Assessment of Left Ventricular Dyssynchrony by Speckle Tracking Strain Imaging

Comparison Between Longitudinal, Circumferential, and Radial Strain in Cardiac Resynchronization Therapy

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Objectives
The objective of this study was to assess the usefulness of each type of strain for left ventricular (LV) dyssynchrony assessment and its predictive value for a positive response after cardiac resynchronization therapy (CRT). Furthermore, changes in extent of LV dyssynchrony for each type of strain were evaluated during follow-up.

Background
Different echocardiographic techniques have been proposed for assessment of LV dyssynchrony. The novel 2-dimensional (2D) speckle tracking strain analysis technique can provide information on radial strain (RS), circumferential strain (CS), and longitudinal strain (LS).

Methods
In 161 patients, 2D echocardiography was performed at baseline and after 6 months of CRT. Extent of LV dyssynchrony was calculated for each type of strain. Response to CRT was defined as a decrease in LV end-systolic volume of 15% at follow-up.

Results
At follow-up, 88 patients (55%) were classified as responders. Differences in baseline LV dyssynchrony between responders and nonresponders were noted only for RS (251 ± 138 ms vs. 94 ± 65 ms; p < 0.001), whereas no differences were noted for CS and LS. A cut-off value of radial dyssynchrony of 130 ms was able to predict response to CRT with a sensitivity of 83% and a specificity of 80%. In addition, a significant decrease in extent of LV dyssynchrony measured with RS (from 251 ± 138 ms to 98 ± 92 ms; p < 0.001) was demonstrated only in responders.

Conclusions
Speckle tracking radial strain analysis constitutes the best method to identify potential responders to CRT. Reduction in LV dyssynchrony after CRT was only noted in responders. (J Am Coll Cardiol 2008;51:1944–52)

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By stimulating the right ventricle and the posterolateral wall of the left ventricle (LV), cardiac resynchronization therapy (CRT) has been shown to decrease LV volumes, increase LV systolic function and improve clinical status in patients with end-stage heart failure (1). However, in earlier studies, the percentage of nonresponders is more than 30% when response to CRT is defined by echocardiographic criteria (e.g., LV reverse remodeling) (2). The lack of mechanical LV dyssynchrony has been suggested as one of the reasons for nonresponse to CRT (3).

In recent years various imaging techniques have been tested for their ability to quantify LV dyssynchrony and for their predictive value for response to CRT, including magnetic resonance imaging, nuclear imaging, and echocardiography (3–7). Most experience has been obtained with echocardiography using color-coded tissue Doppler imaging (TDI) by measuring peak-systolic velocities in different segments of the LV. Several studies in CRT patients proved that TDI was highly predictive for response to CRT and event-free survival at 1-year follow-up (3,5,8,9).

Speckle tracking strain analysis is a novel method based on grayscale 2-dimensional (2D) images, which permits the assessment of myocardial deformation in 2 dimensions. Using apical and parasternal short-axis views, 3 different patterns of myocardial deformation can be assessed: radial strain (RS)
represents the myocardial thickening in a short-axis plane; circumferential strain (CS) represents myocardial shortening in a short-axis plane; and longitudinal strain (LS) represents the myocardial shortening in the long-axis plane (10). To date, few studies used either RS, CS, or LS to assess LV dyssynchrony, and it is unclear which type of strain used for LV dyssynchrony assessment best predicts response to CRT (11–14). Furthermore, data on changes in LV dyssynchrony after CRT according to the different strain types are scarce.

Therefore, using 2D speckle tracking echocardiography, the aims of the present study were: 1) to determine which type of strain for assessment of LV dyssynchrony best predicts echocardiographic response after 6 months of CRT; and 2) to evaluate changes in LV dyssynchrony, as derived from RS, CS, and LS, after 6 months of CRT. In addition, the predictive value of the strain parameters was compared with the established value of TDI (3).

**Methods**

**Population and study protocol.** One hundred sixty-one consecutive patients who were scheduled for CRT were included in the present study. The selection criteria used for CRT were drug-refractory symptomatic heart failure with patients in New York Heart Association (NYHA) functional class III or IV and depressed LV ejection fraction (%35%) with wide QRS complex (%120 ms) (15). The study protocol included evaluation of clinical status and transthoracic echocardiography before CRT implantation, with follow-up evaluation after 6 months of CRT.

**Device implantation.** The coronary sinus was cannulated with the use of a guiding balloon catheter, and a venogram was obtained. Thereafter, the LV pacing lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic, Minneapolis, Minnesota) was inserted into the coronary sinus, and positioned in a lateral or posterolateral vein. The right atrial and ventricular leads were traditionally positioned, and all leads were connected to a dual-chamber biventricular implantable cardioverter-defibrillator (Contak CD or TR, Guidant Corporation; or Insync III or CD, Medtronic).

**Clinical follow-up.** Clinical status was evaluated at baseline and after 6 months of follow-up. Assessed parameters included NYHA functional class, quality-of-life score according to the Minnesota Living with Heart Failure questionnaire (16), and 6-min walking distance (17).

**Echocardiography.** Baseline and follow-up echocardiographic studies were performed with the patient in the left lateral decubitus position using commercially available equipment (Vingmed Vivid-7, General Electric Vingmed, Milwaukee, Wisconsin). Data acquisition was performed with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard 2- and 4-chamber images). Standard M-mode and 2D images were obtained during breath hold and stored in cineloop format from 3 consecutive beats. The LV end-diastolic diameter was obtained from the M-mode images of the parasternal long-axis view. The LV end-diastolic and end-systolic volumes were measured from the apical 2- and 4-chamber views, and the LV ejection fraction was calculated using the Simpson rule (18). The LV volumes were also indexed to the body surface area.

The LV diastolic function was evaluated by the mitral inflow pattern obtained by pulsed-wave Doppler echocardiography and classified as normal filling, abnormal relaxation, pseudonormal filling, or restrictive filling pattern (19).

In addition, conventional color-coded TDI was performed to determine LV dyssynchrony (EchoPac 6.1, GE Medical Systems, Horten, Norway) (3). The sector width and the depth were adjusted to obtain the highest frame rate (100 to 120 frames/s) and pulse repetition frequencies between 500 Hz to 1 KHz were used, resulting in aliasing velocities between 16 and 32 cm/s. The extent of LV dyssynchrony was calculated as the maximum time delay between peak-systolic velocities of basal septal, lateral, anterior, and inferior LV segments (3).

**Speckle tracking strain analysis.** For speckle tracking analysis, standard grayscale 2D images were acquired in the 2- and 4-chamber apical views as well as the parasternal short-axis views at the level of the papillary muscles. Special care was taken to avoid oblique views from the mid-level short-axis images and to obtain images with the most circular geometry possible. All of the images were recorded with a frame rate of at least 30 fps to allow for reliable operation of the software (EchoPac 6.1) (14).

From an end-systolic single frame, a region of interest was traced on the endocardial cavity interface by a point-and-click approach. Then an automated tracking algorithm followed the endocardium from this single frame throughout the cardiac cycle. Further adjustment of the region of interest was performed to ensure that all of the myocardial regions were included. Next, acoustic markers, the so-called speckles, equally distributed in the region of interest, could be followed throughout the entire cardiac cycle. The distance between the speckles was measured as a function of time, and parameters of myocardial deformation could be calculated. Finally, the myocardium was divided into 6 segments that were color coded as previously described (20) and displayed into 6 segmental time-strain curves for RS, CS, and LS (Fig. 1).

For each type of strain analyzed, 2 different parameters for dyssynchrony were obtained: maximal time delay between peak systolic strain of 2 segments (most frequently
observed between the \([\text{antero}]\)septum and \([\text{postero}]\)lateral wall) as well as an asynchrony index of the LV by calculating the standard deviation of time to peak-systolic strain.

For RS and CS, difference between time to peak-systolic strain of the \((\text{antero})\)septal and posterior segments (AS-P delay) and the standard deviation of time to peak-systolic strain for all 6 segments (SD\(t_{6S}\)) were measured. For LS, the 2- and 4-chamber views were used to calculate the difference between time to peak-systolic strain of the basal-septal and basal-lateral LV segment (BS-BL delay) as well as the standard deviation of time to peak-systolic strain for 12 LV segments (SD\(t_{12S}\)).

**Definition of response to CRT.** Response to CRT was defined as displaying a reduction of \(\geq 15\%\) in LV end-systolic volume at 6-month follow-up (2). Patients who died within the 6-month follow-up period or underwent heart transplantation were classified as nonresponders.
Statistical analysis. Continuous variables are presented as mean ± SD and compared using 2-tailed Student t test for paired and unpaired data. Categorical data are presented as number and percentage and compared using chi-square test. Linear regression analysis was performed to assess the relation between the changes in LV end-systolic volume and baseline LV dyssynchrony. In addition, the extent of baseline LV dyssynchrony, as assessed with the different echocardiographic methods, needed to predict response to CRT was determined by receiver operating characteristic curve analysis. The optimal cut-off value was defined as the value for which the sum of sensitivity and specificity was maximized. Finally, 20 patients were randomly selected to test the intra- and interobserver variability for the LV dyssynchrony measurements. Subsequently, linear regression analysis and Bland-Altman analysis were performed. A p value <0.05 was considered to be statistically significant.

Results

Patient baseline characteristics. The baseline characteristics of the 161 patients (mean age 66 ± 11 years, 125 men) included in the present study are summarized in Table 1. According to the inclusion criteria, all patients had severe heart failure (mean NYHA functional class 3.0 ± 0.5), with severe LV dysfunction (mean LV ejection fraction 23 ± 7%) and wide QRS complex (mean 164 ± 32 ms). Mean LV dyssynchrony as assessed with TDI was 84 ± 55 ms. All patients had optimized medical therapy, including angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists (85%), beta-blockers (62%), diuretics (85%), and spironolactone (40%), at maximum tolerated dosages. Device implantation was successful in all patients, and no complications were observed.

Speckle tracking strain analysis and LV dyssynchrony. All patients were analyzed at baseline and at 6-month follow-up. In the midventricular short-axis images, RS by speckle tracking was possible in 90% of 1,896 attempted segments. Reliable CS-time curves were obtained in 85% of the same 1,896 attempted segments. The feasibility for LS in 2- and 4-chamber views was 79%; only 2,990 segments from 3,792 attempted segments could be reliably evaluated. The lesser feasibility for assessment of LS was due to nonvalid tracking at the apical segments, where 30% of the segments had to be discarded. Furthermore, reproducibility for the different time delays was better when 2D RS was used (Table 2).

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<th>Table 1 Baseline Characteristics of the Study Population</th>
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<td>All Patients</td>
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<td>Age (yrs)</td>
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<td>LV dyssynchrony by TDI (ms)</td>
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AS-P delay = difference between time to peak systolic strain of the anteroseptal and posterior segments; BS-BL delay = difference between time to peak systolic strain of the basal-septal and basal-lateral segments; CS = circumferential strain; LS = longitudinal strain; LV = left ventricular; NYHA = New York Heart Association; RS = radial strain; SDT12S = standard deviation of the time to peak systolic strain of 6 segments; SDT12S = standard deviation of the time to peak systolic strain of 12 segments; TDI = tissue Doppler imaging.
In the overall population, substantial baseline dyssynchrony was present, as indicated by long time delays in peak-systolic strain between the anteroseptal and posterior wall, as well as high standard deviations by RS and CS (Table 1). Also, an important BS-BL delay was observed with longitudinal strain, as well as an important SDt12S.

**Response to CRT.** Before the 6-month follow-up evaluation, 2 patients underwent heart transplantation and 4 died from worsening heart failure. In the entire patient group, a significant improvement in clinical status was noted, with a reduction in NYHA functional class (from 3.0 ± 0.5 to 2.1 ± 0.7; p < 0.001), a reduction in quality-of-life score (from 41 ± 16 to 27 ± 19; p < 0.001), and an increase in 6-minute walking distance (from 279 ± 132 m to 377 ± 139 m; p < 0.001).

On echocardiography, LV ejection fraction improved significantly, from 23 ± 7% to 30 ± 9% (p < 0.001), and significant reductions in LV end-diastolic volume (245 ± 89 ml to 215 ± 81 ml; p < 0.001) and LV end-systolic volume (191 ± 82 ml to 155 ± 71 ml; p < 0.001) were observed.

In Table 3, the different parameters for LV dyssynchrony are reported at baseline and at 6-month follow-up. Both the AS-P delay and SDt6s, as assessed with RS, showed a significant reduction in time delay at 6-month follow-up. In contrast, for the same parameters assessed with CS, only the significant reduction in time delay at 6-month follow-up, whereas the SDt12s remained unchanged.

**Responders versus nonresponders to CRT.** At 6-month follow-up, 88 patients (55%) were classified as responders to CRT, according to the predefined criterion of a reduction in LV end-systolic volume by more than 15%. Conversely, 73 patients (45%) were nonresponders, including the 6 patients who died or underwent heart transplantation before the 6-month follow-up.

Responders showed (by definition) a reduction in LV end-systolic volume (from 208 ± 85 ml to 140 ± 72 ml; p < 0.001) and in LV end-diastolic volume (from 260 ± 90 ml to 203 ± 82 ml; p < 0.001) (Fig. 2). Furthermore, an improvement in LV ejection fraction was noted (from 21 ± 6% to 33 ± 9%; p < 0.001). In contrast, nonresponders showed no improvement in LV ejection fraction (from 25 ± 8% to 25 ± 7%; p = NS) and showed a trend toward an increase in both LV end-systolic volume (from 171 ± 75 ml to 175 ± 66 ml; p = 0.05) and LV end-diastolic volume (from 226 ± 86 ml to 230 ± 77 ml; p = NS) at 6-month follow-up (Fig. 2).

Baseline clinical and echocardiographic parameters between responders and nonresponders were similar, except for smaller LV volumes, higher LV ejection fraction, and shorter QRS duration in nonresponders. Furthermore, responders exhibited more baseline LV dyssynchrony as assessed with TDI compared with nonresponders (Table 1).

Concerning the LV dyssynchrony parameters assessed with speckle tracking analysis at baseline, AS-P delay and SDt6s, as assessed by RS, were significantly larger in responders compared with nonresponders (251 ± 138 ms vs. 94 ± 65 ms [p < 0.001] and 130 ± 67 ms vs. 79 ± 65 ms [p < 0.001], respectively). However, there were no differences between the groups in AS-P delay and SDt6s by either CS or BS-BL delay and SDt12s evaluated by LS (Table 1). Linear regression analysis demonstrated a modest but significant relationship between baseline AS-P delay as assessed by RS and extent of LV reverse remodeling (Fig. 3). Similarly, a relationship between baseline SDt6s as assessed by RS and LV reverse remodeling was noted (Fig. 3). A higher value of baseline radial dyssynchrony corresponded with a larger reduction in LV end-systolic volume after 6 months of CRT.

Furthermore, after 6 months of CRT, responders showed a significant reduction in AS-P delay and SDt6s as assessed by RS and in the BS-BL delay assessed by LS (Fig. 4). In nonresponders, none of the dyssynchrony parameters showed a significant reduction.

**Prediction of response to CRT.** Receiver operating characteristic curve analysis was performed to define the optimal cut-off value for both AS-P delay and SDt6s, as assessed with RS to predict response to CRT. In addition, the optimal cut-off value for LV dysynchrony as assessed by TDI was calculated.

The area under the curve for AS-P delay was 0.88, and the optimal cut-off value to predict response to CRT was 130 ms, yielding a sensitivity and specificity of, respectively, 83% and 80% (Fig. 5A). In addition, the area under the curve for SDt6s was 0.74 and the optimal

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<th>Table 2 Intraobserver and Interobserver Variability for the Different LV Dyssynchrony Parameters</th>
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<td>BS-BL delay by LS (ms)</td>
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<td>SDt12s by LS (ms)</td>
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*a p < 0.001; † p < 0.05.

Abbreviations as in Table 1.
The present study demonstrates that evaluation of LV dyssynchrony using speckle tracking strain analysis is feasible and that substantial LV dyssynchrony is present in all 3 deformation types—radial, circumferential and longitudinal—in CRT candidates with depressed LV function and dilated cardiomyopathy. Furthermore, only baseline LV dyssynchrony parameters assessed with RS (both AS-P delay and SDt6S delay) were able to identify potential responders to CRT, defined as a decrease of $\geq 15\%$ in LV end-systolic volume after 6 months of CRT. In addition, a decrease in extent of LV dyssynchrony during follow-up was only noted in responders to CRT for parameters assessed by RS (both AS-P delay and SDt6S delay) and LS (BS-BL delay); no changes in LV dyssynchrony were observed with CS in responders to CRT. Nonresponders to CRT did not show any significant change in extent of LV dyssynchrony using RS, LS, or CS.

**Changes in LV dyssynchrony after CRT.** Three forms of strain were assessed before and 6 months after CRT to assess the effect of biventricular pacing: radial, circumferential and longitudinal strain. Only few data are available on the changes in strain (assessed by 2D speckle tracking analysis) after CRT. Knebel et al. (13) evaluated 38 heart failure patients and demonstrated that responders to CRT revealed a significant decrease in time delays assessed with RS (from $168 \pm 104$ ms at baseline to $98 \pm 44$ ms at follow-up; $p = 0.04$) and LS (from $168 \pm 104$ ms at baseline to $112 \pm 81$ ms at follow-up; $p = 0.02$), whereas nonresponders did not show reductions in dyssynchrony according to RS and LS analyses during follow-up. The results of the present study are in agreement with these earlier findings. In the present study, responders to CRT demonstrated a significant decrease in LV dyssynchrony as...
assessed with RS (using both the AS-P delay and the SDt6S) and LS (using only the BS-BL delay). However, evaluation of dyssynchrony changes for CS did not reveal significant changes after CRT.

Initially, tagged magnetic resonance imaging was used for assessment of myocardial strain in radial, circumferential, and longitudinal orientation. Feasibility of this magnetic resonance imaging technique for assessment of LV mechanical dyssynchrony has been demonstrated in earlier studies (21,22). Currently, no magnetic resonance imaging studies have evaluated assessment of dyssynchrony with RS. However, Leclercq et al. (23) used tagged magnetic resonance imaging with CS in an animal model on heart failure and demonstrated that biventricular pacing resulted in acute reduction of LV dyssynchrony. In a subsequent animal study from the same group, both CS and LS analyses were used to evaluate LV dyssynchrony (12). Biventricular pacing improved synchronicity for both parameters, however this improvement was more pronounced using CS maps. In line with these results, although different parameters of LV dyssynchrony were used, CRT resulted in improvement of most dyssynchrony parameters. However, reductions in dyssynchrony parameters were largest using RS compared with LS and CS.

**Speckle tracking strain analysis and response to CRT.** In the present study, 2D speckle tracking strain analysis was applied to 161 heart failure patients, and 3 forms of strain were derived to assess LV dyssynchrony and predict response to CRT: radial, circumferential, and longitudinal strain. Currently, data on 2D speckle tracking strain analysis in CRT candidates and prediction of response are scarce. Radial strain was first applied in 64 heart failure patients by...
Suffoletto et al. (14). Baseline AS-P delay was significantly higher in patients who showed acute response, defined as an increase in stroke volume of \( \geq 15\% \), compared with patients who did not show an acute response (261 \( \pm \) 90 ms vs. 168 \( \pm \) 69 ms; \( p < 0.001 \)), and a predefined cut-off value of \( \geq 130 \) ms predicted acute response after CRT with 91% sensitivity and 75% specificity. This same cut-off value predicted long-term response (an increase \( \geq 15\% \) in LVEF after 8 \( \pm \) 5 months) with 89% sensitivity and 83% specificity (14). In contrast, the study by Knebel et al. (13) evaluated 38 heart failure patients undergoing CRT implantation and reported that RS derived from 2D speckle tracking analysis could not predict response to CRT (13). The present findings are in line with the results presented by Suffoletto et al. (14); a cut-off value of \( \geq 130 \) ms for AS-P delay assessed with RS was able to predict response with good sensitivity and specificity (Fig. 4A). In addition, the results from the present study revealed that SDt_{6S} measured with RS is also a useful parameter to predict long-term response to CRT (Fig. 4B), although the area under the curve was less than the area under the curve for the AS-P delay.

Two-dimensional CS has been applied in only 1 previous study to assess LV dyssynchrony in patients undergoing CRT (11). Although that study was more focused on the effect of LV lead position in relation to outcome after CRT, the results also indicated that CS was not different between patients with and without response to CRT (161 \( \pm \) 32 ms vs. 159 \( \pm \) 35 ms; \( p = 0.84 \)) (11). Similarly, the present results showed no differences in dyssynchrony assessed by CS between responders and nonresponders; neither the baseline AS-P delay nor the SDt_{6S} delay could identify patients who responded to CRT.

Data on LS assessed by 2D speckle tracking analysis are also limited. Knebel et al. (13) reported more extensive LV dyssynchrony according to LS (217 \( \pm \) 125 ms vs. 168 \( \pm \) 91 ms), although prediction of response to CRT was not possible with LS (13). The present findings are in agreement with those results; regardless of the parameters used (BS-BL delay or SDt_{12S}), LS was not able to predict response to CRT.

Finally, the value of the LV dyssynchrony parameters assessed by novel 2D RS in CRT candidates was similar to the conventional TDI parameter of LV dyssynchrony (3,24).

### Value of speckle tracking strain analysis in CRT

The myofiber orientation in the human heart is complex, with a characteristic helical distribution of the muscular fibers (25). In summary, the typical arrangement of the myocardial layers and its changes during the cardiac cycle has been related to the LV deformation in 3 directions: radial thickening, circumferential shortening, and longitudinal shortening (10,25). Two-dimensional speckle tracking imaging is a new echocardiographic technique which allows the study of all 3 types of deformation. Measurement of RS, CS, and LS has recently been validated by cardiac magnetic resonance imaging (26). More importantly, 2D speckle tracking imaging is angle independent and, as a strain imaging technique, enables differentiating those myocardial segments with active movement from those with passive movement (i.e., scarred tissue tethered by the nonscarred segments) (27,28).

In the present study, both parameters measured with RS were able to predict response to CRT, whereas neither LS nor CS were able to predict response. However, focusing on the SDt_{6S} or SDt_{12S}, a decrease in their values at follow-up was observed in the overall population. A possible explanation may be that radial thickening mirrors the circumferential and longitudinal shortening (28,29); the decrease in SDt_{6S} assessed with RS could be accounted for by a decrease in both SDt_{6S},
Assessed with CS and SD-t12, assessed with LS. As a consequence, the evaluation of LV dyssynchrony by RS with speckle tracking may provide more information in a single assessment than CS and LS could provide separately.

**Study Limitations.** Superior feasibility and reproducibility were noted for assessment of the RS parameters, which may have influenced the results. Larger studies are needed to further elucidate the relationship between electrical and mechanical activation of the LV and its impact on benefit from CRT.

**Conclusions.**

Two-dimensional speckle tracking RS enables the assessment of LV dyssynchrony and constitutes the best deformation study to identify potential responders to CRT. In addition, the predictive value of 2D RS was similar to color-coded TDI. Furthermore, the long-term effect of CRT on LV dyssynchrony is better characterized with RS compared with CS or LS. Reduction in LV dyssynchrony after CRT was noted only in responder patients, whereas in nonresponders no changes were demonstrated.

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**REFERENCES.**