Abstract: Experimental studies have shown that biventricular pacing can improve systolic function in the failing heart with bundle branch block. The goal of this study was to develop and validate a three-dimensional computational model of the dilated failing heart with left bundle branch block to investigate how biventricular pacing can improve systolic mechanical performance and synchrony. In an anatomically detailed model of canine ventricular geometry, fiber architecture and Purkinje fiber network structure, a monodomain solution for anisotropic impulse conduction gave rise to electrical activation sequences that were consistent with experimentally observed patterns. Coupling this with regional myocardial mechanics computed for left branch bundle block and biventricular pacing showed good agreement with published regional fiber strains measured in dogs by using magnetic resonance imaging tagging. Biventricular pacing improved mechanical synchrony and systolic function in the computational model. The model may be a useful tool for investigating the pacing conditions required to achieve optimal mechanical improvement in the failing heart, especially because electrical synchrony does not correlate directly with mechanical synchrony and performance. Key words: Biventricular pacing, cardiac resynchronization therapy, finite element method, heart failure.

Cardiac resynchronization is becoming an increasingly popular therapy for improving ventricular function in the failing heart. Left bundle branch block (LBBB) is a common complication of dilated cardiomyopathy that affects over 3 million patients in the United States alone (1). During LBBB, cardiac pump function is most likely impaired because of disturbed synchrony of regional myocardial contraction (2).

To investigate the mechanical effects of altered cardiac activation sequence, some investigators have mapped ventricular electrical activity and regional contraction simultaneously in experimental animals (3,4). In these studies, bipolar electrograms were mapped on the epicardium in anesthetized dogs, and the activation patterns were registered with the sequence of local midwall fiber shortening measured in the same preparation by magnetic resonance imaging tagging under various pacing conditions.
Although regional strains and epicardial activation patterns have been measured in the intact heart (3,4), practical experimental methods for mapping three-dimensional distributions of other important variables such as stress, strain energy, or transmembrane potential are still not available.

A recent computational model of normal cardiac electromechanics (5) and the effects of ventricular pacing (6) showed good agreement with experimental measurements in anesthetized dogs. The goal of present study was to develop and validate a numerical model of the dilated failing canine heart with LBBB and investigate how biventricular pacing may improve ventricular electrical and mechanical synchrony and systolic pumping performance.

**Materials and Methods**

We rescaled a three-dimensional model of canine left and right ventricular anatomy with a detailed Purkinje fiber network, myofiber and sheet architecture (5,7) to approximate the measured diastolic dimensions of the dilated failing dog heart induced by three weeks of rapid pacing (3,8). In this commonly used experimental model, mean left ventricular end-diastolic diameter was 49 \pm 5 \text{ mm} (3), wall thickness was 8.7 \pm 0.3 \text{ (8) and left ventricular end diastolic axis ratio was 1.34 \pm 0.05 (8). The resulting 48-element tricubic Hermite mesh had 1,200 degrees of freedom and was used as the computational domain for simulating passive inflation and active contraction of the left and right ventricles. The model for electrical impulse propagation was based on the same anatomical mesh but required additional refinement to 768 tricubic elements and 19,200 nodal degrees of freedom.

In the present analysis, the resting myocardium was modeled as a nonlinear, orthotropic and nearly incompressible material (9). Pressure boundary conditions were specified on the left and right ventricular endocardial surfaces during filling, with left ventricular end diastolic pressure 14.0 \text{ mm Hg (LBBB)} and 11 \text{ mm Hg (biventricular pacing)}, which was consistent with experimental observation of failing dog heart (3,8).

Nonlinear membrane ionic kinetics were modeled using the two-variable modified FitzHugh-Nagumo (10,11) equations, and impulse propagation was modeled by using a monodomain formulation (10,11). The contribution of the Purkinje fiber network to ventricular conduction was modeled by adding an extra diagonal diffusion tensor, representing conductivity along the Purkinje fibers (5) on the luminal surfaces of the endocardial elements. Electrical activation time was defined as the instant when transmembrane potential reached 40 mV and it was used to initiate regional systolic tension development after a constant delay of 8.4 ms (4). This latter time (electrical activation time plus 8.4 ms) is referred to as “contractile activation time.” To model electrical propagation in the dilated failing heart with LBBB, we applied an initial stimulus at the right bundle branch, in contrast to our earlier model of normal activation (5) where both sides of the septum were stimulated simultaneously. In the model of biventricular pacing, stimuli were applied simultaneously on the LV midlateral epicardium and at the RV free wall epicardium.

The model of active contraction included sarcomere length-, time- and calcium-dependent active systolic tension development with transverse active stress components (9,12). To approximate twitch kinetics, a modified Hill equation was scaled by the internal scaling coefficient, a function of time after onset of contraction and sarcomere length, as described previously (12). Peak tension and the duration of relaxation in the model were chosen to match experimental measurements in dilated failing canine cardiac muscle summarized by Spinale (1), who reported time to peak isometric contraction of 252 \pm 2 \text{ ms and time to 50\% relaxation of 114\pm 1 \text{ ms. A Windkessel model for arterial impedance was coupled to ventricular pressure and volume to compute the hemodynamic boundary conditions. Ventricular cavity volume constraints were imposed during the isovolumic phases (5). The details of the formulation and solution of the electromechanical model have been described in detail previously for the case of normal activation (5) and ventricular pacing (6).

In keeping with the definition of “mechanical activation time” used by Wyman et al (4), we determined shortening onset time in the model as the time of maximum stretch in regions with a positive strain peak. Activation-shortening delay was computed as the difference between contractile activation time and shortening onset time at each point in the model. A negative delay means that the region began to shorten before the myofilaments at that site had begun to develop systolic tension.

**Results**

The computation of passive and active mechanics required 125 MB of main memory and ran for
approximately 20 minutes and 6 hours, respectively, on a SGI Origin 2100 (Silicon Graphics, Inc, Mountain View, CA). The model of electrical propagation required 2.8 GB of main memory and ran for approximately 72 hours on this platform.

To model activation of the dilated failing heart with LBBB, we applied a single stimulus at the right bundle branch. In general, activation proceeded quickly along the right ventricular side of the Purkinje fiber network and much more slowly through the septal wall. Propagation on the right ventricle occurred from endocardium to epicardium and was

![Fig. 1](image) Left-hand 2 columns: Model results for electrical activation times and shortening onset times during LBBB and biventricular BiV pacing. Right-hand 3 columns: Midwall fiber strain distributions at three phases during systole for both pacing conditions. For biventricular pacing, regional fiber shortening was more synchronous.

![Fig. 2](image) Fig. 2. Comparison between model results and experimental measurements (3) for electrical activation delay (relative to earliest activation) at various sites for both pacing conditions. Biventricular pacing reduced the gradient of activation delay. RV-pace, right ventricular pacing site for biventricular pacing; Ant, anterior wall; Sep, septum; Post, posterior wall; LV-pace, left ventricular pacing site during biventricular pacing.
not very different from that in a model of the normal heart. Activation of the left ventricle was more heterogeneous with breakthrough at the mid-septum after a 25-ms delay compared with right ventricular activation. A right-to-left contribution was present in the middle part on the right septal surface. Total electrical activation time was 108 ms with the latest area of activation occurring at the left ventricular free wall near the base. The model of biventricular pacing showed propagation along the left and right ventricular endocardium, from pacing sites to the septum, with a total electrical activation time of 86 ms and the latest activation occurring near the septum. In general agreement with experimental findings (3), these results are seen in Figure 1, which shows maps of electrical activation times for both pacing conditions (first column from left). This figure also maps shortening onset times (second column). The delay between electrical activation time and initial shortening varied significantly; it was as late as 40 ms in some regions but was also as early as −40 ms in others. This large variation in delay times was attributable to several factors including local anatomic variations, the location of the site relative to the activation wavefront, and regional end-diastolic strain. Group data for electrical activation delay (relative to earliest activation) at various sites are shown in Figure 2 for both pacing models along with experimental findings (3).

Biventricular pacing enhanced systolic mechanics in the model, as shown in Table 1. The slope of left ventricular pressure was calculated during isovolumic contraction and isovolumic relaxation and compared with experimental data (3), as shown in Table 1. Figure 1 also shows three-dimensional fiber strains for each pacing condition at the time of mitral valve closure (third column), mid-systole (fourth column), and late systole (fifth column).

### Table 1. Hemodynamics in Models of Dilated Failing Dog Hearts With LBBB

<table>
<thead>
<tr>
<th></th>
<th>LBBB Model</th>
<th>LBBB Experiment</th>
<th>BIV Pacing Model</th>
<th>BIV Pacing Experiment</th>
<th>Improvement, %</th>
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<tr>
<td>dP/dt max, mm Hg/s</td>
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<td>1048 ± 242</td>
<td>1680</td>
<td>1392 ± 413</td>
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<tr>
<td>dP/dt min, mm Hg/s</td>
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<td>−960 ± 162</td>
<td>−1210</td>
<td>−1152 ± 250</td>
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<td>Ejection fraction, %</td>
<td>21.2</td>
<td>23 ± 12.7</td>
<td>25.6</td>
<td>27.5 ± 16.2</td>
<td>4.4</td>
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</tbody>
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### Discussion

Biventricular pacing was first proposed to treat failing hearts with discoordinate contraction, as a simple way to achieve mechanical resynchronization. To date, most clinical studies have used this method, using simultaneous stimuli intended to maximize QRS narrowing.

A three-dimensional computational model of ventricular electromechanics was developed to study the role of biventricular pacing on regional myocardial mechanics during the cardiac cycle of the dilated failing heart. A previous electromechanical model of the normal heart (5) showed good agreement with experimental data in healthy dogs. The results also demonstrated the significant role of the Purkinje fiber system during normal rhythm and ventricular pacing on the mechanical activation sequence, as expected.

The new computational model showed that biventricular pacing improved mechanical synchrony and systolic function. Experimental studies suggest that electrical synchrony does not correlate directly with mechanical synchrony and systolic performance (3). For example, sequential cardiac resynchronization therapy can improve cardiac performance and mechanical synchrony better than simultaneous biventricular pacing (13). This computational model should be useful for future investigations of the optimal pacing conditions for enhanced mechanical synchrony and systolic ventricular function.

### References