Novel Speckle-Tracking Radial Strain From Routine Black-and-White Echocardiographic Images to Quantify Dyssynchrony and Predict Response to Cardiac Resynchronization Therapy

Matthew S. Suffoletto, MD; Kaoru Dohi, MD; Maxime Cannesson, MD; Samir Saba, MD; John Gorcsan III, MD

Background—Mechanical dyssynchrony is a potential means to predict response to cardiac resynchronization therapy (CRT). We hypothesized that novel echocardiographic image speckle tracking can quantify dyssynchrony and predict response to CRT.

Methods and Results—Seventy-four subjects were studied: 64 heart failure patients undergoing CRT (aged 64±12 years, ejection fraction 26±6%, QRS duration 157±28 ms) and 10 normal controls. Speckle tracking applied to routine midventricular short-axis images calculated radial strain from multiple circumferential points averaged to 6 standard segments. Dyssynchrony from timing of speckle-tracking peak radial strain was correlated with tissue Doppler measures in 47 subjects (r=0.94, P<0.001; 95% CI 0.90 to 0.96). The ability of baseline speckle-tracking radial dyssynchrony (time difference in peak septal wall–to–posterior wall strain ≥130 ms) to predict response to CRT was then tested. It predicted an immediate increase in stroke volume in 48 patients studied the day after CRT with 91% sensitivity and 75% specificity. In 50 patients with long-term follow-up 8±5 months after CRT, baseline speckle-tracking radial dyssynchrony predicted a significant increase in ejection fraction with 89% sensitivity and 83% specificity. Patients in whom left ventricular lead position was concordant with the site of latest mechanical activation by speckle-tracking radial strain had an increase in ejection fraction from baseline to a greater degree (10±5%) than patients with discordant lead position (6±5%; P<0.05).

Conclusions—Speckle-tracking radial strain can quantify dyssynchrony and predict immediate and long-term response to CRT and has potential for clinical application. (Circulation. 2006;113:960-968.)

Key Words: echocardiography □ heart failure □ pacemakers

Cardiac resynchronization therapy (CRT) has made a large impact on improving symptoms and survival in heart failure (HF) patients. Randomized clinical trials have demonstrated that a significant minority of patients do not favorably respond to CRT with standard clinical selection criteria.1–4 Accordingly, quantification of left ventricular (LV) dyssynchrony by echocardiography has emerged as an important potential means to predict patient response.5–14 Several studies have suggested that measures of mechanical dyssynchrony by cardiac imaging are superior markers of response to CRT compared with ECG QRS duration.5–10 Although tissue Doppler measures have been used most often, they are limited by Doppler angle of incidence. A novel approach to quantify regional LV function from routine gray-scale 2D echocardiographic images, known as speckle tracking, calculates myocardial strain independent of angle of incidence. Accordingly, we designed this prospective study with the objective to test the following hypotheses: (1) Measures of radial dyssynchrony determined by speckle-tracking strain compare favorably with tissue Doppler strain in the same patients; (2) speckle-tracking measures of dyssynchrony can predict immediate and long-term response to CRT; and (3) patients who had LV lead tip position concordant with the site of latest mechanical activation identified by speckle-tracking radial strain had a greater degree of LV ejection fraction (EF) increase after CRT than patients with discordant LV lead position.

Methods

The study group began with 69 consecutive HF patients referred for CRT. The protocol was approved by the Institutional Review Board.
for Biomedical Research, and all patients gave informed consent consistent with this protocol. Sixty-seven patients were classified as New York Heart Association functional class III and 2 were class IV at the initial evaluation. Twenty-four were female. The group mean age was 64±12 years, EF was 26±6% (all ≥35%), and QRS duration was 157±28 ms (all >120 ms). No patients had atrial fibrillation. CRT was initiated with implantation of a biventricular pacing system (CONTAK CD H115, CD II H119, RENEWAL H135, or III H170, H175, H177, Guidant Corp; InSync ICD 7272, Marquis 7277, or InSync ICD II Marquis 7289, Medtronic). Biventricular pacing systems were implanted with LV lead placement in epicardial veins via the coronary sinus in 67 patients and in the tricuspid pacing systems were implanted with LV lead placement in 3 patients without long-term follow-up data either were included in this program, and frame rates of 30 to 90 Hz were used for routine gray-scale imaging.17,18 The speckle-tracking analysis introduced by Reinsier and Leitman was used to generate regional LV strain, as developed by Friedman and Lysyansky.17,18 Briefly, routine B-mode gray-scales images were analyzed by novel software for frame-by-frame movement of stable patterns of natural acoustic markers, or speckles, present in ultrasound tissue images over the cardiac cycle. Parasternal short-axis views at the mid-LV level were used for the present study because previous investigations have shown septal wall-to-free wall mechanical activation as a major feature of dyssynchrony.10,19,20 In addition, the speckle-tracking algorithm appeared to track more reliably in this view than longitudinal images from apical windows during our initial experience with the prototype software.

User Interface
End systole was chosen as the single frame for the endocardial to epicardial region of interest to include the maximal wall thickness for strain calculation. A circular region of interest was traced on the endocardial-cavity interface of the mid-LV short-axis view at end systole (minimum cavity area) by a point-and-click approach with special care taken to adjust tracking of all endocardial segments. On completion of this endocardial circle, a second larger concentric circle was then automatically generated that was near the epicardium, with a default width of 15 mm. The region of interest then included the entire myocardial wall, and a click feature increased or decreased the width of the 2 circles for thicker or thinner walls, respectively. The tracking algorithm followed the endocardium from this 1 frame throughout the cardiac cycle. Because LV dyssynchrony by definition involves temporal heterogeneity of wall motion, with septal inward motion usually appearing early in the cardiac cycle and free-wall motion appearing delayed, the region of interest was fine-tuned by visual assessment during the cineloop play feature to ensure that all wall regions were included throughout the cardiac cycle.

Automated Speckle Tracking
The image-processing algorithm automatically subdivided the user-defined region of interest above into blocks of approximately 20 to 40 pixels containing stable patterns of speckles.17,18,21–24 Subsequent frames were then analyzed automatically by searching for the new location of each of the blocks with correlation criteria and the sum of absolute differences (Figure 1). The location shift of these acoustic markers from frame to frame, which represents tissue movement, provides the spatial and temporal data used to calculate velocity vectors. Temporal alterations in these stable speckle patterns are identified as moving further apart or closer together, and a series of regional strain vectors are calculated as change in length/initial length. Accordingly, myocardial thickening was represented as strain with a positive value, color-coded as red, and thinning was represented as strain with a negative value, color-coded as blue, and these were then superimposed on the conventional 2D image (Figures 2 and 3; movie files available in the online Data Supplement). The software then automatically divided the short-axis image into 6 standard segments and provided an automated tracking score, similar to statistical standard deviation, as feedback of the stability of the
regional speckle tracking, ranging from 1.0 to 3.0 in arbitrary units. A tracking score value of \( \leq 2.5 \) was determined as acceptable as previously described, and slight adjustments were made to the placement of the region of interest in regions with greater SDs to attempt to improve tracking stability.\(^24\) Radial strain values from multiple circumferential points were calculated and data averaged into 6 segmental time-strain curves, as previously validated in humans.\(^24\) Time to peak strain from each of the 6 regional color-coded time-strain curves was determined with dyssynchrony defined as the difference between earliest and latest segments (Figure 3).

**Results**

**Comparison of Speckle-Tracking Strain With Tissue Doppler Strain**

Overall, speckle tracking was possible in 96% of 444 attempted segments from the 74 subjects with technically adequate images, with only 4% of segments eliminated with tracking variation scores \( > 2.5 \). Overall tracking variation scores were \( < 2.0 \) in 75%. Paired radial tissue Doppler strain and speckle-tracking radial strain studies were performed for comparison in 47 subjects: 10 normal control subjects and the first 37 HF patients in the study. The time to peak strain by speckle tracking was compared with tissue Doppler radial strain in the anterior septum and posterior wall, where there was a favorable Doppler angle of incidence. Data from the same image and anatomic region were analyzed by both methods. Respective measurements of time to peak radial strain were correlated for the anterior septum (\( r = 0.93, P < 0.001, 95\% \text{ CI } 0.88 \) to 0.96) and the posterior wall (\( r = 0.83, P < 0.001, 95\% \text{ CI } 0.71 \) to 0.90; Figure 4). Bland-Altman analysis revealed no significant bias, with a mean of 0.61 ms and \( \pm 45.7\)-ms limits of agreement. Dyssynchrony,
defined as the time difference between septal to posterior wall peak strain, by speckle-tracking strain and tissue Doppler strain were highly correlated ($r=0.94, P<0.001, 95\% CI 0.90$ to $0.97$; Figure 5). Bland-Altman analysis revealed no significant bias, with a mean of $-3.96$ ms and ±56.4-ms limits of agreement. Control subjects had minimal radial dyssynchrony ($26\pm 18$ ms), whereas CRT patients had significant dyssynchrony ($224\pm 116$ ms, $P<0.001$) with speckle tracking. A similar relationship was seen by tissue Doppler assessment of radial strain dyssynchrony in control patients with $28\pm 20$ ms versus CRT patients with $221\pm 117$ ms of measured dyssynchrony. We observed that the amplitude of strain was diminished, as expected, in regions of high-grade wall-motion abnormalities; however, time to peak strain values used for dyssynchrony analysis could still be detected in these regions. Intraobserver variability for determining speckle-tracking strain data from the identical digital cine loops used for dyssynchrony was $6\pm 6\%$, and interobserver variability was $8\pm 7\%$.

**Prediction of Immediate Response to CRT**

Baseline characteristics of patient subgroups with follow-up data appear in the Table. Acute echocardiographic hemodynamic studies were possible the day after CRT in 48 patients with favorable posterior or lateral LV lead position. Overall, small but significant increases in stroke volume (from $31\pm 16$ to $35\pm 16$ mL; $P<0.001$) and EF (from $26\pm 7\%$ to $29\pm 7\%$; $P<0.05$) were observed for the group, although individual
responses were variable. Thirty-two (67%) had an immediate response to CRT, defined as ≥15% increase in LV stroke volume. Radial dyssynchrony by speckle tracking was significantly greater in the immediate responders than in the nonresponders (261±86 vs 90±69 ms, P<0.001). Speckle-tracking radial dyssynchrony ≥130 ms predicted an immediate response with 91% sensitivity (95% CI 76% to 97%) and 75% specificity (95% CI 51% to 90%; Figure 6). Receiver operator characteristic curve analysis also determined similar sensitivity and specificity.

Figure 6. Scatterplot of the relationship between baseline radial dyssynchrony by speckle tracking and short-term response to CRT in 48 patients. A cutoff of ≥130 ms of radial dyssynchrony was predictive of short-term response (defined as ≥15% increase) in stroke volume with 91% sensitivity and 75% specificity.

**Prediction of Long-Term Improvement in EF**
Fifty patients had echocardiographic studies 8±5 months after CRT, with a minimum of 3 months’ follow-up in all to determine long-term response. Overall, significant changes in the entire CRT group were observed. LV end-systolic volume decreased from 167±73 to 139±77 mL (P<0.001), EF increased from 26±7% to 33±10% (P<0.001), and mitral regurgitation decreased by regurgitant jet area from 5.0±4.8 to 3.1±3.1 cm² (P<0.05). Individual responses, however, were variable. When biplane EF was used as the principal outcome marker for response to CRT because of its well-established prognostic value in HF patients, 26,27 38 patients (76%) were long-term responders, and 12 (24%) were nonresponders. A speckle-tracking radial strain cutoff value ≥130 ms predicted a ≥15% increase in EF with 91% sensitivity (95% CI 76% to 96%) and 83% specificity (95% CI 55% to 95%; Figure 7). Receiver operator characteristic curve analysis similarly determined 130 ms as the cutoff for optimal sensitivity and specificity.

**Determination of Site of Latest Activation**
We then tested the hypothesis that the response to CRT site may be influenced by concordance of LV lead position with the site of latest mechanical activation identified by speckle tracking. Only patients with baseline dyssynchrony could be analyzed in this way, because patients without dyssynchrony had similar segmental timing, by definition. Accordingly, the 36 patients with baseline dyssynchrony who had long-term follow-up data were included in this analysis. The latest site was lateral in 11 patients (31%), posterior in 11 (31%), posterolateral in 10 (28%), and anterolateral in 4 (11%). LV lead placement performed routinely by electrophysiologists with no knowledge of speckle-tracking or tissue Doppler data was lateral in 23 patients (64%), posterolateral in 9 (25%), posterior in 2 (6%), and anterolateral in 2 (6%). Lead placement was confirmed by fluoroscopy and posteroanterior and lateral chest x-ray projections in all patients. Although overall group mean LV EF improved, the 22 patients who had LV lead tip position concordant with the site of latest

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**Baseline Characteristics of Patients and Their Response to Resynchronization Therapy**

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Patients With Acute Studies (n=48)</th>
<th>Patients With Chronic Studies (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute Responders (n=32)</td>
<td>Acute Nonresponders (n=16)</td>
</tr>
<tr>
<td></td>
<td>Chronic Responders (n=38)</td>
<td>Chronic Nonresponders (n=12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63±10</td>
<td>68±9</td>
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<td></td>
<td>64±13</td>
<td>66±8</td>
</tr>
<tr>
<td>Gender (male/female), n</td>
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<td>11/5</td>
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<tr>
<td></td>
<td>26/12</td>
<td>10/2</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>159±25</td>
<td>155±34</td>
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<tr>
<td></td>
<td>158±27</td>
<td>155±41</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>20 (63)</td>
<td>12 (75)</td>
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<tr>
<td></td>
<td>22 (58)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>26±6</td>
<td>27±6</td>
</tr>
<tr>
<td></td>
<td>26±7</td>
<td>27±4</td>
</tr>
<tr>
<td>Radial dyssynchrony by speckle tracking, ms</td>
<td>257±89</td>
<td>102±75*</td>
</tr>
<tr>
<td></td>
<td>223±107</td>
<td>120±86*</td>
</tr>
</tbody>
</table>

*P<0.05 vs acute and chronic responders.
mechanical activation by radial strain had a greater degree of LV EF increase from baseline (10 ± 5%) than the 14 patients with discordant LV lead position (6 ± 5%; P < 0.05; Figure 8).

Additive Value of Radial Strain by Speckle Tracking

Because dysynchrony analysis by longitudinal tissue Doppler velocities has been well described,⁵⁻⁷,⁹ we sought to determine the additive value of radial strain to predict response to CRT. We found routine longitudinal velocity tissue Doppler measures of dysynchrony in the same patients using either the opposing wall method with a cutoff ≥ 65 ms or the 12-segment SD method with a cutoff of 34 ms to yield sensitivities of 89% (95% CI 76% to 96%) and specificities of 75% (95% CI 47% to 91%). When we used a combined approach of either dysynchrony by radial strain or dysynchrony by longitudinal velocities, this increased the sensitivity of detecting a favorable long-term response to CRT to 97% with a specificity of 67%. This combined approach prospectively identified nearly all patients who had significant long-term improvement in EF with CRT; however, it was at the sacrifice of some degree of specificity.

We observed either an immediate or long-term favorable response to CRT in 5 patients (10%) in whom there was significant radial dyssynchrony (≥ 130 ms) by speckle tracking but no longitudinal dyssynchrony by tissue Doppler longitudinal velocities. Four of 5 of these patients with isolated radial dyssynchrony had significant apical wall-motion abnormalities from prior infarction, which apparently diminished longitudinal shortening and masked dyssynchrony by longitudinal velocities, likely due to loss of apical rotation.²⁴ To then determine the potential additive value of speckle tracking to determine site of latest activation, we compared the previously described approach of site of latest activation using longitudinal tissue Doppler velocity data from different apical views in the same patients.²⁸ We observed that the site of latest activation was more apparent by speckle tracking, occurring at least 20 ms later than the alternate segments in 93% of patients compared with 76% of patients by longitudinal tissue Doppler velocity (P < 0.05).

Discussion

This is the first study to demonstrate that a novel speckle-tracking algorithm applied to routine gray-scale images can quantify radial LV dyssynchrony in HF patients and predict both immediate and long-term response to CRT. This extends the ability of echocardiography to quantify mechanical LV dyssynchrony noninvasively, which is emerging as potentially an important step in the selection of patients for CRT.²⁹ The addition of radial mechanical information to longitudinal...
mechanical information is a logical extension of the standard clinical echocardiographic examination in which LV function is routinely assessed by parasternal and apical views. Furthermore, radial strain may likely be complementary and potentially superior to assessment of longitudinal dyssynchrony. The timing of speckle-tracking radial strain correlated well with similar measures by tissue Doppler radial strain in anteroseptal and posterior sites to determine dyssynchrony. Because speckle-tracking strain was not dependent on Doppler angle, it was able to determine the timing of multiple other sites whose timing could not be determined by tissue Doppler. We observed sites of latest radial mechanical activation identified by speckle tracking to be associated with greater improvements in EF when LV lead position was concordant with these sites. Furthermore, speckle tracking detected radial dyssynchrony in a subset of patients with apical dysfunction who did not appear to have dyssynchrony by routine longitudinal tissue Doppler but who had a favorable response to CRT. We see the addition of radial dyssynchrony information to tissue Doppler data to be complementary to determine dyssynchrony, in particular when tissue Doppler data may be unclear or ambiguous. Accordingly, speckle-tracking radial strain may supplement, or potentially be an alternative to, the tissue Doppler approach to quantify LV dyssynchrony in patients being evaluated for CRT.

CRT has established itself as an effective treatment for HF patients with impaired ventricular function and abnormal electrical activation, improving symptoms and survival. The benefits are thought to be secondary to acute resynchronization of regional LV mechanics, decreasing mitral regurgitation, and reverse remodeling. CRT trials consistently demonstrated heterogeneous responses with a subset of nonresponders whose clinical status and LV function did not improve with CRT. Most previous studies to quantify LV dyssynchrony and predict response to CRT have focused on longitudinal velocities by tissue Doppler or radial wall motion by M-mode scanning or tissue Doppler strain. Previous tissue Doppler approaches include a method by Søgaard et al that correlated the percentage of the LV base that displayed basal longitudinal contraction delay with improvements in EF after CRT. Yu et al used time to peak longitudinal systolic velocities from 12 sites to quantify LV dyssynchrony, demonstrating that an increased SD was predictive of clinical response to CRT. Notabartolo et al also used differences in peak tissue Doppler velocities from opposing walls to quantify LV dyssynchrony and predict response to CRT. Our past work with tissue synchronization imaging, which automatically color-codes temporal motion information, defined an opposing wall delay of ≥65 ms as a predictor of immediate response to CRT. Subsequent studies found that a similar longitudinal time to peak velocity delay predicted reverse remodeling and clinical outcomes. Although these approaches are useful, they may have limitations in patients with infarction or complex dyssynchrony. Strain imaging provides an approach to assess myocardial thickening in a manner less affected by passive translational motion or tethering, which makes strain an attractive modality to assess regional myocardial dyssynchrony. MRI studies have recently demonstrated that circumferential myocardial dynamics may characterize LV dyssynchrony in a more sensitive manner than longitudinal dyssynchrony and support our current approach to radial dyssynchrony. The present report highlights the role that radial mechanics may play and their potential additive value in the overall assessment of LV dyssynchrony to achieve a higher sensitivity. The recent work by Notomi et al and others demonstrate that apical rotation is an important component of longitudinal shortening. Our ability to detect radial dyssynchrony in a subgroup of patients with apical infarcts who did not have longitudinal dyssynchrony but responded to CRT suggests the potential additive value of radial assessment. Because we have a small sample of patients with this scenario, further investigation is warranted to confidently elucidate the precise mechanism.

The echocardiographic speckle-tracking method of Friedman and Lysyansky used in the present study is not affected by angle of incidence, as tissue Doppler imaging techniques are. The acoustic markers, or speckles, used for these measurements are the result of backscattered ultrasound from neighboring structures within the myocardial wall, which generate a unique pattern that can be tracked frame by frame to produce a 2D map of myocardial motion and deformation. Kaluzynski and colleagues initially demonstrated how speckle tracking could generate regional strain maps from ultrasound images of a phantom model. D’hooge et al then applied this method to an in vivo beating human heart, producing good agreement to 1D M-mode strain techniques. Reisner et al used strain by speckle tracking to calculate global strain in myocardial infarction patients to show a close correlation to wall-motion score index, and Leitman et al used a regional speckle-tracking strain measurements to differentiate infarct from normal myocardial segments. Most recently, Notomi et al used speckle tracking to measure angular mechanics, or torsion, in short-axis views and validated these measures by tagged MRI.

Previous investigators have inferred that LV lead position impacts patient response to CRT. Ansalone et al demonstrated that LV lead placement at the most delayed segment resulted in the greatest immediate improvements from CRT. They also showed that the LV segment with the greatest delay in activation was most commonly the posterior or lateral wall. Although Gasparini et al demonstrated significant improvements in LV function and symptoms after CRT regardless of LV lead site, the preponderance of available data support the importance of proper LV lead position to optimize clinical outcomes. The present study demonstrates the feasibility of speckle tracking to detect the site of latest radial mechanical activation and has a potential advantage over longitudinal velocities because it may be done in a single image that follows the plane of the coronary sinus into which the LV coronary vein leads are placed.

Study Limitations
A technical limitation is that speckle-tracking echocardiography is dependent on frame rates, as well as image resolution. Low frame rates result in the speckle pattern changing too much from frame to frame, which prevents the precise characterization of regional myocardial motion and impacts
the overall temporal resolution of the regional strain map. In contrast, increasing the frame rate reduces scan-line density, which reduces image resolution.17,18,21 The optimal frame rate for precise detection of myocardial motion in routine clinical use has not yet been determined; however, we found that a minimum frame rate of 30 Hz was required for the speckle-tracking algorithm to calculate strain and that the algorithm did not perform well with frame rates >100 Hz. Accordingly, we found frame rates in the range of 30 to 90 Hz with a mean of 65 Hz suitable for speckle-tracking analysis. Another limitation of speckle tracking is the user interface required for endocardial border tracing. Care must be taken to manually fine-tune the region of interest to capture the early anterior septal motion in left bundle-branch block for dysynchrony analysis before generating and measuring regional strain.

However, the remaining steps were automated and highly reproducible, and further variations of speckle tracking are being developed.28 Another limitation is that long-term clinical outcome data, such as exercise capacity or quality-of-life assessment, were not part of the present study. We chose to use improvement in EF as the marker for patient response in this initial study because it is an objective measure with significant prognostic importance.26,27 Several previous studies have used similar echocardiographic measures as an appropriate initial step, with more detailed clinical follow-up studies subsequently.5–14 Prospective testing of this approach with clinical outcome markers is warranted in a larger patient series.

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Disclosure

GE Medical Systems donated the software and technical support for this study.

References

Clinical Perspective

Quantification of mechanical dyssynchrony by cardiac imaging is emerging as a potential means to predict response to cardiac resynchronization therapy (CRT). Although tissue Doppler is currently used most frequently, a new approach using speckle-tracking software applied to routine black-and-white echocardiographic images was used to calculate strain. Radial dynamics were assessed from short-axis views, which may complement longitudinal dynamics by tissue Doppler from apical views. In 64 heart failure patients studied, a baseline septal wall-to-posterior wall delay in peak radial strain >130 ms predicted an immediate increase in stroke volume in response to CRT with 91% sensitivity and 75% specificity and a long-term improvement in ejection fraction (8±5 months later) with 89% sensitivity and 83% specificity in respective subsets of patients. Left ventricular lead position concordant with the site of latest mechanical activation by radial strain was associated with a greater increase in ejection fraction (10±5%) than in patients with discordant lead position (6±5%; P<0.05). A subset of patients (10%) with a favorable response to CRT had radial dyssynchrony but lacked longitudinal dyssynchrony by tissue Doppler, in which prior apical infarction may diminish longitudinal shortening velocities and apparently mask dyssynchrony. The clinical role that speckle-tracking radial strain will play in the assessment of patients before CRT is yet to be determined. These data support the predictive value of mechanical dyssynchrony by cardiac imaging and suggest that speckle tracking may supplement or potentially be an alternative to M-mode or tissue Doppler approaches.
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