Recent clinical studies have demonstrated that long-term right ventricular apical (RVA) pacing imposes a risk of heart failure, ventricular arrhythmias, and cardiac death.1–5 RVA pacing causes left ventricular (LV) mechanical dyssynchrony because of altered ventricular excitation that bypasses the His–Purkinje system.6–9 Long-term RVA pacing results in LV dilatation associated with asymmetric LV hypertrophy,10,11 regional myocardial perfusion defects12–14 and a decrease in the LV ejection fraction (LVEF).12,15,16 Pacing on the right ventricular (RV) septum, RV outflow tract and His or para-His bundle has been introduced as a potentially favorable alternative to RVA pacing to preserve a more physiologic ventricular activation.8 However, previous investigations of alternative pacing sites have yielded inconsistent results,17–23 which may be attributable, in part, to the fact that the pacing site was determined on a topological rather than functional basis.24 Indeed, acute hemodynamic studies have demonstrated that individual optimization of the RV pacing sites could preserve LV performance in patients without LV dysfunction, and that there are substantial individual variations in the optimal pacing sites.25,26 The paced QRS duration seems to be a practical indicator for determining the optimal RV pacing site.14,19,22,23 However, information on the most appropriate pacing site to preserve long-term LV function is still limited.

Methods

Patients
We retrospectively studied 55 patients (22 men, 32 women; 70±10 years) undergoing dual-chamber pacemaker implantation for advanced atrioventricular block (AVB; n=33) or sinus node dysfunction (SND, n=22). In 40 patients (n=24 for AVB, n=16 for SND), pace mapping was carried out at the junction between the upper and middle segments of the RV septum using a hand-shaped stylet under fluoroscopy.
guidance. The RV lead was screwed into the septum at a site that produced the shortest QRS duration possible after comparing at least 5 pace maps. The septal position of the pacing lead tip was assessed by fluoroscopy and by the following 2 ECG criteria as reported by Muto et al:\textsuperscript{23} (1) paced QRS in the lead I was positive or biphasic and (2) paced QRS axis was concordant with the electrical axis of the baseline QRS (sinus or escaped rhythm) (Figure 1). The RV lead was positioned in the apex in the conventional manner in 15 patients (n=9 for AVB, n=6 for SND). Abnormal AV conduction was recognized in 5 patients with SDN: 3 in the RVS pacing group and 2 in the RVA pacing group. The atrial leads were positioned either in the appendage or septum of the right atrium. Patients were excluded from the study if they had LVEF <40\% on the baseline echocardiogram or a wide QRS duration (>120 ms) on the baseline ECG.

All patients were followed up for >2 years with DDD or DDR pacing at a rate ≥60 beats/min. In the patients with no or impaired AV conduction, the AV delay was optimized as described below. In the patients with intrinsic AV conduction, an AV interval ≥250 ms was ensured to minimize unnecessary ventricular pacing. The mean cumulative percentage of the ventricular pacing in the respective patients was assessed by the pacemaker diagnostics during each follow-up visit.

**Echocardiography**

The LV dimensions and LVEF were assessed by 2-dimensional M-mode echocardiography before the pacemaker was implanted and at the last follow-up visit after implantation. In patients possessing intrinsic AV conduction, the pacemaker was switched to single-chamber atrial (AAI) pacing. Echocardiography was performed after a 20-min stabilization at a rate ≥60 beats/min. In patients with no or impaired AV conduction, echocardiography was carried out during DDD pacing. The AV delay was set to ensure the onset of the first heart sound (S-I) at the end of the left atrial filling wave.\textsuperscript{11,27} ECGs were recorded at a paper speed of 100 mm/s, and the QRS duration was measured as the average of the 12 leads.

LV dyssynchrony was assessed at the last follow-up visit using color-coded tissue Doppler imaging (TDI: Prosound SSD-αD, ALOKA, Tokyo, Japan).\textsuperscript{28,29} Two-dimensional TDI views (apical 4-chamber, 2-chamber and long-axis views) were optimized to allow the highest possible frame rate (≥100 frames/s). The sample volume was placed in 12 segments of the LV wall according to the method of Yu et al:\textsuperscript{28} a 6-basal and 6-mid segmental mode was obtained in the LV, namely the septal, lateral, anteroseptal, posterior, anterior and inferior segments. The peak myocardial sustained systolic velocity (S\textsubscript{SM}) was recognized, and the time-to-S\textsubscript{M} to the beginning of the QRS complex was measured in the 12 segments. The average of at least 3 consecutive beats was used for comparison. LV dyssynchrony was estimated by the difference between the longest and shortest T\textsubscript{SM} (T\textsubscript{SM} dispersion) in the 12 LV segments. The intra- and interobserver variability of T\textsubscript{SM} measurement in the present study was 3.5 and 6.5\%, respectively, for a serial measurement of 120 segments.

Interventricular dyssynchrony was assessed by measuring the interventricular mechanical delay (IVMD) using pulsed-wave Doppler echocardiography.\textsuperscript{11} The time intervals from the onset of the QRS complex to the onset of the pulmonary flow velocity curve and to the onset of the aortic flow velocity curve were measured as the RV pre-ejection interval and LV pre-ejection interval, respectively; the IVMD was defined as their time difference.
The study was approved by the Institutional Ethics Committee of the hospital, and all patients gave their written informed consent.

**Statistical Analysis**

Statistical significance was analyzed using the Mann-Whitney U test for comparisons of data between the different patient groups, and Student’s paired t-test for comparisons of data in the same patient group. Analysis of variance followed by Bonferroni’s test was used for multiple comparisons. P<0.05 was considered significant.

**Results**

**Table 1** lists the baseline characteristics of the patients for RVA and RVS pacing. There were no significant differences between the 2 groups of patients in terms of age at pacemaker implantation, gender distribution, LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LVEF, or QRS duration (sinus or escaped rhythm) before pacemaker implantation.

**Long-Term Effect of RV Pacing on LV Function**

During the entire follow-up period of 4.2±1.4 years in the 55 patients after pacemaker implantation, none was hospitalized for any treatment of heart failure or coronary intervention. Eleven of 15 patients with RVA pacing and 27 of 40 patients with RVS pacing were under full (>95%) ventricular pacing, whereas the remaining 4 with RVA pacing and 13 with RVS pacing were under partial (<50%) ventricular pacing.

Echocardiography was performed at a rate of 65±6 beats/min in the 15 patients with RVA pacing, and at 65±5 beats/min in the 40 patients with RVS pacing at the end of the follow-up period (4.2±1.4 years). LV function on echocardiography was assessed under AAI pacing mode in the 17 patients exhibiting intrinsic AV conduction (partial pacing groups), whereas it was under DDD (RVA, RVS) pacing mode in the 38 patients exhibiting no intrinsic AV conduction (full pacing groups). The AV delay of the DDD pacing mode was 140±15 ms in the full RVA pacing group (n=11) and 138±20 ms in the full RVS pacing group (n=27).

In the 11 patients with full (99.3±1.2%) RVA pacing, the LVEF after a follow-up of 4.2±1.2 years decreased significantly from baseline (64±12 vs 71±7%, P=0.018). In the 27 patients with full (98.9±2.0%) RVS pacing, the LVEF after a follow-up of 4.3±1.6 years did not change from baseline (69±7 vs 70±8%, P=0.70). In the 13 patients with partial (11.0±16.2%) RVS pacing, the LVEF after a follow-up of 4.1±1.3 years was also unchanged (67±6 vs 68±6%, P=0.42). The 10th percentile for a change in the LVEF during the follow-up period was −8% in the 17 patients with partial ventricular pacing. When this value was taken as a cut-off level, a critical decrease in the LVEF was recognized in 5/11 patients (45.5%) with full RVA pacing, but only in 2/27 patients (7.5%) with full RVS pacing (Figure 2A). There was no significant difference in the cumulative percentage of RV pacing (P=0.63) or the follow-up period (P=0.85) between the 2 full ventricular pacing groups.

**LV Dyssynchrony With RV Pacing**

The TDI recordings were obtained under AAI or DDD (RVA, RVS) pacing mode as employed for 2-dimensional M-mode echocardiography. **Table 2** summarizes the LV dyssynchrony parameters during the 3 pacing modes. The QRS durations during RVA and RVS pacing were both significantly longer than that during AAI pacing (P=0.0001), but the prolongation with RVS pacing was significantly less than that with RVA pacing (P<0.001). The QRS axis

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tr>
<td>RVA pacing (n=15)</td>
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<tr>
<td>Age at implantation (years)</td>
</tr>
<tr>
<td>M/F</td>
</tr>
<tr>
<td>AVB/SND</td>
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<tr>
<td>Baseline LVEDD (mm)</td>
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<tr>
<td>Baseline LVESD (mm)</td>
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<tr>
<td>Baseline LVEF (%)</td>
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<td>Baseline QRS duration (ms)</td>
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</table>

Values are mean±SD.

RVA, right ventricular apical; RVS, right ventricular septal; AVB, atrioventricular block; SND, sinus node dysfunction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction.

**Figure 2.** Left ventricular ejection fraction (LVEF) at baseline and after long-term right ventricular apical (RVA) and septal (RVS) pacing. (A) Data obtained from 11 patients with full (>95%) RVA pacing and 27 with full RVS pacing. (B) Critical decrease in the LVEF can be seen in 5/11 patients (45.5%) with full RVA pacing, but only in 2/27 patients (7.4%) with full RVS pacing. B/L, baseline; F/U, follow-up. Data are mean±SD. *P<0.05 vs baseline.
Table 2. Parameters of Electrical and Mechanical Dyssynchrony

<table>
<thead>
<tr>
<th></th>
<th>AAI pacing (n=17)</th>
<th>RVA pacing (n=11)</th>
<th>RVS pacing (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration (ms)</td>
<td>89±18</td>
<td>158±13*</td>
<td>137±13*</td>
</tr>
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<td>QRS axis (degree)</td>
<td>24±33</td>
<td>−65±25*</td>
<td>23±56*</td>
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<tr>
<td>T$_{sys}$ dispersion (ms)</td>
<td>55±19</td>
<td>110±30*</td>
<td>75±32*</td>
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<tr>
<td>IVMD (ms)</td>
<td>−2±11</td>
<td>26±17*</td>
<td>20±20*</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*P<0.05 vs AAI pacing, #P<0.05 vs RVA pacing.

$T_{sys}$ dispersion, difference between the longest and shortest time-to-peak systolic velocity in 12 segments of the left ventricular wall; IVMD, interventricular mechanical delay. Other abbreviations see in Table 1.

during RVA pacing was significantly deviated from that during AAI pacing (P<0.0001), but the axis during RVS pacing was comparable to that during AAI pacing. The $T_{sys}$ dispersion during RVA pacing was significantly larger than during AAI pacing (P<0.0001) and RVS pacing (P<0.001), whereas the $T_{sys}$ dispersion during RVS pacing was comparable to that during AAI pacing. The IVMDs during RVA and RVS pacing were both significantly larger than that during AAI pacing (P<0.0001 for RVA, P<0.001 for RVS); no significant difference was recognized between RVA and RVS pacing.

The mean values of the $T_{sys}$ in the 12 LV segments during AAI and the 2 RV (RVA, RVS) pacing modes are plotted in Figure 3. During AAI pacing there was no sig-

Figure 3. Regional time-to-peak systolic velocity in 12 left ventricular (LV) segments assessed by tissue Doppler imaging. The plotted data were obtained during AAI (triangles, n=17), right ventricular apical (RVA) (squares, n=11) and right ventricular septal (RVS) (circles, n=27) pacing at the end of the follow-up period (4.2±1.4 years). There is a significant positive correlation between the 2 parameters (R=0.65, P<0.0001, n=38). $T_{sys}$ dispersion, difference between the longest and shortest time-to-peak systolic velocity in the 12 segments of the left ventricular wall.

Figure 4. Relationship between paced QRS duration and $T_{sys}$ dispersion in 38 patients with full (>95%) ventricular pacing. The plotted data were obtained during right ventricular apical (RVA) (closed squares, n=11) and right ventricular septal (RVS) (open circles, n=27) pacing at the end of the follow-up period (4.2±1.4 years). There is a significant positive correlation between the 2 parameters (R=0.65, P<0.0001, n=38). $T_{sys}$ dispersion, difference between the longest and shortest time-to-peak systolic velocity in the 12 segments of the left ventricular wall.

Figure 5. Relationship between the $T_{sys}$ dispersion and percentage decrease in the left ventricular ejection fraction (LVEF) during the follow-up period in 38 patients with full (>95%) ventricular pacing. The plotted data were obtained during right ventricular apical (RVA) (closed squares, n=11) and right ventricular septal (RVS) (open circles, n=27) pacing at the end of the follow-up period (4.2±1.4 years). There is a significant positive correlation between the 2 parameters (R=0.42, P=0.008, n=38). $T_{sys}$ dispersion, difference between the longest and shortest time-to-peak systolic velocity in the 12 segments of the left ventricular wall.
nificant regional variability of $T_{sys}$ among the 12 LV segments ($P=0.80$), indicating a synchronous LV contraction. The $T_{sys}$ values during the RVA pacing were significantly longer than those during AAI pacing, except for the septal and anteroseptal segments in the basal and mid levels (BS, BAS, MS and MAS). Compared with those 4 segments, the $T_{sys}$ values in the lateral segments (BL and ML) were significantly longer during RVA pacing ($P<0.05$). Similarly, the $T_{sys}$ in the basal posterior (BP) segment was significantly longer than those in the MS and MAS segments ($P<0.05$), indicating an appreciable LV dyssynchrony. The $T_{sys}$ values during RVA pacing were significantly longer than during AAI pacing, except for the BAS segment. In contrast to RVA pacing, no significant regional variability of $T_{sys}$ was present in the 12 LV segments during RVS pacing ($P=0.71$), suggesting an almost synchronous LV contraction. The $T_{sys}$ values in the BL, ML and BP segments during RVS pacing were significantly shorter than during RVA pacing ($P<0.05$).

In Figure 4, the $T_{sys}$ dispersion of the 12 LV segments during RVA or RVS pacing is plotted as a function of paced QRS duration. There was a positive correlation between the 2 parameters: the longer the QRS duration, the larger the $T_{sys}$ dispersion ($R=0.65$, $P<0.0001$, $n=38$). In contrast, there was no significant correlation between the IVMD and paced QRS duration ($P=0.21$). These observations suggest that LV mechanical dyssynchrony in patients during RV pacing depends primarily on the LV excitation delay.

In Figure 5, the percentage decrease in the LVEF after the follow-up period ($\Delta$EF) in the 38 patients with full RV pacing (11 with RVA, 27 with RVS pacing) from the respective baselines is plotted against the $T_{sys}$ dispersion ($R=0.42$, $P=0.008$, $n=38$): the larger the $T_{sys}$ dispersion, the greater the $\Delta$EF. Similarly, there was a significant correlation between the $\Delta$EF and paced QRS duration ($R=0.35$, $P=0.029$, $n=38$). In contrast, there was no significant correlation between the $\Delta$EF and IVMD ($P=0.44$).

Discussion

To the best of our knowledge, this is the first report of the long-term effect of RVA pacing on LV function with reference to pacing-induced LV dyssynchrony. The key observations are as follows. First, RVA pacing caused a significant conduction delay in the LV posterolateral wall in association with a prominent QRS prolongation; RVS pacing caused a much smaller LV contraction delay and QRS prolongation. Second, LV dyssynchrony associated with the RV pacing positively correlated with the paced QRS duration. Third, long-term RVA pacing resulted in a significant decrease in the LVEF; long-term RVS pacing did not affect the LVEF. The LV dysfunction after long-term RV pacing significantly correlated with the LV dyssynchrony induced by RV pacing.

RVA Pacing-Induced LV Dyssynchrony and Dysfunction

RVA pacing causes an electrical activation delay in the LV free wall, and this electrical dyssynchrony, like left bundle branch block, is expected to have a deleterious influence on LV performance.6,7,9 Previous experimental studies have demonstrated that LV dyssynchrony associated with RVA pacing increases wall stress heterogeneity, and decreases myocardial efficiency, resulting in decreased systolic and diastolic function.30,31 The wall stress is highest in the late-activated myocardial regions because of an exaggerated stretch in early systole (secondary to the septal contraction) and late systolic contraction against an increased after-load,4,5,9,31 leading to dilatation of the LV cavity and asymmetric hypertrophy.10,11 Myofibrillar cellular disarray, disorganized mitochondria and downregulation of proteins involved in Ca$^{2+}$ homeostasis have been demonstrated in the hypertrophied wall.12,33 Recent clinical studies have shown that long-term RVA pacing induces a reduction in the LVEF by 5–15% in patients with normal baseline LV function.14,15

In accordance with those previous studies, we demonstrated in the TDI that RVA pacing produces a significant contraction delay in the posterolateral LV wall in patients with normal baseline QRS duration. Long-term RVA pacing (~4 years) caused a 10% reduction in the LVEF.

Minimization of Pacing-Induced LV Dyssynchrony and LV Dysfunction With RVS Pacing

RVS pacing guided by the paced QRS duration may have an advantage over RVA pacing in terms of LV function. In a crossover studies of patients with permanent atrial fibrillation and AV node ablation, Mera et al19 and Victor et al22 showed that the LVEF during RVS pacing was significantly higher than that during RVA pacing in association with a shorter QRS duration. Tse et al14 demonstrated that RVS pacing minimized the regional myocardial perfusion defect and decrease in the LVEF. In those studies, however, the pacing-induced LV dyssynchrony was not quantified and the follow-up period was limited to 3–18 months. The present study investigated longer term (~4 years) effects of RVS pacing on LV mechanical synchrony and function. Our data provide clear evidence that RVS pacing can preserve long-term LV function by minimizing pacing-induced LV electrical and mechanical dyssynchrony.

In experimental studies, RVS pacing using a screw-in electrode was shown to produce a synchronous LV electrical activation via stimulation of the genuine intraventricular conduction system deep in the septum, and to prevent the development of adverse cellular changes.34,35 In our study, RVS pacing in human patients caused a significant increase in the IVMD compared with AAI pacing, which indicates that the onset of the LV activation is delayed even during RVS pacing. Such an increase in interventricular dyssynchrony may be a result of the initial impulse propagation through a slow muscular conduction region. The increase in $T_{sys}$ during RVS pacing compared with AAI pacing may also be attributable to the initial delay of the impulse propagation.

Clinical Significance

Tops et al15 recently reported that long-term RVA pacing can induce LV dysfunction in association with LV dyssynchrony in almost 50% of patients treated with AV node ablation for permanent atrial fibrillation. In view of the potential harmful effects of RVA pacing on LV function, efforts should be made to minimize ventricular dyssynchrony. In patients without significant distal conduction abnormalities, His or para-His bundle pacing might be optimal, but its feasibility is limited by the technical difficulties.36,37 RVS pacing guided by paced QRS morphology would be more useful in routine clinical practice and may be applicable in patients for standard ventricular pacing.
A recent study has also suggested that RVS pacing may have an advantage over RVA pacing, even in patients with biventricular pacing, as the RV pacing mode.38

Study Limitations
First, the size of the population was small, and the patients were not randomly assigned to RVA or RVS pacing. Second, LVEF was estimated by M-mode echocardiography. The blipane Simpson’s method would be more appropriate for estimating LVEF in patients showing LV dyssynchrony. However, this may not invalidate our conclusion because the extent of LVEF reduction following long-term RVA pacing was comparable to that reported by other investigators using Simpson’s method or radionuclide ventriculography.14,15 Third, a total assessment of the clinical outcome, such as exercise capacity and quality of life, was not made. Fourth, the lead position was optimized during RVS pacing, but not during RVA pacing. Finally, the present results were obtained only in patients with normal QRS duration and preserved LV function at baseline, so whether the findings of this study are applicable to patients with LV dysfunction is an issue for further investigation.

Conclusion
RVS pacing guided by paced QRS morphology preserves long-term LV function via minimizing pacing-induced electrical and mechanical LV dyssynchrony in patients with normal QRS duration and preserved LV function at baseline.

References
LV Dyssynchrony With RV Pacing


