Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 48, No. 10, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.049

FOCUS ISSUE: CARDIAC IMAGING

Cardiovascular Magnetic Resonance, Fibrosis, and Prognosis in Dilated Cardiomyopathy

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OBJECTIVES We studied the prognostic implications of midwall fibrosis in dilated cardiomyopathy (DCM) in a prospective longitudinal study.

BACKGROUND Risk stratification of patients with nonischemic DCM in the era of device implantation is problematic. Approximately 30% of patients with DCM have midwall fibrosis as detected by late gadolinium-enhancement (LGE) cardiovascular magnetic resonance (CMR), which may increase susceptibility to arrhythmia and progression of heart failure.

METHODS Consecutive DCM patients (n = 101) with the presence or absence of midwall fibrosis were followed up prospectively for 658 ± 355 days for events.

RESULTS Midwall fibrosis was present in 35% of patients and was associated with a higher rate of the predefined primary combined end point of all-cause death and hospitalization for a cardiovascular event (hazard ratio 3.4, p = 0.01). Multivariate analysis showed midwall fibrosis as the sole significant predictor of death or hospitalization. However, there was no significant difference in all-cause mortality between the 2 groups. Midwall fibrosis also predicted secondary outcome measures of sudden cardiac death (SCD) or ventricular tachycardia (VT) (hazard ratio 5.2, p = 0.03). Midwall fibrosis remained predictive of SCD/VT after correction for baseline differences in left ventricular ejection fraction between the 2 groups.

CONCLUSIONS In DCM, midwall fibrosis determined by CMR is a predictor of the combined end point of all-cause mortality and cardiovascular hospitalization, which is independent of ventricular remodeling. In addition, midwall fibrosis by CMR predicts SCD/VT. This suggests a potential role for CMR in the risk stratification of patients with DCM, which may have value in determining the need for device therapy. (J Am Coll Cardiol 2006;48:1977–85) © 2006 by the American College of Cardiology Foundation

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Nonischemic dilated cardiomyopathy (DCM) is associated with significant morbidity and premature mortality (1). Several trials have shown the outcome benefits from device implantation in this group of patients (2–5), but at considerable cost (6) and risk of complications (7). In addition, a proportion of patients with cardiac resynchronization therapy (CRT) do not seem to respond (8), whereas many patients with an implantable cardioverter-defibrillator will not experience device activation (9). There is therefore a pressing need for improved identification of those at risk of progressive deterioration requiring hospitalization and sudden cardiac death (SCD).

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In patients with ventricular dysfunction, an important mechanism for the occurrence of arrhythmias and failure to respond to treatment is the presence of myocardial fibrosis (10–12). Although there is extensive evidence to implicate the role of fibrosis after infarction, the significance of fibrosis in DCM is unclear. Approximately 30% of patients with DCM have midwall fibrosis as determined by late gadolinium-enhancement (LGE) cardiovascular magnetic resonance (CMR) (13). This midwall fibrosis is distinct from infarction in sparing the subendocardium. We have speculated that fibrosis in DCM might predict outcome (13). We tested this hypothesis in a prospective study comparing the clinical outcomes in DCM patients with or without midwall fibrosis.

METHODS

Patient population. Patients with DCM (n = 101) and impaired systolic function were prospectively recruited between June 2000 and December 2003 from consecutive referrals from centers in southeast England. The diagnosis

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Manuscript received February 21, 2006; revised manuscript received May 25, 2006, accepted July 12, 2006.

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
CMR = cardiovascular magnetic resonance
CRT = cardiac resynchronization therapy
DCM = dilated cardiomyopathy
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LGE = late gadolinium enhancement
LV = left ventricle/ventricular
RV = right ventricle/ventricular
SCD = sudden cardiac death
VT = ventricular tachycardia

of DCM was made according to World Health Organization/International Society and Federation of Cardiology criteria (14). All patients had chronic heart failure of at least 12 months' duration and had presented with symptoms and onset typical of chronic heart failure, including slowly progressive breathlessness, fatigue, and palpitations. None of the patients in this study had clinical symptoms or signs of ongoing myocarditis. Significant coronary artery disease (CAD) (>50% diameter luminal stenosis in any coronary artery) was excluded in 98 patients by coronary angiography. Two patients declined coronary angiography but had normal myocardial perfusion scans. One asymptomatic patient, age 18 with a strong family history of DCM, did not undergo either test. Any patients with clinical evidence of left ventricular (LV) damage caused by CAD were excluded. These included patients with a clinical history and typical electrocardiogram associated with biochemical, angiographic, or CMR evidence of previous myocardial infarction. Patients with a normal CMR-derived ejection fraction (EF) were also excluded (EF >56%, n = 21). These 21 excluded patients had been referred for CMR with possible ventricular dysfunction based on echocardiography with poor acoustic windows, but none showed evidence of midwall fibrosis, none were on treatment for heart failure at the time of referral, and none are currently receiving heart failure treatment. Other exclusion criteria were the presence of any contraindications to CMR, significant valvular disease, hypertrophic cardiomyopathy, or any evidence of infiltrative heart disease. All participants gave written informed consent. The project was approved by our institutional ethics committee.

CMR. Cardiovascular magnetic resonance (Siemens Sonata 1.5-T, Erlangen, Germany) was performed using steady-state, free precession breath-hold cines (TE [echo time]/TR [repetition time] 1.6/3.2 ms, flip angle 60°) in long-axis planes and sequential 7-mm short-axis slices (3-mm gap) from the atrioventricular ring to the apex. The LGE images were acquired 10 min after intravenous gadolinium-DTPA (Schering, Berlin, Germany; 0.1 mmol/kg) in identical short-axis planes using an inversion-recovery gradient echo sequence (13). Inversion times were adjusted to null normal myocardium (typically 320 to 440 ms; pixel size 1.7 × 1.4 mm). In all patients, imaging was repeated for each short-axis image in 2 separate phase-encoding directions to exclude artifact. Midwall LGE was only deemed to be present when the area of signal enhancement could be seen in both phase-swapped images and in a cross-cut long-axis image by the independent observers (Fig. 1). The LGE was assessed visually, and the volume was measured by manual planimetry by 2 independent readers blinded to all patient details. The planimetered areas had a signal intensity of >2 SD above the mean intensity of remote myocardium in the same slice (15). Patients were divided into those with enhancement (LGE+) and those without (LGE−). Fibrosis volume was expressed as a percentage of total myocardial mass (%LGE). Ventricular volumes and function were measured for both ventricles using standard techniques (16), and analyzed using semiautomated software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom).

Event data. Patient events were recorded by communication with patients, their cardiologists, and general practitioners. Medical records were reviewed after attendance at outpatient clinics or hospitalization. All patients were directly contacted at enrollment and at 3-month to 6-month intervals during follow-up. If the general practitioner had not contacted the patient for >3 months, the patient was directly contacted. In one case, in which the patient could not be reached, a national death register showed that the patient had died of heart failure. No patient was lost to follow-up. The prespecified primary end point was a composite of all-cause mortality or hospitalization for a cardiovascular event (2,5). Secondary end points were the occurrence of SCD or sustained ventricular tachycardia (defined as ventricular extrasystoles at >120 beats/min lasting for >30 s on an electrocardiogram or 24-h tape) and all-cause mortality alone. Patient data were censored at the time of any transplantation. The cause of death was identified in all cases. Death caused by heart failure was defined as death preceded by signs or symptoms of heart failure; SCD was defined as death with or without documented ventricular arrhythmia within 1 h of new symptoms, or nocturnal death with no antecedent history of worsening symptoms (17).

Statistical analysis. Continuous data are expressed as a mean values ± SD. The baseline characteristics of the 2 groups were compared with the independent sample *t* test for continuous variables, and chi-square or Fisher exact tests for categorical variables. Survival estimates and cumulative event rates were compared by the Kaplan-Meier method using the time to first event for each end point. The log-rank test was used to compare the Kaplan-Meier survival curves. The hazard ratio was calculated using a Cox regression model with computed 95% confidence intervals (CI). Multivariate analysis was also performed using covariates known to affect the end points, namely age, LV end-systolic volume (ESV), LV end diastolic volume (EDV), LVEF, right ventricular ejection fraction (RVEF), and digoxin therapy. Linear regression and Bland-

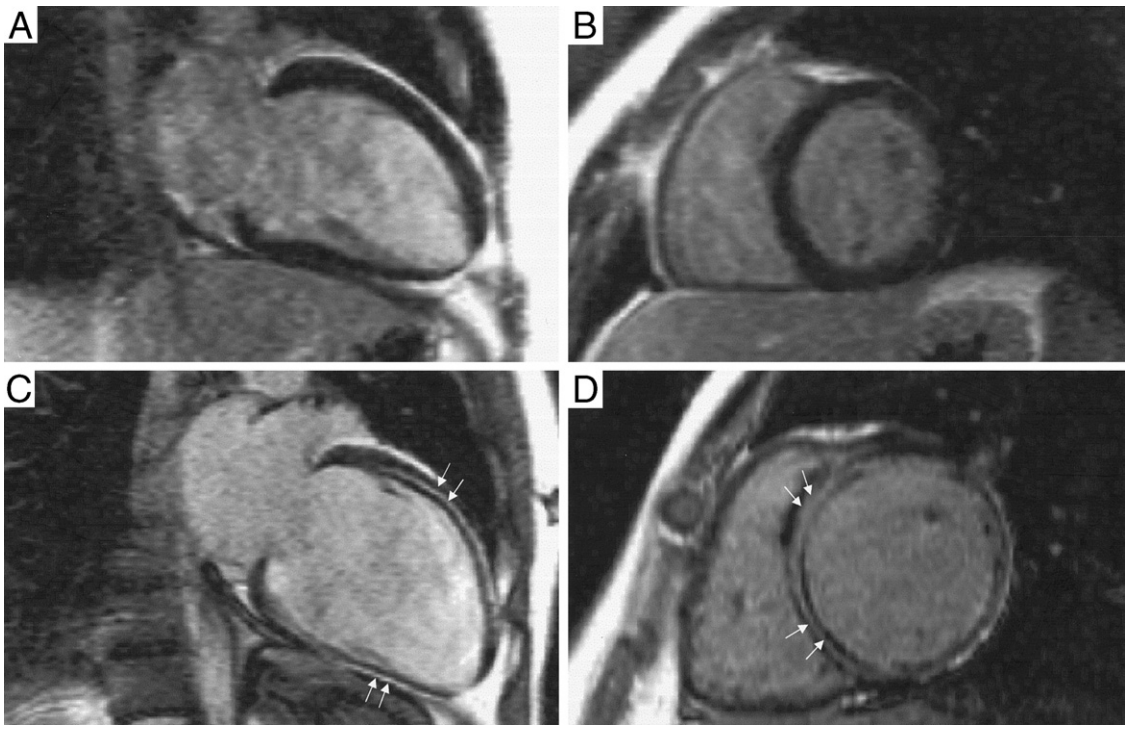

Figure 1. Late gadolinium enhancement patterns in dilated cardiomyopathy in vertical long axis **(A and C)** and short axis **(B and D)**. A patient without late enhancement is shown in **A** and **B**, and a patient with marked midwall enhancement is shown in **C** and **D**. The enhancement pattern **(arrows)** is distinct from that associated with coronary artery disease because of endocardial sparing and noncoronary territory distribution.

Altman analysis were used to assess the correlation between the 2 independent observers performing LGE planimetry. Odds ratios and CIs were calculated using binary logistic regression analysis to investigate for the presence of any significant associations between the primary end point (categorical data) and %LGE, LVEDV, LVESV, or LVEF (continuous data).

The duration of follow-up was computed using the date of entry into the study (day of the CMR scan) to the date of the first end point reached. For patients who did not reach an end point, follow-up data were collected to the time of their last clinical follow-up. A p value of <0.05 was deemed significant, and SPSS for Windows (version 12.0, SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

RESULTS

Baseline characteristics. Group baseline characteristics are summarized in Table 1. The LGE+ patients were younger, with larger LV volumes and a lower LV EF. The RV volumes were not significantly different, but LGE+ patients had a lower RV EF. Baseline medical treatment of the 2 groups was comparable, except that a higher proportion of LGE+ patients received digoxin. There was no difference in the duration of heart failure before enrollment.

Autopsy data. One patient with familial DCM who died underwent autopsy. Comparison of the macroscopic appearance of the cut surface of the heart suggested midwall fibrosis particularly affecting the inferior and lateral walls, and fibrosis was confirmed using Sirius-red staining. There was excellent agreement between the pathological location of the midwall fibrosis and the premortem location of the midwall LGE (Fig. 2).

Survival analysis. Data were collected for a total of 182 patient-years of follow-up. The mean duration of follow-up was 658 ± 355 days. There were 10 deaths (6 LGE+ patients [17%]; 4 LGE− [6%] patients), resulting in an annual mortality rate of 5.4% per year. In the LGE+ group, 3 patients died of heart failure, 2 of SCD, and 1 of drug-related acute hepatic failure. In the LGE− group, 2 patients died of heart failure and 2 patients of SCD. Kaplan-Meier analysis showed no significant difference in all-cause mortality between the 2 groups ($p = 0.10$).

There were episodes of hospitalization for 13 patients. None of the patients had been hospitalized in the 3 months before enrollment. Four patients each in the LGE+ group (11%) and LGE− (6%) group were admitted for unplanned treatment of decompensated heart failure with intravenous diuretics. Three patients in the LGE+ group were admitted with sustained ventricular tachycardia (VT) requiring emergency cardioversion (9%). Finally, 1 patient in each of the LGE+ (3%) and LGE− (2%) groups was admitted with syncope. Orthotopic cardiac transplantation was performed in 3 patients (all LGE+, 9%) for end-stage progressive heart failure.

The LGE+ patients had a significantly higher incidence of the primary end point (all-cause mortality or hospitalization for cardiovascular causes [hazard ratio 3.4; 95% CI 1.4 to 8.7; $p = 0.01$]) (Fig. 3A). Using a Cox regression model including presence of LGE, age, LVESV, LVEDV, LVEF,

Table 1. Baseline Characteristics of the Two Study Groups

Characteristic	LGE− (n = 66)	LGE+ (n = 35)	p Value
Age (yrs) (SD)	53 (13)	48 (14)	0.045
Male (%)	47 (71)	23 (66)	0.57
Family history of DCM (%)	9 (14)	8 (23)	0.23
History of diabetes (%)	4 (6)	1 (3)	0.48
History of hypertension (%)	12 (18)	2 (6)	0.084
History of smoking (%)	5 (8)	2 (6)	1.0
History of alcohol excess (%)	10 (15)	3 (9)	0.53
Increased BMI (%)	10 (15)	2 (6)	0.20
Heart failure duration (months)	28 (40)	24 (24)	0.61
Systolic BP (mm Hg)	120 (16)	115 (21)	0.19
Diastolic BP (mm Hg)	74 (9)	72 (14)	0.39
Heart rate (beats/min)	74 (14)	76 (14)	0.66
NYHA functional class (%)			
I	20 (30)	3 (9)	0.10
II	29 (44)	20 (57)	
III	16 (24)	11 (31)	
IV	1 (2)	1 (3)	
Medication (%)			
ACEi	51 (77)	28 (80)	0.75
AT II blocker	9 (13)	8 (23)	0.24
Beta-blocker	38 (57)	24 (69)	0.28
Spironolactone	14 (21)	13 (37)	0.085
Digoxin	7 (11)	10 (29)	0.022
Diuretics	27 (41)	21 (60)	0.068
Anticoagulation	16 (24)	12 (34)	0.28
Amiodarone	6 (9)	3 (9)	0.93
Statins	4 (6)	3 (9)	0.69
CMR dimensions and function (SD)			
LV EDV (ml)	235 (70)	284 (108)	0.020
LV ESV (ml)	150 (67)	199 (96)	0.0082
LV EF (%)	38 (12)	31 (12)	0.0064
LV mass (g)	139 (66)	134 (63)	0.69
RV EDV (ml)	185 (57)	177 (51)	0.46
RV ESV (ml)	112 (46)	98 (42)	0.12
RV EF (%)	48 (22)	41 (11)	0.044

ACEi = angiotensin-converting enzyme inhibitor; AT II = angiotensin 2 receptor blocker; BMI = body mass index; BP = blood pressure; DCM = dilated cardiomyopathy; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LGE+ = patients with late gadolinium enhancement; LGE− = patients without late gadolinium enhancement; LV = left ventricular; NYHA = New York Heart Association; RV = right ventricular.

RVEF, and treatment with digoxin, the presence of LGE was the sole significant predictor of outcome (hazard ratio 3.1; 95% CI 1.1 to 8.5; p = 0.03) (Fig. 3B). The difference between the two groups was accentuated if elective admissions for biventricular/right ventricular pacemakers were included (hazard ratio 3.6; 95% CI 1.6 to 7.8, p < 0.001).

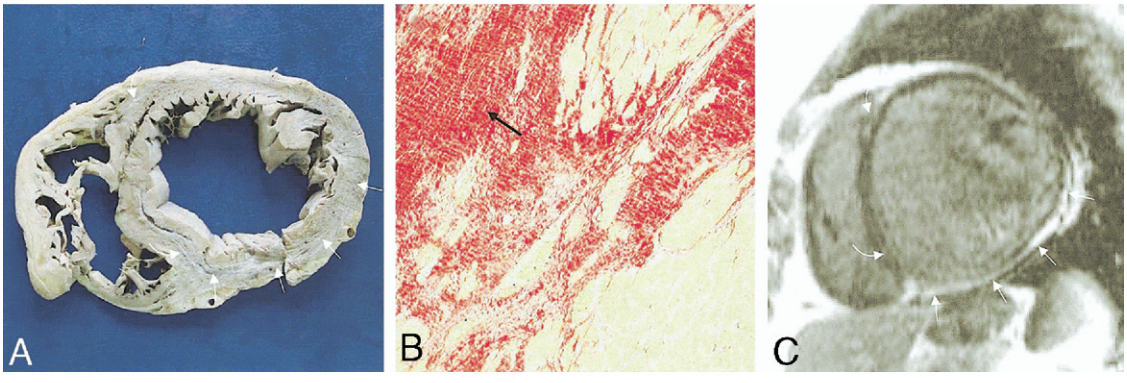

Figure 2. **(A)** Macroscopic short-axis section of the right and left ventricle at a midventricular level from a patient with dilated cardiomyopathy showing midwall fibrosis **(straight arrows)**, mainly in the inferior and lateral walls, but also in the lower and upper septum **(curved arrows)**. **(B)** Microscopic section of the heart in which Sirius red staining confirms collagen **(arrow)** in areas of fibrosis seen macroscopically. Myocytes **(stained yellow)** are admixed with the collagen **(red)**. **(C)** Premortem cardiovascular magnetic resonance of the same slice, with excellent accord between the areas of macroscopic fibrosis and areas of late gadolinium enhancement **(matching arrows)**.

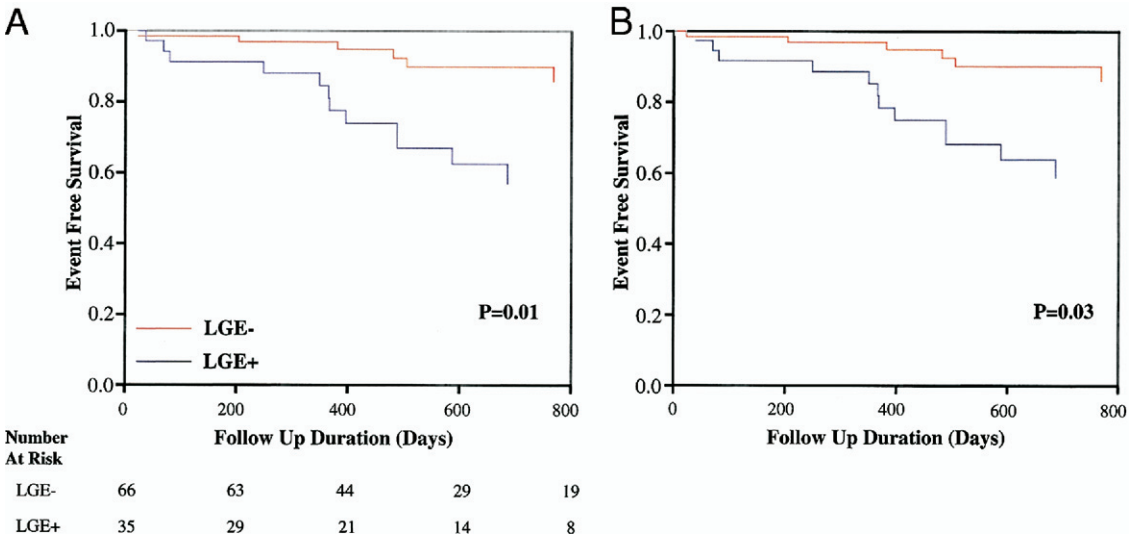

Figure 3. **(A)** Kaplan-Meier survival estimates for the primary end point of all-cause mortality or hospitalization due to cardiovascular causes. **(B)** Same data adjusted for baseline differences in age, left ventricular (LV) end-systolic volume, LV end-diastolic volume, LV ejection fraction, right ventricular ejection fraction, and treatment with digoxin. LGE+ = patients with late gadolinium enhancement; LGE− = patients without late gadolinium enhancement.

For the secondary end points, LGE+ patients had a higher incidence of SCD/VT (hazard ratio 5.2; 95% CI 1.0 to 26.9; p = 0.03) (Fig. 4A). Because of the low event rates (seven events in total), multivariate analysis was performed using only LVEF because this is the most widely used clinical marker of arrhythmic risk in patients with heart failure (5). The LGE remained a significant predictor of outcome when multivariate analysis correcting for LVEF was performed (hazard ratio 5.9; 95% CI 1.1 to 32.2; p = 0.04) (Fig. 4B).

Correlation between extent of LGE and outcome. Linear regression analysis showed a high correlation between the 2 observers for planimetry of %LGE (r = 0.95, p < 0.01). The median %LGE in LGE+ patients was 4.6%, with a range of 0.8% to 21%. In addition, Bland-Altman analysis showed a mean difference in observations of 0.19% with a standard deviation of differences of 3.62%. Using binary logistic regression to derive the probability of having an event, the extent of late enhancement expressed as %LGE was strongly associated with outcome and was found to be the sole significant predictor of an event when compared with LVESV, LVEDV, and LVEF for the primary end point of death or hospitalization (odds ratio 1.12; 95% CI 1.03 to 1.24; p = 0.02) (Fig. 5A). In addition, when considering just the 35 patients in the LGE+ group, a receiver-operating characteristic analysis showed the optimal %LGE, which predicts that outcome was 4.8%. When the LGE+ group was further subdivided into LGE < 4.8% and LGE > 4.8%, Kaplan-Meier analysis showed a strong trend

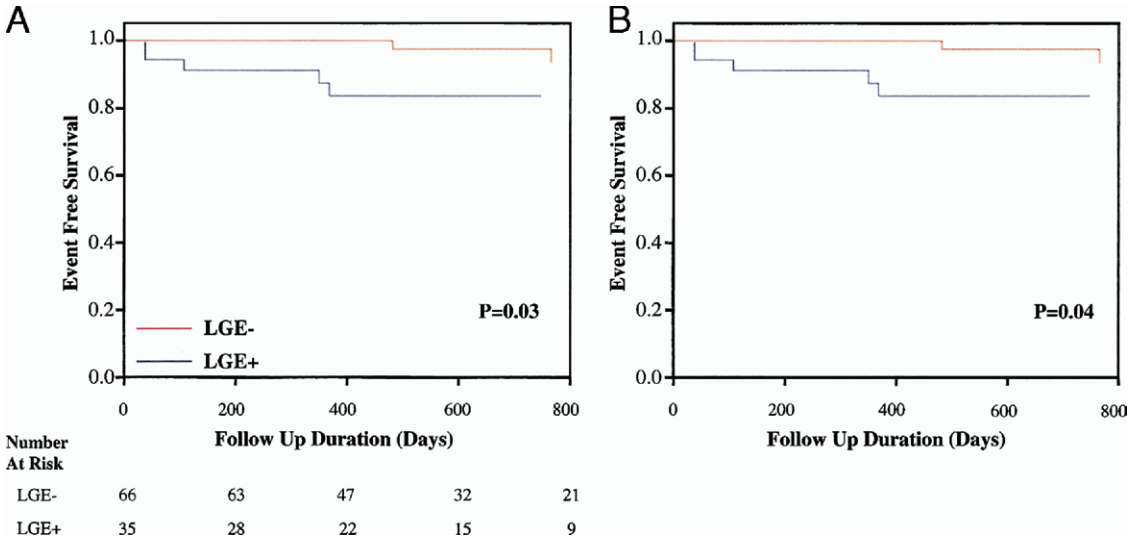

Figure 4. **(A)** Kaplan-Meier survival estimates for the secondary end point of sudden cardiac death or sustained ventricular tachycardia. **(B)** Same data adjusted for baseline differences in left ventricular ejection fraction. LGE+ = patients with late gadolinium enhancement; LGE− = patients without late gadolinium enhancement.

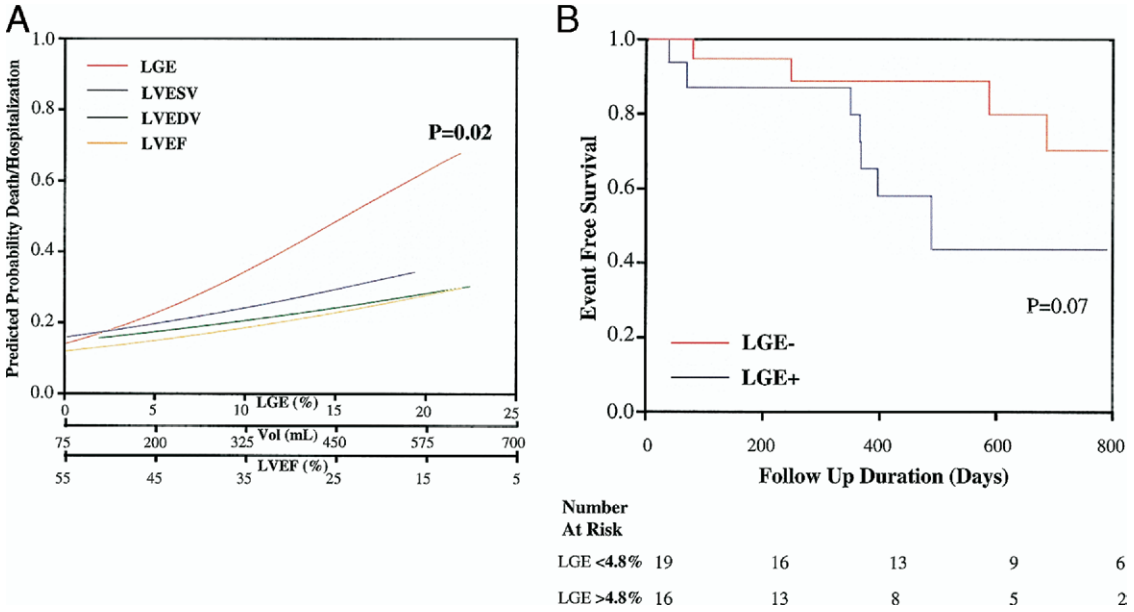

Figure 5. **(A)** Binary logistic regression analysis comparing the extent of late enhancement (%LGE), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF) as predictors of death or hospitalization. There was a strong association between %LGE and outcome, and %LGE was the sole significant predictor of the primary end point (odds ratio 1.12, 95% confidence interval 1.03 to 1.24, p = 0.02). **(B)** Kaplan-Meier subgroup analysis of the 35 patients in the LGE+ group divided into high and low LGE (division point 4.8% LGE). The analysis shows a trend (p = 0.07) toward a significant difference in outcome for the primary end point between the 2 subgroups. LGE+ = patients with late gadolinium enhancement; LGE− = patients without late gadolinium enhancement.

toward a significant difference in outcome between the two groups for the primary end point of all-cause mortality and hospitalization (Fig. 5B).

DISCUSSION

Patients with DCM have increased mortality because of progressive heart failure and SCD (18). Accurate risk stratification is important in identifying those patients who would benefit from costly and invasive procedures such as device implantation. In this prospective study, we investigated the prognostic implications of midwall fibrosis (LGE+) in a cohort of patients with confirmed nonischemic DCM. The overall occurrence of LGE (35%) was similar to that found in previous studies (13). The data show that patients with fibrosis had a significantly worse outcome of the primary end point, all-cause death or cardiac hospitalization. In addition, despite the relatively low number of events, patients with fibrosis had a significantly greater incidence of the secondary end point of SCD/VT. Importantly, by multivariate analysis, the prognostic value of the presence of fibrosis was independent of established markers of adverse outcome, including age and LV and RV volume/function (19,20). There was a trend toward a higher rate of all-cause mortality in the patients with fibrosis, but the study seems underpowered for this comparison.

Our results also suggest that %LGE has a role in predicting outcome. The %LGE was associated with a higher probability of the primary end point of death and hospitalization. The association between %LGE and outcome was better than for established prognostic parameters such as LVESV, LVEDV, and LVEF. We believe that the current study is the first to identify the prognostic significance of in vivo detection of myocardial fibrosis in patients with DCM.

In the current era of device implantation, LVEF is a major determinant of stratification to therapy, and yet it is a poor guide to outcome and treatment benefit. In DCM, a high proportion of patients show evidence of myocardial fibrosis in addition to LV dilatation and global hypokinesis. This has been shown in explanted hearts from transplantation and postmortem studies and, in this study, in the autopsy case available. Both reactive (interstitial and perivascular) and reparative (replacement) patterns of fibrosis are seen in DCM (21,22). The fibrosis may reflect inflammation as well as microvascular ischemia (23,24).

The mechanisms for midwall fibrosis are thought to be the result of a combination of factors including genetic predisposition, exposure to toxins and pathogens, microvascular ischemia, and abnormal modulation of immune and metabolic responses such as overactivity of the renin angiotensin aldosterone system (21,23,25–28). Case reports exist of midwall fibrosis in familial conditions such as muscular dystrophy (29). In the cohort of patients described in the present study, 8 patients with familial cardiomyopathy had midwall fibrosis. The underlying pathological mechanisms for this familial propensity to fibrosis may be explained by the fact that a number of defective genes implicated in familial DCM have also been found to code for cytoskeletal proteins (25), and this could set up a chronic injury–repair scenario resulting in fibrosis. Exposure to pathogens such as

viruses triggers fibrosis. Early CMR imaging of patients with acute myocarditis shows characteristic epicardial or midwall late enhancement in the acute phase (15), which may persist in the subset of patients in whom DCM subsequently develops. Histopathological studies of hearts from patients with myocarditis confirm fibrosis and inflammatory exudates (30). However, other histopathological studies of patients with end-stage DCM do show interstitial fibrosis in the absence of any histological features of inflammation, suggesting that fibrosis may exist in the absence of myocarditis (21). Previous studies have implicated myocarditis as the cause of fibrosis in 10% of cases (31), and we would speculate that a proportion of patients in our study with DCM, including those with fibrosis, may have had a myocarditis at some time with subsequent development to DCM.

The occurrence of sustained monomorphic VT is linked to a scar-related re-entrant mechanism similar to that of CAD. The arrhythmia is uniformly inducible and is often refractory to pharmacological therapy. In animal studies and pretransplantation heart assessments, sustained VT is associated with more extensive myocardial fibrosis and nonuniform anisotropy, involving both the endocardium and epicardium, compared with those without sustained re-entry (32,33). Myocardial fibrosis is also associated with adverse ventricular remodeling leading to the development of heart failure in animal and human studies (26,27).

Although previous invasive studies in DCM patients have shown myocardial fibrosis, these studies have relied on tissue biopsy, which may miss affected areas, resulting in a high sampling error; CMR is able to detect replacement fibrosis in cardiomyopathy caused by both ischemic and nonischemic causes (13,35–37). In ischemic heart disease, detection of fibrosis is useful in viability assessment (12), and recent work has shown that infarct size characterized by CMR is a better identifier of patients with substrate for sustained VT than LV EF (10). Our study using CMR to detect myocardial fibrosis accords with studies in other conditions. Recently published data have also shown that fibrosis as detected by LGE-CMR is significantly predictive of inducible VT in DCM, even after adjustment for LV EF in a multivariate model (38). In arrhythmogenic RV cardiomyopathy, RV myocardial fibrosis detected by CMR had an excellent correlation with histopathology and predicted inducible VT (37). However, there is controversy over the positive predictive accuracy of inducibility of VT alone in consecutive series of patients (39).

Patients with fibrosis also have a higher incidence of hospitalizations. This may be the result of several mechanisms. Fibrosis may predispose to arrhythmia, and paroxysmal tachycardia can result in heart failure decompensation (40). The presence of fibrosis may also render the ventricle less compliant, thereby impairing diastolic function with increasing filling pressures and producing a restrictive filling pattern (41). This may also precipitate pulmonary edema or atrial tachycardias, resulting in decompensation, necessitating hospital admission. To date, there have been few outcome data reflecting the prognostic implications of identifying myocardial fibrosis in vivo.

In our study, the presence of fibrosis predicted a poorer outcome of the primary end point in patients with DCM. Our data imply that patients with DCM and fibrosis may benefit from early and more aggressive treatment of their LV dysfunction with currently available pharmacotherapy and mechanical resynchronization treatment. In addition, our study showed a significantly higher rate of SCD/VT in patients with midwall fibrosis even after adjustment for LVEF. However, because of the low number of events in the cohort, this finding should be interpreted with caution. We propose that CMR could therefore potentially play an important role in early stratification of treatment in patients with DCM. Our findings also emphasize the pressing need for larger studies to further evaluate the possible incidence of higher arrhythmic episodes in patients with midwall fibrosis, because these have important clinical implications for risk stratification of patients requiring implantable cardioverter-defibrillators.

Study limitations. The LGE+ patients were significantly younger than the LGE− patients. The importance of this seems limited because multivariate analysis using age did not alter the findings. Potentially this may reflect a different etiology, although there was no evidence for this. LGE+ patients also had more adverse LV remodeling at baseline. By multivariate analysis, however, LGE was a better marker of outcome than LVESV, LVEDV, LVEF, or RVEF. This finding supports earlier work showing that in ischemic heart disease, the presence of fibrosis is a better marker of VT inducibility than LVEF (10). None of the patients underwent myocardial biopsy for the diagnosis of DCM, as is normal in our center and per guidelines (42). The diagnosis of DCM was based on clinical history and examination coupled with findings from echocardiography and normal findings at coronary angiography. It was not considered ethical to put forward patients for biopsy because this investigation is associated with significant clinical risk and is subject to sampling error (34,43). At baseline, there was a significant difference between groups in use of digoxin. There are, however, no prognostic data to indicate that this would make a difference in the primary end point in DCM (44). By contrast, overall use of beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was similar between groups, with a high usage rate comparable with that of SCD-HEFT (Sudden Cardiac Death in Heart Failure Trial). Another limitation is the assessment of VT. Not all patients had regular investigations for arrhythmia monitoring. A "real-life" approach was used, in which referring physicians investigated for the presence of arrhythmias as was clinically indicated. There is no evidence of bias between groups because the proportion of patients receiving Holter monitors was not significantly different (47% in LGE+ group vs. 46% in the LGE− group, $p = 0.90$).

Conclusions. This is the first study to evaluate the prognostic significance of detecting myocardial fibrosis in DCM. Patients with myocardial fibrosis had a higher incidence of the combined primary end point of all-cause mortality and hospitalization, and this finding persisted after correction for baseline patient differences in LV/RV volumes/function, age, and treatment with digoxin. Patients with fibrosis also had a higher incidence of SCD/VT. These findings have potentially important implications for the risk stratification of DCM patients and may have application for refinement of patient groups suitable for device therapy.

Acknowledgments

We thank Juanra Gimeno for assistance in setting up the patient database and Jane McCrohon for assistance. We also thank all of the participating cardiologists and general practitioners who contributed patients to the project and who assisted with the clinical follow-up.

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