Relationship of Echocardiographic Dyssynchrony to Long-Term Survival After Cardiac Resynchronization Therapy

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Background—The ability of echocardiographic dyssynchrony to predict response to cardiac resynchronization therapy (CRT) has been unclear.

Methods and Results—A prospective, longitudinal study was designed with predefined dyssynchrony indexes and outcome variables to test the hypothesis that baseline dyssynchrony is associated with long-term survival after CRT. We studied 229 consecutive class III to IV heart failure patients with ejection fraction \( \leq 35\% \) and QRS duration \( \geq 120 \) milliseconds for CRT. Dyssynchrony before CRT was defined as tissue Doppler velocity opposing-wall delay \( \geq 65 \) milliseconds, 12-site SD (Yu Index) \( \geq 32 \) milliseconds, speckle tracking radial strain anteroseptal-to-posterior wall delay \( \geq 130 \) milliseconds, or pulsed Doppler interventricular mechanical delay \( \geq 40 \) milliseconds. Outcome was defined as freedom from death, heart transplantation, or left ventricular assist device implantation. Of 210 patients (89\%) with dyssynchrony data available, there were 62 events: 47 deaths, 9 transplantations, and 6 left ventricular assist device implantations over 4 years. Event-free survival was associated with Yu Index \((P=0.003)\), speckle tracking radial strain \((P=0.019)\), and interventricular mechanical delay \((P=0.003)\). When adjusted for confounding baseline variables of ischemic origin and QRS duration, Yu Index and radial strain dyssynchrony remained independently associated with outcome \((P<0.05)\). Lack of radial dyssynchrony was particularly associated with unfavorable outcome in those with QRS duration of 120 to 150 milliseconds \((P=0.002)\).

Conclusions—The absence of echocardiographic dyssynchrony was associated with significantly less favorable event-free survival after CRT. Patients with narrower QRS duration who lacked dyssynchrony had the least favorable long-term outcome. These observations support the relationship of dyssynchrony and CRT response. (Circulation. 2010;122:1910-1918.)

Key Words: echocardiography ■ heart failure ■ pacemakers ■ survival

Cardiac resynchronization therapy (CRT) is an important therapy for patients with symptomatic heart failure, widened ECG QRS, and reduced ejection fraction (EF).\(^1\)\(^-\)\(^3\) Despite significant morbidity and mortality benefits from CRT, approximately one third of patients do not appear to benefit from therapy. The prevailing concept is that correction of mechanical dyssynchrony is the principal mechanism for CRT and that patients who lack significant dyssynchrony despite having QRS widening may not respond.\(^4\)\(^-\)\(^8\) Although a large body of literature supports echocardiographic dyssynchrony as a prognostic marker for patient response to CRT, the recent Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study failed at its attempt to define the optimal echocardiographic dyssynchrony approach.\(^9\)\(^,\)\(^10\) Furthermore, PROSPECT raised concerns about the feasibility and reproducibility of echocardiographic methods.\(^11\)\(^,\)\(^12\) As a result, there is no consensus as to the predictive value of echocardiographic dyssynchrony, and current clinical selection criteria for CRT include QRS widening as a surrogate for dyssynchrony. Acknowledged limitations of PROSPECT include confounding variables of different acquisition and analysis approaches, suboptimal end points, and follow-up limited to 6 months after CRT.\(^11\)\(^,\)\(^12\) Accordingly, our objective was to test the hypothesis that echocardiographic dyssynchrony is associated with outcome after CRT. We used a prospective longitudinal study design with unified echocardiographic analysis and predefined important end points of death, cardiac transplantation, or left ventricular (LV) assist device (LVAD) implantation after CRT.

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Methods

We prospectively studied a series of 229 consecutive heart failure patients referred for routine CRT indications. The protocol was approved by the Institutional Review Board on Biomedical Research, and all patients gave informed consent consistent with this protocol. All patients had New York Heart Association functional class III or IV heart failure despite optimal pharmacological therapy,
QRS duration ≥120 milliseconds, and LV EF ≤35%. Optimal pharmacological therapy included angiotensin-converting enzyme inhibitors or receptor blockers, β-blockers, and spironolactone as tolerated. A biventricular pacing system was implanted with a standard right ventricular (RV) apical lead and LV lead positioned through the coronary sinus in an epicardial vein targeting posterolateral or lateral branches. In the event that a lead could not be placed transvenously because of anatomic constraints, epicardial LV leads were surgically implanted with a minithoracotomy in a small subset (<5%) of patients.

Echocardiography

All echocardiographic studies and offline analyses were performed with a standard imaging system and software (VIVID 7, EchoPac BT08 GE-Vingmed, Horton, Norway). Briefly, routine digital 2-dimensional and tissue Doppler imaging (TDI) cine loops were obtained, including mid-LV short-axis views at the level of the papillary muscle, apical views, and pulsed Doppler of the RV and LV outflow. Mitral regurgitation was assessed semiquantitatively by color Doppler jet area and vena contract width. EF was calculated by the biplane Simpson rule. Intraventricular dyssynchrony was determined by TDI and speckle tracking as previously described in detail (Figure 1). TDI regions of interest (7×15 mm) were placed in the basal and mid-LV segments for the 3 standard views for 12 sites, adjusted for the most reproducible peak systolic velocities and time to peak calculated from the onset of the QRS.6,8,15 Longitudinal dyssynchrony was opposing-wall delay (OWD), defined as the maximal difference in peak velocity at basal and mid segments in opposing walls for each view. The Yu Index was calculated as the 12-site SD. OWD was predefined as significant as the Yu Index of ≥32 milliseconds.6,8,16

Speckle tracking of routine grayscale mid-LV short-axis images was performed as previously described to assess radial dyssynchrony. 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 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. Radial dyssynchrony was determined as the time difference between the anteroseptal and posterior walls with ≥130 milliseconds predefined as significant.6,15 Interventricular dyssynchrony was calculated from routine pulsed Doppler as previously described.6,16 LV pre-ejection delay was
attempted echocardiographic studies, 19 (8%) had technically poor windows and were excluded from all further analysis. Of these 210 patients, TDI analysis for the OWD and Yu Index was feasible in 205 (96%); speckle tracking radial strain was feasible in 197 (91%). Routine pulsed Doppler for IVMD was added to the protocol after the first 27 patients and was feasible in 180 of 202 (90%). From 20 randomly selected studies, intraobserver variability for determining routine pulsed Doppler dyssynchrony measures was ±3 milliseconds (±4%), and interobserver variability was 5±5 milliseconds (±4%). Intraobserver variability for dyssynchrony by TDI using identical digital cine loops was 6±5 milliseconds (±7%), and interobserver variability was 8±7 milliseconds (±7%). Intraobserver variability for dyssynchrony by speckle tracking strain from the identical digital cine loops was 17±10 milliseconds (±7%), and interobserver variability was 22±14 milliseconds (±7%).

### Dyssynchrony and Baseline Characteristics

The baseline characteristics of the 210 patients with echocardiographic data are shown in the Table. The prevalence of TDI dyssynchrony by OWD ≥65 milliseconds and Yu Index ≥32 milliseconds was 78% and 72%, respectively. The 205 patients with and without dyssynchrony by TDI indexes had similar age, proportion of female gender, EF, mitral regurgitation, and QRS duration. However, significant dyssynchrony was observed less often in those with ischemic disease compared with nonischemic disease as follows: 53% versus 71% for OWD ≥65 milliseconds and 51% versus 73% for Yu Index ≥32 milliseconds (all P<0.05). The 197 patients with and without significant radial dyssynchrony ≥130 milliseconds by speckle tracking radial strain also had similar age, percent of female gender, EF, and mitral regurgitation. Patients with ischemic disease had less prevalent radial dyssynchrony than those with nonischemic disease, 50% versus 76%, respectively (P<0.05). QRS duration was greater in patients with significant radial dyssynchrony (161±26 milliseconds) compared with those without radial dyssynchrony (148±23 milliseconds; P<0.05). The 180 patients with IVMD data available with and without dyssyn-
chrony had similar age, percent of female gender, EF, and mitral regurgitation. Once again, patients with ischemic disease had less prevalent dyssynchrony by IVMD 40 milliseconds compared with those with nonischemic disease (43% versus 69%). Similar to radial dyssynchrony, significant IVMD dyssynchrony was associated with wider QRS duration (171±27 milliseconds versus 147±21 milliseconds in those without significant IVMD; P<0.05).

Outcome Events and Dyssynchrony
Follow-up for the 210 patients with available echocardiographic dyssynchrony data was for a period of 4 years. CRT implantations occurred throughout this period in this single-center experience, and the numbers reflect the variable follow-up duration, ranging from a minimum of 1 to 4 years. During this period, 62 outcome events occurred, including 47 deaths, 9 transplantations, and 6 LVAD implantations. Notably, one of these unfavorable clinical events occurred <6 months after CRT implantation in 30 patients. Patients with IVMD ≥40 milliseconds had a significantly more favorable outcome after CRT than those with IVMD <40 milliseconds (P=0.019; Figure 2). OWD by TDI using our predefined cutoff of ≥65 milliseconds had a trend for a better outcome, but this only came close to statistical significance (P=0.075; Figure 3A) We then performed posthoc analysis with an OWD cutoff of ≥80 milliseconds, which was associated with a statistically significant more favorable event-free survival after CRT (P=0.011; Figure 3B). The Yu Index as prospectively defined (≥32 milliseconds) was predictive of survival free from transplantation or LVAD implantation (P=0.003; Figure 4). Radial dyssynchrony ≥130 milliseconds by speckle tracking was highly associated with event-free survival after CRT (P=0.003; Figure 5). Importantly, when adjusted for the covariates of ischemic pathogenesis and QRS duration using a Cox proportional-hazards model, the Yu Index and radial strain remained independently predictive of event-free survival (P<0.05). The hazard ratio of radial dyssynchrony for predicting survival was 2.21 (95% CI, 1.35 to 4.79; P=0.003). When adjusted for QRS, the instantaneous relative risk was 0.55 (95% CI, 0.32 to 0.94; P=0.03). When adjusted for ischemic disease, the instantaneous relative risk was 0.53 (95% CI, 0.31 to 0.92; P=0.03). The hazard ratio of the Yu Index for predicting survival was 2.13 (95% CI, 1.38 to 4.46; P=0.003). When adjusted for QRS, the instantaneous relative risk was 0.51 (95% CI, 0.30 to 0.85; P=0.01), and when adjusted for ischemic disease, the instantaneous relative risk was 0.53 (95% CI, 0.31 to 0.90; P=0.02). In contrast, IVMD and OWD were too closely associated with ischemic origin to be independently predictive.

With receiver-operating characteristic curve analysis, the Yu Index with a cutoff of 32 milliseconds was highly specific at 78% but less sensitive at 40% for predicting death, transplantation, or LVAD implantation (Figure 6). Radial strain with a cutoff of 130 milliseconds was similarly specific.
at 79% and less sensitive at 39% for predicting clinical outcome. Accordingly, excluding dyssynchrony by Yu Index or radial strain was specifically associated with death, transplantation, or LVAD implantation after CRT. For comparison, the area under the curve for radial strain at 0.65 was greater than the Yu Index at 0.55.

Subgroup analysis was performed to examine the potential relationship of QRS width and dyssynchrony to survival after CRT using a predefined QRS cutoff. Patients with narrower QRS width of 120 to 150 milliseconds (n=122) were compared with those with a QRS width >150 milliseconds (n=136). Dyssynchrony by the Yu Index was associated with a more favorable outcome in either QRS duration group, with wider-QRS patients with dyssynchrony having the best outcome and narrower-QRS patients without dyssynchrony having the poorest outcome (Figure 7). With regard to radial dyssynchrony, patients with QRS width >150 milliseconds had a similarly favorable outcome; however, those with a QRS width of 120 to 150 milliseconds who lacked radial dyssynchrony had a particularly poor prognosis (P=0.003 versus all other groups; Figure 8).

Discussion

This study demonstrated the relationship between several echocardiographic dyssynchrony markers and the important outcome variable of long-term survival after CRT. A large series of consecutive patients were included using a prospective longitudinal study design with prespecified end points. The echocardiographic approach revealed a relatively high yield (89%) in consecutive patients referred for CRT. Baseline clinical variables were balanced overall in those patients with and without dyssynchrony; however, the lack of dyssynchrony was significantly more prevalent in those with ischemic disease. Radial dyssynchrony and IVMD were also related to baseline QRS width. As expected from this severely ill group of heart failure patients, there was a large number of the unfavorable events of death, heart transplantation, or LVAD implantation. With the use of predefined cutoffs, baseline dyssynchrony before CRT by the Yu Index, speckle tracking radial strain anteroseptal-to-posterior wall delay, and IVMD were all associated with more favorable survival free from transplantation or LVAD implantation. The TDI OWD with the predefined cutoff of ≥65 milliseconds had a trend for association with event-free survival (P=0.075); however, an OWD cutoff of ≥80 milliseconds by posthoc analysis became significantly associated (P=0.011). Of note, the Kaplan–Meier curves for each of these TDI indexes did not diverge until after the first 6 months after CRT, which was the follow-up interval of PROSPECT. Of the 191 patients with both Yu Index and radial dyssynchrony data available, 128
(67%) were concordant for dyssynchrony using prespecified cutoff values. When 8 additional patients with borderline dyssynchrony values \( \pm 5 \) milliseconds for Yu Index and \( \pm 10 \) milliseconds for radial dyssynchrony were considered, concordance increased to 71%. The exact reason for the discordance is unknown. Perhaps TDI longitudinal velocity and speckle tracking radial strain assess different aspects of dyssynchrony and provide additional information. When adjusted for covariates of ischemic origin and QRS width, the Yu Index and radial strain remained independently predictive of outcome. Subgroup analysis demonstrated that patients with narrower QRS width (120 to 150 milliseconds) who lacked radial dyssynchrony had a particularly poor survival. These observations strongly support the association of echocardiographic dyssynchrony with long-term patient outcome after CRT.

Several previous studies have also shown the ability of echocardiographic mechanical dyssynchrony to predict response to CRT. Baseline dyssynchrony has been related to improvement in heart failure class, 6-minute walk distance, quality-of-life score, EF, and reductions in end-systolic volumes. However, the multicenter PROSPECT study of predictors of response to CRT failed to show conclusively that a single echocardiographic dyssynchrony measure was highly predictive. Although there have been >100 published articles supporting the utility of echocardiographic dyssynchrony to predict CRT response, PROSPECT has had a particularly high impact on clinical opinion because of its prospective multicenter design. CRT guidelines continue to use QRS width as a surrogate for mechanical dyssynchrony. Several acknowledged limitations of PROSPECT included a low yield of feasibility, high variability using 3 different echocardiographic systems and software, and 3 different echocardiography core laboratories. For example, the overall yield for routine measures in PROSPECT such as end-systolic volumes was \( \approx 67\% \), indicating poor image quality in a third of the patients. Furthermore, TDI Yu Index was feasible in only 50% of attempted studies, in contrast to the present study with a yield of 89% of consecutive CRT patients. Importantly, the follow-up was limited to 6 months in PROSPECT, which may have been too short a duration to demonstrate the relationship of dyssynchrony with patient outcome.

Specific echocardiographic measures of dyssynchrony predictive of outcome after CRT have been reported by several authors. Bax et al demonstrated that a TDI OWD of \( \geq 65 \) milliseconds was associated with a lower incidence of heart failure hospitalizations and death in the first year after CRT. This OWD cutoff of 65 milliseconds in our present study had a strong trend to significantly predicting survival free from transplantation or LVAD implantation; however, we did not
include heart failure hospitalizations as an end point. Pitzalis et al.\textsuperscript{23} used M-mode echocardiography to show that an anteroseptal-to-posterior wall delay of \(130\) milliseconds successfully predicted outcome. We and others have had more success with speckle tracking radial strain in assessing anteroseptal-to-posterior wall delay with a favorable predictive value using the same \(130\)-millisecond cutoff value.\textsuperscript{7} Bank et al.\textsuperscript{27} showed that radial strain by speckle tracking was also predictive of response to CRT in a multicenter study. Analyses from the CARE-HF trial used a cutoff of \(49\) milliseconds for IVMD to demonstrate its value to predict outcome after CRT.\textsuperscript{28} We selected a predefined IVMD cutoff of \(40\) milliseconds as originally described and used in the PROSPECT trial.\textsuperscript{9,18} More recently, Chalil et al.\textsuperscript{29} used cardiac MRI to assess dyssynchrony and to predict mortality after CRT. Others have shown that mechanical dyssynchrony, either independently or when combined with clinical markers, is associated with a more favorable survival after CRT.\textsuperscript{30} Furthermore, echocardiographic dyssynchrony has been shown to be a marker for mortality in heart failure patients with narrow QRS duration using TDI or after myocardial infarction using velocity vector imaging.\textsuperscript{31} We observed the absence of radial dyssynchrony in patients with QRS of 120 to 150 milliseconds to be associated with a particularly high probability of death, transplantation, or LVAD implantation. Radial dyssynchrony was not associated with outcome in patients with QRS \(>150\) milliseconds. However, we observed that the Yu Index was particularly associated with outcome in patients with QRS \(>150\) milliseconds. The exact reason for these results is unclear, but they suggest that the TDI Yu Index and speckle tracking radial strain may be assessing different aspects of LV dyssynchrony.\textsuperscript{15} More recently, radial and transverse strain by speckle tracking was shown to be associated with EF response and survival after CRT in a separate multicenter study using different echocardiographic equipment and software.\textsuperscript{31} In summary, the present study demonstrates that baseline echocardiographic dyssynchrony is associated with a more favorable outcome after CRT and that patients who lack dyssynchrony may be identified as being at comparatively higher risk for death, transplantation, or LVAD implantation after CRT.

Limitations
The present study was not part of a randomized trial, and the relationship of echocardiographic dyssynchrony to survival in those who do not undergo CRT remains unknown. Although
the absence of echocardiographic dyssynchrony appears to be a marker for a worse prognosis in patients after CRT, the potential influence of CRT on outcome in patients without dyssynchrony remains unknown. However, it is currently difficult to withhold CRT from patients who meet current CRT implantation criteria to elucidate this point. Another limitation was that echocardiographic dyssynchrony analysis could not be performed successfully on all consecutive CRT patients, and 10% to 11% of patients did not have adequate image quality for quantification. Furthermore, high-quality images appear to be especially important for speckle tracking analysis.\textsuperscript{7,15,32} It is acknowledged that these echocardiographic methods are operator dependent and require user experience. In particular, technical difficulties with speckle tracking strain occurred in regions of myocardial scar and appeared to be more robust in patients with nonischemic cardiomyopathies. However, reproducible results may be achieved with a systematic core laboratory approach, as detailed in Methods. A limitation of the study design may be that all survival free from heart transplantation or LVAD implantation, rather than all-cause mortality, was used as the primary end point. However, heart transplantation and LVAD implantation in our institution are used only in heart failure patients with a very limited lifespan anticipated without these interventions. Another limitation was that markers of CRT response used in other clinical trials such as heart failure hospitalizations, 6-minute walk distance, peak myocardial oxygen consumption, LV reverse remodeling, or EF improvement were not part of the present study. It may be considered a limitation that ischemic origin may influence response to CRT from scar burden or lead positioning and have confounding effects.\textsuperscript{33,34} Analysis of scar burden and lead positioning was not part of the present study. We demonstrated that with adjustment specifically for ischemic origin, the Yu Index and speckle tracking radial strain remained independently associated with survival. Our subgroup analysis on heart failure origin and QRS width provided additive information that may be of clinical impact. Recent data support the potential utility of echocardiographic dyssynchrony in patients with narrower QRS duration as an adjunct to clinical decision making.\textsuperscript{22} It remains uncertain how these data will directly influence clinical practice, and ongoing further study is warranted.

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Disclosures
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CLINICAL PERSPECTIVE

This study demonstrated the association of echocardiographic dyssynchrony with long-term survival after cardiac resynchronization therapy (CRT). We studied 229 consecutive patients with routine CRT indications (symptomatic heart failure, reduced ejection fraction, and widened QRS (≥120 milliseconds), of whom 210 (89%) had baseline echocardiographic dyssynchrony data available. Dyssynchrony was prespecified as tissue Doppler longitudinal velocity opposing-wall delay (≥65 milliseconds), 12-site SD (Yu Index) ≥32 milliseconds, speckle tracking radial strain anteroseptal-to-posterior wall delay ≥130 milliseconds, or pulsed Doppler interventricular mechanical delay ≥40 milliseconds. Of 210 patients, there were 62 unfavorable events over 4 years after CRT: 47 deaths, 9 transplantations, and 6 left ventricular assist device implantations. All echocardiographic dyssynchrony indexes were significantly associated with a more favorable long-term prognosis than for patients without dyssynchrony, except tissue Doppler velocity opposing-wall delay became significant at ≥80 milliseconds. When adjusted for covariates of ischemic pathogenesis and QRS width, the Yu Index and speckle tracking radial strain remained independently predictive of outcome. Subgroup analysis demonstrated that patients with narrower QRS width of 120 to 150 milliseconds who lacked radial dyssynchrony had a particularly poor survival. Although this study has identified the absence of echocardiographic dyssynchrony as a marker for a less favorable prognosis in patients who undergo CRT for routine indications, the potential influence of CRT on outcome in patients without dyssynchrony remains unknown. These observations strongly support the association of echocardiographic dyssynchrony with long-term patient outcome after CRT.
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