

Usefulness of Echocardiographic Dyssynchrony in Patients With Borderline QRS Duration to Assist With Selection for Cardiac Resynchronization Therapy

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OBJECTIVES To test the hypothesis that echocardiographic dyssynchrony may assist in the selection of patients with borderline QRS duration for cardiac resynchronization therapy (CRT).

BACKGROUND Although echocardiographic dyssynchrony is currently not recommended to select patients with QRS duration widening for CRT, its utility in patients with borderline QRS widening is unclear.

METHODS Of 221 consecutive heart failure patients with an ejection fraction (EF) $\leq 35\%$ referred for CRT, 86 had a borderline QRS duration of 100 to 130 ms (115 ± 8 ms) and 135 patients had wide QRS > 130 ms (168 ± 26 ms). Dyssynchrony was assessed using interventricular mechanical delay, tissue Doppler imaging longitudinal velocity opposing wall delay, and speckle tracking radial strain for septal to posterior wall delay. Response to CRT was defined as $\geq 15\%$ increase in EF, and reverse remodeling as $\geq 10\%$ decrease in end-systolic volume.

RESULTS There were 201 patients with baseline quantitative echocardiographic data available, and 187 with follow-up data available 8 ± 5 months after CRT. A smaller proportion of borderline QRS duration patients (53%) were EF responders compared with 75% with widened QRS ($p < 0.05$). Interventricular mechanical delay ≥ 40 ms and opposing wall delay ≥ 65 ms were predictive of EF response in the wide QRS duration group, but not the borderline QRS duration group. Speckle tracking radial dyssynchrony ≥ 130 ms, however, was predictive of EF response in both wide QRS interval patients (88% sensitivity, 74% specificity) and borderline QRS interval patients (79% sensitivity, 82% specificity) and associated reverse remodeling with reduction in end-systolic volume ($p < 0.0005$).

CONCLUSIONS Radial dyssynchrony by speckle tracking strain was associated with EF and reverse remodeling response to CRT in patients with borderline QRS duration and has the potential to assist with patient selection. (J Am Coll Cardiol Img 2010;3:132–40) © 2010 by the American College of Cardiology Foundation

Current clinical guidelines support cardiac resynchronization therapy (CRT) for symptomatic heart failure patients with a depressed ejection fraction (EF) and electrocardiographic widened QRS duration ≥ 120 ms (1). Although imaging measures of mechanical dyssynchrony have shown promise to improve patient response rate to CRT, they have not yet replaced widened QRS duration as a surrogate for mechanical dyssynchrony in current practice guide-

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lines (2–8). Furthermore, the existing studies using dyssynchrony for selection of patients for CRT with narrow QRS interval have been inconclusive (9–11). Although this field continues to evolve, scenarios currently exist in clinical practice in which a patient may be considered a borderline candidate for CRT, and imaging markers of mechanical dyssynchrony may assist in patient selection. A recent consensus report by the American Society of Echocardiography and the Heart Rhythm Society advocated echocardiographic dyssynchrony as a possible adjunct to the selection criteria for CRT in patients with borderline QRS duration (12). Because data are limited in this specific patient group, our objective was to test the hypothesis that echocardiographic measures of mechanical dyssynchrony may assist in the selection of patients for CRT with borderline QRS duration.

METHODS

The study included 221 consecutive patients in sinus rhythm with left ventricular (LV) ejection fraction (EF) $\leq 35\%$ and New York Heart Association functional class III or IV heart failure despite optimal pharmacological therapy referred for CRT. The protocol was approved by the Institutional Review Board on Biomedical Research, and all patients gave informed consent consistent with protocol. Patients with borderline QRS duration were prospectively defined as those with QRS interval width between 100 ms and 130 ms inclusive. The borderline group consisted of 86 patients. The mean age was 60 ± 11 years, 24 (28%) patients were female, the mean EF was $24 \pm 5\%$, the mean QRS duration was 115 ± 8 ms, and 55% had ischemic cardiomyopathy. The remaining 135 CRT patients with widened QRS duration >130 ms had similar demographic data: mean age 64 ± 12 years, 43 female (32%), mean EF $24 \pm 6\%$, 58% ischemic cardiomyopathy, but greater

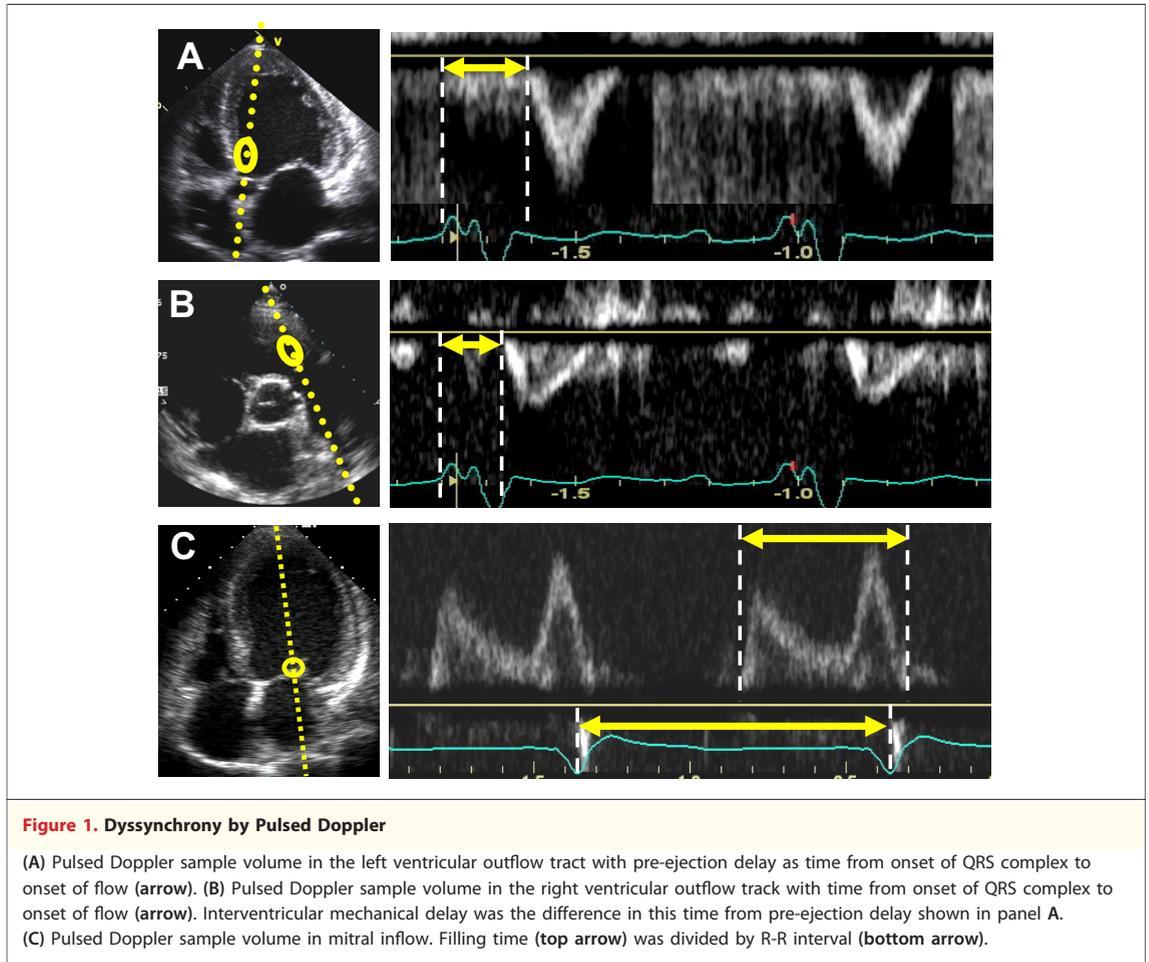
mean QRS duration of 168 ± 26 ms, by definition. A biventricular pacing system was implanted with a standard right ventricular apical lead and left ventricular lead positioned in a posterior or lateral epicardial vein through the coronary sinus. All patients were receiving optimal pharmacological therapy, including angiotensin-converting enzyme inhibitors, β -blockers, and spironolactone, if tolerated.

All echocardiographic studies and off-line analyses were performed using standard imaging systems (VIVID 7; GE-Vingmed, Horton, Norway, or Siemens Medical Solutions, Mountain View, California). Briefly, routine digital gray-scale 2-dimensional and tissue Doppler imaging cine loops were obtained, including mid-LV short axis views at the level of the papillary muscle, routine apical views, and pulsed Doppler interrogation of the right ventricular and LV outflow tract as well as mitral inflow. EF was calculated by biplane Simpson's rule (13). Routine pulsed Doppler was used as previously described (7,12). Left ventricular pre-ejection delay (PED) was determined as the interval from the onset of the electrocardiographic QRS complex to the onset of LV ejection velocity in the outflow tract (Fig. 1). Interventricular mechanical delay (IVMD) was determined as the time difference in onset of right ventricular ejection velocity to PED. The filling time ratio (FT/RR) was calculated from the mitral inflow velocity duration from the onset of E wave to the end of A wave divided by the R-R interval and expressed as a percentage. Pre-defined cutoff values considered consistent with significant dyssynchrony were ≥ 140 ms for PED, ≥ 40 ms for IVMD, and $\leq 40\%$ for FT/RR (12,14).

Intraventricular dyssynchrony was determined using tissue Doppler imaging and/or speckle tracking as previously described in detail (6,12,15,16). For tissue Doppler imaging, regions of interest (7×15 mm) were placed in the basal and midventricular segments for each of the 3 standard views for 12-site time to peak velocity analysis. Manual adjustments were made so that the regions of interest had the most reproducible peak velocities (Fig. 2). Segmental time to peak systolic wave velocity was calculated from the onset of the QRS complex. For longitudinal speckle tracking by velocity vector imaging, endocardial to mid-wall tracing of routine digital cineloops was performed. Velocity was determined toward a point of reference placed at the LV apex for generation of time-velocity curves from all 3 apical views. Longitudinal dyssynchrony was defined as the maximal

ABBREVIATIONS AND ACRONYMS

CRT	= cardiac resynchronization therapy
EF	= ejection fraction
FT/RR	= filling time ratio
IVMD	= interventricular mechanical delay
LV	= left ventricular
PED	= pre-ejection delay



difference in peak velocity at basal and mid segments in opposing walls per view. Significant longitudinal dyssynchrony was defined as the maximal time difference between opposing walls in one view ≥ 65 ms, or the 12-site time to peak SD (Yu Index) of ≥ 33 ms. For uniformity, the same cutoffs were used for either software approach (3,4).

Speckle tracking of routine grayscale mid-LV short-axis images was also performed as previously described to assess radial dyssynchrony (6,16,17). Briefly, an end-diastolic circular region of interest was traced slightly within the endocardial cavity, 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. Time to peak segmental radial strain was determined from the highest peak positive strain value throughout the cardiac cycle, beginning slightly before the onset of the QRS complex to include very early mechanical activation (17) (Fig. 3). Radial dyssynchrony was then determined by measuring the time difference between

the anteroseptal and posterior wall with ≥ 130 ms pre-defined as significant (6,16).

Group data were presented as means \pm SD and were compared using the Student *t* test for paired and unpaired data. Proportional differences were evaluated using the Fisher exact test, and the chi-square test was used for noncontinuous variables. Receiver-operator characteristic (ROC) curves were constructed for dyssynchrony variables to determine the sensitivity, specificity, and areas under the curves at pre-defined cutoffs. Least-squares linear regression analysis was used to determine potential associations between IVMD with longitudinal and radial opposing wall delays. Response to CRT was prospectively defined as a relative increase in EF of $\geq 15\%$ from baseline to 6-month follow-up, and reverse remodeling was defined as a decrease in end-systolic volume $\geq 10\%$, as used in previous studies (6,15,16). All follow-up EF and volume data were acquired by investigators who were blind to baseline data.

Table 1. Prevalence of Dyssynchrony in Borderline QRS Duration and Wide QRS Duration Patients

Dyssynchrony Index	Cutoff	Wide QRS Duration (n = 123)	Borderline QRS Duration (n = 78)	Significance
Pre-ejection delay	≥140 ms	73/106 (69%)	16/70 (23%)	<0.0001
IVMD	≥40 ms	53/98 (54%)	11/61 (18%)	<0.001
FT/RR	≤40%	29/90 (32%)	7/60 (12%)	<0.005
Longitudinal opposing wall delay	≥65 ms	78/110 (70%)	38/67 (58%)	NS
Yu Index	≥33 ms	76/118 (64%)	35/67 (52%)	NS
Radial septal to posterior wall delay	≥130 ms	80/104 (71%)	36/76 (47%)	<0.05

IVMD = interventricular mechanical delay; FT/RR = filling time ratio; NS = not significant.

RESULTS

Of the 221 consecutive patients referred for CRT, 20 (9%) had poor echocardiographic windows with technically inadequate images and were prospectively excluded from all subsequent analyses. Accordingly, the study group consisted of 201 patients: 78 patients with borderline QRS duration between 100 and 130 ms and 123 patients with wide QRS duration >130 ms. All baseline demographic data were similar between groups, except for QRS duration by definition. Follow-up echocardiographic data were available on 187 of these patients 8 ± 5 months after CRT; 72 in the borderline QRS duration group and 115 in the wide QRS duration group.

With the exception of longitudinal opposing wall delay by tissue Doppler imaging, there was significantly less prevalent dyssynchrony using pre-defined cutoff values in the borderline QRS duration patients compared with the wide QRS duration patients (Table 1). PED, IVMD, and FF/RR occurred infrequently in the borderline QRS duration patients. In the borderline QRS duration group, IVMD was weakly associated with longitudinal velocity opposing wall delay ($r = 0.25$, $p < 0.01$), but more closely associated with radial strain dyssynchrony ($r = 0.56$, $p <$

0.0001). Among the 187 patients with follow-up LV volume and EF data, a significantly smaller proportion of patients in the borderline QRS duration group were CRT responders (38 [53%] compared with 86 [75%] patients). The association of dyssynchrony indices with EF response is shown in Table 2, and the individual ROC curves are shown in Fig. 4. Among the pulsed Doppler dyssynchrony markers, only IVMD seemed to be significantly predictive of EF response in the wide QRS duration group. Neither IVMD, PED, nor FT/RR was found to be predictive of EF response in the borderline QRS duration group. Although these pulsed Doppler indexes at the pre-determined cutoff values were found to have high specificities, their low sensitivities resulted in relatively modest area under the ROC curve values. Longitudinal dyssynchrony by either opposing wall delay or Yu Index was predictive of EF response in the wide QRS duration group, but not in the borderline QRS duration group.

The presence of radial dyssynchrony by speckle tracking was the most predictive of EF response in both wide QRS duration and borderline QRS duration patient groups (Fig. 5). Speckle tracking radial dyssynchrony ≥130 ms was predictive of EF response in the wide QRS duration patients (88%

Table 2. Association of Dyssynchrony Indexes With Ejection Fraction Response to Resynchronization Therapy in Wide QRS Duration and Borderline QRS Duration Patients

Dyssynchrony Index	Cutoff	Wide QRS Duration (n = 115)		Borderline QRS Duration (n = 72)	
		Sensitivity	Specificity	Sensitivity	Specificity
Pre-ejection delay	≥140 ms	76%	50%	31%	83%
IVMD	≥40 ms	66%	85%	23%	92%
FT/RR	≤40%	31%	67%	15%	96%
Longitudinal opposing wall delay	≥65 ms	78%	76%	64%	54%
Yu Index	≥33 ms	72%	64%	55%	57%
Radial septal to posterior wall delay	≥130 ms	88%	74%	79%	82%

Abbreviations as in Table 1.

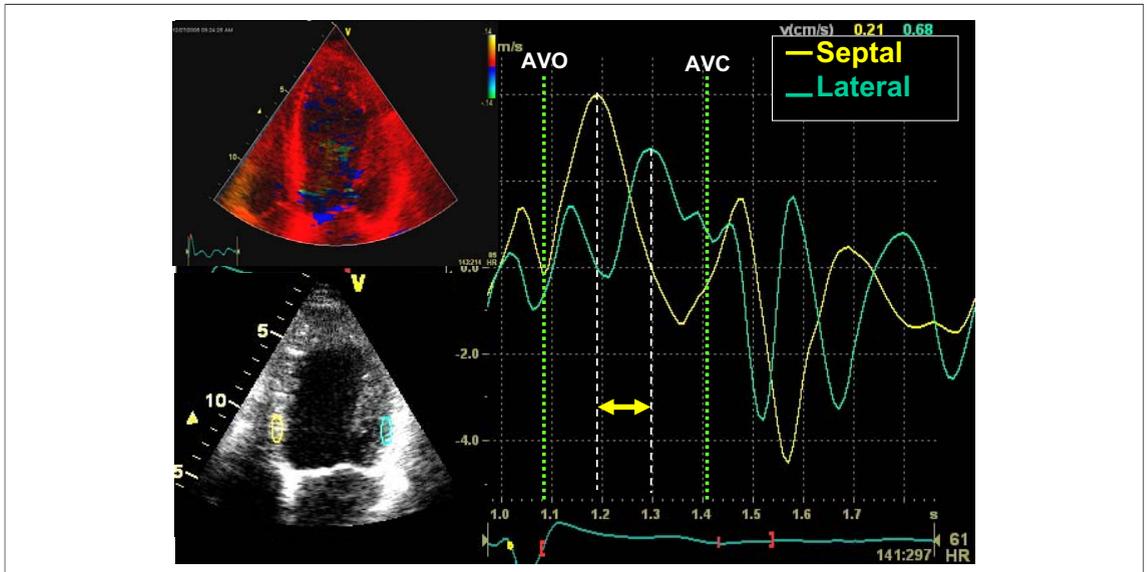


Figure 2. Tissue Doppler Velocity Opposing Wall Delay
 Time-velocity plots from septum (yellow line) and lateral wall (blue line) using the apical 4-chamber view and demonstrating the opposing wall delay in peak velocities (arrow) during the ejection interval. AVC = aortic valve closure; AVO = aortic valve opening.

sensitivity, 74% specificity). Although less sensitive, radial dyssynchrony was a relatively specific predictor of EF response in the borderline QRS duration patients (79% sensitivity, 82% specificity). Radial dyssynchrony was also associated with significant reverse remodeling demonstrated by reductions in end-systolic volume from 155 ± 72 ml to 119 ± 71 ml in the wide QRS duration group and 155 ± 56

to 119 ± 57 ml in the borderline QRS duration group (both $p < 0.0005$). Borderline QRS duration patients who lacked radial dyssynchrony did not have a significant reverse remodeling response to CRT (Fig. 6).

Intraobserver variability for determining routine pulsed Doppler dyssynchrony measures was $3 \pm 4\%$ and interobserver variability was $4 \pm 5\%$. Intraob-

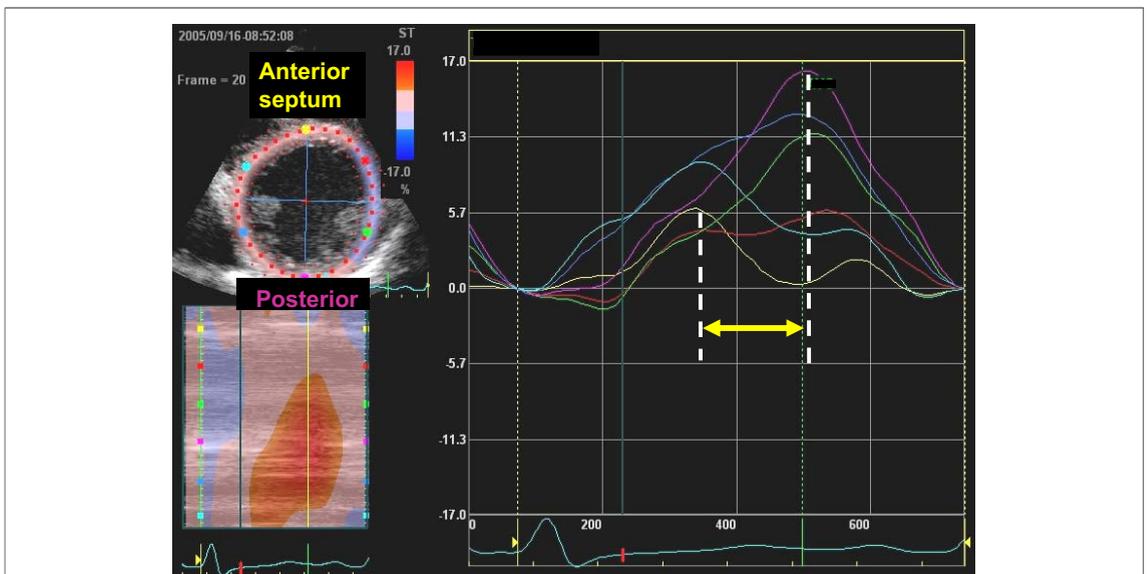


Figure 3. Speckle Tracking Radial Strain
 Time strain plots from the mid-ventricular short-axis view demonstrating anterosseptal (yellow line) to posterior wall (purple line) delay in peak strain (arrow).

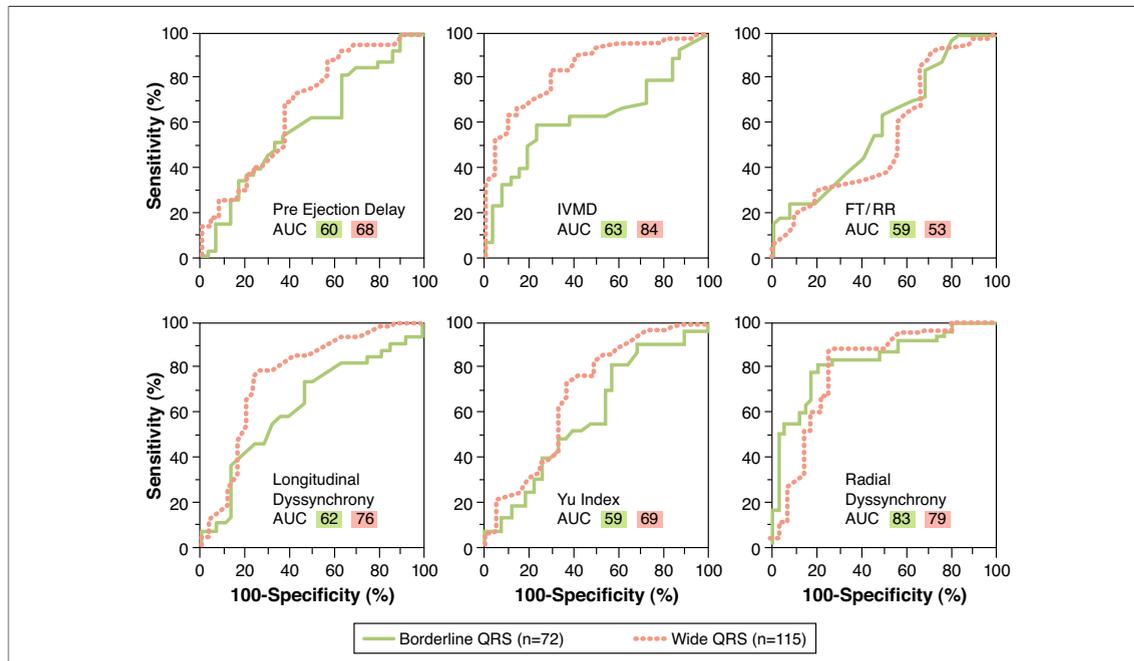


Figure 4. Receiver-Operator Characteristic Curves

Analysis of 6 dyssynchrony indexes and their association with ejection fraction response to cardiac resynchronization therapy in borderline QRS duration patients (solid green lines) and wide QRS duration patients (dashed pink lines). Area under the curve (AUC) values appear in each plot. FT/RR = filling time ratio; IVMD = interventricular mechanical delay.

server variability for determining tissue Doppler imaging longitudinal dyssynchrony was $6 \pm 7\%$ and interobserver variability was $8 \pm 7\%$. Intraobserver variability for determining speckle tracking strain data from the identical digital cineloops used for dyssynchrony was $8 \pm 7\%$ and interobserver variability was $9 \pm 7\%$.

DISCUSSION

This study of a large series of consecutive patients referred for CRT demonstrates that differences in mechanical dyssynchrony and response to CRT in patients with borderline QRS duration of 100 to 130 ms compared with those with widened QRS

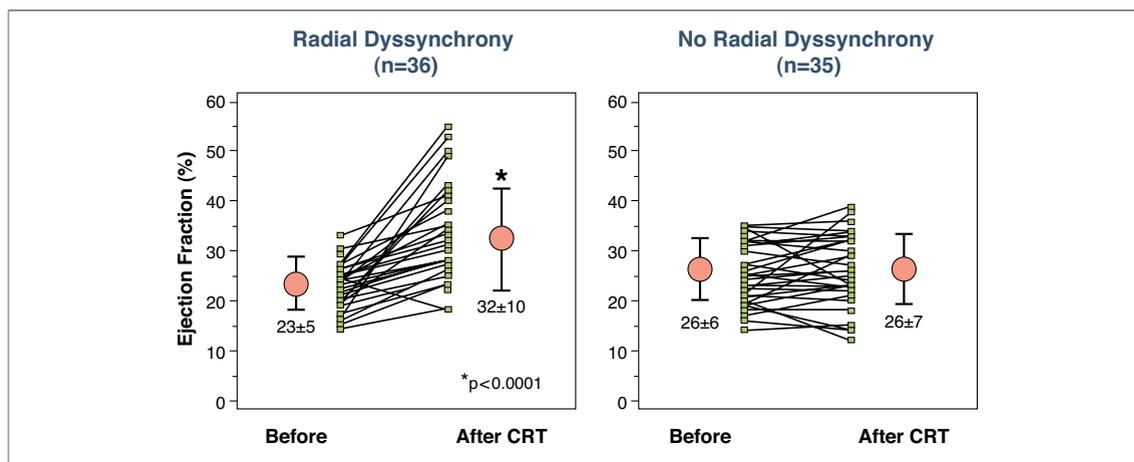
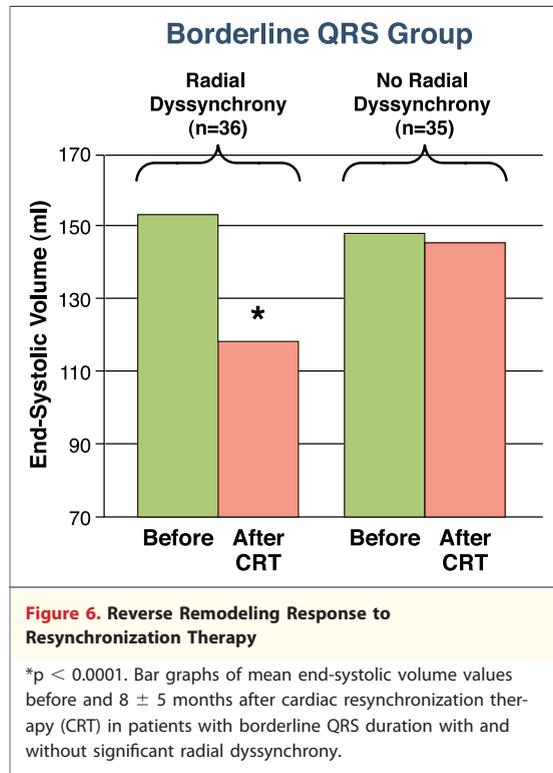


Figure 5. Ejection Fraction Response to Resynchronization Therapy

Line plots of ejection fraction values before and 8 ± 5 months after cardiac resynchronization therapy (CRT) in patients with borderline QRS duration with and without significant radial dyssynchrony.



duration >130 ms. Specifically, the prevalence of dyssynchrony by PED, IVMD, FT/RR, or radial septal to posterior wall delay was less in the borderline QRS duration patients compared with the wide QRS duration patients and the overall EF response rate to CRT was less in the borderline QRS duration patients. The markers of IVMD and longitudinal dyssynchrony were comparatively more predictive of response in the wide QRS duration patients. However, radial strain dyssynchrony by speckle tracking echocardiography was associated with response to CRT in both borderline QRS and wide QRS duration patients, with significant improvements observed in EF and end-systolic volume. These observations have the potential to extend the use of echocardiographic dyssynchrony assessment, in particular by speckle tracking radial strain, to patients with borderline QRS duration who are being considered as potential candidates for CRT.

Several clinical trials have previously confirmed that the majority of patients with heart failure, reduced EF, and widened QRS duration benefit from CRT (18–22). However, it has been shown that approximately 25% to 30% of patients with wide QRS duration do not seem to benefit from CRT, and several echocardiography studies have

associated lack of mechanical dyssynchrony with nonresponse to CRT (2–6,16,23). A recent multicenter study of the predictors of responders to CRT, known as the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study, failed to show conclusively that a single echocardiographic dyssynchrony measure can be highly predictive of response (8). Although problems with technical acquisition and variability interfered with precise interpretation of the results of the PROSPECT study, the conclusion was that routine clinical selection criteria for CRT, including QRS duration, have not yet been replaced (12,24,25). Because the benefits of CRT have been of great clinical significance, it is desirable to provide this therapy to individuals who may possibly benefit from CRT. Accordingly, clinicians have used dyssynchrony information to assist in patient selection for CRT in patients with borderline QRS duration for compassionate use, recognizing that the 120-ms cutoff may be somewhat arbitrary. A potential mechanistic explanation for why radial dyssynchrony was more predictive of response than longitudinal dyssynchrony in the borderline QRS duration patients is that the radial pattern of dyssynchrony is more pronounced than in the longitudinal dimension, as shown by Helm et al. (26) in an elegant tagged cine magnetic resonance study. They observed that circumferential strain in the short-axis plane was much more sensitive to detect dyssynchrony than longitudinal strain. Because the degree of dyssynchrony may be more subtle in patients with narrow QRS duration, it is possible that radial dyssynchrony was more predictive than longitudinal dyssynchrony, although the precise reason was uncertain.

Only 1 randomized CRT trial, known as Re-thinQ (Resynchronization Therapy in Patients with Narrow QRS), was performed to date in heart failure patients with narrow QRS duration <130 ms and dyssynchrony, primarily measured by tissue Doppler imaging (9). This study failed to reach statistical significance for the primary end point of peak myocardial oxygen consumption; however, CRT seemed to benefit patients in terms of New York Heart Association functional class and 6-min walk distance in the nonischemic subgroup. The authors concluded that CRT did not benefit patients with narrow QRS duration; however, the subgroup of patients with borderline QRS duration of 120 to 130 ms showed significant benefit with CRT in the primary end point. Accordingly, the interaction of QRS duration, the presence of me-

chanical dyssynchrony, and the response to CRT is not entirely clear in patients with borderline QRS duration. The results of this study are in agreement with RethinQ results in that the response to CRT seems to be less prevalent in patients with narrower QRS duration compared with clearly widened QRS duration and adds the marker of radial dyssynchrony as a potential predictor of response to CRT in the borderline QRS duration patients.

Study limitations. An important limitation of this study is that the decision for CRT implantation was made by clinicians caring for these patients, and this was not a randomized clinical trial. Accordingly, the echocardiographic dyssynchrony results may have influenced the decision for CRT implantation in the borderline QRS duration patients. However, because we studied several measures of interventricular and intraventricular dyssynchrony as part of our baseline assessment, it is unlikely that an individual measure would selectively influence the decision for implantation. The true value of echocardiographic measures of dyssynchrony in assisting patient selection for CRT among patients who are viewed as borderline candidates because of borderline QRS duration must be tested further in a clinical trial in a larger series. Another limitation of this study is that change in EF and end-systolic volumes were used to define response to CRT and clinical outcome measures such as 6-min walk distance and quality-of-life questionnaires were not systematically performed as part of this study. Measures of reverse LV remodeling have been shown to be objective measures of response to CRT and associated with patient survival, so these measures seem to be clinically relevant (16,27). There are several possible technical limitations with variability in both tissue Doppler imaging and speckle tracking analysis (8,16). These data were derived from a single laboratory with a small group of investigators who perform off-line analysis with a very similar approach. A possible limitation is that the dyssynchrony analysis was performed using software from 2 different vendors; however, we recently demon-

strated that they produce similar results (17). Another important limitation is that factors other than dyssynchrony affect LV functional and reverse remodeling response, including contractile reserve, arrhythmias, scar burden, and lead location in relation to scar and area with latest activation (28–32). An analysis of all these factors in comparison with radial dyssynchrony in these patients was beyond the scope of the present investigation, but is warranted for future studies. Technological advances in echocardiography hardware and software continue, but training and experience continue to be important to achieve reproducible results.

CONCLUSIONS

This study demonstrated that echocardiographic dyssynchrony was less prevalent in patients with borderline QRS duration as compared with those with wide QRS duration using routine pulsed Doppler measures or speckle tracking radial septal-to-posterior wall delay. Although IVMD and longitudinal dyssynchrony were comparatively more predictive of CRT response in patients with wide QRS duration, radial dyssynchrony by speckle tracking was associated with CRT response in both borderline QRS and wide QRS duration patients. These observations have the potential to extend the use of echocardiographic dyssynchrony assessment, in particular by speckle tracking radial strain, to patients with borderline QRS duration to assist with selection for CRT.

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