Risk Stratification of Future Left Ventricular Dysfunction for Patients with Indications for Right Ventricular Pacing due to Bradycardia

Junichi Ooka, MD, Hidekazu Tanaka, MD, Yutaka Hatani, MD, Keiko Hatazawa, MD, Hiroki Matsuoe, MD, Hiroyuki Shimoura, MD, Hiroyuki Sano, MD, Takuma Sawah, MD, Yoshiki Motoji, MD, Yasuhide Mochizuki, MD, Keiko Ryo-Koriyama, MD, Kensuke Matsumoto, MD, Koji Fukuzawa, MD and Ken-ichi Hirata, MD

Summary

Although right ventricular (RV) pacing is the only effective treatment for patients with symptomatic bradycardia, it creates left ventricular (LV) dyssynchrony, which can induce LV dysfunction and heart failure. The current criterion for consideration of cardiac resynchronization therapy (CRT) is LV ejection fraction (LVEF) ≤ 35%, but indication for CRT in patients required for RV pacing with LVEF > 35% remains unclear.

We studied 40 patients, all LVEF ≥ 35%, who had undergone implantable cardioverter-defibrillator implantation with RV pacing < 5%. Echocardiography was performed at baseline and during RV pacing. LV dyssynchrony was defined as anteroseptal-to-posterior wall delay from the mid-LV short-axis view using two-dimensional speckle-tracking radial strain (significant: ≥ 130 ms). Patients were divided into two groups based on baseline LVEF; normal LVEF (≥ 50%; n = 20) and mildly reduced LVEF (35-50%; n = 20).

LVEF and LV dyssynchrony in patients with mildly reduced LVEF deteriorated significantly during RV pacing compared to those in patients with normal LVEF. Moreover, changes in LV dyssynchrony during RV pacing significantly correlated with changes in LVEF (r = -0.44, P < 0.01). Multivariate logistic regression analysis showed that baseline LVEF was the only independent predictor and baseline LVEF < 48% predictive of significant LV dyssynchrony during RV pacing.

The extent of RV pacing-induced LV dysfunction may be associated with baseline LV function. These adverse effects on patients with mildly reduced LVEF of 35-50% and indications for RV pacing due to bradycardia can thus be prevented by CRT.

(Key words: Echocardiography, Right ventricular pacing, Heart failure, Left ventricular function, Dyssynchrony)

Methods

Study population: For this study, 54 consecutive patients with LVEF ≥ 35% who underwent ICD implantation at Kobe University Hospital between August 2005 and July 2015 were prospectively analyzed. The RV lead in all patients was positioned at the RV apex through a transvenous route. Excluded were patients with one or more of the following: 1) chronic RV pacing ≥ 5% determined during device interrogation at the time of enrollment; 2) coronary artery disease, defined as a single coronary artery stenosis of > 50% of the diameter of a major epicar-
Left ventricular dyssynchrony is shown as the interval (white arrow) between the time-to-peak speckle-tracking radial strain in the anteroseptal and peak radial strain to the posterior wall.

LV short-axis images was used to assess LV dyssynchrony as previously described in detail.8-12) LV dyssynchrony was defined as the time difference from the anteroseptal to the posterior wall segmental peak strains and measured using speckle-tracking radial strain, and was considered significant at ≥ 130 ms.8-11) (Figure 1).

Statistical analysis: Continuous variables are expressed as mean ± SD or percentages or median (interquartile range), while categorical data are summarized as frequencies and percentages. The parameters of the two subgroups were compared by using Student t test or Mann-Whitney U test as appropriate. Proportional differences were evaluated with Fisher's exact test. Correlation analysis was performed by using linear regression and expressed as a Pearson correlation coefficient. The initial univariate logistic regression analysis to identify univariate predictors of LV dyssynchrony caused by RV pacing was followed by a multivariate logistic regression model using stepwise selection, with the p levels for entry from the model set at < 0.10. The optimal cutoff value of LVEF for predicting significant LV dyssynchrony during RV pacing was determined with the aid of receiver-operator characteristics (ROC) curve analysis. The inter-observer and intra-observer variabilities for LV dyssynchrony were assessed by means of intra-class correlation coefficients from 10 randomly selected patients. Statistical significance was basically defined as P value < 0.05 for each step. MedCalc version 15.11.4 (MedCalc Software, Mariakerke, Belgium) was used for all analyses.

Results

Baseline characteristics: The baseline clinical and echocardiographic characteristics of the 40 patients are summarized in Table I. In this study, patients were divided into two groups according to their baseline LVEF. In total, 20 patients were classified as the normal LVEF group with LVEF ≥ 50%, and the remaining 20 patients as the mildly reduced LVEF group with LVEF of 35-50%. All
baseline clinical characteristics were similar except that the mildly reduced LVEF group was likely to have more ischemic etiology (55% versus 20%; \( P < 0.01 \)). As expected, LV dimensions and volumes of the mildly reduced LVEF group were significantly larger than those of the normal LVEF group.

**Effect of RV pacing on LV performance:** No significant change was observed in LVEF of the normal LVEF group during RV pacing from 60 ± 6% to 58 ± 8% \( (P = 0.57) \), but LVEF of the mildly reduced LVEF group was significantly reduced during RV pacing from 43 ± 4% to 38 ± 6% \( (P < 0.01) \) (Figure 2). In addition, change in LV dyssynchrony of the normal LVEF group during RV pacing was similar, from 16.5 ms (0.0-18.5) to 27.5 ms (14.3-75.5) \( (P = 0.14) \), whereas that of the mildly reduced LVEF group was significantly larger during RV pacing, increasing from 56.5 ms (16.0-81.1) to 169.9 ms (107.9-251.3) \( (P < 0.01) \) (Figure 3). Also, change in LV dyssynchrony during RV pacing correlated significantly with that in LVEF during RV pacing \( (r = -0.44, \ P < 0.01) \) (Figure 4).

**Changes in time-to-peak strain during RV pacing:** Table II shows changes in time-to-peak strain during RV pacing of the two groups. No significant changes were observed in time-to-peak radial strain of the anteroseptal and posterior wall during RV pacing in the normal LVEF group. In the mildly reduced LVEF group, however, time-to-peak radial strain of the anteroseptal wall tended to occur earlier during RV pacing, but without statistical significance \( (316.6 ± 113.5 \text{ ms versus } 277.8 ± 126.4 \text{ ms}; \ P = 0.21) \), and time-to-peak radial strain of the posterior wall occurred significantly later during RV pacing from 383.2 ± 102.9 ms to 459.1 ± 131.3 ms \( (P < 0.01) \).

**Predictor of significant LV dyssynchrony during RV pacing:** The odds ratio and 95% confidence interval (CI) for each baseline parameter for predicting significant LV dyssynchrony during RV pacing and determined with univariate and multivariate logistic regression analysis are shown in Table III. An important finding of the multivariate logistic regression analysis was that baseline LVEF
These boxplots show changes in left ventricular ejection fraction (LVEF) during right ventricular (RV) pacing in the normal and the mildly reduced LVEF group. No significant change in LVEF was observed in the normal LVEF group during RV pacing, but LVEF in the mildly reduced LVEF group was significantly reduced during RV pacing.

These boxplots show changes in left ventricular (LV) dyssynchrony during right ventricular (RV) pacing in the normal LV ejection fraction (EF) group and the mildly reduced LVEF group. LV dyssynchrony in the normal LVEF group during RV pacing was remained similar, whereas that in the mildly reduced LVEF group was significantly larger during RV pacing.

Reproducibility of LV dyssynchrony: The intra-class correlation coefficients for intra-observer reproducibility was 0.892 (95% CI: 0.627-0.9720).

Discussion

The findings of our study demonstrated that LV performance of patients with mildly reduced LVEF of 35-50% was more impaired during RV pacing than that of patients with normal LVEF of ≥ 50%. In addition, change in LVEF during RV pacing correlated with that in LV dyssynchrony. It was a significant finding that baseline LVEF plays an important role in the development of LV dyssynchrony during RV pacing even in patients with LVEF ≥ 35%.
Adverse effect of RV pacing on LV performance: Permanent RV pacing is the only effective treatment for patients with symptomatic AV conduction disturbance, but it is associated with LV dysfunction and an increased risk of HF and death.\(^{15-16}\) It is also associated with adverse outcomes even for patients with bradycardia and preserved LVEF who had standard indications for RV pacing.\(^{1,2,17}\) Furthermore, it is estimated that up to 40% of patients with permanent pacemakers have HF or LV systolic dysfunction because of frequent RV pacing and their underlying cardiac disease.\(^{18}\) Thus, upgrading of RV pacing systems to CRT devices is often performed for patients who develop LV dysfunction due to RV pacing.\(^{19,20}\) The possible cause of the harmful effects of RV pacing is that RV pacing may create LV mechanical dyssynchrony, which may then induce LV dysfunction and clinical HF. The benefit of upgrading of RV pacing systems to CRT devices seems to be related to the resultant correction of LV dyssynchrony.

**CRT for patients with bradycardia and mildly reduced LVEF:** Although CRT is a well-established therapy for advanced HF patients with LVEF \(\leq 35\%\) and wide QRS complex,\(^{21}\) the potential benefit of CRT for patients with bradycardia and mildly reduced LVEF remains uncertain. A direct comparison between biventricular pacing and RV pacing for patients with bradycardia who required permanent RV pacing was previously performed.\(^{22-24}\) For the BLOCK HF trial, 691 patients with atrioventricular block, New York Heart Association functional class I-III HF, and LVEF \(\leq 50\%\) were randomized to biventricular or RV pacing.\(^{24}\) With a mean follow-up of 37 months, patients receiving biventricular pacing showed a significant 26% reduction in the combined end point such as all-cause mortality, urgent care for HF or increase in LV end-systolic volume index >15% when compared with patients receiving RV pacing. The benefits were similar for the CRT-P and CRT-D groups. In addition to these previous studies, we demonstrated the association of change in LV dyssynchrony with that in LVEF during RV pacing, with patients with LVEF < 48% in particular being more likely to be affected by RV pacing related LV dysfunction as well as deterioration of LV dyssynchrony.

**Clinical implications:** Baseline LVEF in our study was strongly associated with the development of LV dyssynchrony and reduced LVEF during RV pacing. In particular, baseline LVEF of < 48% was linked to significant LV dyssynchrony of 130 ms as assessed by speckle-tracking radial strain during RV pacing. In addition, baseline LVEF of < 42% was also linked to LVEF \(\leq 35\%\) during RV pacing may create LV mechanical dyssynchrony, which may then induce LV dysfunction and clinical HF. The benefit of upgrading of RV pacing systems to CRT devices seems to be related to the resultant correction of LV dyssynchrony.

![Figure 4](image-url) **Figure 4.** Relationship between change in left ventricular ejection fraction (LVEF) during right ventricular (RV) pacing and that in LV dyssynchrony. Correlation is significant.

### Table II. Changes in Time-to-peak Strain during RV Pacing

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During RV Pacing</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal LVEF group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-to-peak radial strain of anteroseptal, ms</td>
<td>372.3 ± 50.2</td>
<td>362.1 ± 88.9</td>
<td>0.66</td>
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<tr>
<td>Time-to-peak radial strain of posterior, ms</td>
<td>394.8 ± 52.4</td>
<td>426.8 ± 55.7</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Mildly reduced LVEF group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-to-peak radial strain of anteroseptal, ms</td>
<td>316.6 ± 113.5</td>
<td>277.8 ± 126.4</td>
<td>0.21</td>
</tr>
<tr>
<td>Time-to-peak radial strain of posterior, ms</td>
<td>383.2 ± 102.9</td>
<td>459.1 ± 131.3</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

### Table III. Univariate and Multivariate Logistic Regression Analysis for Predicting Significant LV Dyssynchrony During RV Pacing

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Univariate OR 95% CI</th>
<th>(P)</th>
<th>Multivariate OR 95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.914-1.054</td>
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<tr>
<td>Gender (female)</td>
<td>0.73</td>
<td>0.180-2.986</td>
<td>0.67</td>
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<tr>
<td>Systolic blood pressure</td>
<td>0.39</td>
<td>0.955-1.018</td>
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<td></td>
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<tr>
<td>QRS duration</td>
<td>1.01</td>
<td>0.987-1.040</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>LV end-systolic volume</td>
<td>1.02</td>
<td>1.001-1.042</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.88</td>
<td>0.801-0.961</td>
<td>&lt; 0.01</td>
<td>0.87</td>
</tr>
<tr>
<td>Left atrial volume</td>
<td>1.00</td>
<td>0.978-1.017</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>0.86</td>
<td>0.558-1.310</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Baseline LV dyssynchrony</td>
<td>1.02</td>
<td>1.001-1.031</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

E/E’ indicates mitral inflow E and mitral E’ annular velocities.
Receiver operating curve (ROC) analysis showed that baseline left ventricular ejection fraction (LVEF) < 48% was predictive of significant LV dyssynchrony during right ventricular (RV) pacing. 

Figure 5. A: Receiver operating curve (ROC) analysis showed that baseline left ventricular ejection fraction (LVEF) < 48% was predictive of significant LV dyssynchrony during right ventricular (RV) pacing. B: ROC curve analysis showed that baseline LVEF < 42% was predictive of LVEF ≤ 35% during RV pacing.

This means that patients with bradycardia and mildly reduced LVEF such as 35-50%, who are undergoing constant RV pacing but do not meet the standard indication for CRT may well become future candidates for CRT due to constant RV pacing. Our findings indicate that the use of biventricular pacing rather than conventional RV pacing can be recommended for patients with bradycardia and mildly reduced LVEF of 35-50% to avoid upgrading to a CRT device and device-related complications. In addition, this may lead to reduce health care cost to avoid hospitalization. However, the difference in effectiveness between bradycardia patients with preserved AV conduction and AV block remains uncertain.

Study limitations: Since this study conducted only acute effect of RV pacing, long-term clinical outcome data during RV pacing, such as exercise capacity, quality-of-life assessment, and survival, were not part of the study. Another limitation is that this study covered a small number of patients at a single-center study, so that future studies of larger patient populations are needed to validate our findings. In addition, we did not provide beneficial data by biventricular pacing in bradycardia patients with mildly reduced LVEF of 35-50% instead of RV pacing. Also, it remains unproved what kind of bradycardia patients were more likely to be adversely affected by RV pacing.

Conclusions

The extent of RV pacing-induced LV dysfunction may be associated with baseline LV function. Thus, these adverse effects on patients with mildly reduced LVEF of 35-50% and indications for RV pacing owing to bradycardia can be prevented by using CRT.

Disclosure

Conflict of interest: The authors declare that they have no competing interests.

References

9. Tanaka H, Nesser HJ, Buck T, et al. Dyssynchrony by speckle-tracking echocardiography and response to cardiac resynchroni-