Systolic Improvement and Mechanical Resynchronization Does Not Require Electrical Synchrony in the Dilated Failing Heart With Left Bundle-Branch Block

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Background—Biventricular (BiV) and left ventricular (LV) pacing similarly augment systolic function in left bundle-branch block (LBBB)–failing hearts despite different electrical activation. We tested whether electrical synchrony is required to achieve mechanical synchronization and functional benefit from pacing.

Methods and Results—Epicardial mapping, tagged MRI, and hemodynamics were obtained in dogs with LBBB-failing hearts during right atrial, LV, and BiV stimulation. BiV and LV both significantly improved chamber hemodynamics (eg, 25% increase in dP/dt max and aortic pulse pressure) compared with atrial pacing–LBBB, and this improvement correlated with mechanical resynchronization. Electrical dispersion, however, decreased 13% with BiV but increased 23% with LV pacing (P<0.01).

Conclusion—Improved mechanical synchrony and function do not require electrical synchrony. Mechanical coordination plays the dominant role in global systolic improvement with either pacing approach. (Circulation. 2002;106:1760-1763.)

Key Words: heart failure ■ pacing ■ electrical stimulation ■ bundle-branch block ■ ventricles

Biventricular (BiV) and left ventricular free-wall (LV) pacing are equally effective for acutely enhancing systolic function in failing human hearts with a left bundle-branch (LBB) type intra-ventricular conduction delay.1–3 Recent studies report positive long-term effects from BiV pacing,4 and LV pacing may achieve similar results.5,6 This has seemed paradoxical, in that LV preexcitation in normal hearts generates dyssynchrony and depresses function.7,8 Although electrical fusion between the LV stimulus and native right bundle conduction might occur, QRS duration remains wide with LV-only pacing2,5,9 and enhances function in patients with atrial fibrillation after atrioventricular (AV)-node ablation, precluding fusion.9 Alternatively, improved mechanical coordination and function maybe inducible in left bundle-branch block (LBBB)–congestive heart failure (CHF) hearts without generating electrical synchrony. The present study addressed this important question by using a novel canine model of cardiac failure combined with LBBB and by obtaining whole heart electrical activation and mechanical strain maps.

Methods

Protocol

Seven adult mongrel dogs underwent LBB radiofrequency-ablation using a 4-mm tipped electrode catheter placed within the LV to record LBB potentials. A right ventricle (RV)-apical endocardial lead was connected to a generator (Medtronic), and animals were rapidly paced (210 to 250 min⁻¹) to into heart failure. Once failure was established, animals were anesthetized (10 to 15 mg/kg thiobarbitral, 1% to 2% halothane), their hearts were exposed via median-sternotomy, and magnetic resonance (MR)–compatible pacing electrodes were sutured to the right atrium, LV midlateral wall, and near the RV-anterior groove. Micromanometers were placed in the central aorta and LV. In 3 animals, an additional endocardial lead was placed in the mid-ventricular septum. A nylon mesh fitted with 128 copper electrodes was placed over the epicardium. Electrodes were radiofrequency-filtered at the MR-scanner interface, and pacing-leads connected via isolation units to stimulators (Grass Instruments). Six to eight (~4-mm outside diameter) glass beads filled with gadolinium-DTPA (~5 mmol/L) were sewn to the sock. BiV and LV pacing were applied at 20 bpm above intrinsic rate while varying the AV delay (0 to 110 ms). The optimal AV delay used in subsequent MR-tagging protocols was that which provided full capture at highest maximal dP/dt (mean 69±17 ms). Tagged cine 3-dimensional LV images10 were obtained (GE Signa 1.5T) with a modified fastcard sequence at 15 ms/frame (30 to 33 frames/beat) during 30-second apneic periods. The scanner was externally triggered to synchronize electrical/mechanical data acquisition. Tagged images were obtained under atrial-LBBB, atrio-BiV, and atrio-LV pacing, in random order. Between each acquisition, unipolar epicardial electrical data were recorded at 1 kHz sampling. Animals were euthanized and their hearts were scanned to locate the gadolinium-DTPA beads. After excision, the heart was filled with vinyl polysi-
Data Analysis

Electrical signals were averaged over ~20 consecutive beats for each pacing mode. Local depolarization at each electrode was at \(-dV/dt_{\text{max}}\) referenced to the earliest ventricular activation time. Short- and long-axis tagged images were processed as described, with the displacement field modeled by a 4-dimensional B-spline, and circumferential strain \(\varepsilon_c\) determined over the entire LV-midwall. LV strain was spatially referenced to electrical maps using the position digitization data.

Mechanical dyssynchrony was indexed by a circumferential uniformity ratio estimate (CURE), \(\varepsilon_c\) at 24 circumferentially-distributed locations around each short-axis section was plotted versus spatial position for each time-frame. The more oscillatory the plot, the more dyssynchrony among segments around the short axis. Plots for ~6 midwall short-axis slices (excluding the most apical and basal regions) were subjected to Fourier analysis, and the results were averaged over space and time to yield CURE.

Results

LV and BiV Pacing Response in PACING-Induced Dilated Cardiomyopathy Combined With LBBB

<table>
<thead>
<tr>
<th></th>
<th>RA (LBBB)</th>
<th>BiV</th>
<th>LV</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min(^{-1})</td>
<td>123±13</td>
<td>123±13</td>
<td>123±13</td>
<td>NS</td>
</tr>
<tr>
<td>AV delay, ms</td>
<td>144±10</td>
<td>69±18*</td>
<td>69±18*</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV systolic pressure, mm Hg</td>
<td>86.6±7.7</td>
<td>97.4±12.6†</td>
<td>19.1±9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>14.0±4.5</td>
<td>11.3±2.1†</td>
<td>10.7±3.1†</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>dP/dt_{\text{max}}, mm Hg/s</td>
<td>1048±242</td>
<td>1392±143*</td>
<td>1390±339*</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>dP/dt_{\text{min}}, mm Hg/s</td>
<td>-960±162.2</td>
<td>-1152±250§</td>
<td>-1125±211§</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>22.8±6.5</td>
<td>28±6.5†</td>
<td>26.5±7†</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>23±12.7</td>
<td>27.5±16.2§</td>
<td>28±16.1§</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\(*P<0.001; †P<0.005; \#P<0.05 vs RA (LBBB). ‡P<0.05 vs LV."

Both LV and BiV Pacing Improve LV Mechanical Synchrony

Figure 2A shows example 3D strain maps for each pacing-mode at time of mitral valve (MV) closure, mid-systole, and late-systole. Displayed numbers are time intervals between septal and lateral wall electrical activation and the mechanical events. RA-LBBB pacing induced both septal shortening (blue) and lateral-wall stretch (yellow) by MV-closure through to mid-systole. Lateral contraction occurred in late systole. With LV-pacing, contraction started at the lateral pacing site with less marked stretch of the opposite (septal) wall. Note that by mitral valve closure, septal electrical-activation had already occurred. Lateral contraction advanced slowly, with shortening observed most prominently in the septum. These 2 areas then converged more synchronously during remaining systole. BiV activation resulted in less asymmetry at MV-closure, with 2 shortening fronts evident by mid-systole that converged during late systole. Thus, mechanical maps at mid- and late systole were similar between LV and BiV modes, both largely eliminating paradox stretch of the opposing wall. Concordant with this example, the CURE synchrony index similarly improved with both modes \((P<0.001)\), correlating with dP/dt_{\text{max}} (adjusted for mean in each animal; \(r=0.84;\) Figure 2B). In contrast, dP/dt_{\text{max}} did not correlate with interelectrode maximal electrical dispersion.
Discussion

BiV pacing was first proposed to treat failing hearts with discoordinate contraction, as it seemed the most logical way to achieve resynchronization. To date, most clinical studies have used this method, using simultaneous stimuli and highlighting QRS narrowing. LV-only pacing, however, produces similar mechanical and energetic effects as BiV pacing. The present study indicates that LV-pacing actually increases electrical dispersion over that from LBBB or BiV pacing, despite improving mechanical function and coordination. Lack of electrical fusion was supported by the electrode-array data, which showed an equal rise in electro-mechanical delay for an increment in AV delay, and the similar mechanical response despite substantially varied AV delays. These results support clinical data showing no correlation between change in QRS duration and mechanical response to LV or BiV pacing. Mechanical dyssynchrony rather than electrical dispersion seems to be the more relevant measure.

LV-pacing started with focal lateral-wall contraction that advanced slowly, with more prominent shortening next appearing in the septum. The precise mechanism for the apparent slow progression of antero-lateral wall shortening despite preexcitation remains to be fully resolved. We speculate that early stimulated regions interact with more pre-stretched (ie, preloaded) distal regions (septum), and that the resulting temporally and spatially varied load yields a nodal zone of apparent less-contracting muscle in the midlateral wall. Reduced and slowed myocardial stiffening, which is typical of failing myocardium, may be important in this regard. Importantly, LV and BiV pacing both generated less early and late systolic stretch of opposing walls versus LBBB, supporting recent clinical data. Further studies will be needed to assess the role of septal/RV loading, systemic afterload, pacing site and extent of stimulation, and underlying cardiomyopathy to these observations. At present, we can conclude that mechanical rather than electrical synchrony

Figure 1. A, Electrical epicardial activation map of whole heart for 3 pacing modes. Activation time is color coded (blue early—red late). With RA pacing (LBBB), electrical activation spread from right to left, whereas LV pacing reversed the pattern but did not reduce conduction delay. BiV pacing, however, showed improved electrical synchrony. B, Short-axis slice demonstrating that activation time at the endocardial septum was similar to that at epicardial electrodes over the same region. C, Group data for electrical activation delay (relative to earliest activation) at various sites for 3 pacing modes. Only BiV pacing reduced the gradient of activation delay.
seems most important for functional improvement with these therapies.

Acknowledgments
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References

Figure 2. A, Mechanical LV activation maps for 3 pacing modes. LV contraction was dysynchronous with RA (LBBB) stimulation, with early septal shortening (blue) and LV-free wall stretch (yellow) followed by lateral shortening. For BiV and LV pacing, mechanical activation was more synchronous, with less early and late systolic dyskinesia, and mechanical maps were remarkably similar by mid-late systole. Numbers shown reflect time duration from electrical stimulation at septal and lateral sites to time when mechanical data were displayed. B, Chamber synchrony (CURE) improved similarly with LV and BiV modes. *P<0.001. C, CURE positively correlated with dP/dtmax but not with electrical delay. dP/dtmax is adjusted for its mean value in each respective animal.
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