Echocardiography and Noninvasive Imaging in Cardiac Resynchronization Therapy

Results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) Study in Perspective

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Over the past decade, cardiac resynchronization therapy (CRT) has changed the treatment of patients with end-stage, drug-refractory heart failure. Evidence of 8 large trials (including 4,017 patients) (1–8) and numerous small studies have demonstrated the benefit of CRT on heart failure symptoms, exercise capacity, and systolic left ventricular (LV) function. Various studies demonstrated reverse remodeling after CRT, with a reduction in severity of mitral regurgitation. Moreover, recent data demonstrated a reduction in heart failure hospitalization and mortality after CRT (6).

Various meta-analyses have subsequently been published and confirmed these beneficial effects when data from the available literature were pooled (9,10). Particularly, when the 5 available randomized, controlled trials that provided data on CRT alone were pooled (including 2,371 patients, with 1,028 control subjects and 1,343 CRT-treated patients), a 29% reduction in all-cause mortality was shown (16.9% mortality in the CRT-treated patients compared with 20.7% in control subjects) (9). Similarly, a 38% reduction in mortality due to progressive heart failure was shown (6.7% in CRT-treated patients vs. 9.7% in control subjects) (9). Based on the available evidence, the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines consider CRT a class I indication in patients with end-stage heart failure (New York Heart Association [NYHA] functional class III or IV) with left ventricular ejection fraction (LVEF) <35% and wide QRS complex (11).

Cardiac dyssynchrony appears to be an important determinant for response to CRT, as demonstrated in numerous small, single-center studies (12), and can be derived from echocardiography. An observational study to identify echocardiographic predictors of response to CRT, known as PROSPECT (Predictors of Response to CRT), was recently published (13). From this study, it appeared that echocardiographic parameters had only modest accuracy to predict response to CRT, in contrast to the results from a multitude of previously published studies. In this review, we aim to explore some details of the PROSPECT study in order to gain a better understanding and to put the PROSPECT data in perspective with the remainder of existing scientific literature. In addition, we will address the contemporary and future roles of noninvasive imaging in candidates for CRT in general.

The Problem of Responder Definition

Despite the impressive results of the large CRT trials, it has been observed that, on an individual basis, about 30% of patients do not respond to CRT. Inherent to this issue is the question: “what is the precise definition of a responder?”

Indeed various end points have been used in the individual studies. These can be divided into 2 main categories: clinical end points indicating improved clinical status (NYHA functional class, quality-of-life score, exercise capacity expressed as 6-min walking distance) and echocardiographic end points indicating improved LV systolic function or reversed LV remodeling. The occurrence of these end points, however, was not equal. Specifically, not all patients who exhibited a favorable response to the clinical end point responded in a similar fashion to the echocardiographic end point and vice versa. This was evaluated...
Recently, Bleeker et al. (14) examined 144 patients undergoing CRT and reported a favorable clinical response in 70% after 6 months of CRT (defined as a reduction in NYHA functional class by ≥1 grade), compared with a salutary echocardiographic response of 56% (defined as a reduction in LV end-systolic volume >15%) in those same patients. The discrepancy between these 2 end points was mainly related to patients who showed clinical improvement but did not show LV reverse remodeling. Although the precise reason for this inconsistency is unknown, it is widely believed to be the (partial) result of a placebo effect with device therapy resulting in subjective clinical improvement without objective improvement in LV systolic function or reduction in LV volumes.

If one pools the data of the 15 largest studies (15) that have reported these end points (Tables 1 and 2), it becomes clear that the weighted mean response rate is 66.9% for clinical end points (3–5,14,16–26) as compared with 56.9% for echocardiographic end points (14,27–40). In addition to the above end points, it has been questioned whether the absence of change (i.e., no deterioration) in clinical or echocardiographic parameters should also be considered a positive response to CRT. Indeed, prevention of the worsening of clinical or echocardiographic status can also be considered a positive response to CRT.

Although the vast majority of studies have used a clinical or echocardiographic end point, ideally one should focus on survival as an end point. Driven by these observations of nonresponse to CRT, substantial effort has been invested to predict response to CRT in order to improve selection of patients who may benefit from CRT. At present, these selection criteria include:

- NYHA functional class III or IV despite optimized medical therapy
- LVEF <35%
- QRS duration >120 ms (11)

The value of cardiac dyssynchrony in response to CRT.

From both experimental and clinical imaging studies, it has become evident that cardiac dyssynchrony is important for response to CRT. Dyssynchrony can occur at 3 levels:

- Atrioventricular dyssynchrony
- Interventricular dyssynchrony
- Intra-(LV) dyssynchrony

The weight of current evidence favors intraventricular or LV dyssynchrony as most associated with response to CRT. In a summary of 24 studies using echocardiography to predict response to CRT, only 2 studies demonstrated some value of interventricular dyssynchrony, whereas all 24 studies showed some predictive value of LV dyssynchrony (12). The lack of QRS duration alone to predict response could be explained by the finding that it is related to interventricular dyssynchrony, but not to LV dyssynchrony (41,42). In general, LV dyssynchrony appears more prevalent among patients with wider QRS complex, but this does not necessarily translate into response to CRT. Indeed, Mollemola et al. (43) recently evaluated 242 heart failure patients with wide QRS complex who underwent CRT implantation; receiver-operator characteristic curve analysis demonstrated an optimal cutoff value for baseline QRS duration to predict clinical response to CRT of 163 ms, which yielded a sensitivity and specificity of 53%. It has been postulated...
that patients with wider QRS complex (≥150 ms) may well respond to CRT (7), but subanalysis in patients with QRS duration ≥150 ms \((n = 189)\) yielded a sensitivity and specificity of 54% (at an optimal cutoff value of 171 ms) to predict clinical response (43). Moreover, as shown in Figure 1, the individualized response rates according to different QRS durations revealed similar nonresponse rate among the spectrum of QRS durations.

In view of the findings as noted in the previous text, many imaging studies examined the ability of LV dyssynchrony to predict the response to CRT. Helm et al. (44) demonstrated that magnetic resonance imaging and strain analysis detected substantial LV dyssynchrony in an animal model of heart failure, which improved after biventricular pacing in association with improved LV function. The vast majority of studies focusing on LV dyssynchrony have been performed with echocardiographic techniques to visualize LV dyssynchrony. The most frequently used techniques include M-mode echocardiography, tissue Doppler imaging (TDI), strain imaging, and three-dimensional (3D) echocardiography (Table 3). In general, these studies showed high sensitivity and specificity (both 80% to 90%) to predict response to CRT (12).

### The PROSPECT Study

The PROSPECT study was an attempt to identify which of several previously published markers of dyssynchrony would forecast success of CRT using a prospective, multicenter approach. The PROSPECT study was a nonrandomized observational study that evaluated pre-defined baseline echocardiographic dyssynchrony parameters for their ability to predict clinical and echocardiographic response to CRT (13). In that study, 426 patients were included according to the traditional selection criteria as recommended by the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines (11). The 6-month end points (response criteria) included a clinical composite score and ≥15% reduction in LV end-systolic volume; the discrepancy in end points was confirmed with 69% showing clinical improvement and 56% showing echocardiographic response.

Despite the intended purpose of the PROSPECT study, the overall results were disappointing with no clear echo-
The Most Frequently Used Echocardiographic Measurements to Detect LV Dyssynchrony and Their Accuracy to Predict Echocardiographic Response to CRT

<table>
<thead>
<tr>
<th>Author (Ref. #)</th>
<th>Patients (n)</th>
<th>Measurement</th>
<th>Echocardiographic Technique</th>
<th>Dyssynchrony Cutoff Value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitzalis et al. (45)</td>
<td>20</td>
<td>Septal-to-posterior wall motion delay</td>
<td>M-mode</td>
<td>≥130 ms</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>Marcus et al. (46)</td>
<td>79</td>
<td>Septal-to-posterior wall motion delay</td>
<td>M-mode</td>
<td>≥130 ms</td>
<td>24</td>
<td>66</td>
</tr>
<tr>
<td>Penicka et al. (47)</td>
<td>49</td>
<td>Sum of LV and VV dysynchrony (pulsed-wave systolic velocities)</td>
<td>Pulsed-wave TDI</td>
<td>≥102 ms</td>
<td>96</td>
<td>77</td>
</tr>
<tr>
<td>Bax et al. (48)</td>
<td>25</td>
<td>Delay in peak systolic velocity (2 segments: basal septum and lateral wall)</td>
<td>Color-coded TDI</td>
<td>≥60 ms</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>Notabartolo et al. (49)</td>
<td>49</td>
<td>Delay in onset of systolic velocity (6 basal LV segments)</td>
<td>Color-coded TDI</td>
<td>≥110 ms</td>
<td>97</td>
<td>55</td>
</tr>
<tr>
<td>Yu et al. (39)</td>
<td>54</td>
<td>Standard deviation of time to peak systolic velocities (12 LV segments)</td>
<td>Color-coded TDI</td>
<td>≥31.4 ms</td>
<td>96</td>
<td>78</td>
</tr>
<tr>
<td>Van de Veire et al. (50)</td>
<td>60</td>
<td>Standard deviation of time to peak systolic velocities (12 LV segments)</td>
<td>Tri-plane TDI</td>
<td>≥33 ms</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>Gorcsan et al. (51)</td>
<td>29</td>
<td>Delay in peak systolic velocity (2 segments: [antero]septal and posterior wall)</td>
<td>Tissue synchronization imaging</td>
<td>≥65 ms</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Suffoletto et al. (52)</td>
<td>64</td>
<td>Delay in peak strain (2 segments: anteroseptal and posterior wall)</td>
<td>2D radial strain</td>
<td>≥130 ms</td>
<td>89</td>
<td>83</td>
</tr>
<tr>
<td>Gorcsan et al. (53)</td>
<td>190</td>
<td>Combination between longitudinal and radial dyssynchrony (strain)</td>
<td>Color-coded TDI and 2D radial strain</td>
<td>≥60 ms</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>Marsan et al. (54)</td>
<td>60</td>
<td>Systolic dyssynchrony index = standard deviation of time to volume shift (16 LV segments)</td>
<td>Real-time 3D echocardiography</td>
<td>≥5.6%</td>
<td>88</td>
<td>86</td>
</tr>
</tbody>
</table>

CRT = cardiac resynchronization therapy; LV = left ventricular; TDI = tissue Doppler imaging; VV = interventricular; 2D = 2-dimensional; 3D = 3-dimensional.

The main question is: why did the PROSPECT study results demonstrate only a modest value of echocardiography to predict response to CRT, in contrast to previously published studies? Although the reported echocardiographic markers of dyssynchrony were of no clinical value. However, we have learned subsequently of several methodological and procedural problems with the PROSPECT study that are worthy of reviewing.

The PROSPECT Study Results in Perspective and How to Improve?

The main question is: why did the PROSPECT study results demonstrate only a modest value of echocardiography to predict response to CRT, in contrast to previously published studies? Although the reported echocardiographic markers of dyssynchrony were of no clinical value. However, we have learned subsequently of several methodological and procedural problems with the PROSPECT study that are worthy of reviewing.

Table 3

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Echocardiographic Technique</th>
<th>Dyssynchrony Cutoff Value</th>
<th>% Echocardiograms Assessable</th>
<th>Intraobserver CV (%)</th>
<th>Interobserver CV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal-to-posterior wall motion delay</td>
<td>M-mode</td>
<td>≥130 ms</td>
<td>72</td>
<td>24.3</td>
<td>72.1</td>
<td>64</td>
<td>52</td>
</tr>
<tr>
<td>LV pre-ejection interval: delay between onset QRS and onset LV ejection</td>
<td>Pulsed-wave Doppler</td>
<td>≥140 ms</td>
<td>95</td>
<td>3.7</td>
<td>6.5</td>
<td>72</td>
<td>44</td>
</tr>
<tr>
<td>Interventricular delay: difference between left and right pre-ejection intervals</td>
<td>Pulsed-wave Doppler</td>
<td>≥40 ms</td>
<td>92</td>
<td>NA</td>
<td>NA</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>LV filling time in relation to cardiac cycle length (pulsed-wave Doppler)</td>
<td>Pulsed-wave Doppler</td>
<td>≥40%</td>
<td>85</td>
<td>NA</td>
<td>NA</td>
<td>41</td>
<td>74</td>
</tr>
<tr>
<td>Delay in peak systolic velocity (2 segments: basal septum and lateral wall)</td>
<td>Color-coded TDI</td>
<td>≥60 ms</td>
<td>67</td>
<td>NA</td>
<td>NA</td>
<td>53</td>
<td>69</td>
</tr>
<tr>
<td>Delay in onset of systolic velocity (6 basal LV segments)</td>
<td>Color-coded TDI</td>
<td>≥110 ms</td>
<td>81</td>
<td>NA</td>
<td>NA</td>
<td>68</td>
<td>34</td>
</tr>
<tr>
<td>Standard deviation of time to peak systolic velocities (12 LV segments)</td>
<td>Color-coded TDI</td>
<td>≥31.4 ms</td>
<td>50</td>
<td>11.4</td>
<td>33.7</td>
<td>78</td>
<td>31</td>
</tr>
</tbody>
</table>
Various potential issues related to the unexpected results reported in the PROSPECT study are summarized in Table 5.

### Patient selection
Most of the patients in small single-center studies were carefully selected, with inclusion of only the most severe heart failure patients. In the PROSPECT study, 20.2% of patients had an LVEF more than 35% and 37.8% had an LV end-diastolic dimension <65 mm, suggesting inclusion of less severe heart failure patients. This is a particularly important confounding variable in the PROSPECT study because reverse LV remodeling was one of the primary end points. In other words, an LV that was not dilated to begin with cannot reverse remodel in response to CRT. Accordingly, larger studies in heart failure patients with severely depressed LVEF (≤35%) and LV dilation (LV end-diastolic diameter >60 or 65 mm) are needed.

### Technical issues
A large percentage of nonassessable echocardiographic data were encountered, both for TDI and M-mode imaging, with feasibility yields ranging from 50% to 81% (as compared with 92% to 95% for the 2-dimensional echocardiography data). Moreover, the interobserver variability of M-mode and TDI measurement was large, indicating lack of standardized data acquisition and analysis. Better training and education might improve the assessability of echocardiographic (M-mode and TDI) parameters, and also reduce interobserver variability. For example, an improvement in the rigor of TDI data analysis is needed, such as size and placement of the regions of interest, to reduce interobserver variability. Also, TDI analysis is based on comparison in timing of peak systolic velocities of different cardiac regions; at times, not 1 but multiple peaks are observed during systole, and a clear and uniform agreement on the selection of peaks that are used to calculate LV dyssynchrony is needed (55,56). Moreover, some studies have included peak systolic velocities occurring after aortic valve closure post-systolic velocities in the calculation of cardiac dyssynchrony, whereas other studies excluded post-systolic signals, and consensus on this issue is currently lacking.
Figure 3  Patient Example of 2D Speckle Tracking Strain Assessment

(Left) The 2-dimensional (2D) strain images and segmental curves in a patient before cardiac resynchronization therapy. The segmental time-strain curves (color-coded) represent the 6 myocardial segments (light blue = septal; yellow = anteroseptal [AS]; red = anterior; green = lateral; purple = posterior [P]; and dark blue = inferior). From these curves, the maximum time difference in peak systolic strain between 2 segments can be determined (in this patient, 228 ms). Resynchronization after 6 months of cardiac resynchronization therapy is shown in the right panel.

Figure 4  Tri-Plane Tissue Synchronization Imaging in a Patient With Dilated Cardiomyopathy Showing Severe LV Dyssynchrony

Using a tri-plane probe, the 2-, 3-, and 4-chamber views are simultaneously acquired. This 3-dimensional assessment of dyssynchrony displays mechanical activation times in colors. The orange-yellow color indicates late activation of the inferior and posterior regions as compared with the remainder of the myocardium (green). The polar map shows the timing from QRS to peak systolic velocity in each of 12 segments that are analyzed (bottom right); the inferior and posterior segments (yellow) show the latest mechanical activation. LV = left ventricular.
Figure 5  Parametric Polar Maps Derived From Real-Time 3-Dimensional Echocardiography

Color-coding (blue indicating early activation and orange-red late activation) represents the time needed to reach the minimum systolic volume, showing that the inferior and posterior left ventricular regions are the latest activated before cardiac resynchronization therapy (A). Six months after cardiac resynchronization therapy (B), the overall green color indicates absence of regions with delayed activation.

Figure 6  Phase Analysis on Gated Myocardial Perfusion SPECT Permits Assessment of LV Dyssynchrony

(A) Shows data from a patient without left ventricular (LV) dyssynchrony. The homogeneous phase angle distribution (non-normalized) is illustrated by a homogeneous color-coding scale (polar map format, left) and a narrow and highly peaked histogram (right). Phase angle reflects timing of conduction within the cardiac cycle (0° to 360°). (B) Shows data from a patient with extensive LV dyssynchrony. The heterogeneous phase angle distribution (non-normalized) is reflected by a heterogeneous color-coding scale (polar map format, left) and a broad and moderate peaked histogram (right). SPECT = single-photon emission computed tomography. Reproduced, with permission, from Henneman et al. (60).
Furthermore, TDI data were obtained using instruments from 3 ultrasound vendors without standardization of frame rates, and 3 different software programs were used for offline data analysis. It seems apparent in retrospect that these technical differences introduced confounding variables that likely affected the PROSPECT study results. When the PROSPECT study began, technological development of offline software for dyssynchrony analysis was relatively new, and improvements by all 3 vendors have occurred subsequently to reduce variability.

In addition, improvement in technology for assessment of LV dyssynchrony is needed. In patients with extensive infarction, both M-mode imaging and TDI fail (to some extent) to provide optimal information on LV dyssynchrony; the septum is frequently a flat line on M-mode imaging (Fig. 2), and TDI provides only information on myocardial velocities, which does not permit differentiation between passive motion and active deformation. In this respect, strain analysis (providing information on active deformation) may be preferred, and novel 2-dimensional strain techniques are promising (Fig. 3). This difficulty has recently been highlighted in various articles, proposing strain as the preferred marker for LV dyssynchrony assessment (55,56).

Still, it is clear that LV dyssynchrony is important in the prediction of response to CRT. Not only have echocardiographic techniques shown this, but other imaging modalities have also reported the value of LV dyssynchrony to forecast the response to CRT, including magnetic resonance (58) and nuclear imaging techniques (59,60) (Fig. 6).

Pathophysiological issues. It has been shown that scar tissue in the region where the LV pacing lead is positioned may reduce the effect of CRT (61,62); of note, the precise extent of scar tissue throughout the wall (transmurality) that would result in nonresponse is not yet clear. In addition, it has been shown that the total extent of scar tissue in the LV is important: too great a scar tissue limits response to CRT (Fig. 7) (63). Most imaging techniques have been used for the assessment of scar tissue, although contrast-enhanced magnetic resonance imaging may be preferred since its high spatial resolution permits precise delineation of transmurality of scar tissue (Fig. 8).

The position of the LV pacing lead is also important; preliminary studies have indicated that positioning the LV

![Figure 7](image7.png)

**A clear relation between the 2 parameters existed. Patients with extensive scar tissue showed virtually no improvement in left ventricular end-systolic volume (LVESV) after cardiac resynchronization therapy (CRT). LV = left ventricle. Reproduced, with permission from Ypenburg et al. (63).**

![Figure 8](image8.png)

**Figure 8 Location and Quantification of Scar Tissue With Contrast-Enhanced MRI**

Contrast-enhanced magnetic resonance imaging (MRI) has excellent spatial resolution and may be the preferred technique for assessment of scar tissue. (A) A patient with transmural infarction in (part of) the lateral wall, the inferior wall, and the septum (the white tissue, arrow). (B) Subendocardial scar formation in a patient with a previous inferior infarction (arrow indicates scar formation).
lead outside of the region of latest activation on echocardiography resulted in poor response to CRT (38,64). In this perspective, it may be important to noninvasively assess the venous anatomy before CRT implantation to decide whether (accessible) veins are present in the target region or whether a surgical approach with epicardial LV lead placement may be preferred. The feasibility of noninvasive assessment of venous anatomy with multislice CT has been demonstrated recently, and results indicated that poor venous anatomy can be encountered in patients with previous infarction (Fig. 9) (65). Moreover, coregistration of multislice computed tomography and 3D dyssynchrony maps may provide the required information (66).

All of these aforementioned issues can potentially influence the response to CRT and may have been more prominently present in the PROSPECT study population, as compared with the carefully selected populations in the small, single-center studies.

While issues concerning the study population and technology can be at least partially resolved in the future, pathophysiological factors that prevent response to CRT cannot be significantly altered. It appears increasingly important to integrate the information on LV dyssynchrony (site of latest mechanical activation), the location and transmural extent of infarction, and the venous anatomy before CRT implantation. Based on this integrated information, it will be possible to determine whether the patient has a high or low likelihood of response to CRT (Fig. 10); this may be more realistic rather than focusing on LV dyssynchrony parameters only, aiming to derive at precise cutoff values to predict response to CRT. One can even foresee that based on an integrated approach, the focus will become to identify nonresponders with high precision, which may be the most important issue from a clinical perspective.

Conclusions

Mechanical LV dyssynchrony appears to be an important pathophysiological feature that is improved by CRT, and this improvement is related to LV reverse remodeling and favorable clinical outcomes. A large body of published evidence from a multitude of independent scientific institutions from around the world have demonstrated promise for echocardiographic measures of LV dyssynchrony to predict response to CRT. Although the results of the
PROSPECT study were modest in comparison with results from many single-center studies, one should not conclude that the PROSPECT study is more correct because of its multicenter design. Clearly, patient selection, technical factors with echocardiographic data acquisition and analysis, and pathophysiological issues are significant confounding variables that need to be considered when interpreting the PROSPECT study results. CRT is undeniably a beneficial therapy for a large number of heart failure patients who are selected properly. The PROSPECT study taken in perspective has taught us some valuable lessons regarding the complexity of echocardiographic dysynchrony analyses and other factors that influence patient response to CRT. Refinements in the technical aspects of data acquisition and analysis along with a greater understanding of pathophysiology will continue to add benefit to the care of CRT patients.

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Key Words: heart failure • cardiac resynchronization therapy • cardiac dyssynchrony • tissue Doppler imaging.