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## Recommended Citation

# Longitudinal Strain Delay Index by Speckle Tracking Imaging
## A New Marker of Response to Cardiac Resynchronization Therapy

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***Background***—In heart failure patients with left ventricular dyssynchrony, contractility in delayed segments does not fully contribute to end-systolic function. We quantified this reserve of contraction related to mechanical dyssynchrony to predict response to cardiac resynchronization therapy by the strain delay index, which was defined as the sum of the difference between peak and end-systolic strain across 16 segments.

***Methods and Results***—In 100 heart failure patients (ejection fraction=26±9%, QRS=154±29 ms, 94% in New York Heart Association class III), we studied left ventricular dyssynchrony before cardiac resynchronization therapy by the strain delay index using longitudinal strain by 2D speckle tracking and by the SD of time to peak myocardial velocity in 12 segments. The optimal cutoff value of the strain delay index to predict response to cardiac resynchronization therapy was determined in a retrospective group (n=65) and then confirmed in a validation group (n=35). Left ventricular end-systolic volume reduction at 3 months >15% (responder) occurred in 64 of 100 patients. In the retrospective group, the strain delay index but not the SD of time to peak myocardial velocity was greater in responders (n=42/65) than nonresponders (35±8% versus 19±7%, *P*<0.0001), and the optimal cutoff value to identify response to cardiac resynchronization therapy was 25%. In the validation group, strain delay index ≥25% identified 82% (18/22) of responders and 92% (12/13) of nonresponders. Among the entire population (n=100), strain delay index correlated with reverse remodeling in both the ischemic (*r*=−0.68, *P*<0.0001) and nonischemic (*r*=−0.68, *P*<0.0001) population.

***Conclusions***—Use of the strain delay index with longitudinal strain by speckle tracking has a strong predictive value for predicting response to cardiac resynchronization therapy in both ischemic and nonischemic patients. (***Circulation***. 2008; 118:1130-1137.)

**Key Words:** heart failure ■ pacemakers ■ echocardiography ■ prognosis ■ mechanics ■ remodeling

Several large clinical trials have established the long-term benefits (such as improvement of symptoms,[1–8] ejection fraction,[2,4,8] mitral regurgitation,[1,4] left ventricular [LV] remodeling,[1,2,4] and survival[8]) with cardiac resynchronization therapy (CRT) in symptomatic patients who have severe LV dysfunction and a wide QRS complex.[1–8] Despite these promising results, ≈30% of patients selected on the basis of QRS duration do not respond to CRT.[8] Observational studies have consistently shown that the main predictor of responsiveness to CRT is mechanical rather than electrical dyssynchrony.[9] Measurement of regional myocardial electrical-mechanical events with velocity data acquired with tissue Doppler imaging (TDI)[10,11] has been shown to enhance identification of mechanical dyssynchrony and can be used to select patients who may better respond to CRT; however,

limitations of this technique still exist, in particular the lack of specificity associated with delayed contraction in patients with ischemic cardiomyopathy.[12,13] Patients with significant mechanical dyssynchrony may be nonresponsive because myocardial segments may be scarred and therefore lack residual contractility. This phenomenon is particularly evident in ischemic patients who have myocardial segments with delayed contraction, which is often caused by scar.[14–16] Current identification of responders by time-delay indexes alone is inherently limited, because residual myocardial contraction is not taken into account. To overcome these limitations, we propose a new method, the strain delay index. The strain delay index can predict response to CRT by directly assessing the potential for incremental contractility gain after resynchronization rather than by simply quantify-
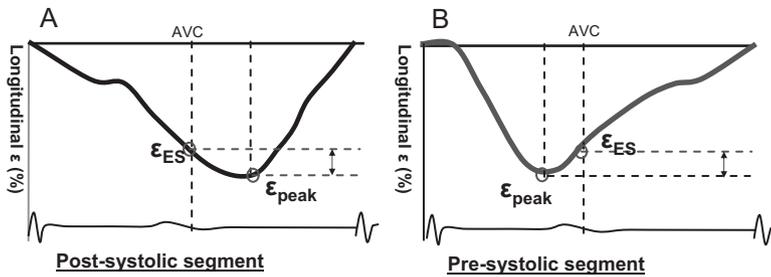
**Figure 1.** In dyssynchronized myocardium, $\varepsilon$-peak of delayed segment does not fully contribute to ES function. The wasted energy due to dyssynchrony is mathematically expressed as the difference ($\varepsilon_{peak} - \varepsilon_{ES}$) in postsystolic (A) and presystolic (B) segments. AVC indicates aortic valve closure.

ing LV dyssynchrony by regional timing. In the present study, the strain delay index was calculated by use of longitudinal strain ($\varepsilon$) assessed by 2D speckle tracking, which was then compared to the SD of time to peak velocity and time to peak longitudinal strain to predict future reverse remodeling after CRT.

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## Methods

### Population

The study included 100 patients with symptomatic heart failure (HF), an ejection fraction <35%, and QRS duration >120 ms who had conventional TDI and longitudinal $\varepsilon$ analysis by 2D speckle tracking before undergoing implantation of a biventricular device. The study was conducted in 2 consecutive groups of patients, with hypothesis testing to determine the optimal cutoff value for the strain delay index to predict response to CRT, which was first assessed in a retrospective cohort (derivation group, n=65) followed by validation in a prospective cohort (validation group, n=35).

### Derivation Group

The derivation group was selected from 589 consecutive HF patients who underwent implantation of a biventricular device at the Cleveland Clinic (Cleveland, Ohio) between January 2005 and December 2006. Patients were selected if they had a complete baseline echocardiographic study performed 3 months before device implantation on a Vivid 7 system (GE, Vingmed System 7, Horten, Norway) and if an echocardiographic follow up (>3 months) was available (120 of 589 patients). Complete baseline echocardiography included standard gray-scale and color TDI in the apical views (2-, 3-, and 4-chamber views) with high frame rates (>35 frames/s). Of these 120 selected patients 50 were excluded (5 with implantation <3 months after an acute coronary syndrome or cardiac surgery, 41 with >2 nonanalyzable segments by 2D speckle tracking or TDI, and 4 with permanent atrial fibrillation). After device implantation, another 5 patients were excluded (inadequate CRT delivery, ie, LV pacing rate was <50%; 3 with paroxysmal atrial fibrillation and 2 owing to an increased LV lead threshold). Ultimately, 65 patients were entered into the derivation group.

### Validation Group

This phase of the study was conducted prospectively in a cohort of HF patients recruited consecutively before biventricular device implantation at Cleveland Clinic from January 2007 to May 2007. Patients were included if they met all of the following criteria: symptomatic HF, age between 18 and 75 years, LV ejection fraction <35%, and sinus rhythm with QRS duration >120 ms. Exclusion criteria were recent cardiac event (<3 months after an acute coronary syndrome or cardiac surgery), inadequate CRT delivery after 3-month follow-up (LV pacing rate <50%), and >2 nonanalyzable segments by either speckle tracking or TDI. Patients in the study (n=40) underwent 2D echocardiographs before device implantation on a Vivid 7 system with a high frame rate and color TDI in the apical views. At 3 months, 2D echocardiography was repeated to quantify reverse remodeling after CRT. Five patients were excluded because of limited echocardiographic images and inadequate CRT delivery during the 3-month follow up. Overall, 35 patients were selected as the validation group. All patients had given informed consent, and the study protocol was approved by the Cleveland Clinic Institutional Review Board.

### Biventricular Pacemaker Implantation

CRT was provided in the standard fashion with 3 transvenous leads inserted. The right atrial and ventricular (apical site) leads were positioned conventionally. The LV lead was inserted through the coronary sinus and positioned into the lateral (n=38), posterolateral (n=43), anterolateral (n=8), or middle (n=4) cardiac vein. Epicardial implantation was required in 7 patients. Biventricular pacing devices used included those manufactured by Medtronic (Minneapolis, Minn; n=59), St Jude Medical (Sylmar, Calif; n=27), and Guidant–Johnson & Johnson (Boston, Mass; n=14). After implantation, the atrioventricular interval was adjusted for optimal diastolic filling by Doppler echocardiographic assessment of mitral inflow, and V-V timing was programmed to be simultaneous in all cases. All devices were interrogated systematically within 3 months after the CRT procedure to ascertain their proper functioning.

### Follow-Up

Baseline and 3-month clinical characteristics were extracted from medical reports. Responders were defined by the presence of significant reverse remodeling (LV end-systolic volume [ESV] reduction >15% by Simpson biplane method) at 3 months after CRT.

### Strain Delay Index

In dyssynchronous ventricles, delayed segments do not contribute fully to end-systolic (ES) function. The wasted energy per segment caused by dyssynchrony can be expressed mathematically as the difference between peak ($\varepsilon_{peak}$) and ES strain ($\varepsilon_{ES}$). Theoretically, this difference ($\varepsilon_{ES} - \varepsilon_{peak}$) increases with the severity of dyssynchrony (Figures 1 and 2A). The wasted energy is expected to be greater in the segment with preserved contractility than in the segment with no or minimal residual contractility at a similar degree of delayed contraction. This can be well appreciated in scar or fibrotic myocardium (Figure 2B). The strain delay index (Figure 3) represents the sum of the wasted energy due to LV dyssynchrony across all (n) myocardial segments:

$$\text{strain delay index} = \sum_{1}^{n}(\varepsilon_{peak} - \varepsilon_{ES})$$

The strain delay index can be computed from any quantitative regional wall-motion method, because it expresses a difference of contractility amplitude; however, its accuracy depends on the precision of the method for quantifying regional wall motion. Prior to this investigation, we compared longitudinal, transversal, circumferential, and radial $\varepsilon$ by 2D speckle tracking, TDI-derived myocardial velocity, and TDI-derived longitudinal $\varepsilon$ in 29 HF patients (Supplemental Table I). We observed that regional peak longitudinal $\varepsilon$ by speckle tracking provided an accurate measure of regional myocardial wall motion, with global peak strain closely correlated to LV ejection fraction ($r = -0.84$, $P<0.0001$; Supplemental Table II). The strain delay index was then computed from longitudinal $\varepsilon$ by 2D
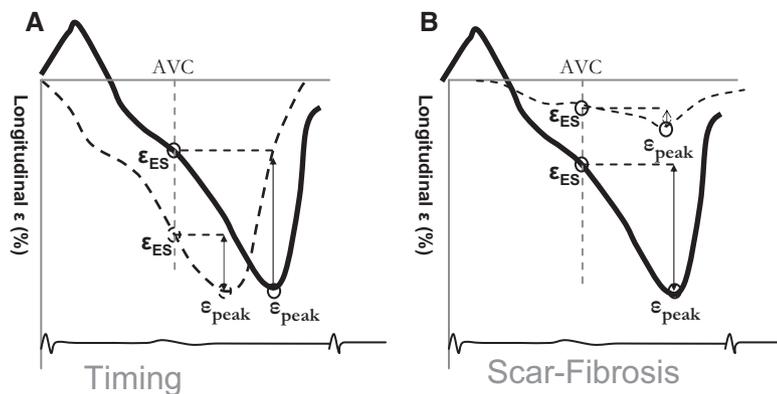
**Figure 2.** Effects of time to peak strain and status of myocardium on wasted contractile energy. Theoretically, the wasted energy due to dyssynchrony ($\varepsilon_{peak}-\varepsilon_{ES}$) in each segment increases with the severity of the delayed contraction (A). For segments with a similar degree of dyssynchrony (B), the difference ($\varepsilon_{peak}-\varepsilon_{ES}$) would be greater in a myocardial segment with preserved contractility than in those with no or minimal residual contractility, as in scar or fibrotic myocardial tissue. AVC indicates aortic valve closure.

speckle tracking (EchoPac version 7.0.0, GE Vingmed). The peak of the R wave on the ECG was used as the reference time point for end diastole. Strain curves derived from a single cardiac cycle were exported for an automatic analysis in Excel. The different steps of strain delay index processing can be summarized as follows: First, we computed a global $\varepsilon$ curve representing LV function by averaging 16 regional LV $\varepsilon$ curves. To average strain curves with different RR intervals and frame rates, we normalized the time as a percent of the RR interval, and strain value at every 2.5% of the RR interval was calculated with linear interpolation for missing values. Second, we used the time to the peak of this global $\varepsilon$ curve to determine the timing of ES and to compute the $\varepsilon_{ES}$ in the 16 segments. Third, we also defined peak and time to peak $\varepsilon$ in the 16 segments as the $\varepsilon$ curve reached its minimum value during the cardiac cycle. Finally, the difference ($\varepsilon_{peak}-\varepsilon_{ES}$) in each segment (all 16 segments) was summed to generate the strain delay index. For a segment that exhibited positive strain or biphasic strain with a peak positive $\varepsilon$ greater than the maximal absolute negative strain, the term



**Figure 3.** A, Strain delay index is defined as the sum of the wasted energy, ie, ($\varepsilon_{ES}-\varepsilon_{peak}$) caused by LV dyssynchrony across the 16 myocardial segments (colored curves) of the LV. B, After CRT, the increase ($\Delta$) of global strain curve (white dashed curve) is supposed to be proportional to strain delay index.

**Table.    Comparison Between Responders and Nonresponders**

| | Retrospective Group (n=65) | | Prospective Group (n=35) | |
|---|---|---|---|---|
| | Responders, n=42 (64%) | Nonresponders, n=23 (36%) | Responders, n=22 (63%) | Nonresponders, n=13 (37%) |
| Age, y | 65±10 | 63±13 | 62±13 | 62±12 |
| Male sex, n (%) | 33 (79) | 18 (78) | 12 (54) | 7 (54) |
| Baseline NYHA class III, n (%) | 39 (93) | 23 (100) | 21 (95) | 11 (85) |
| QRS duration, ms | 157±28 | 144±26 | 156±26 | 159±37 |
| Baseline ejection fraction, % | 26±10 | 23±6 | 27±10 | 27±9 |
| End-diastolic volume, mL | 225±85 | 260±87 | 205±72 | 243±122 |
| ESV, mL | 169±75 | 200±72 | 152±63 | 187±120 |
| Ischemic, n (%) | 14 (33) | 11 (48) | 5 (23) | 5 (38) |
| Baseline medications, n (%) | | | | |
| β-Blockers | 36 (86) | 20 (87) | 18 (82) | 11 (85) |
| ACEI/ARB | 35 (83) | 22 (95) | 21 (95) | 12 (92) |
| Spironolactone | 17 (40) | 14 (61) | 10 (45) | 6 (46) |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

($\varepsilon_{peak}-\varepsilon_{ES}$) was entered as zero for the calculation of strain delay index. This methodology is based on the assumption that dyskinetic segments with predominant stretch are unlikely to be improved immediately by CRT. Time to peak longitudinal $\varepsilon$ by speckle tracking was used to calculate the 12-segment (base and mid) SD of time to peak-$\varepsilon$ (SD$-\varepsilon$). In segments with positive or biphasic strain curve, time to absolute maximal $\varepsilon$ was chosen to compute SD-$\varepsilon$.

## TDI Analysis

We also defined LV dyssynchrony using the SD in 12 segments of time to peak velocity by TDI (SD-TDI) and the septal-lateral delay of time to peak velocity ($T_{SL}$). These indexes were computed automatically with modified software developed in our laboratory. Automatic and manual measurements were compared in 20 random patients and results reported with Bland-Altman analysis (Data Supplement, Figure I). The process can be summarized as follows: (1) Basal and midventricular velocity curves (n=12) derived from color TDI sequences (EchoPac version 7.0.0) were exported for analysis in Excel. (2) Time to peak velocity was defined when peak velocity reached its maximum positive value during the systolic ejection period. (3) The reference timing point was defined at end diastole (at the peak of the R wave on the ECG tracing), and the systolic period was defined by aortic valve opening and closure with LV outflow tract pulse-wave Doppler flow. (4) Segments with only negative velocity during the systolic ejection period were excluded from the calculation of SD-TDI and $T_{SL}$. Significant LV dyssynchrony was considered when SD-TDI was >33 ms[10] and $T_{SL}$ was ≥65 ms.[11]

## Statistical Analysis

Continuous variables with normal distribution are expressed as mean±SD. Dichotomous data are expressed as percentages. To compare numerical data between 2 groups, paired and unpaired Student tests were used when appropriate. Dichotomized comparisons were assessed by $\chi^2$ test or the Fisher exact test. Receiver operating characteristic curves were determined to evaluate the diagnostic performance of LV dyssynchrony indexes to detect responders to CRT. An optimal cutoff value for the diagnosis of responders was chosen to maximize the Youden index (sensitivity+specificity−1). The optimal cutoff value of strain delay index was assessed in the derivation group, and then the accuracy was confirmed in the validation group. Linear correlation was used to compare LV ESV reduction and strain delay index. Reproducibility was performed in 10 randomly selected patients. Interobserver and intraobserver variability were expressed as the SD of the difference between 2 paired measurements and as a percentage of variability (SD was divided by the

average value of the variable). Two-tailed probability values <0.05 were considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

## Results

The entire study population averaged 63±12 years of age; 94% were in New York Heart Association class III, with ejection fraction of 26±9% (35% with ischemic origin of HF) and QRS duration of 154±29 ms. Baseline characteristics of the derivation and validation populations are summarized in Supplemental Table III. After 3 months of CRT, 53 of 100 patients were clinically improved by CRT, 35 (54%) of 65 in the derivation group and 18 (51%) of 35 in the validation group. Eleven patients experienced worsening symptoms, 7 (11%) in the derivation group (4 died and 2 underwent heart transplantation) and 4 (11%) in the validation group (1 died). The overall population had a mean LV ESV reduction of 17.6±24% (range −54% to 66%); 64 patients had ESV reduction >15%, 14 had reductions between 0% and 15%, and 22 had increased ESV. Baseline clinical and echocardiographic parameters were similar between responders and nonresponders in the 2 populations (Table 1).

## Derivation Group

### *TDI and Strain for Reverse Remodeling*

In the initial 65 patients, ESV reduction at 3 months was 16±24% (range −54% to 59%). In 42 (65%) of 65 patients, ESV reduction was >15%; in 6 (9%), it was between 0% and 15%; and in 17 (26%), the ESV increased. Neither SD-TDI (52±17 ms, range 19 to 93 ms) nor the opposing-wall $T_{SL}$ (100±51 ms, range 0 to 250 ms) correlated with QRS duration or reverse remodeling (r=0.2, P=0.1 for SD-TDI; r=0.2 P=0.1 for $T_{SL}$). Significant dyssynchrony by TDI (SD-TDI >33ms) was observed in 59 (91%) of 65 patients and did not differ between responders and nonresponders (37/42 versus 22/23, P=0.3; mean 51±16 versus 56±14 ms, P=0.2). Similarly, $T_{SL}$ ≥65 ms was observed in 51 (78%) of 65 patients and did not
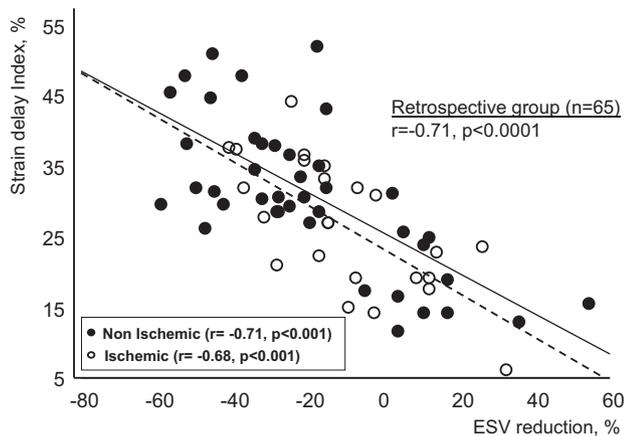
**Figure 4.** Correlation between strain delay index and ESV reduction after CRT in ischemic and nonischemic patients in the derivation group (n=65).

provide significant predictive value for CRT response. In contrast, SD-ε did correlate with baseline QRS duration ($r=0.42$, $P<0.001$) and ESV reduction ($r=-0.38$, $P=0.002$). Finally, the correlation between reverse remodeling and SD-ε was significant in nonischemic patients ($r=-0.4$, $P=0.01$) but not in ischemic patients ($r=-0.35$, $P=0.08$).

### Strain Delay Index for Reverse Remodeling

The strain delay index ($29\pm10\%$, range 6% to 52%) was found to be higher in responders than nonresponders ($35\pm7\%$ versus $19\pm6\%$, $P<0.0001$). Furthermore, the strain delay index increased with QRS duration ($r=0.32$, $P=0.01$) and was closely correlated with reverse remodeling ($r=-0.71$ for all, $P<0.0001$; Figure 4) in both the ischemic ($r=-0.68$, $P<0.001$) and nonischemic ($r=-0.71$, $P<0.0001$) patients. All patients with a strain delay index ≥75th percentile (≥35%) exhibited a significant LV ESV reduction ($33\pm13\%$, range 15% to 57%), whereas all patients with a strain delay index below the 25th percentile (<20%) showed ESV reduction ≤10% (mean $-12\pm18\%$, range $-54\%$ to 10%). The optimal cutoff value to predict response to CRT determined from the receiver operating characteristic curve of the derivation group was a strain delay index ≥25% (Figure 5). The sensitivity, specificity, negative predictive value, and positive predictive value were 95% (95% CI 87% to 99%), 83% (95% CI 72% to 91%), 90% (95% CI 81% to 96%), and 90% (95% CI 81% to 96%), respectively.

### Validation Group

#### Validation of Strain Delay Index

The mean ESV reduction at 3 months was $20\pm25\%$ (range $-40\%$ to 70%). ESV reduction was >15% in 22 (63%) of 35 patients and between 0% and 15% in 8 (23%), and ESV increased in 5 (14%). Strain delay index ($28\pm9\%$, range 10 to 47%) was significantly greater in responders than nonresponders ($32\pm8\%$ versus $20\pm5\%$, $P<0.0001$). A strain delay index cutoff ≥25% was observed in 18 of 22 patients (82%; 95% CI 66% to 93%) among responders and was <25% in 12 (92%; 95% CI 77% to 98%) of 13 nonresponders. The positive predictive value was 75% (95% CI 57% to 87%) with a cutoff ≥25% and increased to 83% (95% CI 66% to
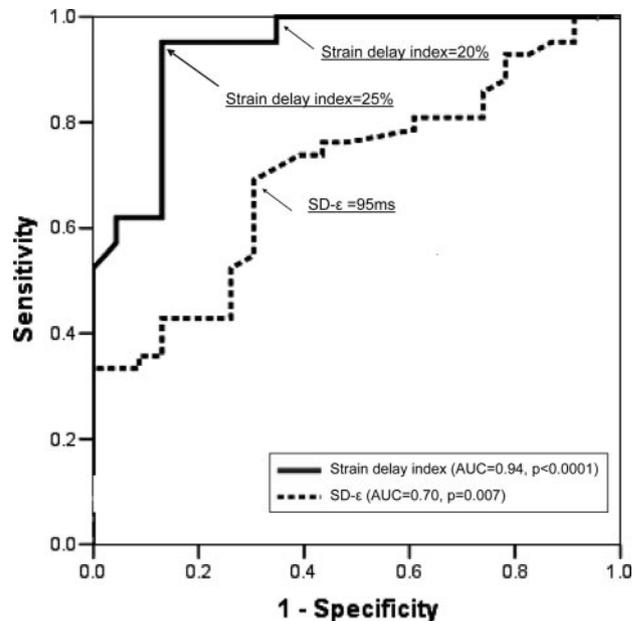


**Figure 5.** Receiver operating characteristic curves for diagnosis of response to CRT from the derivation group (n=65). *P* value for area under the curve (AUC) vs the null hypothesis of a true area=0.5.

93%) with a strain delay index >20%. Conversely, the negative predictive value was 95% (95% CI 81% to 99%) with a cutoff ≥25% and decreased to 73% (95% CI 54% to 85%) with a strain delay index >20%. Similar to the derivation group, the strain delay index correlated to reverse remodeling after CRT ($r=-0.68$, $P<0.0001$ for all) in the ischemic ($r=-0.68$, $P=0.04$) and nonischemic ($r=-0.68$, $P<0.001$) population. The correlation between strain delay index and ESV reduction for the entire population (n=100) is displayed in Figure 6. In the validation group, SD-ε tended to correlate with reverse remodeling ($r=-0.37$, $P=0.05$), whereas no significant association was observed for either SD-TDI ($r=0.15$, $P=0.5$; Supplemental Figure II) or the opposing-wall $T_{SL}$ ($r=0.1$, $P=0.6$).
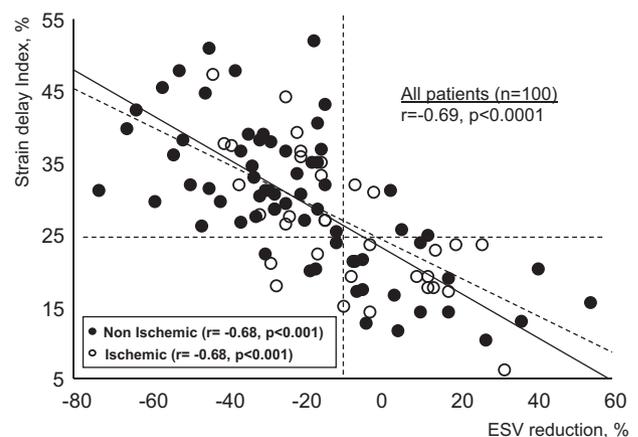


**Figure 6.** Correlation between strain delay index and ESV reduction after CRT in ischemic and nonischemic patients among the entire population of patients (n=100).

## Reproducibility

Intraobserver and interobserver variability were, respectively, 20 mL (10%) and 25 mL (13%) for LV volume, 7 ms (13%) and 9 ms (17%) for SD-TDI, 15 ms (17%) and 18 ms (21%) for $T_{SL}$, 19 ms (17%) and 27 ms (24%) for SD-ε, and 4% (13%) and 6% (20%) for strain delay index.

## Discussion

Reverse remodeling of the LV after CRT provides an objective measurement for CRT response, which is correlated to improved survival and LV function. In the present study, we defined CRT response as ESV reduction >15%. This reduction was only observed in 64% of patients despite the presence of a significant prolonged QRS duration. LV mechanical dyssynchrony indexes derived from time-delay measurements with TDI failed to improve patient selection. In contrast, the strain delay index, which quantifies the amount of wasted energy due to LV dyssynchrony, was found to correlate closely with reverse remodeling after CRT in both ischemic and nonischemic patient populations ($r=-0.69$, $P<0.0001$; Figure 6).

CRT has been shown to improve both the symptoms[1–8] and the prognosis[8] of HF patients with depressed LV function and a wide QRS complex; however, most CRT studies have demonstrated that one third of patients are nonresponders, presumably because mechanical dyssynchrony was absent despite a wide QRS duration.[8] Several methods based on the time-delay measurement of regional wall motion have been proposed to quantify LV dyssynchrony.[9] Values for most of these methods are obtainable with echocardiographic techniques and are usually derived from longitudinal myocardial velocity data by TDI.[9] Several single-center studies have demonstrated that a 12-segment SD-TDI >33 ms and an opposing-wall delay $T_{SL} \geq 65$ ms correlated to the clinical response to CRT.[17] However, in a prospective, multicenter setting in the Predictors of Response to CRT (PROSPECT) study,[18] which sought to test the performance of these mechanical dyssynchrony markers, neither the SD-TDI nor the opposing-wall delay was predictive of response to CRT. In addition, the TDI parameters were highly variable, with an interobserver variability >30%. In the present study, these markers were also computed automatically with dedicated software to improve reproducibility. Despite an objective determination of time to peak velocity and a careful review of velocity curves, neither an SD-TDI >33 ms nor an opposing-wall $T_{SL} \geq 65$ ms correlated with response to CRT. The limitations of time delay by TDI to assess LV dyssynchrony to predict response to CRT in HF patients have also been reported by others (Soliman et al[19] and the REsynchronization THerapy In Normal QRS [RETHINQ] trials[20]). The suboptimal accuracy of TDI to predict response to CRT may be explained by a drawback of the Doppler technique in HF patients in which the signal-to-noise ratio of TDI is particularly affected by myocardial dysfunction (minimal base to apex motion), translational and tethering effects,[21] and malalignment of the Doppler sample volume, which increases as LV geometry changes to a globular shape. These issues may explain the difficulty in identifying peak contraction in the flat velocity contour of the failing heart.[22] This is particularly salient in the present study, because the patients had significantly larger LV volumes than those in the validation study by Yu et al[12] ($231\pm90$ versus $193\pm81$ mL, $P<0.05$).

Time delay from speckle tracking correlated with reverse remodeling after CRT better than TDI and QRS duration. The apparent superiority of the speckle tracking technique to quantify intraventricular mechanical dyssynchrony is believed to be related to a lesser ultrasonic angle dependency of the speckle tracking technique, as well as a better signal-to-noise ratio of the strain signal than with TDI. Furthermore, the predictive value of mechanical dyssynchrony for responsiveness to CRT also depends on the ability to detect viable versus scarred myocardium, because this varies significantly between ischemic and nonischemic or dilated cardiomyopathies. Delayed contraction by TDI is a nonspecific marker for myocardial dysfunction[23,24] that can be seen in scar,[14–16] fibrosis,[25,26] and viable myocardium and may be further impacted by loading conditions.[14] Recently, several investigators have suggested interrogating myocardial viability[27–29] and contractile reserve[30,31] as a complement to LV dyssynchrony to better identify responders; however, this multimodality approach can be costly and time-consuming, is possibly oversimplified, and may not be practical in some centers.

In the present study, we proposed a new method to overcome many of these limitations by applying a strain amplitude technique from the baseline 2D echocardiographic data rather than applying a time-delay–based measurement alone. This concept to predict response to CRT is based on the assessment of a component of wasted contractility related to dyssynchrony that can be inferred as the acute gain of contractility expected after resynchronization. The acute increase in myocardial performance plays an important role in the long-term effects of CRT, because it will help to reduce LV wall stress and mitral regurgitation and trigger the reverse-remodeling process. The degree of impaired contractility expressed by the strain delay index was not only derived from delayed segments but also included presystolic segments. Time to peak strain in presystolic segments is also expected to change under CRT with the improved synchronicity of the LV[32] to enable segments with early contraction to more fully contribute to myocardial function.

Importantly, the strain delay index had similar accuracy in patients with ischemic and nonischemic cardiomyopathies. This may be explained by the robustness of the index, which considers all 16 myocardial segments of the ventricle, and the fact that the strain delay index is not a simple measurement of contractility or time delay but a combination (and relative weighting) of both of these parameters. Indeed, the delayed myocardial segments incrementally impact the strain delay index value not only in proportion to the severity of dyssynchrony but also relative to the amplitude of their residual contractility (Figure 2). Figure 7 demonstrates that the difference ($\varepsilon_{peak}-\varepsilon_{ES}$) is low ($\leq1\%$) in a segment with limited dyssynchrony (<5% delay from ES), as well as in a dyssynchronized segment with severely impaired contractility ($\varepsilon_{peak}$ less than $-5\%$). This supports the concept that a scarred segment with minimal contractility, which is less likely to improve with CRT, will barely increase the strain delay index primarily because of the small difference between $\varepsilon_{peak}$ and $\varepsilon_{ES}$ despite the presence of significantly delayed contraction.
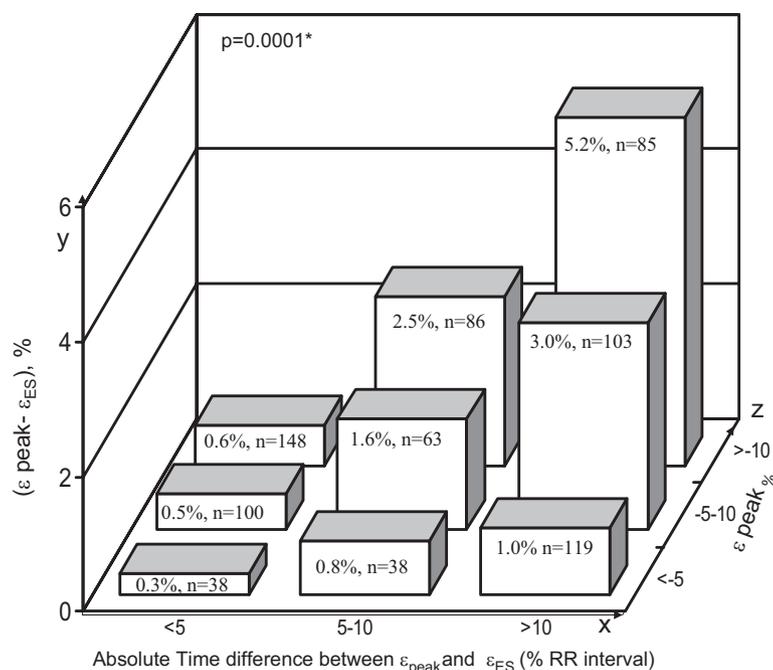
**Figure 7.** Data from the 780 mid and basal segments of the derivation group demonstrating that the wasted energy ($\varepsilon_{peak} - \varepsilon_{ES}$) is related to the severity of dyssynchrony (x-axis) and to the residual contractility (z-axis).

## Study Limitations

The results of the present study are limited to patients with wide QRS duration and should not be extended to patients with QRS <120 ms until a specific validation study can be conducted in this population. In addition, the quality of echocardiographic images is important for all strain-based analysis; therefore, our index may not reach its full capability if the image quality is suboptimal. However, the strain delay index can be applied to other imaging modalities. Next, LV ESV is critical for defining responders to CRT. Other accurate measures, such as 3D echocardiography, should be used in the future to reduce observer-related variability. In the present study, the SD-TDI was computed automatically with modified software rather than manually as reported by Yu et al.[10,17] We reported that SD-TDI computed automatically was not accurate for identification of responders to CRT, and according to recently published studies,[18–21] this appears to be related to TDI limitations. However, we cannot exclude the possibility that the automated approach may be less accurate than the manual approach, which may be effective in predicting response to CRT if performed in a laboratory with special expert knowledge, skill, and experience.

## Conclusions

The strain delay index from a longitudinal strain amplitude measurement by 2D speckle tracking appears to be an accurate predictor of CRT response both in ischemic and nonischemic patients alike.

## Sources of Funding

## Disclosures

## References

1. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873–880.
2. Lozano I, Bocchiardo M, Achtelik M, Gaita F, Trappe HJ, Daoud E, Hummel J, Duby C, Yong P. Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. *Pacing Clin Electrophysiol*. 2000;23:1711–1712.
3. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schondube F, Wolfhard U, Bocker D, Krahnefeld O, Kirkels H. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:2026–2033.
4. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
5. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kirkels JH, Kramer A, Huvelle E. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol*. 2003;42:2109–2116.
6. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA*. 2003; 289:2685–2694.
7. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150.
8. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
9. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, Garrigue S, Gorcsan J III, Hayes DL, Kass DA, Knuuti J, Leclercq C, Linde C, Mark DB, Monaghan MJ, Nihoyannopoulos P, Schalij MJ, Stellbrink C, Yu

CM. Cardiac resynchronization therapy: part 1: issues before device implantation. *J Am Coll Cardiol*. 2005;46:2153–2167.

10. Yu CM, Zhang Q, Fung JW, Chan HC, Chan YS, Yip GW, Kong SL, Lin H, Zhang Y, Sanderson JE. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. *J Am Coll Cardiol*. 2005;45:677–684.

11. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2004;44:1834–1840.

12. Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, Kum LC, Kong SL, Zhang Y, Sanderson JE. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation*. 2004;110:66–73.

13. Kanhai SM, Viergever EP, Bax JJ. Cardiogenic shock shortly after initial success of cardiac resynchronization therapy. *Eur J Heart Fail*. 2004;6: 477–481.

14. Skulstad H, Edvardsen T, Urheim S, Rabben SI, Stugaard M, Lyseggen E, Ihlen H, Smiseth OA. Postsystolic shortening in ischemic myocardium: active contraction or passive recoil? *Circulation*. 2002;106:718–724.

15. Ryf S, Rutz AK, Boesiger P, Schwitter J. Is post-systolic shortening a reliable indicator of myocardial viability? An MR tagging and late-enhancement study. *J Cardiovasc Magn Reson*. 2006;8:445–451.

16. Lim P, Pasquet A, Gerber B, D'Hondt A-M, Vancraenest D, Gueret P, Vanoverschelde JL. Is postsystolic shortening a marker of viability in chronic left ventricular ischemic dysfunction? Comparison with late enhancement magnetic resonance imaging. *J Am Soc Echocardiogr*. 2008;21:452–457.

17. Yu C, Gorcsan J III, Bleeker GB, Zhang Q, Schalij MJ, Suffoletto MS, Fung JW, Schwartzman D, Chan YS, Tanabe M, Bax JJ. Usefulness of tissue Doppler velocity and strain dyssynchrony for predicting left ventricular reverse remodeling response after cardiac resynchronization therapy. *Am J Cardiol*. 2007;100:1263–1270.

18. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J III, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*. 2008;117:2608–2616.

19. Soliman OI, Theuns DA, Geleijnse ML, Anwar AM, Nemes A, Caliskan K, Vletter WB, Jordaens LJ, Cate FJ. Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy. *Europace*. 2007;9:113–118.

20. Beshai J, Grimm R, Nagueh S, Baker JN, Beau S, Greenberg S, Pires L, Tchou PJ; RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med*. 2007;357:2461–2471.

21. Miyazaki C, Powell BD, Bruce CJ, Espinosa RE, Redfield MM, Miller FA, Hayes DL, Cha YM, Oh JK. Comparison of echocardiographic dyssynchrony assessment by tissue velocity and strain imaging in subjects with or without systolic dysfunction and with or without left bundle-branch block. *Circulation*. 2008;117:2617–2625.

22. Marwick TH. Hype and hope in the use of echocardiography for selection for cardiac resynchronization therapy: the Tower of Babel revisited. *Circulation*. 2008;117:2573–2576.

23. Ehring T, Heusch G. Left ventricular asynchrony: an indicator of regional myocardial dysfunction. *Am Heart J*. 1990;120:1047–1057.

24. Jamal F, Szilard M, Kukulski T, Liu XS, D'Hooge J, Bijnens B, Rademakers F, Hatle L, Descheerder I, Sutherland GR. Changes in systolic and postsystolic wall thickening during acute coronary occlusion and reperfusion in closed-chest pigs: implications for the assessment of regional myocardial function. *J Am Soc Echocardiogr*. 2001;14:691–697.

25. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, de Jonge N, Lahpor JR. Fractionated electrograms in dilated cardiomyopathy: origin and relation to abnormal conduction. *J Am Coll Cardiol*. 1996;27:1071–1078.

26. Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, Hauer RN, Kirkels H, Janse MJ, de Bakker JM. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. *Circulation*. 2001;104:3069–3075.

27. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation*. 2006;113:969–976.

28. Hummel JP, Lindner JR, Belcik JT, Ferguson JD, Mangrum JM, Bergin JD, Haines DE, Lake DE, DiMarco JP, Mounsey JP. Extent of myocardial viability predicts response to biventricular pacing in ischemic cardiomyopathy. *Heart Rhythm*. 2005;2:1211–1217.

29. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J*. 2007;28:33–41.

30. Da Costa A, Thevenin J, Roche F, Faure E, Romeyer-Bouchard C, Messier M, Convert G, Barthelemy JC, Isaaz K. Prospective validation of stress echocardiography as an identifier of cardiac resynchronization therapy responders. *Heart Rhythm*. 2006;3:406–413.

31. Lim P, Bars C, Mitchell-Heggs L, Roiron C, Elbaz N, Hamdaoui B, Lellouche N, Dubois-Rande JL, Gueret P. Importance of contractile reserve for CRT. *Europace*. 2007;9:739–743.

32. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation*. 2002;105:438–445.

## CLINICAL PERSPECTIVE

Recent results from the PROSPECT and RETHINQ trials might suggest that a relatively limited and simple quantification of left ventricular dyssynchrony has suboptimal accuracy for the identification of responders to cardiac resynchronization therapy. In the present study, we introduce a new method, the strain delay index, to quantify response to cardiac resynchronization therapy. Rather than simply measuring left ventricular dyssynchrony, we propose to quantify the potential gain of contractility expected after the best possible cardiac resynchronization. The potential gain, in turn, should predict reverse remodeling after resynchronization therapy. The strain delay index combines the importance of left ventricular dyssynchrony and residual contractility and provides a better understanding of the physiological response to cardiac resynchronization therapy. This index should improve the ability to identify potential responders to cardiac resynchronization therapy in the future. The sophistication of the strain delay index relative to Doppler-derived parameters might be of particular importance in the narrow-QRS population, in whom the degree of dyssynchrony may be less and thus more challenging to quantify. Future efforts should focus on validation of the method in current clinical practice along with implementation of software modifications to facilitate ease of use. Additionally, because the strain delay index is computed from regional strain curves, its accuracy is dependent on the precision of the method used to quantify myocardial contractility. Importantly, therefore, the strain delay index can be computed from imaging modalities other than ultrasound (ie, cardiac magnetic resonance and CT) and should be tested in patients with poor acoustic windows.

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Pascal Lim, Adisai Buakhamsri, Zoran B. Popovic, Neil L. Greenberg, Dimpi Patel, James D. Thomas and Richard A. Grimm

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