Speckle-tracking strain echocardiography for detecting cardiac dyssynchrony in a canine model of dyssynchrony and heart failure

Takeshi Arita,1 George P. Sorescu,1,3 Brian T. Schuler,1 Laura S. Schmarkey,3 John D. Merlino,1,3 Jakob Vinten-Johansen,2,3 Angel R. Leon,1,3 Randolph P. Martin,1 and Dan Sorescu1
1Division of Cardiology, Department of Medicine, 2Division of Cardiothoracic Surgery, Department of Surgery, and 3Carlyle Fraser Heart Center, Emory University School of Medicine, Emory University, Atlanta, Georgia

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CARDIAC RESYNCHRONIZATION therapy (CRT) improves clinical status and promotes reverse remodeling in patients with advanced heart failure (5). CRT corrects the mechanical dyssynchrony that worsens systolic (18, 21) and diastolic dysfunction (19, 29) and creates functional mitral regurgitation (11). However, those same clinical trial results suggest that 30–35% of patients with systolic dysfunction and ventricular conduction delay with QRS exceeding 120 ms fail to respond to CRT. Absence of dyssynchrony in the presence of wide QRS may explain the observed failure to respond. Conversely, detecting dyssynchrony independent of QRS duration may identify other potential responders. Therefore, optimizing patient selection for CRT depends on accurate detection of cardiac dyssynchrony. Methods to detect mechanical dyssynchrony include magnetic resonance imaging (26), radionuclear scintigraphy (12), invasive conductance catheter recordings (23), and echocardiography. Preliminary clinical studies suggest echocardiography with tissue Doppler imaging (TDI) as an effective and practical modality to assess mechanical dyssynchrony by analyzing time to peak systolic velocity (TPV) (4, 6, 22, 28). However, the physical properties of Doppler imaging limit assessment of motion and deformation to the longitudinal axis lying parallel to the transducer, whereas ventricular motion occurs in three dimensions.

Recent developments in speckle tracking (13) allow assessment of radial and circumferential strain on B-mode echocardiography similar to tagged magnetic resonance imaging (1, 7). Whether conventional echocardiography, TDI, or novel speckle tracking accurately detect mechanical dyssynchrony remains undetermined; the various clinically utilized echocardiography-Doppler techniques have not undergone extensive testing in an experimental model of dyssynchrony. The present study tests the accuracy of detecting dyssynchrony of multiple echocardiography parameters in an experimental canine model of dyssynchrony with or without heart failure, with specific attention to a comparison between novel speckle tracking-derived radial and circumferential strain and widely adopted TDI-derived longitudinal velocity methods.

METHODS

Animal Models

The experimental procedures complied with Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication No. 85-23, revised 1996) and were approved by The Institutional Animal Care and Use Committee of Emory University. (Supplemental data for this article is available online at The American Journal of Physiology-Heart and Circulatory Physiology website).

Adult mongrel dogs underwent atrioventricular junction ablation followed by implantation of a dual-chamber pacing system. Atrioventricular pacing (atrioventricular interval of 150 ms) at 110 bpm induced dyssynchrony and wide QRS without heart failure (D group, n = 12), and right-ventricular (RV) pacing at 170 bpm induced dyssynchrony and wide QRS with heart failure (DHF group, n = 9). A third group underwent implantation of a dual-chamber pacing system without junctional ablation and received atrial pacing at 190 bpm for 4 wk to induce heart failure with narrow QRS (HF group, n = 8). Intracardiac recordings confirmed the absence of intrinsic atrioventricular conduction in the animals that underwent junctional ablation. We measured QRS duration on surface lead II.
Echocardiography

We performed tissue Doppler and two-dimensional echocardiography (Vivid 7; General Electric, Vingmed, Norway) at baseline and 4 wk after pacing with animals under general anesthesia (closed chest). All the echocardiographic images were obtained at intrinsic normal sinus rhythm both at baseline and 4 wk later. One cardiologist (D. Sorescu) obtained the images, and a second investigator (T. Arita) analyzed them offline. We derived the ventricular volumes and ejection fractions by using the Simpson biplane method. Color-coded tissue Doppler images were obtained on apical two-, three-, and four-chamber views with a frame exceeding 150 frames/s (see supplemental video online). Pulse-wave tissue Doppler images were obtained on apical two-, three-, and four-chamber views. We excluded the foreshortened apical image view for measurement. TDI involved sampling a region of interest in the basal six and mid-six segments. The speckle-tracking analysis used two-dimensional images obtained in the mid-level short axis with a frame rate of 70–110 frames/s. We generated the mid-level short-axis images at the level of both papillary muscles perpendicular to the long axis of the ventricle. We recorded and stored at least three clips of three to five consecutive cardiac cycles of each apical and short-axis image for offline digital analysis. All the measured parameters except speckle-tracking analysis were calculated as the average of three consecutive beats.

Assessment of Dyssynchrony

Color-coded tissue Doppler image. We measured longitudinal dyssynchrony as the standard deviation (SD) of time from onset of QRS to peak systolic velocity (TPVs) within the ejection phase across 12 (6 basal and 6 mid) segments according to a previously described method (28) (Fig. 1A).

Pulse-wave tissue Doppler image. We also used an alternative method to assess longitudinal dyssynchrony by calculating the SD of time from onset of QRS to peak S wave (pkS) by using pulse-wave TDI in the 12 segments (6) (Fig. 1B).

M mode. We defined the septal-to-posterior wall motion delay (SPWMD) as the time difference between the peak inward excursions of the interventricular septum and left posterior wall on M-mode images obtained from the mid-level short-axis view (17) (Fig. 1C).

Speckle tracking of short-axis B-mode image. Analysis of mid-level short-axis images used dedicated software (EchoPac PC, BT05.0.1; General Electric) to determine radial and circumferential dyssynchrony (Fig. 1, D and E). After tracing the endocardial border at the

Fig. 1. A: color-coded tissue Doppler imaging (TDI). Time from onset of QRS to peak systolic velocity (TPVs) was measured (apical 4-chamber view). B: pulse-wave TDI. AVO, aortic valve opening; AVC, aortic valve closure. Time to peak S wave (pkS) was measured. C: septal-to-posterior wall motion delay (SPWMD) obtained as timing difference between most inward excursion point of interventricular septum and posterior wall in M mode. D: radial strain curve by speckle-tracking analysis. Time to peak radial strain (Er) was obtained from 2-dimensional image of short axis. Top shows radial strain waveform obtained from control animal (at baseline), and bottom shows radial strain waveform obtained from an animal with dyssynchrony and heart failure. E: circumferential strain curve by speckle-tracking analysis. Time to peak circumferential strain (Ec) was obtained from 2-dimensional image of short axis. Top shows circumferential strain waveform obtained from control animal (at baseline), and bottom shows circumferential strain waveform obtained from an animal with dyssynchrony and heart failure.
end systole, we set the region of interest from the endocardium to the epicardial edge. Automatic speckle tracking analyzed each short-axis image to track motion of speckles contained within the region of interest on a frame-to-frame basis. The software automatically computed distances between adjacent speckles to obtain the radial and circumferential strain curves as a function of time. Assessing radial and circumferential dyssynchrony involved exporting the strain data for automatic processing on a customized program (Matlab; MathWorks, Natick, MA) to calculate the SD of time from onset of QRS to peak radial and circumferential strain ($E_{rr}$ and $E_{cc}$, respectively) across the six mid-level segments.

Reproducibility of Echocardiographic Analysis

We used the Bland-Altman method and standard error of the mean to assess inter- and intraobserver variability.

Intraobserver variability. Bland-Altman analysis computed the limits of agreement for TPVs ($5.2$ ± $12.9$ ms), pkS ($-4.3$ ± $14.4$ ms), SPWMD ($-2.6$ ± $28.9$ ms), $E_{rr}$ ($-1.4$ ± $15.8$ ms), and $E_{cc}$ ($11.6$ ± $76.4$ ms). The variability for each parameter measured $7.0$, $6.8$, $14.4$, $2.3$, and $10.4\%$, respectively.

Interobserver variability. To determine the interobserver variability, two independent observers (T. Arita and G. P. Sorescu) performed independent analysis of the same echocardiographic images. Average differences were as follows: TPVs, $-1.3$ ± $19.4$ ms; pkS, $0.25$ ± $24.5$ ms; $E_{rr}$, $-6.2$ ± $33.4$ ms; and $E_{cc}$, $-4.7$ ± $81.0$ ms. The variability for each parameter measured $9.8$, $7.9$, $17.3$, $6.3$, and 15.4%, respectively.

Statistical Analysis

All data appear as means ± SD. For statistical analysis, we used the Wilcoxon t-test or Mann-Whitney U-test to analyze differences in the means. Receiver-operating curve (ROC) analysis was performed to obtain the cutoff point for determining intraventricular mechanical dyssynchrony with or without heart failure. Area under the curve (AUC) was computed for each significant parameter. In ROC analysis, the DHF and D groups served as separate positive controls, with the combined baseline group serving as a negative control. The relationship between dyssynchrony parameters and basic echocardiographic parameters was analyzed by using linear regression and is expressed as a Pearson’s correlation coefficient followed by stepwise multivariate regression analysis. Statistical analysis was performed with commercial software (SPSS 13.0; SPSS, Chicago, IL). We defined the two-sided $P$ value of $<0.05$ as statistically significant.

RESULTS

Baseline Characteristics

Figure 2 and Table 1 contain the results of the ablation and pacing intervention in the three groups of animals. RV pacing after His-bundle ablation increased the QRS duration from $91.2$ ± $12.9$ to $166.7$ ± $14.6$ ms but did not affect ejection fraction (D group). Rapid atrial pacing caused systolic dysfunction (left-ventricular ejection fraction reduced from $58.7$ ± $6.0$ to $22.2$ ± $4.7\%$) but produced no significant change in QRS duration (HF group). Rapid RV pacing and His-bundle ablation worsened left-ventricular ejection fraction (58.4 ± 9.4 to $21.4$ ± $7.6\%$) and prolonged QRS duration ($93.7$ ± $6.0$ to $166.1$ ± $17.5$ ms ) to produce dyssynchrony and heart failure (group DHF).

Echocardiographic Parameters of Dyssynchrony

Color-coded and pulse-wave tissue Doppler analysis of longitudinal dyssynchrony. Functional ablation or rapid pacing alone did not change the color-coded tissue Doppler-derived TPVs in the D and HF groups. The combination of ablation and rapid RV pacing increased TPVs in the DHF group (Table 2 and Fig. 3A). Rapid atrial pacing-induced heart failure (HF with narrow QRS) and the ablation/rapid RV pacing combina-
tion (DHF, heart failure with wide QRS) increased the pulse-wave tissue Doppler-derived pkS; dyssynchrony alone (D group) did not affect the pkS (Table 2 and Fig. 3B). Applying multiple published color-coded and pulse-wave tissue Doppler methods found no statistical significant difference in time to peak longitudinal velocity in the D group; ablation and rapid RV pacing (DHF group) did affect some parameters (see Supplemental Table 1 online).

M mode measurement of dyssynchrony. The M mode-derived SPWMD did not change as a result of either dyssynchrony or heart failure alone but did increase with the combination of dyssynchrony and heart failure (Table 2 and Fig. 3C).

Radial and circumferential strain analysis from short axis. The Er, increased significantly in all three groups (Table 2 and Fig. 3D). The DHF group demonstrated the greatest change in the Er, (greater than fivefold increase in mean SD; P < 0.001), with less change in the HF and D groups [twofold (P = 0.019) and greater than threefold (P = 0.018) increase over baseline, respectively]. The DHF group showed significantly greater Er, than the D and HF groups (both P < 0.001). The results suggest that Er, detects dyssynchrony irrespective of heart failure and may also reflect the degree of dyssynchrony.

The circumferential short-axis strain increased in all three groups (Table 2 and Fig. 3E). Circumferential dyssynchrony increased in the D and DHF groups (P = 0.03 and P < 0.001, respectively). However, the lack of difference in the changes detected in the HF and DHF groups (P = 0.20) suggests that, compared with radial strain analysis, circumferential strain analysis has sensitivity but lacks specificity in detecting dyssynchrony.

**ROCs for Echocardiographic Parameters of Dyssynchrony**

Using the D group as the positive control for dyssynchrony shows that Er (AUC = 0.819) and Echo (AUC = 0.874) effectively detect dyssynchrony without heart failure (Table 3). Using the DHF group as the positive control shows that radial and circumferential dyssynchrony detect dyssynchrony in heart failure better (AUC = 1) than tissue Doppler- and M-mode-derived parameters (Table 4). Tissue Doppler and M-mode parameters appear insensitive, whereas radial and circumferential dyssynchrony appear more sensitive and specific for detecting dyssynchrony independent of QRS duration. All parameters detect dyssynchrony with adequate sensitivity and specificity in heart failure associated with prolonged QRS, but radial dyssynchrony had the best overall sensitivity and specificity.

**Detecting Dyssynchrony in Heart Failure with Narrow QRS**

 Adopting cutoff values from the ROC analysis (using DHF as positive control) yields the following results. With cutoff point for Er, > 63.94 ms, 37.5% (3 of 8) of heart failure animals demonstrated radial dyssynchrony; with a cutoff value for Echo > 107.69 ms, 50% (4 of 8) showed circumferential dyssynchrony, but results were less specific.

**Relationship Between Echocardiographic Dyssynchrony Parameters and Global Cardiac Function**

The longitudinal dyssynchrony parameters (i.e., TPV and pkS) correlated with ejection fraction, end-diastolic volume,
and end-systolic volume but not with QRS duration during univariate analysis. The radial strain-derived dyssynchrony parameter correlated with ejection fraction, end-diastolic volume, end-systolic volume, and QRS. The circumferential strain-derived dyssynchrony parameter and SPWMD correlated with ejection fraction, end-systolic volume, and QRS but not end-diastolic volume (Table 5). Multivariate analysis showed that TPVs and pkS independently correlated with ejection fraction (P < 0.001) but not with QRS duration. In contrast, SPWMD and Err correlated both with ejection fraction and QRS duration (P < 0.01) and Ecc correlated with ejection fraction, end-diastolic volume, and QRS duration (P < 0.01; Table 6).

**DISCUSSION**

**Differences among Various Parameters to Assess Dyssynchrony**

Preliminary clinical reports demonstrate the value of echocardiography for assessing cardiac dyssynchrony and predict-

![SD of time to peak systolic velocity](image1)

![SD of time to PW peak S wave](image2)

![SPWMD](image3)

![SD of time to peak radial strain](image4)

![SD of time to peak circumferential strain](image5)

Table 2. Dyssynchrony parameter analysis by echocardiography

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<table>
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<th>HF</th>
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<th>DHF</th>
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<td>TPVs, ms</td>
<td>17.7±5.2</td>
<td>22.4±10.9</td>
<td>24.9±11.5</td>
<td>35.5±8.3†</td>
<td>21.8±5.4</td>
<td>42.0±13.4‡</td>
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<td>pkS, ms</td>
<td>16.2±10.3</td>
<td>21.8±9.2</td>
<td>19.7±11.6</td>
<td>36.3±10.2‡</td>
<td>19.3±4.7</td>
<td>35.4±10.1‡</td>
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<td>SPWMD, ms</td>
<td>74.4±34.0</td>
<td>139.2±110.2</td>
<td>85.5±37.8</td>
<td>127.8±122.7</td>
<td>75.4±40.8</td>
<td>253.2±118.7‡</td>
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<td>Eerr, ms</td>
<td>16.6±12.0</td>
<td>53.1±32.2*</td>
<td>24.5±22.5</td>
<td>52.0±26.6*</td>
<td>27.3±16.5</td>
<td>137.5±39.7‡</td>
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<tr>
<td>Ecc, ms</td>
<td>48.9±23.0</td>
<td>95.9±40.7*</td>
<td>60.1±35.7</td>
<td>116.4±40.3*</td>
<td>31.8±26.0</td>
<td>139.0±22.7‡</td>
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</tbody>
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Values are means ± SD. TPVs, time to peak systolic volume; pkS, time to peak S wave; SPWMD, septal-to-posterior wall motion delay; Eerr, time to peak radial strain; Ecc, time to peak circumferential strain. *P < 0.05 vs. pre; †P < 0.05 HF or DHF vs. D; ‡P < 0.05 DHF vs. HF.

Fig. 3. Parameters of dysynchrony by echocardiography for each group. A: standard deviation of (SD) of TPV, by color-coded TDI. B: SD of pkS by pulse-wave (PW) TDI. C: SPWMD on M-mode tracings. D: SD of Eerr by speckle-tracking analysis of B-mode mid-short axis image. E: SD of Ecc by speckle-tracking analysis of B-mode mid-short axis image (*P < 0.05, post vs. pre).
Table 3. Receiver-operator curve analysis using D group as control

<table>
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<tr>
<th>Variables</th>
<th>AUC</th>
<th>P Value</th>
<th>95% CI</th>
<th>Cutoff, ms</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>TPV,</td>
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<td>0.886</td>
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</tr>
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<td>pkS</td>
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<td>0.477</td>
<td>0.375–0.776</td>
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<td>SPWMD</td>
<td>0.690</td>
<td>0.069</td>
<td>0.511–0.869</td>
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<tr>
<td>$E_\text{cc}$</td>
<td>0.874</td>
<td>0.001</td>
<td>0.755–0.993</td>
<td>43.8</td>
<td>100</td>
<td>59.3</td>
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</table>

AUC, area under the curve; CI, confidence interval.

resolution compared with color-coded TDI (16). The multivariate regression analysis demonstrated that both color-coded and pulse-wave tissue Doppler indices correlated better with ejection fraction (systolic dysfunction) and less with QRSD duration. Yu et al. (27) reported that TPV correlated with left-ventricular end-systolic volume in heart failure patients with narrow and wide QRSD duration during multivariate regression analysis. Their results and ours suggest that global ventricular size and function, and not the timing of the altered sequence of contraction, affect longitudinal velocity.

The SPWMD has also been proposed to quantitatively assesses dyssynchrony in patients with heart failure (17). Because the acquisition measures the timing of excursion points, the angle of acquisition and translation can affect the measurement and distort displacement. Factors that independently affect septal movement such as RV pressure overload or prior cardiac surgery could impact radial septal motion and decrease the reliability of this measurement for the detection of dysynchrony. Also, although relatively easy to obtain, the low reproducibility of the SPWMD, as shown in our study and also by Marcus et al. (15), limits its value in clinical use.

Radial or Circumferential Strain from Speckle-Tracking Analysis

Speckle-tracking analysis provides angle-independent information on motion and deformation in any direction of a cardiac coordinate system. Several studies demonstrated its validity against sonomicrometry (1) and tagged MRI (7). Speckle-tracking echocardiography offers higher temporal resolution than MRI, making it suitable for assessing the timing of cardiac motion. Speckle tracking offers easier access, costs less, and consumes less time compared with tagged MRI. In our study, the processing and analysis of echocardiographic data was automatically performed by the software and was therefore independent of the operator. The limitations of speckle tracking include its dependence on the angle of acquisition in the short axis. In the present study, this limitation had greater impact on the measurement of circumferential (especially posterior wall) rather than radial strain, and this might explain the observed large variability in circumferential strain determination even in the presumably normal ventricles (baseline dog). With less variability and similar accuracy in detecting dysynchrony, the radial strain derived from short-axis views was superior to circumferential strain. Our observations agree with Suffoletto et al. (24), who reported that speckle tracking-derived radial dysynchrony has high sensitivity and specificity in predicting response in CRT in humans. That analysis used the difference in $E_\text{cc}$ between two segments (anteroseptal and posterior wall) to measure dysynchrony. We used the SD in $E_\text{cc}$ across six segments in the mid-short axis view to achieve

Table 4. Receiver-operator curve analysis using DHF as control

<table>
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<tr>
<th>Variables</th>
<th>AUC</th>
<th>P Value</th>
<th>95% CI</th>
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<th>Sensitivity</th>
<th>Specificity</th>
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<td>pkS</td>
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<td>SPWMD</td>
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<td>0.001</td>
<td>0.685–1.068</td>
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<td>$E_\text{rr}$</td>
<td>1.000</td>
<td>&lt;0.001</td>
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<td>$E_\text{cc}$</td>
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<td>107.69</td>
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greater accuracy. We observed that the difference in $E_s$ between the anteroseptal and posterior wall segments increased in the D group ($P = 0.047$, AUC = 0.776) and also in DHF ($P = 0.0019$, AUC = 0.977). However, differences were lower than those calculated using the SD in the six-segment model (Tables 3 and 4).

**Mechanical Dyssynchrony with Narrow QRS**

The atrial pacing cardiomyopathy model in this study produced a valid representation of heart failure with normal QRS duration (fast atrial pacing with normal atrioventricular node conduction). In our study, 30% of the animals in the HF group displayed radial or circumferential dyssynchrony according to the criteria derived from analysis of the DHF group. However, although this method is very sensitive to detect mechanical dyssynchrony per se, it does not identify the threshold value, which defines the response to cardiac resynchronization therapy in subjects with heart failure and normal QRS. Whether echocardiography and TDI can detect dyssynchrony accurately enough to predict CRT response remains to be determined, and further studies are required to test this notion. Our results suggest that longitudinal velocity-derived parameters do not detect dyssynchrony well; therefore, the role of these methods in expanded clinical application of CRT in the narrow QRS population remains unproven.

Finally, our data suggest that systolic dysfunction may beget intraventricular mechanical dyssynchrony. Severe systolic dysfunction caused radial dyssynchrony of similar magnitude to that observed in D group, and this was further enhanced in DHF group. The pattern of mechanical dyssynchrony caused by systolic dysfunction likely differs from that associated with echocardiogram-defined dyssynchrony (such as in left bundle branch block) (9). Whether CRT corrects heart failure-related dyssynchrony with normal QRS duration as effectively as it improves dyssynchrony in heart failure associated with left bundle branch block needs further testing in prospective human clinical studies.

**Limitations of Our Study**

The current study suggests that speckle tracking-derived strain analysis is more sensitive and specific than velocity-based echocardiographic methods to detect cardiac dyssynchrony in a canine model of cardiomyopathy with dyssynchrony. The purpose of our study was to generate a relative homogenous model of dyssynchrony (electrical dyssynchrony with left-ventricular systolic dysfunction) so we could compare various echocardiographic methods that have been proposed in the human studies to detect dyssynchrony. Therefore, to induce dyssynchrony we chose a model of RV pacing with nonischemic cardiomyopathy. Obviously, our current results cannot be automatically extrapolated to all various subgroups of cardiac dyssynchrony encountered in human heart failure (for example, ischemic cardiomyopathy).

One limitation of this model is that we were unable to analyze speckle tracking-derived longitudinal strain because the quality of our echocardiographic images from apical views in dogs was inadequate to perform this analysis. In humans, with current technology this can be performed reliably and reproducibly. Furthermore, the specific cutoffs for various dyssynchrony parameters need to be validated against response to cardiac resynchronization therapy in humans. Nonetheless, our study suggests that speckle-tracking strain analysis is superior to longitudinal velocity data and provides the scientific basis to design further studies in which radial, circumferential, or longitudinal strain are compared with longitudinal velocity to test response from cardiac resynchronization therapy, especially in patients with narrow QRS and heart failure.

**Conclusion**

We demonstrated that radial and circumferential strains derived by speckle tracking in short-axis images accurately identify mechanical dyssynchrony in the presence or absence of left-ventricular dysfunction. The majority of the animals with heart failure and narrow QRS showed mechanical dyssynchrony during speckle-tracking analysis. Prospective ran-

### Table 5. Univariate analysis for relationship between dyssynchrony parameters and basic characteristics

<table>
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<tr>
<th></th>
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<th>pkS</th>
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<td>$P$</td>
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### Table 6. Multivariate stepwise regression analysis for relationship between dyssynchrony parameters and basic characteristics

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domized clinical studies will need to determine whether speckle tracking radial or circumferential strain detects dys-synchrony in humans with heart failure accurately enough to identify appropriate candidates for CRT.

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REFERENCES


