations) in the DE(+) group. Among the rehospitalizations in the DE(+) group, there were 2 cases of non-sustained ventricular tachycardia, which was treated medically. In the DE(–) group, however, there were no fatal arrhythmic events (data not shown). In the comparison of the occurrence of cardiac events, there was a significantly higher percentage of DE in the cardiac event-positive group than in the cardiac event-negative group. There were also significant differences in the cardiac events in terms of the different patterns of DE (FPE and DME) between the 2 groups (FPE: 8.3% vs 50.0%; DME: 91.7% vs 50.0%) (Table 2). There was a significant difference in the mean event-free survival between groups (38.9±1.0 months vs 28.4±2.7 months, P<0.01) (Figure 4). The multivariate regression analysis revealed that the presence of DE was the most potent, independent predictor of cardiac events (hazard ratio (HR) 8.06, confidence interval 1.03–1.03±63.41, P<0.063.4, P<0.05) (Table 3). In the subgroup analysis, the extent of DE influenced event-free survival: the DME group had a shorter event-free survival than the FPE group (37.6±2.4 vs 24.0±3.5, P<0.05) (Figure 5).

Table 3. Multivariate Regression Analysis for Cardiac Events

	HR	CI	P value
Initial NYHA class >III	2.10	0.19–2.29	0.06
Presence of DE	8.06	1.03–63.41	0.04*
QRS duration >120 ms	5.28	1.53–18.17	0.05*
β-blocker usage	0.20	0.06–0.74	0.05*

*P<0.05.
HR, hazard ratio; CI, Confidence interval. Other abbreviations see in Table 1.

Discussion

In this study, we evaluated the association between DE-CMR and cardiac events in a group of patients with NICM during a sufficiently long follow-up period (33.4±1.7 months). Our results demonstrated that the presence of DE was the most significant prognostic predictor of future cardiac events, along with other established predictors such as β-blocker use, increased QRS duration and NYHA class ≥III. Furthermore, to our knowledge this is the first demonstration of an association between differential patterns of DE-CMR and clinical outcome, as well as functional recovery, in patients with NICM.

DE-CMR in NICM

Because gadolinium-DTPA is a biologically inert product that diffuses passively into the extracellular space, expansion of that space by fibrous replacement tissue will result in increased distribution of contrast agents with subsequent increased accumulation. Also, slower distribution kinetics may account for DE in regions of fibrosis in the heart.[9–11] McCrohon et al[12] demonstrated DE-CMR in patients with DCM. Interestingly, there were 3 types of DE in those patients: no enhancement, enhancement indistinguishable from patients with ischemic cardiomyopathy (ie, subendocardial or transmural) and patchy

or longitudinal striae of midwall enhancement. The patchy or longitudinal striae pattern was reported to be similar to fibrosis found at autopsy, so it was thought to be associated with idiopathic DCM. In the present study, there were patchy or longitudinal enhancement lesions along the mid-myocardial layer. To assess the amount of DE semi-quantitatively in each subject, we categorized the myocardial pattern of enhancement as focal patchy or diffuse, according to the extent of myocardium with DE, as previously defined in the Methods section. In a study by Bello et al, they performed gadolinium-CMR in a patient with heart failure and concluded that the amount of viable myocardium (as opposed to myocardial segment with DE) was an independent predictor of change in LVEF, mean wall motion score, and the LV end-diastolic/end-systolic volume index.[13] Our group previously demonstrated that the absence of DE can be useful in predicting functional recovery in patients with NICM.[3] In the present study, the percentage of functional recovery was significantly higher in the DE(–) group than in the DE(+) group (67.6% vs 12.0%, P<0.01). Although statistically not significant, there was a numerically higher percentage of functional recovery in the FPE group than in the DME group (11.1% vs 8.3%).

The different patterns of DE (ie, subendocardial/transmural, patchy or longitudinal striae), as McCrohon et al reported, are largely based on specific CMR findings. In practice, there are many more patterns of DE in patients with NICM, so for clinical purposes, the extent of DE should be emphasized, rather than a prespecified morphologic pattern.

DE and Prognosis of NICM

There are few reports regarding prognosis and DE in patients with NICM. In one report by Assomull et al suggested the prognostic implications of midwall fibrosis in DCM.[14] In their report, 101 consecutive DCM patients with presence or absence of midwall fibrosis detected by DE-CMR were followed for 22±12 months. Midwall fibrosis was present in 35% of patients and was associated with a higher rate of cardiac events (HR 3.4) and it was the sole significant predictor of outcome (HR 3.1). In that study population with DCM, patients with DE only have midwall enhancement. In our study, however, we found varying patterns of DE, except for subendocardial/transmural patterns, and categorized these as the FPE or DME group, which may explain the high percentage of DE in patients with NICM from our study (42 of 79, 53.2%), compared with the study by Assomull et al. In a small observational study by Nanjo et al, they reported as high as 88% DE in Japanese patients with DCM, with varying patterns,[15] which could also be supporting evidence of the relatively higher prevalence of DE in patients with NICM in our study.

NICM, by definition, includes a variety of etiologies and the underlying etiology can be a determinant of prognosis. So, there is increased concern about the relationship between DE patterns and specific pathologic characteristics. In a recent report by Zimmermann et al,[16] 42 patients with DCM and 42 control subjects underwent DE-CMR and all patients with DCM underwent endomyocardial biopsy. None of the control subject showed DE whereas in 29 DCM patients (69%) DE (50% midwall, 17% patchy, 2% typical for ischemic heart disease) was detectable. Interestingly, the pattern of DE and myocardial biopsy findings did not significantly correlate, suggesting that endomyocardial biopsy cannot be replaced by DE-CMR for the differential diagnosis of DCM. However, endomyocardial biopsy inherently carries potentially complications, such as pericardial effusion and cardiac tamponade, so for practical purposes, endomyocardial biopsy is not always necessary in the management of patients with NICM.[17]

The higher percentage of reversibility of depressed LV systolic function in the DE(–) group is a noteworthy finding in our study. Among them, heavy alcoholics (>8 standard drinks/day over a period at least 5 years, by interview) were the most frequent (21%). It has been reported that the prevalence of spontaneous recovery in alcoholic cardiomyopathy is relatively high.[18] The pathologic studies shown that myocyte hypertrophy, fibrosis, and nuclear changes are significantly less frequent in alcoholic cardiomyopathy compared with idiopathic DCM.[19] However, in the present DE(+) group, cardiomyopathy without definite cause (namely, idiopathic) was the most frequent (90.5%), as expected.

The role of medication on cardiovascular outcome in patients with NICM should not be overlooked. There have been large randomized studies demonstrating that β-blockers improve survival in patients with heart failure.[20] However, not all patients responds uniformly to this therapy and those without improvement of LV function may not have improved survival because of having less viable myocardium to respond to β-blockers.[21,22] So, if there were more viable myocardium (ie, less myocardial fibrosis), then the patients can respond well to β-blockers (consequently tolerate well) and may have improved survival. There was an association between the degree of myocardial fibrosis and response to β-blockers in our study, there were a relatively high percentage of β-blocker usage by all patients (71.5%). Because β-blockers are known to have protective effects against fatal ventricular arrhythmias, these results might be a reason for the relatively few fatal arrhythmic events in the study patients. In addition, β-blockers were more frequently used in the DE(–) group than in the DE(+) group (**Table 1**), as well as in the FPE group compared with the DME group, suggesting that less improvement in myocardial function did not allow introduction of β-blockers. This could also be a partial explanation for the better event-free survival in the FPE group compared with the DME group, even though other parameters only showed favorable trends towards better outcome in the former group.

Study Limitations

This study had a purely observational basis and non-randomized design, so there might have been a selection bias in the enrollment of study patients. Patients with severe arrhythmias (atrial fibrillation etc), which make CMR possible, or those with any implantable devices (pacemaker or implantable cardioverter-defibrillator), who cannot undertake CMR will inevitably be excluded and this would also contribute to the selection bias.

Clinical Implications

The prognosis of NICM is variable. In such patients, myocardial fibrosis is reported to be associated with cardiovascular outcome. DE-CMR is directly associated with fibrosis. In this regard, DE-CMR can be useful to predict cardiovascular outcome in patients with NICM, regardless of its etiology.

In conclusion, DE-CMR should be considered as a useful clinical tool to investigate the degree of myocardial fibrosis in the evaluation of LV systolic function.

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