His-bundle and left bundle pacing with optimized atrioventricular delay achieve superior electrical synchrony over endocardial and epicardial pacing in left bundle branch block patients

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BACKGROUND His-bundle pacing (HBP) and left bundle pacing (LBP) are emerging as novel delivery methods for cardiac resynchronization therapy (CRT) in heart failure patients with left bundle branch block (LBBB). HBP and LBP have never been compared to biventricular endocardial (BiV-endo) pacing. Furthermore, there are indications of negative effects of LBP on right ventricular (RV) activation times (ATs), but these effects have not been quantified.

OBJECTIVE The purpose of this study was to compare changes in ventricular activation induced by HBP, LBP, left ventricular (LV) septal pacing, BiV-endo, and biventricular epicardial (BiV-epi) pacing using computer simulations.

METHODS We simulated ventricular activation on 24 four-chamber heart meshes inclusive of the His-Purkinje network in the presence of LBBB. We simulated BiV-epi pacing, BiV-endo pacing with left ventricular (LV) lead at the lateral wall, BiV-endo pacing with LV lead at the LV septum, HBP, and LBP.

RESULTS HBP was superior to BiV-endo and BiV-epi in terms of reduction in LV ATs and interventricular dyssynchrony (P < .05). LBP reduced LV ATs but not interventricular dyssynchrony compared to BiV-epi and BiV-endo pacing. RV latest AT was higher with LBP than with HBP (141.3 ± 10.0 ms vs 111.8 ± 10.4 ms). Optimizing AV delay during LBP reduced RV latest AT (104.7 ± 8.7 ms) and led to comparable response to HBP. In case of complete AV block, BiV-epi septal pacing was equivalent to LBP.

CONCLUSION HBP is superior to BiV-epi and BiV-endo. To achieve comparable response to HBP, AV delay optimization during LBP is required in order to reduce RV ATs.

KEYWORDS Cardiac resynchronization therapy; Heart failure; His-bundle pacing; Left bundle branch block; Left bundle pacing

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Introduction
Cardiac resynchronization therapy (CRT) is one of the most effective treatments of heart failure (HF). However, between 30% and 40% of patients indicated for CRT do not experience target clinical improvements.1

Biventricular epicardial (BiV-epi) pacing is the standard clinical form of delivering CRT, with a right ventricular (RV) apical lead and a left ventricular (LV) lead in one of the coronary sinus (CS) tributaries.2 Response to BiV-epi pacing is strongly determined by the location of the LV lead,3,4 which is limited by local CS anatomy. In contrast, biventricular endocardial (BiV-endo) pacing5,6 allows for testing more potential LV lead targets. However, clinical studies indicate that the optimal endocardial lead location is highly patient specific.7 Despite efforts to find novel methods for optimal pacing site selection,5,7 optimal epicardial or endocardial LV lead placement remains a challenge.

Resynchronization through BiV-epi or BiV-endo pacing is caused by the addition of a wavefront traveling from the pacing site at the LV free wall to the septum. This is the opposite of intrinsic synchronous activation, in which activation spreads from the septum to the LV free wall. Pacing the ventricular fast conducting system (His-Purkinje system) instead of the slow-conducting myocardium might restore native synchronous activation.8 His-bundle pacing (HBP) below the conduction block leads to better LV function compared to BiV-epi and BiV-endo pacing,9–13 reduces all-cause mortality compared to RV pacing,9 and is comparable or superior to BiV-epi pacing.8,14 However, HBP is technically challenging, as the His bundle is located at different depths in the myocardium.15 Furthermore, HBP requires high pacing thresholds.15 Pacing the LV septum to capture the left bundle might overcome some of the challenges associated with HBP and maintain the benefits of pacing the Purkinje system.15–17 Lin et al15 showed the feasibility of HBP and left bundle pacing (LBP) to correct left bundle branch block (LBBB) in 1 patient. LBP required lower thresholds than HBP. However, achieving response through LBP involved atrioventricular (AV) delay optimization, which was not required with HBP. Although there are indications of negative effects of LBP on RV activation,15,18 such effects have not been quantified. Both HBP and LBP constitute intriguing alternatives to BiV-epi and BiV-endo pacing to correct LBBB. More studies are needed to assess HBP and LBP feasibility in larger cohorts and to provide a better understanding of the effects of these novel pacing strategies.

To facilitate the design of larger clinical studies and predict the mechanisms underpinning these new therapies, we created and performed simulations in a virtual patient cohort. We compared activation times with HBP, LBP, and LV septal pacing with BiV-endo and BiV-epi pacing. We also investigated the effect of LBP on RV activation times and determined whether response to LBP can be improved with AV delay optimization.

Methods
Patient cohort
Data were gathered as part of 2 clinical trials: clinical trial REC numbers 14/WM/1069 and 18/LO/07652 approved by the West Midlands Coventry & Warwick ethics committee and by the London-Harrow ethics committee, respectively. Data were analyzed anonymously.

We used data from 24 patients recruited for CRT upgrade. Patients underwent electrocardiography (ECG)-gated computed tomography before the upgrade procedure. Baseline conditions were assessed with 12-lead ECG and 2-dimensional echocardiographic LV ejection fraction. Patient demographics are listed in Table 1.

Anatomic models
We built 24 four-chamber heart models inclusive of ventricular myofiber orientation using a pipeline described previously.19,20 We included a His-Purkinje network on the LV and RV endocardium using a publicly available tool (https://github.com/fsahli/fractal-tree). We studied the effect of Purkinje network height and density on simulated ventricular activation (Online Supplemental Material). We simulated LBBB by disconnecting the LV Purkinje network along the His. (For more details about Purkinje network generation, see the Online Supplemental Material.)

Electrophysiological simulations
Ventricular tissue was simulated as transversely isotropic, with conduction velocity (CV) of 0.6 and 0.24 m/s in the fiber and in the transverse direction, respectively.21 CV along the Purkinje network was set to 4.0 m/s.22 Ventricular cellular dynamics were modeled with the Ten Tusscher model.23 We used a reaction-eikonal model to compute ventricular activation times and transmembrane potential transient over time (Figure 1, left).24

Computing ECGs requires knowing the position of the heart within the chest. However, segmentation of the whole torso was not possible because the computed tomographic images did not cover the torso volume. Therefore, we registered all our heart geometries to a heart enclosed in a pre-existing whole torso model using the LV long axis.25 We then selected locations of the 12 lead-ECG electrodes on the torso skin (Figure 1, right) and simulated the extracellular potential at these locations.24 We used simulated 12-lead ECG signals to compute QRS duration (QRSd).26

A validation of our baseline LBBB simulation is provided in the Online Supplemental Material. To confirm that the

<table>
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<tr>
<th>Table 1</th>
<th>Patient cohort demographics</th>
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<tr>
<td>Age (y)</td>
<td>67 ± 14</td>
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<tr>
<td>Sex (male)</td>
<td>23 (96)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>159 ± 23</td>
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<tr>
<td>LV ejection fraction (%)</td>
<td>34 ± 10</td>
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Values are given as mean ± SD or n (%). LV = left ventricle.
models are representative of CRT patients, we compare simulated measurements of electrical activation with values available in the literature and from the clinical data from our cohort. We show that the modeled LBBB activation sequence and ECG morphology are similar to those reported in the literature for LBBB patients.

**CRT simulation**  
Figure 2 shows simulated CRT delivery methods: BiV-epi, BiV-endo with LV lead in the lateral wall, BiV-endo with LV lead in the septum, selective and nonselective HBP, and LBP. We quantified the role of prolonged AV delay and the presence of intrinsic activation on LBP activation. Details about pacing locations and simulations with different AV delays are detailed in the Online Supplemental Material.

We used the following electrical measures to compare response to different CRT delivery methods: QRSd; LV 95% activation time (LVAT-95), computed as the time interval spanning activation of 95% of the LV; BiV 90% AT (BIVAT-90), computed as the time interval spanning activation of 90% of the ventricles; and BiV dyssynchronous index (DI), computed as the standard deviation of ventricular activation times, which gives a measure for spatial synchronicity of ventricular activation.\(^{27}\) To compare HBP and LBP with BiV-epi and BiV-endo pacing, we selected the best epicardial and endocardial locations for each patient. We computed RV latest activation time (LAT) to quantify the effect of each pacing modality on RV activation. We tested the effect of Purkinje CV, CV in the fiber direction, and CV in the transverse direction on our results (Online Supplemental Material).

**Statistical analysis**  
All variables were normally distributed according to the Shapiro-Wilk test, with a 0.05 significance level. We compared different CRT delivery methods with paired Student t tests, with \(P < .05\) level considered significant.
Results

**HBP is superior to BiV pacing in resynchronizing ventricular activation**

Figure 3 shows the response for all tested CRT delivery methods. Selective and nonselective HBP are superior to both BiV-epi and BiV-endo pacing with optimized LV lead location regardless of the response metric used, with all statistical differences being significant ($P < .05$). Selective and nonselective LBP are also superior to both BiV-epi and BiV-endo pacing in terms of LVAT-95 ($P < .05$) (Figure 3B). However, selective LBP is comparable to BiV-endo pacing ($P = .63$), and nonselective...
LBP is comparable to BiV-epi pacing in terms of BIVAT-90 ($P = .26$). Compared to BiV-epi pacing, selective and nonselective LBP had similar QRSd ($P = .28$ and $P = .36$) and BIV DI ($P = .30$ and $P = .86$). Selective and nonselective HBP improve ventricular activation dynamics compared to other CRT delivery methods. In contrast, LV activation times, but not inter-ventricular dyssynchrony, benefit from LBP compared to BiV-epi and BiV-endo. (Discussion of how these conclusions do not depend on model parameters is given in the Online Supplemental Material.)

**Improved response to LBP through AV delay optimization**

Differences in interventricular dysynchrony between HBP and LBP (when performed in the presence of AV block) are caused by differences in RV activation times. RV LAT was higher with LBP than with HBP ($141.3 \pm 10.0$ ms vs $111.8 \pm 10.4$ ms). LBP increases RV LAT compared to baseline (Figure 3E) and induces right bundle branch block (RBBB)-like activation, with a wave spreading from the LV to the RV (Figure 4B). RV activation with LBP improves with AV delay optimization. Figure 4A shows simulated

![Figure 4](Image)

**Figure 4** Response to LBP with optimized AV delay. A: Response measures simulated with different AV delays. Positive and negative delays mean that the left bundle is paced before and after the stimulus enters the His, respectively. Gray lines represent the patients. Red lines represent the mean. B: Activation times with selective HBP, selective LBP with complete AV block and with optimal AV delay. C: Boxplots of change in QRSd, LVAT-95, BIVAT-90, BIV DI, and RV LAT for selective HBP, selective LBP with complete AV block and with optimal AV delay. Light blue circles represent mean values. Plus symbols represent outliers. AV = atrioventricular; BIV DI = biventricular dyssynchronous index; BIVAT-90 = 90% biventricular activation time; HBP = His-bundle pacing; LBP = left bundle pacing; LVAT-95 = 95% left ventricular activation time; QRSd = QRS duration; RV LAT = right ventricular latest activation time.
response measures for LBP with different AV delays. If the left bundle is stimulated before the stimulus enters the His-Purkinje system (negative delays), then pacing completely overwrites intrinsic activation, RV activation is slow, and interventricular dysynchrony increases. With positive delays, the patient’s intrinsic rhythm induces a wave traveling from the atria to the ventricles that activates the RV. At the same time, LBP maintains synchronous LV activation (Figure 4A, second plot from the left). This decreases RV LAT, and synchronous activation is restored.

LBP with optimized AV delay is comparable to HBP. Figure 4C shows changes in all response measures for selective HBP, selective LBP with complete AV block, and selective LBP with optimized AV delay. If AV delays are optimized, RV LATs are reduced compared to LBP without optimized AV delays (104.7 ± 8.7 ms vs 141.3 ± 10.0 ms), leading to comparable response to HBP. LVAT-95, BIVAT-90, and BIV DI achieved with LBP with optimized AV delay are similar to HBP (P > .05). LBP with optimized AV delay is even superior to HBP in terms of QRSd reduction (P < .05). Activation time distribution shows that optimized AV delay solves RBBB-like activation induced by LBP in the presence of complete AV block (Figure 4B). When the patient does not suffer from complete AV block and there is a viable conduction pathway from atria to the ventricles, response to LBP can be improved by optimizing the AV delay. In case of complete AV block, the benefits of LBP are limited to LV activation times.

BiV-endo septal pacing is superior to LBP in patients with AV block

BiV-endo septal pacing without targeting the LB might be as beneficial as LBP in patients with AV block. Selective and nonselective LBP outperform BiV-endo septal pacing in terms of LVAT-95 because of capture of the fast conduction system and correction of LBBB (Figure 3B). However, BiV-endo septal pacing is superior to both selective and nonselective LBP in terms of QRSd and BIV DI (P < .05) (Figures 3A and 3D), indicating better ventricular resynchronization. BIVAT-90 achieved with BiV-endo septal pacing is superior to nonselective LBP (P < .05). In case of complete AV block, targeting the LB seems to be unnecessary. Generically placing the LV lead in the middle of the septum and pacing the RV apex might be more effective and maintain physiological activation (Figure 5).

Discussion

We quantified changes in ventricular electrical activation induced by HBP and LBP on LBBB patients with the use of computer simulations. We found that HBP is superior to BiV-endo and BiV-epi pacing in terms of both LV activation times and interventricular dyssynchrony. The benefits of LBP are restricted to LV activation times, as LBP induces RBBB-like activation. RV activation times during LBP can be reduced by optimizing AV delay. This leads to a comparable response between HBP and LBP. In the presence of complete AV block, prolonged RV activation times due to LBP cannot be corrected. In this case, BiV-endo pacing with the LV lead positioned in the center of the septum is as effective as LBP, indicating that targeting the LB in patients with AV block is not necessary.

HBP restores native synchronous activation

We found that HBP improves ventricular electrical activation, as shown by previous studies.8,10,15,17,28 Similar to our results (Figure 3A), Lustgarten et al14 reported significantly shortened QRSd with selective HBP compared to BiV-epi in patients with prolonged QRSd. However, Lustgarten et al14 also reported similar QRSd with nonselective HBP and BiV-epi pacing. We found nonselective HBP to be inferior to selective HBP but still superior to BiV-epi pacing. Our results are in agreement with those reported by Arnold et al,8 who measured improved LV activation times (LVAT-95 and LV DI) with HBP compared to BiV-epi.
pacing. HBP represents a novel CRT delivery method that can potentially restore the patient’s native activation before the conduction block. However, due to concerns about challenging lead implantation, high pacing thresholds, and lead stability, large cohort studies are needed to assess HBP long-term feasibility and outcomes.

**LBP with optimized AV delay as a valuable alternative to HBP**

LBP is emerging as a less challenging but equivalent alternative to HBP.\(^{15,17}\) Our results show that LBP leads to slow RV activation (Figures 3E and 4). Consistent with our findings, Lin et al\(^{15}\)’s reported increased RV activation times as a consequence of LBP. Furthermore, RBBB ECG morphology has been used to detect the correct implantation of LBP lead by Wang et al.\(^{18}\) indicating that LBP induces RBBB-like activation. We showed that optimized AV delay improves response to LBP and restores ventricular synchrony similar to HBP. Similarly, Lin et al\(^{15}\) reduced RV activation times by optimizing AV delays and achieved similar response with HBP and LBP. Despite some advantages, LBP requires LV endocardial pacing, which can increase the risks of cerebrovascular accidents and embolic events.\(^{19}\) To prevent these events, LBP could necessitate long-term anticoagulation that would need to be offset against any benefits. However, recent developments in leadless endocardial pacing by EBR Systems (Sunnyvale, CA) may provide a lower-risk delivery system.\(^{17}\)

In the presence of complete AV block, response to LBP cannot be improved with AV delay optimization as there are no viable conduction pathways from atria to ventricles. This makes LBP a poor choice for patients receiving pharmacologic block or AV nodal ablation to treat atrial fibrillation (AF) because of its deleterious effects on the RV. This is relevant for the 20%–35% of CRT recipients who suffer from AF,\(^{20}\) in whom the AV node is blocked pharmacologically or through ablation and in congestive HF patients who can receive CRT with AV nodal ablation to treat AF if the preferred option of performing pulmonary vein isolation is unsuccessful or not possible. In patients receiving CRT with or likely to develop AF, HBP may offer a better outcome over conventional CRT, while LBP is to be avoided. LBP with AV delay optimization could be a valuable alternative in some classes of patients but should be delivered with care considering the patient’s AF history. Furthermore, clinical studies investigating the feasibility of AV delay optimization during LBP in patients with no AV block are required.

**BiV-endo septal pacing leads to activation sequence similar to HBP and LBP**

Similarly to HBP and LBP, LV septal pacing aims to restore physiological activation patterns. We found that BiV-endo pacing with a septal LV lead is inferior to BiV-endo at the lateral wall, but the difference in change in QRSd was only 7.1 ms (BiV-endo septal: –17.3 ± 9.3 ms vs BiV-endo lateral: –24.4 ± 8.3 ms). Similarly, Rademakers et al\(^{12}\) showed that BiV-endo pacing with the LV lead at the septum is comparable to BiV-endo pacing with the LV lead at the lateral wall in terms of QRSd shortening. Whereas BiV-endo lateral pacing leads to a nonphysiological wavefront from the LV free wall to the septum, BiV-endo septal pacing leads to physiological activation with the depolarization wave traveling from the septum to the free wall, similarly to HBP and LBP (Figure 5). Although potentially less effective than directly pacing the His-Purkinje system, LV septal pacing is easier to perform than HBP, does not require targeting the LB, and still allows for physiological ventricular activation.

**Study limitations**

Our simulation study provides useful insight into improved response to CRT through HBP and LBP but has some limitations. Our results were based on a cohort of 24 patient-specific anatomic models generated from HF patients and on synthetically defined His-Purkinje networks. Although the network reflects known anatomic structure and recapitulates physiological activation patterns (Online Supplemental Material Sections 2 and 4), it may not reflect the network for a specific patient, and our results should be interpreted with care. Invasive mapping data would facilitate constraining and validating the model, but these data are not recorded routinely in CRT patients. However, in our sensitivity analysis we show that although perturbations in the properties of the His-Purkinje network affect activation times, they do not alter study conclusions.

In our study, we assumed acute LV activation times to be the main determinant of CRT outcome. Although in general CRT clinical outcome is not solely determined by LV activation, improved LV dyssynchrony is an important determinant of CRT response in case of LBBB.\(^{32}\) If LBBB is the only cause of dyssynchrony, then improved LV activation times reflect the extent of restored synchrony between the ventricles. This may not be the case if dyssynchrony was caused by other underlying pathologies, such as presence of myocardial infarction or compromised myocardial contraction.\(^{24}\) In addition, predicting long-term CRT outcomes remains challenging due, in part, to the confounding effects of anatomic remodeling, device failure, and comorbidities. However, patients who do not have a good acute response are unlikely to have the capacity to improve significantly in the long term.\(^{33}\)

**Conclusion**

HBP is superior to BiV-epi and BiV-endo pacing in terms of electrical resynchronization in LBBB patients. Response to LBP is equivalent to HBP if AV delay can be optimized in order to improve RV activation times. With complete AV block, LV activation times but not interventricular dysynchrony improve with LBP. In this case, BiV-endo septal pacing is equivalent to LBP.

**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at https://10.1016/j.hrthm.2020.06.028.
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