Simultaneous His Bundle and Left Ventricular Pacing for Optimal Cardiac Resynchronization Therapy Delivery
Acute Hemodynamic Assessment by Pressure–Volume Loops

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Background—Previous studies have investigated the role of intrinsic conduction in optimizing cardiac resynchronization therapy. We investigated the role of fusing pacing-induced activation and intrinsic conduction in cardiac resynchronization therapy by evaluating the acute hemodynamic effects of simultaneous His-bundle (HIS) and left ventricular (LV) pacing.

Methods and Results—We studied 11 patients with systolic heart failure and left bundle-branch block scheduled for cardiac resynchronization therapy implantation. On implantation, LV pressure–volume data were determined via conductance catheter. Standard leads were placed in the right atrium, at the right ventricular apex, and in a coronary vein. An additional electrode was temporarily positioned in the HIS. The following pacing configurations were systematically assessed: standard biventricular (right ventricular apex+LV), LV-only, HIS, simultaneous HIS and LV (HIS+LV). Each configuration was compared with the AAI mode at multiple atrioventricular delays (AVD). In comparison with the AAI, right ventricular apex+LV and LV-only pacing resulted in improved stroke volume (85±32 mL and 86±33 mL versus 58±23 mL; P<0.001), stroke work, maximum pressure derivative, and systolic dyssynchrony at individually optimized AVD. The optimal AVD was close to the P-H interval in the majority of patients. By contrast, HIS-LV pacing improved hemodynamic indexes at all AVD (stroke volume >76 mL at all fixed intervals and 88±31 mL at optimal interval; all P<0.001).

Conclusions—Standard right ventricular apex+LV and LV-only pacing enhanced systolic function and LV synchrony at individually optimized AVD close to the measured intrinsic P-H interval. By contrast, HIS+LV pacing yielded improvements, regardless of AVD setting. These findings support the hypothesis of the crucial role of intrinsic right ventricular conduction in optimal cardiac resynchronization therapy delivery. (Circ Arrhythm Electrophysiol. 2016;9:e003793. DOI: 10.1161/CIRCEP.115.003793.)

Key Words: CRT ◼ fusion ◼ heart failure ◼ His bundle ◼ pressure volume loop ◼ resynchronization

The beneficial effects of cardiac resynchronization therapy (CRT) have been evaluated in several trials, and different degrees of response to CRT have been reported; indeed, the optimization of pacing sites and stimulation timing seems to be a major determinant of the hemodynamic response.

For standard CRT delivery, the atrioventricular pacing interval is shortened to ensure consistent left ventricular (LV) and right ventricular (RV) capture. However, it has been suggested that in addition to the activation wavefronts generated by RV and LV pacing, the physiological activation propagated through the right bundle branch may be part of the resynchronization mechanism. Moreover, it has been hypothesized that the atrioventricular interval could influence the contribution of intrinsic conduction to total ventricular activation by fusing the intrinsic activation wave with the activation wave originating from pacing sites. The role of pacing-induced activation and intrinsic conduction in CRT optimization has been investigated in previous studies in canine models.

In the present study, we investigated the role of fusing pacing-induced activation and intrinsic conduction in CRT by evaluating the effects of atrioventricular interval modulation and right ventricular electrode positioning on LV function. To study these effects, we evaluated the acute hemodynamic effects of simultaneous His bundle (HIS) and LV pacing for CRT delivery in heart failure patients by analyzing LV pressure–volume relationships.

Methods

Patient Selection and Procedure
We enrolled 12 consecutive heart failure patients with indications for CRT. The Institutional Review Board approved the protocol,
WHAT IS KNOWN

- Different degrees of response to cardiac resynchronization therapy (CRT) have been reported, and the optimization of pacing sites and stimulation timing seems to be a major determinant of the hemodynamic response.
- In addition to the activation wavefronts generated by right ventricular and left ventricular pacing, the physiological activation propagated through the right bundle-branch may be part of the resynchronization mechanism.
- The atrioventricular interval could influence the contribution of intrinsic conduction to total ventricular activation by fusing the intrinsic activation wave with the activation wave originating from pacing sites.

WHAT THE STUDY ADDS

- During standard biventricular pacing (right ventricular apex+left ventricle) and left ventricular-only pacing, the optimal systolic function was obtained with atrioventricular intervals close to the measured intrinsic P-H interval, due to the contribution from intrinsic right ventricular conduction.
- The simultaneous stimulation of the His bundle and the left ventricle yielded results comparable to those obtained with individually optimized standard biventricular and left ventricular-only pacing, regardless of the atrioventricular interval setting.
- These findings support the hypothesis of the crucial role of intrinsic right ventricular conduction for optimal CRT delivery.

Pacing Protocol

Hemodynamic status was evaluated under steady state conditions after a minimum of 2 minutes of stabilization in each pacing configuration. Stimulation was delivered by means of an external stimulator (Analyzer model 2290; Medtronic, Minneapolis, MN). To obtain simultaneous biventricular pacing, a splitter was used to join the RVA lead or the temporary lead in the HIS to the coronary sinus lead. All pacing interventions were tested at a fixed rate of 10 beats per minute higher than the sinus heart rate, and the baseline values were recorded during continuous atrial overdrive pacing with spontaneous ventricular activation (AAI mode). We tested the following pacing configurations: standard biventricular pacing (RVA+LV), LV-only pacing, HIS, and simultaneous HIS and LV pacing (HIS+LV). The sequence of pacing configurations and atrioventricular intervals was randomly assigned. The pacing configurations (DDD mode) were assessed at multiple atrioventricular intervals. For HIS and HIS+LV configurations, the longest time interval was programmed at 10 ms shorter than the measured intrinsic P-H interval. The remaining atrioventricular intervals were programmed at 66% and 33% of this value. For RVA+LV and LV-only configurations, the interval was also programmed at 10 ms shorter than the measured P-Q interval.

At the end of the pacing protocol, the temporary catheter was removed and a biventricular cardioverter-defibrillator was implanted.

Data Analysis

Each configuration was compared with the AAI mode at multiple atrioventricular intervals. In all patients, the atrioventricular interval that elicited the best hemodynamic response was identified for each configuration tested, and the hemodynamic response at the optimal atrioventricular interval setting was measured. The criterion used to identify the optimal pacing configuration in each patient was the maximization of stroke volume.

Several indexes of LV performance (LV end-systolic and end-diastolic pressure, maximum and minimum LV pressure derivative, LV end-diastolic volume, stroke volume, stroke work, and the time constant of isovolumetric relaxation) were calculated and averaged over 8 to 10 beats at end expiration from the raw LV pressure and conductance volume data by means of commercially available software (Conduct NT, Leycom). End diastole was identified immediately before the isovolumetric increase in the LV pressure derivative, and end systole was defined as the maximum ratio of LV pressure to volume. Nonuniform LV performance was determined from the segmental LV conductance signals and quantified by calculating the percentage of time within the cardiac cycle that a specific segment was dysynchronous (ie, opposite in phase to the global LV volume signal). Overall, LV mechanical dyssynchrony was determined as the mean of the segmental dyssynchronies within each specified time interval: during systole and diastole.

Data are expressed as means±standard deviation. One-way analysis of variance for repeated measures was used to test for differences in hemodynamic data obtained during pacing with different configurations and atrioventricular delays. A Student–Neuman–Keuls test was used for post hoc comparisons. A P value <0.05 was considered significant for all tests. All statistical analyses were performed by means of SPSS software (SPSS Inc, Chicago, IL).

Results

One patient was excluded from the analysis because the pressure-volume catheter could not be properly placed in the LV cavity. Demographic data of the 11 patients included in the analysis are listed in Table 1. All patients were presented with systolic heart failure and left bundle-branch block (QRS duration 151±19 ms; PQ interval 204±35 ms) and met the criteria for CRT. Four patients had documented coronary artery disease. The temporary electrode was positioned in the HIS, and its location was confirmed in all patients. In no cases HIS pacing resulted in narrower QRS compared with native conduction. No
changes in hemodynamics were observed during His stimulation at different atrioventricular intervals on AAI pacing (Figure 1 and Table 2). In the 11 patients included in the analysis, all biventricular pacing conditions were successfully assessed.

In comparison with the AAI mode, the RVA+LV and LV-only configurations resulted in improved stroke volume, stroke work, and maximum pressure derivative at intermediate atrioventricular intervals, that is, 66% (PH-10 ms) and PH-10 ms (Figure 2, analysis of variance followed by pairwise comparisons). A shorter atrioventricular interval, that is, 33% (PH-10 ms) seemed to produce less hemodynamic benefit and proved to be the optimal interval only in 2 patients on RVA+LV and 1 patient on LV-only pacing. Similarly, a longer interval (PQ-10 ms) resulted in optimal response only in 1 patient on LV-only pacing. The optimal atrioventricular interval was 140±83 ms on RVA+LV pacing and 152±43 ms on LV-only pacing. At individual optimal intervals, the mean QRS duration was 133±20 ms on RVA+LV pacing and 125±18 ms on LV-only pacing (both P<0.05 versus AAI). The hemodynamic benefit of RVA+LV and LV-only pacing at individually tailored optimal intervals was significantly higher than that obtained with fixed short or long atrioventricular intervals (Figure 2, analysis of variance followed by pairwise comparisons). By contrast, HIS-LV pacing improved hemodynamic indexes at all atrioventricular intervals, the optimal interval being 132±36 ms and the QRS duration 127±17 ms (P<0.05 versus AAI). Diastolic function, as expressed by the minimum pressure derivative, improved at the majority of

Table 1. Demographics and Baseline Clinical Parameters

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Pathogenesis</th>
<th>NYHA Class</th>
<th>LV Ejection Fraction, %</th>
<th>PQ Interval, ms</th>
<th>QRS Duration, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>70</td>
<td>CAD</td>
<td>II</td>
<td>20</td>
<td>240</td>
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<td>2</td>
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<td>DC</td>
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<tr>
<td>3</td>
<td>M</td>
<td>82</td>
<td>CAD</td>
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<td>4</td>
<td>F</td>
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<td>DC</td>
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<td>30</td>
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<tr>
<td>5</td>
<td>M</td>
<td>75</td>
<td>DC</td>
<td>II</td>
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<tr>
<td>6</td>
<td>M</td>
<td>66</td>
<td>DC</td>
<td>II</td>
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<tr>
<td>7</td>
<td>F</td>
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<td>DC</td>
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<tr>
<td>8</td>
<td>M</td>
<td>75</td>
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<td>23</td>
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<td>9</td>
<td>F</td>
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<td>DC</td>
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<tr>
<td>11</td>
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<td>55</td>
<td>CAD</td>
<td>III</td>
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<td>140</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; DC, dilated cardiomyopathy; F, female; LV, left ventricle; M, male; and NYHA, New York Heart Association.
atrioventricular intervals in all pacing configurations, whereas systolic and diastolic indexes of dyssynchrony improved only at intermediate intervals on RVA+LV and LV-only pacing and at all intervals on HIS-LV pacing (Table 3, analysis of variance followed by pairwise comparisons). Figure 3 shows representative pressure–volume loops obtained in one patient undergoing CRT with the tested pacing configurations at optimal atrioventricular intervals.

**Discussion**

In the present study on heart failure patients with left bundle-branch block, analysis of pressure–volume loops revealed that CRT significantly enhanced systolic function and LV synchrony, irrespective of the pacing configuration (ie, standard RVA+LV, LV-only, and simultaneous HIS+LV pacing). During standard RVA+LV and LV-only pacing, the optimal systolic function was obtained with atrioventricular intervals close to the measured intrinsic P-H interval, perhaps because such intervals allow a contribution from the intrinsic right ventricular conduction. By contrast, the original simultaneous HIS+LV pacing yielded results comparable to those obtained with individually optimized RVA+LV and LV-only pacing, regardless of the atrioventricular interval setting.

It has previously been hypothesized that during standard CRT, the activation wavefront generated by the LV lead could variably interact with those generated by the intrinsic conduction and the right ventricular lead. A previous animal study showed that in hearts with left bundle-branch block, the activation front generated by the right ventricular lead dominates and fully collides with the one generated by the LV lead at short atrioventricular intervals. By contrast, at longer intervals, the intrinsic conduction emerges and contributes to resynchronization. The present human study confirmed those findings. Indeed, unlike RVA pacing, HIS pacing does not deliver an additional electric wavefront to the right ventricle, but takes advantage of the right bundle branch, which is preserved in patients with left bundle-branch block, and enables fusion between the LV-pacing–induced wavefront and intrinsic conduction, irrespective of the atrioventricular interval setting.

Strik et al elegantly investigated the interplay of electric wavefronts as a possible determinant of the response to CRT by adopting a canine model of complete atrioventricular block. Indeed, in hearts with complete atrioventricular block, resynchronization can only result from biventricular pacing because activation via the right bundle branch is nonexistent. In their model, the best hemodynamic response was achieved at a fixed interventricular interval over a wide range of atrioventricular intervals. The simultaneous HIS+LV pacing that we tested in the present study reproduced that model in humans because it allowed us to modulate the atrioventricular interval (within the limits of the spontaneous P-H interval to ensure consistent His capture) without changing the degree of electric and mechanical resynchronization. Moreover, our results confirmed that the optimal acute hemodynamic response during CRT is achieved in association with mechanical resynchronization, whereas changes in ventricular filling do not seem to play a role. Indeed, in agreement with previous results, we observed no notable changes in LV end-diastolic volume over the range of atrioventricular intervals tested.

During LV-only pacing, short atrioventricular intervals were not associated with optimal hemodynamic response. It has previously been shown that on LV-only pacing, the typical left bundle-branch block activation pattern is reversed, with latest activation of the right ventricular free wall, but with increased total activation time. Similarly, at long atrioventricular intervals (close to the P-Q interval), standard RVA+LV and LV-only pacing yielded suboptimal results. In both configurations, an intrinsic activation wave originates from the right bundle branch and collides with a lately initiated LV activation wavefront. In this case, the typical left bundle-branch block pattern is known to persist, with the most delayed activation in the LV-free wall.

In our population, the extent of the additional improvement after interval optimization on RVA+LV and LV-only pacing was considerable, in agreement with published clinical data. However, the optimal atrioventricular interval showed considerable individual variation, thus suggesting the need for individual (and possibly time-consuming) optimization.
Various techniques have been proposed for the optimization of CRT, some guided by echo-derived indexes of LV filling or systolic function\textsuperscript{16} and others by device-based algorithms.\textsuperscript{17,18} In particular, an algorithm has been developed to synchronize LV pacing with the intrinsic activation.\textsuperscript{18} To achieve this, the device periodically measures the delay between atrial- and
RV-A sensed signals and provides LV pacing that preempts intrinsic conduction by imposing an empirically determined interval of \(\approx 40\) ms.\(^{19}\) Indeed, as confirmed by our tests with atrioventricular delays close to the P-Q interval, stimulation delivered simultaneously with the RV-A sensed signal would not result in effective resynchronization. Nonetheless, our results suggest that optimal results can be obtained in the majority of patients by positioning a pacing lead at the HIS. This would enable His-synchronized LV pacing by means of a triggered pacing mode or equally effective simultaneous HIS+LV pacing at any atrioventricular interval.

These acute results should be confirmed in the medium and long terms, and of course, the benefits of this approach should be weighed against the higher complexity of the procedure. Indeed, although the success rate of HIS pacing has improved in recent years, the methodology still remains more complex than standard RV-A lead placement.\(^{20}\) Interestingly, preliminary observations have suggested that HIS pacing may be useful and may yield significant narrowing of the QRS complex in some patients requiring CRT if the site of an intra-Hisian lesion responsible for left bundle-branch block is above the pacing site.\(^{21}\) However, in these cases, the relative, and possibly additive, effect of His and LV pacing would require specific assessment. In a previous study, we directly compared the changes in LV function associated with pacing from the HIS and the LV in a population of patients with no indications for CRT, using pressure–volume plane analysis.\(^{22}\) Our results suggested that, despite retaining the intrinsic QRS duration, direct His pacing resulted in decreased stroke work and stroke volume in comparison with AAI and LV pacing. The present results, obtained in patients with heart failure and CRT indications, confirmed that LV pacing is superior to His pacing, but no differences emerged between HIS pacing and AAI pacing.

Previous results on direct HIS pacing in patients with dilated cardiomyopathy have also been reported by Deshmukh et al.\(^{5}\) In a subset of patients with chronic atrial fibrillation,
they recorded a reduction in LV dimensions and an improvement in cardiac function over long-term follow-up.

Actually, the possible application of simultaneous HIS+LV pacing in patients with atrial fibrillation and CRT indications is particularly intriguing. Indeed, in this setting, positioning a pacing lead at the HIS could enable HIS+LV pacing in the presence of slowly conducted atrial beats without impairing the rate-stabilizing effect of pacing\(^2\) and optimal LV-only pacing in the case of rapidly conducted beats. However, this would also require direct verification.

**Limitations**

The present results should be interpreted within the constraints of the study limitations. In particular, the number of patients included in the present study was small, and we did not assess CRT effects beyond acute hemodynamic response. Moreover, although QRS duration during His pacing was similar in both morphology and duration to atrial pacing, we cannot exclude local right ventricular capture, which typically occurs during HIS pacing. Finally, we tested only a limited number of atrioventricular intervals and only simultaneous biventricular pacing.

**Conclusions**

In heart failure patients with left bundle-branch block, standard RVA+LV and LV-only pacing significantly enhanced systolic function and LV synchrony at individually optimized atrioventricular intervals close to the measured intrinsic P-H interval. By contrast, the original simultaneous HIS+LV pac ing yielded improvements, regardless of the atrioventricular interval setting. These findings support the hypothesis of the crucial role of intrinsic right ventricular conduction for optimal CRT delivery.

**Disclosures**

F. Picariello and Dr Valsecchi are employees of Boston Scientific, Inc. The other authors report no conflicts.

**References**


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