Differential effects of left ventricular pacing sites in an acute canine model of contraction dyssynchrony

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Johnson L, Kim HK, Tanabe M, Gorcsan J, Schwartzman D, Shroff SG, Pinsky MR. Differential effects of left ventricular pacing sites in an acute canine model of contraction dyssynchrony. Am J Physiol Heart Circ Physiol 293: H3046–H3055, 2007. First published September 14, 2007; doi:10.1152/ajpheart.00728.2007.—The goal of the present study was to assess the effects of left ventricular (LV) pacing sites (apex vs. free wall) on radial synchrony and global LV performance in a canine model of contraction dyssynchrony. Ultrasound tissue Doppler imaging and hemodynamic (LV pressure-volume) data were collected in seven anesthetized, opened-chest dogs. Right atrial (RA) pacing served as the control, and contraction dyssynchrony was created by simultaneous RA and right ventricular (RV) pacing to induce a left bundle-branch block-like contraction pattern. Cardiac resynchronization therapy (CRT) was implemented by adding simultaneous LV pacing to the RV pacing mode at either the LV apex (CRTa) or free wall (CRTf). A new index of synchrony was developed via pair-wise cross-correlation analysis of tissue Doppler radial strain from six midmyocardial cross-sectional regions, with a value of 15 indicating perfect synchrony. Compared with RA pacing, RV pacing significantly decreased radial synchrony (11.1 ± 0.8 vs. 4.8 ± 1.2, P < 0.01) and global LV performance (cardiac output: 2.0 ± 0.3 vs. 1.4 ± 0.1 l/min and stroke work: 137 ± 22 vs. 60 ± 14 mJ, P < 0.05). Although both CRTa and CRTf significantly improved radial synchrony, only CRTa markedly improved global function (cardiac output: 2.1 ± 0.2 l/min and stroke work: 113 ± 13 mJ, P < 0.01 vs. RV pacing). Furthermore, CRTa decreased LV end-systolic volume compared with RV pacing without any change in LV end-systolic pressure, indicating an augmented global LV contractile state. Thus, LV apical pacing appears to be a superior pacing site in the context of CRT. The dissociation between changes in synchrony and global LV performance with CRTf suggests that regional analysis from a single plane may not be sufficient to adequately characterize contraction synchrony.

cardiac resynchronization therapy; left ventricular global performance; myocardial strain; tissue Doppler imaging

EFFECTIVE MYOCARDIAL CONTRACTION requires not only shortening of contractile myocardial elements but also the synchronization of contraction across elements. Myocardial contraction dyssynchrony can occur from structural changes to the His-Purkinje system, functional changes in regional myocardial contractility, or both (32). Alterations in the His-Purkinje system include left bundle-branch block (LBBB) or other intraventricular conduction defects, manifested as nonspecific widening of the QRS (12, 32). Functional abnormalities of the myocardium include myocardial ischemia, stunning, hibernation, and infarction. Contraction dyssynchrony is the most common form of myocardial contraction dysfunction and can be characterized as regional wall motion abnormalities (5, 13, 18, 19, 22, 33, 40). Dyssynchronous myocardial contraction decreases mechanical efficiency by a variety of mechanisms, including having regional segments reach their maximal shortening at different times and dysfunction of the mitral valve apparatus leading to incompetence through dyssynchronous papillary muscle contraction.

Cardiac resynchronization therapy (CRT) is used to minimize left ventricular (LV) contractile dyssynchrony. In CRT, selective ventricular multisite pacing is used to optimize LV mechanical function. The clinical efficacy of CRT is generally quantified in terms of its effects on LV systolic function and other hemodynamic indexes, such as LV ejection fraction, stroke volume (SV), stroke work (SW), maximum rate of LV pressure increase (dP/dt max), and aortic pulse pressure (11, 17, 35–37). Several clinical trials have documented that CRT improves functional status and survival (1–3, 6–8, 26, 41), but 20–30% of patients do not benefit from this therapy (4). Several factors may contribute to this variability in CRT benefit: limited knowledge regarding the mechanisms underlying the beneficial effects of CRT, lack of robust algorithms for identifying the optimal pacing site(s) that maximizes LV ejection effectiveness and/or minimizes contraction dyssynchrony, and limited choices of pacing sites available in the clinical setting.

A variety of echocardiographic techniques are currently used to quantify dyssynchrony, including M-mode, two-dimensional echocardiography, and tissue Doppler (TD) imaging (TDI). Although several studies have focused on deriving an algorithm to assess contraction dyssynchrony (9, 31, 39, 43), an ideal standard is yet to be developed, particularly from the perspective of robustness and ease of use. In addition, there is no general agreement regarding the optimal pacing site(s) for CRT.

The primary goal of the present study was to assess the effects of LV pacing sites (apex vs. free wall) on restoration of radial contraction synchrony and global LV performance in a canine model of contraction dyssynchrony. We also report a new robust algorithm to quantify radial synchrony.

MATERIALS AND METHODS

Preparation

The protocol was approved by the Institutional Animal Care and Use Committee and conformed to the position of the American...
Physiological Society on research animal use. Seven mongrel dogs, weighing 21.0 ± 1.5 kg, were studied after an overnight fast. All dogs were anesthetized with pentobarbital sodium (30 mg/kg induction and 1.0 mg·kg\(^{-1}\)·h\(^{-1}\) with intermittent boluses, as needed) and their tracheas were intubated (8-Fr Portex endotracheal tube) and mechanically ventilated (Harvard dual-phase animal ventilator) with a 10 mg/kg tidal volume. Frequency was adjusted to maintain an arterial P\(_{\text{CO}}\_2\) between 35 and 40 mmHg. A 6-Fr 11-pole multielectrode conductance catheter (Webster Laboratories, Irvine, CA) and a LV micromanometer catheter (MPC-500, Millar, Houston, TX) were placed for LV pressure-volume analysis via the right internal carotid artery and left common carotid artery, respectively, as previously described by us (30). These devices allowed for the continuous measurement of LV pressure and volume allowing the calculation of LV SV and SW. The pericardium was opened, and epicardial pace-maker leads were placed on the right atrium (RA), right ventricular (RV) free wall near the anterior infundibulum, mid-LV free wall near the midposterior-lateral wall, and LV apex for multisite stimulation. The pericardium was reopposed with multiple interrupted sutures, and positive end-expiratory pressure (PEEP) was applied to reexpand the lungs. Afterward, 5 cmH\(_2\)O PEEP was applied to maintain end-expiratory lung volume for the remainder of the experiment. Fluid resuscitation was performed prior to starting the protocol to restore apneic LV end-diastolic volume to values similar to where they were prior to sternotomy.

**Protocol**

All measurements were made with respirations suspended at an end-expiration of 5 cmH\(_2\)O PEEP to control for the effects of cardiopulmonary interactions. The protocol consisted of pacing and then creating a stable apneic steady state for data acquisition. To avoid retrograde conduction for all pacing steps of the protocol, RA pacing was performed at frequencies 5–10 beats/min above the intrinsic rhythm. Right atrial pacing is defined as normal ventricular contraction for subsequent comparisons. All succeeding ventricular pacing experiments were then done with sequential pacing at an atrioventricular (A-V) delay of 30 ms. This pacing delay prevented ventricular fusion beats from contaminating the ventricular pacing effects of CRT. Contraction dyssynchrony was created by simultaneous RA and high RV free wall pacing, which induced a LBBB-like contraction pattern. We then compared the impact of counterclocking at two different LV sites on the RV pacing-induced dyssynchronous contraction pattern. We chose to simultaneously pace at either the LV apex or posterior-lateral LV free wall at the midventricular level below the left circumflex artery to mimic CRT (referred to as CRT\(_a\) and CRT\(_f\), respectively). The order of apical and free wall pacing was alternated among sequential animals to eliminate any sequencing effects. Pacing was sustained for >30 s before measurements were made for each step so that a hemodynamic equilibrium could be established. In practice, hemodynamic stability usually took <15 s to occur. Between each ventricular paced rhythm interval, the animals were returned to RA pacing, and all hemodynamic variables were stabilized to baseline levels before the next step in the protocol was initiated.

**Echocardiographic TDI and Tissue Strain Imaging**

An echocardiographic system with TDI capabilities was used (Aplio SSA-770A, Toshiba Medical Systems, Tokyo, Japan) with a 3.0-MHz transducer. Digitized routine and color-coded TD images were acquired from mid-LV short-axis levels using epicardial imaging and a transducer stand. TD system frame rates were a minimum of 49 frames/s with a pulse repetition frequency of 4.5 kHz. Velocity ranges were from ±17.0 to ±13.0 cm/s to select the lowest possible range to maximize the sensitivity of low velocity values while aliasing did not occur. Color TD video data were analyzed off-line using custom software (TDI-Q, Toshiba Medical Systems) as described by us for this canine preparation (9). Briefly, the myocardial vector (V) of motion toward a manually placed point of contraction center was calculated as follows: \(V_{\text{motion}} = V_{\text{beam}} \cdot \cos(\theta)\), where \(\theta\) is the angle of incidence of the ultrasound beam. Sectors were masked where the angle of incidence approached 90° and Doppler calculations are not possible. Strain was calculated as time integral of the velocity gradient that was calculated along radii of a distance (\(\Delta r\)) toward the contractile center. Angle-corrected, color-coded Lagrangian strain was calculated as percent wall thickening toward the contraction center and displayed on a continuous scale from dark red to bright orange-yellow as positive strain corresponding to wall thickening. The six segments of interest in the mid-LV short-axis view were midseptum, anteroseptum, anterolateral, posterolateral, posterior, and inferior and were manually drawn as linear polygons placed in the inner third of the wall (Fig. 1). This subendocardial region was selected to represent the major component of transmural thickening and to minimize translational or RV effects on regional LV wall dynamics. A tracking algorithm was employed with manual adjustment of the size and shape of the regions of interest to maintain its subendocardial location throughout the cardiac cycle.

**Regional Contraction Synchrony Analysis**

Regional radial synchrony was analyzed by implementing a newly developed algorithm on time-strain curves constructed from color-coded strain data at the mid-LV level. The new index derived from this algorithm was compared with other commonly used indexes of dyssynchrony.

**Cross-correlation synchrony index.** A new index of synchrony was developed in the time domain via a pair-wise correlation analysis of radial strain waveforms over systole for six myocardial segments. The peak of the QRS wave on ECG defined the onset of systole. Off-line analysis of data indicated that global end systole, defined by the diastolic notch of aortic pressure waveform, and time of latest peak strain occurred in close proximity. Thus, end systole was defined by the time of latest peak strain. Only the systolic portion of the strain waveforms was used for all cross-correlation analyses. Given that strain data were acquired for 6 segments, there are 15 segment pairs. For each segmental pair, the cross-correlation coefficient was calculated using a custom-written MATLAB (version R2006a, The MathWorks) program (Fig. 2). All cross-correlation coefficients were summed and used as an overall index of synchrony; a value of 15 for this index would imply perfect synchrony, and lower values for this index would correspond to progressively greater dyssynchrony.

**Additional dyssynchrony indexes.** Two commonly used indexes of dyssynchrony were also calculated to provide a preliminary validation of our new index and to confirm that our findings were not a result of the specific algorithm used in the analysis. These two indexes were 1) maximal time delay of peak systolic strain calculated from data for multiple segments (9) and 2) SD of time to peak systolic strain calculated from data for multiple segments (44). Although Yu et al. (44) used velocity instead of strain to calculate the SD index in their study, the conceptual underpinnings are the same: a higher value of SD indicates a greater degree of dyssynchrony.

**Global LV Performance Analysis**

Indexes of global performance [e.g., LV SV, LV SW, LV dP/d\(_{\text{max}}\), and minimum rate of LV pressure increase (dP/d\(_{\text{min}}\))] were calculated from LV pressure-volume data obtained under steady-state apneic conditions for each pacing modality using standard formulas (30).

**Statistical Analysis**

Data are expressed as means ± SE. One-way ANOVA with repeated measures was used to evaluate the effects of different pacing modalities on regional LV synchrony and indexes of global LV...
performance. The Tukey-Kramer test was employed for post hoc pair-wise comparisons following each ANOVA. Significance was determined as $P < 0.05$. Linear regression analysis was used to compare the newly developed index of contraction synchrony with the existing dyssynchrony indexes.

RESULTS

Induction of LV Contraction Dyssynchrony

RV pacing induced radial contraction dyssynchrony manifested as a significant decrease in the synchrony index from $11.1 \pm 0.8$ (RA pacing) to $4.8 \pm 1.2$ ($P < 0.01$; Fig. 3). Regional dyssynchrony was correlated with a marked depression in LV pressures, volumes, and global LV functional indexes [e.g., SV: $15 \pm 2$ to $10 \pm 1$ ml, cardiac output (CO): $2.0 \pm 0.3$ to $1.4 \pm 0.1$ l/min, SW: $137 \pm 22$ to $60 \pm 14$ mJ, LV $dP/dt_{\text{max}}$: $1,346 \pm 144$ to $1,087 \pm 166$ mmHg/s, and LV $dP/dt_{\text{min}}$: $-1,679 \pm 221$ to $-1,072 \pm 165$, all $P < 0.05$]. Hemodynamic data and calculated variables under the control condition (RA pacing) and contraction dyssynchrony model (RV pacing) are shown in Table 1. Overall, RV pacing was associated with both marked radial dyssynchrony and depression of global LV performance.

CRT and Regional LV Contraction Synchrony

As shown in Fig. 3, CRTa restored radial synchrony to that seen with RA pacing, with the synchrony index increasing to

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**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RV Pacing</th>
<th>CRTa</th>
<th>CRTf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchrony Index</td>
<td>$11.1 \pm 0.8$</td>
<td>$4.8 \pm 1.2$</td>
<td>$10.2 \pm 1.1$</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>$15 \pm 2$</td>
<td>$10 \pm 1$</td>
<td>$8 \pm 1$</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>$2.0 \pm 0.3$</td>
<td>$1.4 \pm 0.1$</td>
<td>$1.2 \pm 0.1$</td>
</tr>
<tr>
<td>SW (mJ)</td>
<td>$137 \pm 22$</td>
<td>$60 \pm 14$</td>
<td>$40 \pm 12$</td>
</tr>
<tr>
<td>$dP/dt_{\text{max}}$ (mmHg/s)</td>
<td>$1,346 \pm 144$</td>
<td>$1,087 \pm 166$</td>
<td>$900 \pm 150$</td>
</tr>
<tr>
<td>$dP/dt_{\text{min}}$ (mmHg/s)</td>
<td>$-1,679 \pm 221$</td>
<td>$-1,072 \pm 165$</td>
<td>$-800 \pm 120$</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Tissue Doppler image (TDI) in short-axis view taken at the mid-left ventricular (LV) location. Strain waveforms were calculated from velocity data obtained at each of the 6 segments under 4 pacing modalities: right atrial (RA) pacing (A), right ventricular (RV) pacing (B), cardiac resynchronization therapy (CRT) at the LV apex (CRTa; C), and CRT at the LV free wall (CRTf; D). Line colors of waveforms correspond to the segments labeled in TDI. Each segment was paired with one another for a pair-wise evaluation of contraction synchrony.
11.7 ± 0.6 [P < 0.01 vs. RV pacing and P = not significant (NS) vs. RA pacing]. Similarly, CRTf also significantly improved radial synchrony by increasing the synchrony index to 9.8 ± 1.1 (P < 0.01 vs. RV pacing and P = NS vs. RA pacing). The synchrony index was not significantly different between the two CRT modes (P = NS, CRTf vs. CRTa).

Although some scatter existed, the newly developed synchrony index (i.e., cross-correlation coefficient sum) was significantly correlated with two commonly used measures of dyssynchrony (Fig. 4, A and B). Analyses of our data for contraction synchrony using these two indexes (Fig. 4, C and D) yielded the same results as those obtained using the cross-correlation analysis (i.e., decreased synchrony with RV pacing and significant improvement of synchrony with both CRT modes).

### CRT and Global LV Performance

Hemodynamic data and calculated variables under RV pacing and both CRT modes (CRTa and CRTf) are shown in Table 1. Below each performance index is the percent change with respect to its value with RV pacing.

When CRTa was used to correct for RV pacing-induced contraction dyssynchrony, mean arterial pressure and LV end-systolic pressure (LVESP) did not change. However, global LV systolic performance was significantly improved with CRTa (SV: 16 ± 2 ml, CO: 2.1 ± 0.2 l/min, and SW: 113 ± 13 mJ, all P < 0.01, CRTa vs. RV pacing). The increase in CO was primarily a result of significantly lower LV end-systolic volume (LVESV: 23 ± 6 ml, P < 0.01, CRTa vs. RV pacing). Although most LV systolic performance indexes were in-

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**Fig. 2. Example of the cross-correlation method developed to analyze contraction synchrony.** Top plots show regional myocardial strain waveforms for all 6 segments under RA pacing (A) and RV pacing (B). End systole was determined by the time to latest peak strain (dashed line). Line colors of waveforms correspond to the segments labeled in Fig. 1. Bottom plots show an example of the cross-correlation analysis applied to one segmental pair [midseptum (MS)-posterolateral (PL)] over systole. With RA pacing (C), the 2 segments contract almost synchronously, as indicated by the high cross-correlation value (0.96) over the systolic duration. In contrast, significant contraction dyssynchrony was evident with RV pacing (D) manifested as a septal to lateral contraction delay and a low cross-correlation value (~0.40) over the systolic duration.

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Differential Effects of LV Pacing

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Differential Effects of LV Pacing

Global LV performance values for different pacing modalities

<table>
<thead>
<tr>
<th></th>
<th>RA Pacing</th>
<th>RV Pacing</th>
<th>CRTa</th>
<th>CRTf</th>
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</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>133±6</td>
<td>133±6</td>
<td>133±6</td>
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<tr>
<td>ΔHR, %</td>
<td>6±2</td>
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<td>6±2</td>
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<tr>
<td>MAP, mmHg</td>
<td>91±7</td>
<td>71±7§</td>
<td>71±6</td>
<td>72±7</td>
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<td>ΔMAP, %</td>
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<td>9±2</td>
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<tr>
<td>ΔLVEDP, %</td>
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<td>-1±2</td>
<td>-1±2</td>
<td>-1±2</td>
</tr>
<tr>
<td>LVESP, mmHg</td>
<td>96±8</td>
<td>77±7§</td>
<td>77±7</td>
<td>77±7</td>
</tr>
<tr>
<td>ΔLVESP, %</td>
<td>1±4</td>
<td>1±4</td>
<td>1±4</td>
<td>1±4</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>46±7</td>
<td>41±6§</td>
<td>39±7</td>
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<tr>
<td>ΔLVEDV, %</td>
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<td>-8±3</td>
<td>-8±3</td>
<td>-8±3</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>31±5</td>
<td>30±6</td>
<td>36±9</td>
<td>27±6*</td>
</tr>
<tr>
<td>ΔLVESV, %</td>
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<td>0±1†</td>
<td>0±1†</td>
<td>0±1†</td>
</tr>
<tr>
<td>SV, ml</td>
<td>15±2</td>
<td>10±1§</td>
<td>16±2†</td>
<td>12±1†</td>
</tr>
<tr>
<td>ΔSV, %</td>
<td>58±16</td>
<td>58±16</td>
<td>53±16</td>
<td>43±10</td>
</tr>
<tr>
<td>CO, l/min</td>
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<td>1±0.1§</td>
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<td>1.5±0.2†</td>
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<td>ΔCO, %</td>
<td>58±16</td>
<td>58±16</td>
<td>53±16</td>
<td>43±10</td>
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<tr>
<td>dP/dtmax, mmHg/s</td>
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<tr>
<td>dP/dtmin, mmHg/s</td>
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<td>-1,072±165§</td>
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<tr>
<td>ΔdP/dtmin, %</td>
<td>17±7</td>
<td>17±7</td>
<td>17±7</td>
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</tr>
<tr>
<td>SW, mJ</td>
<td>137±22</td>
<td>60±14§</td>
<td>113±13§</td>
<td>75±12*</td>
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<td>ΔSW, %</td>
<td>180±94</td>
<td>65±43</td>
<td>153±9</td>
<td>87±16</td>
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</table>

Data are means ± SE; n = 7. RA, right atrial; RV, right ventricular; CRTa, cardiac synchronization therapy (CRT) at the left ventricular (LV) apex; CRTf, CRT at the LV free wall; HR, heart rate; MAP, mean arterial pressure; LVEDP, LV end-diastolic pressure; LVESP, LV end-systolic pressure; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; SV, stroke volume; CO, cardiac output; dP/dtmax, maximum rate of change of LV pressure; dP/dtmin, minimum rate of change of LV pressure; SW, LV stroke work. For CRT, below each performance index is the percentage change with respect to RV pacing. *P < 0.05 and †P < 0.01, CRTf vs. CRTa; ‡P < 0.01, CRTa vs. RV pacing or CRTf vs. RV pacing; §§P < 0.05, RV pacing vs. RA pacing.

Effects of LV Pacing Alone

Given that LV pacing can create dyssynchronous contraction by itself (24), we assessed radial dyssynchrony under LV apical and LV free wall pacing alone (i.e., in the absence of simultaneous RV pacing). With LV apical pacing alone, our synchrony index decreased slightly (9.8 ± 1.1); however, this was not significantly different from the RA pacing value (11.1 ± 0.8, P = 0.23). In contrast, LV free wall pacing alone significantly decreased the synchrony index to 4.5 ± 1.7 (P = 0.01 vs. RA pacing). Thus, there seems to be discordance between restoration of radial synchrony and global LV performance following CRTf.

The differential response with respect to the improvement in global LV systolic function between the two CRT modes can be better appreciated from the data shown in Fig. 5. For CRTf, the changes in global LV systolic performance indexes hovered around zero, even when there was significant improvement in radial synchrony. In contrast, CRTa resulted in improvements in both radial synchrony and global LV systolic performance. Despite the variability in global LV performance (especially for dP/dtmax), the changes in these indexes were proportional to the improvements in radial synchrony with CRTa (Fig. 5).

Representative pressure-volume loops for RV pacing and both CRT modes are shown in Fig. 6. Compared with RV pacing (i.e., the dysynchrony model), CRTa significantly decreased LVESV, without any change in LVESP (Table 1), indicating an augmented global LV contractile state. Although a similar pattern of changes in LVESV and LVESP was seen with CRTf, the decrease in LVESV did not reach statistical significance (Table 1), indicating a modest or no change in global LV contractility with respect to RV pacing.

Table 1. Global LV performance values for different pacing modalities

*P < 0.05 and †P < 0.01, CRTf vs. CRTa; ‡P < 0.01, CRTa vs. RV pacing or CRTf vs. RV pacing; §§P < 0.05, RV pacing vs. RA pacing.
0.002, LV free wall vs. RA). Thus, the observation that CRTf failed to improve global LV systolic performance despite a significant improvement in radial synchrony may be a consequence of the dyssynchronous effects of LV free wall pacing alone. In addition, radial synchrony may not have been restored with CRTf at all cross-sectional planes (we only examined synchrony at the mid-LV level).

**DISCUSSION**

The present study reports three primary findings. First, although both modes of CRT (CRTa and CRTf) significantly restored radial synchrony, only CRTa increased global LV systolic function. Second, the improvement in global LV systolic function with CRTa appears to be driven by increased LV contractility, as indicated by an increase in SV with unchanged LVEDV, LVESP, and heart rate. Finally, the dissociation between changes in synchrony and global LV performance with CRTf suggests that regional analysis from a single plane may not be sufficient to adequately characterize contraction synchrony. We also report a new index to quantify LV synchrony using pair-wise cross-correlations of six LV wall regions. Before we discuss the present findings, we will first address certain methodological considerations.

**Methodological Considerations**

**Dysynchrony model.** Two relevant issues need to be noted here. First, we did not study the impact of dyssynchrony or CRT in the setting of chronic structural conduction abnormalities such as blockage of the His-Purkinje system or myocardial ischemia/infarction. Instead, we used RV pacing as a model of the LBBB-like contraction pattern. RV pacing is known to produce delayed LV contraction (19) and, consequently, LV contraction dyssynchrony, which has been shown to decrease SV, SW, and LV pressures (9). Although RV pacing-induced dyssynchrony has been used previously (9, 16, 19), functional differences in contraction resynchronization using an intact conduction system may not extrapolate to studies where anatomical LBBB is present. Second, we studied the effect of dyssynchrony and CRT in healthy, nonfailing hearts. Contractile and structural changes occur in heart failure that may alter the response of CRT. Future studies involving a heart failure model with structural defects will address these issues.

**Consequence of short A-V delay.** The animal model used in the present study involved an intact conduction system; therefore, a short A-V delay was necessary to avoid intrinsic activation of the ventricles (i.e., fusion beats). However, a short A-V delay often leads to inefficient atrial emptying because the atrium is forced to contract against the closed mitral valve (15), which adversely affects A-V coupling by decreasing LV preload. Therefore, the observed lower end-diastolic volumes with RV pacing and CRT may be a consequence of the short A-V interval used in the present study. It should be noted, however, that our inferences regarding the differential effects of the modes of CRT (CRTa vs. CRTf) on LV global performance are
not confounded by the short A-V delay because this short delay existed for all three conditions (RV pacing, CRTa, and CRTf) that were included in the statistical analysis. Furthermore, in a previous study using this model, we performed A-V nodal ablation and saw no differences in regional or global function with CRT compared with the intact A-V node condition (data not shown).

Quantification of dyssynchrony. Quantification of contraction dyssynchrony is an emerging interest in cardiology, and several different indexes have been reported to assess it. We developed a new algorithm to quantify LV synchrony by pair-wise cross-correlation analysis of LV regional TD segmental strain. Previously, mechanical dyssynchrony has been quantified using time to peak systolic longitudinal velocity using TD from echocardiographic apical views and expressed principally as either the standard deviation of 12 segments or the maximum opposing wall delay (10, 20, 27, 43). Cut-off values to predict the response to CRT in terms of absolute time have been devised; however, difficulties may exist with TD angle dependence, signal noise, translational effects of scar, and variations in heart rate (4, 11, 42, 43), which can make this approach less robust. Angle-corrected TDI minimizes some but not all of the TD angle dependence bias. Importantly, tissue strain echocardiography has the advantage over TD velocity with respect to differentiating active contraction from passive motion or tethering, which are important confounding variables in patients with ischemic heart disease (9). Dyssynchrony indexes can therefore be derived using tissue strain data based on the extent and timing of myocardial deformation over systole.

Midventricular cross-sectional radial strain has recently been shown to predict both acute and chronic clinical response to CRT using the maximal time delay between earliest and latest peak strain (10, 31). Although our new index significantly correlated with this index, cross-correlation analysis is expected to be superior in assessing LV contraction synchrony. Our synchrony algorithm assesses the entire systolic portion of the time-strain waveform and thus offers a more robust method in assessing contraction synchrony. It also overcomes the
limitation of variations in heart rate because each region is compared with a common end systole. However, because our new algorithm was applied to a nonischemic, non-heart failure model, we cannot prove superiority over other indexes at this time. Future studies involving an ischemic model will address this issue.

The present study used TD radial strain at a midpapillary view to assess contraction dyssynchrony. Although 12 longitudinal segments were used to calculate the dyssynchrony index in other studies (44), we were limited to 6 segments in our analysis for two reasons: 1) Doppler calculations are not possible where the angle of incidence approaches 90° and 2) increasing the number of segments in processing TD data increases the signal-to-noise ratio, which jeopardizes the reliability of the data. We plan to improve our analysis in future studies by using speckle-tracking algorithm of routine echocardiographic images, which will allow us to apply our cross-correlation analysis on more LV regions to better quantify contraction synchrony.

LV Pacing Sites: Implications for CRT and Contraction Synchrony Analysis

We saw significant improvements in global LV performance compared with RV pacing only with CRTa, even though both CRTa and CRTf significantly improved contraction synchrony. Thus, it appears that LV apical pacing is superior to LV free wall pacing in CRT if no structural limitations to cardiac conduction coexist. Recently, Helm et al. (14) reported that the CRT response was better with LV apical pacing compared with more basal stimulation. They used a custom epicardial sock with 128 stimulating/recording electrodes and showed that mechanical synchrony and global LV function were better preserved as the LV pacing site was moved more apically. Similarly, Peschar et al. (23) and Prinzen et al. (25) reported beneficial effects on global LV performance following biventricular (RV apex + LV apex) pacing in healthy dogs. Furthermore, Vanagt et al. (34) showed that the LV apex was the optimal pacing site in both canines and humans. Apical stimulation may be more beneficial to global LV function because it triggers mechanical activity closest to the intrinsic pattern of contraction. Propagation of electrical signals is fastest when the stimulation is nearest to the sites where the intrinsic impulses exit the Purkinje system (24). Since impulses exit the Purkinje system in the lower third of the LV wall (21), apical stimulation should induce an activation pattern similar to intrinsic myocardial activation, thus contributing to improved global LV performance.

We used changes in the end-systolic pressure-volume point to draw the conclusion that only CRTa significantly increased LV contractile state compared with RV pacing. It is acknowledged that the entire end-systolic pressure-volume relationship (ESPVR) would have been better for this purpose. However, significant reductions in LVESV with little or no change in LVEESP provide a reasonably sound basis for our conclusion. Although ESPVR has been used to quantify changes in LV contractile state following restoration of synchrony (28, 29), most previous studies have used dP/dt max as the index of LV contractility. In the present study, CRTa did not increase the group average value of dP/dt max, but this response was variable among different experiments (Fig. 5). We attribute this variability to concomitant changes in LV end-diastolic volume, which, together with LV contractility, can affect LV dP/dt max (38).

In contrast to our results regarding CRTf, some studies have reported a benefit in LV global function with LV free wall pacing. Leclercq et al. (17) induced LBBB via radiofrequency ablation in canines and showed that both single-site and multistim LV free wall pacing significantly increased dP/dt max and aortic pulse pressure compared with their LBBB mode. Verbeek et al. (36) also showed increases in dP/dt max and SW with LV free wall pacing relative to LBBB values. The differences in the dyssynchrony model may contribute to the discrepant observations. Whereas we used a pacing-induced model of dyssynchrony, Leclercq et al. and Verbeek et al. used a structural insult to induce dyssynchrony. However, it is important to note that several other studies have supported our finding that LV free wall pacing is an inferior pacing site in the context of resynchronization (14, 23, 25, 34). The conflicting results concerning the benefits of LV free wall pacing remain an unresolved issue in CRT research that needs further clarification.

We were also surprised to find that improvements in regional contraction synchrony with CRTf were not accompanied by improvements in global LV function (Fig. 5). This apparent disconnect may be due to the limitations of synchrony analysis using single-plane views. Because the LV free wall pacing site was in the same cross-sectional plane (mid-LV) as that used for TDI, it is not surprising that electrical stimulation synchronized contraction in this plane. However, due to slow conducting myocardium (24), delayed activation of the remainder of the LV free wall may have failed to correct contraction dyssynchrony at other planes. Therefore, the failure of global function to improve with CRTf may be a result of the continued presence of contraction dyssynchrony at sites outside of the mid-LV plane. Multiplane assessment of synchrony is necessary for a more comprehensive characterization.

Conclusions

Following RV pacing-induced LBBB-like contraction patterns, differential effects were observed with two different LV pacing sites during CRT. Although both modes of CRT significantly improved radial contraction synchrony, only CRTa improved global LV performance and contractility. Thus, the LV apex appears to be a superior pacing site in the context of CRT. The observed dissociation between changes in regional contraction synchrony and changes in global LV performance with CRTf suggests that regional contraction data obtained from a single cross-sectional plane may not be sufficient to adequately characterize contraction synchrony of the LV as a whole; a three-dimensional dataset may be necessary.

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