cardiac resynchronization therapy in a chronic canine model of ischemic heart failure

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Left ventricular endocardial or triventricular pacing to optimize cardiac resynchronization therapy in a chronic canine model of ischemic heart failure. Am J Physiol Heart Circ Physiol 303: H207–H215, 2012. First published May 4, 2012; doi:10.1152/ajpheart.01117.2011.—Cardiac resynchronization therapy (CRT) is a recommended treatment for heart failure but ~30% of patients appear to not benefit from the therapy. Left ventricular (LV) endocardial and multisite epicardial [triventricular (TriV)] pacing have been proposed as alternatives to traditional LV transvenous epicardial pacing, but no study has directly compared the hemodynamic effects of these approaches. Left bundle branch block ablation and repeated microembolizations were performed in dogs to induce electrical dyssynchrony and to reduce LV ejection fraction to <35%. LVEDP/dP/dtmax and other hemodynamic indexes were measured with a conductance catheter during LV epicardial, LV endocardial, biventricular (BiV) epicardial, BiV endocardial, and TriV pacing performed at three atrioventricular delays. LV endocardial pacing was obtained with a clinically available pacing system. The optimal site was defined as the site that increased dP/dtmax by the largest percentage. Implantation of the endocardial lead was feasible in all canines (n = 8) without increased mitral regurgitation seen with transesophageal echocardiography and with full access to the different LV endocardial pacing sites. BiV endocardial pacing increased dP/dtmax more than BiV epicardial and TriV pacing on average (P < 0.01) and at the optimal site (P < 0.01). There were no significant differences between BiV epicardial and TriV pacing. BiV endocardial pacing was superior to BiV epicardial and to TriV pacing in terms of acute hemodynamic response. Further investigation is needed to confirm the chronic benefit of this approach in humans.

multisite left ventricular pacing

Cardiac resynchronization therapy (CRT) is a recommended treatment for patients with symptomatic heart failure, severely impaired left ventricular (LV) function, and ventricular dyssynchrony. Large randomized trials have demonstrated that CRT improves quality of life and symptoms and reduces heart failure-related hospitalizations, as well as mortality (1, 5, 18, 20). However, ~30% of patients implanted with a single LV transvenous lead placed in a lateral or posterolateral tributary of the coronary sinus or a surgical epicardial lead appear nonresponsive to CRT. Adjusting the LV pacing site probably has the most potential to influence the effectiveness of CRT in certain patients. Optimal pacing position is highly variable between patients, and the site is often constrained by coronary sinus anatomy. Alternative pacing strategies such as LV endocardial pacing and multisite epicardial (i.e., triventricular) pacing have been proposed to improve hemodynamic and clinical response.

In cases of unsuccessful implantation via the coronary sinus, a few operators have implanted an LV endocardial lead via an atrial transseptal approach (12, 13, 19, 28). This approach is currently limited by technical difficulties and the thromboembolic risk associated with the presence of a lead inside the LV cavity. The interest in LV endocardial pacing was recently renewed by studies in animal models and humans. Hemodynamic studies (11, 27, 29) in animals performed in an acute left bundle branch block (LBBB) with or without heart failure showed a highly significant superiority of LV endocardial over epicardial stimulation. While the heart failure models more closely mimic the clinical and electrophysiologic characteristics of patients suffering from advanced heart failure, cardiac mechanics are altered during open-chest experiments (23, 30). The extensive nature of the instrumentation in these studies, while providing important insight into the mechanisms of benefit from endocardial pacing, also could impact cardiac mechanics, and the comparison to triventricular pacing was not investigated. Moreover, endocardial stimulation was obtained with plunged electrodes and not with a clinically relevant pacing system. In a study performed in patients with dilated cardiomyopathy, LV endocardial pacing appeared very promising with access to more sites but the superiority over epicardial stimulation was not clearly demonstrated when pacing was performed at the site transmural to the epicardial electrode (4, 8, 26). Nonetheless, a superior hemodynamic response could be achieved with endocardial pacing.

Stimulation of more than one LV epicardial site has also drawn interest to improve CRT. Acute hemodynamic studies have provided conflicting evidence on the benefits of this approach (21, 22). This approach is also limited by the availability of only three pacing channels in currently marketed pacing systems and the known limitations of the coronary sinus approach.

Endocardial and triventricular pacing have been studied separately, but there has been no head-to-head comparison of both techniques on their ability to improve cardiac function. In this animal study, we performed LV endocardial pacing via an atrial transseptal puncture with a new dedicated system and compared the hemodynamic response between epicardial, endocardial and triventricular pacing with two LV electrodes in a chronic canine model of ischemic heart failure with dyssynchrony.
Canine Model of LV Dysfunction with Dyssynchrony

Ablation of left bundle branch and implantation of epicardial leads. Antibiotics (cefazolin, 700 mg iv) were administered to canines (n = 10) within 48 h of the first procedure. They were premedicated with morphine (1 mg/kg im), and anesthesia was induced with propofol (120 mg iv) and isoflurane to effect. Epicardial leads (model no. 4968; Medtronic) were sutured to four locations on the LV via left thoracotomy and connected to an implantable pulse generator (INSYNC III model no. 8042; Medtronic). The locations included the LV apex, LV lateral wall, LV base, and LV posterior wall. Creation of left bundle branch block (LBBB) was then performed as previously described with an ablation catheter (ATAKII RF Ablation System; Medtronic) placed inside the LV cavity through a carotid arterial approach (10). The aim of the procedure was to increase the QRS duration by twofold. The incisions were closed, and the implanted system was documented with lateral and dorsoventral X-rays. The animals recovered for 4 wk before the microembolization procedures began.

Microembolization. Microembolization procedures with microspheres were initiated after 4 wk. An ultrasound exam was repeated while the animals were under sedation (butorphanol, 0.22 to 0.44 mg/kg iv) before the first microembolization to measure the LV ejection fraction. After anesthesia was induced, heparin (1,000 units iv) was administered before injection of the microspheres. A Judkins 6-Fr catheter (Medtronic) was placed in the left anterior descending or left circumflex artery. Microspheres were mixed in a syringe with saline and Isovue to create a 1.5-mL solution. The solution was then delivered to the target artery during diastole, and an additional 2 mL of saline were injected to flush the syringe. Selection of the target artery for embolization was guided by qualitative assessment of contractile function of the LV segment fed by either the left anterior descending or left circumflex artery. The segment with higher contractile function was embolized. The injections were repeated until a sustained change in the ECG was observed (e.g., ST segment elevation, ST segment inversion, or QRS widening). Injections were stopped if a pronounced increase in heart rate or decrease in blood pressure occurred. Metoprolol (0.1–0.5 mg/kg iv) was used to reduce the incidence of arrhythmias. Protamine (5 mg iv) was used to reverse anticoagulation.

The procedures were repeated every 1–3 wk until LV ejection fraction decreased <35% (24). The LV ejection fraction was measured at least once between each microembolization procedure. The hemodynamic study was performed once the LV ejection fraction was confirmed stable for two consecutive studies. LV pressure-volume relations. The LV epicardial leads were connected to an EP recording station (Prucka, GE Medical Systems) for stimulation control.

Implantation of the LV endocardial lead. A transesophageal echo probe was placed in the esophagus to monitor the transeptal puncture and mitral regurgitation. Mitral regurgitation was quantified with ultrasound immediately before LV endocardial lead implant, after implant, during LV endocardial, and during LV epicardial pacing at a posterior location with an apical four-chamber apical view. The LV endocardial delivery system consisted of a deflectable catheter system with an inner dilator, needle, and SelectSecure lead (model no. 3830; Medtronic). First, the atrial septum was punctured with the needle and dilator. A guidewire was then passed through the mitral valve into the LV cavity. An Attain Select II catheter (Medtronic) was then advanced into the LV to position the endocardial lead.

Measurements. After placing the lead inside the LV cavity, we compared endocardial and epicardial pacing by changing the position of the endocardial lead to face each of the four epicardial leads in a randomized order. At each endocardial and epicardial pair, LV only and biventricular (BiV) pacing was performed with three atroventricular (AV) delays corresponding to 40, 60, and 80% of paced PR interval. The right and left ventricles were paced simultaneously. After pacing was completed, the LV endocardial lead was repositioned to the next site until all sites were tested. Triventricular pacing was then performed with up to six combinations of LV epicardial sites in a randomized order. Repeated baseline measurements with right atrial pacing (or right ventricular pacing in the case of AV block) were performed before each ventricular pacing intervention to account for baseline variation during the study.

Data acquisition and analysis. LV pressure, five conductance segments, and lead two ECG were recorded with IOX version 2.5.1.10 data acquisition software (EMKA Technologies) and sampled at 1,000 Hz. QRS duration during sinus rhythm was manually measured. Data were exported to text format for analysis with custom Matlab software (The Mathworks). The conductance calibration factors were calculated during each baseline by scaling and shifting the conductance signal to match the echocardiographic measured LV volumes using 3DQ Advanced software with transesophageal echocardiography imaging (Philips Medical Systems, Eindhoven, The Netherlands). These factors were then applied to the following ventricular pacing intervention. End-diastole was defined as 10% of LVdP/dt max, LVdP/dt end-diastole and end-diastolic pressure were calculated for each dataset. End-diastolic volume, end-systolic volume, stroke volume, and stroke work (SW) were also calculated. The difference and percent change from baseline were calculated for each intervention.

Statistical Analysis

Optimal pacing sites during LV endocardial, LV epicardial, BiV endocardial, BiV epicardial and triventricular pacing were defined as the combination that resulted in the largest percent increase in dp/dt max from baseline. Both the optimal and average improvements in cardiac function were calculated for each approach. Changes from baseline during LV and BiV pacing for endocardial and epicardial pacing were assessed with a paired t-test for all sites and at the optimal site. A repeated-measures ANOVA with Dunnett posttest was used to compare triventricular to BiV endocardial and BiV epicardial pacing. A repeated-measures ANOVA with Tukey posttest was used to compare changes in LV ejection fraction and QRS duration at baseline, after LBBB, and after LBBB with microembolizations before the hemodynamic study. Data are expressed as means ± SD.
and with full access to the different LV endocardial pacing sites. The pacing thresholds were acceptable for most of the animals except in one canine where we could not obtain ventricular capture with the LV epicardial apical and lateral electrodes and in one canine where we could not obtain ventricular capture with the epicardial lateral electrode. A total of 260 ventricular pacing interventions were collected with baselines for comparison. The first canine was excluded from the triventricular analysis due to lack of data collection. Mitral regurgitation data was collected in only six canines during the termination procedure. In some cases, only the LV endocardial lead was within the LV cavity during ultrasound scan. In others, the stiffer Attain Select II catheter was also present. The severity of mitral regurgitation was less than “mild” in all animals at baseline, after positioning of the lead and after pacing. Baselines and paced values on average and at the optimal site are included in Tables 1 and 2.

### RESULTS

#### Chronic Canine Model of Ischemic Heart Failure with Dyssynchrony

Two animals died during the course of the microembolization procedures. In the remaining eight animals, ablation of the LBB significantly increased QRS duration. Complete AV block appeared in one animal after successful LBB. At the end of the ablation procedure, the mean QRS duration significantly increased by 74 ± 18 ms and the mean LV ejection fraction decreased by 3 ± 6% (Fig. 1); 4 ± 2 embolizations were required to reduce ejection fraction <35%. Six canines received a mix of both left anterior descending or left circumflex artery embolizations to meet the ejection fraction criteria, while two other canines received only a single left anterior descending or left circumflex artery embolization to reduce ejection fraction. Before the hemodynamic study, the average intrinsic QRS duration was 133 ± 4 ms and the average ejection fraction was 33 ± 2%.

#### Hemodynamic Study

Implantation of the endocardial LV lead and measurements. Implantation of the endocardial lead was feasible in all canines except in one canine where we could not obtain ventricular capture with the LV epicardial apical and lateral electrodes and in one canine where we could not obtain ventricular capture with the epicardial lateral electrode. A total of 260 ventricular pacing interventions were collected with baselines for comparison. The first canine was excluded from the triventricular analysis due to lack of data collection. Mitral regurgitation data was collected in only six canines during the termination procedure. In some cases, only the LV endocardial lead was within the LV cavity during ultrasound scan. In others, the stiffer Attain Select II catheter was also present. The severity of mitral regurgitation was less than “mild” in all animals at baseline, after positioning of the lead and after pacing. Baselines and paced values on average and at the optimal site are included in Tables 1 and 2.

#### Comparison of endocardial vs. epicardial pacing: LV pacing.

On average (i.e., all sites and AV delays), LV epicardial pacing significantly increased \( \text{LVdP/dt}_{\text{max}} \) by 7 ± 5% from baseline \( (P = 0.003; \text{Fig. 2}) \). There were no significant changes in \( \text{LVdP/dt}_{\text{min}} \), stroke volume, SW, end-diastolic volume, and end-systolic volume \( (P > 0.05) \). Similarly, epicardial pacing at the optimal LV site increased \( \text{LVdP/dt}_{\text{max}} \) by 15 ± 8% \( (P = 0.0017) \). At the pacing combination that resulted in the largest percent increase in \( \text{dP/dt}_{\text{max}} \), there were no significant changes in other hemodynamic variables compared with baseline \( (P > 0.05) \).

LV endocardial pacing increased \( \text{LVdP/dt}_{\text{max}} \) on average by 12 ± 5% from baseline \( (P = 0.005) \); SW also increased by 30 ± 24% \( (P = 0.007) \). Endocardial pacing increased \( \text{LVdP/dt}_{\text{max}} \) more on average than LV epicardial pacing \( (4.5 ± 2.4\% \; (P < 0.01; \text{Fig. 2}) \). End-diastolic pressure was significantly smaller with endocardial pacing \( (7.0 ± 7.2\% \; (P = 0.03) \). LV endocardial pacing at the optimal site increased \( \text{LVdP/dt}_{\text{max}} \) by 20 ± 8% from baseline \( (P = 0.0001) \); and SW also increased by 27 ± 23% \( (P = 0.001) \). Endocardial pacing at the optimal site significantly increased \( \text{LVdP/dt}_{\text{max}} \) compared with the optimal epicardial site \( (5.9 ± 4.5\% \; (P = 0.008; \text{Fig. 2}) \).

**BiV pacing.** BiV epicardial pacing on average significantly increased \( \text{LVdP/dt}_{\text{max}} \) by 11 ± 6% from baseline \( (P = 0.0001; \text{see Fig. 4}) \); \( \text{LVdP/dt}_{\text{min}} \) improved by 5 ± 7% \( (P = 0.046) \); and SW increased by 19 ± 16% \( (P = 0.006) \). At the optimal site, \( \text{LVdP/dt}_{\text{max}} \) increased by 20 ± 10% from baseline \( (P = \ldots) \).

#### Table 1. Comparison of hemodynamics during LV and BiV pacing

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Average</th>
<th>Optimal</th>
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<tbody>
<tr>
<td></td>
<td>LV Epi, %</td>
<td>LV Endo, %</td>
<td>BiV Epi, %</td>
</tr>
<tr>
<td>dp/dt(_{\text{max}})</td>
<td>1,090 ± 209</td>
<td>7 ± 5*</td>
<td>12 ± 5†</td>
</tr>
<tr>
<td>dp/dt(_{\text{min}})</td>
<td>1,579 ± 316</td>
<td>-6 ± 6</td>
<td>-1 ± 5</td>
</tr>
<tr>
<td>EDP</td>
<td>7.7 ± 2.3</td>
<td>7.8 ± 12.1</td>
<td>0.8 ± 9.5†</td>
</tr>
<tr>
<td>EDV</td>
<td>60.6 ± 18.0</td>
<td>2.1 ± 3.0</td>
<td>2.9 ± 3.5</td>
</tr>
<tr>
<td>ESV</td>
<td>47.0 ± 16.3</td>
<td>-2.8 ± 5.8</td>
<td>-2.2 ± 3.3</td>
</tr>
<tr>
<td>SV</td>
<td>16.9 ± 5.6</td>
<td>11.9 ± 16.8</td>
<td>11.4 ± 13.7</td>
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<tr>
<td>SW</td>
<td>901 ± 279</td>
<td>21 ± 25</td>
<td>30 ± 24*</td>
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Values are means ± SD; \( n = 8 \). Baseline is calculated from all baselines for the pacing configurations shown. Average is the average of all sites and atrophicventricular delays at each configuration. Optimal is the average of each configuration’s optimal site defined by the largest percent increase in \( \text{dP/dt}_{\text{max}} \); LV, left ventricular; BiV, biventricular; EDP, end-diastolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; SW, stroke work; Epi, epicardial; Endo, endocardial. *\( P < .05 \) vs. each configuration’s baseline; †\( P < .05 \) vs. epicardial at the same configuration (i.e., LV or BiV, average or optimal).
There were no significant changes in the other variables on average or at the optimal site (P > 0.05).

BiV endocardial pacing on average significantly increased LVdP/dt\(_{\text{max}}\) by 16 ± 6\% (P = 0.0001) and SW by 28 ± 17\% (P = 0.0008) from baseline. BiV endocardial pacing at the optimal site increased LVdP/dt\(_{\text{max}}\) by 25 ± 11\% (P = 0.0003). At the combination that resulted in the largest percent increase in dP/dt\(_{\text{max}}\), SW increased by 18 ± 21\% (P = 0.047). Endocardial pacing significantly increased LVdP/dt\(_{\text{max}}\) compared with epicardial pacing on average (5.0 ± 2.8\%; P = 0.001) and at the optimal site (5.1 ± 3.2\%; P = 0.003; Fig. 3). There were no significant differences in the other variables (P > 0.05).

### Influence of the pacing site

We observed significant influence of the pacing site during both epicardial and endocardial pacing (Fig. 4). The optimal site varied between canines, pacing mode (i.e., LV vs. BiV), and whether the pacing was endocardial or epicardial (Table 3). For LV only pacing, the optimal endocardial and epicardial site was the same for only three canines. The LV lateral site was most often optimal during LV epicardial pacing, while the apical and basal sites were most often optimal for LV endocardial pacing. The basal site was most often optimal for both endocardial and epicardial pacing when the pacing mode was changed to BiV.

### Table 2. Comparison of hemodynamics during BiV and TriV pacing

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Average</th>
<th>Optimal</th>
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<tbody>
<tr>
<td></td>
<td>BiV Epi, %</td>
<td>TriV Epi, %</td>
<td>BiV Endo, %</td>
</tr>
<tr>
<td>dp/dt(_{\text{max}})</td>
<td>1,117 ± 234</td>
<td>11 ± 6*</td>
<td>12 ± 7*</td>
</tr>
<tr>
<td>dp/dt(_{\text{min}})</td>
<td>1,556 ± 336</td>
<td>5 ± 7</td>
<td>5 ± 8</td>
</tr>
<tr>
<td>EDP</td>
<td>8.6 ± 2.3</td>
<td>-2.0 ± 6.5</td>
<td>0.5 ± 4.8</td>
</tr>
<tr>
<td>EDV</td>
<td>64.3 ± 19.2</td>
<td>1.5 ± 3.0</td>
<td>0.7 ± 3.3</td>
</tr>
<tr>
<td>ESV</td>
<td>49.2 ± 16.0</td>
<td>-1.5 ± 2.6</td>
<td>-5.2 ± 5.9</td>
</tr>
<tr>
<td>SV</td>
<td>18.0 ± 7.9</td>
<td>6.8 ± 11.4</td>
<td>13.7 ± 13.6</td>
</tr>
<tr>
<td>SW</td>
<td>969 ± 442</td>
<td>19 ± 18*</td>
<td>20 ± 19</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 7. Baseline is calculated from all baselines for the pacing configurations shown. Average is the average of all sites and atrioventricular delays at each configuration. Optimal is the average of each configuration’s optimal site defined by the largest percent increase in dp/dt\(_{\text{max}}\). TriV, triventricular. *P < 0.05 vs. each configuration’s baseline; †P < 0.05 vs. TriV on average; ‡P < 0.05 vs. TriV at the optimal site.

Fig. 2. Percent change in dp/dt\(_{\text{max}}\) (A and B), dp/dt\(_{\text{min}}\) (C and D), and stroke work (SW; E and F) from baseline during LV epicardial (Epi) and endocardial (Endo) pacing on average and at the optimal site. SW, stroke work. *P < 0.01 vs. LV Epi.
Comparison of triventricular pacing to endocardial and epicardial pacing. Triventricular pacing increased dP/dt max by 12 ± 7% on average and by 23 ± 12% at the optimal site compared with baseline (P = 0.0005 for both comparisons). SW also significantly increased at the optimal site by 28 ± 25% (P < 0.05). There were no significant differences between BiV epicardial and triventricular pacing at the optimal site and on average (P > 0.05). At the optimal site, the percent increase in dP/dt max was significantly higher with BiV endocardial than during triventricular pacing by (3.4 ± 3.5%; P < 0.05; Fig. 5).

The increase in dP/dt max and SW was also significantly higher on average (4.6 ± 4.1 and 11.0 ± 12.8%; P < 0.05). There were no significant differences in any of the other hemodynamic parameters (P > 0.05). During triventricular pacing, the optimal sites were most often the LV basal + LV posterior sites (43%). The optimal sites differed in each of the four remaining canines. The sites included apex + lateral, apex + basal, apex + posterior, and lateral + posterior.

DISCUSSION

Since the main limitation of CRT is the predictable proportion of nonresponders, any new approach that can lower this percentage of patients is welcome. Inadequate delivery of the therapy may play a critical role in nonresponse to CRT. The results of the present study highlight the importance of alternatives to coronary sinus pacing, including the future role of LV endocardial stimulation in candidates for CRT. Indeed, the major insights of this study were as follows: 1) this novel canine model of dysynchrony with ischemic heart failure induced through combined left anterior descending or left circumflex artery microembolization was stable and responsive to pacing. 2) LV endocardial pacing was achieved with a clinically relevant pacing system and leads could easily be maneuvered to predefined locations marked by the epicardial electrodes without appreciable mitral regurgitation. 3) The percent increase in dP/dt max on average, as well as at the optimal site, was significantly higher during BiV endocardial pacing than during BiV epicardial pacing. 4) We found considerable variation in the pacing site that produced the maximal acute hemodynamic response during both epicardial and endocardial LV pacing. The best and worst pacing sites appeared to be animal specific. 5) We could not obtain further hemodynamic improvement with triventricular pacing.

Animal Model and Technique for LV Endocardial Pacing

A recent hemodynamic animal study showed a highly significant superiority of LV endocardial compared with epicardial stimulation in canines that had undergone LBBB ablation both with and without heart failure (27, 29). LV endocardial pacing was obtained with an electrode plunged through the
myocardial wall, a pacing system that is not clinically available at this time. We believe that the model used in our study is highly relevant since we obtained progressive and stable deterioration of the ejection fraction, with characteristics close to those of patients with ischemic cardiomyopathy who are candidates for CRT: reduced ejection fraction, LV remodeling, and electrical dyssynchrony (24). LV endocardial pacing was achieved with a clinically relevant pacing system via a superior approach without mitral regurgitation and every predefined site could be reached easily, including the septum.

Comparison of Endocardial to Epicardial LV Pacing

In the present animal study in a model of ischemic heart failure with dyssynchrony, we demonstrated unequivocally the superiority of endocardial over epicardial stimulation on hemodynamic measurements measured invasively. A total of 260 ventricular pacing interventions were collected with repeated baselines, allowing reliable comparison between epicardial and endocardial sites. Endocardial pacing increased $dP/dt_{\text{max}}$ more than epicardial pacing during LV and BiV pacing at the optimal site and on average (i.e., all sites and AV delays). This significant superior improvement may be related to the following: 1) a faster endocardial than epicardial conduction, and 2) a smaller, central endocardial vs. epicardial circumference (3, 29). Both mechanisms were recently confirmed in animal models of heart failure with concentric and eccentric remodeling (27).

We observed significant influence of the pacing site during both epicardial and endocardial pacing in agreement with previous studies (11, 27). We found a wide interanimal disparity in the location of the optimal and least favorable site of stimulation, such that a predictably best or worst site was not identified for all animals. The search for an optimal site allowed a significant improvement compared with the choice of any predefined LV epicardial or endocardial site. Despite the wide variation in location of the optimal site between canines, pacing at a basal location was most often optimal during BiV endocardial, BiV epicardial, and triventricular pacing. These results are supported by a recent study in a similar model of left anterior descending or left circumflex artery microembolization. Canines that received left anterior descending artery occlusions received a larger benefit, in terms of $dP/dt_{\text{max}}$ and SW, from pacing sites remote to the site of infarction (e.g., basal sites) while canines receiving left circumflex artery

Table 3. Distribution of optimal sites during epicardial and endocardial pacing

<table>
<thead>
<tr>
<th>Pacing Site</th>
<th>LV Epi, %</th>
<th>LV Endo, %</th>
<th>BiV Epi, %</th>
<th>BiV Endo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVA</td>
<td>0</td>
<td>38</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>LVL</td>
<td>50</td>
<td>12</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>LVB</td>
<td>25</td>
<td>38</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>LVPOST</td>
<td>25</td>
<td>12</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

LVA, LV apex; LVL, LV lateral; LVB, LV basal; LVPOST, LV posterior.
embolizations benefited most from pacing sites in the anterior region close to the infarct. Since the majority of the canines in the present study had combined left anterior descending and left circumflex artery, we would expect the majority of the optimal sites, as defined by dP/dt max, would be located in a basal location. Besides location of infarction, scar burden and proximity of the LV lead to scar also impact response to CRT. The position of the LV lead at a segment with transmural scar was previously associated with lack of reverse remodeling at 6 mo, and a larger amount of viable myocardium was associated with more reverse remodeling (31). A larger report from >500 patients showed that MRI-guided lead placement improved cardiovascular death and hospitalization when the lead was positioned in an area without scar instead of within scar (17).

Comparison of triventricular pacing vs. epicardial and endocardial pacing. Increasing the number of pacing sites has been proposed to improve the response after CRT (14–16). The potential benefit of a triventricular pacing approach would involve two mechanisms. First, by increasing the number of pacing sites, the probability of reaching a more efficient site may increase. Secondly, stimulating more sites on the LV could provide a faster and more physiologic LV activation. In the present study, optimizing the triventricular configuration (best pair of sites and best AV delay) was not associated with a significant improvement in any of the measured parameters compared with the optimal BiV epicardial configuration. The results were even worse than those observed with the optimal endocardial configuration. This confirms the mixed results observed in humans without clear demonstration of the superiority of triventricular vs. BiV pacing.

Today, the triventricular approach in clinical practice involves implanting two LV leads as far apart as possible (2, 16). Success rates of ~85% have been reported using available tools (16). The complicated implant, coupled with the lack of tools to determine the optimal sites and longevity concerns with multiple LV pacing outputs makes this approach difficult to implement in routine clinical practice. The absence of hemodynamic improvement with triventricular pacing described in this study favors the development of LV endocardial pacing. Today, triventricular pacing is technically restricted to the implantation of only two LV leads. However, in the future, implantation of more than two leads or stimulating electrodes may be possible and the hemodynamic impact of such a strategy will have to be evaluated at that time.

Clinical Implications

LV endocardial pacing offers several notable advantages. The transseptal approach allows the freedom to choose a stimulation site, as opposed to being constrained by the anat-
omy of the coronary sinus. LV endocardial pacing appears more physiologic, preserving the transmural activation and repolarization sequence; therefore, it may lower the risk of arrhythmia development (25). Moreover, we have demonstrated that LV endocardial stimulation and optimization of the pacing site significantly improved systolic function compared with standard LV epicardial pacing. Therefore, LV endocardial stimulation may represent a very promising option to lower the proportion of nonresponders.

A number of issues need to be resolved before an approach of individually tailoring LV endocardial pacing is adopted in routine clinical practice. An LV lead implanted through the interatrial septum crosses the mitral valve, which may increase the risk of insufficiency and endocarditis. We did not observe any appreciable mitral regurgitation with the LV endocardial lead implant. This finding is important because all of the animals had evidence of heart failure with LV dysfunction and if the LV endocardial lead could create appreciable mitral regurgitation, we would be more likely to observe changes in this model than in animals with normal LV function and structure. Furthermore, previous studies focusing on the hemodynamic effect of endocardial pacing have not evaluated mitral regurgitation. Bordachar et al. (3) previously reported higher mitral integral time-velocity with endocardial pacing than during epicardial pacing, which could result from reduced mitral regurgitation. The results of this study will need to be confirmed in patients undergoing chronic LV endocardial pacing. The risk of thrombus formation on the lead is a major concern with LV endocardial leads. Even small emboli may cause major systemic complications, including stroke. The safety of this new approach first needs to be rigorously assessed in a prospective study.

The implementation of endocardial stimulation will ultimately depend on three factors: 1) there is a need to develop dedicated instrumentation to facilitate the implant procedure and disseminate this strategy on a wider scale. 2) Development of a reliable and reproducible method is needed to identify the optimal site of stimulation during the procedure; indeed, LV endocardial stimulation allows greater access to potential pacing sites and provides the ability to screen them in an attempt to determine the position that results in the greatest improvement in cardiac function. Studies with chronic followup are required to answer the question of which intraoperative measurement might best predict patient benefit and outcome after CRT. 3) Finally, controlled trials are necessary to confirm the safety and potential benefits of these new pacing strategies and to confirm the superiority of LV endocardial pacing compared with standard CRT.

Feedback at the time of the CRT implant to predict successful therapy is still lacking. We focused on dP/dt max with standard CRT. To confirm the superiority of LV endocardial pacing compared with standard CRT.

Limitations

Limitations of this study are driven by the relatively small number of animals studied. While the animal model is a good representation of ischemic cardiomyopathy with LBBB, validation of these findings in humans is required. The results may have been different if another model, such as coronary ligature, was used. We investigated only a few LV sites, and the results may have varied if additional sites were studied. The conditions under which mitral regurgitation occurred varied slightly between animals, but in no cases did we detect mild or greater mitral regurgitation. We also did not perform a detailed analysis of infarct location, burden, and transmurality. Most of our findings rest on acute differences in dP/dt max and the best parameter to optimize CRT still requires definition. We chose to focus on invasive hemodynamic measurements to characterize myocardial function instead of MRI or tridimensional echocardiography to focus on global cardiac function and because this technique may be easier to implement at the time of LV lead implant. We decided not to explore the electrophysiological mechanisms involved in the improvement provided by endocardial pacing to remain in clinically relevant closed-chest conditions and not to alter cardiac mechanics through open-chest experiments. We did not characterize the location of the LV electrodes with respect to scar location in the present study and thus cannot comment further on how the vicinity of LV pacing to scar may have impacted our results.

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DISCLOSURES


AUTHOR CONTRIBUTIONS

Author contributions: P.B., N.G., P.J., P.R., C.L., J.M.M., D.G., and P.Y. conceived and designed the experiments; P.B., N.G., P.J., and P.Y. performed the experiments; P.B., N.G., P.J., and P.Y. drafted the manuscript; P.B., N.G., and P.Y. edited and revised the manuscript; P.B., N.G., P.J., P.R., C.L., J.M.M., D.G., and P.Y. interpreted the data; P.B., N.G., and P.Y. interpreted results of experiments; N.G. and P.Y. prepared figures.

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