Selecting patients for cardiac resynchronization therapy: electrical or mechanical dyssynchrony?

Nathaniel M. Hawkins1*, Mark C. Petrie2, Michael R. MacDonald2, Kerry J. Hogg1, and John J.V. McMurray3

1Department of Cardiology, Stobhill Hospital, Balornock Road, Springburn, Glasgow G21 3UW, UK; 2Royal Infirmary, Glasgow, UK; and 3Western Infirmary, Glasgow, UK

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Cardiac resynchronization therapy (CRT) markedly reduces morbidity and mortality in patients with heart failure and prolonged QRS duration. Landmark trials have included over 4000 patients based on their electrocardiogram. A few small, observational, non-randomized, single centre studies of short duration have suggested that echocardiographic measurement of mechanical dyssynchrony may better identify patients likely to benefit from CRT. We objectively review the meaning and measurement of electrical and mechanical dyssynchrony, the strengths and weaknesses of echocardiographic indices of dyssynchrony, and the controversial issue of predicting response to treatment. We conclude that proposals to alter current guidelines for patient selection, and include echocardiography, are misguided. Echocardiographic assessment will only become credible and applicable to clinical practice once used to select patients for large prospective randomized trials which show an improvement in clinical outcome.

KEYWORDS
Cardiac resynchronization therapy; Dyssynchrony; Tissue Doppler imaging

Introduction
Cardiac resynchronization therapy (CRT) improves functional status and reduces hospitalizations and mortality in patients with heart failure (HF). In the pivotal large randomized trials, patients were selected on the basis of three main criteria: impaired functional status (New York Heart Association class III or IV), reduced left ventricular (LV) ejection fraction (<0.35), and prolonged QRS duration (>120 ms). The latter was considered a marker of underlying ventricular dyssynchrony (so-called 'electrical dyssynchrony') (Table 1). Consequently, international guidelines recommend CRT based on the electrocardiographic (ECG) inclusion criteria in those trials.1

Some have stated that around one-third of patients appear not to improve clinically or exhibit favourable echocardiographic remodelling (so-called 'non-responders').2,3 It has been proposed that echocardiography may better identify those likely to respond to treatment by measuring actual mechanical dyssynchrony.4 If correct, this alternate approach to patient selection has two important clinical consequences. First, non-responders with a broad QRS would be spared an ineffective and invasive procedure, with resultant cost savings to healthcare providers. Conversely, patients with mechanical dyssynchrony but a narrow QRS complex, who were excluded from the landmark clinical trials, may benefit from CRT.

We review the meaning and measurement of electrical and mechanical dyssynchrony, the strengths and weaknesses of echocardiographic indices of dyssynchrony, and the controversial issue of predicting response to treatment. How valid is the concept of 'responders' vs. 'non-responders'? Should patients eligible for treatment based on inclusion criteria for clinical trials be excluded from that treatment in clinical practice? Why is such an approach advocated for devices but not for drug therapy?

Electrical dyssynchrony
What is electrical dyssynchrony?
The QRS complex represents the vectorial sum of electrical forces generated by myocardial masses over time. Normal electrical activation propagates as a uniform high-velocity wavefront through the myocardial Purkinje network. In damaged myocardium, altered conduction properties impair the velocity and direction of electrical propagation. Abnormal ventricular depolarization, manifesting as QRS prolongation, generates regions of both early and delayed ventricular contraction. The delayed segments accommodate contractile force and volume, reducing systolic function.

Why is electrical dyssynchrony important?
A direct relationship exists between QRS duration and ejection fraction.5-7 Prevalence of bundle branch block (BBB) varies from around 20% in the general HF population5,6 to 35% among patients with more severely impaired systolic function.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Follow-up (months)</th>
<th>QRS duration (ms)</th>
<th>LVEDD (mm)</th>
<th>Echo</th>
<th>LVEF (%)</th>
<th>NYHA class</th>
<th>SR/AF</th>
<th>ICD</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATH-CHF&lt;sup&gt;21&lt;/sup&gt;</td>
<td>41</td>
<td>Cross-over</td>
<td>1</td>
<td>≥ 120</td>
<td>No cut-off</td>
<td>No</td>
<td>No cut-off</td>
<td>III, IV</td>
<td>SR</td>
<td>No</td>
<td>6MWT + 44m; MLHFQ – 19.3; NYHA; Peak VO₂ + 1.8;</td>
</tr>
<tr>
<td>PATH-CHF II&lt;sup&gt;20&lt;/sup&gt;</td>
<td>86</td>
<td>Cross-over</td>
<td>3</td>
<td>≥ 120</td>
<td>No cut-off</td>
<td>No</td>
<td>≤ 30</td>
<td>II–IV</td>
<td>SR</td>
<td>Yes</td>
<td>6MWT + 47m; MLHFQ – 8.1; Peak VO₂ + 2.5;</td>
</tr>
<tr>
<td>MUSTIC-SR&lt;sup&gt;19&lt;/sup&gt;</td>
<td>48</td>
<td>Cross-over</td>
<td>3</td>
<td>&gt; 150</td>
<td>&gt; 60</td>
<td>No</td>
<td>&lt; 35</td>
<td>III</td>
<td>SR</td>
<td>No</td>
<td>6MWT + 73m; MLHFQ – 13.6; MLHFQ – 4.3; Peak VO₂ + 1.7;</td>
</tr>
<tr>
<td>MUSTIC-AF&lt;sup&gt;71&lt;/sup&gt;</td>
<td>37</td>
<td>Cross-over</td>
<td>3</td>
<td>&gt; 200 paced</td>
<td>&gt; 60</td>
<td>No</td>
<td>&lt; 35</td>
<td>III</td>
<td>AF</td>
<td>No</td>
<td>6MWT + 32m; MLHFQ – 4.3; MLHFQ – 9.0; NYHA;</td>
</tr>
<tr>
<td>MIRACLE&lt;sup&gt;2&lt;/sup&gt;</td>
<td>453</td>
<td>Parallel</td>
<td>6</td>
<td>≥ 130</td>
<td>≥ 55</td>
<td>No</td>
<td>≤ 35</td>
<td>III, IV</td>
<td>SR</td>
<td>No</td>
<td>6MWT + 29m; MLHFQ – 9.0; MLHFQ – 1.1; Peak VO₂ + 1.7;</td>
</tr>
<tr>
<td>MIRACLE-ICD&lt;sup&gt;72&lt;/sup&gt;</td>
<td>369</td>
<td>Parallel</td>
<td>6</td>
<td>≥ 130</td>
<td>≥ 55</td>
<td>No</td>
<td>≤ 35</td>
<td>III, IV</td>
<td>SR</td>
<td>Yes</td>
<td>6MWT + 2m; MLHFQ – 6.5; NYHA;</td>
</tr>
<tr>
<td>MIRACLE-ICD II&lt;sup&gt;73&lt;/sup&gt;</td>
<td>186</td>
<td>Parallel</td>
<td>6</td>
<td>≥ 130</td>
<td>≥ 55</td>
<td>No</td>
<td>≤ 35</td>
<td>II</td>
<td>SR</td>
<td>Yes</td>
<td>6MWT + 9m; MLHFQ – 2.6; MLHFQ – 2.3; Peak VO₂ – 0.3;</td>
</tr>
<tr>
<td>CONTAK-CD&lt;sup&gt;74&lt;/sup&gt;</td>
<td>490</td>
<td>Parallel</td>
<td>6</td>
<td>≥ 120</td>
<td>No cut-off</td>
<td>No</td>
<td>≤ 35</td>
<td>II–IV</td>
<td>SR</td>
<td>Yes</td>
<td>6MWT + 20m; MLHFQ – 2; MLHFQ – 0.49; Peak VO₂ + 0.8;</td>
</tr>
<tr>
<td>COMPANION&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1520</td>
<td>Parallel</td>
<td>16.2 (median)</td>
<td>≥ 120</td>
<td>≥ 60</td>
<td>No</td>
<td>≤ 35</td>
<td>III, IV</td>
<td>SR</td>
<td>Yes</td>
<td>Death, admission HR 0.81; Death HR 0.76; HF death, admission HR 0.76;</td>
</tr>
<tr>
<td>CARE-HF&lt;sup&gt;23&lt;/sup&gt;</td>
<td>813</td>
<td>Parallel</td>
<td>29.4 (mean)</td>
<td>≥ 150; ≥ 120</td>
<td>30 height</td>
<td>Yes</td>
<td>≤ 35</td>
<td>III, IV</td>
<td>SR</td>
<td>No</td>
<td>Death or MACE HR 0.63; Peak VO₂ + 0.002;</td>
</tr>
</tbody>
</table>

6MWT, 6 minute walk test; AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end diastolic diameter; MACE, major adverse cardiovascular event; MLHFQ, Minnesota Living with Heart Failure Questionnaire; SR, sinus rhythm; VO₂, oxygen consumption (mL/min/kg).
function. Reversal of maladaptive remodelling. 15–18 CRT improves symptoms, quality of life and functional class, increases exercise tolerance, and reduces hospitalizations and improvement. 10–13 Reduced mitral regurgitation, and tricular (BiV) pacing resynchronizes both intra- and interventricular contractions. The result is haemodynamic improvement, 10–13 reduced mitral regurgitation, and reversal of maladaptive remodelling. CRT improves symptoms, quality of life and functional class, increases exercise tolerance, and reduces hospitalizations and mortality. 22,23 In a recent study, RV lead to produce maximal QRS shortening may improve correlation between QRS narrowing and clinical efficacy suggests that after LV lead implantation, positioning the RV lead was positioned for maximum reduction to all major CRT trials to date (Table 1). National guidelines recommend CRT in patients with medically refractory, symptomatic (NYHA III/IV) HF, with prolonged QRS duration ≥120 ms, and ejection fraction ≤35%. Simultaneous biventricular (BiV) pacing resynchronizes both intra- and interventricular delays. The RV lead to produce maximal QRS shortening may improve correlation between QRS narrowing and clinical efficacy suggests that after LV lead implantation, positioning the RV lead to produce maximal QRS shortening may improve resynchronization. In a recent study, ΔQRS was an independent predictor of response after multivariate adjustment. The RV lead was positioned for maximum reduction in QRS duration at the apex, septum, anterior wall, or RV outflow tract, guided by intra-operative biventricular pace mapping.

Mechanical dyssynchrony

What is mechanical dyssynchrony?

Mechanical dyssynchrony may be considered in terms of inter- and intraventricular components. Intraventricular dyssynchrony refers to delayed activation of the LV relative to the right ventricle. Intraventricular dyssynchrony refers to delayed activation of one LV region relative to another. Correction of intraventricular delay frequently simultaneously improves interventricular delay through ventricular interdependence. CRT aims to correct both aspects of mechanical dyssynchrony.

Why is mechanical dyssynchrony important?

Baseline QRS duration consistently fails to predict response (Tables 2 and 7). However, change in QRS duration (ΔQRS) following CRT differs significantly between responders and non-responders in a number of studies. This correlation between QRS narrowing and clinical efficacy suggests that after LV lead implantation, positioning the RV lead to produce maximal QRS shortening may improve resynchronization. In a recent study, ΔQRS was an independent predictor of response after multivariate adjustment. The RV lead was positioned for maximum reduction in QRS duration at the apex, septum, anterior wall, or RV outflow tract, guided by intra-operative biventricular pace mapping.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Inclusion QRS duration (ms)</th>
<th>Follow-up (months)</th>
<th>Response criteria</th>
<th>Non-responders (%)</th>
<th>QRS responders vs. non-responders (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecoz et al. 24</td>
<td>139</td>
<td>&gt;150</td>
<td>6</td>
<td>Survival, and HF hospitalization, and NYHA ≥ 1 class, or peak VO₂ ≥ 10% or 6-min walk ≥ 10%</td>
<td>28</td>
<td>192 vs. 180; P = 0.018; 37 vs. 11; P &lt; 0.001</td>
</tr>
<tr>
<td>Pitzalis et al. 25</td>
<td>60</td>
<td>&gt;130</td>
<td>14</td>
<td>Survival, and heart failure hospitalization</td>
<td>27</td>
<td>168 vs. 179; P = NS; 45 vs. 31; P &lt; 0.05</td>
</tr>
<tr>
<td>Bax et al. 26</td>
<td>85</td>
<td>≥120</td>
<td>6</td>
<td>NYHA ≥ 1 class, and 6-min walk ≥ 25%</td>
<td>26</td>
<td>174 vs. 171; P = NS; 32 vs. 6; P &lt; 0.01</td>
</tr>
<tr>
<td>Molhoek et al. 27</td>
<td>61</td>
<td>&gt;120</td>
<td>6</td>
<td>NYHA ≥ 1 class</td>
<td>26</td>
<td>179 vs. 171; P = NS; 29 vs. 11; P = 0.07</td>
</tr>
<tr>
<td>Alonso et al. 27</td>
<td>26</td>
<td>&gt;120</td>
<td>6</td>
<td>Survival, and NYHA ≥ 1 class, and peak VO₂ ≥ 10%</td>
<td>27</td>
<td>179 vs. 176; P = NS; 23 vs. 4; P = 0.04</td>
</tr>
<tr>
<td>Penicka et al. 28</td>
<td>49</td>
<td>≥130</td>
<td>6</td>
<td>≥25% LVEF</td>
<td>45</td>
<td>190 vs. 171; P &lt; 0.01; 38 vs. 17; NS</td>
</tr>
<tr>
<td>Pitzalis et al. 27</td>
<td>20</td>
<td>≥140</td>
<td>1</td>
<td>≥15% LVESV</td>
<td>40</td>
<td>173 vs. 164; P = NS; 21 vs. 22; P = NS</td>
</tr>
<tr>
<td>Yu et al. 35</td>
<td>30</td>
<td>&gt;140</td>
<td>3</td>
<td>≥15% LVESV</td>
<td>43</td>
<td>166 vs. 150; P = NS; 24 vs. 19; P = NS</td>
</tr>
</tbody>
</table>

VO₂, oxygen consumption.
significant increase in QRS duration.\textsuperscript{30,31} This suggests that benefit from CRT relates to improved mechanical rather than electrical coordination.

How do we measure mechanical dyssynchrony?

Mechanical dyssynchrony may be assessed using conventional M-mode and Doppler echocardiography. Newer modalities include tissue Doppler imaging (TDI), strain rate imaging (SRI), and tissue synchronization imaging (TSI).

**Interventricular dyssynchrony—conventional measurement**

Interventricular mechanical delay (IVMD) is the difference in left and right ventricular pre-ejection intervals (LPEI and RPEI), measured from QRS onset to the beginning of aortic and pulmonary Doppler flow velocity curves respectively.\textsuperscript{32} An IVMD $\geq 40$ ms, 2 SD above the mean of normal controls,\textsuperscript{33} represents interventricular dyssynchrony.\textsuperscript{32,34,35} The predictive utility is doubtful as multiple factors influence ventricular ejection, including changes in preload and afterload. In particular, prolonged RPEI in pulmonary hypertension or right ventricular dysfunction reduces IVMD and accuracy of assessment.\textsuperscript{34} Precisely identifying QRS onset may also be difficult, depending on QRS morphology and electrical trace clarity.

**Intraventricular dyssynchrony—conventional measurement**

Three conventional parameters of intraventricular dyssynchrony have been described. LPEI, the time interval between QRS onset and beginning of the aortic Doppler flow velocity curve,\textsuperscript{32} represents a complex interaction between ventricular contraction, preload, and afterload. A delay $\geq 140$ ms is considered indicative of intraventricular dyssynchrony.\textsuperscript{32,35,36}

Left lateral wall contraction (LLWC) suggests severe intraventricular dyssynchrony, defined as overlap of lateral wall contraction (using M-mode) and onset of diastolic filling (transmitral Doppler E-wave onset).\textsuperscript{32} Such co-existence of systole and diastole has a relatively high specificity but low sensitivity for identifying dyssynchrony.\textsuperscript{32} Septal-to-posterior wall motion delay (SPWMD) measures time between maximal displacement of the septum and posterior wall on M-mode, with delay $\geq 130$ ms considered significant intraventricular dyssynchrony.\textsuperscript{25,37,38} Several limitations exist. It is one-dimensional, comparing only two basal segments and neglecting the more frequently delayed lateral wall. Perpendicular M-mode sections of the proximal LV are often not possible. A calculated ‘anatomical’ M-mode lowers temporal resolution, whereas a skewed M-mode produces artefactual dyssynchrony by comparing segments at different longitudinal positions. Maximal septal or posterior wall endocardial excision may be diminished and unclear in ischaemic populations, causing inaccurate assessment.\textsuperscript{38} Finally, the parameter reflects interventricular in addition to intraventricular dyssynchrony, as passive septal motion occurs due to right ventricular contraction.

**Intraventricular dyssynchrony—TDI**

TDI evaluates long-axis myocardial contraction in varying numbers of basal and mid-segments from apical 4, 3, and 2 chamber views. Either time to peak systolic velocity (Ts) or time to onset of systolic velocity (electromechanical delay, EMD) is measured relative to QRS onset. LV dyssynchrony is quantified either by the standard deviation of 12 segments.
(Ts-SD-12 or ‘dyssynchrony index’) or the maximal temporal difference between two (Ts-2, EMD-2) or more LV segments (e.g. Ts-6, Ts-12). Larger values of any parameter indicate more severe dyssynchrony.

Limitations of TDI are similar to conventional Doppler. Notably, the angle between the incident ultrasound beam and vector of myocardial motion influences measurements, and excessive gain causes spectral broadening and velocity overestimation. Pulsed wave TDI restricts sampling to a single position during each cardiac cycle. Comparison of multiple myocardial segments requires separate acquisitions in different cycles and is consequently limited by differences in heart rate, loading conditions, and respiration. By contrast, colour-coded TDI stores time velocity data superimposed on 2D cine loops, allowing rapid offline analysis of multiple segments simultaneously during the same cardiac cycle.

**Intraventricular dyssynchrony—TSI**

TSI software automatically measures Ts, colour codes delays, then superimposes colour mapping on real-time two-dimensional images. This allows immediate visual identification of regional delay, ranging from green (normal) to red (severe delay). Dedicated algorithms calculate dyssynchrony parameters involving all 12 segments within minutes, using three apical images.

**Intraventricular dyssynchrony—SRI**

TDI myocardial velocities are inherently inaccurate through incorporation of translational cardiac motion, rotation and ‘tethering’ contraction of adjacent segments. SRI reduces this by measuring localized myocardial deformation, thus differentiating between passive displacement and active systolic contraction. Unfortunately, low signal-to-noise ratio, artefacts, and complex data processing overshadow these theoretical merits, resulting in high intra- and interobserver variability (>16%) limiting reproducibility.

**Which level of the ventricle should we assess for dyssynchrony?**

The level of the ventricle at which to assess dyssynchrony is unclear. The LV base contains the largest myocardial mass and is potentially of most haemodynamic significance, especially with regard to mitral annular function and mitral regurgitation. However, in 158 consecutive patients the most delayed segments were mid-ventricular rather than basal in over two-thirds of cases. Dyssynchrony was also evenly distributed between basal and mid-ventricular segments in a second smaller study (n = 25). Only basal dyssynchrony reduced acutely following CRT, although mid-ventricular improvement followed in the long-term. Basal rather than mid-level assessment may therefore be more important in predicting response to CRT.

**Which walls of the ventricle should we assess for dyssynchrony?**

The number of ventricular walls requiring assessment is equally unclear. A compromise is necessary between optimal detection of mechanical delay and feasibility of examining numerous segments in clinical practice. Measuring time between peak velocities in opposing basal septal and lateral segments, without utilizing QRS onset as a reference point, permits rapid analysis (septal to lateral delay, Ts-2). However, in four studies using different TDI parameters, the wall exhibiting maximal delay was lateral in just one-third of patients (30–35%).

**Prevalence and prognostic implications**

In five studies, intraventricular dyssynchrony correlated poorly with QRS duration, being absent in around one-third of patients with an intermediate or wide QRS, and conversely present in many with a normal QRS duration (27–56%) (Table 3). The latter patients may potentially benefit from CRT. The difference in prevalence between studies almost certainly reflects the varying parameters.

By contrast, IVMD correlates significantly with QRS duration (Table 4) and is accordingly less common (5–18%) than intraventricular dyssynchrony in patients with a narrow QRS. Given this similarity to QRS duration, IVMD may have only limited additional value over the baseline ECG in predicting response to CRT. The only study examining the prognostic implications of mechanical dyssynchrony supports this notion. In that study (n = 104), intraventricular dyssynchrony was the most powerful independent predictor of HF hospitalization [hazard ratio, HR 3.39 (95% CI: 2.12–6.05), P < 0.001], independent of QRS duration and left ventricular ejection fraction (LVEF). However, while QRS width >140 ms was also an independent, although less potent risk factor [1.86 (1.11–3.21), P = 0.022], intraventricular dyssynchrony was not [1.18 (0.71–1.86), P = 0.433].

**Predicting response to therapy**

Numerous parameters of intraventricular dyssynchrony have been suggested as predictors of potential responders to CRT (Table 5). These almost universally derive from retrospective, exploratory analyses of multiple measurements in small, single centre, non-randomized studies. In single centres, it is unclear whether patients from earlier studies were included in subsequent ones. Interpretation is confounded by varying definitions of both dyssynchrony and response. Direct comparisons between parameters are virtually absent. The duration of CRT was frequently only 3 months or less, arguably too short a period in which to identify measurable LV remodelling. The manuscripts are often not specific regarding whether or not consecutive patients were recruited and whether or not observers performing analysis were blinded. Many studies fail to define all standard statistical parameters of accuracy, which may be calculated from data presented using a standard ‘accuracy matrix’ (Table 6). Intra- and interobserver variability are frequently either not presented or quoted from previous separate studies.

**Predicting response using conventional parameters**

Pitzalis *et al.* initially demonstrated that SPWMD ≥130 ms, but not LPEI or IVMD, predicted reverse remodelling in 20 patients, with 63% specificity and 85% accuracy. Subsequently, in 60 patients with predominantly non-ischaemic cardiomyopathy, SPWMD ≥130 ms independently
predicted long-term clinical improvement following CRT (median follow-up of 14 months). Despite defining response differently in the two studies, predictive accuracy (84 and 85%) and correlation between SPWMD and volumetric change were remarkably consistent (Table 7).

The clinical applicability and predictive value of SPWMD were strongly disputed in a recent retrospective analysis of the CONTAK-CD trial involving 79 patients with predominantly ischaemic cardiomyopathy (72%). SPWMD failed to correlate with left ventricular end systolic volume (LVESV) reduction, predicting response with just 24% sensitivity and 66% specificity. Feasibility of obtaining measurements and inter-observer reproducibility were very poor, with only 45% of patients having a definitive septal and posterior wall motion deflection.

Echocardiographic inclusion criteria in the Cardiac Resynchronization in Heart Failure (CARE-HF) study were in addition to, rather than replacing, intermediate QRS prolongation (120–150 ms). Ninety two (11%) patients were enrolled, requiring two of three echocardiographic indicators of dyssynchrony: LPEI > 140 ms; IVMD > 40 ms; or delayed LLWC. All three are relatively insensitive markers of dyssynchrony. Furthermore, by definition IVMD and LPEI are highly inter-dependent, the variance in the first largely attributable to the latter. Although the original report dichotomized results using a high cut-off for IVMD of 49.2 ms, subgroup analysis is unpublished.

### Predicting response using TDI

The simplest tissue Doppler assessment, septal to lateral delay, was initially evaluated in 22 patients. Mean delay decreased from 97 to 28 ms immediately after CRT ($P < 0.05$) and returned to baseline after discontinuing pacing. In a subsequent study, baseline delay was the only variable differentiating responders and non-responders (86 vs. 39 ms, $P < 0.01$) and the only independent predictor of improved LVEF. Delay $> 60$ ms predicted response with 80% overall accuracy.

Bax et al. then measured the maximal temporal difference between peak systolic velocities in four basal segments (anterior, inferior, septal, and lateral). In 85 patients, responders and non-responders were differentiated by baseline delays similar to the 2-segment model (87 vs. 35 ms, $P < 0.01$). Dyssynchrony $> 65$ ms yielded a sensitivity and specificity of 80% to predict clinical improvement and of 92% to predict reverse remodelling. Patients with dyssynchrony $> 65$ ms had an excellent prognosis compared with those without (6 vs. 50% one year composite mortality or HF hospitalization, $P < 0.001$).

### Table 5 Design of studies investigating parameters predicting response to CRT

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Follow-up (months)</th>
<th>Dyssynchrony parameter</th>
<th>Cut-off (ms)</th>
<th>Cut-off derivation</th>
<th>Consecutive patients</th>
<th>Blinded analysis</th>
<th>Observer variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitzalis et al.</td>
<td>20</td>
<td>1</td>
<td>SPWMD</td>
<td>130</td>
<td>ROC curve</td>
<td>+</td>
<td>+</td>
<td>0.96</td>
</tr>
<tr>
<td>Marcus et al.</td>
<td>51</td>
<td>14</td>
<td>SPWMD</td>
<td>130</td>
<td>Previous study</td>
<td>+</td>
<td>+</td>
<td>0.91</td>
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<tr>
<td>Bax et al.</td>
<td>79</td>
<td>6</td>
<td>SPWMD</td>
<td>130</td>
<td>Previous study</td>
<td>–</td>
<td>+</td>
<td>High</td>
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<tr>
<td>Bax et al.</td>
<td>25</td>
<td>Acute</td>
<td>Ts-2</td>
<td>60</td>
<td>Selected</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Yu et al.</td>
<td>80</td>
<td>6</td>
<td>Ts-4</td>
<td>65</td>
<td>ROC curve</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Notabartalo et al.</td>
<td>30</td>
<td>3</td>
<td>Ts-SD-12</td>
<td>32.6</td>
<td>2 SD normal controls</td>
<td>–</td>
<td>–</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Yu et al.</td>
<td>49</td>
<td>3</td>
<td>Ts-SD-12</td>
<td>31.4</td>
<td>ROC curve</td>
<td>–</td>
<td>–</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Penicka et al.</td>
<td>49</td>
<td>6</td>
<td>EMD-3</td>
<td>60</td>
<td>ROC curve</td>
<td>+</td>
<td>+</td>
<td>6.8%</td>
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<td></td>
<td></td>
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<td>EMD LV-RV</td>
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<td></td>
<td></td>
<td></td>
<td>EMD Sum</td>
<td>102</td>
<td></td>
<td></td>
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<td>6.1%</td>
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<tr>
<td></td>
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<td>EMD Lat Delay</td>
<td>–</td>
<td>ROC curve</td>
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<td>7.2%</td>
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<td></td>
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<td></td>
<td>TSI Ts-2</td>
<td>65</td>
<td>ROC curve</td>
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<td>TSI Ts-SD-12</td>
<td>34.4</td>
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<td></td>
<td></td>
<td>TSI Ts-12</td>
<td>105</td>
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<td></td>
<td></td>
<td>TSI Ts-SD-6</td>
<td>34.5</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TSI Ts-6</td>
<td>78</td>
<td></td>
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</table>

### Table 6 Accuracy matrix

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>No disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +ve</td>
<td>True positive (TP)</td>
<td>False positive (FP)</td>
</tr>
<tr>
<td>Test -ve</td>
<td>False negative (FN)</td>
<td>True negative (TN)</td>
</tr>
</tbody>
</table>

Sensitivity, $Sn = TP/(TP + FN)$ Specificity, $Sp = TN/(TN + FP)$

Positive predictive value, $PPV = TP/(TP + FP)$ Negative predictive value, $NPV = TN/(TN + FN)$

Accuracy, $Acc = TP + TN/(TP + FP + TN + FN)$
<table>
<thead>
<tr>
<th>Dyssynchrony parameter</th>
<th>Responder definition</th>
<th>% Non-responders</th>
<th>Responders vs. non-responders</th>
<th>Correlation*</th>
<th>Accuracy parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>QRS (ms) P</td>
<td>Parameter (ms) P</td>
<td>r</td>
</tr>
<tr>
<td>SPWMD&lt;sup&gt;37&lt;/sup&gt; 15% LVESV</td>
<td>40</td>
<td>173 vs. 164 NS</td>
<td>246 vs. 110 &lt;.001</td>
<td>0.70 &lt;.001</td>
<td>100</td>
</tr>
<tr>
<td>SPWMD&lt;sup&gt;25&lt;/sup&gt; 5% LVEF</td>
<td>53</td>
<td>— — — —</td>
<td>77 vs. 59 0.63</td>
<td>0.10 0.41</td>
<td>24</td>
</tr>
<tr>
<td>SPWMD&lt;sup&gt;38&lt;/sup&gt; 15% LVESV</td>
<td>—</td>
<td>—</td>
<td>86 vs. 39 &lt;.01</td>
<td>0.47 0.017</td>
<td>76</td>
</tr>
<tr>
<td>Ts-2&lt;sup&gt;6&lt;/sup&gt; 5% LVEF</td>
<td>32</td>
<td>— NS</td>
<td>87 vs. 35 &lt;.01</td>
<td>— —</td>
<td>80</td>
</tr>
<tr>
<td>Ts-4&lt;sup&gt;6&lt;/sup&gt; Clinical</td>
<td>26</td>
<td>174 vs. 171 NS</td>
<td>87 vs. 35 &lt;.01</td>
<td>— —</td>
<td>78</td>
</tr>
<tr>
<td>Ts-SD-12&lt;sup&gt;55&lt;/sup&gt; 15% LVESV</td>
<td>43</td>
<td>166 vs. 150 NS</td>
<td>45.0 vs. 24.8 &lt;.001</td>
<td>0.76 &lt;.001</td>
<td>100</td>
</tr>
<tr>
<td>Ts-6 (PVD)&lt;sup&gt;57&lt;/sup&gt; Clinical&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24</td>
<td>162 vs. 151 NS</td>
<td>264 vs. 198 — —</td>
<td>78</td>
<td>33</td>
</tr>
<tr>
<td>Ts-6 (PVD)&lt;sup&gt;57&lt;/sup&gt; 15% LVESV</td>
<td>41</td>
<td>166 vs. 150 NS</td>
<td>289 vs. 188 &lt;.01</td>
<td>— —</td>
<td>97</td>
</tr>
<tr>
<td>Ts-SD-12&lt;sup&gt;52&lt;/sup&gt; 15% LVEF</td>
<td>43</td>
<td>155 vs. 147 NS</td>
<td>— —</td>
<td>0.74 &lt;.001</td>
<td>96</td>
</tr>
<tr>
<td>EMD-358&lt;sup&gt;58&lt;/sup&gt; 25% LVEF</td>
<td>45</td>
<td>190 vs. 171 &lt;.01</td>
<td>84 vs. 38 &lt;.0001</td>
<td>— —</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>EMD LV-RV&lt;sup&gt;58&lt;/sup&gt;</td>
<td>—</td>
<td>84 vs. 43 &lt;.0001</td>
<td>— —</td>
<td>— —</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>EMD Sum&lt;sup&gt;58&lt;/sup&gt;</td>
<td>—</td>
<td>167 vs. 81 &lt;.0001</td>
<td>0.73 &lt;.0001</td>
<td>— —</td>
<td>96</td>
</tr>
<tr>
<td>SR&lt;sup&gt;61&lt;/sup&gt; 15% SV</td>
<td>45</td>
<td>164 vs. 169 NS</td>
<td>249 vs. 137 &lt;.005</td>
<td>0.93 &lt;.0001</td>
<td>95</td>
</tr>
<tr>
<td>TSI Ts-2&lt;sup&gt;63&lt;/sup&gt; 15% SV</td>
<td>48</td>
<td>164 vs. 187 NS</td>
<td>161 vs. 18 &lt;.001</td>
<td>— —</td>
<td>87</td>
</tr>
<tr>
<td>TSI Lat Delay&lt;sup&gt;46&lt;/sup&gt; 15% LVESV</td>
<td>46</td>
<td>— — — —</td>
<td>47.3 vs. 29.2 &lt;.001</td>
<td>0.61 &lt;.001</td>
<td>87</td>
</tr>
<tr>
<td>TSI Ts-12&lt;sup&gt;46&lt;/sup&gt;</td>
<td>—</td>
<td>133.9 vs. 83.7 &lt;.001</td>
<td>83</td>
<td>85</td>
<td>81&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TSI Ts-SD-6&lt;sup&gt;46&lt;/sup&gt;</td>
<td>—</td>
<td>42.9 vs. 26.6 &lt;.001</td>
<td>70</td>
<td>92</td>
<td>73&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TSI Ts-6&lt;sup&gt;46&lt;/sup&gt;</td>
<td>—</td>
<td>105.2 vs. 65.5 &lt;.001</td>
<td>0.53 &lt;.001</td>
<td>73</td>
<td>77</td>
</tr>
</tbody>
</table>

ACC, accuracy; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; SV, stroke volume.

*Correlation between dyssynchrony parameter and responder definition.

Accuracy parameters calculated from data presented.

Clinical responder: improvement in NYHA ≥ 1 and 6-min walking distance ≥ 25%.

Clinical responder: two of three improvements: NYHA ≥ 1; 6-min walking distance 50 m; quality of life score 15 points.
Using a 12-segment model (6-basal, 6-mid), Yu et al. demonstrated improved synchronicity and reverse remodelling following CRT. LV EF improved from 28% to 40% after 3 months. Coordinated systolic contraction occurred through delay of early contracting segments, decreasing the standard deviation of $T_s$ ($TS_{SD-12}$) (29.3 vs. 37.7 ms, $P < 0.05$). As observed by Bax et al., improvements were pacing-dependent: withholding pacing immediately reduced LVEF and increased dyssynchrony ($TS_{SD-12}$ 41.1 vs. 29.3 ms, $P < 0.01$). In a second study ($n = 33$), $TS_{SD-12}$ decreased similarly within 30 min of biventricular but not RV pacing, again correlating with acute volumetric improvements.

Yu et al. examined predictors of reverse remodelling in 30 patients. Cardiac function and clinical status improved significantly over 3 months in responders, associated with a reduction in systolic dyssynchrony ($TS_{SD-12}$ 32.5 vs. 45.0 ms, $P = 0.003$). The ‘dyssynchrony index’ ($TS_{SD-12}$) was the only independent predictor of reverse remodelling, with a pre-implant cut-off of 32.6 ms (two SD from the mean of 88 normal controls) remarkably separating responders from non-responders completely.

In a similar prospective 3-month study involving 58 patients, greater clinical and volumetric improvements occurred in patients with wide compared with intermediate QRS durations. This related to a higher prevalence of interventricular dyssynchrony in the wide QRS group, correlating closely with reverse remodelling ($r = -0.78$, $P < 0.001$). The systolic ‘dyssynchrony index’ was again the only independent predictor of reverse remodelling, with a sensitivity of 94% and specificity of 83% using the predefined cut-off of 32.6 ms.

Recently, two further studies used TDI to predict responders. In the first, the only independent determinant of remodelling was a peak velocity difference (PVD) $> 110$ ms, defined as the maximal difference in time to peak velocity between six basal segments. Although specificity was low (55%), this would be improved at the expense of sensitivity (97%) by increasing the threshold characterizing dysynchrony. Comparison of six ventricular walls ($TS_{6}$ and $TS_{12}$) requires a much higher cut-off to identify dysynchrony than 2- or 4-segment models. This supports the earlier observation that myocardial delay is distributed around the entire ventricle, suggesting optimal assessment of dysynchrony requires inclusion of all six walls.

In the second study, Penicka et al. used pulsed wave TDI to measure maximal difference in EMD between three basal LV segments (septal, lateral, and posterior). Interventricular dyssynchrony (EMD LV-RV) was assessed by comparing the RV basal lateral segment to the most delayed LV segment, and added to intraventricular dyssynchrony for a combined index (sum asynchrony). The predictive value of TDI interventricular dyssynchrony was almost that of interventricular assessment, unlike measurement of conventional IVMD in previous studies. More importantly, 'sum asynchrony' identified all but one responder, suggesting for the first time that combining both inter- and intra-ventricular assessments may improve patient selection.

**Predicting response using SRI**

Several studies have demonstrated improvement in strain parameters following CRT, but only two have examined their ability to predict response. In a comprehensive study comparing 18 parameters, all TDI measurements significantly predicted reverse remodelling after 3 months. While the two segment models correlated modestly with remodelling, the higher predictive value of basal $TS_{6}$ and $TS_{12}$ was identical ($r = -0.60$, $P < 0.001$). However, $TS_{SD-12}$ was again the most powerful, and only independent, predictor in both ischaemic and non-ischaemic patients ($r = -0.74$, $P < 0.001$ overall). By contrast, all strain rate parameters failed to predict response. The superiority of TDI is unsurprising as translational motion, the inherent limitation, influences all segments equally and myocardial velocity rather than timing, thus having minimal impact on dispersion of timing within the ventricle.

More recently, dyssynchrony was defined by the temporal difference in peak radial strain between the anterosepal and posterior walls, as compared by Pitizalis et al. using M-mode. Baseline delay differed significantly between acute haemodynamic responders and non-responders (249 vs. 137 ms, $P < 0.005$), predicting response with 95% sensitivity and 88% specificity using the 130 ms cut-off introduced by Pitizalis et al. Interestingly, changes in stroke volume immediately after CRT correlated strongly with baseline delay until 200 ms ($r = 0.93$, $P < 0.0001$), after which a plateau was observed, similar to the pattern observed by Bax et al. Obviously ventricular haemodynamic or volumetric improvement following CRT is limited, no matter the severity of dyssynchrony.

**Predicting response using TSI**

The same two groups predicted acute or longer term response after CRT using TSI. In 29 patients, 65 ms delay between the anterosepal and posterior wall predicted acute response, defined by 15% increase in stroke volume, with 87% sensitivity and 100% specificity. However, no baseline TSI pattern predicted long-term reverse remodelling, which correlated poorly with early haemodynamic response.

In a more substantive study involving 56 patients, Yu et al. examined both qualitative visual TSI images and quantitative TSI parameters, comparing the latter with traditional TDI velocity data. $T_s$ measurements by TSI and TDI velocity curves correlated very highly ($r = 0.97$, $P < 0.001$), validating the TSI software. Of all baseline TSI visual patterns, only severe lateral wall delay (coloured red) predicted reverse remodelling, with high specificity (89%) but low sensitivity (47%). All the quantitative TSI parameters were significantly higher in responders and correlated with volumetric changes (Table 7).

In contrast to their earlier study, parameters based on standard deviation or range yielded similar overall accuracy and correlations ($r = 0.52$ vs. 0.53 and $r = 0.61$ vs. 0.60) in both the 6- and 12-segment models respectively. This suggests the method of quantifying 'spread' is only of minor importance. Much emphasis was placed on the higher correlations and accuracy of the 12-segment compared to the 6-segment parameters. However, in the previous study $TS_{6}$ and $TS_{12}$ demonstrated identical correlations ($r = 0.60$). Herein lies the Achilles heel of the dyssynchrony debate: minor differences in small patient groups are frequently over-interpreted, without statistical confidence that disparities are not simply the play of chance.
Cautions regarding responders and non-responders

Clinical responders

Clinical response is variably defined. The clinical composite score, used in the Multicentre InSync Randomized Clinical Evaluation (MIRACLE), classifies patients as improved, unchanged, or worsened. The score combines measures of functional status (NYHA class or moderate change in patient global assessment) with major adverse clinical outcomes (death, hospitalization) and withdrawal of study medication relating to worsening HF. However, different clinical composite endpoints in other studies limit comparisons, with components including transplantation, 6 minute walking distance, peak oxygen consumption, and quality of life scores. Furthermore, clinical measures are subject to placebo effect: 39% of controls as well as 67% of the treatment group were responders in the MIRACLE study.

Volumetric responders

A 15% reduction in LVESV is considered indicative of reverse remodelling (Table 7). In CRT studies, as with trials of drug therapy, the onset of remodelling often coincides with clinical improvement, in terms of NYHA class, exercise capacity, or quality of life score. Changes in cardiac size and function, quantified by LVESV and LVEF respectively, provide objective measures independent of placebo effect. However, definitions are arbitrary and magnitude of either response may not reach a specific threshold. Clinical response may occur without volumetric change or vice versa. Correlations between the two are weak.

Clinical outcomes improve with CRT irrespective of HF aetiology. By contrast, echocardiographic reverse remodelling is significantly greater in patients with non-ischaemic compared with ischaemic cardiomyopathy. The discrepancy is also apparent in echocardiographic studies, in which TDI parameters predict clinical response less accurately than reverse remodelling (Table 7).

Non-responders

In around one-quarter to one-half of patients, clinical and volumetric non-responders are consistently observed, the latter being more frequent (Tables 2 and 7). The disparity between clinical and volumetric responses relates in part to arbitrary volumetric cut-offs and different parameters defining clinical response. This serves to highlight limitations in characterizing response and cautions against substituting remodelling for clinical efficacy. Moreover, failing to achieve selected ‘response’ criteria is not necessarily ‘non-response’. Without CRT, a patient may have undergone further adverse remodelling, been unable to achieve their current walking distance, or indeed be dead. A crucial weakness of echocardiographic studies is the absence of ‘hard’ endpoints—all cause mortality, cardiovascular death, and hospitalizations.

The PROSPECT study: predictors of response to CRT

The PROSPECT study is currently evaluating the ability of conventional and TDI parameters to predict a positive clinical and echocardiographic response in approximately 300 patients in up to 75 centres. Entry criteria include a QRS duration ≥130 ms, although centres outside the United States may enrol patients with a QRS duration <130 ms with echocardiographic evidence of dys synchrony. Although larger-scale and a prospective study, PROSPECT is not enrolling sequential patients and suffers from the interpretative limitations alluded to above.

Reasons for non-response

Lack of response has been attributed to the absence of sufficient baseline dyssynchrony to allow improvement with therapy. However, no echocardiographic indicator of dyssynchrony will completely predict a successful response, given the numerous other potential reasons for non-response: sub-optimal lead placement; non-viable ischaemic or infarcted myocardium; poor threshold or inadequate device optimization; severe LV dilatation; irreversible mitral annular dilatation and severe regurgitation; and development of atrial fibrillation after implantation. Most important of all, perhaps, is the duration of CRT. It is highly unlikely, for example, that β-blockers would have showed clear-cut clinical or volumetric benefits in similar small-scale and short-duration studies with the endpoints used.

Summary

Improving clinical outcomes is clearly desirable. However, current proposals that would deny patients an effective treatment with a Class I, Level A guideline recommendation are misguided, unique to devices (as opposed to drugs), and driven in part by limited healthcare budgets. Echocardiographic parameters of dyssynchrony are not robust enough to withhold CRT, with proven morbidity and mortality benefits, from patients. Landmark trials have randomized over 4000 patients based on their electrocardiogram as opposed to 92 by echocardiogram (in conjunction with a borderline QRS duration). Although PROSPECT is a fairly large study, it is observational and primarily serves to generate a hypothesis requiring validation in a prospective randomized trial, i.e. that treatment of patients selected on the basis of mechanical dyssynchrony with biventricular pacing will lead to improved morbidity and mortality.

Extending CRT to patients with narrow QRS complexes based on echocardiographic parameters is currently unfounded. Echocardiographic assessment will only become credible and applicable to clinical practice once used to select patients for large prospective randomized trials which show an improvement in clinical outcome. An obvious target population is patients with mechanical dyssynchrony but narrow QRS complexes. From existing evidence, contrary to recent opinion, we believe it neither mandatory to alter current guidelines for patient selection (to either restrict or expand the indication for CRT) nor essential to include echocardiographic assessment. For now, the cornerstone of dyssynchrony assessment remains the parameter prospectively validated in landmark clinical trials—the ECG-documented QRS duration.

Conflict of interest. The authors have no conflict of interest to declare regarding companies’ manufacturing devices or echocardiography systems.
References


A 51-year-old man was referred to our hospital for recurrences of palpitation due to atypical atrial flutter. The patient reported several episodes of hemoptysis only during the childhood. No other symptom was present. Chest plain radiograph showed a mild displacement of the heart to the right while only a mild enlargement of both atria was observed by echocardiography. Axial images and three-dimensional reconstructions (volume rendering) of lung and mediastinum using 16-slices Multidetector computed tomography demonstrated: (i) the absence of right pulmonary artery (Panels A–C); (ii) a less expanded and dystrophic right lung with evidence of several bullous cavities (Panel A); (iii) the presence of collateral vessels for the right lung mainly arising from a dilated right internal mammary artery and from the celiac trunk. Other smaller vessels came from the aortic arch and descending aorta (Panels B and C).

A ventilation-perfusion scintigraphy (Tc-99 m Pertechnetate Aerosol + Tc-99 m MacroAggregates of human serum Albumin) showed the absence of perfusion in the right lung with almost normal ventilation; a normal ventilation and perfusion was found in the left lung (Panel D).

Catheter ablation of a left atrial flutter was successfully performed. Since there were no other symptoms, we decided to carefully follow this patient and not perform any more intervention at that time.

Panel A. Multidetector computed tomography axial image demonstrates the absence of right pulmonary artery and right lung dystrophy. Panels B and C. Multidetector computed tomography volume rendering reconstructions (Panel B: antero-posterior view; Panel C: right postero-lateral view) show the presence of collateral vessels for right lung arising from: (i) a large right mammary artery (white arrow); (ii) the celiac trunk through an infra-diaphragmatic vessel (red arrow); (iii) the aortic arch and descending aorta through several small peri-bronchial arteries (arrowheads).

Panel D. Ventilation-perfusion scintigraphy (Tc-99 m Pertechnetate Aerosol + Tc-99 m MAA). The ventilation examination of both lungs (Sections a and b) shows a mild reduction of activity at the third medium of the right lung. Homogeneous distribution of aerosol was seen in whole left lung and in the remaining right lung. The perfusion examination (Sections c and d) shows only a faint amount of activity in the right lung while a homogeneous tracer distribution in left lung is detected.