Vagal Modification Can Also Help Prevent Late Recurrence of Atrial Fibrillation After Segmental Pulmonary Vein Isolation

Naoki Yoshida, MD; Takumi Yamada, MD*; Yoshimasu Murakami, MD**; Taro Okada, MD**; Yuichi Ninomiya, MD***; Junji Toyama, MD***; Yukihiro Yoshida, MD†; Naoya Tsuboi, MD††; Masahiro Muto, MD; Yasuya Inden, MD; Makoto Hirai, MD‡; Toyoaki Murohara, MD

Background: The relationship between vagal modification and paroxysmal atrial fibrillation (PAF) recurrence after segmental pulmonary vein (PV) isolation (S-PVI) was investigated.

Methods and Results: S-PVI was performed in 77 PAF patients using a multielectrode basket or circular catheter to achieve electrical disconnection of all 4 PVs independent of eliminating vagal reflexes. Serial Holter-recordings were obtained at baseline, immediately and 1, 3, 6, and 12 months after S-PVI to analyze the heart rate variability. Fifty-one patients were free from symptomatic PAF (Group A) and 26 had late PAF recurrences (Group B) at 12-month follow-up. Immediately after S-PVI, the root mean square of the successive differences (rMSSD) and high-frequency (HF) power, which reflected parasympathetic nervous activity, were significantly lower in Group A than in Group B (rMSSD: 33.6±26.0 vs 60.6±23.2 ms², P<0.05; ln HF: 8.73±0.84 vs 9.31±0.95 ms², P<0.05). There were no significant differences in the average heart rate or ratio of the low-frequency to HF powers between the 2 groups. By multivariate analysis, only the HF immediately after S-PVI was an independent predictor of PAF recurrence (hazard ratio 1.707, 95% confidence interval 1.057–2.756, P<0.05).

Conclusions: Vagal modification after S-PVI could also help prevent late recurrence of PAF. (Circ J 2009; 73: 632–638)

Key Words: Atrial fibrillation; Autonomic nervous system; Heart rate variability; Radiofrequency catheter ablation

Segmental catheter ablation (SCA) of the pulmonary veins (PVs) is an effective technique for curing paroxysmal atrial fibrillation (PAF). It has been reported that adding an ablation aimed at vagal denervation that is adequate for eliminating the vagal reflexes or targeting ganglionic plexi in the left atrium (LA) may reduce atrial fibrillation (AF) recurrence. Those reports suggest that modification of autonomic nervous function may prevent PAF recurrence. SCA alone has induced an immediate decrease in the autonomic nervous function, but the relationship between modification of autonomic nervous function and PAF recurrence after SCA remains unknown. This study was undertaken to reveal that relationship by analyzing heart rate variability (HRV).

Methods

Patient Characteristics

The study population consisted of 97 patients (74 men, 58±12 years) with symptomatic PAF refractory to 2±1 class I or class III antiarrhythmic drugs (not including amiodarone). The mean PAF history was 4±4 years (0–17). The mean echocardiographic dimension of the LA was 35±5 mm (25–46) and mean left ventricular ejection fraction 68±9% (50–89%). Three patients had a history of an old myocardial infarction (MI) and 3 had had prior embolic episodes. The exclusion criteria were sick sinus syndrome, diabetes mellitus, thyroid dysfunction, recent MI (<6 months), history of a prior thoracotomy, β-blocker therapy, and a pacing rhythm. Each patient gave written informed consent, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the study.

Electrophysiologic Study

A 7-French decapolar catheter with 1.5-1-mm interelectrode spacing between each electrode pair (St Jude Medical, AF Division, Minnetonka, MN, USA) was placed in the coronary sinus via the subclavian vein. The transeptal procedure was performed with intracardiac echocardiography guidance recorded with a 9-French transducer catheter (Boston Scientific, Natick, MA, USA) operating at 9 MHz. Catheterization into the LA was performed with a 1-puncture and 2-sheath technique (1 sheath (8-French, St Jude Medical, AF Division) for an ablation catheter and another (8.5-French, Soft Tip EP Sheath™, EP Technologies, Boston Scientific Corporation/San Jose, CA, USA) for a mapping catheter). After the transeptal procedure, sys-
PV Mapping With Multielectrode Basket Catheter (MBC)

In all cases, PV mapping and SCA were performed by the same technique as we previously reported. All 4 PVs were targeted for this SCA technique according to the evidence reported in previous studies. When the right inferior PV was difficult to cannulate with a MBC, it was isolated with a circular catheter as previously reported. The heart rate (HR) and time- and frequency-domain power were targeted for this SCA technique according to the evidence reported in previous studies.

Vagal Modification in S-PVI Reduces AF Recurrence

Late recurrence

No Yes

Minimum HR, beats/min 46.0±6.9 48.3±7.6 0.32
Average HR, beats/min 67.2±11.9 69.3±8.1 0.55
Maximum HR, beats/min 118.9±21.7 115.3±21.0 0.61
PACs, % 3.2±4.1 3.4±3.4 0.83
ASDNN, ms 61.6±14.2 63.6±10.2 0.76
SDANN, ms 126.6±29.2 119.9±50.8 0.58
SDNN, ms 152.0±32.7 150.8±72.3 0.94
rMSSD, ms 59.0±26.7 59.2±41.1 0.99
ln LF, ms² 8.99±0.52 8.79±0.42 0.21
ln HF, ms² 9.36±0.56 9.06±0.51 0.10
LF/HF 0.72±0.23 0.78±0.19 0.42

HR, heart rate; HRV, HR variability; PAC, premature atrial contraction; ASDNN, mean of the standard deviation of all NN intervals for all 5-min segments; SDANN, standard deviation of the average of the NN intervals in all 5-min segments; SDNN, standard deviation of all NN intervals; rMSSD, root mean square successive differences; ln, natural logarithm; LF, low-frequency power; HF, high-frequency power; LF/HF, ratio of LF to HF.

Figure 1. Clinical outcome after segmental ostial catheter ablation in the 77 patients with paroxysmal atrial fibrillation.
HRV were analyzed from the Holter recordings using an analysis program (Philips Zymed Holter 2010 Plus). Supraventricular premature beats, AF, ventricular premature beats, electrical noise, and other aberrant ECG signals were excluded from the HRV analysis. The underlying rhythm was carefully analyzed, and only artifact-free episodes of sinus rhythm were included in further analyses. HRV was used as an indicator of autonomic activity in accordance with the guidelines for standardization.\textsuperscript{12} The time-domain measures of the HRV included the standard deviation (SD) of all NN intervals (SDNN), SD of the averages of the NN intervals in all 5-min segments (SDANN), mean of the SD of all NN intervals for all 5-min segments (ASDNN), and root mean square successive differences (rMSSD). The frequency-domain measures of the HRV included the low-frequency (LF: 0.04–0.15 Hz) power, high-frequency (HF: 0.15–0.40 Hz) power, and ratio of the LF to HF powers (LF/HF). The frequency-domain HRV was calculated by a fast Fourier transform for each 5-min segment of data. All values of the frequency-domain HRV were expressed as the average of all 5-min segments of the 24-h recordings and were logarithmically transformed to avoid the undue influence of extreme values. The rMSSD and HF were used to reflect parasympathetic nervous activity, and the LF/HF was used to reflect sympathetic nervous activity.

Follow-up
During the follow-up period, none of the patients was administered antiarrhythmic drugs. Clinical follow up was performed at 2 weeks, 1 month and every month until 12 months after the procedure, using 24-h Holter and cardiac recordings. All patients who reported symptoms were given an event monitor to document the cause of the symptoms. Enhanced electron beam tomography was performed in all the patients at 3 and 6 months after the procedure for the detection of PV stenosis.

Statistical Analysis
All values are expressed as the mean±SD. The frequency-domain measurements of the HRV (LF and HF) were expressed in squared milliseconds. Comparisons of continuous variables were analyzed using the Student’s t-test. Categorical variables expressed as numbers and percentages in different groups were compared with a chi-square test. Multivariate Cox regression analysis was performed to determine the independent predictors of AF recurrence. Statistical significance was considered to be present for \( P < 0.05 \).

Results

Catheter Ablation
In all the study patients, successful SCA of all 4 PVs was achieved. In 34 right inferior PVs in which QMS mapping was not available, successful SCA was achieved with a circular catheter. In 20 patients, spontaneous AF was induced after successful SCA and additional SVC isolation and/or focal ablation targeting the triggers was performed. All 20 cases were excluded from the analysis because any additional ablation might have affected autonomic nervous function. The average total procedure and fluoroscopy times was 209±51 min and 87±22 min, respectively. The

\[\text{Figure 2. Serial changes in heart rate (HR), percentages of premature atrial contractions (PACs), and heart variability before, immediately (1 day), 1 month (1M), 3 months (3M), 6 months (6M), and 12 months (12M) after segmental ostial catheter ablation (SCA) in Group A patients.}^* P < 0.05 \text{ vs before ablation.} \text{LF, low-frequency; HF, high-frequency; LF/HF, ratio of the LF to HF powers; rMSSD, root mean square of the successive differences; SDNN, standard deviation of all NN intervals.}\]
average total RF duration needed to complete the SCA was 70±23 min for 66±18 RF applications. During SCA of the left PVs, transient AV block was elicited in 3 patients. During SCA of the right PVs, sinus bradycardia with hypertension was elicited in 2 patients.

Clinical Outcomes

Six patients had early PAF recurrence within 24 h of SCA and all of them also had late PAF recurrences. Of the 77 patients, 51 were free from symptomatic PAF without any antiarrhythmic drugs (Group A) and 26 had a late PAF recurrence (Group B) at 12 months follow-up (Figure 1). There were no significant differences between the 2 groups in the total number of RF applications (66±16 vs 67±21, P=0.85), total RF energy delivery (68,127±26,054 vs 69,864±32,541 J, P=0.82) or extent of the targeted regions (69±13 vs 70±12% of the circumference, P=0.71).

HR and HRV Changes

In Group A, the minimum and average HR increased immediately after SCA and remained elevated for 6 months. The time- and frequency-domain HRV parameters, including the SDNN, rMSSD and HF, decreased immediately after SCA and remained attenuated for 3–6 months. The LF/HF did not change significantly immediately after SCA, but minimum average HR also increased immediately after the SCA, but the time- and frequency-domain HRV parameters, excepting the SDANN and SDNN, did not change significantly (Tables 2, 4). Because 21 of 26 (76.9%) Group B patients underwent another ablation procedure (n=18) and/or took antiarrhythmic drugs or β-blockers (n=10) because of PAF recurrence, subsequent Holter recordings after those interventions were excluded from the HRV analyses of those patients.

Comparisons of the HR and HRV in the 2 groups immediately after SCA are shown in Table 4. The rMSSD and HF, which reflect parasympathetic nervous activity, were significantly lower in Group A than in Group B (rMSSD: 33.6±26.0 vs 60.6±25.2 ms, P<0.05; ln HF: 8.73±0.84 vs 9.11±0.11, P=0.05).

### Table 3. Comparison of the Changes in HR and HRV Before and After Ablation in Group A

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 day</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum HR, beats/min</td>
<td>46.0±6.9</td>
<td>58.6±10.7*</td>
<td>55.2±10.5*</td>
<td>53.5±8.6*</td>
<td>53.1±7.0*</td>
<td>49.3±5.1</td>
</tr>
<tr>
<td>Average HR, beats/min</td>
<td>67.2±11.9</td>
<td>76.9±8.9*</td>
<td>76.9±9.2*</td>
<td>74.9±7.9*</td>
<td>76.2±4.9*</td>
<td>72.1±4.8</td>
</tr>
<tr>
<td>Maximum HR, beats/min</td>
<td>118.9±21.7</td>
<td>120.0±17.1</td>
<td>123.3±14.1</td>
<td>121.3±13.3</td>
<td>121.5±13.7</td>
<td>118.7±10.5</td>
</tr>
<tr>
<td>PACs, %</td>
<td>3.2±4.1</td>
<td>1.2±2.0*</td>
<td>0.9±1.7*</td>
<td>0.5±1.2*</td>
<td>0.7±1.7*</td>
<td>0.5±0.9*</td>
</tr>
<tr>
<td>ASDNN, ms</td>
<td>61.6±14.2</td>
<td>37.2±20.0*</td>
<td>50.3±30.0</td>
<td>45.4±26.4*</td>
<td>44.0±15.5*</td>
<td>48.3±12.3*</td>
</tr>
<tr>
<td>SDANN, ms</td>
<td>126.6±29.2</td>
<td>79.1±29.1*</td>
<td>107.3±27.0*</td>
<td>113.7±35.6</td>
<td>111.0±24.4*</td>
<td>128.9±21.7</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>152.0±32.7</td>
<td>92.0±36.0*</td>
<td>131.0±39.6*</td>
<td>130.0±45.4*</td>
<td>126.8±36.7*</td>
<td>140.9±23.7</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>59.0±26.7</td>
<td>33.6±26.0*</td>
<td>36.0±28.6*</td>
<td>37.9±24.8*</td>
<td>47.4±24.9</td>
<td>50.7±22.0</td>
</tr>
<tr>
<td>ln LF, ms²</td>
<td>9.99±0.52</td>
<td>8.36±0.90*</td>
<td>8.56±0.82*</td>
<td>8.59±0.70*</td>
<td>8.82±0.69</td>
<td>8.87±0.56</td>
</tr>
<tr>
<td>ln HF, ms²</td>
<td>9.36±0.56</td>
<td>8.73±0.84*</td>
<td>8.85±0.80*</td>
<td>8.72±0.81*</td>
<td>9.03±0.87</td>
<td>9.08±0.61</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.72±0.23</td>
<td>0.75±0.29</td>
<td>0.79±0.27</td>
<td>0.89±0.17*</td>
<td>0.84±0.23*</td>
<td>0.84±0.28</td>
</tr>
</tbody>
</table>

*P<0.05 vs before ablation.

Abbreviations as in Table 2.

### Table 4. Comparison of HR and HRV Immediately After SCA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No</th>
<th>Yes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum HR, beats/min</td>
<td>58.6±10.7</td>
<td>55.8±7.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Average HR, beats/min</td>
<td>76.9±8.9</td>
<td>78.7±8.1</td>
<td>0.40</td>
</tr>
<tr>
<td>Maximum HR, beats/min</td>
<td>120.0±17.1</td>
<td>123.2±17.7</td>
<td>0.46</td>
</tr>
<tr>
<td>PACs, %</td>
<td>1.2±2.0</td>
<td>2.5±3.2</td>
<td>0.049</td>
</tr>
<tr>
<td>ASDNN, ms</td>
<td>37.2±20.0</td>
<td>50.1±26.1</td>
<td>0.02</td>
</tr>
<tr>
<td>SDANN, ms</td>
<td>79.1±29.1</td>
<td>83.0±21.8</td>
<td>0.56</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>92.0±36.0</td>
<td>111.2±39.2</td>
<td>0.046</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>33.6±26.0</td>
<td>60.6±23.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>ln LF, ms²</td>
<td>8.36±0.90</td>
<td>8.68±0.95</td>
<td>0.16</td>
</tr>
<tr>
<td>ln HF, ms²</td>
<td>8.73±0.84</td>
<td>9.31±0.95</td>
<td>0.009</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.75±0.29</td>
<td>0.63±0.23</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

### Table 5. Results of Cox Regression Analysis in 77 PAF Patients

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Coefficient</th>
<th>P value</th>
<th>Hazard ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>−0.019</td>
<td>0.38</td>
<td>0.981</td>
<td>0.940–1.024</td>
</tr>
<tr>
<td>Sex (1/0=m/F)</td>
<td>0.067</td>
<td>0.91</td>
<td>1.069</td>
<td>0.358–3.194</td>
</tr>
<tr>
<td>Duration of PAF</td>
<td>−0.009</td>
<td>0.89</td>
<td>0.991</td>
<td>0.877–1.120</td>
</tr>
<tr>
<td>SHD (0/1=nlésyès)</td>
<td>−1.188</td>
<td>0.29</td>
<td>0.305</td>
<td>0.034–2.741</td>
</tr>
<tr>
<td>LAD</td>
<td>0.041</td>
<td>0.45</td>
<td>1.042</td>
<td>0.936–1.159</td>
</tr>
<tr>
<td>LVEF</td>
<td>−0.015</td>
<td>0.65</td>
<td>0.985</td>
<td>0.925–1.050</td>
</tr>
<tr>
<td>Average HR</td>
<td>0.017</td>
<td>0.59</td>
<td>1.017</td>
<td>0.956–1.082</td>
</tr>
<tr>
<td>ln HF</td>
<td>0.535</td>
<td>0.03</td>
<td>1.707</td>
<td>1.057–2.756</td>
</tr>
<tr>
<td>LF/HF</td>
<td>−1.536</td>
<td>0.13</td>
<td>0.215</td>
<td>0.029–1.587</td>
</tr>
<tr>
<td>No. of RF lesions</td>
<td>−0.016</td>
<td>0.45</td>
<td>1.010</td>
<td>0.984–1.037</td>
</tr>
</tbody>
</table>

CI, confidence interval; RF, radiofrequency. Other abbreviations as in Tables 1, 2.

Circulation Journal  Vol.73, April 2009
The percentage of PACs out of the total beats in the Holter recordings was significantly lower in Group A than in Group B (PACs: 1.2±2.0 vs 2.5±3.2%, \(P<0.05\)). There was a significant correlation between the HF and percentage of PACs immediately after SCA \(r(15) = 0.525, P<0.0001\). There were no significant differences between the 2 groups in the minimum, average or maximum HR and LF/HF.

Repeat Procedures
In total, 18 (69%) of 26 Group B patients underwent a second procedure, and 17 (94%) of them exhibited the recovery of the electrical connections between the LA and PVs in 11 left superior PVs, 12 right superior PVs, 11 left inferior PVs, and 6 right inferior PVs. In all of those PVs, a successful electrical disconnection could be achieved by the same technique used in the first procedure.

Predictors of AF Recurrence
After 12 months of follow-up since the first SCA procedure, 66% of the patients were free from symptomatic AF. By multivariate Cox regression analysis, only the HF immediately after SCA was an independent predictor of PAF recurrence (Table 5).

Discussion
Major Findings
Vagal modification varied among the patients after SCA, the end point of which was PV electrical disconnection independent of whether or not the vagal reflexes were completely eliminated. Parasympathetic nervous activity after SCA was significantly lower in the patients without PAF recurrence than in the patients with PAF recurrence, and that remained attenuated for 3–6 months in the patients without PAF recurrence. Most of time-domain HRV parameters (ASDNN, SDNN, and rMSSD) after SCA tended to be lower in the patients without PAF recurrence than in the patients with PAF recurrence. This study demonstrated that further vagal modification and HRV attenuation after SCA resulted in greater suppression of PAF recurrence. The study results also suggest that the HF alone could be a valid predictor of PAF recurrence after SCA.

Parasympathetic Attenuation and AF Recurrence
After SCA
An anatomical study has recently demonstrated that the adrenergic and cholinergic nerve densities are highest in the LA within 5 mm of the LA–PV junction and are not homogeneous around the PV ostium, independent of the distribution of the myocardial fibers. Therefore, in the present study vagal modification might have varied among the patients after SCA in which RF energy was delivered segmentally around the PVs, targeting the myocardial connection between the LA and PVs. The main cause of AF recurrence after SCA is the fairly high occurrence of recovery of the electrical connections between the LA and PVs which was also observed in this study. On the other hand, it has been recently reported that there are no statistically significant differences in the persistence of PV disconnections in the patients with and without recurrence after an AF ablation procedure, although that was not demonstrated in the present study. One possibility that may explain the results of these 2 studies is that recovery of the electrical connections happens to occur in the arrhythmogenic PVs in the patients with AF recurrence, whereas it does not occur in the arrhythmogenic PVs in the patients without AF recurrence.

Recovery of the electrical connections of the PVs in the patients after SCA in which RF energy was delivered segmentally around the PVs, targeting the myocardial connection between the LA and PVs.
reasons: (1) SCA is an easier technique for achieving PV electrical disconnection than LACA, (2) it was recently reported that there is no superiority of LACA over SCA for the treatment of AF in terms of efficacy and safety27,28 and (3) LACA can have some life-threatening complications such as atrio-esophageal fistula29 or congestive heart failure associated with LA edema30,31. Therefore, we believe that our study provides some important evidence for an advance in the catheter ablation of AF.

Study Limitations
We did not investigate the difference in vagal modification between patients with and without vagal reflexes during SCA, because coronary sinus pacing during SCA in the left PVs might have masked some vagal reflexes. However, Hsieh et al reported that regardless of the appearance of vagal reflexes during PV ablation, the HRV parameters described above showed similar changes32. Therefore, we believe that the appearance of vagal reflexes did not significantly change the results of this study.

Recent reports have revealed by the use of transtelephonic and long-term Holter monitoring that asymptomatic AF recurrence after AF ablation occurs more often than might be expected and thus freedom from AF after AF ablation may be overestimated33,34. In this study, asymptomatic PAF recurrences might have been missed and the cure rate might have been overestimated because intermittent Holter recordings alone were performed as clinical follow up.

Conclusions
Parasympathetic nervous activity after SCA was significantly lower in the patients without PAF recurrence than in those with PAF recurrence. This study suggests that vagal modification during SCA could also help prevent late recurrence of PAF.

Disclosure
There was no financial support for this study.

References


