Interplay of Electrical Wavefronts as Determinant of the Response to Cardiac Resynchronization Therapy in Dyssynchronous Canine Hearts

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Background—The relative contribution of electromechanical synchronization and ventricular filling to the optimal hemodynamic effect in cardiac resynchronization therapy (CRT) during adjustment of stimulation-timings is incompletely understood. We investigated whether optimal hemodynamic effect in CRT requires collision of pacing-induced and intrinsic activation waves and optimal filling of the left ventricle (LV).

Methods and Results—CRT was performed in dogs with chronic left bundle–branch block (n=8) or atrioventricular (AV) block (n=6) through atrial (A), right ventricular (RV) apex, and LV-basolateral pacing. A 100 randomized combinations of A-LV/A-RV intervals were tested. Total activation time (TAT) was calculated from >100 contact mapping electrodes. Mechanical interventricular dyssynchrony was determined as the time delay between upslopes of LV and RV pressure curves. Settings providing an increase in LVdp/dt_max (maximal rate of rise of left ventricular pressure) of ≥90% of the maximum LVdp/dt_max value were defined as optimal (CRT_opt). Filling was assessed by changes in LV end-diastolic volume (EDV; conductance catheter technique). In all hearts, CRT_opt was observed during multiple settings, providing an average LVdp/dt_max increase of >15%. In AV-block hearts, CRT_opt exclusively depended on interventricular-interval and not on AV-interval. In left bundle–branch block hearts, CRT_opt occurred at A-LV intervals that allowed fusion of LV-pacing–derived activation with right bundle–derived activation. In all animals, CRT_opt occurred at settings resulting in the largest decrease in TAT and mechanical interventricular dyssynchrony, whereas LV EDV hardly changed.

Conclusions—In left bundle–branch block and AV-block hearts, optimal hemodynamic effect of CRT depends on optimal interplay between pacing-induced and intrinsic activation waves and the corresponding mechanical resynchronization rather than filling. (Circ Arrhythm Electrophysiol. 2013;6:924-931.)

Key Words: bundle–branch block ■ cardiac resynchronization therapy ■ electrophysiology

In patients with chronic heart failure with delayed ventricular activation (most often in the form of left bundle–branch block, LBBB) and decreased left ventricular (LV) ejection fraction (<35%), cardiac resynchronization therapy (CRT) has been shown to improve cardiac pump function, symptoms, hospitalizations, and survival.1 Optimizing the CRT-device is important because CRT response is heterogeneous among patients and up to half of implanted patients fail to respond to the therapy. During optimization, the timing between atrial pacing or sensing and stimulation of right ventricular (RV) and LV (A-RV and A-LV intervals) is varied. However, the exact mechanism behind CRT optimization is not well understood.

Clinical Perspective on p 931

In hearts with LBBB, ventricular activation is preserved via the right bundle branch.2 During CRT, ventricular activation may result from fusion of 3 activation wavefronts generated by (1) intrinsic conduction, (2) the RV-pacing lead, and (3) the LV-pacing lead. At certain atrioventricular (AV)-intervals, the activation front generated by the RV-pacing lead dominates, and it fully collides with the one generated by the LV lead. In patients with complete AV-block, 1 component (activation via right bundle branch) is inexistent; this is an ideal situation to clarify the importance and relative role of activation generated via right bundle as well as whether ventricular filling is determinant to the hemodynamic outcome of CRT. As consequence of the different mechanism of optimization of CRT, different protocols are being used for optimization of CRT, using either filling (E-A-wave separation, diastolic filling times) or systolic parameters with respect to the latter either externally measured indices, like aortic velocity–time integral and systolic blood pressure are being used, as well as device-based algorithm using signals from lead electrograms or accelerometer sensors.3,5 Clearly, better insight into the mechanisms of

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CRT optimization may help to further improve the clinical approaches to create the largest benefit of CRT. This is particularly true in consideration of a possible expansion of the indication to CRT after the BLOCK-HF study supporting previous single-center observations that biventricular pacing may be preferred instead of RV-pacing in patients with heart failure.6

It was the aim of the present study to evaluate the acute hemodynamic response during CRT optimization, focusing on the fusion of the activation wavefronts originating from pacing electrodes and intrinsic conduction, the effects of AV-intervals on ventricular filling, and the resulting changes in LV pump function. To investigate these effects, electric mapping and hemodynamic measurements were performed in the established canine models7 of LBBB and AV-block during extensive CRT optimization. Comparison between these 2 animal models will indicate the role of intrinsic conduction in optimization and may show whether CRT optimization protocol can be similar in both patients with complete AV-block and those presenting ventricular conduction disturbance as LBBB.

**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. The protocol was approved by the Animal Experimental Committee of Maastricht University.

**Experimental Model**

The experiments were performed on 14 adult mongrel dogs of either sex and unknown age. Animals were induced by IV pentothal administration and anesthetized by continuous infusion of midazolam (0.25 mg/kg per hour IV) and sufentanyl (3 µg/kg per hour IV). Radiofrequency ablation was used to create LBBB in 8 dogs and complete AV-block in 6 dogs.8 In the LBBB dogs, CRT studies were performed 16 weeks after ablation, to allow for ventricular remodeling to occur.9

One 7F catheter-tip manometer (CD-Leycom Zoetermeer, the Netherlands) was used to measure RV pressure, whereas a 7F combined catheter-tip manometer and conductance catheter was used to measure LV pressure and volume. A pacing lead was transvenously inserted into the right atrium. After thoracotomy, 2 multielectrode bands holding 102 contact electrodes were placed around the heart, which measured local LV and RV epicardial electrograms, a basal posterolateral electrode was selected for LV-pacing.9,10 An additional electrode was placed at the apex. A multielectrode catheter (Daig Livewire TC, Minnetonka, MN) placed in the RV was used for mapping, and its most distal electrode was used for RV apical pacing.

A schematic overview of the experiment is shown in Figure 1A. For baseline measurements, atrial pacing occurred at a rate of ≈10 beats per minute above the intrinsic sinoatrial rate (see Figure 1B for an example of an LVdP/dt [first derivative of LV pressure] tracing). In

![Figure 1A](https://example.com/figure1a.png)

**A** Schematic set-up of pacing system & LVdP/dt measurements

![Figure 1B](https://example.com/figure1b.png)

**B** Example of LV dP/dt trace during baseline atrial pacing

![Figure 1C](https://example.com/figure1c.png)

**C** Example of LV dP/dt during multiple A-LV and A-RV intervals

![Figure 1D](https://example.com/figure1d.png)

**D** % change in LV dp/dtmax for all A-LV and A-RV intervals in a single subject

*Figure 1.* Methods for measuring relative change in LVdP/dtmax (maximal rate of rise of left ventricular pressure) for 100 atrio-right ventricular (A-RV)/atrio-left ventricular(A-LV) intervals. **A**, Schematic setup of pacing leads and LV pressure-catheter. **B**, An example of an LVdP/dt tracing during baseline atrial pacing (C) and during 4 A-RV/A-LV interval-combinations flanked by baseline recordings. **D**, A quadratic fit was applied on the LVdP/dtmax data (black circles) to minimize the effects of measurement variation.
the AV-block dogs, additional RV apical pacing was used for baseline measurements (at an AV-interval of 125 ms). AV-intervals were then programmed individually for the RV and the LV, ranging from 50 to 230 ms in randomized steps of 20 ms, resulting in a 100 possible combinations of A-LV and A-RV intervals. Baseline recordings were performed before every fourth setting (as shown in Figure 1C), which were used to calculate relative changes. Hemodynamic and ECG data were recorded for a minimum of 2 respiratory cycles.

Data Analysis
From the surface-ECG, PR, and QRS durations were determined. Depolarization times were calculated for all cardiac mapping electrodes, with total activation time (TAT) defined as the maximal depolarization time difference, and electric resynchronization was expressed as the percentage decrease in TAT when compared with baseline. Electric activation maps were created by plotting the depolarization times on models of cardiac shape using custom MATLAB software (MathWorks, Natick, MA). Mechanical interventricular dyssynchrony (MIVD) was determined as the absolute time delay between normalized upslopes of simultaneously recorded LV and RV pressure curves. Stroke work was calculated as the area of the pressure–volume diagram. Electric resynchronization, MIVD, and relative change in LVDp/dtmax and stroke work were plotted in relation to the A-LV/A-RV interval in contour plots. Quadratic fitting was applied to account for measurement variability (Figure 1D). Simultaneous LV- and RV-pacing at an AV-interval of 110 ms (CRT110) ensured full biventricular capture in all dogs and was regarded as out-of-the-box CRT. When a setting resulted in a percentage LVDp/dtmax increase of ≥90% of the maximal LVDp/dtmax value, the setting was identified as optimal (CRTopt).

Statistical Analysis
Continuous data are presented as mean±SD and median with first and third quartiles (Q1–Q3). Continuous variables were compared using the Wilcoxon signed-rank test or Mann–Whitney U test for dependent or independent observations, respectively. A probability value <0.05 was considered statistically significant. Statistics were performed using MATLAB (MathWorks, Natick, MA).

Results
The baseline characteristics of the LBBB group and the complete AV-block group are described in Table I in the online-only Data Supplement. There were no significant differences found in measures of ventricular dyssynchrony or systolic pump function between the 2 groups. PR-duration was shorter in the dogs with complete AV-block (P=0.03) because AV-interval during RV apex pacing was set at 125 ms, whereas intrinsic PR-duration in the LBBB dogs ranged from 108 to 218 ms (median 162 ms).

Electrophysiological Effects of Altering Ventricular Stimulation Timings in CRT
Figure 2 shows electric contact maps acquired from an LBBB dog during 4 settings: atrial pacing without ventricular capture (LBBB), single-site LV-pacing, out-of-the-box CRT (CRT110, A-LV, and A-RV 110 ms), and CRTopt (A-LV 110 ms, A-RV 180 ms). During A-LV and A-RV of 230 ms, ventricular capture is lost (indicated by the dashed lines), and a typical LBBB electric activation pattern was observed with most delayed activation in the LV free wall (top-left). During single-site LV-pacing at a short AV-interval (top-right), the activation pattern as observed during LBBB was largely reversed, with latest activation of the RV free wall. The reversed activation pattern coincided with an increase in TAT during LV-pacing (121 ms) as compared with LBBB (98 ms), also indicated by the larger and darker blue latest activation region. During CRT110, 2 activation wavefronts originating from the stimulated RV and LV electrodes fuse and resynchronized the heart as evidenced by a decrease of TAT to 79 ms. In the CRTopt example, RV capture is lost (A-RV 180 ms) but the LV activation wavefront (A-LV 110 ms) fuses with an intrinsic activation wave originating from the right bundle. The electric activation wavefronts resulted in an alternative electric resynchronization of the heart with a TAT decrease to 78 ms, comparable with simultaneous biventricular pacing. The top of Figure 3 displays electric resynchronization, defined as the percentage reduction in TAT, for all 100 settings. LV-pacing at short A-LV increased electric dispersion, whereas biventricular pacing at short AV-intervals resulted in a greater homogeneous electric activation. Intrinsic conduction through the AV-node and right bundle was possible, enabling fusion between LV-pacing–induced wavefront and intrinsic conduction. This is shown by the leftward turn where pacing at an A-LV interval resulting in at least partial LV capture and a delayed A-RV interval resulting in loss of RV capture allows similar electric resynchronization as biventricular pacing at short AV-interval. In a dog with AV-block, electric resynchronization was identical over a range of AV-intervals and a set offset between A-LV and A-RV (Figure 3, top-right). Because there was no conduction possible through the bundle branches, only the interventricular delay (offset A-LV and A-RV) determined TAT. On average, TAT could be decreased by an average of 22% (median of 20%, Q1–Q3: 17%–25%) during the optimization protocol, a decrease that was similar to that in LBBB dogs: mean value 22% (median 24%, Q1–Q3: 19%–26%; P=0.67 between the 2 groups).
Hemodynamic Effects of Altering Ventricular Stimulation-Timings in CRT

The pattern of MIVD (Figure 3) matched well with that of electric resynchronization. MIVD could be diminished to less negative values during biventricular capture and during LV fusion-pacing in the LBBB heart. Consequently, the ridge of minimal MIVD showed a similar leftward turn as seen during electric resynchronization. In the LBBB hearts, CRT at the out-of-the-box setting (CRT
\textsubscript{110}) increased LVdP/dt\textsubscript{max} by 10±4% (median 11%, Q1–Q3: 8%–13%) as compared with baseline atrial pacing (P=0.008). The optimization protocol effectuated a further increase in LVdP/dt\textsubscript{max} to 15±4% above baseline (median 16%, Q1–Q3: 11%–19%; P=0.008 versus baseline and versus CRT\textsubscript{110}). The LVdP/dt\textsubscript{max} surface plot showed a ridge of optima rather than a sharp peak, indicating that CRT\textsubscript{opt} could be reached at multiple settings. CRT\textsubscript{opt} settings were found during biventricular pacing, but also during LV pre-excitation at longer AV-intervals where the leftward ridge indicates fusion between pacing induced activation wavefront(s) and the intrinsic activation wavefront. For all LBBB experiments, optimal acute response was found during simultaneous biventricular pacing (n=4), LV pre-excitation (20 ms, n=3; 40 ms, n=1), or RV pre-excitation (20 ms, n=1). The leftward ridge (fusion with intrinsic conduction) occurred during A-LV intervals ranging from 70 to 190 ms. Between experiments, the number of A-LV/A-RV interval-combinations, which resulted in CRT\textsubscript{opt} varied between 2 and 6 combinations out of a possible 100 (median of 4 combinations).

Contrary to observations in LBBB, in hearts with complete AV-block, changes were similar for a fixed ventriculoventricular (VV)-interval over a large range of AV-intervals. The optimal settings for the example shown in Figure 3 (right) were consistently seen at 20 ms LV pre-excitation, expressed in the surface plot as a straight ridge. For all AV-block experiments, the LVdP/dt\textsubscript{max} increase at CRT\textsubscript{opt} was 15±6% (median 14%, Q1–Q3: 9%–21%) compared with RV-pacing (P=0.03), an increase similar to what was found in the LBBB dogs (P=0.95; Figure 4A). In all AV-block hearts, LVdP/dt\textsubscript{max} showed optima at LV pre-excitation ranging from 20 to 40 ms, over the whole range of AV-intervals. Figure 4B indicates the importance of ventricular synchronization and the limited influence of atrial contraction on LVdP/dt\textsubscript{max} in the range of AV-intervals tested.

Figure 5 shows that the ridge of highest LVdP/dt\textsubscript{max} values (top) matched with that of highest stroke work (middle) and of lowest TAT (bottom) in 2 LBBB and 1 AV-block experiment. In addition, the leftward turn in LVdP/dt\textsubscript{max} seen in the LBBB hearts (left and middle) was also observed for stroke work and TAT, which strongly indicates contribution of intrinsic conduction at these settings. The location of the leftward turn in
the matrix was mainly dependent on PQ-interval during baseline LBBB. The individual behavior for all 14 experiments is depicted in the figures in the online-only Data Supplement for TAT, LVdP/dt max, and stroke work.

Effects of AV/VV Intervals on LV Filling
In dogs with LBBB, the differences in LV end-diastolic volume (EDV) between baseline atrial pacing, CRT at shortest AV-interval (50 ms), and at CRT TIV, and CRT min were small, whereas changes in LVdP/dt max were apparent (Figure 6A). Also in dogs with complete AV-block, simultaneous biventricular pacing over a wide range of AV-intervals did not induce notable changes in LV EDV (Figure 6B). For most experiments, EDV remained stable over a wide range of AV-intervals (Figure 7) and did not show parabola patterns such as for LVdP/dt max.

Discussion
The present animal study shows that in hearts with AV-block, the best hemodynamic response, as quantified by LVdP/dt max, is achieved at a fixed VV-interval over a wide range of AV-intervals, whereas in hearts with LBBB, the optimal response can also be achieved during AV-intervals that allow contribution from intrinsic activation. The common denominator in both models is that optimal acute hemodynamic response during CRT is achieved by proper electric and mechanical resynchronization rather than by improvement in filling. These findings may help to design better protocols for CRT optimization in different patient populations.

Resynchronization Versus Filling
The present study demonstrates that changing AV-intervals in hearts with LBBB can change the degree of electric and

Figure 4. Average percentage LVdP/dt max (maximal rate of rise of left ventricular pressure) increase in left bundle-branch block (LBBB) (blue color) and atrioventricular (AV)-block dogs (red color) at (A) cardiac resynchronization therapy (CRT) opt (small dots are individual data) and (B) during simultaneous biventricular pacing at increasing AV-intervals. Means±SD are shown.

Figure 5. Contour plots of percentage change in LVdP/dt max (maximal rate of rise of left ventricular pressure; top), stroke work (middle), and electric resynchronization (bottom) during a 100 possibilities of atrio-left ventricular (A-LV) and atrio-right ventricular (A-RV) interval-combinations in 3 experiments with varying underlying intrinsic atrioventricular (AV)-conduction: ranging from PQ duration of 143 ms (left, same experiment as in Figures 2 and 3A) to 201 ms (middle) to complete AV-block (right, same experiment as in Figure 3B).
mechanical resynchronization. In hearts with complete AV-block, resynchronization can only result from biventricular pacing, whereas in LBBB hearts, intrinsic conduction can deliver an alternative or additional wavefront that contributes to resynchronization. Our results confirm previous data where it was shown that the effective VV-interval, correcting for the contribution by intrinsic conduction, predicts the hemodynamic response during LV, simultaneous, and sequential biventricular pacing. In hearts with complete AV-block, the AV-interval was varied over a wide range, and little changes were noted in ventricular filling volume or pressure. Similarly, in LBBB hearts, maximal values of \( \text{LVdP/dt}_{\text{max}} \) were achieved despite minor changes in ventricular filling. Although the degree of dilatation is undoubtedly more pronounced in patients with CRT than in the dog models used in this study, clinical studies have indicated that AV-intervals influence ventricular filling only to a limited extent. This has been demonstrated by acute studies using PV-loop analysis in patients with CRT and measurements of LV end-diastolic pressure. In addition, a recent subanalysis of the MADIT-CRT (The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) trial revealed that the lowest incidence of heart failure events and mortality (combined end point) and largest echocardiographic response were found in patients with programmed AV-interval between 80 and 99 ms, which is shorter than commonly found for achieving optimal E-A wave separation.

### Hemodynamic Effects of Cardiac Resynchronization Therapy Optimization

The observation that optimization leads to an additional relative increase in \( \text{LVdP/dt}_{\text{max}} \) of \( \approx 50\% \) on top of that achieved by out-of-the-box CRT (from \( \approx 10\% \) to \( \approx 15\% \) above baseline LBBB), is in agreement with clinical data. Interestingly, the surface plots do not show a steep peak of a single optimum but rather a ridge of multiple optima, matching with findings from Zuber et al who showed that, in most of 20 matrix-optimized patients, no global optimum was seen but rather several optimal AV/VV interval combinations. More abrupt peaks, as shown by other studies, may have been caused by variability in the measurement of \( \text{LVdP/dt}_{\text{max}} \) which we accounted for by quadratic fitting of relative changes. A recent study shows that stroke work is a better predictor of long-term CRT response than \( \text{LVdP/dt}_{\text{max}} \). In the present study, we found that the optimal pacemaker settings for \( \text{LVdP/dt}_{\text{max}} \) closely matched those for optimal stroke work. The differences in the patterns of optimization between the 2 hemodynamic parameters may be because of the fact that \( \text{LVdP/dt}_{\text{max}} \) reflects only the isovolumic contraction of cardiac systole, whereas LV SW comprises the full systolic phase and incorporates both pressure and volume changes, and that catheter movement artifacts add to the variability of this measurement.

### Potential Clinical Implications

Extrapolation of data from the experimental to the clinical situation should always be done with care. However, the canine models of AV-block and LBBB have been shown to provide data that apply quite well to the human situation because of the similarities in anatomy and conduction system. A first important potential implication is that CRT can provide similar hemodynamic benefit in hearts with LBBB and hearts with AV-block or in those with chronic atrial fibrillation and slow ventricular conduction requiring continuous pacing. The latter condition is present in patients with AV-block (intrinsic or after His-ablation) receiving a de novo implant or who are...
upgraded to CRT. It has been shown in single-center studies and the BLOCK-HF study that CRT preserves LV function better and reduces mortality and heart failure events than RV-pacing in patients with AV-block.\(^2\)\(^{21}\) Furthermore, for these patients, the present data imply that a proper setting of VV-interval seems more critical than that of AV-interval.

For LBBB patients, an implication of the present results is that optimization of the interventricular delay or allowing contribution of intrinsic conduction may improve the benefit of CRT as compared with out-of-the-box settings, as has been recognized earlier.\(^2\)\(^5\) As a consequence, the present study provides a rationale for identifying and modifying the electromechanical substrate for CRT optimization. Evidence for this idea has already been observed in an analysis of data from the PATH-CHF-I (Pacing Therapies in Congestive Heart Failure [study 1]) study because MIVD could predict optimal increase in LVdP/dt\(_{\max}\) without changing LV EDP (end diastolic pressure).\(^1\)\(^4\) Furthermore, the data show that LV fusion–pacing may be at least as efficacious as BiV pacing, as also has been demonstrated by van Gelder et al.\(^2\)\(^1\) A novel algorithm for automated optimization of AV- and VV-intervals uses information on the A-RV sensing interval to allow such RV-synchronized LV-pacing.\(^2\)\(^2\) Summarizing, the present study indicates the value of the proper interplay of electrical wavefronts for the most effective application of CRT.

Limitations

This animal study investigated the acute hemodynamic improvement by CRT without evaluation of its long-term benefit. Acute response may not always predict chronic outcome.\(^2\)\(^3\) Moreover, the dog models may not recapitulate all characteristics of dysynchronous heart failure and LBBB occurring in patients. The canine model used is representative of nonischemic LBBB hearts in patients, but may not reflect all abnormalities present in patients with ischemic hearts. However, previous studies from our laboratory showed that in dogs with myocardial infarction on top of LBBB a similar acute hemodynamic can be achieved as in LBBB dogs without infarction, albeit that more attention has to be paid to pacing site and AV-interval.\(^2\)\(^5\)

Conclusion

In canine hearts with LBBB and AV-block, optimal acute hemodynamic response during CRT is achieved at AVVV settings that provide the best electromechanical resynchronisation. In hearts with LBBB, this optimum is reached by interplay of activation waves originating from pacing electrodes and from intrinsic conduction, whereas in hearts with AV-block, resynchronisation is governed entirely by VV-interval. Changes in ventricular filling do not seem to play a role in achieving the optimal acute hemodynamic effect.

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Disclosures

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References

It is incompletely understood to what extent electromechanical synchronization and ventricular filling contribute to the hemodynamic effect of cardiac resynchronization therapy (CRT) during adjustment of stimulation-timing. We investigated whether the optimal hemodynamic effect in CRT requires collision of pacing-induced and intrinsic activation waves and optimal filling of the left ventricle (LV). In established canine models of left bundle-branch block and atroventricular (AV) block, electric mapping and hemodynamic measurements were performed during a wide range of atrio-right ventricular and atrio-LV stimulation intervals. In hearts with AV-block, the best hemodynamic response, as quantified by LVdP/dt_max (maximal rate of rise of left ventricular pressure) and stroke work, was achieved at a fixed ventriculoventricular (VV)-interval over a wide range of AV-intervals. In contrast, in hearts with left bundle-branch block, the optimal response was also achieved during AV-intervals that allow collision of the LV-pacing induced activation wavefront with that originating from intrinsic activation. The common denominator in both animal models was that optimal acute hemodynamic response during CRT is achieved by the best possible electric and mechanical resynchronization rather than by improvement in filling. These findings show the importance of fusion-pacing in left bundle-branch block and VV-optimization in AV-block and may help to design better protocols for optimization of CRT.
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Supplemental table 1. Baseline electrocardiographic and hemodynamic characteristics from LBBB dogs during atrial pacing (n=8) and AV-block dogs during atrial and RV pacing (n=6).

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<th>LBBB</th>
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<td>(n=8)</td>
<td>(n=6)</td>
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<td><strong>Electrocardiography parameters</strong></td>
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<td>PR time (ms)</td>
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Means ± S.D. are given; *p<0.05 as compared with LBBB.
Supplemental Figure 1. Contour plots of electrical resynchronization (percentage decrease in TAT) of all experiments grouped by LBBB or AV-block dogs and sorted according to intrinsic PQ-duration. Arrows show ridge of optima.
Supplemental Figure 2. Contour plots of percentage change in LVdP/dt\textsubscript{max} of all experiments grouped by LBBB or AV-block dogs and sorted according to intrinsic PQ-duration. Arrows show ridge of optima.
Supplemental Figure 3. Contour plots of percentage change in Stroke Work of all experiments grouped by LBBB or AV-block dogs and sorted according to intrinsic PQ-duration. Dashed arrows show ridge of LVdP/dt\textsubscript{max} optima (supplemental figure 2).