Three-Dimensional Mapping of Optimal Left Ventricular Pacing Site for Cardiac Resynchronization

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Background—The efficacy of cardiac resynchronization therapy (CRT) depends on placement of the left ventricular lead within the late-activated territory. The geographic extent and 3-dimensional distribution of left ventricular (LV) locations yielding optimal CRT remain unknown.

Methods and Results—Normal or tachypacing-induced failing canine hearts made dyssynchronous by right ventricular free wall pacing or chronic left bundle-branch ablation were acutely instrumented with a nonconstraining epicardial elastic sock containing 128 electrodes interfaced with a computer-controlled stimulation/recording system. Biventricular CRT was performed using a fixed right ventricular site and randomly selected LV sites covering the entire free wall. For each LV site, global cardiac function (conductance catheter) and mechanical synchrony (magnetic resonance imaging tagging) were determined to yield 3-dimensional maps reflecting CRT impact. Optimal CRT was achieved from LV lateral wall sites, slightly more anterior than posterior and more apical than basal. LV sites yielding ≥70% of the maximal dP/dtmax increase covered ≈43% of the LV free wall. This distribution and size were similar in both normal and failing hearts. The region was similar for various systolic and diastolic parameters and correlated with 3-dimensional maps based on mechanical synchrony from magnetic resonance imaging strain analysis.

Conclusions—In hearts with delayed lateral contraction, optimized CRT is achieved over a fairly broad area of LV lateral wall in both nonfailing and failing hearts, with modest anterior or posterior deviation still capable of providing effective CRT. Sites selected to achieve the most mechanical synchrony are generally similar to those that most improve global function, confirming a key assumption underlying the use of wall motion analysis to optimize CRT. (Circulation. 2007;115:953-961.)

Key Words: bundle-branch block ■ heart failure ■ pacing

Cardiac resynchronization therapy (CRT) obtained from biventricular (BiV) stimulation has emerged as an important new treatment for selected heart failure patients.1,2 CRT enhances systolic function and cardiac energetics,3 reverses chamber remodeling,4 and improves clinical symptoms and outcome.5-7 Despite its overall efficacy, ≈30% of CRT recipients do not appear to benefit.8-10 This may stem from inappropriate patient selection or suboptimal implementation of the therapy; both aspects have become the focus of many recent investigations aimed at better targeting and delivering CRT.

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CRT typically involves placement of a right ventricular (RV) endocardial and left ventricular (LV) free wall epicardial lead, the setting of intraventricular and interventricular delay times, and adjustment of simulator parameters to ensure consistent delivery of BiV excitation. Among these factors, LV lead placement is particularly important.10,11 Although it is generally recommended that the lead be placed in the midlateral free wall, this is not always feasible because of suboptimal venous anatomy. Yet, the full 3-dimensional (3D) distribution of efficacious LV sites and just how anterior or posterior a lead might be positioned before losing CRT efficacy remain unknown. Furthermore, the extent of the LV pacing region yielding both optimal global hemodynamic responses and mechanical synchrony has not been previously defined. This extent is increasingly relevant because many have turned to motion-based analysis of dyssynchrony to help identify candidates and to optimize lead position.

To address these questions, we developed a custom epicardial stimulation/recording system to randomly vary the LV pacing site over the entire free wall and to generate 3D maps relating pacing site to functional and mechanical synchrony...
responses. LV sites yielding effective CRT covered a substantial area of the lateral free wall in both normal and failing hearts. The results further support a strong relationship between functional hemodynamics and global mechanical resynchronization.

Methods

Acute pacing studies were conducted in 10 adult anesthetized mongrel dogs with LV mechanical dyssynchrony. In 5 animals, dyssynchrony was generated by RV free wall pacing (nonfailing) and CRT achieved by combining this with LV stimulation at various LV sites. The remaining animals underwent combined radiofrequency ablation of the left bundle, followed by 3 to 4 weeks of tachypacing (210 minutes¹ for 3 weeks) to induce dyssynchronous heart failure. In these dogs, CRT was implemented with an RV lead (free wall, n=3; apical, n=2) combined with LV stimulation.

At the time of study, dogs were anesthetized (thiopental 12.5 mg/kg, isoflurane 1% to 2%) and underwent a midline thoracotomy to expose the heart. The epicardium was fitted with a magnetic resonance imaging (MRI)-compatible, 128-electrode nylon sock secured along the AV junction. The density of the sock electrodes was distributed so that ~90 leads were dispersed over the LV epicardium. Interlead spacing varied with the contour and size of a given heart but was generally <1 cm. A custom-designed computer-interface pacing program provided random selection of a given LV lead combined with constant RV stimulation to vary the configuration of BiV pacing. Cardiac function was assessed by a pressure-volume catheter (SPR-550-7, Millar Instruments Inc, Houston, Tex) inserted through a carotid artery into the LV. Bipolar pacing electrodes were sewn to the right atrium and ground reference electrodes to the aortic root fat pad. For studies conducted with MRI, the chest was closed with the pacing and sock electrode wires exiting superiorly. Electrodes were radiofrequency filtered at the MR scanner interface and right atrial leads connected via isolating units to a stimulator (Grass Technologies, West Warwick, RI).

The 128 sock electrodes were interfaced with a custom computer-controlled stimulator recording system that determined the spatial and temporal output for each electrode. Stimulator circuits were optically isolated to eliminate ground loops and to protect the heart from 60-Hz leakage currents. Four additional outputs provided triggering of external devices for right atrial pacing, initiation of MRI scanning, ventilation breathholding, and acquisition of hemodynamics. This technique allowed rapid and random testing of multiple pacing protocols while simultaneously recording hemodynamic and mechanical data. Hearts were paced at 10 to 20 bpm above the intrinsic sinus rate with an AV delay of 40 to 70 ms to ensure ventricular preexcitation.

Animals were euthanized on completion of the protocol, and hearts were excised and filled with vinyl polysiloxane to maintain end-diastolic shape. The 3D location of each sock electrode was then digitized (MicroScribe 3DLX, Immersion Corporation, San Jose, Calif) to generate a 3D finite-element rendering of the pacing sites (Figure 1). This rendering formed the basis for color-encoded 3D maps with the magnitude of a given hemodynamic or mechanical synchrony parameter plot at each electrode position.

MRI Studies

In a subset of animals, hemodynamic measurements were supplemented by 3 to 4 cross-sectional, tagged cine MRIs (GE Sigma, Huntley, Ill; 1.5 T) obtained for each selected LV lead position using a modified fast-card sequence at 15 ms per frame (30 frames per beat). Imaging was acquired during 30-second breathholds. The tagging pulse sequence consisted of nonselective radiofrequency pulses separated by a spatial modulation of magnetization–encoding gradient to generate 2 orthogonal sets of parallel planes of magnetic saturation with a tag separation of ~7 mm. The scanner was set to the following: field of view, 36 cm; slice thickness, 8 mm; temporal resolution, ~38 ms; echo time, minimum full; flip angle, 32°; imaging matrix, 256×128; and views per segment, 8. Tagged cine MRIs were analyzed with harmonic-phase image analysis to derive circumferential strain at 24 equally spaced segments about a short-axis slice.

Data Analysis

Hemodynamic pressure-volume data were recorded at 250 Hz, and results for each pacing site were derived from an average of 10 sequential cycles. These data were used to derive arterial pulse pressure (dP/dtmax), time constant of relaxation (τ), and stroke work (pressure-volume loop area), reflecting ejection and isovolumic phases of contraction. We derived τ from logistic approximation of the isovolumic relation time curve.12

Mechanical dyssynchrony was indexed by the circumferential uniformity ratio estimate (CURE).13,14 CURE is generated by plotting instantaneous circumferential strains at 24 equally spaced segments around a short-axis slice at each time point, subjecting each plot to Fourier analysis, and determining the ratio of first- to zero-order power.13 CURE ranges from 0 (pure dyssynchrony) to 1 (synchronous). In dyssynchronous failing hearts, CURE was determined for each LV pacing site during BiV pacing and compared with the baseline (right atrial pacing, dyssynchronous contraction) CURE index for that animal.

Functional and dyssynchrony 3D maps were used to define regions of effective CRT (ie, the LV epicardial zone containing electrodes that yielded a given percent or greater of the maximal possible response for any given hemodynamic/dyssynchrony parameter). The optimal pacing region was determined using a cost function defined as the ratio of the mean benefit from pacing within a given region divided by its relative size as a percentage of the LV surface. Very selective regions (ie, small regions) may have the highest mean CRT response but would be considered less optimal than those with lower mean response thresholds but greater 3D distribution.

To define the relationship between function and mechanical response to CRT, functional (hemodynamic) maps and mechanical synchrony maps were compared. Then, 3D plots of overlapping territories with >70% maximal stroke work improvement and mechanical resynchronization were determined. In addition, regression plots of functional versus mechanical response to CRT were generated from pooled data from all 5 dyssynchronous failing animals.

Computational and Statistical Analyses

The 3D surface geometries were reconstructed for each heart based on digitized electrode data fit to a piecewise polynomial using prolate spherical coordinates. Color maps encoding functional or mechanical metrics were fit using a similar process. Finite-element
rendering and computational analysis were performed with Matlab (MathWorks, Natick, Mass) software.

Baseline dyssynchrony data (atrial pacing, left bundle-branch block [failing dogs] and right ventricular pacing [nonfailing dogs]) were measured throughout the pacing protocol, and values for each animal were derived from the mean of these repeated observations. Optimal CRT response was obtained by averaging data from the 10 most responsive LV electrodes. To compare CRT responses, the LV surface region providing a given percent or more of maximal CRT effect was determined for each animal, and CRT response was derived from the average for each pacing site within this region. The region size was expressed as percent of LV surface area.

Within-animal comparisons (ie, dyssynchrony versus CRT) were analyzed through the use of paired /tests; between-group analysis (nonfailing versus failing) was done by nonpaired /tests. Assessment of the mechanical response to CRT as a function of pacing site was performed by multivariate linear regression on pooled data from the 5 failure animals, with pacing site circumferential (anterior, lateral, and posterior) and longitudinal (basal, mid, and apical) location serving as independent variables. The data from each animal were first mean adjusted (average of both absicissa and ordinate was 0) to correct for interanimal variance. Statistical analysis was performed with Systat software (Systat Software, Inc, San Jose, Calif).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Hemodynamics
Summary baseline hemodynamics for dyssynchronous nonfailing and failing hearts before and after optimal CRT are provided in Table 1. Baseline cardiac function in failing hearts was significantly reduced. Both RV single-site pacing and left bundle-branch block right atrium pacing increased QRS duration \( \propto 2\)-fold. (Normal canine QRS duration is \( \approx 80\) ms; data not shown.) Optimal CRT resulted in an \( \approx 30\% \) increase in dP/dtmax, an \( \approx 10\% \) increase in pulse pressure, and an \( \approx 20\% \) decrease in \( \tau \) in both types of hearts. These responses are similar to changes reported in human subjects with dilated cardiomyopathy and left bundle-branch block.13 QRS narrowing with CRT reached significance in nonfailing but not failing hearts despite similar hemodynamic improvements in both.

3D Maps of Global Function (Hemodynamic) Response Versus LV Pacing Site
Figure 2 shows representative 3D functional maps from a dyssynchronous nonfailing (Figure 2A through 2D) and failing (Figure 2E through 2G) heart. Maps for percent change in dP/dtmax, pulse pressure, stroke work, or \( \tau \) as a function of pacing site are provided. Hearts are oriented to displayed both anterolateral and posterolateral walls. In general, pacing over the lateral wall was most optimal (darker orange/red) independently of the functional index used. This optimal region was broad and fairly uniform from base to apex. Map reproducibility was tested in 2 animals and found to be highly consistent, and overall data were similar among animals. Distributions of optimal CRT for both nonfailing and failing hearts were similar. In a subset of dogs, we tested whether RV pacing at the free wall or apex influenced the data. This pacing site had no influence (\( P > 0.8 \)).

Characterization of the Optimal Pacing Region
To determine the largest region on the LV surface in which pacing resulted in a physiologically meaningful response, isocontours were generated to delineate territories over the LV surface reflecting a given percent or greater of the maximal CRT response. Peak response was derived from the mean of the top 10 electrode responses for a given index. Figure 3A is a sample of the isocontours over the LV surface defining regions \( > 70\% \), \( > 80\% \), and \( > 90\% \) of the maximal dP/dtmax response. As the percent threshold rises, the mean response increases but the territory area declines. Figure 3B shows the cost function (ratio of mean response to size of region for nonfailing and failing hearts). Because the cost function was optimal at the 70% threshold, this level was used to define the optimal pacing region.

The mean functional response (for dP/dtmax) and relative surface size of 70%, 80%, and 90% response regions are provided in Table 2. The optimal pacing area (\( > 70\% \) peak response) covered \( \approx 40\% \) of the LV surface in both nonfailing and failing dyssynchronous hearts. Limiting the region to that achieving 90% of the peak response yielded an \( \approx 3\% \) increase in mean dP/dtmax increase but a nearly 3-fold reduction in territory size.

The anatomic position for the optimal pacing region is shown in Figure 3C, displayed on a short-axis mid LV slice. The anterior edge of the region is expressed by angle \( \gamma \) from the RV-LV groove, whereas its breadth is given as the angle \( \theta \) from this boundary. Summary data for both angles are displayed in Figure 3D and show that the radial location and overall breadth of these territories were similar for normal and failing hearts.

The size of the optimal pacing region was similar when characterized using diastolic optimization maps (ie, plots of \( \tau \) versus LV stimulation site; Figure 2D and 2H). In the nonfailing and failing canine, the optimal diastolic pacing region was 40.7 \( \pm 1.2\% \) and 41.4 \( \pm 1.4\% \) of the LV surface, respectively.

| Table 1. Effects of Optimal CRT (Mean of LV Sites With Response \( > 90\% \) of Maximum Effect) Obtained in Dyssynchronous Nonfailing and Failing Hearts |
|---|---|---|---|---|---|---|---|
| | Nonfailing | | Failing | |
| | Dyssynchrony | Optimal CRT | Percent Change | Dyssynchrony | Optimal CRT | Percent Change |
| QRS duration, ms | 114.8 \( \pm 5.6 \) | 82.0 \( \pm 6.1 \)* | \(-26.1 \pm 4.3 \) | 150.2 \( \pm 9.8 \) | 136.6 \( \pm 8.1 \)† | \(-7.9 \pm 6.2 \) |
| dP/dtmax | 1212.1 \( \pm 158.7 \) | 1607.9 \( \pm 70.4 \)* | 33.73 \( \pm 2.91 \) | 737.1 \( \pm 78.0 \) | 970.1 \( \pm 24.2 \)* | 32.84 \( \pm 0.79 \) |
| Pulse pressure | 36.1 \( \pm 3.7 \) | 39.4 \( \pm 1.1 \)† | 9.8 \( \pm 1.5 \) | 21.4 \( \pm 1.4 \) | 23.8 \( \pm 0.8 \)* | 10.5 \( \pm 0.4 \) |
| \( \tau \) | 24.7 \( \pm 1.2 \) | 19.3 \( \pm 0.4 \) | \(-21.7 \pm 1.9 \) | 36.3 \( \pm 3.7 \) | 30.1 \( \pm 0.5 \)† | \(-18.1 \pm 1.0 \) |

* \( P \leq 0.002 \), † \( P < 0.05 \) vs baseline; ‡ nonsignificant difference vs baseline.
Mechanical Dyssynchrony Assessment in the Dyssynchronous Failing Canine

Figure 4A is a representative rendering of the relative mechanical activation (time to peak circumferential strain) in the dyssynchronous failing dog at baseline and with CRT. The figure is colored according to the time of activation, with blue being early activated and red being late activated. The red dot denotes the septum. At baseline, the observed degree of mechanical dyssynchrony in this representative dog yielded a CURE index of 0.53. During BiV pacing with a given LV pacing site (green dot), more homogeneous mechanical activation is observed, and the CURE index in-
creased to 0.82. This figure highlights the ability of CURE to quantify global mechanical synchrony. On average, the 5 dyssynchronous failing dogs had a baseline CURE index of 0.56 ± 0.08; with optimal resynchronization (>90% of maximal response), the CURE index increased to 0.87 ± 0.01.

3D Maps of Global Mechanical Response (CURE) Versus LV Pacing Site

Figure 4B shows a representative 3D mechanical synchrony map in a dyssynchronous failing animal, with the value of CURE depicted at each LV pacing site. The heart is oriented to show the anterolateral wall (left) and posterolateral wall (right). Pacing over the lateral wall resulted in the greatest (darker orange/red) enhancement in global mechanical synchrony. The region of efficacious sites was similar to that derived from functional/hemodynamic indexes, was highly reproducible for all failing animals, and was independent of the RV pacing site. The optimal CURE region was 32.2 ± 6.6% of the total LV surface, and pacing within this region resulted in a CURE index of 0.81 ± 0.01. The 80% and 90% response regions were 21.6 ± 6.1% and 8.6 ± 2.6% of the total LV surface, respectively, and pacing within these regions resulted in average CURE indexes of 0.84 ± 0.01 and 0.87 ± 0.01, respectively.

3D Maps of Functional Response and Mechanical Synchrony Versus LV Pacing Site

Figure 4C displays a representative union plot for the LV region that provided >70% of the maximal functional response defined by stroke work and mechanical synchrony indexed by CURE. Union plots for 4 dogs are shown in Figure 4D. The union region (green territory) was smaller (20.4 ± 1.4% of the LV surface) and favored apical regions, although there was still a substantial area of the midlateral wall. This distribution was also independent of RV pacing site.

TABLE 2. Magnitude of Mean Systolic Improvement From Different LV Stimulation Electrode Groups With Each Group Selected to Provide >70%, >80%, or >90% of the Maximal Response and Percent of the LV Surface Covered by These Stimulation Electrode Groups (Response Regions)

<table>
<thead>
<tr>
<th>Response Region</th>
<th>Nonfailing</th>
<th>70%</th>
<th>Nonfailing</th>
<th>80%</th>
<th>Failing</th>
<th>Nonfailing</th>
<th>90%</th>
<th>Failing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of increase in dP/dtmax with CRT</td>
<td>29.0 ± 1.0</td>
<td>27.67 ± 0.4</td>
<td>32.4 ± 1.5</td>
<td>30.4 ± 0.5</td>
<td>33.7 ± 2.9</td>
<td>32.84 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of LV surface</td>
<td>44.0 ± 4.5</td>
<td>41.7 ± 2.9</td>
<td>28.5 ± 4.5</td>
<td>27.8 ± 3.6</td>
<td>11.3 ± 2.7</td>
<td>16.8 ± 3.5</td>
<td></td>
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</tr>
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</table>

A response of >70% of the peak response was obtained over ~40% of the LV free wall.

Figure 4. A, 3D plot of relative mechanical activation time (time from QRS to peak circumferential strain) in a dyssynchronous failing heart (left bundle-branch block) and during BiV pacing. The green dot shows the LV stimulation site. B, Synchrony indexed by CURE was calculated as a function of varying LV pacing site and plotted on 3D maps. The red region denotes the territory in the lateral wall that achieved optimal mechanical resynchronization. C, Full maps derived for ventricular stroke work and synchrony (CURE) were determined in 4 failing hearts, and the territories producing optimal responses (>70% maximal) for both were calculated and are displayed in green (far right). This region was somewhat smaller and located in the midlateral (midapical) wall. D, Overlay maps generated for all 4 animals revealing similarly sized, shaped, and localized co-optimal regions. Dogs A and B had RV free-wall stimulation during BiV pacing; dogs C and D had RV apical pacing during BiV pacing.
Correlating Functional Response and Mechanical Synchrony: Regression Analysis

Figure 5A shows the relation between functional response to CRT (stroke work) versus mechanical synchrony (CURE) as a function of varying LV pacing site from multiple electrodes in dyssynchronous failing hearts. Pacing over the lateral wall achieved greater synchrony and global work over anterior and posterior regions \( (P < 0.001) \). As shown by the 3D plots (Figure 5B), there was a gradient of responsiveness with better CRT in apical versus basal regions for all sectors of the LV free wall \( (P < 0.001) \). This was similar regardless of the RV pacing site.

Discussion

The present study provides the first full 3D characterization of the location and extent of optimal LV pacing region for BiV CRT in both normal and failing dyssynchronous hearts. The main findings are that (1) the optimal LV pacing region is fairly broad and centered over the mid to apical lateral LV wall, (2) the anatomic extent and location of this region are not altered by heart failure per se, and (3) reasonable concordance exists between regions that yield the most mechanical synchrony and those that achieved optimal LV systolic and diastolic performance. These data have implications for successful CRT implementation and efforts to achieve optimal therapy.

Optimal CRT Pacing Region: The Sweet Spot

The present data support prior although fairly limited clinical data suggesting that optimal CRT is achieved by pacing the lateral wall when this territory contracts last. The finding that this territory is fairly large (>40% of the LV free wall) is new but provides reassurance for those responsible with implanting a lead in this region. Indeed, clinical implementation of the LV lead has always been an inexact science, and the general efficacy of CRT without knowledge of the precise optimal region has suggested that this territory may indeed be fairly sizable. The homogeneity of the region in the present study probably reflects the nature of the models used (ie, normal or tachypacing failing hearts) but could differ in ischemic ventricles. If severe coronary artery disease exists subtending one region more than another or heterogeneous tissue damage associated with patchy ischemic injury, more regional disparities in electromechanical properties may exist. Consequently, the distribution of optimal pacing sites during CRT may be altered. However, rather than displace this territory or make it larger, one would most likely observe variability of CRT response within the zone as a result of conduction delay or block or infarction (scar). Although it is likely that the overall placement and extent would be similar to what we have observed, the present data should not necessarily be used to guide lead placement in patients with ischemic cardiomyopathy.

Our results also suggest that CRT response within the optimal territory is better preserved moving apically compared with basally. This might seem a bit surprising in that one would suspect that at the apex, LV activation is closer to that achieved by the RV apical lead. Previous canine pacing studies have demonstrated similar benefit of LV
apical pacing, and when translated clinically, Vanagt et al. observed similar benefit of apical pacing in children undergoing cardiovascular surgery. Other clinical studies in patients with heart failure and dyssynchrony have yet to corroborate these observations. One possibility is that smaller hearts (ie, those in children and dogs) may yield somewhat different contraction/excitation patterns that favor more apical placement over what is observed in much lager adult human hearts. The benefit of more apical versus basal stimulation may relate to faster radial dispersion (anterior-posterior), followed by apex-base activation based on fiber architecture to provide faster activation synchrony and better LV function. In contrast, basal stimulation may lead to less efficient ejection because blood is displaced toward both the LV apex and the LV outflow tract. Finally, apical stimulation may reduce mitral regurgitation by resulting in earlier activation of the papillary muscles.

An early focus was on increasing the distance between the RV and LV stimulation sites to yield more efficacious CRT, but recent studies have turned instead to identifying the region of latest mechanical activation. We found that with BiV pacing using a fixed RV stimulation site, there was a broad area of optimal LV stimulation with varying distance to the RV lead, including LV apical regions. Sites closer to the RV lead (ie, midapical) proved superior to more distal sites (basal) with RV free wall or RV apical stimulation. Thus, the physical distance between RV and LV stimulation appears less important than getting into the region of later contraction.

The finding of a similar size and distribution of the optimal LV pacing region in both normal and failing hearts deserves comment. Chronic dyssynchronous failure in the present canine model not only generates mechanical dyssynchrony but also results in underlying molecular changes noted and further supports prior work indicating that electrical synchrony is not required to achieve mechanical synchrony. Thus, geographic location appears more important than electrical dispersion in defining the optimal pacing region. Although we are cautious in extending implications to patients with ischemic cardiomyopathy, the extent of the optimal region is likely similar to what we observed; however, the response to CRT may be more variable within this distribution because of ischemia and scar as previously discussed.

Global Function Versus Mechanical Synchrony

There has been a growing appreciation for the prognostic utility of measure of regional dyssynchrony based on wall motion analysis over QRS duration for chronic CRT response. Nelson et al. were among the first to demonstrate that although QRS grossly correlated with acute hemodynamic improvement from CRT, 3D analysis of basal dyssynchrony provided a far better correlation. Numerous studies have since demonstrated that dyssynchrony measures based on longitudinal tissue Doppler imaging, color-coded dyssynchrony imaging, and myocardial speckle tracking can be used to predict chronic cardiac and clinical improvement from CRT. Global invasive LV function is rarely ever assessed yet is arguably the key factor that predicts whether CRT will impart hemodynamic and ultimately symptomatic benefit. In this regard, our analysis comparing the distribution of LV pacing sites that optimally resynchronize the heart with those that provide optimal cardiac work is reassuring but highlights a somewhat complex relation between the 2 properties. Although the overall overlap region was similarly centered in the lateral-apical wall, it was smaller in extent because bordering pacing sites improved work or dyssynchrony, but not always both, at the >70% optimal level. The mechanisms for areas that do not overlap include signal noise and potential mechanical effects other than synchrony such as papillary muscle contraction timing and mitral regurgitation. Nonetheless, overall considerable concordance exists between these regions.

Study Limitations

Our study has several limitations. Although the dyssynchronous failing model used recapitulates many of the pathophysiological features of human dilated cardiomyopathy, as already noted, it is not a model of ischemic heart disease. Greater heterogeneity of electrical and mechanical properties of ischemic myocardium could alter optimal LV pacing site, although we suspect that the major impact would be to enhance the variability of response within the region rather than fundamentally alter its size, shape, and location. Another potential limitation of the study is that the RV was stimulated epicardially rather than endocardially, as is performed clinically. It is likely that the transmural spread of electrical and mechanical activation is slightly different between epicardial and endocardial RV stimulation during BiV pacing, although further work is required to isolate and quantify these differences.

We generated mechanical dyssynchrony in 2 ways: RV free wall pacing and right atrial pacing with a left bundle-branch block. On the basis of previous studies by our laboratory, these approaches appear to generate the same response with respect to inducing mechanical dyssynchrony, molecular changes, and altering LV function and therefore were not expected to influence the analysis of the present study.

Finally, current clinical work focuses on measuring the region of latest activation using cardiac MRI or tissue Doppler to help guide LV lead placement, and there continues to be growing interest in the ability to identify the geographic extent of the optimal pacing region directly
from noninvasive tagging MRI. Although possible, such information requires acquisition of activation time at each pacing electrode and implementation of complex registration techniques\(^\text{14}\) that were not used in the present study for practical reasons. Rather, we used a simplified MRI approach (harmonic-phase image analysis) to maximize the number of electrode configurations that could be tested while reducing the required MR imaging and analysis time.

Conclusions
From the outset, the notion that an epicardial BiV stimulation approach could achieve clinically relevant mechanical resynchronization in select heart failure patients required an underlying presumption: that the optimal region for LV lead placement was sizable enough that one would land there without knowing precisely where it was. Unfortunately, coronary venous anatomy is highly variable from patient to patient; it is not always possible to target a specific LV location by this route. This, and the appreciation that 30% of CRT recipients do not demonstrate clinical benefit, has led to substantial recent research on how to best optimize treatment delivery.\(^\text{29}\) Our data show that for nonischemic hearts, the LV lateral pacing territory is fairly large, that one can pace somewhat anteriorly or posteriorly and still achieve efficacy, and that more apical sites provide improved responses. Although obtained in an animal rather than a human model, these findings should help current efforts to improve CRT implementation.

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Drs Lardo and Kass are paid consultants for Guidant/Boston Scientific.

References
Cardiac resynchronization therapy (CRT) requires the placement of a left ventricular (LV) pacing lead, typically via an epicardial vein. Prior studies have shown that the lateral wall is generally the optimal pacing site, although the geographic size and more precise location of this region remain unknown. This is clinically relevant because coronary venous anatomy varies among patients, and it is not always possible to target a specific LV location via this route. Furthermore, little clinical response to CRT occurs in \( \sim 30\% \) of patients, raising questions about optimal lead placement. We therefore generated a canine model of cardiac dyssynchrony in both normal and dilated failing hearts and determined the full 3-dimensional LV pacing region for optimal CRT. The latter was defined by improved global function and analysis of dyssynchronous wall motion using magnetic resonance imaging. The data reveal the optimal LV pacing territory to be fairly large, covering \( \sim 40\% \) of the LV free wall and positioned slightly more apical than basal. Furthermore, the LV pacing territory yielding optimal improvement in global function is quite similar to that which best reduces regional wall motion dyssynchrony. This finding is important because many current clinical assessments of CRT are based on tissue Doppler–derived measures of regional dyssynchrony, and this correlation is tacitly assumed. Although these data have been obtained in an animal model free of ischemic disease, they probably are applicable to various forms of heart failure and provide new insight into the placement of the LV lead to optimize CRT.
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