Clinical Outcome After Permanent Pacemaker Implantation in Patients With a High Percentage of Ventricular Pacing

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SUMMARY

Previous reports have suggested that right ventricular apical pacing may lead to cardiac dysfunction. Septal pacing is thought to be superior to apical pacing in the prevention of cardiac dyssynchrony, however, there have been no reports on the contribution of septal pacing to improving clinical outcome. We retrospectively evaluated factors associated with cardiac events in patients with right ventricular pacing. The study population consisted of 256 consecutive patients newly implanted with permanent pacemakers and followed-up for 29 ± 18 months. Cardiac events, consisting of cardiac death or heart failure requiring hospitalization, occurred in 22 patients. Kaplan-Meier curves revealed that patients with a high percentage of ventricular pacing (> 90%, n = 101, group H) had a higher incidence of cardiac events than patients with a low percentage of ventricular pacing (< 10%, n = 83, group L) (P = 0.002). In group H, multivariate analysis showed that age (HR: 1.174, 95%CI: 1.066-1.291, P = 0.001), ejection fraction (EF) (HR: 0.898, 95%CI: 0.836-0.964, P = 0.003), QRS duration during cardiac pacing (HR: 1.059, 95%CI: 1.017-1.103, P = 0.006), and existing basal cardiac diseases (HR: 13.080, 95%CI: 2.463-69.479, P = 0.003) were significant predictors of cardiac events, although pacing site had no significant association with prognosis (P = 0.56).

Higher age, lower EF, longer QRS duration during cardiac pacing, and existing basal cardiac diseases are associated with poor prognosis in patients with a high percentage of ventricular pacing. (Int Heart J 2015; 56: 622-625)

Key words: Right ventricular pacing, Pacing site, Follow-up

Cardiac pacing is the established treatment for patients with bradyarrhythmia. The right ventricular apex is commonly selected as the site of ventricular lead placement. However, many previous reports have suggested that right ventricular apical pacing may lead to cardiac dyssynchrony and cause left ventricular dysfunction.1-3 The right ventricular septum was suggested as an alternative site, and was shown to be superior to apical pacing in the prevention of cardiac dysfunction caused by left ventricular dyssynchrony.4-7 However, to the best of our knowledge, no studies have shown that septal pacing contributes to an improved prognosis.8-10 Pacing itself may reduce cardiac function regardless of pacing position. Cardiac resynchronization therapies (CRT) minimize cardiac dysfunction induced by right ventricular pacing, and a recent report suggested that CRT was superior to right ventricular pacing in patients with reduced cardiac function.10 However, the indications of CRT without decreased cardiac functions are limited by the guidelines. If a poor prognosis caused by right ventricular pacing can be predicted, CRT may be selected instead of right ventricular pacing.

In this study, we assessed the characteristics of patients who had a poor outcome with right ventricular pacing and evaluated candidates for CRT.

METHODS

Patients: The study population consisted of 268 consecutive patients newly implanted with permanent pacemakers in our institution from January 2009 to December 2013. All patients had standard indications of cardiac pacing, including sick sinus syndrome (n = 136), atrioventricular block (n = 109), and atrial fibrillation with low ventricular response (n = 23). All patients underwent electrocardiography, echocardiography, chest X-rays, and blood exams before implantation. Echocardiography was performed using a commercially available system (Sonos5500, Phillips, Netherlands) to obtain the left ventricular ejection fraction (LVEF). The chest to thoracic ratio was calculated from chest X-rays and was defined as the index of cardiac enlargement. Blood exams were performed to obtain levels of brain-type natriuretic peptide (BNP) and hemoglobin. After the operation, both the PA and left lateral positions were checked by X-rays to confirm the position of the pacing leads and QRS duration on standard 12-channel electrocardiography.
during ventricular pacing.

Pacemaker implantation: Pacemaker implantation was performed under local anesthesia. The pacing lead was inserted from the right or left subclavian vein. Atrial leads were positioned at the right atrial appendage or right atrial septum. Ventricular leads were positioned at the right ventricular apex or septum. Atrium and ventricle pacing sites depended on each operator. Implantation of the right ventricular septum lead was performed by advancing into the apex and pushing up with counter-clockwise rotation using a 3-dimensional stylet. Differentiation between the right ventricular septum and right ventricular free wall was confirmed by a lateral view chest X-ray. If the right ventricular septum leads were positioned at the most suitable site, a relatively narrow QRS complex was obtained. The devices used were from Medtronic (St Paul, Minnesota, USA), St Jude Medical (Sylmar, California, USA), Biotronik (Berlin, Germany), and Sorin (Milan, Italy).

Follow-up: All patients were followed up every 6 months in our outpatient clinic after implantation. The endpoint of the study was defined as cardiac death or hospitalization for heart failure. We retrospectively analyzed the characteristics of patients with a poor outcome.

Statistical analysis: Variables are expressed as the mean ± standard deviation. Continuous variables were analyzed by Student’s t-test, and categorical data were compared using the chi square test. Cumulative event rates were calculated by the Kaplan-Meier method, and differences were assessed with the log-rank test. Multivariate analysis was performed by Cox proportional regression analysis, in which age, gender, ejection fraction, QRS duration, position of ventricular pacing, and combination with other cardiac diseases were entered into the analysis. A P < 0.05 was considered statistically significant.

RESULTS

The study population consisted of 268 patients who were followed up for 29 ± 18 months. Pacemakers were successfully implanted in all patients; however, 12 patients were excluded from the study because the right ventricular lead had been positioned at the right ventricular free wall as detected by chest X-rays after pacemaker implantation.

During the follow-up period, 22 patients had cardiovascular events, including hospitalization for heart failure (n = 13) and sudden cardiac death (n = 9). To investigate the influence of right ventricular pacing on cardiac events, we compared patients with a high percentage of ventricular pacing (> 90%, n = 101; group H) to patients with a low percentage of ventricular pacing (< 10%, n = 83; group L) (Table I). Cardiac events occurred in 14 patients in group H and in 3 patients in group L. Cardiac function before pacemaker implantation was approximately similar between the two groups, although both age and number of male patients were significantly higher in group H. Kaplan-Meier curves revealed that patients with a high percentage of ventricular pacing had a higher incidence of cardiac events than patients with a low percentage of ventricular pacing (P = 0.002) (Figure 1). Table II shows a comparison of clinical, electrocardiographic, and echocardiographic characteristics by right ventricular lead position in group H. QRS duration during ventricular pacing was significantly longer in pa-

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<th>Table I. Patient Clinical Characteristics</th>
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<td>Ventricular pacing</td>
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<td>Age (years)</td>
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<td>Gender (male : female)</td>
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<td>Ventricular lead position</td>
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<td>Basal disease (n, %)</td>
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<td>Ventricular pacing (%)</td>
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Data are expressed as the mean value ± standard deviation or number (%). BMI indicates body mass index; LVEF, left ventricular ejection fraction; CTR, chest to thoracic ratio; BNP, brain natriuretic peptide; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; and CI, confidence interval.

![Figure 1. Kaplan-Meier curves for time to cardiac events in patients with high (> 90%) and low (< 10%) ventricular pacing. Patients requiring a high percentage of ventricular pacing had a higher incidence of cardiac events than patients requiring a low percentage of ventricular pacing (P = 0.002).](image)

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<th>Table II. Comparison of the Characteristics According to the Right Ventricular Lead Position</th>
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<td>Septum (n = 78)</td>
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<td>Age (years)</td>
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<td>Gender (male : female)</td>
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<td>BMI (kg/m²)</td>
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<td>Echocardiography</td>
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Data are expressed as the mean value ± standard deviation. Abbreviations are same as in Table I.
tients with apical pacing than septal pacing. However, there was no significant difference between the two groups in the event-free rate ($P = 0.69$) (Figure 2). Table III shows the results of univariate and multivariate analysis identifying factors for prediction of cardiac events among patients in group H. Univariate analysis revealed a significant association between cardiac events and age, gender, LVEF, BNP, chest to thoracic ratio, QRS duration, and existing basal cardiac diseases. Multivariate analysis showed age (HR: 1.174, 95% CI: 1.066-1.291, $P = 0.001$), LVEF (HR: 0.898, 95% CI: 0.836-0.964, $P = 0.003$), QRS duration during cardiac pacing (HR: 1.059, 95% CI: 1.017-1.103, $P = 0.006$), and existing basal cardiac diseases (HR: 13.080, 95% CI: 2.463-69.479, $P = 0.003$) were significant predictors of cardiac events, although pacing site had no significant association with prognosis ($P = 0.56$).

**DISCUSSION**

In the present study, we demonstrated that a high percentage of ventricular pacing was associated with a higher rate of cardiac events. Moreover, in patients with higher ventricular pacing demand, age, LVEF, QRS duration during ventricular pacing, and existing basal cardiac diseases were significant predictors of cardiac events.

Many previous reports have suggested that ventricular pacing, in particular right ventricular apical pacing, should be avoided due to the possibility of causing left ventricular dysynchrony. An abnormal electrical activation sequence leads to increased mitral regurgitation, asymmetrical hypertrophy, or decreased ejection fraction. On the other hand, right ventricular septal pacing, rather than apical pacing, has been reported to be better suited for protecting ventricular function. It has been reported that right ventricular septal pacing reduced left ventricular dyssynchrony. Indeed, septal pacing reduces paced QRS duration on electrocardiography and decreased dyssynchrony indices on echocardiography. However, it remains to be clarified whether septal pacing is preferable to apical pacing in reducing cardiac mortality.

Our data suggest that right ventricular septal pacing did not reduce the incidence of cardiac events compared with apical pacing. Right ventricular septal pacing reduced left ventricular mechanical dyssynchrony, but this did not contribute to improvement in chronic clinical outcome. For septal pacing, it is very important to place the ventricular lead close to the conduction system, but it is known to be difficult to implant pacing leads at the right ventricular septum and capture the right bundle branch. Conflicting data on right ventricular pacing and its association with left ventricular function may be due to a high degree of heterogeneity in correct pacing sites between patients. Although right ventricular septum pacing decreases QRS duration, one of the prognostic indicators in patients with heart diseases, this too does not contribute to improved clinical outcome. This may be explained by the fact that QRS duration reflects various ventricular conditions, such as conduction disturbance or ventricular fibrosis, as well as mechanical left ventricular dyssynchrony. In the present study, only a small number of patients suffered from structural heart diseases. Right ventricular apical pacing, as compared with septal pacing, has an disadvantage in preventing mechanical dyssynchrony; however, dyssynchrony induced by cardiac pacing may be tolerated in patients with preserved left ventricular function.

CRT is known to be one of the most effective therapies in patients with advanced heart failure combined with left ven-

![Figure 2. Kaplan-Meier curves for time to cardiac events in patients with high (> 90%) ventricular pacing. Ventricular pacing position had no association with prognosis ($P = 0.69$). RVS indicates right ventricular septal pacing and RVA, right ventricular apical pacing.](image-url)

| Table III. Univariate and Multivariate Analysis for Predicting Cardiac Events |
|------------------|------------------|------------------|------------------|------------------|
|                  | **Hazard ratio** | **95% CI**      | **P**            | **Hazard ratio** | **95% CI**      | **P**            |
| Age              | 1.107            | 1.047-1.170     | < 0.001          | 1.174           | 1.066-1.291     | 0.001            |
| Gender           | 0.212            | 0.047-0.946     | 0.042            |                 |                 |                  |
| Electrocardiography | 1.037          | 1.008-1.067     | 0.012            | 1.059           | 1.017-1.103     | 0.006            |
| QRS duration     | 0.922            | 0.880-0.965     | < 0.001          | 0.898           | 0.836-0.964     | 0.003            |
| Echocardiography |                 |                 |                  |                 |                 |                  |
| LVEF             | 1.119            | 1.031-1.214     | 0.007            |                 |                 |                  |
| Chest X ray      |                 |                 |                  |                 |                 |                  |
| CTR              | 1.001            | 1.000-1.003     | 0.021            |                 |                 |                  |
| Blood exam       | 0.758            | 0.574-1.001     | 0.0505           |                 |                 |                  |
| Haemoglobin      | 0.935            | 0.849-1.030     | 0.17             |                 |                 |                  |
| Ventricular lead position | 1.398          | 0.464-4.213     | 0.55             | 1.543           | 0.357-6.662     | 0.56             |
| Basal Cardiac disease | 4.438           | 1.537-12.816    | 0.006            | 13.080          | 2.463-69.479    | 0.003            |

CI indicates confidence interval. Other abbreviations are expressed as in Table I.
tricular dyssynchrony, which was mainly generated by intra-
ventricular conduction disturbance. In contrast, left ventricular
dyssynchrony induced by right ventricular pacing was com-
monly observed to some degree regardless of pacing site. Yu, et al reported that CRT prevented left ventricular remodeling
induced by right ventricular apical pacing in patients with nor-
mal systolic function. Moreover, Curtis, et al suggested that
in patients with atrioventricular block and systolic dysfunction,
CRT provided better clinical outcome than conventional right
ventricular pacing. There have been many reports that pacing
itself reduces cardiac function regardless of pacing position.
Thus, present most pacemakers have an algorithm to mini-
mize ventricular pacing. The advantage of right ventricular
septal pacing for improving clinical outcome has not yet been
established. Accordingly, in patients with high ventricular pac-
ing demand, CRT may be preferable to right ventricular septal
pacing, particularly in patients with a higher age or decreased
cardiac function.

Limitations: There are several limitations in this study. First,
this was not a randomized study. Pacing sites depended on
each operator. Accordingly, the number of patients with septal
and apical pacing was quite different. We demonstrated that
multivariate analysis revealed ventricular pacing site had no impact on cardiac events. Second, we did not conduct an analy-
thesis of patients with a medium percentage of ventricular pac-
ing (10%-90%). The percentage of ventricular pacing detected
by a programmer is sometimes unreliable, especially in pa-
ients without complete atrioventricular block, because intrin-
sic atrioventricular conduction diminishes the pacing effects
even if event markers on programmers indicate “pacing”. Re-
cent pacemakers have excellent functions by which ventricular
pacing is minimized. If the entire study population had these
types of pacemakers, we would not need to pay attention to the
“fusion” beats for analysis of pacing effects. Third, we have
not presented clinical data from patients who needed up-grading
for CRT. It is very important to predict patients with a poorer outcome after pacemaker implantation. In this study, we have demonstrated the risk factors for cardiac events in pa-

cients with a high percentage of ventricular pacing. We should
analyze the clinical course in patients who received CRT for
atrioventricular block combined with multiple risk factors and
clarify which of the patients may benefit most from CRT in a
future study.

Conclusion: Higher age, lower LVEF, longer QRS duration
during cardiac pacing, and existing basal cardiac diseases are
associated with a poor prognosis in patients with high ven-
tricular pacing demand.

DISCLOSURE

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

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