Is Assessment of Systolic Dyssynchrony for Cardiac Resynchronization Therapy Clinically Useful?

Assessment of Systolic Dyssynchrony for Cardiac Resynchronization Therapy Is Clinically Useful

Victoria Delgado, MD, PhD; Jeroen J. Bax, MD, PhD

The beneficial effects of cardiac resynchronization therapy (CRT) on morbidity and mortality of heart failure patients with wide QRS complex have been demonstrated extensively. Various single-center and multicenter randomized, clinical trials have shown that CRT improves heart failure symptoms and left ventricular (LV) function and induces a significant reduction in LV volumes and mitral regurgitation. In addition, CRT reduces the number of heart failure hospitalizations and improves long-term survival. More important, unlike other heart failure medical therapies that may lose their effects over time, CRT is a long-term effective therapy. Accordingly, current American Heart Association/American College of Cardiology/Heart and Rhythm Society guidelines consider CRT a class I indication for patients with drug-refractory heart failure symptoms, LV ejection fraction <35%, and wide QRS complex (>120 ms).

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Despite these encouraging results, cumulative evidence shows that only 60% to 80% of patients exhibit a favorable clinical or echocardiographic response to CRT. For example, in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) and the MIRACLE-ICD (Multicenter InSync Implantable Cardioverter Defibrillator) trials, more than 30% of the patients fulfilling the aforementioned inclusion criteria did not show a favorable clinical response to CRT. Several single-center studies have reported similar nonresponse rates and have questioned the accuracy of these inclusion criteria to identify patients who will respond to CRT, which has encouraged the research of novel indices and strategies that can reliably predict response to CRT.

One of these indices is LV mechanical dyssynchrony. In the last decade, multiple single-center trials and the Cardiac Resynchronization in Heart Failure (CARE-HF) trial have demonstrated that LV mechanical dyssynchrony indices (most of which are based on echocardiographic measures) have superior accuracy compared with LV electric dyssynchrony (based on QRS duration) to predict response to CRT and long-term outcome. However, those results were challenged recently by the multicenter PROSPECT (Predictors of Response to CRT) trial, in which no single LV mechanical dyssynchrony parameter could accurately predict response to CRT.

In this controversy, we advocate the use of LV mechanical dyssynchrony as an additional selection criterion for CRT and address the strengths of current imaging modalities to evaluate LV mechanical dyssynchrony. In addition, the different pathophysiological factors that may determine CRT response will be discussed. Finally, the use of an integrated approach, including LV mechanical dyssynchrony, LV lead position, and extent of myocardial scar, will be proposed as a potential optimal strategy to evaluate candidates for CRT.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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How to Define Response to CRT

The majority of the CRT trials have defined response to CRT as improvement in clinical variables (New York Heart Association functional class, quality of life, 6-minute walk distance) or improvement in LV systolic function and LV reverse remodeling at 3- to 6-month follow-up; however, it has been shown repeatedly that the agreement between clinical and echocardiographic improvement is poor. A significant percentage of patients with improvement in clinical status do not exhibit improvement in LV systolic function or reverse LV remodeling (reduction in LV volumes). In the PROSPECT trial, for example, 68% of patients showed improvement in the clinical composite score at 6-month follow-up, whereas 56% of patients showed a reduction in LV end-systolic volume. Pooled data from the 15 largest trials demonstrated that the weighted mean clinical response rate was 66.9% compared with a weighted mean echocardiographic response rate of 56.9%. The subjective improvement in clinical status without improvement in LV performance may be explained in part by a placebo effect. These results fuel the ongoing debate regarding what is the most appropriate definition of CRT response. It has been suggested that no deterioration of clinical or echocardiographic parameters might be considered as a favorable response to CRT. In the PROSPECT trial, the clinical status or LV end-systolic volumes remained unchanged at 6-month follow-up in 15% and 35% of the patients, respectively. It is possible that the best end point would be improvement in long-term survival; in CRT studies, a significant reduction in LV end-systolic volume at 3- to 6-month follow-up was directly related to improved long-term survival. Conversely, from a patient’s perspective, improvement in clinical status may be more relevant. In light of this discussion, research of new selection criteria that can accurately predict response to CRT may be challenging.

Accuracy of QRS Duration to Predict Response to CRT

Duration of the QRS complex is the most controversial criterion to select patients for CRT. Landmark randomized CRT trials included patients with QRS duration of approximately 160 ms (Table 1). However, those studies with available data on CRT response rate demonstrated that 30% of the patients did not benefit from CRT, which suggests that QRS duration might not be ideal to predict response to CRT. The reduced accuracy of QRS duration to predict response to CRT was demonstrated recently by Mollema and coworkers. In a series of 242 heart failure patients with prolonged QRS complex who were treated with CRT, the accuracy of baseline QRS duration to predict response to CRT was poor. Analysis of 626 consecutive heart failure patients from our center, with a QRS duration ≥120 ms, confirmed these results (Victoria Delgado, MD, PhD, et al, unpublished data, 2010). Response to CRT was defined by the presence of LV reverse remodeling (≥15% reduction in LV end-systolic volume) after 6 months. Figure 1 shows that echocardiographic CRT response and nonresponse rates were comparable in the different QRS durations. In addition, the accuracy of baseline QRS duration to predict response to CRT was suboptimal (area under the curve 0.58). A cutoff value of 163 ms yielded a sensitivity and specificity of 57% and 53%, respectively.

These results suggest that duration of the QRS complex may not be specific enough to characterize the exact electric and mechanical LV activation pattern. Indeed, high-
resolution endocardial and epicardial mapping studies have shown that left bundle-branch block may result in different and heterogeneous electric and mechanical LV activation delay patterns, despite similar surface ECG morphology and duration (Figure 2). This heterogeneity is determined by several pathophysiological factors that may influence CRT response. One of these factors is the anatomic level of the conduction delay. In left bundle-branch block, the conduction delay resides mainly within the interventricular septum; however, the pattern of transseptal activation delay is highly variable and results in different LV activation patterns that determine LV mechanics. In failing remodeled LVs, the increased myocardial fibrosis content may result in lines of fixed conduction blocks. In contrast, functional conduction blocks are related to stretching of delayed-activated areas, heart rate, or diastolic depolarization, and the location of these functional conduction blocks can be changed by pacing. Finally, the pathological substrate also determines the LV activation pattern. In ischemic dilated cardiomyopathy, LV endocardial activation is characterized by slow conduction velocities across regions of scar, whereas in nonischemic cardiomyopathy, rapid LV endocardial activation after single-point breakthrough can be observed.

This heterogeneous LV activation pattern was demonstrated in a series of 24 heart failure patients with left bundle-branch block configuration. Auricchio et al, using 3-dimensional (3D) nonfluoroscopic contact and noncontact mapping, studied the LV activation pattern (including LV...
endocardial breakthrough site, transseptal activation time, and duration of LV endocardial activation). The LV endocardial breakthrough site was identified on the 3D color map, and transseptal activation time was defined as the time delay between the onset of the QRS and the detected LV endocardial breakthrough. The duration of LV endocardial activation was derived as the time difference between the LV breakthrough and the latest activated region. In the majority of the patients, activation spreads superiorly and inferiorly from the site of earliest breakthrough. The activation wave reached the lateral or the posterolateral regions by propagating inferiorly around the apex and across the inferior wall (so-called U-shaped pattern of activation); however, the LV breakthrough site and transseptal time determined different LV activation patterns, which have been related to variable response rates to CRT.23,24

The advent of newer imaging technologies such as tissue Doppler imaging (TDI) permits noninvasive characterization of the LV mechanical activation pattern. Previous studies demonstrated that 11% to 38% of heart failure patients with a QRS duration ≥120 ms did not exhibit systolic LV mechanical dyssynchrony.25–27 Recently, the poor correlation between QRS duration and mechanical LV dyssynchrony was confirmed in 103 heart failure patients with various QRS durations and 59 healthy control subjects with normal QRS duration (<100 ms).28 Although LV mechanical dyssynchrony was more frequently observed in patients with left bundle-branch block (60%), up to 40% of patients with normal QRS duration (<100 ms) also showed significant LV systolic dyssynchrony.28 On the basis of these experiences, it can be concluded that QRS duration does not reliably characterize both electric and mechanical LV dyssynchrony and may not accurately predict response to CRT. In addition, it has been demonstrated that the hemodynamic benefits of CRT depend on whether LV mechanical dyssynchrony can be restored. Accordingly, assessment of LV mechanical dyssynchrony may be a more robust criterion to predict response to CRT.

Initial Echocardiographic Approaches to Predict CRT Response
Heart failure patients may exhibit 3 different types of cardiac dyssynchrony: Atrioventricular dyssynchrony, interventricular dyssynchrony, and intraventricular or LV mechanical dyssynchrony. Only interventricular and LV mechanical dyssynchrony have been associated with response to CRT and long-term survival.

Few studies have demonstrated the value of interventricular dyssynchrony assessment to predict response to CRT.29,30 The results of the CARE-HF trial showed that the presence of baseline significant interventricular dyssynchrony as assessed with pulsed-wave Doppler echocardiography was related to a higher likelihood of a favorable response to CRT.7,29 In patients with a QRS duration between 120 and 149 ms, 2 of 3 additional criteria for cardiac dyssynchrony were required: an aortic preejection delay ≥140 ms, an interventricular mechanical delay ≥40 ms (measured as the time delay between the left and right ventricular preejection intervals [Figure 3A]), or delayed activation of the posterolateral LV wall. However, only interventricular mechanical delay ≥40 ms was demonstrated to predict response to CRT (hazard ratio 0.99, 95% confidence interval 0.98 to 1.00).7,29

The measurement of LV mechanical dyssynchrony provides the largest body of evidence of the value of this parameter in prediction of response to CRT and long-term survival. Multiple LV dyssynchrony parameters, mainly based on echocardiographic imaging, have been proposed in the last decade to quantify LV dyssynchrony and predict response to CRT. The use of M-mode echocardiography pioneered the measurement of LV mechanical dyssynchrony (Figure 3B).31,32 The measurement of a septal-to–posterior wall motion delay ≥130 ms was shown to predict response to CRT and long-term clinical outcome in a very small sample population31,32; however, subsequent studies that included larger populations questioned the feasibility and accuracy of this parameter to predict response to CRT.33,34 For example, in patients with ischemic heart failure with akinetic interventricular septum or posterior wall, this parameter cannot be measured properly. The introduction of novel techniques such as TDI permitted the assessment of myocardial velocities, and the LV mechanical activation pattern could be evaluated on the basis of time to onset or peak systolic velocity (Figure 3C). The majority of the TDI-derived dyssynchrony indices are based on differences in time to onset or time to peak systolic velocity between 2, 4, or more opposing LV walls.11,12,35,36 For example, the measurement of the maximum peak systolic velocity time delay between 4 opposing walls yielded a cutoff value of 65 ms to indicate the presence of significant LV dyssynchrony.11 This TDI-derived LV dyssynchrony parameter yielded a sensitivity and specificity of 92% to predict significant LV reverse remodeling after CRT.11 Recently, these results were confirmed in a series of 361 heart failure patients undergoing CRT implantation, in whom the presence of significant LV dyssynchrony (measured as the maximum time difference between peak systolic velocities of 4 opposing walls) was a strong and independent determinant of clinical and echocardiographic CRT response (odds ratio 1.02, 95% confidence interval 1.02 to 1.03; \( P < 0.001 \)).12 In contrast, QRS duration was not related to response to CRT (odds ratio 1.00, 95% confidence interval 0.99 to 1.01; \( P = \text{NS} \)).12 In addition, LV dyssynchrony can be quantified by measurement of the dispersion of time to peak systolic velocity for the entire LV. Thus, a standard deviation of time to peak systolic velocity of 12 LV segments ≥31.4 ms indicates the presence of significant LV dyssynchrony and has been related to a high likelihood of a favorable response to CRT (sensitivity and specificity 90% and 83%, respectively).35

Unlike TDI velocity imaging, TDI-derived strain and strain rate imaging enable identification of myocardial segments...
with active deformation (contraction) and myocardial segments with passive motion (scar tissue). Therefore, particularly in patients with ischemic heart failure (and previous infarction), strain may be preferred for assessment of dyssynchrony. A few studies have demonstrated the feasibility of TDI-derived radial strain to quantify LV mechanical dyssynchrony and to predict LV functional improvement; however, assessment of LV longitudinal TDI-derived strain and strain rate has not provided any parameter of LV mechanical dyssynchrony that could accurately predict CRT response (Figure 3D). The measurement of myocardial velocities or strain and strain rate with TDI depends on the angle of insonation of the ultrasound beam, and high expertise in acquiring TDI data is mandatory to obtain reliable analysis of LV dyssynchrony.

The ability of the aforementioned LV mechanical dyssynchrony parameters to predict response to CRT was evaluated in the large-scale PROSPECT trial, which included 498 heart failure patients who fulfilled the standard inclusion criteria for CRT. The vast majority of the LV dyssynchrony parameters evaluated in the study showed only modest ability to predict response to CRT. Various issues, including patient selection and echocardiographic data acquisition and analysis, may explain these results. A significant percentage of patients (24%) with an LV ejection fraction >35% and a less dilated LV were included in the study. In addition, analysis and postprocessing of the echocardiographic data depended on the expertise of the center. Finally, it has become evident over time that other factors such as LV lead position and the presence or extent of myocardial scar are important in CRT response; these factors were not evaluated in the PROSPECT trial.

Improving Assessment of LV Dyssynchrony: Shift Toward 3D Imaging

Despite the results of the PROSPECT trial, the cumulative evidence shows that the study of LV mechanical dyssynchrony is clinically relevant. Indeed, a recent substudy of the...
The PROSPECT trial showed that the magnitude of LV mechanical dyssynchrony at baseline was related to the extent of reduction in LV end-systolic volume. Patients with more LV mechanical dyssynchrony at baseline demonstrated more LV reverse remodeling at 6-month follow-up. In addition, LV resynchronization after CRT is associated with LV reverse remodeling, reduction in mitral regurgitation, improvement in clinical symptoms, and superior long-term survival. As mentioned previously, the echocardiographic modalities evaluated in the PROSPECT trial had several technical limitations that could partially explain the negative results. Advances in echocardiographic techniques and other imaging modalities have provided novel and robust indices of LV mechanical dyssynchrony with increased accuracy to predict CRT response.

One of these novel technologies is 2-dimensional strain imaging or speckle-tracking echocardiography. Unlike TDI-derived strain, speckle-tracking strain imaging enables angle-independent multidirectional analysis of myocardial deformation. Several studies have demonstrated the value of this novel technique in predicting response to CRT. In a series of 161 patients undergoing CRT implantation, a time difference between peak radial strain of the anteroseptal and posterior segments ≥130 ms predicted CRT response with a sensitivity and specificity of 83% and 80%, respectively. In addition, 2-dimensional speckle-tracking longitudinal strain has provided a novel marker of LV dyssynchrony. The longitudinal strain delay index combines the assessment of LV mechanical dyssynchrony and the evaluation of LV contractile efficiency (wasted energy; Figure 4A). A longitudinal strain delay index ≥25% yielded a sensitivity of 95% and a specificity of 83% to predict CRT response at 3-month follow-up.

3D echocardiography is another important breakthrough in the assessment of LV dyssynchrony. Unlike 2-dimensional echocardiographic modalities, 3D echocardiographic techniques permit assessment of LV mechanical dyssynchrony within the entire ventricle and provide a global measurement of the time dispersion to peak systolic contraction (Figure 5). Several LV mechanical dyssynchrony indices based on volumetric analysis or triplane tissue synchronization imaging have been proposed to predict response to CRT. More recently, 3D speckle-tracking imaging has been proposed for the assessment of LV mechanical dyssynchrony by evaluation of myocardial deformation within the LV full volume (Figure 5). In 54 heart failure patients and 10 healthy volunteers, Tanaka et al assessed LV mechanical dyssynchrony with 3D speckle-tracking imaging. The maximal opposing wall delay and the standard deviation of time to peak radial strain of 16 LV segments were derived as indices of LV dyssynchrony. Compared with healthy volunteers, heart failure patients showed significantly larger maximal opposing wall delay (316±112 versus 59±12 ms; P<0.001) and standard deviation of time to peak radial strain (124±48 versus 28±11 ms; P<0.001), which reflected greater LV dyssynchronous contraction.

In a subgroup of 11 heart failure patients treated with CRT, 3D speckle-tracking imaging demonstrated effective LV resynchronization with significant improvement in LV systolic function.

Various magnetic resonance imaging (MRI) techniques have been developed for assessment of LV mechanical dyssynchrony. The circumferential uniformity ratio estimate (CURE) index is based on tagged MRI and ranges from 0 (dysynchronous) to 1 (synchronous). In a recent series of 43 heart failure patients treated with CRT, the CURE index showed an accuracy of 90% to predict clinical improvement at 6-month follow-up, with a negative predictive value of 87% and a positive predictive value of 100% (Figure 6A). Vector-velocity–encoded magnetic resonance permits the assessment of LV mechanical dyssynchrony by measuring differences in regional time to peak myocardial velocities, similar to echocardiography with TDI (Figure 6B). Finally, the assessment of segmental radial motion or radial thickness of the LV along the cardiac cycle with MRI has provided novel indices of LV mechanical dyssynchrony (Figure 6C). The standard deviation of time to peak radial motion or thickness of 16 or more LV segments is used as a marker of LV mechanical dyssynchrony. This approach was applied in 35 heart failure patients undergoing CRT. The responder patients showed more extensive LV dyssynchrony at baseline (90 versus 60 ms; P<0.001), and multivariate analysis confirmed that LV mechanical dyssynchrony was independently related to CRT response (odds ratio 6.3, [95% confidence interval 3.1 to 9.9]; P<0.001).

Nuclear imaging has also been used for assessment of LV mechanical dyssynchrony. Gated blood-pool ventriculography, gated blood-pool single photon emission computed tomography (SPECT), and gated myocardial perfusion SPECT permit characterization of LV contraction patterns. Boogers et al have developed a novel count-based approach to assess LV dyssynchrony with gated myocardial perfusion SPECT. From the short-axis images, the amplitude (which reflects systolic wall thickening) and phase (reflecting onset of mechanical contraction) are calculated. Five different quantitative LV dyssynchrony indices can be derived (peak phase, phase standard deviation, bandwidth, phase histogram skewness, and kurtosis), and the normal range for each parameter has been reported. The phase standard deviation and the histogram bandwidth are the most commonly used parameters to assess LV mechanical dyssynchrony (Figure 7).

In 40 patients with advanced heart failure treated with CRT, LV mechanical dyssynchrony was assessed with gated myocardial perfusion SPECT. Responders had significantly larger bandwidth histogram (94±23° versus 68±21°; P<0.01) and phase standard deviation (26±6° versus 18±5°; P<0.01) at baseline than nonresponders. Receiver operating characteristic curve analysis showed a high accuracy of the bandwidth histogram and phase standard deviation to predict response to CRT, with respective areas under the
Figure 4. Novel echocardiographic LV mechanical dyssynchrony indices: 2-Dimensional speckle-tracking imaging. A, Two-dimensional radial strain speckle-tracking imaging enables the assessment of LV mechanical dyssynchrony. A time difference between the peak strain of the septal segment and the posterolateral segments ≥130 ms predicts LV reverse remodeling after CRT. B, In addition, from LV apical views, LV dyssynchrony can be analyzed with 2-dimensional longitudinal strain speckle tracking and the strain delay index. This index indicates the amount of inefficient contraction of the LV induced by the dyssynchronous activation (wasted energy). A longitudinal strain delay index ≥25% predicted LV reverse remodeling.
curve of 0.83 and 0.85. The optimal cutoff value for the bandwidth histogram was 72°, which yielded a sensitivity and specificity of 83% and 81%, respectively. For phase standard deviation, the optimal cutoff value was 19.6°, with a sensitivity and specificity of 83% and 81%, respectively, to predict CRT response.55

All of these studies with different imaging modalities indicate that LV mechanical dyssynchrony assessment has
gradually shifted toward a 3D approach, which provides more comprehensive information on LV mechanics. Large-scale clinical trials evaluating the performance of these novel indices to predict response to CRT will establish the role of these techniques to evaluate patients who are candidates for CRT.

**LV Mechanical Dyssynchrony and CRT: Focus on Predicting Long-Term Outcome**

The initial, smaller studies used LV dyssynchrony to predict CRT response defined by surrogate endpoints such as New York Heart Association functional class, 6-minute walk distance, or LV reverse remodeling; more recent, larger

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**Figure 6. LV mechanical dyssynchrony assessed with MRI.**

A, 3D tagged MRI data are postprocessed with harmonic phase imaging to obtain the circumferential strain-time curves (left). LBBB indicates left bundle-branch block; csh, circumferential shortening; and AVC, aortic valve closure. The dispersion in time to peak circumferential strain within the LV (SDI) and the CURE index can be calculated as measures of LV dyssynchrony. This information can also be displayed as a polar map, with the latest activated areas coded in red (middle). SDI indicates systolic dyssynchrony index. Adapted with permission from Rutz et al.51 B, Velocity-encoded MRI assesses LV dyssynchrony by measuring the time difference between the peak systolic velocity of the septum and the lateral wall (arrows). Adapted with permission from Westenberg et al.52 C, On the basis of the measurement of time to peak radial motion, MRI can assess LV dyssynchrony and display the time dispersion graphically. Three slices are selected from the complete short-axis data set of the LV. Radial segmental motion-time curves indicate the presence of LV mechanical dyssynchrony as dispersion in time to peak radial motion. The motion-time curve graphs show the example of 2 patients with dysynchronous mechanical activation of the LV (left) and synchronous activation (right). Adapted with permission from Marsan et al.54
studies have shifted to prediction of long-term outcome after CRT, which is a more important end point.\textsuperscript{6,7} These studies are summarized in Table 2.\textsuperscript{7,30,58–60} In the CARE-HF trial, during a mean follow-up of 29.4 months, the all-cause mortality rate for the overall population was almost 25%.\textsuperscript{7} The analysis of the effect of CRT on the primary end point (composite of death due to any cause or an unplanned hospitalization for a major cardiovascular event) in predefined groups showed that patients with significant cardiac dyssynchrony at baseline (assessed by an interventricular mechanical delay $/H1/1350 \geq 49.2$ ms) had superior long-term survival compared with patients with more synchronous interventricular activation.\textsuperscript{7} These results were extended by Wiesbauer et al,\textsuperscript{30} who reported an all-cause mortality rate of 10% in 200 patients undergoing CRT; patients with an interventricular mechanical delay $/H1/11350 \geq 60$ ms at baseline showed a better outcome than patients with a delay $<60$ ms. Other studies have demonstrated the relationship between LV mechanical dyssynchrony and long-term outcome.\textsuperscript{36,53,58–60} In 239 heart failure patients treated with CRT, Zhang et al\textsuperscript{36} evaluated the relation between LV dyssynchrony (using TDI and $\geq 65$-ms difference in time to peak velocity between 2 opposing walls) and cardiovascular mortality. LV dyssynchrony at baseline was an independent determinant of cardiovascular mortality (hazard ratio 0.463, 95% confidence interval 0.720 to 0.972; $P=0.005$).\textsuperscript{36} Leyva et al\textsuperscript{60} demonstrated the prognostic value of LV mechanical dyssynchrony assessed with MRI. In 148 heart failure patients, LV mechanical dyssynchrony was measured as the temporal dispersion of peak inward myocardial motion throughout the cardiac cycle. During a median follow-up of 2.5 years, 37 cardiovascular deaths were recorded. Again, the presence of baseline LV mechanical dyssynchrony was related to cardiovascular mortality (hazard ratio 1.01,95% confidence interval 1.00 to 1.02; $P=0.001$).\textsuperscript{60} All of these studies, using different techniques, have shown in large cohorts that cardiac dyssynchrony is a strong predictor of long-term outcome after CRT.

However, there are still areas of controversy. The effects of CRT on morbidity and mortality of heart failure patients who fulfill current inclusion criteria for CRT but do not show LV mechanical dyssynchrony remain unclear. In addition, the results of recent trials that included patients with narrow QRS complex and substantial LV mechanical dyssynchrony (the RethinQ [Resynchronization Therapy in Normal QRS] trial and the ESTEEM-CRT [Evaluation of CRT in Narrow QRS Patients with Mechanical Dyssynchrony from a Multi-center Trial] trial) are still pending.

Table 2. Studies Evaluating the Role of Cardiac Dyssynchrony to Predict Long-Term Outcome After CRT

<table>
<thead>
<tr>
<th>First Author</th>
<th>Patients, n</th>
<th>Follow-Up, mo</th>
<th>Cardiac Dyssynchrony Parameter</th>
<th>End Point</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland et al\textsuperscript{7}</td>
<td>813</td>
<td>29.4</td>
<td>IVMD $\geq 49.2$ ms</td>
<td>All-cause mortality or hospitalization for heart failure</td>
<td>0.50 (0.36–0.70)</td>
</tr>
<tr>
<td>Wiesbauer et al\textsuperscript{30}</td>
<td>200</td>
<td>10</td>
<td>IVMD $\geq 60$ ms</td>
<td>All-cause mortality</td>
<td>0.21 (0.07–0.6)</td>
</tr>
<tr>
<td>Cho et al\textsuperscript{58}</td>
<td>106</td>
<td>17±11</td>
<td>TDI maximal opposing delay (8 LV segments) $&gt;91$ ms</td>
<td>All-cause mortality</td>
<td>9.02 (2.42–33.57)</td>
</tr>
<tr>
<td>Zhang et al\textsuperscript{36}</td>
<td>239</td>
<td>37±20</td>
<td>TDI maximal opposing delay $\geq 65$ ms</td>
<td>Cardiac mortality</td>
<td>0.463 (0.270–0.792)</td>
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<tr>
<td>Cho et al\textsuperscript{59}</td>
<td>167</td>
<td>33</td>
<td>TDI maximal opposing delay $\geq 65$ ms</td>
<td>Cardiac mortality and hospitalization for heart failure</td>
<td>2.37 (1.39–4.04)</td>
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<tr>
<td>Leyva et al\textsuperscript{60}</td>
<td>148</td>
<td>30</td>
<td>SD of time to peak radial motion-MRI</td>
<td>Cardiac mortality</td>
<td>1.01 (1.00–1.02)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; IVMD, interventricular mechanical delay; and TDI, tissue Doppler imaging.
Study] trial) have not convincingly demonstrated that CRT provides an incremental clinical benefit over optimized medical therapy. The ongoing EchoCRT (Echocardiography-guided Cardiac Resynchronization Therapy) trial will help elucidate the benefits of CRT in a large group of heart failure patients with narrow QRS and documented LV mechanical dyssynchrony.

**Prediction of Response to CRT: Beyond LV Dyssynchrony**

It is important to recognize that the response to CRT is also influenced by other pathophysiological factors, including the position of the LV pacing lead and the extent and location of myocardial scar. The aforementioned imaging techniques, including 2-dimensional and 3D speckle-tracking imaging, MRI, and nuclear imaging, permit an integrated approach to evaluate candidates for CRT by providing information on LV dyssynchrony and site of latest activation and extent and location of myocardial scar tissue.

Although an increasing distance between the right ventricular and LV pacing leads was initially the target of CRT implantation, several imaging studies have shown that positioning the LV pacing lead in the region of the most delayed LV mechanical activation may provide superior hemodynamic benefit and increase the percentage of patients who respond to CRT. With tagged MRI, Helm et al assessed LV mechanical dyssynchrony with the CURE index and identified the apical and middle segments of the LV lateral wall as the latest mechanically activated areas in sophisticated 3D maps; pacing of these regions yielded the largest hemodynamic benefit after CRT. More recently, Ypenburg et al demonstrated that an optimal LV lead position (concordant with the site of most delayed LV mechanical activation) determined superior long-term survival. In a series of 244 heart failure patients undergoing CRT implantation, LV dyssynchrony and the most delayed mechanically activated areas of the LV were assessed by 2-dimensional speckle-tracking imaging (Figure 8A). In addition, the position of the LV pacing lead was assessed on chest radiograph. The lateral and posterior walls of the LV were the areas of latest mechanical activation, and a concordant LV lead position was observed in 63% of patients. At 6-month follow-up after CRT, patients with an optimal LV lead position exhibited more LV reverse remodeling and improvement in LV systolic function. More important, at 32 months of follow-up, patients with an optimal LV lead position had superior survival over patients with a discordant LV lead position (85% versus 79%; log-rank \( P=0.048 \)). Additional prospective randomized studies on LV lead positioning are needed to establish the most appropriate locations.

The other important issue in response to CRT is scar formation in the LV. The extent of myocardial scar tissue has been associated with LV dyssynchrony in patients with acute myocardial infarction; however, in heart failure patients, this association remains unclear, because patients with nonischemic cardiomyopathy and without myocardial scar may also show LV mechanical dyssynchrony. Myocardial scar tissue may influence CRT response through different pathophysiological pathways. First, in ischemic heart failure patients, LV endocardial activation is slowed across the regions of scar, which results in LV mechanical activation patterns that may be less amenable to correction with CRT. Second, the presence of transmural scar tissue in the area where the LV pacing lead is positioned limits the efficacy of CRT. In 40 patients with heart failure, the location and transmurality of scar tissue were evaluated with contrast-enhanced MRI in the area where the LV pacing lead was positioned. The LV lead was positioned in the posterolateral region. At 6-month follow-up, the response rate in patients with transmural myocardial scar (>50% wall thickness) in the posterolateral region was significantly less than that in patients without transmural scar (14% versus 81%; \( P<0.001 \)). Third, the extent of myocardial scar may reduce LV reverse remodeling. Data from the large randomized clinical trials have shown that ischemic heart failure patients in general show less LV reverse remodeling than patients with nonischemic cardiomyopathy. For example, a subanalysis of the MIRACLE trial that included 228 heart failure patients showed a greater reduction in LV volumes after CRT in patients with nonischemic cardiomyopathy. These observations suggest that the presence of extensive scar tissue is an important determinant of negative response to CRT. This was recently demonstrated in a series of 34 patients with ischemic cardiomyopathy scheduled for CRT implantation. The extent of myocardial scar tissue (total scar burden) was evaluated with contrast-enhanced MRI. At 6-month follow-up, 53% of the patients showed a significant reduction in LV volumes. Of interest, the reduction in LV volumes was inversely related to the total scar burden, and patients showing extensive myocardial scar tissue (total scar burden >1.2) had the lowest probability of responding to CRT (Figure 8B). Various imaging techniques can detect scar tissue, including contrast echocardiography and nuclear imaging with SPECT or positron emission tomography. The most accurate technique for assessment of scar tissue is contrast-enhanced MRI, which has the highest spatial resolution and permits assessment of the transmural extent of scar tissue.

Given the importance of positioning the LV lead in the area of latest mechanical activation and avoiding areas of scar tissue, knowledge of the cardiac venous anatomy is critical in planning the LV lead implantation. Preprocedural venography is the most commonly used method to visualize the precise number and location of tributaries of the coronary sinus, but recent advances in multidetector computed tomography also permit noninvasive 3D assessment of the cardiac venous anatomy. Patients with extensive areas of scar tissue due to previous infarction frequently exhibit less extensive venous anatomy (Figure 8C), and a minimally invasive surgical approach may be preferred over a transvenous approach for LV lead positioning.
Figure 8. Multimodality imaging integrating different information determining CRT response. A, Example of a patient with dysynchronous LV mechanical activation as assessed with 2-dimensional speckle-tracking radial strain imaging. The sites of latest LV mechanical activation are the posterior and lateral segments, as indicated by the arrows. B, Contrast-enhanced MRI demonstrates the presence and extent of myocardial scar. Transmural scar at the posterolateral regions has been related to lower likelihood of CRT response. In addition, the total scar burden, reflecting the extent of LV myocardial scar, has been inversely related to CRT response at 6-month follow-up. In patients with a total scar burden <0.9, the percentage of response to CRT is 100% (open bars). In contrast, patients with a total scar burden >1.2 do not show response to CRT (solid bars). Adapted with permission from Ypenburg et al.\textsuperscript{64} C, The presence of favorable cardiac vein anatomy to place the LV lead can be assessed by multidetector computed tomography. Left, An example of a patient with dilated cardiomyopathy with left marginal vein where the LV pacing lead can be placed. Middle, An ischemic heart failure patient with a great posterior interventricular vein (first tributary of the coronary sinus) but without suitable cardiac veins at the posterolateral regions. Right, The prevalence of a suitable posterior vein of the LV and left marginal vein in ischemic heart failure patients (red bar) is significantly lower than in control subjects (green bar) and coronary artery disease patients (blue bar). Adapted with permission from van de Veire et al.\textsuperscript{67} CS indicates coronary sinus; LMV, left marginal vein; PIV, posterior interventricular vein; and PVLV, posterior vein of the LV.
Conclusions

CRT has changed the management of heart failure patients, resulting in significant improvement in clinical status, LV performance, and long-term survival. Consequently, the number of CRT implantations has increased substantially over the last several years. However, this therapy still faces a 30% nonresponse rate based on current inclusion criteria, which suggests inadequate specificity in the CRT selection process. The width of the QRS complex is a crude parameter of LV dyssynchrony and has shown a poor ability to predict response to CRT. In contrast, LV mechanical dyssynchrony assessed with echocardiography has demonstrated superior accuracy to identify responders to CRT. Recent evidence shows that LV mechanical dyssynchrony is an independent determinant of long-term survival, and therefore, the evaluation of this parameter in candidates for CRT is clinically relevant. Recent research has focused on 3D imaging modalities that can provide more robust and accurate parameters of LV mechanical dyssynchrony to predict CRT response and long-term survival. In addition, it has been demonstrated that CRT response is not solely determined by LV mechanical dyssynchrony. Other pathophysiological factors, such as extent and location of myocardial scar and LV lead position, have been associated with response to CRT. Current 3D imaging modalities, including echocardiography, MRI, and nuclear imaging, provide comprehensive and robust information on the main determinants of CRT response: LV mechanical dyssynchrony and site of latest mechanical activation, extent and location of myocardial scar, and venous anatomy.

At present, the current inclusion criteria for CRT implantation remain New York Heart Association functional class III-IV heart failure symptoms despite optimized medical therapy, LV ejection fraction ≤35%, and QRS duration ≥120 ms. However, measurement of LV dyssynchrony, detection of the presence and extent of myocardial scar tissue, and assessment of the site of latest mechanical activation may help to improve selection of patients who will benefit from CRT.

Disclosures

Dr Bax receives grants from Biotronik, Lantheus Medical Imaging, Boston Scientific, Edwards Lifesciences, GE Healthcare, Medtronic, and St. Jude Medical. Dr Delgado reports no conflicts.

References


Drs Delgado and Bax have provided an elegant argument for the clinical use of systolic dyssynchrony, summarizing the evidence supporting the measurement of baseline mechanical dyssynchrony. We agree that it is worthwhile to try to identify potential cardiac resynchronization therapy (CRT) nonresponders, and that mechanical dyssynchrony is a possible component in determining a patient’s response to CRT. However, lacking from their treatise is a practical, reproducible, and widely applicable approach to patient selection. The authors acknowledge the unpredictability of clinical benefit with CRT in patients whose results do not cross an arbitrary threshold of left ventricular mechanical dyssynchrony yet meet all other inclusion criteria. The studies cited, which show correlation between left ventricular dyssynchrony and long-term mortality, are nonrandomized and fail to account for differences in all baseline characteristics, including New York Heart Association functional class, ischemic etiology, QRS duration, presence of left bundle branch block, and scar burden, known to affect long-term mortality. Additionally, without a suitable control group, these observational studies cannot distinguish the mortality benefit of CRT over medical therapy alone. We are concerned that specifying mechanical dyssynchrony as a requirement for CRT could needlessly deny a valuable, life-saving therapy to patients who may still derive benefit. Despite its limitations, the Predictors of Response to CRT (PROSPECT) trial demonstrates that there is no method with sufficient specificity and predictive value that permits a clinician to say with confidence that our hypothetical patient would not derive benefit from resynchronization. PROSPECT highlights the variability and difficulty in widespread application of these methods, making them unfeasible for use in guiding therapy at the current time.
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