**Easy-to-Use Comprehensive Speckle-Tracking Approach for Cardiac Resynchronization Therapy**

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**Background:** Left ventricular (LV) dyssynchrony has emerged as an important mechanism contributing to the patient’s response to cardiac resynchronization therapy (CRT), but other potential factors, especially LV myocardial viability, are also influential.

**Methods and Results:** We studied 132 patients undergoing CRT. LV dyssynchrony was determined by anteroseptal-to-posterior wall delay on the mid-LV short-axis view using 2-dimensional speckle-tracking radial strain (≥130 ms as significant). Global circumferential strain (GCS), considered as a parameter of LV intrinsic myocardial function, was also determined as the peak GCS from the same view. Long-term follow-up was tracked over 40 months. Kaplan-Meier analysis indicated that patients with GCS >3.9% experienced fewer cardiovascular events overall (log-rank P=0.034). Similarly, patients with GCS >3.9% and ≥6.6% experienced fewer cardiovascular events than those with GCS ≤3.9% and <6.6% among patients with and without LV dyssynchrony (log-rank P=0.025 and P=0.029, respectively). An important finding from multivariate Cox proportional hazards analysis was that LV dyssynchrony and GCS were independently associated with cardiovascular events. Of note, only 2±1 min per patient were needed to analyze both LV dyssynchrony and GCS from the same routine mid-LV short-axis view.

**Conclusions:** This easy-to-use combined assessment of LV dyssynchrony and myocardial function using speckle-tracking strain from the same mid-LV short-axis view may well have clinical implications for CRT. (Circ J 2014; 78: 2250–2258)

**Key Words:** Asynchrony; Echocardiography; Heart failure; Resynchronization

Cardiac resynchronization therapy (CRT) is an established therapeutic option for advanced heart failure (HF) patients with severe symptoms and wide QRS duration.\(^1\)\(^–\)\(^5\) It is well known that roughly one-third of patients do not respond to CRT when they are selected using standard criteria, and the quantification of left ventricular (LV) mechanical dyssynchrony has therefore gained prominence as an important potential means of predicting responders. Although the PROSPECT (Predictors of Responders to Cardiac Resynchronization Therapy) study suggested that standard echocardiographic parameters, including tissue Doppler velocity, did not have enough predictive value of responders after CRT,\(^6\) 2-dimensional (D) speckle-tracking radial strain to quantify LV dyssynchrony has proved to be a promising approach to predicting the response to CRT. Previous investigators have demonstrated that LV dyssynchrony, defined as a time difference in the peak anterior septal-to-posterior wall speckle-tracking radial strain ≥130 ms on the mid-LV short-axis view, predicted the response to CRT.\(^7\)\(^–\)\(^14\) LV dyssynchrony has emerged as an important mechanism contributing to the response to CRT, but other potential factors, especially LV myocardial viability, are also influential.\(^14\)\(^–\)\(^17\) Therefore, combined assessment of LV dyssynchrony and myocardial function may well be required to avoid nonresponse to CRT. Additionally, more simple and reliable parameters for clinical use may be required.

It was recently reported that global circumferential strain (GCS) assessed by 2D speckle-tracking strain in the mid-LV short-axis view reflects LV intrinsic myocardial function,\(^18\)\(^,\)\(^19\) and constitutes an independent prognostic marker for the prediction of cardiovascular events regardless of markers of LV global function such as ejection fraction (EF) in HF patients.\(^19\)

Accordingly, our objective was to test the hypothesis that an easy-to-use comprehensive speckle-tracking approach that combined assessment of LV radial dyssynchrony and GCS...
Echocardiography

All echocardiographic studies were performed using commercially available echocardiography systems (Vivid 7; GE-Vingmed, Horten, Norway, or Aplio SSA-770A; Toshiba Medical Systems, Tochigi, Japan) before and 3.4±1.0 months after CRT. Digital routine grey-scale 2D cine loops from 3 consecutive beats were obtained during end-expiratory apnea from standard LV apical views and mid-LV short-axis view at depths of 13–17 cm. Mean frame rates were 64±5 frames/s in the mid-LV short-axis view for grey-scale imaging used for speckle-tracking analysis. For patients with atrial fibrillation, measurements of standard echocardiographic and speckle-tracking parameters were obtained as averages of ≥4 cardiac cycles. LV volumes and EF were obtained with the modified biplane Simpson’s method.20

Speckle-Tracking Strain Analysis

Speckle-tracking strain analysis was performed for each patient with the aid of dedicated software (Ultra Extend; Toshiba Medical Systems) to avoid any difference between vendors. Speckle-tracking radial and circumferential strains were as-

Methods

Study Populations
We retrospectively studied a series of 139 consecutive HF patients undergoing CRT at 2 centers, Kobe University Graduate School of Medicine (Kobe, Japan) and Himeji Cardiovascular Center (Himeji, Japan), between July 2004 and January 2012. All patients had New York Heart Association functional class III or IV HF despite optimal pharmacological therapy that included angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, and diuretic, QRS duration ≥120 ms, and EF ≤35%. A biventricular pacing system was implanted with a standard right ventricular apical lead and LV lead positioned through the coronary sinus in an epicardial vein targeting the posterolateral or lateral branches. This study was approved by the local ethics committees of both institutions, and written informed consent was given by all patients.
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ical data are summarized as frequencies and percentages. The contentious variables of the 2 subgroups were compared by unpaired t-test. Proportional differences were evaluated with Fisher’s exact test. Relationships between 2 variables were analyzed by linear regression and expressed as Pearson correlation coefficients. Optimal cutoff values for association of baseline GCS with long-term cardiovascular events were determined by receiver-operator characteristics curve analysis, as well as calculating the area under the curve (AUC) and 95% confidence intervals (CI). Event-free survival curves were determined by Kaplan-Meier method and comparisons of cumulative event rates were performed with log-rank test. After performing the initial univariate Cox proportional hazards regression analysis to identify univariate predictors of long-term cardiovascular events, we proceeded with a multivariate Cox model on the basis of stepwise selection, with the P level for removal from the model set at >0.15. Candidate predictors were coronary disease, left bundle branch block (LBBB), LV dyssynchrony, and GCS. Furthermore, sequential Cox models were constructed to determine the incremental prognostic benefit of combined assessment of GCS and LV dyssynchrony over LBBB. A statistically significant increase in the global log-likelihood $\chi^2$ value of the model defined the incremental prognostic value. The intraclass correlation coefficient was then used to determine inter- and intraobserver reproducibility for LV dyssynchrony and GCS from 30 randomly selected patients using the identical cine-loop for each view. For all

### Table 1. Clinical, Hemodynamic, and Echocardiographic Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=132)</th>
<th>Patients without cardiovascular events (n=100)</th>
<th>Patients with cardiovascular events (n=32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, years</td>
<td>68±11</td>
<td>68±10</td>
<td>66±12</td>
<td>0.30</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>33 (25)</td>
<td>25 (25)</td>
<td>8 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>164±25</td>
<td>164±23</td>
<td>163±28</td>
<td>0.91</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>32 (24)</td>
<td>21 (21)</td>
<td>11 (34)</td>
<td>0.16</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>108 (82)</td>
<td>81 (81)</td>
<td>27 (93)</td>
<td>0.10</td>
</tr>
<tr>
<td>$\beta$-blockers</td>
<td>113 (86)</td>
<td>89 (89)</td>
<td>24 (75)</td>
<td>0.08</td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>108 (82)</td>
<td>89 (89)</td>
<td>19 (66)</td>
<td>0.01</td>
</tr>
<tr>
<td>QRS morphology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td>73 (55)</td>
<td>62 (62)</td>
<td>11 (34)</td>
<td>0.01</td>
</tr>
<tr>
<td>RBBB</td>
<td>12 (9)</td>
<td>8 (8)</td>
<td>4 (14)</td>
<td>0.30</td>
</tr>
<tr>
<td>Intraventricular conduction delay</td>
<td>13 (10)</td>
<td>7 (7)</td>
<td>6 (21)</td>
<td>0.04</td>
</tr>
<tr>
<td>RV pacing</td>
<td>34 (26)</td>
<td>22 (22)</td>
<td>12 (38)</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhythm, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>88 (67)</td>
<td>71 (71)</td>
<td>17 (53)</td>
<td>0.08</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10 (8)</td>
<td>5 (5)</td>
<td>5 (16)</td>
<td>0.01</td>
</tr>
<tr>
<td>RV pacing</td>
<td>34 (26)</td>
<td>22 (22)</td>
<td>12 (38)</td>
<td>0.10</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>192±70</td>
<td>190±67</td>
<td>197±77</td>
<td>0.68</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>143±59</td>
<td>141±56</td>
<td>148±66</td>
<td>0.62</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>26±6</td>
<td>26±6</td>
<td>26±6</td>
<td>0.94</td>
</tr>
<tr>
<td>LV dyssynchrony, ms</td>
<td>253±132</td>
<td>268±134</td>
<td>206±113</td>
<td>0.01</td>
</tr>
<tr>
<td>GCS, n (%)</td>
<td>6.2±2.8</td>
<td>6.5±3.0</td>
<td>5.3±1.9</td>
<td>0.03</td>
</tr>
<tr>
<td>GRS, n (%)</td>
<td>12.5±7.7</td>
<td>12.5±7.7</td>
<td>10.4±9.2</td>
<td>0.24</td>
</tr>
<tr>
<td>LV dyssynchrony ≥130 ms, n (%)</td>
<td>100 (76)</td>
<td>78 (78)</td>
<td>22 (69)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GCS, global circumferential strain; GRS, global radial strain; LBBB, left bundle branch block; LV, left ventricular; RBBB, right bundle branch block; RV, right ventricular.

sessed from the mid-LV short-axis view as previously described in detail. Briefly, a circular region of interest was traced on the endocardium using a point-and-click approach, with special care taken to adjust the tracking of all endocardial segments. A second larger concentric circle was then generated and manually adjusted near the epicardium. The mid-LV image was divided into 6 standard segments and each time-train curve and global strain curves were generated. LV dyssynchrony was defined as the time difference from the anteroseptal to the posterior wall segmental peak strains using speckle-tracking radial strain (Figure 1A). LV dyssynchrony ≥130 ms was considered to constitute significant dyssynchrony. GCS was determined as the peak GCS, and was expressed as an absolute value (Figure 1B). In addition, global radial strain (GRS) was also determined as the peak GRS from the same view.

### Definitions of Response and Long-Term Outcome Analysis

Mid-term response to CRT was defined as LV reverse remodeling detected at 3-month follow-up as a relative reduction ≥15% in end-systolic volume. Long-term unfavorable outcome events were prespecified as primary endpoints of death from worsening HF or hospitalization for deteriorating HF. Long-term follow-up after CRT was tracked over 40 months.

### Statistical Analysis

Continuous variables are expressed as mean±SD and categorical data are summarized as frequencies and percentages. The contentious variables of the 2 subgroups were compared by unpaired t-test. Proportional differences were evaluated with Fisher’s exact test. Relationships between 2 variables were analyzed by linear regression and expressed as Pearson correlation coefficients. Optimal cutoff values for association of baseline GCS with long-term cardiovascular events were determined by receiver-operator characteristics curve analysis, as well as calculating the area under the curve (AUC) and 95% confidence intervals (CI). Event-free survival curves were determined by Kaplan-Meier method and comparisons of cumulative event rates were performed with log-rank test. After performing the initial univariate Cox proportional hazards regression analysis to identify univariate predictors of long-term cardiovascular events, we proceeded with a multivariate Cox model on the basis of stepwise selection, with the P level for removal from the model set at >0.15. Candidate predictors were coronary disease, left bundle branch block (LBBB), LV dyssynchrony, and GCS. Furthermore, sequential Cox models were constructed to determine the incremental prognostic benefit of combined assessment of GCS and LV dyssynchrony over LBBB. A statistically significant increase in the global log-likelihood $\chi^2$ value of the model defined the incremental prognostic value. The intraclass correlation coefficient was then used to determine inter- and intraobserver reproducibilities for LV dyssynchrony and GCS from 30 randomly selected patients using the identical cine-loop for each view. For all
after CRT in patients with cardiovascular events was similar (from 5.5 ± 2.0% to 6.2 ± 2.8%, P=0.24), but that in patients without cardiovascular events was significantly increased (from 6.5 ± 2.9% to 9.0 ± 3.2%, P<0.0001). In total, 100 patients (76%) were characterized as exhibiting significant LV dyssynchrony according to the predefined criteria, and the remaining 32 patients (24%) were classified as non-dyssynchronous. Additionally, the time-phase mismatch of LV contraction because of significant LV dyssynchrony may underestimate GCS because the peak GCS does not mean just the average of each peak strain value. In fact, GCS inversely correlated with LV dyssynchrony in the entire patient cohort (r=–0.31, P=0.0003). Because a larger degree of LV dyssynchrony can influence GCS analysis, patients were divided into 2 groups based on the presence or absence of LV dyssynchrony for further analysis. Receiver-operator characteristic curve analysis revealed that optimal cutoff values of GCS for predicting cardiovascular events were 3.9% for all patients (AUC 0.60, 95% CI 0.495–0.693), 6.6% for patients without LV dyssynchrony (AUC 0.74, 95% CI 0.578–0.897), and 3.9% for patients with LV dyssynchrony (AUC 0.60, 95% CI 0.516–0.688). When using these cutoff values, the Kaplan-Meier curve indicated that patients with GCS >3.9% experienced fewer cardiovascular events than those with GCS ≤3.9% among the overall patient group (log-rank P=0.034).

Prediction of Cardiovascular Events Using the Combined Method
For patients with LV dyssynchrony (n=100), the prevalence of event-free survival among those with GCS >3.9% was significantly higher than among patients with GCS ≤3.9% (84%
**Figure 3.** Kaplan-Meier curves show that (A) for patients with left ventricular (LV) dyssynchrony, those with global circumferential strain (GCS) >3.9% experienced fewer cardiovascular events than those with GCS ≤3.9% and (B) for patients without LV dyssynchrony, those with GCS ≥6.6% experienced fewer cardiovascular events than those with GCS <6.6%. CRT, cardiac resynchronization therapy.

**Figure 4.** Among the patients with left ventricular (LV) dyssynchrony, event-free survival for patients with global circumferential strain (GCS) >3.9% was significantly better than for patients with GCS ≤3.9%. For patients without LV dyssynchrony, event-free survival was better for patients with GCS ≥6.6% than for patients with GCS <6.6%.
Association of GCS With Mid-Term Responders and Long-Term Outcome After CRT

Of the 132 patients, 84 (64%) were characterized as mid-term responders according to the predefined criteria, and the remaining 48 patients (36%) were classified as mid-term non-responders. Baseline GCS was similar between mid-term responders and non-responders (6.2±3.0% vs. 6.4±2.5%, P=0.67). The multiple logistic regression analysis for detecting mid-term responders showed that baseline LV dyssynchrony was the only independent associated factor (odds ratio 1.001, 95% CI 1.003–1.010), and the baseline LV dyssynchrony of mid-term responders was significantly greater than that of mid-term non-responders (297±125 vs. 183±118, P<0.0001). As expected, mid-term responders had a significantly more favorable long-term outcome after CRT (log-rank P<0.001, Figure 5). Interestingly, among the mid-term responders, the baseline GCS in

Figure 5. Kaplan-Meier curves of event-free survival after cardiac resynchronization therapy (CRT) show that mid-term responders had a significantly more favorable long-term outcome.

Figure 6. (A) Among the mid-term responders, global circumferential strain (GCS) in patients without cardiovascular events was significantly higher than that in patients with cardiovascular events. (B) Among the mid-term non-responders, patients without cardiovascular events also had a trend for a higher GCS, but was not statistically significant.
patients without cardiovascular events was significantly higher than that in patients with cardiovascular events (4.1±1.4% vs. 6.4±3.0%, P=0.003, Figure 6A), even though baseline EF was not significantly different (25±8% vs. 25±6%). Among the mid-term nonresponders, patients without cardiovascular events also had a trend for a higher GCS, but not statistically significant (5.7±1.9% vs. 7.1±2.8%, P=0.064, Figure 6B).

**Predictors of Long-Term Outcome**

Univariate and multivariate Cox proportional hazards analyses for predicting long-term cardiovascular events are shown in Table 2. An important finding of the multivariate Cox proportional hazards analysis was that both LV dyssynchrony and GCS were independently associated with cardiovascular events (hazard ratio, 0.997 and 0.994–0.999; 95% CI, 0.994–0.999, respectively, Table 2A). In addition, sequential Cox models showed a baseline model of LBBB was improved by the addition of GCS and LV dyssynchrony (χ²=19.5, P=0.004; Table 2B).

**Discussion**

The findings of our study demonstrated that baseline GCS was associated with long-term outcome. Furthermore, GCS in patients with mid-term LV reverse remodeling who had cardiovascular events was significantly lower than that in patients with mid-term LV reverse remodeling who did not have cardiovascular events. Furthermore, combining LV dyssynchrony and GCS may be even more effective for predicting cardiovascular events during long-term follow-up. It is noteworthy that LV dyssynchrony and GCS were found to be independently associated with cardiovascular events following CRT. The combined assessment of LV dyssynchrony and intrinsic myocardial function using speckle-tracking strain from the same mid-LV short view may well have clinical implications for CRT.

**Prognostic Value of GCS in HF Patients**

Speckle-tracking strain was originally used for regional myocardial assessment, and the averaged strain values of several segments taken together may represent alternative global myocardial function and have recently been applied to prognostic evaluation of patients with HF. Cho et al demonstrated that GCS assessed by 2D speckle-tracking strain constitutes an independent prognostic marker of cardiovascular events regardless of age, EF, or E/E’ during a follow-up period of 39 months, and they reported that patients with GCS ≤–10.7% had better outcome than those with GCS >–10.7% on the basis of their study of 201 acute HF patients with depressed EF. LV myocardial damage starts with longitudinal shortening, which occurs in the early stage of HF, and impairment of circumferential shortening develops at a later stage of HF. This phenomenon may lead to the different cutoff values of GCS for predicting long-term outcome in patients with HF between the study of acute HF by Cho et al and that of chronic HF by us (10.7% vs. 6.6%). In addition, global LV function such as LV volume and EF failed to be a valuable additive factor in predicting long-term responders after CRT in this study. Thus contraction of muscle fibers in the mid-wall, which is linearly related to circumferential strain, may better reflect intrinsic contractility in HF patients. Although GCS was an independent predictor of long-term outcome, there was no relationship between baseline GCS and mid-term response in this study. The precise reason remains unknown, but multiple logistic regression analysis for detecting mid-term responders showed that LV dyssynchrony was the only independently associated factor. Thus, we speculate that LV reverse remodeling mid-term after CRT primarily depends on the degree of baseline LV dyssynchrony rather than on baseline LV intrinsic myocardial function.
Clinical Utility of Combined Assessment of LV Dyssynchrony and GCS

The PROSPECT study suggested that standard echocardiographic dyssynchrony parameters do not have enough predictive value to replace routine selection criteria for CRT, but several investigators have demonstrated the utility of speckle-tracking radial strain for identifying responders following CRT. In particular, LV dyssynchrony, defined as a time difference ≥130 ms between the peak anteroseptum to posterior wall speckle-tracking radial strain was associated with mid-term LV reverse remodeling after CRT. Although, LV dyssynchrony appears to play a major pathophysiologic role in patients undergoing CRT and has emerged as an important mechanism contributing to the response to CRT, other factors, especially LV intrinsic myocardial function, also influence the response to CRT, regardless of LV dyssynchrony. Low-dose dobutamine stress echocardiography or cardiac magnetic resonance imaging is widely used to assess LV intrinsic myocardial function in HF patients, and the safety and utility of these techniques are well established. However, analysis of LV wall motion, including EF, during dobutamine infusion is subjective as well as highly load-dependent, and its accuracy depends largely on the experience of the operator; cardiac magnetic resonance imaging is also costly, time-consuming, and may not be suitable for patients with a previously implanted right ventricular pacemaker. Furthermore, Zhang et al. reported that short-term LV reverse remodeling after CRT was primarily associated with improvement of LV short-axis function, including LV radial and circumferential myocardial function, but not long-axis function. Therefore, a comprehensive approach to the assessment of LV dyssynchrony and myocardial function may well be required to avoid nonresponse to CRT. However, this combined assessment should be more simple and intelligible to any cardiologist for clinical utility because various parameters using various modalities exist for predicting the response to CRT. In the present study, we found GCS was a valuable additive factor associated with the response to CRT, especially in patients without LV dyssynchrony. Although LV dyssynchrony could be a major contributor to the predicted response to CRT, as shown by our multivariate Cox proportional hazards analysis, a comprehensive approach to evaluating LV dyssynchrony and myocardial function may well be required to avoid nonresponse to CRT of approximately one-third of CRT candidates. Of note, only 2±1 min per patient were needed to analyze both LV dyssynchrony and GCS from the same, routine mid-LV short-axis view. Therefore, measuring LV dyssynchrony and GCS proved to be simple, highly feasible, not time-consuming and to have sufficient reproducibility, and may well have clinical implications for CRT.

Study Limitations

This study was not randomized and the number of patients may not be enough, especially patients without LV dyssynchrony (n=32), so future studies of larger patient populations are necessary to assess our findings. Only 24% of patients in this study had ischemic cardiomyopathy. A possible reason could be the difference in etiology between patients with advanced HF in Japan and in other countries, especially the United States and Europe. We assessed only mid-LV short-axis views for measuring GCS using 2D speckle-tracking strain. GCS assessed by recently developed 3D speckle-tracking strain may be a more robust prognostic parameter than that assessed by the 2D method. Furthermore, assessment of scar burden by mean of cardiac magnetic resonance imaging or myocardial perfusion imaging was not part of this study. The LV lead position in relation to scar and the site of latest activation was not also part of this study. Finally, this combined assessment of LV dyssynchrony and intrinsic myocardial function using 2D speckle-tracking strain from the same mid-LV short-axis view was "easy-to-use", but speckle-tracking strain analysis requires both a training period and experience to achieve reproducible results.

Conclusions

The combined assessment of LV dyssynchrony and intrinsic myocardial function using 2D speckle-tracking strain from the same view proved to be simple and not time-consuming and had sufficient reproducibility. This easy-to-use combined approach may well have clinical implications for better management of CRT patients.

References


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