Biventricular Pacing With Ventricular Fusion by Intrinsic Activation in Cardiac Resynchronization Therapy

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Summary

We sought to evaluate the impact of biventricular (BiV) pacing with ventricular fusion by intrinsic atrioventricular nodal (AVN) conduction (BiV + intrinsic pacing) on clinical outcomes in patients with chronic heart failure (CHF) receiving cardiac resynchronization therapy (CRT).

A total of 44 patients were randomized to receive either BiV or BiV + intrinsic pacing for one month. Echocardiographic optimization was performed for the BiV pacing mode, while the BiV + intrinsic pacing mode was achieved by titrating AV delay under electrocardiography (ECG) monitoring. Symptoms, quality of life, ECG, echocardiography, and cardiovascular events were recorded at baseline and the end of the follow-up for each pacing mode.

Patients undergoing BiV + intrinsic pacing mode had shorter QRS duration compared to those with conventional BiV pacing (118.4 ± 21.6 ms versus 146.4 ± 5.3 ms, \( P < 0.0001 \)). Also, these patients had improved echocardiographic left ventricular fractional shortening (LVFS) (17.4 ± 5.9 versus 15.7 ± 4.9, \( P = 0.019 \)), higher left ventricular ejection fraction (LVEF) (35.5 ± 9.7 versus 32.7 ± 9.7, \( P = 0.048 \)), longer 6-minute walk test (6MWT) (372.5 ± 80.9 m versus 328.7 ± 108.9 m, \( P = 0.0001 \)), and better Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores (12.5 ± 6.6 versus 18.2 ± 12.3, \( P = 0.0001 \)).

Treating CHF patients with BiV+intrinsic pacing resulted in improved cardiac function and quality of life. BiV + intrinsic pacing can be used in CHF patients with sinus rhythm and normal AV nodal conduction to improve CRT efficacy. (Int Heart J 2015; 56: 000-000)

Key words: Intrinsic conduction, Heart failure, Electrocardiography, Echocardiography

Congestive heart failure (CHF) is a major public health problem associated with high mortality and morbidity. Common causes of CHF include, but are not limited to ischemic heart disease, hypertension, arrhythmias, valvular diseases, cardiomyopathies, and congenital heart diseases. Cardiac resynchronization therapy (CRT), also known as biventricular pacing (BiV) or multisite ventricular pacing, simultaneously paces the right ventricle and the left ventricle. Large randomized clinical trials have shown that CRT improves symptoms, cardiac functions, and survival in patients with heart failure who have electrical dyssynchrony. CRT has been recommended by the American Heart Association (AHA) guidelines for patients with recurrent symptoms of systolic heart failure and a wide QRS complex, despite being on optimal medical therapy.

CRT allows for more efficient blood ejection by reducing mechanical inefficiency from dyssynchronous contraction. However, there is a wide spectrum of clinical responses to CRT and one third of the patients who are selected for CRT fail to demonstrate any benefit from it. Therefore, the current clinical focus in CRT is to maximize the benefit from this therapy.

A physiological approach to pacing is important for patients with CHF. It can be achieved by a number of methods including CRT, rate adaptation, sinus node preference pacing, and pacing in the right ventricular outflow tract. With respect to the CRT procedure, current recommendations in AHA guidelines emphasize that both left and right ventricles should be totally captured by a CRT device. However, the CRT pacing mode shortens the AVN. In addition, the activations from the leads in the right ventricular apex and coronary sinus are different from the physiological activations propagating through the AVN. These conduction variations make CRT challenging for pacing patients with CHF.

The lack of a physiological excitation process in myocardium in patients with CHF can compromise CRT efficacy, even if the AV conduction is functional in these patients. Several studies have been conducted to explore the feasibility of preserving normal AV nodal conduction by pacing the left ventricle (LV) only or appropriately setting atrioventricular de-
lay (AVd) to obtain ventricular fusion in every beat in patients with sinus rhythm and normal AV nodal conduction in CRT.\textsuperscript{11-15} For example, Vatasescu, \textit{et al} observed a better CRT responder rate by BiV pacing with fusion than by conventional BiV pacing.\textsuperscript{15}

In the present study, we evaluated the impact of biventricular pacing with ventricular fusion by intrinsic AV nodal conduction (BiV + intrinsic) on cardiac function, exercise capacity, quality of life, and electrocardiographic and echocardiographic features in patients with CHF who received CRT.

**METHODS**

**Population:** Forty-four patients with CHF, (34 males and 10 females, with a mean age of 62.1 ± 9.0 years,) were recruited from January 2008 to December 2009 at the First Affiliated Hospital of Kunming Medical College and The First Kunming People’s Hospital. Inclusion criteria were: 1) New York Heart Association (NYHA) category III/IV on optimal medical therapy; 2) sinus rhythm with intrinsic AV conduction; 3) QRS duration > 120 ms; and 4) left ventricular ejection fraction (LVEF) < 35%. Among these 44 patients, 25 (56.8%) were diagnosed with dilated cardiomyopathy and 19 (43.2%) with ischemic heart diseases (IHD); and 12 (27.3%) were in NYHA class IV, 13 (29.5%) had mild to moderate aortic valve regurgitation (AR), and 29 (65.9%) had mild mitral valve regurgitation (MR). Of the 44 inserted devices in CRT, 23 (52.3%) were pacemaker function (CRT-P) and 21 (47.7%) were defibrillator function (CRT-D) (St Jude, Medical, Saint Paul, MN, USA; Medtronic, Inc, Fridley, MN, USA).

The present study was approved by the hospital IRB committee and complied with the Declaration of Helsinki. Consent forms were obtained from all patients for CRT implantation and study participation.

**CRT programming:**

**Conventional BiV pacing** The conventional BiV pacing optimization was achieved by using Doppler echocardiography. The optimal variables for BiV pacing were selected when the maximal velocity-time integral (VTI) of the LV outflow tract and aorta (LV VTI) was achieved. After being programmed in the range during which both ventricles were totally captured, VV delay was first optimized at 7 different V-V intervals (from LV before RV by 60 ms to RV before LV by 60 ms, in steps 20 ms apart). Once the V-V interval giving rise to the maximal VTI was determined, the A-V interval optimization was performed by altering AV timing during the intrinsic sinus rhythm. The AV timing was shortened at a step of 20 ms from the intrinsic AV interval. The optimal AV delay (AVd) was selected when the new maximal VTI was reached. The optimized BiV pacing parameters were then used in the follow-ups.

**BiV + intrinsic pacing** A 12-lead electrocardiogram (ECG) was recorded at a paper speed of 50 mm/s, and QRS duration in ms was measured in the lead with the largest QRS width. To program BiV + intrinsic, the optimal V-V delay was first determined by identifying the V-V interval with the narrowest QRS width. Next, the AV interval was titrated under ECG monitoring in steps of 10 ms in sinus rhythm, until the ventricles were activated by both BiV and AVN propagation, indicated by a “fusion” QRS wave on ECG. After this programming, the ventricles were activated by sinus activation from the AVN and electrical pulses from both ventricular leads resulted in the narrowest QRS waveform (Figure). This pacing mode for the patient was then set as BiV + intrinsic pacing. Echocardiographic monitoring was performed after the programming for the BiV + intrinsic pacing.

**Follow-up** All 44 patients were randomized to one of the two groups for CRT for 1 month: the BiV group or the BiV + intrinsic group, followed by group switch by device programming for another month. The patients were assessed preoperatively and 1 month after each pacing mode. At the end of each follow-up, the patients were kept in the programming with the narrowest QRS waveform.

**Outcome assessment:**

**ECG** Resting 12-lead ECG was performed to measure QRS duration in each lead during sinus rhythm, BiV pacing, and BiV pacing with ventricular fusion by intrinsic AVN conduction (fusion), respectively. The largest QRS duration out of 12 leads was chosen for comparison and CRT optimization.

**Echocardiography** Echocardiography after establishing a 15-minute resting condition was conducted to assess the following parameters: aortic valvular insufficiency (AVI), mitral valvular insufficiency (MVI), left ventricular filling time (LVFT), interventricular mechanical delay (IVMD), the standard deviation of Ts of 12 left ventricular segments in ejection phase (TS-SD12), left atrial dimension (LA), right atrial dimension (RA), velocity-time integral (VTI), left ventricular end-diastolic dimension (LVEDd), abnormality of the interventricular septum (IVS), left ventricular fractional shortening (LVFS), left ventricular ejection fraction (LVEF), and severity of mitral valve regurgitation (MR) and aortic valve regurgitation (AR). Echocardiography was performed preoperatively as baseline and at the end of each follow-up.

**Clinical assessment** Symptom severity was assessed using a

![Figure](https://example.com/figure.png)

**Figure.** QRSd changes during the BiV pacing mode and the BiV + intrinsic pacing mode in a female patient, 55 years old, with dilated cardiomyopathy, sinus rhythm, LBBB, NYHA III, LVEDd dimension 67 mm, and LVEF 19%. A: Before CRT, sinus rhythm, PR duration 210 ms, LBBB, QRS duration 180 ms. B: BiV pacing after CRT-D insertion, LV > RV 20 ms and 110 ms device AV delay, RBBB, QRS duration 160 ms, 100% captured by CRT. C: BiV + intrinsic pacing, 100% ventricular fusion, LV > RV 20 ms and 150 ms device AV delay, QRS duration 120 ms.
6-minute walk test (6MWT), Minnesota Living with Heart Failure questionnaire (MLHFQ), and NYHA classification. Adverse events, rehospitalization for heart failure, and death were also recorded.

Statistics: Continuous variables are presented as the mean ± standard deviation (SD). SPSS11.5 (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. Comparisons between two pacing modes were performed using the paired t test for quantitative variables and chi-square test for binary variables. A two-tailed P value < 0.05 was considered significant.

RESULTS

All 44 patients received optimal medical therapy including angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARB), β-blockers, aldosterone antagonists, diuretics, and digoxis when necessary. There was no significant difference in medication between the two pacing groups. Twenty-three CRT-Ps and 21 CRT-Ds were successfully implanted. Two patients experienced single ventricular tachycardia and fibrillation at 10 and 12 months after CRT, and these two arrhythmias were successfully converted by ATP and shock, respectively. There was no death or rehospitalization due to CHF deterioration within 12 months post implant. The time required for optimization of programming in CRT was significantly shorter for the BiV + intrinsic pacing (26.23 ± 10.51 minutes) than that for the conventional BiV pacing (112.39 ± 25.28 minutes, P < 0.001).

ECG and echocardiographic features during different pacing modes: AV delay was longer for the BiV + intrinsic mode (164 ± 36 ms) than that for the BiV pacing (128 ± 29 ms, P < 0.001). QRS duration was shorter during the BiV + intrinsic pacing (118.35 ± 21.59 ms) than during the standard BiV pacing (164 ± 36 ms) than that for the BiV + intrinsic pacing (128 ± 29 ms, P < 0.001). However, no difference was observed between QRS duration during the conventional BiV pacing and that of baseline (P = NS).

With respect to the echocardiographic measurements (Table), LVFT was longer when the BiV+intrinsic pacing (0.49 ± 0.08 ms) was programmed compared to that at the baseline (0.43 ± 0.07, P = 0.001). In addition, compared with the conventional BiV pacing group (Table), the BiV + intrinsic pacing showed significantly larger LVFS (17.41 ± 5.9 versus 15.66 ± 4.90, P = 0.019), greater LVEF (35.50 ± 9.72 versus 32.68 ± 9.74, P = 0.048), and a wider peak aortic valve velocity-time integral (115.00 ± 20.93 m/s versus 106.80 ± 20.87 m/s, P = 0.002). However, there were no significant differences in other echocardiographic parameters between the two pacing modes at the comparable follow-up time point (Table).

Clinical assessments following CRT: Following CRT, either in the conventional BiV or the BiV + intrinsic pacing mode, the patients all experienced significant clinical improvement in values of NYHA classification, 6MWT, and MLHFQ, compared to those baseline levels (Table). The BiV + intrinsic pacing mode demonstrated superior clinical improvement compared to the conventional BiV pacing mode, in terms of parameters of NYHA classification (1.82 versus 1.98, P = 0.008), 6MWD (372.51 ± 80.88 m versus 328.66 ± 108.89 m, P = 0.0001) and MLHFQ scores (12.48 ± 6.56 versus 18.16 ± 12.25, P = 0.0001). These data indicated that BiV + intrinsic pacing offered greater clinical benefits for the patients than did the conventional BiV pacing.

DISCUSSION

CRT is often used to restore synchrony of the left ventricle in patients with dilated cardiomyopathy and a widened QRS by placing a coronary sinus lead for LV pacing, plus a conventional right ventricular endocardial lead.23,16 The present study demonstrated that biventricular pacing with ventricular fusion by intrinsic AV nodal conduction is a simple.

Table. Echocardiographic Measurements and Clinical Evaluation Before and After CRT

<table>
<thead>
<tr>
<th></th>
<th>Baseline (before CRT)</th>
<th>BiV + intrinsic</th>
<th>BiV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVI (cm)</td>
<td>17.25 ± 4.51</td>
<td>19.79 ± 5.43</td>
<td>19.91 ± 5.53</td>
<td>0.830</td>
</tr>
<tr>
<td>MVI (cm)</td>
<td>16.91 ± 4.25</td>
<td>17.28 ± 4.05</td>
<td>17.36 ± 4.60</td>
<td>0.940</td>
</tr>
<tr>
<td>LVFT (cm/s)</td>
<td>0.43 ± 0.10</td>
<td>0.49 ± 0.08</td>
<td>0.44 ± 0.08</td>
<td>0.092</td>
</tr>
<tr>
<td>TVs-SD12 (cm/s)</td>
<td>62.33 ± 25.23</td>
<td>47.95 ± 25.18</td>
<td>58.35 ± 43.60</td>
<td>0.231</td>
</tr>
<tr>
<td>LVFS (%)</td>
<td>34.20 ± 28.72</td>
<td>32.00 ± 26.65</td>
<td>30.85 ± 22.50</td>
<td>0.681</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>14.91 ± 3.27</td>
<td>17.41 ± 5.97</td>
<td>15.66 ± 4.90</td>
<td>0.019</td>
</tr>
<tr>
<td>VTI (m/s)</td>
<td>30.66 ± 6.17</td>
<td>35.93 ± 9.72</td>
<td>32.68 ± 9.74</td>
<td>0.048</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>116.48 ± 23.50</td>
<td>115.00 ± 20.93</td>
<td>106.80 ± 20.87</td>
<td>0.002</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>40.73 ± 6.70</td>
<td>39.15 ± 6.33</td>
<td>40.18 ± 6.92</td>
<td>0.159</td>
</tr>
<tr>
<td>RA (mm)</td>
<td>36.01 ± 6.37</td>
<td>36.80 ± 4.99</td>
<td>37.14 ± 5.30</td>
<td>0.610</td>
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<tr>
<td>MR (n)</td>
<td>29</td>
<td>33</td>
<td>33</td>
<td>0.317</td>
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<tr>
<td>AR (n)</td>
<td>13</td>
<td>16</td>
<td>16</td>
<td>0.564</td>
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<tr>
<td>NYHA class</td>
<td>2,3,16</td>
<td>2,3,16</td>
<td>2,3,16</td>
<td>0.524</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>192.20 ± 133.19</td>
<td>372.51 ± 80.88</td>
<td>328.66 ± 108.89</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MLHFQ (score)</td>
<td>43.07 ± 18.13</td>
<td>12.48 ± 6.56</td>
<td>18.16 ± 12.25</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Comparison between BiV + intrinsic and BiV only, *Comparison with baseline, P < 0.05. AVI indicates aortic valve dysasia; MVI, mitral valve insufficiency; LVFT, left ventricular filling time; IVMD, left ventricular mechanical delay; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameters; LA, left atrium; RA, right atrium; MR, mitral regurgitation; AR, atrial regurgitation; 6MWT, 6 minute walk test; VTI, aortic velocity-time integral; and MLHFQ, Minnesota Living with Heart Failure questionnaire.
safe, and less time-consuming way for CRT optimization. This BiV + intrinsic mode could be performed conveniently under 12-lead ECG monitoring to obtain a narrower QRS waveform, while conventional biventricular pacing requires echocardiography for optimization. More importantly, the BiV + intrinsic mode provided better clinical outcomes, as exemplified by improvements in 6MWT, MLHFQ score, NYHA classification, and echocardiographic parameters. No cardiac re-hospitalization or mortality was observed one year post device implant, indicating the general safety of this therapy. In the published guidelines of device implantation, CRT is recommended for systolic heart failure patients with wide QRS and sinus rhythm (class IA), which potentially provides an opportunity for biventricular pacing with ventricular fusion via intrinsic AV nodal conduction.

The mechanisms underlying the improved clinical outcomes by BiV + intrinsic pacing may be explained by the involvement of multiple-site activations that enhance ventricular synchronization and cardiac contraction. For instance, in the BiV + intrinsic programming, the ventricles can be activated from 3 sites: 2 ventricular pacing sites localized in the left and right ventricles and the AVN (the sinus activation through AVN). Leclercq, et al and Yoshida, et al have reported that multi-site pacing demonstrates superior reverse remodeling of the left ventricle, together with increased LV dp/dt and cardiac output. Consistent with our findings in the present study, Vatasescu, et al showed a shorter LV activation time and a better CRT responder rate during bi-ventricular pacing with fusion, when compared to the results with conventional CRT. In addition, van Gelder, et al found that LV pacing with fusion produces a significantly higher acute hemodynamic response than does bi-ventricular pacing. Taken together, we believe that the BiV + intrinsic pacing mode allows multi-site activations and therefore reduces ventricular activation time (narrower QRS duration) and dysynchronization, resulting in better cardiac function. In this study, the optimal AV delay was determined by identifying the AV interval with the narrowest QRS width in the BiV + intrinsic pacing group, which was performed by ECG but not echocardiography. Chirife, et al showed that inter-atrial and inter-ventricular electromechanical delays can be determined by P-wave and QRS durations, indicating that AV delay optimization in CRT could be predicted by ECG with no need for echocardiography, which supported our study findings.

The AVN preference pacing is considered as a more physiological pacing mode. Deshmukh, et al performed direct His-bundle pacing in 14 patients with dilated cardiomyopathy, and found prominent echocardiographic improvement in heart function. Fröhlig recommended His-bundle pacing instead of LV pacing for avoiding right ventricular apical pacing. Moreover, the AVN preference mode helps to obtain the narrowest QRS. It has been found that shortening of the QRS duration after CRT correlates with the improvement of LVEF and benefits the patients. In the present study, BiV + intrinsic pacing provided physiological activation through both His-bundle and BiV pacing, and hence further improved cardiac function. This is evidenced by the fact that short QRS duration could be achieved by activations from the AVN and appropriate AV timing for BiV pacing (eg, BiV + intrinsic pacing). This ventricular resynchronization could help to rebuild centric contraction of the ventricles.

Cardiac dyssynchrony is usually caused by conduction deficiency in the left/right bundle branches and Purkinje fibers, but not in the AV node or His bundle. In the conventional CRT pacing mode, AV delay is set to a relatively small value to ensure the ventricles are totally captured by the pacemaker. However, this mode shorts the AVN and leads to delayed activation of the septum near the His-bundle. Thus, in patients with an unchanged or even wider QRS waveform after CRT, efforts to diminish the regional dyssynchrony and widen QRS are necessary. Theoretically, the BiV + intrinsic programming integrates activations from the pacemaker and sinus node, thus minimizing the possible dysynchrony caused by apical pacing in the right ventricle for maximized clinical benefit.

Limitations: There are several limitations in the present study. First, it had a small sample size with a limited follow-up interval. A long-term follow-up would confirm the duration of clinical benefits observed in this study. Second, the current CRT program does not allow automatic adjustment of the AV delay with a simultaneous change of P waveform and PR duration, especially when varied heart rate and physiological conditions may lead to “pseudo-fusion” or ventricular activation without pacing. Third, the BiV + intrinsic programming will not resolve a CRT non-response due to ischemia, scar, absence of target veins, or malposition of the LV lead. Based on our experience, the selection of patients is very important for ensuring the clinical benefits with the BiV + intrinsic programming, i.e., it is only suitable for those with sinus rhythm and normal AV nodal conduction.

Conclusion: The conventional CRT pacing mode does not promote the distribution of ventricular excitation through activation of the AV node and His bundle. This method may result in wider QRS width and shorter AV delay. In contrast, the BiV + intrinsic pacing mode not only simplifies CRT optimization, but also provides superior clinical benefits, such as improvement in cardiac function as well as quality of life in patients with CHF. If patients who selected for CRT do not respond well, if they have sinus rhythm and normal AV nodal conduction, optimization of CRT with BiV + intrinsic programming should be considered for maximal therapy efficacy.

Disclosure

Conflict of interest: We have no conflict of interest to declare.

References

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-847.
3. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Associa-
tion (HFA) of the ESC. Eur J Heart Fail 2012; 14: 803-69.