Appropriate cardiac resynchronization therapy (CRT) enhances quality of life and improves survival in patients with refractory heart failure due to systolic dysfunction and mechanical dyssynchrony. On the assumption that the main therapeutic mechanism of CRT is the correction of dyssynchronous myocardial contraction, imaging-based measures of dyssynchrony have been intensely investigated with the aim of predicting response to therapy. Numerous echocardiographic dyssynchrony parameters have been proposed, but no large prospective trial have been published to prove the clinical utility of any of these indexes. Moreover, the methodology to derive the proposed dyssynchrony indexes has not been standardized. Therefore, the purpose of this article is to critically review the current status of proposed dyssynchrony indexes by echocardiography for patient selection and to recommend future investigations in this area.

CRT: From Origins to Routine Clinical Practice

The adverse effects of dyssynchronous activation\(^1\) and the ability to correct these abnormalities with biventricular stimulation\(^2\) were described long ago, but the potential therapeutic application was not realized until an unprecedented study in 1990 reported recovery from intractable heart failure in 16 patients implanted with conventional dual-chamber pacemakers programmed to a short atrioventricular (AV) delay.\(^3\) Although these results could not be reproduced in prospective studies\(^4,5\) and improvements could only be demonstrated short-term in highly selected patients,\(^6\) the race to find a pacing therapy for heart failure had begun.

On the hypothesis that the disappointing results of dual-chamber pacing in prospective studies were due to cancelling or overcoming the beneficial effects of AV synchronisation by the adverse effect of RV pacing-induced dyssynchrony,\(^7,8\) Cazeau and colleagues proposed a 4-chamber pacing mode and reported the first successful permanent implant in 1994.\(^9\) Early randomized controlled trials confirmed short-term improvements in functional capacity and quality of life for patients.\(^10–13\) However it was the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION; \(n=1520\) patients) and the Cardiac Resynchronisation in Heart Failure (CARE-HF; \(n=804\) patients) trials that firmly established the role of CRT in contemporary heart failure therapy by demonstrating a significant reduction in combined all-cause mortality and hospital admissions.\(^14,15\)

Selection of Candidates in CRT Clinical trials

The prerequisites of refractory cardiac failure (New York Heart Association class 3 or 4 and optimal medical therapy) and severe left ventricular (LV) impairment were apparent and have not varied between trials. The requirement of sinus rhythm to combine both AV and ventricular resynchronization was stipulated in all the randomized controlled trials with the exception of a substudy of 39 patients in the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial.\(^16\) However, the choice of a surrogate marker for LV electromechanical dyssynchrony was more problematic and varied between the acknowledged “empirical choice” of a QRS >150 ms in MUSTIC, to inclusion of all patients with QRS >120 ms in COMPANION, to combined ECG and echo inclusion criteria in CARE-HF (QRS >150 ms or QRS >120 ms plus 2 out of 3 of aortic preejection delay >140 ms, interventricular delay >40 ms, and maximal contraction of the posterolateral wall occurring after the onset of LV filling).

Defining Response to Therapy

The best measure for defining response to CRT has not been established. However, nonresponse to CRT was recognized early on,\(^12,17,18\) spawning a plethora of small nonrandomized echocardiographic studies aiming to predict response to CRT. “Response” was usually defined by echocardiographic rather than clinical parameters, and cutoffs for response differed, resulting in varying proportions of “nonresponders.” Furthermore, dyssynchrony indexes did not predict clinical response so well as reverse remodeling.\(^19,20\) However, Yu and colleagues justified the use of echocardiographic parameters by reporting...
that reverse remodeling (reduction in LV end-systolic volume \( \geq 10\% \)) predicted 1-year survival but that clinical parameters (New York Heart Association class and 6-minute walk and quality of life scores) were unrelated to survival in these heart failure patients. A recent study comparing clinical and echocardiographic responses to CRT demonstrated clinical improvement in 70\% but reverse remodeling, defined as reduction in LV end-systolic volume \( \geq 15\% \), in only 56\%. Interestingly, when change in LV end-systolic volume was subdivided into quintiles of response, a clear relationship was seen between the percent-

### Table 1. Proposed Echocardiographic Measures of Intraventricular Dyssynchrony to Predict Response to CRT

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Method</th>
<th>Parameter for Regional Timing</th>
<th>No. of Segments Measured</th>
<th>Follow-Up, mo</th>
<th>Definition of Response</th>
<th>Criteria, ( \geq )</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitzalis</td>
<td>20</td>
<td>M-mode</td>
<td>SPWMD</td>
<td>2 (AS-P)</td>
<td>1</td>
<td>ESV ( \downarrow ) 15%</td>
<td>130 ms</td>
<td>100</td>
<td>63</td>
<td>(b) SPWMD &lt;130 ms separated event-free curve of hospitalization or death</td>
</tr>
<tr>
<td>Pitzalis</td>
<td>(a) 51</td>
<td>M-mode</td>
<td>SPWMD</td>
<td>2 (AS-P)</td>
<td>( \geq 6 )</td>
<td>(a) EF ( \uparrow ) ( \geq +5% )</td>
<td>130 ms</td>
<td>(a) 92</td>
<td>(a) 78</td>
<td></td>
</tr>
<tr>
<td>Marcus</td>
<td>79</td>
<td>M-mode</td>
<td>SPWMD</td>
<td>2 (AS-P)</td>
<td>6</td>
<td>(a) ESI ( \downarrow ) ( \geq 15% )</td>
<td>130 ms</td>
<td>(a) 24</td>
<td>(a) 66</td>
<td>Low feasibility of SPWMD (45%)</td>
</tr>
<tr>
<td>Diaz-Infante</td>
<td>67</td>
<td>M-mode</td>
<td>SPWMD</td>
<td>2 (AS-P)</td>
<td>6</td>
<td>(b) NYHA ( \geq 1 )</td>
<td>130 ms</td>
<td>(b) 24</td>
<td>(b) 66</td>
<td>SPWMD did not correlate with BNP level at follow-up</td>
</tr>
<tr>
<td>Sassone</td>
<td>48</td>
<td>M-mode</td>
<td>(1) Presence of LWPSD</td>
<td>(1) 1 (lateral, 4 chamber)</td>
<td>6</td>
<td>ESV ( \downarrow ) ( \geq 15% )</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) SPWMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jensen</td>
<td>53</td>
<td>2D</td>
<td>Presence of abnormal motion pattern</td>
<td>3</td>
<td>ESV ( \downarrow ) ( \geq 10% )</td>
<td>(1) Shuffle</td>
<td>(1) 73–87</td>
<td>(1) 75–88</td>
<td>Good concordance between visual assessment and To-SD in 6 basal segments</td>
<td></td>
</tr>
<tr>
<td>Penicka</td>
<td>49</td>
<td>PWTDI</td>
<td>Sum asynchrony*</td>
<td>3 + RV</td>
<td>6</td>
<td>EF ( \uparrow ) ( \geq 25% )</td>
<td>102 ms</td>
<td>96</td>
<td>77</td>
<td>No difference in clinical and echo outcome in patients with or without dyssynchrony</td>
</tr>
<tr>
<td>Jansen</td>
<td>69</td>
<td>PWTDI</td>
<td>(1) To-SD</td>
<td>6 (basal)</td>
<td>3</td>
<td>ESV ( \downarrow ) ( \geq 15% )</td>
<td>(1) 20.4 ms</td>
<td>(1) 97</td>
<td>(1) 74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Ts-SD</td>
<td>6 (basal)</td>
<td></td>
<td></td>
<td></td>
<td>(2) 31.3 ms</td>
<td>(2) 78</td>
<td>(2) 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3) To-Diff</td>
<td>2 (S-L)</td>
<td></td>
<td></td>
<td></td>
<td>(3) 25 ms</td>
<td>(3) 79</td>
<td>(3) 58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4) Ts-Diff</td>
<td>2 (S-L)</td>
<td></td>
<td></td>
<td></td>
<td>(4) 33 ms</td>
<td>(4) 76</td>
<td>(4) 57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(5) To-Diff</td>
<td>2 (AS-P)</td>
<td></td>
<td></td>
<td></td>
<td>(5) 30 ms</td>
<td>(5) 84</td>
<td>(5) 84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(6) To-Diff</td>
<td>2 (AS-P)</td>
<td></td>
<td></td>
<td></td>
<td>(6) 45 ms</td>
<td>(6) 81</td>
<td>(6) 71</td>
</tr>
<tr>
<td>Soliman</td>
<td>60</td>
<td>PWTDI</td>
<td>(1) To-Diff</td>
<td>2 (S-L)</td>
<td>12</td>
<td>(a) NYHA ( \geq 1 ) and 6MWD ( \uparrow ) ( \geq 25% )</td>
<td>(1) (2) 60 ms</td>
<td>NA</td>
<td>NA</td>
<td>No difference in clinical and echo outcome in patients with or without dyssynchrony</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Ts-Diff</td>
<td></td>
<td></td>
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</tbody>
</table>

(Continued)
nage of clinical responders and degree of reverse remodeling, suggesting a spectrum rather than an absolute response/nonresponse to CRT.21

Current Recommended Selection Criteria for CRT
As successive publications each proposed a new dyssynchrony measure to reliably predict outcome, the clinician was presented with a bewildering array of echo determinants on which to base his or her selection. The publication of almost identical European22 and American Heart Association/American College of Cardiology (AHA/ACC)23 guidelines for CRT in 2005 that omitted any reference to echocardiographic measures of dyssynchrony was therefore met with relief by heart failure specialists and electrophysiologists alike. However, recent UK National Institute for Health and Clinical Excellence (NICE) guidelines24 may be interpreted as a retrograde step by

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Method</th>
<th>Parameter for Regional Timing</th>
<th>No. of Segments Measured</th>
<th>Follow-Up, mo</th>
<th>Definition of Response</th>
<th>Criteria, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achilli34</td>
<td>133</td>
<td>PWTDI (1) Interventricular delay</td>
<td>(2) 2 (S-L)</td>
<td>6</td>
<td>Combined outcome (clinical improvement and EF ↑ ≥ 5%)</td>
<td>(1) 44 ms</td>
<td>66</td>
<td>55</td>
<td>Intraventricular dyssynchrony did not differ in responders and nonresponders</td>
<td></td>
</tr>
<tr>
<td>M-mode (2) To-diff (3) LWPSD</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bax 26</td>
<td>25</td>
<td>CCTDI</td>
<td>Ts-Diff 2 (S-L) Acute</td>
<td>6</td>
<td>EF ↑ ≥ 5%</td>
<td>60 ms</td>
<td>76</td>
<td>87.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bax 19</td>
<td>85</td>
<td>CCTDI</td>
<td>Ts-Diff (max opposing wall delay) 2 (4C or 2C)</td>
<td>6</td>
<td>(a) ESV ↓ ≥15%</td>
<td>65 ms</td>
<td>(a) 92</td>
<td>(a) 92</td>
<td>(c) S-L delay ≥65 ms was able to separate event curve (hospitalization or death)</td>
<td></td>
</tr>
<tr>
<td>Van De Vaire36</td>
<td>60</td>
<td>TSI</td>
<td>Ts-Diff 2 (S-L)</td>
<td>6</td>
<td>(a) NYHA ↓ ≥1 and 6MWD ↑ ≥25%</td>
<td>65 ms</td>
<td>(a) 80</td>
<td>(a) 92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleecker37</td>
<td>98</td>
<td>M-mode</td>
<td>(1) Ts-Diff 2 (S-L)</td>
<td>6</td>
<td>(a) NYHA ↓ ≥1 and 6MWD ↑ ≥25%</td>
<td>65 ms</td>
<td>(b) 81</td>
<td>(b) 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorcsan38</td>
<td>29</td>
<td>CCTDI</td>
<td>Tpss-Diff 2 (AS-P) Acute</td>
<td>6</td>
<td>SV ↑ ≥15%</td>
<td>65 ms</td>
<td>87</td>
<td>100</td>
<td>Concordance in LV lead location and the delayed segments were associated to more frequent acute response</td>
<td></td>
</tr>
<tr>
<td>Notabartoro39</td>
<td>49</td>
<td>CCTDI</td>
<td>Tpss-Diff 6 (basal)</td>
<td>3</td>
<td>(a) ESV ↓ ≥15%</td>
<td>110 ms</td>
<td>(a) 97</td>
<td>(a) 97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu 39</td>
<td>30</td>
<td>CCTDI</td>
<td>Ts-SD 12</td>
<td>3</td>
<td>ESV ↓ ≥15%</td>
<td>32.6 ms</td>
<td>100</td>
<td>100</td>
<td>Strain rate–derived parameters were not predictive of reverse remodelling</td>
<td></td>
</tr>
<tr>
<td>Yu 40</td>
<td>54</td>
<td>CCTDI, strain rate</td>
<td>Ts-SD 12</td>
<td>&gt;3</td>
<td>ESV ↓ ≥15%</td>
<td>31.4 ms</td>
<td>96</td>
<td>78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
some. Echocardiographic measures of “mechanical dyssynchrony” are required for patients with QRS of 120 ms to 150 ms, with no guidance on how best to measure this dyssynchrony, the cutoffs to use, or indeed whether AV, interventricular or LV dyssynchrony is required.

### Proposed Echocardiographic Dyssynchrony Parameters

In the following section, we describe the currently proposed echocardiographic intra- and interventricular dyssynchrony parameters, their technical pros and cons, and existing prog-
nostic data for each technique, which are not all consistent. Key features and findings of published reports of echocardiographic intraventricular dyssynchrony parameters for the prediction of response to CRT are summarized in Table 1. Disadvantages and advantages of each echocardiographic method for the quantification of intraventricular mechanical dyssynchrony are listed in Table 2.

### Intraventricular Dyssynchrony

#### M-Mode Echocardiography

Septal-posterior wall motion delay, the time difference between peak inward motion of the ventricular septum and the posterior wall, is obtained from parasternal short axis M-mode images. An initial report showed septal-posterior wall motion delay $\geq 130$ ms to predict reduction in LV end-systolic volume index $>15\%$ with a sensitivity of $100\%$ and a specificity of $63\%$ in 20 patients at 1 month and later to predict improvement in LV ejection fraction (LVEF) $>5\%$ and better prognosis at 6 months after CRT. However, such a delay could only be quantified in regions that were perpendicular to the ultrasound beam and was feasible in only half of patients. M-mode of color tissue Doppler imaging enhances timing measurements (Figure 1) but is still limited to assessments of the septum and the posterior wall. In 3 subsequent reports, septal-posterior wall motion delay did not predict outcome after CRT.

#### Tissue Velocity

Tissue Doppler imaging (TDI) allows measurement of either longitudinal tissue velocity or deformation (strain) of myocardium, both of which have been used to measure mechanical dyssynchrony. Most publications have employed tissue velocity dyssynchrony measurements, but its methods have not been standardized in following areas:

Both pulsed-wave TDI and color-coded TDI have been used to identify peak systolic velocity.
Both time to peak velocity and time to onset of systolic velocity have been measured to calculate dyssynchrony index. The number (2, 6, or 12) and location of segments sampled to obtain dyssynchrony index have varied. Both the standard deviation and the maximum difference of timing intervals have been used to calculate a dyssynchrony index. Velocity peaks were measured during the ejection period only or in both the ejection and the postejection period.

The advantage of pulsed-wave TDI is that it does not require high-end equipment, specific software, or offline analysis, and its drawback is that it requires sampling of multiple regions from different cardiac cycles, which is time consuming and renders tissue velocity peaks more difficult to identify. A sum of dyssynchrony index measured from the time to onset of tissue velocity in each of the basal septal, lateral, inferolateral, and right ventricular free walls showed a sensitivity of 96% and specificity of 77% to predict increase in LVEF \( \geq 25\% \) after CRT.\textsuperscript{31} However more recently, no significant difference in septal–lateral delay in time to onset of systolic velocity using pulsed-wave TDI was found between responders and nonresponders.\textsuperscript{34} Furthermore, neither septal–lateral delay

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-mode echocardiography</td>
<td>No specific ultrasound equipment is needed</td>
<td>Difficult to determine the timing of inward motion if the wall is akinetic or has plateau in motion</td>
</tr>
<tr>
<td></td>
<td>Easy to perform</td>
<td>Only can assess limited walls (anteroseptal and inferolateral wall)</td>
</tr>
<tr>
<td>Tissue velocity imaging</td>
<td>High temporal resolution (&gt;1000–3000 fps)</td>
<td></td>
</tr>
<tr>
<td>Pulsed-wave doppler</td>
<td>High temporal resolution</td>
<td>Does not allow simultaneous sampling in multiple segments</td>
</tr>
<tr>
<td></td>
<td>Does not require specific ultrasound equipment</td>
<td>Requires multiple imaging to map the entire heart</td>
</tr>
<tr>
<td>Color-coded tissue doppler</td>
<td>Relatively high temporal resolution (&gt;100 fps)</td>
<td>Requires high-end ultrasound equipment</td>
</tr>
<tr>
<td></td>
<td>Allows sampling of multiple segments simultaneously from one image</td>
<td>Susceptible to translational motion or tethering effect</td>
</tr>
<tr>
<td>Tissue synchronization imaging</td>
<td>Same as color-coded TDI</td>
<td>Same as color-coded TDI</td>
</tr>
<tr>
<td></td>
<td>Enables quick measurement of timing</td>
<td>Color-coding can change substantially depending on time window setting</td>
</tr>
<tr>
<td>Strain imaging</td>
<td>Relatively high temporal resolution (&gt;200 fps for individual wall imaging, &gt;100 for whole apical views)</td>
<td>Time-consuming image analysis</td>
</tr>
<tr>
<td>TDI-derived</td>
<td>Less affected by translational and tethering motion</td>
<td>High angle dependency: difficult in spherical heart</td>
</tr>
<tr>
<td>Speckle tracking</td>
<td>Nearly automated analysis: less variability</td>
<td>Less reproducibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires specific software</td>
</tr>
<tr>
<td>3-D echocardiography</td>
<td>Enables the dyssynchrony assessment in one image</td>
<td>Highly dependent on image quality: not feasible in all patients</td>
</tr>
<tr>
<td></td>
<td>Nearly automated analysis</td>
<td>Highly dependent on 2-D image quality: not feasible in all patients</td>
</tr>
<tr>
<td></td>
<td>Option to display the temporal and spatial distribution of timing in bull’s eye plot</td>
<td>Low temporal (15–25 fps) and spatial resolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires specific high-end ultrasound equipment and probe</td>
</tr>
<tr>
<td>3-D echocardiography</td>
<td></td>
<td>Highly dependent on image quality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incomplete inclusion of dilated apex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires several regular heart beats: cannot perform in atrial fibrillation or frequent ectopic beats</td>
</tr>
</tbody>
</table>

fps indicates frames per second; 2-D, 2-dimensional; and 3-D, 3-dimensional.
in time to peak nor onset of systolic velocity predicted clinical improvement or reverse remodeling.\textsuperscript{33}

Most published data on mechanical dyssynchrony have used color-coded TDI, which allows simultaneous processing of multiple sample points on the same image for a more comprehensive assessment of dyssynchrony. Bax and colleagues reported that basal septal–lateral delay $>60$ ms in time to peak systolic velocity predicted a short-term improvement in EF,\textsuperscript{35} and similar dyssynchrony index (maximum difference in opposing basal segment delay in the apical 4-chamber or 2-chamber view) $>65$ ms predicted reverse remodeling at 6 months after CRT.\textsuperscript{19} Yu and colleagues proposed a dyssynchrony index of standard deviation in time to peak systolic velocity among 12 basal and mid segments (Ts-SD) (Figures 2 and 3). Ts-SD $>32.6$ ms predicted reverse remodeling 3 months after CRT with a sensitivity and specificity of 100% in the initial 30 patients\textsuperscript{39} and Ts-SD $>31.4$ ms with a sensitivity of 96\% and specificity of 78\% in a subsequent 54 patients.\textsuperscript{40} Yu and colleagues also showed that correlation with reverse remodeling after CRT was better with Ts-SD than any other tissue Doppler parameters, including 2-segment delay, 6–basal segment delay, and maximum difference in 12 segments.\textsuperscript{40} On the other hand, the Resynchronization Therapy in Normal QRS (RethinQ) study recently found no benefit to CRT in patients with heart failure with a narrow QRS interval ($<130$ ms) when study entry was determined by a delay of at least 65 ms between 2 opposing walls using color-coded tissue velocity technique.\textsuperscript{51}

Why is there this discrepancy? Determining which “peak” to measure may be a part of the problem. Difficulty in identifying a correct peak to measure is illustrated by several examples in Figure 4. Two distinct peaks of tissue velocity during the ejection period are not uncommon from the free wall even in normal subjects\textsuperscript{52} (Figures 4 and 5). Such double peaks often show beat-to-beat variability in velocities (Figure 4). Besides, patients with conduction delay and impaired systolic function often show more prominent positive velocities during isovolumic contraction or in the postsystolic period than in the ejection period and sometimes do not show a distinct peak during the ejection period (Figure 4). Therefore, considerable variations in measurements may arise depending on which peak is selected.

The aforementioned studies\textsuperscript{19,35,39,40} of tissue velocity–derived dyssynchrony indexes used peaks only within the ejection period. However, it is also known that dyssynchronous motion in electrical activation delay is characterized by early septal motion frequently seen in the isovolumic contraction period and delayed lateral motion during the postsystolic period.\textsuperscript{53} Assessments of myocardial motion that include pre- or postejection periods, or both, may have more value for dyssynchrony measurement than those that focus on motion solely during the ejection period. When postsystolic peak velocities were included, an anteroseptal-posterior delay $>65$ ms predicted improvement in stroke volume $>15\%$ with a specificity of 92\%.\textsuperscript{38} On the other hand, the maximum difference in time to peak velocity predicted reverse remodeling with a poor specificity of 55\% three months after CRT when postsystolic peaks were included.\textsuperscript{20} Yu and colleagues reported a similar detrimental effect for predicting response to CRT when postsystolic peaks were included.\textsuperscript{40,41} In another study, the percentage of segments showing delayed longitudinal contraction after aortic valve closure correlated with response to CRT.\textsuperscript{46}
Dependence of tissue velocity dyssynchrony parameters on longitudinal motion to represent regional contraction in this population may also be problematic. In hearts with left bundle branch block (LBBB) and reduced LV contraction, long-axis forces are frequently unbalanced, both in their timing and magnitude of contraction. In such “rocking” hearts, overall rotational motion may be greater than any local velocity induced by regional contraction, and thus the local long-axis velocity curve may no longer reflect the timing and magnitude of regional contraction, and the timing of radial motion may better reflect regional contraction as it is less dependent on long-axis rotation.

**Strain Imaging**

Strain can be measured by TDI or by 2-dimensional speckle tracking and, as it is less affected by tethering or translation induced by unbalanced rocking motion, would theoretically be a more reliable measure of regional myocardial contraction. Tissue Doppler–derived strain is highly angle dependent and may be difficult to measure in patients with a spherical dilated heart and highly angulated basal segments. 2-dimensional speckle tracking based on speckle pattern recognition in B-mode echocardiography may prove to be superior because it is angle independent, allowing assessment of radial, circumferential, and longitudinal strain in all segments. The theoretical disadvantage of speckle tracking is its temporal resolution, which is lower than in tissue velocity–derived strain, especially in dilated hearts requiring large sector size for the imaging.

Using TDI, an abnormal strain pattern (premature early systolic shortening of the septum accompanied by lateral prestretch and followed by postsystolic lateral wall shortening) and its reversal immediately after CRT has been described in patients with left bundle branch block (Figure 6). A delay >130 ms in time to peak radial strain in the anteroseptal and inferolateral walls predicted a short-term increase in stroke volume, and the standard deviation in time to peak longitudinal strain among 12 basal and mid segments predicted reverse remodeling 6 months after CRT.

Using 2-dimensional speckle tracking, a delay >130 ms in time to peak systolic radial strain among 6 mid segments in the parasternal short-axis view (Figure 7) predicted increase in LVEF >15% with a sensitivity of 89% and a specificity of 83% at 8 months after CRT.

In contrast to these positive results, Yu and colleagues reported that standard deviation in time to peak systolic TDI-derived strain in 12 segments did not predict the response to CRT in 2 studies (a first study in 55 patients and a second in 256 patients). Another study also showed dyssynchrony indexes derived from speckle tracking and
tissue Doppler strain did not correlate with reverse remodeling 6 months after CRT.44

**Three-Dimensional Echocardiography**

Three-dimensional echocardiography enables the measurement of dyssynchrony indexes derived from the difference in minimal segmental volume and the standard deviation in time to minimal volume among 16 segments. Short-term improvement in 3-dimensional dyssynchrony index is seen after CRT.55,56 To date, no published study has assessed whether 3-dimensional echocardiography predicts response to CRT.

Poor temporal resolution compared with 2-dimensional or tissue Doppler echocardiography prevents precise measurement of timing and may result in failure to detect the brief early abnormal septal motion typical of left bundle branch block. Moreover, 3-dimensional full-volume image acquisition requires several consecutive beats with regular R-R intervals, limiting its application in patients with atrial fibrillation or frequent ectopic beats.

**Interventricular Dyssynchrony**

The preejection period difference between pulsed-wave Doppler flow in the aorta and pulmonary artery is used to represent interventricular dyssynchrony, correlates with QRS duration, and typically exceeds 40 ms in patients with QRS >150 ms.57 Although initially overlooked,25,58 the predictive value of preejection period difference was recently highlighted in 2 multicenter prospective trials. The Selection of Candidates for CRT (SCART) group reported that interventricular dyssynchrony >44 ms and smaller end-systolic diameter were the only independent predictors for combined clinical and echocardiographic response.54 and the CARE-HF group found that a cutoff value of 49.2 ms separated event-free curves after CRT.59

The tissue velocity delay between RV and LV free walls has also been used to represent interventricular dyssynchrony. However, contrary to the positive results from large prospective studies using pulsed-wave Doppler, interventricular dyssynchrony measured from tissue velocity either using time to peak19,40 or onset34 was not predictive for the effect of CRT.

**Cardiac Time Intervals**

Delayed electrical activation results in slow pressure development within the LV with delay in aortic valve opening and closure.60 Isovolumic relaxation can be prolonged because of continuing depolarization in late-activated segments and elastic recoil in early-activated segments after passive stretch by later-activated segments. The filling period shortens and is accentuated by concomitant AV delay. Isovolumic periods are prolonged at the expense of both ejection and filling.

![Figure 3. Color-coded tissue velocity recordings from 12 LV segments before (a) and after (b) CRT in 71-year-old patient with ischemic cardiomyopathy whose LVEF improved by 19% at 6 months after CRT. Apical 4-chamber (left), long-axis (middle), and 2-chamber (right) views are shown. Before CRT (a), marked difference in time to peak systolic velocity was noted among multiple segments (arrows). b, Six months after CRT, no improvement had occurred in the difference in time to peak systolic velocity.](http://circ.ahajournals.org/doi/abs/10.1161/CIR.0000000000000000)
period. Shortening of isovolumic contraction and prolongation of filling time are seen acutely after CRT and persist at follow-up, suggesting that these changes are related to an immediate change in electrical activation rather than subsequent reverse remodeling. Simple measurements of cardiac time intervals using pulsed-wave Doppler have been proposed as indirect measures of dyssynchrony and predictors of response to CRT. Total isovolumic time (sum of isovolumic contraction and relaxation times) correlated with the improvement of exercise capacity and cardiac output after CRT.

**Current Role of Echocardiography Before and After CRT**

High-quality echocardiography imaging is vital in the work-up of patients before beginning CRT. In addition to assessing ejection fraction for standard inclusion criteria, echocardiography plays a key role in determining pathogenesis, provides information on the extent of viable myocardium, which is relevant for extent of response to CRT, and is also essential for ruling out treatable valvular and ischemic pathologies. Echocardiography is also important after CRT for optimization of pacemaker AV delay. The defining CRT trials aimed to synchronize both atrioventricular and ventricular dyssynchrony (hence the inclusion requirement of sinus rhythm), and protocols required AV optimization (using either echocardiographic or intracardiac electrical delay method) in all patients. However, at present, most publications in this field are small nonrandomized studies. Clear guidance on the requirement for routine AV optimization or agreement on the “best method” is lacking, and as a result wide variations in practice exist. Larger randomized trials are required therefore to establish (1) the relative additional effect of AV delay optimization and (2) the best...
(echocardiographic or intracardiac electrical delay) method to use. In an ideal scenario, echocardiographic dyssynchrony measurements would guide the electrophysiologist in obtaining the ideal lead position. However, in practice this is often determined by venous anatomy and there may be more potential for echocardiographic lead position guidance during surgical epicardial lead placement. Currently, a major limitation of echocardiography,
as well as of other studies, is not being able to identify nonresponders with a very high accuracy. Although some centers may select patients for CRT on the basis of echocardiography measurement of dyssynchrony, we do not yet have an echocardiography parameter with a very high specificity or negative predictive value, on the basis of which CRT could be denied to patients who meet conventional selection criteria.

Figure 7. Radial strain curves from short-axis view of speckle tracking echocardiography. Significant timing difference was found among time to peak radial strain before CRT (a), and it was reduced after CRT (b).
**Conclusion and Recommendations**

Despite the huge output of publications in this field, we do not presently advise incorporating echocardiographic dyssynchrony parameters for the selection of candidates for CRT for the following reasons: First, no large published clinical trials exist to demonstrate benefit with a particular dyssynchrony index. Second, conflicting results are emerging on the predictive value of dyssynchrony indexes. Third, all the parameters described to date have either technical or theoretical limitations. A practical parameter or index for selection of appropriate patients for CRT should be simple and preferably should not require offline analysis. Clinically, it will be more important to identify nonresponders to CRT using various clinical, laboratory, and echocardiographic data with a very high accuracy. This ideal parameter has not been found.

Echocardiography also has an ongoing role in helping us to understand how CRT actually works. It is possible that response or nonresponse to CRT involves multiple interrelated mechanisms (myocardial viability within the paced area, underlying myocardial conditions such as fibrosis and hyper trophy, and location of the pacing lead) rather than a single mechanism of LV dyssynchrony. Before we hastily exclude potential candidates on the basis of indexes that are not yet validated in large clinical trials, we should try to better comprehend the pathophysiological mechanisms underlying response and nonresponse to therapy. Prospective randomized trials incorporating echocardiography are likely to play an important role in establishing extended indications for CRT. It may require several parameters, which could be used in a stepwise fashion, different parameters for different groups of patients (for example, ischemic versus nonischemic patients), or a combination of these methods, to select or exclude patients for CRT. Until we have a clinically reliable and practical parameter, inclusion criteria based on the major randomized trials should be employed to provide CRT to all deserving patients.

**Appendix: Current ACC/AHA/NASPE 2005 Guideline Update**

Patients with LVEF ≤35%, sinus rhythm, and New York Heart Association functional class III or ambulatory class IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration >120 ms, should receive CRT unless contraindicated (Class: I, Level of Evidence: A).

**Disclosures**

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Lisa J. Anderson, Chinami Miyazaki, George R. Sutherland and Jae K. Oh

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