Left Ventricular Endocardial or Triventricular Pacing to Optimize Cardiac Resynchronization Therapy in a Chronic Canine Model of Ischemic Heart Failure

Authors: Pierre Bordachar\textsuperscript{2*}, Nathan Grenz\textsuperscript{1*}, Pierre Jais\textsuperscript{2}, Philippe Ritter \textsuperscript{2}, Christophe Leclercq\textsuperscript{3}, John M. Morgan\textsuperscript{4}, Daniel Gras\textsuperscript{5}, Ping Yang\textsuperscript{1}

\textsuperscript{1}CRDM Therapy Delivery Systems Research, Medtronic Inc., US
\textsuperscript{2}Hospital Haut Leveque, Service Pr. Haissaguerre, Pessac 33604, France
\textsuperscript{3}Hospital Pontchaillou, Service Pr. Mabo, Rennes, France
\textsuperscript{4}Wessex Cardiothoracic Unit, Southampton University Hospital, Southampton, UK
\textsuperscript{5}Nouvelles Cliniques Nantaises, Nantes, France

*The 2 first authors contributed equally to this work.

Running Head: LV Endocardial and Triventricular Pacing in Heart Failure

Correspondence: Dr. Pierre Bordachar, Hopital Cardiologique Haut Leveque, Avenue Magellan, Bordeaux-Pessac, France.

Fax: 00 33 5 57 65 65 09

Phone: 00 33 5 57 65 65 65

Email: bordacharp@hotmail.com
Abstract

Background: Cardiac resynchronization therapy (CRT) is a proven treatment for heart failure but approximately 30% of patients appear to not benefit from the therapy. Left ventricular (LV) endocardial and multisite epicardial (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.

Methods and Results: Left bundle branch block ablation and repeated microembolizations were performed in dogs to induce electrical dysynchrony and to reduce LV ejection fraction to less than 35%. LV dP/dt\text{max} and other hemodynamic indices were measured with a conductance catheter during LV epicardial, LV endocardial, Biventricular (BiV) epicardial, BiV endocardial and TriV pacing performed at 3 atrioventricular delays. LV endocardial pacing was obtained with a clinically-available pacing system. The optimal site was defined as the site that increased dP/dt\text{max} 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/dt\text{max} more than BiV epicardial and TriV pacing on average (p<.01) and at the optimal site (p<.01). There were no significant differences between BiV epicardial and TriV pacing.

Conclusions: 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.

Key Words: cardiac resynchronization therapy, LV endocardial pacing, multisite LV pacing
Introduction

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, about 30% of patients implanted with a single LV transvenous lead placed in a lateral or postero-lateral tributary of the coronary sinus or a surgical epicardial lead appear non-responsive 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 multi-site 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 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 (11; 27; 29). 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 1 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 3 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 2 LV electrodes in a chronic canine model of ischemic heart failure with dyssynchrony.

Methods

The study was reviewed and approved by Medtronic’s Institutional Animal Care and Use Committee.

Canine Model of Left Ventricular Dysfunction with Dyssynchrony

Ablation of Left Bundle Branch and Implantation of Epicardial Leads
Antibiotics (cefazolin, 700 mg intravenous) were administered to canines (n=10) within 48 hours of the first procedure. They were premedicated with morphine (1mg/kg intramuscular) and anesthesia was induced with propofol (120 mg intravenous) and isoflurane to effect. Epicardial leads (Model 4968, Medtronic, US) were sutured to 4 locations on the LV via left thoracotomy and connected to an implantable pulse generator (INSYNC® III Model 8042, Medtronic, US). 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 (ATAKR® II RF Ablation System, Medtronic, US) placed inside the LV cavity through a carotid arterial approach (10). The aim of the procedure was to increase the QRS duration by 2 fold. The incisions were closed and the implanted system was documented with lateral and dorsoventral X-rays. The animals recovered for 4 weeks before the microembolization procedures began.

**Microembolization**

Microembolization procedures with microspheres were initiated after 4 weeks. An ultrasound exam was repeated under sedation (butorphanol, 0.22 to 0.44 mg/kg intravenous) prior to the first microembolization to measure the LV ejection fraction. After anesthesia was induced, heparin (1000 units intravenous) was administered prior to injecting the microspheres. A Judkins 6 Fr catheter (Medtronic, US) 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 was 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 - .5 mg/kg intravenous) was used to reduce the incidence of arrhythmias. Protamine (5 mg intravenous) was used to reverse anticoagulation.

The procedures were repeated every 1 to 3 weeks until LV ejection fraction decreased below 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 2 consecutive studies. QRS duration was measured throughout the study.

Echocardiography

LV ejection fraction at baseline, post LBBB and prior to the hemodynamic study was quantified with triplane imaging on a Vivid 7 ultrasound system with a transthoracic probe (GE Medical Systems, Horten, Norway). Mitral regurgitation was quantified after the LV endocardial lead or delivery system was placed inside the LV cavity using iE33 ultrasound system with transesophageal echocardiography by inspecting the mitral regurgitant jet from an apical 2, 3 and 4 chamber view (Philips Medical Systems, Eindhoven, Netherlands). The proximal isovelocity surface area method could not be used due to lack of a quantifiable continuous wave Doppler waveform. Thus, mitral regurgitation was quantified as trace, mild, moderate or severe depending on the qualitative size of the jet using previously published criteria (32).

Acute Hemodynamic Closed-Chest Study

The animals were premedicated with morphine and anesthesia was induced with propofol and isoflurane. Fentanyl (5 to 10 μg/kg/hr intravenous) was infused to preserve hemodynamic
function while lowering the amount of isoflurane necessary to maintain anesthesia. A jugular venotomy was performed to introduce pacing leads into the right atrium and right ventricle. A conductance catheter (CD Leycom, The Netherlands) was inserted into the LV via a retrograde aortic approach to measure LV pressure-volume relations. The LV epicardial leads were connected to an EP recording station (Prucka, GE Medical Systems, US) for stimulation control. **Implantation of the Left Ventricular Endocardial Lead**

A transesophageal echo probe was placed in the esophagus to monitor the transseptal 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 4-chamber apical view. The LV endocardial delivery system consisted of a deflectable catheter system with an inner dilator, needle and SelectSecure™ lead (Model 3830, Medtronic, US). 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, US) 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 4 epicardial leads in a randomized order. At each endocardial and epicardial pair, LV only and biventricular (BiV) pacing was performed with 3 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 6 combinations of LV epicardial sites in a randomized
order. Repeated baseline measurements with right atrial pacing (or right ventricular pacing in the
case of atrioventricular block) were performed before each ventricular pacing intervention to
account for baseline variation during the study.

Data Acquisition and Analysis

LV pressure, 5 conductance segments and Lead 2 ECG were recorded with IOX version 2.5.1.10
data acquisition software (EMKA Technologies, France) and sampled at 1000 Hz. QRS duration
during sinus rhythm was manually measured. Data were exported to text format for analysis with
custom Matlab software (The Mathworks, US). 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 LV $dP/dt_{max}$. LV $dP/dt_{max}$, LV $dP/dt_{min}$ and end-diastolic pressure (EDP) were
calculated for each dataset. End-diastolic volume (EDV), end-systolic volume (ESV), stroke
volume (SV) and stroke work (SW) were also calculated. The difference and percent change
from baseline was 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 (RM) analysis of variance (ANOVA) with Dunnett post-test was used to
compare triventricular to BiV endocardial and BiV epicardial pacing. An RM-ANOVA with Tukey post-test was used to compare changes in LV ejection fraction and QRS duration at baseline, after LBBB and after LBBB with microembolizations prior to the hemodynamic study. Data are expressed as mean ± standard deviation.

**Results**

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

Two animals died during the course of the microembolization procedures. In the remaining 8 animals, ablation of the LBB significantly increased QRS duration. Complete atrioventricular block appeared in 1 animal after successful LBBB. 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% (Figure 1). 4 ± 2 embolizations were required to reduce ejection fraction below 35%. 6 canines received a mix of both left anterior descending or left circumflex artery embolizations to meet the ejection fraction criteria, while 2 other canines received only a single left anterior descending or left circumflex artery embolization to reduce ejection fraction. Prior to 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 and with full access to the different LV endocardial pacing sites. The pacing thresholds were acceptable for most of the animals except in 1 canine where we could not obtain ventricular capture with the LV epicardial
apical and lateral electrodes and in 1 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 6 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 Table 1 and 2.

Comparison of Endocardial versus Epicardial pacing

LV pacing

On average (i.e., all sites and AV delays), LV epicardial pacing significantly increased LV
dP/dt_max by 7 ± 5% from baseline (p=.003, Figure 2). There were no significant changes in LV
dP/dt_min, SV, SW, EDV or ESV (p>.05). Similarly, epicardial pacing at the optimal LV site
increased dP/dt_max by 15 ± 8% (p=.0017). At the pacing combination that resulted in the largest
percent increase in dP/dt_max, there were no significant changes in other hemodynamic variables
compared to baseline (p>.05).

LV endocardial pacing increased LV dP/dt_max on average by 12 ± 5% from baseline (p=.005).
SW also increased by 30 ± 24% (p=.007). Endocardial pacing increased LV dP/dt_max more on
average than LV epicardial pacing (4.5 ± 2.4 %, p<.01, Figure 2). EDP was significantly smaller
with endocardial pacing (7.0 ± 7.2 %, p=.03). LV endocardial pacing at the optimal site
increased LV dP/dt_max by 20 ± 8% from baseline (p=.0001) and SW also increased by 27 ± 23%
Endocardial pacing at the optimal site significantly increased LV dP/dt_{max} compared to
the optimal epicardial site (5.9 ± 4.5%, p=.008, Figure 2).

BiV pacing

BiV epicardial pacing on average significantly increased LV dP/dt_{max} by 11 ± 6% from baseline
(p=.0001, Figure 4). LV dP/dt_{min} improved by 5 ± 7% (p=.046) and SW increased by 19 ± 16%
(p=.006). At the optimal site, LV dP/dt_{max} increased by 20 ± 10% from baseline (p=.0003).

There were no significant changes in the other variables on average or at the optimal site (p>.05).

BiV endocardial pacing on average significantly increased LV dP/dt_{max} by 16 ± 6% (p=.0001)
and SW by 28 ± 17% (p=.0008) from baseline. BiV endocardial pacing at the optimal site
increased LV dP/dt_{max} by 25 ± 11% (p=.0003). At the combination that resulted in the largest
percent increase in dP/dt_{max}, SW increased by 18 ± 21% (p=.047). Endocardial pacing
significantly increased LV dP/dt_{max} compared to epicardial pacing on average (5.0 ± 2.8 %, p=.001) and at the optimal site (5.1 ± 3.2 %, p=.003, Figure 3). There were no significant
differences in the other variables (p>.05).

Influence of the Pacing Site

We observed significant influence of the pacing site during both epicardial and endocardial
pacing (Figure 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 3 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.

Comparison of Triventricular pacing to Endocardial and Epicardial Pacing
Triventricular pacing increased \( \frac{dP}{dt_{\text{max}}} \) by 12 ± 7% on average and by 23 ± 12% at the optimal site compared to baseline (\( p=.0005 \) for both comparisons). SW also significantly increased at the optimal site by 28 ± 25% (\( p<.05 \)). There were no significant differences between BiV epicardial and triventricular pacing at the optimal site and on average (\( p>.05 \)). At the optimal site, the percent increase in \( \frac{dP}{dt_{\text{max}}} \) was significantly higher with BiV endocardial than during triventricular pacing by (3.4 ± 3.5 %, \( p<.05 \), Figure 5). The increase in \( \frac{dP}{dt_{\text{max}}} \) and SW was also significantly higher on average (4.6 ± 4.1 % and 11.0 ± 12.8%, \( p<.05 \)). There were no significant differences in any of the other hemodynamic parameters (\( p>.05 \)). During triventricular pacing, the optimal sites were most often the LV basal + LV posterior sites (43%). The optimal sites differed in each of the 4 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 non-responders, any new approach that can lower this percentage of patients is welcome. Inadequate delivery of the therapy may play a critical role in non-response 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: 1) This novel canine model of dyssynchrony 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 \( \frac{dP}{dt_{\text{max}}} \) on average, as well
as at the optimal site, was significantly higher during biventricular endocardial pacing than
during biventricular 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_{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: 1) a faster endocardial than epicardial conduction, and 2) a smaller, central endocardial versus 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 inter-animal 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 to 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 which received left anterior descending artery occlusions received a larger benefit, in terms of dP/dtmax and stroke work, from pacing sites remote to the site of infarction (e.g. basal sites) while canines receiving left circumflex artery 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/dtmax, 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 months and a larger amount of viable myocardium was associated with more reverse remodeling (31). A larger report from over 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 versus 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, best AV delay) was not associated with a significant improvement in any of the measured parameters compared to 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 versus BiV pacing.

Today, the triventricular approach in clinical practice involves implanting 2 LV leads as far apart as possible (2; 16). Success rates of around 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 2 LV leads. However, in the future, implantation of more than 2 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 anatomy 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 non-responders.

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. Garrigue et al. previously reported higher mitral integral time-velocity with endocardial pacing than during epicardial pacing, which could result from reduced mitral regurgitation (11). 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 3 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.

3) Studies with chronic follow-up 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 to standard CRT.

Feedback at the time of the CRT implant to predict successful therapy is still lacking. We focused on dP/dt max to define the optimal site of pacing. Previous studies have shown that changes in dP/dt max may have no correlation with changes in stroke work and therefore ‘optimal’ lead position may differ depending on the optimization parameter (6; 7). LV dP/dt max depends on LV pressure during isovolumic contraction, while stroke work reflects LV pressure and volume throughout the cardiac cycle and provides a more global metric of LV function. These 2 factors likely explain why we observed similar changes in dP/dt max and stroke work in some pacing conditions but not others. Although there is the limited data demonstrating the relationship between acute hemodynamic response and chronic benefit, percentage change in dP/dt max during LV pacing was recently shown to be highly predictive of at least a 15% reduction in end-systolic volume after 6 months of CRT (9). Other investigators have preferred stroke work because it reflects global pump function throughout the cardiac cycle, but the technique is more complex.
than measuring only LV pressure (7). Further investigation is required to determine the best acute measurement to easily implement at implant in order to improve the benefits of 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 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\textsubscript{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.
Acknowledgements

We would like to thank Dr. Nancy Rakow, Dr. Linnea Lentz, Ms. Hanna Robinson, Ms. Renee Gerhart, Mr. Jason Bourgoin at the Physiological Research laboratory, Medtronic Inc., for their support and technical assistance of this study.

Funding Sources

This study was funded by Medtronic Inc.

Disclosures

Pierre Bordachar, Philippe Ritter, Daniel Gras and John M. Morgan serve as consultants for Medtronic. Nathan A. Grenz and Ping Yang are employees of Medtronic.
Figure 1. Significant changes in QRS width and LV ejection fraction after ablation of the left bundle branch and after microembolizations; *, p<.0001 vs. baseline. **, p<.0001 vs. baseline; LBBB: left bundle branch block; MI: microembolizations; LV EF: left ventricular ejection fraction.

Figure 2. Percent change in dP/dt\text{max} (A&B), dP/dt\text{min} (C&D) and stroke work (E&F) from baseline during LV epicardial and endocardial pacing on average and at the optimal site. *, p<.01 vs. LV Epi.
LV Epi: left ventricular epicardial; LV Endo: left ventricular endocardial; SW: stroke work.

Figure 3. Percent change in dP/dt\text{max} (A&B), dP/dt\text{min} (C&D) and stroke work (E&F) from baseline during BiV epicardial and endocardial pacing on average and at the optimal site. *, p<.01 vs. BiV epicardial.
BiV Epi: biventricular epicardial; BiV Endo: biventricular endocardial; SW: stroke work.

Figure 4. Variation in hemodynamic response in each canine for different pacing sites and AV delays (best and worst sites) for A) LV epicardial, B) LV endocardial, C) BiV epicardial and D) BiV endocardial pacing.
Figure 5. Percent increase in dP/dt_{max} (A&B), dP/dt_{min} (C&D) and stroke work (E&F) from baseline during triventricular and BiV endocardial pacing on average and at the optimal sites. *, p<.0001 vs. triventricular.

TriV: triventricular
<table>
<thead>
<tr>
<th></th>
<th>Average Baseline (%)</th>
<th>LV Epi (%)</th>
<th>LV Endo (%)</th>
<th>BiV Epi (%)</th>
<th>BiV Endo (%)</th>
<th>LV Epi (%)</th>
<th>LV Endo (%)</th>
<th>BiV Epi (%)</th>
<th>BiV Endo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dp/dt&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1090±209</td>
<td>7±5*</td>
<td>12±5*†</td>
<td>11±6*</td>
<td>16±6*†</td>
<td>15±8*</td>
<td>20±8*†</td>
<td>20±10*</td>
<td>25±11*†</td>
</tr>
<tr>
<td>dp/dt&lt;sub&gt;min&lt;/sub&gt;</td>
<td>1579±316</td>
<td>-0±6</td>
<td>-1±5</td>
<td>5±7*</td>
<td>5±7</td>
<td>1±7</td>
<td>2±8</td>
<td>5±9</td>
<td>7±11</td>
</tr>
<tr>
<td>EDP</td>
<td>7.7±2.3</td>
<td>7.8±12.1</td>
<td>0.8±9.3†</td>
<td>-1.6±6.1</td>
<td>-1.5±7.0</td>
<td>7.5±19.9</td>
<td>-1.0±13.4</td>
<td>8.5±12.5</td>
<td>1.8±11.5</td>
</tr>
<tr>
<td>EDV</td>
<td>60.6±18.0</td>
<td>2.0±3.0</td>
<td>2.9±3.5</td>
<td>1.6±2.8</td>
<td>1.9±3.2</td>
<td>2.7±6.3</td>
<td>2.6±2.4</td>
<td>0.2±3.9</td>
<td>1.0±3.7</td>
</tr>
<tr>
<td>ESV</td>
<td>47.0±16.3</td>
<td>-2.8±5.8</td>
<td>-2.2±3.3</td>
<td>-1.5±2.4</td>
<td>-2.5±2.0</td>
<td>-1.4±7.0</td>
<td>-1.1±5.1</td>
<td>-0.6±4.5</td>
<td>-1.1±3.4</td>
</tr>
<tr>
<td>SV</td>
<td>16.9±5.6</td>
<td>11.9±16.8</td>
<td>11.4±13.7</td>
<td>6.5±10.6</td>
<td>12.1±10.3</td>
<td>11.3±29.5</td>
<td>11.7±13.5</td>
<td>8.1±14.1</td>
<td>6.4±12.5</td>
</tr>
<tr>
<td>SW</td>
<td>901±279</td>
<td>21±25</td>
<td>30±24*</td>
<td>19±16*</td>
<td>28±17*</td>
<td>21±46</td>
<td>27±23*</td>
<td>15±18</td>
<td>18±21*</td>
</tr>
</tbody>
</table>

‘Baseline’ is calculated from all baselines for the pacing configurations shown. ‘Average’ is the average of all sites and AV delays at each configuration. ‘Optimal’ is the average of each configuration’s optimal site defined by the largest percent increase in dp/dt<sub>max</sub>. Values are mean ± SD. 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).
Table 2. Comparison of Hemodynamics during BiV and TriV Pacing (n=7)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>BiV Epi (%)</th>
<th>TriV Epi (%)</th>
<th>BiV Endo (%)</th>
<th>BiV Epi (%)</th>
<th>TriV Epi (%)</th>
<th>BiV Endo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dp/dt\text{max}</td>
<td>1117±234</td>
<td>11±6*</td>
<td>12±7*</td>
<td>17±7*†</td>
<td>21±10*</td>
<td>23±9*</td>
<td>26±12*‡</td>
</tr>
<tr>
<td>dp/dt\text{min}</td>
<td>1556±336</td>
<td>5±7</td>
<td>5±8</td>
<td>5±8</td>
<td>5±10</td>
<td>5±10</td>
<td>7±11</td>
</tr>
<tr>
<td>EDP</td>
<td>8.6±2.3</td>
<td>-2.0±6.5</td>
<td>0.5±4.8</td>
<td>-1.0±7.4</td>
<td>8.7±13.5</td>
<td>11.2±15.5</td>
<td>-0.6±10.0</td>
</tr>
<tr>
<td>EDV</td>
<td>64.3±19.2</td>
<td>1.5±3.0</td>
<td>0.7±3.3</td>
<td>2.2±3.4</td>
<td>-0.2±4.1</td>
<td>2.1±3.1</td>
<td>1.3±4.0</td>
</tr>
<tr>
<td>ESV</td>
<td>49.2±16.0</td>
<td>-1.5±2.6</td>
<td>-5.2±5.9</td>
<td>-2.5±2.2</td>
<td>-0.8±4.8</td>
<td>-6.0±6.8</td>
<td>-1.7±3.2</td>
</tr>
<tr>
<td>SV</td>
<td>18.0±7.9</td>
<td>6.8±11.4</td>
<td>13.7±13.6</td>
<td>13.0±10.7</td>
<td>9.0±15.0</td>
<td>25.3±24.3*</td>
<td>8.7±11.4</td>
</tr>
<tr>
<td>SW</td>
<td>969±442</td>
<td>19±18*</td>
<td>20±19</td>
<td>31±17*†</td>
<td>15±19</td>
<td>28±25</td>
<td>21±22</td>
</tr>
</tbody>
</table>

‘Baseline’ is calculated from all baselines for the pacing configurations shown. ‘Average’ is the average of all sites and AV 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}.

Values are mean ± SD. EDP, end-diastolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; SW, stroke work; Epi, Epicardial; Endo, Endocardial; TriV, Triventricular. *, p<.05 vs. each configuration’s baseline, †, p<.05 vs. TriV on average, ‡ vs. TriV at the optimal site.
<table>
<thead>
<tr>
<th>Site</th>
<th>Pacing</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>
<td></td>
</tr>
<tr>
<td>LVL</td>
<td>50%</td>
<td>12%</td>
<td>13%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>LVB</td>
<td>25%</td>
<td>38%</td>
<td>50%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>LVPOST</td>
<td>25%</td>
<td>12%</td>
<td>25%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

LVA: LV apex; LVL: LV lateral; LVB: LV basal; LVPOST: LV posterior


