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Dyssynchrony, Contractile Function, and Response to Cardiac Resynchronization Therapy

Dorit Knappe, MD*; Anne-Catherine Pouleur, MD*; Amil M. Shah, MD; Susan Cheng, MD; Hajime Uno, PhD; W. Jackson Hall, PhD; Mikhail Bourgoun, MD; Elyse Foster, MD; Wojciech Zareba, MD, PhD; Ilan Goldenberg, MD; Scott McNitt, MS; Marc A. Pfeffer, MD, PhD; Arthur J. Moss, MD; Scott D. Solomon, MD; for the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy Investigators

Background—Despite benefits of cardiac resynchronization therapy (CRT) in patients with severe but less symptomatic heart failure, approximately 30% of patients do not fully respond to treatment. We hypothesized that a combined assessment of left ventricular (LV) dyssynchrony and contractile function by strain-based imaging would identify patients who would most benefit from CRT.

Methods and Results—We studied 1077 patients with New York Heart Association class I/II, LV ejection fraction $\leq 30\%$ and QRS width ≥ 130 ms enrolled in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy trial with sufficient echocardiographic image quality for cardiac deformation analysis (implantable cardioverter-defibrillator [ICD], $n=416$; CRT, $n=661$). Patients were assigned to CRT plus an ICD or to ICD alone in 3:2 random assignment. We assessed the degree to which baseline echocardiographic assessments of dyssynchrony, measured as the standard deviation of time-to-peak transverse strain over 12 segments, contractile function, measured as global longitudinal strain, or both predicted the effect of treatment on the primary outcome of death or heart failure. With 213 primary events occurring over a mean of 2.4 years, the benefit of CRT plus an ICD relative to ICD alone was greatest in patients with mild to moderate dyssynchrony (time-to-peak transverse strain standard deviation, 142 to 230 ms) and greater baseline contractile function (global longitudinal strain $\leq -8.7\%$). Overall, those patients with mild to moderate dyssynchrony and those with best contractile function at baseline demonstrated the greatest benefit from CRT (adjusted hazards ratio, 0.20; 95% confidence interval, 0.09 to 0.44). Dyssynchrony and global longitudinal strain predicted response to CRT independent of each other, QRS width, LV ejection fraction, and presence versus absence of left bundle-branch block, although the observed benefit remained greatest in patients with left bundle-branch block.

Conclusions—Both mechanical dyssynchrony and contractile function are important independent correlates of benefit from CRT.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00180271.

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Key Words: cardiac resynchronization therapy ■ outcomes ■ heart failure ■ echocardiography ■ strain imaging

Cardiac resynchronization therapy (CRT) has been shown to reduce cardiovascular morbidity and mortality in patients with heart failure symptoms and left ventricular (LV) dysfunction in patients with advanced heart failure.^{1,2} The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT), Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE), and Resynchronization/defibrillation for Ambulatory Heart Failure Trial (RAFT) trials have extended these benefits of CRT to patients with less advanced

heart failure.^{3–6} However, despite current selection criteria based on New York Heart Association (NYHA) functional class, ejection fraction (LVEF), and ECG QRS duration, up to 30% of the patients do not benefit from CRT with respect to clinical outcomes or echocardiographic parameters of LV remodeling.^{1,7,8}

Clinical Perspective on p ●●●

The exact criteria by which patients should be selected for CRT remain controversial. LV mechanical dyssynchrony con-

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From the Cardiovascular Division (D.K., A.C.P., A.S., S.C., H.U., M.B., M.A.P., S.D.S.), Brigham and Women's Hospital, Boston, MA; the University of California, San Francisco (E.F.); and the University of Rochester Medical Center (W.J.H., W.Z., I.G., S.M., A.J.M.), Rochester, NY.

*Drs Knappe and Pouleur contributed equally to this article.

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Correspondence to Scott D. Solomon, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail ssolomon@rics.bwh.harvard.edu

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tinues to be considered a potentially important predictor of response to CRT, with several measures of dyssynchrony having been shown to predict the response to CRT.^{9–12} Nevertheless, the Predictors of Response to CRT (PROSPECT) study suggested that echocardiographic and tissue Doppler parameters may have limited predictive accuracy.¹³ Contractile function measured by global longitudinal strain has been shown to be feasible, reliable, and a major predictor of cardiac events.^{14,15} However, few studies have looked at a combined assessment of dyssynchrony and contractile function.¹⁶

Additional factors, such as myocardial viability and burden of myocardial scarring, have also been suggested as possible markers of response to CRT.¹⁷ Detailed echocardiographic assessments of both LV mechanical dyssynchrony and contractile function, which can reflect the extent of myocardial viability and scar burden, now can be performed in a highly reproducible and angle-independent manner with the use of speckle-tracking analysis. We used echocardiographic myocardial deformation techniques to comprehensively assess these factors as possible predictors of long-term benefit from CRT. We hypothesized that both dyssynchrony measured by the standard deviation of time-to-peak transverse strain and contractile function measured by global longitudinal strain would potentially help identify patients who would be most likely to respond to CRT.

Methods

Patient Population

MADIT-CRT enrolled patients with ischemic heart disease in NYHA class I or II or patients with nonischemic heart disease in NYHA class II, an LVEF $\leq 30\%$, and a QRS duration ≥ 130 ms. From December 2004 through April 2008, a total of 1820 patients were enrolled at 110 hospital centers: 88 centers in the United States, 2 centers in Canada, and 20 centers in Europe. Patients were randomly assigned in a 3:2 ratio to receive CRT-D (CRT plus an implantable cardioverter-defibrillator [ICD]) or ICD alone. Additional details regarding inclusion and exclusion criteria have been previously reported.^{3,18} Two-dimensional echocardiography was performed at baseline and at 1-year follow-up. Echocardiograms were obtained according to a study-specific protocol at baseline, which was done before device implantation, and at 1 year. A total of 1077 patients (ICD, $n=416$; CRT, $n=661$) had image quality sufficient for analyzing dyssynchrony and global longitudinal strain, based on B-mode speckle-tracking methods. We excluded 607 patients from the analysis because images were in non-DICOM format or the frame rate was <30 Hz; 136 patients were excluded from the analysis because of missing 4- or 2-chamber views, insufficient 2D image quality, use of echocardiographic contrast agent, presence of endocardial dropout, or out-of-plane images.

Echocardiographic Analyses

Standard echocardiographic parameters, including ventricular volumes and LVEF, were analyzed using an offline analysis workstation as previously described.¹⁹ Dyssynchrony and contractile function indices were measured using B-mode speckle-tracking software (TomTec Imaging Systems, Unterschleissheim, Germany) that circumvents angle dependency and identifies cardiac motion by tracking multiple reference points over time; this method has been validated against sonomicrometry²⁰ and has demonstrated excellent reproducibility in our laboratory.^{15,21} The endocardial borders were traced in the end-systolic frame of 2D images acquired from the apical 4- and 2-chamber views. Speckles were tracked frame by frame throughout the LV myocardium over the course of ≥ 2 cardiac cycles; basal, mid, and apical regions of interest were created. Semiquantitative segment tracking was carefully inspected for each

image and manually adjusted as needed. If ≥ 2 segments could not be tracked, the measurements were considered unreliable and the study was excluded from the analysis. Tracings in each view were performed by a single investigator blinded to treatment assignment, clinical/demographical data, and clinical outcomes.

Mechanical dyssynchrony of the LV was determined as the standard deviation of regional time-to-peak transverse strain, measured during systole, across all 12 anatomic wall segments of the ventricle (SD-TTS) (Figure 1A).^{22–24} Global longitudinal strain, a detailed measure of LV contractile function, was calculated as the average across the apical 4- and 2-chamber views (AV-LS) (Figure 1B). Intraobserver and interobserver variation for dyssynchrony and global longitudinal strain was assessed in a sample of 75 randomly selected patients with a broad range of LVEF: coefficients of variation were 13.8% and 15.4% for time-to-peak transverse strain and 7.7% and 8.0% for global longitudinal strain, respectively.

Outcomes

The primary end point for the MADIT-CRT trial was all-cause death or nonfatal heart failure events. The diagnosis of heart failure required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay. End point adjudication was performed, according to prespecified criteria, by an independent mortality committee and by a heart failure committee that was unaware of study group assignments, as described previously.¹⁸

Statistical Analyses

We categorized the study sample by quartiles according to degree of dyssynchrony, measured by time-to-peak transverse strain, and contractile function, measured by global longitudinal strain. We applied a nonparametric trend test, an extension of the Wilcoxon rank-sum test, across the ordinal categories.²⁵ We determined event rates across quartiles of dyssynchrony and global longitudinal strain in each of the treatment arms. We examined the treatment effect comparing CRT-D with ICD alone within quartiles of dyssynchrony and global longitudinal strain and combined groups of dyssynchrony quartile and global longitudinal strain either above or below the median value in adjusted Cox proportional hazards analyses. We adjusted for the 11 strongest conventional predictors of the primary outcome (identified using a stepwise backward selection Cox regression model that originally included 30 covariates, was based on a probability value threshold of 0.1 for selecting variables, and forced in variables considered to be clinically relevant): age, sex, QRS duration, left bundle-branch block (LBBB), indexed left atrial volume, LVEF, LV end-systolic volume, estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease (MDRD) equation, diuretic drug use, heart rate, and ischemic status at study enrollment. Although a strong predictor of heart failure, B-type natriuretic peptide was omitted because it was only available in a subset of the patients. Because previous analyses have demonstrated the importance of LBBB on outcome in MADIT-CRT,²⁶ we repeated analyses in patients with and those without LBBB.

To further assess the incremental value of including dyssynchrony and strain in prediction models for outcomes among patients randomly assigned to the CRT-D treatment arm, we used the likelihood ratio test to test whether these novel measures significantly improve model fit in which these parameters were included over the multivariable baseline model. We further assessed whether there was effect modification by sex, baseline ischemic status, or presence versus absence of LBBB on the association of dyssynchrony and global longitudinal strain with the primary treatment effect. For the assessment of the effect modification, we fit and tested interaction terms in the model.

All analyses were performed using STATA version 10 (Stata Corporation, College Station, TX). For all analyses, a probability value of <0.05 was considered statistically significant.

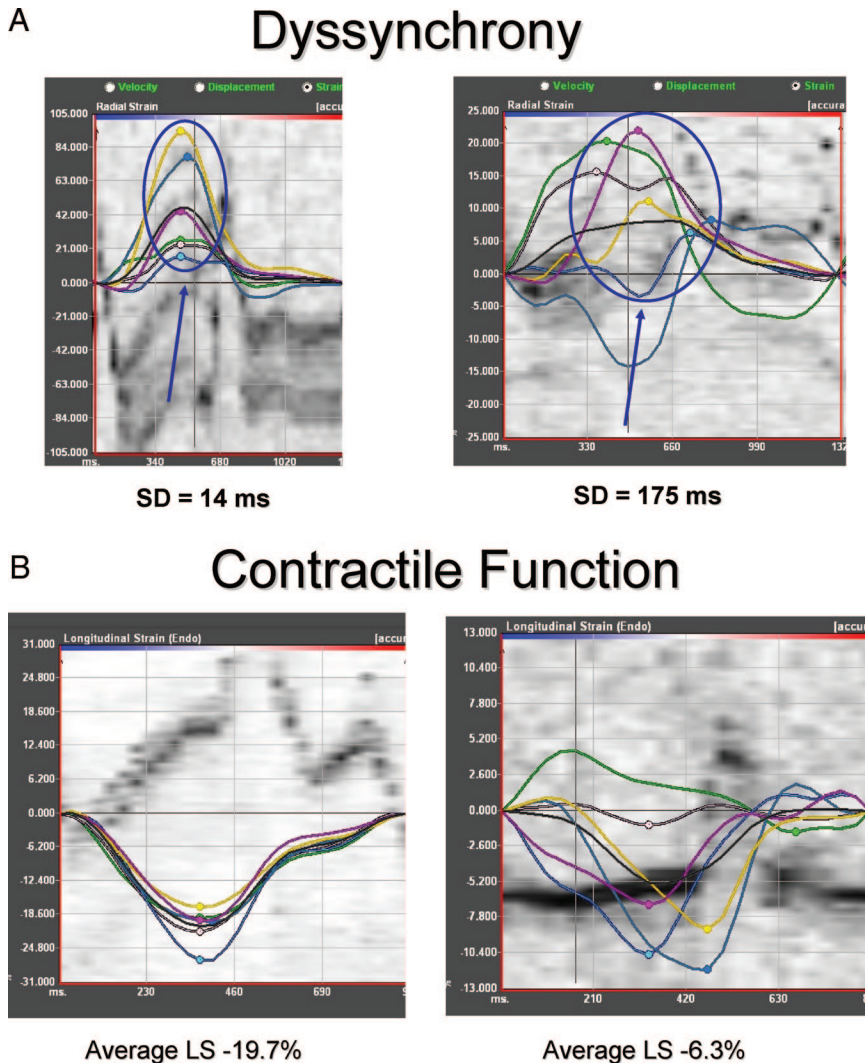


Figure 1. A, Assessment of LV dyssynchrony by standard deviation (SD) of time-to-peak systolic transverse strain of the 12 segments from the apical 4- and 2-chamber views. Left panel, Example of a synchronous contraction, with all segments contracting at the same time resulting in a very low SD; right panel, example of a dyssynchronous contraction: peak contraction for each segment occurs at different time points, which results in a larger SD. **B,** Assessment of global longitudinal strain (LS). Average peak longitudinal strain between all 12 segments (4Ch/2Ch) was used as a measure of contractile function, as illustrated. Left panel, Example of a normal contraction, with average LS of -19.7% ; right panel, abnormal LV function, with average LS of -6.3% .

Results

Baseline characteristics of the study sample are shown in Table 1 by quartiles of dyssynchrony and quartiles of global longitudinal strain. Patients included in the present analysis were comparable to patients in the remainder of the MADIT-CRT study sample with respect to age, sex, NYHA functional class, ischemic status, QRS morphology, systolic and diastolic blood pressure, estimated glomerular filtration rate, LV end-diastolic and end-systolic volumes, and use of medications. Compared with excluded patients, those in the present analysis had shorter QRS duration (160 ± 21 ms versus 157 ± 19 ms; $P=0.009$) and a lower frequency of reported diabetes mellitus (35% versus 28%; $P=0.001$). The point estimate for the efficacy of CRT in the included cohort was 0.61 (95% confidence interval [CI], 0.47 to 0.80), which was comparable to that in the entire MADIT-CRT population (hazards ratio [HR], 0.66; 95% CI, 0.52 to 0.84).

Baseline dyssynchrony was greater in women than in men and was associated with history of diabetes mellitus, longer QRS duration, and greater frequency of LBBB; dyssynchrony was inversely related to right bundle-branch block, end-systolic volumes, atrial volume indices, and longitudinal strain (Table 1). Worse longitudinal strain was associated with younger age, male

sex, ischemic etiology, history of diabetes mellitus, higher heart rate, longer QRS duration, lower LVEF, lower right ventricular fractional area change, higher end-systolic volumes, higher atrial volume index, and greater transverse dyssynchrony. During an average follow-up of 2.4 years, 213 patients had events: 105 in the ICD alone group and 108 in the CRT-D group. In total, 30 patients (14%) died, 158 (74%) were hospitalized for heart failure, and 25 (12%) had a heart failure event that occurred outside the hospital. The number for nonresponders, based on the primary outcome of death or nonfatal heart failure events, was 17% in the MADIT-CRT Trial; the number for nonresponders, based on a lack of a 15% improvement in end-systolic volume, was 32%.

Influence of Global Longitudinal Strain and Dyssynchrony on Efficacy of Treatment

There was no clear relationship between the degree of dyssynchrony and outcomes in the ICD-alone group (Figure 2, left panel). However, in the CRT-D group, patients in the lowest dyssynchrony quartile had the highest event rates, with reduced event rates in the 2 middle quartiles of dyssynchrony, whereas we observed an increase in the event rate for the fourth quartile, suggesting a potential J-shaped relationship.

Table 1. Baseline Characteristics of Patients by Quartiles of Dyssynchrony Measured by Transverse Strain and Global Longitudinal Strain

	Quartiles of Dyssynchrony, ms					Quartiles of Global Longitudinal Strain, %				
	Less	→			More	Better Contractile	→			Worse Contractile
	Dyssynchrony 38–141 (n=272)	142–180 (n=273)	181–230 (n=269)	231–496 (n=263)	Dyssynchrony P Trend	Function –19.0 to –10.6 (n=271)	–10.59 to –8.7 (n=269)	–8.69 to –6.94 (n=269)	–6.93 to –2.0 (n=268)	Function P Trend
Clinical parameters										
Age, y	65±11	64±11	63±11	65±11	0.92	65±11	66±11	64±11	62±11	0.0001
Female, n (%)	46 (17)	77 (28)	69 (26)	76 (29)	0.005	81 (30)	61 (23)	70 (26)	56 (21)	0.045
NYHA II, n (%)	225 (83)	228 (84)	226 (84)	227 (86)	0.26	222 (82)	231 (86)	217 (81)	236 (88)	0.19
Ischemia, n (%)	170 (63)	150 (55)	133 (49)	148 (56)	0.071	128 (47)	156 (58)	167 (62)	150 (56)	0.03
Hypertension, n (%)	169 (63)	166 (61)	157 (58)	171 (65)	0.74	155 (57)	184 (68)	169 (63)	155 (58)	0.83
Diabetes mellitus, n (%)	81 (30)	85 (31)	73 (27)	57 (22)	0.02	62 (23)	73 (27)	78 (29)	83 (31)	0.03
eGFR, mL/min	68±20	71±21	70±21	67±21	0.73	71±22	68±20	68±19	68±21	0.14
BNP, pmol/L, median (interquartile range)*	71.6 (31–152)	65 (25–139)	67 (27–155)	94 (37–197)	0.09	45 (20–100)	69 (32–149)	87 (34–176)	118 (56–249)	<0.001
ECG parameters										
Heart rate, bpm	65±12	66±11	65±11	58±9	<0.0001	59±10	62±10	63±11	70±11	<0.0001
QRS, ms	152±17	156±19	160±19	161±20	<0.0001	153±16	157±19	165±19	163±21	<0.0001
RBBB, n (%)	52 (19)	28 (10)	21 (8)	25 (10)	<0.001	37 (14)	38 (14)	25 (9)	26 (10)	0.06
LBBB, n (%)	165 (61)	198 (73)	214 (80)	187 (71)	0.002	192 (71)	183 (68)	190 (71)	199 (74)	0.29
Echocardiographic parameters										
LVEF, %	29.8±3.4	29.4±3.3	28.8±3.4	29.0±3.5	0.0004	31.1±3.3	29.4±3.1	29.0±2.9	27.5±3.4	<0.0001
LVEDV, mL	237±48	243±58	253±56	257±67	<0.0001	219±39	238±43	249±51	284±74	<0.0001
LVESV, mL	167±39	173±47	181±45	184±55	<0.0001	151±31	168±34	178±40	207±60	<0.0001
LAVI, mL/m ²	45±10	45±10	47±9	48±12	0.002	42±9	45±10	47±9	50±12	<0.0001
RVFAC, %	43±6	43±6	42±6	43±6	0.63	44±6	42±6	43±6	41±5	0.0002
Longitudinal strain, %	–9.5±3.0	–8.9±2.8	–8.5±2.9	–8.8±2.7	0.001	...	...	...	...	...
Transverse dyssynchrony, ms	...	...	...	...	...	177±68	190±70	189±64	195±61	0.003

eGFR indicates estimated glomerular filtration rate; BNP, B-type natriuretic peptide; RBBB, right bundle-branch block; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; LAVI, left atrial volume index; and RVFAC, right ventricular fractional area change.

*Missing values=353.

Patients who demonstrated mild to moderate dyssynchrony appeared to derive the greatest benefit (Figure 2, left panel). In contrast, the relationship between contractile function (measured as average longitudinal strain) and outcomes appeared linear in both treatment arms, with worse global

longitudinal strain associated with higher event rates (Figure 2, right panel).

The HRs associated with CRT efficacy across quartiles of transverse dyssynchrony and global longitudinal strain are shown for all patients and for those with and those without

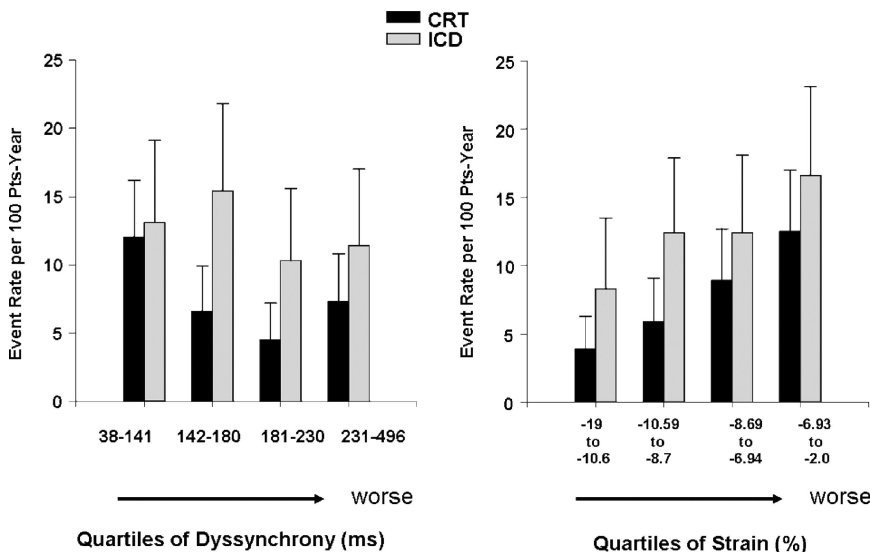


Figure 2. Relation of quartiles of dyssynchrony measured by transverse dyssynchrony (left panel) and quartiles of global longitudinal strain (right panel) to the primary outcome event rate in the CRT and ICD arms.

Table 2. HRs for Primary End Points by Quartiles of Dyssynchrony Measured by Transverse Strain and Global Longitudinal Strain in All Patients and by LBBB Status

	Quartiles of Dyssynchrony, ms			
	→			More Dyssynchrony 231 to 496
	Less Dyssynchrony 38 to 141	142 to 180	181 to 230	
All patients, HR (95% CI)	0.86 (0.52–1.42), <i>P</i> =0.55	0.42 (0.24–0.73), <i>P</i> =0.002	0.34 (0.18–0.66), <i>P</i> =0.001	0.65 (0.37–1.16), <i>P</i> =0.15
LBBB	0.64 (0.33–1.26), <i>P</i> =0.20	0.26 (0.12–0.54), <i>P</i> <0.001	0.27 (0.13–0.57), <i>P</i> =0.001	0.52 (0.27–1.03), <i>P</i> =0.06
Non-LBBB	1.37 (0.58–3.28), <i>P</i> =0.47	0.92 (0.36–2.38), <i>P</i> =0.87	0.23 (0.005–11.45), <i>P</i> =0.46	1.23 (0.29–5.21), <i>P</i> =0.78
	Quartiles of Global Longitudinal Strain, %			
	→			Worse Contractile Function –6.93 to –2.0
	Better Contractile Function –19.0 to –10.6	–10.59 to –8.7	–8.69 to –6.94	
All patients	0.51 (0.25–1.04), <i>P</i> =0.07	0.43 (0.24–0.77), <i>P</i> =0.005	0.71 (0.41–1.23), <i>P</i> =0.22	0.76 (0.47–1.21), <i>P</i> =0.24
LBBB	0.37 (0.15–0.89), <i>P</i> =0.026	0.25 (0.11–0.57), <i>P</i> =0.001	0.59 (0.30–1.15), <i>P</i> =0.12	0.47 (0.27–0.83), <i>P</i> =0.009
Non-LBBB	0.32 (0.06–1.60), <i>P</i> =0.17	0.89 (0.33–2.46), <i>P</i> =0.83	1.25 (0.38–4.12), <i>P</i> =0.71	1.38 (0.50–3.85), <i>P</i> =0.53

HRs (95% CIs) are for the primary outcome, comparing the treatment effect (among patients who received CRT-D and those who received an ICD only). Analyses are adjusted for age, sex, QRS duration, LBBB, LVEF, LV end-systolic volume, estimated glomerular filtration rate, diuretic use, heart rate, ischemic status, and indexed left atrial volume. The test for overall differences in CRT-D benefit did not differ significantly across the 4 quartiles of dyssynchrony or strain.

LBBB in Table 2. In multivariable analyses, the greatest benefit from CRT was noted in the second (adjusted HR, 0.42; 95% CI, 0.24 to 0.73) and third (adjusted HR, 0.34; 95% CI, 0.18 to 0.66) quartiles of dyssynchrony, suggesting a potential J-shaped relationship. Conversely, treatment benefit steadily increased as longitudinal strain improved, with the greatest benefit noted for patients who had global longitudinal strain measures below the median of -8.7% (longitudinal strain $\leq -8.7\%$: HR, 0.43; 95% CI, 0.28, 0.67; longitudinal strain $> -8.7\%$: HR, 0.72; 95% CI, 0.51, 1.01). Patients with better global longitudinal strain and mild to moderate dyssynchrony (SD-TTS between 142 and 230 ms) had the greatest treatment benefit (HR, 0.20; 95% CI, 0.09, 0.44) (Figure 3). This pattern was observed primarily in patients with LBBB.

In an analysis of the CRT-D group patients, the direct measures of LV dyssynchrony, measured by transverse strain, and LV contractile function, assessed by global

longitudinal strain, provided incremental value over baseline covariates for predicting the primary outcome with respect to model fit ($P<0.001$). Based on the trends among CRT-D patients seen in Figure 2, we modeled strain as a linear variable and dyssynchrony as both linear and quadratic terms. Models for the endpoint of heart failure or death were fitted using the previously described list of covariates alone and then additionally with these strain and dyssynchrony parameters. A 3-degrees-of-freedom χ^2 test for the joint significance of these parameters, based on the difference in the likelihoods, was found to have a *P* value less than 0.001. The variables were all individually significant at $P<0.01$. In secondary analyses, we observed no significant effect modification by sex, baseline ischemic status, or presence versus absence of LBBB on the association of dyssynchrony and global longitudinal strain with the primary treatment effect.

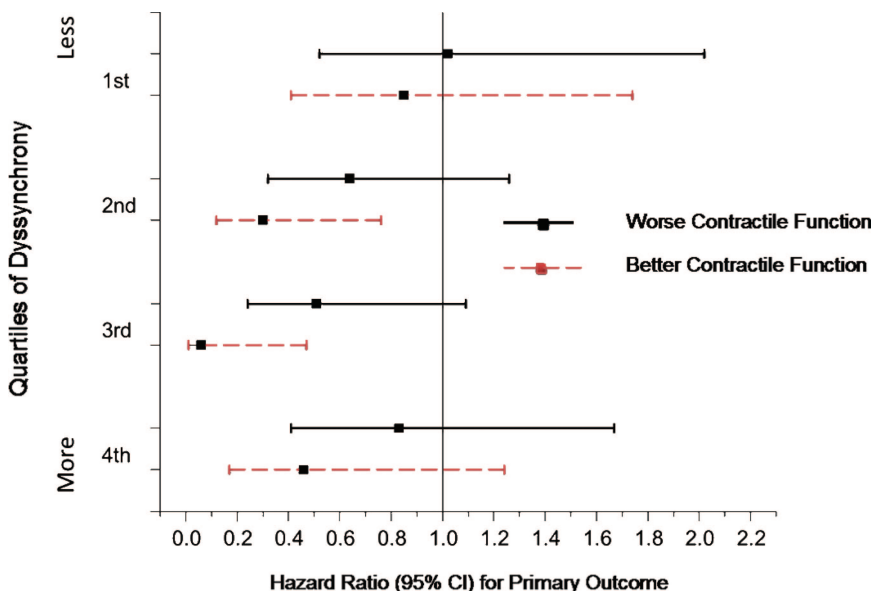


Figure 3. HRs for primary outcome, comparing the treatment effect (among patients who received CRT-D and those who received an ICD only) by quartiles of dyssynchrony and contractile function (as measured by longitudinal strain) above and below the median, adjusting for clinical covariates (described in the text).

Discussion

In this analysis of dyssynchrony, assessed as the standard deviation of time-to-peak transverse strain, and contractile function, assessed by global longitudinal strain, in the MADIT-CRT trial, we observed the greatest benefit from CRT-D compared with ICD alone in patients with mild to moderate dyssynchrony and best contractile function. These results suggest that both factors—degree of mechanical dyssynchrony and contractile function—may be important determinants of benefit in CRT and that these measures may provide incremental value over traditional characteristics such as LVEF, QRS duration, and LBBB.

LVEF, QRS duration, and LBBB are widely accepted as important predictors of response to CRT, but these measurements have well-recognized limitations. Almost one-third of patients do not respond to CRT, even when carefully selected according guidelines-based criteria that include NYHA class, LVEF, and QRS duration. This consistent finding probably is due to the fact that response to CRT is determined by the interaction of a large number of factors. Thus, in recent years, assessment of LV mechanical dyssynchrony has been suggested as a method for overcoming the limitations of conventional methods for estimating electric dyssynchrony. However in the PROSPECT study,¹³ which tested the performance of mechanical dyssynchrony measures, the tissue Doppler-based assessments lacked meaningful predictive value and lacked reproducibility, with an interobserver variability >30%. On the other hand, the 2D speckle-tracking method of assessing mechanical dyssynchrony, which was used in the present study, offers several advantages: angle-independent image acquisition, the ability to differentiate myocardial segments with active movement from those with passive movement, and high reproducibility. Thus, speckle-tracking-based methods may demonstrate greater utility than Doppler-based methods for assessing mechanical dyssynchrony as well as global longitudinal strain.

As a marker for dyssynchrony, we chose the standard deviation of time-to-peak systolic transverse strain of the 12 segments from the apical 4- and 2-chamber views, as has been previously used by Delgado et al²³ and Miyazaki et al.²⁴ In a comparison of radial/transverse strain with longitudinal and circumferential strain, Delgado et al have shown that radial/transverse strain (myocardial thickening) analysis performed best to identify potential responders to CRT. In their analyses, 2 different parameters for dyssynchrony were obtained: maximal time delay between peak systolic strain of 2 segments observed between the anteroseptum and posterolateral wall as well as an asynchrony index of the LV by calculating the standard deviation of time-to-peak systolic strain. We used the standard deviation in time to peak strain from the 12 segments because this method is more comprehensive than methods that compare a limited number of specific regions. Miyazaki et al have shown that the strain-derived dyssynchrony index is a better measurement than the tissue velocity dyssynchrony index for monitoring changes in mechanical dyssynchrony after CRT and for predicting reduction in LV volume after CRT. The recent published STAR trial by Gorcsan et al²⁷ showed that dyssynchrony by speckle-tracking echocardiography using radial and transverse strain

was associated with better EF response and long-term outcome after CRT. Circumferential and longitudinal strain predicted response when dyssynchrony was detected but failed to identify dyssynchrony in one-third of patients who responded to CRT. In a study of patients with NYHA class III and IV heart failure, mechanical dyssynchrony defined by opposite-wall, time-to-peak radial strain and peak transverse strain was significantly associated with increased risk of death, transplantation, or need for an LV assist device.²⁸

Our data suggest that the relationship between LV mechanical dyssynchrony and treatment benefit is complex. We believe that the lack of relationship between the degree of dyssynchrony and outcomes in this wide QRS population in the ICD-only group reflects the fact that these patients were selected to have a QRS width of ≥ 130 ms, and thus all would be expected to be dyssynchronous by standard ECG criteria. We have previously shown that in a post-myocardial infarction population in which the vast majority of patients had QRS width <120 ms, dyssynchrony was related to clinical outcomes.²¹ In this analysis, those patients with mild to moderate dyssynchrony and preserved contractile function at baseline demonstrated a 37% improvement in LV end-systolic volume. We observed that patients with the least dyssynchrony at baseline benefited least from CRT, whereas the greatest benefit was observed among patients in the middle 2 quartiles of the dyssynchrony spectrum. We speculate that the most dyssynchronous patients in this cohort may have derived less benefit from CRT because they were at higher risk to begin with, as also suggested by the higher B-type natriuretic peptide values in this cohort. Although limited by the absence of outcomes data, most prior smaller studies have shown that dyssynchrony was associated with echocardiographic response to CRT such as improvement in LVEF.^{10,29}

The relationship between longitudinal strain and treatment benefit suggests that patients with the best contractile function at baseline demonstrated the greatest benefit from CRT. As a sensitive measure of LV contractile function and, by extension, the amount of viable contractile myocardium present, LV longitudinal strain has been associated inversely with total scar burden assessed by MRI.^{30,31,32} Accordingly, longitudinal strain has also been shown to predict an echocardiographic response to CRT, defined as an increase in LV end-systolic volume by $\geq 15\%$, in a study of 45 patients with ischemic dilated cardiomyopathy.³⁰ These data suggest that the presence of preserved contractile function myocardium may be critically important for predicting response to CRT and highlight the role of the myocardial substrate in determining the LV functional response and possible reverse remodeling that may result from biventricular pacing. Our study extends the findings of smaller studies that also highlight the importance of viability and synchrony¹⁶ to a large sample of patients with both ischemic and nonischemic heart failure with hard outcomes of death and heart failure events and suggests that despite all patients in this cohort having a reduced EF, those with the most preserved baseline strain measures, indicating a higher degree of inherent contractile function, derive the greatest benefit from CRT. That patients with mild to moderate dyssynchrony and better contractile

function derived the greatest overall benefit from CRT suggests that to benefit from CRT, the ventricle may need to be both dyssynchronous and have a relatively preserved contractile function. We consider the data from these post hoc analyses hypothesis-generating.

We observed no significant effect modification by sex, ischemic versus nonischemic etiology of HF, or presence versus absence of LBBB in our study sample, despite the fact that the most profound benefit for CRT was observed in patients with LBBB, patients who were female, and patients with nonischemic etiology. We cannot rule out the possibility that our interaction analyses may have been underpowered to detect effect modification. Previous post hoc analyses from MADIT-CRT have demonstrated an interaction between bundle-branch block status and treatment effect such that patients with LBBB derived by far the greatest benefit. Similarly, we found that regardless of global longitudinal strain or dyssynchrony measures, patients with LBBB received the greatest benefit. Although we were unable to identify by these measures the patients in the non-LBBB group who were more likely to benefit, the small number of patients in MADIT-CRT without left bundle severely limits this analysis, and we cannot exclude the possibility that measures of synchrony or global longitudinal strain could be useful in identifying non-LBBB patients who are more likely to respond.

Several limitations of our analysis should be noted. Speckle-tracking strain and dyssynchrony analysis was not possible in 30% of our cohort because of their original acquisition and storage in videotape format. Those studies were excluded at the outset to ensure a feasible frame rate for image analyses. Among the 1213 remaining studies, we also excluded 11% because of insufficient image quality or missing views. Although strain-based assessments of myocardial performance are known to be much less load-dependent than conventional measures of LV function, particularly EF, variation in hemodynamic loading conditions may yet have contributed confounding effects. Nevertheless, our findings remained robust after adjustment for several surrogates of hemodynamic status including blood pressure indices, LV volumes, heart rate, and diuretic medication use. Notwithstanding these limitations, our analysis is strengthened by the availability of detailed clinical characteristics and advanced echocardiographic measures in a large sample size, the availability of long-term clinical outcomes data, and the presence of a control group (ICD alone) that allowed estimation of the treatment effect (CRT).

In summary, we observed that both mechanical dyssynchrony and contractile function are important determinants of CRT benefit and that these assessments may help to identify patients who stand to derive the greatest benefit from CRT therapy. These results suggest that mechanical dyssynchrony and myocardial viability may be more directly related to clinical response and outcomes with CRT than conventional measurements of electric dyssynchrony.

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Disclosures

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CLINICAL PERSPECTIVE

Although cardiac resynchronization therapy (CRT) has been shown to reduce cardiovascular outcomes in patients with heart failure and left ventricular dysfunction, almost one-third of patients who receive CRT do not respond to treatment. Determining which patients are more or less likely to benefit from CRT remains a therapeutic challenge. Left ventricular mechanical dyssynchrony has been suggested as a method for overcoming the limitations of estimating electric dyssynchrony. Echocardiographic assessments of both left ventricular mechanical dyssynchrony and discrete contractile function, which can reflect the extent of myocardial viability and scar burden, now can be performed in a highly reproducible and angle-independent manner by using speckle-tracking analysis. Therefore, in a sample of 1077 patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy Trial, we used echocardiographic myocardial deformation analyses to investigate whether or not mechanical synchrony and contractility might predict response to CRT. We observed that the combination of mechanical dyssynchrony and preserved contractile function significantly predicted lower risk for recurrent heart failure or death after CRT, even after adjusting for factors conventionally associated with CRT response. Our results indicate that the ventricle must be dyssynchronous but also viable, as reflected by contractile function, to benefit from CRT. These findings suggest that mechanical dyssynchrony and contractile function may be more directly related to clinical response and outcomes than conventionally measured electric dyssynchrony. Our analyses were strengthened by the availability of a large sample size, data on long-term clinical outcomes, and the presence of a control group that allowed estimation of the treatment effect.