Initiation of Atrial Fibrillation by Ectopic Beats Originating From the Pulmonary Veins

Electrophysiological Characteristics, Pharmacological Responses, and Effects of Radiofrequency Ablation

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Background—Atrial fibrillation (AF) can be initiated by ectopic beats originating from the atrial or great venous tissues. This study investigated the anatomic characteristics and electrophysiological properties of pulmonary veins (PVs), as well as the possible mechanisms and response to drugs of ectopic foci, and assessed the effects of radiofrequency (RF) ablation on AF initiated by ectopic beats originating from PVs.

Methods and Results—Seventy-nine patients with frequent episodes of paroxysmal AF and 10 control patients were included. Distal PVs showed the shortest effective refractory periods (ERPs), and right superior PVs showed a higher incidence of intra-PV conduction block than left superior PVs. Superior and left PVs had longer myocardial sleeves than inferior and right PVs, respectively. These electrophysiological characteristics were similar between AF and control patients. Propranolol, verapamil, and procainamide suppressed ectopic beats that originated from the PVs. Of 116 ectopic foci that initiated AF, 103 (88.8%) originated from PVs. A mean of 7.63 RF applications completely eliminated 110 ectopic foci (94.8%). During the 6.6-month follow-up period, 68 patients (86.1%) were free of AF without any antiarrhythmic drugs. Follow-up transesophageal echocardiogram showed 42.4% of ablated PVs had focal stenosis. One patient had mild exertional dyspnea after ablation, but it resolved 3 months later; 1 patient had onset of mild exertional dyspnea 5 months after ablation.

Conclusions—Electrophysiological characteristics of PVs are different from those in the atria. Ectopic beats from PVs can initiate AF, and β-adrenergic receptor blocker, calcium channel blockers, and sodium channel blockers can suppress these ectopic beats. Careful mapping and elimination of these ectopic foci can cure paroxysmal AF.

Key Words: ablation ■ fibrillation ■ veins ■ electrophysiology

Atrial fibrillation (AF) can be initiated by ectopic beats from the cristal terminalis, ostium of the coronary sinus, interatrial septum, atrial free wall, and pulmonary veins (PVs).1-5 The mechanism of AF initiated by ectopic beats from PVs is not clear; furthermore, the effects of antiarrhythmic drugs on these ectopic beats have not been reported.1-10 Haissaguerre et al and this laboratory have demonstrated that radiofrequency (RF) catheter ablation can effectively eliminate AF initiated by ectopic beats from a focal area.1-5 However, the possible side effects, such as RF energy-induced PV stenosis, have not been studied in detail.

This study investigated the anatomic characteristics and electrophysiological properties of PVs, as well as possible mechanisms and the response to drugs of ectopic foci, and assessed the effects of RF ablation on AF initiated by ectopic beats originating from PVs.

Methods

Group I consisted of 79 patients with frequent, daily attacks of paroxysmal AF (PAF). Group II consisted of 10 patients with a concealed left-side free-wall accessory pathway (without AF); these patients underwent the study protocol of PV electrophysiology after successful ablation of accessory pathways. None of the group II patients had other cardiovascular diseases. As described previously, all antiarrhythmic drugs except amiodarone were discontinued for ≥5 half-lives before the study.1,4,5,11,12

Catheter Positions

As described previously, 3 multipolar electrode catheters (Mansfield or Daig Co) were placed in the anterolateral right atrium (RA), the His bundle area, and the coronary sinus. A 7F, 20-pole, deflectable halo catheter (Cordis-Webster Co) was positioned around the tricuspid annulus to simultaneously record RA activation in the lateral wall and the low RA isthmus; the cristal terminalis and superior vena cava were also mapped if RA ectopic foci were suspected.4,5,11,12

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Effects of Propranolol, Verapamil, and Procainamide on Spontaneous APC/AF
The density of APCs and burst AF (number of APCs and episodes of burst AF within 5 minutes) was measured during baseline or after isoproterenol infusion. Thirty patients were further randomized to receive propranolol (0.02 mg/kg of body weight for the loading dose over 10 minutes and 0.04 mg·kg⁻¹·h⁻¹ for maintenance), verapamil (0.15 mg/kg of body weight for the loading dose over 10 minutes and 0.3 mg·kg⁻¹·h⁻¹ for maintenance), or procainamide (15 mg/kg of body weight for the loading dose at a rate of 50 mg/min and 4 mg/min for maintenance). Spontaneous APCs and AF were assessed 10 minutes after the loading dose was given.

Radiofrequency Ablation
As described previously, the presumed ablation site showed the earliest bipolar activity and/or a local unipolar QS pattern of ectopic beats preceding AF from PVs. The ablation catheter (4-mm-tip electrode, Mansfield, Boston Scientific) was connected with an EPT-1000 generator (EP Technology) delivering a 550-kHz sine wave output between the distal electrode of the ablation catheter and the cutaneous patch electrode placed over the left scapula. A temperature-control model with a maximal temperature setting of 60°C was used. Each application of RF energy was delivered for 20 to 40 seconds. If patients had cough, burning pain, or severe bradycardia, RF energy was stopped, and a maximal temperature setting of 50°C to 55°C was used. The protocols used to induce spontaneous initiation of AF before ablation were repeated to assess the effects of RF ablation at 30 minutes after the last pulse. Procedural success was defined as the absence of ectopic beats and inability to reinitiate AF with the same protocols used before ablation. Heparin (1000 U/h) was continuously administered for 24 hours, and oral coumadin was continued for 2 months with an international normalized ratio (INR) level between 2.0 and 3.0.

Follow-Up
Close clinical follow-up (2 weeks, 1 month, and then every 2 months), 24-hour Holter monitoring, cardiac event recorder, and transthoracic echocardiography (within 3 days and 1 to 6 months after ablation) were obtained in the patients at this institution. Serial follow-up transesophageal echocardiograms were performed in 48 patients within 3 days and 1 to 6 months after ablation to evaluate stenosis of PVs. If patients experienced palpitation, another 24-hour Holter monitoring or cardiac event recorder was used to evaluate their condition.

Statistical Analysis
Parametric data are presented as mean±SD. Paired t test was used to analyze changes in parametric data before and after an intervention in the same group. Nonparametric data were analyzed by the χ² test with Yates correction or Fisher exact test. ANOVA was used for comparison of ERPs at different sites. The effects of antarrhythmic drugs on the incidence of APCs and AF were analyzed with the sign test. A P value <0.05 was considered significant.

Results
Clinical Characteristics
All 79 patients had frequent attacks of clinically documented PAF on 24-hour Holter recordings (6±4 episodes/d; duration 28±30 min/d; 4±4 episodes/d with symptoms and 2±3 episodes/d without patient events; mean, median, and range of APC number were 892±311, 863, and 267 to 3256, respectively). These episodes of PAF were refractory to or intolerant of 3±1 antarrhythmic drugs. Thirty-nine patients (50%) had other associated diseases (Table 1).

Electrophysiological Characteristics
Effective Refractory Periods
In patients with AF, the longest and shortest ERPs were at the Bachmann bundle and distal RSPV, respectively. ERPs at proximal sites of the RSPV and LSPV were significantly higher.
**TABLE 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group I (AF)</th>
<th>Group II (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>79</td>
<td>10</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>66 ± 12 (27–83)</td>
<td>58 ± 6 (34–72)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>67/13</td>
<td>8/2</td>
</tr>
<tr>
<td>Associated CVD and systemic disease, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive CVD</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Atrial enlargement</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>COPD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Left-side concealed FW accessory pathway</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Atrial diameter by echocardiogram, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>40 ± 8</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>RA</td>
<td>32 ± 4</td>
<td>24 ± 3</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; COPD, chronic obstructive pulmonary disease; FW, free wall; and LA, left atrium.

longer than those at the distal sites. After isoproterenol infusion, ERP at the distal RSPV was shorter than at the proximal RSPV, but ERP at the distal LSPV was similar to that at the proximal LSPV. The mean slopes of ERP against pacing cycle length were significantly lower at the low lateral RA than at other sites. Comparisons between patients with AF and control subjects did not show any difference in ERPs and slopes of ERP (Table 2 and Figure 2).

**Local PV Electrogamis**

PV potentials (with a sharp upstroke, narrow duration <50 ms, and an amplitude >0.05 mV) were preceded by far-field atrial potential with a slow slope (depolarization rate dV/dt <0.5 mV/s). The length of the myocardial sleeve showing PV potentials calculated from the number of bipolar recordings was significantly less in the right side and inferior PVs than those in the left side and superior PVs, respectively. Control subjects showed similar characteristics of PV potentials (Figures 3 and 4).

**Ectopic Beats With Initiation of AF**

Seventy-three patients (92%) had spontaneous initiation of sustained (>30 seconds) AF during baseline observation or after different maneuvers. Six patients (7.6%) had only burst ectopic beats without initiation of sustained AF (Figure 1). During ectopic beats from PVs, PV potentials preceded atrial potentials. During the initial 5 seconds of spontaneous depolarization of ectopic foci, 27 patients (34.2%) showed conduction block; 19 ectopic foci were in the RSPV (Figure 5).

**Electropharmacological Characteristics**

Sixteen patients had spontaneous APCs or burst AF during the baseline study. After propranolol (n = 5), verapamil (n = 5), or procainamide (n = 6) infusion, the density of PV ectopic beats and episodes of burst AF decreased significantly. Fourteen patients had spontaneous APCs or burst AF after isoproterenol infusion. After pretreatment with propranolol (n = 5), verapamil (n = 5), or procainamide (n = 4), isoproterenol infusion could not induce any episode of sustained AF; the density of APCs and density of burst AF were significantly decreased (Figures 6 and 7).

**RF Ablation**

**Results**

Table 3 and Figure 8 show the 116 ectopic foci that initiated spontaneous AF. Forty-four patients had 1, 33 patients had 2, and 2 patients had 3 ectopic foci. Among the 103 ectopic foci

<table>
<thead>
<tr>
<th></th>
<th>AF</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCL=700</td>
<td>PCL=500</td>
</tr>
<tr>
<td>High lateral RA</td>
<td>265±38</td>
<td>254±26</td>
</tr>
<tr>
<td>Middle lateral RA</td>
<td>228±36</td>
<td>218±34</td>
</tr>
<tr>
<td>Low lateral RA</td>
<td>223±29</td>
<td>216±31</td>
</tr>
<tr>
<td>Bachmann's bundle</td>
<td>277±31*</td>
<td>266±35*</td>
</tr>
<tr>
<td>Proximal CS</td>
<td>260±36</td>
<td>249±36</td>
</tr>
<tr>
<td>Distal CS</td>
<td>256±32</td>
<td>246±35</td>
</tr>
<tr>
<td>Proximal LSPV</td>
<td>252±36</td>
<td>239±38</td>
</tr>
<tr>
<td>Distal LSPV</td>
<td>228±30</td>
<td>216±34</td>
</tr>
<tr>
<td>Proximal LIPV</td>
<td>243±34</td>
<td>227±32</td>
</tr>
<tr>
<td>Proximal RSPV</td>
<td>259±37</td>
<td>241±29</td>
</tr>
<tr>
<td>Distal RSPV</td>
<td>215±25</td>
<td>205±20</td>
</tr>
<tr>
<td>Proximal RIPV</td>
<td>226±35</td>
<td>223±39</td>
</tr>
<tr>
<td>High anterior LA</td>
<td>271±23</td>
<td>251±19</td>
</tr>
<tr>
<td>Low anterior LA</td>
<td>258±19</td>
<td>246±32</td>
</tr>
<tr>
<td>High posterior LA</td>
<td>260±28</td>
<td>246±30</td>
</tr>
<tr>
<td>Low posterior LA</td>
<td>256±25</td>
<td>247±29</td>
</tr>
</tbody>
</table>

PCL indicates pacing cycle length (in ms); CS, coronary sinus; LIPV, left inferior PV; RIPV, right inferior PV; and LA, left atrium.

*Site with longest ERP; †site with lowest slope.
from PVs, 40 (38.8%) were in the ostium and proximal PV (<20 mm inside the PV), and 63 (61.2%) were in the distal PV (20 to 40 mm inside the PV). Bipolar electrograms in the successful ablation sites were 84±63 ms (range 40 to 150 ms) before the ectopic P wave. After 7±6 (range 2 to 13) applications of RF energy (mean 25±12 W), 97 of 103 ectopic foci from PVs were completely eliminated; the other 6 ectopic foci were partially eliminated (APCs were still present, but spontaneous AF could not be initiated). The mean procedure time required for mapping and ablation was 90±32 minutes, and fluoroscopic time was 42±20 minutes.

Complications and Follow-Up

Two patients had transient cerebral ischemic attack within 24 hours after ablation; fortunately, they recovered well. One patient had hemothorax and hemopericardium immediately after successful ablation; after pericardiocentesis and pleural tapping, the patient recovered well.

Forty-two patients underwent follow-up transthoracic echocardiogram, and 2 had pericardial effusion (5 mm in width) without any symptoms on the second day; it resolved spontaneously at 1 month follow-up. An iatrogenic small atrial septal defect with trivial shunt (width of shunt 2.6±1.0 mm) was found in 43 of 45 patients within 3 days; in each case, it had closed spontaneously 3 months later. Injury of valvular function or thrombus was not found. Twenty-five (42.4%) of 59 PV foci showed peak PV flow velocity >80 cm/s obtained from transesophageal echocar-
diagram within 3 days after ablation (65±7 versus 125±10 cm/s; P<0.01); these 25 foci also showed an increase in peak PV flow velocity (120±12 cm/s), with a mean pressure gradient of 4.9±2.3 mm Hg at 3-month follow-up. Three patients had a double stenosis: 1 patient was completely asymptomatic; 1 had mild exertional dyspnea after RF ablation, which resolved 3 months later; and the remaining patient had onset of mild exertional dyspnea 5 months after RF ablation, with 12 and 18 mm Hg pressure gradients within the RSPV and LSPV, respectively. Among 7 patients who

Figure 5. Spontaneous onset of AF from LSPV; rapid activation from LSPV-2 or LSPV-3 conducted to left atrium with 2:1 block. HRA and CSP, CSM, and CSD are recordings from high lateral RA and proximal, middle, and distal coronary sinus, respectively. Other recordings as indicated in Figure 4.

Figure 6. Effects of antiarrhythmic drugs on APC/AF from PVs. CI indicates coupling interval; SR-APC, CI between sinus beat and APC; and SR-AF, CI between sinus beat and the first initiating beat of AF.
underwent repeated ablation, PV angiography did not reveal any stenotic lesion or pressure gradient within the PV or between the PV and left atrium.

During the follow-up period (mean 6±2 months, range 2 to 13 months), 11 patients (13.9%) had early recurrence of AF within 72 hours after ablation. In all 11 patients, AF was converted to sinus rhythm after 24-hour intravenous administration of amiodarone (1200 mg). Four of the 11 patients had late (1±1 month) recurrence of AF, and they underwent a repeated ablation with success. Among the other 68 patients without early recurrence, 4 had late recurrence of AF (1±1 month); 3 of these 4 patients underwent a repeated ablation with success, and the other patient underwent AV junction ablation with implantation of a permanent pacemaker. In the 7 patients who received repeated ablation of ectopic foci, 5 foci were from the original sites and 2 were from the left atrial posterior wall. In total, 68 patients (86.1%) were free of symptomatic AF without any antiarrhythmic drug, and 10 (12.7%) were free of symptomatic AF with 1 type of antiarrhythmic drug (which failed to control AF before ablation) during the follow-up period. Late follow-up 24-hour Holter monitoring was obtained in 49 patients and showed a significant decrease in ectopic beats compared with baseline (892±311 versus 210±66 beats/d; P<0.01); symptomatic and sustained AF was not found, and nonsustained (asymptomatic) AF was found in 12 patients (3±1 episode/d, duration 8±3 s/episode).

Discussion

Cardiac Muscle in the PVs

This study found longer myocardial sleeves with PV potentials in the superior than in the inferior PVs and confirmed the previous anatomic and pathological findings that superior PVs had longer and better-developed myocardial sleeves than inferior PVs.13 These results might explain the fact that most of the ectopic foci that initiate AF were from the superior PVs, because myocardial sleeves in the inferior PVs were shorter and less developed.

Electrophysiology of Atria and PVs

Regional Difference of ERPs

Previous human studies included no systemic study of atrial ERP in different sites; thus, the results were controversial.14–18 The present study first showed similar atrial ERP distribution patterns between AF patients and control subjects; furthermore, the longest and shortest ERPs were in the Bachmann bundle area and the distal PVs, respectively. In the pericarditis and atrial rapid pacing models of AF,19,20

**Figure 7.** A, Coupling interval between sinus beat and initiating beat of AF was 300 ms. B, After infusion of propranolol, burst AF was suppressed, and coupling interval between sinus beat and APC was prolonged to 340 ms. HRA indicates high lateral RA; HIS, His bundle area; and CS, coronary sinus. Other abbreviations as in Figure 4.

**Figure 8.** Distribution of ectopic foci that initiate spontaneous AF. RAA/LAA indicate right/left atrial appendage; SN, sinus node; SVC, superior vena cava; CT, crista terminalis; RAFW, RA free wall; IVC, inferior vena cava; CSO, coronary sinus ostium; IAS, interatrial septum; and LAFW, left atrial free wall.

**TABLE 3. Number and Distribution of Ectopic Foci**

<table>
<thead>
<tr>
<th>Ectopic Foci</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single focus</td>
<td></td>
</tr>
<tr>
<td>RSPV</td>
<td>18</td>
</tr>
<tr>
<td>LSPV</td>
<td>26</td>
</tr>
<tr>
<td>Double foci</td>
<td></td>
</tr>
<tr>
<td>RSPV+LSPV</td>
<td>22</td>
</tr>
<tr>
<td>RSPV+LA posterior free wall</td>
<td>4</td>
</tr>
<tr>
<td>RSPV+cristal terminalis</td>
<td>2</td>
</tr>
<tr>
<td>RSPV+LA posterior free wall</td>
<td>5</td>
</tr>
<tr>
<td>Triple foci</td>
<td></td>
</tr>
<tr>
<td>RSPV+LSPV+cristal terminalis</td>
<td>1</td>
</tr>
<tr>
<td>RSPV+LSPV+LA posterior free wall</td>
<td>1</td>
</tr>
</tbody>
</table>

LA indicates left atrium.
the anatomic distribution of atrial ERP is also similar to that observed in normal dogs.

**Maladaptation of ERP**
Maladaptation of atrial ERP has been considered to be related to AF. The present study found that the rate adaptation response was different between the low RA and other areas in both the control group and patients with AF. We also demonstrated the site difference of maladaptation and its correlation with reinitiation of AF. These findings suggest the site difference of atrial electrophysiology. However, maladaptation of PV ERP was not found in any patient.

**ERP at Proximal and Distal Portions of PVs**
This study showed longer ERPs in the proximal than the distal PV, and this finding might be similar to Cheung’s report that action potential duration was longer in the proximal PV than in the distal PV. Longer ERPs in proximal than in distal PVs could block the impulses originating from the distal PV and reduce the possibility of AF. However, the differences in ERP between proximal and distal PVs were decreased after isoproterenol infusion; this finding possibly suggests that isoproterenol can attenuate the protection mechanism of the proximal PV, and fast, spontaneous activation from the distal PV could be conducted to the proximal PV and left atrium and initiate AF, in the same way that burst pacing of atrial tissue can induce AF.

**Conduction Block Within the PV**
This study demonstrated that 34.2% of patients had intra-PV conduction block, and 70.4% of these cases had conduction block in the RSPV. Haissaguerre et al demonstrated concealed discharges and speculated that decremental conduction properties existed in PVs. A more complex arrangement of the myocardial sleeve with more anisotropic conduction properties in the RSPV than in the LSPV and a significant difference in ERP between the proximal and distal RSPV might be possible mechanisms. The other possible mechanism is impedance mismatch. Because the proximal PV has a relatively larger mass than the distal PV, impulses from distal PVs would be blocked in the proximal PVs or blocked in the PV/atrial junction.

**Spontaneous Activity Originating From PVs**
This laboratory showed that spontaneous activity from the atria or PVs can initiate AF. Previous studies demonstrated that ouabain infusion or norepinephrine infusion could trigger the onset of rapid repetitive activity from the distal PV. Jais et al first described the focal source AF of in humans and found that most spontaneous AF originated from PVs. The present study found that a β-receptor blocker, a calcium channel blocker, and procainamide could suppress spontaneous ectopic beats and AF from PVs. This laboratory has demonstrated that β-receptor blockers and calcium channel blockers can effectively terminate or prevent induction of focal-type atrial tachycardia, including atrial tachycardias originating from PV ostia, and that the mechanism of this type of atrial tachycardia is abnormal automaticity or triggered activity. Furthermore, our previous study proved that procainamide could prevent secondary AF caused by accumulation of intracellular calcium after rapid atrial pacing. Because the β-receptor blocker and procainamide were less effective in suppressing triggered activity, the mechanism of the ectopic beats that initiate AF might be abnormal automaticity.

**RF Ablation of AF Initiated by Ectopic Beats**
The present study showed a higher success rate and a lower recurrence rate than that by Haissaguerre et al. It is difficult to define which type of APCs should be ablated to prevent initiation of AF; in the present study, a single-beat APC that did not induce a burst of rapid, repetitive atrial beats or initiation of AF was not chosen for RF ablation. Some patients with drug-refractory AF can be treated with original antiarrhythmic drugs after catheter ablation of PV foci; thus, hybrid therapy may be an alternative choice for management of AF. The true incidence of recurrent AF after initially successful ablation is unknown because attacks of AF were paroxysmal in these patients, and the methods used to evaluate and follow up were not perfect. We also found that all recurrences occurred within the first 2 months after ablation. The potential risk of cardiac perforation during transseptal catheterization and catheter ablation should be considered. Extensive linear ablation of atrial tissue and PVs includes the risk of PV stenosis, cardiac tamponade, cerebral emboli, or death. Focal ablation around or inside the PV may be a relatively safe procedure. Although 42.4% of patients showed an increase in PV flow velocity, a larger number of patients and a longer follow-up period are necessary to prove safety and efficacy.

**Study Limitations**
The first limitation of this study is that there is no uniform definition of focal AF. Further confirmation of the continuous or intermittent firing of PV activity during AF would be helpful to define the term focal AF. In this study, AF was initiated by ectopic beats originating from a single or multiple foci in the PVs. Second, this study only included 3 patients who also had RA ectopic foci; thus, the results cannot be extrapolated to all AF. Third, we used a bipolar pacing technique to measure ERP; unipolar pacing may be a better technique in small tissue.

**Conclusions**
The electrophysiological characteristics of PVs are different from those in the atria. Ectopic beats from PVs can initiate AF, and β-adrenergic receptor blockers and calcium and sodium channel blockers can suppress these ectopic beats. Careful mapping and elimination of these ectopic foci can cure PAF.

**Acknowledgments**
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References


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