Radial Strain Delay Based on Segmental Timing and Strain Amplitude
Predicts Left Ventricular Reverse Remodeling and Survival following
Cardiac Resynchronization Therapy

Kydd et al: Radial Strain Delay and CRT

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DOI: 10.1161/CIRCIMAGING.112.000191

Journal Subject Codes: [31]Echocardiography,[110]Congestive Heart Failure,
[120]Pacemaker
Abstract

Background—Dyssynchrony assessment based on the timing of regional contraction is inherently independent of underlying myocardial contractility. We tested the hypothesis that patient selection for cardiac resynchronization therapy (CRT) would be enhanced using a parameter derived from the net radial strain delay for the 12 basal and mid left ventricular (LV) segments (RSDc), based not only on timing but also amplitude of segmental strain.

Method and Results—Echocardiographic data was analysed in 240 patients with symptomatic heart failure undergoing CRT (NYHA class III/IV, QRS>120ms, ejection fraction 23±7%). RSDc was calculated as the sum of difference between peak radial strain and radial strain at aortic valve closure before CRT implantation. CRT response was defined as >15% reduction in LV end-systolic volume (LVESV) at 6 months. In a derivation group (n=102) RSDc was higher in responders compared to non-responders (74±39 vs. 29±15%, p<0.001), and related to the change in LVESV (r=-0.53, p<0.001). RSDc >40% predicted remodeling (sensitivity 87%, specificity 88%). In the validation group (n=108) RSDc similarly predicted response (sensitivity 89%, specificity 84%). Survival at long-term follow up was greater in patients with RSDc >40 (p<0.001).

Conclusions—RSDc, based on both the timing and amplitude of segmental strain, has a strong predictive value for CRT remodeling response and long-term survival.

Key Words: speckle tracking echocardiography, cardiac dysfunction, cardiac resynchronization therapy
Echocardiographic parameters using dyssynchrony measurement by tissue Doppler and strain imaging have been disappointing for predicting CRT response\(^1\)\(^2\). Although most major trials and current guidelines recommend CRT on the basis of QRS width (>120ms), several studies recognise identification of mechanical dyssynchrony may enhance patient selection\(^3\)\(^4\). However, the use of these techniques was not supported in two major multicentre trials. In the PROSPECT\(^5\) study of nearly 500 patients, echocardiographic parameters of dyssynchrony offered limited sensitivity, specificity and reproducibility for predicting CRT response. In the ReThinQ trial\(^6\) of patients with a narrow QRS duration and severe left ventricular (LV) dysfunction, including evidence of mechanical dyssynchrony, CRT conferred no benefit. Extensive myocardial scar also limits CRT response suggesting that characterization of the underlying myocardial substrate should be considered together with timing of segmental contraction to predict LV reverse remodeling\(^7\)\(^8\). Speckle-tracking analysis has emerged as a technique with the potential to enhance patient selection for CRT with a >130ms difference in the delay between the time to peak antero-septal and posterior wall radial strain predicting response (sensitivity 88%, specificity 83%)\(^9\). We therefore tested the hypothesis that patient selection for CRT would be enhanced using a strain-based parameter incorporating both timing of myocardial segmental motion and amplitude of deformation, a potential measure of contractile reserve. We assessed a radial strain delay parameter (based conceptually on the strain delay index reported by Lim et al\(^{10}\)) and compared this to previously reported dyssynchrony measures to determine improvements in predefined endpoints of LV volume following CRT, as well as prognosis.
Methods

Patient Population and Study Protocol

Two hundred and forty patients were assessed in two consecutive groups. In the first cohort (n=120), the optimal cut off for radial strain delay to predict CRT response was assessed (derivation group) followed by validation in a prospective group (n=120). Inclusion criteria included sinus rhythm with left bundle branch block (QRS width ≥ 120ms), New York Heart Association (NYHA) functional class III or IV heart failure and impaired LV systolic function (LV ejection fraction ≤ 35%), despite optimal medical treatment. All patients underwent detailed clinical assessment including a 6-minute walk test (6-MWT) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) and baseline echocardiography prior to scheduled device therapy. Radial strain speckle tracking analysis was performed on the parasternal 2D gray scale images of the 12 non-apical segments in each patient. Following CRT, baseline clinical and echocardiographic assessments were repeated at 6 months and response defined as a ≥15% reduction in LVESV. Mortality data was collected with the longest follow-up of almost 4 years. The study was approved by the local ethics committee and all participants gave fully informed written consent.

CRT Implantation

An 8F guiding catheter was used to position the LV lead. Final LV lead position was determined by biplane fluoroscopy and lateral and frontal chest radiographs. The right atrial lead was positioned in the right atrial appendage and the right ventricular (RV) lead was placed according to operator preference in the mid-septum or RV apex. Atrioventricular (AV) and interventricular (VV) delays were optimized by echocardiography in all patients according to the highest velocity time integrals (VTI) from the pulsed wave Doppler of the transmiatral inflow and left ventricular outflow tract respectively as previously described11.
Devices were programmed in DDD-Mode (lower rate limit 40) to achieve atrial synchronous biventricular pacing.

**Echocardiography**

Standard two-dimensional and tissue Doppler imaging was performed in all subjects using a 3.5MHz phased array transducer (Vivid 7, General Electric Medical Systems, Horten, Norway). The gray-scale, colour Doppler and tissue colour Doppler data were acquired in a cine-loop format and digitally stored for post-processing offline (GE EchoPAC, version 7.0, Horten, Norway). LV end diastolic and end-systolic volumes (LVEDV, LVESV) and LV ejection fraction (EF) were calculated using the Simpson biplane method in accordance with the American Society of Echocardiography guidelines. Interventricular mechanical dyssynchrony (IVMD) was determined as the difference in time from QRS onset and the beginning of pulmonary and aortic ejection from pulsed wave Doppler measurements in the pulmonary and aortic outflow tracts respectively. Intraventricular dyssynchrony was assessed in all patients by speckle tracking echocardiography and tissue Doppler imaging.

**Speckle Tracking Echocardiography**

Speckle tracking analysis of the pre-implantation gray scale basal and mid-LV short-axis images was performed using a standardized approach as previously described. All images were recorded with a frame rate of >40 Hz. The endocardial border was traced just within the endocardium using a point-and-click technique in end-systole, and particular care was taken to adjust tracking of all segments. A second larger concentric circle was then automatically generated and manually adjusted near the epicardium such that the area of interest included the entire myocardial wall. The width of the epicardial circle was either increased or decreased where necessary to account for variation in wall thickness. The image was then
played so that tracking in the region of interest could be fine-tuned by visual assessment, to ensure that all wall segments tracked appropriately throughout the cardiac cycle and that the sectors defining each wall segment were adjusted appropriately.

**Radial Strain Delay**

The derived measure of radial strain delay (RSD\textsubscript{c}) is designed to incorporate both the amplitude and timing of myocardial regional deformation. Areas of scar do not contribute effectively to myocardial ejection and the extent of myocardial scar is inversely proportional to the extent of LV reverse remodeling following CRT\textsuperscript{7}. Myocardial deformation analysis has the inherent advantage of distinguishing active contraction from passive movement or tethering. Analysis of the amplitude of regional strain by speckle tracking echocardiography has the potential to identify potentially recruitable myocardium (Figure 1). Areas of low amplitude probably represent scar and LV lead placement over areas of low amplitude radial strain is associated with a poor response to CRT\textsuperscript{13}. Intraventricular conduction delay induces both early and late segmental contraction either before peak ejection or after closure of the aortic valve, thereby reducing the efficiency of myocardial contraction resulting in wasted energy. As the amplitude of myocardial strain is not measured in standard dyssynchrony parameters, which are based on timing alone, the extent of wasted energy is not taken into account. This concept of wasted energy has been proposed and quantified previously using speckle tracking longitudinal strain delay\textsuperscript{10} and has shown promise in identifying responders and non-responders to CRT\textsuperscript{14}. Using a similar principle, we quantified the extent of wasted energy using RSD\textsubscript{c} calculated as peak radial strain minus radial strain at peak ejection (aortic valve closure, AVC) for the 12 non-apical segments, expressed as $\Sigma_{12} (RS_{Peak} - RSAVC)$(Figure 2). RSD\textsubscript{c(mid)} for the 6 mid-myocardial segments only, expressed as $\Sigma_{6mid} (RS_{Peak} - RSAVC)$, was also calculated.
Timing Based Dyssynchrony Parameters

In addition to the RSD dyssynchrony parameters based on the timing from onset of the QRS to peak strain were assessed. Anteroseptal to posterior wall delay (AS-P) using radial speckle tracking was calculated as the difference between time to peak radial strain from QRS onset of the anteroseptal and posterior segments of the mid LV. RsSD12, defined as the standard deviation of the time to peak strain of the 12 non-apical segments using speckle tracking radial strain was also assessed. Dyssynchrony was additionally assessed by tissue Doppler imaging techniques in all patients. Dyssynchrony by TDI was determined as the maximal time difference in peak systolic velocities between the basal septum and lateral segment (Ts-SL delay) and the standard deviation of the time to peak systolic velocity of the 12 non-apical segments (Ts-SD12) as previously reported.

Follow up

The primary endpoint of LV remodeling at 6 months was defined as a >15% reduction in LVESV. Secondary endpoints were clinical response of >1 class improvement in NYHA functional status at 6 months and survival.

Statistical Analysis

Data are presented as mean ± SD. For continuous data, student’s t-test was used to compare means between paired and unpaired groups. A p value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were determined to evaluate the potential of each dyssynchrony parameter to predict CRT response. Optimal cut off values for the AS-P, Ts SL and Ts-SD12 were taken as 130ms, 65 ms and 33ms respectively as previously reported. For the remaining dyssynchrony parameters optimal cut off values
were chosen to maximize the Youden index (sensitivity+specificity-1). Correlation was used to compare LV ESV reduction and each of the dyssynchrony parameters. Kaplan-Meier curves were plotted for survival and the log rank test used to compare the groups. Reproducibility was assessed in 20 randomly selected datasets. Interobserver and intraobserver variability were expressed as the SD of the difference between 2 paired measurements and as a percentage of variability (SD divided by the average value of the variable). Intraobserver and interobserver variability for RSDc by speckle tracking strain was based on identical datasets.

Results

Patient Baseline Characteristics

In 240 consecutive patients assessed for CRT, a total of 18 (8%) subjects (n=11 in the derivation group) had inadequate echocardiographic images for analysis. Implantation of a LV lead was not possible in 5 (2%) patients (n=3, in the derivation group). Follow-up data was incomplete at 6 months in 7 patients due to failure to attend for echocardiography (n=4 in the derivation group) resulting in complete data in 102 patients in the derivation group and 108 patients in the validation group. The baseline characteristics of all patients are presented in Table 1.

Feasibility and Reproducibility of Dyssynchrony Parameters and RSDc

Feasibility for dyssynchrony parameters were: Ts SL in 178 (85%) patients, Ts SD12 in 170 (81%) patients), AS-P delay in 181 (86%) patients, RsSD12 in 177 (84%) patients, RSDc in 178 (85%) patients, and IVMD in 195 (93%) patients. Intraobserver and interobserver reproducibility were respectively; 5% (10%) and 7% (14%) for calculation of the RSDc. For additional dyssynchrony parameters intraobserver and interobserver reproducibility were
respectively: 20ms (10%) and 28ms (14%) for AS-P delay, 15ms (12%) and 21ms (16%) for RsSD12, 4ms (10%) and 5ms (12%) for IVMD, 8ms (11%) and 11ms (15%) for Ts SL and 4ms (10%), and 5ms (13%) for Ts SD12.

**Derivation Group**

**Response to CRT**

After 6 months of CRT, NYHA class improved in 71 (69.6%) patients, was unchanged in 16 (15.7%) patients, worsened in 11 (10.8%) patients and 4 patients had died and were classified as non-responders. Of the remaining patients in whom LV reverse remodeling data was available, LVESV reduced by >15% in 62 patients, between 0 and 15% in 29 (28.4%) patients and increased in 9 (8.8%) patients giving a response rate of 60.8% for the total cohort. The changes in functional and echocardiographic variables before and 6 months after treatment are reported in Table 2. Responders by volume reduction, compared to non-responders exhibited lower NYHA class, greater 6 minute walk test distances and improved quality of life scores.

**Dyssynchrony Parameters between Responders and Non-responders**

Dyssynchrony parameters that differed between volumetric responders and non-responders were the RSDc (74 ± 39 vs. 29 ± 15%, p<0.001), RSDd(mid) (45.8 ± 29 vs. 16.4 ± 12.3%, p<0.001), AS-P delay (226 ± 154 vs. 122 ± 93ms, p<0.001), RsSD12 (144 ± 100 vs. 100 ± 58%, p<0.001) and IVMD (42 ± 22 vs. 35 ± 26%, p=0.02). Neither the Ts SL nor the Ts SD12 differed significantly between the two groups (Table 3).
Prediction of LV Reverse Remodeling post CRT

RSD_τ was related to the reduction in LVESV at 6 months (r=-0.53, p<0.001, Figure 3), and did not differ in those with an ischemic and non-ischemic basis for their heart failure (r=-0.51, p<0.001 vs. r= 0.54, p<0.001). RSD_{c(mid)} was similarly related to reduction in LVESV at 6 months (r=-0.53, p<0.001). Both parameters displayed a stronger correlation LV reverse remodeling than the AS-P delay (r=-0.28, p=0.02), Rs SD12 (r=-0.29, p=0.007), and IVMD (r=-0.29, p=0.008). However, there was no correlation with the change in LVESV at 6 months for either Ts SL (r=-0.18, p=0.11) or Ts SD12 (r=-0.19, p=0.12). Using receiver operating characteristic (ROC) curve analysis a cut off value of 40% for RSD_τ predicted a >15% reduction of LVESV with a sensitivity of 87% and specificity of 88% (Figure 4). A cut off value of 23% for RSD_{c(mid)} predicted >15% reduction of LVESV with a sensitivity of 81% and specificity of 83%. ROC curve analysis and the sensitivities and specificities of all dyssynchrony parameters assessed are presented in Table 3. RSD_τ had the highest sensitivity and specificity and was evaluated in a validation cohort.

Validation Group

Radial Strain Delay and Prediction of CRT Response

Seventy-four (68.5%) of the validation group had a clinical response to CRT and 67 (62.0%) patients showed a volumetric response at 6 months (Table 2). RSD_τ was higher in responders than non-responders (66 ± 35 vs. 38 ± 24%, p<0.001) and correlated with LVESV reduction (r=-0.48, p<0.001). Using the derived cut off of 40%, RSD_τ predicted CRT response with a sensitivity of 89% (95% CI: 79-94%) and specificity of 84% (95% CI: 69-95%). This gave a positive predictive value of 84% and a negative predictive value of 85%. A RSD_τ >40% at baseline appeared to identify those with greater LV reverse remodeling following CRT (28 ± 11 vs. 9 ± 8%, p<0.001).
All Patients

Relationship of Radial Strain Delay to QRS Duration and Heart Failure Aetiology

A great proportion of patients with non-ischaemic aetiology demonstrated remodeling response following CRT when compared to ischaemic aetiology (68% vs. 56%). Although patients with non-ischaemic and ischaemic aetiology had similar baseline RSD_c (60±36 vs. 52±36%, p=0.1) RSD_c was greater in CRT responders irrespective of aetiology (Figure 5).

We examined the relationship between RSD_c, QRS duration, using a cut off of 150ms, and CRT remodeling response. RSD_c was greater in CRT responders than non-responders irrespective of baseline QRS duration (Figure 5).

Relation of Radial Strain Delay to Survival

Follow up survival data was available for all 210 patients over a mean length of 855±315 days, there were a total of 45 deaths (21%). In patients with a RSD_c >40% (n=131) there were a total 17 deaths compared to 28 deaths in patients with a radial strain delay of <40% (n=79).

The presence of dyssynchrony assessed by RSD_c was associated with improved survival (p<0.001, Figure 6). Outcomes remained similar in each group when stratified according to baseline QRS duration (Figure 6).

Discussion

The present study assesses the utility of a radial strain delay dyssynchrony parameter to potentially enhance the selection of patients for CRT. The radial strain delay is able to predict LV reverse remodeling with a higher sensitivity and specificity, and has better correlation with reduction of LVESV at 6 months than measures based on the regional timing of either myocardial velocity or 2D strain. Our findings suggest that a parameter incorporating both the regional timing and amplitude of myocardial deformation is superior in predicting CRT
response, including LV reverse remodeling and survival, than parameters based on timing alone. Similar predictive potential is seen in patients irrespective of underlying aetiology. These findings support the superiority of strain over velocity and demonstrate additional refinement in CRT patient selection by inclusion of measures of residual contraction.

A reduction of LVESV of >15% following CRT is associated with improved prognosis\textsuperscript{17} but is not realized in approximately 30% of all heart failure patients undergoing device therapy. Mechanical dyssynchrony assessment using echocardiography may enhance patient selection and tissue velocity imaging of longitudinal wall motion is the most widely reported method\textsuperscript{16,18}. Unlike strain, velocity based measures are unable to differentiate active contraction from passive motion and have a low specificity for patient selection. This is demonstrated in a recent study by Miyakazi et al, who report that up to 68% of normal individuals with normal LV function and normal QRS duration have tissue velocity parameters that exceed the cut offs for recommending CRT implant. When tissue strain is used, however, there is minimal overlap between groups of patients with and without LBBB, with and without LV impairment\textsuperscript{19}. In the present study, both dyssynchrony parameters based on tissue velocity (namely the Tv-SL and Tv-SD12) were similar in responders and non-responders. Although this is in conflict with the study by Yu et al\textsuperscript{3}, our findings are in line with more recent reports. Mele et al report a comparison of tissue myocardial strain and velocity dyssynchrony and found that strain derived regional timing of 12 non-apical segments better identified CRT responders\textsuperscript{20}. Likewise Porciani et al report a very low specificity of only 39% for the Tv SD12 using a cut off of 33ms to predict response at 6 month follow up\textsuperscript{21}.

Even though strain appears to be superior to velocity, not all strain is the same. Delgado et al in 242 CRT patients with 6 months follow up showed that segmental timing of radial and not
longitudinal strain by speckle tracking analysis predicted response\textsuperscript{22}. We hypothesized, that a strain-based approach, although an advancement on velocity based parameters, still inherently fails to take into account residual contraction by being limited only to the timing and not the extent of myocardial deformation. Myocardial viability assessed by \textsuperscript{18}F-Fluro-Deoxy-Glucose and positron emission tomography (PET-FDG) predicts response with a sensitivity of 74\% and a specificity of 87\% and similarly, extensive LV scar is associated with poor outcomes after CRT\textsuperscript{7, 23}. Speckle tracking strain analysis has been shown to correctly identify segmental LV dysfunction due to scar following myocardial infarction in an animal model and can correctly identify reversible myocardial dysfunction in humans\textsuperscript{24, 25}. Strain analysis by speckle tracking echocardiography therefore has the potential to identify viable myocardium as well as heterogeneity in segmental timing\textsuperscript{26}. The RSD\textsubscript{c} is a parameter based on both of these elements and is conceptually based on a previous report by Lim et al who have pioneered the approach of quantifying wasted energy as a predictor of LV reverse remodeling. The authors report the use of a strain-delay parameter based on speckle tracking longitudinal motion of 16 myocardial segments and show a sensitivity of 91\% and specificity of 90\% for predicting the same pre-specified endpoint as in this study\textsuperscript{10}. Furthermore they have used this approach in a multicentre observation study of 189 CRT patients with analyzable echo data using this pre defined cut off to predict response with a sensitivity of 92\%, and specificity of 65\%\textsuperscript{14}.

The present study is the first to report the benefit of quantifying wasted energy as a marker of CRT response using speckle tracking radial strain analysis. The RSD\textsubscript{c} can theoretically be calculated in several ways and we elected to use speckle tracking strain analysis which, unlike Doppler strain is less affected by insonation angle, a particular concern in the failing heart where spherical geometry is often encountered. This study highlights the limitations of
a timing based approach without consideration of the underlying myocardial substrate. Based on this principle, Carasso et al report that the absence of passively compliant segments (defined as >5% holosystolic stretching) using longitudinal speckle strain analysis in a predominantly ischemic population predicts response with a sensitivity of 98% and specificity of 88%26. The RSDc is just one possible method of incorporating elements of timing and residual contraction but is not the only one and may not be the most optimal technique. As the move from velocity based timing to strain based timing gathers momentum, this study provides further support, albeit in a small cohort, for an even further shift from the timing of regional strain alone to incorporate elements of strain amplitude.

Limitations of our study

Although promising, the RSDc has only been assessed in the present study in a relatively small cohort of patients in a single centre and further investigation is warranted in particular its use in patients with coronary artery disease. Validation with formal quantification of scar burden should be undertaken to clarify its utility. The calculation of the RSDc was restricted to the 12 basal and mid segments in the radial vector due to a higher proportion of non-valid tracking of the apical segments. A more comprehensive approach using three dimensional speckle tracking may yield better sensitivities and specificities. An automated software based calculation of the RSDc may further widen the application of this method. Our current findings are restricted to patients with LBBB and may not be suitable for patients with a QRS of <120ms or with right bundle branch block and this requires further assessment. Finally, we acknowledge that the use of a reduction in LVESV as a remodeling parameter to dichotomise the response to CRT alone has limitations and does not encompass both clinical and structural data that are included in a composite score.
Conclusions

A novel RSD_e dyssynchrony parameter incorporating the timing and amplitude of dyssynchronous myocardial segmental motion accurately may offer a reliable single measure to predict response to CRT with high sensitivity and specificity and is related to long term survival.

Acknowledgements

The authors wish to thank Addenbrooke’s Charitable Trust, Papworth Hospital Research and Development Department and Cambridge Biomedical Research Centre funded from the UK NIHR for their support in conducting this work.

Disclosures

None.

References


Table 1. Baseline Characteristics of all Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=210)</th>
<th>Derivation Group (n=102)</th>
<th>Validation Group (n=108)</th>
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<tr>
<td>Age (yrs.)</td>
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<td>69 ± 10</td>
<td>72 ± 11</td>
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<td>Male</td>
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<td>Previous CABG</td>
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<td>Diabetes Mellitus</td>
<td>49 (35.0)</td>
<td>34 (33.3)</td>
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<td>QRS duration (ms)</td>
<td>160 ± 22</td>
<td>158 ± 21</td>
<td>163 ± 23</td>
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<tr>
<td>LVEDV (ml)</td>
<td>201 ± 85</td>
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<td>202 ± 91</td>
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<td>LVESV (ml)</td>
<td>152 ± 71</td>
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<td>154 ± 75</td>
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<tr>
<td>LVEF (%)</td>
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<td>23 ± 7</td>
<td>23 ± 7</td>
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<td>Moderate/severe mitral regurgitation</td>
<td>62 (29.5)</td>
<td>27 (26.5)</td>
<td>35 (32.4)</td>
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<td>ACEI or ARB</td>
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<td>91 (43.3)</td>
<td>43 (42.2)</td>
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<td>CRT – Pacemaker</td>
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CABG – Coronary Artery Bypass Grafting; LVEDV – Left ventricular end diastolic volume; LVESV – left ventricular end-systolic volume; LVEF – left ventricular ejection fraction; ACEI – Angiotensin converting enzyme inhibitors; ARB – Angiotensin receptor blockers; AS-P – Anteroseptal to posterior wall delay.

Data are presented as mean±SD or n or n(%)
Table 2. Clinical and Echocardiographic Variables between Responders and Non Responders

<table>
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<tr>
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<th>Derivation Group n=102</th>
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<td></td>
<td>(mean ± SD)</td>
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<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
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<td>Baseline</td>
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<td>Follow Up</td>
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<tr>
<td>Baseline</td>
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<td>198 ± 91</td>
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<tr>
<td>Follow Up</td>
<td>320 ± 112</td>
<td>221 ± 82</td>
<td>&lt;0.001</td>
<td>295 ± 102</td>
<td>223 ± 84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Change</td>
<td>+36</td>
<td>+12</td>
<td>0.001</td>
<td>+37</td>
<td>+9</td>
<td>0.01</td>
</tr>
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<td><strong>MLHFQ</strong></td>
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</tr>
<tr>
<td>Baseline</td>
<td>52 ± 18</td>
<td>57 ± 21</td>
<td>0.24</td>
<td>55 ± 18</td>
<td>54 ± 21</td>
<td>0.43</td>
</tr>
<tr>
<td>Follow Up</td>
<td>27 ± 19</td>
<td>46 ± 19</td>
<td>&lt;0.001</td>
<td>29 ± 19</td>
<td>50 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Change</td>
<td>-48</td>
<td>-19</td>
<td>&lt;0.001</td>
<td>-47</td>
<td>-7</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>LVEDV</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>194 ± 81</td>
<td>202 ± 91</td>
<td>0.25</td>
<td>201 ± 81</td>
<td>210 ± 91</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Follow Up</td>
<td>% Change</td>
<td>Follow Up</td>
<td>% Change</td>
<td>Baseline</td>
<td>% Change</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>144 ± 79</td>
<td>-26</td>
<td>190 ± 78</td>
<td>-6</td>
<td>152 ± 79</td>
<td>-24</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.56</td>
<td>0.56</td>
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<tr>
<td><strong>LVESV</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>146 ± 79</td>
<td>-33</td>
<td>152 ± 78</td>
<td>-10</td>
<td>153 ± 79</td>
<td>-33</td>
</tr>
<tr>
<td>Follow Up</td>
<td>98 ± 79</td>
<td>&lt;0.001</td>
<td>137 ± 78</td>
<td>&lt;0.001</td>
<td>103 ± 79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>23 ± 7</td>
<td>+39</td>
<td>24 ± 6</td>
<td>+13</td>
<td>23 ± 7</td>
<td>+43</td>
</tr>
<tr>
<td>Follow Up</td>
<td>32 ± 9</td>
<td>&lt;0.001</td>
<td>27 ± 7</td>
<td>&lt;0.001</td>
<td>33 ± 9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Comparison of Dyssynchrony Parameters between Responders and Non responders and ROC analyses

<table>
<thead>
<tr>
<th>Dyssynchrony Parameter</th>
<th>Responders (mean ± SD)</th>
<th>Non responders (mean ± SD)</th>
<th>P value</th>
<th>Cut Off Value</th>
<th>AUC (ROC)</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSDc (%)</td>
<td>74 ± 39</td>
<td>29 ± 15</td>
<td>&lt;0.001</td>
<td>40%</td>
<td>0.91</td>
<td>87 (74-94)</td>
<td>88 (72-93)</td>
</tr>
<tr>
<td>RSDc(mid) (%)</td>
<td>46 ± 29</td>
<td>16 ± 12</td>
<td>&lt;0.001</td>
<td>23%</td>
<td>0.87</td>
<td>81 (68-91)</td>
<td>83 (66-93)</td>
</tr>
<tr>
<td>AS-P (ms)</td>
<td>226 ± 154</td>
<td>122 ± 93</td>
<td>&lt;0.001</td>
<td>130 ms</td>
<td>0.75</td>
<td>73 (57-92)</td>
<td>74 (52-94)</td>
</tr>
<tr>
<td>Rs-SD12 (ms)</td>
<td>144 ± 100</td>
<td>100 ± 58</td>
<td>&lt;0.001</td>
<td>122 ms</td>
<td>0.71</td>
<td>69 (51-86)</td>
<td>68 (50-82)</td>
</tr>
<tr>
<td>Ts S-L (ms)</td>
<td>70 ± 31</td>
<td>60 ± 26</td>
<td>0.17</td>
<td>65 ms</td>
<td>0.65</td>
<td>61 (29-82)</td>
<td>59 (33-80)</td>
</tr>
<tr>
<td>Ts SD12 (ms)</td>
<td>39 ± 12</td>
<td>34 ± 11</td>
<td>0.12</td>
<td>33 ms</td>
<td>0.59</td>
<td>58 (28-89)</td>
<td>61 (35-86)</td>
</tr>
<tr>
<td>IVMD (ms)</td>
<td>42 ± 22</td>
<td>35 ± 26</td>
<td>0.02</td>
<td>40 ms</td>
<td>0.69</td>
<td>67 (52-83)</td>
<td>64 (49-83)</td>
</tr>
</tbody>
</table>

RSDc – calculated radial strain delay

RSDc(mid) – calculated radial strain delay (mid myocardial level only)
Figure Legends

Figure 1. Concept of the radial strain delay using speckle tracking analysis

Schematic representation of wasted energy according to timing of myocardial deformation (dyssynchrony) and amplitude (contractility) by radial strain. (A) In a normal segment (gray) peak deformation occurs close to aortic valve closure contributing fully to end-systolic function. Peak ejection is assumed to occur at end-systole, at the point of AVC defined by pulsed wave Doppler. Early and late deformation in segments with preserved contractility will not fully contribute to end-systolic function. The wasted energy is represented by the difference in strain amplitude at peak and end-systole for these segments (red). (B) The degree of wasted energy increases as segments with preserved contractility become more delayed. (C) In delayed segments with preserved amplitude (contractility) the degree of wasted energy is greater than in low amplitude segments (minimal residual contractility or scar). ES – end-systole; AVC - aortic valve closure.

Figure 2. Calculation of Radial Strain Delay

Speckle tracking radial strain curves from the mid LV level in a patient with dilated cardiomyopathy and LBBB prior to CRT implantation (A). Early peak deformation is seen in the anteroseptum (yellow). Remaining segments demonstrate late peak deformation occurring after aortic valve closure. An example calculation of the difference between peak and end-systolic strain is shown for the anteroseptum (yellow) and posterior (purple) segments. RSDc is calculated by summing peak radial strain (%) - radial strain (%) at AVC for all 12 basal and mid myocardial segments. Following CRT implantation with >15% reduction in LVESV (B) there is
a reduction in RSDc as the late segments are ‘resynchronized’ resulting in minimal residual difference between peak strain and strain at AVC for the 6 mid myocardial segments shown, the anteroseptum (yellow) and posterior (purple) segments are highlighted.

Figure 3. Relationship between baseline radial strain delay and change in left ventricular end-systolic volume change at 6 months

Figure 4. Receiver Operating Characteristic Curve for the Radial Strain Delay
Area under the curve (AUC), sensitivities and specificities are given for proposed a cut off values of 40%.

Figure 5. Radial Strain Delay in CRT responders (>15% reduction in LVESV) and non-responders according to actiology and baseline QRS duration.

Figure 6. Kaplan Meier Curve showing Survival for all patients according baseline radial strain delay and stratified according to baseline QRS duration.
C

Radial strain %

Late Peak: Preserved Amplitude

Late Peak: Low Amplitude

ES

AVC
$$RSD_c = \sum_{12} (RS_{\text{Peak}} - RS_{\text{AVC}})$$

**RSD_c** = Sum of peak strain (%) – strain at AVC (%) (end systole) for all 12 basal and mid myocardial segments
* p<0.001
Percent survival vs. Days from CRT for two groups: RSD >40 and RSD <40.

- **RSD >40**
  - Blue line
  - Lower survival rate compared to RSD <40

- **RSD <40**
  - Red line
  - Higher survival rate compared to RSD >40

Statistical note:

- **n=210**
- **p<0.0001**

The graph indicates a statistically significant difference in survival rates between the two groups.
Radial Strain Delay Based on Segmental Timing and Strain Amplitude Predicts Left Ventricular Reverse Remodeling and Survival following Cardiac Resynchronization Therapy

Anna C. Kydd, Fakhar Z. Khan, Denis O'Halloran, Peter J. Pugh, Munmohan S. Virdee and David P. Dutka

*Circ Cardiovasc Imaging.* published online January 30, 2013;

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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