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CLINICAL RESEARCH

Cardiac Magnetic Resonance Assessment of Dyssynchrony and Myocardial Scar Predicts Function Class Improvement Following Cardiac Resynchronization Therapy

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OBJECTIVES We tested a circumferential mechanical dyssynchrony index (circumferential uniformity ratio estimate [CURE]; 0 to 1, 1 = synchrony) derived from magnetic resonance-myocardial tagging (MR-MT) for predicting clinical function class improvement following cardiac resynchronization therapy (CRT).

BACKGROUND There remains a significant nonresponse rate to CRT. MR-MT provides high quality mechanical activation data throughout the heart, and delayed enhancement cardiac magnetic resonance (DE-CMR) offers precise characterization of myocardial scar.

METHODS MR-MT was performed in 2 cohorts of heart failure patients with: 1) a CRT heart failure cohort (n = 20; left ventricular ejection fraction of 0.23 ± 0.057) to evaluate the role of MR-MT and DE-CMR prior to CRT; and 2) a multimodality cohort (n = 27; ejection fraction of 0.20 ± 0.066) to compare MR-MT and tissue Doppler imaging septal-lateral delay for assessment of mechanical dyssynchrony. MR-MT was also performed in 9 healthy control subjects.

RESULTS MR-MT showed that control subjects had highly synchronous contraction (CURE 0.96 ± 0.01), but tissue Doppler imaging indicated dyssynchrony in 44%. Using a cutoff of <0.75 for CURE based on receiver-operator characteristic analysis (area under the curve: 0.889), 56% of patients tested positive for mechanical dyssynchrony, and the MR-MT CURE predicted improved function class with 90% accuracy (positive and predictive values: 87%, 100%); adding DE-CMR (% total scar <15%) data improved accuracy further to 95% (positive and negative predictive values: 93%, 100%). The correlation between CURE and QRS duration was modest in all cardiomyopathy subjects ($r = 0.58$, $p < 0.001$). The multimodality cohort showed a 30% discordance rate between CURE and tissue Doppler imaging septal-lateral delay.

CONCLUSIONS The MR-MT assessment of circumferential mechanical dyssynchrony predicts improvement in function class after CRT. The addition of scar imaging by DE-CMR further improves this predictive value. (J Am Coll Cardiol Img 2008;1:561–8) © 2008 by the American College of Cardiology Foundation

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Cardiac resynchronization therapy (CRT) has been shown to improve heart failure symptoms and survival (1,2), yet 30% or more patients do not derive a clinical benefit from the therapy (3). The current criteria for receiving treatment include the presence of a QRS duration (QRSd) ≥120 ms. Yet direct pre-CRT assessments of mechanical dyssynchrony using tissue Doppler imaging (TDI)/echocardiography (4) are common despite many limitations, including the poor intraobserver variability shown in the PROSPECT (Predictors of Response to CRT) trial (3), dependence on longitudinal and radial motion rather than circumferential strain, limited acoustic windows, and ambiguities in the interpretation of these studies.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CRT = cardiac resynchronization therapy

CURE = circumferential uniformity ratio estimate

DE-CMR = delayed enhancement-cardiac magnetic resonance

HF = heart failure

MR-MT = magnetic resonance-myocardial tagging

NPV = negative predictive value

PPV = positive predictive value

QRSd = QRS duration

ROC = receiver-operating characteristic

TDI = tissue Doppler imaging

See page 569

Magnetic resonance-myocardial tagging (MR-MT) provides quantitative and highly reproducible circumferential and longitudinal myocardial activation data along all 3 dimensions of the heart that are largely operator- and patient-independent (5), as well as characterization of myocardial scar and scar distribution (6). Myocardial fiber orientation is principally circumferential (7), and the circumferential strain data provided by MR-MT appear to have a much greater dynamic range for assessing mechanical dyssynchrony than longitudinal or radial strain (8). We have previously evaluated MR-MT for assessment of the acute hemodynamic response to left ventricular pacing (9), but the role of MR-MT for clinical response after CRT implantation has not yet been defined. Accordingly, this study examined an MR-MT–based metric of global circumferential mechanical dyssynchrony in combination with MR scar imaging in patients with heart failure to test its predictive value for function class improvement in those receiving CRT, clarify its relation to TDI metrics, and determine whether scar imaging provides additional value for identifying responsive patients.

METHODS

Clinical study groups. The study protocol was approved by the Johns Hopkins Hospital Institutional Review Board, and all patients gave written informed consent. We studied 43 subjects with cardiomyopathy (divided into CRT heart failure [HF] and multimodality cohorts) and 9 control subjects (total N = 52). The CRT-HF cohort (n = 20) included subjects referred for CRT, all New York Heart Association function class III, in whom MR-MT was obtained prior to implantation. These patients all received an implantable cardioverter defibrillator and CRT between August 2003 and May 2007. Implantable cardioverter defibrillator selection and exclusion were based on MADIT II (Second Multicenter Automated Defibrillator Implantation Trial) (10) or SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (11) criteria, and the decision to implant a CRT device was made based on approved clinical recommendations (12,13). As in prior studies (14), clinical improvement was defined as improvement to at least New York Heart Association functional class II or better by 6 months as assessed by history, patient symptoms (e.g., dyspnea on exertion and/or fatigue), and functional capacity. Follow-up clinical status was assessed by staff different from those analyzing the MR-MT and echo imaging data.

The multimodality cohort (n = 27) was used to determine discordance rates between MR-MT dyssynchrony and the most commonly used clinical measure of mechanical dyssynchrony, the TDI septal-lateral delay. Four subjects in this cohort also received CRT and were included in the CRT-HF cohort. The MR-MT studies and dyssynchrony echo studies with TDI were also obtained in a group of 9 normal volunteers.

Cardiac magnetic resonance (CMR) protocol. All patients in the CRT-HF cohort underwent CMR studies using a 1.5-T clinical scanner (Signa CV/I, GE Medical Systems, Waukesha, Wisconsin) with a phased array receiver coil on the chest. After localization of the heart, 8 to 10 contiguous short-axis slices were prescribed to cover the entire left ventricle from base to apex. Cine images were acquired using a steady-state free precession pulse sequence. MR-MT was performed using 5 to 8 tagged short-axis slices acquired at the left ventricular base, mid-level, and apex (repetition time: 3.5 to 7.2 ms, echo time: 2.0 to 4.2 ms, flip angle: α = 12°, 40-cm field of view, 8- to 10-mm slice thickness, matrix size: 256 × 96 to 140, 4 to 9 phase-encoding views per segment, bandwidth of 49 MHz with range of 24.9 to 62.5, and tag spacing: 7 mm). Tagging was prescribed as a grid matrix in orthogonal orientations (0° and 90°) using an electrocardiogram-triggered spoiled gradient echo pulse sequence with spatial modulation of magnetization (15,16). The multimodality group studies were performed on a

Philips 3.0-T clinical scanner (Philips, Bothell, Washington) with a nearly identical protocol.

Delayed-enhancement images in locations identical to the cine images were acquired 10 to 15 min after a bolus injection of 0.2 mmol/kg gadodiamide (Omniscan, GE Healthcare, Buckinghamshire, United Kingdom) in patients with glomerular filtration rates of at least 60 cc/min, and with gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Tarrytown, New York) in selected patients if the glomerular filtration rate was 45 to 60 cc/min. An inversion recovery fast gradient-echo pulse sequence was used for the acquisition. Imaging parameters for both 1.5- and 3.0-T were: repetition time: 5.4 ms, echo time: 1.3 ms, 36- to 40-cm field of view, 8-mm slice thickness, matrix: 256 × 192, inversion recovery time: 150 to 250 ms (adjusted to null the signal of normal myocardium), and flip angle $\alpha = 20^{\circ}$.

Image and strain analysis. Short-axis tagged slices were analyzed in blinded fashion by the harmonic phase method (HARP, Diagnosoft, Palo Alto, California) to assess strain (17). Regional systolic circumferential strains and time from end diastole to peak circumferential strain were determined in 24 left ventricular segments from the midwall layers using the HARP method and a custom MATLAB program (The MathWorks, Natick, Massachusetts).

Mechanical dyssynchrony was indexed by the circumferential uniformity ratio estimate (CURE) (18,19) (Fig. 1). Values for CURE range from 0 (pure dyssynchrony) to 1 (perfectly synchronous). Circumferential uniformity ratio estimate was measured in 3 evenly spaced myocardial slices over the left ventricle, each containing approximately 15 cardiac phases. Slice-based CURE was measured by averaging CURE values for all systolic phases and several diastolic phases. The 3 slice-based CUREs were then averaged to yield a composite, patient-level CURE.

Delayed enhancement-cardiac magnetic resonance (DE-CMR) was analyzed for percent total scar and posterolateral scar by standard methods (20). Abnormally enhanced myocardium (scar) was defined as high-signal intensity regions with signal intensity at least 2 standard deviations or more relative to a remote region of interest, then percent left ventricular scar volume was calculated using standard methods (20,21).

Echocardiography. Complete dyssynchrony echo studies equivalent to the clinical protocol at our hospital were performed in all multimodality cohort subjects. This included standard 2-dimensional views, TDI in 3 views (apical 4-, 2-, and 3-chamber), and M-mode left ventricular images. Timing delays by TDI were determined in a blinded fashion and reported as the septal-lateral delay, primarily based on peaks of tissue velocity in both basal and midwall planes in each view.

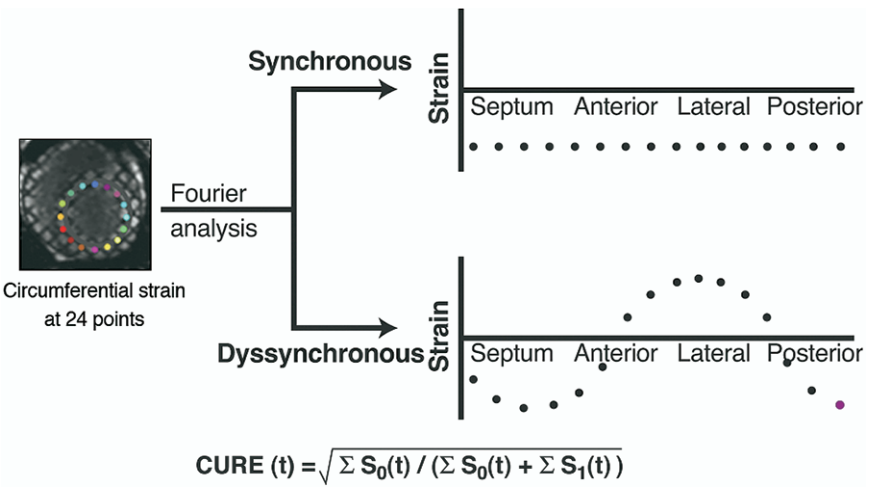

Figure 1. Quantification of Circumferential Mechanical Dyssynchrony from MR-MT Strain Map

Calculation of the circumferential uniformity ratio estimate (CURE) for mechanical dyssynchrony using Fourier analysis with extreme examples of spatial distribution of strain for synchrony **(straight line)** versus dyssynchrony (sine wave pattern). S0 is the zero-order or constant term of the Fourier transform, and S_1 is the first-order term, representing low frequency changes at a given time. The CURE for a given short-axis slice is generated first by determining instantaneous circumferential strains at 24 equally spaced segments in a short-axis slice at each time point, then subjecting this strain v. segment data to Fourier analysis with determination of the ratio of first- to zero-order power. MR-MT = magnetic resonance-myocardial tagging.

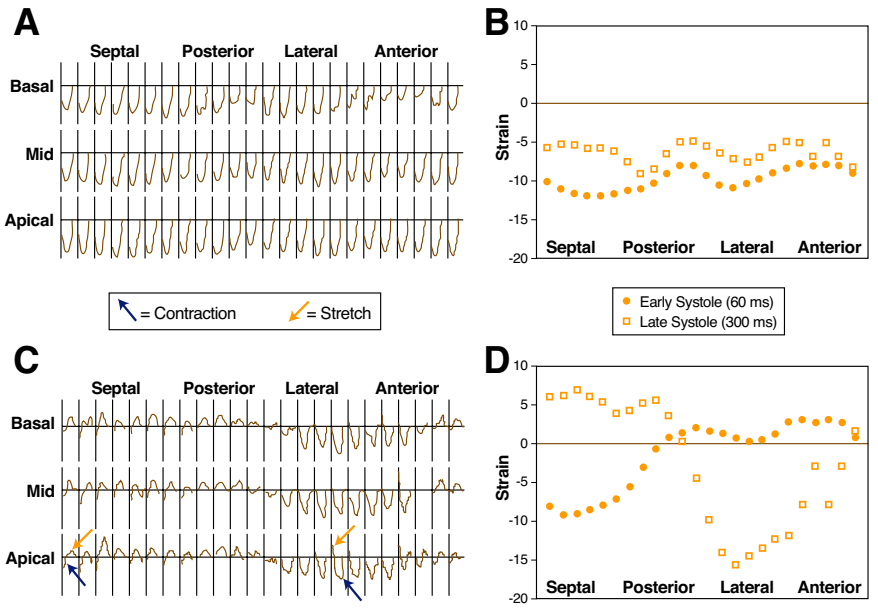

Figure 2. MR-MT Temporal and Spatial Circumferential Strain Maps for a Normal Subject and a Subject With Cardiomyopathy and Dyssynchrony

In the normal subject, the progression of the strain versus time (negative strain represents systole) is uniform in each of the 24 segments in each slice **(A)**, and there is synchronous negative strain for each segment along the circumference of the left ventricle **(B)**. In the subject with dyssynchrony and cardiomyopathy, the strain versus time maps show variable timing of contraction (**blue arrows** = negative strain) and stretch (**orange arrows** = positive strain) in septal versus lateral segments **(C)**. In this subject, some segments have positive strain (stretch) and others have negative strain (contraction) during systole **(D)**. See Online Video. Abbreviation as in Figure 1.

Statistical analysis. Mean, standard deviation, and standard error of the mean were determined for continuous variables, and the Student *t* test was used where appropriate. Fisher exact test (SAS 9.1.3, SAS Institute Inc., Cary, North Carolina) was used for selected 2 × 2 comparisons. Correlation and linear regression analyses were used to compare CURE and TDI with QRSd (SAS). Receiver-operator characteristic (ROC) analysis was performed using Johns Hopkins Web-based ROC analysis software (22), and the optimal cutoffs for dyssynchrony determined by maximization of sensitivity with preservation of a reasonable specificity. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for CRT response were calculated for CURE, DE-CMR, and QRSd. McNemar exact test (SAS) was used to compare MR-MT and TDI for dyssynchrony assessment in subjects with a narrow QRS in the multimodality cohort.

RESULTS

Baseline characteristics. Baseline demographic and left ventricular structural characteristics for the multimodality and CRT-HF cohorts are given in Table 1. All 9 normal subjects in the control group had normal left ventricular systolic function and normal QRSd.

Strain analysis. Figure 2 displays strain plots for a normal control (Figs. 2A and 2B) and a patient with dyssynchronous cardiomyopathy (Figs. 2C and 2D). The important findings in these strain maps are described in the figure legends. The Online Video shows the MR-MT images for the dyssynchronous subject, including color coding for varying stretch (positive strain) and contraction (negative strain).

Relationship of MR-MT CURE to QRSd. In cardiomyopathy subjects, there was a modest correlation between mechanical dyssynchrony by MR-MT (CURE) and the QRSd ($r = -0.58$, $p < 0.001$) (Fig. 3A). As anticipated, this correlation weakened when including only CRT-HF (wider QRS) patients ($r = -0.40$, $p = 0.08$), as the variance range of QRSd was more limited (Fig. 3C). Consistent with prior results, we found no correlation between the TDI septal-lateral delay and QRSd ($r = 0.04$, $p = 0.83$) (Fig. 3B).

MR-MT CURE in normal subjects. The CMR studies from 9 normal volunteers (mean [standard devia-

tion] age 47 [13] years) with normal QRSd were also analyzed. In these 9 subjects, CURE approached unity with mean (standard deviation) 0.96 (0.01), and the strain maps were similar to those shown in Figures 2A and 2B. Despite synchronous cardiac function, 44% had a TDI septal-lateral delay of at least 65 ms, indicating dyssynchrony based on published data (23).

ROC of MR-MT for prediction of CRT response. Based on ROC analysis, the area under the curve (standard error) for CURE for prediction of improvement in function class was 0.889 (0.098) in the CRT-HF cohort. Based on this analysis, a cutoff of 0.75 for CURE was chosen because this was associated with maximal sensitivity and preserved specificity. For comparison purposes, QRSd was associated with an area under the curve (standard error) of 0.5077 (0.157).

Prediction of function class improvement after CRT using CURE. Improvement in function class was much more likely for subjects with dyssynchrony by CURE as compared with subjects without dyssynchrony by CURE ($p < 0.001$) (Fig. 4B). With a cutoff of <0.75, CURE had 90% accuracy for predicting CRT response (PPV: 87%; NPV: 100%) (Table 2). As expected, QRSd did not predict function class improvement after CRT (Fig. 4A) in the CRT-HF cohort. One of the 2 subjects with CURE between 0.50 and 0.75 who did not improve had extensive scar as determined by DE-CMR (37% of total), as shown in Figure 5.

Table 1. Baseline Characteristics

	CRT-HF Cohort (n = 20)	Multimodality Cohort (n = 27)
Age, yrs, mean (SD)	58 (10)	50 (15)
Gender, n (%)		
Male	13 (65)	16 (59)
Female	7 (35)	11 (41)
Cardiomyopathy, n (%)		
Ischemic	8 (40)	8 (30)
Nonischemic	12 (60)	19 (70)
LVEF, mean (SD)	0.23 (0.057)	0.20 (0.066)
QRSd, ms, mean (SD)	151 (26)	138 (34)
NYHA functional class, n (%)		
I	0 (0)	3 (11)
II	0 (0)	12 (44)
III	20 (100)	12 (44)
IV	0 (0)	0 (0)
Medication use, n (%)		
Beta-blocker	19 (90)	26 (96)
Amiodarone	3 (15)	1 (4)

CRT = cardiac resynchronization therapy; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QRSd = QRS duration.

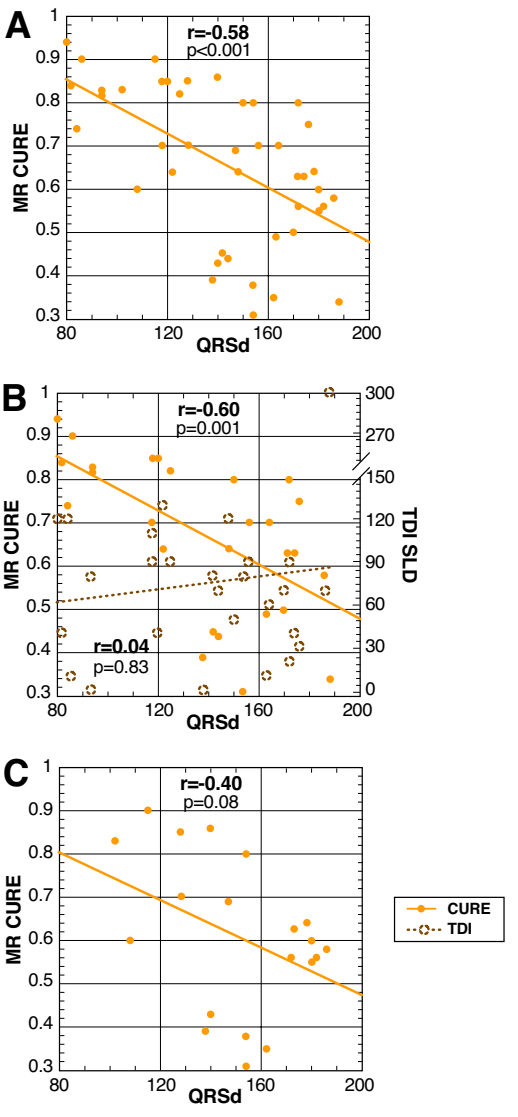

Figure 3. Correlations for MR-MT Circumferential Dyssynchrony (CURE), TDI Septal-Lateral Delay, and QRSd

The modest correlation between CURE and QRS duration (QRSd) is shown ($r = -0.58$, $p < 0.001$) for all 43 subjects in the cardiac resynchronization therapy heart failure (CRT-HF) and multimodality cohorts **(A)**. For the multimodality cohort only **(B)**, CURE and the tissue Doppler imaging (TDI) septal-lateral delay are shown versus QRSd. As expected (based on prior published data), there is no correlation between TDI and QRSd ($r = 0.04$, $p = 0.83$), but there is a significant correlation between CURE and QRSd ($r = -0.60$, $p = 0.001$) **(B)**. The CURE-QRSd correlation is also shown **(C)** for the CRT-HF cohort only ($r = -0.40$, $p = 0.08$). Abbreviations as in Figure 1.

Scar imaging findings by DE-CMR. With scar imaging of CRT-HF patients with an acceptable glomerular

filtration rate (90%), 25% met the previously published criterion of percent total scar less than 15% (21) associated with CRT response. The CRT response rate in subjects with percent total scar <15% was significantly better that for subjects with percent total scar of 15% or greater ($p = 0.047$) (Fig. 4C). This criterion was associated with a PPV of 77%, NPV of 80%, and accuracy of 78% for CRT response. A CURE value <0.75 without evidence of extensive (15% or more) left ventricular scar resulted in the most accurate prediction of CRT response, with a PPV of 93%, NPV of 100%, and accuracy of 95% ($p < 0.001$) (Table 2).

Application of CURE cutoff to standard clinical dyssynchrony assessment. In the multimodality cohort ($n = 27$), the mean (standard error) for CURE was 0.68 (0.03) and for TDI septal-lateral delay was 74 (7.0) ms. Using the ROC-based CURE cutoff of 0.75, 56% of patients tested positive for mechanical dyssynchrony using either MR-MT or TDI, but the patients testing positive by MR-MT were not necessarily the same patients testing positive with TDI (discordance rate: 30%).

In half of these discordant cases (15% of total), MR-MT indicated dyssynchrony and TDI did not, but in the other half of discordant cases (15% of total), TDI indicated dyssynchrony and MR-MT did not. TDI was more likely than MR-MT to indicate dyssynchrony in both cardiomyopathy subjects with a narrow QRS (63% vs. 25%, TDI vs. MR-MT, respectively) and control group subjects (44% vs. 0%), who all had a narrow QRS ($p = 0.016$ for all subjects with a narrow QRS). Of note, 77% of subjects with TDI/MR-MT *discordance* had 2 systolic peaks in the TDI tissue velocity versus time tracing from the septal or lateral walls, but only 33% of subjects with TDI/MR-MT *concordance* had double systolic velocity peaks in the septal or lateral walls.

DISCUSSION

Main findings. This is the first published series evaluating MR-MT assessment of circumferential mechanical dyssynchrony in patients referred for CRT with respect to prediction of clinical improvement after implantation. The most significant find-

Table 2. MR-MT and DE-CMR for CRT Response

	Sensitivity	Specificity	PPV	NPV	Accuracy
% total scar <15%*	91	57	77	80	78
MR-MT CURE <0.75*	100	71	87	100	90
Both present*	100	86	93	100	95

*All numbers reported are percentages.
CRT = cardiac resynchronization therapy; CURE = circumferential uniformity ratio estimate; DE-CMR = delayed enhancement-cardiac magnetic resonance; MR-MT = magnetic resonance-myocardial tagging; NPV = negative predictive value; PPV = positive predictive value.

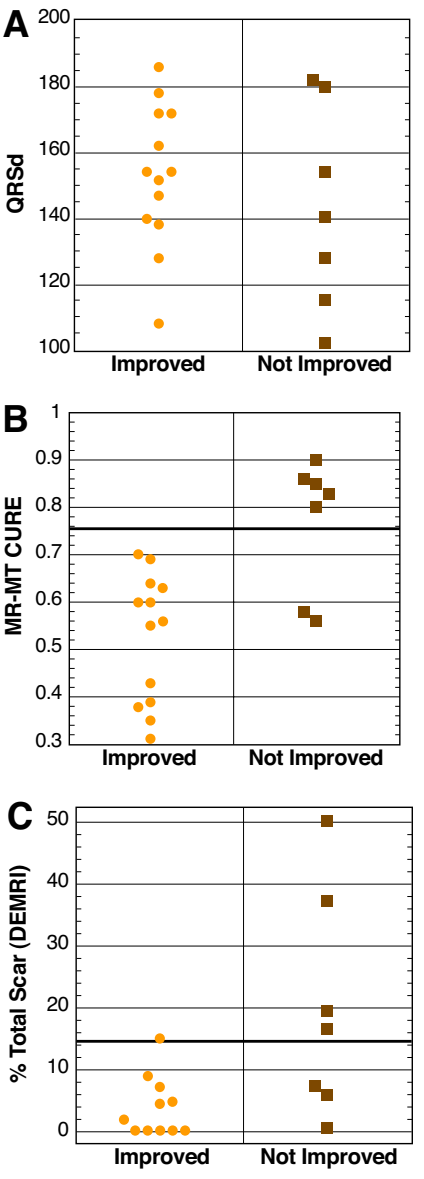

Figure 4. Clinical Response to CRT Based on CMR Findings

These plots show data for individual improvement in function class for patients in the CRT-HF cohort based on baseline characteristics such as QRSd **(A)**, CURE **(B)**, and percent left ventricular scar volume by delayed enhancement-cardiac magnetic resonance (DE-CMR) **(C)**. Those with function class improvement are shown in the **left column of each panel**, and those without improvement are shown in the **right column of each panel**. The QRSd **(A)** has no association with improvement in function class. MR-MT **(B)** has better accuracy (90%) than DE-CMR (78%) and **(C)** MR-MT and DE-CMR combined have superior accuracy (95%). This highlights the superior accuracy of CURE for predicting function class improvement. Abbreviations as in Figures 1 and 3.

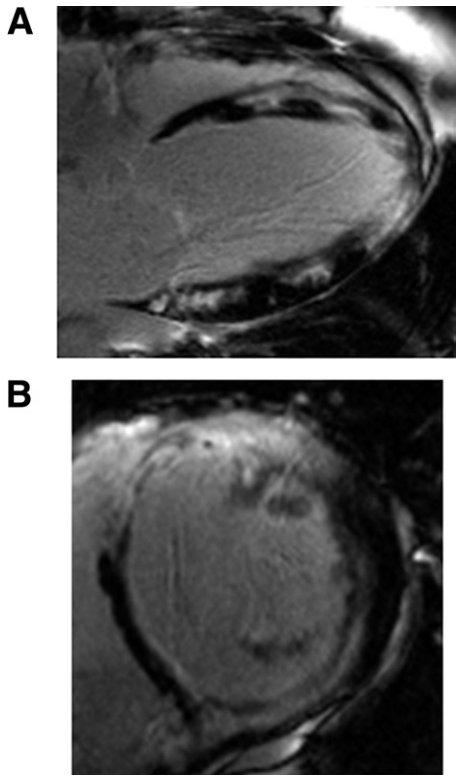

Figure 5. CRT Nonresponse Due to Extensive Scar

Scar imaging from a subject with significant circumferential dyssynchrony but CRT nonresponse shows extensive left ventricular scar on long-**(A)** and short-axis **(B)** images. This underscores the importance of CMR relative to echocardiography in the assessment of CRT candidates. Not only does MR-MT provide a very accurate measure of dyssynchrony, but the scar imaging data provide important information regarding the myocardial substrate such as extent and distribution of scar. Abbreviations as in Figures 1 and 3.

ing of this study is that MR-MT assessment of circumferential mechanical dyssynchrony had excellent predictive value for improved function class after CRT, and its accuracy could be further improved by combining MR-MT with scar imaging by DE-CMR. This result is likely due to the precise circumferential strain map along all 3 dimensions of the heart provided by the MR-MT technique, integration of the entire strain map into a physiologic mechanical dyssynchrony index, and simultaneous evaluation of the underlying tissue substrate.

The CURE cutoff was based on ROC analysis. MR-TDI discordance was likely related to the use of circumferential strain by MR-MT (rather than longitudinal tissue velocity with TDI), as well as certain limitations of TDI for determining accurate time delays. Of note, our finding that TDI was more likely to indicate dyssynchrony in subjects with a narrow QRS (including normal subjects) is consistent with recent data from the RETHINQ (Resynchronization Therapy in Patients with Narrow QRS) study, in which TDI failed to identify narrow QRS patients who would benefit from CRT (24).

Present findings in the context of prior CMR dyssynchrony studies. This is the first study to support the use of MR-MT circumferential strain for CRT selection based on long-term function class improvement. Other MR protocols such as radial motion analysis (25) and CMR longitudinal phase velocity have essentially mimicked TDI by determining radial or longitudinal timing delays and have not been shown to identify CRT responders. Of note, the usefulness of MR-MT circumferential strain for dyssynchrony had been suggested by prior small acute hemodynamic studies of left ventricular or biventricular pacing (9,26).

CRT selection. We have shown that MR-MT assessment of mechanical dyssynchrony has excellent predictive accuracy for improvement in function class after CRT and may be enhanced by DE-CMR scar imaging. These findings highlight the unique value of MR-MT/DE-CMR to characterize both mechanical function and scar extent/distribution in CRT candidates prior to implantation.

Study limitations. There are several limitations to the study. Due to the retrospective nature of the assessment of clinical response, routine post-CRT echocardiographic studies and functional studies such as the 6-min walk were not performed. Even so, the optimal CRT study end point is controversial, improvement in heart failure class is recognized as a valid post-CRT end point, and the overall agreement between clinical response (heart failure class improvement) and echocardiographic response was noted to be 76% in a recent series (14). Of note, the number of patients in the CRT-HF cohort was somewhat limited, and not all patients had pre-CRT TDI studies. Another limitation is that CURE was evaluated during the systolic and early diastolic frames, as the tags may fade somewhat after early diastole. The effect of not including a complete diastolic evaluation of dyssynchrony is likely minor, as dyssynchrony has been shown to peak in systole. Also, although the signal-to-noise ratio in MR-MT circumferential strain data is quite good, and the CURE filters out almost all of the noise based on exclusion of second-order and higher Fourier terms, further refinement of the CMR protocol and analysis may be helpful.

CONCLUSIONS

Magnetic resonance-myocardial tagging–based analysis of circumferential mechanical dyssynchrony with precise

strain maps over all 3 dimensions of the heart is feasible, has excellent predictive accuracy for improvement in New York Heart Association functional class after CRT, and is complemented by substrate characterization using DE-CMR scar imaging.

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Key Words: cardiac magnetic resonance ■ cardiac resynchronization therapy ■ biventricular ■ dyssynchrony ■ heart failure

APPENDIX

For an accompanying video, please see the online version of this article.