Dyssynchrony by speckle-tracking echocardiography and response to cardiac resynchronization therapy: results of the Speckle Tracking and Resynchronization (STAR) study

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Aims

The Speckle Tracking and Resynchronization (STAR) study used a prospective multi-centre design to test the hypothesis that speckle-tracking echocardiography can predict response to cardiac resynchronization therapy (CRT).

Methods and results

We studied 132 consecutive CRT patients with class III and IV heart failure, ejection fraction (EF) ≤35%, and QRS ≥120 ms from three international centres. Baseline dyssynchrony was evaluated by four speckle tracking strain methods; radial, circumferential, transverse, and longitudinal (≥130 ms opposing wall delay for each). Pre-specified outcome variables were EF response and three serious long-term events: death, transplant, or left ventricular assist device. Of 120 patients (91%) with baseline dyssynchrony data, both short-axis radial strain and transverse strain from apical views were associated with favourable EF response 7±4 months and long-term outcome over 3.5 years (P, 0.01). Radial strain had the highest sensitivity at 86% for predicting EF response with a specificity of 67%. Serious long-term unfavourable events occurred in 20 patients after CRT, and happened three times more frequently in those who lacked baseline radial or transverse dyssynchrony than in patients with dyssynchrony (P < 0.01). Patients who lacked both radial and transverse dyssynchrony had unfavourable clinical events occur in 53%, in contrast to events occurring in 12% if baseline dyssynchrony was present (P < 0.01). Circumferential and longitudinal strains predicted response when dyssynchrony was detected, but failed to identify dyssynchrony in one-third of patients who responded to CRT.

Conclusion

Dyssynchrony by speckle-tracking echocardiography using radial and transverse strains is associated with EF response and long-term outcome following CRT.

Keywords

Echocardiography • Heart failure • Pacing therapy

Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for selected heart failure (HF) patients. Current selection criteria for CRT include patients with New York Heart Association functional class III or IV on optimal pharmacologic therapy, QRS ≥120 ms, and ejection fraction (EF) ≤35%. Because significant subgroups of patients do not experience benefits of CRT, such as improved symptoms, ventricular function, or survival,2–5 echocardiographic techniques have been of interest to quantify LV mechanical dyssynchrony as a means to predict patient response.6–10 However, the PROSPECT (predictors of responders to cardiac resynchronization therapy) study suggested that echocardiographic dyssynchrony, such as tissue Doppler, did not have enough predictive value to replace routine selection criteria for CRT.11 Speckle-tracking echocardiography is a more recent approach that allows

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for strain imaging to assess dyssynchrony.\textsuperscript{12–19} Four different types of speckle-tracking approaches have been described included radial strain (myocardial thickening) and circumferential strain (myocardial shortening) assessed from short-axis views; and transverse (myocardial thickening) and longitudinal strains (myocardial shortening) assessed from apical views.\textsuperscript{10,12–14,16,18} Our objectives were to test the hypothesis that speckle-tracking strain can quantify dysynchrony and predict response to CRT in a prospective, multicentre, long-term study and to elucidate which of the above speckle-tracking strain approaches were most closely associated with outcome.

Methods
A series of 132 consecutive HF patients were prospective enrolled in the Speckle Tracking and Resynchronization (STAR) study from three international centres. This protocol was approved by the Institutional Review Board on Biomedical Research at the University of Pittsburgh, PA, USA, and ethics committees of the Elisabethinen University Teaching Hospital, Linz, Austria and University of Essen, Essen, Germany. All patients gave informed consent consistent with this protocol. No patients had atrial fibrillation. The mean age was 65 ± 13 years, 51 (39%) patients were female, the mean EF was 24 ± 6% (all ≤35%), the mean QRS duration was 159 ± 25 ms (all ≥120 ms), and 65 (49%) had ischaemic cardiomyopathy. All patients were classified as New York Heart Association functional class III or IV on optimal pharmacological therapy HF including angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and spironolactone, if tolerated. All patients had biventricular pacing systems with cardioverter–defibrillators implanted with a standard right ventricular apical lead and LV lead positioned through the coronary sinus in an epicardial vein targeting posterolateral or lateral branches.

Echocardiography
Echocardiographic studies were performed with commercially available systems (Aplio 80 or Aplio Artida, Toshiba Medical Systems Corporation, Tokyo, Japan). Digital routine greyscale two-dimensional cine loops from three consecutive beats were obtained at end-expiratory apnoea from standard apical views (four-chamber, two-chamber, and long-axis) mid-LV short-axis views at depths of 11–20 cm (mean 16 ± 2 cm). Frame rates were 44–90 Hz (mean 59 ± 11 Hz) for grey-scale imaging. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate. All data were prospectively and blindly analysed by the coordinating echo core lab at the University of Pittsburgh. The LV volumes and EF were assessed with the two-tailed Student’s t-test for unpaired data. Proportional differences were evaluated with Fisher’s exact test or the Chi-square test. Receiver operating characteristic (ROC) curves were constructed for each dyssynchrony parameter individually to test predefined cut-offs and to determine sensitivities and specificities. Areas under curve (AUCs) by ROC analysis were compared by logistic regression analysis. Event-free survival curves were determined according to the Kaplan–Meier method, with comparisons of cumulative event rates by the log-rank test. Any potential influence of covariates, a Cox proportional hazard model was used. Inter- and intra-observer variability analysis for speckle tracking was performed in 20 randomly selected patients using the identical cine-loop for each view. Inter- and intra-observer variabilities were expressed as the absolute differences divided by the mean value of the measurements. Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and MedCalc software

Speckle-tracking strain analysis
Routine B-mode greyscale images were analysed for frame-by-frame movement of stable patterns of natural acoustic markers or speckles, described previously in detail.\textsuperscript{16,21} Dyssynchrony was assessed for each patient by four different types of speckle-tracking strain using off-line software (Toshiba Medical Systems Corporation, Tokyo, Japan). Radial and circumferential dyssynchrony were assessed from mid-LV short-axis views, and transverse and longitudinal dyssynchrony were assessed from basal and mid-levels in apical four-chamber, two-chamber, and long-axis views.

Radial and circumferential dyssynchrony
A circular region of interest traced the endocardium counterclockwise beginning at 9 o’clock at end-systole using a point-and-click approach. A second larger concentric circle was then automatically generated and manually adjusted near the epicardium or manually traced. Special care was taken to fine-tune the region of interest, using visual assessment during cineloop playback to ensure that segments were tracked appropriately. The mid-LV image was divided into six standard segments and time-strain curves were generated from each segment. Radial and circumferential dyssynchrony were defined as a time difference between the anteroseptal and posterior wall segmental peak strain (Figure 1) using a pre-defined cut-off ≥130 ms considered as significant dyssynchrony.\textsuperscript{14}

Transverse and longitudinal dyssynchrony
A region of interest was traced counterclockwise direction on the endocardium starting from the right-hand mitral annulus at end-diastole in each three apical view using a point-and-click approach. A second larger region of interest was then generated and manually adjusted near the epicardium. Special care was taken to fine-tune the region of interest, using visual assessment during cineloop playback to ensure that segments were tracked appropriately. Apical images were divided into six standard segments (at basal, mid, and apical levels) and six corresponding time–strain curves were generated. Transverse and longitudinal dyssynchrony were defined as maximum opposing wall delay in time-to-peak strain among the three apical views from basal and mid-levels (Figure 2) using a pre-defined cut-off ≥130 ms considered as significant dyssynchrony.

Definitions of response and long-term outcome analysis
Response to CRT was pre-specified as a relative increase in EF ≥15% from baseline as used in previous studies.\textsuperscript{13,14,16} In addition, response to CRT was also investigated as an absolute increase in EF ≥5% in EF units and a relative decrease in LV end-systolic volume ≥15%.6,8,9,11,12,18,19,22 Long-term unfavourable outcome events were pre-specified as death, heart transplant, or left ventricular assist device (LVAD) implantation. These events were pre-determined because only patients with end-stage HF with limited anticipated survival would undergo transplant or LVAD in these institutions. Accordingly, death, transplant, or LVAD were pre-specified as primary endpoints. Long-term follow-up after CRT was tracked over 3.5 years.

Statistical analysis
All group data were presented as mean ± SD and were compared with the two-tailed Student’s t-test for unpaired data. Proportional differences were evaluated with Fisher’s exact test or the Chi-square test. Receiver operating characteristic (ROC) curves were constructed for each dyssynchrony parameter individually to test predefined cut-offs and to determine sensitivities and specificities. Areas under curve (AUCs) by ROC analysis were compared by logistic regression analysis. Event-free survival curves were determined according to the Kaplan–Meier method, with comparisons of cumulative event rates by the log-rank test. Any potential influence of covariates, a Cox proportional hazard model was used. Inter- and intra-observer variability analysis for speckle tracking was performed in 20 randomly selected patients using the identical cine-loop for each view. Inter- and intra-observer variabilities were expressed as the absolute differences divided by the mean value of the measurements. Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and MedCalc software
version 10.4.0.0 (MedCalc Software, Inc., Mariakerke, Belgium) were used. Statistical significance was $P < 0.05$.

**Results**

**Feasibility and variability of speckle-tracking dyssynchrony analysis**

Of the 132 consecutive HF patients who underwent CRT, 8 (6%) had poor echocardiographic windows and were prospectively excluded from all subsequent analyses. Overall, speckle-tracking dyssynchrony analysis was feasible from at least one view in 120 patients (91%), with details appearing in Figure 3. Speckle tracking was possible only from short-axis views in eight patients (6%) and only from apical views in six patients (5%). The inter- and intra-observer variabilities were $17 \pm 14$ and $10 \pm 6$% for radial dyssynchrony, $18 \pm 8$ and $11 \pm 7$% for circumferential dyssynchrony, $17 \pm 16$ and $11 \pm 6$% for transverse dyssynchrony, and $19 \pm 9$ and $13 \pm 7$% for longitudinal dyssynchrony, respectively.

**Individual and combined predictors of ejection fraction response to cardiac resynchronization therapy**

Of 97 patients who had follow-up EF data 7 ± 4 months after CRT, an EF response was observed in 63 patients (65%), predefined as relative change in EF ≥ 15% (Table 1). Responders, compared with non-responders, had similar age, gender distribution, and EF.
However, responders were more likely to have wider QRS duration (166 ± 24 vs. 150 ± 25 ms) and less likely to have ischaemic heart disease (36 vs. 62%) (both P < 0.05 vs. non-responders). Similar baseline characteristics were observed when grouping patients as event-free survivors and patients with serious clinical events (Table 2). Radial and transverse dyssynchrony were significantly greater in the responders than in the non-responders (both P < 0.001 vs. non-responders). EF significantly improved after CRT in patients with baseline radial and transverse dyssynchrony from 24 ± 7 to 36 ± 13% and 24 ± 7 to 35 ± 13%, respectively (both P < 0.001, Figure 4). However, patients who lacked radial and transverse dyssynchrony did not have a significant EF response to CRT from 24 ± 7 to 26 ± 11% and 26 ± 7 to 28 ± 12%, respectively. Furthermore, EF response rate was higher in patients with radial and transverse dyssynchrony than in patients who lacked dyssynchrony (80 vs. 29% and 71 vs. 22%, respectively, both P < 0.001) (Table 3). Of individual measures, radial dyssynchrony was the best predictor of EF response with sensitivity of 87%, specificity of 67%, and ROC AUC of 0.79 (P < 0.001, Figure 5). Transverse dyssynchrony yielded a sensitivity of 83%, specificity of 63%, and AUC of 0.75 (P < 0.001).

We also observed similar results that radial and transverse dyssynchrony were associated with an absolute 5% increase in EF (Table 4) and a relative decrease in end-systolic volume ≥15% (AUC = 0.79 and 0.73 for an absolute 5% increase in EF, and 0.78 and 0.71 for the relative decrease in end-systolic volume ≥15%, respectively, all P < 0.005). In addition, the combination of either radial or transverse dyssynchrony using 130 ms cut-off for each was the most highly predictive of EF response to CRT with AUC of 0.82. The presence of circumferential and longitudinal dyssynchrony was associated with EF response to CRT, when detected (Table 5). However, circumferential and longitudinal

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/31/14/1690/439529/1693)
strains were not associated with overall EF response following CRT, because they were unable to detect significant dyssynchrony in approximately one-third of patients who responded to CRT.

Individual and combined predictors of event-free survival after cardiac resynchronization therapy

Of the 120 patients where speckle-tracking analysis was feasible, long-term outcome data after CRT were available on 110 patients over 3.5 years. The mean follow-up duration was 2.1 ± 1.5 years, with shorter follow-up intervals were related to primary endpoints occurring. The primary endpoint of a pre-specified clinical event occurred in 20 patients (18%) as follows: 13 deaths, 3 heart transplants, and 4 LVAD implants. Both radial and transverse dyssynchrony were associated with probability of freedom from death, transplant, or LVAD after CRT ($P < 0.05$, Figure 6, Table 5). Radial dyssynchrony using the pre-defined cut-off of 130 ms predicted the probability of event-free survival with 56% sensitivity and 76% specificity with AUC = 0.71 (Figure 5). Transverse dyssynchrony using the same cut-off also successfully predicted probability of event-free survival with 61% sensitivity and 74%
and transverse dyssynchrony remained independently associated with event-free survival after CRT. For radial dyssynchrony, the hazard ratio was 4.73 with 95% confidence intervals of 1.83–12.23, \( P = 0.02 \) and for transverse dyssynchrony the hazard ratio was 4.32 with 95% confidence intervals of 1.73–10.84, \( P = 0.03 \).

**Discussion**

STAR is the first prospective multicentre study to assess the utility of speckle-tracking strain to quantify LV dyssynchrony and investigate their associations with EF response and important long-term outcome events of death, heart transplant, or LVAD implant after CRT. Of individual speckle-tracking strain dyssynchrony approaches, radial strain from short-axis views and transverse strain from apical views were both significantly associated with EF response and long-term survival following CRT. Importantly, patients who lacked dyssynchrony before CRT by either radial or transverse strain approach had serious unfavourable clinical events occur three times more frequently than those with significant baseline dyssynchrony. Lack of dyssynchrony before CRT by both radial and transverse strains when used in combination was associated with death, heart transplant, or LVAD in approximately 50% of patients, in contrast to these unfavourable events occurring in 11–13% of patients if baseline radial or transverse dyssynchrony were present. The precise meaning of this observation is unclear because a control group whom did not undergo CRT was not part of this study for comparison. However, it appeared that lack of baseline radial or transverse dyssynchrony was a marker for a poor prognosis following CRT. Dyssynchrony by circumferential or longitudinal strain was also successfully predictive of EF response and long-term outcome, when detected. However, circumferential and longitudinal strains failed to detect significant dyssynchrony in one-third of patients who responded to CRT, which was approximately 20% less detected by radial and transverse strains. Accordingly, speckle-tracking radial and transverse strains appeared to be comparatively more robust to quantify dyssynchrony associated with CRT response.

**Dyssynchrony analysis by speckle-tracking strain**

Dyssynchrony analysis by echocardiography has been mostly reported using LV longitudinal velocities by tissue Doppler imaging from the apical views.6–9 The PROSPECT study, however, suggested that echocardiographic parameters including tissue Doppler velocity did not have enough predictive value to replace routine selection criteria for CRT.11 Speckle tracking utilized in the present study has the advantage of differentiating active motion from passive motion independent of Doppler angle of incidence and may be used to assess dyssynchrony.10,12–14,16,18 Becker et al.23 used circumferential strain to determine that optimal CRT LV lead position, defined as concordance of the segment with latest motion from passive motion independent of Doppler angle of incidence. However, it appeared that lack of baseline radial or transverse dyssynchrony was a marker for a poor prognosis following CRT.

### Table 2 Baseline characteristics of heart failure patients and their long-term outcome response to cardiac resynchronization therapy

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Event-free survivors (n = 90)</th>
<th>Patients with unfavourable events (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 ± 13</td>
<td>66 ± 11</td>
<td>0.84</td>
</tr>
<tr>
<td>Heart rate, ms</td>
<td>68 ± 14</td>
<td>67 ± 10</td>
<td>0.69</td>
</tr>
<tr>
<td>Gender (female), n (%)</td>
<td>36 (40)</td>
<td>6 (30)</td>
<td>0.46</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>162 ± 26</td>
<td>148 ± 19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>36 (40)</td>
<td>13 (65)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>25 ± 6</td>
<td>24 ± 8</td>
<td>0.60</td>
</tr>
<tr>
<td>End-diastolic volume, mL</td>
<td>205 ± 78</td>
<td>194 ± 40</td>
<td>0.60</td>
</tr>
<tr>
<td>End-systolic volume, mL</td>
<td>154 ± 74</td>
<td>148 ± 28</td>
<td>0.96</td>
</tr>
<tr>
<td>Speckle-tracking strain dyssynchrony</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial dyssynchrony, ms</td>
<td>244 ± 123</td>
<td>155 ± 109</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circumferential dyssynchrony, ms</td>
<td>207 ± 132</td>
<td>167 ± 111</td>
<td>0.22</td>
</tr>
<tr>
<td>Transverse dyssynchrony, ms</td>
<td>255 ± 131</td>
<td>179 ± 111</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Longitudinal dyssynchrony, ms</td>
<td>200 ± 106</td>
<td>169 ± 96</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Long-term outcome was defined as freedom from death, heart transplant, or left ventricular assist device.

specifity with AUC = 0.67. The combination of radial and transverse dyssynchrony was the most highly specific for predicting unfavourable clinical events with 67% sensitivity and 80% specificity with AUC = 0.73. When significant dyssynchrony was detected by circumferential or longitudinal strain, it was similarly associated with EF response and long-term outcome (Table 5). However, circumferential or longitudinal strain failed to detect dyssynchrony in many patients who responded to CRT, and the absence of circumferential or longitudinal dyssynchrony was not predictive of unfavourable events (Table 5, Figure 7).

Remarkably, 34–36% of patients had a serious unfavourable clinical event if they lacked radial or transverse dyssynchrony before CRT in contrast to 11–13% of patients who had an unfavourable event if baseline dyssynchrony was present (\( P < 0.01 \)) (Figure 8). Patients who lacked both radial and transverse dyssynchrony before CRT had a particularly poor prognosis with 53% having either death, transplant, or LVAD over 3.5 years, in contrast to 12% having these serious events occur if baseline dyssynchrony by either approach was detected (\( P < 0.01 \)). Importantly, when adjusted for the covariates of ischaemic aetiology and QRS duration using a Cox proportional hazard model, radial
CRT. Furthermore, Lim et al.\textsuperscript{19} recently reported that dyssynchrony by a longitudinal strain delay index $\geq 25\%$ strongly predicted response to CRT with sensitivity of 95\% and specificity of 83\%, and correlated with reverse remodelling. Our study confirms a previous report by Delgado et al.\textsuperscript{12} who concluded that radial dyssynchrony was superior to circumferential and longitudinal speckle-tracking strain to predict response to CRT in 161 CRT patients. Since this group used an entirely different echo system and a different vendor’s speckle-tracking software, these findings suggest that the success of radial strain over circumferential or longitudinal strain is not specific to a particular brand of speckle-tracking software. A possible reason for these observations is that the timing of wall thickening represented by radial or transverse strain is more sensitive for speckle tracking to detect than circumferential or transverse stain. Of note, other investigators have reported the utility of circumferential strain using magnetic resonance imaging for quantifying dyssynchrony,\textsuperscript{25–28} suggesting that there are differences in imaging approaches.

**Clinical implications**

The results of this study support the potential for radial and transverse strains by speckle-tracking echocardiography to quantify dyssynchrony associated with response to CRT. In particular, the absence of radial or transverse dyssynchrony was shown to be associated with a high rate of unfavourable clinical events following CRT in patients with routine indications. Regarding potential future applications, the effects of CRT in patients with narrow QRS duration $<120$ ms and speckle-tracking dyssynchrony are presently unknown. The only randomized CRT trial in patients with narrow QRS width, known as RethinQ (Resynchronization...
Figure 5  Receiver operating characteristics curve analysis of speckle-tracking strain approaches to dyssynchrony for predicting outcome after cardiac resynchronization therapy. (A) Ejection fraction (EF) response $\geq 15\%$ and (B) event-free survival (freedom from death, transplant, or left ventricular assist device). Radial and transverse strain dyssynchrony were successfully predictive of response to CRT; however, circumferential and longitudinal strains were not. The combination of radial and transverse dyssynchrony was the most predictive of EF response and long-term outcome following CRT.

Table 4  Response defined as absolute increase in ejection fraction $\geq 5\%$

<table>
<thead>
<tr>
<th>Speckle-tracking approach</th>
<th>Dyssynchrony ($\geq 130$ ms)</th>
<th>No dyssynchrony ($&lt;130$ ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Non-responders</td>
</tr>
<tr>
<td>Radial strain ($n = 94$)</td>
<td>53 (79%)*</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>Circumferential strain ($n = 92$)</td>
<td>39 (70%)*</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>Transverse strain ($n = 93$)</td>
<td>51 (77%)*</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>Longitudinal strain ($n = 91$)</td>
<td>38 (63%)*</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Radial and transverse strains ($n = 93$)</td>
<td>57 (71%)*</td>
<td>23 (29%)</td>
</tr>
</tbody>
</table>

*P < 0.01 vs. dyssynchrony non-responders.
†P < 0.05 vs. circumferential and longitudinal strains.
‡P < 0.01 vs. no dyssynchrony responders.

Table 5  Response defined as freedom from death, transplant, or left ventricular assist device

<table>
<thead>
<tr>
<th>Speckle-tracking approach</th>
<th>Dyssynchrony ($\geq 130$ ms)</th>
<th>No dyssynchrony ($&lt;130$ ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event-free survivors</td>
<td>Patients with adverse events</td>
</tr>
<tr>
<td>Radial strain ($n = 110$)</td>
<td>71 (89%)*</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Circumferential strain ($n = 106$)</td>
<td>56 (84%)*</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Transverse strain ($n = 108$)</td>
<td>69 (87%)*</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Longitudinal strain ($n = 105$)</td>
<td>54 (81%)*</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>Radial and transverse strain ($n = 108$)</td>
<td>80 (88%)*</td>
<td>11 (12%)</td>
</tr>
</tbody>
</table>

*P < 0.01 vs. dyssynchrony patients with adverse events.
‡P < 0.05 vs. circumferential or longitudinal strain.
Therapy in Patients with Narrow QRS), primarily measured dysynchrony by tissue Doppler imaging. Although current patient selection guidelines for CRT utilize QRS width as a surrogate for dyssynchrony, this present study supports the potential for speckle-tracking dyssynchrony to be used as an adjunct to decision making, perhaps in patients with borderline QRS duration.

**Study limitations**

A limitation was that this was not a randomized study, and routine implantation criteria for CRT were used. Accordingly, a control group of patients who did not undergo CRT was not compared. Although the absence of radial or transverse dyssynchrony was a marker for unfavourable clinical events after CRT, it remains unknown what the outcome would be if these patients did not have CRT. Another limitation is that the exact cause of death was not specifically adjudicated as part of this study. However, all patients with a limited prognosis due to other disease, such as carcinoma, were excluded from CRT. It may be considered a limitation that the largest proportion of patients was enrolled from the Pittsburgh site; however, the influence of a centre effect was minimized by utilizing a similar approach to CRT implantation, similar echo hardware and software, and a single echo core lab for analysis. Another limitation was that other clinical endpoints, such as quality of life questionnaire or 6 min walk distance.
were not included; we chose the hard endpoints of death, transplant, and LVAD, because they are important and more objective. Left ventricular lead position, scar position, and scar burden have all been shown to have an impact on response to CRT regardless of dyssynchrony, but were not part of this present study.\textsuperscript{14,22,31–34}

Another limitation was that neither atrio-ventricular dyssynchrony nor dyssynchrony assessment after CRT was part of this study. Technical limitations of each speckle-tracking method include endocardial border tracing, where care must be taken to manually fine-tune the width or the region of interest for appropriate tracking. A relatively high degree of intra-observer variability of speckle tracking analysis was observed in this present study, even with an experienced core lab. Accordingly, speckle tracking, similar to tissue Doppler dyssynchrony analysis, requires training and experience to achieve reproducible results.\textsuperscript{11,35} There are hopes that future technological improvements with automation of speckle tracking will reduce variability. Another limitation is that two-dimensional speckle tracking was used, and the heart is a three-dimensional object. A newly developed three-dimensional speckle-tracking system could overcome this problem.\textsuperscript{15,17}

Another limitation was that other measures of dyssynchrony, such as using tissue Doppler, were not compared in this same group of patients. However, this multiple method comparison was beyond the scope of the present study which focused on speckle-tracking echocardiography. Future larger studies would be useful to further elucidate the role of speckle-tracking echocardiography for predicting response to CRT.

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