

Evaluating multisite pacing strategies in cardiac resynchronization therapy in the preclinical setting

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BACKGROUND Multisite pacing strategies that improve response to cardiac resynchronization therapy (CRT) have been proposed. Current available options are pacing 2 electrodes in a multipolar lead in a single vein (multipoint pacing [MPP]) and pacing using 2 leads in separate veins (multizone pacing [MZP]).

OBJECTIVE The purpose of this study was to compare in a systematic manner the acute hemodynamic response (AHR) and electrophysiological effects of MPP and MZP and compare them with conventional biventricular pacing (BiVP).

METHODS Hemodynamic and electrophysiological effects were evaluated in a porcine model of acute left bundle branch block (LBBB) (n = 8). AHR was assessed as LVdP/dtmax. Activation times were measured using >100 electrodes around the epicardium, measuring total activation time (TAT) and left ventricular activation time (LVAT).

RESULTS Compared to LBBB, BiVP, MZP, and MPP reduced TAT by 26% ± 10%, 32% ± 13%, and 32% ± 14%, respectively (P = NS between modes) and LVAT by 4% ± 5%, 11% ± 5%, and 12% ± 5%,

respectively (P < .05 BiVP vs MPP and MZP). On average, BiVP increased LVdP/dtmax by 8% ± 4%, and optimal BiVP increased LVdP/dtmax by 13% ± 4%. The additional improvement in LVdP/dtmax by MZP and MPP was significant only when its increase during BiVP and decrease in TAT were poor (lower 25% of all sites in 1 subject). The increase in LVdP/dtmax was larger when large inter-electrode distances (>5 cm vs <2.2 cm) were used.

CONCLUSION In this animal model of acute LBBB, MPP and MZP create similar degrees of electrical resynchronization and hemodynamic effect, which are larger if interelectrode distance is large. MPP and MZP increase the benefit of CRT only if the left ventricular lead used for BiVP provides poor response.

KEYWORDS Acute hemodynamics; Cardiac resynchronization therapy; Electrical mapping; Multipoint pacing; Multizone pacing

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Introduction

Up to 30% of heart failure patients exhibit left ventricular (LV) conduction abnormalities that lead to slow electrical activation and discoordination of contraction.¹ For these

patients, biventricular pacing (BiVP) has been proven to be a valuable therapy. BiVP restores ventricular synchrony and therefore is also referred to as cardiac resynchronization therapy (CRT).

Response to CRT is complex and multifactorial, and although it is in general positive, it varies considerably among individual patients. An important determinant of CRT response is delivery of optimal LV pacing. Most LV pacing leads are implanted conventionally in an LV (postero-)lateral vein, but the pacing site yielding the maximum hemodynamic effect differs considerably among individuals.²

In addition to optimal positioning of the (single) LV lead, another strategy proposed to improve response to CRT is pacing from multiple LV sites. Conceptually, capturing a larger tissue area provides better resynchronization and, as

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KEY FINDINGS

- Compared to baseline left bundle branch block, multipoint pacing (MPP) and multizone pacing (MZP) create similar degrees of ventricular resynchronization and hemodynamic improvement.
- Although biventricular pacing (BiVP) often is sufficient, both MPP and MZP can create a beneficial effect beyond BiVP when the left ventricular (LV) site used for BiVP does not lead to adequate hemodynamic benefit.
- During multiple LV pacing, the increase in LVdp/dtmax compared to baseline left bundle branch block was significantly larger for the largest interelectrode distances (>5.0 cm) compared to the smallest distances (<2.2 cm).

a consequence, cardiac function. Several single-center and multicenter studies have suggested a benefit of multiple LV pacing using an additional LV lead in a second vein,^{3,4} which we refer to as multizone pacing (MZP). However, implantation of a second LV lead comes at the cost of longer procedural times and higher periprocedural complication rates.^{5,6} These disadvantages are not encountered when multipoint pacing (MPP) (ie, stimulating multiple electrodes on a single quadripolar lead) is used. Several clinical studies showed a small hemodynamic benefit and/or increased electrical resynchronization with MPP over conventional BiVP,⁷⁻⁹ although other studies were not able to demonstrate such benefit.^{10,11}

Studies directly comparing MPP and MZP are scarce and focused mainly on hemodynamic differences.^{9,12,13} Sohal et al¹³ showed the importance of the electrical substrate for the hemodynamic response to multiple LV pacing using invasive electroanatomic mapping in patients, but little attention was paid to the pattern of electrical synchronization created during MPP and MZP.

The aim of the present study was to assess in a systematic manner the electrophysiological and hemodynamic effects of MPP and MZP compared to BiVP. We determined the acute electrical and hemodynamic effects of pacing from a large number of single LV sites and multiple combinations of 2 LV sites in a porcine model of acute left bundle branch block (LBBB).

Methods

Animal experiments

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive on the Protection of Animals used for Scientific Purposes (2010/63/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

Experimental setup

The experiments were performed on 8 adult pigs (weight 71.1 ± 0.6 kg). Animals were premedicated with Zoletil (5–8 mg/kg intramuscularly). After thiopental induction (5–15 mg/kg intravenously), anesthesia was maintained by continuous infusion of propofol (2.5–10 mg/kg/h), sufentanil (4–8 µg/kg/h), and rocuronium (0.1 mg/kg/h). A thermal mattress was used to maintain adequate body temperature. Electrocardiography was derived from limb leads.

Left bundle branch block (LBBB) was either created by radiofrequency ablation (n = 4) using an ablation catheter (MarinR; Medtronic, Minneapolis, MN) and a radiofrequency power generator (Atakr; Medtronic),¹⁴ or (if ablation created atrioventricular block) mimicked through right ventricular (RV) free-wall pacing (n = 4).

LV and RV pressures were measured using 7F catheter-tip manometers. The catheters were introduced through the carotid artery and jugular vein, respectively. After thoracotomy and pericardiotomy, 2 custom-made multielectrode bands were placed around the heart. These bands consisted of 2 of electrodes (2×30 and 2×22 electrodes) and were used for stimulation of the heart as well as for electrical mapping. One electrode band was positioned at the basal level and 1 at the mid-level of the ventricles.

Pacing protocol

Right atrial and RV pacing leads were positioned transvenously. For each electrode, the pacing threshold was determined separately, and output was set at twice the threshold. Baseline was measured during AAI pacing. The ventricular pacing protocol was performed in DOO mode, 10 bpm above sinus rhythm. To ensure full ventricular capture, the paced AV interval was set at 70% of the intrinsic PQ interval (LBBB by radiofrequency ablation) or 30 ms shorter than the A-RV free-wall pacing interval (LBBB through RV free-wall pacing).

BiVP, MPP, and MZP configurations were created by unipolarly pacing the RV apical lead simultaneously with ≥1 band electrodes situated on the LV. Dual LV pacing combinations were classified as MPP if the paced electrodes were apico-basally aligned or as MZP if the electrodes were circumferentially aligned. Electrode combinations were chosen with varying interelectrode distances (IEDs) and at different LV levels (basal and mid) and LV segments (anterior, lateral, posterior) (Figure 1).

Six different combinations of 4 LV electrodes were tested in each animal. Therefore, the pace protocol consisted of pacing at 24 LV single sites and 36 LV dual-site combinations. All configurations were combined with endocardial RV apex pacing.

Results were calculated by averaging values for all parameters over a 20- to 30-second period, excluding inappropriate beats such as ventricular extrasystoles and 2 subsequent beats.

Data analysis

Analysis of recorded experimental data was performed using custom MATLAB software (MathWorks, Natick, MA).

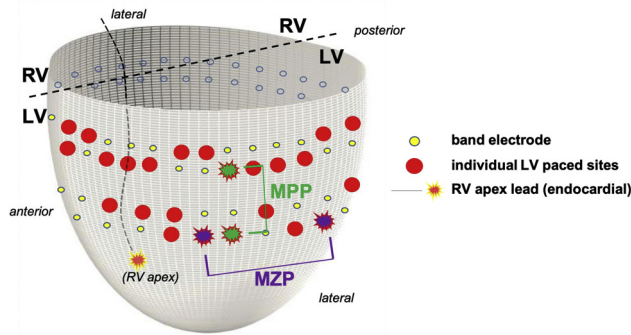


Figure 1 Schematic overview of paced locations on the porcine epicardium, showing the 2 multi-electrode bands (2×30 and 2×22 electrodes) around the right ventricle (RV) and left ventricle (LV). Individual electrodes are illustrated by dots. Large red dots indicate electrodes that have been used in any pacing mode (single or dual). Green and purple stars indicate examples of dual LV paced configurations, resembling either multipoint pacing (MPP) (vertically aligned) or multizone pacing (MZP) (horizontally aligned). All nonpaced electrodes were used for electrical mapping.

Systolic and diastolic pressures, and LV and RV dP/dt_{max} and dP/dt_{min} were derived from LV and RV pressure signals.¹⁴ Local activation times were calculated as the time difference between onset of Q wave (LBBB by radiofrequency ablation) or pacing artifact (LBBB through RV free-wall pacing) and the timing of the steepest negative deflection on the local unipolar electrogram. If activation time calculation was not possible for an electrode due to pacing artifact, it was excluded. A septal decapolar catheter was used to determine activation at the RV side of the interventricular septum, in order to distinguish RV from LV. From these data, total activation time in both ventricles (TAT), left ventricular activation time (LVAT), and right ventricular activation time (RVAT) were determined. Interventricular electrical delay (IVED) was defined as the difference between the median values of LVAT and RVAT. Left ventricular electrical delay (Q-LV) was measured as the interval from the onset of the QRS complex to the fastest negative deflection of the local LV electrogram during intrinsic activation.

To account for baseline drift, the effect of pacing on hemodynamic parameters was quantified as a percentage change compared with the mean of the 2 adjoining baseline measurements.

Statistical analysis

Statistical analyses were performed using the SPSS Version 25.0 (IBM Corp, Armonk, NY). Values are given as mean \pm SD. All hemodynamic and electrical results are expressed as percent changes relative to the corresponding baseline. Two-way analysis of variance for repeated measurements was used to evaluate between-group differences in relative changes between pacing modes and/or sites. When necessary due to sample size distributions, the Levene test was used to assess heterogeneity. Bonferroni multiple comparison analysis was performed and applied to pairwise comparisons. Differences between individual group means

were tested by independent-samples Student *t* tests. $P < .05$ was considered significant.

Results

Induction of LBBB resulted in a $75\% \pm 23\%$ increase in QRS duration compared to intrinsic conduction (to 93 ± 14 ms).

Electroanatomic assessment of different pacing sites

Activation times and sequences were dependent on the LV pacing site. The longest TAT occurred during LV pacing in the anterior and posterior walls, as evident from the blue color in the opposing wall shown in Figure 2A.

For the entire group, stimulation sites on the lateral wall provided better resynchronization than those on the anterior or posterior wall, as evidenced from significantly larger reductions in TAT, LVAT, and IVED (Figure 2B, upper row). There were no significant differences in TAT and IVED between basal or mid-level pacing sites (Figure 2B), but pacing mid-LV regions provided a significantly larger LVAT reduction ($19\% \pm 11\%$ vs $13\% \pm 6\%$; $P < .05$).

Acute hemodynamic response during BiVP

The acute hemodynamic response (AHR), defined as relative change in $LVdP/dt_{max}$ compared to baseline LBBB, varied widely among and within individuals. The pacing site yielding the highest AHR was animal specific and ranged from 7.9% to 17.4%. The pacing site yielding the lowest AHR also was animal specific and ranged from -3.6% to 7.7% (Figure 3A). The range between the highest and lowest AHR per experiment was 8.8 ± 4.4 percent points. On average, BiVP increased $LVdP/dt_{max}$ by $8\% \pm 4\%$, and optimal BiVP increased $LVdP/dt_{max}$ by $13\% \pm 4\%$.

There was a moderate correlation between the reduction in TAT and the increase in $LVdP/dt_{max}$ in BiVP (Figure 3B).

Electrophysiological effects of multiple LV pacing strategies

Figure 4 shows representative examples of 3-dimensional activation maps during baseline LBBB, BiVP, and both multisite pacing strategies. The examples show that MPP and MZP reduce TAT, LVAT, and IVED to similar extents.

Figure 5A shows that BiVP, MZP, and MPP reduced TAT significantly compared to baseline LBBB, but that the reduction was not significantly different among the three modes.

Figure 5A, right panels, show the reduction in activation time for both MZP and MPP, differentiating between the first and fourth quartiles of IED. In neither MPP nor MZP was a significant effect of IED on TAT observed.

Hemodynamic effect of multiple LV pacing

Both MPP and MZP increased $LVdP/dt_{max}$ by $7\% \pm 3\%$ compared to LBBB (Figure 5B, left). Optimal MPP and MZP increased $LVdP/dt_{max}$ by $13\% \pm 4\%$ and $11\% \pm 2\%$, respectively (NS). Importantly, a large IED

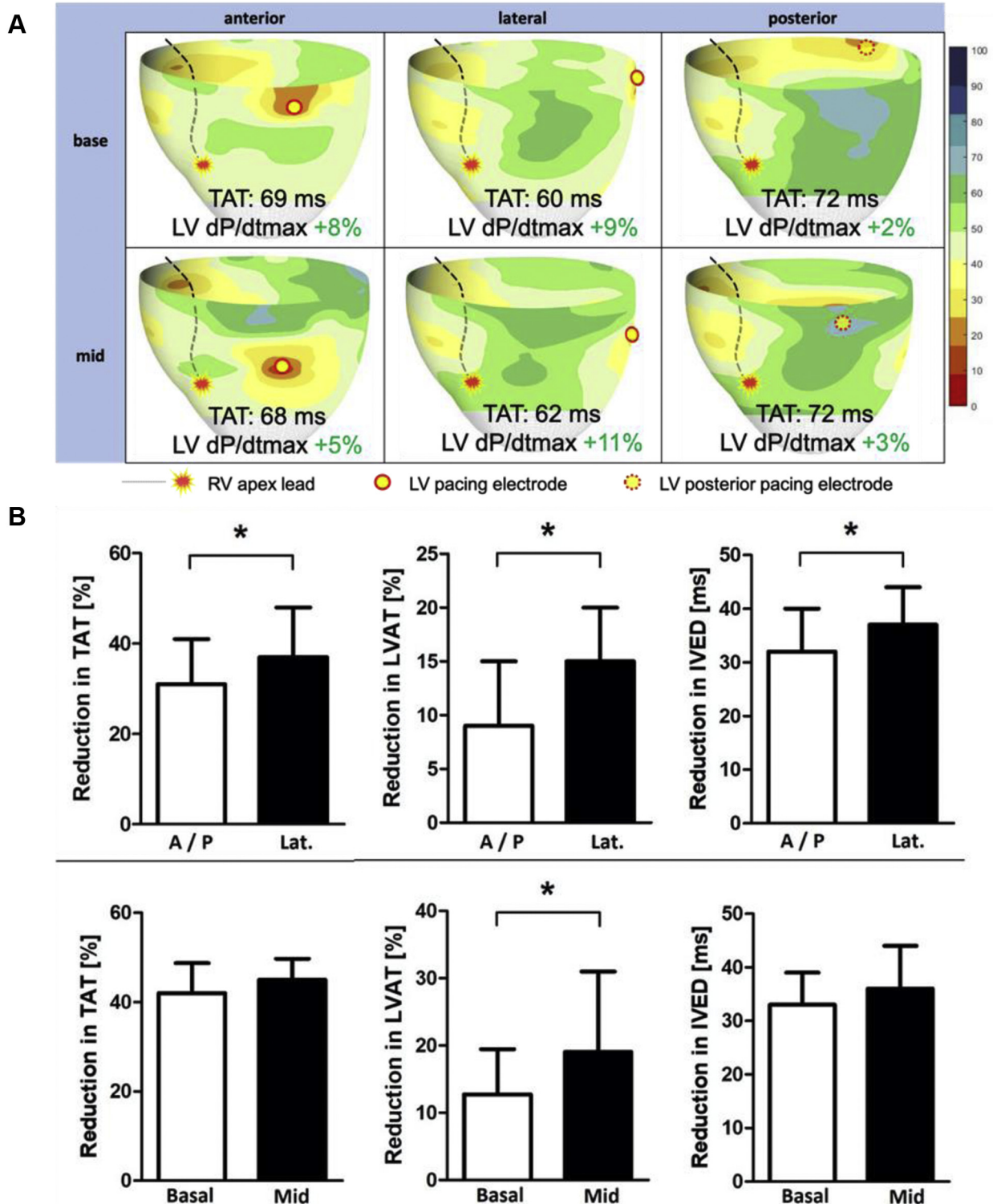


Figure 2 Acute effects of different left ventricular (LV) pacing sites during biventricular pacing (BiVP). **A:** Typical examples of 3-dimensional epicardial activation maps in the same porcine heart during BiVP. Lateral LV pacing sites provide better resynchronization over anterior or posterior sites. Compared within the same segment, activation times and sequence are comparable between basal and mid-level pacing sites. The apical region is not depicted due to the absence of electrodes. **B:** Reduction in dyssynchrony parameters for LV anterior/posterior (A/P) vs lateral (Lat.) sites (**top**) and for basal vs mid-level sites (**bottom**) during conventional BiVP. **P* < .05 vs lowest reducing segment or level. IVED = interventricular electrical dyssynchrony; LVAT = left ventricular total activation time; TAT = total activation time.

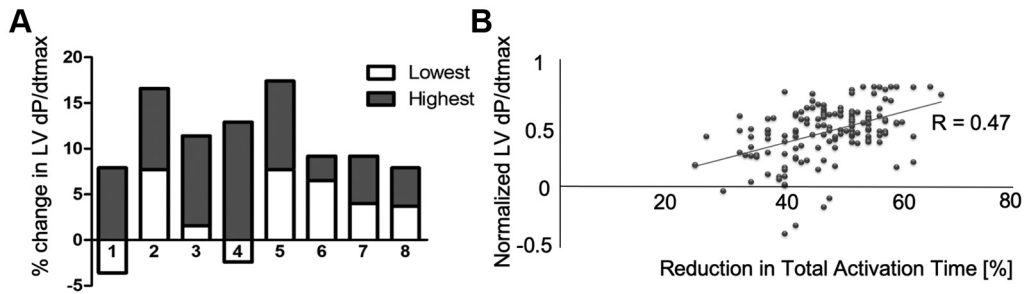


Figure 3 Hemodynamic response per experiment and correlation with activation time. **A:** Lowest and highest acute hemodynamic response (AHR) to biventricular pacing (BiVP) in the 8 individual experiments (numbers along the horizontal axis). *White bars* represent the lowest AHR. *Gray bars* represent the highest AHR. **B:** Correlation between normalized LVdP/dtmax and reduction in total activation time for the individual left ventricular (LV) sites during BiVP. Values were normalized to the maximum of the individual experiment.

provided a significantly larger AHR during both MPP and MZP (Figure 5B, right).

Figure 4 shows an example in which pacing from 2 LV sites resulted in better electrical resynchronization but not necessarily a higher increase of LVdP/dtmax. This issue is further addressed in Figure 6, which shows that pacing from 2 LV sites (Figures 6C and 6D) increased LVdP/dtmax compared to single posterior wall pacing (Figure 6A), but LVdP/dtmax was not increased compared with LV lateral wall pacing (Figure 6B).

In order to investigate this finding for the entire group and all sites, LV sites were grouped according to the size of AHR during BiVP into subgroups with the highest 25%, the lowest 25%, and the intermediate 50% change in each experiment. Each site was then used in an MPP and an MZP configuration, and changes in LVdP/dtmax were

compared to those during BiVP. Figure 7A shows that MPP and MZP provided a significant additional increase in AHR only in the group with the 25% lowest AHR. The highest 25% group consisted of $75\% \pm 10\%$ of lateral sites, whereas the lowest 25% group consisted of $61\% \pm 14\%$ of anterior/posterior sites. Anatomic electrode positions on the lateral LV wall that produced poor hemodynamic improvement (lowest 25%) were not consistent among different experiments.

When performing the same analysis after dividing the pacing sites according to the lowest 25%, intermediate 50%, and largest 25% reduction in TAT, LV sites yielding the smallest initial decrease in TAT benefited most from upgrading to MZP/MPP, an increase that was at least as large as that observed after MPP/MZP using sites showing the lowest increase in LVdP/dtmax (Figure 7B). In the

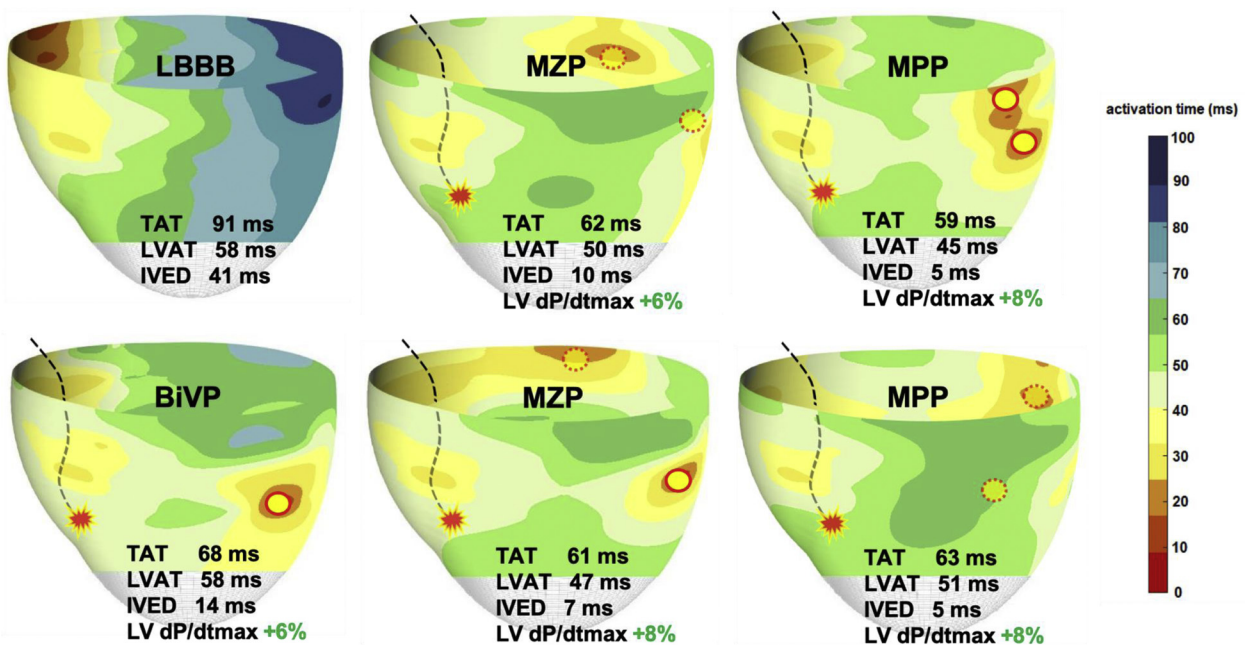


Figure 4 Three-dimensional activations maps of the epicardium during left bundle branch block (LBBB), biventricular pacing (BiVP), multizone pacing (MZP), and multipoint pacing (MPP) in the same heart. **Left:** Activation patterns during LBBB (top) and BiVP (bottom), during which the LV is paced from the anterolateral wall. **Center:** MZP with small (top) and large (bottom) interelectrode distance. **Right:** Activation maps during MPP with small (top) and large (bottom) interelectrode distance. IVED = interventricular electrical dyssynchrony; LVAT = left ventricular activation time; TAT = total activation time.

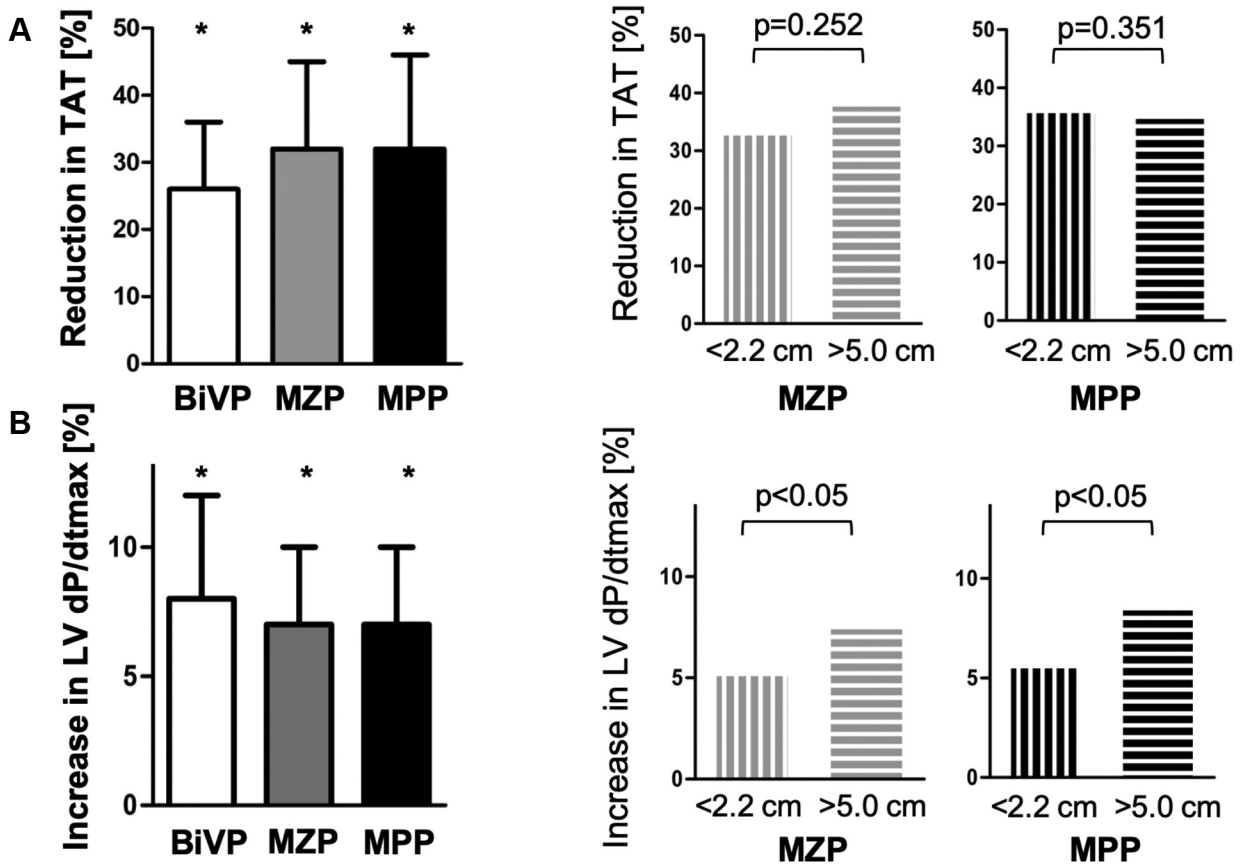


Figure 5 Resynchronization during BiVP, MZP, and MPP. Reduction in TAT (A) and increase in LVdP/dtmax (B) during BiVP, MZP, and MPP, expressed as percent of left bundle branch block for all pacing combination (left) and for the first and fourth interelectrode distance quartiles (right). * $P < .05$ vs baseline. Abbreviations as in Figure 4.

lowest 25% group, LVdP/dtmax increased from $4.0\% \pm 4.4\%$ to $8.8\% \pm 1.5\%$ above baseline during MZP and to $9.8\% \pm 2.1\%$ during MPP (both $P < .05$ vs BiVP). No statistically significant changes in LVdP/dtmax occurred in the 2 other subgroups.

Discussion

The principal findings of the present study are as follows. (1) MPP and MZP create similar degrees of ventricular electrical resynchronization and hemodynamic effect. (2) Although BiVP often is sufficient, MPP and MZP can create a beneficial effect beyond BiVP only when the LV site used for BiVP does not lead to adequate hemodynamic benefit. (3) A large IED increases the benefit of MPP and MZP.

Electrical resynchronization by multiple LV pacing

The finding that multiple LV pacing significantly reduces electrical activation time and dyssynchrony compared with BiVP pacing is in accordance with previous animal¹⁵ and patient studies.¹³ Whereas most of the electrical dyssynchrony in LBBB-like conduction abnormalities are in the circumferential direction, pacing in 2 veins (MZP), so largely circumferentially aligned, did not provide significantly better intra- or interventricular resynchronization compared to pacing with more apico-basally aligned electrodes (MPP). This similarity in degree of electrical resynchronization

also seems to be present in clinical studies, which reported comparable reductions in QRS duration⁹ and epicardial activation time.¹³ The electrical maps in the present study may provide an explanation for these observations, as late activated regions are observed both more basal and more anterior and posterior from LV lateral wall electrodes (blue regions in Figure 4) (BiVP), which disappear during both MPP and MZP.

Hemodynamic consequences of LV multisite pacing strategies

The observation in the present study that MPP- and MZP-like pacing strategies do not lead to improved AHR compared to BiVP seems in contradiction with several clinical studies that demonstrated a small but significant positive hemodynamic effect of MPP and MZP over BiVP.^{3,7-9} However, several other studies were not able to show a positive effect.^{10,11} One possible explanation may be related to statistical analysis. Most studies compared the best of several options of multisite pacing with fewer (sometimes just one) BiVP measurements.^{16,17} In contrast, we compared each dual LV mode with its corresponding BiVP measurement. In this respect, it is interesting that a study that specifically accounted for randomized and repeated measurements using appropriate controls was not able to find acute hemodynamic benefits of MPP.¹¹

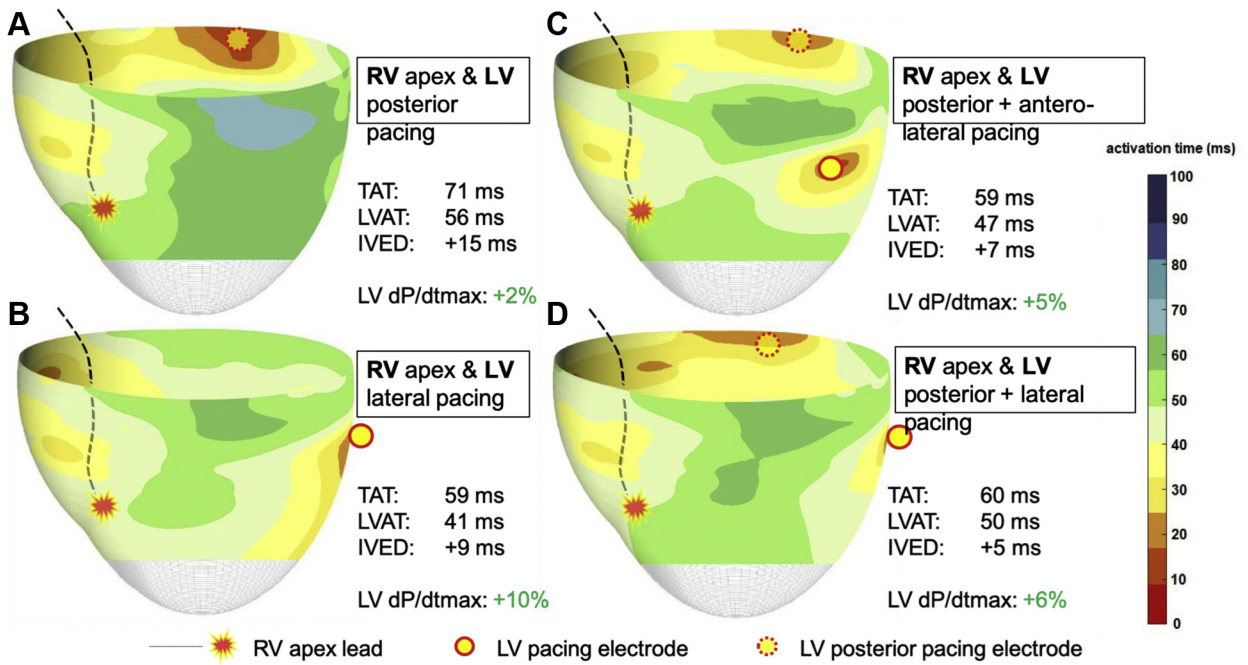


Figure 6 Effect of left ventricular (LV) pacing locations on acute hemodynamic effect during multiple LV pacing. Representative 3-dimensional epicardial activation maps of the ventricles during BiVP (A, B) and multiple LV pacing (C, D) in the same heart. A, B: Configurations yielding the lowest and highest acute hemodynamic response (AHR), respectively. C: In an attempt to increase the initial AHR, a second pacing site was added in the delayed activated anterolateral area of A, resulting in the activation map shown. D: Effects of the simultaneously paced combination of A and B. RV = right ventricle; other abbreviations as in Figure 4.

An implication of the present study, and supported by other studies,^{10,11} is that choosing the best possible single LV site is sufficient to achieve optimal CRT benefit.

Although on average MPP and MZP did not significantly improve hemodynamic response beyond that achieved by BiVP, they may be beneficial if the initial electrophysiological (TAT) or hemodynamic (LVdP/dtmax) effect of BiVP is poor. This is an extension of previous clinical studies in which the LV location determined the magnitude of the hemodynamic effect of BiVP. A considerable effect was seen when MPP was compared to “poorer” LV sites, but the benefit was small when MPP was compared to the BiVP configuration, which yielded the largest AHR.^{8,9} These

findings are in line with previous work from our group in a nonischemic canine LBBB model¹⁵ and from Bordachar et al¹⁸ in a canine model of chronic ischemic heart failure. Even increasing the number of LV pacing sites to 6 resulted in a better AHR only if AHR during BiVP was poor.¹⁵ In agreement with the study by Ploux et al,¹⁵ we also found that better electrical resynchronization during multiple LV pacing did not always coincide with a better hemodynamic response.

The finding that pacing the lateral wall in LBBB was more beneficial compared to pacing the anterior or posterior wall is not new, but it confirms the suitability of the LBBB animal model. In clinical situations, the lateral wall may not be

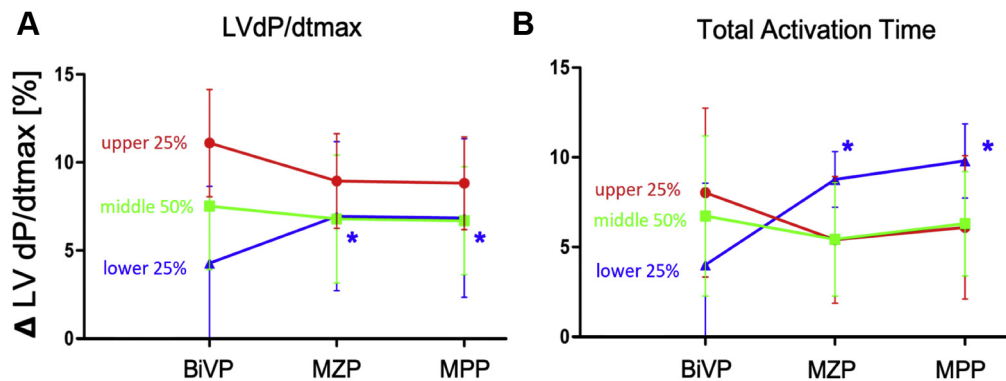


Figure 7 Acute hemodynamic response during multiple left ventricular (LV) pacing based on initial acute hemodynamic and electrical response during biventricular pacing (BiVP). Relative increase in LVdP/dtmax compared to baseline during BiVP, multipoint pacing (MPP), and multizone pacing (MZP), distinguishing between single initial LV pacing sites with upper 25%, middle 50%, and lower 25% change in LVdP/dtmax (A) and total activation time (B). Values are given as mean and SD. **P* < .05 vs BiVP.

targetable due to the lack of suitable veins or the presence of scar. The results of the present study show that MPP or MZP can be considered in such situations. If used, multiple LV pacing configurations should be programmed with large electrode distance, because we found that MZP- and MPP-like configurations consisting of more widely spaced electrodes yielded higher AHRs than more closely spaced combinations. This seems in line with the MORE-CRT MPP (MORE REsponse on Cardiac Resynchronization Therapy With MultiPoint Pacing) study,¹⁹ which showed that using MPP with a large anatomic separation of cathodal electrodes resulted in a larger conversion of nonresponders to responders than MPP with small electrode distance. An implication of the present study is that the design of pacing leads for MPP and MZP may be adapted to allow for larger electrode spacing.

Impact on battery longevity

The impact of MPP and MZP on battery longevity might be a different reason to opt for BiVP over MPP or MZP. An IRON-MPP (Italian Registry On Multipoint Left Ventricular Pacing) study subanalysis showed that early MPP activation was associated with a <1-year reduction in projected battery life compared to single-site biventricular pacing, with follow-up of 1.9 ± 0.8 years.²⁰ In a small multicenter trial, MPP also significantly shortened battery longevity for all 3 pacing capture threshold cutoffs.²¹

Study limitations

The data from this preclinical porcine model should be extrapolated with care to the clinical situation. The degree of dyssynchrony, created by ablation of the left bundle, is relatively small in porcine hearts,²² evidenced, for example, by QRS duration of 93 ms during LBBB (instead of ~50 ms before LBBB) in the present study. From previous studies in our laboratory, a more severe degree of dyssynchrony can be achieved in canine hearts.²³ However, experiments in dogs are becoming increasingly scrutinized due to ethical issues. Along with the smaller degree of dyssynchrony, the AHR achievable by CRT is smaller in porcine hearts compared to canine hearts, yet several observations such as the better performance of LV lateral wall sites over anterior or posterior wall sites mimics the clinical situation.

An advantage of the present study is that it allows extensive and systematic comparison of the electrophysiologic and hemodynamic effects of MPP and MZP strategies, including different combinations of pacing sites and distances between pacing sites. The importance of the present study may be illustrated by the fact that, to the best of our knowledge, only 1 study on direct comparison of multiple LV configurations has been published.⁹ In that clinical study, no difference in AHR was found between MPP and multivein pacing, although patients with ischemic cardiomyopathy were included.⁹

The present study was performed in a nonischemic, acute (nonmyopathic) LBBB model. Because different studies have shown conflicting results as to whether multiple LV

pacing has a greater benefit in ischemic compared to nonischemic cardiomyopathy patients,^{17,24} we opted for a nonischemic model. This approach allows for comparison of AHR generated by sites that are considered to be best (ie, lateral wall) with fewer optimal sites, without the potential influence of a scar or ischemic region.

Two methods were used to create an LBBB-like dyssynchrony model. In 2 cases in which radiofrequency ablation for LBBB led to complete atrioventricular block, RV free-wall pacing was used. These two approaches may have led to slightly different activation sequences, but extensive electrical mapping revealed no significant differences in wavefront propagation or activation times.

Finally, acute effects such as changes in LVdP/dtmax do not necessarily relate to long-term benefits of CRT.²⁵

Conclusion

In this acute porcine LBBB model, MPP and MZP create similar degrees of electrical resynchronization and hemodynamic improvement. However, the AHR of MPP and MZP is significantly better than conventional BiVP only if the corresponding LV site provides poor hemodynamic improvement during BiVP. In MPP and MZP, a larger IED increases the hemodynamic response.

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