Delayed Trans-Septal Activation Results in Comparable Hemodynamic Effect of Left Ventricular and Biventricular Endocardial Pacing: Insights from Electro-Anatomical Mapping

Running title: Sohal et al.; Endocardial CRT and delayed trans-septal activation

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Abstract:

Background - We sought to compare left ventricular (LV_epi) and biventricular epicardial pacing (BIV_epi) with left ventricular (LV_endo) and biventricular endocardial pacing (BIV_endo) in patients with chronic heart failure with an emphasis on the underlying electrophysiological mechanisms and hemodynamic effects.

Methods and Results - 10 patients with chronically implanted cardiac resynchronization devices underwent temporary LV_endo and BIV_endo pacing with an LV endocardial roving catheter. A pressure wire and non-contact mapping array were placed to the LV cavity to measure LVdP/dt_{max} and perform electroanatomical mapping. At the optimal endocardial position the acute hemodynamic response (AHR) was superior to epicardial stimulation, the AHR to BIV_endo pacing and LV_endo pacing being comparable (21±15% vs 22±17%; P=NS). During intrinsic conduction QRS duration (QRS_d) was 185±30ms, endocardial LV total activation time (LVTAT) 92±27ms and trans-septal activation time (TSAT) 60±21ms. With LV_endo pacing QRS_d (187±29ms; P=NS) and endocardial LVTAT (91±23ms; P=NS) were comparable to intrinsic conduction. There was no significant difference in endocardial LVTAT between LV_endo and BIV_endo pacing (91±23 vs 85±15ms; P=NS). Assessment of isochronal maps identified slow trans-septal conduction with both LV_endo and BIV_endo pacing resulting in activation of almost the entire LV endocardium prior to septal breakout thereby limiting any possible fusion with either pacing mode.

Conclusions - The equivalent AHR to LV_endo and BIV_endo pacing may be explained by prolonged trans-septal conduction limiting electrical fusion. The optimal AHR was associated with predominantly LV pre-excitation and depolarization. Our results suggest that LV pacing alone may offer a viable endocardial stimulation strategy to achieve cardiac resynchronization.

Key words: pacing, heart failure, cardiac resynchronization therapy, left bundle branch block, electroanatomic mapping
Background

The last two decades have seen cardiac resynchronization therapy (CRT) establish itself as a powerful tool in selected heart failure patients with evidence of electrical dyssynchrony. However, when applying internationally recognized selection criteria for CRT there is a non-response rate of 30-40%\(^1,2\). CRT is conventionally delivered as biventricular pacing with endocardial stimulation of the right ventricle and epicardial left ventricular (LV) stimulation via the coronary sinus (BIVepi). Clinical studies have shown similar outcomes with LV and BIV pacing suggesting that epicardial LV only pacing (LVepi) may be as beneficial as BIVepi.\(^3\) A recent canine study suggested delayed trans-septal activation results in the majority of LV depolarisation occurring prior to any contribution from right ventricular (RV) stimulation thereby limiting fusion of electrical wave-fronts.\(^4\) LV pacing alone has potential advantages over BiV pacing as it may preserve intrinsic conduction, avoid detrimental effects of RV pacing and reduce the number of electrodes making implantation less technically challenging. Endocardial LV pacing (BIVendo) pacing is not limited by CS anatomy and has been shown to improve acute and medium-term CRT response\(^5-8\) due to a more physiological electrical and mechanical propagation.\(^9,10\) The relative effect of endocardial pacing (LVendo) alone compared to BIVendo pacing is not well defined. We therefore sought to compare the hemodynamic effects of LVepi and BIVepi with LVendo and BIVendo pacing in patients with chronic heart failure with an emphasis on the underlying electrophysiological mechanisms that might explain the response to these different pacing modalities.

Methods

The study was approved by the local ethics committee and informed consent was obtained from each patient. The study population consisted of 10 patients with a chronically implanted CRT.
system in-situ for at least three months (St Jude Medical, Sylmar, CA, USA). All patients fulfilled standard criteria for CRT (NYHA class II-IV drug refractory heart failure, LVEF ≤35% and QRS ≥ 120ms (9 patients had left bundle branch block, 1 patient was dependent on RV pacing). Patients with a mechanical aortic valve or significant peripheral vascular disease were excluded. Baseline assessment included NYHA functional class, ECG and 2D echocardiography prior to the original CRT implant. Each patient’s heart failure etiology was confirmed on the basis of clinical history, coronary angiography and/or cardiac magnetic resonance (CMR) imaging. In all cases a temporary LV endocardial lead was used to perform LV endocardial stimulation.

Invasive Hemodynamic and Electro-anatomical Study

The protocol used has previously been described.11 Patients were lightly sedated using diazepam (5-10mg). A steerable 6Fr Livewire decapolar catheter (St Jude Medical, Sylmar, CA, USA) was passed from the left femoral artery retrogradely to the LV cavity to stimulate multiple sites within the LV. A non-contact mapping (NCM) array was passed retrogradely into the LV cavity and an 0.014 inch diameter high fidelity Certus PressureWire and PhysioMon software (RADI Medical Systems, Uppsala, Sweden) with a 500Hz frequency response and 50Hz filter bandwidth were used to assess real-time mean peak LVdP/dt\textsubscript{max}.7

Acute Hemodynamic Measurement

LVdP/dt\textsubscript{max} was recorded for at least 20 s to ensure steady-state conditions during any pacing modality. LVdP/dt\textsubscript{max} during atrial pacing (AAI) or RV pacing (if the patient was in AF) at 5-10 beats above intrinsic rate was used as baseline. A waiting period of at least 20 s was respected after any change in pacing settings or lead position to achieve hemodynamic stabilization. These methods have previously been shown to reliably measure LVdP/dt\textsubscript{max}.12-17 Results at each pacing
site were expressed as a percentage change from baseline. To minimize baseline drift in AHR the baseline was reassessed prior to and after every change in pacing modality and comparisons were made to a mean of these two readings. Data from premature ventricular complexes were discarded.

**Pacing protocol**

A pacing protocol was performed: (5-10bpm above intrinsic rate, paced and sensed AV delay 100ms, AAI pacing as baseline and repeated after each pacing mode):

i) DDD-RV only

ii) DDD-LV only from the chronic epicardial CS lead (LV_{epi})

iii) DDD-BIV from the chronically implanted epicardial LV lead plus RV pacing with 0ms V-V delay (BIV_{epi})

iv) LV only pacing from the endocardial catheter at multiple endocardial sites (LV_{endo})

v) LV endocardial and RV endocardial pacing from multiple LV endocardial sites with 0ms V-V delay (BIV_{endo})

BIV_{endo} and LV_{endo} stimulation was repeated with the LV roving catheter in a random order in up to 4 different LV endocardial positions including anterior, lateral, and posterior sites. Capture was verified for each pacing modality by looking for a change in QRS morphology at a paper speed of 200mm/s. This was also validated with reference to LV pacing by analysis of the activation wavefront on non-contact mapping. For the purposes of this study the endocardial position producing the best AHR with BiV_{endo} pacing was chosen as the position used for analysis.

**Electro-anatomical mapping**

Analysis of the non-contact mapping data was performed by 2 independent observers blinded to
the hemodynamic results. Endocardial maps were obtained at baseline and in each pacing configuration. The virtual unipolar electrograms recorded at 1200Hz (temporal resolution of 0.83ms) from the endocardial surface were used to measure the endocardial left ventricular total activation time (LVTAT). The high pass filter was set at 8Hz. The onset of LV activation was defined as the first peak negative dV/dt at any point in the LV and the end of LV activation was defined as the time of the latest peak negative unipolar electrogram on the virtual endocardial surface. The trans-septal activation time (TSAT) was defined as the time from the onset of the earliest QRS complex to the time of the first detected LV endocardial breakthrough as described previously by Auricchio et al.19

**Statistical Analysis**

Statistical analysis was performed on PASW Statistics 20 (SPSS Inc, Chicago, IL, USA). Data were analyzed using generalized estimating equations using an exchangeable correlation structure, to explore the extent of differences between pacing methods. Pacing methods were compared to each other and to avoid type 1 errors, P values were corrected using the Bonferroni adjustment. Descriptive results are expressed as mean± SD.

**Results**

**Patient demographics (table 1)**

Baseline characteristics are shown in table 1. All patients were male with a mean age of 62 ± 8 yrs. The mean LVEF was 26 ± 8% and there were equal numbers of ischemic and non-ischemics (5/5). The mean QRS duration was 186±27 ms and morphology was LBBB in 9 and RV paced rhythm in the remaining patient. The epicardial LV lead was in a lateral or postero-lateral position in 8 (80%) patients and in an anterior position in 2 (20%) patients. Table 2 displays the
epicardial LV lead positions for each patient along-side the optimal LV endocardial pacing position in each case. There was concordance in four cases (table 2).

**Acute hemodynamic response (figure 1 and table 3):**

LV $dP/dt_{max}$ whilst AAI pacing 5-10 beats above intrinsic rate was taken as the baseline to which all pacing measurements were compared in each patient. Table 3 shows the mean (SD) percentage increase in LV $dP/dt_{max}$ for each pacing mode over baseline. Compared to baseline, $LV_{epi}$ pacing from the chronically implanted epicardial lead gave a 10±14% increase in LV $dP/dt_{max}$. $BIV_{epi}$ pacing increased LV $dP/dt_{max}$ over baseline by 15±15% whilst $LV_{endo}$ and $BIV_{endo}$ pacing increased LV $dP/dt_{max}$ over baseline by 22±17% and 21±15% respectively. The P value for the overall test for variability across all pacing modalities was significant at 0.001 (figure 1). $BIV_{epi}$ increased LV $dP/dt_{max}$ by a mean of 4.1% (95% CI 1.2 to 7.0). However the AHR to $BIV_{endo}$ pacing and $LV_{endo}$ pacing were comparable with a mean difference of 1.1% (95% CI -5.5 to 7.8). At the optimal endocardial position, hemodynamics were superior to epicardial stimulation with a mean difference of 6.2% (95% CI 0.5 to 11.8 for $BIV_{endo}$ vs $BIV_{epi}$ pacing).

**QRS duration, LVTAT and Transeptal Activation Times (TSAT) (figure 1 and table 3):**

Intrinsic QRSd was 185±30ms and the intrinsic endocardial LVTAT was 92±27ms. Four patients exhibited a type I pattern of endocardial activation (homogenous spread from the septum to lateral wall) whilst 6 patients exhibited a type II pattern of activation (characterized by a line of functional block between the septum and lateral wall). TSAT in intrinsic rhythm was 60±21ms and lengthened with RV pacing to 71±13ms (mean difference 10.4, 95% CI 0.6 to 20.2). Figure 2 demonstrates the delay in endocardial breakout on the left side of the interventricular septum following RV pacing. $LV_{epi}$ pacing resulted in a similar QRSd to
intrinsic (187±25ms vs 185±30ms) and a similar endocardial LVTAT (93±17). BIV_epi however, significantly reduced QRSd to 142±12ms (mean difference -42.3; 95% CI -61.0 to -23.6) and shortened endocardial LVTAT to 72±15ms (mean difference -20.1; 95% CI -41.4 to 1.2) suggesting a degree of fusion of RV and LV wavefronts. The mean QRSd and endocardial LVTAT with LV_endo pacing were comparable to intrinsic rhythm (187±29ms and 91±23ms respectively). BIV_endo pacing from the same position as LV_endo reduced QRSd over intrinsic rhythm to 155±28ms  however there was no significant difference between the endocardial LVTAT between LV_endo and BIV_endo pacing (91±23 vs 85±15ms; mean difference -5.9; 95% CI -14.6 to 2.8).

Assessment of the isochronal activation maps of the LV during the various pacing modes demonstrated fusion of electrical wave-fronts with BIV_epi pacing (figure 3). LV_epi pacing resulted in minimal fusion of RV and LV activation wave fronts. No significant fusion was seen with BIV_endo pacing and the activation maps were strikingly similar to LV_endo pacing (figure 3). The non-contact maps identified slow trans-septal conduction during both LV_endo and BIV_endo pacing. This resulted in activation of almost the entire LV endocardium prior to septal breakout, thereby limiting any possible fusion with either pacing mode. With BIV_epi pacing, endocardial breakthrough from the epicardial LV lead was sufficiently delayed to allow fusion of electrical wave fronts.

**Discussion**

The present study provides new insights into the electrical mechanisms of epicardial and endocardial CRT. The principal findings of our study are as follows: 1) trans-septal LV activation was prolonged during both intrinsic rhythm and RV pacing (equivalent to approximately 33% of the QRSd); 2) there was no significant difference between the AHR
derived from \( L_{\text{endo}} \) and \( B_{\text{endo}} \) at the optimal site whereas \( B_{\text{epi}} \) appeared superior to \( L_{\text{epi}} \) pacing; 3) Endocardial LVTAT and LV endocardial activation patterns were comparable between \( B_{\text{endo}} \) and \( L_{\text{endo}} \) pacing suggesting minimal fusion of LV and RV wave-fronts. 4) \( L_{\text{endo}} \) pacing may be equivalent to \( B_{\text{endo}} \) pacing.

**Endocardial pacing hemodynamics and electrical changes**

\( B_{\text{endo}} \) stimulation at the optimal site gave a superior AHR to epicardial pacing which was site specific. \( L_{\text{endo}} \) stimulation at a short AV delay produced a similar AHR to \( B_{\text{endo}} \) pacing (22±17% vs 21±15%, \( P=\text{NS} \)) suggesting no incremental benefit in \( B_{\text{endo}} \) over \( L_{\text{endo}} \) pacing (when pacing at a short AV delay) in comparison to epicardial stimulation. Our findings may be explained on the basis of the long trans-septal activation times seen in our patients with LBBB so that by the time the RV pacing impulse had broken through the septum into the LV cavity (approximately 70msecs) the majority of LV endocardial activation had already occurred. This is supported by examination of the isochronal activation maps of \( B_{\text{endo}} \) and \( L_{\text{endo}} \) pacing which were almost identical, suggesting an absence of fusion (figure 3). The short AV interval of 100ms used in our study may explain the apparent lack of fusion seen with \( L_{\text{endo/epi}} \) pacing and the PR interval in our group was 182±19ms therefore at an AV delay of 100ms one would not expect any fusion from intrinsic activation via the right bundle branch. A reduction in QRSd was noted with \( B_{\text{endo}} \) pacing but endocardial LVTAT remained similar between LV and \( B_{\text{endo}} \) pacing. The surface QRSd represents a summation of LV and RV activation times and therefore the QRS reduction seen with BIV pacing may reflect a reduction in RV (and not LV) activation time. We measured only LV endocardial activation time (and not epicardial) and the reduction may be related to changes occurring in the epicardium as has been shown in the canine model.\(^4\) We saw divergent findings for \( L_{\text{epi}} \) and \( B_{\text{epi}} \) pacing with an improvement in AHR
with BIV_epi pacing over LV_epi accompanied by a reduction in both QRS_d and endocardial LVTAT. The electrical findings may be accounted for by the fact that pacing from the epicardium resulted in a sufficient delay to compensate for prolonged trans-septal conduction thereby allowing fusion of electrical wave-fronts from RV and LV stimulation. A reduction in RV activation time (which was not measured) may have also contributed to the reduction in QRS_d with BIV_epi pacing (the reduction in QRS_d between LV_epi and BIV_epi was greater than the reduction between LV_endo and BIV_endo). Our results would suggest a mismatch between hemodynamic response and electrical parameters with the best hemodynamic response being relatively equal between LV_endo and BIV_endo pacing, however with epicardial pacing this differed. This may suggest that optimal pacing LV endocardially may only require a single lead. The long TSAT seen in our group would suggest that most LV depolarization occurs via the LV pacing impulse in both LV_endo and BIV_endo modes.

Comparison with previous studies

Our findings of improved hemodynamic response with endocardial CRT are in keeping with other groups. Strik et al demonstrated in a chronic canine heart failure model improved hemodynamics as a result of LV endocardial pacing compared to conventional epicardial CRT which could be explained by the shorter path length and more rapid conduction resulting from endocardial LV pacing. Derval et al found better hemodynamic effects with LV_endo versus LV_epi and in keeping with our study showed that there is not one pacing site (or combination of pacing sites) that is best for all patients. The benefits of LV endocardial pacing seen in our patients are likely to be due to a reduction in total LV activation time (endocardial and epicardial activation) with the reduction predominantly in epicardial LV activation time (which we did not specifically measure in this study. Our findings of slow trans-septal conduction are strikingly
similar to those recently found in canines. Strik et al found a TSAT of 67±9ms in a canine model of LBBB and pacing induced dysynchrony compared to 60±21ms in our patients with LBBB and heart failure. In the same study there was no incremental benefit in BIV compared to LV only pacing and this was due to predominant LV stimulation in both modes due to long trans-septal activation times. This is in keeping with our findings with endocardial stimulation where we saw no incremental benefit with RV and LV pacing due to apparent lack of fusion with both modalities. Our results do however differ in that we found an incremental hemodynamic benefit with BIV_epi compared to LV_epi associated with a reduction in the LVTAT and a degree of fusion of wave fronts, which may be explained by much longer endocardial LVTAT than in the dogs. Additionally, we saw that there was a delay between epicardial stimulation and endocardial breakthrough (as seen in figure 3) thereby allowing for a delay in trans-septal conduction and resulting in fusion of RV and LV wave fronts. We saw minimal fusion with LV_epi pacing and this may have been as a result of the short AV delay used in the study (100ms) versus the longer mean PR interval (182ms) in intrinsic rhythm. The short AV delay when the RV was paced with BIV_epi pacing may have provided a sufficient head start and therefore earlier breakthrough into the LV endocardium. The difference may also be explained by the differences between the animal model in our patients with chronic heart failure, significantly dilated ventricles and the presence of scar (50% of our patients were ischemic). Also the PR interval in our patients of over 180ms is longer in comparison to the canine model and likely explains the difference on the basis of fusion with BIV_epi pacing.

Human studies comparing LV_epi pacing with BIV_epi pacing would also seem to suggest that there is little difference in terms of acute hemodynamics or medium-term clinical response between the two. \(^3, 21-23\) We found a small (but statistically significant) benefit in AHR with
BIVepi pacing over LVepi pacing. The reason behind this may lie behind the fact that we utilized a short AV delay of 100ms compared to a long mean intrinsic PR interval of 182ms. This meant that we saw minimal fusion with LVepi pacing (see figure 3) and this in turn may have attenuated the AHR. Auricchio et al also studied the differences in LVdP/dtmax between LVepi and BIVepi pacing and found LVepi to be associated with a slightly greater AHR.24 Crucially, pacing was performed in VDD mode (atrial sensing) and so did not control for heart rate which is one of the key determinants that affects absolute values of LVdP/dtmax. Additionally, most LV leads were positioned apically and this has been shown to attenuate the response to BIV stimulation.25 These differences may also explain why our results vary in this respect.

**Study Limitations**

This study is limited by its small sample size, however given the highly invasive and time-consuming nature of the study the size was limited to the smallest size needed to provide significant results in this proof of principle study. Ideally a range of AV delays and VV delays would have been assessed but this was not possible because of time constraints and will need to be assessed in future studies. Our study used a short AV delay of 100ms and this may in some part explain the results. With such a short AV delay there was likely to be little intrinsic fusion in the LV only modes (intrinsic PR interval was over180ms). At a short AV delay, LV and BIV endocardial pacing appear equivalent, although we cannot rule out the possibility that at different AV delays this may have differed due to ‘LV fusion’ pacing. Our measures of LV activation were endocardial and we did not study epicardial activation specifically. We do, however, have data on QRS duration which is a measure of total electrical activation of the heart. We did not specifically look at areas of myocardial scar in relation to lead positioning in our patients may
which may be important in determining both the optimal epicardial and endocardial stimulation sites. There was concordance between epicardial and endocardial lead position in only four cases meaning that comparisons between endocardial and epicardial CRT should be made with caution and the benefits of LV endocardial pacing seen in this study may be related to the lack of being constrained by coronary venous anatomy and so being able to pace from a more optimal position. Our assessment of CRT response using AHR may not necessarily translate into chronic response, however, previous work from our institution has suggested a good correlation with chronic response albeit predominantly in non ischemic patients.17

Clinical implications

Our findings may have important implications for the practice of endocardial CRT. This type of CRT may become more prevalent in an attempt to improve CRT response. Our results would suggest that in such patients LVendo pacing may be a viable treatment strategy and that in patients not requiring an RV lead (for potential defibrillation) it may be reasonable to implant an LV lead alone.

Conclusion

Endocardial LV pacing from the optimal site is hemodynamically superior to conventional epicardial CRT, but biventricular endocardial pacing did not produce an incremental hemodynamic benefit over endocardial LV pacing alone. This may be due to long trans-septal activation times resulting in lack of fusion of LV and RV wavefronts. Indeed the optimal hemodynamic response would appear to be associated with predominantly LV pre-excitation and depolarization. Our results suggesting that LV pacing alone may offer a viable endocardial stimulation strategy to achieve CRT.
Conflict of Interest Disclosures: Drs. Sohal and Shetty are supported by an educational grant from St. Jude Medical. Dr. Niederer receives research support from Boston Scientific Corp. Professor Razavi receives research support from Philips Healthcare. Professor Prinzen has received research grants from Medtronic Inc., Boston Scientific Corp., MSD, Biological Delivery System (Cordis) and EBR Systems. Dr. Rinaldi receives research support form St. Jude Medical and Medtronic Inc. All other authors state that they have no conflicting interests to declare.

References:


Table 1: Patient characteristics

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<th>Characteristic</th>
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<td>Age (years)</td>
<td>62 ± 8</td>
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<tr>
<td>Gender n(%)</td>
<td></td>
</tr>
<tr>
<td>Male 10 (100)</td>
<td></td>
</tr>
<tr>
<td>Female 0 (0)</td>
<td></td>
</tr>
<tr>
<td>Etiology n(%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic 5 (50)</td>
<td></td>
</tr>
<tr>
<td>Non-ischemic 5 (50)</td>
<td></td>
</tr>
<tr>
<td>NYHA class n(%)</td>
<td></td>
</tr>
<tr>
<td>Class II 4 (40)</td>
<td></td>
</tr>
<tr>
<td>Class III 6 (60)</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction* (%)</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>Intrinsic PR interval (ms)</td>
<td>182 ± 19</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>185 ± 30</td>
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<tr>
<td>QRS morphology n(%)</td>
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</tr>
<tr>
<td>LBBB 9 (90)</td>
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<tr>
<td>RV paced 1 (10)</td>
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<tr>
<td>Epicardial LV lead position n(%)</td>
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</tr>
<tr>
<td>Lateral 4 (40)</td>
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<tr>
<td>Posterolateral 4 (40)</td>
<td></td>
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<tr>
<td>Anterior 2 (20)</td>
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- derived from 2D echocardiography using the modified Simpson’s biplane method
- Continuous variables are expressed as mean ± standard deviation

Table 2: Comparison between the position of the chronically implanted epicardial LV lead and the optimal position for LV endocardial pacing

<table>
<thead>
<tr>
<th>Patient</th>
<th>Epicardial lead position</th>
<th>Optimal endocardial lead position</th>
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<tbody>
<tr>
<td>1</td>
<td>Posterolateral</td>
<td>Posterolateral</td>
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<td>2</td>
<td>Posterolateral</td>
<td>Inferoseptal</td>
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<tr>
<td>3</td>
<td>Lateral</td>
<td>Lateral</td>
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<tr>
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<tr>
<td>5</td>
<td>Anterior</td>
<td>Lateral</td>
</tr>
<tr>
<td>6</td>
<td>Lateral</td>
<td>Posterior</td>
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<tr>
<td>7</td>
<td>Lateral</td>
<td>Septal</td>
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<tr>
<td>8</td>
<td>Lateral</td>
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<td>Posterolateral</td>
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<tr>
<td>10</td>
<td>Anterior</td>
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Table 3: Hemodynamic and electrical parameters compared across pacing modalities

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<thead>
<tr>
<th>Modality</th>
<th>% change in dP/dt\text{max} over baseline</th>
<th>QRS\text{d} (ms)</th>
<th>Mean change in QRS\text{d} over baseline</th>
<th>TSAT (ms)</th>
<th>Mean change in TSAT over baseline</th>
<th>LVTAT (ms)</th>
<th>Mean change in LVAT over baseline</th>
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<tr>
<td>Baseline</td>
<td>n/a</td>
<td>185±30</td>
<td>n/a</td>
<td>60±21</td>
<td>92±27</td>
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<tr>
<td>RV</td>
<td>1±3</td>
<td>195±30</td>
<td>10.0</td>
<td>71±13</td>
<td>10.4</td>
<td>93±26</td>
<td>1.6 (-8.6 to 11.8; P=0.730)</td>
</tr>
<tr>
<td>LVepi</td>
<td>10±14</td>
<td>187±25</td>
<td>2.3</td>
<td>94±17</td>
<td>1.8</td>
<td>93±17</td>
<td>1.8 (-19.6 to 23.2; P=0.853)</td>
</tr>
<tr>
<td>BiVepi</td>
<td>15±15</td>
<td>142±12</td>
<td>-42.3</td>
<td>72±15</td>
<td>72±15</td>
<td>72±15</td>
<td>-20.1 (-41.4 to 1.2; P=0.062)</td>
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<tr>
<td>LVendo</td>
<td>22±17</td>
<td>187±29</td>
<td>2.8</td>
<td>91±23</td>
<td>91±23</td>
<td>91±23</td>
<td>-0.4 (-21.5 to 20.7; P=0.967)</td>
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<tr>
<td>BiVendo</td>
<td>21±15</td>
<td>155±28</td>
<td>-30.1</td>
<td>85±15</td>
<td>85±15</td>
<td>85±15</td>
<td>-6.3 (-21.4 to 8.8; P=0.369)</td>
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</table>

Abbreviations: LVepi – AV synchronous LV pacing from the epicardial LV lead; BiVepi – AV synchronous biventricular pacing using the chronically implanted CRT system; LVendo – AV synchronous LV pacing from the temporary endocardial LV pacing catheter; BiVendo – AV synchronous biventricular stimulation using the temporary endocardial LV pacing catheter for LV stimulation; QRS\text{d} – QRS duration; TSAT – transseptal activation time; LVAT – endocardial LV activation time
Figure Legends:

**Figure 1:** Mean change from baseline in dP/dt\textsubscript{max}, QRS duration and LV activation time for each pacing modality. This is displayed as the percentage mean change each variable resulting from pacing in each pacing configuration, compared with baseline (AAI pacing). Abbreviations as for table 2.

**Figure 2:** Isochronal map derived from non-contact mapping in a patient with RV pacing (referenced to RV stimulation artifact). The left hand panel is in a right anterior oblique (RAO) orientation and the right panel is in a left anterior oblique (LAO) orientation. Septal breakout is identified as the site of earliest onset in the LV (white colour scale on the map). Inspection of the scale bar on the left shows that it takes approximately 65ms from the onset of RV stimulation before septal breakout occurs and begins spreading across the LV.

**Figure 3:** Isochronal maps from the same patient as figure 2, with LVepi pacing (top panels) and BIVepi pacing (bottom panels). There is a change in endocardial electrical activation between LVepi and BIVepi modalities. Inspection of the colour scale bar on the left shows that there is a delay between epicardial stimulation and endocardial breakthrough and this is sufficient to allow some fusion of endocardial activation of the LV from RV and LV epicardial stimulation.

**Figure 4:** Isochronal maps from the same patient as figure 2, with LVendo pacing (top panels) and BIVendo pacing (bottom panels). Endocardial stimulation results in a broad region of early activation with both pacing modalities and endocardial activation that is broadly similar for both (implying minimal fusion of RV and LV stimulation wavefronts).
Overall test of variability across all pacing modes: $P=0.012$

Change in LV $dP/dt_{max}$ from baseline (%)
Overall test of variability across all pacing modes: P<0.001

Change in QRS duration from baseline (%)
Overall test of variability across all pacing modes: P<0.001
Delayed Trans-Septal Activation Results in Comparable Hemodynamic Effect of Left Ventricular and Biventricular Endocardial Pacing: Insights from Electro-Anatomical Mapping
Manav Sohal, Anoop Shetty, Steven Niederer, Zhong Chen, Tom Jackson, Eva Sammut, Julian Bostock, Reza Razavi, Frits Prinzen and C. Aldo Rinaldi

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