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.2006.07.046

Delayed Enhancement Magnetic Resonance Imaging Predicts Response to Cardiac Resynchronization Therapy in Patients With Intraventricular Dyssynchrony

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OBJECTIVES We evaluated the ability of delayed enhancement magnetic resonance imaging (DE-MRI) to predict clinical response to cardiac resynchronization therapy (CRT).

BACKGROUND Cardiac resynchronization therapy reduces morbidity and mortality in selected heart failure patients. However, up to 30% of patients do not have a response. We hypothesized that scar burden on DE-MRI predicts response to CRT.

METHODS The DE-MRI was performed on 28 heart failure patients undergoing CRT. Patients with QRS ≥120 ms, left ventricular ejection fraction ≤35%, New York Heart Association functional class II to IV, and dyssynchrony ≥60 ms were studied. Baseline and 3-month clinical follow-up, wall motion, 6-min walk, and quality of life assessment were performed. The DE-MRI was performed 10 min after 0.20 mmol/kg intravenous gadolinium. Scar measured by planimetry was correlated with response criteria.

RESULTS Twenty-three patients completed the protocol (mean age 64.9 ± 11.7 years), with 12 (52%) having a history of myocardial infarction. Thirteen (57%) patients met response criteria. Percent total scar was significantly higher in the nonresponse versus response group (median and interquartile range of 24.7% [18.1 to 48.7] vs. 1.0% [0.0 to 8.7], p = 0.0022) and predicted nonresponse by receiver-operating characteristic analysis (area = 0.94). At a cutoff value of 15%, percent total scar provided a sensitivity and specificity of 85% and 90%, respectively, for clinical response to CRT. Similarly, septal scar ≤40% provided a 100% sensitivity and specificity for response. Regression analysis showed linear correlations between percent total scar and change in each of the individual response criteria.

CONCLUSIONS The DE-MRI accurately predicted clinical response to CRT. This technique offers unique information in the assessment of patients referred for CRT. (J Am Coll Cardiol 2006;48: 1953–60) © 2006 by the American College of Cardiology Foundation

Heart failure is a major cause of morbidity and mortality, contributing significantly to global health expenditure (1). Despite significant advancements in the medical management of heart failure, the morbidity and mortality in this patient population remains high (2). Cardiac resynchronization therapy (CRT) is a valuable therapeutic option for such patients with intraventricular conduction delay and has been shown to improve heart failure symptoms, improve mitral regurgitation, reduce hospitalization, and improve exercise performance in carefully selected patients (3–9). Recently, a mortality benefit from CRT has also been reported (7,8). However, up to 30% of these carefully selected patients do not receive benefit from this invasive and costly intervention (10), with up to 40% having a progressive worsening of their heart failure (8). The ability to identify patients not likely to benefit from CRT is therefore desirable.

Tissue Doppler imaging can identify intraventricular dyssynchrony in patients with systolic heart failure, and is a useful tool in the selection of candidates for CRT (11–19). However, patients with documented dyssynchrony may still have marked heterogeneity with respect to their pathophysiology and related myocardial scar burden. Patients with heart failure often show varying patterns of scarring despite similar degrees of myocardial dysfunction (20). The burden of global and regional scar may have a significant influence on the ability of the myocardium to respond to CRT. Characterization of scar distribution may therefore aid in the identification of responders to CRT.

This study was designed to investigate the utility of scar imaging by delayed enhancement magnetic resonance imaging (DE-MRI) to predict response to CRT in patients

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Manuscript received February 23, 2006; revised manuscript received May 22, 2006, accepted July 10, 2006.

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
DE-MRI = delayed-enhancement magnetic resonance imaging
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

with drug-refractory systolic heart failure and mechanical dyssynchrony.

METHODS

Patient population. Twenty-eight consecutive patients undergoing CRT were recruited. For inclusion in the study, patients were required to have: 1) symptomatic congestive heart failure (New York Heart Association [NYHA] functional class II or higher), 2) left ventricular ejection fraction (LVEF) ≤35% as measured by 2-dimensional echocardiography or radionuclide angiography, 3) QRS duration of ≥120 ms, and 4) intraventricular dyssynchrony ≥60 ms. All patients were required to be on stable, optimal drug therapy for at least 6 weeks before enrollment. In addition, patients with NYHA functional class II symptoms were required to have been hospitalized with heart failure within the preceding 12 months. Intraventricular dyssynchrony was defined as the maximal difference in time to peak systolic velocity (T_s) between any 2 basal myocardial segments on tissue Doppler imaging. Patients were excluded for the following reasons: myocardial infarction within 1 month, revascularization procedure within 3 months, and standard contraindications to MRI imaging.

All patients agreed to participation with both oral and written informed consent. The study was approved by the University of Western Ontario research ethics board.

Baseline assessment. Transthoracic echocardiography, including tissue Doppler imaging, radionuclide angiography, 6-min walk test, and a Minnesota Living With Heart Failure questionnaire, were performed on all patients within 48 h of MRI imaging.

MRI protocol. The DE-MRI imaging was performed on a Signa 1.5-T magnet (General Electric, Inc., Milwaukee, Wisconsin) with electrocardiographic gating within 48 h before scheduled biventricular pacemaker insertion. Images were obtained using a 4-channel phased-array radiofrequency coil during repeated breath holds (approximately 7 to 15 s). Cine images were obtained in long-axis (4-chamber) and multiple short-axis planes in 10-mm intervals (8-mm slice thickness, 2-mm gap) from the mitral annulus to the left ventricular (LV) apex using the Fiesta pulse sequence. Gadolinium diethylene triamine pentaacetic acid contrast (0.2 mmol/kg, Magnevist, Berlex, Canada) was infused over 2 min via a peripheral vein, followed by delayed enhancement imaging at 10 min using a segmented inversion-recovery pulse sequence in imaging planes identical to the cine images. The inversion time was adjusted to optimally null (darken) the myocardium as previously described (21).

Each short-axis image was divided into 6 equal wall segments (septal, anteroseptal, anterior, inferior, posterior, and lateral walls) for segmental analysis. Total wall area was measured for each slice by area planimetry of the epicardial and endocardial borders of the LV (OsiriX, version 1.7.1, 2005, open-source software [22]). Nonviable scar tissue (bright on DE-MRI imaging) was also measured by area planimetry (Fig. 1). Regions of interest were accepted as hyperenhanced if the mean signal intensity was at least 2 SD above that of nulled (viable) myocardium. Percent scar was determined for each segment by dividing scar area by total wall area. The summing of respective area measurements for each wall assignment and multiplying by slice thickness determined measurements of both total wall volume and total scar volume. Dividing total scar volume by total wall volume and multiplying by 100 then obtained percent total scar. A blinded investigator performed all MRI analysis.

Echocardiography protocol. Standard 2-dimensional echocardiography and tissue Doppler imaging were performed on a commercially available ultrasound system (Agilent Sonos 5500, Andover, Massachusetts) using a 3-MHz phased-array transducer. Tissue Doppler imaging was performed at the apical window and was optimized using gain and filter settings while maintaining maximal obtainable frame rates. Long-axis motion of the LV was then recorded by pulsed-wave tissue Doppler at 6 basal segments in accordance with the apical 4-, 3- (long axis),

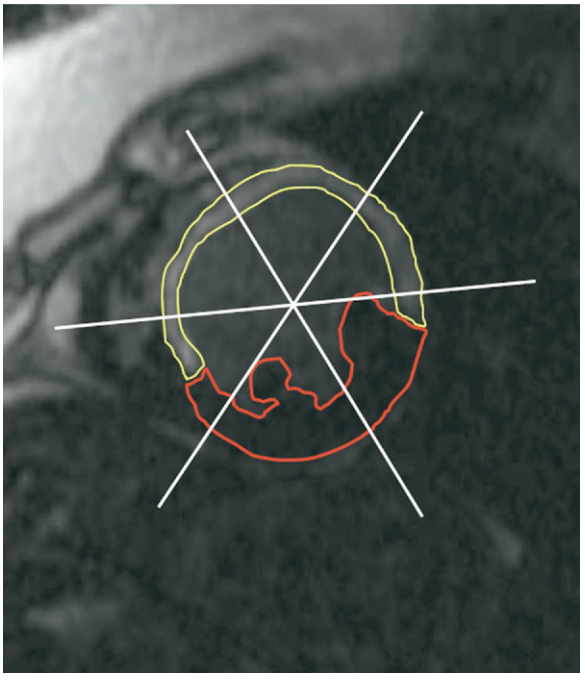

Figure 1. Short-axis delayed-enhancement magnetic resonance image showing a large area of scarred **(bright)** myocardium in the septal, anteroseptal, and anterior walls. Area planimetry of viable myocardium **(red line)** and scarred myocardium **(yellow line)** was performed as illustrated.

Table 1. Baseline Characteristics of All Patients, Clinical Responders, and Nonresponders to Cardiac Resynchronization Therapy

	All Patients (n = 23)	Responders (n = 13)	Nonresponders (n = 10)	p Value*
Clinical characteristics				
Age (yrs)	64.9 ± 11.7	66.2 ± 10.4	63.2 ± 13.6	0.56
Male†	15 (65%)	8 (62%)	7 (70%)	1.00‡
Prior myocardial infarction†	12 (52%)	4 (31%)	8 (80%)	0.04‡
Prior coronary artery bypass graft†	5 (22%)	4 (31%)	1 (10%)	0.34‡
Diabetes†	7 (30%)	5 (38%)	2 (20%)	0.41‡
Hypertension†	12 (57%)	7 (54%)	6 (60%)	1.00‡
Hypercholesterolemia†	20 (87%)	11 (85%)	9 (90%)	1.00‡
Current smoker†	3 (13%)	2 (15%)	1 (10%)	1.00‡
QRS duration (ms)	165.7 ± 24.2	171.8 ± 21.7	157.9 ± 26.1	0.17
New York Heart Association mean	3.0 ± 0.6	3.0 ± 0.6	2.9 ± 0.7	0.72
Class II	5	2	3	
Class III	14	9	5	
Class IV	4	2	2	
Ejection fraction by WMS	27.0 ± 10.6	28.5 ± 13.1	25.0 ± 6.1	0.80
6-min walk (m)	307.0 ± 88.8	299.0 ± 89.9	317.4 ± 91.1	0.63
Quality of life (MLHF)	55.3 ± 17.0	52.3 ± 17.8	59.6 ± 15.7	0.34
Intraventricular dyssynchrony (ms)	114.3 ± 26.5	116.5 ± 26.6	111.5 ± 27.5	0.66
CMR characteristics				
LVEDV (ml)	179.5 ± 52.2	177.3 ± 53.6	182.4 ± 45.6	0.82
LVESV (ml)	142.2 ± 53.0	140.2 ± 60.6	144.7 ± 44.2	0.85
Ejection fraction	22.0 ± 9.7	22.5 ± 11.5	21.4 ± 7.1	0.80
Percent total scar§	11.8 (0.6–23.3)	1.0 (0.0–8.7)	24.7 (18.1–48.7)	0.002
Percent scar in septal wall§	13.0 (0.0–83.0)	0.0 (0.0–8.5)	89.5 (54.8–97.0)	0.0005

*The p value represents a comparison between responder and nonresponder groups. †Categorical variable (unmarked represent continuous variable). ‡Fisher exact test (2-tailed). §Comparison by Wilcoxon test, shown as median (interquartile range).

CMR = cardiac magnetic resonance; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; MLHF = Minnesota Living With Heart Failure Questionnaire; WMS = wall motion study.

and 2-chamber views to obtain measurements corresponding to the septal, lateral, anteroseptal, posterior, anterior, and inferior walls. Time to peak systolic velocity (T_s) was measured for each segment, with the onset of the QRS as a reference point. Maximal intraventricular dyssynchrony was defined as the maximal difference in T_s obtained from any 2 of the 6 basal myocardial segments. Averages of 3 consecutive beats were used for all measurements and were performed by a blinded investigator.

Implantation technique. A cardiac resynchronization device was implanted after MRI evaluation. Right atrial and right ventricular lead placement was performed followed by a coronary sinus lead positioned to the lateral wall of the LV. All device systems were programmed to DDD mode. Atrioventricular intervals were optimized to maximize duration of biventricular pacing.

Follow-up assessment. Follow-up was performed at 3 months and consisted of the assessment of NYHA functional class, 6-min walk test, LVEF by radionuclide angiography, and Minnesota Living With Heart Failure Quality of Life Questionnaire. Individual response criteria were prospectively defined for each of the 4 parameters used: 1) increase in LVEF by ≥5%, 2) improvement in NYHA functional class by ≥1 class, 3) improvement in 6-min walk test by ≥30 m, and 4) decrease in Minnesota Living With Heart Failure score by ≥10 points. Clinical response was defined as an improvement in either ejection fraction or 6-min walk plus ≥1 other response criteria at follow-up.

Statistics. Continuous data are presented as mean values ± SD, except where noted. Between-group comparisons of discrete data were made using chi-square tests; in those cases in which the expected cell count was <5, the Fisher exact test was used. Between-group comparisons of continuous data were made using 2-sample *t* tests. Non-normally distributed continuous data were compared using the Wilcoxon test. Univariate and multivariate logistic regression analyses were performed to assess the relationship between clinical response and baseline clinical variables shown in Table 1, as well as with cardiac MRI variables, also shown in Table 1. Only variables significant at $p < 0.30$ were considered for inclusion in the multivariate model. Changes from baseline to follow-up in the 4 individual response criteria were evaluated using paired *t* tests. Linear regression analysis was used to assess the relationship of these changes to total percent scar. Receiver-operating characteristic analysis of total percent scar and overall responders as well as responders to each of the 4 individual criteria were performed. All statistical tests were 2-tailed, and $p < 0.05$ was regarded as significant.

RESULTS

Baseline characteristics. Twenty-three patients completed the investigations and underwent successful device implantation. One patient did not complete MRI imaging because of claustrophobia, 2 patients had spontaneous improvement

in systolic function at time of MRI, and 2 had unsuccessful LV lead implantation.

The mean age of the 23 patients was 64.9 ± 11.7 years (15 male, 8 female). Mean baseline NYHA functional class was 3.0 ± 0.6 with a QRS duration of 165.7 ± 24.2 ms, 6-min walk test of 307.0 ± 88.8 m, and Minnesota Living With Heart Failure Questionnaire score of 55.3 ± 17.0 (Table 1). Nineteen of the 23 patients had left bundle branch block, whereas 3 had bifascicular block and 1 had right bundle branch block. Ischemia was thought to be the underlying cause of heart failure in 12 patients (52%).

Clinical response. Thirteen of 23 (57%) patients had a clinical response to CRT pacing as was prospectively defined in this study. Of the 10 nonresponders, 8 (80%) had a history of ischemic heart disease. Multivariate analysis of all clinical baseline characteristics showed only prior myocardial infarction to be independently predictive of clinical response to CRT. No significant difference was seen in mean baseline T_s between nonresponders and responders (111.5 ± 27.5 ms vs. 116.5 ± 26.6 ms, p = 0.66), and the degree of baseline dyssynchrony was not predictive of response. The multivariate analysis was then performed, including all MRI parameters. In this analysis only percent total scar by DE-MRI was an independent predictor of clinical response. Changes in ejection fraction, 6-min walk, quality-of-life score, and NYHA functional class are shown in Table 2.

DE-MRI findings. Overall, 17 of 23 patients (74%) had evidence of scar on DE-MRI imaging. One hundred percent of patients with a previous myocardial infarction and 45% of nonischemic patients had detectable scar on DE-MRI. The mean percent scar was significantly greater in those with a history of ischemic heart disease than in those with no such history (25.3 ± 15.7% vs. 8.1 ± 19.5%). Of the 11 patients studied with presumed nonischemic cardiomyopathy, 1 patient had a hyperenhancement pattern consistent with an anterolateral wall myocardial infarction that was previously not suspected. The remaining 4 patients in this group with detectable scar had a nonischemic midwall pattern.

Percent total scar was significantly greater in the clinical nonresponder group versus the responder group, with a median and interquartile range of 24.7% (18.1 to 48.7) and 1.0% (0.0 to 8.7), respectively (p = 0.002). Scarring in the nonresponder group involved the septal and anteroseptal walls in all cases and was a transmural ischemic pattern injury (>50% wall thickness) in 8 of the 10 patients (Fig. 2). The remaining 2 patients in this group had dense midwall scarring that was suggestive of a nonischemic cardiomyopathy. Clinical responders with scarring showed 1 of 2 patterns. Those with a history of ischemic heart disease showed subendocardial (<50% wall thickness) scarring involving multiple vascular territories, whereas patients with no history of ischemic heart disease showed midwall hyperenhancement (Fig. 3).

Receiver-operating characteristic analysis of total percent scar for the prediction of clinical response to CRT is shown in Figure 4, with an area under the curve of 0.94. A cutoff value of 15% total scar provided a sensitivity and specificity of 85% and 90%, respectively, for the prediction of clinical response. Septal wall scar showed a sensitivity and specificity of 100% for clinical response using a cutoff of value of ≤40%. Receiver-operating characteristic analysis of each individual response criterion showed similar relationships with the area under the curve for change in LVEF, 6-min walk test, quality-of-life score, and NYHA functional class being 0.71 ± 0.11, 0.80 ± 0.10, 0.87 ± 0.08, and 0.87 ± 0.08, respectively. Linear regression analysis of total percent scar to change in LVEF, quality-of-life score, and NYHA functional class showed statistically significant correlations, whereas a strong trend was seen with the 6-min walk test (Fig. 5).

DISCUSSION

This study shows the ability of DE-MRI to predict response to CRT in patients with drug-refractory systolic heart failure and intraventricular dyssynchrony. A percent total scar of ≤15% or a percent septal scar ≤40% accurately identified patients with a clinical response to CRT. This finding suggests additive prognostic value of DE-MRI for the assessment of patients referred for this therapy.

Cardiac resynchronization therapy aims to restore mechanical synchrony through simultaneous stimulation and subsequent coordinated contraction of dyssynchronous ventricular walls (23). Previous studies have shown that up to 30% of carefully selected patients do not derive benefit from this therapy (10). A recent analysis of the MUSTIC

Table 2. Changes in Individual Response Criteria at Follow-Up for All Patients, Clinical Responders, and Nonresponders to Cardiac Resynchronization Therapy

Response Criterion	All Patients (n = 23)	Responders (n = 13)	Nonresponders (n = 10)	p Value*
Ejection fraction (%)	4.5 ± 6.9	8.2 ± 5.3	−0.9 ± 5.2	0.0007
p vs. baseline	0.006	<0.0001	0.621	
New York Heart Association functional class	−0.6 ± 0.7	−1.1 ± 0.3	0.1 ± 0.6	0.0002
p vs. baseline	0.001	<0.0001	0.594	
Quality-of-life score	−17.0 ± 16.1	−24.4 ± 12.8	−5.0 ± 14.0	0.042
p vs. baseline	<0.0001	<0.0001	0.346	
6-min walk (m)	34.0 ± 54.0	61.1 ± 55.8	−2.0 ± 21.4	0.0027
p vs. baseline	0.009	0.003	0.781	

*The p value represents a comparison between responder and nonresponder groups.

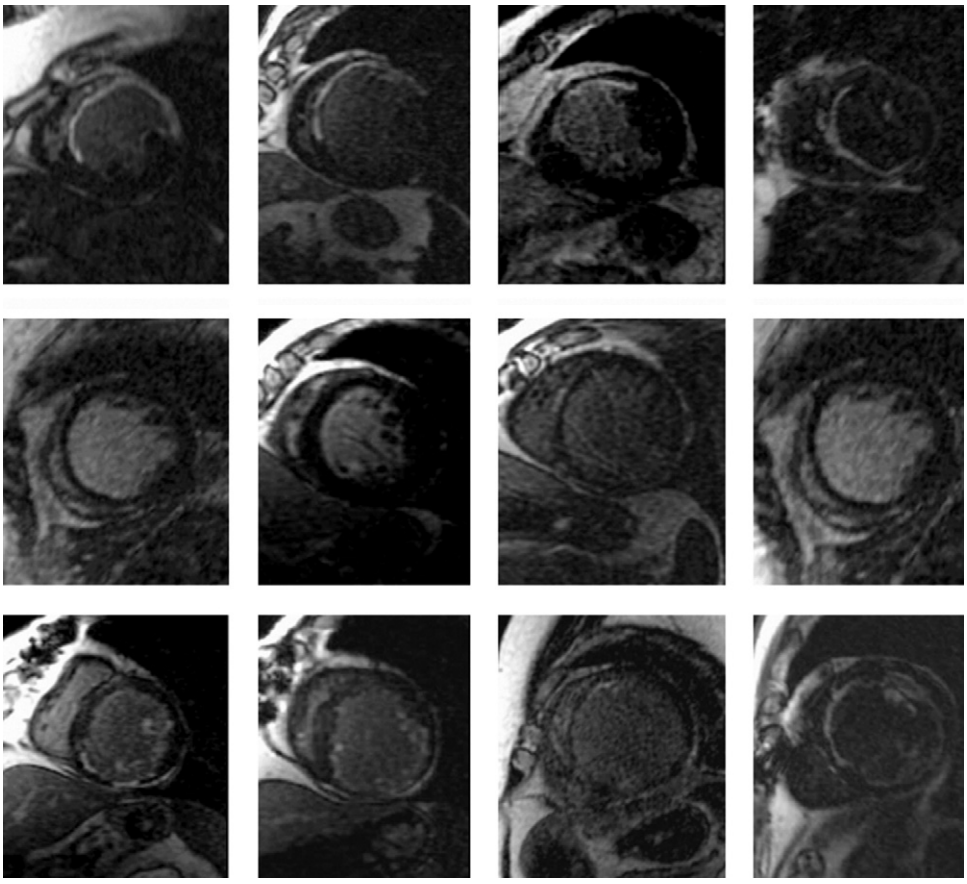

Figure 2. Examples of scar distribution **(bright signal)** on delayed-enhancement magnetic resonance imaging from clinical nonresponders **(top row)**, responders without scar **(middle row)**, and responders with scar **(bottom row)**.

(Multisite Stimulation in Cardiomyopathies) trial data identified that patients with previous myocardial infarction are more likely to have a failed CRT than patients with idiopathic dilated cardiomyopathy (24). Although this relationship has been challenged by others (25), the ability of diseased myocardium to respond to and propagate electrical stimulation during CRT may be influenced by the underlying pathology. More specifically, the amount and distribution of myocardial scar may be an important determinant of response.

Patients with systolic heart failure have heterogeneous patterns of myocardial scarring despite similar alterations in contractile function (20). In patients with severe LV dysfunction, the percentage of patients with detectable scar by DE-MRI ranges from 12% to 100% depending on the underlying cause of heart failure (20,26,27). The volume, location, and transmurality of this scarring are similarly heterogeneous between individuals (20).

Regional nonviability may be assumed using functional imaging techniques that show an absence of contractile function, especially when provided with a history of myocardial infarction. However, patients were identified in this study who had relatively little scar despite a history of ischemic heart disease and severe LV dysfunction (Fig. 3A), suggesting a nonischemic component to their myocardial dysfunction. Therefore, a history of ischemic heart disease should not exclude nonischemic components to progressive LV dysfunction. Conversely, a lack of scar tissue should not be assumed in the setting of normal contractile function. In patients with ischemic heart disease, preservation of contractile function has been seen in myocardial segments with up to 50% transmural scarring (28,29). Therefore, when prescribing therapy thought to be influenced by myocardial scar burden, functional imaging and patient history are insufficient surrogates of viability.

The relationship between myocardial viability and response to medical heart failure therapies has been previously examined. Bello et al. (26) investigated the role of DE-MRI for the prediction of response to beta-blocker therapy in 45 heart failure patients. This study showed a similar burden of scar tissue compared with the current series, with 67% of all patients and 100% of patients with a history of ischemic heart disease showing detectable scar on DE-MRI. An inverse relationship was seen between absolute scar burden and functional recovery at 6 months as assessed by cine MRI imaging (26). Recovery of systolic function after revascularization is also predicted through the use of this technique. The likelihood of functional recovery is inversely proportional to the transmural extent of scarring in functionally impaired myocardial segments (30).

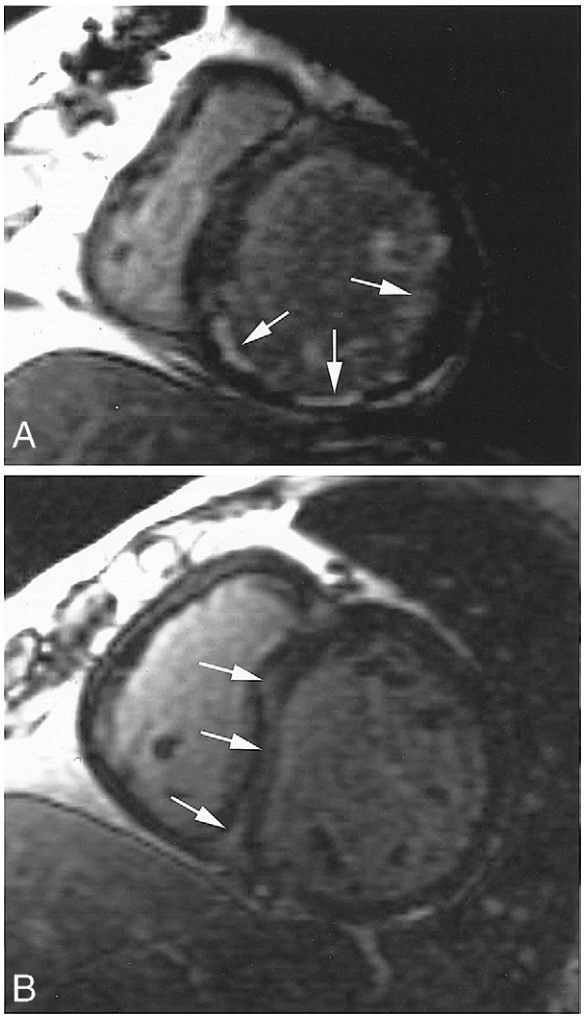

Figure 3. Typical scar patterns seen on delayed-enhancement magnetic resonance imaging in clinical responders with **(A)** history of myocardial infarction and **(B)** no history of myocardial infarction (scar indicated by **white arrows**).

There are limited published data on the prediction of response to CRT through the assessment of myocardial viability. Sciagra et al. (31) showed that large resting perfusion defects on single-photon emission computed tomography perfusion imaging predicted a lack of ventricular remodeling with CRT. These patients also had significantly less improvement in ejection fraction, 6-min walk test, and quality of life compared with those without such defects.

Left ventricular pacing from geographically different sites has been shown to yield varying changes in systolic performance (32,33). A study using electromechanical endocardial mapping to assess regional viability in patients with dilated cardiomyopathy showed that pacing from sites with reduced local viability yielded less improvement in maximal LV dp/dt, a measure of LV performance (34).

A recently published study by Bleeker et al. (35) was the first to examine the role of DE-MRI for the prediction of response to CRT. This study examined the predictive utility of >50% scar in the posterolateral wall with respect to clinical and echocardiographic indices of response. This scar pattern was seen in 35% of patients and reliably predicted nonresponse. The effect of scarring in the septal wall was not examined in this study. Our study offers complimentary data showing that septal wall scarring is equally important for response to CRT. Together, these findings suggest a substantial influence of regional viability on clinical response to CRT. This seems to be important for each of the 2 sites typically targeted for this therapy, the septal and posterolateral walls.

Future considerations. Techniques have been developed for the mapping of mechanical dyssynchrony using tagged cine MRI imaging (36–40). This offers the potential to obtain measurement of both myocardial dyssynchrony and viability in a single setting, avoiding the need for multiple imaging investigations. Other dedicated pulse sequences can be included within the imaging protocol to provide stress perfusion imaging and the identification of LV thrombus, when clinically indicated. Such a comprehensive cardiovascular MRI study can be performed in approximately 45 min and provides a detailed characterization of cardiac morphology, function, perfusion, and viability.

Advanced 3-dimensional imaging of the coronary venous anatomy has also been recently described (41,42). A customized approach to resynchronization therapy may be feasible by implementing image-guided delivery of LV leads to dyssynchronous but viable myocardial segments via the coronary venous system.

Study limitations. This study was performed in a small patient population. There were few patients with large-sized myocardial infarctions in territories outside of the anterior and septal walls. This may reflect a higher likelihood of referral for CRT in patients with large anteroseptal myocardial infarctions because of more severe LV dysfunction. The previously discussed study by Bleeker et al. (35) offers insight into a population of patients with posterolateral wall injury, although it was similarly limited by a small sample

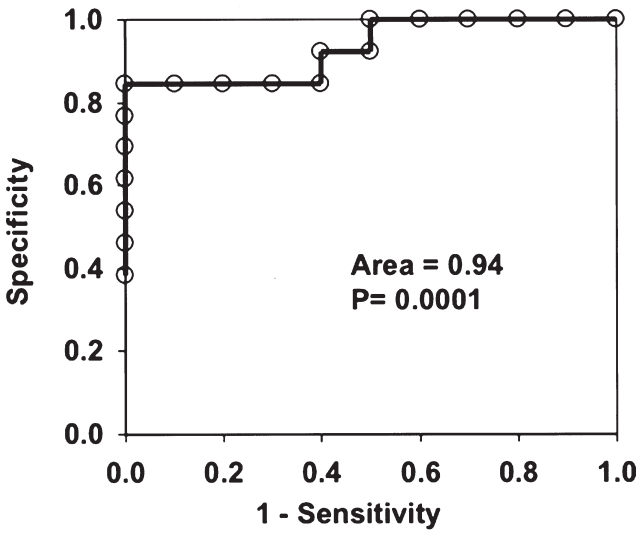

Figure 4. Receiver-operating characteristic analysis of total percent scar for the prediction of clinical response to cardiac resynchronization therapy.

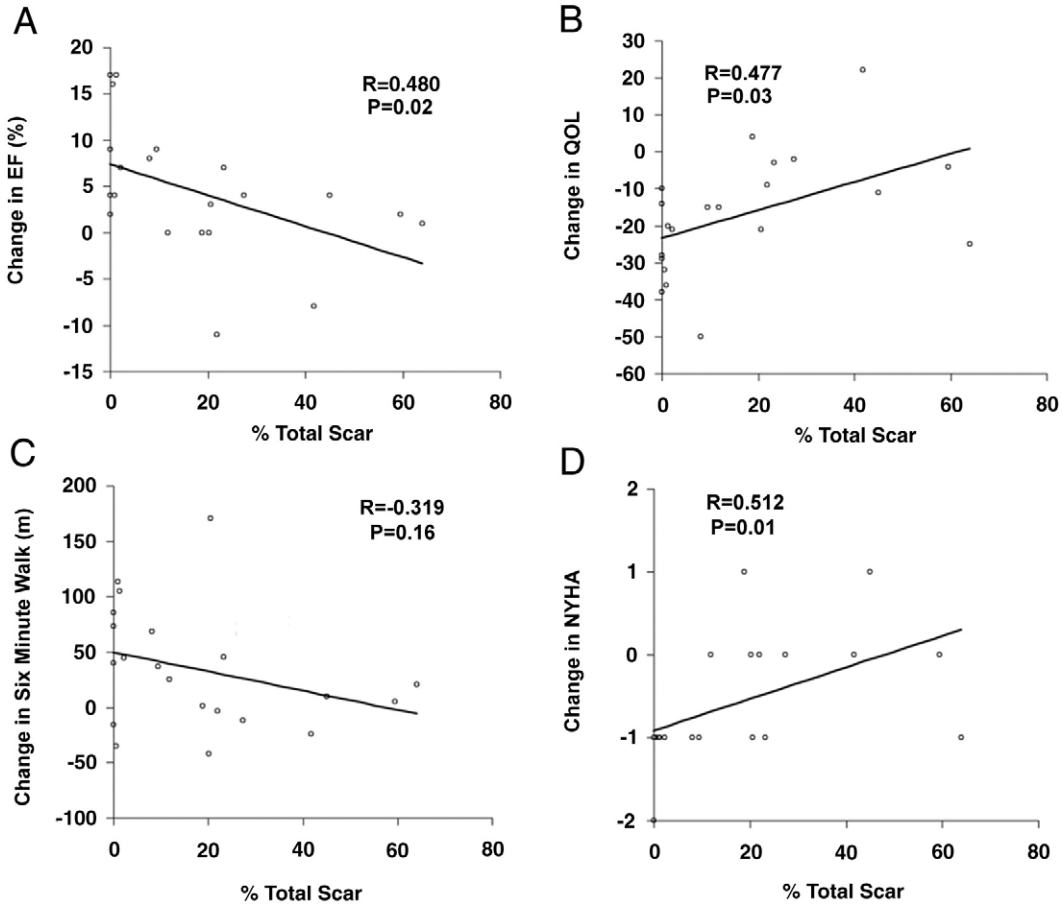

Figure 5. Linear regression plots showing the relationship between total percent scar and change in **(A)** left ventricular ejection fraction (EF), **(B)** quality-of-life (QOL) score, **(C)** 6-min walk, and **(D)** New York Heart Association (NYHA) functional class at follow-up.

size. Larger studies examining a wide range of ischemic injury are warranted.

Conclusions. In a population with intraventricular dyssynchrony, DE-MRI can accurately predict clinical response to CRT. This technique offers unique and predictive information in the assessment of patients referred for CRT.

Acknowledgments

Our thanks to Rhonda Walcarius and Kathy Blackler for their assistance in this study.

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