Utility of a new left ventricular asynchrony index as a predictor of reverse remodelling after cardiac resynchronization therapy

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Aims The majority of tissue Doppler indexes proposed to predict left ventricular (LV) reverse remodelling in cardiac resynchronization therapy (CRT) reflects LV asynchrony as assessed in ejection phase. We evaluated the predictive value of a new strain-imaging parameter reflecting the total amount of time spent by 12 LV segments in contracting after aortic valve closure.

Methods and results Fifty-nine patients who fulfilled current treatment recommendations were studied before and 6 months after CRT. Time to tissue Doppler systolic peak velocity (Ts) and time exceeding aortic closure (ExcT) in strain curves were measured in 12 LV segments. Ts standard deviation (Ts-SD) and sum of ExcT of overall 12 LV segments (oExcT) were analysed. After 6 months, responders were defined according to 15% LV end-systolic volume reduction. Responders (47%) when compared with non-responders (53%) had significantly higher baseline Ts-SD and oExcT values. Receiver operating characteristic (ROC) curve analysis demonstrated that an optimal cutoff value of 760 ms for oExcT yielded 93.5% sensitivity and 82.8% specificity. For Ts-SD at the cutoff of 32 ms, 82% sensitivity and 39% specificity were obtained. Area under ROC was significantly larger for oExcT than for Ts-SD.

Conclusion o-ExcT is able to predict LV reverse remodelling after CRT.

Introduction

In the last few years, cardiac resynchronization therapy (CRT) has been widely used as an effective therapy for patients with heart failure (HF) and LV conduction disturbances.1–5 However, despite enthusiasm regarding the use of therapy for patients who fulfill current treatment recommendations,6 about 50%7,8 of patients may not show clinical or left ventricular (LV) reverse remodelling response. The reasons for lack of response are not well known. From the initial focus on electrical markers, recent interest has shifted towards a more direct assessment of mechanical dysynchrony by means of tissue Doppler imaging (TDI). At present, many predictors of CRT response indexes have been proposed, the majority of them reflecting LV asynchrony as assessed in the ejection phase.9–12 Among them, the standard deviation of the time to the systolic peak velocity (Ts-SD) has been demonstrated to be the most powerful predictor of LV reverse remodelling.7 Only few previous studies showed the finding of LV contraction in diastolic phase to be useful in determining haemodynamic improvement after CRT.13,14 Using strain imaging that reflects myocardial deformation, we proposed a new index quantitatively reflecting the whole temporal amount spent by 12 LV segments in contracting after aortic valve closure. In our study, we prospectively compared the relative predictive value of this new index and of Ts-SD on the CRT-induced reverse remodelling.

Methods

Inclusion criteria and study protocol

The study population comprised 59 patients who (from January 2004 to October 2005) underwent biventricular pacing device implantation for HF according to current guidelines.6 Briefly, inclusion criteria were New York Heart Association (NYHA) classes III–IV despite maximum well-tolerated medical therapy, LVEF ≤ 35%, and QRS duration ≥ 130 ms. They were treated with maximal tolerable doses of HF medications and remained clinically stable for ≥ 1 month before enrolment. Patients with atrial fibrillation (AF) or with a previously implanted pacemaker were excluded.

Standard and TDI echocardiography was performed before and 6 months after biventricular pacing device implant. At the 6-month follow-up, patients were divided into responders and non-responders on the basis of at least 15% LV end-systolic volume (ESV) reduction according to the literature data.15,16 Our Institutional Review Board approved the study and witnessed informed consent was obtained from each patient.

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Biventricular pacemaker implantation

Three transvenous pacing leads were inserted. The right atrial and ventricular leads were positioned conventionally. The LV lead was inserted through the coronary sinus into either the lateral (28 patients, 47%) or posterolateral cardiac vein (31 patients, 53%). The biventricular devices used were InSync (Medtronic Inc., Minneapolis, MN, USA) in 25 patients and Contak TR CHFD (Guidant Inc., St Paul, MN, USA) in 34 patients. After implantation, the atroventricular interval was optimized for maximal diastolic filling using Doppler echocardiography.17

Echocardiography

Standard echocardiography, including Doppler studies, was performed using a Vivid 7 System (Vingmed-General Electric, Horten, Norway). The following parameters were evaluated: LV end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) assessed by Simpson’s equation using the apical four-chamber view,18 myocardial performance index (MPI) as the sum of isovolumic contraction and relaxation times divided by ejection time,19 the time of strain tracing exceeding aortic valve closure (E/W), deceleration time of E-wave (DTE), isovolumic relaxation time (IVRT) as the interval between the end of mitral flow and the sum of isovolumic contraction and relaxation time was derived from the interval between the end of mitral inflow and the onset of the next mitral inflow signal minus ejection time, the ratio of peak flow velocity in early diastole and peak flow velocity in late diastole during atrial contraction (E/W), deceleration time of E-wave (DTE), isovolumic relaxation time (IVRT) as the interval between the end of aortic flow and the beginning of mitral inflow, and the jet mitral regurgitant area (JA) relative to left atrial size in the apical four-chamber view (JA/LAA) as mitral regurgitation severity parameter.20 The interventricular electromechanical delay (IVD) was also calculated as the time difference between the aortic and pulmonary pre-ejection time intervals where aortic and pulmonary ejection flows were recorded in the five-chamber apical and parasternal views, respectively.

Tissue Doppler and strain Doppler imaging evaluation

TDI and strain Doppler colour imaging (SDI) were performed with a 2.5 or 3.5 MHz phase array transducer for the long axis motion of the ventricles. Gain setting, filters, and pulse repetition frequency were adjusted to optimize colour saturation; sector size and depth were optimized for the highest frame rate. At least three consecutive beats were stored, and the images were digitized and computer-analysed offline (EchoPac 6.3.6, Vingmed-General Electric, Horten, Norway). Myocardial pulse-Doppler velocity profile signals were reconstituted offline from the TDI colour images that provided regional myocardial velocity curves.

From the apical four-chamber, two-chamber, and long-axis views, a six-basal and six-mid segmental models were obtained in the LV, namely the septal, lateral, anteroseptal, posterior, anterior, and inferior segments at both basal and mid-levels. The time to the systolic peak velocity (Ts) was measured in every segment. For Ts, the beginning of the QRS complex was used as the reference point. Ts-SD was assumed as LV asynchrony index as proposed by Yu et al.9

For SDI, the image sector width was set as narrow as possible to allow a frame rate acquisition >140 frames/s. As with the TDI measurements, three beats were measured and averaged for each measurement. A region of interest (ROI), 6 × 6 mm² sized, was used with careful alignment of the cursor with the wall direction in any given region measured. A semi-automatic tracking algorithm was applied to maintain the sample volume in the ROI throughout the cardiac cycle. Myocardial strain is a measure of the regional deformation, and by definition, for the apical views, negative strain reflects shortening, whereas positive strain indicates elongation.21,22 The time of strain tracing exceeding aortic valve closure (ExcT) was measured in each segment as the interval between the marker of aortic closure and the nadir of the strain tracing as illustrated in Figure 1. ExcT was considered 0 when the nadir of strain curve did not exceed aortic valve closure. The overall time of strain exceeding aortic valve closure (oExcT) was computed as the sum of the 12 segmental ExcTs. Reproducibility of oExcT was assessed in 10 randomly chosen baseline echocardiograms by Bland–Altman method. Mean ± SD difference between two expert echocardiographers for oExcT was 95 ± 124 ms (r = 0.97) (95% CI 6.1–183.8 ms).

Statistical analysis

Continuous variables are expressed as mean ± SD. Baseline categorical data were compared by means of the x² test. For the comparison of continuous variables before and after CRT, paired sample t-test was performed. The comparison of clinical and echocardiographic parameters between responder and non-responder groups was performed by unpaired t-test. Linear regression analysis was performed to assess the relationship between the two chosen parameters of LV asynchrony (i.e. Ts-SD and oExcT) at baseline and changes in ESV. Receiver operating curve (ROC) analysis was performed to determine sensitivity and specificity of Ts-SD and oExcT in predicting CRT response. The value corresponding with the highest accuracy (i.e. minimal false negative and false positive result) was chosen as the optimal cutoff. The reliability of the cutoff was validated using bootstrap resampling (n = 5000) (90% confidence intervals are presented). CMDT software (version 1.0 β, Berlin University) was used for bootstrapping analysis.

We derived from our previously published population study8 an area under curve (AUC) of 0.68 for Ts-SD and decided to enrol at least 50 patients (80% of power with a difference between AUC of 0.17, given a one-sided a value of 0.05 and responders of 50%). For all tests, a P-value <0.05 was considered significant.
Results

Of 69 initially assessed patients, seven had poor echocardiographic images (bad alignment in five cases and missed anterior wall in two cases) and strain analysis was not possible with a final feasibility of 89%. Three patients died before the 6-month follow-up visit. Fifty-nine patients constitute the final population. The baseline characteristics are shown in Table 1. Pacemaker implantation was successful in all patients and no procedure-related complications were observed.

After 6 months of CRT, among the 59 patients, there were 28 responders (47%) to LV reverse remodelling with reduction of >15% ESV and 31 non-responders (53%) in whom the reduction in ESV was ≤15%. No significant differences were observed in baseline clinical and demographic characteristics between the two groups (Table 2).

Among the baseline echocardiographic parameters, in responders when compared with non-responders, DTE and IVRT were significantly longer and MPI significantly higher, and LV dyssynchrony resulted more extensively as indicated by significantly larger Ts-SD and oExcT values (Table 2).

At the 6-month follow-up, in responders, ESV was reduced by 20% in all patients with a mean reduction of 36 ± 11% (20–61%). In non-responders, ESV was stable in 12 patients and further dilated in the remaining 19 patients with a mean increase of 16 ± 12% (2–41%). Both EDV and ESV were significantly decreased in responders when compared with baseline, whereas in non-responders, they were significantly further diluted. In responders, EF (P = 0.000), MPI (P = 0.000), and MR (P = 0.0005) improved and IVRT shortened (P = 0.015); in non-responders, all these parameters remained unchanged, with exception for MR, which significantly improved (P = 0.03). Intraventricular synchronism

### Table 1  Responder and non-responder patient baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Population (n = 59)</th>
<th>Responders (n = 28)</th>
<th>Non-responders (n = 31)</th>
<th>P-value (responders vs. non-responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70 ± 10.4</td>
<td>70.3 ± 11</td>
<td>69 ± 10</td>
<td>0.63</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (19)</td>
<td>7 (25)</td>
<td>4 (13)</td>
<td>0.39</td>
</tr>
<tr>
<td>Ischaemic, n (%)</td>
<td>30 (51)</td>
<td>13 (46)</td>
<td>17 (54)</td>
<td>0.72</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.2 ± 0.43</td>
<td>3.1 ± 0.37</td>
<td>3.2 ± 0.46</td>
<td>0.36</td>
</tr>
<tr>
<td>ACE-I/ARBs, n (%)</td>
<td>54 (92)</td>
<td>26 (92)</td>
<td>28 (90)</td>
<td>0.85</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>53 (90)</td>
<td>26 (92)</td>
<td>27 (87)</td>
<td>0.84</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>59 (100)</td>
<td>28 (100)</td>
<td>31 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>35 (59)</td>
<td>17 (61)</td>
<td>18 (58)</td>
<td>0.97</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>28 (47)</td>
<td>12 (43)</td>
<td>16 (51)</td>
<td>0.72</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>10 (17)</td>
<td>6 (21)</td>
<td>4 (13)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

### Table 2  Conventional and tissue Doppler echocardiographic parameters of responders and non-responders at baseline and at the 6-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± SD)</th>
<th>Follow-up (mean ± SD)</th>
<th>P vs. baseline</th>
<th>Non-responders (mean ± SD)</th>
<th>Follow-up (mean ± SD)</th>
<th>P vs. baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV (mL)</td>
<td>216 ± 79</td>
<td>166 ± 51*</td>
<td>0.000</td>
<td>209 ± 64</td>
<td>223 ± 68</td>
<td>0.016</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>161 ± 64</td>
<td>102 ± 37**</td>
<td>0.000</td>
<td>158 ± 53</td>
<td>168 ± 60</td>
<td>0.045</td>
</tr>
<tr>
<td>EF (%)</td>
<td>26 ± 6</td>
<td>40 ± 8**</td>
<td>0.000</td>
<td>24 ± 8</td>
<td>25 ± 8</td>
<td>0.873</td>
</tr>
<tr>
<td>MPI</td>
<td>1.02 ± 0.29***</td>
<td>0.65 ± 0.18*</td>
<td>0.000</td>
<td>0.88 ± 0.33</td>
<td>0.85 ± 0.32</td>
<td>0.393</td>
</tr>
<tr>
<td>E/A</td>
<td>1.18 ± 0.92</td>
<td>0.98 ± 0.63*</td>
<td>0.208</td>
<td>1.3 ± 0.86</td>
<td>1.65 ± 0.92</td>
<td>0.114</td>
</tr>
<tr>
<td>DTE (ms)</td>
<td>218 ± 108***</td>
<td>240 ± 87***</td>
<td>0.298</td>
<td>172 ± 55</td>
<td>179 ± 45</td>
<td>0.538</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>145 ± 41****</td>
<td>113.9 ± 34****</td>
<td>0.015</td>
<td>97.2 ± 37.5</td>
<td>94.5 ± 49</td>
<td>0.569</td>
</tr>
<tr>
<td>JA/LAA (%)</td>
<td>23 ± 12</td>
<td>12 ± 9**</td>
<td>0.000</td>
<td>30 ± 18</td>
<td>24 ± 17</td>
<td>0.030</td>
</tr>
<tr>
<td>IVD (ms)</td>
<td>44 ± 30</td>
<td>23 ± 27</td>
<td>0.007</td>
<td>42 ± 30</td>
<td>32 ± 36</td>
<td>0.253</td>
</tr>
<tr>
<td>Ts-SD (ms)</td>
<td>49.5 ± 17****</td>
<td>35.3 ± 14****</td>
<td>0.002</td>
<td>37 ± 10</td>
<td>42.9 ± 14</td>
<td>0.083</td>
</tr>
<tr>
<td>oExcT (ms)</td>
<td>1087 ± 307****</td>
<td>566 ± 355****</td>
<td>0.000</td>
<td>663 ± 446</td>
<td>757 ± 328</td>
<td>0.275</td>
</tr>
</tbody>
</table>

*P < 0.01, responders vs. non-responders at 6 months.

**P < 0.001, responders vs. non-responders at 6 months.

***P < 0.05, responders vs. non-responders at baseline.

****P < 0.001, responders vs. non-responders at baseline.

*****P < 0.05, responders vs. non-responders at 6 months.

******P < 0.01, responders vs. non-responders at baseline.
improved only in responder group, as indicated by a significant reduction in Ts-SD and oExcT ($P = 0.002$ and $P = 0.000$, respectively). No significant changes in IVD were observed in the both groups (Table 2).

In overall population, linear regression analysis showed a significant correlation between changes in ESV and baseline Ts-SD and oExcT ($r = -0.32\), $P = 0.01$ and $r = -0.48\), $P = 0.0001$, respectively) (Figure 2).

**Prediction of response**

ROC analysis showed that oExcT had 93.5% of sensitivity and 82.8% of specificity to predict CRT response with an optimal cutoff value of 760 ms (90% CI by bootstrapping 725–879.5) (area under curve 0.86; 95% CI 0.75–0.94, $P = 0.000$). Ts-SD with a cutoff of 32 ms as proposed had 82% of sensitivity and 39% of specificity (area under curve 0.69; 95% CI 0.56–0.8, $P = 0.004$). Area under the ROC curves was significantly larger for oExcT than for Ts-SD ($P = 0.03$) (Figure 3).

**Discussion**

In this study, for the first time, a parameter measuring the overall time wasted by the LV in contracting after aortic valve closure has been introduced for LV dyssynchrony evaluation. Our data show that this parameter can predict LV reverse remodelling in patients treated with CRT. Previously, several TDI parameters, generally using the variation or the difference in time to the peak of systolic sustained velocity, were proposed for asynchrony evaluation. Of them, the Ts-SD has been recently demonstrated to be the most powerful predictor of LV reverse remodelling. All these parameters have the common attribute of focusing exclusively on the mechanical asynchrony in the ejective phase. They do not take into account the contractile events occurring after aortic valve closure. Sogaard et al. for the first time highlighted the presence of delayed longitudinal contraction and demonstrated that the greater the number of segments displaying longitudinal contraction during diastole, the more severe is the degree of dys synchrony. This finding was shown to be predictive of CRT efficacy. In this study, the authors performed a dichotomic analysis of each segment on the basis of the presence or absence of delayed longitudinal contraction using tissue-tracking technique. Although this method immediately shows the region with delayed longitudinal contractions, it cannot evaluate the degree of the temporal delay. To better describe such phenomenon, we proposed a quantitative parameter. Using strain imaging, we measured the total amount of time spent by 12 LV segments in contracting after aortic valve closure. Thus, a quantitative measurement in time domain of the whole LV segmental deformation occurring outside ejective phase was obtained. This parameter reflects a severe asynchrony degree in which regional electromechanical delays are prolonged to an extent that some regional contractile events are shifted in diastolic phase. We considered two different patterns of contractile asynchrony: a ’systolic contractile asynchrony’ in which there is a temporal dispersion of the regional electromechanical delays although they remain confined inside ejective phase and a ’contractile diastolic asynchrony’ in which the contractile events exceed ejective phase. The latter cannot be disclosed analysing only the ejection phase. Figure 4 shows an example of patient with baseline low Ts-SD (left side) and prolonged oExcT (right side) in whom after 6 months of CRT, a 32% LV ESV reduction was observed. According to the Ts-SD criterion, this patient should not have benefited from CRT.

Strain is a measure of true myocardial deformation. Although it can reflect both active contraction and passive recoil, it is less influenced by overall heart motion and tethering effects than TDI. Strain imaging in patients

![Figure 2](http://eurheartjournals.org/download/figure2.png) ![Figure 3](http://eurheartjournals.org/download/figure3.png)

**Figure 2** Linear regression analysis between changes of oExcT and ESV ($P < 0.00001$) and between Ts-SD and ESV ($P < 0.005$).

**Figure 3** Comparison of ROC curve analysis between oExcT and Ts-SD showed better sensitivity and specificity for the first ($P < 0.05$ between curves).
Clinical studies. This phenomenon defined as postsystolic contraction in the rate of the LV falling pressure. responders is likely due to contrasting effects of the diastolic IVRT observed at baseline in responders compared with non-responders is likely due to contrasting effects of the diastolic IVRT observed at baseline in responders compared with non-responders. However, strain rate signal is more disturbed by noising artefacts than the strain that we used, and this could explain the discordant results. We found ExcT a better predictor of positive response to CRT than Ts-SD. The longer oExcT (right panel) in whom after 6 months of CRT a 32% ESV reduction was observed.

Conclusions
Currently, in the setting of CRT responders’ identification, attention is focused on LV dyssynchrony analysis, as assessed in the systolic phase. This study highlights the importance of LV dyssynchrony occurring in the diastolic phase. The presence of delayed longitudinal contraction had been previously demonstrated to be useful in predicting CRT benefits, but the semi-quantitative nature of the method employed may limit its efficacy. In our cohort of patients, we found that a quantitative measurement in the time domain of the whole LV segmental deformation occurring after aortic valve closure is able to predict LV functional recovery and reversal remodelling after CRT.

Conflict of interest: none declared.

References


