Impact of pulmonary vein isolation on the autonomic modulation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses

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Aims

The efficacy of catheter-based pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (AF) and prolonged sinus pauses [bradycardia–tachycardia syndrome (BTS)] has been already described. However, the effects of PVI on autonomic modulation in BTS patients remain to be determined. We, therefore, examined the alteration in the autonomic modulation through the PVI procedure by using a heart rate variability (HRV) analysis of 24 h ambulatory monitoring.

Methods and results

This study consisted of 26 symptomatic paroxysmal AF patients either with prolonged sinus pauses on termination of AF (>3.0 s, BTS group, n = 11) or without any evidence of sinus node dysfunction (control group, matched for sex and age, n = 15) who underwent PVI. All 11 BTS patients became free from both AF and prolonged sinus pauses without pacemaker implantation (23 ± 14 months of observation). The mean heart rate significantly increased in the control group (P < 0.05), but not in the BTS group after the PVI procedure, although the HRV parameters of root-mean-square successive differences in the adjacent NN intervals, standard deviation of the NN intervals, and high frequency did significantly decrease in both groups (P < 0.05).

Conclusion

Although the parasympathetic modulation was significantly attenuated after the PVI procedure, the mean heart rate did not increase in the BTS patients, probably due to the pre-existing sinus node dysfunction.

Keywords

Atrial fibrillation • Bradycardia–tachycardia syndrome • Pulmonary vein isolation • Heart rate variability • Autonomic modulation

Introduction

Prolonged sinus pauses on termination of atrial fibrillation (AF) are sometimes observed in patients with paroxysmal AF [bradycardia–tachycardia syndrome (BTS)] who often require implantation of permanent pacemakers. Recently, catheter-based pulmonary vein isolation (PVI) has been widely performed for patients with paroxysmal AF. The elimination of AF by PVI has been shown to resolve the clinical manifestation of sinus node dysfunction in patients with both paroxysmal AF and BTS. There has been evidence that radiofrequency (RF) applications for the pulmonary vein (PV) or around the PV antrum often induce both a significant reduction in parasympathetic activity and a significant increase in the mean heart rate after these procedures. Pappone et al. described a significant reduction in the parasympathetic heart rate variability (HRV) parameters and an increase in the mean and minimum heart rates for 1 week to 3 months after the PVI, which were closely associated with the reduction of subsequent AF recurrences. In patients with both paroxysmal AF and BTS, however, there have been no data available.
regarding the effects of PVI procedure on autonomic modulation. We herein examined the changes in heart rate and the autonomic modulation through the PVI procedure, as determined by the HRV analysis of 24 h ambulatory monitoring in the BTS patients.

**Methods**

**Patient population**

This study consisted of 26 patients (19 men and 7 women; mean age: 60.9 ± 6.9 years; range: 43–75 years) with drug-refractory symptomatic paroxysmal AF who were referred to our institution and underwent catheter-based PVI. The BTS group included 11 patients with prolonged sinus pauses (≥3.0 s) on termination of AF, and the control group included 15 patients, matched for sex and age, without any evidence of sinus node dysfunction. All patients in the BTS group had at least one episode of syncope or dizziness correlated with prolonged sinus pauses documented during 24 h ambulatory monitoring with or without anti-arrhythmic or rate-controlling drugs. Patients with sinus pauses, which were recorded independently of the AF terminations, were not included in this study. All studied BTS patients preferred to undergo the curative catheter- ablation procedures for paroxysmal AF rather than to receive the implantation of pacemakers.

**Electrophysiological study**

After written informed consent was obtained from each patient, the electrophysiological study and catheter ablation were performed, as described previously, under the approval protocol of the institution. All patients had effective anticoagulation for at least 1 month and underwent transoesophageal echocardiography to exclude left atrial (LA) thrombus formation before the procedure. All anti-arrhythmic drugs were discontinued for at least five half-lives before the study.

The electrophysiological study was performed in a post-absorptive state. Surface ECG and bipolar endocardial electrograms were continuously monitored and recorded on polygrams (EP Med Systems, Inc., West Berlin, NJ, USA).

**Catheter ablation of atrial fibrillation**

The LA and PVS were examined through the trans-septal route with three catheters: two for the circumferential PV mappings and the other for the RF ablation. The PV mapping was performed using a steerable circular catheter with a diameter of either 20, 25, or 30 mm equipped with 20 mm electrodes in a loop made of shape-retaining material orthogonal to the shaft (Lasso, Biosense Webster, Diamond Bar, CA, USA). A dosage of 5000 U of heparin was administered intravenously after the trans-septal procedure, followed by a continuous infusion of ~1000 U/h of heparin to maintain an active clotting time >250 s. Each of the four PVS was individually isolated from the LA as proximal as possible at the PV antrum under ongoing rhythm (sinus rhythm or AF). The RF applications were delivered at the segments of the earliest PV potential deviations or electrogram polarity reversal on the perimeter of the PV antrum. The RF energy was delivered with an 8 mm tip thermocouple-equipped ablation catheter (Blazer II, Boston Scientific, CA, USA). The PVI was performed with a target temperature of 50°C, a power limit of 30 W for a duration of 30–60 s. The endpoint of the PVI was the establishment of the bidirectional conduction block between the LA and PV, confirmed by the elimination of the PV potentials and the absence of PV to LA conductions. In patients with a history of common right atrial flutter, the bidirectional blockline of the cavo-tricuspid isthmus was created in the same session.

**Estimation of sinus node function**

The SNRT was estimated at the beginning of the study. The SNRT recovery time (SNRT), evaluated by 30 s burst pacing trains at every 50 ms from 600 to 300 ms, was determined as the longest time from the stimulus artifact to the earliest atrial activity. The corrected SNRT was determined by correcting for the underlying sinus cycle length.

**Analysis of mean heart rate and heart rate variability**

The mean heart rate and HRV were analysed using 24 h ambulatory monitoring before the procedure and at the first week, 1, 3, 6, 9, and 12 months after ablation. These monitoring were performed in ambulatory settings, except for the monitoring at the first week which performed in hospital. The autonomic modulation was assessed by time- and frequency-domain HRV analysis with commercially available software (MemCalc/CHIRAM, GMS, Tokyo, Japan). The analysis was automatically performed in short segments and averaged subsequently. The time-domain HRV analysis, including root-mean-square successive differences in the adjacent NN intervals (rMSSD) and the standard deviation of the NN intervals (SDNN), was obtained by using the continuous data during 24 h. The frequency-domain analysis was performed by a fast Fourier transform of the NN intervals. The low frequency (LF; range: 0.04–0.15 Hz), high frequency (HF; range: 0.15–0.40 Hz), and LF/HF ratio were calculated. During the analysis, only normal beats were measured, and all AF, extrasystolic beats, and artefacts were eliminated. The records with normal beats that were ≥5% of the available beats were excluded.

**Patient follow-up**

All patients were monitored in the hospital at least for 4 days after ablation. The patients were given a 3-month follow-up in an outpatient clinic (once a month) and re-evaluated by 24 h ambulatory monitoring without taking any anti-arrhythmic drugs. A recurrence of AF was defined as the appearance of AF lasting more than 1 min. A repeat ablation session was recommended for patients who were judged to have an unsuccessful procedure at 3 months after the initial procedure.

**Statistical analysis**

All variables are expressed as mean ± SD. The sequential data measurements were analysed by repeated-measures ANOVA followed by Fisher’s PLSD for multiple comparisons. Comparisons between groups were performed with Student’s t-test or the 2 × 2 χ² tests. Statistical significance was established at P < 0.05.

**Results**

**Patients’ characteristics**

The clinical characteristics of all 11 BTS patients (7 men; mean age: 61.9 ± 7.8 years) and 15 control group patients (12 men; mean age: 60.1 ± 6.4 years) are shown in Table 1. The history of AF duration and the diameter of LA were not significantly different between the two groups. Although there was one patient with hypertension in the BTS group, no patient was observed to have structural heart disease in either group.
Sinus node function

In the BTS group, although symptomatic prolonged sinus pauses on termination of AF (3.9–10.6 s, average 6.6 ± 2.2 s) were documented, the measured corrected SNRT was shorter than expected (0.5–4.9 s, average 2.3 ± 1.4 s). In the control group, there was no evidence of sinus node dysfunction during the session and throughout the observation period.

Ablation of atrial fibrillation and clinical outcome

All four PVs were successfully isolated from the LA in all patients of this study during the first session. Subsequently, 8 (72.7%) and 10 (66.7%) patients in the BTS and the control group, respectively, became free from AF after the first procedure. After the initial procedure, AF recurred in three (27.3%) and five (33.3%) patients in the BTS and the control group, respectively, during the first 3 months of observation period. All three patients in the BTS group experienced further episodes of syncope or dizziness correlated with prolonged sinus pauses, but not five patients in the control group. Subsequently, repeat procedures were performed in all eight patients in both groups. In total, after an average of 1.4 procedures, all 11 BTS patients became free from both AF and prolonged sinus pauses during a mean observation period of 22 ± 14 months from the last ablation session. As a result, no patient required pacemaker implantation. In the control group, all 15 patients also remained free from AF after an average of 1.5 procedures for 20 ± 9 months of observation from the last ablation session. In addition, no life-threatening complications were observed including PV stenosis in this study population.

**Table 1 Patients’ characteristics**

<table>
<thead>
<tr>
<th></th>
<th>BTS group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
<td>61.9 ± 7.8</td>
<td>60.1 ± 6.4</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Male/female (n)</strong></td>
<td>7/4</td>
<td>12/3</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>AF duration (year)</strong></td>
<td>3.0 ± 2.1</td>
<td>3.9 ± 5.5</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>LAD (mm)</strong></td>
<td>36.8 ± 5.1</td>
<td>37.8 ± 4.7</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Longest pause (s)</strong></td>
<td>6.6 ± 2.2</td>
<td>2.1 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Corrected SNRT (s)</strong></td>
<td>2.3 ± 1.4</td>
<td>0.4 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>PVI session (n)</strong></td>
<td>1.4</td>
<td>1.5</td>
<td>0.74</td>
</tr>
</tbody>
</table>

BTS, bradycardia–tachycardia syndrome; AF, atrial fibrillation; LAD, diameter of left atrium; SNRT, sinus node recovery time; PVI, pulmonary vein isolation.

**Table 2 Changes of heart rate variability and mean heart rate through the pulmonary vein isolation procedure**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 week</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rMSSD (ms)</td>
<td>40.0 ± 18.6</td>
<td>20.4 ± 8.2*</td>
<td>20.7 ± 12.3*</td>
<td>24.3 ± 11.8*</td>
<td>22.0 ± 9.1*</td>
<td>28.7 ± 21.8</td>
<td>26.4 ± 15.8*</td>
<td>0.032</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>149.7 ± 37.3</td>
<td>79.8 ± 29.0*</td>
<td>115.8 ± 10.9*</td>
<td>115.1 ± 35.7*</td>
<td>129.9 ± 40.5</td>
<td>133.6 ± 22.9</td>
<td>137.2 ± 40.5</td>
<td>0.002</td>
</tr>
<tr>
<td>HF (s)</td>
<td>51.0 ± 24.6</td>
<td>27.5 ± 15.5*</td>
<td>25.5 ± 13.2*</td>
<td>28.3 ± 21.6*</td>
<td>25.5 ± 13.7*</td>
<td>25.6 ± 19.9*</td>
<td>30.2 ± 18.0*</td>
<td>0.036</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.22 ± 0.42</td>
<td>0.93 ± 0.58</td>
<td>1.09 ± 0.50</td>
<td>0.91 ± 0.54</td>
<td>0.92 ± 0.39</td>
<td>1.16 ± 0.74</td>
<td>1.47 ± 0.92</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean RR (ms)</td>
<td>969 ± 126</td>
<td>905 ± 131</td>
<td>923 ± 156</td>
<td>949 ± 130</td>
<td>953 ± 135</td>
<td>979 ± 158</td>
<td>968 ± 170</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control group</td>
<td>n = 15</td>
<td>n = 15</td>
<td>n = 15</td>
<td>n = 15</td>
<td>n = 15</td>
<td>n = 15</td>
<td>n = 15</td>
<td></td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>40.8 ± 19.7</td>
<td>21.2 ± 8.2*</td>
<td>21.6 ± 11.8*</td>
<td>28.2 ± 17.6*</td>
<td>27.6 ± 12.2*</td>
<td>21.7 ± 6.6*</td>
<td>17.8 ± 3.2*</td>
<td>0.045</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>163.9 ± 53.8</td>
<td>77.2 ± 28.9*</td>
<td>120.9 ± 49.1*</td>
<td>119.6 ± 45.5*</td>
<td>119.5 ± 38.3*</td>
<td>95.6 ± 6.6*</td>
<td>106.4 ± 9.1*</td>
<td>0.001</td>
</tr>
<tr>
<td>HF (s)</td>
<td>39.5 ± 14.6</td>
<td>16.4 ± 6.1*</td>
<td>19.5 ± 22.5*</td>
<td>20.0 ± 18.0*</td>
<td>28.9 ± 27.8</td>
<td>30.7 ± 19.2</td>
<td>39.6 ± 39.6</td>
<td>0.042</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.37 ± 1.34</td>
<td>0.64 ± 0.37</td>
<td>1.40 ± 1.09</td>
<td>1.74 ± 1.28</td>
<td>1.27 ± 0.77</td>
<td>2.06 ± 0.84</td>
<td>1.33 ± 0.84</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean RR (ms)</td>
<td>895 ± 113</td>
<td>752 ± 108*</td>
<td>802 ± 99*</td>
<td>811 ± 102*</td>
<td>839 ± 116</td>
<td>796 ± 74</td>
<td>842 ± 50</td>
<td>0.041</td>
</tr>
</tbody>
</table>

BTS, bradycardia–tachycardia syndrome; rMSSD, root-mean-square successive differences in the adjacent NN intervals; SDNN, standard deviation of the NN intervals; HF, high frequency; LF, low frequency.

*P < 0.05 vs. baseline.
control group for the first 3 months (68.1 ± 8.9 bpm at baseline, 81.2 ± 10.3, 76.3 ± 11.1, 75.8 ± 9.0, 72.7 ± 9.6, 75.8 ± 7.4, 71.5 ± 4.1 bpm at first week, 1, 3, 6, 9, and 12 months after PVI, respectively, *P < 0.05 vs. baseline).

As shown in Figure 3B, the normalized value of the mean RR trends was significantly smaller in the control group than that in the BTS group at the first week and 3 months after the procedure (P < 0.05).

**Discussion**

The present study demonstrates that catheter-based PVI eliminated not only paroxysmal AF but also prolonged sinus pauses in all 11 BTS patients. A significant reduction in the parasympathetic modulation after PVI was observed in both the BTS patients and the control group patients; however, a transient increase in the mean heart rate after PVI was only observed in the control group patients. As far as we know, this is the first study examining the effects of the PVI procedure on the autonomic modulation and mean heart rate in the BTS patients.

Although the efficacy of catheter-based PVI for patients with paroxysmal AF has already been established, there have so far only been a few reports describing the efficacy of PVI in cases with both paroxysmal AF and BTS. Hocini et al. demonstrated that prolonged sinus pauses could be eliminated by the curative ablation of paroxysmal AF and the discontinuation of antiarrhythmic or rate-controlling drugs. Transient sinus node remodeling induced by 10–15 min of rapid atrial pacing even in patients without sinus node dysfunction has been demonstrated by Hadian et al. The elimination of paroxysmal AF by catheter-based PVI can therefore be one of the therapeutic choices in patients with both paroxysmal AF and BTS.

In paroxysmal AF patients without sinus node dysfunction, it has been already reported that RF applications for PV or around the PV antrum often induced sinus bradycardia, sinus pauses, atrioventricular block, or hypotension through vagal reflexes during the
procedure. Subsequently, these vagal reflexes would reduce parasympathetic activities and increase heart rates after the procedure.3–7 The ganglionated plexi, which exist on the epicardium of the PV antrum, were shown to be closely related to these reflexes.11 Hsieh et al.5 demonstrated a significant increase in the mean heart rate and a significant decrease in the parasympathetic HRV parameters after RF applications for focal AF originating from PVs. Pappone et al. also reported that vagal reflexes and complete vagal denervations were obtained in 34.3% of the patients who underwent circumferential PV ablation for paroxysmal AF. These vagal denervations were closely associated with a reduction in the subsequent AF recurrences, which might therefore play an additional anti-arrhythmic role in paroxysmal AF patients.6 Regardless of such accumulated evidence in patients with normal sinus node function, there are no previous data regarding the effects of PVI on the autonomic modulation in BTS patients. In the present study, a significant parasympathetic attenuation was observed in the BTS patients as well as in the control group patients. The HRV parameters of rMSSD, SDNN, and HF were significantly decreased after segmental PVI from 1 week to 3 months (P < 0.05 vs. baseline), suggesting the persistence of the parasympathetic attenuation for at least 3 months after the procedure. This transient attenuation of parasympathetic modulation has been already described in some literature.5,12 Bauer et al.12 mentioned the difference of the time course of parasympathetic attenuation according to different strategies for ablation of AF. Anatomically guided circumferential PVI induced a decrease of autonomic function for at least 1 year, whereas it returned to baseline value within 1 month in the segmental PVI group.

In this study, no significant difference could be noted in the mean heart rate after PVI when compared with the baseline value in the BTS group, in spite of a significant reduction in the parasympathetic modulation, which seems to be contradicted to the demonstration already published by Hocini et al. They found a significant increase in the mean heart rate (P = 0.001) after the PVI procedure in patients with BTS (n = 20, 14 men, mean age: 56.0 ± 12.1 years).2 Although the precise mechanism of this discrepancy remains to be determined, the changes in mean heart rate would be influenced by the differences of sample size, age, sex, pre-existing sinus node dysfunction, and strategies for ablation of AF between these two studies.

**Study limitation**

First, the clinical outcome was evaluated by the patients' symptoms, electrocardiograms at the outpatient clinic, and 24 h ambulatory monitoring. Therefore, asymptomatic episodes of AF might be overlooked in a recurrence of AF, although most of all patients included in this study were symptomatic before ablation. Second, all the BTS patients in this study had sinus pauses only after the termination of AF. As a result, the findings of this study should not be applied to patients with sinus pauses independent of AF terminations. Third, since sinus node function was not estimated after the PVI procedure, the degree of participation of both ‘structural’ and neurally mediated components of sinus node dysfunction was not known. Fourth, autonomic modulation would be influenced by various factors such as age, sex, daily activity, structural heart disease, anti-arrhythmic drugs, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, smoking, and alcohol drinking. Further specifically designed experimental protocol that can exclude the influence of above factors may help to clarify more precise mechanisms underlying these autonomic modifications.
Conclusion

The parasympathetic modulation was found to be significantly attenuated after the PVI procedure in the BTS patients as well as in the control group patients without any sinus node dysfunction; therefore, this phenomenon is considered to be an essential effect of PVI. Although the mean heart rate significantly increased in the control group, it did not significantly change in the BTS group, probably due to the pre-existing sinus node dysfunction. These observations may ultimately shed some light on the pathophysiology of BTS.

Conflict of Interest: none declared.

References


