

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

Hidekazu Tanaka¹, Hans-Joachim Nesser², Thomas Buck³, Olusegun Oyeyuga¹, Rolf Alexander Jánosi³, Siegmund Winter², Samir Saba¹, and John Gorcsan III^{1*}

¹University of Pittsburgh, Scaife Hall 564, 200 Lothrop Street, Pittsburgh, PA15213-2582, USA; ²Elisabethinen University Teaching Hospital, Linz, Austria; and ³University Hospital Essen, Essen, Germany

Received 26 April 2010; revised 17 May 2010; accepted 31 May 2010; online publish-ahead-of-print 8 June 2010

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) $\leq 35\%$, 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 \pm 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) $\leq 35\%$.¹ 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

* Corresponding author. Tel: +1 412 647 6570, Fax: +1 412 647 0568, Email: gorcsanj@upmc.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org. The online version of this article has been published under an open access model. Users are entitled to use, reproduce, disseminate, or display the open access version of this article for non-commercial purposes provided that the original authorship is properly and fully attributed; the Journal, Learned Society and Oxford University Press are attributed as the original place of publication with correct citation details given; if an article is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For commercial re-use, please contact journals.permissions@oxfordjournals.org

for strain imaging to assess dyssynchrony.^{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.^{10,12–14,16,18} Our objectives were to test the hypothesis that speckle-tracking strain can quantify dyssynchrony 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 $24 \pm 6\%$ (all $\leq 35\%$), 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 (Aplo 80 or Aplo 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 greyscale 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 by biplane Simpson rule using manual tracing of digital images.²⁰

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.^{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 cine-loop 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.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 cine-loop 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 $\geq 15\%$ from baseline as used in previous studies.^{13,14,16} In addition, response to CRT was also investigated as an absolute increase in EF $\geq 5\%$ in EF units and a relative decrease in LV end-systolic volume $\geq 15\%$.^{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 \pm 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

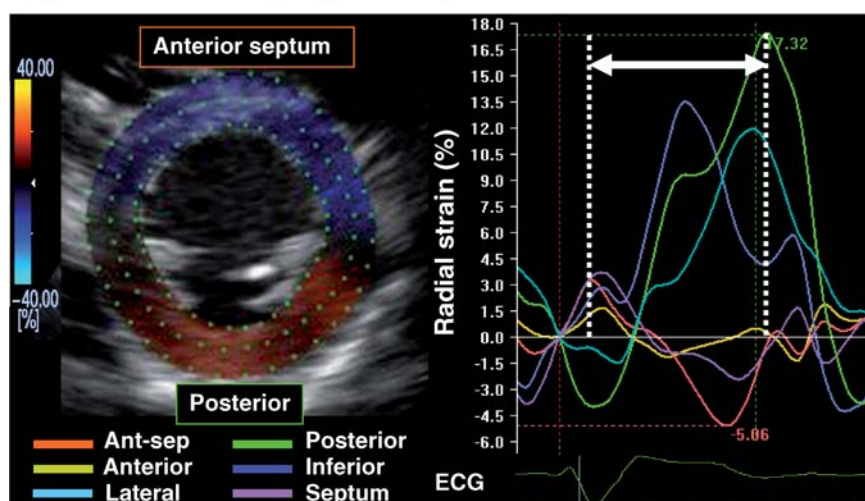
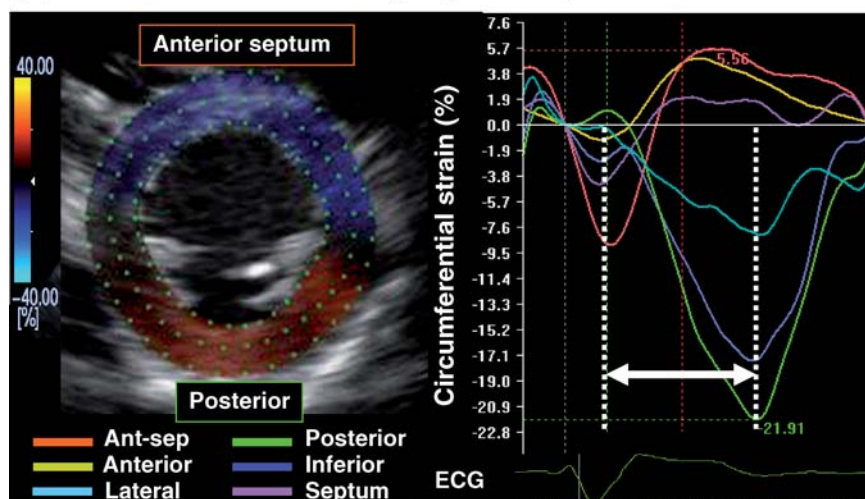
(A) Radial strain dyssynchrony**(B) Circumferential strain dyssynchrony**

Figure 1 An example of speckle-tracking dyssynchrony analysis from mid-ventricular short-axis views demonstrating radial (A) and circumferential (B) time–strain curves in a heart failure patient with left bundle-branch block. Dyssynchrony is shown as a time difference (arrow) between time to peak strain in the anterior septum (orange curve) and posterior wall peak strain (green curve). ECG, electrocardiogram; Ant-sep, anterior septum.

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 ± 14 and $10 \pm 6\%$ for radial dyssynchrony, 18 ± 8 and $11 \pm 7\%$ for circumferential dyssynchrony, 17 ± 16 and $11 \pm 6\%$ for transverse dyssynchrony, and 19 ± 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 $\geq 15\%$ (*Table 1*). Responders, compared with non-responders, had similar age, gender distribution, and EF.

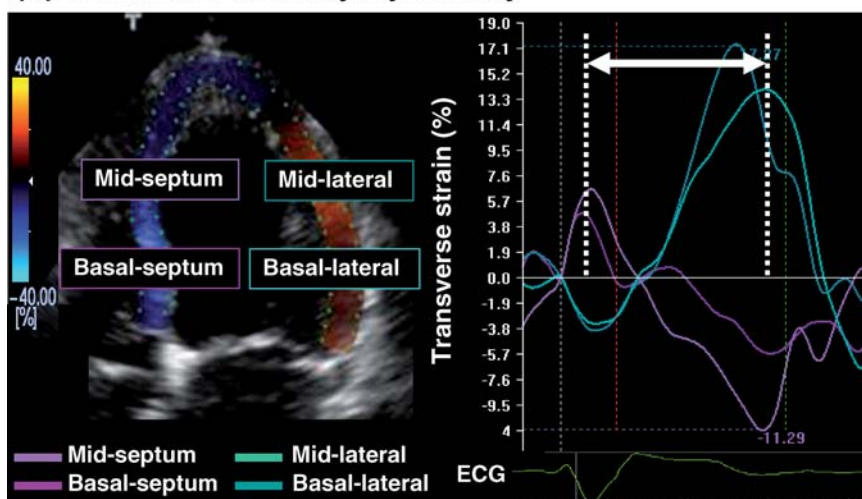
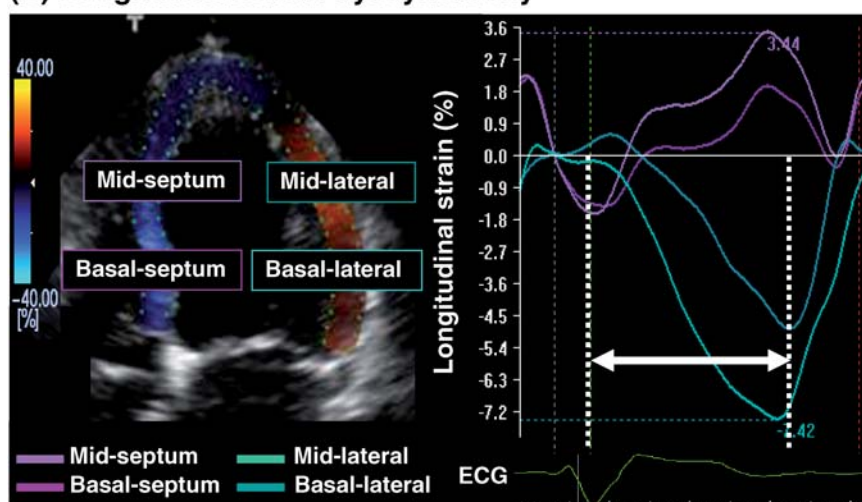
(A) Transverse strain dyssynchrony**(B) Longitudinal strain dyssynchrony**

Figure 2 An example of speckle-tracking dyssynchrony analysis from an apical four-chamber view demonstrating transverse (A) and longitudinal (B) time–strain curves in a heart failure patient with left bundle-branch block. Dyssynchrony is shown as a maximum opposing wall delay (arrow) in time-to-peak strain among three apical views; four-chamber, two-chamber, and long-axis. ECG, electrocardiogram.

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 $36 \pm 13\%$ and 24 ± 7 to $35 \pm 13\%$, 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 $26 \pm 11\%$ and 26 ± 7 to $28 \pm 12\%$, 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 $\geq 15\%$ (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 $\geq 15\%$, 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

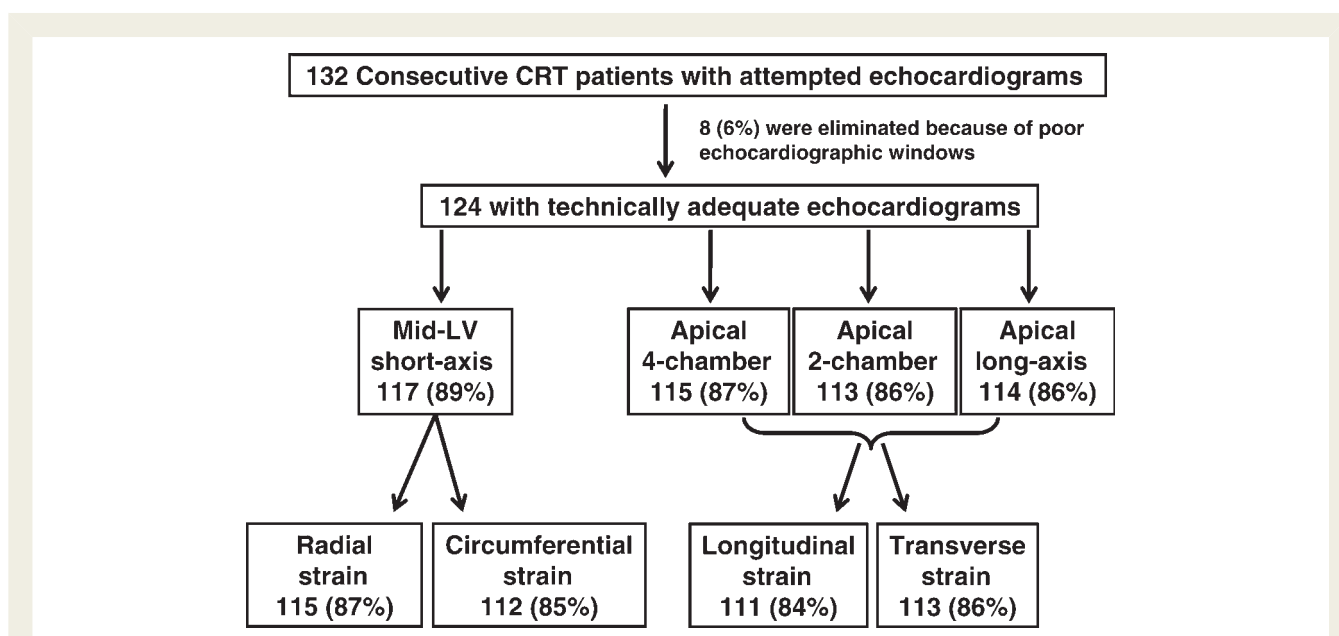


Figure 3 Feasibility of speckle-tracking dyssynchrony analysis in consecutive patients with attempted echocardiograms. CRT, cardiac resynchronization therapy; LV, left ventricular.

Table 1 Baseline characteristics of heart failure patients and their ejection fraction response to cardiac resynchronization therapy

Baseline variable	Ejection fraction responders (n = 63)	Ejection fraction non-responders (n = 34)	P-value
Age, years	65 ± 14	67 ± 10	0.53
Heart rate, ms	68 ± 14	67 ± 15	0.56
Gender (female), n (%)	27 (43)	10 (29)	0.10
QRS duration, ms	166 ± 24	150 ± 25	<0.05
Coronary disease, n (%)	22 (35)	21 (62)	<0.05
Ejection fraction, %	25 ± 7	23 ± 6	0.21
End-diastolic volume, mL	186 ± 81	219 ± 79	0.06
End-systolic volume, mL	143 ± 75	170 ± 70	0.08
Speckle-tracking strain dyssynchrony			
Radial dyssynchrony, ms	272 ± 131	148 ± 91	<0.001
Circumferential dyssynchrony, ms	209 ± 135	168 ± 119	0.15
Transverse dyssynchrony, ms	281 ± 131	180 ± 110	<0.001
Longitudinal dyssynchrony, ms	196 ± 109	170 ± 90	0.25

Ejection fraction response defined as a relative increase $\geq 15\%$ from baseline values.

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%

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

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

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

specificity 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

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 strain resulted in greater improvements in LV function compared with those with non-optimal LV lead position. Knebel et al.²⁴ reported that longitudinal dyssynchrony from standard apical views significantly decreased after CRT in the responders, but baseline longitudinal strain dyssynchrony failed to predict response to

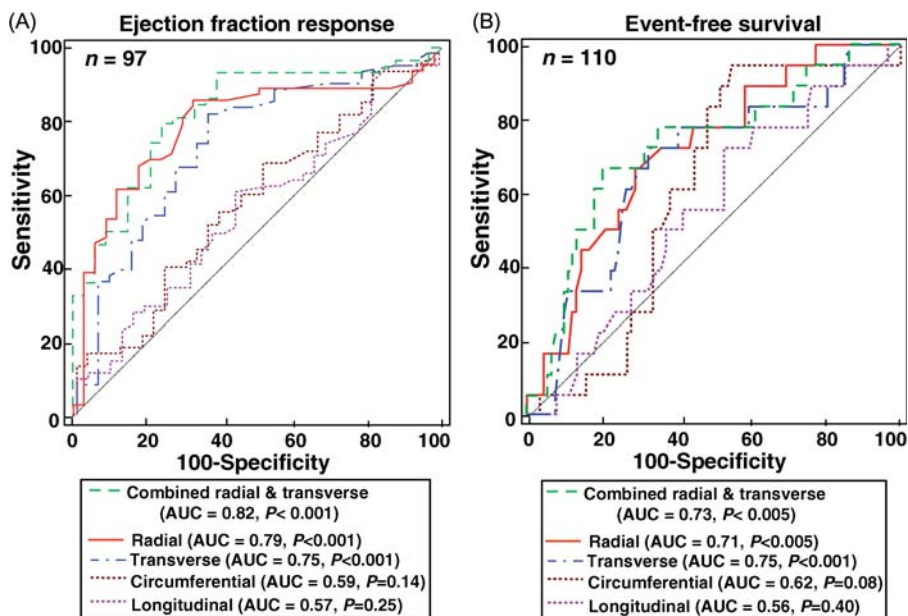


Figure 5 Receiver operating characteristics curve analysis of speckle-tracking strain approaches to dyssynchrony for predicting outcome after cardiac resynchronization therapy. (A) Ejection fraction (EF) response $\geq 15\%$ and (B) event-free survival (freedom from death, transplant, or left ventricular 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 $\geq 5\%$

Speckle-tracking approach	Dyssynchrony (≥ 130 ms)		No dyssynchrony (<130 ms)	
	Responders	Non-responders	Responders	Non-responders
Radial strain (n = 94)	53 (79%)*	14 (21%)	9 (31%)	20 (70%) ^{#†}
Circumferential strain (n = 92)	39 (70%)*	17 (30%)	19 (53%)	17 (47%)
Transverse strain (n = 93)	51 (77%)*	15 (23%)	8 (30%)	19 (70%) ^{#†}
Longitudinal strain (n = 91)	38 (63%)*	22 (37%)	20 (65%)	11 (35%)
Radial and transverse strains (n = 93)	57 (71%)*	23 (29%)	2 (15%)	11 (85%) ^{#†}

*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

Speckle-tracking approach	Dyssynchrony (≥ 130 ms)		No dyssynchrony (<130 ms)	
	Event-free survivors	Patients with adverse events	Event-free survivors	Patients with adverse events
Radial strain (n = 110)	71 (89%)*	9 (11%)	19 (63%)	11 (36%)*
Circumferential strain (n = 106)	56 (84%)*	10 (15%)	31 (78%)	9 (23%)
Transverse strain (n = 108)	69 (87%)*	10 (13%)	19 (66%)	10 (34%)*
Longitudinal strain (n = 105)	54 (81%)*	12 (18%)	32 (84%)	6 (16%)
Radial and transverse strain (n = 108)	80 (88%)*	11 (12%)	8 (47%)	9 (53%) ^{#†}

*P < 0.01 vs. dyssynchrony patients with adverse events.

†P < 0.05 vs. circumferential or longitudinal strain.

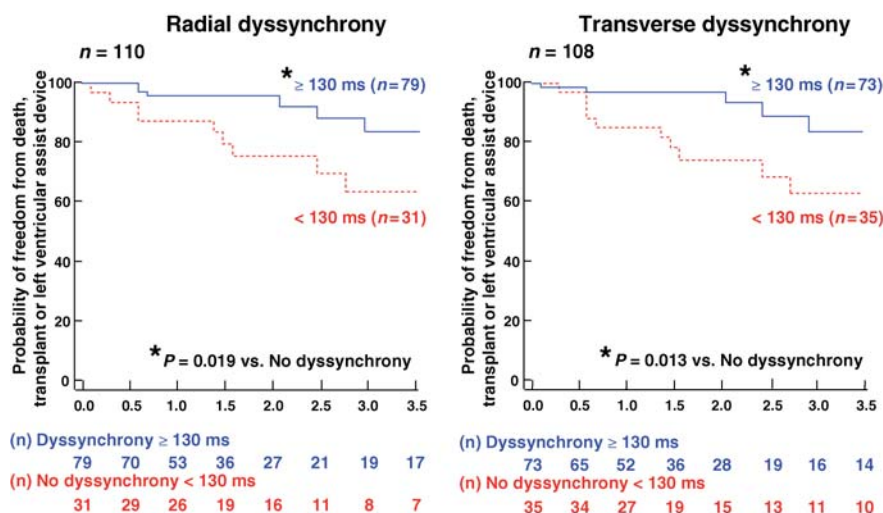


Figure 6 Kaplan–Meier curves of probability of freedom from death, transplant, or left ventricular assist device after cardiac resynchronization therapy (CRT). Baseline radial and transverse dyssynchrony ≥ 130 ms were associated with a significantly more favourable outcome.

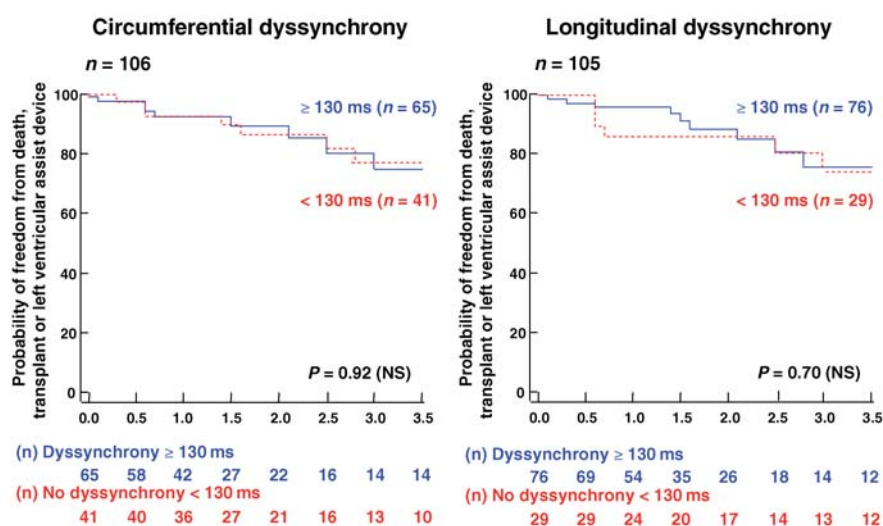


Figure 7 Kaplan–Meier curves of probability of freedom from death, transplant, or left ventricular assist device after cardiac resynchronization therapy (CRT). Neither circumferential nor longitudinal dyssynchrony was associated with outcome.

Therapy in Patients with Narrow QRS), primarily measured dyssynchrony by tissue Doppler imaging.²⁹ 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.³⁰

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

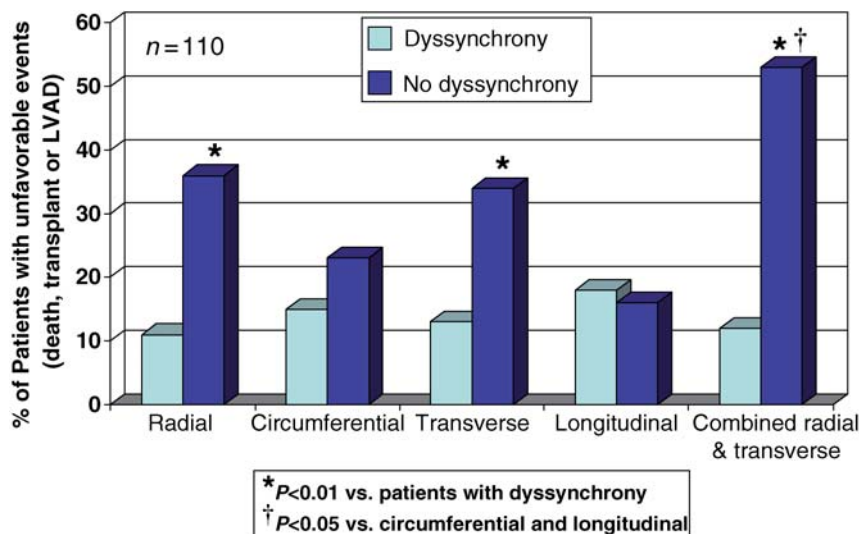


Figure 8 Bar graph of per cent of patients with serious unfavourable events of death, heart transplant, or left ventricular assist device (LVAD) after cardiac resynchronization therapy. Patients with dyssynchrony identified by all speckle-tracking strain approaches had a low adverse event rate. Patients who had dyssynchrony excluded by radial or transverse strain had a significantly higher per cent of unfavourable events, in particular when combined.

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.^{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.^{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.^{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.

Acknowledgements

The authors are grateful for the support of the entire staff of the echocardiography and electrophysiology laboratories of the University of Pittsburgh Presbyterian University Hospital, Elisabethinen

University Teaching Hospital in Linz, Austria and University of Essen, Essen, Germany. The authors thank Willem Gorissen and the Toshiba Corporation for technical support.

Funding

J.G. was supported in part by National Institutes of Health Award 2 K24 HL004503-06 from the National Institutes of Health, Bethesda, Maryland. Funding to pay the Open Access publication charges for this article was provided by the Toshiba Medical Corporation.

Conflict of interest: this study was sponsored by Toshiba Medical Corporation, which provided equipment and technical support.

References

- Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;**51**:e1–e62.
- 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.
- Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC. Long-term benefits of biventricular pacing in congestive heart failure: results from the Multisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;**40**:1111–1118.
- 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.
5. 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.
 6. 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.
 7. Gorcsan J 3rd, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. *Am J Cardiol* 2004;**93**:1178–1181.
 8. 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.
 9. Yu CM, Gorcsan J 3rd, 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.
 10. Gorcsan J 3rd, Abraham T, Agler DA, Bax JJ, Derumeaux G, Grimm RA, Martin R, Steinberg JS, Sutton MS, Yu CM. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting—a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. *J Am Soc Echocardiogr* 2008;**21**:191–213.
 11. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
 12. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;**51**:1944–1952.
 13. Gorcsan J 3rd, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, Tops LF, Schalij MJ, Bax JJ. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol* 2007;**50**:1476–1483.
 14. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;**113**:960–968.
 15. Tanaka H, Hara H, Adelstein EC, Schwartzman D, Saba S, Gorcsan J 3rd. Comparative mechanical activation mapping of right ventricular pacing to left bundle branch block by two-dimensional and three-dimensional speckle tracking and association with response to resynchronization therapy. *JACC Cardiovasc Imaging* 2010;**3**:461–471.
 16. Tanaka H, Hara H, Saba S, Gorcsan J 3rd. Prediction of response to cardiac resynchronization therapy by speckle tracking echocardiography using different software approaches. *J Am Soc Echocardiogr* 2009;**22**:677–684.
 17. Tanaka H, Hara H, Saba S, Gorcsan J 3rd. Usefulness of three-dimensional speckle tracking strain to quantify dyssynchrony and the site of latest mechanical activation. *Am J Cardiol* 2010;**105**:235–242.
 18. Tops LF, Suffoletto MS, Bleeker GB, Boersma E, van der Wall EE, Gorcsan J 3rd, Schalij MJ, Bax JJ. Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. *J Am Coll Cardiol* 2007;**50**:1180–1188.
 19. Lim P, Buakhamsri A, Popovic ZB, Greenberg NL, Patel D, Thomas JD, Grimm RA. Longitudinal strain delay index by speckle tracking imaging: a new marker of response to cardiac resynchronization therapy. *Circulation* 2008;**118**:1130–1137.
 20. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–1463.
 21. Tanabe M, Lamia B, Tanaka H, Schwartzman D, Pinsky MR, Gorcsan J 3rd. Echocardiographic speckle tracking radial strain imaging to assess ventricular dyssynchrony in a pacing model of resynchronization therapy. *J Am Soc Echocardiogr* 2008;**21**:1382–1388.
 22. Ypenburg C, van Bommel RJ, Delgado V, Mollema SA, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;**52**:1402–1409.
 23. Becker M, Kramann R, Franke A, Breithardt OA, Heussen N, Knackstedt C, Stellbrink C, Schauer P, Kelm M, Hoffmann R. Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodeling. A circumferential strain analysis based on 2D echocardiography. *Eur Heart J* 2007;**28**:1211–1220.
 24. Knebel F, Schattke S, Bondke H, Walde T, Eddicks S, Reibis R, Baumann G, Borges AC. Evaluation of longitudinal and radial two-dimensional strain imaging versus Doppler tissue echocardiography in predicting long-term response to cardiac resynchronization therapy. *J Am Soc Echocardiogr* 2007;**20**:335–341.
 25. Zwaneburg JJ, Gotte MJ, Marcus JT, Kuijper JP, Knaepen P, Heethaar RM, van Rossum AC. Propagation of onset and peak time of myocardial shortening in time of myocardial shortening in ischemic versus nonischemic cardiomyopathy: assessment by magnetic resonance imaging myocardial tagging. *J Am Coll Cardiol* 2005;**46**:2215–2222.
 26. Lardo AC, Abraham TP, Kass DA. Magnetic resonance imaging assessment of ventricular dyssynchrony: current and emerging concepts. *J Am Coll Cardiol* 2005;**46**:2223–2228.
 27. Bilchick KC, Dimaano V, Wu KC, Helm RH, Weiss RG, Lima JA, Berger RD, Tomaselli GF, Bluemke DA, Halperin HR, Abraham T, Kass DA, Lardo AC. Cardiac magnetic resonance assessment of dyssynchrony and myocardial scar predicts function class improvement following cardiac resynchronization therapy. *JACC* 2008;**1**:561–568.
 28. Helm RH, Leclercq C, Faris OP, Ozturk C, McVeigh E, Lardo AC, Kass DA. Cardiac dyssynchrony analysis using circumferential versus longitudinal strain: implications for assessing cardiac resynchronization. *Circulation* 2005;**111**:2760–2767.
 29. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**:2461–2471.
 30. Oyenu O, Hara H, Tanaka H, Kim HN, Adelstein EC, Saba S, Gorcsan J 3rd. Usefulness of echocardiographic dyssynchrony in patients with borderline QRS duration to assist with selection for cardiac resynchronization therapy. *JACC* 2010;**3**:132–140.
 31. Adelstein EC, Saba S. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. *Am Heart J* 2007;**153**:105–112.
 32. 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.
 33. Bleeker GB, Schalij MJ, Bax JJ. Importance of left ventricular lead position in cardiac resynchronization therapy. *Eur Heart J* 2007;**28**:1182–1183.
 34. 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.
 35. Yu CM, Bax JJ, Gorcsan J 3rd. Critical appraisal of methods to assess mechanical dyssynchrony. *Curr Opin Cardiol* 2009;**24**:18–28.