Endocardial Left Ventricular Pacing Improves Cardiac Resynchronization Therapy in Chronic Asynchronous Infarction and Heart Failure Models

Running title: Strik et al.; Endocardial CRT in infarcted and failing canine hearts

Marc Strik, MD¹; Leonard M. Rademakers, MD, PhD¹; Caroline J.M. van Deursen, MD¹;
Arne van Hunnik, BSc¹; Marion Kuiper BSc¹; Catherine Klersy, MD, MSc²;
Angelo Auricchio, MD, PhD³; Frits W. Prinzen, PhD¹

¹Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University,
Maastricht, Limburg, the Netherlands; ²Biometry and Clinical Epidemiology, Scientific
Direction, IRCCS Policlinico San Matteo Foundation, Pavia, Italy; ³Fondazione Cardiocentro
Ticino, Lugano, Ticino, Switzerland

Corresponding Author:

Dr. Frits W. Prinzen
Department of Physiology
Cardiovascular Research Institute Maastricht,
P.O. Box 616, 6200MD Maastricht, The Netherlands
Tel:+31-43-3881080
Fax:+31-43-3884166
E-mail: frits.prinzen@maastrichtuniversity.nl

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Animal models of human disease
Abstract:

Background - Studies in canine hearts with acute left bundle branch block (LBBB) showed that endocardial left ventricular (LV) pacing improves efficacy of Cardiac Resynchronization Therapy (CRT) as compared to conventional epicardial LV pacing. The present study explores the efficacy of endocardial CRT in more compromised hearts and the mechanisms of such beneficial effects.

Methods and Results - Measurements were performed in 22 dogs, 9 with acute LBBB, 7 with chronic LBBB combined with infarction (embolization; LBBB+MI, concentric remodeling) and 6 with chronic LBBB and heart failure (rapid pacing, LBBB+HF, eccentric remodeling). Head-to-head comparison was performed of the effects of endocardial and epicardial LV pacing at 8 sites. LV activation times were measured using ≈100 endocardial and epicardial electrodes and non-contact mapping. Pump function was assessed from right ventricular and LV pressures. Endocardial CRT resulted in better electrical resynchronization than epicardial CRT in all models, though the benefit was larger in concentrically remodeled LBBB+MI than in eccentrically remodeled LBBB+HF hearts (19 vs. 10%, respectively). In LBBB and LBBB+HF animals endocardial conduction was ≈50% faster than epicardial conduction and in all models transmural impulse conduction was ≈25% faster when pacing from the endocardium than from the epicardium. Hemodynamic effects were congruent with electrical effects.

Conclusions - Endocardial CRT improves electrical synchrony of activation as well as LV pump function compared to conventional epicardial CRT in compromised canine LBBB hearts. This benefit can be explained by shorter pathlength along the endocardium and by faster circumferential and transmural impulse conduction during endocardial LV pacing.

Key words: pacing, heart failure, cardiac resynchronization therapy, electrophysiology, bundle-branch block
Introduction

Cardiac Resynchronization Therapy (CRT) is an established treatment for patients with moderate-to-severe heart failure and a wide QRS complex. However, the amount of reverse remodeling and clinical improvement is highly variable and a considerable amount of patients respond poorly to the therapy.

In conventional CRT, the left ventricular (LV) lead is transvenously positioned in a coronary vein, which results in epicardial (EPI) LV pacing. As a consequence, the initiated electrical wavefront propagates over the epicardium and through the LV wall towards the endocardium. Under physiological conditions, electrical activation of the LV initiates at the endocardium. Endocardial (ENDO) LV pacing results in less asynchronous activation of the LV free wall than EPI LV pacing. In dogs with acute left bundle branch block (LBBB), ENDO LV pacing during CRT (ENDO-CRT) has indeed been shown to increase the benefits of CRT. As compared to EPI-CRT, ENDO-CRT improved LV systolic pump function in combination with better electrical resynchronization and less dispersion of repolarization.

Three possible mechanisms explaining the more rapid electrical activation during ENDO-CRT were proposed: i) shorter path length of conduction, ii) faster endocardial than epicardial conduction as well as iii) faster conduction from endocardium to epicardium than vice versa.

While all three factors may contribute in the setting of acute LBBB in otherwise healthy canine hearts, several factors may potentially diminish the benefit of ENDO-CRT in patients. Firstly, the influence of an infarct on impulse conduction in asynchronous hearts is not understood and may differ between myocardial layers. Secondly, ventricular dilatation and wall thinning would reduce the difference in conduction pathlength between endocardium and epicardium, potentially reducing the advantage of ENDO-CRT in patients with dilated cardiomyopathy. In addition,
Spragg et al showed that in canine hearts with chronic LBBB, impulse conduction was reduced especially in the endocardium of the late activated regions, exactly the region where one would position the ENDO LV pacing lead. Better understanding of the various factors determining the benefits of ENDO-CRT in animal models with compromised hearts are warranted also to better understand the ambivalent results reported from the few small clinical studies on endocardial CRT.6-9

To this purpose we investigated the efficacy of ENDO-CRT in three animal models: canine hearts with acute LBBB and in chronic LBBB in combination with myocardial infarction (LBBB+MI, induced by coronary embolization) or with dilated cardiomyopathy (LBBB+HF, induced by rapid pacing). In order to better understand the mechanisms of ENDO-CRT we also performed more detailed electrophysiological measurements as compared to our earlier studies in acute LBBB.4

Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

Experimental models

Twenty-two adult mongrel dogs of either sex and unknown age, weighing 29.5±2.0kg, were divided into three groups; acute LBBB (n=9, of which some data were already reported previously4), LBBB+MI (n=7) and LBBB+HF (n=6). Animals were induced by intravenous
pentothal administration and anesthetized by continuous infusion of midazolam (0.25mg/kg/h iv) and sufentanil (3μg/kg/h iv).

In the LBBB+MI group, transmural infarction was created by embolization of the LCX (n=3) and LAD (n=4) artery using a suspension of ≈1cc dry volume polyvinyl alcohol foam particles and four weeks later, LBBB was induced. Infarct size (% LV mass) and transmurality was determined by triphenyltetrazolium chloride staining postmortem. In the LBBB+HF group, LBBB was created and, during the same procedure, a standard pacing lead was placed in the apex of the right ventricle (RV) and connected to a pacemaker (Medtronic InSync® III). After a week of recovery, the heart was paced at a rate of 220 beats per minute for 4 weeks to induce systolic LV dysfunction, as described by other groups. In both models, M-mode recordings of 2D echocardiography measurements from the mid-ventricular papillary muscle level were obtained at baseline and just before the final measurements.

Cardiac Resynchronization Therapy studies

Five weeks after creating the infarction (LBBB+MI) or four weeks after turning on the pacemaker (LBBB+HF), the animals were anesthetized again, as described above, for the acute CRT studies. RV and LV pressure catheters were positioned as reported earlier. After opening the chest, two multi-electrode arrays holding 102 contact electrodes were placed around the heart, which measured epicardial electrical potentials (figure 1). Additional EPI LV electrodes were placed at the apex and lateral apex. An octapolar electrode catheter (Daig Livewire TC, Minnetonka, MN) was positioned against the RV-septum. Eight LV EPI electrodes were selected for pacing at various wall regions; anterior base, lateral base, posterior base, mid anterior, mid lateral, mid posterior, lateral apex and apex. For a paired comparison between EPI and ENDO
LV pacing, custom-made plunge electrodes were inserted at these exact sites to enable ENDO-CRT and endocardial LV mapping (figure 1).

**Pacing protocol**

All pacing was performed in D00 mode, using atrial pacing at approximately 10 beats per minute above intrinsic rate. Between each switch of LV pacing site (8 EPI and 8 ENDO), baseline atrial pacing measurements were made during three respiratory cycles. During biventricular (BiV) pacing, the RV apex was stimulated simultaneously with the selected EPI or ENDO LV electrode, using the longest atrioventricular (AV) interval that ensured complete biventricular capture.

After hemodynamic measurements in the LBBB and LBBB+HF dogs, a non-contact multi-electrode array (EnSite 3000®, figure 1) was introduced into the LV to enable localization of the LV endocardium and plunge electrodes.13 Subsequently, the pacing protocol was repeated while deriving 2048 virtual electrograms around the endocardial LV simultaneously and storing them for offline analysis.

**Data analysis**

From the surface ECG, QRS-width and time from T-peak to T-end were determined.4 For all electrodes, depolarization times were calculated as the time difference between onset of the Q-wave (during baseline) or ventricular pacing artifact (during CRT) and the time of steepest deflection in the electrogram (-dV/dtmax). Three-dimensional depolarization time maps were created by plotting the depolarization times on epicardial and endocardial models using custom MATLAB software (MathWorks, Natick, MA).14 Activation times (AT) were defined as the maximum depolarization time difference and were calculated for specific LV layers (endocardium, epicardium and transmural) and of the total LV. LV EPI electrodes were
considered to be the band electrodes on the LV wall, the LV apical plunge electrodes and the RV septal electrodes.

Since endocardial LV AT was derived from a small amount of plunge electrodes, the 2048 virtual electrograms as derived from the multi-electrode array (EnSite 3000®) were used to calculate endocardial LV AT in an alternative way to compare with the plunge electrode measurements. Conduction velocities were calculated in the acute LBBB and LBBB+HF groups for anterior, lateral and posterior regions between the paced electrode and their neighboring electrodes in the same myocardial layer by dividing the inter-electrode distance by the difference in AT. For epicardial conduction velocity, this distance was equal to the inter-electrode distance on the epicardial bands. For the endocardial conduction velocity, the endocardial inter-electrode distance was derived from the shortest path length between these electrodes over the endocardial contour as calculated by the EnSite® system. Hemodynamic data analysis was performed as described previously.4

**Statistical analysis**

Continuous data are presented as mean±standard deviation, and discrete variables as counts and percentage. A series of general linear regression models were used to compare pacing sites and experimental models for the several endpoints, with identity or logistic link function according to the dependent variable assessed. To account for intra-individual correlation of measurements (panel data), Huber-White robust standard-errors were calculated. No missing data imputation was performed. Stata 10 (StataCorp, College Station, TX, USA) was used for computation. A two-sided *P*-value<0.05 was considered statistically significant. The Bonferroni correction was used for post-hoc comparisons.
**Results**

In all 22 experiments, 8 EPI-ENDO pairs of LV pacing sites were evaluated during BiV pacing. Due to occasional misplacement of the endocardial electrode or unstable hemodynamic conditions, 151 out of the possible 176 paired datasets were successfully acquired.

**Experimental Models**

Table 1 summarizes baseline characteristics of hearts with acute LBBB, LBBB+MI and LBBB+HF during the CRT protocol. All infarctions were transmural and infarct size accounted for 20±16% (range 14-32%) of LV mass. As compared to the acute LBBB group, LV function was depressed in the LBBB+MI group, as indicated by lower stroke work and elevated LV and RV end-diastolic pressures. Echocardiographically, LV end-diastolic diameter remained constant while wall thickness increased (Table 1). Consequently, the ratio of outer to inner LV radius was higher in the LBBB+MI group as compared with the acute LBBB group (1.88 versus 1.61, respectively, general linear model (post-hoc comparison) p<0.05), indicating concentric remodeling. In the LBBB+HF group, four weeks of rapid pacing induced an increase in LV end-diastolic diameter and a decrease in LV wall thickness. In this model, the ratio of outer LV radius and inner LV radius was decreased to 1.36 (general linear model (post-hoc comparison) p<0.05), reflecting eccentric remodeling, which was accompanied by severe systolic dysfunction as evidenced by an LV ejection fraction of ≥15% in combination with ≥50% reduction of LV dP/dt\text{max}, and elevated LV EDP (Table 1).

*Effects of ENDO-CRT on impulse conduction*

Typical examples of electrical activation in the ventricles for all three groups are shown in figure 2. During baseline LBBB (left panels), the electrical wavefront initiated at the RV endocardium and gradually spread through the interventricular septum towards the latest activated LV lateral
wall, consistent with electrical maps from an earlier high-resolution mapping study.\(^\text{15}\) During
conventional EPI-CRT, activation wavefronts (red-yellow) generated in the RV and LV merged
near the septum and anterior wall (green), thus resynchronizing the ventricles as compared to
baseline LBBB. ENDO-CRT (right panels) resulted in more pronounced resynchronization than
EPI-CRT, as is depicted by the more homogeneous color pattern (lack of green color) and less
crowding of isochrone lines.

These mapping studies revealed that in all models, ENDO-CRT significantly reduced total LV
AT as compared with EPI-CRT, which was associated with reduced QRS duration (figure 3,
table 2). The shorter total LV AT during ENDO-CRT was caused by shorter epicardial LV AT as
well as shorter transmural LV AT. The latter is depicted in figure 3 by the dashed arrow lines as
the time to the first endocardial activation during EPI-CRT and time to first epicardial activation
during ENDO-CRT. A detailed indication of the spread of activation in the short axis is provided
by figure 4. This figure also explains why endocardial LV AT was paradoxically increased by
ENDO-CRT as compared to EPI-CRT in figure 3. During EPI-CRT, a broad wavefront slowly
approached the endocardium but caused almost simultaneous activation of a large part of the LV
endocardium, whereas during ENDO-CRT the earliest endocardial activation occurred in a small
region that took time to spread to more remote areas of the LV endocardium. The endocardial
LV AT as derived from the LV contact electrodes corresponded closely with those derived from
multi-electrode array mapping (plot in figure 4), albeit that the plunge electrodes underestimated
endocardial LV AT at higher values, presumably because the multi-electrode array is more likely
to include small late activated regions.

Comparing all measurements to baseline LBBB, ENDO-CRT reduced total LV AT significantly
more than EPI-CRT in all three models (bottom panel of figure 5; table 2) The improved
resynchronization during ENDO-CRT was associated with approximately 50% higher circumferential conduction velocities at the endocardium than at the epicardium (figure 6A). This difference was consistent for all LV segments and was observed in hearts with acute LBBB and in the LBBB+HF hearts. The added benefit of ENDO-CRT to resynchronize was larger in concentrically remodeled hearts (LBBB+MI) and least (19 vs. 10%, respectively) in eccentrically remodeled hearts (LBBB+HF; figure 6B), indicating that the smaller path length along the endocardium partly explains the benefit of endocardial CRT on electrical resynchronization.

**Effects of ENDO-CRT on hemodynamic performance**

The superior electrical resynchronization by ENDO-CRT coincided with larger increases in LV dP/dt\textsubscript{max} than during EPI-CRT and the absolute increase was similar for the three models (≈10% on top of EPI-CRT effect; upper panel in figure 5). Larger LV contractility improvement during ENDO-CRT was consistent for all paced regions and groups (with the exception of apicolateral pacing in the LBBB+HF group; Figure 7). Defining ≥10% increase in LV dP/dt\textsubscript{max} as acute hemodynamic response to CRT, ENDO-CRT resulted in a hemodynamic response in 90% cases, whereas EPI-CRT only resulted in a 59% response rate. Generally, the optimal sites during ENDO-CRT were located at the same wall regions as the optimal sites during EPI-CRT (Figure 8). However, endocardial sites providing a significant effect, encompassed a larger LV area and magnitude of improvement was larger than for epicardial sites, as indicated by the more intense red colors. In LBBB hearts with LAD infarction the best pacing sites were the basolateral LV wall, whereas in LBBB hearts with LCX infarction, LV mid-lateral to apicolateral wall sites provided the best results. In the acute LBBB and LBBB+HF group, lateral and apicolateral pacing sites tended to perform better than anterior and posterior sites but there was not an identifiable 'optimal' ENDO or EPI pacing site (Figure 8). ENDO-CRT tended to increase
stroke work as compared to EPI-CRT and in the LBBB+HF group, ENDO-CRT also resulted in larger decreases in LV $dP/dt_{\text{min}}$ than EPI-CRT (Table 2).

**Discussion**

The present study shows that endocardial CRT produces more uniform ventricular depolarization as well as larger hemodynamic benefit as compared to conventional epicardial CRT in three models of experimental dyssynchrony: acute LBBB and chronic LBBB in combination with heart failure and with myocardial infarction. The advantage of endocardial over epicardial CRT can to a large extent be understood from higher endocardial impulse conduction velocities, shorter transmural activation times and shorter conduction path length, the latter explaining the less pronounced resynchronization in eccentrically remodeled LBBB+HF.

**Mechanisms of better electrical resynchronization by LV Endocardial Pacing**

From the data of our previous study in canine hearts with acute LBBB we suggested that the electrical benefits of endocardial CRT could be explained by three factors: (i) a shorter path length for the depolarization wave to reach all regions of the ventricles, (ii) more rapid impulse conduction in the endocardium than in the epicardium, (iii) a more rapid transmural conduction from endocardium to epicardium than in the opposite direction. The present study extends these observations and provides more robust and more detailed evidence for these mechanisms.

While obviously the path for impulse conduction is always shorter along the endocardium than along the epicardium, the difference depends on the eccentricity of ventricular remodeling. The finding that the added benefit of endocardial over epicardial CRT on electrical resynchronization was greater in hearts with concentric than with eccentric remodeling supports the idea of a role...
for the shorter path length in the benefits of endocardial CRT. However, even in the most eccentrically remodeled hearts a clear benefit remained, indicating important roles for other factors.

The most predominant factor in respect to the added benefit of endocardial pacing appears to be the faster impulse conduction in the endocardial layers. This fast conduction was even observed in the chronically dyssynchronous failing hearts and without regional differences. These results seem to contradict results from in vitro mapping studies by Spragg et al, who showed endocardial conduction slowing in lateral regions of chronically dyssynchronous canine hearts. These contradictory findings might be explained by the difference in setup (perfused wedge preparations versus in vivo). Factors like hypoxia, tissue damage during isolation of the wedge and perfusion with crystalline medium may have influenced the in vitro measurements. On the other hand, distance along the endocardium may have been assessed less accurately in our in vivo preparation. Finally, Spragg et al measured along the main axis of a diagonally propagating wavefront, whereas we selectively measured velocity in circumferential direction.

Beside a faster endocardial than epicardial impulse conduction we also consistently found that impulse conduction across the LV wall was ≈25% faster when pacing the LV endocardium than pacing the LV epicardium, thus adding to the more rapid total LV resynchronization. This difference in transmural conduction velocity is not well understood, because it would be expected that the conduction path is the same. Interestingly, this effect was observed even in the LBBB+HF group, even though LV wall thickness was decreased by ≈21%, thus contributing to the better electrical resynchronization during endocardial CRT.

Comparison with clinical studies
LV endocardial pacing in humans can be established through an atrial transseptal approach.\textsuperscript{6-8} The results of our study are, at least in part, supported by a few small observational studies in human CRT patients where such approach has been followed. In these clinical studies, LV dP/dt$_{\text{max}}$ at the best LV endocardial site was significantly greater than that with device pacing via the coronary sinus.\textsuperscript{7-9} Recently, these findings were debated to be subjected to statistical bias as the best LV ENDO site was selected among many (up to 51) LV endocardial sites, which were compared to a single LV EPI site (via the coronary sinus).\textsuperscript{16} Using this method, a relatively small measurement error could project into a rather wide range of extreme results.\textsuperscript{16} In contrast, in our study we used 8 sites, evenly spread over the LV free wall, and used back-to-back comparison of endocardial and epicardial CRT, thus eliminating these site-specific biological pacing effects and statistical bias. In the clinical studies that compared the effect of pacing the coronary sinus electrode with the corresponding, immediately opposite LV endocardium the statistical significance was lost, but the trend still was towards a better effect of endocardial CRT.\textsuperscript{7, 8} A possible explanation for the lack of statistical significance in the clinical studies may be the fact that one study only investigated single-site LV pacing\textsuperscript{7}, which in the present canine study also did not result in significant LV dP/dt$_{\text{max}}$ differences when using short AV-intervals (data not shown). In another study\textsuperscript{8} the direct comparison could only be made in 7 patients, which resulted in very low statistical power. An additional advantage of our animal experiment may have been the higher accuracy of positioning the pacing leads at directly opposite sides of the LV wall because of the direct access to the heart. Clearly, a more systematic study is required to certify the benefit of endocardial over epicardial CRT in patients.
Most clinical studies used either QRS duration or solely epicardial or endocardial activation time to assess electrical asynchrony while few studies measured total (epicardial and endocardial activation time). Like in our study, Ginks et al employed multi-electrode array (EnSite®) measurements of endocardial LV AT and found no reduction in this variable when moving from epicardial to endocardial CRT. This observation was also made in our study, actually demonstrating an increase of endocardial LV AT upon endocardial CRT. However, this paradoxical increase was inconsequential, due to the reduction in epicardial LV as well as transmural AT, such that total LV AT was reduced. Comparable to our results achieved in canine hearts, Ginks et al found that endocardial LV AT encompassed ≈40% of the QRS duration. Therefore, endocardial conduction velocity is most likely similarly higher than epicardial conduction in patients, which is an important factor in the mechanism of endocardial CRT. The present study shows one possible reason why endocardial CRT may be less beneficial in patients with dilated heart failure. The smaller endocardial to epicardial path length difference in patients with dilated hearts could preclude the better resynchronization but the hemodynamic benefits remain in favor of endocardial CRT, presumably due to the role of faster transmural and endocardial conduction.

In the latter respect Ginks et al made an important observation, in that they observed smaller benefits at endocardial sites with slow conduction, possibly related to scar or hypoperfusion. This observation may seem in contradiction with our observation that the benefit of endocardial pacing was largest in the LBBB+MI group. However, it should be kept in mind that in our study we avoided to pace inside the infarcted area. In fact, myocardial infarction does not preclude benefits of CRT, but the efficacy is more dependent on location and timing of stimulation, as has also been shown in a previous report. Also, a recent publication provides evidence that pacing
in the scar strongly reduces the benefit of CRT. Therefore, it is still plausible that ENDO-CRT can increase therapy response in ischemic patients. In this respect an important benefit of endocardial CRT is that more pacing sites can be reached than usually with coronary venous implants. Exploring the sites appears important in the light of the findings of Ginks et al as well as of our finding that there was no single optimal endocardial pacing site that showed consistently better hemodynamics. Helm et al investigated over one hundred pacing sites in failing and non-failing asynchronous canine hearts and found, in agreement with our results, that average CRT response was excellent in a fairly broad range of the LV lateral wall. Individual tailoring of endocardial CRT by searching the optimal pacing site within the endocardium is thus warranted. The fact that endocardial CRT provides consistently better electrical resynchronization as well as hemodynamic improvement in the three different animal models further supports the idea that endocardial CRT is the ultimate preference in a wide variety of patients with dyssynchrony. This benefit may be enhanced by the larger range of accessible locations at the endocardium.

**Endocardial CRT in specific LBBB models**

It was interesting to observe that despite all differences between the three models, CRT resulted in a similar absolute increase in LV $dP/dt_{max}$ (all $\approx 150$ mmHg/s with EPI-CRT and $\approx 250$ mmHg/s with endocardial CRT). Because baseline LV $dP/dt_{max}$ was considerably lower in the LBBB+HF group, this translated to higher relative increases in LV $dP/dt_{max}$ during CRT, relative increases that are similar to those found in patients. Interestingly, in CRT patients, a wide range of baseline LV $dP/dt_{max}$ is observed, yet the increase in LV $dP/dt_{max}$ upon CRT is also $\approx 200$ mmHg/s. This indicates that there is an almost fixed increase in this parameter by CRT, which, as we show, can be increased by using a better (endocardial) pacing site.
Limitations

Even though current chronic animal models resemble CRT candidates better than the acute LBBB model, our data should be extrapolated to patients with care. The LBBB+MI model has been introduced in a previous publication. It is characterized by preserved LV ejection fraction, but elevated LV and RV filling pressures and reduced stroke work. It should be realized that in this model, LBBB was induced by ablation of the proximal left bundle branch. The thus induced conduction abnormality may differ from that in patients with ischemic etiology of heart failure, where the ischemia may be the underlying cause of the conduction abnormality.

The LBBB+HF model has been used before by other groups. Even in these 'chronic' animal models the disease history is shorter than in patients, and in addition, fibrosis and molecular remodeling may differ between animals and patients. Furthermore, the present study investigated the acute hemodynamic response, whereas the long term response, reverse remodeling and survival are more relevant. Long term follow up of patients with endocardial CRT is limited to a small study, comparing 8 patients with endocardial CRT with 17 conventional (epicardial) CRT patients. This study found a more homogenous intraventricular resynchronization, better LV filling and increased systolic performance after 6 months. Clearly, larger long term follow up of endocardial CRT in patients is indicated.

Conclusions

In the canine model of chronic LBBB combined with myocardial infarction or dilated cardiomyopathy, endocardial CRT improves electrical synchrony of activation as well as LV function as compared with conventional epicardial CRT. The extent of additional electrical
resynchronization by endocardial CRT is dependent on cardiac remodeling but the functional response is not. Therefore, this study further emphasizes the relevance of investigating the benefits of endocardial LV stimulation in CRT patients.

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Conflict of Interest Disclosures: AA has received research grants from Medtronic Inc., Boston Scientific Corp., St.Jude Medical and Biotronic and is advisor to EBR Systems, Medtronic and Sorin. FWP has received research grants from Medtronic Inc., Boston Scientific Corp. and EBR Systems and is advisor to Medtronic Inc.

References:


**Table 1:** Baseline electrocardiography, echocardiography and hemodynamic characteristics of the LBBB group, LBBB+MI group and LBBB+HF group.

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<th></th>
<th>LBBB (n=9) mean±SD</th>
<th>LBBB+MI (n=7) mean±SD</th>
<th>LBBB+HF (n=6) mean±SD</th>
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<tr>
<td><strong>Electrocardiography parameters</strong></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>117±11</td>
<td>125±16</td>
<td>135±10*</td>
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<td>QRS width (ms)</td>
<td>116±8</td>
<td>106±9</td>
<td>123±10</td>
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<td><strong>Echocardiography parameters</strong></td>
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<td>LV end-diastolic diameter (cm)</td>
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<td>LV posterior wall thickness (cm)</td>
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<td>LV septum wall thickness (cm)</td>
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<td>LV Ejection Fraction (%)</td>
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<td><strong>Hemodynamic parameters</strong></td>
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<td>LV dP/dt_{max} (mmHg/s)</td>
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<td>RV PSP (mmHg)</td>
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<td>RV EDP (mmHg)</td>
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<td>Mech.InterVentr.Asynch. (ms)</td>
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<td>-22±7</td>
<td>-23±11</td>
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Mech.InterVentr.Asynch.: mechanical interventricular asynchrony. *p<0.05 compared to LBBB group, using a general linear model for repeated measures and Bonferroni correction for post-hoc comparisons.
Table 2A: Electrophysiological and hemodynamic variables during baseline LBBB conduction and during epicardial and endocardial CRT in dogs with LBBB and myocardial infarction. Corresponding data for the acute LBBB group have been published previously.4

<table>
<thead>
<tr>
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<th>Baseline LBBB+MI</th>
<th>EPI-BiV</th>
<th>ENDO-BiV</th>
<th>ΔEPI vs ΔENDO</th>
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<td><strong>HR (bpm)</strong></td>
<td>mean±SD</td>
<td>mean±SD</td>
<td>mean±SD</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>125±16</td>
<td>124±17</td>
<td>124±18</td>
<td>0.486</td>
</tr>
<tr>
<td><strong>QRS width (ms)</strong></td>
<td>106±9</td>
<td>96±17*</td>
<td>79±12*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total LV AT (ms)</strong></td>
<td>88±7</td>
<td>81±16*</td>
<td>66±12*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Epicardial LV AT (ms)</strong></td>
<td>88±7</td>
<td>81±16*</td>
<td>40±11*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Endocardial LV AT (ms)</strong></td>
<td>52±16</td>
<td>47±15</td>
<td>54±10*</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Transmural AT (ms)</strong></td>
<td>36±21</td>
<td>21±11</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>T_peak-T_end (ms)</strong></td>
<td>63±4</td>
<td>52±12</td>
<td>49±11</td>
<td>0.358</td>
</tr>
<tr>
<td><strong>Tau (ms)</strong></td>
<td>43±6</td>
<td>45±5</td>
<td>45±5</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>LV P_max (mmHg)</strong></td>
<td>87±12</td>
<td>88±12</td>
<td>88±13</td>
<td>0.183</td>
</tr>
<tr>
<td><strong>LV dP/dt_max (mmHg/s)</strong></td>
<td>1410±282</td>
<td>1527±320*</td>
<td>1673±382*</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>LV dP/dt_min (mmHg/s)</strong></td>
<td>-1495±344</td>
<td>-1550±340</td>
<td>-1551±375</td>
<td>0.711</td>
</tr>
<tr>
<td><strong>LV EDP (mmHg)</strong></td>
<td>13±7</td>
<td>14±8</td>
<td>14±7</td>
<td>0.362</td>
</tr>
<tr>
<td><strong>SV (ml)</strong></td>
<td>20±7</td>
<td>21±8</td>
<td>21±8</td>
<td>0.384</td>
</tr>
<tr>
<td><strong>SW (mmHg*ml)</strong></td>
<td>1208±594</td>
<td>1403±692*</td>
<td>1586±775*</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>RV P_max (mmHg)</strong></td>
<td>30±5</td>
<td>28±4</td>
<td>26±4</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>RV dP/dt_max (mmHg/s)</strong></td>
<td>490±129</td>
<td>531±148</td>
<td>517±139</td>
<td>0.066</td>
</tr>
<tr>
<td><strong>RV dP/dt_min (mmHg/s)</strong></td>
<td>-280±75</td>
<td>-272±69</td>
<td>-288±90</td>
<td>0.351</td>
</tr>
<tr>
<td><strong>RV EDP (mmHg)</strong></td>
<td>9±4</td>
<td>10±4</td>
<td>9±3</td>
<td>0.408</td>
</tr>
<tr>
<td><strong>Mech.InterVentr.Async. (ms)</strong></td>
<td>-22±7</td>
<td>-16±9</td>
<td>-9±10</td>
<td>0.052</td>
</tr>
</tbody>
</table>

Mech.InterVentr.Asynchr: mechanical interventricular asynchrony; data from 51 paired measurements in 7 experiments. *p<0.05 compared to baseline LBBB. In the last column, p-values are presented for the differences in relative change (Δ) by EPI-CRT versus ENDO-CRT. All p-values are based on the general linear model for repeated measures.
**Table 2B:** Electrophysiological and hemodynamic variables during baseline LBBB conduction and during epicardial endocardial CRT in dogs with LBBB and dilated cardiomyopathy.

<table>
<thead>
<tr>
<th></th>
<th>Baseline LBBB+HF</th>
<th>EPI-CRT</th>
<th>ENDO-CRT</th>
<th>ΔEPI vs ΔENDO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>mean±SD</td>
<td>mean±SD</td>
<td>mean±SD</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>135±10</td>
<td>135±9</td>
<td>135±9</td>
<td></td>
</tr>
<tr>
<td><strong>QRS width (ms)</strong></td>
<td>123±10</td>
<td>116±16</td>
<td>99±20*</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Total LV AT (ms)</strong></td>
<td>97±16</td>
<td>87±13*</td>
<td>76±17*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Epicardial LV AT (ms)</strong></td>
<td>97±16</td>
<td>85±12*</td>
<td>49±16*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Endocardial LV AT (ms)</strong></td>
<td>37±10</td>
<td>42±11</td>
<td>61±13*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Transmural AT (ms)</strong></td>
<td>35±11</td>
<td>26±9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tpeak-Tend (ms)</strong></td>
<td>56±8</td>
<td>44±13*</td>
<td>45±18*</td>
<td>0.883</td>
</tr>
<tr>
<td><strong>Tau (ms)</strong></td>
<td>57±20</td>
<td>49±22</td>
<td>46±21</td>
<td>0.297</td>
</tr>
<tr>
<td><strong>LV Pmax (mmHg)</strong></td>
<td>76±10</td>
<td>78±9</td>
<td>78±10</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>LV dP/dtmax (mmHg/s)</strong></td>
<td>842±82</td>
<td>1009±153*</td>
<td>1090±221*</td>
<td>0.106</td>
</tr>
<tr>
<td><strong>LV dP/dtmax/Pnormed (mmHg/s)</strong></td>
<td>22.3±5</td>
<td>26.9±7*</td>
<td>29±7*</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>LV dP/dtmin (mmHg/s)</strong></td>
<td>-976±175</td>
<td>-1091±241*</td>
<td>-1177±281*</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>LV EDP (mmHg)</strong></td>
<td>18.3±11</td>
<td>18.3±14</td>
<td>17.7±15</td>
<td>0.386</td>
</tr>
<tr>
<td><strong>SV (ml)</strong></td>
<td>15±5</td>
<td>20±9*</td>
<td>20±10</td>
<td>0.556</td>
</tr>
<tr>
<td><strong>SW (mmHg*ml)</strong></td>
<td>1088±398</td>
<td>1363±644*</td>
<td>1467±767*</td>
<td>0.170</td>
</tr>
<tr>
<td><strong>RV Pmax (mmHg)</strong></td>
<td>30±10</td>
<td>28±9*</td>
<td>28±9*</td>
<td>0.640</td>
</tr>
<tr>
<td><strong>RV dP/dtmax (mmHg/s)</strong></td>
<td>426±125</td>
<td>442±102</td>
<td>437±142</td>
<td>0.823</td>
</tr>
<tr>
<td><strong>RV dP/dtmin (mmHg/s)</strong></td>
<td>-388±165</td>
<td>-384±172</td>
<td>-412±176</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>RV EDP (mmHg)</strong></td>
<td>8±5</td>
<td>8±7</td>
<td>8±7</td>
<td>0.662</td>
</tr>
<tr>
<td><strong>Mech.InterVentr.Async. (ms)</strong></td>
<td>-23±11</td>
<td>-16±9</td>
<td>-9±10*</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Mech.InterVentr.Async: mechanical interventricular asynchrony; data from 48 paired measurements in 6 experiments. *p<0.05 compared to baseline LBBB. In the last column, p-values are presented for the differences in relative change (Δ) by EPI-CRT versus ENDO-CRT. All p-values are based on the general linear model for repeated measures.
Figure Legends:

Figure 1: Schematic set-up of the experiment (left panel) with mapping electrodes depicted as yellow dots; The 8 pacing electrodes have an additional blue (EPI) or red (ENDO) border. The fluoroscopic image (right panel) shows the mapping electrodes and multi-electrode array in place.

Figure 2: Typical examples of 3D electrical activation in the LBBB group, LBBB+MI group and LBBB+HF group during baseline LBBB (left panels), CRT with EPI LV pacing (middle panels) and ENDO LV pacing (right panels). In both modes of CRT the LV pacing lead was positioned at the mid-level of the LV wall. The size of cavity and the wall thickness correspond approximately with the echocardiographic measurements.

Figure 3: Overview of mean QRS duration, epicardial LV AT (activation time) and endocardial LV AT during EPI versus ENDO-CRT in dogs with LBBB, LBBB+MI and LBBB+HF. Dashed bars indicate total LV AT and dashed arrows show transmural LV AT. All EPI-ENDO comparisons are statistically significant (p<0.01), see table 2 for absolute values and p-values (all p-values are based on the general linear model for repeated measures).

Figure 4: Typical examples of short-axis electrical activation during baseline LBBB (left), EPI-CRT (top right) and ENDO-CRT (bottom right), obtained by electrode band and multi-electrode array mapping. Transmural and epicardial isochrone broadening during ENDO-CRT indicate faster depolarization but the endocardium is depolarized later than during EPI-CRT as indicated
by the isochrone narrowing. Dotted lines indicate the electrodes from which activation times were derived and divided by their distance to the pacing electrode to obtain conduction velocity. The graph plot shows the correlation between ENDO AT derived by the plunge electrodes and by the multi-electrode array during EPI and ENDO-CRT in the LBBB and LBBB+HF groups.

**Figure 5:** Percent change in LV dP/dt$_{max}$ (top panel) and during LV total activation duration (bottom panel) during EPI versus ENDO-CRT in dogs with LBBB, LBBB+MI and LBBB+HF. *p<0.05 compared with baseline atrial pacing. # p<0.05 comparing ENDO-CRT with EPI-CRT. (all p-values are based on the general linear model for repeated measures).

**Figure 6:** A: Means (±SD) of conduction velocities (in m/s) of the epicardium and endocardium in anterior, lateral and posterior regions in dogs with acute LBBB and chronic LBBB+HF. #p<0.05 EPI versus ENDO. B: Percent change in total LV AT during EPI versus ENDO-CRT as a function of the ratio of outer LV radius to inner LV radius in the three experimental groups. P-values signify a statistical difference in ENDO-EPI difference between groups. (all p-values are based on the general linear model for repeated measures).

**Figure 7:** Increase in LV dP/dt$_{max}$ (mean values and S.D., pooled by regions, as compared to baseline) during ENDO-CRT as a function of the % increase in LV dP/dt$_{max}$ during EPI-CRT in dogs with LBBB, LBBB+MI and LBBB+HF.

**Figure 8:** Spatial distribution of pacing sites (indicated by grey circles) that provide a certain % increase in LV electrical resynchronization and LV dP/dt$_{max}$ during EPI-CRT and ENDO-CRT as
compared to baseline atrial pacing. Plots are based on mean values from 6 LBBB hearts (top left panels), 6 LBBB+HF hearts (top right panels), 4 LBBB+MI with LAD infarction (bottom left panels) and 3 LBBB+MI hearts with LCX infarction (bottom right panels). Dashed lines indicate region of infarction and arrows indicate rotation of LAD versus LCX. Impression of variation in measurements can be obtained from the error bars in figure 7.
multi-electrode catheter
epicardial multi-electrode arrays
RV apex
mapping electrode
EPI pace electrode
ENDO pace electrode
apex
posterior
lateral
antero
base
mid
Acute LBBB

LBBB + MI

LBBB + HF
LBBB

EPI CRT

RV apex

ENDO CRT

LV ENDO AT (plunge electrodes)

LV ENDO AT (multi electrode array)

○ EPI CRT (LBBB)
■ ENDO CRT (LBBB)

○ EPI CRT (LBBB+HF)
■ ENDO CRT (LBBB+HF)

pacing electrode
■ mapping electrode
measurement of conduction velocity
% decrease in Total LV Activation Time

% increase in LV dp/dt max

EPI CRT
ENDO CRT

LBBB
LBBB + MI
LBBB + HF

* #
Endocardial Left Ventricular Pacing Improves Cardiac Resynchronization Therapy in Chronic Asynchronous Infarction and Heart Failure Models
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