Distinctive Electrophysiological Properties of Pulmonary Veins in Patients With Atrial Fibrillation

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Background—Atrial fibrillation (AF) is frequently initiated from pulmonary veins (PVs), but little is known of the electrophysiological properties of PVs.

Methods and Results—Two groups were studied: 28 patients (49±13 years old) with paroxysmal AF and 20 control patients (49±14 years old) without AF. Effective and functional refractory period and conduction time from PV to left atrium (LA) were compared in the 2 groups by use of programmed stimulation with a single extrastimulus in the PVs and LA. In the AF group, the venous effective refractory periods (ERPs) were shorter than that of the LA: 185±71 versus 253±21 ms, \( P<0.001 \), whereas in the control group, they were longer (282±45 versus 253±41 ms, \( P=0.009 \)). The venous ERPs and functional refractory periods in patients with AF were also shorter than that observed in control subjects (185±71 versus 282±45 ms and 210±77 versus 315±43 ms, respectively, \( P<0.001 \)), whereas LA ERPs were not significantly different. Decremental conduction in PVs was more frequent (93% versus 56%, \( P=0.01 \)) and had a greater increment (102±65 versus 42±40 ms, \( P<0.001 \)) in patients with AF. Finally, AF was more frequently induced when pacing was performed in PVs (22 of 90) versus LA (1 of 81) in patients with AF (\( P<0.001 \)).

Conclusions—The PVs of patients with AF exhibited distinctive electrophysiological properties, which were strikingly different from those of patients devoid of AF, potentially explaining their arrhythmogenicity. (Circulation. 2002;106:2479-2485.)

Key Words: fibrillation ■ electrophysiology ■ lung ■ veins

Atrial fibrillation (AF) is the most common arrhythmia in humans. Its maintenance is thought to be due to multiple wavelets reentry occurring in both atria. AF initiation has been shown to be due to triggers predominantly clustered within thoracic veins, particularly pulmonary veins (PVs), but the reasons for this arrhythmogenic behavior are unknown. Moreover, little is known of the electrophysiological characteristics of these veins, particularly focusing on patients with or without AF.

Methods

Patients

Twenty-eight consecutive patients (3 women) 49±13 years old (24 to 72 years) were referred for paroxysmal AF ablation. The arrhythmia was documented for 86±72 months (12 to 300 months), and at the time of inclusion, patients had at least 1 episode every 10 days. The most recent AF episode was noted within the last 48 hours preceding the procedure in 11 patients. A mean of 4.4±1.7 antiarhythmic drugs had been administered unsuccessfully, including amiodarone in 22 patients. Ten patients were treated with amiodarone during the 3 months preceding the procedure. Eight patients had additional cardiovascular diagnoses, including systemic hypertension in 3, dilated cardiomyopathy in 3, mitral regurgitation in 1, and hypertrophic cardiomyopathy in 1.

This group of patients with AF was compared with 20 control patients (6 women, 49±14 years old) referred for ablation of various arrhythmias, requiring a transeptal approach, in whom AF had not previously been documented. Fifteen patients had a left-sided accessory pathway, and 3 had a left ventricular tachycardia requiring transeptal access for successful ablation. Two patients had a LA tachycardia, 1 with an incessant focal arrhythmia from the roof of the LA at the junction with the ostium of the right superior PV (RSPV) and 1 with a perimitral circuit. Three patients were treated with amiodarone during the 3 months preceding the procedure (\( P=\text{NS} \) versus patients with AF). Clinical and echocardiographic parameters of the 2 groups are presented in Table 1.

Electrophysiological Study

Written informed consent was obtained from all patients. Patients were on oral anticoagulation at least 1 month before the ablation, and transthoracic and transesophageal echocardiography was performed to exclude LA thrombi. Antiarrhythmic drugs were discontinued 5 half-lives before ablation, except for amiodarone. Electrophysiological study was performed with 3 catheters introduced percutaneously through the right femoral vein. A 6F quadripolar deflectable catheter was placed in the coronary sinus (X-trem ELA Medical). A trans-
septal approach was performed with an 8F long sheath (Preface, Biosense Webster) both for the puncture and for introducing the circumferential mapping catheter dedicated to PV mapping. This 10-pole circular catheter (Lasso, Biosense Webster) was used to sequentially map the ostium of the 4 PVs except when it was not possible to access the right inferior PV (RIPV). In 4 patients, PV mapping was performed with a basket (64-pole) catheter (Boston Scientific). A 4-mm-tip conventional ablation catheter (Biosense Webster or Bard) was also introduced into the left atrium (LA) for stimulation purposes.

A 6F or 7F NIH catheter (Cordis Europa) was used for direct PV angiography to assess PV dimensions and to appropriately size the Lasso catheter to PV diameter. One patient with common ostia was excluded from the study so as to have a homogenous population. The proximal part of the PVs was defined as the ostial side of the veins, and distal referred to lung side of the veins.

The 20 control patients were studied similarly with the exception that oral anticoagulation and transesophageal echocardiography were not performed.

**Stimulation Protocol**

The ablation catheter was used to pace the PVs, distal to the Lasso position, and sequentially from the top and bottom of each vein when possible. It was also used to pace 2 to 4 different sites within the LA, including the lateral wall or appendage, superior, posterior, and/or inferior areas. A Biotronik stimulator (UHS 20) was used to deliver electrical impulses of 2-ms duration at twice the diastolic threshold, the negative pole being connected to the distal electrode of the pacing catheter. Stable pacing sites were considered only if threshold was ≤4 V. ECG leads and intracardiac electrograms filtered at 30 to 500 Hz were recorded simultaneously with a polygraph (Midas PPG Biomedical system or Laboratory system Bard). After a basic drive cycle of 8 stimuli at a cycle length of 600 ms, a single extrastimulus coupled at 400 ms was decremented automatically in steps of 20 ms to the effective refractory period (ERP). The following variables were measured: (1) PV ERP at each stimulation site within each assessed PV. The ERP of PVs was defined as the longest coupling interval at which a premature impulse (S₂) failed to capture local PV musculature. (2) The ERP of the LA was defined as the longest coupling interval at which a premature impulse (S₂) failed to capture local atrial muscle. LA ERP was determined at 2 to 4 different sites and averaged. (3) The ERP of the LA anteroposterior, mm 34±8

<table>
<thead>
<tr>
<th>Patients</th>
<th>Control</th>
<th>AF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>20</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (70)</td>
<td>25 (89)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>49±14</td>
<td>49±13</td>
<td>NS</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>1 (20)</td>
<td>8 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Amiodarone during the past 3 mo, n (%)</td>
<td>3 (15)</td>
<td>10 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic LV, mm</td>
<td>51±4</td>
<td>53±7</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic LV, mm</td>
<td>32±5</td>
<td>31.5±9</td>
<td>NS</td>
</tr>
<tr>
<td>% Shortening</td>
<td>38±7</td>
<td>38±8</td>
<td>NS</td>
</tr>
<tr>
<td>LA anteroposterior, mm</td>
<td>34±8</td>
<td>40±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA inferosuperior, mm</td>
<td>41±5</td>
<td>52±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PV diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSPV</td>
<td>15±2</td>
<td>17±3</td>
<td>NS</td>
</tr>
<tr>
<td>RSPV</td>
<td>17±3</td>
<td>17±3</td>
<td>NS</td>
</tr>
<tr>
<td>LIPV</td>
<td>17±3</td>
<td>17±3</td>
<td>NS</td>
</tr>
<tr>
<td>RIPV</td>
<td>18±2</td>
<td>17±3</td>
<td>NS</td>
</tr>
</tbody>
</table>

LV indicates left ventricle.

**Results**

Sixty-three PVs were studied at 90 pacing sites in patients with AF and 55 PVs with 87 pacing sites in control patients.

**Refractory Period**

In patients with AF, the ERPs of PVs were significantly shorter than those of atrial tissue: 185±71 ms (range, 60 to 340 ms) versus 253±21 ms (range, 120 to 320 ms), P<0.001. This was also true of the ERPs of each left superior PV (LSPV), RSPV, and left inferior PV (LIPV) compared with those of the LA. This difference was not significant for the RIPV (assessed in only 6 cases). At 89% of venous pacing...
sites, ERPs were shorter than that of the LA, whereas at 11%, they were longer.

Moreover, ERPs and FRPs of PVs were significantly shorter in patients with AF than in control patients: 185 ± 71 ms versus 282 ± 45 ms (P < 0.001) and 210 ± 77 versus 315 ± 43 ms (P < 0.001), respectively. This was also true of ERPs of the LA, whereas at 19%, they were longer. The mean ERPs of the LA were significantly longer than that observed in control patients (282 ± 45 ms), with a mean difference ranging from 12 ± 33 to 34 ± 36 ms. At 84% of venous pacing sites, ERPs were longer than that of LA, whereas at 16%, they were shorter. The mean ERPs of the LA (253 ± 41 ms in patients with AF) were not significantly different.

Decremental PV-LA Conduction
Decremental conduction properties were significantly (P = 0.01) more frequent in patients with AF (84 of 90 of the venous pacing sites, 93%) than in patients without AF (49 of 87, 56%). The mean increment in conduction time ranged from 88 ± 66 (RIPV) to 114 ± 70 (LSPV) ms and was significantly higher than that observed in control patients (102 ± 65 versus 42 ± 40 ms, P = 0.001).

PV Activation Pattern and Conduction Block During Decremental Pacing
During premature stimulation, activity in the veins changed from short-duration high-frequency signals to fragmented long-duration potentials (indicating slow conduction) before the occurrence of conduction block. The increasing delay from pacing artifact to atrial potential was shown, in the 4 patients studied with a basket catheter, to be occupied by long-duration and fractionated potentials recorded at various levels in the veins (Figure 2). Circumferential activation sequence of venous potentials, including the LA breakthrough and exit point, changed (Figure 3, A and B) with shortening the coupling interval of extrastimulus in 81% of patients with AF (62% of PVs).

In the majority of patients, the FRP of the PVP was longer than the ERP of the LA component recorded with the Lasso catheter, thus resulting in conduction block between pacing artifact and PVP, as shown in Figure 3B. The opposite was observed in 17 PV pacing sites (19%) in 11 patients (40%), where conduction block occurred between the PVs and LA.

A more complex electrophysiological pattern was observed in 6 patients. During programmed stimulation, conduction block occurred between the PVs and LA as extrastimuli were progressively decremented. Then, extrastimuli at even shorter coupling intervals resulted in so long a delay in venous activation that PV-LA conduction resumed before PV ERP was reached (Figure 4). As a consequence, the interval between venous and atrial activation was shortened. PVP-LA block was observed at a mean coupling interval of 190 ± 33 ms, and conduction resumed at 140 ± 33 ms.

AF Initiation During Pacing Protocol
In patients with AF, at least 1 episode of sustained AF (>3 minutes) was induced by the stimulation protocol when performed from within 22 of 90 PV pacing sites (25%) in 15
patients (54%) (Figure 5). This was observed in only 1 case when LA pacing was performed (1 of 81 pacing sites; \( P < 0.001 \)). Multiple paroxysms of induced AF in 9 patients (7 from LSPVs and 2 from RSPVs) prevented venous ERP assessment. AF was never induced in the control group during the stimulation protocol either in the PVs or in the LA.

Discussion
PVs are of major interest as a result of their prominent arrhythmogenic role in AF.\(^2\)–\(^4\) This study describes specific electrophysiological properties of PVs in human beings, distinguishing patients with from those without AF.

Programmed stimulation from multiple sites showed that in patients with AF, venous ERPs are significantly shorter than LA ERPs and significantly shorter than PV ERPs of patients without AF. The PVP FRPs of patients with AF are also significantly shorter than those of control patients, whereas the FRPs of the PV-LA junction and the LA ERPs are comparable, demonstrating that the main difference between patients with and without AF is observed in PVs rather than at the junction with the LA or in the LA itself. PV ERPs and FRPs were found to be as short as 60 and 100 ms, respectively. Such short functional refractory periods have never been reported previously in any part of the human heart and may explain why rapid high-frequency activity is consistently recorded in the PV area during AF.\(^5\)\(^,\)\(^6\)

On the contrary, venous ERPs in control patients were found to be significantly longer than that of the LA. These parameters clearly differ in patients with and without AF and may be responsible or play a major role for the development of AF. However, we cannot rule out the opposite, short venous ERPs being the consequence of AF by a remodeling process. This is less likely, because in our patient population, AF was paroxysmal, with episodes separated by hours or days, and it has been shown that atrial ERPs recovered to baseline values within 10 minutes after an episode of AF.\(^7\)

Furthermore, it is difficult to surmise that the remodeling process would have selectively affected the PVs, sparing the rest of the LA, because the LA ERPs were not different from those of controls.
Figure 3. A. Panel 1, with an extrastimulus coupling interval (S2) of 280 ms, LSPV activation sequence recorded is similar on Lasso catheter to that observed during basic cycle drive. Panel 2, shortening coupling interval to 260 ms results in delayed PV and LA activation with changes in intra-PV activation sequence. This is better seen in panel 3, with an extrastimulus at a coupling interval of 240 ms. Long-duration and fractionated potentials suggesting slow conduction are clearly visible in Lasso 6 to 7. Dashed arrows indicate PVPs; solid vertical arrows, LA potentials. B, Panel 4, with a coupling interval of 220 ms, an abrupt delay is observed between S2 artifact and PVP, associated with a significant change in intra-PV course, resulting in prolongation of S2-LA from 118 ms (panel 3, Figure 2) to 213 ms. Panel 5, with a coupling interval of 200 ms, a different intra-PV route is observed, and S2-LA interval is further delayed to 227 ms. Panel 6, with a coupling interval of 180 ms, venous ERP is reached. Open arrow indicates absence of venous activity.
Electrical properties of the thoracic veins have been assessed in animals, but currently, there are no animal models of AF spontaneously induced from PVs, and as a result, few experimental data are available to substantiate our findings. However, action potentials at the distal end of PVs were previously reported to be shorter than those of more proximal segments and LA in guinea pigs, consistent with the results of the present study.

The other significant result in the present study is the pronounced decremental conduction properties of PVs. This probably explains the marked conduction delay in the PVs observed during AF initiation or ectopics, as well as the phenomenon of concealed venous ectopics blocked within the vein. The same phenomenon was mimicked during programmed stimulation, with a block occurring between venous potentials and LA. A recent study conducted in dogs reported conduction patterns in PVs similar to those described here. The activation delay was correlated with complex fiber arrangement and particularly with abrupt changes in their direction. These decremental conduction properties could therefore be related to anisotropic conduction, with the fractionated venous potentials and associated changes in activation sequence and exits probably correlating with the complex arrangement of venous muscular sleeves reported by pathologists in humans. In a previous human study by Chen et al, the distal ERPs of superior PVs, although significantly shorter than those of the proximal venous musculature, were not significantly different from atrial ERPs and from those of control patients. Moreover, there was no mention of the extremely short venous ERPs as observed in our AF population. This may be related to differences in populations or in methods, but limited details were provided. The use in our study of circular PVs or basket mapping has probably been a significant improvement to the evaluation of electrophysiological PV properties.

Finally, the preferential induction of AF after a single extrastimulus from the vein (compared with the LA) is remarkable and suggests that inducibility depends on proximity to critical areas (with short ERP and long conduction time) such as PVs.

Using the findings of the present study, it may be possible to identify the potential arrhythmogenicity of PVs based on short ERPs and inducibility with possible extrapolation to other thoracic veins but with the limitation that ERP may vary significantly in different areas of a given vein.

In association with long conduction times in PVs, these short ERPs and FRPs provide a very favorable milieu for arrhythmogenicity, particularly reentry in or around the veins.

Figure 4. "Gap"-like behavior during programmed stimulation from LSPV. Panel 1, S2 delivered with a coupling interval of 220 ms is followed by venous potentials (dashed arrow) with an S2-PVP delay of 20 ms. Atrial potential (solid arrow) recorded in bipolar 3 to 4 occurs 170 ms after local PVP. Panel 2, with a coupling interval of 200 ms, a venous response is recorded (dashed arrow), with an S2-PVP interval of 20 ms. There is no atrial response, demonstrating that refractory period of PV-LA junction was reached. Same phenomenon was observed with coupling intervals of 200 to 100 ms (panel 3). Panel 4, with an S2 delivered at a coupling interval of 100 ms, very slow conduction occurring in vein allows impulse to arrive at venoatrial junction late enough to be conducted. FRP of PVP is as short as 110 ms. Panel 5, with an S2 coupling interval of 80 ms, venous ERP is reached.
which may perpetuate arrhythmia and thus act as a substrate for AF maintenance.

The main limitation to this study is that the pacing protocol used may occasionally have resulted in capture with long latencies, thus producing false “decremental” conduction. The chance of latency polluting the results was exactly the same in both groups, because all patients were studied in the same way, without significant differences in PV thresholds. The longer PV ERPs without pronounced slow conduction observed in the control group does not favor an important role for latency in this study protocol. Latency could have been ruled out by systematically using basket catheters. Unfortunately, they are limited by important artifacts recorded during PV pacing.

Conclusions
This study demonstrates very distinctive electrophysiological properties of PVs in patients with AF, consisting of short or extremely short ERPs and FRPs, with decremental and slow conduction properties probably playing a major role in arrhythmogenicity.

References

Figure 5. Programmed stimulation performed within LSPV from the ablation catheter placed distal to the Lasso. An extrastimulus (S2), coupled at 200 ms, results in long duration and fractionated potentials in Lasso bipolar 3–4 (indicating slow conduction), with significant changes in intra PV course. Latency can be ruled out in this example, as proximal bipolar of the pacing catheter (PV 3–4) is not showing any delay (†). When S2 is decremented to 180 ms, AF is initiated. Fractionated potentials recorded by the Lasso catheter during the first 2 beats nearly cover the entire CL and are consistent with a complex reentrant mechanism.
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