Cardiac resynchronization therapy (CRT) is an effective treatment in patients with medically refractory heart failure. Several clinical trials have shown improvement in both left ventricular (LV) function and symptoms with CRT compared with controls, with the 2 largest trials showing a reduction in rates of hospitalization and death. On the basis of data from these studies, most international guidelines agree on the standard indications for CRT: impaired functional status with New York Heart Association functional class III or IV, LV ejection fraction (LVEF) ≤35%, and prolonged QRS duration ≥120 ms in the setting of optimal medical therapy. However, not all patients experienced improvement in symptoms or LV function, and numerous studies have focused on improving the selection criteria for CRT in the hopes of excluding these “nonresponders.” One of the most frequently studied modalities for patient selection is echocardiographic measurement of LV systolic dyssynchrony based on the supposition that there is a threshold for mechanical dyssynchrony below which there is no therapeutic benefit. Despite these studies, we argue that current echocardiographic methods of measuring dyssynchrony should not be used to exclude patients who are otherwise candidates for CRT. Conversely, in patients with narrow QRS, echocardiographic evidence of dyssynchrony is insufficient to warrant CRT on the basis of current data.

Response by Delgado and Bax on p 663

There are important unresolved issues regarding the use of mechanical dyssynchrony measurements for determining CRT eligibility in an individual patient. Let us examine the case of a 60-year-old man with ischemic cardiomyopathy, recurrent hospitalizations, and New York Heart Association functional class III despite an excellent heart failure drug regimen. He inquires about additional therapy to help improve his symptoms and keep him out of the hospital. His LVEF is 30% by echocardiogram, and the ECG shows a QRS duration of 150 ms in a left bundle-branch block configuration. Current guidelines clearly state that this patient qualifies for CRT. However, proponents of mechanical dyssynchrony would require additional evaluation before referring him for CRT. If evaluation for mechanical dyssynchrony is undertaken, many issues are unresolved, including the value of measuring intraventricular and/or interventricular dyssynchrony, the best modality to use for intraventricular dyssynchrony, and the threshold values that define the presence of mechanical dyssynchrony. Most importantly, if mechanical dyssynchrony is not demonstrated, is the weight of this evidence sufficient to advise against CRT implantation in the patient, contrary to guidelines?

After reviewing the available data, we will present the case that current measures of mechanical dyssynchrony do not add clinical utility in selecting patients for CRT beyond current guidelines. Key issues to be addressed include the following: (1) defining “response” to CRT; (2) the clinical relevance of employing echocardiographic surrogate end points for CRT response; (3) the limitations inherent in studies of dyssynchrony; and (4) the false presumption that mechanical dyssynchrony is the only factor predicting CRT response.

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

From the Division of Cardiology, University of California, San Francisco.

This article is Part II of a 2-part article. Part I appears on p 640.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.954420/DC1.

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The Definition of Response
The 2 largest randomized, controlled clinical trials on CRT have demonstrated its positive effects on rates of death and hospitalization in comparison to a control group. In the United States, the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial enrolled 1520 heart failure subjects with standard indications for CRT, including QRS duration ≥120 ms, randomizing treatment to CRT with or without a defibrillator or optimal medical therapy. Compared with medical therapy alone, patients undergoing CRT with or without a defibrillator demonstrated a significant decrease in the primary end point of all-cause hospitalization or death over the course of 12 months. In contrast to COMPANION, the European Cardiac Resynchronisation in Heart Failure (CARE-HF) trial enrolled 813 patients with standard CRT indications if the QRS exceeded 150 ms. When the QRS duration was 120 to 149 ms, the investigators required 2 of 3 criteria for dyssynchrony (aortic prejection delay >140 ms, interventricular mechanical delay >40 ms, and delayed activation of the posterolateral LV wall). Over a mean follow-up period of 29.4 months, patients receiving CRT had a decrease in the primary end point of all-cause mortality and hospitalization for a cardiovascular event. In this study, despite the demonstration of mechanical dyssynchrony in patients with narrower QRS duration, the subgroup analysis of patients with QRS <160 ms did not exhibit a statistically significant benefit with CRT, exposing the questionable role of mechanical dyssynchrony in predicting morbidity and mortality response to CRT.6

Nevertheless, ongoing investigations, predominantly with the use of echocardiographic techniques, attempt to find a “magic bullet” that identifies all “nonresponders” to minimize the number of patients unnecessarily exposed to this expensive and invasive therapy. Most of these studies have used short-term echocardiographic surrogate end points, such as the decrease in LV end-systolic volume (LVESV) or increase in LVEF, in lieu of the hard end points of death or hospitalization to define a CRT responder. Few studies have included clinical or symptomatic improvement (see the online-only Data Supplement). The major clinical trials published to date have not linked hard end points of mortality or hospitalization to early LV reverse remodeling with CRT. How strong is this association between these surrogate end points and hard clinical end points of death and hospitalization?

Is Reverse LV Remodeling an Appropriate Surrogate for Response to CRT?
As listed in the Table, several observational studies have attempted to correlate short-term clinical and echocardiographic changes with long-term prediction of mortality. Unfortunately, the results are varied and conflicting. In 1 study prospectively evaluating 141 nonconsecutive patients for a mean follow-up of 22.9 months, LVESV reduction ≥10% at 3 to 6 months was associated with reduced long-term mortality. However, the clinical significance was modest, with a receiver operating characteristic area under the curve of 0.69, resulting in sensitivity and specificity of 70% on univariate analysis. No confidence interval was reported for the calculated sensitivity/specificity, which undoubtedly would have given a lower boundary of <70%, reinforcing the modest association, at best, between short-term LVESV improvement and prediction of long-term mortality. A second, larger study prospectively evaluating 286 patients over a mean long-term follow-up of 22 months took a different approach in correlating LVESV change with mortality. At the short-term follow-up period of 6 months, quartile analysis based on the magnitude of reduction in LVESV (decrease in LVESV ≥30%, 15% to 29%, 0% to 14%, or increase in LVESV) revealed an incremental decrease in mortality, with the lowest mortality seen in the highest decrease of LVESV. However, the investigators did not demonstrate that the change in LVESV was an independent predictor of mortality because they did not correct for baseline differences in NYHA class IV, ischemic etiology, QRS duration, presence of left bundle-branch block, and degree of LV dyssynchrony. All of these baseline differences correlated directly with change in LVESV, making it impossible to determine whether baseline clinical variables or the change in LVESV was responsible for the mortality difference. In contrast to the aforementioned studies, an observational study of 174 patients with a short-term follow-up of 5.4 months showed that change in LVESV was not associated with long-term survival at a median follow-up interval of 16.7 months. The long-term follow-up substudy of the CARE-HF trial also demonstrated that reverse remodeling, as defined by improved LVEF or decreased LVESV index at a short-term follow-up of 3 months, was not an independent predictor of mortality on multivariate analysis. This unclear association between reduced LVESV and mortality becomes even more apparent when one considers that, whereas subjects with ischemic cardiomyopathy consistently demonstrate less reverse remodeling with CRT than subjects with nonischemic cardiomyopathy, there is no attenuation of the survival benefit in this group. These observational studies do not compare outcomes with a control group of untreated patients, and thus may miss clinical benefit in the highest-risk groups.

Most recently, an echocardiographic substudy of the Multi-center Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT) provides the only convincing prospective data that support the link between reverse remodeling and clinical benefit (reduced mortality and fewer heart failure hospitalizations). However, this study evaluated fewer symptomatic patients and did not use mechanical dyssynchrony as a criterion for study inclusion, which limits the applicability to the standard CRT population.

Echocardiographic Dyssynchrony Parameters
Two recent reviews have detailed the various echocardiographic dyssynchrony parameters and their individual
strengths and pitfalls. The online-only Data Supplement summarizes key features and findings of published studies on echocardiographic dyssynchrony parameters, limited to those reports with a minimum of 50 subjects. With few exceptions, the vast majority of studies defined CRT response as LVESV decrease of $\approx 15\%$ at short-term follow-up of 3 to 6 months. Four of the studies evaluated clinical improvement by measuring decrease in NYHA functional class. Furthermore, there is a concerning lack of consistency among the studies, which are primarily single-center studies. For example, the recommended thresholds for dyssynchrony with the use of the same parameter differ among investigators. For speckle tracking, the optimal cutoff value for the standard deviation in time to peak radial strain ranges from 55.3 to 76 ms, and in real-time 3-dimensional echocardiography, the optimal cutoff value for a 16-segment systolic dyssynchrony index ranges from 6.4% to $>10\%$. Finally, well-established echocardiography sites with strong research backgrounds have rarely been able to reproduce published findings and often have found frankly contradictory results.

Table. Association Between Short-Term Variables and Long-Term Outcomes in CRT

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Study Type</th>
<th>Consecutive Patients</th>
<th>Long-Term Follow-Up Time, mo</th>
<th>Median Short-Term Follow-Up Time, mo</th>
<th>Short-Term Variable (Degree Change)</th>
<th>Long-Term End Points</th>
<th>Strength of Association</th>
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<td>Kronborg</td>
<td>171</td>
<td>Retrospective, observational</td>
<td>Yes</td>
<td>48 (median)</td>
<td>8.4</td>
<td>(1) Age (older age per year)</td>
<td>Mortality</td>
<td>HR: 1.05 (1.02–1.08)*</td>
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<tr>
<td>Ypenburg</td>
<td>286</td>
<td>Prospective, observational</td>
<td>Yes</td>
<td>22 (mean)</td>
<td>6</td>
<td>ESV (quartile analysis)</td>
<td>Mortality, heart transplant, heart failure hospitalization</td>
<td>Higher ESV improvement quartile associated with lower events†</td>
</tr>
<tr>
<td>Yu</td>
<td>141</td>
<td>Prospective, observational</td>
<td>No</td>
<td>22.9 (mean)</td>
<td>3–6</td>
<td>(1) NYHA (improvement)</td>
<td>Mortality</td>
<td>‡</td>
</tr>
<tr>
<td>Cha</td>
<td>174</td>
<td>Retrospective, observational</td>
<td>Yes</td>
<td>16.7 (median)</td>
<td>5.4</td>
<td>(1) NYHA (per ↓ 1 class)</td>
<td>Mortality</td>
<td>RR 0.43 (0.26–0.69)*</td>
</tr>
<tr>
<td>Cleland</td>
<td>813</td>
<td>Randomized controlled trial, subanalysis</td>
<td>Yes</td>
<td>37.6 (median)</td>
<td>3</td>
<td>(1) NYHA (class IV status)</td>
<td>Mortality</td>
<td>2.39 (1.61–3.54)$§</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; ROC AUC, receiver operating characteristic area under the curve; and RR, relative risk.
*Multivariate analysis.
†Significant baseline differences in percent NYHA class IV, ischemic etiology, QRS duration, left bundle branch block, moderate to severe mitral regurgitation, and degree of LV dyssynchrony between quartiles.
‡Not statistically significant.
§Univariate analysis.
||In multivariate analysis, only change in NYHA class was statistically significant, not change in LVEF.
tional limitations of these studies include small sample sizes (mostly from 50 to 70 subjects) and suboptimal study design, which are mostly retrospective and often unblinded. Finally, the 95% confidence intervals are rarely reported, and when they are available, the boundaries are wide, limiting their clinical relevance.

**Mechanical Dyssynchrony Is Not Sufficient to Predict CRT Response in the Absence of Significant Electric Dyssynchrony**

Three small single-center studies examined the response to CRT in patients with narrow QRS and echocardiographic evidence of mechanical dyssynchrony, all demonstrating promising results.\(^{37-39}\) To further evaluate these preliminary findings, 2 multicenter studies were performed to investigate the role of CRT in heart failure patients with narrow QRS but evidence of mechanical dyssynchrony.

The Evaluation of Screening Techniques in Electrically-Normal, Mechanically-Dysynchronous Heart Failure Patients (ESTEEM-CRT) trial was a multicenter, single-arm, unblinded study evaluating 68 patients with QRS <120 ms. With the use of the same tissue Doppler imaging measure of dyssynchrony described in the study of Yu et al of patients with narrow QRS, there was improvement in subjective symptoms (NYHA functional class and quality of life score), whereas objective measures of peak exercise, LVEF, LVESV, and LV end-diastolic volume were unchanged from baseline.\(^{38,40}\) The larger Resynchronization Therapy in Normal QRS (RETHINQ) study was a prospective randomized controlled clinical trial enrolling 172 patients randomized to implantable cardioverter-defibrillator versus implantable cardioverter-defibrillator with CRT in subjects with narrow QRS duration (<130 ms) but with evidence of mechanical dyssynchrony with the use of tissue Doppler imaging and conventional parameters.\(^{41}\) Despite the presence of mechanical dyssynchrony, the primary end point of increase in peak oxygen consumption at 6 months did not differ significantly between groups undergoing CRT versus control (46% and 41%, respectively; \(P=0.63\)). These data suggest that without the minimum substrate of significant electric dyssynchrony, mechanical dyssynchrony alone is not predictive of hemodynamic response to CRT. They also reiterate the subgroup analysis from CARE-HF, in which patients with QRS <160 ms treated with CRT did not have a statistically significant reduction in mortality or hospitalization compared with controls despite the fact that the presence of dyssynchrony was required for all patients with QRS <150 ms.\(^{8}\) Moreover, these studies highlight the issues encountered in other studies utilizing dyssynchrony to predict CRT response, namely, small sample size, lack of reproducibility in a multicenter study, and inability to assess true outcome differences without an adequate control group.

**Predictors of Response to CRT Study: Evidence of Mechanical Dyssynchrony Is Not Necessary to Predict CRT Response**

The Predictors of Response to CRT (PROSPECT) study was a large, prospective, blinded analysis clinical trial examining the potential of echocardiographic dyssynchrony to predict response to CRT, involving 53 recruiting centers in Europe, Hong Kong, and the United States, enrolling 498 patients with standard clinical CRT indications and QRS \(\geq 130\) ms.\(^{42}\) The study evaluated 12 distinct dyssynchrony parameters on the basis of both conventional and tissue Doppler–based methods. The end points evaluated at 6 months included both an improvement in clinical composite score as well as LV reverse remodeling with LVESV reduction \(\geq 15\%\). Despite formal training in image acquisition at all participating centers and expert analysis at 3 core laboratories, no dyssynchrony parameter was able to meaningfully distinguish responders from nonresponders, with the lower confidence interval boundary <50% for either sensitivity or specificity for all 12 dyssynchrony parameters evaluated. This study highlights the variability and difficulty in widespread applications of these methods.

**Other Mechanisms of CRT Response**

The exact mechanism responsible for reverse remodeling and hemodynamic improvement with CRT is not well understood and likely involves a complex interplay of several factors specific to each individual. In addition to the role of baseline mechanical dyssynchrony, other determinants of CRT response include LV lead position,\(^{43-49}\) scar burden,\(^{50-53}\) electric dyssynchrony as measured by intracardiac electrogram (Q-LV interval),\(^{54}\) and device optimization.\(^{55}\) With so many variables at play, it is not surprising that dyssynchrony alone is inadequate to predict response to CRT.

Several retrospective studies evaluated whether concordance between LV lead position and the most delayed area of mechanical activation was correlated with improved response rate in patients undergoing CRT. With the use of pulse wave Doppler imaging,\(^{46}\) tissue synchronization imaging,\(^{47}\) real-time 3-dimensional echocardiography,\(^{48}\) or 2-dimensional strain with speckle tracking,\(^{49}\) the wall demonstrating maximal mechanical delay was identified and targeted for the LV lead position, leading to improved CRT response over non-optimized lead localization. The degree of scar burden, as assessed by varied modalities, has also been associated with echocardiographic response to resynchronization therapy. Myocardial perfusion imaging was utilized to generate a summed perfusion score, with higher scores (more scar) correlating with lower LVEF response.\(^{50}\) Similarly, echocardiography and contrast-enhanced magnetic resonance imaging were able to identify reverse remodeling responders on the basis of the number of LV scar segments identified, with the presence of fewer scar segments better identifying CRT responders.\(^{52,53}\)
A novel approach to evaluating electric dyssynchrony comes from a small prospective study on intracardiac electric dyssynchrony as measured by duration from the onset of the surface Q wave to the intrinsic deflection of the LV lead electrogram (Q-LV interval).54 A Q-LV interval >80 ms was able to reliably predict >10% increase in LV $dP/dt_{\text{max}}$. Interestingly, the lower Q-LV intervals did not correlate with narrower QRS, suggesting that surface electric dyssynchrony is not necessarily indicative of intraventricular dyssynchrony.

In regard to device optimization, several methods have been proposed for atrioventricular and interventricular timing in CRT, including the Ritter, iterative, and aortic outflow methods for atrioventricular optimization and the aortic velocity time integral for interventricular optimization.56,57 Although the clinical benefits of optimizing atrioventricular and interventricular timing are uncertain, several studies have demonstrated improved hemodynamic performance with atrioventricular and interventricular optimization.3,58–60 A randomized, multicenter, double-blinded trial is currently under way to investigate the role of atrioventricular delay optimization on short-term reverse remodeling.61

Conclusions
Because of the lack of evidence that there is a direct link between the presence of mechanical dyssynchrony and the clinical benefit derived from CRT, we do not recommend echocardiographic assessment of mechanical dyssynchrony for patient selection. Despite the numerous trials utilizing echocardiographic measures of mechanical dyssynchrony parameters to predict response to CRT in patients with narrow or wide QRS, their small numbers, poor reproducibility, lack of a control group, and use of surrogate markers for therapeutic response make it impossible to translate the results of these studies into clinical practice.

Proponents for the use of mechanical dyssynchrony point to the lack of appropriate sonographer training at centers without reproducible results.62,63 We argue that the degree of sonographer training in the PROSPECT trial likely represents the real-world training that could be expected at most laboratories. Newer methods appear to hold promise from a technical standpoint because of the lack of angle dependency as well as the obvious advantages of 3-dimensional methods. However, more recent studies evaluating speckle tracking and 3-dimensional imaging show findings similar to those of previous dyssynchrony parameters.24,26,27

The decision to offer CRT to an individual patient is based on a number of factors, many of which are included in the current guidelines. However, given the high cost and the risk associated with this invasive therapy, we agree that further research is needed to tailor this therapy to patients who derive benefit while minimizing the use of this therapy in patients who do not. The guidelines must be reassessed continually so that they evolve with emerging data, and revised only when the data are clinically compelling and firmly established.

In summary, published studies evaluating baseline mechanical dyssynchrony have not yet established the minimum requirements to affect current medical decision making. Mechanical dyssynchrony, at least as measured currently, is not the sole determinant of response to resynchronization. The surrogate end points measured in studies of mechanical dyssynchrony may not be sufficient markers of improved clinical outcomes. Finally, parameters of mechanical dyssynchrony based on echocardiographic imaging lack sufficient reproducibility and predictive value to reliably identify patients who stand to derive significant mortality benefit and/or hospitalization reduction with CRT.

Although there are some gray areas even within the established guidelines for CRT, including its use in the presence of narrower QRS (<150 ms) and right bundle-branch block, we know that, as a population, patients with standard indications for CRT have experienced proven benefits in mortality and hospitalization. Thus, let us revisit our ischemic patient who meets all standard clinical indications for CRT. Two different echocardiographic measures of mechanical dyssynchrony are negative. Detractors may argue about his reduced chances at reverse remodeling; we say that he deserves the proven benefit of reduced hospitalization and death with CRT, at least for now.

Disclosures
Dr Foster reports significant grant support from Boston Scientific Corporation, EBR Systems, Inc, Guided Delivery Systems, Inc, and Abbot Vascular Structural Heart and is a consultant for Actelion. Dr Sung reports no conflicts.

References


Response to Sung and Foster

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

In this controversy, Drs Sung and Foster agree with us on the fact that QRS duration lacks the accuracy to select the patients who will respond to cardiac resynchronization therapy (CRT). In contrast, they argue that echocardiography measurements of left ventricular (LV) dyssynchrony have failed to accurately predict CRT response, and advocate the use of novel methods such as the intracardiac electrogram to assess electric dyssynchrony and predict response to CRT. Interestingly, the value of the intracardiac electrogram to predict CRT response has not been demonstrated, except in a small population of 80 patients, whereas the predictive value of LV dyssynchrony as assessed with echocardiographic techniques has been demonstrated in numerous single and multicenter trials that have enrolled >2000 patients. Therefore, it is important to validate the reproducibility and robustness of intracardiac electrograms in further studies before its incorporation into day-to-day clinical practice. Furthermore, there is substantial cumulative evidence showing that the measurement of LV dyssynchrony with echocardiography is strongly related to long-term prognosis, which is the preferred end point in heart failure trials. Therefore, the measurement of LV dyssynchrony is of clinical relevance. Finally, we believe that several other pathophysiological factors play a role in the response to CRT, and that assessment of LV mechanical dyssynchrony should be integrated with quantification and localization of LV scar tissue and identification of the site of latest mechanical activation to further improve selection of patients for CRT.
Assessment of Systolic Dyssynchrony for Cardiac Resynchronization Therapy Is Not Clinically Useful
Raphael K. Sung and Elyse Foster

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## SUPPLEMENTAL MATERIAL

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

<table>
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<tr>
<th>Study Type</th>
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<th>N</th>
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<th>Blinded Analysis</th>
<th>Method</th>
<th>Parameter (No. of Segments Measured)</th>
<th>Follow-up, mo</th>
<th>Definition of Response</th>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>Yes</td>
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<td>SPWMD</td>
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<td>EF ↑ ≥ 5%</td>
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<td>Yes</td>
<td>Yes</td>
<td>PWD</td>
<td>IVMD</td>
<td>6</td>
<td>Improved CCS + EF ↑ ≥ 5%</td>
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<td></td>
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<td>53</td>
<td>Yes</td>
<td>Yes</td>
<td>2D</td>
<td>Presence of abnormal motion</td>
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<td>ESV ↓ ≥ 10%</td>
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<td>Yes</td>
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<td>a) NYHA ↓ ≥ 1</td>
<td>65 msec</td>
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<td>ESV ↓ &gt; 15%</td>
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<td>96</td>
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<td>78</td>
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<td>75 msec</td>
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<td>Speckle</td>
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<td>&gt;10%</td>
<td>96 (88-99)</td>
<td>88 (66-97)</td>
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6MWD, 6-minutes walk distance; AS-P, anteroseptal and posterior delay; CCS, clinical composite score; CC(PW)TDI, color coded (pulsed wave) tissue Doppler imaging; Conven, conventional echocardiographic parameters; ESV, end systolic volume; ESVI, end systolic volume index; IVMD, interventricular
mechanical delay; MOWD, maximum opposing wall delay; oExcT, overall time of strain exceeding aortic valve closure; PWD, pulsed wave Doppler; RT3D, real time 3D; S-L, septal and posterior delay; SPWMD, septal-posterior wall motion delay; SRI, strain rate imaging; Ts (To)-Diff, difference in time to peak (onset) of systolic velocity; T*-Diff, difference in time to peak strain; Ts (To)-SD, standard deviation in time to peak (onset) systolic velocity; Td-SD, standard deviation in time to peak displacement; T*-SD, standard deviation in time to peak strain; TSI, tissue synchronization imaging; RS/CS/LS, radial/circumferential/longitudinal strain; GRS/GCS, global radial/circumferential strain; GLPSS, global longitudinal peak systolic strain.

* Sensitivity/specificity not reported due to lack of statistical significance

† Cutoff value not reported
Supplemental References:


12. Yu CM, Zhang Q, Chan YS, Chan CK, Yip GW, Kum LC, Wu EB, Lee PW, Lam YY, Chan S, Fung JW. Tissue doppler velocity is superior to displacement and strain mapping in predicting left ventricular reverse remodelling response after cardiac resynchronisation therapy. *Heart*. 2006;92:1452-1456


