Beneficial Effect on Cardiac Resynchronization From Left Ventricular Endocardial Pacing Is Mediated by Early Access to High Conduction Velocity Tissue Electrophysiological Simulation Study

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Background—Cardiac resynchronization therapy (CRT) delivered via left ventricular (LV) endocardial pacing (ENDO-CRT) is associated with improved acute hemodynamic response compared with LV epicardial pacing (EPI-CRT). The role of cardiac anatomy and physiology in this improved response remains controversial. We used computational electrophysiological models to quantify the role of cardiac geometry, tissue anisotropy, and the presence of fast endocardial conduction on myocardial activation during ENDO-CRT and EPI-CRT.

Methods and Results—Cardiac activation was simulated using the monodomain tissue excitation model in 2-dimensional (2D) canine and human and 3D canine biventricular models. The latest activation times (LATs) for LV endocardial and biventricular epicardial tissue were calculated (LVLAT and TLAT), as well the percentage decrease in LATs for endocardial (en) versus epicardial (ep) LV pacing (defined as %dLV=100×(LVLAT−LVLAT)/LVLAT and %dT=100×(TLAT−TLAT)/TLAT, respectively). Normal canine cardiac anatomy is responsible for %dLV and %dT values of 7.4% and 5.5%, respectively. Concentric and eccentric remodeled anatomies resulted in %dT values of 15.6% and 1.3%, respectively. The 3D biventricular-paced canine model resulted in %dLV and %dT values of −7.1% and 1.5%, in contrast to the experimental observations of 16% and 11%, respectively. Adding fast endocardial conduction to this model altered %dLV and %dT to 13.1% and 10.1%, respectively.

Conclusions—Our results provide a physiological explanation for improved response to ENDO-CRT. We predict that patients with viable fast-conducting endocardial tissue or distal Purkinje network or both, as well as concentric remodeling, are more likely to benefit from reduced ATs and increased synchrony arising from endocardial pacing. (Circ Arrhythm Electrophysiol. 2015;8:1164-1172. DOI: 10.1161/CIRCEP.115.002677.)

Key Words: cardiac resynchronization therapy ■ electrophysiology ■ electric stimulation ■ heart failure ■ heart ventricles

Dysynchronous heart failure (HF) is routinely treated with cardiac resynchronization therapy (CRT). During conventional biventricular (BV) CRT, pacing is applied to the right ventricle (RV) endocardium and the left ventricle (LV) epicardium via the coronary sinus (EPI-CRT). Current best practice results in 30% to 40% of CRT patients failing to display improved clinical response. Recent clinical1-3 and experimental4,5 evidence suggests that BV CRT with an endocardial (en) LV pacing (ENDO-CRT) can provide an improvement in acute hemodynamic response and stroke work over EPI-CRTen and offers a novel approach for increasing CRT response rates. However, the relative importance of cardiac physiology or better access to optimal pacing sites in causing this improved outcome remains controversial. Identifying and understanding physiological mechanisms behind improved ENDO-CRTen response are crucial for optimizing clinical procedures and identifying patients who will receive the maximal benefit from this therapy.

In acute left bundle branch block (LBBB) canine studies, ENDO-CRTen improved the systolic LV function over conventional EPI-CRTen.6 Electric activation times (ATs) as measured by contact mapping were decreased with ENDO-CRTen.
WHAT IS KNOWN

• Biventricular endocardial pacing can improve left ventricular acute hemodynamic response over conventional epicardial pacing. However, the mechanism underlying this improvement is unknown.

• Endocardial pacing leads to a reduction in epicardial and endocardial latest activation times compared to epicardial pacing in acute left bundle branch block canine electrophysiological studies.

• The relative importance of myocardial anatomical and physiological effects responsible for the observed decrease of activation times with endocardial pacing has not been established.

WHAT THE STUDY ADDS

• Fast endocardial conduction (FEC), whether via specialized high-conduction endocardial tissue and/or retrograde activation of the Purkinje network, is required to explain the experimental observations.

• Simulations predict that for endocardial pacing, early stimulation of the FEC region is the primary factor in reducing ventricular activation time. A secondary but significant factor is the shorter pathway from the stimulus site to the remainder of the myocardium.

• Patients with concentric as opposed to eccentric remodelling may be more likely to experience reduced activation times and increased synchrony resulting from endocardial pacing.

Hyde et al  Mechanisms of Endocardial CRT Improvement 1165

over EPI-CRT BV, consistent with concurrent improvements in systolic LV function and more synchronous electric activation compared with EPI-CRT BV. Specifically, ENDO-CRT BV resulted in an average decrease in LV endocardial and BV epicardial latest ATs (LATs; measured as time from stimulus) of ≈16% and 11%, respectively, when compared with EPI-CRT BV at the equivalent transmural epicardial location. Similar improvements in electric synchrony have been reported for canines undergoing ENDO-CRT BV with LBBB and myocardial infarction, or LBBB with HF. These invasive measures are replicable in canine ECG recordings, where a 20% decrease in QRS duration (QRSd) with ENDO-CRT BV was observed relative to EPI-CRT BV.9

The exact mechanisms underlying the decreases in ATs for ENDO-CRT BV versus EPI-CRT BV have not been fully elucidated. It has been hypothesized that the differences are caused by (1) shorter activation path lengths in ENDO-CRT BV allowing earlier activation in remote regions; (2) earlier activation of fast-conducting endocardial tissue, which has been shown to have a higher conduction velocity (CV) than epicardial tissue in canines and in humans; and (3) bulk tissue anisotropy, which may be important in dysynchronous HF patients where major fiber remodeling and redistribution of gap junction proteins, such as Connexin 43, are known to occur.9,14,15

To test the role and relative importance of these hypotheses, we used computational models of tissue excitation to quantify the mechanisms listed above in terms of their impact on ATs and to investigate if the combined or individual effects of these mechanisms can plausibly explain the observed reduction in ATs with LV endocardial pacing. A 2-dimensional (2D) short-axis model was created to allow for a tractable model sensitivity analysis, and results were subsequently confirmed in 3D models.

Methods

Excitation

Cardiac tissue electrophysiology was simulated by the monodomain equation

\[ \beta \left( \frac{\partial V}{\partial t} + I_{ion}(V_{m}, I) \right) = V \cdot (\sigma \nabla V_{m}) + I_{st}, \]

where \( \beta = 0.14 \, \mu m^{-1} \) is the membrane surface/volume ratio, \( C_{m} = 1 \, \mu F/cm^2 \) is the membrane capacitance, \( V_{m} \) is the transmembrane potential and is dependent on time \( t \), \( I_{st} \) is the density of the total ionic current, \( \sigma \) is the conductivity tensor, \( I_{ion} \) is the cell model state variables, and \( I_{st} \) is a transmembrane stimulus current. As we solely simulate activation, in both human and canine models, electric \( I_{ion} \) was calculated using the ten Tusscher 2006 human cardiac myocyte model.16 The Cardiac Arrhythmia Research Package (CARP17,18) was used to numerically solve the equation via the finite element method using a global time step of 25 \( \mu s \).

Quantifying the Role of Anatomy

The role of anatomy in dictating myocardial ATs for endocardial and epicardial pacing strategies was quantified in a 2D short-axis BV geometry derived from canine histological data (see Data Supplement for a description of the 2D model construction; Figures I–III in the Data Supplement).19,20 This generic tissue domain was characterized by ecc, a measure of the epicardial short-axis elliptical eccentricity (ratio of RV–LV free wall dimension to anterior–posterior wall dimension), and rLV, the endocardial LV radius. Setting these values to ecc=0.5 and rLV=20.5 mm generated a representative average canine cross-section with a lateral RV–LV distance of 82 mm.21 By varying the values of ecc and rLV, a wide range of short-axis anatomies can be generated which reflect variability of cardiac shape and structural remodeling that may occur during cardiomyopathy (Figure 1: Figure III in the Data Supplement). The 2 geometric parameters were conservatively perturbed by ±20% to ensure that the physiologically relevant remodeled geometries were contained within the space of simulated geometries, for example, canine HF models result in a 20% reduction in wall thickness which corresponds to a 48% increase in ecc and rLV. The ratio of LV wall thickness/rLV, denoted ‘\( h \)’, was also introduced as a dependent variable that is easily measured within the clinic. A similar 2D human cardiac anatomy was generated by uniformly scaling the canine toplometry to achieve an LV blood pool diameter of 66 mm.22

A generic 3D BV canine geometry was constructed to test the efficacy of the 2D model results and allow for BV pacing. This geometry had ventricular blood pool volumes of 43 and 22 mL for the LV and RV, respectively, corresponding to previously obtained experimental canine ventricular geometries.23 The apex–base length was 60 mm, the anterior–posterior length was 54 mm, and the short-axis RV–LV length was 80 mm. LV and septal wall thickness was 8±8 mm (Figure 2B). The corresponding tetrahedral finite element mesh had over 55M elements and a mean edge length of 0.25 mm.

Tissue Microstructure and Conductivity

The fiber imbrication angle was assumed to be negligible, consistent with reported imbrication angles of 3° to 5° in the canine.24 The effect
Simulations were performed to test the impact of cardiac anatomy, FEC, and bulk tissue anisotropy on myocardial ATs. For each model combination of anatomy and conductivity, the percentage decrease in LVLAT (%dLV) and in TLAT (%dT) was calculated between epicardial and endocardial LV pacing conditions (denoted by subscripts ep and en, respectively). These values were compared with the experimentally observed values for %dLV and %dT of 16% and 11%, respectively, as found in the canine study of van Deursen et al.6 The 2D anatomy sensitivity analysis required 484 simulations to be run (11×11 uniform parameter grid, endocardial/epicardial pacing, with/without FEC). Furthermore, 2D simulations were performed on a human scale model to ensure that the conclusions were consistent with respect to alterations of local tissue curvature across canine and human scales. The 2D canine model results were subsequently extended to a 3D canine model to confirm their validity in whole-heart geometries and to investigate the effect of bulk tissue anisotropy.

Effect of Anatomy
Simulated activation times for the default 2D canine geometry without FEC are presented in Figure 3A and 3B, and the corresponding values for %dLV and %dT are 7.4% and 5.5%, respectively (Table 1). Although this decrease in LAT is a direct consequence of the inherent cardiac geometry alone, it is approximately half of that observed experimentally.

The sensitivity of %dLV and %dT to cardiac anatomy changes was examined in the canine 2D model by varying the geometric parameters ecc and rLV within the range of ±20%. The LATs for ENDO-CRTLV and EPI-CRTLV converge for eccentric remodeling, that is, increasing epicardial eccentricity and decreasing LV wall thickness, whereas conversely the LATs diverge for concentric remodeling (Figure 4A and 4B). The 95% confidence interval for the experimentally observed mean values for %dLV and %dT is denoted by the area within the green isolines, which can be seen to lie in the strongly concentrically remodeled portion of the parameter space. The simulated ranges of %dLV and %dT were 0.6% to 16.1% and
0.4% to 12%, respectively. Qualitatively similar results were also obtained for the 2D human scale model (Table 1).

**Effect of Fast Endocardial Conduction**

The presence of FEC results in a significant alteration to the activation pattern and excitation wavefront curvature, particularly for EPI-CRT. In the 2D model, the wavefront initially expands from the sole stimulus site, but there is a manifest discontinuity in wavefront propagation direction resulting from the rapidly activated LV endocardium in both anterior and posterior regions (Figure 3D). Thus, relatively rapid endocardial activation causes an increase of effective epicardial CV remote from the stimulus site, as epicardial points are activated transmurally via an effective secondary wavefront initiating from the endocardium, as opposed to circumferentially by the stimulus wavefront. Such an increase in effective epicardial CV has been measured experimentally.26

In terms of bulk tissue activation, increasing the LV endocardial CV reduced all measured LATs (Table 1). The 2D default canine model values for %dLV and %dT are 13.2% and 8.4%, respectively (Table 1), with similar findings for the human model (Table 1) and the 3D canine with FEC and bulk tissue isotropy under LV-only pacing (Table 2).

The sensitivity of the 2D canine models with FEC to variations in anatomy can be seen in Figure 4C and 4D. The influence of anatomy on LATs has been enhanced, as illustrated by the enlarged ranges of %dLV and %dT which are 2% to 22.8% and 1.3% to 15.6%, respectively. Furthermore, the increased confidence interval area indicates that the range of anatomies consistent with experiments has increased significantly, on average from 3% of the tested parameter space to 16% (Figure V in the Data Supplement). Importantly, the confidence interval representing the experimental findings are more central in simulations with FEC compared with the simulation results in the absence of FEC, that is, a smaller deviation from the average canine anatomy is required to achieve similar results to the experimental data when FEC is present in the model. The human scale model results are similar, with the most extreme concentric (eccentric) remodeled anatomy having a %dT value of 15.9% (1.8%; Table 1). Of the 3 geometric variables (ecc, rLV, and h), h consistently correlated the best with the percentage decreases in LATs, with the minimum absolute correlation coefficient being 0.97 (Table 3).

The isotropic 3D canine model with FEC, under similar BV pacing conditions as were applied experimentally, resulted in %dLV and %dT values of 5.2% and 0.1%, respectively (Table 2; Figure 5). The absence of tissue anisotropy resulted in the TLAT being dependent on the RV apical pacing site only and so no change in %dT was observed when switching between ENDO and EPI-CRT. In general, the strong influence of FEC on LVLATs is clearly observed on the 17-segment LV endocardial surfaces (Figure 5, insets).

**Table 1. LATs (Units of ms) and Percentage Decreases in Related Activation Measurements With Varying Model Conductivity Assumptions for the 2D Canine Model and the 2D Human Scale Model (CV=0.65 m/s, LV-only pacing)**

<table>
<thead>
<tr>
<th>Model</th>
<th>Conductivity Type</th>
<th>ecc Perturbation</th>
<th>rLV Perturbation</th>
<th>LVLAT&lt;sub&gt;en&lt;/sub&gt;</th>
<th>TLAT&lt;sub&gt;en&lt;/sub&gt;</th>
<th>LVLAT&lt;sub&gt;ep&lt;/sub&gt;</th>
<th>TLAT&lt;sub&gt;ep&lt;/sub&gt;</th>
<th>%dLV</th>
<th>%dT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canine</td>
<td>Homogenous</td>
<td>−20%</td>
<td>−20%</td>
<td>94.3</td>
<td>130.6</td>
<td>112.3</td>
<td>148.5</td>
<td>16.1</td>
<td>12</td>
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<tr>
<td>Canine</td>
<td>Homogenous</td>
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<td>0</td>
<td>103</td>
<td>142.3</td>
<td>111.3</td>
<td>150.5</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Canine</td>
<td>Homogenous</td>
<td>+20%</td>
<td>+20%</td>
<td>113.7</td>
<td>151.4</td>
<td>114.4</td>
<td>152</td>
<td>0.6</td>
<td>0.4</td>
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<tr>
<td>Canine</td>
<td>FEC</td>
<td>−20%</td>
<td>−20%</td>
<td>73.9</td>
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<td>95.7</td>
<td>139.9</td>
<td>22.8</td>
<td>15.6</td>
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<td>0</td>
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<td>128.6</td>
<td>89.2</td>
<td>140.4</td>
<td>13.2</td>
<td>8.4</td>
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<tr>
<td>Canine</td>
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<td>+20%</td>
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<td>139.5</td>
<td>93.8</td>
<td>141.4</td>
<td>2</td>
<td>1.3</td>
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<td>−20%</td>
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<td>210.3</td>
<td>181.4</td>
<td>239.6</td>
<td>16.2</td>
<td>12.2</td>
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<td>0</td>
<td>166</td>
<td>229.7</td>
<td>179.7</td>
<td>243.4</td>
<td>7.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Human</td>
<td>Homogenous</td>
<td>+20%</td>
<td>+20%</td>
<td>183.3</td>
<td>244.5</td>
<td>185.1</td>
<td>246.2</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Human</td>
<td>FEC</td>
<td>−20%</td>
<td>−20%</td>
<td>118</td>
<td>189.2</td>
<td>153.7</td>
<td>224.9</td>
<td>23.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Human</td>
<td>FEC</td>
<td>0</td>
<td>0</td>
<td>122.5</td>
<td>206.1</td>
<td>142.2</td>
<td>225.7</td>
<td>13.8</td>
<td>8.7</td>
</tr>
<tr>
<td>Human</td>
<td>FEC</td>
<td>+20%</td>
<td>+20%</td>
<td>139.6</td>
<td>220.7</td>
<td>143.7</td>
<td>224.8</td>
<td>2.9</td>
<td>1.8</td>
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</tbody>
</table>

Subscripts en and ep indicate endocardial and epicardial LV stimulation, respectively. 2D indicates 2-dimensional; %dLV, percentage decrease in LVLAT; %dT, percentage decrease in TLAT; ecc, eccentricity parameter; FEC, fast endocardial conduction; LAT, latest activation times; LV, left ventricular; LVLAT, LAT for the LV endocardium; rLV, LV blood pool radius parameter; and TLAT, LAT for the total myocardium as represented by the electric activity recording sites in Figure 1.
Figure 4. Sensitivity analysis of myocardial latest activation times (LATs) to changes in the cardiac short-axis geometry. The effect of perturbations in the left ventricular (LV) blood pool radius (rLV, horizontal axis) and epicardial eccentricity (ecc, vertical axis) on the percentage decrease in left ventricular (%dLV, A and C) and total (%dT, B and D) LATs is presented using a common color scale. Experimentally observed mean values for %dLV and %dT of 16% and 11%, respectively, are indicated by the thicker inner green isolines, and 95% confidence intervals for these means are denoted by the outer thinner lines (Data Supplement). The percentage of the parameter space enclosed by the confidence interval is also reported in the top right corner of each figure. Two conductivity models are considered, homogeneous isotropic conductivities without (A and B) and with (C and D) fast endocardial conduction (FEC). The presence of FEC results in LATs for the average short-axis geometry that are more consistent with experimental observations as opposed to without FEC, as indicated by the relative closeness of the experimental values to the values simulated at the default geometry (white +).

Effect of Bulk Tissue Anisotropy
Anisotropic bulk tissue without FEC in the 3D model gives %dLV values of −3.3% and −7.1% for the LV and BV pacing protocols, respectively. These results are both quantitatively and qualitatively different from experimental findings, despite being a more biophysically realistic approach to modeling cardiac tissue excitation compared with isotropic bulk tissue. We found that under LV pacing, the introduction of FEC was sufficient to improve the qualitative match, with %dLV and %dT values becoming 24.8% and 14.5%, respectively (Table 2). Switching to BV pacing to arrive at the simulation, most representative of the canine experiments of van Deursen et al further altered the results quantitatively to give %dLV and %dT equal to 13.1% and 10.1%, respectively (Table 2). The switch from LV-only to BV pacing also resulted in a significant decrease in TLATen (173.3 to 89 ms).

Focusing on the TLATen results for the anisotropic 3D simulations (which one may take to be a surrogate for QRSd under EPI-CRTBV pacing conditions), there was a 3.8% reduction in this TLAT when FEC was introduced into the model (Table 2).

Both anisotropic bulk tissue models with and without FEC predicted an increase in LV endocardial first-to-last AT (13% and 35% increases, respectively) when EPI-CRTBV was compared with ENDO-CRTBV in qualitative agreement with experimental contact mapping measurements.7

Discussion
We investigated the effects of ventricular shape, FEC, and tissue anisotropy on myocardial ATs resulting from epicardial and endocardial pacing protocols using computational models of cardiac electrophysiology. Our results indicate that FEC and early endocardial activation are key factors in reducing activation times that may play an important role in reducing mechanical dyssynchrony and improving patient response to endocardial CRT strategies.

Table 2. LATs (Units of ms) and Percentage Decreases in Related Activation Measurements With Varying Model Conductivity Assumptions for the 3-Dimensional Canine Model With LV-Only and BV Pacing

<table>
<thead>
<tr>
<th>Pacing Mode</th>
<th>Conductivity Type</th>
<th>LVLATen (ms)</th>
<th>TLATen (ms)</th>
<th>LVLATep</th>
<th>TLATep (ms)</th>
<th>%dLV</th>
<th>%dT</th>
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<tbody>
<tr>
<td>LV-only pacing</td>
<td>Isotropic bulk</td>
<td>107.5</td>
<td>144.8</td>
<td>111.4</td>
<td>151.2</td>
<td>3.5</td>
<td>4.3</td>
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<tr>
<td>LV-only pacing</td>
<td>Isotropic bulk and FEC</td>
<td>74.8</td>
<td>129.1</td>
<td>83.4</td>
<td>139.2</td>
<td>10.3</td>
<td>7.3</td>
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<tr>
<td>LV-only pacing</td>
<td>Anisotropic bulk</td>
<td>147.8</td>
<td>177.4</td>
<td>143.2</td>
<td>181.6</td>
<td>−3.3</td>
<td>2.4</td>
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<tr>
<td>LV-only pacing</td>
<td>Anisotropic bulk and FEC</td>
<td>73.5</td>
<td>148.2</td>
<td>97.7</td>
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<td>24.8</td>
<td>14.5</td>
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<tr>
<td>BV pacing</td>
<td>Isotropic bulk</td>
<td>74.2</td>
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<td>75.2</td>
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<td>Isotropic bulk and FEC</td>
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<td>BV pacing</td>
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<td>89</td>
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<td>10.1</td>
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Subscripts en and ep indicate endocardial and epicardial LV stimulation, respectively. %dLV indicates percentage decrease in LVLAT; %dT, percentage decrease in TLAT; BV, biventricular; FEC, fast endocardial conduction; LAT, latest activation times; LV, left ventricular; LVLAT, LAT for the LV endocardium; and TLAT, LAT for the total myocardium as represented by the electric activity recording sites in Figure 2B.
in ATs experimentally observed between ENDO-CRT and EPI-CRT pacing is a key finding of this study. For example, the anisotropic 3D BV-paced model without FEC produced a negative value of %dLV which is contrary to the experimental findings of Strik et al, whereas the introduction of FEC correctly predicted a reduction of LV LAT under endocardial pacing. Furthermore, we have demonstrated that the 2D canine model findings are robustly applicable to the upscale human model, despite scale-dependent changes in local geometric curvature (Table 1).

Regardless of FEC presence, the 3D anisotropic bulk models consistently report a significant reduction of TLAT ep when LV pacing is switched to BV pacing (Table 2). Although there is some conflicting data on the effect of such a pacing change on QRSd, for example, some studies have shown a negligible difference in QRSd between LV and BV pacing, whereas other studies have shown a clear reduction in QRSd with BV over LV-only pacing. This simulation result is consistent with experimental contact mapping findings.

FEC has a large impact on both myocardial ATs and the pattern of activation, not just on the endocardium but also throughout the LV (Figure 5), and thus FEC will also affect the onset of tissue contraction. The underlying cause of FEC, when the heart is activated from an external stimulus, remains controversial. Researchers have attributed FEC to either the intrinsic properties of the LV endocardium or retrograde activation of the Purkinje network which may manifest as fast conduction. This latter study by Taccardi et al experimentally investigated the effect of myocardial structure and FEC on ATs under intrinsic and transmural pacing protocols. The presence of canine FEC was clearly demonstrated by a short-axis isochronal map of activation resulting from LV epicardial pacing whereby measurements were made using a series of transmural electrodes, and the resulting activation pattern is qualitatively similar to the activation pattern of Figure 3D. However, although the authors exclusively refer to FEC because of retrograde activation of the Purkinje system, the data presented are not sufficient to determine the causative form of the FEC. For example, their endocardial application of Lugol solution to prevent Purkinje activation could also potentially inactivate specialized high-conducting endocardial myocytes.

Transmural gradients in myocardial CV have been reported in several studies. The presence of a region of relatively high conductivity endocardial tissue is supported by reports of increased cell area, higher gap junction density, and higher sodium channel density at the endocardium as opposed to epicardium. However, to achieve a near doubling of endocardial CV, as reported in experimental measurements, requires a nearly 4-fold increase in conductivity because of the approximate square root dependence of CV on conductivity. This significant increase in conductivity is not clearly supported by these observed transmural gradients.

An alternative cause of FEC is the recruitment of fast conducting subendocardial Purkinje fibers that quickly spread activation across the endocardium resulting in a rapid effective endocardial conductivity. In canines, Purkinje fiber potentials are reported to be found at depths of 2 to 4 mm into the subendocardium, and the Purkinje network covers the apex, the lower half of septum, and the lower third of the LV free wall. Retrograde activation of the Purkinje system has been found to occur at junctions between the Purkinje network and the myocardium, measured directly during RV pacing, and observed during sinus rhythm in idiopathic ventricular tachycardia patients. A role for the Purkinje network in CRT activation implies that early access to the network would improve CRT response via the rapid and homogeneous activation of the LV as opposed to slow activation through the bulk tissue. Interestingly, LV apical or septal pacing sites are more optimal in terms of acute hemodynamic response in canines, where the Purkinje network is coupled with the myocardium. In human cases, however, basal LV pacing, which is an area predominantly absent of Purkinje fibers, tends to result in improved clinical outcomes.

There is insufficient experimental or clinical evidence to clearly differentiate between fast-conducting endocardial

### Table 3. Pearson Correlation Coefficients Relating Geometric Variables With the Decrease in LV and Total LATs for Endocardial Versus Epicardial Pacing

<table>
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<tr>
<th>Variables</th>
<th>Homo %dLV</th>
<th>Homo %dT</th>
<th>FEC %dLV</th>
<th>FEC %dT</th>
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<tr>
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<td>-0.51</td>
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<td>-0.68</td>
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<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
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</table>

All coefficients were determined with \( P < 0.001 \). %dLV indicates percentage decrease in LV endocardial LAT; %dT, percentage decrease in total LAT; ecc, eccentricity parameter; FEC, fast endocardial conduction, h, ratio of LV wall thickness/LV blood pool radius; Homo, homogeneous conductivity; LAT, latest activation time; LV, left ventricular; and rLV, LV blood pool radius parameter.
This article has focused on understanding the causative mechanisms of these clinical findings from a cardiac electrophysiological viewpoint. It has been argued that the benefit of LV endocardial pacing may be derived from the ability to access the optimal pacing site when the anatomy of the coronary sinus limits access to the epicardial site in the same region.3 Our results identify an important role for early access to FEC in achieving synchronous activation with ENDO-CRT. If the Purkinje network is recruited during CRT then the ability to map Purkinje potentials37 offers an interesting opportunity to guide ENDO-CRT implantation procedures.

Our findings also suggest that ENDO-CRT may be more likely to benefit patients with higher h values, that is, reduced LV blood pool radii and thicker LV walls. This is quantitatively demonstrated by the 9-fold and 8-fold increases in %dLV and %dT, respectively, for the FEC sensitivity analysis (Figure 4C and 4D), suggesting that patients with concentric cardiac structural remodeling may observe a larger benefit from endocardial pacing than patients with decompensated eccentric remodeling.

Comparison With Previous Studies
This study has focused on modeling results in comparison with canine rather than human data. This reflects the greater availability of electric activation data under a range of pacing protocols in canine models relative to similar human measurements. There is a scarcity of human data relating to ATs with canine rather than human data. This reflects the greater availability of electric activation data under a range of pacing protocols in canine models relative to similar human measurements. There is a scarcity of human data relating to ATs with endocardial compared with epicardial pacing, and results from these few relevant studies are often conflicting.

Some human studies have found limited difference in hemodynamics between endocardial and epicardial pacing,1,4,9 in contrast to findings in canines.6,9 This may be because of interspecies physiological differences or optimal response may be dependent on the mode of stimulus delivery because roving catheters were used in patients, whereas plunge electrodes were used in canine experiments.

The effect of endocardial pacing on QRSd remains controversial. Recent studies in patients that compared the mean QRSd across multiple pacing sites did not report a significant decrease in QRSd or in the time from first-to-last activation of the LV endocardial surface for ENDO-CRT relative to conventional CRT,3,5,39 whereas a decrease in QRSd was found in human and canine cases when comparing paired transmural pacing sites.9,41 One possible explanation for the former finding is that CRT patients tend to have a reduced ejection fraction which is associated with eccentric remodeling, and as we have shown in this article, this remodeling type is less sensitive to LV pacing strategy.

Clinical Implications
The potential benefit to patient outcome resulting from endocardial pacing strategies has already been extensively documented in several small-scale clinical studies.2,3,5,39,42 This study has focused on understanding the causative mechanisms of these clinical findings from a cardiac electrophysiological viewpoint. It has been argued that the benefit of LV endocardial pacing may be derived from the ability to access the optimal pacing site when the anatomy of the coronary sinus limits access to the epicardial site in the same region.3 Our results identify an important role for early access to FEC in achieving synchronous activation with ENDO-CRT. If the Purkinje network is recruited during CRT then the ability to map Purkinje potentials37 offers an interesting opportunity to guide ENDO-CRT implantation procedures.

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Limitations
All the electrophysiological models used in this study are approximations and aim to capture the salient system features of interest. A short-axis tissue model based on 2 variables may be overconstrained to model all possible pathological cardiac anatomies. For example, increasing the LV blood pool radius via the rLV variable causes a decrease in septal and LV wall thickness. However, given the computational efficiencies and the fact that the key simulation results are the relative differences in LATs (and thus the same geometry is used for comparing endocardial with epicardial pacing types), we think that this limitation is warranted and acceptable.

Tissue function is also an important factor in patients undergoing CRT, as they frequently have myocardial fibrosis/sca which will have a significant effect on tissue conduction properties and the response to CRT. This modeling study did not specifically explore the effects of localized scar which may be an important factor when extrapolating these results to clinical practice.

Conclusions
We have shown using a computational model of cardiac electrophysiology that the presence of and early access to fast-conducting endocardial tissue are predicted to be the primary factor in reducing ventricular AT during ENDO-CRT. The benefit by accessing a shorter pathway to the remainder of the myocardium is also significant, and patients with concentric remodeling are more likely to experience reduced ATs and increased synchrony arising from ENDO-CRT as opposed to patients with eccentric remodeling. Our results suggest a plausible biological explanation for the observed benefit of LV endocardial pacing compared with epicardial pacing.

myocardium and Purkinje fiber network recruitment–mediated FEC. However, it would seem that early access to the fast-conducting region improves activation synchrony in canines, regardless of the causative mechanism. Furthermore, our results suggest that determining whether or not FEC recruitment has been captured may be clinically difficult. Using our most experimentally relevant model (3D anisotropic), we have shown that EPI-CRTVW without FEC results in a TLatVW of 92.5 ms, whereas the inclusion of FEC only reduces TLatVW by 3.8% to 89 ms (Table 2). Thus, the clinical evaluation of total AT, via measuring modalities, such as ECG, may fail to successfully delineate between FEC capture and noncapture.

Although thus far primary consideration has been paid to the acute LBBB model scenario, there are limited structurally remodeled data that can be compared with the simulated results. In Strik et al.,7 their LBBB+myocardial infarction animal model resulted in increased %dLV and %dT values (34% and 16%, respectively), which is predicted by the concentrically remodeled geometry with FEC (%dLV=27% and %dT=18%) and to a lesser extent without FEC (%dLV=16% and %dT=12%). Their tachypacing-induced LBBB+HF animal model, however, resulted in %dLV=20% and %dT=18%, whereas the eccentrically remodeled simulation that most closely matches the experimental geometry (default ecc and rLV +8% perturbation) predicted changes %dLV=9% and %dT=5.7%. This discrepancy could be explained by the observed one-third reduction in CV for tachypacing-induced nonischemic dilated cardiomyopathy canines.15 Accounting for this CV reduction in the bulk myocardium in a new simulation for the corresponding geometry increased %dLV to 20% and %dT to 9%.
Acknowledgments
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Dr Niederer is also supported by British Heart Foundation for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. Circulation. 2012;125:1835–1847. doi: 10.1161/CIRCULATIONAHA.111.047274.

Disclosures
None.

References


Beneficial Effect on Cardiac Resynchronization From Left Ventricular Endocardial Pacing Is Mediated by Early Access to High Conduction Velocity Tissue: Electrophysiological Simulation Study

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SUPPLEMENTAL MATERIAL

Electronic Supplementary Material 1

The 2D tissue domains were constructed as follows, with all constant values being based on canine histologic data $^1$–$^3$:

(i) A unitless ellipse with constant semi-major axis $a=1.0$ and variable eccentricity, denoted $ecc$, was constructed to form the outer epicardial boundary. A second ellipse of equal eccentricity, was constructed with semi-major axis $a_2=a-t_{RV}$, where $t_{RV}$ is the right ventricle (RV) wall thickness. A constant value of $t_{RV}=0.15$ and a default variable value of $ecc=0.5$ were used (Figure S1(a)).

(ii) The location of the LV centre was determined. This was done by constructing a circular arc with the desired LV blood pool radius, denoted $r_{LV}$, centred at a point $(c^*,0)$ with $0<c^*<a-t_{RV}$, and with the arc angle ranging from $-45^\circ$ to $45^\circ$ relative to the positive x axis. The variance of the wall thickness of the region defined by this arc and its equivalent outer elliptical boundary was determined for this $c^*$ by calculating the transmural distance at 100 equally spaced radial lines throughout this segment. The value of $c^*$ that minimises this variance (see Figure S2) was taken to be the LV centre, $c$ (Figure S1(b)). The LV endocardial boundary was then given by the circle with radius $r_{LV}$ centred at $(c,0)$.

(iii) Septal thickness was taken to be equal to lateral LV thickness, thus a circular arc was constructed of radius $a-c$ centred at the LV centre and extended between the two points of intersection of this arc and the inner ellipse in the negative x plane (Figure S1(c)).

Finally, two lines were constructed that start at the outer ellipse, passed through the same two points of intersection and met at the LV centre (Figure S1(d)). These lines partitioned the geometry into three regions of interest, the RV, the LV and the septum (Figure S1(e)).

For Finite Element Method modelling purposes, the default anatomical model was discretised as a triangular mesh with 212,329 elements, with mean edge length of 0.18 mm,
created using the 2D meshing software *Triangle*. By varying the geometric parameters, a variety of cardiac geometries can be created (Figure S3).

**Figure S1**

Fig. S1. Template design for the 2D short-axis geometry. Sub-figures a-d, in conjunction with the description in ESM1, outline the geometry generation process. (a) The outer ellipse forms the epicardial boundary, while the inner ellipse forms a portion of the RV free wall endocardium and defines the RV free wall thickness. (b) The LV centre is positioned along the positive x-axis such that the variance of the lateral LV wall thickness (shaded region) is minimised. (c) The RV-septal arc is added with thickness equal to the lateral LV wall. (d) Two lines are extended from the LV centre to the epicardium, passing through the points of intersection of the RV-septal boundary and the inner elliptical boundary in the negative x-plane. (e) Schematic indicating the key geometric parameters and regions. a; epicardial semi-major axis length. b; epicardial semi-minor axis length. c; LV centre x-coordinate. rLV; LV blood pool radius. tRV; thickness of the RV wall.

* http://www.cs.cmu.edu/quake/triangle.html
Fig. S2. Due to the geometric construction of our tissue domain, there is a uniquely defined minimum for the variance of the lateral LV thickness. The lateral LV region was defined to be the LV portion within ±45° of the LV centre point being evaluated with respect to the positive x-axis. Here, we explicitly show the global minimum of this variance for all geometries using an extreme geometric parameter value, and the default geometry.
**Fig. S3.** All simulated geometries on an 11x11 grid of uniform parameter distribution in the range of ±20% perturbations.
Electronic Supplementary Material 2

The three anatomical regions of interest (RV, LV and septum) were linearly partitioned into 10 transmural segments which had a piecewise constant transmurality-dependent fibre angle assigned to each region as determined from canine histology (Figure S4)\textsuperscript{4,5}.

Increasing the number of discrete transmural regions to 12 was found to alter the latest ATs by less than 1%.

Figure S4

(a) Cubic functions (full lines) fit to experimental data (+ from Nielsen et al.\textsuperscript{5}, ∙ from Streeter et al.\textsuperscript{4}) for the out-of-plane fibre angles assigned to the LV, septal and RV regions respectively. For the LV and RV, transmurality is taken to be zero at their respective endocardial surface, whereas for the septum it is zero at the LV endocardium. (b) Line glyphs representing the fitted fibre directions on a 2D short-axis slice, coloured by positive angle with the xy-plane.
Electronic Supplementary Material 3

The reduction in latest activation times (LATs) for the 2D short-axis canine model when LV pacing is switched from a lateral epicardial to endocardial location for CV=0.3 m/s and CV=0.475 m/s are presented in Table S1.

### Table S1

Demonstration of the dependency of %dLV and %dT on the ratio of bulk tissue vs fast endocardial conduction CV for CV=0.3 m/s (A) and CV=0.475 m/s (B). Latest activation times (LATs; units of ms) and percentage decreases in related activation measurements with varying model conductivity assumptions for the 2D canine model and the 2D human scale model. Subscripts en and ep indicate endocardial and epicardial LV stimulation, respectively. LVLAT; LAT for the LV endocardium. TLAT; LAT for the total myocardium as represented by the electrical activity recording sites in Figures 1. %dLV; percentage decrease in LVLAT. %dT; percentage decrease in TLAT. Pert; perturbation. FEC; fast endocardial conduction. Ecc; eccentricity parameter. rLV; LV blood pool radius parameter.

#### (A) CV 0.3 m/s, LV only pacing

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#### (B) CV 0.475 m/s, LV only pacing

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Electronic Supplementary Material 4

Bootstrapping was applied to the available experimental data to estimate the 95% confidence interval in the average decrease in LVLATs and TLATs under endocardial pacing compared to epicardial pacing. The approximating distributions were assumed to be normal with means and standard deviations as reported in the original experimental literature. A specific example is now provided for the %dLV confidence interval estimator. LVLAT_{ep} and LVLAT_{en} were assumed to be normally distributed via N(82.4,8.8) and N(69.3,7.8), respectively (Fig. S5(A)). A thousand samples are drawn from each distribution to build a frequency chart of the percentage decrease in LV LAT when using endocardial pacing, from which the mean %dLV is calculated (Fig. S5(B)). This process is repeated a thousand times to construct a frequency chart of the average mean %dLV, and a normal distribution is fitted to this latter data from which the 95% confidence interval is derived (Fig. S5(C)).

**Fig. S5.** Statistical bootstrap method used to estimate the 95% confidence interval (Conf.Int.) from averaged experimental data. Presented are the results related to the decrease in left ventricular endocardial latest activation times (LATs) for endocardial pacing as opposed to epicardial pacing, with the same method being applied to the total myocardial LATs (results not shown). Firstly, the reported statistics for the LATs under epicardial and endocardial pacing are assumed to be normally distributed (A)(see Table 1 of van Deursen et al ). A thousand samples are drawn from each distribution to build a frequency chart of the percentage decrease in LV LAT when using endocardial pacing, from which the mean %dLV is calculated (B). This process is repeated a thousand times to construct a frequency chart of the average mean %dLV, and a normal distribution is fitted to this latter data from which the 95% confidence interval is derived (C).
Supplement References


