Diminished Left Ventricular Dyssynchrony and Impact of Resynchronization in Failing Hearts With Right Versus Left Bundle Branch Block

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Objectives
We compared mechanical dyssynchrony and the impact of cardiac resynchronization therapy (CRT) in failing hearts with a pure right (RBBB) versus left bundle branch block (LBBB).

Background
Cardiac resynchronization therapy is effective for treating failing hearts with conduction delay and discoordinate contraction. Most data pertain to LBBB delays. With RBBB, the lateral wall contracts early so that biventricular (BiV) pre-excitation may not be needed. Furthermore, the magnitude of dyssynchrony and impact of CRT in pure RBBB versus LBBB remains largely unknown.

Methods
Dogs with tachypacing-induced heart failure combined with right or left bundle branch radiofrequency ablation were studied. Basal dyssynchrony and effects of single and BiV CRT on left ventricular (LV) function were assessed by pressure-volume catheter and tagged magnetic resonance imaging, respectively.

Results
Left bundle branch block and RBBB induced similar QRS widening, and LV function (ejection fraction, maximum time derivative of LV pressure [dP/dt\text{max}]) was similarly depressed in failing hearts with both conduction delays. Despite this, mechanical dyssynchrony was less in RBBB (circumferential uniformity ratio estimate [CURE] index: 0.80 ± 0.03 vs. 0.58 ± 0.09 for LBBB, p < 0.04; CURE 0–1 is dyssynchronous—synchronous). Cardiac resynchronization therapy had correspondingly less effect on hearts with RBBB than those with LBBB (i.e., 5.5 ± 1.1% vs. 29.5 ± 5.0% increase in dP/dt\text{max}, p < 0.005), despite similar baselines. Furthermore, right ventricular-only pacing enhanced function and synchrony in RBBB as well or better than did BiV, whereas LV-only pacing worsened function.

Conclusions
Less mechanical dyssynchrony is induced by RBBB than LBBB in failing hearts, and the corresponding impact of CRT on the former is reduced. Right ventricular-only pacing may be equally efficacious as BiV CRT in hearts with pure right bundle branch conduction delay. (J Am Coll Cardiol 2007;50:1484–90) © 2007 by the American College of Cardiology Foundation.

The presence of a left- or right-sided intraventricular conduction delay increases mortality risk in patients with cardiac failure (1,2). Conduction delay generates dyssynchrony of left ventricular (LV) contraction (3), reducing systolic function and energetic efficiency (4), triggering regional molecular and metabolic abnormalities (5), and exacerbating the evolution of chamber dysfunction. Biventricular (BiV) stimulation, or cardiac resynchronization therapy (CRT), improves cardiac contractile synchrony and mechano-energetics, and morbidity and mortality of affected patients (6–10).

The vast majority of experimental and clinical data on dyssynchrony and CRT effects derive from hearts with a left-bundle delay pattern in which lateral wall contraction is delayed (11). Right-bundle pattern delay occurs, but remains a small subset in clinical trials; thus, the magnitude of dyssynchrony and potential benefits of CRT in this setting remain uncertain. The few studies examining the role of CRT in right bundle branch block (RBBB) patients have
yielded conflicting results supporting (12) or lacking support for CRT (13) in this setting. Since a right bundle branch-type delay means the LV free wall is activated early, discoordination may be less than with a left bundle branch block (LBBB) where this wall contracts late and distends the septum. Furthermore, it remains unclear if an LV lead is required to achieve CRT functional benefit, or if right ventricular (RV) pacing alone would be sufficient. Accordingly, the present study examines the relative magnitude of basal dyssynchrony and effects of CRT in a canine model of cardiac failure superimposed with either an RBBB or LBBB induced by radiofrequency ablation. We tested the hypotheses that: 1) RBBB induces less discoordinate contraction and reduced CRT improvement as compared with LBBB; and 2) that RV-only stimulation achieves similar or better CRT effects as traditional BiV stimulation in failing hearts with an RBBB. Right bundle branch block data were compared with LBBB data previously acquired in our laboratory as part of another study.

Methods

Protocol. Twelve adult mongrel dogs were subjected to left (n = 6) or right (n = 6) bundle radiofrequency ablation using a 4-mm tipped electrode catheter positioned in the proximal (infundibular) LV or RV, respectively. The LBBB studies were performed as part of a previous investigation reported by our laboratory (11). In both sets of ablated animals, an endocardial lead was placed in the right atrium, connected to a modified subcutaneous generator (Medtronic, Minneapolis, Minnesota), and animals chronically paced at 210 beats/min for 3 to 4 weeks to induce dysynchronous heart failure (HF). Once failure was induced, animals were anesthetized (10 to 15 mg/kg pentothal, 1% to 2% isoflurane) and the heart exposed by a midline thoracotomy. Magnetic resonance imaging (MRI)-compatible pacing electrodes were sutured to the right atrium, RV free wall, RV apex, and LV lateral wall, and transvenously in the RV septum in RBBB-HF dogs, and to the right atrium, LV lateral, and RV apex in LBBB-HF dogs. An MRI-compatible micromanometer-tipped catheter was placed in the LV chamber for pressure recording. Cardiac resynchronization therapy was tested using BiV pacing (RV + LV) sites. In RBBB animals only, additional tests were made using several RV sites (RV free wall, apex, and septum) only, and LV free wall pacing only, to contrast these responses to standard BiV CRT. Cardiac resynchronization therapy was induced at ~20 beats/min above the intrinsic heart rate. Atrioventricular delay was set to a value that achieved full pre-excitation and generated the optimal maximum time derivative of LV pressure (dP/dt max) response with BiV stimulation (~70 ms).

MRI protocol. Tagged MRI data were obtained using a Signa CVi 1.5-T scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with a fast gradient echo sequence. A maximum of 4 cross-sectional, tagged MRI cine planes were acquired for each pacing protocol using a modified fast-card sequence at 15 ms/frame (30 frames/beat). Imaging was acquired during 30-s breath hold periods. The tagging spatial modulation of magnetization pulse sequence consisted of non-selective radiofrequency pulses separated by encoding gradient to generate a set of parallel planes of magnetic saturation to produce images with a tag separation of about 7 mm. Two orthogonal sets of tag lines were acquired to analyze the motion of the myocardium. Imaging parameters were as follows: field of view 40 cm, slice thickness 8 to 10 mm, repetition time 3.5 to 7.2 ms, echo time 2.0 to 4.2 ms, flip angle 120°, matrix size 256 × 96 to 140, 4 to 9 phase-encoding views per segment (range 4 to 9), bandwidth of 49 MHz (range 24.9 to 62.5), temporal resolution 15.6 to 50 ms, and tag spacing 7 mm. Modification to the standard pulse sequence allowed for external triggering of the scanner to facilitate synchronous electrical/mechanical data acquisition.

Data and image analysis. Hemodynamic data were determined from an average of ~20 consecutive beats for each pacing combination and the percentage change from baseline determined for dP/dt max, stroke work, and isovolumic relaxation time constant (Tau). Short-axis tagged images were analyzed using the harmonic phase method (Diasonoft HARP, Diasonoft, Inc., Palo Alto, California), which provides circumferential strain over 6 myocardial segments. Analysis was performed by 1-way analysis of variance (ANOVA) to test for differences between percent change from baseline for RBBB-HF and LBBB-HF animals with respect to CURE, dP/dt max, the.

Abbreviations and Acronyms

BiV = biventricular
cCRT = cardiac resynchronization therapy
cCURE = circumferential uniformity ratio estimate
cdP/cdt max = maximum time derivative of left ventricular pressure
cEF = ejection fraction
cHF = heart failure
cLBBB = left bundle branch block
cLV = left ventricle/ventricular
cMRI = magnetic resonance imaging
cRBBB = right bundle branch block
cRV = right ventricle/ventricular
standard deviation of time to peak strain, and EF. Effects of CRT pacing configuration were determined by 1-way repeated measures ANOVA analysis. Post-hoc comparisons were determined using a Tukey test. A 2-way ANOVA with dummy variable coding for the animal was employed for comparison involving multiple measurements from each animal across different groups. Effects of CRT pacing configuration were determined by 2-way repeated measures ANOVA analysis. Post-hoc comparisons were determined using a Tukey test.

Results

Baseline electrophysiology and hemodynamics: RBBB-HF versus LBBB-HF model. Table 1 provides summary characteristics for the 2 dyssynchrony HF models. Baseline QRS duration was 46 ± 2.5 ms, and both LBBB and RBBB models increased the duration similarly to 110 ms (both p < 0.0001). With tachypacing-induced HF, LV systolic function (dP/dt_max and LV EF) was similarly depressed in both groups (both p < 0.049), to values near half those previously reported in control animals (5). Right ventricular EF tended toward being lower in RBBB-HF dogs as compared with that in LBBB-HF (p = 0.079).

Cardiac dyssynchrony in failing hearts with RBBB or LBBB. Figure 1 shows example strain maps for LBBB-HF and RBBB-HF models. With LBBB-HF (Fig. 1A), there was septal shortening and lateral stretch during early systole, followed by septal stretch and lateral shortening later in systole. However, with RBBB-HF, strain was more uniform (Fig. 1B), with little dyssynchrony in early systole, and postero-septal shortening late in systole without reciprocal stretch. Plots of instantaneous strain versus short-axis segment location (i.e., used for CURE determination) for each model are shown in Figures 1C and 1D. These plots represent an instantaneous distribution of strain throughout all myocardial segments at 2 different time points in the cardiac cycle. Note the more sinusoidal strain profile during early systole in the LBBB model, reflecting a larger disparity of strains. For the RBBB case (Fig. 1D), segment-to-segment variation was noted in late systole but was lower in magnitude than that seen with LBBB. Early systolic strain distribution in RBBB was nearly uniform.

Table 1 Baseline Characteristics

<table>
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<th>Normal*</th>
<th>RBBB-HF</th>
<th>LBBB-HF</th>
<th>ANOVA</th>
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<tr>
<td>QRS (ms)</td>
<td>46 ± 2.5</td>
<td>110 ± 4.1†</td>
<td>113 ± 4.0†</td>
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<td>CURE</td>
<td>0.97 ± 0.01</td>
<td>0.80 ± 0.03‡</td>
<td>0.58 ± 0.09§</td>
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<td>+dP/dt_max</td>
<td>2.301 ± 890.0</td>
<td>928.0 ± 66.1§</td>
<td>981.7 ± 73.9</td>
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<td>LVEF (%)</td>
<td>51.8 ± 2.8</td>
<td>32.6 ± 7.5§</td>
<td>25.1 ± 3.8</td>
<td>0.005</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>49.1 ± 3.2</td>
<td>15.5 ± 1.6†</td>
<td>25.1 ± 3.2†</td>
<td>&lt;0.0001</td>
</tr>
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</table>

*Previously reported control animals; †p < 0.0001 as compared with baseline; ‡p = 0.044 as compared with left bundle branch block (LBBB) heart failure (HF); §p < 0.005 as compared with baseline; p < 0.048 as compared with baseline.

ANOVA = analysis of variance; CURE = circumferential uniformity ratio estimate; dP/dt_max = maximum time derivative of left ventricular pressure; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; RVEF = right ventricular ejection fraction.

Figure 1 Strain Plots Comparing Mechanical Dyssynchrony in Failing Hearts With RBBB and LBBB

Temporal strain maps for (A) left bundle branch block (LBBB) + heart failure; (B) right bundle branch block (RBBB) + heart failure during right atrial pacing; (C) corresponding LBBB + heart failure strain plot; and (D) corresponding RBBB + heart failure strain plot during early and late systole.
Dyssynchrony quantified by CURE was significantly greater in LBBB than RBBB failing hearts (CURE = 0.80 ± 0.03 for RBBB-HF, 0.58 ± 0.09 for LBBB-HF, p = 0.044). Despite similar QRS widening and a somewhat lower mean value, CURE was not significantly different between RBBB failing hearts and normal control hearts (0.97 ± 0.01, p = 0.191) (5), and was very similar to that obtained with BiV CRT in LBBB failing hearts (0.82 ± 0.06, p = 0.205). Additional analysis of dyssynchrony was obtained by assessing the time to peak strain in each region and standard deviation of these times (Figs. 2A to 2C). This also revealed greater dyssynchrony with LBBB versus RBBB. Figure 2D shows example mechanical activation maps for both pure RBBB and LBBB. The maps demonstrate the temporal evolution of mechanical activation, with the zero or reference point being the early activated region (i.e., the ventricular septum and the LV lateral wall for the LBBB and RBBB maps, respectively). The degree color heterogeneity within a map reflects the magnitude of mechanical dyssynchrony—as blue represents early activated regions and red represents late activated regions. In the LBBB map, the septum is early activated followed by various timing delays across the ventricular myocardium with late activation of the LV lateral wall (CURE = 0.53). The RBBB map, however, demonstrates more homogenous color distribution throughout the myocardium, starting with early activation of the LV lateral wall and then late activation of the septum (CURE = 0.79).

Cardiac resynchronization in RBBB-HF. In RBBB-HF hearts, both RV single site and BiV pacing similarly reduced QRS duration compared with right atrial-paced baseline (RV single site: −28.1 ± 3.3%; BiV: −33.5 ± 3.25% change from baseline, whereas QRS duration was unaltered by LV-only pacing (−0.83 ± 4.3%). Figure 3 summarizes the functional and mechanical synchrony response to various modes of CRT in RBBB-HF hearts. Single site RV-only pacing in RBBB-HF significantly improved CURE (p = 0.007) and dP/dt max (p = 0.001) but had no impact on stroke work (p = 0.965) or Tau (p = 0.638). Biventricular pacing improved both dP/dt max (p < 0.001) and stroke work (p = 0.010), but prolonged isovolumic relaxation (p = 0.036) and did not improve CURE (p = 0.203). Biventricular CRT improved dP/dt max far less in RBBB than LBBB failing hearts (5.5 ± 1.1% vs. 29.5 ± 4.9%, respectively, p < 0.001). Right ventricular EF improved similarly with RV-only and BiV pacing in RBBB-HF hearts (RV-only 62.18 ± 15.20%; BiV 55.43 ± 13.01% change from baseline, p < 0.001). Left ventricular-only pacing, which provides substantial CRT benefit in LBBB-HF hearts (15,16), was detrimental in RBBB-HF hearts, worsening both dyssynchrony and global function. For LBBB-HF animals, LV and BiV pacing improved synchrony (CURE 61.2 ± 31.4% and 68.14 ± 24%, p < 0.031, respectively) and function (dP/dt max 23.4 ± 3.6% and 29.5 ± 4.9%, p < 0.041, respectively) similarly.

Figure 2 Comparison of Regional and Global Strain in Failing Hearts With RBBB and LBBB
Time to peak strain as a percentage of R-R interval for (A) RBBB + heart failure; (B) LBBB + heart failure; and (C) the standard deviation of time to peak strain for RBBB + heart failure and LBBB + heart failure. (D) Examples of mechanical activation delay maps for both RBBB and LBBB (see text for details). Color bar: blue = early activation; red = late activation. Data expressed as mean ± standard error of the mean. (A and B) *p < 0.001 as compared with septum; †p < 0.030 as compared with septum; ‡p < 0.001 as compared with septum; §p < 0.001 as compared with septum. Ant. = anterior; CURE = circumferential uniformity ratio estimate; Lat. = lateral; Post. = posterior; Sept. = septal; other abbreviations as in Figure 1.
We further examined whether the precise RV pacing site (septum, free wall, or apex) was important to generating CRT effects in RBBB-HF hearts (Table 2). While there were some small disparities, responses with each RV site were not significantly different from one another whether employed as single-site pacing or in a BiV mode.

**Discussion**

Cardiac resynchronization therapy is an effective treatment for patients with HF and wide QRS (>120 ms) most commonly in a left bundle conduction block pattern. The mechanisms are thought related to reduction in LV dyssynchrony and corresponding stress-strain disparities and inefficient contraction of the ventricle. Patients with HF and an RBBB pose some similarities but also differences to the LBBB condition, it strengthens our analysis based on differences in pure RBBB. Assessment of mechanical contraction and dyssynchrony in RBBB patients for whom CRT is considered would seem particularly relevant. Further, while clinical CRT data require a greater basal QRSd than is generally observed with a pure RBBB, the present study assessed truly pure RBBB in a failing heart reveals that the dyssynchrony induced is indeed less than with an LBBB. Corresponding improvement in synchrony (and function) with CRT in hearts with RBBB delay is less than in those with LBBB.

The strain maps reveal more pronounced reciprocal stretch/shortening in opposing walls in hearts with LBBB versus RBBB (Fig. 1). Higher RV loading at the start of systole may help stent the septum preventing early stretch despite initial LV free-wall stimulation. Reduced lateral stretch during septal contraction may relate to the disparity in size of the 2 regions as noted in the preceding text.

The current models examined pure RBBB and LBBB pathophysiology, whereas clinical conduction block often combines components of each. This may underlie the observation of Fantoni et al. (12), who found both pre-stretch of the LV lateral wall in HF patients with RBBB, but also delay in lateral wall contraction. In contrast, we observed early lateral wall contraction with isolated RBBB. This distinction is likely important; patients with an electrocardiogram suggesting RBBB but who have either underlying dual-branch delay or intrinsic myocardial disease and, hence, late LV conduction are more likely to have a substrate suitable for traditional CRT than those with a pure RBBB. Assessment of mechanical contraction and dyssynchrony in RBBB patients for whom CRT is considered seems particularly relevant. Further, while clinical CRT data require a greater basal QRSd than is generally observed with a pure RBBB, the present study assessed truly pure RBBB, and we note that QRS prolongation in this canine model with both RBBB and LBBB ablation was not statistically different. While this may differ from the human condition, it strengthens our analysis based on differences in regional mechanics that are triggered by the 2 different conduction block patterns.

While less than in LBBB failing hearts, CRT in hearts with an RBBB conferred some systolic benefit. However, not a symmetric structure, in that the septum is loaded from both right and left hearts, while the free wall is less so. The septal region is also smaller geographically (approximately one-third the LV) as compared with the LV free wall. Thus, the extent of discoordinate contraction and impact of CRT are not implicitly the same as with an LBBB.

The present study employing an experimental model of pure RBBB in a failing heart reveals that the dyssynchrony induced is indeed less than with an LBBB. Corresponding improvement in synchrony (and function) with CRT in hearts with RBBB delay is less than in those with LBBB. The strain maps reveal more pronounced reciprocal stretch/shortening in opposing walls in hearts with LBBB versus RBBB (Fig. 1). Higher RV loading at the start of systole may help stent the septum preventing early stretch despite initial LV free-wall stimulation. Reduced lateral stretch during septal contraction may relate to the disparity in size of the 2 regions as noted in the preceding text.

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While less than in LBBB failing hearts, CRT in hearts with an RBBB conferred some systolic benefit. However,
the mode of CRT did not necessarily require BiV stimulation. Single-site RV pacing generally produced similar improvements in global mechanical function and synchrony as with BiV pacing, and in some instances appeared superior to BiV stimulation. Interestingly, significant narrowing of the QRS complex with both RV-only and BiV pacing did not translate to a large functional improvement, supporting prior data showing lack of correlation between these parameters (17). Pacing combinations that produced LV functional benefit were also those that improved RV EF, suggesting that CRT with underlying RBBB may involve improvement of RV function, which assists in filling and function of the LV.

In failing hearts with an LBBB, both BiV and LV-only stimulation have been shown to be similarly effective in improving cardiac mechanics both acutely and chronically. In the current study, hearts with RBBB were worsened by LV-only pacing. This is perhaps expected, since under the conditions of the RBBB, the LV was stimulated early but in a more rapid coordinate manner via the conducting left bundle. Left ventricular pacing slows this activation by requiring intramyocardial conduction, perhaps worsening dyssynchrony. This would also explain why BiV stimulation was not better than RV-only pacing in such hearts. With BiV, one combined a useful phase-advance stimulation of the RV with a less beneficial advance of the already early activated LV, and the mechanical results were either similar to RV-only or halfway between RV- and LV-only responses.

Our finding of a limited benefit of CRT in RBBB-HF are, in part, supported by a recent retrospective analysis of the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) and CONTAK CD trials examining the role of CRT in RBBB and HF patients. With the exception of New York Heart Association functional class, the authors found no demonstrable benefit in hemodynamics after 6 months of follow-up (13). The improvement in New York Heart Association functional class was also observed in the control group and may be attributed to placebo effect. Other studies, however, have found that patients with RBBB and with significant intraventricular mechanical delay respond to CRT (18), suggesting the latter may be a key determinant rather than the pattern of block per se.

Finally, the improvement in RV EF with CRT in RBBB hearts deserves comment. While the focus of resynchronization has been to improve LV function, very few studies have evaluated the effect of pacing on RV function. In the present study, tachypacing animals with pure RBBB versus pure LBBB resulted in significantly worse RV function. Right ventricular-only pacing and BiV pacing improved RV EF by \( \sim 14\% \). This is similar to the 22% enhancement in function \((dP/dt_{max})\) with RV pacing that Dubin et al. (19) demonstrated in patients with isolated right HF. This may be due to improved RV mechanical synchrony, energetics, and/or reduced tricuspid and pulmonary insufficiency, and warrants further evaluation.

The current study has some admitted limitations. The HF model was nonischemic, and the conduction blocks induced were relatively pure and distinct. This certainly differs from the clinical situation in many patients where combined conduction delay occurs still with a predominant RBBB electrocardiographic pattern. Ischemic disease may further alter the timing of LV activation in hearts with an underlying RBBB, and could be a source for greater intraventricular conduction delay in this setting. Additionally, the model did not account for pulmonary hypertension, which is commonly present in patients with RBBB and HF and may have an independent effect on mechanical dyssynchrony and the effect of CRT due to changes in septal loading and contraction patterns. Pulmonary pressures are elevated in the tachypacing model (35 to 40 mm Hg mean), however, so some of this pathophysiology did apply (20). One might expect an even smaller impact of dyssynchrony with more pronounced pulmonary hypertension, as the septal wall would be stented with reduced motion. Lastly, the results described here apply only to rest conditions.

**Conclusions**

The magnitude of cardiac dyssynchrony in a failing heart with a pure RBBB is considerably less than in hearts with an LBBB, despite similar prolongation of the QRS. This is due to asymmetry in the freedom of wall movement between septal and lateral walls, as RBBB generates relatively little early septal stretch with the pre-excited lateral wall and less lateral stretch when the septum contracts. Though CRT improves dyssynchrony in RBBB-HF hearts, this effect is smaller than observed in LBBB hearts. Lastly, with a pure RBBB conduction delay, there is little to no advantage of BiV over RV single-site pacing therapy to improve LV synchrony, and both modes can enhance RV EF.

**References**


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