Alterations of Heart Rate Variability After Radiofrequency Catheter Ablation of Focal Atrial Fibrillation Originating From Pulmonary Veins

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Background—Transient sinus bradycardia and hypotension have been reported as complications during radiofrequency (RF) ablation of focal atrial fibrillation (AF) originating from pulmonary veins (PVs). This study used heart rate variability (HRV) to evaluate the effects of focal PVs ablation on autonomic function.

Methods and Results—Thirty-seven patients with paroxysmal AF were referred for ablation. The study group included 30 patients who underwent transseptal ablation of PVs, and the control group included 7 patients who underwent the transseptal procedure without ablation. The mean sinus rate and time-domain (standard deviation of RR intervals and root-mean-square of differences of adjacent RR intervals) and frequency-domain (low frequency, high frequency, and low-frequency/high-frequency ratio) analyses of HRV were obtained by use of 24-hour Holter monitoring before and 1 week, 1 month, and 6 months after ablation. All the triggering points of AF were from PVs, and they were successfully ablated. Severe bradycardia and hypotension were noted during ablation of PVs in 6 patients (group IA); 24 patients without the above complication belonged to group IB. Compared with preablation values, a significant increase in mean sinus rate and low-frequency/high-frequency ratio and a significant decrease in standard deviation of RR intervals, root-mean-square of differences of adjacent RR intervals, low frequency, and high frequency were noted in groups IA and IB patients 1 week after ablation. The changes in HR and HRV recovered spontaneously in the 2 subgroups by 1 month later. These parameters of HRV did not change in the control group after the transseptal procedure.

Conclusions—Transient autonomic dysfunction with alterations in HR and HRV occurred after ablation of focal AF originating from PVs. (Circulation. 1999;100:2237-2243.)

Key Words: fibrillation ■ veins ■ ablation

Autonomic dysfunction has been reported as a consequence of radiofrequency (RF) catheter ablation of various kinds of supraventricular tachycardia.1–6 Several reports have demonstrated an increase in heart rate (HR) and a decrease in HR variability (HRV) after ablation of slow atrioventricular nodal, posteroseptal, and para-hisian accessory pathways.2–6 These reports suggested that transient parasympathetic nervous withdrawal might be one of the mechanisms that causes these HR effects when RF energy is applied around these pathways. Recently, RF catheter ablation of pulmonary veins (PVs) has been demonstrated to cure focal atrial fibrillation (AF).7–10 However, transient sinus bradycardia, sinus arrest, and hypotension have been reported as complications during focal ablation of PVs, and thermal stimulation of vagus nerve fibers might play an important role in these complications.9 Therefore, the purpose of the present study was to evaluate the effects of focal PVs ablation on autonomic function by using HRV.

Methods

Thirty-seven patients (26 men, 11 women; mean age, 58±11 years; range, 27 to 75 years) with frequent attacks of paroxysmal AF were referred for electrophysiological study or catheter ablation. The study group included 30 patients (group I) who underwent the transseptal procedure for ablation of PVs, and a control group (group II) who underwent the transseptal procedure for ablation of PVs, and a control group (group II) who underwent the transseptal procedure for ablation of PVs, and a control group (group II) who underwent the transseptal procedure for ablation of PVs.
II) included 7 patients who only underwent the transseptal procedure without ablation. These patients gave informed consent. As described previously, all antiarrhythmic drugs were discontinued for at least 5 half-lives before the study.9,10 The patients who took amiodarone for management of AF were excluded.

Twenty-Four-Hour Holter Monitoring
All the patients received ambulatory 24-hour Holter monitoring before, 1 week, and 1 and 6 months after focal ablation of PVs. We did not perform Holter monitoring 1 day after ablation, because postprocedural pain, hypovolemia, and anxiety may contribute to the alterations in HR and HRV.1 Holter monitoring was performed using a 3-channel bipolar recorder and was evaluated after digitization by an Oxford Medilog Excel II analysis system. For each hour, the following data were computed and tabulated: maximal and minimal HR; total number of ventricular premature beats, including couplets and ventricular tachycardia; and total number of supraventricular premature beats. The mean sinus rate was derived from the mean RR intervals (after exclusion of abnormal beats), and the maximal sinus rate was derived from the maximal HR after exclusion of nonsinus rhythm. Inappropriate sinus tachycardia was defined as a resting mean sinus rate of >100 bpm without physiological or hemodynamic causes.

Heart Rate Variability
The analysis technique has been well established in this laboratory.11,12 In brief, HRV was analyzed from the Holter recordings using a commercially available software algorithm (Oxford Medilog Excel II). During the analysis, only normal beats were measured, and all artifacts or extrasystolic beats were eliminated. The beat classification was verified, manually read, and corrected appropriately by an experienced cardiologist. The beats before the onset of AF (total, 30 seconds), during the AF episode, and after the termination of AF (total, 30 seconds) were also excluded. All the beats of exclusion must be <1% of totally available beats. The time-domain measures of HRV, including standard deviation of RR intervals (SDRR) and root-mean-square of differences of adjacent RR intervals (rMSSD), were obtained by using the continuous data throughout 24 hours. The frequency-domain analysis of HRV was performed by a fast Fourier transform of the RR intervals, which produced a power spectrum from the 0.01- to 1.0-Hz unit (1 cycle per second). Three frequency-domain measures of HRV, including low frequency (LF; range, 0.04 to 0.15 Hz), high frequency (HF; range, 0.15 to 0.40 Hz), and LF/HF ratio were calculated. The SDRR, rMSSD, and HF are known to reflect the activity of the parasympathetic nervous system, and LF/HF ratio is interpreted to be a marker of sympathovagal balance.11–15

Electrophysiological Study and Catheter Ablation
As described previously, 2 multipolar electrode catheters were placed at the anterolateral right atrium and His bundle area for recording and pacing.10 A 7F decapolar catheter was inserted into the coronary sinus. After a successful atrial transseptal puncture, 2 exchange guidewires were introduced into the left atrium through the interatrial septum, and then 2 long sheaths (8F SR0 for left superior pulmonary vein [LSPV] and 8.5F SL1 for right superior pulmonary vein [RSPV]; Daig Co) were advanced along the guidewires into the left atrium. Two 6F decapolar catheters were put into the RSPV and LSPV, guided by the pulmonary venography (Figure 1). Intravenous heparin was administered at a dosage of 1000 to 2000 U at 1-hour intervals, if needed, to maintain activated clotting time >250 seconds after the atrial transseptal procedure.

Because these patients were suspected to have spontaneous onset of AF, we first tried to find spontaneous AF at the baseline or after infusion of isoproterenol (≤4 μg/min). If spontaneous AF did not appear, a short duration of burst pacing from right atrium and coronary sinus was used to facilitate spontaneous AF onset during isoproterenol infusion. If spontaneous AF could not be initiated, high-current burst pacing from right atrium or coronary sinus was used to induce AF; after the episode of pacing-induced AF was sustained for >5 minutes, external cardioversion was attempted to convert AF to sinus rhythm and observe the spontaneous reinitiation of AF. The methods used to induce spontaneous AF were tried at least twice to ensure reproducibility. The details of these techniques have been described in our laboratory.10,11 The presumed ablation site was chosen on the basis of the earliest bipolar activity of the triggering ectopic beats preceding AF from PVs (Figure 2). The ablation catheter (4-mm tip electrode, Mansfield, Boston Scientific) was put into the PV with 1 guiding catheter in situ, and ablation was performed. A temperature control model with maximal temperature setting of 60°C was used. Each application of RF energy was delivered for 20 to 40 seconds. Application of energy was stopped immediately if the patients felt burning pain or bradycardia and/or hypotension occurred. Procedural success was defined as that AF was noninducible with the same protocols before ablation.

Postablation Follow-Up
All the procedures and follow-up studies were performed at this institution. Close clinical follow-up and 24-hour Holter monitoring (1 week, 1 month, and 6 months after ablation) were scheduled and performed to assess the effects of catheter ablation.

Statistical Analysis
The parametric data were presented as mean ± SD. Comparisons of the parametric data among the groups obtained at different time.
sequences were made by 1-way ANOVA with the Bonferroni correction for comparison between means. An unpaired t test was used to compare data among groups. A value of $P < 0.05$ was considered statistically significant.

**Results**

**Clinical Characteristics and Ablation Results**

All 37 patients had frequent attacks of clinically documented paroxysmal AF ($2 \pm 2$ episodes per day; duration, $7 \pm 3$ min/d; range, 1 to 12 minutes) and were refractory to or intolerant of 2±1 antiarrhythmic drugs. The mean number of atrial premature beats was $412 \pm 102$ beats per day. Fourteen of 37 patients had associated cardiovascular disease, including hypertensive heart disease (9 patients), ischemic heart disease (2), dilated cardiomyopathy (2), and hypertrophic cardiomyopathy (1). Twenty-one patients (57%) had no associated cardiovascular or other medical diseases.

All of the study patients had spontaneous initiation of AF, as follows: during the baseline observation (1 patient), after isoproterenol infusion (5), after a short duration of atrial pacing under isoproterenol infusion (11), or after cardioversion of pacing-induced AF (13). All of the triggering points of AF in the study group were from the PVs, including 12 in the LSPV, 8 in the RSPV, and 10 in the RSPV and LSPV. Successful ablation of the PVs was achieved in all patients. Severe bradycardia (HR <40 bpm), sinus arrest, or hypotension (systolic blood pressure <90 mm Hg) was noted during applications of RF to the PVs in 6 patients (group IA); the ablation site was $7 \pm 9$ mm inside the LSPV (4 patients) or $9 \pm 13$ mm inside the RSPV (2 patients). The other 24 patients without this complication during ablation belonged to group IB. The ablation site was $11 \pm 10$ mm inside the LSPV (10 patients), $13 \pm 12$ mm inside the RSPV (6), or both in the RSPV and LSPV (8). The mean number of RF applications was $9 \pm 5$ in group IA and $7 \pm 3$ in group IB patients. None of the patients had bradycardia-hypotension response during the transseptal puncture. Three patients (1 in group IA and 2 in group IB) had recurrent asymptomatic AF, which was noted during 1-month follow-up Holter monitoring. Because the duration of AF attack was short (all <1 minute) and the frequency of AF was less than before ablation, the patients did not need any antiarrhythmic drug.

**Acute Changes in HRV**

Comparisons with the baseline data before ablation, the mean sinus rate, and maximal sinus rate were significantly higher at
Acute Changes in Time-Domain and Frequency-Domain Measures of HRV

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>1 wk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group IA (n=6)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Maximum SR, bpm</td>
<td>126±15</td>
<td>142±16</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean SR, bpm</td>
<td>68±6</td>
<td>79±12</td>
<td>0.01</td>
</tr>
<tr>
<td>SDRR, ms</td>
<td>104±35</td>
<td>82±25</td>
<td>0.02</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>24±10</td>
<td>14±8</td>
<td>0.03</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>276±88</td>
<td>172±75</td>
<td>0.04</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>132±70</td>
<td>72±55</td>
<td>0.02</td>
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<tr>
<td>LF/HF ratio</td>
<td>2.0±0.5</td>
<td>2.4±0.6</td>
<td>0.04</td>
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<tr>
<td>Group IB (n=24)</td>
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<tr>
<td>Maximum SR, bpm</td>
<td>130±14</td>
<td>145±12</td>
<td>0.02</td>
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<tr>
<td>Mean SR, bpm</td>
<td>71±10</td>
<td>81±12</td>
<td>0.02</td>
</tr>
<tr>
<td>SDRR, ms</td>
<td>109±31</td>
<td>79±27</td>
<td>0.01</td>
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<tr>
<td>rMSSD, ms</td>
<td>27±12</td>
<td>16±7</td>
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<tr>
<td>LF, ms²</td>
<td>303±90</td>
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</tr>
<tr>
<td>HF, ms²</td>
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<td>84±50</td>
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<tr>
<td>LF/HF ratio</td>
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<td>0.02</td>
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<tr>
<td>Group II (n=7)</td>
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<tr>
<td>Maximum SR, bpm</td>
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<td>Mean SR, bpm</td>
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<td>rMSSD, ms</td>
<td>28±7</td>
<td>26±8</td>
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<td>LF, ms²</td>
<td>304±78</td>
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<tr>
<td>HF, ms²</td>
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<td>LF/HF ratio</td>
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<td>0.95</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. SR denotes sinus rate. P indicates paired t test between baseline and 1 week after ablation.

1 week after ablation of PVs in groups IA and IB (Table). Two patients (6.7%) presented with inappropriate sinus tachycardia (mean sinus rate increased from 83 and 79 bpm to 110 and 104 bpm, respectively). SDRR, rMSSD, LF, and HF were all significantly decreased after ablation in the 2 subgroups; LF/HF ratio was also increased significantly. Furthermore, these parameters obtained before or after ablation were similar between groups IA and IB patients. In group II patients, no significant change occurred among the parameters obtained at baseline and 1 week after the transseptal procedure.

Chronic Changes in HRV

One month after ablation, the mean and maximal sinus rates of all the study patients (including the 2 patients with inappropriate sinus tachycardia) returned to the baseline level; no significant change of the mean and maximal sinus rates was noted in the data before and 1 month after ablation (Figure 3A). SDRR, rMSSD, LF, HF, and LF/HF were not significantly different in the data obtained at before and 1 month after ablation (Figures 3B through 3F). These changes showed the same trends in groups IA and IB. The HRV parameters obtained at 6 months after ablation were similar compared with those obtained at baseline and 1 month after ablation (Figures 3A through 3F).

Discussion

Major Findings

The present study demonstrated that focal ablation of PVs may result in a transient increase in HR and a transient decrease of time-domain and frequency-domain HRV, which indicates autonomic dysfunction (enhanced sympathetic activity or parasympathetic nervous withdrawal); these changes recovered spontaneously 1 month later. However, these changes were not present in the patients who only underwent the transseptal procedure without ablation of PVs.

Autonomic Dysfunction After Ablation of PVs

Previous studies have reported inappropriate sinus tachycardia as a complication after ablation of supraventricular tachycardias.1–2,16–19 Some possible mechanisms have been discussed, and a change of autonomic tone is the most likely explanation in these reports. These researchers used HRV to evaluate the autonomic function and found that parasympathetic nervous withdrawal occurred after ablation of supraventricular tachycardias.1–6,16–19 In the present study, the prevalence of inappropriate sinus tachycardia was 6.7%, similar to that in previous reports regarding ablation of supraventricular tachycardias.1–3,17,18 We also found decreases in SDRR, rMSSD, and HF and increases in mean and maximal sinus rate and LF/HF ratio, which indicates autonomic dysfunction, just like the findings after ablation of supraventricular tachycardias. Furthermore, no significant
recently, Marron et al. identified widely the right vagus penetrate epicardium adjacent to the origin of the common PV complex. Furthermore, the projections of vagus to the sinus node penetrate the epicardium in the region of the canine heart that the intrapericardial projections of the left sympathetic activity and parasympathetic nervous withdrawal.

Therefore, an increase in HR and a decrease in HRV after ablation of PVs was not related to the transseptal procedure.

Although autonomic dysfunction may play an important role in changes in HR and HRV after ablation of slow pathway, posteroseptal space, and PVs, the precise mechanism is not clear. An increase of sympathetic tone, a decrease of parasympathetic tone, or a combination of both factors is the possible explanations. Ardell and Randall20 have shown in the canine heart that the intrapericardial projections of the left vagus to the sinus node penetrate the epicardium in the region of the common PV complex. Furthermore, the projections of the right vagus penetrate epicardium adjacent to the origin of the right PV. 21–23 Recently, Marron et al.24 identified widely distributed specialized nerve terminals in the human heart, and numerous nonmyelinated C-fibers terminals, which are believed to be responsible for cardiac depressing baroreflexes, were identified in the roof of the left atrium and around the 4 PVs. Therefore, focal ablation of PVs could result in stimulation (induced bradycardia-hypotension response) or destruction (induced parasympathetic nervous withdrawal or denervation) of postganglionic parasympathetic fibers or specialized nerve terminals in PVs, which are destined to innervate the sinus node (Figure 4). 25

The other possibility of changes in HR and HRV is mediated by cardiac sympathovagal (so-called cardiocardiac) reflex. 26 In acute myocardial infarction, the necrotic scar alters the geometry of the beating heart, which results in an increased activity of sympathetic afferent fibers secondary to distortion of their sensory endings; this change produces an inhibition of vagal efferent activity to the heart (including the sinus node) and increases efferent sympathetic activity. Therefore, an increase in HR and a decrease in HRV after myocardial infarction are the results of an enhanced sympathetic activity and parasympathetic nervous withdrawal.

Some previous reports have demonstrated that cardiac sympathetic nerves form an important afferent pathway and the receptor endings of the fibers consist of free terminals scattered diffusely in the heart. 22,26–28 These sympathetic fibers are distributed throughout the atria, but the vagal branches have a more-limited distribution to specific sites. This explains why multiple lesions in the atria (including slow atrioventricular node, para-hisian pathway, posteroseptal space, and PVs) affect preferentially the sympathetic endings and elicit an increase in HR and a decrease in HRV (Figure 5). Vagal fiber endings would be less affected.

Relation Between Parasympathetic Stimulation and Autonomic Dysfunction Caused by RF Energy

Friedman et al. 1 have shown that ablation of slow pathway or posteroseptal area could result in profound sinus bradycardia. They suggested that RF current directly stimulated parasympathetic fibers traveling from the site of RF application to the sinus node. The finding was similar to that of our previous report regarding the effect of direct intracardiac stimulation of human afferent vagal fibers. 29 Because focal ablation of supraventricular tachycardias could result in stimulation of parasympathetic nerve fibers or terminals, the presence of a bradycardia-hypotension phenomenon may be related to the distribution and density of parasympathetic nerve fibers around the ablation areas. Previous animal and human studies have demonstrated numerous parasympathetic nerve terminals in the PV area, and the incidence of ablation-induced bradycardia-hypotension response was higher than with ablation of other atrial tissues. 2,9,20–24 In the present study, we found no significant difference in HR and HRV between patients with bradycardia-hypotension response and those without this complication during ablation of PVs. The 2 subgroups showed transient autonomic dysfunction after ablation. This finding suggested that transient autonomic dysfunction occurred even in the absence of bradycardia-hypotension response (parasympathetic stimulation) during ablation of PVs.
Recovery of Autonomic Dysfunction After Ablation of PVs

Previous reports showed that autonomic dysfunction developed immediately after ablation of slow pathway or posteroseptal area and spontaneous resolution of HRV occurred 1 to 6 months later. Therefore, we performed 24-hour Holter monitoring at 1 and 6 months after ablation of PVs, respectively, to see the chronic changes in HRV. The results showed that an increase in HR and a decrease in HRV recovered at 1 month after ablation of PVs, indicating a transient dysfunction of autonomic nervous system, just as the findings after ablation of supraventricular tachycardias.

Clinical Implications

The present study provided some clinical implications in the patients who underwent ablation of PVs. First, the incidence of bradycardia-hypotension response induced by the transseptal puncture was low, and no evidence of autonomic dysfunction after the transseptal procedure was noted in the present study. However, focal PV ablation could induce a higher incidence of bradycardia-hypotension response and transient autonomic dysfunction. The transient alterations of autonomic function could explain the possible mechanism of palpitation (sinus tachycardia, without recurrence of paroxysmal AF) after ablation of PVs. Second, the change in autonomic function with enhanced sympathetic tone or parasympathetic withdrawal could cause atrial premature beats and spontaneous AF.

Study Limitations

The present study had several limitations. First, HRV is used to evaluate the variability of sinus node, and all of the beats not from the sinus node should be eliminated. Our patients had frequent attacks of paroxysmal AF, and the patients with abnormal beats that were >1% of the available beats were excluded. Thus, the patients with very frequent attacks of AF were not included. On the other hand, in patients with recurrence of AF after ablation of PVs who had abnormal beats that were >1% of sinus beats were also excluded. Otherwise, an increase in HR and a decrease in HRV might result from elevated sympathetic activity, decreased parasympathetic activity, or a combination of the 2 factors. Any factor that could affect autonomic tone also interfered with the HRV; these factors included postprocedural hypovolemia, pain, emotional stress, and some drugs (such as sedative or isoproterenol used during the procedure). To avoid the effects of these factors, we performed postablation 24-hour Holter monitoring 1 week after ablation. Finally, we could not rule out the possibility that the autonomic dysfunction was induced by transient edema of autonomic nerve fibers after PV ablation.

Conclusions

Focal ablation of PVs could result in an increase in HR and a decrease in time-domain and frequency-domain measures of HRV, which indicates autonomic dysfunction. These changes were transient and could resolve spontaneously 1 month later, which represents recovery of autonomic dysfunction.

Acknowledgments

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