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Combined Longitudinal and Radial Dyssynchrony Predicts Ventricular Response After Resynchronization Therapy

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Objectives The purpose of this study was to test the hypothesis that a combined echocardiographic assessment of longitudinal dyssynchrony by tissue Doppler imaging (TDI) and radial dyssynchrony by speckle-tracking strain may predict left ventricular (LV) functional response to cardiac resynchronization therapy (CRT).

Background Mechanical LV dyssynchrony is associated with response to CRT; however, complex patterns may exist.

Methods We studied 190 heart failure patients (ejection fraction [EF] 23 ± 6%, QRS duration 168 ± 27 ms) before and after CRT. Longitudinal dyssynchrony was assessed by color TDI for time to peak velocity (2 sites in all and 12 sites in a subgroup of 67). Radial dyssynchrony was assessed by speckle-tracking radial strain. The LV response was defined as ≥15% increase in EF.

Results One hundred seventy-six patients (93%) had technically sufficient baseline and follow-up data available. Overall, 34% were EF nonresponders at 6 ± 3 months after CRT. When both longitudinal dyssynchrony by 2-site TDI (≥60 ms) and radial dyssynchrony (≥130 ms) were positive, 95% of patients had an EF response; when both were negative, 21% had an EF response ($p < 0.001$ vs. both positive). The EF response rate was lowest (10%) when dyssynchrony was negative using 12-site TDI and radial strain ($p < 0.001$ vs. both positive). When either longitudinal or radial dyssynchrony was positive (but not both), 59% had an EF response. Combined longitudinal and radial dyssynchrony predicted EF response with 88% sensitivity and 80% specificity, which was significantly better than either technique alone ($p < 0.0001$).

Conclusions Combined patterns of longitudinal and radial dyssynchrony can be predictive of LV functional response after CRT. (J Am Coll Cardiol 2007;50:1476–83) © 2007 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) is an important therapy for heart failure patients using standard selection criteria of a widened electrocardiograhic QRS complex and low ejection fraction (EF). Randomized clinical trials have shown that the majority of patients benefit from CRT using this approach; however, the desire to predict patient response using measures of mechanical dyssynchrony continues to exist (1–4). An important subset of patients who have a widened electrocardiograhic QRS lack significant mechanical dyssynchrony, although the pathophysiologic reason for this phenomenon is unclear (5–11). Several studies have shown that these patients without dyssynchrony despite having a widened QRS do not respond to CRT and have a worse prognosis than those with significant mechanical dyssynchrony (12–21). Although several promising approaches to quantify dyssynchrony have been reported, difficulties have been encountered with complex patterns of dyssynchrony, particularly in patients with ischemic wall motion abnormalities (6,13,15,18,22). Accordingly, our objective was to test the hypothesis that a combined assessment of longitudinal dyssynchrony by tissue Doppler imaging (TDI) and radial dyssynchrony by speckle tracking can predict left ventricular (LV) function response to CRT superior to either approach alone, particularly to identify patients without dyssynchrony who have a low probability of LV functional response to CRT.

Methods

The initial patient group consisted of 190 consecutive heart failure patients referred for CRT from 2 centers. The

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protocol was approved by the Institutional Review Boards for Biomedical Research at the University of Pittsburgh and Leiden University Medical Center, and all patients gave informed consent consistent with this protocol. This was a prospective study design where investigators from one institution traveled to the other institution to analyze echo data in a uniform core lab approach. The study group consisted of 176 patients with complete baseline TDI, speckle tracking, and follow-up datasets; 7% were excluded with technically insufficient or missing data. One hundred fifty-nine patients were New York Heart Association (NYHA) functional class III and 17 were class IV at the initial evaluation. Forty-one were female. The group mean age was 64 ± 11 years, EF was 23 ± 7% (all ≤35%), and QRS duration was 168 ± 27 ms (all >120 ms). Sixty percent of patients had ischemic heart disease, and 40% had nonischemic causes of heart failure. No patients had atrial fibrillation. The CRT was initiated with implantation of biventricular pacing systems in routine clinical use with the LV lead placement via the coronary sinus targeting the posterior or lateral wall using routine angiographic and fluoroscopic guidance. All patients were on optimal pharmacologic therapy, including angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone as tolerated.

Echocardiography. All echocardiographic studies were performed with a commercially available echocardiography system (Vivid 7, GE-Vingmed, Horten, Norway). Patients were studied before and after (mean 6 ± 3 months) CRT to assess EF response. Digital routine grayscale 2-dimensional and TDI cine loops from 3 consecutive beats were obtained at end-expiratory apnea from standard apical and mid-LV short-axis views at depths of 12 to 20 cm as previously described (14,15,23). Frame rates were 30 to 100 Hz (mean 65 ± 15 Hz) for grayscale imaging used for speckle tracking and 72 to 154 Hz for TDI with a velocity range of ±16 cm/s. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate. Gain settings were adjusted for routine clinical grayscale 2-dimensional imaging to optimize endocardial definition. Specific views used for this study included: mid-LV short-axis views at the papillary muscle level, routine apical views, and pulsed-wave Doppler of the LV outflow tract. The color TDI protocol varied slightly between the 2 institutions, with recordings only from the 4-chamber view at one institution (15) and color TDI data from apical 4-chamber, 2-chamber, and apical long-axis views at the other. The LV volumes and EF were assessed by biplane Simpson rule using manual tracing of digital images, and wall motion analysis was performed for hypokinesis, akinesis, or dykinesis using the American Society of Echocardiography standard (24).

Longitudinal dyssynchrony analysis. Quantitative analysis was performed on all digitally stored images (EchoPAC version BTO6, GE-Vingmed). The ejection interval from aortic valve opening to aortic valve closure was indicated from the LV outflow tract spectral Doppler signal and appeared on the time–velocity analysis screen with care taken to ensure that the heart rates were consistent. The TDI data using regions of interest (approximately 7 mm × 15 mm) were placed in the basal segments from the 4-chamber view in all patients (15) and in basal and mid segments of each of 3 standard apical views in a subgroup of 67 patients (Figs. 1 and 2). Tissue synchronization imaging was used to help guide placement of the region of interest, but time-to-peak data were derived from the time–velocity curves in all (14). For all patient studies, regions of interest were manually adjusted within the segment in the longitudinal plane of the LV and within the wall to identify the most reproducible peak velocity during ejection. In other words, the most representative peak of the segment was searched for, particularly where there were multiple peaks. Post-systolic peaks after aortic valve closure were not included. Segmental time to peak systolic wave velocity was calculated from the onset of the QRS complex or, if the onset was unclear, a uniform point on the electrocardiogram. Dyssynchrony by TDI was determined as the maximal time difference in peak systolic velocities from available data: 2-site basal septal to lateral delay in all 176 patients and maximum opposing wall delay using 12 segments in a subgroup of 67 patients (14,15). The standard deviation of 12-site time from QRS onset to peak systolic velocity (Yu index) was also calculated in this subgroup (6,17,19).

Radial dyssynchrony analysis. Speckle tracking of routine grayscale mid-LV short-axis images was performed as previously described in detail (23). Briefly, a minimum frame rate of 30 Hz was required with frame rate range of 30 to 100 Hz (23,25,26). An end-systolic circular region of interest was traced on the endocardial cavity (minimum cavity area), using a point-and-click approach with special care taken to adjust tracking of all endocardial segments. A second larger concentric circle was then automatically generated and manually adjusted near the epicardium. Speckle tracking automatically analyzed frame-by-frame movement of the stable patterns of natural acoustic markers, or speckles, over the cardiac cycle (26). The location shift of these acoustic markers representing tissue movement provided spatial and temporal data used to calculate regional strain vectors as change in length/initial length, with myocardial thickening toward the LV center represented as a positive value. The short-axis image was then divided into 6 standard segments with corresponding time-strain curves from each segment. A tracking score, similar to statistical standard deviation, was provided as feedback of the stability of the regional speckle tracking, and slight adjustments were

Abbreviations and Acronyms

CI = confidence interval
CRT = cardiac resynchronization therapy
EF = ejection fraction
LV = left ventricular
NYHA = New York Heart Association
ROC = receiver operator characteristic
TDI = tissue Doppler imaging

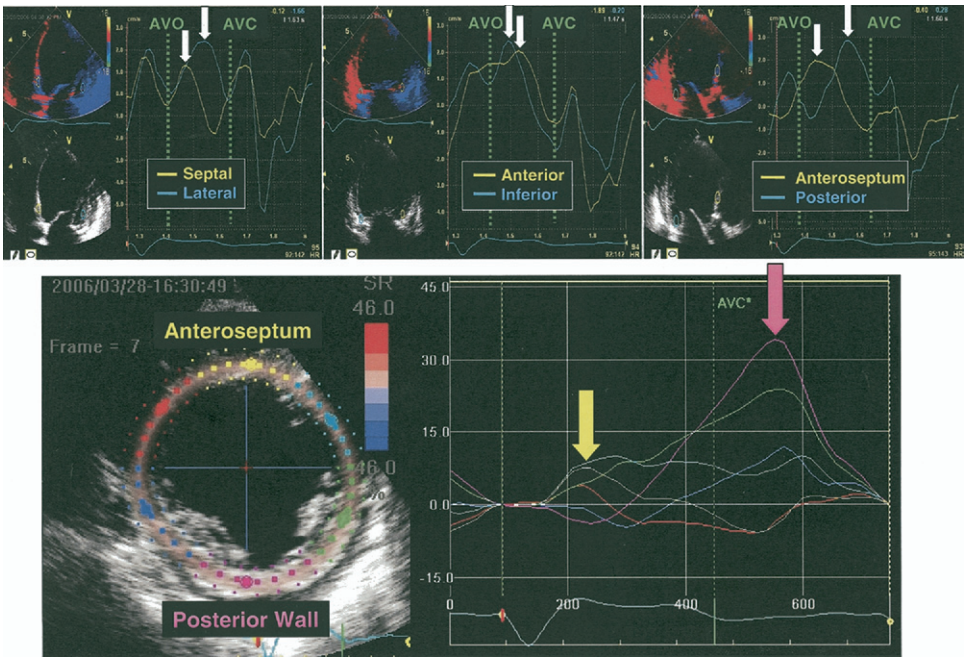

Figure 1 **Combined Analysis in a Patient With Significant Dyssynchrony Prior to Resynchronization Therapy**

(Top) Tissue Doppler time-velocity curves were derived from 12 sites: basal and mid levels from apical 4-chamber, 2-chamber, and long-axis views. Representative paired curves from 6 sites are shown illustrating a significant opposing wall delay of 110 ms **(white arrows). (Bottom)** Speckle-tracking time-strain curves of 6 radial sites are shown from the midventricular short-axis view with a significant anterior septum to posterior wall delay of 310 ms **(yellow and purple arrows).** AVC = aortic valve closing; AVO = aortic valve opening.

made to the placement of the region of interest to improve tracking stability (23,27). Because LV dyssynchrony typically involved inward septal motion early in the cardiac cycle with free wall motion appearing delayed, care was taken so that the region of interest was fine-tuned using visual assessment during the cine loop play feature to ensure that all segmental wall motions were included throughout the cardiac cycle. Significant radial dyssynchrony was defined as a time difference between the anteroseptal and posterior wall segmental peak strain ≥130 ms (23). No corrections for heart rate were performed; heart rate was in the range of 50 to 100 beats/min.

Statistical analysis. Group data were presented as mean ± standard deviation and were compared using the 2-tailed Student *t* test for paired and unpaired data. Chi-square analysis was used for variables that were not continuous. Proportional differences were evaluated with Fisher exact test. Correlations were determined with Pearson product moment correlation analysis, with 95% confidence interval (CI) calculated by Fisher r-to-z transformation. Receiver-operating characteristic (ROC) curves were constructed first for longitudinal and radial dyssynchrony individually to determine optimal sensitivities and specificities and then for the combined approach with areas under the ROC curves initially compared by logistic regression analysis. Individual predictors were further compared with the combined predictor from the areas under the ROC curves using the method of Delong et al. (28). Statistical significance was $p < 0.05$.

Results

Ventricular function response to resynchronization therapy. The study group consisted of 176 patients with complete data sets consisting of baseline TDI longitudinal dyssynchrony analysis, speckle-tracking radial dyssynchrony analysis, and follow-up volume and EF data. Follow-up LV volume and EF data were available 6 ± 3 months after CRT. All patients, except for 3 who were lost to follow-up after 3 months, had follow-up of at least 6 months, representing 98% (range 3 to 24 months). An LV functional response, defined as percentage change in EF ≥15%, was observed in 116 patients, corresponding to a 34% EF nonresponder rate (Table 1). Ninety-five percent of EF nonresponders also failed to decrease end-systolic volume by at least 15%. Nonresponders, compared with responders, were more likely to have ischemic heart disease (75% vs. 52%), slightly wider QRS duration (171 ± 27 ms vs. 162 ± 26 ms), and slightly lower baseline EF (21 ± 7% vs. 25 ± 7%); all $p < 0.05$ versus responders.

Individual and combined predictors of response. The opposing wall delay using the 2-site method was performed in all patients, using the cut-off of ≥60 ms determined by ROC curve analysis. The sensitivity was

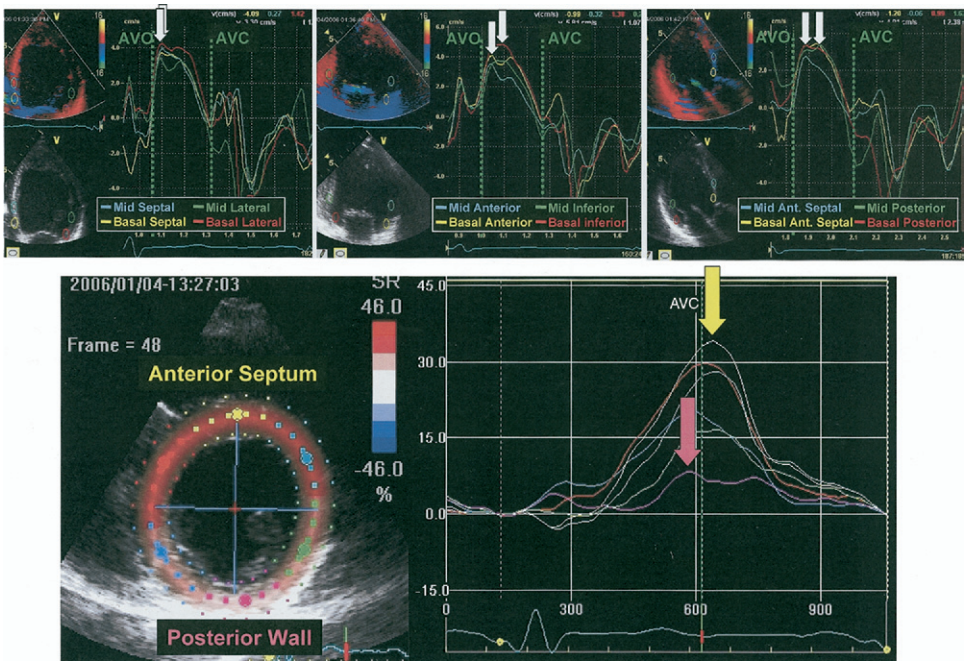

Figure 2 Combined Analysis in a Patient With No Significant Dyssynchrony Prior to Resynchronization Therapy

(Top) Tissue Doppler time-velocity curves derived from 12 sites: basal and mid levels from apical 4-chamber, 2-chamber, and long-axis views. The maximum opposing wall delay of only 50 ms was not considered to be significant **(white arrows). (Bottom)** Speckle-tracking time-strain curves of 6 radial sites are shown from the midventricular short-axis view. The maximum opposing wall delay of only 85 ms was not considered to be significant **(yellow and purple arrows)**. Abbreviations as in Figure 1.

72% (95% CI 64% to 80%) and the specificity 77% (95% CI 66% to 86%) for predicting EF response (14,15). A subgroup of 67 patients had data analysis using a 12-site TDI model with a cut-off value of ≥65 ms determined by ROC curve analysis, with a slightly better sensitivity of 84% (95% CI 70% to 93%) and specificity of 76% (95% CI 41% to 87%) for predicting EF response. The Yu index, using a 32 ms cut-off, yielded a similar sensitivity of 80% (95% CI 66% to 89%) and specificity of 78% (95% CI 55% to 91%) for predicting EF response (6,17). Speckle-tracking radial dyssynchrony, using an anterior-septal to posterior wall delay ≥130 ms determined by ROC curve analysis as previously described, had a sensitivity of 84% (95% CI 77% to 91%) and specificity of 73% (95% CI 60% to 84%) for predicting EF response (23).

Table 1 Baseline Patient Characteristics

	Responders (n = 116)	Nonresponders (n = 60)	Significance
Age (yrs)	64 ± 12	65 ± 10	NS
Female gender	31 (27%)	10 (17%)	NS
NYHA functional class (III/IV)	105/11	54/6	NS
Ischemic etiology	60 (52%)	45 (75%)	$p < 0.05$
QRS duration (ms)	171 ± 27	162 ± 26	$p < 0.05$
Ejection fraction (%)	21 ± 7	25 ± 7	$p < 0.05$

Response defined as ≥15% improvement in ejection fraction.
NS = not significant; NYHA = New York Heart Association.

The combined longitudinal and radial dyssynchrony information using these same cut-offs predicted EF response statistically better than either technique alone. The combined approach for the whole 176-patient group, using a ≥60 ms 2-site TDI cut-off and a ≥130 ms radial strain cut-off, resulted in a sensitivity of 88% and specificity of 80% for predicting EF response. The area under the ROC curve (Fig. 3) was 84.6 for the combined approach versus 77.5 for longitudinal dyssynchrony (2-site TDI method) and 80.5 for radial dyssynchrony individually (both $p < 0.0001$) (29).

Positive longitudinal and radial dyssynchrony. There were 79 patients (45%) with both longitudinal dyssynchrony positive ≥60 ms by the 2-site opposing wall delay and radial dyssynchrony positive ≥130 ms by radial strain (Fig. 4). Fifty-two percent of this group had ischemic heart disease, which was a significantly smaller proportion than seen in the other patient groups ($p < 0.05$). This pattern of both longitudinal and radial dyssynchrony positivity was associated with a high incidence of LV functional improvement, with an EF response rate of 95% (95% CI 88% to 98%). Of note, 92% (95% CI 84% to 96%) also had reverse remodeling with a decrease in end-systolic volume. Among the subgroup of 67 patients with 12-site TDI analysis with longitudinal dyssynchrony positive and radial dyssynchrony positive, a similar 93% (95% CI 81% to 98%) had an EF response to CRT.

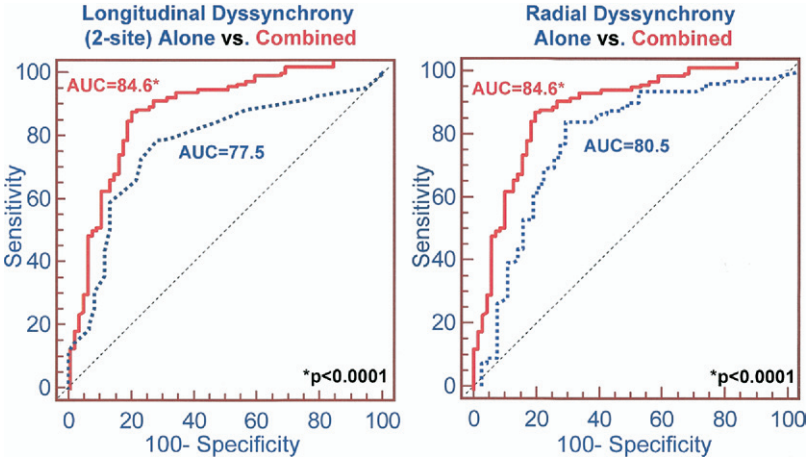

Figure 3 **Receiver-Operating Characteristic Curves for Individual Dyssynchrony Methods and the Combined Method**

The comparison with the 2-site tissue Doppler longitudinal dyssynchrony data appears on the **left**, and the comparison with radial dyssynchrony by speckle-tracking radial strain appears on the **right**. The areas under the curves (AUCs) were significantly greater with the combined approach than with either individual approach and support its favorable ability to predict ejection fraction response to cardiac resynchronization therapy. Sensitivities and specificities were 72% and 77% for the 2-site tissue Doppler method, 84% and 73% for the radial strain method, and 88% and 80% for the combined method. **Blue dashed lines** = individual dyssynchrony methods; **red solid lines** = combined method.

Negative longitudinal and radial dyssynchrony. There were 43 patients (24%) with no significant radial dyssynchrony and no significant longitudinal dyssynchrony detected by the 2-site TDI method. Their EF response rate was 21% (95% CI 11% to 35%; $p < 0.05$ vs. both-positive or heterogeneous groups). Only 9% (95% CI 4% to 22%) had reverse remodeling with improvement in end-systolic volume ($p < 0.05$ vs. both-positive or heterogeneous groups). Among the subgroup of 67 patients with 12-site TDI analysis where dyssynchrony could be more completely excluded, 10 (15%) had no dyssynchrony by either method, and only 10% (95% CI 2% to 40%) of these patients had an EF response to CRT ($p < 0.05$ vs. both-positive or heterogeneous groups). Similarly, only 10% of the same

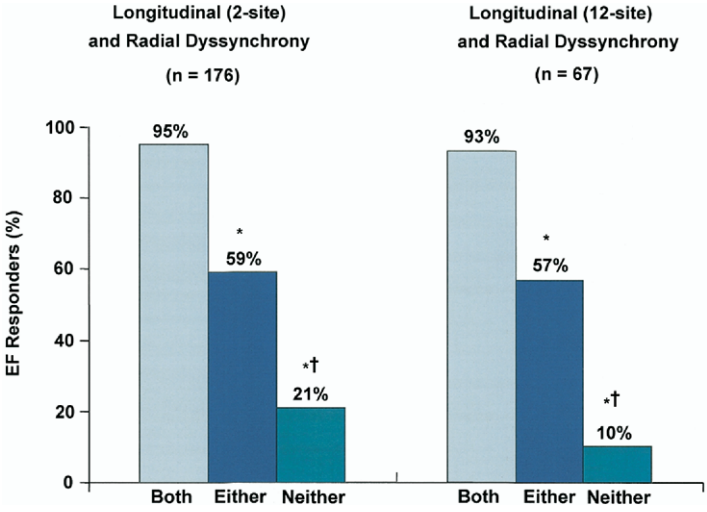

Figure 4 **Proportion of Patients Who Were EF Responders to Resynchronization Therapy**

All patients had 2-site tissue Doppler measures of longitudinal dyssynchrony along with radial strain dyssynchrony **(left)**, and a subgroup of 67 patients had 12-site tissue Doppler measures of longitudinal dyssynchrony along with radial strain dyssynchrony **(right)**. A pattern of both longitudinal and radial dyssynchrony was associated with ejection fraction (EF) response, whereas a pattern of neither longitudinal nor radial dyssynchrony was associated with EF nonresponse, particularly when the 12-site tissue Doppler method excluded dyssynchrony. A heterogeneous pattern of either longitudinal or radial dyssynchrony (but not both) had an intermediate proportion of responders. *$p < 0.05$ versus both groups; †$p < 0.05$ versus either group.

patients had a decrease in end-systolic volume ($p < 0.05$ vs. both-positive or heterogeneous groups). Accordingly, the absence of 12-site longitudinal dyssynchrony accompanied by the absence of radial dyssynchrony was associated with nonresponse to CRT.

Heterogeneous patterns of longitudinal and radial dyssynchrony. There were 54 patients (31%) with heterogeneous patterns of either positive radial dyssynchrony or positive longitudinal dyssynchrony: 19 had positive longitudinal dyssynchrony but negative radial dyssynchrony, and 35 had negative longitudinal dyssynchrony but positive radial dyssynchrony. The EF response rate of patients with heterogeneous dyssynchrony patterns was 59% (95% CI 4% to 71%), and a similar 56% had reverse remodeling with a decrease in end-systolic volume ($p < 0.05$ vs. both-positive group). Among the subgroup of 67 patients with 12-site TDI analysis, a similar 57% (95% CI 33% to 79%) had an EF response to CRT ($p < 0.05$ vs. both-positive group). Accordingly, a heterogeneous pattern of either longitudinal dyssynchrony or radial dyssynchrony, but not both, was associated with an intermediate response to CRT. Sixty-one percent of these patients with heterogeneous dyssynchrony patterns had ischemic heart disease with wall motion abnormalities versus 52% in the patients with both positive longitudinal dyssynchrony and positive radial dyssynchrony.

Clinical response to resynchronization therapy. The NYHA functional class assessments at follow-up were available in a subset of 164 patients, which was 92% of patients with follow-up EF data. The dyssynchrony patterns corresponded to similar levels of group mean NYHA functional class response to CRT as follows: patients with both positive longitudinal and radial dyssynchrony had the greatest improvement in NYHA functional class, at 1.03 ± 0.69; patients with neither longitudinal nor radial dyssynchrony had the least improvement in NYHA functional class, at 0.59 ± 0.77 ($p < 0.001$ vs. both-positive group); and patients with heterogeneous patterns of dyssynchrony had an intermediate improvement in NYHA functional class, at 0.80 ± 0.71.

Discussion

This is the first study to use a combined approach of assessing longitudinal and radial dyssynchrony to predict EF response to CRT. Patients who had both positive longitudinal dyssynchrony by TDI and positive radial dyssynchrony by speckle-tracking strain had a high likelihood of response to CRT; conversely, patients with neither longitudinal nor radial dyssynchrony had a lower likelihood of EF response. A more complete exclusion of dyssynchrony using 12 TDI sites and radial strain in a subgroup had the lowest probability of EF response to CRT. Patients with a heterogeneous pattern of either longitudinal or radial dyssynchrony, but not both, often had ischemic wall motion abnormalities and had a less predictable EF response to CRT. Similar degrees of NYHA functional class response were associated with dyssynchrony patterns, with patients with both longitudinal and radial dyssynchrony having the greatest improvements in NYHA functional class and patients with absence of dyssynchrony having the least NYHA functional class improvements. Although the TDI longitudinal velocity method and speckle-tracking radial strain methods had similar sensitivities and specificities for predicting reverse remodeling by themselves, their positive and negative predictive values were more favorable when combined.

This study extends earlier work that supports the hypothesis that markers of mechanical dyssynchrony by cardiac imaging have potential clinical utility to predict response to CRT (5,6,14–16,19,23). It demonstrates that consistent patterns of dyssynchrony in longitudinal and radial planes, either both positive or both negative, have predictive value regarding reverse remodeling after CRT. The subgroup of patients with either longitudinal or radial dyssynchrony, but not both, comprised an important 31% and were characterized by ischemic disease where the response rate was less predictable, at 59%.

Most earlier studies to quantify LV dyssynchrony and predict response to CRT have focused on longitudinal velocities by TDI (6,14,15,19) or radial wall motion by M-mode scanning or TDI strain (13,16,20,21,23). An advantage of longitudinal TDI appears to be the favorable Doppler angle of incidence for a robust signal, and multiple clinical studies have demonstrated its utility. Yu et al. used time to peak longitudinal systolic velocities from 12 sites to quantify LV dyssynchrony, demonstrating that an increased standard deviation was predictive of clinical response to CRT, and this remains to have a high sensitivity (6,17,19,30). Søgaard et al. (5) used the percentage of the LV base displaying basal longitudinal contraction delay to predict improvements in EF after CRT. Notabartolo et al. (31) also used differences in peak TDI velocities from opposing walls, including postsystolic peaks, to quantify LV dyssynchrony and predict response to CRT, although subsequent studies have shown superiority when limiting analysis to the ejection interval (17). Other studies found that a longitudinal time to peak velocity delay predicted reverse remodeling and clinical outcomes (14,15). Although TDI is useful, limitations may occur in patients with infarction or complex dyssynchrony where motion along the longitudinal axis does not completely describe LV mechanics. Magnetic resonance imaging and 3-dimensional echocardiography studies have demonstrated that circumferential myocardial dynamics may characterize LV dyssynchrony in a more sensitive manner than longitudinal dyssynchrony (21,32). The echocardiographic speckle-tracking method of Friedman and Lysyansky used in this study was not affected by angle of incidence as TDI imaging techniques are, although it is affected by frame rates and image quality (25–27,33–35). The acoustic markers, or speckles, used are the result of backscattered ultrasound from within the myocardial wall that are tracked frame-by-frame to calculate myocardial thickening, motion, or deformation. Our previous work

with radial strain by TDI or speckle tracking characterized mechanical dyssynchrony to predict response to CRT (16,23). Strain imaging may assess myocardial thickening in a manner less affected by passive translational motion or tethering and appears favorable to M-mode scanning to characterize radial mechanics (16,36). The present study demonstrated the additive role of radial mechanical assessment to longitudinal TDI in the overall more complete assessment of LV dyssynchrony. In particular, our ability to exclude significant dyssynchrony by using both a 12-site longitudinal TDI approach and a radial strain approach improved the ability to identify patients with a low chance of response to CRT.

Study limitations. The presence or absence of dyssynchrony does not completely describe response to CRT. Other important confounding variables include LV lead position, scar burden in patients with ischemic disease that cannot reverse remodel, disease progression, impact of medical therapy, and spontaneous improvement (22,37,38). The present study extends the evaluation of dyssynchrony to multiple anatomic LV planes but cannot account for these other potential factors. This study highlights the complexity of dyssynchrony patterns that may occur in a large group of patients referred for CRT, but EF response appears to be more clearly associated with homogeneously positive or negative dyssynchrony patterns. A limitation is that long-term clinical outcome data, such as exercise capacity, quality of life assessment, or survival, were not part of the study. We chose to use EF response and reverse remodeling by end-systolic volume as the markers for patient response in this study, because they are objective measures with significant prognostic importance (10,11). Several earlier studies have used similar echocardiographic measures (5,6,15,18,19,23). Another limitation is that only a subgroup of 67 patients had a more complete 12-site TDI data analysis. There are limitations with TDI data analysis, including signal noise affecting peak velocity measures and ambiguous time-velocity curves. Care was taken to move the region of interest within the segment and determine the most reproducible peak velocity with a uniform approach in all patients. Limitations of speckle tracking include endocardial border tracing, where care must be taken to manually fine-tune the region of interest to capture the early anterior septal motion in left bundle branch block and adjust its width for dyssynchrony analysis before generating and measuring regional strain.

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